

**Lithiation-Trapping of Saturated
Oxygen and Sulfur Heterocycles**

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Doctor of Philosophy

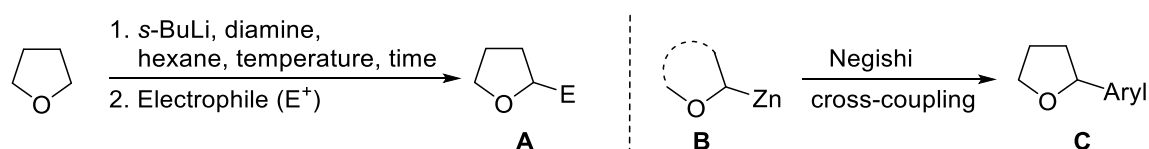
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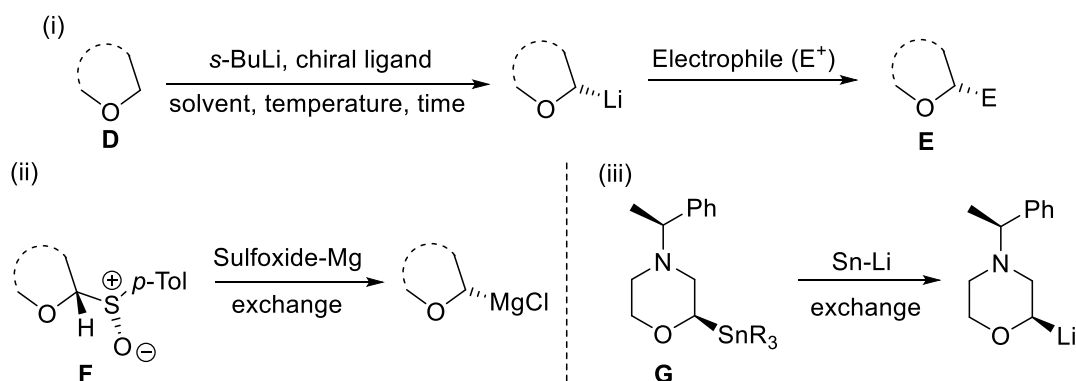
March 2020

Abstract

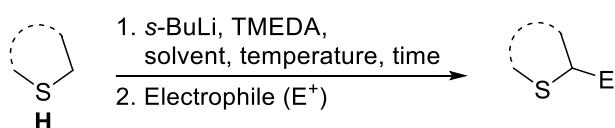
Substituted oxygen and sulfur heterocycles form the core of a number of drug molecules and natural products. In this thesis, the α -functionalisation of saturated oxygen and sulfur heterocycles, *via* direct lithiation and *via* Sn-Li exchange reactions from organostannanes, using organolithium reagents is described. Chapter 2 details the synthesis of α -substituted tetrahydrofurans (THFs) **A** *via* racemic lithiation and subsequent trapping with electrophiles. In addition, the arylation of saturated oxygen heterocycles *via* the generation of an organozinc species **B** and subsequent Negishi cross-coupling to give α -aryl oxygen heterocycles **C** is presented. Two routes towards the organozinc species, direct lithiation of oxygen heterocycles and transmetalation with ZnCl_2 and starting from organostannanes, Sn-Li exchange and transmetalation, are described.



In chapter 3, three approaches to enantioenriched α -substituted oxygen heterocycles **E** are described: (i) asymmetric deprotonation of oxygen heterocycles **D** using chiral diamines; (ii) synthesis and sulfoxide-Mg exchange of α -sulfinyl substituted oxygen heterocycles **F**; (iii) synthesis of enriched α -substituted morpholines using α -stannyl morpholines **G**.



In chapter 4, the lithiation-trapping of saturated sulfur heterocycles **H** is presented. This includes development of lithiation conditions for 5- and 6-membered saturated sulfur heterocycles and regio- and stereoselective lithiation-trapping processes.



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Author's Declaration

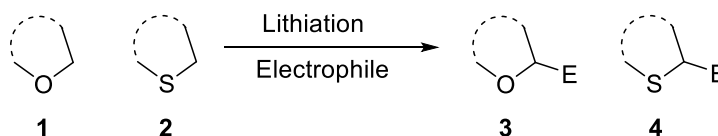
I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Nico Seling

Chapter 1: Introduction

Saturated and aromatic oxygen heterocycles are the second most common structures in FDA approved pharmaceuticals.¹ Among the 311 approved drugs bearing such oxygen heterocycles, 73% contained saturated 5- and 6-membered ring oxygen heterocycles. In addition, saturated 5- and 6-membered ring oxygen heterocycles appear in a wide range of natural products.²⁻³ Although less common than their oxygen analogues, α -substituted saturated sulfur heterocycles are present in pharmaceutically relevant compounds.⁴⁻⁵ Therefore, the development of new synthetic pathways to saturated α -substituted oxygen heterocycles and their sulfur analogues is of current interest.

This thesis is concerned with the α -functionalisation of saturated oxygen and sulfur heterocycles **1** and **2** to give **3** and **4** respectively (Scheme 1.1). Our strategy is to start with an intact saturated oxygen or sulfur heterocycle and carry out α -lithiation and subsequent electrophilic trappings. Lithiation, transmetallation and cross-coupling to introduce α -aryl groups will also be explored.



Scheme 1.1 Lithiation-Trapping of Oxygen and Sulfur Heterocycles.

In section 1.1, a brief introduction to selected oxygen and sulfur-containing pharmaceutically relevant compounds as well as natural products is presented. Current approaches that use α -functionalisation of intact saturated oxygen or sulfur heterocycles are mainly limited to radical processes. Therefore, in section 1.2, an overview of approaches that start with 5- and 6-membered cyclic ethers and sulfides and use radical processes for carbon-carbon bond formation are presented. In contrast to the relatively underrepresented metallation of oxygen and sulfur heterocycles, the lithiation of *N*-Boc heterocycles and trapping with electrophiles or transmetallation and cross-coupling is well explored. In section 1.3.1, a brief overview of the functionalisation of *N*-Boc heterocycles using organolithium reagents is presented. Finally, a summary of the metallation of saturated oxygen and sulfur heterocycles is given in sections 1.3.2 and 1.3.3 respectively and this is followed by the outline of the project in section 1.4.

1.1 Introduction to Saturated α -Substituted Oxygen and Sulfur Heterocycles

Saturated oxygen and sulfur heterocycles are present in a range of natural products and pharmaceutically relevant molecules.¹⁻² α -Substituted saturated tetrahydrofuran (THF) is present in the stimulant drug Zylofuramine[®] which was used as an appetite suppressant and in the treatment of senile dementia (Figure 1.1).⁶ In addition, α -substituted THF forms the core of bromuconazol, a fungicide developed by Rhône-Poulenc and marketed as a mixture of two diastereomers.⁷ Naftidrofuryl, marketed as Praxilene[®], is a mixture of two diastereomers and was used historically in the treatment of idiopathic hearing loss and tinnitus.⁸ Today, it is marketed as a vasodilator and used in the regulation of peripheral vascular disorders. Another example is terazosin (marketed as Hytrin[®]), an α blocker used for the treatment of high blood pressure.⁹ The methacrylic ester THFM is used as a methacrylate monomer in the synthesis of adhesives.¹⁰ Faropenem, marketed as Farom[®] in Japan, is an antibiotic bearing a 4-membered β -lactam ring fused to a 5-membered sulfur heterocycle. It is in clinical trials in the USA for the treatment of sinusitis and chronic bronchitis.¹¹

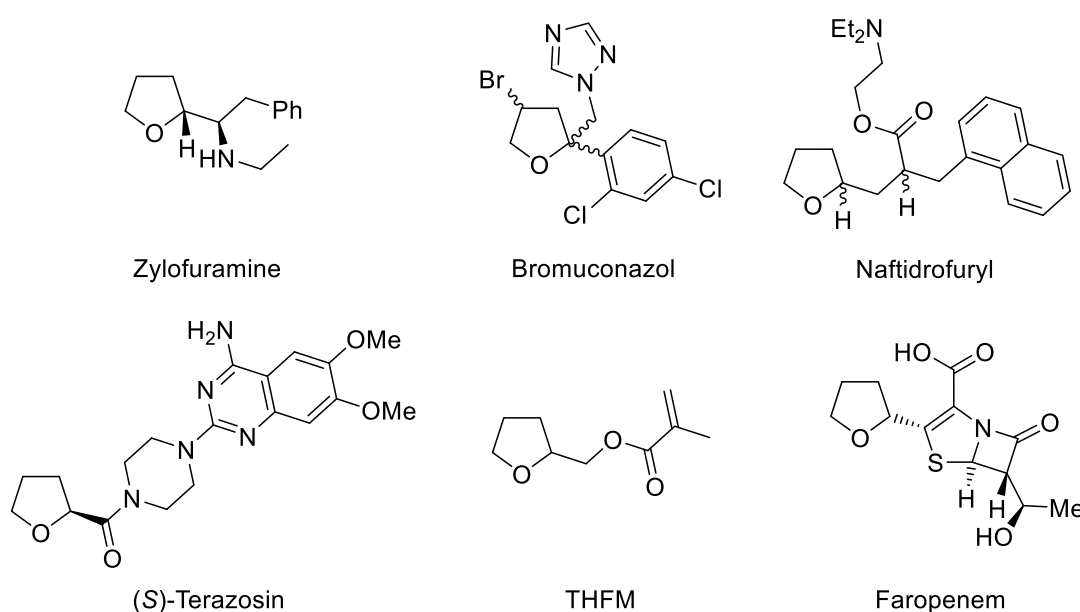


Figure 1.1 α -Functionalised Tetrahydrofurans.

The α -substituted tetrahydropyran (THP) scaffold is found in numerous natural products. One example is the monoterpene rose oxide. The (–)-2,4-*cis* configured rose oxide is responsible for the characteristic smell of roses.¹² A 2,4,6-*cis*-substituted THP *cis*-5 has been extracted from the leaves of the plant *Plectranthus Sylvestris*.¹³ In addition, oliceridine, an

opioid drug, bearing a THP core, is in clinical trials for the treatment of acute pain. Developed by Trevena, it is a potential μ -opioid receptor agonist (Figure 1.2).¹⁴

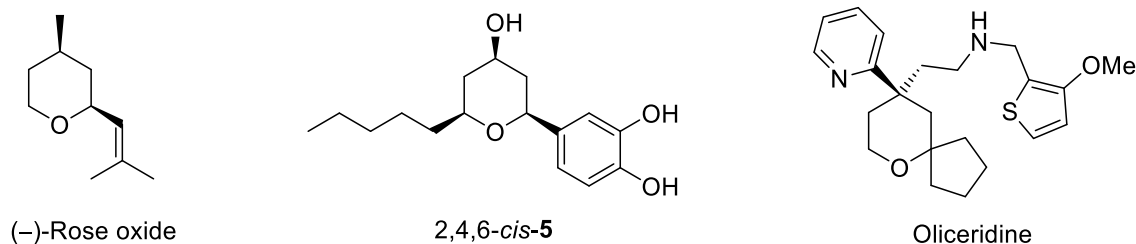


Figure 1.2 α -Functionalised Tetrahydropyrans.

α -Substituted morpholines are particularly common in pharmaceutically relevant compounds (Figure 1.3). For example, PF-219,061 is a selective antagonist for the dopamine D3 receptor,¹⁵ morpholine (*R,S*)-**6** is a key intermediate in the synthesis of a TPK1 inhibitor developed by Mitsubishi Tanabe Pharma and Sanofi-Aventis¹⁶ and oxaflozane is an antidepressant drug introduced by Solvay.¹⁷ The morpholine scaffold also forms the core of reboxetine, an antidepressant marketed by Pfizer. It is commercially available as the racemate of a specific diastereomer and acts as a norepinephrine reuptake inhibitor.¹⁸

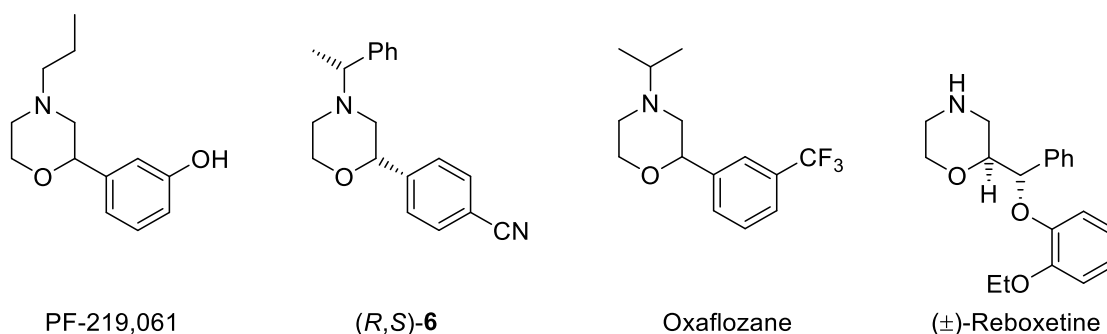


Figure 1.3 α -Functionalised Morpholines.

Although less common than their oxygen analogues, saturated sulfur heterocycles that have a substituent in the α -position to sulfur do feature in pharmaceutically relevant compounds. For example, they form the core of the orexin antagonist **7** developed by Merck Sharp Dohme and the CXCR antagonist **8** synthesised by Nestle and currently in clinical trials showing efficiency in inflammation models.^{4, 19} The 5-membered cyclic sulfide sets the scaffold of the natural product biotin²⁰ and the core of the naturally occurring antibiotic penicillin G.²¹ In catalysis, α -substituted sulfides **9** and **10** have been used as organocatalysts for asymmetric epoxidation and for the enantioselective synthesis of chiral aziridines respectively (Figure 1.4).²²⁻²⁴

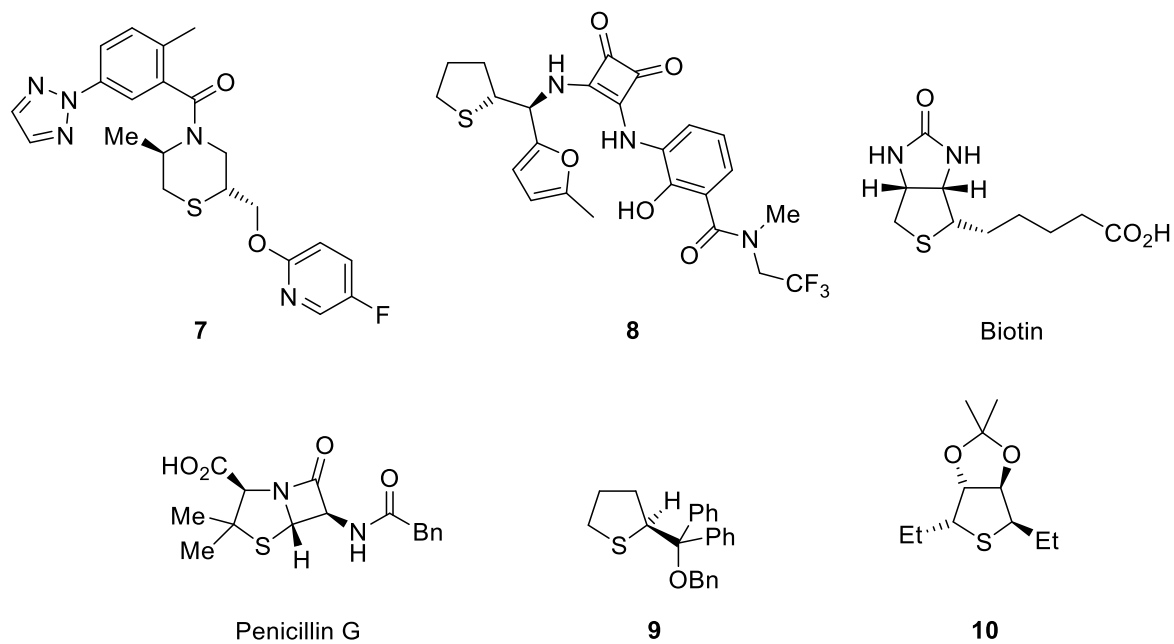
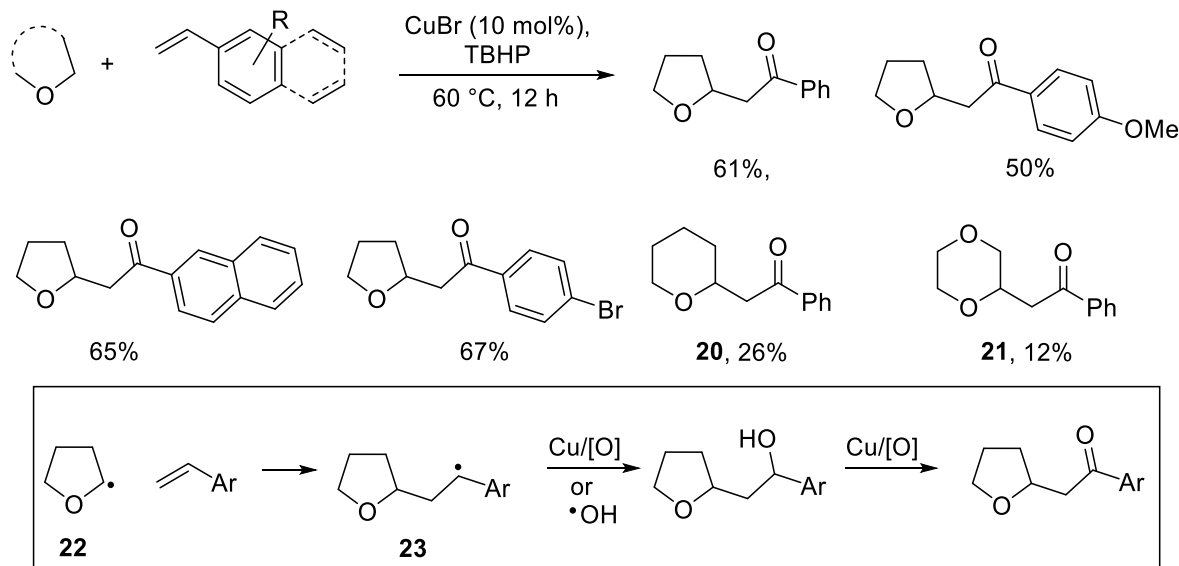


Figure 1.4 α -Functionalised Sulfur Heterocycles.

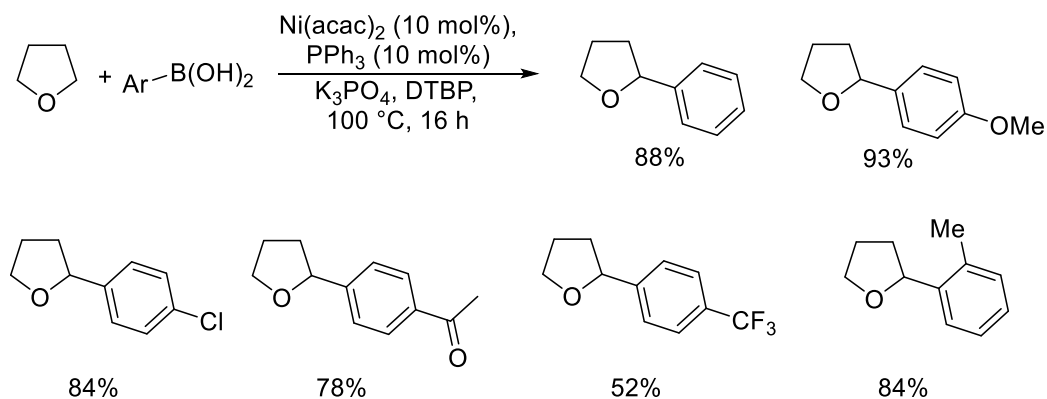
Gong and Fuchs proposed two mechanisms for the formation of the product (Scheme 1.3). In one mechanism, the alkalkoxy radical reacts with the β -carbon of the triflone to give the vinyl radical **17**, which fragments to the vinylidene carbene **18**. Subsequent Fritch-Buttenberg-Weichell rearrangement results in the product. An alternative mechanism from the vinyl radical **17** is the formation of vinyl radical **19** via a 1,2-shift which fragments to give the product.

Zhang et al. presented an approach towards α -substituted oxygen heterocycles via Cu-catalysed cross-dehydrogenative coupling of vinylarenes.²⁶ Addition of the oxygen heterocycles to vinyl arenes in the presence of CuBr and TBHP gave α -substituted THFs in 50-67% yield (Scheme 1.4). Using 6-membered THP and dioxane, α -substituted oxygen THP **20** and dioxane **21** were obtained in 26% and 12% yield respectively. Zhang et al. suggested the following mechanism for the α -substitution. Fragmentation of TBHP leads to the formation of *t*-butoxy and hydroxyl radicals which both can abstract a hydrogen atom from THF to give the alkalkoxy radical **22**. The THF radical then adds to the alkene to give radical **23**. Subsequent recombination with a hydroxyl radical or Cu-mediated oxidation results in an alcohol which is oxidised to the ketone.



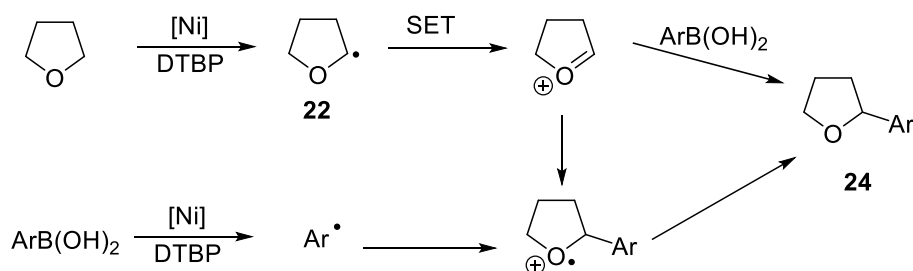
Scheme 1.4 Cu-Catalysed Cross-Dehydrogenative Coupling of Vinylarenes.

In 2013, Lei et al. reported the Ni-catalysed oxidative arylation of THF using arylboronic acids.²⁷ The cross-dehydrogenative coupling required the use of DTBP and catalytic Ni(acac)₂ and PPh₃. Reaction of THF with aryl boronic acids gave α -arylated oxygen heterocycles in up to 88% yield (Scheme 1.5). Electron-withdrawing and donating aryl substituents were tolerated.



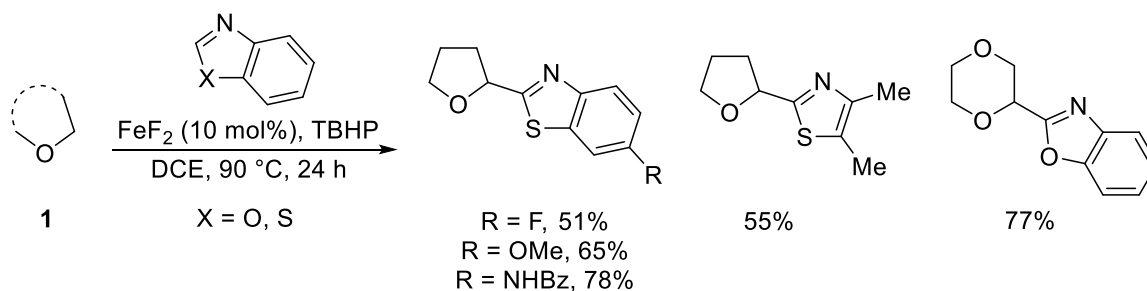
Scheme 1.5 Ni-Catalysed Oxidative Arylation of THF.

In the reaction mechanism proposed by Lei et al., Ni-catalysed hydrogen atom abstraction leads to radical **22** (Scheme 1.6). Subsequent single electron transfer would give an oxonium ion which could then react with the boronic acid to give the α -arylated THF **24**. Alternatively, the oxonium ion could react with the aryl radical, generated by homolytic cleavage of the boronic acid mediated by the oxidant and Ni catalyst.



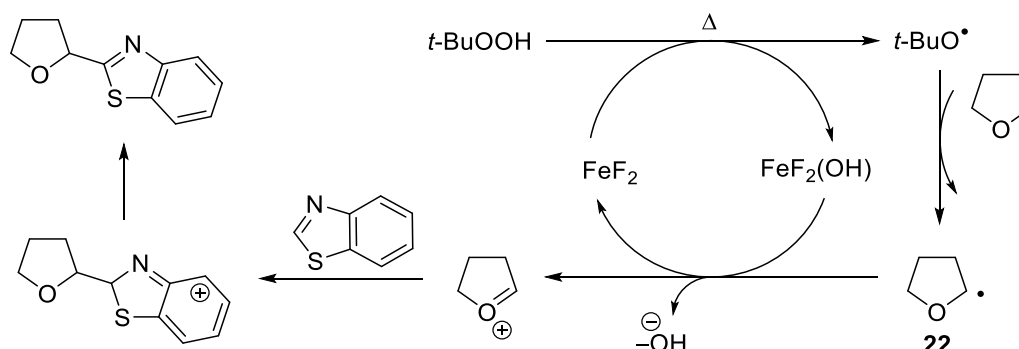
Scheme 1.6 Proposed Mechanism for the Ni-Catalysed Oxidative Arylation of THF.

The synthesis ofazole-substituted oxygen heterocycles using transition metal-catalysed cross-dehydrogenative coupling has received high interest over the last decade. TBHP and catalysts such as $\text{Cu}(\text{OTf})_2$, CoCO_3 , Co/ETS-10 and CuI have been employed in the coupling.²⁸⁻³¹ In addition, Correra et al. presented the Fe-catalysed coupling of azoles with oxygen heterocycles (Scheme 1.7).³² The oxygen heterocycles **1** were treated with azole derivatives in the presence of FeF_2 and TBHP to give α -azole substituted heterocycles. Coupling of THFs with thiazoles gave the α -substituted THF in 51-78% yield. Apart from THF, azoles were coupled to oxolanes and dioxanes in good yield (59-78%).



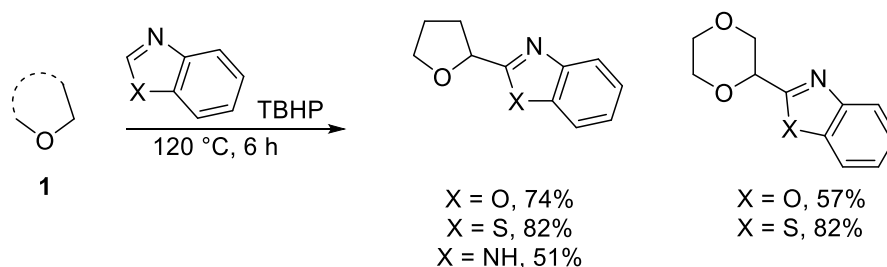
Scheme 1.7 Fe-Catalysed Coupling of Azoles with Oxygen Heterocycles.

To gain insight into the mechanism of the reaction, a range of control experiments was carried out. Addition of a radical scavenger such as BHT to the reaction inhibited the formation of the α -substituted oxygen heterocycle. Based on DFT studies the radical pathway as depicted in Scheme 1.8 is likely. Thermal induced homolytic cleavage of TBHP leads to the generation of $\text{FeF}_2(\text{OH})$ and the *t*-butoxy radical which abstracts a hydrogen atom from the oxygen heterocycles to give the alkylalkoxy radical **22**. Subsequent $\text{FeF}_2(\text{OH})$ assisted oxidation *via* SET would lead to the oxonium ion and the regeneration of the FeF_2 catalyst. The oxonium ion is then attacked by the azole to give a carbocation which undergoes rearomatisation to result in the product.



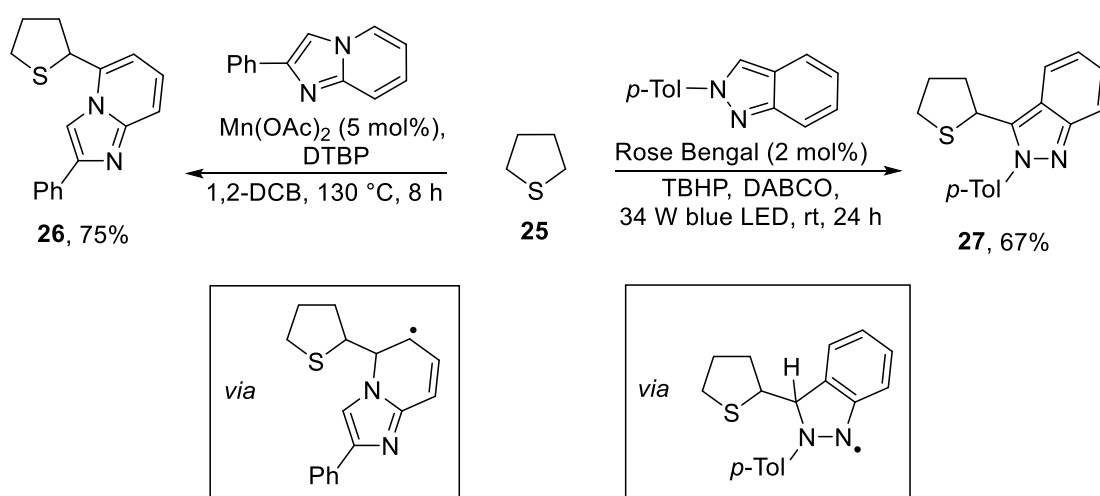
Scheme 1.8 Postulated Mechanism for the Fe-Catalysed Coupling.

As well as the transition metal-catalysed cross dehydrogenative coupling reactions, several groups have reported metal-free coupling reactions. Ueno and Shirakawa published a base-promoted synthesis of α -substituted cyclic ethers.³³ Wang et al., Cai et al. and Kwong et al. developed metal-free cross-decarboxylative coupling reactions using only the oxidant DTBP or TBHP and high reaction temperatures to access α -indolyl, α -pyridyl substituted oxygen heterocycles in high yields.³⁴⁻³⁷ For example, Wang et al. reported the metal-free coupling of azoles with THF and dioxane (Scheme 1.9).³⁸ Simply, reaction of TBHP with the oxygen heterocycles **1** and azole at high temperature for 6 h gave α -arylated THFs in 51-82% yield and α -arylated dioxanes in 57-82% yield (Scheme 1.9).



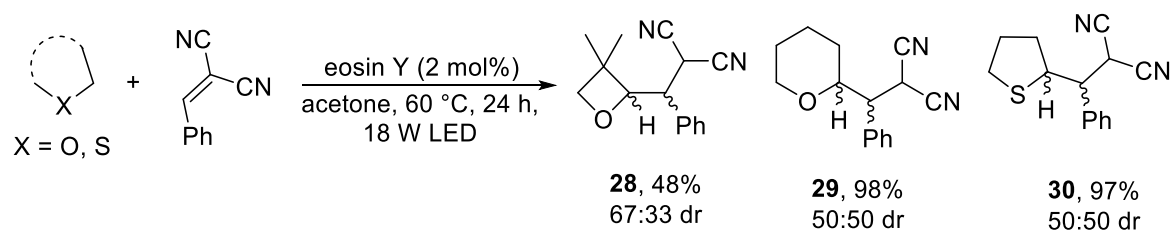
Scheme 1.9 Metal-Free Coupling of Azoles with Oxygen Heterocycles.

Recently, Hajra et al. used the cross-dehydrogenative coupling for the synthesis of 2*H*-indazolyl- and imidazopyridyl-substituted cyclic ethers and sulfides.³⁹ Two examples with cyclic sulfides **25** are shown in Scheme 1.10. For the imidazopyridine, an approach with a $\text{Mn}(\text{OAc})_2$ catalyst in combination with DTBP was used to give the α -arylated sulfide **26** in 75% yield. The formation of the indazolyl-substituted sulfide **27** (67% yield) used TBHP as the oxidant, Rose Bengal as a photocatalyst and a blue LED.⁴⁰ The key step in both reactions is the cross-dehydrogenative coupling step in which the sulfide radical attacks into the aromatic system to give the intermediate radical species shown. Subsequent rearomatisation resulted in the desired products.



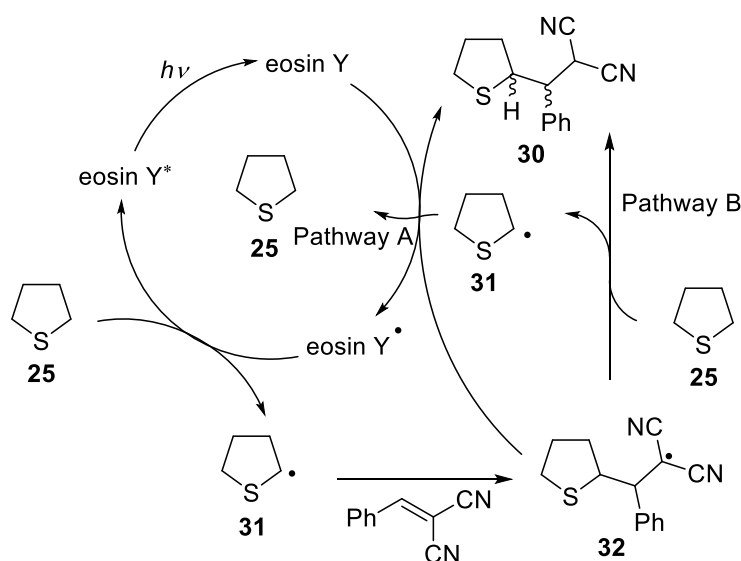
Scheme 1.10 Cross-Dehydrogenative Couplings Developed by Hajra.

In recent years, several research groups have become interested in the light-mediated α -functionalisation of saturated oxygen and sulfur heterocycles. Wu et al. reported the use of eosin Y as a hydrogen atom transfer (HAT) photocatalyst in the α -alkylation of cyclic ethers and sulfides with electron-deficient dicyanide alkenes using a white LED light source (Scheme 1.11).⁴¹ For example, α -substituted oxetane **28** was isolated in 48% yield (67:33 dr) and THP derivative **29** was formed in 98% yield (50:50 dr). In addition, the α -alkylated sulfide **30** was obtained in 97% yield (50:50 dr).



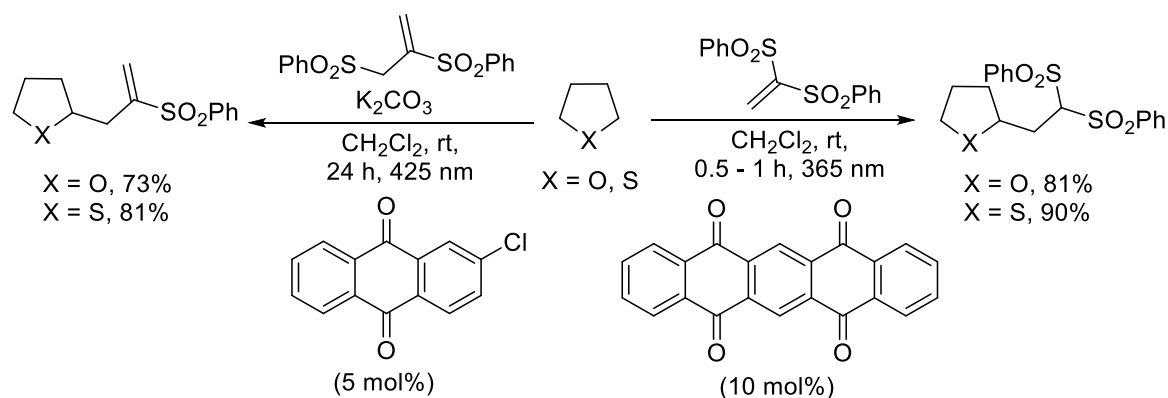
Scheme 1.11 Light-Mediated α -Functionalisation using Eosin Y.

The proposed mechanism, illustrated for cyclic sulfide **25**, is shown in Scheme 1.12. Wu et al. stated that in the first step of the catalytic cycle, a HAT of eosin Y* and cyclic sulfide **25** leads to cyclic sulfide radical **31** which reacts with the electron-deficient alkene to form radical species **32**. In the next step (pathway A), another HAT of eosin Y could result in the desired α -alkylated product **30** and the eosin Y radical. An alternative pathway (pathway B) is a HAT of a second cyclic sulfide by radical **32** to give the product **30**. The generated radical **31** could then undergo a HAT to regain the cyclic sulfide while forming the eosin Y radical.



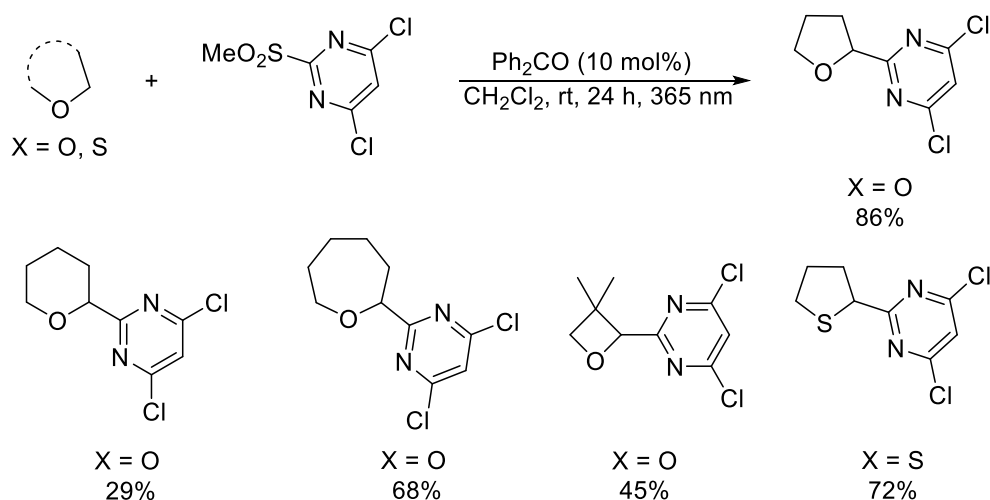
Scheme 1.12 Proposed Mechanism for the Light-Mediated α -Functionalisation Using Eosin Y.

The group of Kamijo reported the use of alkyl-, allyl- and aryl-substituted sulfones in light-mediated coupling reactions with cyclic ethers and sulfides.⁴²⁻⁴⁵ An approach towards α -alkylated and allylated heterocycles was reported by the group using sulfonyl alkenes (Scheme 1.13). Starting from THF or sulfide **25**, two different hydrogen abstracting reagents were used to form a radical α to oxygen or sulfur which was mediated by 365 nm or 425 nm light sources. Allylation using the sulfonyl propene gave α -substituted products in 73-81% yield. Reaction with a sulfonyl alkene gave α -substituted products in 81-90% yield.



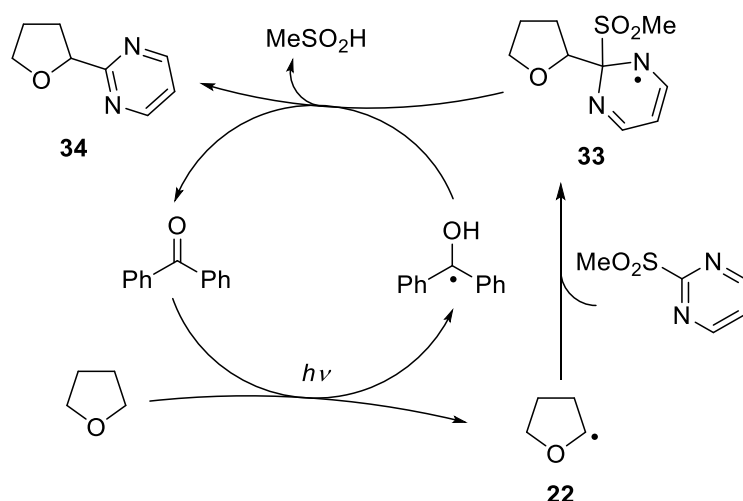
Scheme 1.13 Light-Mediated Coupling of Oxygen and Sulfur Heterocycles with Sulfonyl Alkenes.

The pyrimidine scaffold and derivatives are present in bases such as adenine, cytosine, thymine and guanine which are essential building blocks of DNA. Therefore, Kamijo et al. extended the light-mediated sulfonyl coupling reactions to couple sulfonyl pyrimidines and cyclic ethers and cyclic sulfides (Scheme 1.14). The reactions were mediated by photoexcited benzophenone and sulfonyl pyrimidines using a 365 nm light source. This gave the desired α -arylated products in up to 86% yield with different oxygen and sulfur heterocycles.



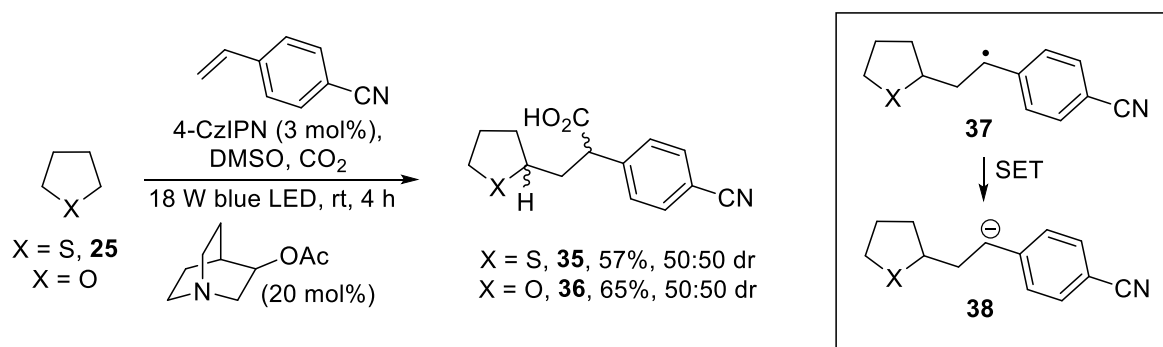
Scheme 1.14 Light-Mediated Coupling with Sulfonyl Pyrimidines.

In the first step of the catalytic cycle, THF radical **22** is generated by HAT to give the ketyl radical obtained from benzophenone (Scheme 1.15). The radical reacts with the pyrimidine derivative to give an intermediate nitrogen-centred radical **33** which undergoes rearomatisation to give the desired product with formation of a sulfonyl radical **34**.



Scheme 1.15 Proposed Mechanism in the Light-Mediated Coupling with Sulfonyl Pyrimidines.

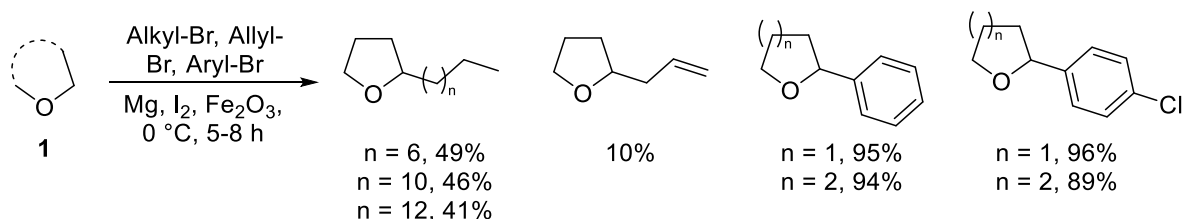
A protocol for a visible light-mediated difunctionalisation of alkenes with CO₂ and THF and cyclic sulfide **25** was presented by Wu et al. (Scheme 1.16).⁴⁶ The reaction allows the coupling of an alkene with cyclic sulfide **25** to form an α -alkylated cyclic sulfide which was then reacted with CO₂ to give carboxylic acid **35** in 57% yield (50:50 dr). Starting from THF, the α -alkylated THF **36** was obtained in 65% yield (50:50 dr). In the proposed mechanism, radical α to sulfur or oxygen is generated which reacts with the alkene to form radical **37**. Subsequent SET transfer leads to the formation of anion **38** which can then be trapped with CO₂ to give the carboxylic acid.



Scheme 1.16 Light-Mediated Difunctionalisation of Alkenes.

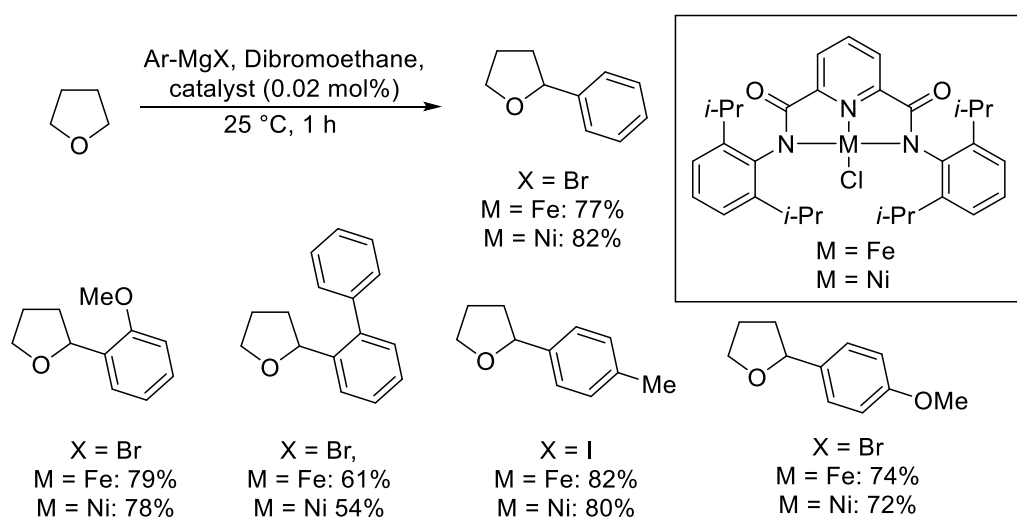
Another approach to α -substituted saturated oxygen and sulfur heterocycles is *via* transition-metal catalysed cross-coupling of alkyl and aryl magnesium halides. Vishwakarma et al. reported the synthesis of α -arylated THF derivatives using Fe₂O₃.⁴⁷⁻⁴⁸ The oxygen heterocycle **1** was treated with the alkyl or aryl halide and magnesium and iodine to form the Grignard reagent which then underwent Fe₂O₃-catalysed cross-coupling to give the α -substituted THFs in 10-49% yield (Scheme 1.17). In addition, coupling was possible with a

range of aryl bromides bearing electron-withdrawing and electron-donating groups to give the α -arylated THF and THP heterocycles in 89-95% yield.



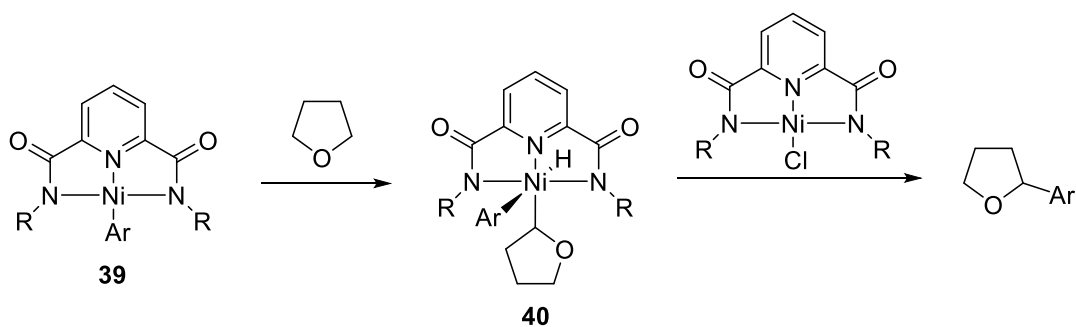
Scheme 1.17 Transition-Metal Catalysed Cross-Coupling of Alkyl and Aryl Magnesium Halides and Oxygen Heterocycles.

In 2014, Gosh et al. reported the coupling of THF and aryl Grignard reagents in the synthesis of α -arylated THF derivatives (Scheme 1.18).⁴⁹⁻⁵⁰ Small quantities (0.02 mol%) of Ni and Fe complexes were used as catalysts to give the desired products in 54-82% yield. The turnover number of the catalyst was between 3490 and 4340 and therefore underlined the high efficiency of the catalyst. Furthermore, the synthesis of α -alkylated and α -allylated THF derivatives was possible using alkyl and allyl Grignard reagents in moderate yields of 12-54%.



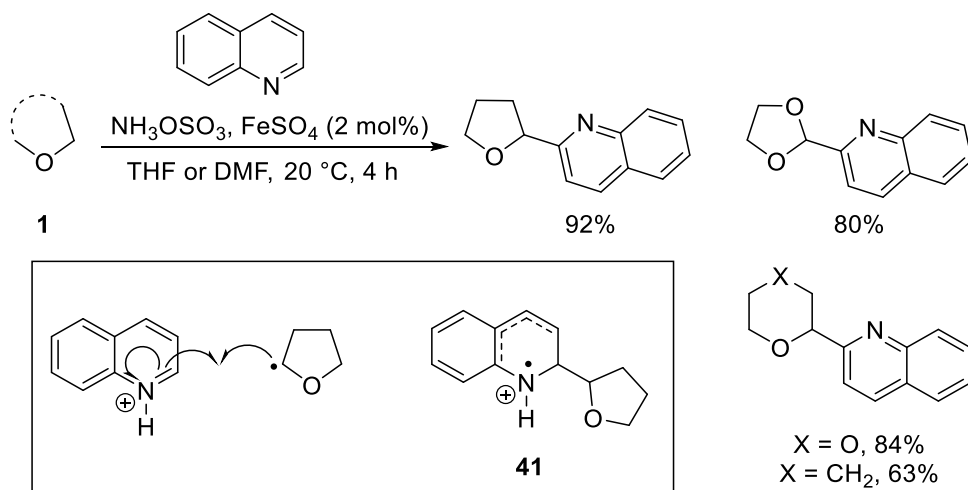
Scheme 1.18 Transition-Metal Catalysed Cross-Coupling of Aryl Magnesium Halides and THF.

Gosh et al. proposed a mechanism in which the Ni complex and the Grignard reagent form a Ni aryl complex **39** (Scheme 1.19). Subsequent oxidative addition of THF leads to the formation of the proposed Ni-alkyl-aryl complex **40**. (No further characterisation data of complex **40** was reported by Gosh et al.). Finally, reductive elimination leads to the α -substituted product and the regeneration of the catalyst.



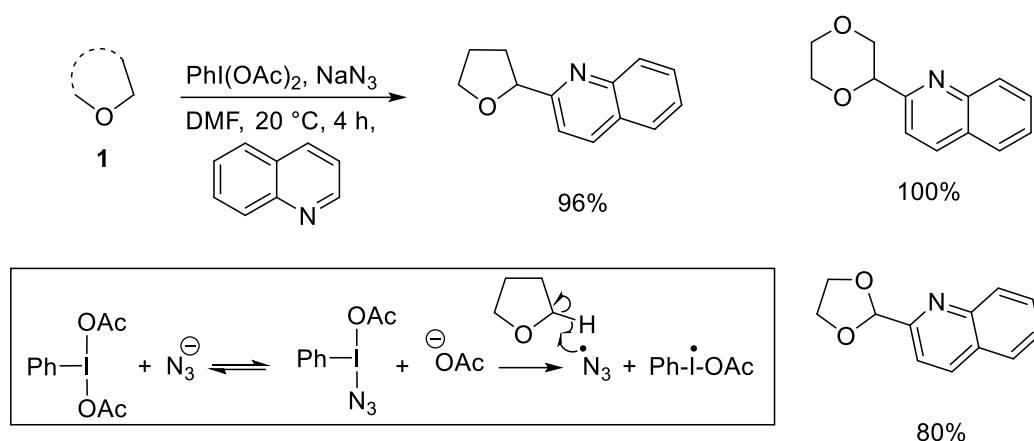
Scheme 1.19 Proposed Mechanism for the Transition-Metal Catalysed Cross-Coupling of Aryl Magnesium Halides and THF.

In 1983, Minisci et al. reported the synthesis of α -arylated saturated oxygen heterocycles from heteroaromatics such as quinoline. The oxygen heterocycles were reacted with quinoline in the presence of FeSO_4 and hydroxylamine-*O*-sulfonic acid to give the α -substituted oxygen heterocycles in 63-92% yield (Scheme 1.20). The key intermediate is radical **41** generated by reaction of the alkalkoxy radical and the protonated quinoline.



Scheme 1.20 Fe-Catalysed Minisci Reaction of Oxygen Heterocycles and Quinoline.

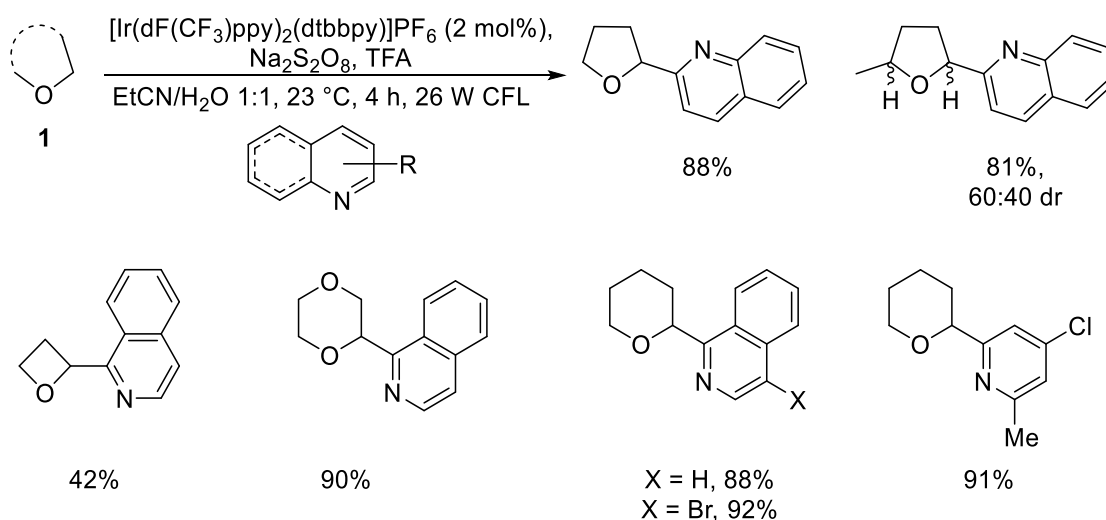
The same transformation can be achieved using PIDA and sodium azide (Scheme 1.21). Coupling with THF, dioxane and 1,3-dioxolane gave the α -arylated oxygen heterocycles in 80-100% yield. Minisci et al. proposed that an azide radical is generated which can then abstract a hydrogen atom from the oxygen heterocycle to form the alkalkoxy radical.



Scheme 1.21 PIDA-Catalysed Minisci Reaction of Oxygen Heterocycles and Quinoline.

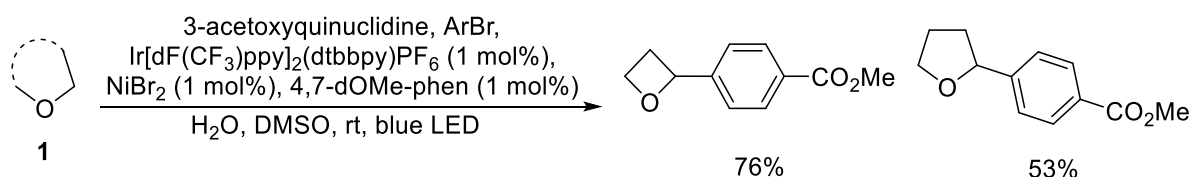
Other groups have subsequently investigated Minisci-type reaction conditions for the synthesis of aryl-substituted oxygen heterocycles. In 2015, Huang et al.⁵¹ reported the synthesis of α -pyridyl-substituted oxygen heterocycles using catalytic Sc(OTf)_3 . Another approach towards α -arylated saturated oxygen heterocycles *via* Minisci-type reactions using TFA and potassium persulfate was reported by Barriault et al.⁵²

In 2015, Jin and MacMillan⁵³ developed a method for the arylation of oxygen heterocycles by combining the Minisci reaction with photoredox-mediated C-H functionalisation. Irradiation of oxygen heterocycles in the presence of an Ir catalyst, pyridine and quinoline derivatives with fluorescent light gave the α -arylated oxygen heterocycles in 42-91% yield (Scheme 1.22). In related work, Devari and Shah and Jin et al. expanded the scope of the reaction using Selectfluor[®] and hydrogen peroxide as oxidants.⁵⁴⁻⁵⁵



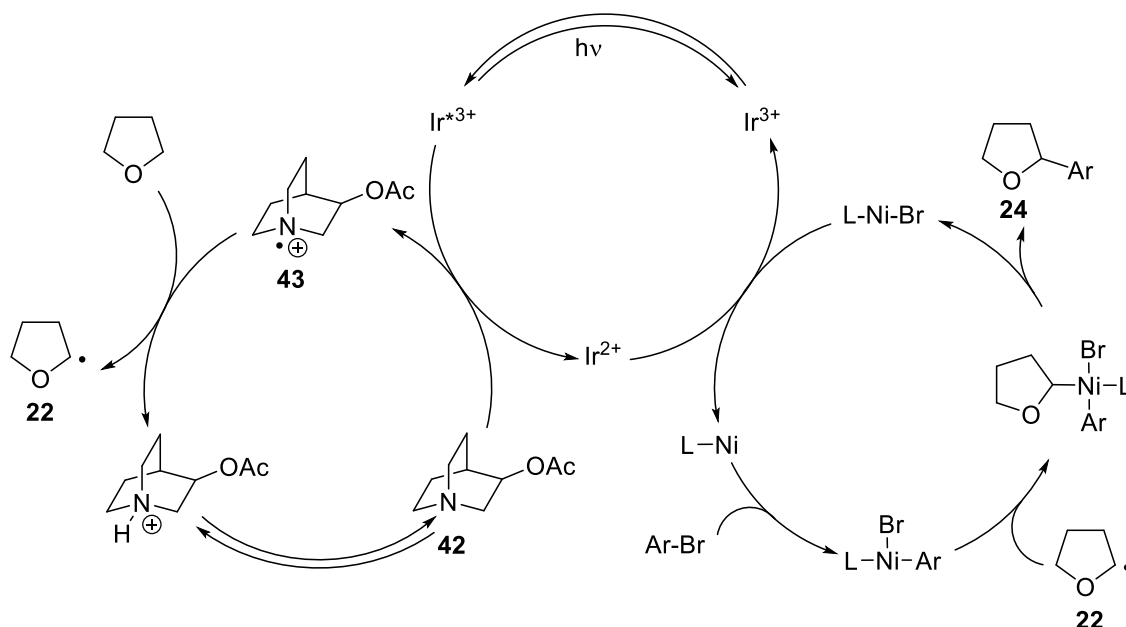
Scheme 1.22 Light-Mediated Minisci Reaction of Oxygen Heterocycles with Pyridine and Quinoline Derivatives.

One year later, MacMillan et al. reported the arylation of saturated oxygen heterocycles using a triple catalytic cross-coupling with aryl bromides (Scheme 1.23).⁵⁶ Photoredox-mediated HAT and organocatalytic regeneration of the photocatalyst were followed by a Ni-catalysed cross-coupling. The four-membered oxetane was coupled with methyl 4-bromobenzoate to give an α -arylated oxetane in 76% yield. In addition, THF underwent the coupling to give an α -aryl-substituted THF in 53% yield. Of note, in addition to oxetane and THF, a variety of saturated *N*-Boc heterocycles were used as starting materials in the α -arylation with methyl 4-bromobenzoate.



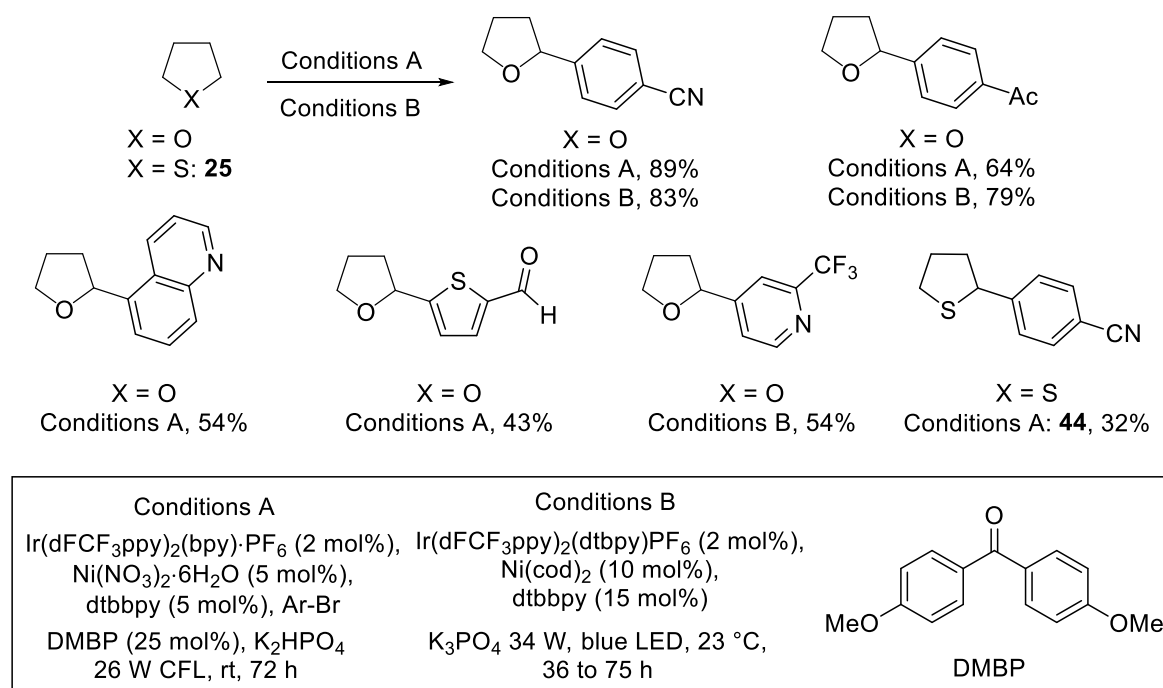
Scheme 1.23 Triple Catalytic Cross-Coupling of Oxygen Heterocycles and Aryl Bromides.

MacMillan et al. proposed the mechanism shown in Scheme 1.24 for these reactions. In the photoredox catalytic cycle, Ir(III) is excited by light. Then, SET to the HAT catalyst **42** results in radical cation **43**. Hydrogen abstraction of THF by the radical cation **43** results in THF radical **22**. In a second SET, Ir(III) is regenerated and leads to the formation of the Ni(0) species. Oxidative addition of the aryl bromide and the THF radical **22** results in a Ni complex. Subsequent reductive elimination leads to the formation of the α -arylated THF **24**.



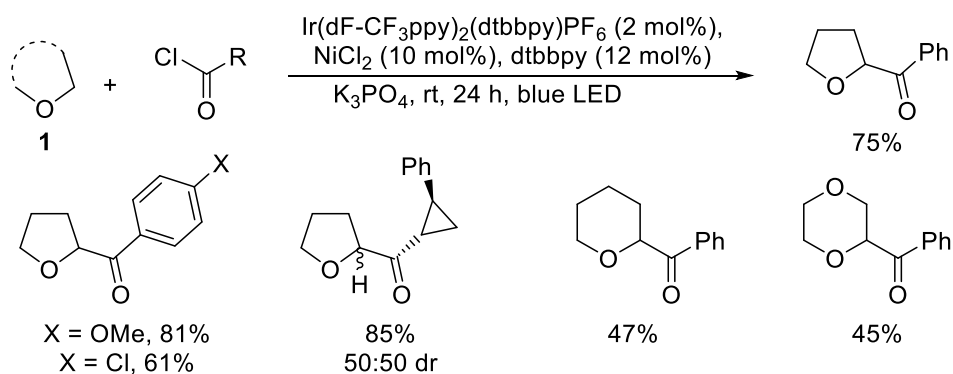
Scheme 1.24 Proposed Mechanism for the Organocatalysis, Photoredox and Ni-Catalysis Cycles.

In 2016, Molander et al. and Shields and Doyle independently reported the light-mediated synthesis of α -arylated oxygen heterocycles.⁵⁷⁻⁵⁸ Both groups used an Ir photocatalyst in combination with a Ni catalyst (Scheme 1.25). Molander et al. used visible light for 72 h (conditions A) to give α -arylated THFs in up to 89% yield. Shields and Doyle reported the synthesis of α -arylated THF (conditions B) in up to 83% yield. Starting from sulfide **25** reaction with 4-bromobenzonitrile using Molander et al.'s reaction conditions gave α -arylated cyclic sulfide **44** in 32% yield. Recently, Wang et al. extended the Ir-catalysed reaction to the arylation of oxygen heterocycles with multi-fluorinated benzene derivatives.⁵⁹



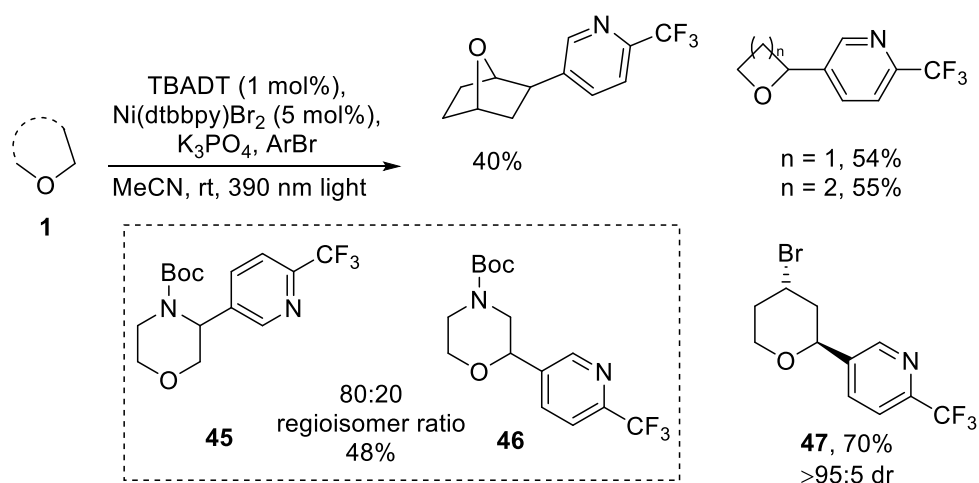
Scheme 1.25 Light-Mediated Arylation of Oxygen and Sulfur Heterocycles using Ir Photocatalysts in Combination with Ni Catalysis.

In the same year, Shibasaki et al. developed a light-mediated α -acylation of cyclic ethers using the combination of Ir and Ni catalysis (Scheme 1.26).⁶⁰ Addition of acid chlorides to 5- and 6-membered oxygen heterocycles in the presence of blue light and an Ir and Ni catalyst with benzoyl chlorides gave the α -acylated THF, THP and dioxane derivatives in 45-75% yield respectively.



Scheme 1.26 Light-Mediated α -Acylation of Oxygen Heterocycles Using Ir Photocatalysts in Combination with Ni Catalysis.

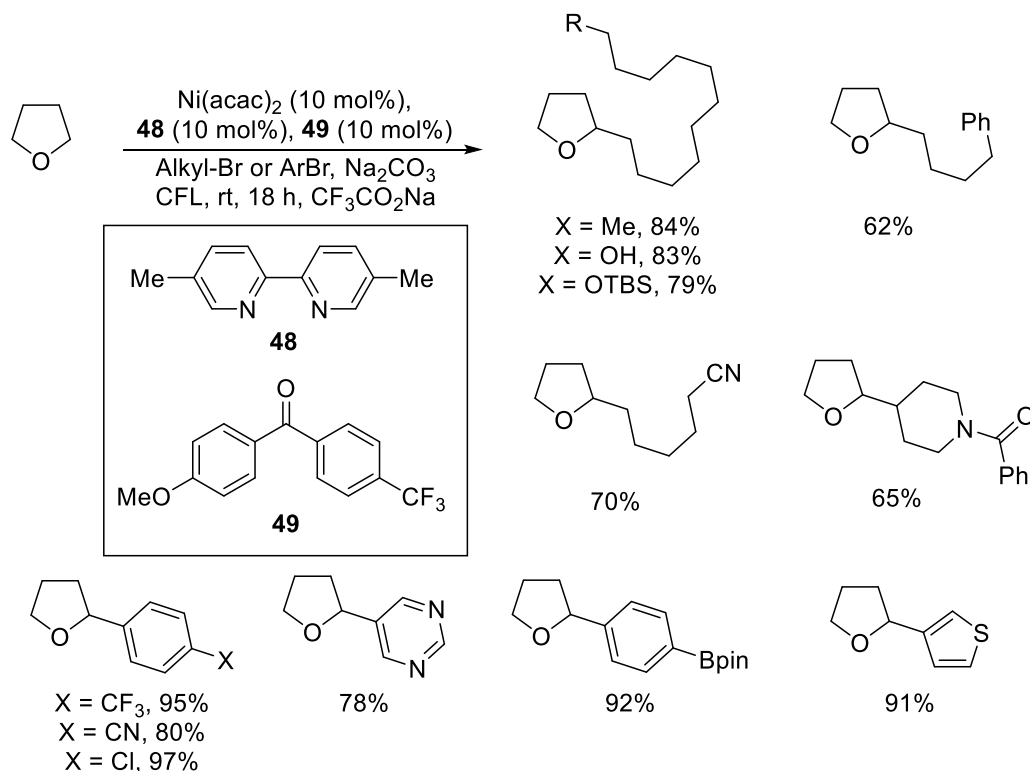
In 2018, an approach towards α -arylated oxygen heterocycles was developed by MacMillan et al. using W- and Ni-mediated photocatalysis.⁶¹ Irradiation of the oxygen heterocycle in the presence of tetrabutylammonium decatungstate (TBADT) and coupling with pyridyl bromides gave arylated oxygen heterocycles in up to 70% yield (Scheme 1.27). Interestingly, the arylation of *N*-Boc morpholine gave an 80:20 mixture of regioisomers **45** and **46** in 48% yield. Starting from 4-bromo THP, a 2,4-*trans* substituted THP **47** was formed in 70% yield and >95:5 dr.



Scheme 1.27 Light-Mediated Arylation of Oxygen Heterocycles Using W and Ni Catalysis.

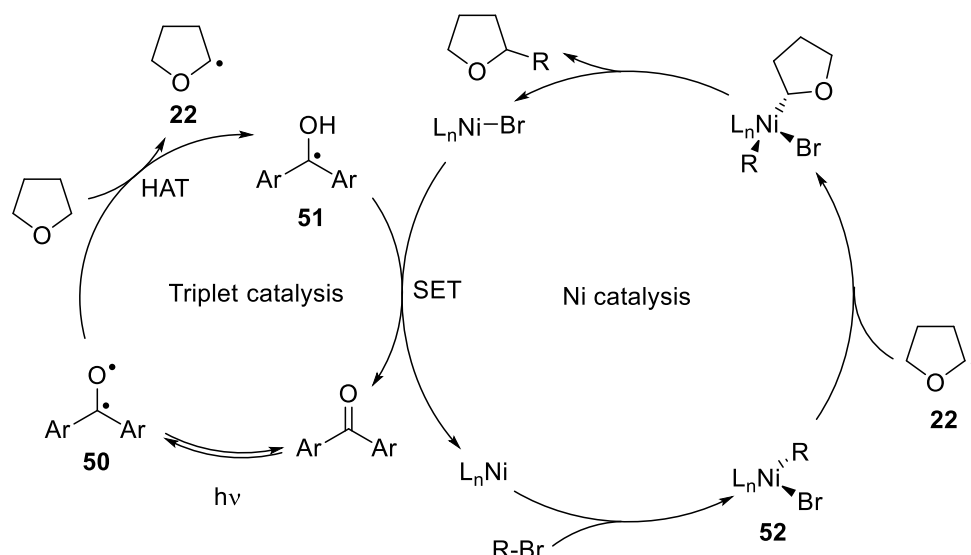
In 2018, Martin et al. presented a protocol to access α -alkylated oxygen heterocycles via combination of triplet excited ketones and Ni catalysis.⁶² THF was treated with Ni(acac)_2 , ligand **48** and photosensitizer **49** and coupled to a range of aryl bromides using a visible light source (CFL) (Scheme 1.28). Coupling with simple alkyl bromides and alkyl bromides bearing free alcohols and silyl esters as well as nitriles resulted in α -alkylated oxygen heterocycles in 80-84% yield. In addition, coupling was possible with secondary alkyl

bromides and with a range of aryl bromides to give the corresponding α -arylated heterocycles in 78-97% yield.



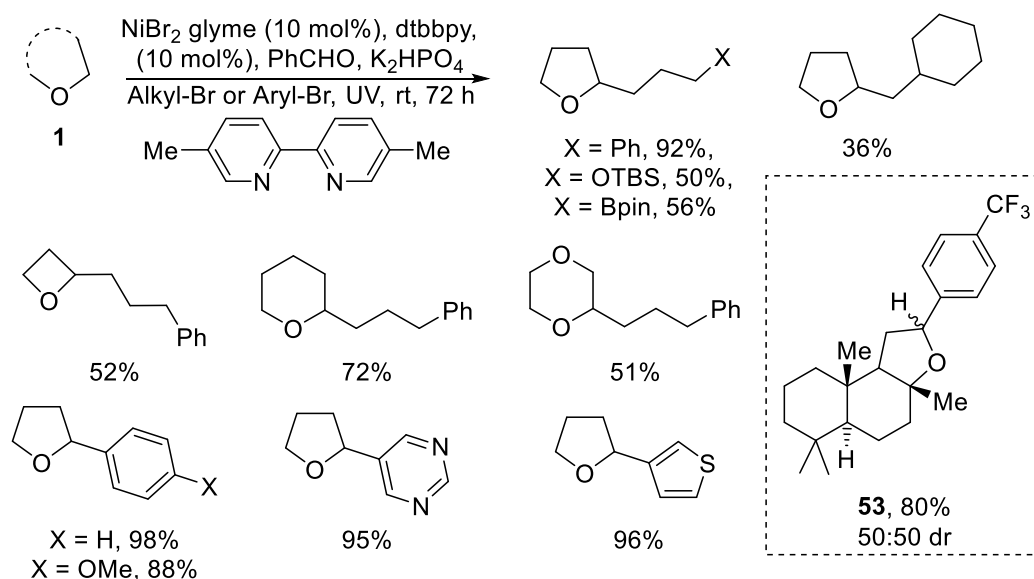
Scheme 1.28 Light-Mediated α -Functionalisation of Oxygen Heterocycles Using Ni Catalysis and Triplet Excited Ketones.

Martin et al.'s mechanistic hypothesis is depicted in Scheme 1.29. THF radical **22** is generated *via* HAT from triplet excited diradical **50**. The formed ketyl radical **51** then undergoes SET to give the Ni(0) species. Oxidative addition of the alkyl bromide results in Ni(II) species **52**. Subsequent radical recombination with the THF radical **22** and reductive elimination results in the α -substituted oxygen heterocycle.



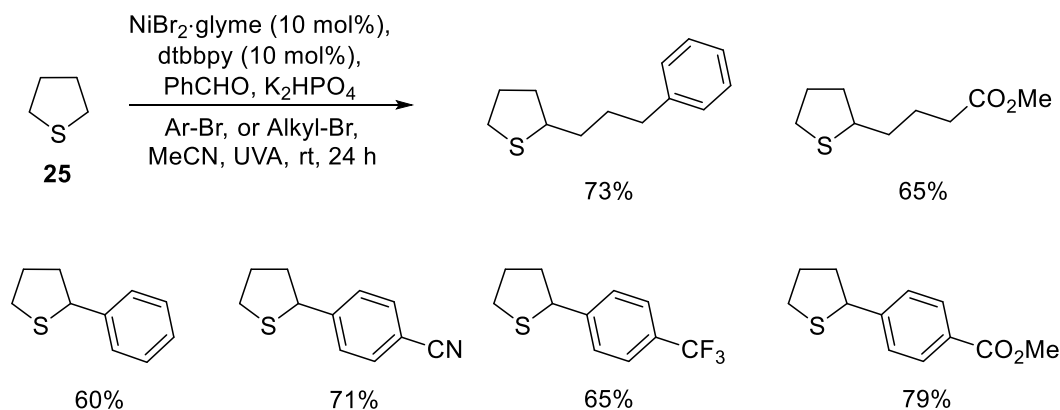
Scheme 1.29 Proposed Mechanism for the Light-Mediated α -Functionalisation of Oxygen Heterocycles Using Ni Catalysis and Triplet Excited Ketones.

Recently, Hashmi et al. reported a complementary approach towards α -alkylated oxygen heterocycles using light-mediated Ni catalysis in combination with benzaldehyde as a photosensitiser (Scheme 1.30).⁶³ Irradiation of the oxygen heterocycles, Ni catalyst and a bipyridine ligand with UV light at rt for 72 h in the presence of alkyl and aryl bromides gave α -substituted tetrahydrofurans in 36-98% yield. In addition, arylation using heteroaryl bromides such as pyridines, pyrimidines and thiophenes introduced in high yields was reported. Finally, Hashmi et al. showed the versatility of the method by introducing a substituent in the position α to the natural product (–)-ambroxide to give arylated ambroxide derivative **53** in 80% yield (50:50 dr).



Scheme 1.30 Light-Mediated α -Functionalisation of Oxygen Heterocycles Using Ni Catalysis and Triplet Excited Benzaldehyde.

Subsequently, Hashmi et al. applied the same method to the α -functionalisation of tetrahydrothiophene **25** (Scheme 1.31).⁶⁴ UV light-mediated coupling using benzaldehyde in combination with $\text{NiBr}_2\cdot\text{glyme}$ and a bispidine ligand with alkyl and aryl bromides bearing esters, nitriles and trifluoromethyl groups gave α -alkyl and α -aryl sulfides in 60–79% yield.



Scheme 1.31 Light-Mediated α -Functionalisation of Sulfur Heterocycles Using Ni Catalysis and Triplet Excited Benzaldehyde.

Regarding the mechanism of the reaction it is postulated that benzaldehyde serves as a photosensitizer and accepts an electron. Subsequent HAT leads to homolytic cleavage of a C-H bond at the α -position in cyclic ether or cyclic sulfide **25**. This forms the alkalkoxy or alkalkthiyl radical which then undergoes the Ni-catalysed coupling with an alkyl or aryl bromide.

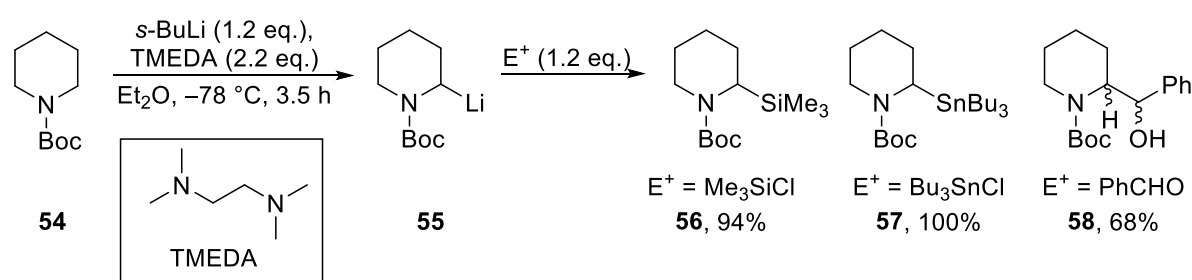
To conclude, radical approaches towards α -substituted oxygen and sulfur heterocycles starting from an intact ring system are a widely explored area. Various activation methods such as classic radical initiation and peroxide initiation have been explored. In addition, Minisci-type approaches have recently been revisited and in recent years, Ir photocatalysts and Ni-mediated cross-coupling have gained much attention in light-mediated α -substitution reactions.

1.3 Metallation of Nitrogen, Oxygen and Sulfur-Containing Heterocycles

1.3.1 Lithiation-Trapping of Saturated Nitrogen-Containing Heterocycles

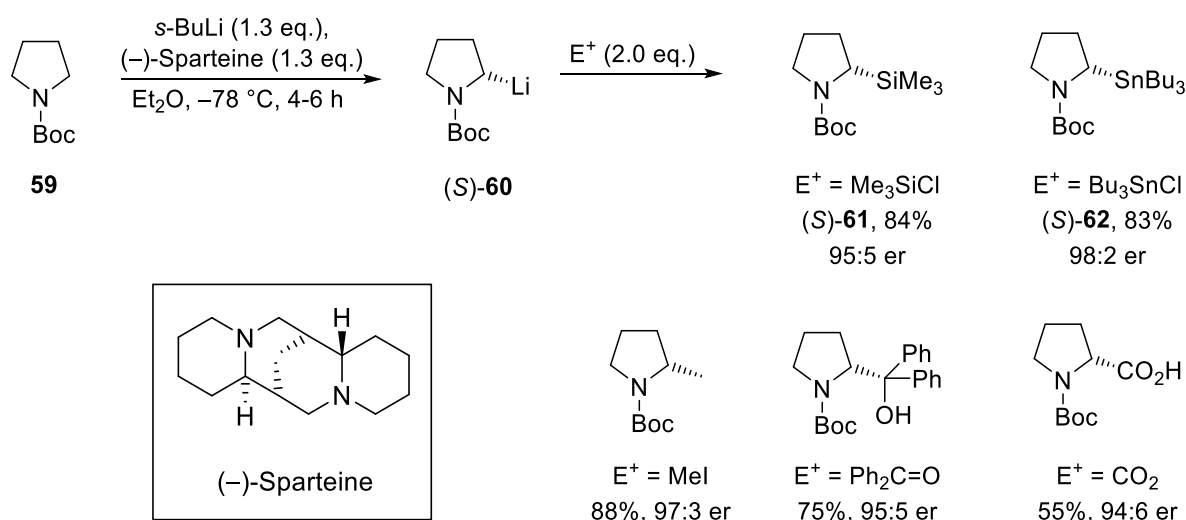
The synthesis of α -substituted nitrogen heterocycles using lithiation-trapping has been intensively investigated over the last 30 years. The pioneering work of Beak et al.,⁶⁵⁻⁶⁶ Meyers and Hellring⁶⁷ and Seebach and Enders⁶⁸ showed that lithiation-trapping using strong organolithium bases is a powerful tool to access and functionalise nitrogen-containing heterocycles. The lithiation-trapping of *N*-Boc pyrrolidines and piperidines has been well explored. Furthermore, solvent effects and the influence of chiral diamines as well as mechanistic details of the lithiation process have recently been reviewed by the O'Brien group.⁶⁹

In 1989, Beak and Lee reported the lithiation-trapping of *N*-Boc protected piperidine **54**.⁶⁶ Lithiation at $-78\text{ }^{\circ}\text{C}$ using *s*-BuLi and TMEDA in Et₂O for 3.5 h gave organolithium **55** and subsequent trapping with different electrophiles resulted in α -substituted *N*-Boc piperidines in **56-58** in 53-100% yield (Scheme 1.32). This paper reported the first examples of the lithiation-trapping of *N*-Boc heterocycles.



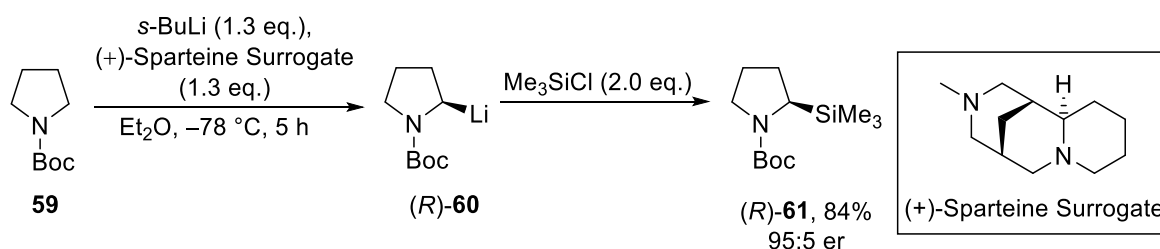
Scheme 1.32 Lithiation of *N*-Boc Piperidine **54** and Trapping with Several Electrophiles.

In follow-up work, Beak et al. revealed a protocol for the asymmetric deprotonation and subsequent trapping of *N*-Boc protected pyrrolidine **59**.⁷⁰ Using *s*-BuLi and (–)-sparteine as a chiral ligand at low temperatures ($-78\text{ }^{\circ}\text{C}$), *N*-Boc-pyrrolidine **59** was asymmetrically deprotonated. After a lithiation-time of 4–6 h, organolithium (*S*)-**60** was trapped with several electrophiles. Trapping with Me₃SiCl gave silane (*S*)-**61** in 84% yield and 95:5 er. Addition of Bu₃SnCl to the lithiated species (*S*)-**60** resulted in stannane (*S*)-**62** in 83% yield and 98:2 er. Further electrophiles gave α -substituted pyrrolidines in up to 88% yield and 97:3 er (Scheme 1.33).



Scheme 1.33 Asymmetric Deprotonation of *N*-Boc Pyrrolidine **59 using *s*-BuLi / (-)-Sparteine and Trapping with Several Electrophiles.**

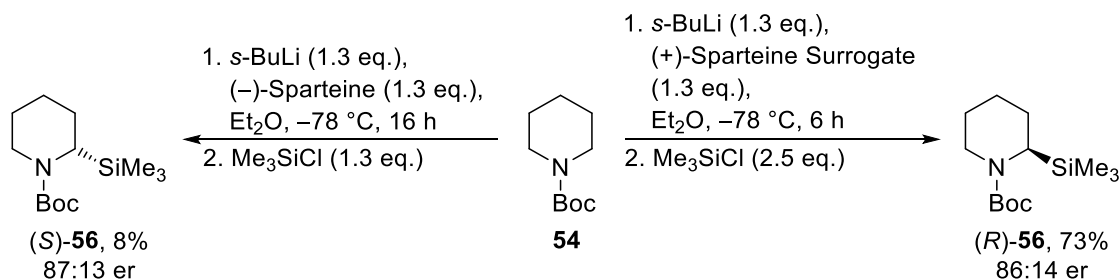
To access the other enantiomeric form of the α -substituted *N*-Boc pyrrolidines, (+)-sparteine could be used as the chiral ligand. However, in contrast to (-)-sparteine, (+)-sparteine was not commercially available up until recently. Therefore, the O'Brien group designed a sparteine surrogate which mimics the (+)-sparteine ligand.⁷¹ Lithiation of *N*-Boc pyrrolidine **59** using *s*-BuLi and the (+)-sparteine surrogate at -78 °C and subsequent trapping with Me₃SiCl gave silane (*R*)-**61** in 84% yield and 95:5 er (Scheme 1.34).



Scheme 1.34 Asymmetric Deprotonation of *N*-Boc Pyrrolidine **59 using *s*-BuLi / (+)-Sparteine Surrogate and Trapping with Me₃SiCl.**

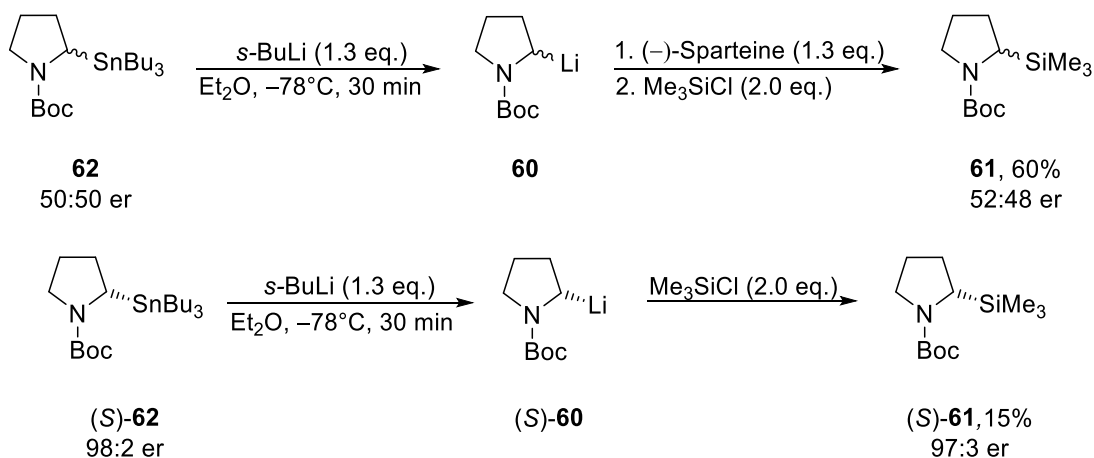
The asymmetric deprotonation of *N*-Boc piperidine **54** has been investigated using (-)-sparteine and the (+)-sparteine surrogate. The ers in the asymmetric deprotonation and trapping were generally lower compared to the 5-membered *N*-Boc pyrrolidine **59**. In addition, significant differences in reactivity of the *s*-BuLi / diamine complexes were observed. Beak et al. reported that deprotonation of *N*-Boc piperidine **54** using *s*-BuLi / (-)-sparteine at -78 °C for 16 h and trapping with Me₃SiCl gave α -substituted *N*-Boc piperidine (*S*)-**56** in only 8% yield and 87:13 er (Scheme 1.35).⁷² In contrast, the O'Brien group used *s*-BuLi / (+)-sparteine surrogate at -78 °C for 6 h and, after trapping with Me₃SiCl, (*R*)-**56**

was obtained in 73% yield (86:14 er). The reactivity of *s*-BuLi / (+)-sparteine surrogate is therefore at least ten times higher compared to *s*-BuLi / (–)-sparteine.⁷³



Scheme 1.35 Comparison of Asymmetric Deprotonation of *N*-Boc Piperidine **54 using *s*-BuLi / (–)-Sparteine and *s*-BuLi / (+)-Sparteine Surrogate.**

The asymmetric deprotonation pathway relies on the formation of a configurationally stable lithiated species.⁷⁴ A reliable way to investigate the configurational stability is using Sn-Li exchange.⁷⁴ Beak and Kerrick proved the configurational stability of lithiated *N*-Boc pyrrolidine **59** at -78°C and thus showed that the mechanism proceeded *via* an asymmetric deprotonation pathway. The two key experiments are shown in Scheme 1.36. Starting from racemic stannyl pyrrolidine **62**, Sn-Li-exchange using *s*-BuLi in Et₂O at -78°C led to racemic lithiated species **60**, which, after adding (–)-sparteine, was trapped with Me₃SiCl to give silane **61** with 52:48 er.⁷⁵ As the er is close to racemic, it shows that no enantioselectivity arose in a post-lithiation process. In addition, starting from stannyl pyrrolidine (S)-**62** (98:2 er), Sn-Li exchange using *s*-BuLi in Et₂O at -78°C gave lithiated species (S)-**60**. Subsequent trapping in the absence of a chiral ligand gave (S)-**61** in 97:3 er, which is close to the er of the starting material.



Scheme 1.36 Study of Configurational Stability for α -Lithio *N*-Boc Pyrrolidine (S)-60**.**

The induced enantioselectivity in asymmetric deprotonation reactions using organolithium reagents and (–)-sparteine is highly dependent on the solvent.⁷⁶ Hoppe and Hense proposed that coordinating solvents such as THF can displace (–)-sparteine in organolithium complexes leading to low enantioselectivity during the deprotonation step.⁷⁷ Hence, the O'Brien group⁷⁸ investigated the complexation of *i*-PrLi with (–)-sparteine and (+)-sparteine surrogate in different solvents, especially Et₂O and THF. In earlier work, Beak had shown that (–)-sparteine and *i*-PrLi in Et₂O resulted in the formation of heterodimer **63** (Figure 1.5) where one lithium is complexed by (–)-sparteine and the other is complexed by Et₂O.⁷⁹ Using the (+)-sparteine surrogate in combination with *i*-PrLi in Et₂O at –80 °C, the O'Brien group showed that a head-to-tail homodimer **64** was formed. Interestingly, spectroscopic analysis of the solution structure of (+)-sparteine surrogate and *i*-PrLi in THF revealed that the (+)-sparteine surrogate readily complexed to *i*-PrLi in THF to give monomer **65**. In contrast, a low complexation of *i*-PrLi to (–)-sparteine in THF was observed which is in accordance with the synthetic results reported by Hoppe and Hense.

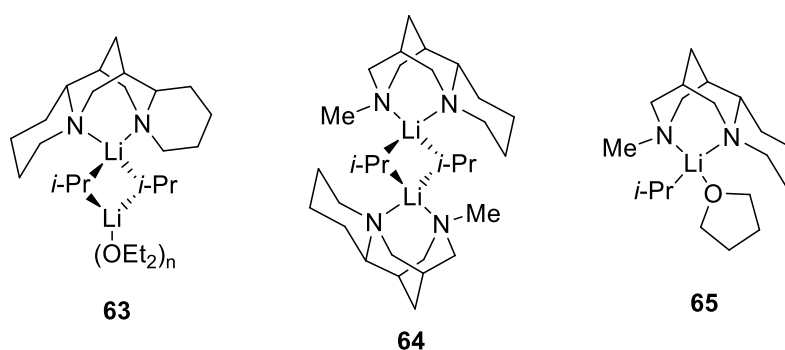
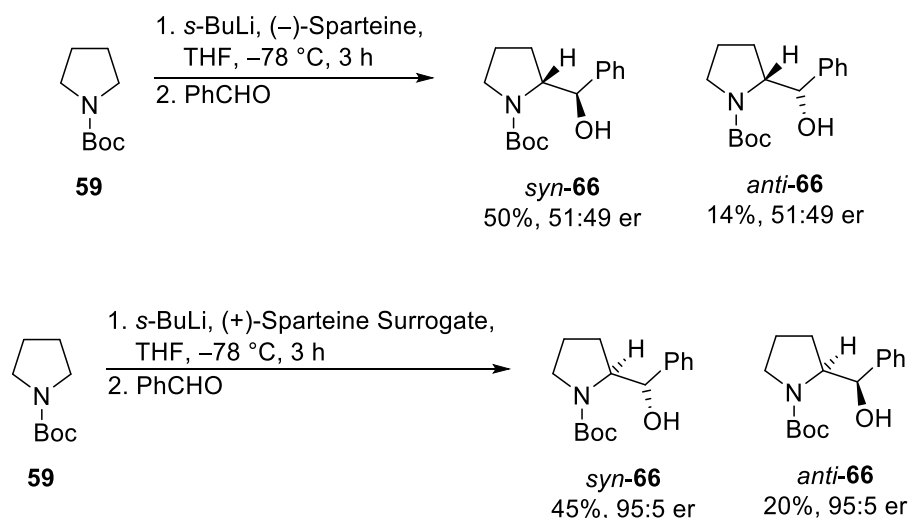


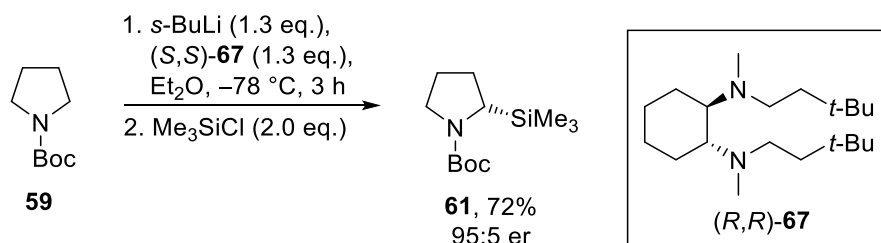
Figure 1.5 Solution Structures of (–)-Sparteine and (+)-Sparteine Surrogate.

The O'Brien group's spectroscopic studies were accompanied with investigations of the asymmetric deprotonation of *N*-Boc pyrrolidine **59** using *s*-BuLi / (–)-sparteine or the (+)-sparteine surrogate in THF and subsequent trapping with benzaldehyde.⁷⁸ Lithiation using *s*-BuLi / (–)-sparteine in THF and trapping with benzaldehyde resulted in a near racemic mixture of *syn*-**66** and *anti*-**66** in 50% and 14% yield respectively (Scheme 1.37). When *N*-Boc pyrrolidine **59** in THF was lithiated in the presence of *s*-BuLi / (+)-sparteine surrogate and then trapped with benzaldehyde, alcohol *syn*-**66** was isolated in 45% yield and 95:5 er and alcohol *anti*-**66** was isolated in 20% and 95:5 er. These results show that asymmetric deprotonation reactions in THF can be carried out using *s*-BuLi and (+)-sparteine surrogate.



Scheme 1.37 Lithiation of *N*-Boc Pyrrolidine **59** in THF using *s*-BuLi / (–)-Sparteine and *s*-BuLi / (+)-Sparteine Surrogate and Trapping with Benzaldehyde.

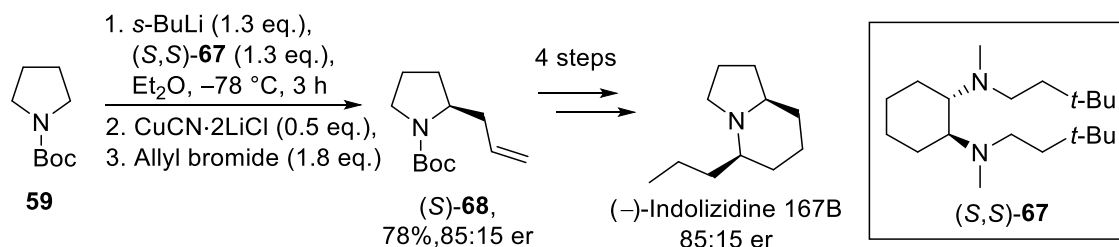
Asymmetric deprotonation of *N*-Boc pyrrolidine **59** using *s*-BuLi and (–)-sparteine or the pseudo-enantiomer, (+)-sparteine surrogate, gives access to products with opposite configurations. However, due to the fluctuations in the commercial availability of (–)-sparteine, the O'Brien group was interested in alternative routes for the synthesis of (–)-sparteine but also in exploring alternative ligands which could mimic (–)-sparteine. In 2018, the gram-scale synthesis of the (–)-sparteine surrogate and (–)-sparteine in eight and ten steps respectively was reported by the O'Brien group.⁸⁰ Alexakis et al. has shown that diamine (*R,R*)-**67**, readily available in either enantiomeric form, can form a complex with organolithium reagents and used this in several asymmetric reactions.⁸¹ The O'Brien group explored the use of *s*-BuLi and diamine (*R,R*)-**67** in the asymmetric deprotonation of *N*-Boc pyrrolidine **59**.⁸² Trapping with Me₃SiCl gave α-substituted *N*-Boc pyrrolidine (*S*)-**61** in 72% yield and 95:5 er, a similar enantioselectivity and yield compared to that obtained with (–)-sparteine (see Scheme 1.38).



Scheme 1.38 Asymmetric Deprotonation of *N*-Boc Pyrrolidine **59** Using Alexakis Diamine (*R,R*)-**67**.

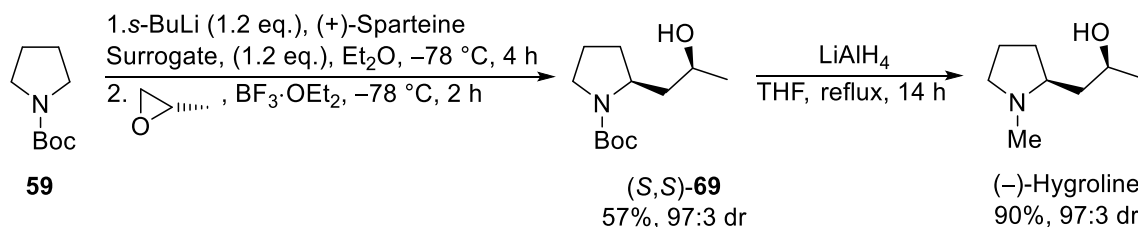
The asymmetric deprotonation of nitrogen heterocycles has been used in the synthesis of pharmaceutically relevant compounds and natural products. Two synthetic examples are

presented in detail in Scheme 1.39 and Scheme 1.40. Asymmetric deprotonation of *N*-Boc pyrrolidine **59** using *s*-BuLi / diamine (*S,S*)-**67**, transmetalation to a cuprate and trapping with allyl bromide resulted in α -allylated *N*-Boc pyrrolidine (*S*)-**68** in 78% yield and 85:15 er. The product was a precursor to indolizidine 167B, an alkaloid found in neotropical frogs.⁸²



Scheme 1.39 Synthesis of α -Allyl Substituted *N*-Boc Pyrrolidine (*S*)-68** in the Synthesis of (-)-Indolizidine 167B.**

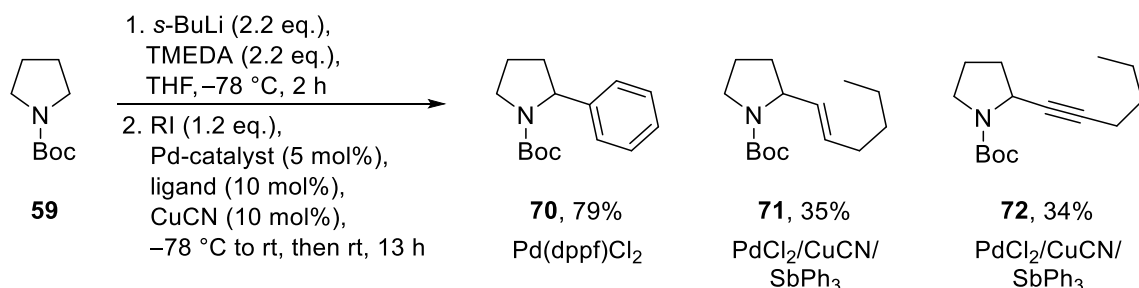
In 2002, Altmann et al. reported the synthesis (-)-hygroline, a natural product isolated from *Erythroxylum coca* extracts, using asymmetric deprotonation of *N*-Boc pyrrolidine **59**.⁸³ Lithiation of *N*-Boc pyrrolidine **59** with *s*-BuLi and the (+)-sparteine surrogate and subsequent trapping with (*S*)-propylene oxide in the presence of BF₃·OEt₂ gave alcohol (*S,S*)-**69** in 57% yield and 97:3 dr (Scheme 1.39). Subsequent *N*-Boc reduction gave (-)-hygroline in 90% yield and 97:3 dr.



Scheme 1.40 Synthesis of (-)-Hygroline.

In 1997, Dieter and Li reported the synthesis of α -arylated *N*-Boc pyrrolidines such as **70** via racemic lithiation of *N*-Boc pyrrolidine **59** and subsequent CuCN-catalysed Pd-mediated cross-coupling. After the lithiation using *s*-BuLi / TMEDA in THF at -78 °C for 2 h, addition of iodobenzene, Pd(dppf)Cl₂ (5 mol%) and CuCN (10 mol%) gave α -phenyl *N*-Boc pyrrolidine **70** in 79% yield (Scheme 1.41).⁸⁴⁻⁸⁵ In this case, it is likely that the active Pd(0) species is initially generated by reductive elimination to give dimerised *N*-Boc pyrrolidine. As well as iodobenzene, the coupling was also possible with heteroaromatic systems as well as alkenes and alkynes in moderate to good yields. The methodology could also be transferred to *N*-Boc piperidine **54**, resulting in 2-aryl *N*-Boc piperidines in yields up to 75%.

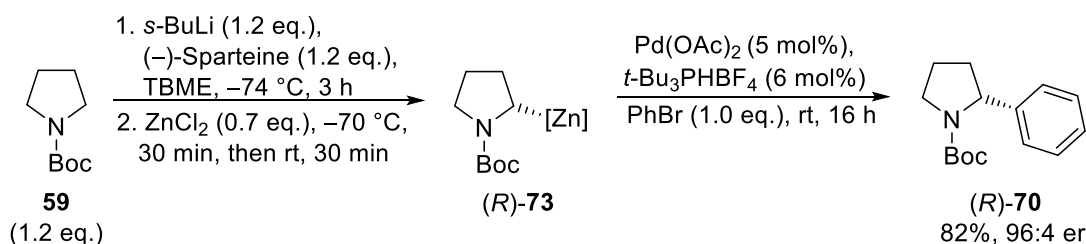
For the introduction of alkenes and alkynes a different catalytic system gave the best results. Thus, Pd(0) was generated by the potassium reduction of a PdCl₂/CuCN mixture and SbPh₃ as a ligand. Using these conditions, unsaturated products **71** and **72** were isolated in 35% and 34% yield respectively (Scheme 1.41).



Scheme 1.41 Lithiation of *N*-Boc Pyrrolidine **59** and Coupling with Aryl-, Alkenyl- and Alkynyl Iodides.

In addition, the influence of different diamines on the α -arylation of *N*-Boc pyrrolidine **59** was investigated. Interestingly, when (–)-sparteine was used instead of TMEDA in THF, only a 39% yield of α -phenyl *N*-Boc pyrrolidine **70** was obtained (er not reported). As subsequent studies in the O’Brien group revealed, (–)-sparteine does not coordinate to *s*-BuLi in THF and so high enantioselectivity would not have been expected (see Scheme 1.37).⁸⁵

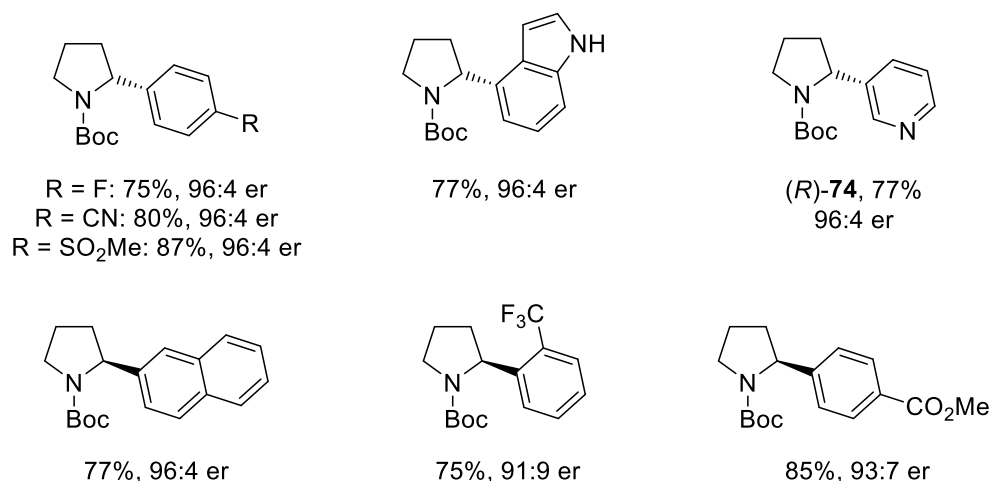
The first example of enantioselective α -arylation *via* lithiation-trapping of a *N*-heterocycle was reported by Campos et al. in 2006.⁸⁶ Lithiation of *N*-Boc pyrrolidine **59** using *s*-BuLi and (–)-sparteine in TBME at -74 °C gave the lithiated species which was then transmetallated using 0.7 equivalents of ZnCl₂ to give an undefined organozinc species **73**. Subsequent Negishi coupling using Pd(OAc)₂, *t*-Bu₃PHBF₄ and bromobenzene gave α -phenyl *N*-Boc pyrrolidine (*R*)-**71** in 82% yield and 96:4 er (Scheme 1.42). In these reactions, the aryl bromide was used as the limiting reagent. The coupling was also possible with aryl chlorides but aryl triflates and tosylates were unreactive.



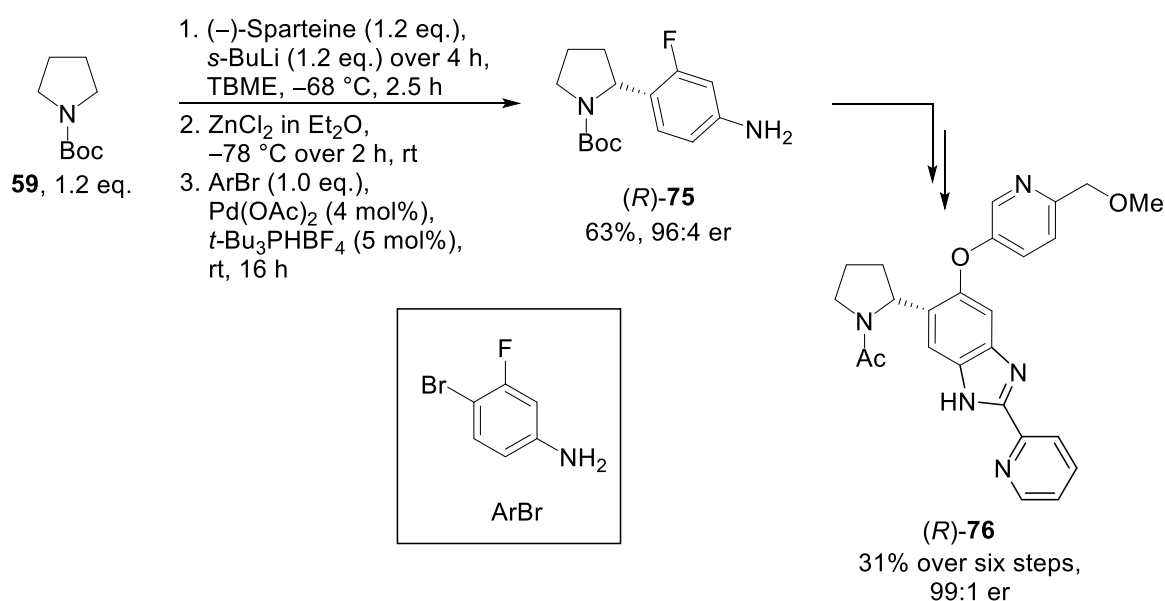
Scheme 1.42 Asymmetric Deprotonation of *N*-Boc Pyrrolidine 59, Transmetalation and Negishi Cross-Coupling.

The Negishi coupling approach for the introduction of the aryl substituent required an extensive optimisation of the reaction conditions. As the lithiated species is configurationally unstable at temperatures above $-40\text{ }^{\circ}\text{C}$, ZnCl_2 was added at $-70\text{ }^{\circ}\text{C}$ to give a configurationally stable organozinc species, which kept its configuration even when warmed up and heated to $60\text{ }^{\circ}\text{C}$. Initially, 0.7 eq. of ZnCl_2 was used in the generation of the organozinc species. However, the amount of ZnCl_2 could be reduced to 0.33 eq. without affecting the enantioselectivity or yield. For that reason, it was assumed that different organozinc species (RZnCl , R_2Zn or R_3ZnLi) could be formed but would exist in an equilibrium and would not affect the reactivity. For the subsequent Negishi coupling, several Pd catalysts were screened. $\text{Pd}(\text{dppf})\text{Cl}_2$, commonly used in Negishi couplings, was unreactive. In contrast, Pd catalysts derived from Ru-Phos, Q-Phos and *t*-Bu₃PHBF₄ gave α -arylated *N*-Boc pyrrolidines in good yields and high ers. $\text{Pd}(\text{OAc})_2$ was superior in the generation of the active catalyst species and a 1:1 or 2:1 ratio of ligand to Pd resulted in the best *in situ* formed active catalytic species. Noteworthy, the *N*-Boc enamide derived from β -hydride elimination was isolated in less than 8% yield from the reactions.

Using the conditions shown in Scheme 1.42, a range of aryl bromides containing electron-donating and electron-withdrawing groups were tolerated and gave (*R*)- α -aryl pyrrolidines in up to 87% yield and 96:4 er. Coupling with 3-bromopyridine required a higher reaction temperature of $60\text{ }^{\circ}\text{C}$ in the coupling step to give the nicotine derivative (*R*)-74 in good yield. Use of *s*-BuLi and a substoichiometric amount of the (+)-sparteine surrogate in the lithiation step gave access to products with the opposite configuration. For example, (*S*)- α -aryl pyrrolidines were formed in 75–85% yield and up to 94:6 er (Figure 1.6).⁸⁷

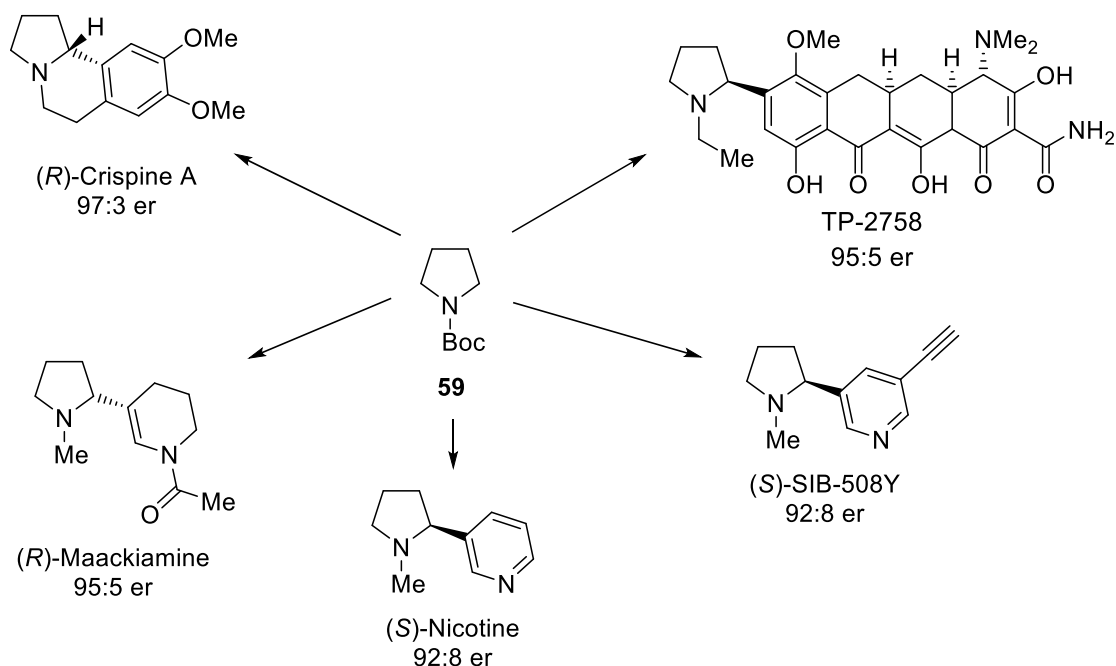
Figure 1.6 *N*-Boc Arylation Scope.

This enantioselective approach towards α -aryl *N*-Boc pyrrolidines has been used by Merck in the synthesis of glucokinase activator (*R*)-**76**.⁸⁸ Lithiation of *N*-Boc pyrrolidine **59**, transmetallation and Negishi coupling gave α -aryl *N*-Boc pyrrolidine (*R*)-**75** in 63% yield and 96:4 er. This reaction was carried out on the kg scale and the aryl bromide was the limiting reagent (Scheme 1.43).

Scheme 1.43 Synthesis of α -Arylated *N*-Boc Pyrrolidine (*R*)-**75** in the Synthesis of Glucokinase Activator (*R*)-**76** by Merck.

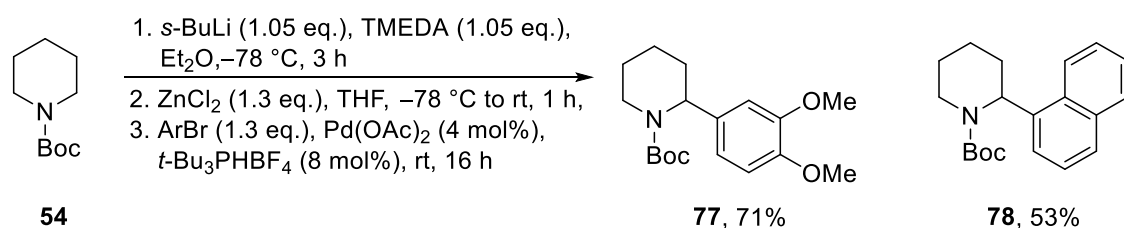
The lithiation, transmetallation and Negishi coupling protocol has been used in the synthesis of a few natural products and potential drug molecules (Scheme 1.44). For example, the synthesis of (*S*)-nicotine was completed in two steps starting from *N*-Boc pyrrolidine **59** in 44% overall yield and 92:8 er. Similarly, potential Parkinson's drug SIB-150BY was

synthesised in two steps with an overall yield of 23% (92:8 er).⁸⁷ Recently, the synthesis of tetracycline TP-2758 using the Negishi approach was reported by Zhang.⁸⁹ In the O'Brien group, the cytotoxic alkaloid (*R*)-crispine A was synthesised in three steps and 97:3 er. In addition, a procedure to (*R*)-maackiamine, an extract from the tree *Maackia amurensis*, was reported by the O'Brien group in three steps and 95:5 er.⁸⁷



Scheme 1.44 Accessed Natural Products and Potential Drug Molecules via Lithiation, Transmetallation and Negishi Cross-Coupling Starting from *N*-Boc Pyrrolidine **59**.

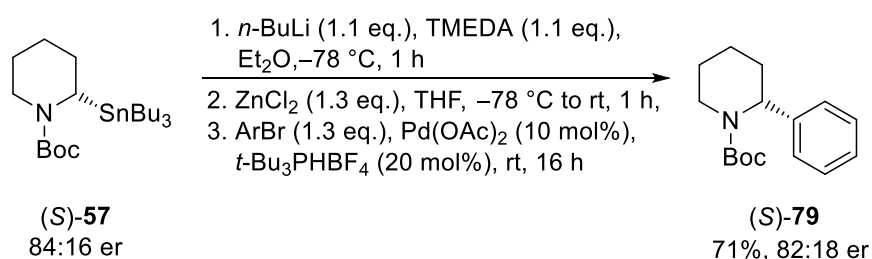
Leonori and Coldham extended the α -arylation protocol to *N*-Boc piperidine **54** using the lithiation, transmetallation and Negishi coupling sequence to generate racemic α -aryl *N*-Boc piperidines such as **77** and **78** (Scheme 1.45).⁹⁰ Lithiation of *N*-Boc piperidine **54** using *s*-BuLi and TMEDA in Et₂O at -78 °C gave the α -lithiated *N*-Boc piperidine. Subsequent transmetallation using ZnCl₂ (1.3 eq.) gave the organozinc species. To the organozinc solution was added a solution of Pd(OAc)₂ (4 mol%), *t*-Bu₃PHBF₄ (8 mol%) and aryl bromide (1.3 eq.). Use of 4-bromoveratrole in the Negishi coupling gave substituted *N*-Boc piperidine **77** in 71% yield. When 1-bromonaphthalene was used, α -naphthyl *N*-Boc piperidine **78** was isolated in 53% yield. In contrast to the coupling with *N*-Boc pyrrolidine **59**, use of a substoichiometric amount of ZnCl₂ gave recovered starting material only. Furthermore, an excess of the aryl bromide (1.3 eq.) gave the best results with *N*-Boc piperidine **54**.



Scheme 1.45 Lithiation, Transmetalation and Negishi Cross-Coupling Starting from *N*-Boc Piperidine 54.

In an initial approach towards enantioenriched α -arylated *N*-Boc piperidines, the O'Brien group reported the asymmetric deprotonation of *N*-Boc piperidine **54** using *s*-BuLi/(+)-sparteine surrogate, transmetalation to an organozinc species and Negishi coupling. Using the conditions reported by Campos et al., α -arylated *N*-Boc piperidine (*S*)-**79** of 82:18 er was formed but in only 33% yield.⁹¹

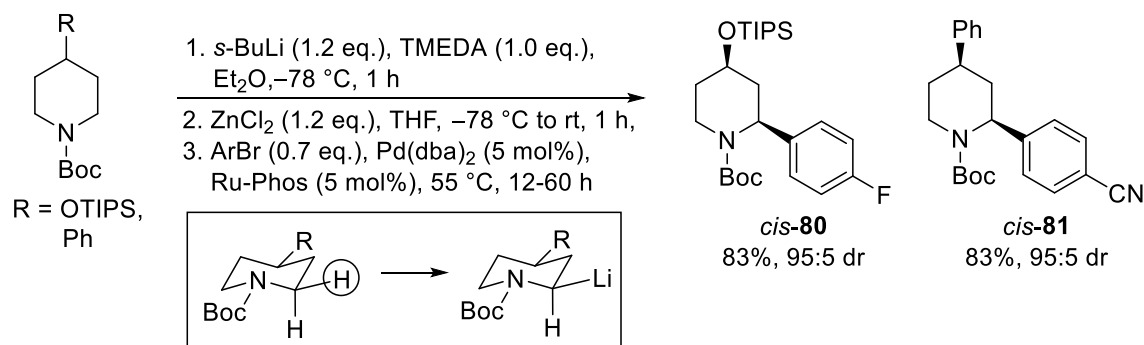
Coldham et al. reported an approach towards enantioenriched α -arylated *N*-Boc piperidines starting from enantioenriched stannane (*S*)-**57** (84:16 er, generated by a dynamic thermodynamic resolution process). Sn-Li exchange of stannane (*S*)-**57** using *n*-BuLi/TMEDA in Et₂O at -78 °C and subsequent transmetalation with ZnCl₂ gave the organozinc species. Subsequent Negishi coupling with bromobenzene gave α -arylated *N*-Boc piperidine (*S*)-**79** in 82% yield and 82:18 er (Scheme 1.7).⁹² The minor change in er from stannane (*S*)-**57** to α -arylated product (*S*)-**79** suggests a stereospecific reaction pathway.



Scheme 1.46 Stereospecific Sn-Li Exchange of α -Stannyl *N*-Boc Piperidine (*S*)-57, Transmetalation and Negishi Cross-Coupling.

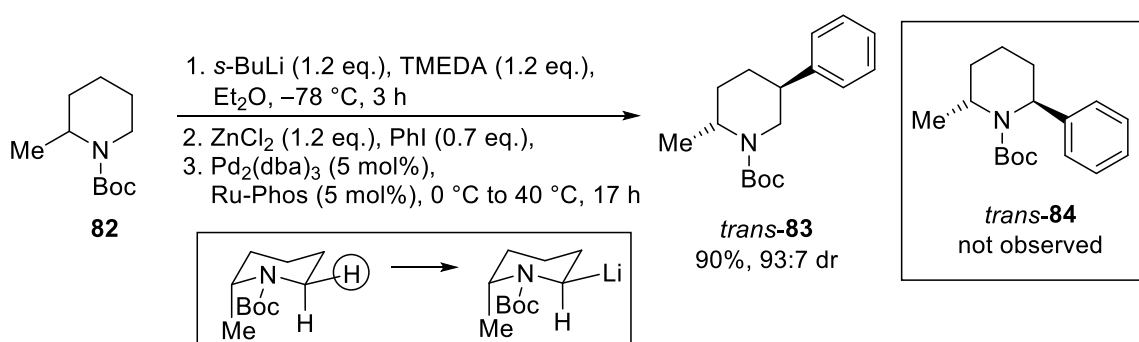
In 2011, Knochel et al. reported the diastereoselective arylation of substituted *N*-Boc piperidines.⁹³ Lithiation of 4-substituted *N*-Boc piperidines using *s*-BuLi / TMEDA in Et₂O at -78 °C and transmetalation gave an organozinc species. Negishi cross-coupling resulted in 2,4-*cis* configured *N*-Boc piperidines *cis*-**80** and *cis*-**81** (83% and 79% yield) in high drs (Scheme 1.47). The high level of diastereoselectivity arises due to predominant equatorial lithiation next to nitrogen from a conformation in which the 4-substituent is in the favoured

equatorial position, as previously established by Beak and Lee.⁹⁴ Subsequent stereospecific transmetallation and Negishi cross-coupling results in the 2,4-*cis* configured products.



Scheme 1.47 Synthesis of 2,4-*cis* Configured *N*-Boc Piperidines via Lithiation, Transmetallation and Negishi Cross-Coupling.

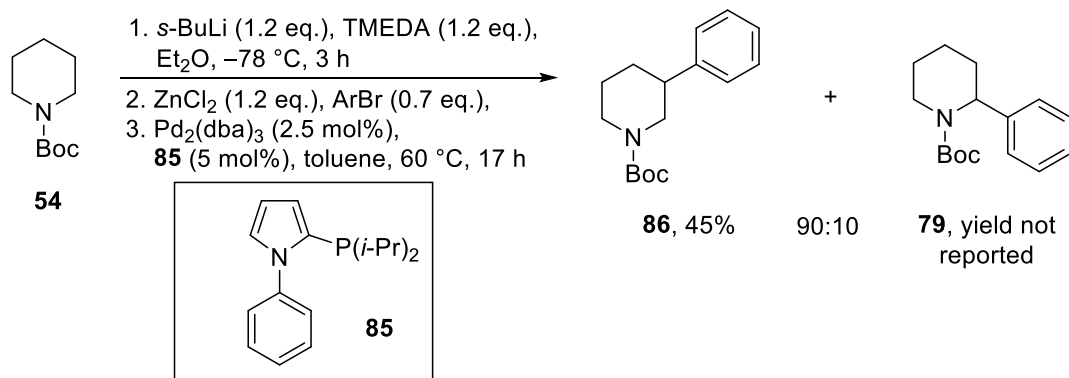
In contrast, the α -methyl substituted *N*-Boc piperidine **82** behaved differently in the α -lithiation-arylation process. Lithiation of α -methyl *N*-Boc piperidine **82** with *s*-BuLi / TMEDA in Et₂O, transmetallation and subsequent cross-coupling with bromobenzene gave 2,5-*trans*-substituted *N*-Boc piperidine *trans*-**83** in 90% yield and 93:7 dr (Scheme 1.48). The expected regioisomer, 2,6-substituted *N*-Boc piperidine *trans*-**84**, was not formed. In previous results,⁹⁴ it was observed that lithiation of α -substituted *N*-Boc piperidines led to equatorial lithiation from a conformation in which the α -substituent was in an axial position. Presumably, 1,2-migration in the cross-coupling step led to 2,5-substituted *N*-Boc piperidine *trans*-**83**. Subsequent work by Baudoin et al. suggests that conformational effects during the Negishi cross-coupling result in the β -arylation.⁹⁵



Scheme 1.48 Synthesis of 2,5-*trans* Configured *N*-Boc Piperidines via Lithiation, Transmetallation and Negishi Cross-Coupling.

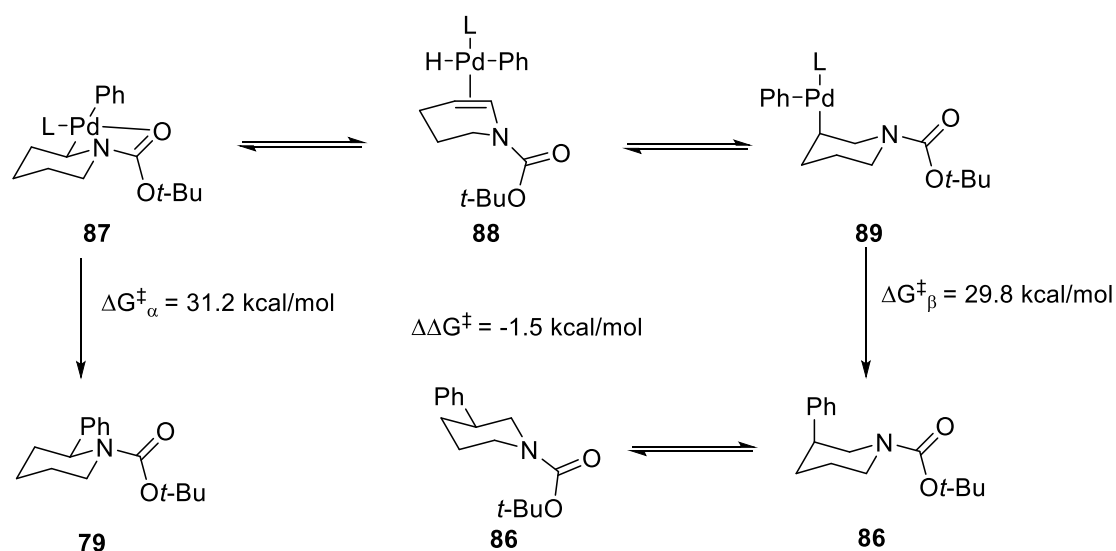
Millet and Baudoin revealed the influence of solvent and ligand on the regioselectivity in the Negishi coupling step of *N*-Boc piperidine **54**. Lithiation of *N*-Boc piperidine **54** using *s*-BuLi and TMEDA in Et₂O at -78 °C for 3 h followed by transmetallation using ZnCl₂ gave the organozinc species.⁹⁵ A subsequent solvent switch to toluene and Negishi coupling

using $\text{Pd}_2(\text{dba})_3$ and pyrrole phosphine ligand **85** at 60 °C for 17 h gave a 90:10 mixture of β -substituted and α -substituted *N*-Boc piperidines **86** and **79**. After purification, the β -substituted *N*-Boc piperidine **86** was isolated in 45% yield (Scheme 1.49).



Scheme 1.49 Synthesis of β -Aryl *N*-Boc Piperidines.

Computational studies suggested that the formation of β -aryl *N*-Boc piperidine **86** is a result of a 1,2-migration of the palladium in the palladium complex **87** (Scheme 1.11). After Zn-Pd-transmetalation, the Pd is attached to the C-2 atom and coordinating to the Boc group resulting in **87**. Decoordination of the Pd-O bond and β -hydride elimination leads to π -complex intermediate **88** and the piperidine ring-flips to a twist-boat conformation. Subsequent insertion of the alkene into the Pd-H bond at C-3 gives Pd complex **89**. The energy difference for reductive elimination from intermediate **87** is slightly higher than that from intermediate **89** ($\Delta\Delta G^\ddagger = 1.5 \text{ kcal/mol}$). In accordance with the Curtin-Hammett principle, the lower energy barrier for the reductive elimination *via* **89** leads to the preferential formation of β -phenyl *N*-Boc piperidine **86**. Sterically less demanding and flexible ligands were found to increase the reductive elimination pathway *via* **89** to give β -aryl substituted products. The DFT-calculated ratio of the β -arylated product **86** to the α -arylated product **79** was 90:10, identical to the experimental outcome.



Scheme 1.50 Computational Study of the α -Arylation and β -Arylation of *N*-Boc Piperidine.

In addition to the arylation of *N*-Boc pyrrolidines and *N*-Boc piperidines, the lithiation, transmetallation and Negishi coupling methodology has been applied to a broad range of other *N*-heterocycles. Selected products are shown in Figure 1.7. The O'Brien group used a diamine-free lithiation, transmetallation and Negishi coupling to obtain racemic α -arylated imidazolidine derivative **90** in a moderate yield of 43%.⁹⁶ Recently, Baudoin et al. reported the synthesis of enantioenriched α -arylated oxazinanes (*S*)-**91** as precursors in the synthesis of β^3 -amino acids.⁹⁷ Metallinos and Xu used the enantioselective α -arylation in the synthesis of urea derivative (*S*)-**92**. For the lithiation step, *i*-PrLi and (–)-sparteine at low temperatures resulted in the asymmetric deprotonation and the organolithium was then transmetallated using ZnCl₂ and coupled to bromobenzene in the subsequent Negishi coupling.⁹⁸ In addition, Leonori and Coldham synthesised α -arylated *N*-Boc azepanes **93** using the Negishi approach.⁹⁰

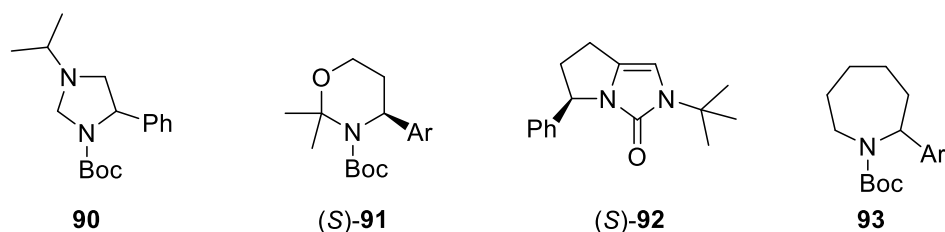
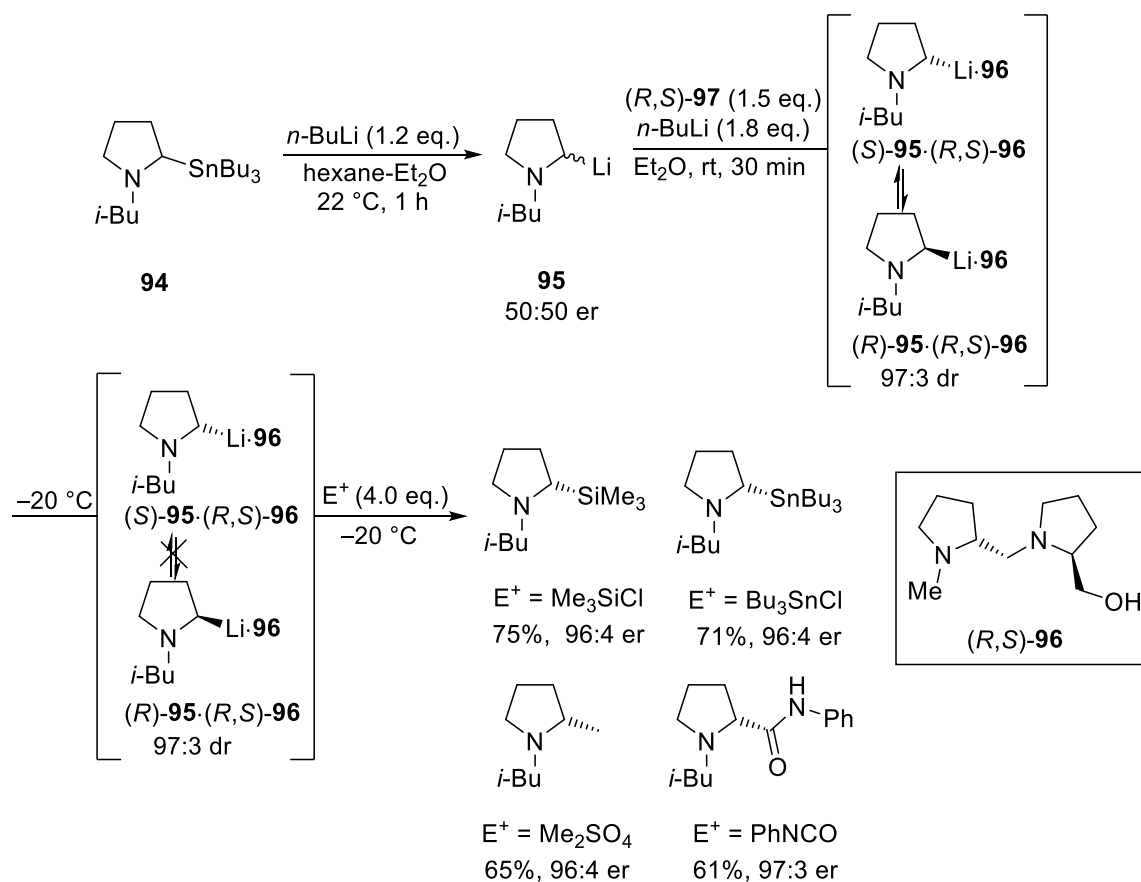


Figure 1.7: Various *N*-Containing Heterocycles Accessed via Negishi Cross-Coupling.

Two other mechanistic pathways, dynamic thermodynamic resolution and dynamic kinetic resolution of organolithium species, have been used in the synthesis enantioenriched α -substituted saturated nitrogen heterocycles. In 2002, Coldham et al. reported the synthesis

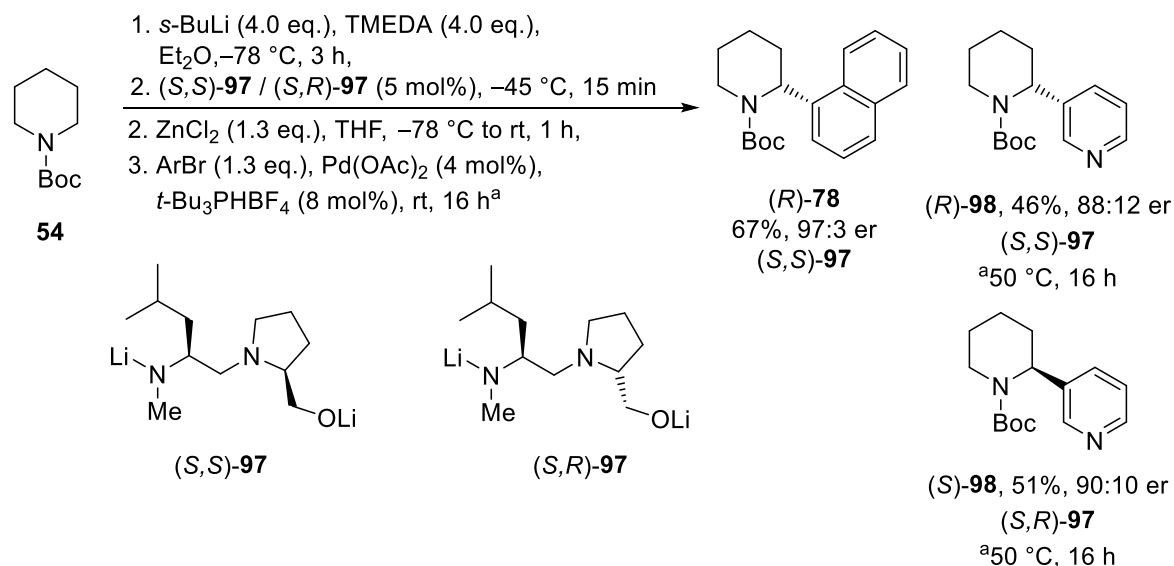
of α -substituted *N*-*i*-butyl pyrrolidines via a dynamic thermodynamic resolution pathway. In the first step, racemic stannane **94** underwent Sn-Li exchange using *n*-BuLi to give the lithiated species **95**. Subsequently, chiral ligand **96**, pretreated with *n*-BuLi was added to give a mixture of two configurationally unstable and ligand-complexed species (*S*)-**97**·**96** and (*R*)-**97**·**96**. After an equilibration phase, the configurationally unstable species (*S*)-**97**·**96** and (*R*)-**97**·**96** equilibrated to a 97:3 ratio. Cooling to $-20\text{ }^{\circ}\text{C}$ locked the configuration and subsequent trapping was performed at $-20\text{ }^{\circ}\text{C}$ with several electrophiles to give α -substituted pyrrolidines in 61-75% yield and 96:4-97:3 er (Scheme 1.51).⁹⁹



Scheme 1.51 Dynamic Thermodynamic Resolution of *N*-*i*-Butyl Pyrrolidine **94**.

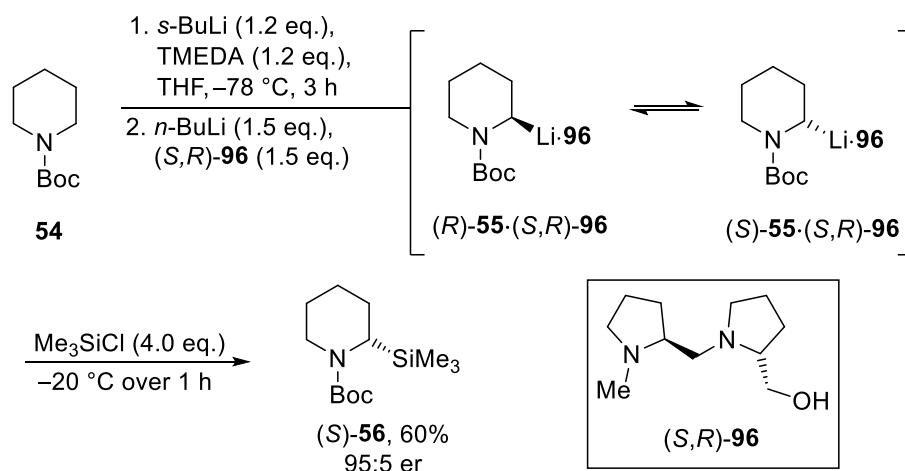
Beng and Gawley reported the synthesis of α -aryl substituted *N*-Boc piperidines using dynamic thermodynamic resolution.¹⁰⁰ Racemic lithiation of *N*-Boc piperidine **54** using *s*-BuLi and TMEDA in Et₂O at $-78\text{ }^{\circ}\text{C}$ for 3 h gave the racemic lithiated species. Subsequent addition of the chiral ligand (*S,S*)-**97** (5 mol%) at $-45\text{ }^{\circ}\text{C}$ and equilibration at $-45\text{ }^{\circ}\text{C}$ for 5 h gave the enantioenriched species which was then cooled to $-78\text{ }^{\circ}\text{C}$. ZnCl₂ was added to give the organozinc species which was then warmed to rt. Subsequent Negishi coupling with Pd(OAc)₂, *t*-Bu₃PBHF₄ and 1-bromonaphthalene gave α -aryl substituted *N*-Boc heterocycle (*R*)-**78** in 67% yield and 97:3 er (Scheme 1.52). Negishi coupling with 3-bromopyridine at

an elevated temperature of 50 °C for 16 h gave *N*-Boc piperidine (*R*)-**98** in 46% yield and 88:12 er. Using the diastereomeric ligand (*S,R*)-**97**, subsequent transmetallation and Negishi coupling gave the enantiomeric *N*-Boc piperidine (*S*)-**98** in 51% yield and 90:10 er. During their optimisation, it was observed that yields and ers were higher when Et₂O was used as a solvent instead of TBME.



Scheme 1.52 Dynamic Thermodynamic Resolution of *N*-Boc Piperidine **54**.

The dynamic kinetic resolution pathway is the least explored approach to enantioenriched *N*-heterocycles. Coldham et al. reported the synthesis of enantioenriched *N*-Boc piperidines **54** via the dynamic kinetic resolution of the organolithium species (Scheme 1.53).⁹² *N*-Boc piperidine **54** was lithiated using *s*-BuLi / TMEDA. Addition of ligand (*S,R*)-**96** pretreated with *n*-BuLi resulted in two configurationally unstable lithiated species (*R*)-**55**·**96** and (*S*)-**55**·**96**. The trapping was performed at -20 °C using a slow trapping electrophile such as Me₃SiCl. At that temperature, the trapping of lithiated species (*S*)-**55**·**96** was faster than trapping of the lithiated species (*R*)-**55**·**96**. In addition, both lithiated species were configurationally unstable and interconversion was faster than the trapping process leading to the α -substituted *N*-Boc piperidine (*S*)-**56** in 60% yield and 95:5 er. However, the method was limited to slow trapping electrophiles.



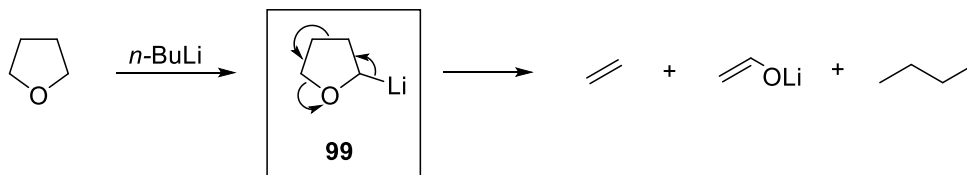
Scheme 1.53 Dynamic Kinetic Resolution of *N*-Boc Piperidine **54**.

In summary, methods for the α -substitution of *N*-Boc pyrrolidine **59** and *N*-Boc piperidine **54** using organolithium chemistry have been well explored. Together with the synthesis of racemic α -substituted saturated *N*-Boc heterocycles, asymmetric deprotonation using *s*-BuLi and (–)-sparteine, the (+)-sparteine surrogate and Alexakis ligand (*S,S*)-**67** resulted in highly enantioenriched products. In addition, approaches using dynamic thermodynamic resolution gave α -substituted *N*-*i*-Bu pyrrolidines and *N*-Boc piperidines in high *ers*. A third less explored method is the generation of enantioenriched α -substituted *N*-Boc piperidines *via* dynamic kinetic resolution. Two pathways for the introduction of aryl substituents have been developed. One approach involves the transmetalation to an organocopper species and Pd-catalysed introduction of the aryl substituent using aryl iodides. A more explored route is the transmetalation of the lithiated species using ZnCl₂ and Negishi coupling. For the Negishi coupling, a combination of *t*-Bu₃PHBF₄, Pd(OAc)₂ and aryl bromides gave the best yields and high *ers* (where applicable).

1.3.2 Metallation-Trapping of Saturated Oxygen-Containing Heterocycles

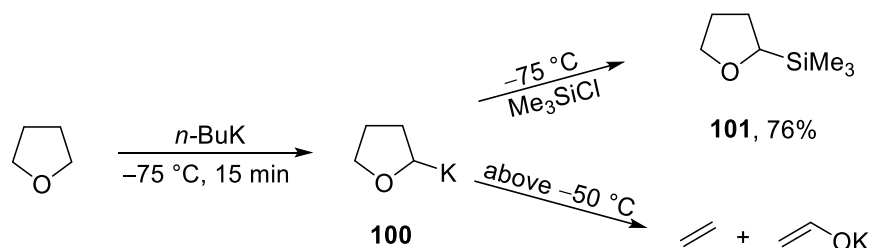
Synthetic access to α -substituted oxygen-containing heterocycles *via* metallation-trapping is under-explored compared to the *N*-Boc heterocycle functionalisation methods discussed in the previous section. In 1972, Bates et al. investigated the synthesis of lithium enolates *via* lithiation of oxygen heterocycles. At room temperature, a solution of *n*-BuLi in THF was found to be unstable. Mixing *n*-BuLi with THF resulted in lithiation and a fast [3+2] cycloreversion. The lithiated species **99** was highly unstable and subsequent fragmentation

gave ethene and a lithium enolate, together with *n*-butane as a by-product of the lithiation step (Scheme 1.54).¹⁰¹



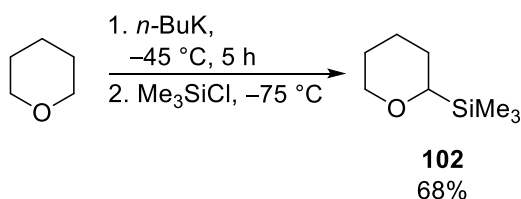
Scheme 1.54 [3+2] Cycloreversion of Lithiated THF 99.

The first successful metallation-trapping of saturated oxygen heterocycles was reported by Lehmann and Schlosser in 1984. Schlosser treated THF, used as a solvent and substrate, with *n*-BuK at $-75\text{ }^{\circ}\text{C}$ and generated the organopotassium species **100**. Addition of Me_3SiCl after 15 min gave α -silyl THF **101** in 76% yield (Scheme 1.55). The main issue with this methodology is that the preparation of the highly reactive *n*-BuK reagent requires the use of stoichiometric amounts of toxic HgCl_2 and a very reactive K alloy. In addition, organopotassium species **100** was shown to be unstable above $-50\text{ }^{\circ}\text{C}$: it fragmented after a few minutes to ethene and a potassium enolate *via* the retro-[3+2] process.¹⁰²



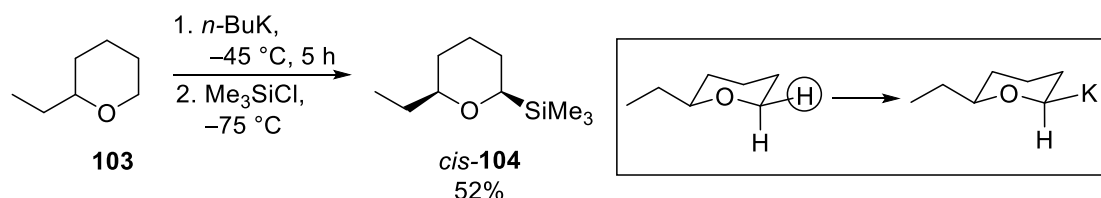
Scheme 1.55 Metallation of THF using *n*-BuK and Trapping with Me_3SiCl .

In further investigations, Lehmann and Schlosser reported that metallation of 6-membered ring THP was 25 times slower than that of THF as shown by a competition experiment. Thus, a higher temperature ($-45\text{ }^{\circ}\text{C}$) was needed for good yields: metallation of THP at $-45\text{ }^{\circ}\text{C}$ for 5 h and subsequent trapping with Me_3SiCl gave α -silyl THP **102** in 68% yield (Scheme 1.56).



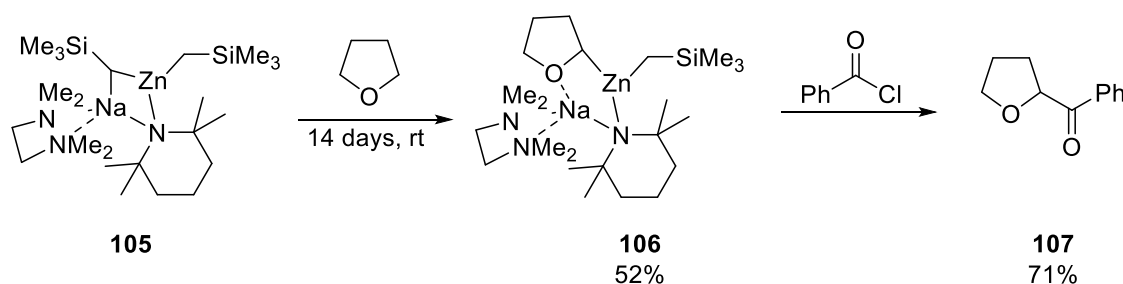
Scheme 1.56 Metallation of THP using *n*-BuK and Trapping with Me_3SiCl .

Additionally, the diastereoselective metallation-trapping of α -ethyl THP **103** was reported. Metallation using *n*-BuK at $-45\text{ }^{\circ}\text{C}$ and subsequent addition of Me_3SiCl exclusively gave *cis*-configured α -silyl THP *cis*-**104** in 52% yield. Although not stated in the paper, the diastereoselectivity probably arises from the ethyl substituent being in an equatorial position and preferential deprotonation of the equatorial proton resulting in the *cis*-organopotassium species (Scheme 1.57).



Scheme 1.57 Metallation of α -Ethyl THP **103 using *n*-BuK and Trapping with Me_3SiCl .**

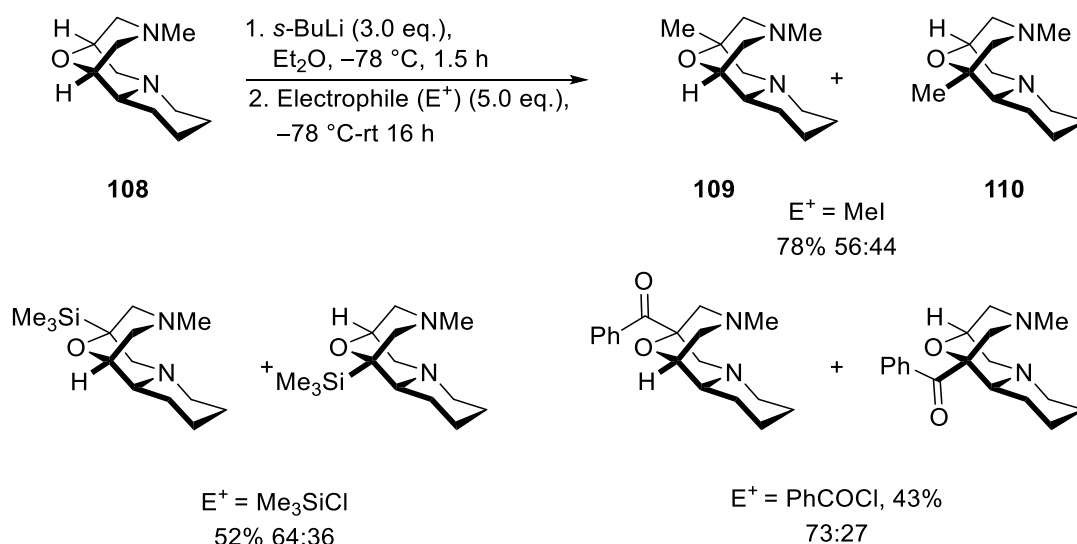
In 2010, Mulvey et al. described the metallation of THF using zincate base **105** which formed the THF zincate **106** (Scheme 1.58). The formation of complex **106** inhibited the decomposition of metallated THF by the ring [3+2] cycloreversion and it was found to be stable at rt. Despite the high stability of this complex, its formation was very slow and a 52% yield of complex **106** was obtained after 14 days and required THF as the solvent and as the substrate. In the next step, the trapping of the coordinated α -THF anion was possible with benzoyl chloride and ketone **107** was isolated in 71% yield.¹⁰³ This approach was subsequently extended to THP.¹⁰³



Scheme 1.58 Metallation of THF using Zincate Base **105 at rt.**

In a final example in the published literature, Breuning et al. explored the lithiation-trapping of tricyclic, morpholine-containing 9-oxabispidine **108**. Oxabispidine **108** is closely related to (–)-sparteine and the (+)-sparteine surrogate and it was hoped that **108** could be used as a chiral ligand in asymmetric deprotonation reactions. However, Breuning et al. reported that deprotonation reactions using *s*-BuLi / oxabispidine **108** were unsuccessful as a result of lithiation at one of the bridgehead carbon atoms of the ligand. *S*-BuLi was essential (no

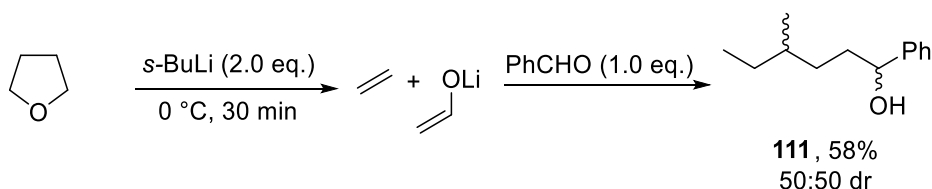
reaction with *n*-BuLi) and a chelating ligand (*e.g.* TMEDA) was not required to promote the lithiation. This is probably because the substrate is a bispidine which is known to coordinate very well to organolithiums. Lithiation of oxabispidine **108** using *s*-BuLi and subsequent trapping with MeI gave a 56:44 mixture of regioisomers **109** and **110** in 78% yield (Scheme 1.59).¹⁰⁴ In addition, trapping with Me₃SiCl and benzoyl chloride resulted in mixtures of regioisomers in 43% and 52% yield respectively.



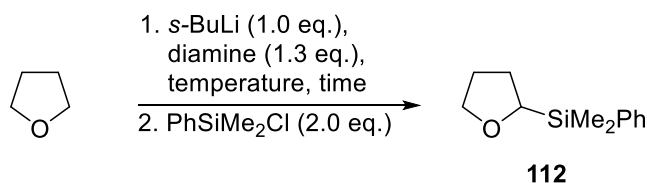
Scheme 1.59 Lithiation-Trapping of Oxabispidine 108.

The mentioned routes to α -substituted oxygen heterocycles required highly toxic reagents and reactive alloys (Lehmann and Schlosser), proceeded *via* the slow formation of the metallated oxygen heterocycles (Mulvey et al.) or needed a very specific 9-oxabispidine **108**. Therefore, the O'Brien group became interested in the metallation of saturated oxygen heterocycles using readily available organolithium reagents and several important results were discovered in the group before the work described in this thesis commenced.^{105 106}

One of the first examples studied in the group was the lithiation-trapping of THF using *s*-BuLi. The lithiation of THF is a balance between lithiation reactivity to generate the lithiated species and stability of the so-formed lithiated species which can undergo fragmentation *via* the [3+2]cycloreversion reaction. Lithiation of THF (substrate and solvent) using *s*-BuLi at 0 °C for 30 min and trapping with benzaldehyde did not give any of the α -substituted THF. Instead, alcohols **111** (50:50 dr) were isolated in 58% yield (yield based on PhCHO) (Scheme 1.60). It was proposed that [3+2] cycloreversion led to the formation of ethene and a lithium enolate. Subsequent carbolithiation of ethene by remaining *s*-BuLi and trapping with benzaldehyde generated alcohols **111**.

Scheme 1.60 Lithiation of THF Using *s*-BuLi at rt.

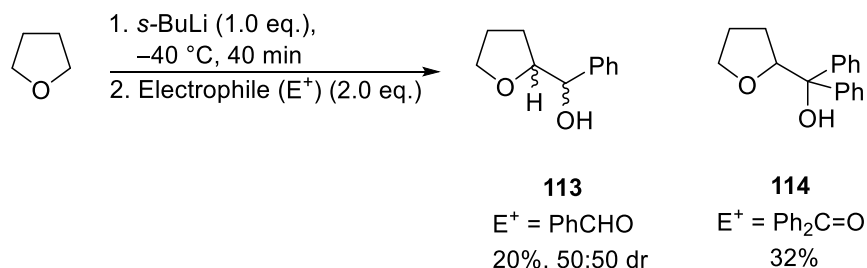
Hence, the lithiation of THF was explored at lower temperatures as it was hoped that the lithiated species would be more stable. However, this would also impact on the rate of lithiation. Indeed, at $-78\text{ }^{\circ}\text{C}$, lithiation of THF (solvent and substrate) using *s*-BuLi / TMEDA gave only traces of α -substituted THF **112** suggesting very low reactivity at that temperature (Table 1.1, entry 1).^{21,22} The lithiation of THF as the substrate and as the solvent was carried out using *s*-BuLi at $-45\text{ }^{\circ}\text{C}$ and lithiation times between 20 min and 60 min. Subsequent trapping with PhSiMe_2Cl gave varying amounts of α -silyl THF **112** (Table 1.1).

Table 1.1 Previous Results in the Lithiation-Trapping of THF with PhSiMe_2Cl .

Entry	Diamine	Temperature / $^{\circ}\text{C}$	Time / min	Yield / %
1	TMEDA	-78	60	1
2	None	-45	20	21
3	TMEDA	-45	20	14
4	None	-45	40	31
5	TMEDA	-45	40	30
6	None	-45	60	29
7	TMEDA	-45	60	29

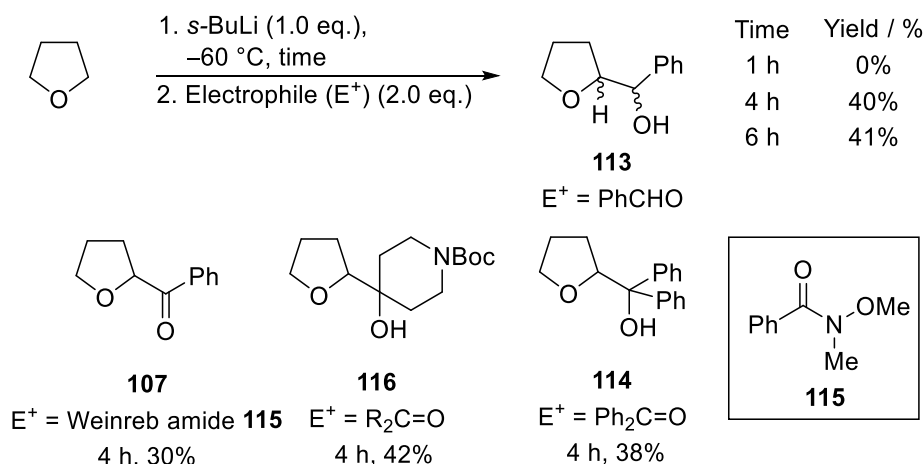
The results revealed that the lithiation of THF as the substrate and as the solvent was not affected by TMEDA (compare entries 4/5 and 6/7), as α -silyl THF **112** was formed in similar yields. A temperature of $-45\text{ }^{\circ}\text{C}$ and a lithiation time of 40 min were the best compromise to achieve sufficient reactivity to allow deprotonation of THF but also to stabilise the resulting lithiated species. Use of these conditions with no TMEDA and trapping with PhSiMe_2Cl gave α -silyl THF **112** in 31% yield (entry 4). A longer lithiation time (60 min) did not result in higher yields (entries 6/7). A shorter lithiation time (20 min) resulted in

lower yields of 14-21% (entries 2/3). Using the best conditions (lithiation with *s*-BuLi at $-40\text{ }^{\circ}\text{C}$ for 40 min), trapping with two other electrophiles was explored and α -substituted THFs **113** and **114** were obtained in 20% and 32% yield respectively (Scheme 1.61).¹⁰⁵



Scheme 1.61 Lithiation-Trapping of THF at $-40\text{ }^{\circ}\text{C}$.

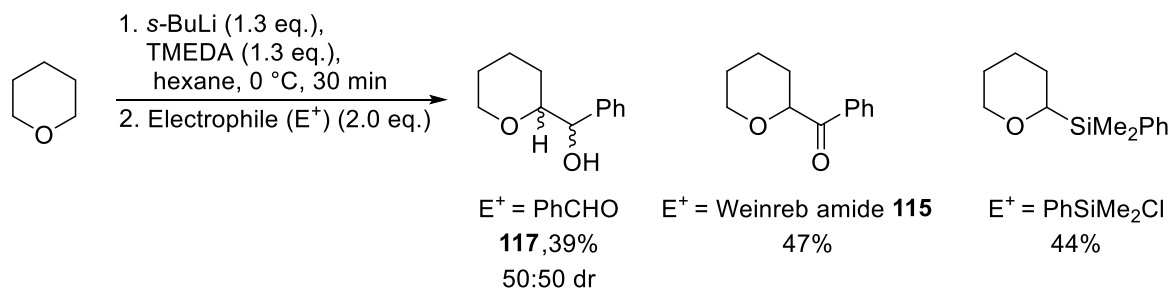
To explain the relatively low yields of 20-32% for the lithiation-trapping of THF at $-40\text{ }^{\circ}\text{C}$, it was proposed that the lithiated species was not sufficiently stabilised. Therefore, lithiation of THF at $-60\text{ }^{\circ}\text{C}$ (trapping with benzaldehyde) was explored in the O'Brien group (Scheme 1.62). Lithiation of THF (substrate and solvent) at $-60\text{ }^{\circ}\text{C}$ for 1 h and subsequent trapping did not give α -substituted THF **113**. Lithiation for 4 h and trapping with benzaldehyde gave the α -substituted THF **113** in 40% yield. However, a longer lithiation time (6 h) did not further increase the yield of α -substituted THF **113** (41% yield). Lithiation conditions of *s*-BuLi at $-60\text{ }^{\circ}\text{C}$ for 4 h were used for trapping with several electrophiles, for example Weinreb amide **115**, and gave the products **107**, **116** and **114** in yields of 30-42% (Scheme 1.62).



Scheme 1.62 Lithiation-Trapping of THF at $-60\text{ }^{\circ}\text{C}$.

The lithiation-trapping of THP was also explored. Initial lithiation of THP as a substrate and as a solvent using *s*-BuLi / TMEDA at $-30\text{ }^{\circ}\text{C}$ for 1 h and trapping with benzaldehyde did not result in the desired α -substituted THPs. Instead, the direct trapped product, resulting

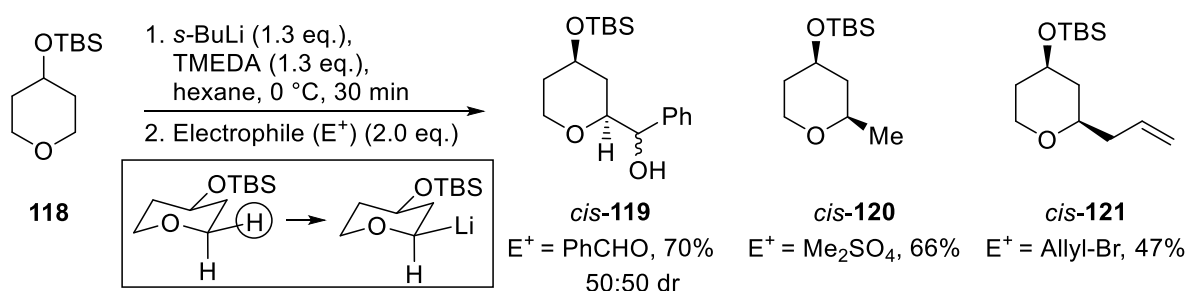
from *s*-BuLi reacting with the electrophile, was observed indicating that the lithiation of THP had not occurred.¹⁰⁵ Therefore, the lithiation of 1 eq. of THP using *s*-BuLi / TMEDA in hexane at higher temperatures (0 °C) was studied. Subsequent trapping with benzaldehyde gave diastereomeric alcohols **117** in 39% yield and 50:50 dr (Scheme 1.63). In total, eight examples were synthesised in yields up to 47%.



Scheme 1.63 Lithiation-Trapping of THP.

Longer lithiation times (1 h and 2 h) at 0 °C resulted in lower yields of alcohols **117** presumably due to degradation of the lithiated species. Based on recent results in the group, it is now believed that the lithiated species can undergo dimerization due to its carbenoid type behaviour.¹⁰⁷

In addition to THP, the lithiation of TBS-protected 4-hydroxy THP **118** was previously explored. Lithiation-trapping of TBS-protected 4-hydroxy THP **118** under the standard THP lithiation conditions (*s*-BuLi / TMEDA, 0 °C, 30 min) resulted in the formation of diastereomeric alcohols 2,4-*cis*-**119** in 70% yield (50:50 dr) (Scheme 1.64). In addition, trapping with Me_2SO_4 and allyl bromide gave the 2,4-*cis*-configured THPs *cis*-**120** and *cis*-**121** in 66% and 47% yield. It is proposed that *cis*-diastereoselectivity arises from the OTBS-substituent being in an equatorial position and favourable deprotonation of the equatorial proton in a similar way to our explanation of Lehmann and Schlosser's result (see Scheme 1.55).¹⁰²



Scheme 1.64 Lithiation-Trapping of TBS-Protected 4-Hydroxy THP 118.

The higher yields in the lithiation-trapping of TBS-protected 4-hydroxy THP **118** compared to the unsubstituted THP suggest that the 4-substituent has an effect on reactivity. Indeed, previous results in the O'Brien group had shown that the rate of lithiation of 4-OTBS *N*-Boc piperidine **122** was faster than the rate of lithiation of *N*-Boc piperidine using ReactIR experiments and monitoring of the lithiated species.¹⁰⁸ In a competition experiment by a co-worker it was found that the TBS-protected 4-hydroxy THP **118** undergoes faster lithiation than the unsubstituted THP.¹⁰⁷ In Figure 1.8, a potential explanation for the high reactivity of TBS-protected 4-hydroxy THP **118** is presented. In the case of 4-TBS-protected *N*-Boc piperidines and TBS-protected 4-hydroxy THPs it is assumed that back-donation from the C-H σ -orbital to the C-O σ^* -orbital could occur leading to an increased acidity of the position α to nitrogen or oxygen.

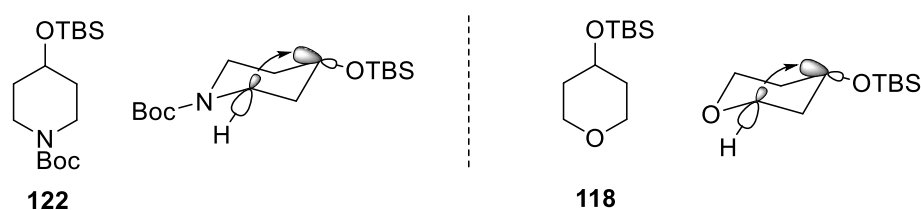


Figure 1.8: Propose Activating Effect via Back-Donation.

In the case of *N*-Boc piperazines **123** and *N*-substituted morpholines **124**, a similar back-donation from the C-H σ -orbital to the C-N σ^* -orbital could lead to a higher acidity of the protons in position α to nitrogen or oxygen (Figure 1.9).¹⁰⁹ In fact, the back-donation model would also account for the high reactivity in the lithiation of oxabispidine **108** reported by Breuning (Scheme 1.59). The oxabispidine system is doubly activated as the protons α to oxygen are activated by double back-donation from the C-H σ -orbital to the C-N σ^* -orbital as a result of the bispidine structure and deprotonation is possible at low temperatures.

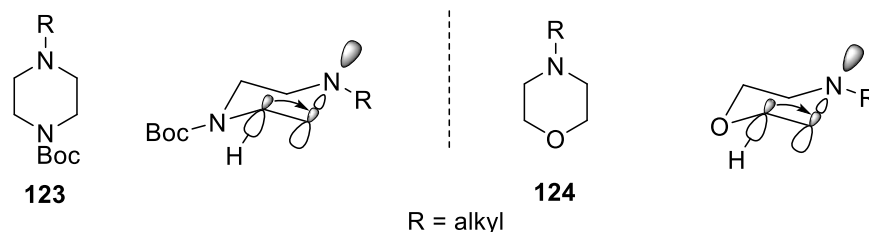
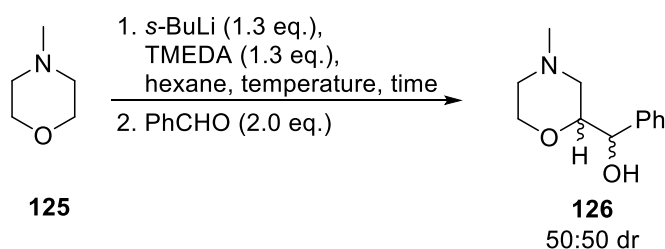


Figure 1.9 Rate of Lithiation for *N*- and *O*-Containing Heterocycles.

As a result of the reported high reactivity towards lithiation in the oxabispidine system by Breuning et al., the O'Brien group became interested in the lithiation of the related *N*-methyl morpholine **125**. To the best of our knowledge, lithiation of that system has not been studied

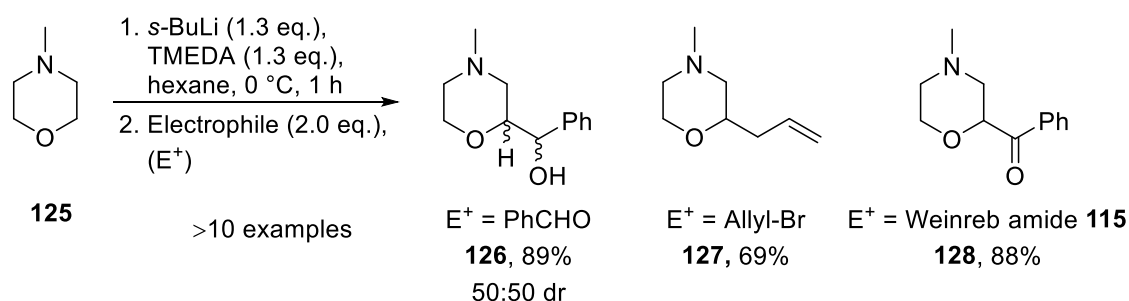
before. Initially, lithiation of *N*-methyl morpholine **125** by a co-worker in the O'Brien group¹⁰⁶ using *s*-BuLi / TMEDA at $-40\text{ }^{\circ}\text{C}$ for 1 h and then trapping with benzaldehyde gave alcohols **126** in 15% yield (entry 1). Lithiation under the same conditions at $-20\text{ }^{\circ}\text{C}$ gave the alcohols **126** in 63% yield (entry 2). At $0\text{ }^{\circ}\text{C}$, lithiation for 1 h resulted in alcohols **126** being formed in 89% yield (entry 3). Lithiation at higher temperatures ($20\text{ }^{\circ}\text{C}$) for shorter reaction times resulted in the desired products in lower yields (entries 4 and 5). Presumably, the lithiated species is unstable at higher temperatures than $0\text{ }^{\circ}\text{C}$.

Table 1.2: Lithiation-Trapping of *N*-Methyl Morpholine **125.**



Entry	Temperature / $^{\circ}\text{C}$	Time / min	Yield / %
1	-40	60	15
2	-20	60	63
3	0	60	89
4	20	10	66
5	20	30	48

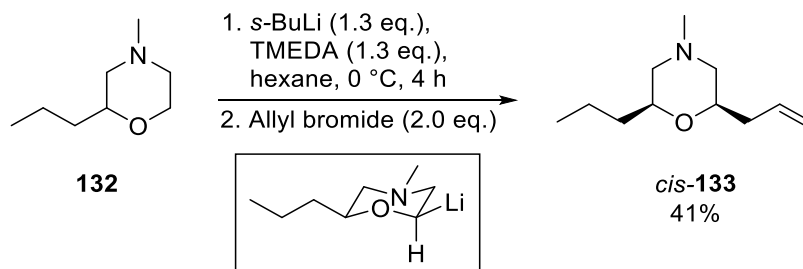
Using the best lithiation conditions (*s*-BuLi / TMEDA in hexane at $0\text{ }^{\circ}\text{C}$ for 1 h), the trapping with a range of electrophiles gave α -substituted morpholines in high yields up to 90% and several examples were synthesised. Three examples **126**, **127** and **128** are shown in Scheme 1.65.



Scheme 1.65 Lithiation-Trapping of *N*-Methyl Morpholine **125.**

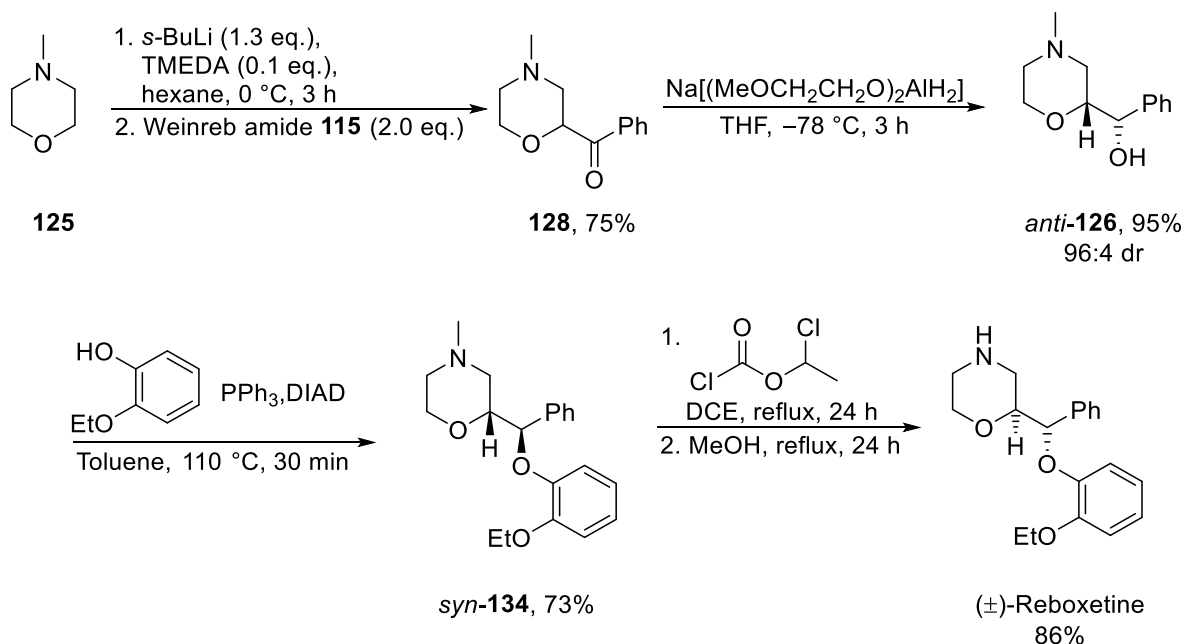
Furthermore, a catalytic lithiation-trapping was reported using substoichiometric amounts of TMEDA (0.1 eq.) and an extended lithiation time of 3 h.¹⁰⁶ Under these conditions, the

1.68). The 2,6-*cis* configuration is assumed to arise due to equatorial lithiation with the *n*-propyl group of morpholine **133** in the equatorial position.



Scheme 1.68 Synthesis of 2,6-*cis*-Configured Morpholines.

With a reliable lithiation-trapping procedure for the α -functionalisation of morpholines in hand, the O'Brien group investigated a new approach for the synthesis of reboxetine (Scheme 1.69).²² Starting from *N*-methyl morpholine **125**, lithiation-trapping with Weinreb amide **115** resulted in ketone **128** in 75% yield. In the next, step Cram chelation-controlled reduction with Red-Al gave morpholine *anti*-**126** in an excellent 95% yield. A Mitsunobu reaction was used to complete the reboxetine backbone by converting the hydroxyl group into an ether group using PPh₃ and DIAD. Ether *syn*-**134** was isolated in 73% yield. Finally, removal of the methyl group following a procedure by Olofson et al. gave reboxetine in 86% yield.¹¹¹ Mechanistically, the addition of α -chloroethyl chloroformate led to the formation of an ammonium species. The methyl group was cleaved by chloride to give a carbamate intermediate. Subsequent MeOH addition led to collapse of the carbamate and the formation of a secondary amine. This entirely new approach to reboxetine was made possible by the newly developed lithiation-trapping in the first step.¹⁰⁶

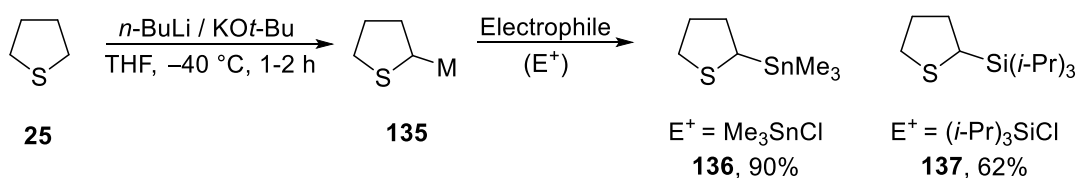


Scheme 1.69 Synthesis of Reboxetine by the O'Brien Group.

The metallation-trapping of oxygen-heterocycles is not very well investigated. Early investigations by Bates and Lehmann and Schlosser on THF proved the instability of the lithiated species. Mulvey et al. reported the stabilisation of a zincated THF species but the formation of the complex was very slow. Finally, unpublished work in the O'Brien group showed that it was possible to perform lithiation-trapping of THF and THP in moderate yields. Furthermore, conditions for the high yielding lithiation-trapping of *N*-methyl morpholine **125** have been discovered, which enabled a catalytic approach to trapped products in high yields at mild reaction temperatures.

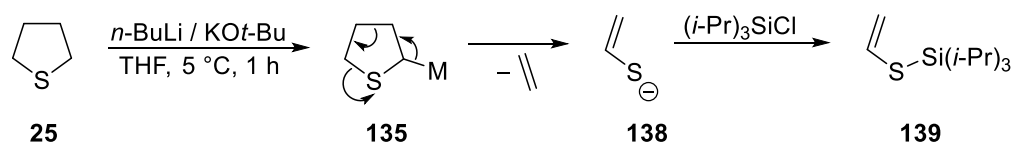
1.3.3 Synthesis of α -Substituted Sulfides Using Organometallic Reagents

To the best of our knowledge, only one group has previously investigated the direct metallation of cyclic saturated sulfur heterocycles to access α -substituted cyclic sulfides. In 1997, Liu and Glass¹¹² reported the synthesis of α -substituted acyclic and cyclic sulfides using a mixture of *n*-BuLi and KO*t*-Bu (Schlosser base). For example, tetrahydrothiophene **25** was treated with *n*-BuLi and KO*t*-Bu in THF at -40 °C to give metallated sulfide **135** which was then trapped with stannyl and silyl chlorides to give α -substituted sulfur heterocycles **136** and **137** in 90% and 62% yield respectively (Scheme 1.70).



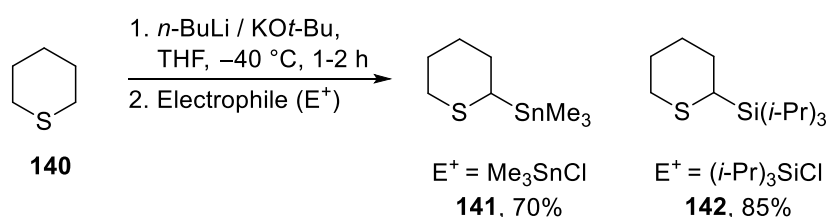
Scheme 1.70 Metallation-Trapping of Cyclic Sulfide 25.

Interestingly, the stability of metallated sulfide **135** was highly dependent on the temperature. The best yields of trapped product were obtained using a temperature of $-40\text{ }^\circ\text{C}$ for the metallation. In contrast, metallation at $5\text{ }^\circ\text{C}$ for 1 h using *n*-BuLi and KOt-Bu resulted in the formation of the fragmentation product **138** (Scheme 1.71). It is assumed that the fragmentation proceeded *via* an analogous [3+2] cycloreversion pathway to α -lithiated THF resulting in thioenolate **138**. Trapping with a silyl chloride gave silyl sulfide **139**.¹⁰¹



Scheme 1.71 Fragmentation of Metallated Cyclic Sulfide 25 at $5\text{ }^\circ\text{C}$.

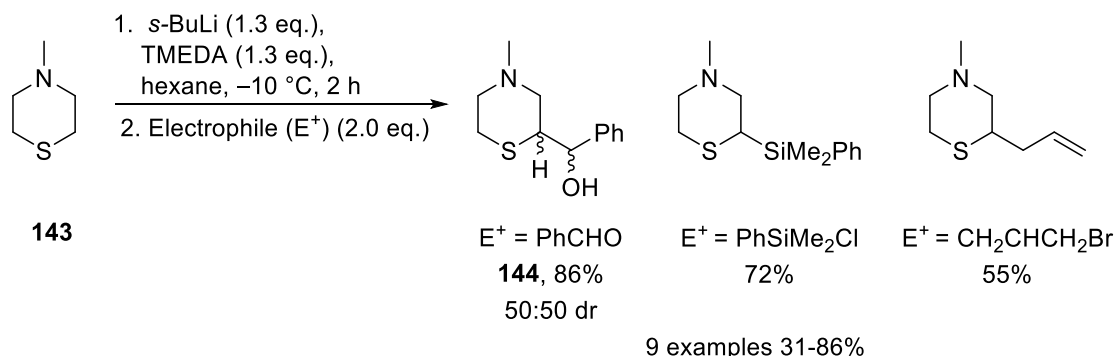
In addition to the 5-membered tetrahydrothiophene **25**, the metallation of 6-membered tetrahydrothiopyran **140** was studied by Liu and Glass. Metallation of tetrahydrothiopyran **140** using the Schlosser base and trapping with stannyl and silyl chlorides gave α -stannyl tetrahydrothiopyran **141** in 70% yield and α -silyl tetrahydrothiopyran **142** in 85% yield (Scheme 1.72).



Scheme 1.72 Metallation-Trapping of Cyclic Sulfide 140.

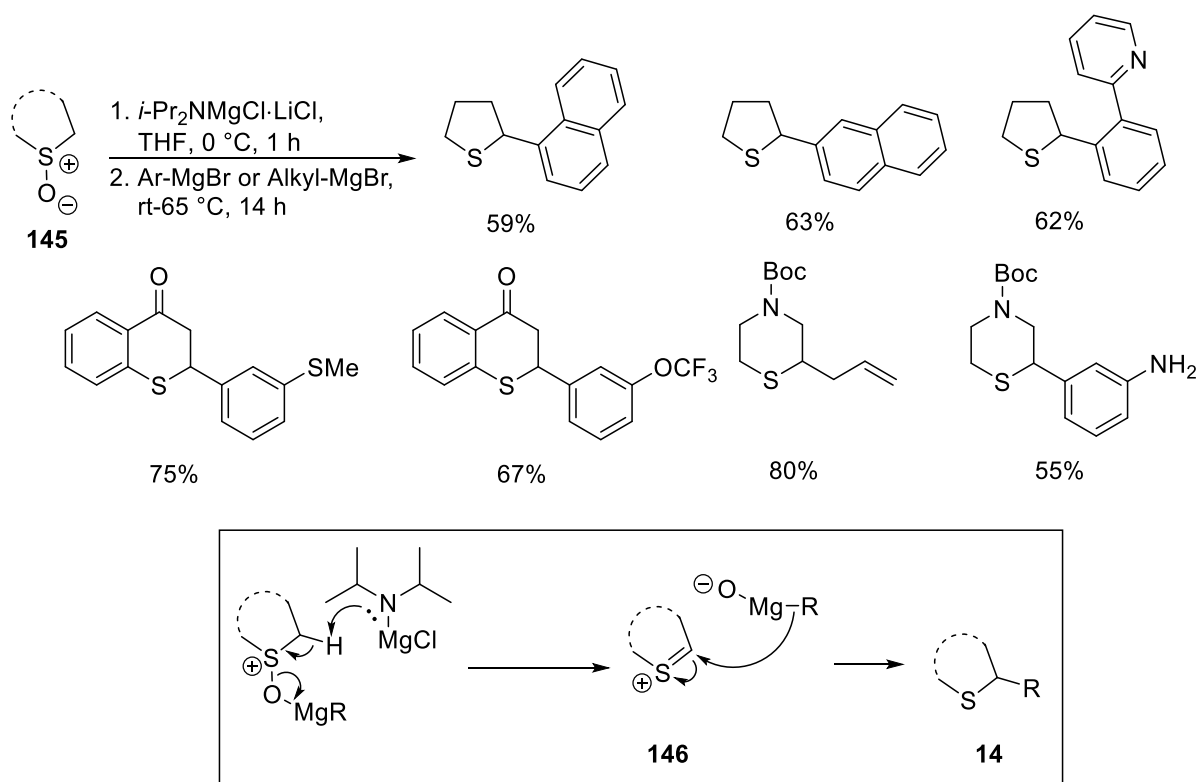
Recently, the O'Brien group has developed a protocol for the lithiation-trapping of thiomorpholine **143**.¹⁰⁶ Based on the previously described conditions for the lithiation of morpholine **125** (*s*-BuLi / TMEDA in hexane at $0\text{ }^\circ\text{C}$ for 1 h), the lithiation-trapping of thiomorpholine was studied. Using *s*-BuLi and TMEDA in hexane at $-10\text{ }^\circ\text{C}$ for 2 h, a slightly lower temperature and an increased lithiation time compared to the lithiation of *N*-methyl morpholine **125** and trapping with benzaldehyde gave α -substituted thiomorpholine

144 in 86% yield (50:50 dr). Under the same reaction conditions further electrophiles were used in the trapping to give α -substituted thiomorpholines in 31-86% yield (Scheme 1.73).



Scheme 1.73 Lithiation-Trapping of *N*-Methyl Thiomorpholine **143**.

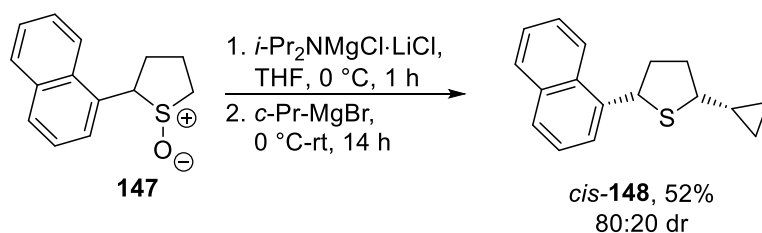
A different organometallic pathway to access α -substituted cyclic saturated sulfides starting from sulfoxides was recently developed by Mendoza et al. based on previous work by Kobayashi et al.¹¹³⁻¹¹⁵ Since sulfoxides are readily available *via* oxidation of the corresponding sulfides, this can be considered a two-step method for the α -functionalisation of cyclic sulfides. In 2017, Mendoza et al. reported that treatment of sulfoxides **145** with Knochel-Hauser bases and subsequent addition of aryl and alkyl Grignard reagents gave the corresponding α -alkyl and α -aryl substituted sulfur heterocycles in moderate to good yield 55-80%. Interestingly, substrates bearing a ketone were tolerated during addition of the Grignard reagents. In particular, the synthesis of α -substituted tetrahydrothiophenes and thiomorpholines was explored by Mendoza et al. (Scheme 1.74).



Scheme 1.74 Synthesis of Cyclic Sulfides *via* Pummerer Rearrangement Starting from Cyclic Sulfoxides **145**.

The reaction proceeds *via* a Pummerer-type rearrangement (Scheme 1.74). Mendoza et al. revealed that the reactivity of the base needed to be adjusted to the reactivity of the sulfoxide. The Knochel-Hauser base in combination with a Grignard reagent allowed the α -deprotonation of the sulfoxide which is activated by the Grignard reagent to form the sulfonium intermediate **146**. Attack of the Grignard species then gives the α -substituted sulfur heterocycle **14**. Strong bases led to competing irreversible deprotonation of the sulfoxide **145** which inhibits the formation of the desired α -substituted products.

Starting from α -substituted sulfoxide **147**, the Pummerer rearrangement was explored. This gave 2,5-*cis* substituted tetrahydrothiophene **148** in 52% yield and a moderate dr of 80:20 (Scheme 1.75).



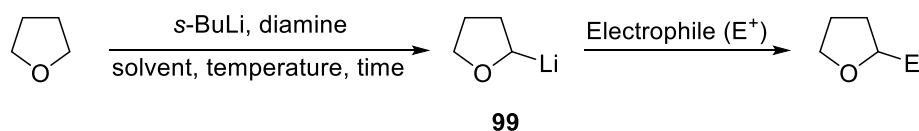
Scheme 1.75 Synthesis of 2,5-*cis*-Configured Cyclic Sulfides *via* Pummerer Rearrangement Starting from Cyclic Sulfoxides.

In summary, the direct metallation-trapping of saturated cyclic sulfides is under-explored. To the best of our knowledge, only Liu and Glass have investigated the α -metallation which was achieved using a Schlosser base. Preliminary results in the lithiation-trapping of thiomorpholines by the O'Brien group show that the use of readily available organolithium reagents allows the synthesis of α -functionalised thiomorpholines in good yields.

1.4 Project Outline

The focus of research described in this thesis is the development of new methods for the α -functionalisation of saturated oxygen and sulfur heterocycles using organolithium reagents.

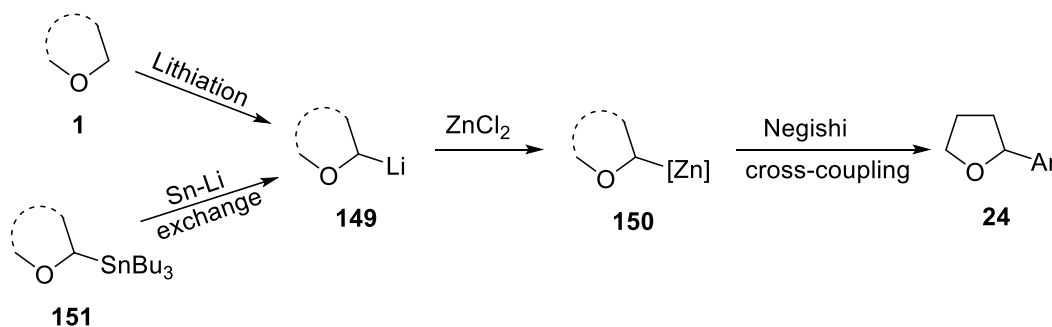
In contrast to the detailed studies in the lithiation-trapping of saturated *N*-Boc heterocycles, the direct α -functionalisation of saturated oxygen heterocycles for example THF *via* metallation and subsequent trapping is underexplored. As presented in section 1.2, it is mainly radical methods that are used to give access to α -substituted saturated oxygen heterocycles. To date, the metallation of THF can be carried out using very reactive organopotassium reagents¹⁰² or requires Na-Zn complexes¹⁰³ and reaction times of two weeks. Building on the expertise in the O'Brien group in the use of organolithium reagents, co-workers started exploring reaction conditions that allow the generation of lithiated THF **100** using readily available organolithium reagents. However, the explored lithiation conditions for THF often did not give reproducible results and did not allow the exploration of a wide scope of electrophiles.¹⁰⁵⁻¹⁰⁶ Therefore, in this thesis efforts towards the study of reliable lithiation conditions for THF are described (Scheme 1.76). It is proposed that employing a *s*-BuLi / diamine complex could lead to a higher reactivity in the α -deprotonation of THF and higher yields in the subsequent trapping and our efforts are presented in chapter 2.



Scheme 1.76 Proposed Lithiation-Trapping Approach for THF.

In the previously developed lithiation-trapping approaches for THF, THP and *N*-methyl morpholine the introduction of aryl-substituents α to oxygen was not explored. To expand the scope, there was a high interest in exploring routes towards α -arylated oxygen heterocycles. In the related saturated *N*-Boc heterocycles, Negishi cross-coupling approaches of organozinc species were successfully reported by Campos et al.⁸⁶ and Coldham and Leonori⁹⁰ in the synthesis of α -arylated of 5- and 6-membered *N*-Boc heterocycles. It was therefore proposed that the organozinc species **150** would be a key intermediate that will allow us to study Negishi cross-coupling to give α -arylated oxygen heterocycles **24** (Scheme 1.77). To access the organozinc species **150**, two different approaches will be investigated. Based on the lithiation protocols for THF, THP and *N*-

methyl morpholine a direct lithiation and subsequent transmetallation using ZnCl_2 was considered. An alternative strategy that could give access to the lithiated species **149** would be starting from organostannanes **151** via Sn-Li exchange. The exploration of both of these approaches is detailed in chapter 2.

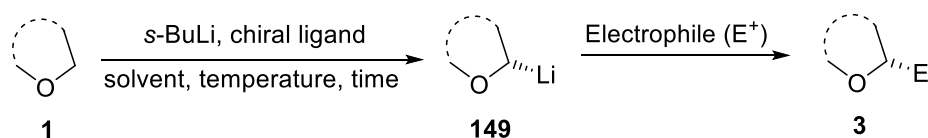


Scheme 1.77 Proposed Generation of the Lithiated Oxygen Heterocycles, Transmetallation and Negishi Cross-Coupling.

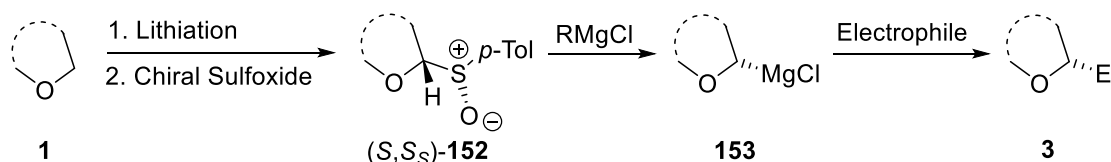
Chapter 3 describes three different investigations into the synthesis of enantioenriched α -substituted oxygen heterocycles **3**. Firstly, it was planned to investigate the asymmetric deprotonation of oxygen heterocycles **1** including THF, THP and morpholine. With the expertise in the asymmetric deprotonation of saturated *N*-Boc heterocycles, reaction conditions using *s*-BuLi and chiral ligands would be studied to enable the asymmetric deprotonation of oxygen heterocycles. In an alternative approach, it was proposed to focus on the synthesis of chiral sulfoxides **152** via lithiation-trapping of oxygen heterocycles with (–)-Andersen's sulfinate.¹¹⁶ The α -sulfinyl substituted oxygen heterocycles **152** would then be used in sulfoxide-Mg exchange reactions to generate an enantioenriched organomagnesium species **153** for subsequent trapping. This approach has previously been carried out by the O'Brien group in the synthesis of enantioenriched *N*-Boc heterocycles and protected carbamates.¹¹⁷

In addition, it was planned to study the synthesis of enantioenriched α -substituted morpholines. It was proposed that lithiation of an enantioenriched *N*-substituted morpholine (*S*)-**154** and trapping with alkyltin chloride should give access to diastereomeric α -stannyl morpholines (*S,R*)-**155** and (*S,S*)-**155**. It is hoped that the diastereomers will be separable by chromatography and subsequent Sn-Li exchange of each stannane and trapping with different electrophiles as well as transmetallation to zinc and Negishi cross-coupling should produce α -substituted morpholines **156**.

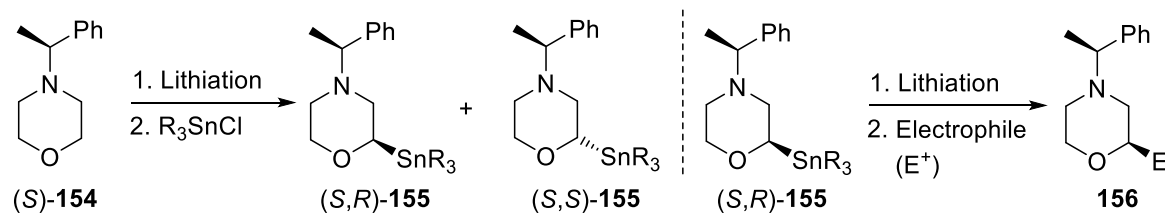
(i) Asymmetric Deprotonation



(ii) Sulfoxide-Mg Exchange

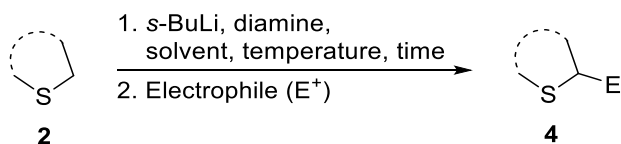


(iii) Sn-Li Exchange



Scheme 1.78 Proposed Approaches for the Synthesis of Enantioenriched α -Substituted Oxygen Heterocycles.

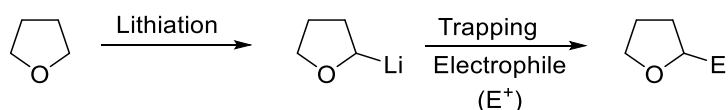
The study of the racemic α -lithiation of saturated sulfur heterocycles was also planned. Very little work has been carried out by Liu and Glass in the metallation of saturated sulfur heterocycles and there are only three examples of the synthesis of α -stannyl and α -silyl substituted cyclic sulfides.¹¹² Based on previous results in the lithiation of saturated oxygen heterocycles, a detailed analysis of lithiation-trapping conditions for various saturated sulfur heterocycles **2** will be carried out (Scheme 1.79). If lithiation conditions for saturated sulfur heterocycles could be developed, the scope of α -substituted sulfur heterocycles **4** and the stereo- and regio selectivity of the lithiation-trapping process would then be explored. The results in this area are described in chapter 4.



Scheme 1.79 Proposed Lithiation-Trapping Approach for Saturated Sulfur Heterocycles.

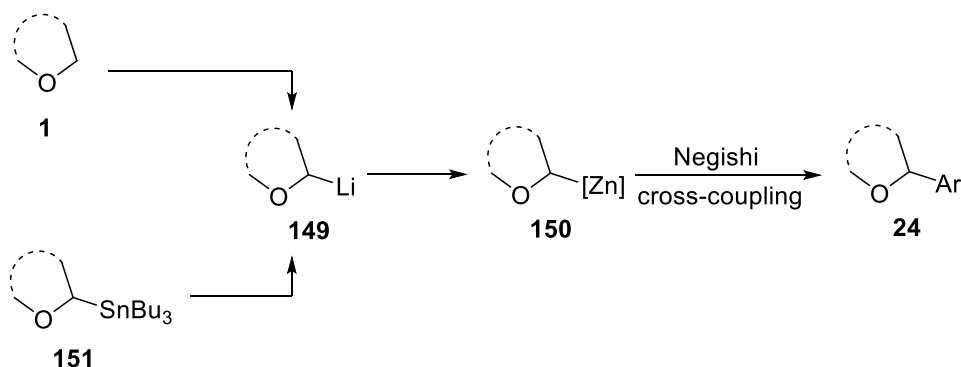
Chapter 2: Racemic Lithiation-Trapping of Tetrahydrofuran and α -Arylation of Saturated Oxygen Heterocycles using Negishi Cross-Coupling

In the first part of this chapter (section 2.1), the racemic lithiation-trapping of THF as an approach to α -substituted THFs is described (Scheme 2.1). Building on previous work in the O'Brien group, new reaction conditions for the lithiation are developed and trapping with a range of electrophiles is presented.



Scheme 2.1 Proposed Lithiation and Trapping Process for THF.

In the second part of the chapter (section 2.2), efforts on the synthesis of α -arylated saturated oxygen heterocycles using organolithium reagents are reported. Two routes to access α -arylated saturated oxygen heterocycles **1** are described (Scheme 2.2). One approach starts from saturated oxygen heterocycles and uses deprotonation to generate a lithiated species **149**. Transmetalation gives an organozinc species **150** which undergoes Negishi cross-coupling to give α -arylated saturated oxygen heterocycles **24**. The second strategy to access α -arylated oxygen heterocycles, which proves to be the more successful approach, starts from organostannanes **151**. Sn-Li exchange and transmetalation generates the same organozinc species **150** and the subsequent Negishi-cross coupling to access α -arylated saturated oxygen heterocycles **24** is described.



Scheme 2.2 Proposed Generation of α -Lithiated Oxygen Heterocycles, Transmetalation and Negishi Cross-Coupling.

2.1 Racemic Lithiation-Trapping of THF

Over the last few years, conditions for the lithiation of THF and subsequent trapping with electrophiles have been studied in the O'Brien group (see section 1.3.2). These studies on the lithiation-trapping of THF (solvent and substrate) identified two useful sets of lithiation conditions: (i) lithiation using *s*-BuLi at $-60\text{ }^{\circ}\text{C}$ for 4 h and (ii) lithiation using *s*-BuLi at $-40\text{ }^{\circ}\text{C}$ for 40 min (see Scheme 1.61 and Scheme 1.62). The two sets of conditions represent a compromise between ensuring high reactivity in the formation of the lithiated species and sufficient stability of the lithiated species to prevent competing [3+2] cycloreversion. However, yields were sometimes not reproducible using either set of conditions and maintaining a consistent temperature of $-60\text{ }^{\circ}\text{C}$ for reaction times of 4 h can be challenging. Performing the reactions using *s*-BuLi in the presence of TMEDA did not seem to enhance the reactivity in the formation of the lithiated THFs and therefore the yields of α -substituted THFs were similar with and without TMEDA (see Table 1.1).

Recently, Aggarwal et al. reported the effect of different diamines on the rate of *s*-BuLi / diamine-mediated lithiation of *O*-alkyl carbamates using ReactIR spectroscopic monitoring (Figure 2.1).¹¹⁸ The slowest lithiation of the carbamates was observed with a *s*-BuLi / (+)-sparteine complex. Lithiation was slightly faster with *s*-BuLi / TMEDA. Use of *s*-BuLi / (+)-sparteine surrogate and *s*-BuLi / *N,N'*-dimethyl bispidine (DMBS) resulted in much faster lithiation rates. As the stability of a lithiated species is harder to predict, we wondered if employing a more reactive *s*-BuLi / bispidine complex in the lithiation of THF would lead to higher yields of α -substituted THF products.

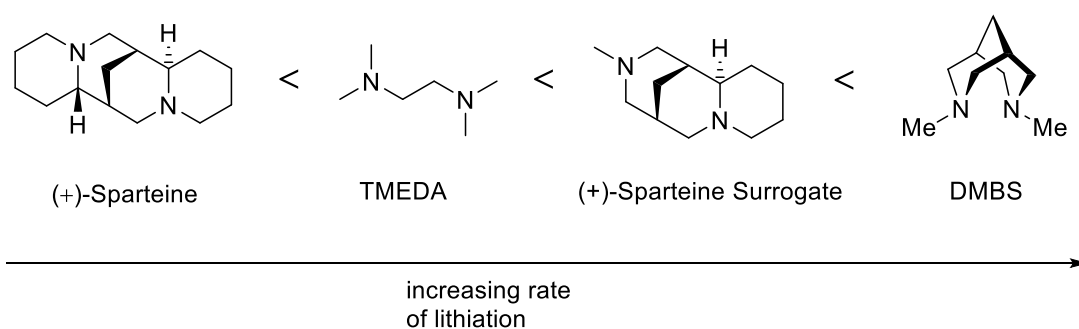
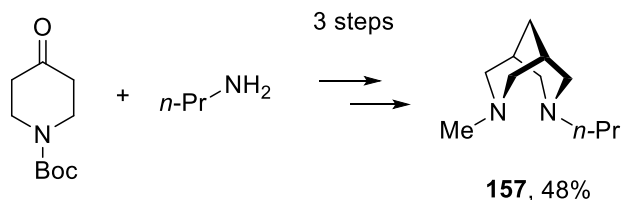


Figure 2.1: Rate of Lithiation for *s*-BuLi / Diamine Complexes.

Unlike TMEDA which is commercially available, most bispidine ligands cannot be purchased and require a multi-step synthesis. In some cases, the synthesis of bispidine ligands can be challenging. For example, Aggarwal et al. reported the synthesis of DMBS in three steps with an overall yield of only 1%.¹¹⁸ In previous work on the synthesis of bispidine

ligands, the O'Brien group reported the generation of *N*-methyl, *N'*-*i*-propyl bispidine in three steps in 37% overall yield.¹¹⁹ Using a similar approach, *N*-methyl, *N'*-*n*-propyl bispidine **157** was synthesised by a co-worker in 48% yield over three steps (Scheme 2.3).¹⁰⁷ Since it was believed that bispidine **157** is likely to be sterically similar to DMBS, it was decided to use bispidine **157** for our studies as it is accessible in higher yields.



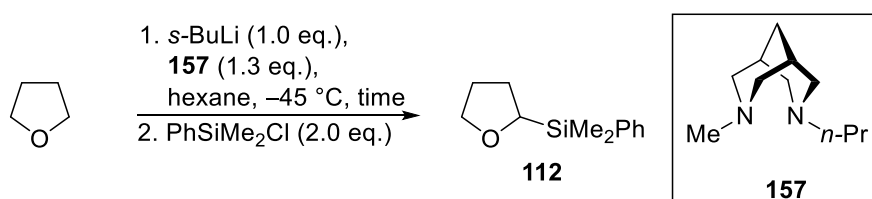
Scheme 2.3 Synthesis of Bispidine 157.

With bispidine ligand **157** available in the group, new conditions for the lithiation of THF were explored. As the previously investigated lithiation conditions of THF (substrate and solvent) using *s*-BuLi at $-60\text{ }^{\circ}\text{C}$ for 4 h resulted in variable yields, the lithiation of THF at $-45\text{ }^{\circ}\text{C}$ (dry ice/MeCN cold bath) in combination with *s*-BuLi / bispidine **157** was studied and the results are presented in Table 2.1. Lithiation of THF as substrate and solvent using *s*-BuLi / bispidine **157** at $-45\text{ }^{\circ}\text{C}$ for 1 h and trapping with PhSiMe₂Cl gave α -silyl THF **112** in 29% yield (entry 1). This is essentially the same result as that obtained with or without TMEDA see Table 1.1, entries 6 and 7). The bispidine ligand and TMEDA appear to have no effect on the lithiation using THF as the solvent. Further stability studies carried out by a co-worker suggest that the stability of lithiated THF in THF is lower than that in hexane (in the presence of TMEDA).¹⁰⁷

Therefore, there was interest in adapting the previously explored lithiation conditions for THP and *N*-methyl morpholine **125** which used 1.0 eq. of the heterocycle in hexane (see Scheme 1.63 and Scheme 1.65). Lithiation of 1.0 eq. THF with *s*-BuLi / bispidine **157** in hexane at $-45\text{ }^{\circ}\text{C}$ for 1 h and trapping with PhSiMe₂Cl gave α -silyl THF **112** in only 4% yield (entry 2). Due to the poor lithiation using 1.0 eq. THF in hexane and *s*-BuLi / bispidine **157**, it was wondered if an amount of THF between 1.0 eq. and using it as a solvent could lead to a higher yield. It was arbitrarily chosen to try the lithiation of THF using 10 eq. of THF and *s*-BuLi / bispidine **157** in hexane. To our surprise and delight, the desired product **112** was isolated in 66% yield (entry 3, yield calculated based on *s*-BuLi as the limiting reagent). It was presumed that 10 eq. of THF leads to more lithiation and produces a relatively stable lithiated THF species since there is no large excess of THF. Decreasing the

lithiation time to 0.5 h gave the α -substituted THF **112** in 49% yield (entry 4). When the lithiation time was increased to 2 h, a yield of 41% was obtained (entry 5), presumably because of further degradation of the lithiated species. Lithiation of THF using 5.0 eq. of THF and *s*-BuLi / TMEDA for 1 h and trapping with PhSiMe₂Cl gave the α -substituted THF **112** in 28% yield (entry 6). The best conditions for the lithiation of THF were 10 eq. of THF in hexane using *s*-BuLi / bispidine **157** at $-45\text{ }^{\circ}\text{C}$ for 1 h in the lithiation process and trapping resulted in the α -silyl THF in 66%, which is the highest yield reported for the lithiation-trapping of THF.

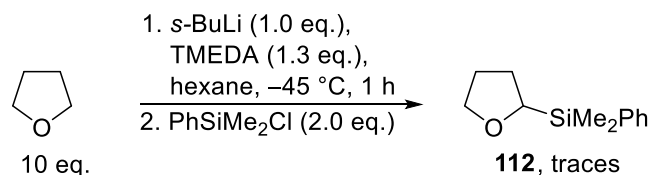
Table 2.1 Lithiation of THF using *s*-BuLi / Bispidine **157**.



Entry	THF / eq.	Time / h	Yield / % ^a
1	Solvent	1	29
2	1.0	1	4
3	10	1	66
4 ^b	10	0.5	49
5	10	2	41
6	5.0	1	28

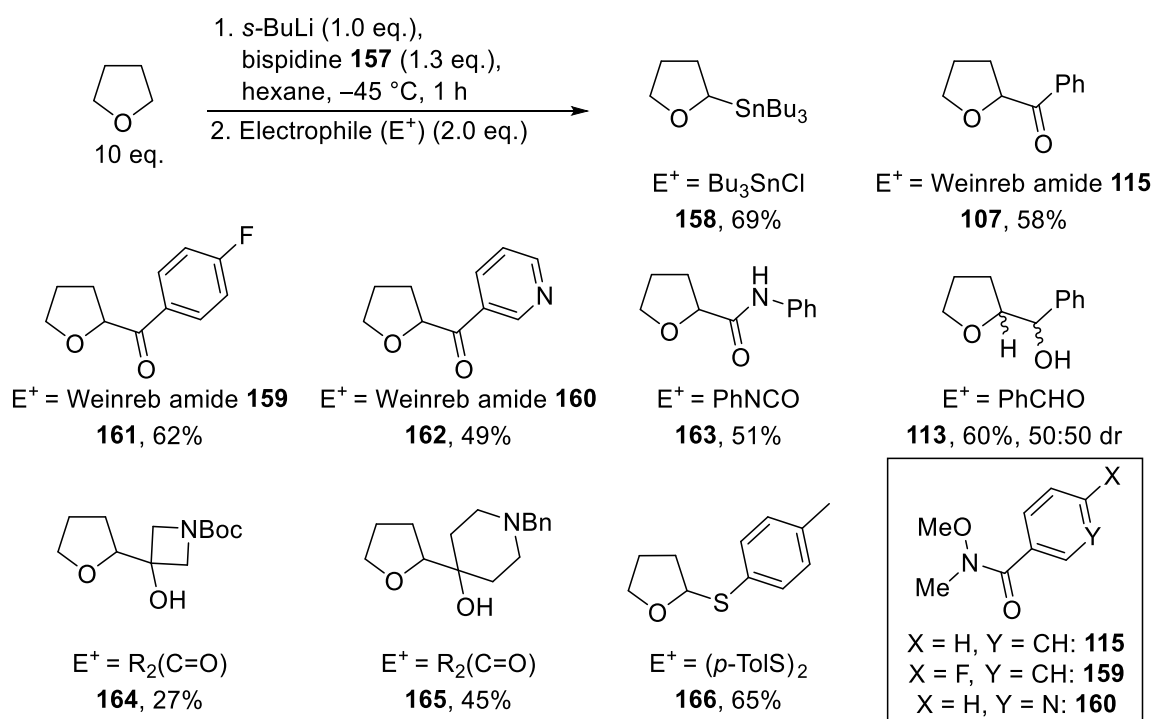
^aYield after purification by chromatography, ^bexperiment carried out by a co-worker.

For comparison, this reaction was carried out using TMEDA in place of bispidine **157** (Scheme 2.4). Trapping, of lithiated THF after lithiation using *s*-BuLi / TMEDA, with PhSiMe₂Cl gave traces of silane α -silyl THF **112**. This result indicates that in the lithiation of THF (10 eq. in hexane) the *s*-BuLi / bispidine **157** complex has a higher reactivity than the *s*-BuLi / TMEDA.



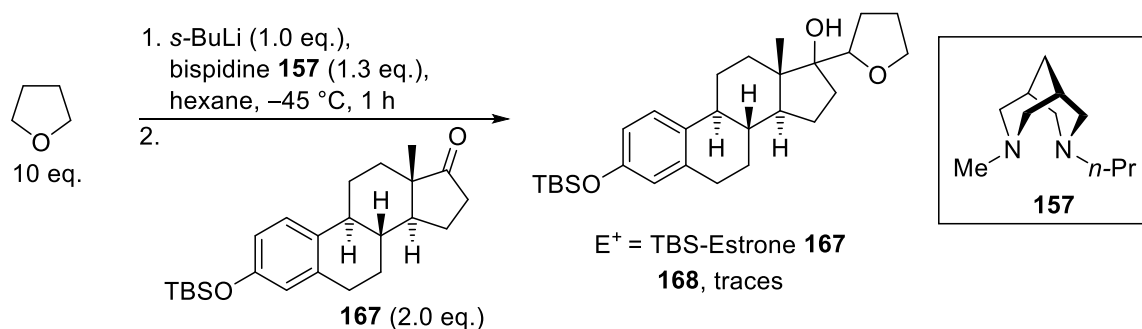
Scheme 2.4 Lithiation of THF (10 eq.) Using *s*-BuLi / TMEDA.

With the new lithiation conditions for THF in hand (10 eq. of THF, *s*-BuLi / bispidine **157** in hexane at $-45\text{ }^{\circ}\text{C}$ for 1 h), the trapping with a range of electrophiles was explored (Scheme 2.5). The lithiated species was trapped with Bu_3SnCl to give the α -stannyl THF **158** in 69% yield. In addition, trapping with Weinreb amides **115**, **159** and **160** was investigated and gave ketones **107**, **161** and **162** in 49-62% yield. The trapping with phenyl isocyanate gave the corresponding amide **163** in 51% yield. When benzaldehyde was used, a 50:50 mixture (by ^1H NMR spectroscopy of the crude product) of diastereomeric alcohols **113** was obtained. The same mixture of diastereomeric alcohols **113** was isolated in 60% yield after chromatography. Unless otherwise stated in this thesis, the diastereomeric ratios mentioned in schemes and tables are based on analysis of the ^1H NMR spectrum of the crude product. If an inseparable diastereomeric mixture of products is isolated after chromatography, the ratio after chromatography can be found in the experimental section. Trapping with ketones generated alcohols **164** and **165** in 27% and 45% yield respectively whereas reaction with $(p\text{-TolS})_2$ produced sulfide **166** in 65% yield.

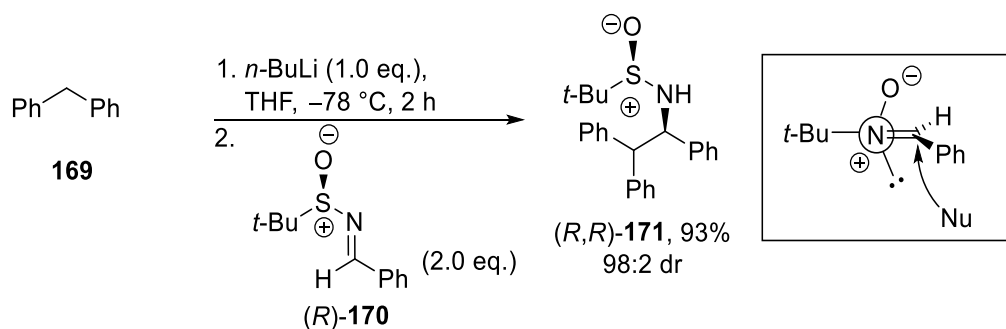


Scheme 2.5 Lithiation of THF and Trapping with Various Electrophiles.

Next, the late-stage functionalisation of TBS-protected estrone **167** was explored (Scheme 2.6). Unfortunately, only traces of product **168** were observed by ^1H NMR spectroscopy of the crude product.

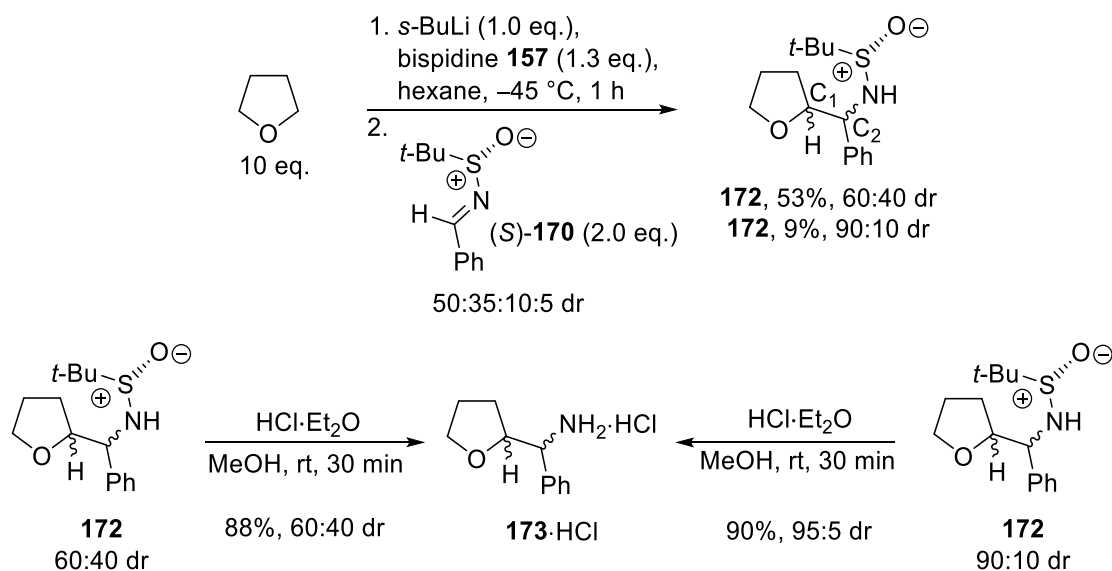

 Scheme 2.6 Lithiation of THF and Trapping with TBS-Estrone **167**.

In addition, the lithiation of THF and subsequent trapping with Ellman's sulfinyl imine (S)-**170** was explored. Ellman's sulfinyl imines have been frequently used as electrophiles in the synthesis of primary amines.¹²⁰⁻¹²¹ The chirality at the sulfur atom can lead to stereoselective attack by nucleophiles at the sp^2 -hybridised carbon of the imine. For example, Reddy has reported a highly diastereoselective synthesis of sulfinamide (*R,R*)-**171** starting from diphenyl methane **169**.¹²² Lithiation of diphenyl methane using *n*-BuLi and subsequent addition of sulfinyl imine (*R*)-**170** resulted in the product (*R,R*)-**171** in 93% yield and 98:2 dr (Scheme 2.7). Although not stated in the paper, the stereochemistry outcome of the reaction can be explained by an open-transition model in which *Re*-face attack of the lithiated diphenyl methane onto the sulfinamide accounts for the high diastereoselectivity.¹²⁰


 Scheme 2.7 Lithiation of Diphenyl Methane **169** and Trapping with Ellman's Sulfinyl Imine (*R*)-**170**.

We wondered if Ellman sulfinamides could also be good electrophiles for trapping lithiated THF. Lithiation of THF (10 eq.) in hexane using *s*-BuLi and bispidine **157** at $-45\text{ }^{\circ}\text{C}$ for 1 h and subsequent addition of Ellman's sulfinyl imine (S)-**170** gave a 50:35:10:5 mixture (by ^1H NMR spectroscopy of the crude product) of diastereomeric sulfinamides **172**. Purification using chromatography gave a 60:40 mixture of sulfinamides **172** and a 90:10 mixture of sulfinamides **172** in 53% and 9% yield respectively. Removal of the sulfinyl substituent of **172** (60:40 dr) with $\text{HCl}\cdot\text{Et}_2\text{O}$ gave a 60:40 diastereomeric mixture of hydrochloride salts **173}\cdot\text{HCl} in 88% yield. Starting from sulfinamides **172** (90:10 dr), removal of the sulfinyl**

group using $\text{HCl}\cdot\text{Et}_2\text{O}$ gave a 95:5 diastereomeric mixture of hydrochloride salts **173** $\cdot\text{HCl}$ in 90% yield. Unfortunately, the relative stereochemistry of **172** and **173** $\cdot\text{HCl}$ could not be determined. However, the 60:40 dr of the primary amines **172** suggest a moderate control over both stereogenic centres: the C_1 / C_2 diastereoselectivity was 60:40 whereas the diastereoselectivity induced by the sulfinamide group must be 85:15, assuming no epimerisation during the deprotection step.



Scheme 2.8 Lithiation of THF and Trapping with Ellman's Sulfinyl Imine (S)-**170**.

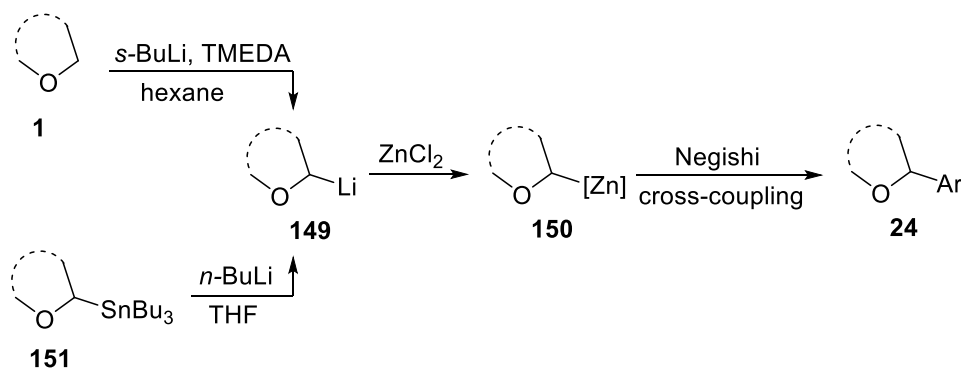
In summary, the lithiation of THF has been explored using *s*-BuLi and bispidine **157**. Under the new lithiation conditions 10 eq. of THF were lithiated in hexane using *s*-BuLi (1.0 eq.) as the limiting reagent and bispidine **157** (1.3 eq.) at $-45\text{ }^{\circ}\text{C}$ for 1 h. Trapping was explored with a range of electrophiles leading to α -substituted THFs in 27-69% yield. These conditions are the best lithiation conditions, developed in the O'Brien group for the α -lithiation-trapping of THF and represent a significant improvement on the previous best conditions.

2.2 α -Arylation of Oxygen Heterocycles via Lithiation, Transmetallation and Negishi Cross-Coupling

2.2.1 Proposed Approaches and Background Literature

As outlined in section 1.1, the lithiation and trapping of oxygen heterocycles had been carried out in the O'Brien group. However, there were no methods for the introduction of aryl and heteroaryl substituents in the α -position. In particular, given the prevalence of the α -aryl oxygen motifs in medicinal chemistry, it was decided to explore α -arylation of oxygen heterocycles. It was wondered if the Negishi approach towards α -arylated saturated nitrogen heterocycles *via* generation of an organozinc species (see section 1.3.1) could be applied to the synthesis of saturated α -aryl oxygen heterocycles such as THF, THP and *N*-methyl morpholine.

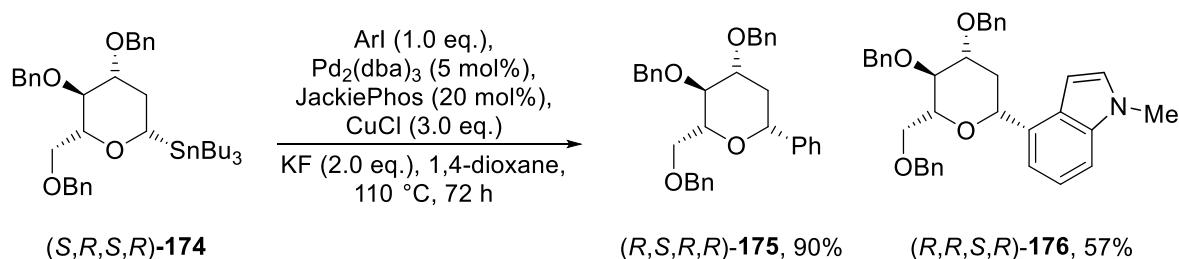
Two approaches were considered for the α -arylation of saturated oxygen heterocycles (Scheme 2.9). In the first approach, direct lithiation of the oxygen heterocycle **1** to give α -lithiated oxygen heterocycles **149**, subsequent transmetallation to organozinc species **150** and Negishi cross-coupling could give the α -aryl oxygen heterocycles **24**. Alternatively, starting from organostannanes **151** (themselves potentially generated by lithiation-trapping), the lithiated species **149** could be generated using Sn-Li exchange and then it could follow the same route of transmetallation and Negishi cross-coupling.



Scheme 2.9 Proposed Strategy for the Synthesis of α -Aryl Substituted Oxygen Heterocycles.

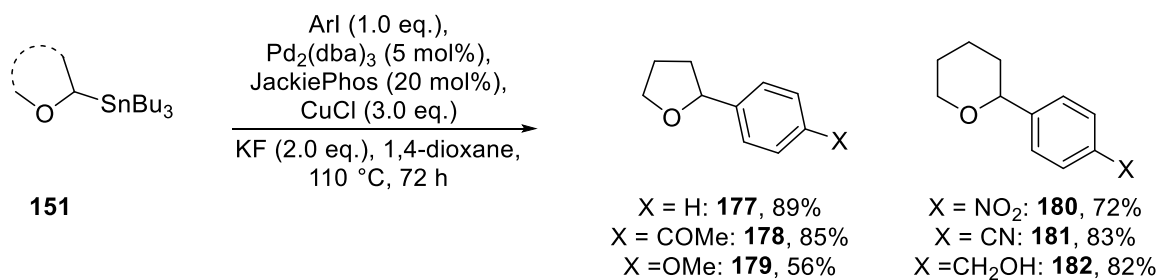
Previously, a variety of groups have investigated the synthesis of α -arylated saturated oxygen heterocycles using radical chemistry (see section 1.2). For example, MacMillan et al., Molander et al. and Shields and Doyle developed the light-mediated synthesis of α -arylated oxygen heterocycles using Ir photocatalysts in combination with Ni catalysis to couple oxetanes and THF with aryl bromides and heteroaryl bromides (see Scheme 1.24 and Scheme 1.25).⁵⁶⁻⁵⁸ In pioneering work by Martin et al., the coupling of THF dioxane and THP with aryl bromides was investigated using triplet excited ketones as photosensitizers in

combination with Ni catalysis (see Scheme 1.28).⁶² Recently Hashmi et al. reported a complementary approach towards α -arylated oxygen and sulfur heterocycles using a Ni catalyst and benzaldehyde as the sensitizer and showed that a wide range of α -arylated saturated oxygen heterocycles could be produced (see Scheme 1.30 and Scheme 1.31).⁶³⁻⁶⁴ A different strategy in the synthesis of α -arylated saturated oxygen heterocycles was reported by Walczak et al. *via* Stille cross-coupling using α -stannyl substituted oxygen heterocycles. Initially, Walczak et al. investigated the synthesis of C-aryl glycosides starting from β -glucoside stannanes such as (*S,R,S,R*)-**174** *via* a stereospecific Stille cross-coupling. The coupling of stannane (*S,R,S,R*)-**174** with aryl iodides using Pd₂(dba)₃, JackiePhos, CuCl and KF at 110 °C for 72 h gave C-aryl glycosides (*R,S,R,R*)-**175** and (*R,R,S,R*)-**176** in 90% and 57% yield respectively (Scheme 2.10).



Scheme 2.10 Synthesis of C-Aryl Glycosides Using Stille Cross-Coupling.

In addition to the arylation of glycosides, Walczak et al. reported the Stille cross-coupling of saturated oxygen heterocycles **151** with aryl iodides (Scheme 2.11).¹²³⁻¹²⁴ Stille cross-coupling using the same conditions with aryl iodides gave α -arylated THFs **177**, **178** and **179** in 56-89% yield. The corresponding α -arylated THPs **180**, **181** and **182** were obtained in 72-83% yield.



Scheme 2.11 Stille Cross-Coupling of α -Stannyl Oxygen Heterocycles.

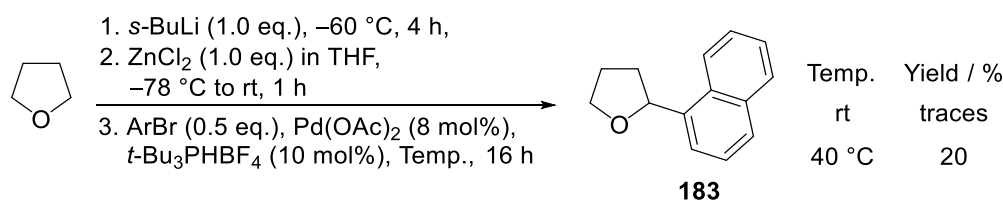
Instead of aryl iodides, the coupling was also possible with diaryliodonium salts as an alternative coupling partner to give the α -arylated THFs, THPs and glycosides in high yields.¹²³ However, the Stille cross-coupling developed by Walczak et al. required the use of 3.0 eq. of CuCl and the coupling was carried out at high temperatures (110 °C) for required long reaction times (72 h). It was hoped that in our complementary approach, such

high reaction temperatures and the use of aryl bromides as coupling partners could be avoided. Furthermore, as previously reported by Campos et al. in the arylation of *N*-Boc heterocycles using the Negishi approach, the transmetallation of an enantioenriched species to the organozinc species and in the Negishi cross-coupling proved to be stereospecific.⁸⁶ If suitable asymmetric deprotonation of oxygen heterocycles could be discovered the Negishi cross-coupling approach should result in highly enantioenriched α -arylated oxygen heterocycles.

2.2.2 Lithiation of Oxygen Heterocycles, Transmetallation and Negishi Cross-Coupling

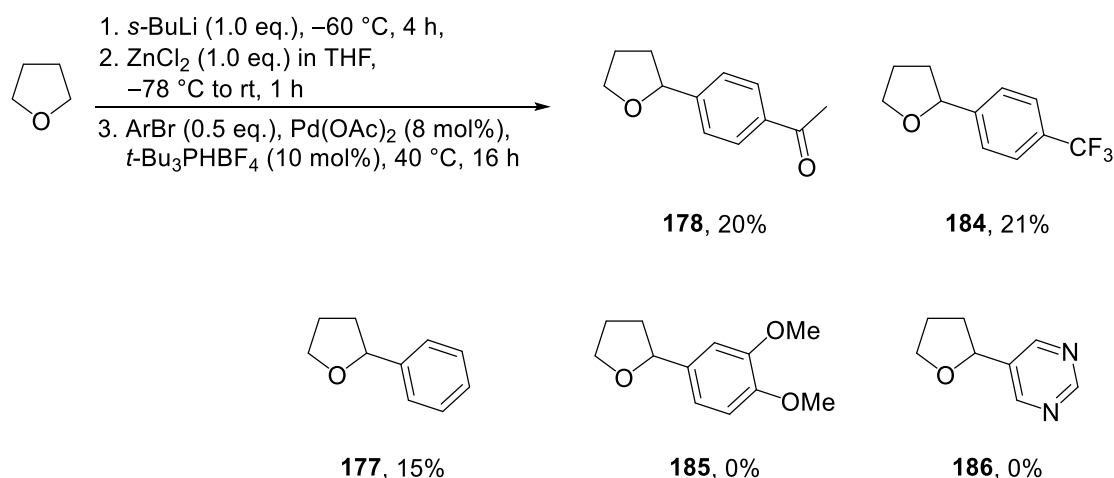
To start with, the α -arylation of THF was investigated. When these studies were started, the best way to generate lithiated THF was treating THF (solvent and substrate) with *s*-BuLi at $-60\text{ }^{\circ}\text{C}$ for 4 h. For the transmetallation to an organozinc species, it was decided to follow procedures by Campos et al.⁸⁶ and by Coldham and Leonori⁹⁰ using ZnCl_2 at $-78\text{ }^{\circ}\text{C}$ for 30 min and then 30 min at rt. It was planned to use $\text{Pd}(\text{OAc})_2$ and *t*-Bu₃PHBF₄, also based on Campos et al. and Coldham and Leonori's precedent. The aryl bromide would be used as the limiting reagent because the highest yields in the lithiation-trapping of THF of ~40% indicate that, under these lithiation conditions, only ~40% lithiated THF (relative to *s*-BuLi) would have formed.

Thus, lithiation of THF using *s*-BuLi at $-60\text{ }^{\circ}\text{C}$ for 4 h and subsequent transmetallation using ZnCl_2 gave the organozinc species. Then, 1-bromonaphthalene (0.5 eq. relative to *s*-BuLi), $\text{Pd}(\text{OAc})_2$ (8 mmol%) and *t*-Bu₃PHBF₄ (10 mmol%) were added in one portion without solvent to the zincated species to form the active Pd species (as described by Coldham and Leonori⁹⁰ in the Negishi cross-coupling of *N*-Boc piperidines). Negishi coupling at rt for 16 h gave only traces of α -naphthyl THF **183**. However, when the Negishi cross-coupling step was heated at $40\text{ }^{\circ}\text{C}$ for 16 h, α -arylated THF **183** was isolated in 20% yield (Scheme 2.12). Since ~40% of lithiated THF forms under these conditions, the synthesis of α -arylated THF **183** in 20% yield represented a promising start.



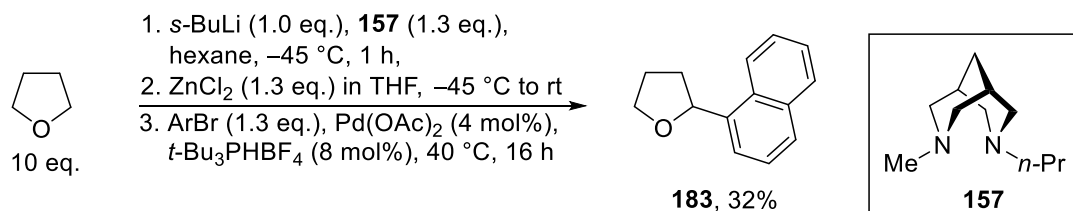
Scheme 2.12 Lithiation of THF, Transmetallation and Negishi Cross-Coupling with 1-Bromonaphthalene.

With an arylation procedure of THF using Negishi cross-coupling in hand, the scope was briefly investigated (Scheme 2.13). Use of 4-bromoacetophenone or 4-bromobenzotrifluoride in the cross-coupling gave the corresponding α -aryl THFs **178** (20% yield) and **184** (21% yield) respectively. Using bromobenzene, a 50:50 mixture of α -phenyl THF **177** (15%) and CH_2Cl_2 was isolated after chromatography. Attempted removal of the CH_2Cl_2 led to evaporation of the volatile α -phenyl THF **177** and none was isolated. Couplings with 4-bromoveratrole and 5-bromopyrimidine to give α -arylated THFs **185** or **186** respectively were, however, not successful with no evidence of product formation in the ^1H NMR spectra of the crude products.



Scheme 2.13 Lithiation of THF, Transmetalation and Negishi Cross-Coupling with Various Aryl Bromides.

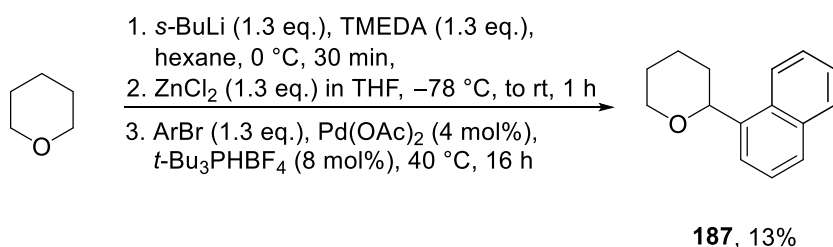
Subsequently, as described in section 2.1, new conditions for lithiation-trapping of THF were developed and these should generate at least ~70% of lithiated THF (see section 2.1). Using the new lithiation conditions, THF (10 eq.) was lithiated using $s\text{-BuLi}$ / bispidine **157** in hexane at $-45\text{ }^\circ\text{C}$ for 1 h. Then, transmetalation and Negishi cross-coupling with 1-bromonaphthalene were carried out to give α -arylated THF **183** in slightly improved 32% yield (Scheme 2.14).



Scheme 2.14 Lithiation of THF using Bispidine **157**, Transmetalation and Negishi Cross-Coupling with 1-Bromonaphthalene.

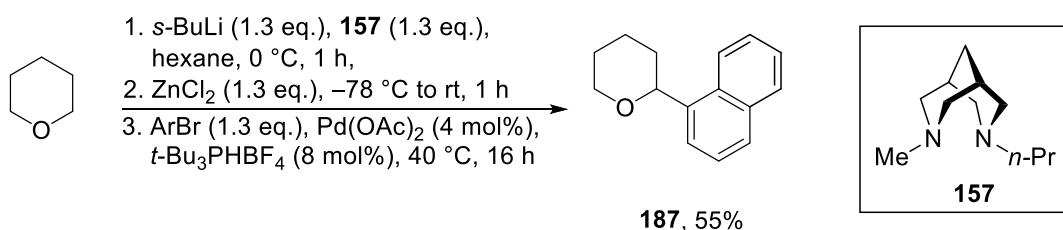
Next, the lithiation, transmetalation and Negishi cross-coupling methodology was applied to THP. At that time, the best method for lithiation of THP involved the use of 1.0 eq. THP

and 1.3 eq. of *s*-BuLi / TMEDA in hexane at 0 °C for 30 min (39-47% yields after trapping, see Scheme 1.63). Therefore, 1.3 eq. of ZnCl₂ would be used in the transmetallation step and the cross-coupling would be carried out with an excess of aryl bromide (1.3 eq.). These conditions using an excess (1.3 eq.) of ZnCl₂ and aryl bromide are similar to the Negishi cross-coupling conditions reported by Coldham for the synthesis of α -arylated *N*-Boc piperidines (see Scheme 1.46).⁹⁰ Thus, lithiation of THP using 1.3 eq. of *s*-BuLi / TMEDA in hexane at 0 °C for 30 min, transmetallation with ZnCl₂ (1.3 eq.) and Negishi coupling using 1-bromonaphthalene (1.3 eq.), Pd(OAc)₂ (4 mol%) and *t*-Bu₃PHBF₄ (8 mol%) at 40 °C for 16 h was carried out. This gave α -naphthyl THP **187** in only 13% yield (Scheme 2.15).



Scheme 2.15 Lithiation of THP, Transmetallation and Negishi Cross-Coupling with 1-Bromonaphthalene.

In recent work, the lithiation of THP was revisited by a co-worker using the *s*-BuLi / bispidine **157** complex.¹⁰⁷ Lithiation of 1.0 eq. THP using *s*-BuLi / bispidine **157** in hexane at 0 °C for 1 h and trapping with several electrophiles resulted in α -substituted THPs in high yields of 63-95%, indicating that these conditions led to a very efficient lithiation. Hence, these lithiation conditions were applied to the Negishi α -arylation of THP. Using these new lithiation conditions, THP was lithiated, transmetallated and cross-coupled to give α -naphthyl THP **187** in a much improved 55% yield (Scheme 2.16).

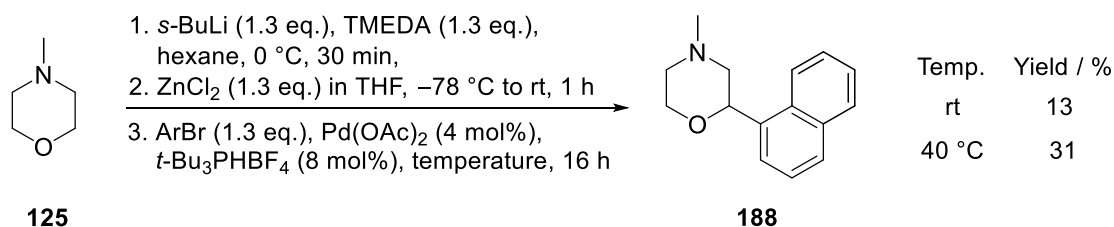


Scheme 2.16 Lithiation of THP using Bispidine **157**, Transmetallation and Negishi Cross-Coupling with 1-Bromonaphthalene.

Finally, the α -arylation of *N*-methyl morpholine **125** via Negishi cross-coupling was explored. It was planned to lithiate *N*-methyl morpholine **125** (1.0 eq.) under the previously explored lithiation conditions for morpholine using *s*-BuLi / TMEDA (1.3 eq.) in hexane at 0 °C for 1 h, as the previously explored trapping with a range of electrophiles resulted in α -substituted *N*-methyl morpholines in ~75-92% yield. Therefore, ~90% of the lithiated *N*-

methyl morpholine was formed in the lithiation step (see section 1.3.2, Scheme 1.66). As it is a 6-membered saturated oxygen heterocycle, the transmetallation and Negishi-cross coupling conditions were based on the explored THP Negishi cross-coupling. *N*-methyl morpholine **125** was used as the limiting reagent and excess of ZnCl_2 (1.3 eq.) in the transmetallation step and of the ArBr (1.3 eq.) in the Negishi step would be used.

As shown in Scheme 2.17, the lithiated *N*-methyl morpholine was generated using 1.0 eq. of *N*-methyl morpholine **125** and 1.3 eq. of *s*-BuLi / TMEDA in hexane at 0 °C for 1 h. Subsequent transmetallation with ZnCl_2 (1.3 eq.) and Negishi cross-coupling with 1-bromonaphthalene in the presence of $\text{Pd}(\text{OAc})_2$ (4 mol%), and *t*-Bu₃PHBF₄ (8 mol%) at rt gave α -naphthyl substituted morpholine **188** in only 13% yield. Increasing the temperature to 40 °C during the Negishi cross-coupling gave α -naphthyl morpholine **188** in 31% yield (Scheme 2.17).



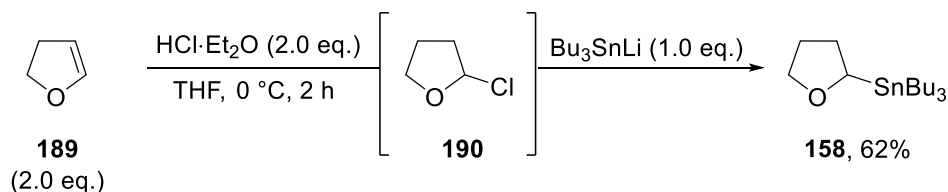
Scheme 2.17 Lithiation of *N*-Methyl Morpholine **125**, Transmetallation and Negishi Cross-Coupling with 1-Bromonaphthalene.

In summary, the α -arylation of THF, THP and *N*-methyl morpholine **125** via direct lithiation, transmetallation to an organozinc species and Negishi cross-coupling was explored. For all three systems the α -arylation yields are significantly lower than direct electrophile trapping and therefore no scope was explored. Having generated the lithiated species in hexane as the solvent using *s*-BuLi / TMEDA or *s*-BuLi / bispidine **157**, it was observed precipitation of a white solid during the addition of the ZnCl_2 (in a THF solution) to form the organozinc species. The precipitation led to an insufficient stirring of the reaction mixture and a cloudy solution was observed after warming the organozinc species to rt and during the Negishi cross-coupling. It was wondered if hexane as the solvent in the lithiation is inhibiting the transmetallation and the Negishi step. Therefore, it was decided to explore generating the lithiated species from an organostannane via Sn-Li exchange, which is typically carried out in THF. Subsequent transmetallation and Negishi cross-coupling in THF would then be investigated for each system.

2.2.3 Sn-Li Exchange, Transmetallation and Negishi Cross-Coupling

Due to the moderate yields in the direct lithiation, transmetallation and Negishi cross-coupling of THF, THP and *N*-methyl morpholine **125**, it was considered to investigate if avoiding hexane during the Negishi reaction would lead to α -arylated oxygen heterocycles in higher yields. It was planned to start from α -stannyl oxygen heterocycles and carry out Sn-Li exchange, transmetallation to an organozinc species and subsequent Negishi cross-coupling in THF.

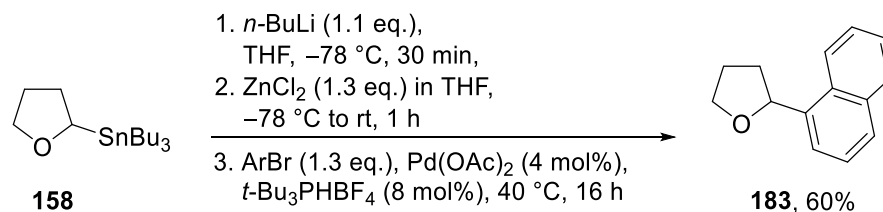
It was decided to start exploring the new approach with α -stannyl THF **158**. As shown in Scheme 2.5, α -stannyl THF **158** was prepared in 69% yield, *via* lithiation-trapping, starting from THF and *s*-BuLi / bispidine **157** and trapping with Bu₃SnCl. α -Stannyl THF **158** was also synthesised *via* an alternative route using 2,3-dihydrotetrahydrofuran **189** according to a procedure by McGarvey et al., which was more convenient on a large scale.¹²⁵ Addition of HCl in Et₂O resulted in the formation of an α -chloro THF **190** *via* oxonium ion formation and nucleophilic attack of the chloride. Subsequent reaction with Bu₃SnLi gave the α -stannyl THF **158** in 62% yield (Scheme 2.18).



Scheme 2.18 Synthesis of α -Stannyl THF **158** *via* α -Chloro THF **190**.

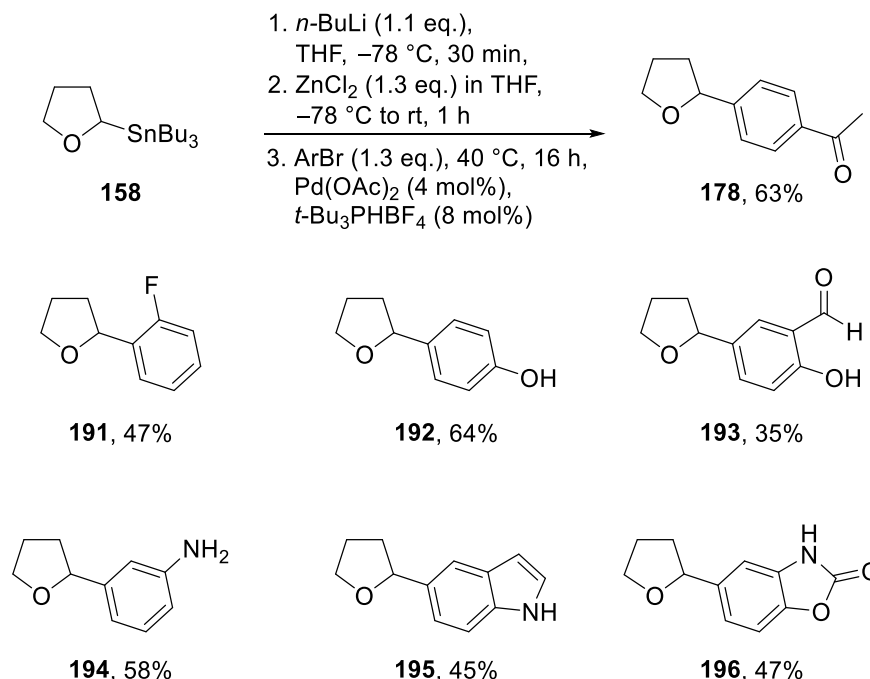
The Sn-Li exchange of α -stannyl THF **158** has previously been investigated by McGarvey et al.¹²⁵ In their work, α -stannyl THF **158** was treated with *n*-BuLi in THF at -78 °C to give the lithiated species. Trapping with benzaldehyde gave a 50:50 mixture of diastereomeric alcohols in 71% yield, indicating that the Sn-Li exchange is efficient.

α -Stannyl THF **158** was then used to explore the Sn-Li exchange, transmetallation and subsequent Negishi cross-coupling. As outlined in Scheme 2.19, addition of *n*-BuLi to α -stannyl THF **158** at -78 °C for 30 min gave the lithiated species, which was transmetallated using ZnCl₂ (1.3 eq.). A clear organozinc solution was obtained and no precipitation was observed. Subsequent Negishi cross-coupling of the zincated species using Pd(OAc)₂ (4 mol%) and *t*-Bu₃PHBF₄ (8 mol%) and 1-bromonaphthalene at 40 °C for 16 h gave α -arylated THF **183** in 60% yield (Scheme 2.19). The yield is only slightly lower than that obtained by McGarvey et al.¹²⁵ in a Sn-Li exchange from α -stannyl THF and trapping with benzaldehyde and much higher than the yield of 40%, obtained using the direct lithiation approach (see Scheme 2.14). This suggested an efficient transmetallation and cross-coupling process.



Scheme 2.19 Sn-Li Exchange of α -Stannyl THF **158**, Transmetallation and Negishi Cross-Coupling with 1-Bromonaphthalene.

Given this successful outcome, the reaction conditions were used to explore the Negishi cross-coupling with other aryl bromides (Scheme 2.20). Cross-coupling was possible with electron-rich and deficient aryl bromides and heteroaryl bromides. For example, cross-coupling was performed with aryl bromides bearing a ketone to give α -arylated THF **178** in 63% yield. When 2-fluorobromobenzene was used, α -arylated THF **191** was isolated in 47% yield. In addition, aryl bromides bearing an unprotected hydroxyl group as well as a primary amine worked well and the corresponding alcohols **192** (64% yield) and **193** (35%) as well as amine **194** (58% yield) were obtained. Arylation with heteroaryl bromides such as 5-bromoindole gave α -arylated THF **195** in 45% yield. Finally, arylation with carbamate-containing aryl bromide gave α -arylated THF **196** in 47% yield.

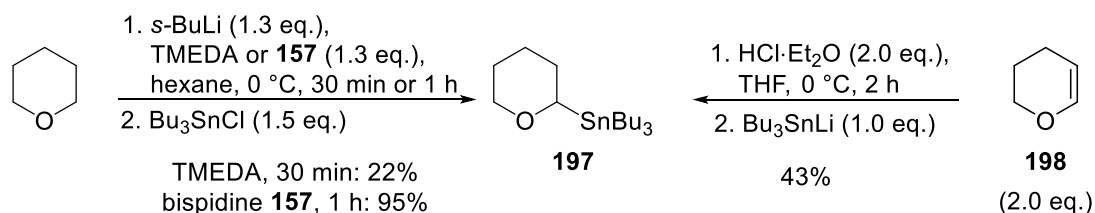


Scheme 2.20 Sn-Li Exchange of α -Stannyl THF **158**, Transmetallation and Negishi Cross-Coupling with Various Aryl Bromides.

Next, the Negishi α -arylation was explored starting from α -stannyl THP **197**. Previously, THP stannane **197** was synthesised starting from THP *via* the standard protocol in the O'Brien group (1.3 eq. of *s*-BuLi / TMEDA in hexane at 0°C for 30 min) and trapping with Bu_3SnCl (see section 1.3.2, Scheme 1.63). This gave THP stannane **197** in 22% yield

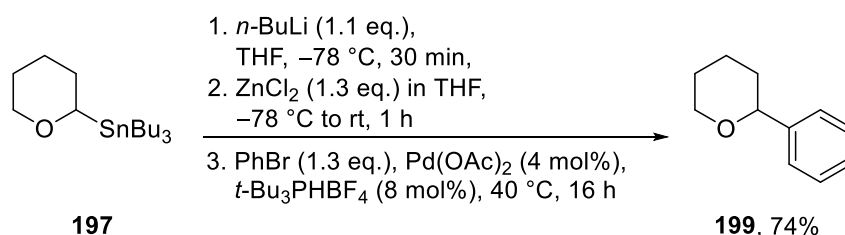
(Scheme 2.21). Higher yields of the α -stannyl THP **197** could be achieved using the recently optimised reaction conditions developed by a co-worker in the group.¹⁰⁷ They found that lithiation of THP using *s*-BuLi / bispidine **157** in hexane at 0 °C for 1 h and trapping with Bu₃SnCl gave the α -stannyl THP **197** in 95% yield.

For the synthesis of α -stannyl THP, the synthesis starting from DHP **198** using HCl in Et₂O to generate an α -chloro THP was also explored which was then reacted with Bu₃SnLi as previously reported by McGarvey et al. (see Scheme 2.18).¹²⁵ DHP **198** was treated with HCl in Et₂O at 0 °C for 2 h to give the α -chloro THP species which was subsequently treated with Bu₃SnLi to give α -stannyl THP **197** in 43% yield.



Scheme 2.21 Synthesis Routes to α -Stannyl THP **197**.

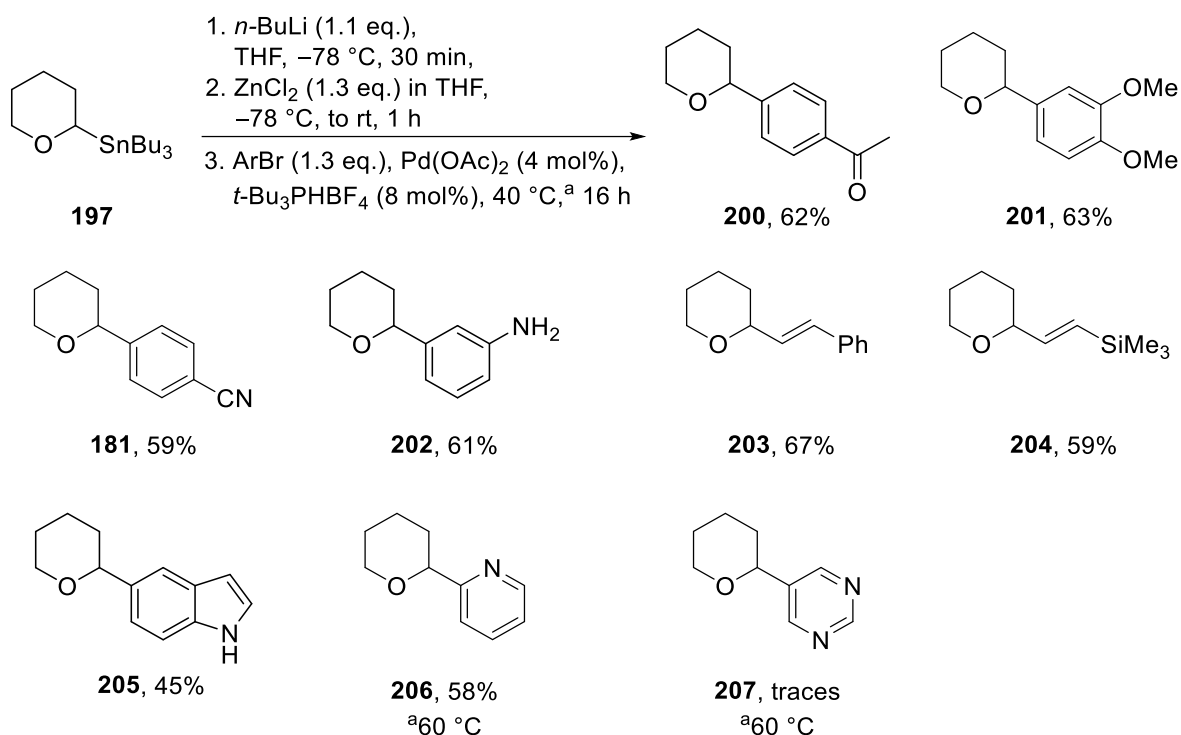
To generate the lithiated THP species, α -stannyl THP **197** was treated with *n*-BuLi in THF at -78 °C for 30 min to achieve the Sn-Li exchange. Then, transmetallation using ZnCl₂ gave the organozinc species. Negishi cross-coupling with bromobenzene under the standard conditions gave α -arylated THP **199** in 74% yield (Scheme 2.22). The good yield in the reaction shows that the transmetallation and the Negishi coupling conditions are efficient, giving a higher yield than direct lithiation, and transmetallation and Negishi reaction (see Scheme 2.15 and Scheme 2.16).



Scheme 2.22 Sn-Li Exchange of α -Stannyl THP **197**, Transmetallation and Negishi Cross-Coupling with Bromobenzene.

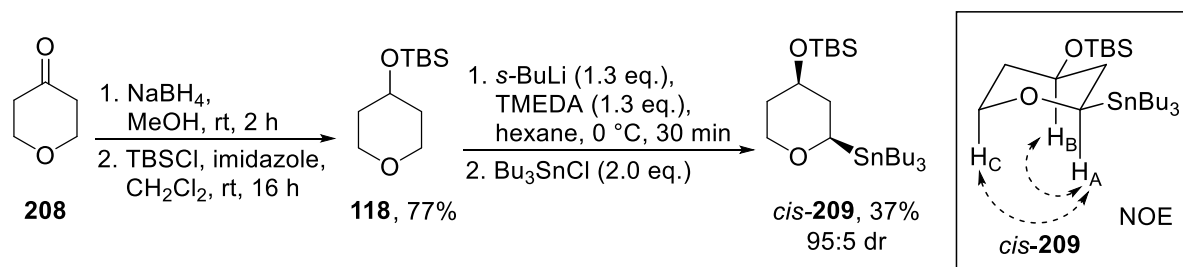
The Negishi coupling of α -stannyl THP **197** with 1-bromobenzene worked very well and the arylation was therefore expanded to various aryl bromides (Scheme 2.23). Arylation with aryl bromides bearing ketones, methoxy groups and a nitrile group were tolerated giving the products **200**, **201** and **181** in 62%, 63% and 59% yield respectively. In addition, 3-bromoaniline could be used in the cross-coupling resulting in the α -arylated THP **202** in 61% yield. Also, coupling with vinyl bromides was explored and α -vinyl THPs **203** and **204** were

obtained in 67% and 59% yield respectively. Finally, heteroaryl bromides were used and the Negishi cross-coupling was carried out at 60 °C as previously reported in the coupling of *N*-Boc pyrrolidines with heteroaryl bromides by Campos et al.⁸⁶ Using 5-bromo indole gave the corresponding substituted indole **205** in 45% yield. Coupling with 2-bromo pyridine gave the α -pyridyl substituted THP **206** in 58% yield. However, arylation using 5-bromo pyrimidine gave only traces of desired product **207**.

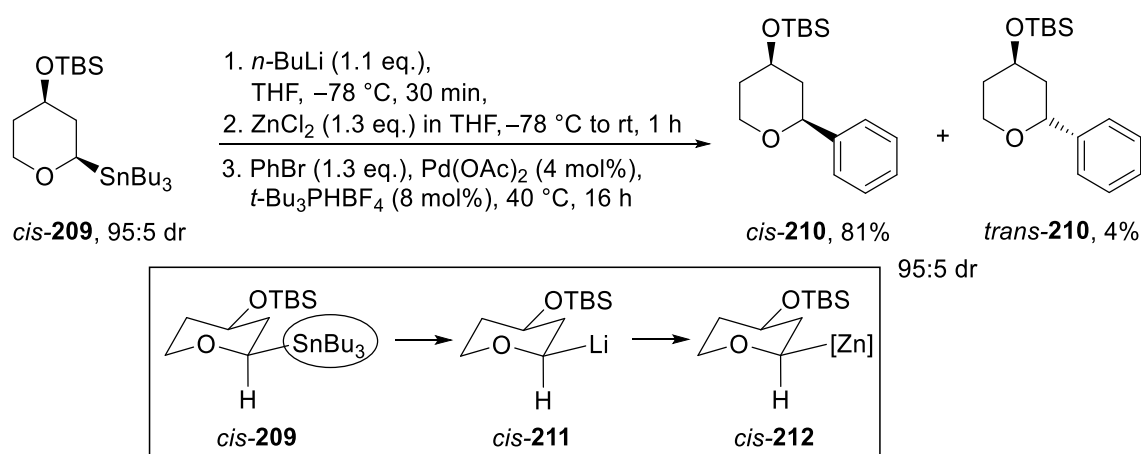


Scheme 2.23 Sn-Li Exchange of α -Stannyl THP **197**, Transmetalation and Negishi Cross-Coupling with Various Aryl Bromides.

Having explored the arylation of α -stannyl THP **197**, the Negishi α -arylation of 4-OTBS substituted α -stannyl THP *cis*-**209** was explored next. It was synthesised starting from tetrahydro-4*H*-pyran-4-one **208**. Reduction using NaBH₄ and protection using TBSCl and imidazole gave 4-OTBS-substituted THP **118** in 77% yield. Lithiation of THP **118** using *s*-BuLi / TMEDA in hexane at 0 °C for 30 min and trapping with Bu₃SnCl gave a 95:5 mixture of *cis*-**209** and *trans*-**209** in 37% yield (Scheme 2.24). The high *cis*-selectivity is in accordance with previous results in the O'Brien group (see Scheme 1.64). The 2,4-*cis* configuration of stannane *cis*-**209** could not be assigned using coupling constant values as the signals were not fully resolved. However, the relative stereochemistry of stannane *cis*-**209** was assigned using NOE experiments, with the protons H_A, H_B and H_C showing clear NOE interactions.


 Scheme 2.24 Synthesis of 2,4-*cis* Configured Stannane *cis*-209.

With the 2,4-*cis* configured stannane *cis*-209 in 95:5 dr in hand, subsequent Sn-Li exchange, transmetallation and Negishi cross-coupling was explored using the established conditions. Starting from stannane *cis*-209 (95:5 dr), cross-coupling with bromobenzene gave a 95:5 mixture of 2,4-disubstituted THPs *cis*-210 and *trans*-210. Purification via chromatography gave *cis*-210 in 81% yield and *trans*-210 in 4% yield (Scheme 2.25). Our result indicates that the overall reaction retains the diastereomeric ratio throughout. Indeed, the 95:5 dr must be maintained during the formation of lithiated species *cis*-211, the transmetallation to the organozinc species *cis*-212 and finally during the Pd-mediated Negishi cross-coupling step. It was expected that the organolithium species would maintain its configuration at -78°C . However, the result also shows that the organozinc species is configurationally stable up to 40°C which is in line with the configurationally stable organozinc species generated in the α -arylation of *N*-Boc pyrrolidine and *N*-Boc piperidine by Campos et al. and Coldham and Leonori.^{86, 126}


 Scheme 2.25 Sn-Li Exchange of 2,4-*cis* Configured Stannane *cis*-209, Transmetallation and Negishi Cross-Coupling with Bromobenzene.

Detailed analysis of the HMBC and ^1H , ^1H COSY spectra gave evidence for a 2,4-disubstituted 6-membered ring system. The stereochemistry of α -phenyl THP *cis*-210 was established by ^1H NMR spectroscopy using ^3J coupling constant values. The most likely

conformation of *cis*-**210** would have the 6-membered oxygen ring in a chair conformation with two equatorial substituents. Part of the ^1H NMR spectrum of α -phenyl THP *cis*-**210** is shown in Figure 2.2. In the case of *cis*-**210**, proton H_A shows a 2.0 Hz $^3J_{\text{ax-eq}}$ coupling and a 11.5 Hz $^3J_{\text{ax-ax}}$ coupling, which indicate that H_A is in an axial position coupling to another axial and equatorial proton. The $^3J_{\text{ax-ax}}$ couplings of H_B of 10.5 Hz and the $^3J_{\text{ax-eq}}$ couplings of H_B in the range of 4.5 Hz are evidence for the equatorial position of the OTBS substituent in the 4-position coupling to two axial and two equatorial protons. Combining all of these ^3J values, the substituents in the 2- and 4-positions must be *cis*.

For the 2,4-*trans* stereochemistry, the 6-membered oxygen ring is assumed to have a chair conformation with an axial and an equatorial substituent. The ^1H NMR spectrum of *trans*-**210** is shown in Figure 2.2. In the case of *trans*-**210**, proton H_E showed a 6.5 Hz axial-equatorial $^3J_{\text{ax-eq}}$ coupling and a 13.5 Hz $^3J_{\text{ax-ax}}$ coupling, which indicate that H_E is in an axial position coupling to another axial and equatorial proton. The phenyl-substituent is therefore in an equatorial position. The two $^3J_{\text{ax-eq}}$ couplings of H_F of 3.5 Hz and two $^3J_{\text{eq-eq}}$ couplings of H_F of 3.5 Hz are evidence for the axial position of the OTBS substituent in the 4-position coupling to two axial and two equatorial protons. Combining all of these ^3J values, the substituents in the 2- and 4-position must be *trans*.

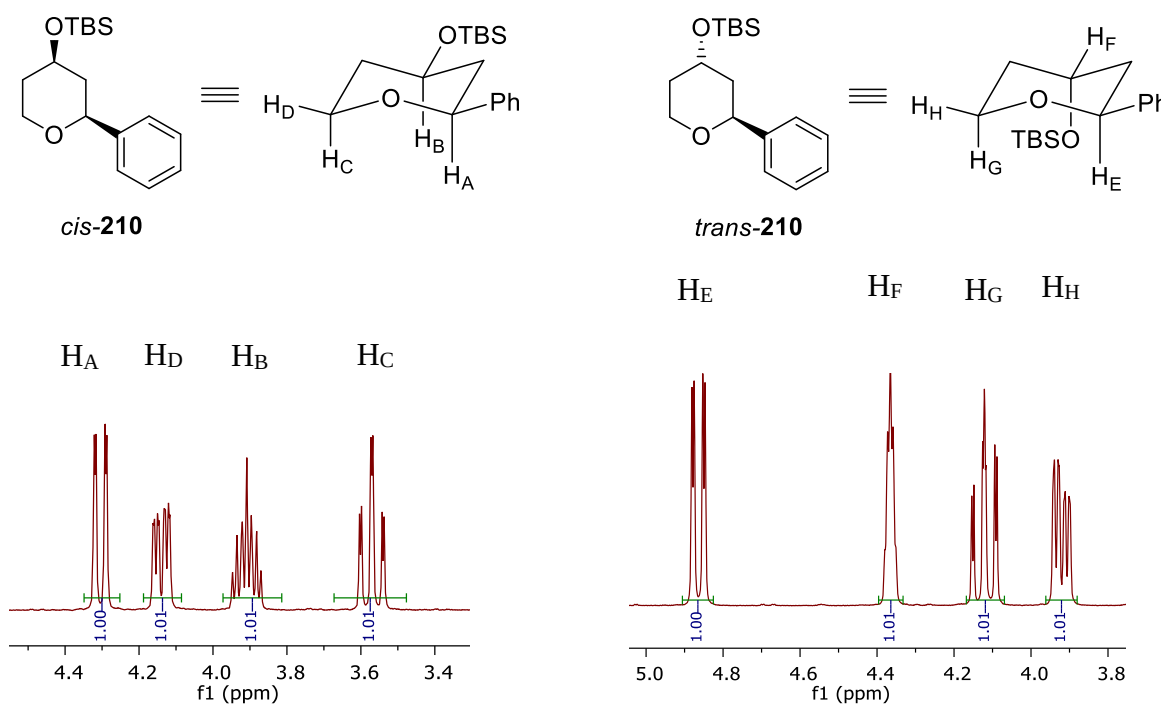
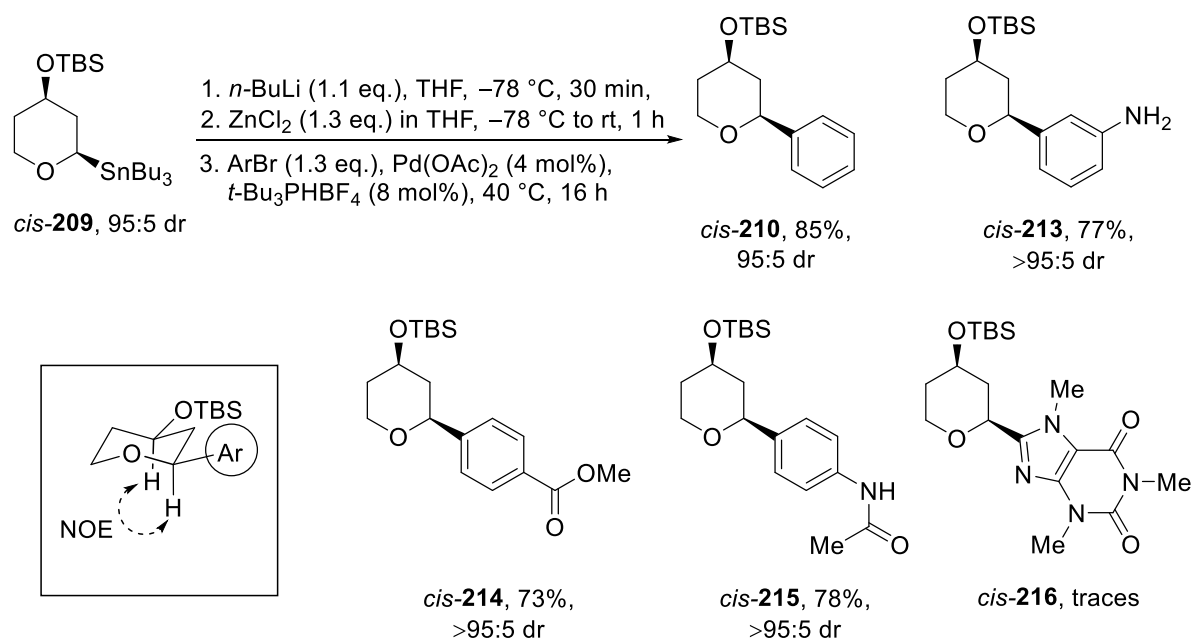


Figure 2.2: Part of the ^1H NMR Spectrum of *cis*-**210** and *trans*-**210**.

Having explored the stereospecific character of the transformation, further examples were synthesised (Scheme 2.26). Sn-Li exchange, transmetalation and Negishi cross-coupling

with 3-bromoaniline gave a >95:5 mixture of *cis*-**213** and *trans*-**213** from which a 77% yield of *cis*-**213** was isolated after chromatography. Coupling using methyl 4-bromobenzoate resulted in a >95:5 mixture of diastereomeric esters *cis*-**214**. After chromatography, α -aryl THP *cis*-**214** was isolated in 73% yield. The Negishi cross-coupling with *N*-(4-bromophenyl)acetamide gave a >95:5 mixture of diastereomeric amides. Subsequent chromatography gave α -aryl THP *cis*-**215** in 78% yield. For all examples, the 2,4-*cis* configuration was assigned by constant coupling values in the ^1H NMR spectra. In addition, the relative stereochemistry for THPs *cis*-**214** and *cis*-**215** was assigned using NOE experiments. The two protons in the 2- and 4-positions showed NOE interaction and hence both protons were assigned as being in axial positions. Finally, 8-bromo caffeine was used in the Negishi cross-coupling but unfortunately, the reaction was not successful.

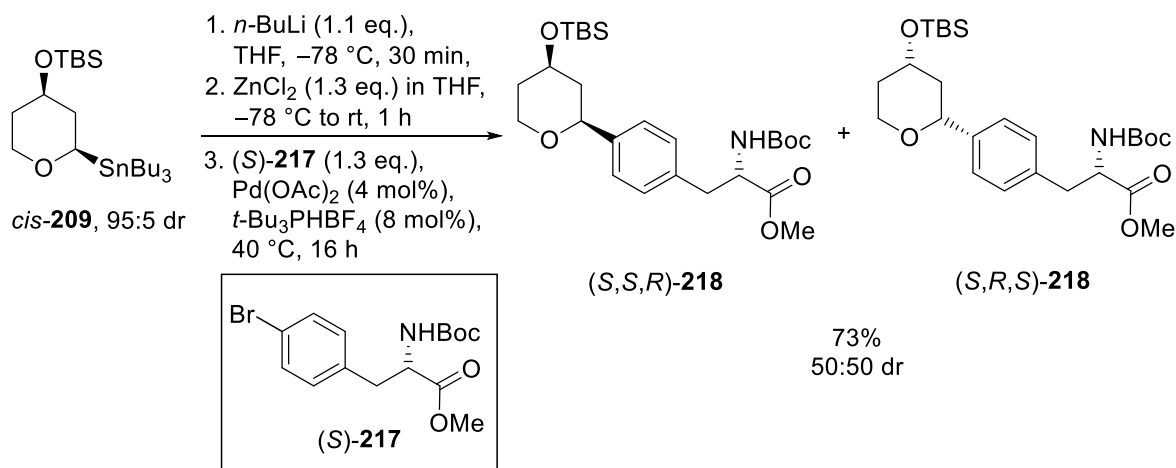


Scheme 2.26 Sn-Li Exchange of 2,4-*cis* Configured Stannane *cis*-**209**, Transmetallation and Negishi Cross-Coupling with Various Aryl Bromides.

Finally, the Negishi cross-coupling of *cis*-**209** was investigated using 4-bromophenylalanine derivative (*S*)-**217**. (*S*)-*N*-Boc 4-bromo-phenylalanine was reacted with trimethylsilyl diazomethane following a procedure by Taylor et al.¹²⁷ to give the methyl ester (*S*)-**217** in 99% yield and then used in the Negishi reaction (Scheme 2.27).

Under the optimised conditions, Sn-Li exchange of stannane *cis*-**209**, transmetallation and subsequent Negishi cross-coupling with 4-bromophenylalanine derivative (*S*)-**217** gave a 50:50 mixture of inseparable diastereomeric 2,4-*cis* substituted THPs (*S,S,R*)-**218** and (*S,R,S*)-**218** in 73% yield (Scheme 2.27). As the stereogenic centre of the amino acid

functionality is far from the THP heterocycle, only one set of signals was observed in the ^1H NMR spectrum. However, ^{13}C NMR spectroscopy showed a set of signals for each diastereomer and confirmed the formation of the expected diastereomeric mixture. The 2,4-*cis*-configuration was assigned by ^1H NMR spectroscopy using coupling constant values in the usual way.



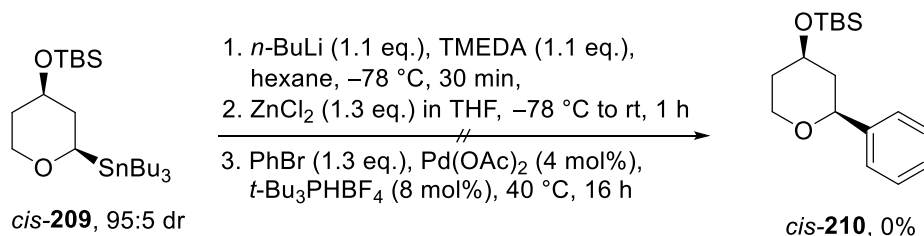
Scheme 2.27 Sn-Li Exchange of 2,4-*cis* Configured Stannane *cis*-**209**, Transmetallation and Negishi Cross-Coupling with 4-Bromo Phenylalanine Derivative (S)-**217**.

Previously in the direct lithiation, transmetallation and Negishi cross-coupling of THF, THP and *N*-methyl morpholine **125** (see section 2.1) it was observed the precipitation of a white solid during the transmetallation to the organozinc species in a hexane / THF mixture and a cloudy solution during the Negishi-cross-coupling. Only moderate yields of the α -arylated products were obtained for each system (see section 2.1). In contrast, no precipitation was observed after Sn-Li exchange of α -stannyl THF **158**, α -stannyl THP **197** and α -stannyl THP *cis*-**209** in THF and subsequent transmetallation with ZnCl_2 also in THF. The organozinc species in THF was observed to be a clear solution in all cases. It was hypothesised that the organozinc species is not very soluble in hexane and as a result, the Negishi cross-coupling is not very efficient resulting in lower yields.

To test this hypothesis, a test reaction using OTBS-substituted THP *cis*-**209** as the substrate was designed. The plan was to generate the lithiated OTBS-substituted THP *via* Sn-Li exchange in hexane using 1.1 eq. of $n\text{-BuLi}$ / TMEDA at -78°C for 30 min and then perform the transmetallation using 1.3 eq. of ZnCl_2 . Subsequent Negishi cross-coupling with bromobenzene, $\text{Pd}(\text{OAc})_2$ (4 mol%) and $t\text{-Bu}_3\text{PHBF}_4$ (8 mol%) would then be explored.

Starting from stannane *cis*-**209**, Sn-Li exchange in hexane using $n\text{-BuLi}$ / TMEDA, subsequent transmetallation to an organozinc species with ZnCl_2 and Negishi cross-coupling

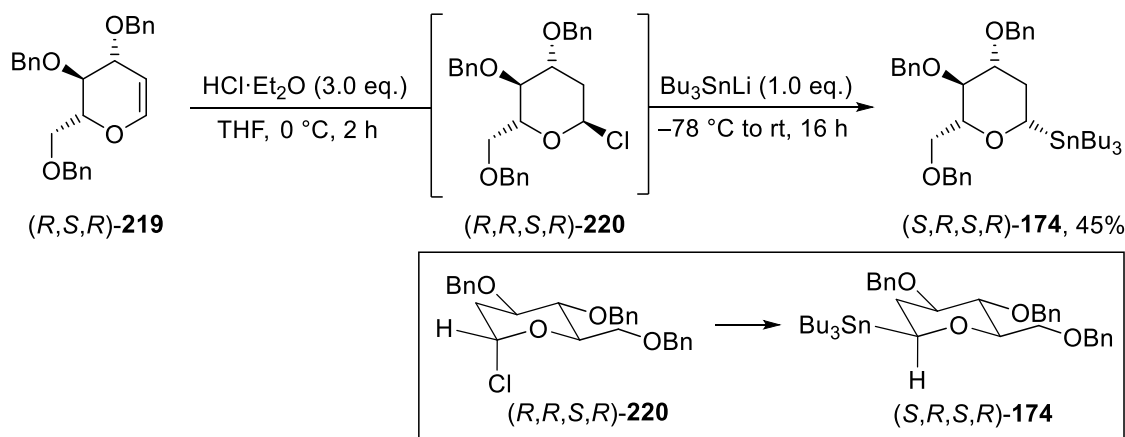
did not give the desired 2,4-*cis* configured α -aryl THP *cis*-**210** but only 4-OTBS-substituted THP **118** (Scheme 2.28). The result clearly shows that THF as the solvent would be better for the transmetallation and Negishi cross-coupling step.



Scheme 2.28 Attempted Sn-Li Exchange of 2,4-*cis*-Configured Stannane *cis*-209** in Hexane, Transmetallation and Negishi Cross-Coupling with Bromobenzene.**

It was wondered if our new Negishi reaction could be applied to the synthesis of C-aryl glycosides starting from the corresponding β -glucoside stannanes. In the literature, the β -glucoside stannanes were synthesised in two steps starting from acetyl protected glucal. The benzyl protecting groups were installed in the first step following a procedure by Misra et al.¹²⁸ In our hands, the acetyl protected was reacted with NaOH, TBAI and BnBr to give benzyl-protected glucal (*R,S,R*)-**219** in 88% yield.

The β -butylstannyl glycopyranoside (*S,R,S,R*)-**174** was then synthesised from the benzyl-protected glucal (*R,S,R*)-**219** using a procedure reported by Beau et al.¹²⁹ Addition of HCl in Et₂O to the benzyl-protected glucal (*R,S,R*)-**219** gave the α -hexopyranosyl chloride (*R,R,S,R*)-**220**. Mechanistically, reversible protonation leads to the formation of an oxonium ion. Nucleophilic attack of the chloride gives the thermodynamically favoured α -axial substituted α -hexopyranosyl chloride (*R,R,S,R*)-**220**. The chloride is introduced in axial position, due to the anomeric effect as reported by Bates and Deng.¹³⁰ As the chloride **220** is known to be unstable when exposed to air, no work-up of the reaction was done and Bu₃SnLi was subsequently added. Nucleophilic S_N2-type attack using Bu₃SnLi gave β -butylstannyl glycopyranoside (*S,R,S,R*)-**174** as a single diastereomer in 45% yield (Scheme 2.29).


 Scheme 2.29 Synthesis of β -Glucoside Stannane (S,R,S,R) -**174**.

The relative stereochemistry of the product was assigned by ^1H NMR spectroscopy. The most likely conformation of (S,R,S,R) -**174** is a 6-membered ring chair conformation with the 2,4,5,6-substituents in equatorial positions. In Figure 2.3, part of the ^1H NMR spectrum of (S,R,S,R) -**174** is presented. Proton H_A shows a 2.0 Hz $^3J_{\text{ax-eq}}$ coupling and a 13.0 Hz $^3J_{\text{ax-ax}}$ coupling, which indicate that H_A is in an axial position coupling to another axial and equatorial proton. The $^3J_{\text{ax-ax}}$ couplings of H_B of 10.5 Hz and of 9.0 Hz and the $^3J_{\text{ax-eq}}$ coupling of H_B in the range of 5.0 Hz are evidence for the equatorial position of the OBn substituent in the 4-position coupling to two axial and one equatorial protons. In addition, the $^3J_{\text{ax-ax}}$ couplings of H_C of 9.0 Hz show that the substituent in the 5-position is axial and couples to two axial protons. Proton H_D exhibits a 9.0 Hz $^3J_{\text{ax-ax}}$ coupling indicating that H_D is in an axial position coupling to another axial proton in the 6-membered ring. In addition, it shows two ^3J couplings of 3.5 Hz and 3.0 Hz to the CH_2 -substituent outside of the ring. Combining all of these ^3J values, the 2,4,5,6-substituents must each be equatorial. The value of the optical rotation of (S,R,S,R) -**173** is -9.3 (c 1.00 in CHCl_3) and matches the optical rotation of -9.1 (c 1.00 in CHCl_3) of the sample reported by Walczak supporting the same configuration of the product.^{124, 131}

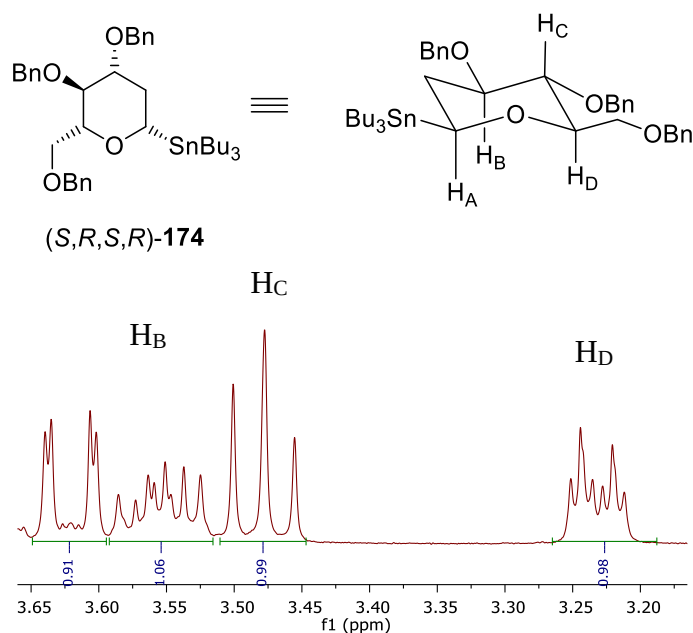
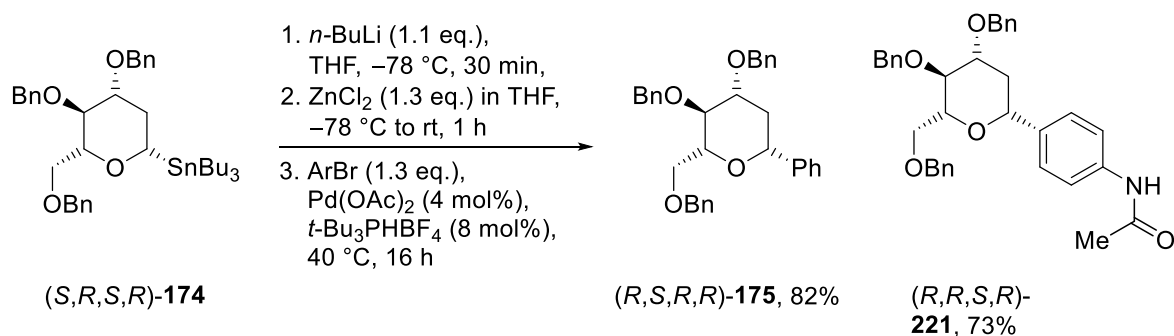


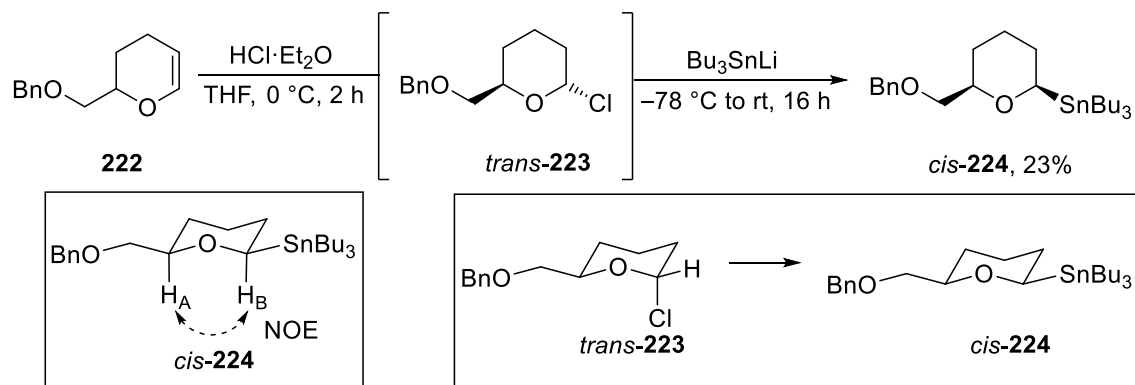
Figure 2.3: Part of the ^1H NMR of (S,R,S,R) -174.

β -Butylstannyl glycopyranoside (S,R,S,R) -174 was then used in the Negishi cross-coupling protocol to investigate the compatibility of benzyl protected ethers with the Sn-Li exchange and subsequent steps. Sn-Li exchange using $n\text{-BuLi}$ at -78°C for 30 min and subsequent transmetallation to an organozinc species using ZnCl_2 were followed by the Negishi cross-coupling with bromobenzene. This gave C -aryl glycoside (R,S,R,R) -175 in 82% yield (Scheme 2.30). Arylation using N -(4-bromophenyl)acetamide gave C -aryl glycoside (R,R,S,R) -221 in 73% yield. The relative configuration of C -phenyl glycoside (R,S,R,R) -175 was assigned using coupling constant values and was assumed for C -aryl glycoside (R,R,S,R) -221 based on analogy. In addition, comparing the value of the optical rotation for C -phenyl glycoside (R,S,R,R) -175 ($+20.0$, c 1.0 in CHCl_3) with the value in the literature ($+21.1$, c 0.9 in CHCl_3) shows that the absolute configuration is the same.¹³²



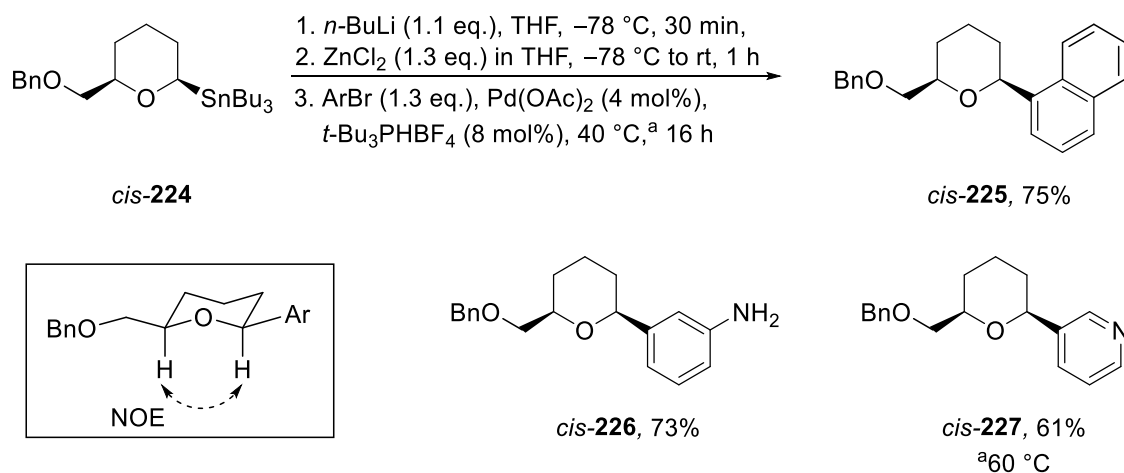
Scheme 2.30 Sn-Li Exchange of β -Glucoside Stannane (S,R,S,R) -174, Transmetallation and Negishi Cross-Coupling with Aryl Bromides.

It was also explored the use of 2,6-disubstituted stannane *cis*-**224** as the starting material for α -arylation reactions. Stannane *cis*-**224** was synthesised starting from (3,4-dihydro-2H-pyran-2-yl)methanol. Benzyl protection using reaction conditions developed by Renaud et al. gave benzyl ether **222** in 93% yield.¹³³ The α -stannyl substituent was introduced in a similar way to that in the synthesis of β -butylstannyl glycopyranoside (*S,R,S,R*)-**174**. Benzyl ether **222** was treated with HCl in Et₂O to give the 2,6-*trans* chloride *trans*-**223**. S_N2 reaction of the chloride with Bu₃SnLi gave stannane *cis*-**224** in 23% yield (Scheme 2.31). The *cis*-configuration of stannane *cis*-**224** could not be assigned using coupling constant values. However, NOE experiments clearly show an interaction of the protons H_B in the 2-position and H_A in the 6-position of the THP ring. Based on that result both protons are assigned to be axial. Hence, the stannyl and the benzyloxymethyl substituent are equatorial resulting in a 2,6-*cis* configuration.



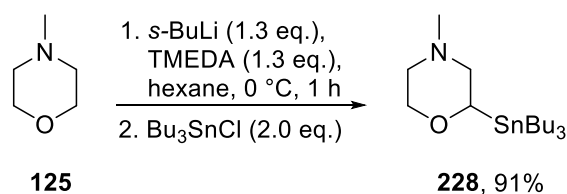
Scheme 2.31 Synthesis of 2,5-*cis* Configured Stannane *cis*-**224**.

Using the standard Negishi arylation protocol, stannane *cis*-**224** was arylated to give *cis*-**225** and *cis*-**226** in 75% and 73% yield respectively (Scheme 2.32). The *cis*-configuration of the arylated products was assigned using coupling constant values as well as using NOE experiments. In addition, the Negishi cross-coupling was performed using 3-bromopyridine and this gave *cis*-**227** in 61% yield (coupling at 60 °C).



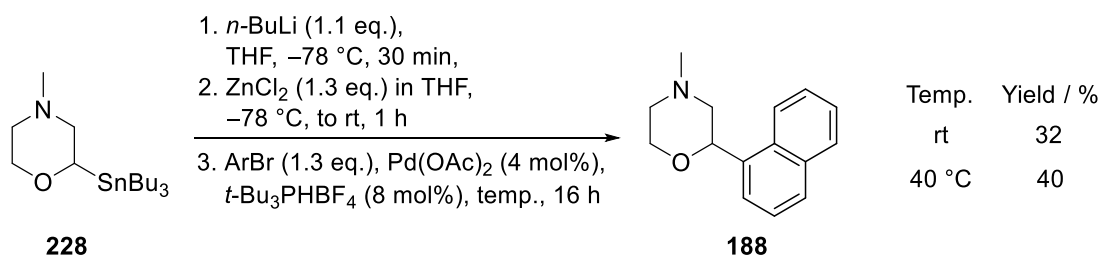
Scheme 2.32 Sn-Li Exchange of 2,5-*cis* Configured Stannane *cis*-224, Transmetallation and Negishi Cross-Coupling with Various Aryl Bromides.

With the success in the synthesis of α -arylated THFs and THPs starting from organostannanes and subsequent Sn-Li exchange, transmetallation and Negishi reaction, our interest turned to use the same strategy with α -stannyl *N*-methyl morpholine **228** as a substrate. The α -stannyl morpholine was synthesised starting from *N*-methyl morpholine **125** using the lithiation-trapping protocol developed in the O'Brien group (Scheme 2.33). Lithiation of *N*-methyl morpholine **125** (1.0 eq.) using *s*-BuLi / TMEDA (1.3 eq.) in hexane at 0 °C for 1 h and trapping with Bu₃SnCl gave α -stannyl morpholine **228** in 91% yield.



Scheme 2.33 Synthesis of α -Stannyl Morpholine **228.**

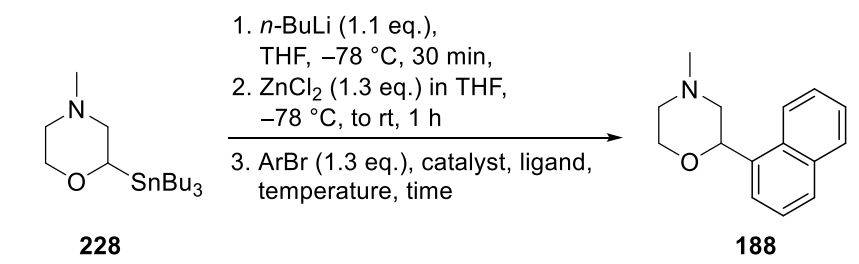
Sn-Li exchange of α -stannyl morpholine **228** with *n*-BuLi in THF at $-78\text{ }^\circ\text{C}$ for 30 min and transmetallation with ZnCl₂ gave the organozinc species. The cross-coupling with Pd(OAc)₂ (4 mol%) and *t*-Bu₃PHBF₄ (8 mol%) and bromobenzene at rt for 16 h gave the desired α -naphthyl morpholine **188** in 32% yield. Increasing the reaction temperature during the Negishi cross-coupling step to 40 °C gave α -naphthyl morpholine **188** in 40% yield (Scheme 2.34).



Scheme 2.34 Sn-Li Exchange of α -Stannyl Morpholine 228, Transmetallation and Negishi Cross-Coupling with 1-Bromonaphthalene.

Due to the moderate yield, of the cross-coupling at rt (Table 2.2, entry 1) and at 40 °C (entry 2), a set of Pd sources and ligands was studied and the results are presented in Table 2.2. Higher catalyst loading of 7 mol% Pd(OAc)₂ and ligand loading of 9 mol% *t*-Bu₃PHBF₄ during the coupling step gave the desired product **188** in 45% yield (entry 3). Increasing the reaction temperature to 60 °C only resulted in a slight increase in yield (entry 4). Changing the catalyst system to a PEPPSI-*i*Pr catalyst gave only a 4% yield of arylated morpholine (entry 5). Using Pd(dba)₂ and X-Phos, a 24% yield of arylated morpholine **188** was isolated (entry 6).

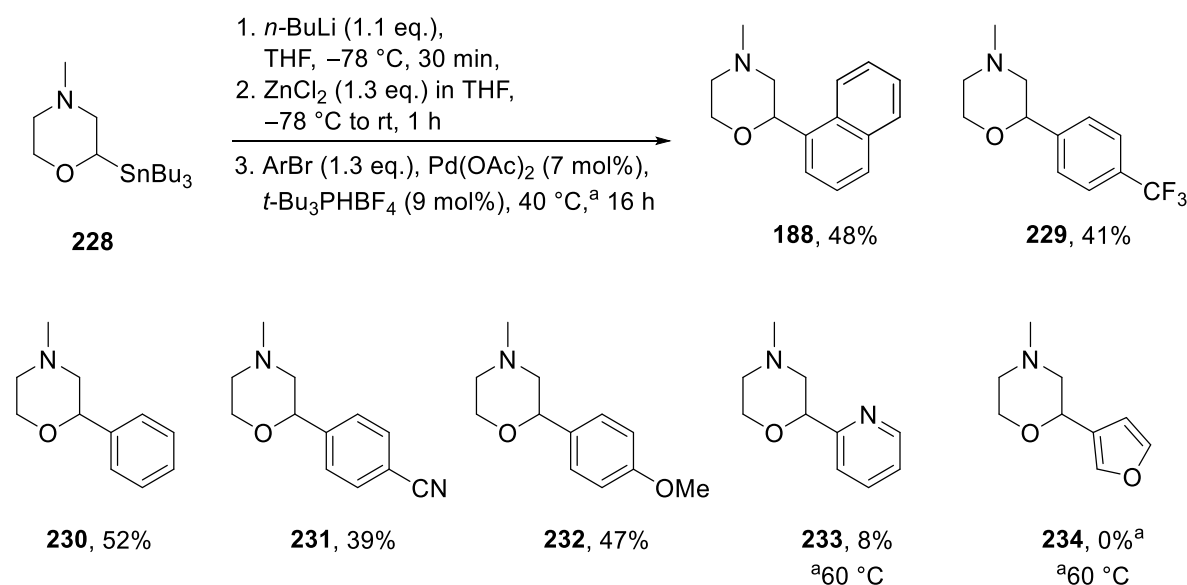
Table 2.2: Optimisation of the Negishi Cross-Coupling Conditions using α -Stannyl Morpholine 228.

							
228							188
Entry	Catalyst	mol%	Ligand	mol%	Time / h	Temperature / °C	Yield / % ^a
1	Pd(OAc) ₂	4	<i>t</i> -Bu ₃ PHBF ₄	8	16	rt	32
2	Pd(OAc) ₂	4	<i>t</i> -Bu ₃ PHBF ₄	8	16	40	40
3	Pd(OAc) ₂	7	<i>t</i> -Bu ₃ PHBF ₄	9	16	40	45
4	Pd(OAc) ₂	7	<i>t</i> -Bu ₃ PHBF ₄	9	16	60	47
5	PEPPSI- <i>i</i> Pr	5	-	-	16	40	4
6	Pd(dba) ₂	5	X-Phos	5	16	40	24

^a Yield after purification by chromatography.

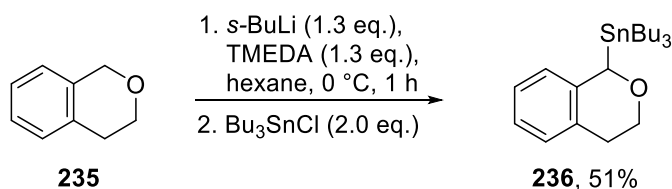
The conditions presented in entry 3 were used as the optimised standard conditions. Compared to the previously used conditions, the catalyst loading of $\text{Pd}(\text{OAc})_2$ was increased to 7 mol% and the loading of the ligand $t\text{-Bu}_3\text{PHBF}_4$ was increased to 9 mol%.

As a temperature rise to 60 °C during the coupling gave only a very small improvement, it was decided to use $\text{Pd}(\text{OAc})_2$ (7 mol%), $t\text{-Bu}_3\text{PHBF}_4$ (9 mol%) and aryl bromides (1.3 eq.) at 40 °C for 16 h as the Negishi cross-coupling conditions to explore the scope. A range of aryl bromides was used to give α -arylated morpholines **188,229-234** in up to 52% yield and the products are shown in Scheme 2.35. Aryl bromides bearing a CF_3 , nitrile and methoxy group were tolerated in this coupling as well as unsubstituted naphthyl and phenyl bromides. Disappointingly, a low yield was obtained for 2-bromopyridine and no product was obtained with 3-bromofuran (coupling at 60 °C).



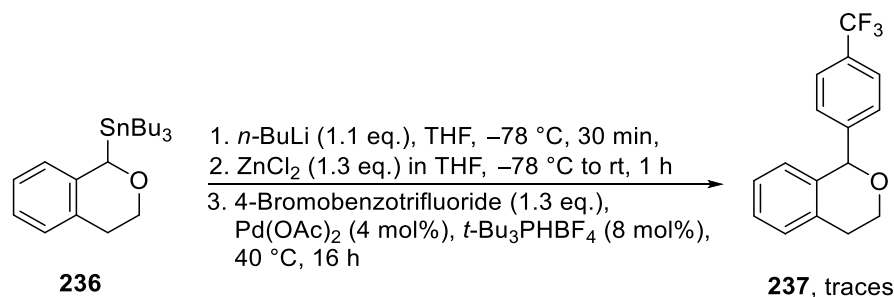
Scheme 2.35 Sn-Li Exchange of α -Stannyl Morpholine **228**, Transmetalation and Negishi Cross-Coupling with Various Aryl Bromides.

Finally, it was tried to expand the methodology to isochromans.¹³⁴ The stannyl isochroman **236** was prepared using the lithiation conditions for N -methyl morpholine. Lithiation of isochroman **235** using $s\text{-BuLi}$ / TMEDA in hexane at 0 °C and trapping with Bu_3SnCl resulted in α -stannyl isochroman **236** in 51% yield (Scheme 2.36).



Scheme 2.36 Synthesis of α -Stannyl Isochroman 236.

Then, Sn-Li exchange, transmetallation and Negishi cross-coupling were then explored. α -Stannyl isochroman **236** underwent the established protocol for the α -arylation starting from organostannanes. Unfortunately, Sn-Li exchange in THF at -78°C for 30 min, transmetallation and Negishi cross-coupling using $\text{Pd}(\text{OAc})_2$ (4 mol%) and $t\text{-Bu}_3\text{PHBF}_4$ (8 mol%) with 4-bromobenzotrifluoride gave only traces of product **237** (Scheme 2.37).

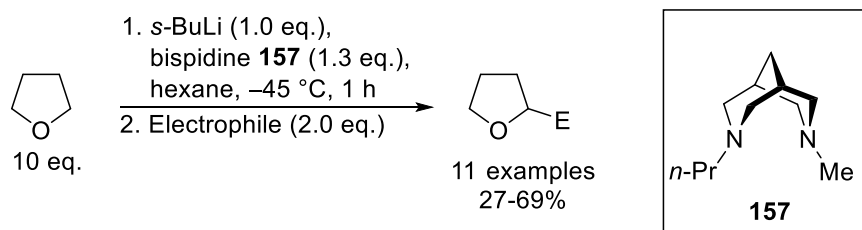


Scheme 2.37 Sn-Li Exchange of α -Stannyl Isochroman 236, Transmetallation and Negishi Cross-Coupling with 4-Bromobenzotrifluoride.

The new protocol for the synthesis of α -arylated saturated oxygen heterocycles such as THF, THP and *N*-methyl morpholine starting from the corresponding organostannanes works very well. Much higher yields of the α -arylated products were obtained compared to the previous explored routes *via* direct lithiation of the oxygen heterocycles (see section 2.1).

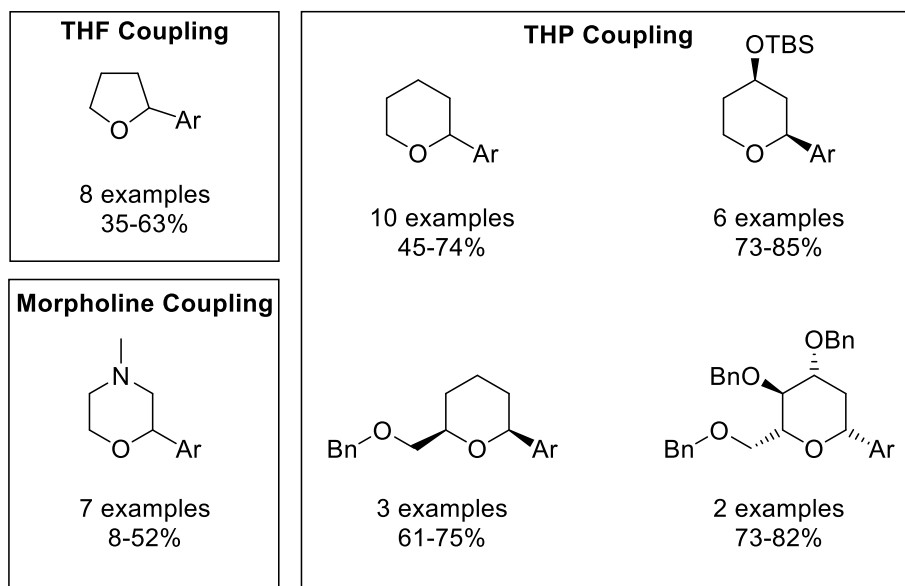
2.3 Conclusions and Future Work

In summary, new conditions for the lithiation-trapping of THF have been developed. The combination of using 10 eq. of THF and the *s*-BuLi / bispidine **157** complex in hexane at $-45\text{ }^{\circ}\text{C}$ for 1 h and subsequent trapping with electrophiles gave the best results. In this way, a range of α -substituted THFs was synthesised in 27-69% yield (Scheme 2.38). The highest yield of 69% compared to a yield of $\sim 40\%$ obtained under the previously explored THF lithiation conditions in the O'Brien group (see section 1.3.2), indicates a much improved lithiation step using the *s*-BuLi / bispidine **157** complex.



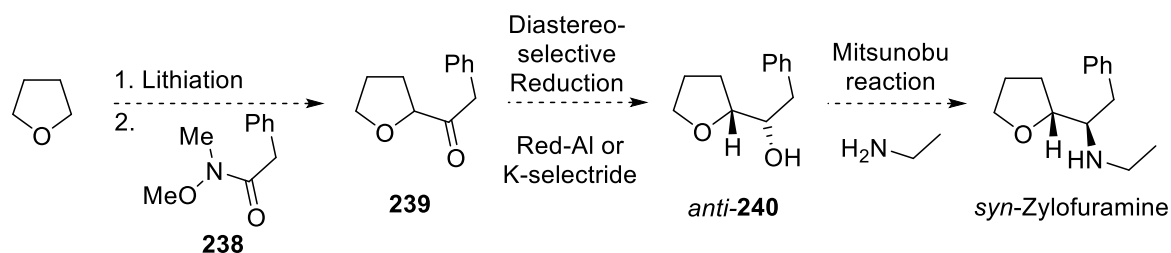
Scheme 2.38 Lithiation-Trapping of THF Using Bispidine **157**.

In addition, reaction conditions for the arylation of oxygen heterocycles were explored. It was found that a direct lithiation of oxygen heterocycles, transmetallation and Negishi cross-coupling resulted in only moderate yields of α -arylated oxygen heterocycles. It is proposed that the low yields are due to the use of hexane in the lithiation step which is believed is incompatible with the subsequent Negishi cross-coupling. As an alternative approach, it was focussed on the use of α -stannyl substituted saturated oxygen heterocycles which underwent Sn-Li exchange, transmetallation and Negishi cross-coupling to give the desired α -arylated saturated oxygen heterocycles. An overview of our results is presented in Figure 2.4. Coupling of α -stannyl-substituted oxygen heterocycles with aryl bromides gave eight α -arylated THFs in moderate to good yields (35-63% yield). Similar yields were obtained in the coupling starting from α -stannyl morpholine and seven examples were completed. The best results were obtained for the synthesis of α -aryl THPs. Four different substrates were explored leading to 21 examples in 58-85% yield. Across all substrates, electron-rich and electron-poor aryl bromides as well as heteroaryl bromides were successfully coupled in the Negishi reaction. An important aspect was the study of stereospecificity. It was shown that the configuration of the stannanes was maintained in the α -aryl oxygen heterocycle products.

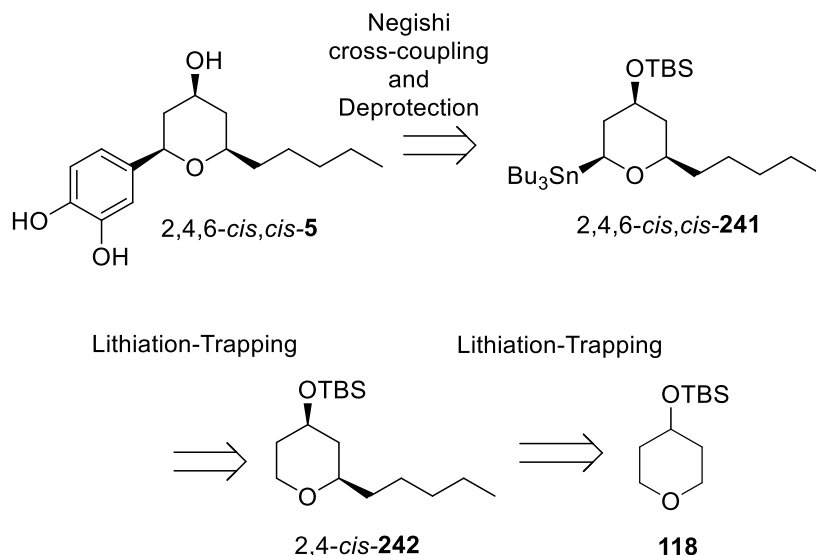

 Figure 2.4 Scope of α -Arylated Saturated Oxygen Heterocycles.

Our new methodology gave α -arylated oxygen heterocycles in good yields and a similar scope to the Stille cross-coupling reported by Walczak et al. The Negishi approach can be considered complementary to this Stille cross-coupling. However, in contrast to Walczak et al.'s approach, the Negishi methodology does not require high temperatures and long reaction times (110 °C for 72 h) and works with aryl bromides. In addition, it was possible to avoid the use of 3.0 eq. of moisture sensitive CuCl and stoichiometric amounts of KF.

In future, it could be envisaged that the new lithiation-trapping methodology could be applied to the synthesis of *syn*-zylofuramine (Scheme 2.39). Lithiation under the best conditions and trapping with Weinreb amide **238** would result in ketone **239**. Subsequent chelate-controlled diastereoselective reduction, for example with Red-Al, as previously described by a co-worker in the synthesis of reboxetine (see Scheme 1.69), could give alcohol *anti*-**240**. In the next step, conditions adapted from a recently reported Mitsunobu reaction that allowed the formation of CN bonds by Huang and Kang¹³⁵ could be employed. In their work, nucleophilic amines were used in the substitution reaction of aliphatic alcohols. This rather unusual Mitsunobu reaction could allow the synthesis of *syn*-Zylofuramine starting from alcohol *anti*-**241** via the reaction with ethyl amine.

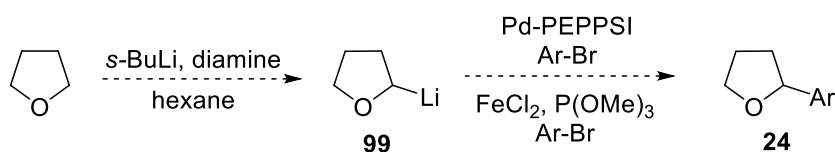

 Scheme 2.39 Proposed Synthesis of *syn*-Zylofuramine.

In addition, it was proposed that the new methodology for α -aryl oxygen heterocycle synthesis could be applied to the synthesis of 2,4,6-*cis,cis*-5, an extract of the plant *Plectranthus Sylvestris*.^{13, 136} It is a 2,4,6-*cis* configured oxygen heterocycle bearing a *n*-pentyl and catechol substituents which exhibits antioxidant activity. Our proposed retrosynthetic pathway is shown in Scheme 2.40. The catechol substituent could be installed starting from α -stannyl THP 2,4,6-*cis,cis*-**241** via Sn-Li exchange, transmetallation and our developed stereospecific Negishi cross-coupling strategy and removal of the TBS protecting group. It is envisaged that α -stannyl THP 2,4,6-*cis,cis*-**241** could be accessed via our developed lithiation-trapping protocol from lithiation-trapping with Bu_3SnCl starting from 2,4-*cis* TBS-protected 4-hydroxy THP **118**. Presumably, lithiation and transmetallation to an organocopper species could allow a high *cis*-selectivity in the subsequent trapping with *n*-pentyl iodide and would result in 2,4-*cis* configured THP *cis*-**242**.


 Scheme 2.40 Retrosynthetic Analysis of 2,4,6-*cis,cis*-5.

One other proposal for future work would be to explore a direct Pd- or Fe-catalysed cross-coupling of lithiated oxygen heterocycles with aryl bromides. Previously, Feringa et al.¹³⁷ and Wong et al.¹³⁸ independently reported cross-couplings of alkyl lithium and aryl halides

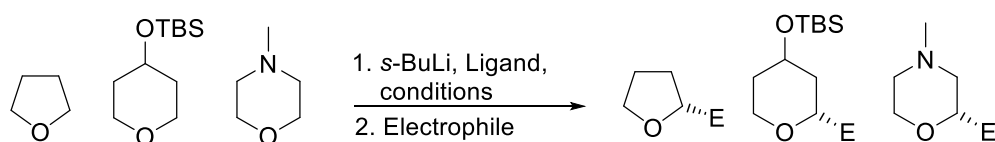
mediated by Pd and Fe catalysts. As a starting point, our developed lithiation conditions could be used to generate lithiated THF **99** which could then be subjected to the reported cross-coupling conditions as outlined in Scheme 2.41. This could allow us to avoid the transmetalation step to an organozinc species but, most importantly, it might be able to avoid the use of organostannanes. However, Feringa et al. and Wong et al. reported the highest yields when carrying out the cross-coupling reactions at rt. Due to the instability of the lithiated THF **99** at rt, it is may needed to explore lower reaction temperatures for the cross-coupling.



Scheme 2.41 Proposed Cross-Coupling of α -Lithio THF and Aryl Bromides.

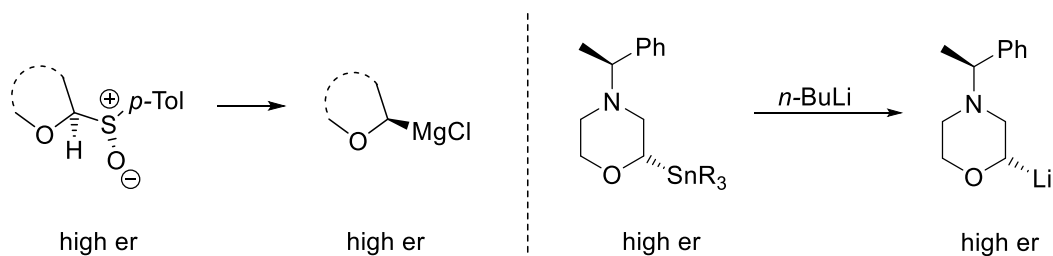
Chapter 3: Synthesis of Enantioenriched Saturated α -Substituted Oxygen Heterocycles

In this chapter, methods based on previous α -lithiation results for the synthesis of enantioenriched saturated α -substituted oxygen heterocycles were developed. There are very limited previous examples to enantioenriched oxygen heterocycles starting from an intact oxygen ring system and these are summarised in section 3.1. It was envisaged three different approaches towards α -substituted enantioenriched oxygen heterocycles. First, it was planned to investigate the asymmetric deprotonation of saturated oxygen heterocycles using chiral diamine ligands (Scheme 3.1) which builds on the expertise in the O'Brien group with the asymmetric deprotonation of *N*-Boc heterocycles. These results are presented in section 3.2.



Scheme 3.1 Asymmetric Deprotonation of Oxygen Heterocycles.

In addition, it was also planned to investigate routes to enantioenriched oxygen heterocycles using enantioenriched sulfoxides (section 3.3) and stannanes (section 3.4) as set out in Scheme 3.2. For the sulfoxides, it was imagined accessing enantioenriched sulfoxides from Andersen's sulfinate. Then, sulfoxide-Mg exchange should give access to enantioenriched Grignard reagents which would be trapped with electrophiles. Alternatively, the synthesis of enantioenriched α -substituted morpholines would be explored *via* the synthesis of enantiopure stannanes containing an α -methylbenzyl group. Sn-Li exchange and trapping would then give access to α -substituted morpholines in high *ers*.

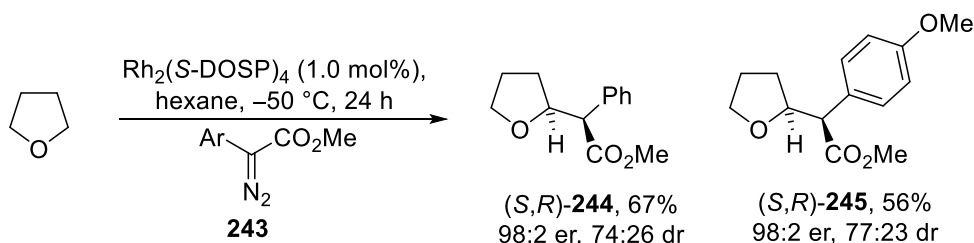


Scheme 3.2 Enantioenriched Sulfoxides and Stannanes.

3.1 Previous Approaches to Enantioenriched Oxygen Heterocycles Starting from Intact Ring Systems

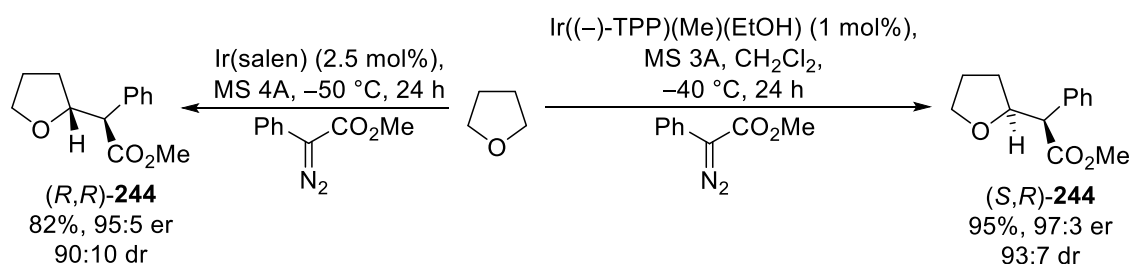
The direct enantioselective α -functionalisation of saturated oxygen heterocycles starting from intact ring system is challenging. To the best of our knowledge there are only two known approaches to enantioenriched oxygen heterocycles: (i) Rh-catalysed,¹³⁹ Ir-catalysed,¹⁴⁰⁻¹⁴² or Cu-catalysed¹⁴³⁻¹⁴⁴ coupling of THF and related oxygen heterocycles to diazoacetates; (ii) one isolated example of Ni-catalysed, light-mediated coupling of THF to an aryl bromide.⁶²

In pioneering work by Davies et al., the Rh-catalysed asymmetric C-H activation of cyclic alkanes and THFs combined with intermolecular C-H insertion of aryldiazoacetates was studied.¹³⁹ CH-Activation of THF was carried out at $-50\text{ }^{\circ}\text{C}$ using a $\text{Rh}_2(\text{S-DOSP})_4$ catalyst, a dinuclear Rh complex bearing four (*S*)-proline derived ligands. Subsequent reaction with aryldiazoacetates **243** gave α -substituted THFs (*S,R*)-**244** and (*S,R*)-**245** in 67% and 56% yield respectively and high ers (98:2) (Scheme 3.3).



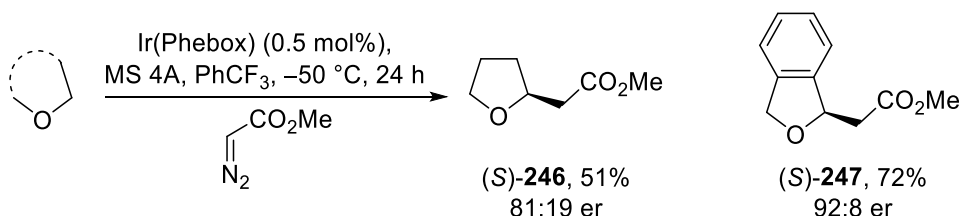
Scheme 3.3 Rh-Catalysed Asymmetric C-H Activation of THF.

In 2009, Che et al.¹⁴⁰ reported the synthesis of the same types of THF carboxylic esters using aryldiazoacetates and an Ir-salen complex (Scheme 3.4). Asymmetric, intermolecular carbene C-H insertion mediated by the Ir(III)-salen complex generated α -substituted THF (*R,R*)-**244** in 82% yield and 95:5 er. In addition, Suematsu and Katsuki¹⁴¹ reported the synthesis of α -substituted THF (*S,R*)-**244** using an Ir((-)-TPP)(Me)(EtOH) catalyst, a hexavalent Ir complex bearing a tetraphenylporphyrin ligand. Carbene insertion of aryldiazoacetates resulted in the α -substituted THF (*S,R*)-**244** in 95% yield and 97:3 er (Scheme 3.4). Both groups explored further aryldiazoacetates bearing electron-donating and electron-withdrawing aryl substituents and use of these gave methyl esters in good diastereoselectivities and high enantioselectivities.



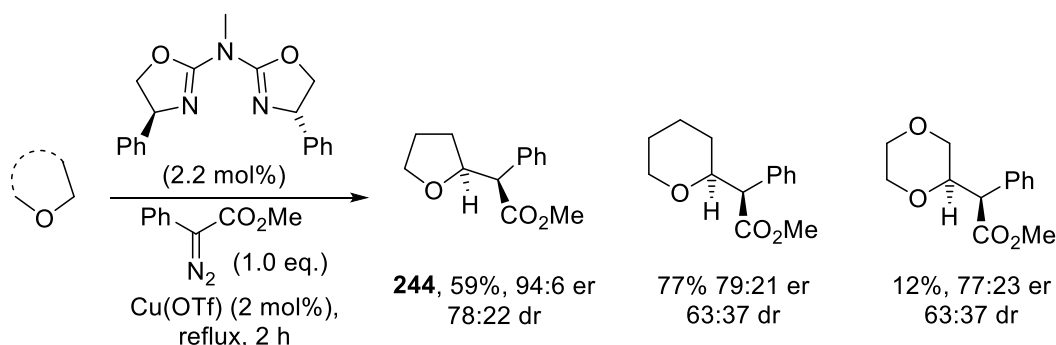
Scheme 3.4 Ir(salen) and Ir((-)-TPP)-Catalysed Asymmetric C-H Activation of THF.

In 2016, Davies et al. developed the Ir-catalysed asymmetric CH-activation of THF and phthalans using Phebox ligands and insertion into a range of diazoacetates (Scheme 3.5).¹⁴² Reaction of the diazoacetate with the oxygen heterocycle and Ir(Phebox) at low temperatures ($-50\text{ }^{\circ}\text{C}$ for 24 h) delivered the α -substituted THFs (**S**)-**246** and (**S**)-**247** in moderate to high ers.



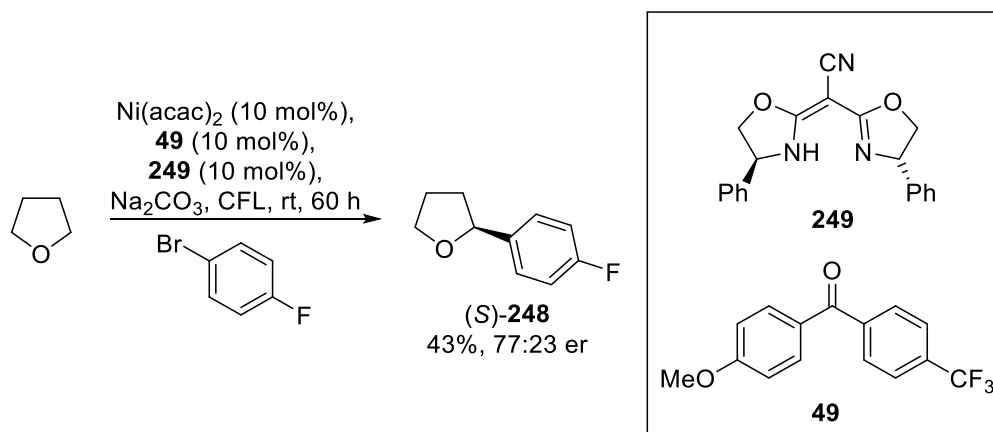
Scheme 3.5 Ir(phebox)-Catalysed Asymmetric C-H Activation of THF.

In related work, Fraile et al. explored a heterogeneous Cu-catalysed enantioselective C-H activation of oxygen heterocycles such as THF, THP and dioxane using box-Cu complexes which were immobilised onto clay.¹⁴³⁻¹⁴⁴ CH-Activation and carbene insertion using aryldiazoacetates gave the α -substituted saturated oxygen heterocycles. A good yield and high enantioselectivity (94:6 er) were reported for 5-membered ring THF. For 6-membered ring THP and dioxanes, the α -substituted products were obtained in moderate ers (Scheme 3.6).



Scheme 3.6 Cu-Catalysed Asymmetric C-H Activation of Oxygen Heterocycles.

As described in section 1.2 (see Scheme 1.28), Martin et al.⁶² reported a protocol to access α -arylated and α -alkylated oxygen heterocycles using a combination of triplet excited ketones, Ni-catalysis and a visible light source. As well as preparing racemic α -arylated THFs, the synthesis of enantioenriched α -aryl THF (**(S)-248**) was presented using chiral ligand **249** in the Ni catalysis step. Light-mediated coupling of THF with the aryl bromide gave α -arylated THF (**(S)-248**) in 43% yield and 77:23 er (Scheme 3.7). This was the only example reported by Martin.



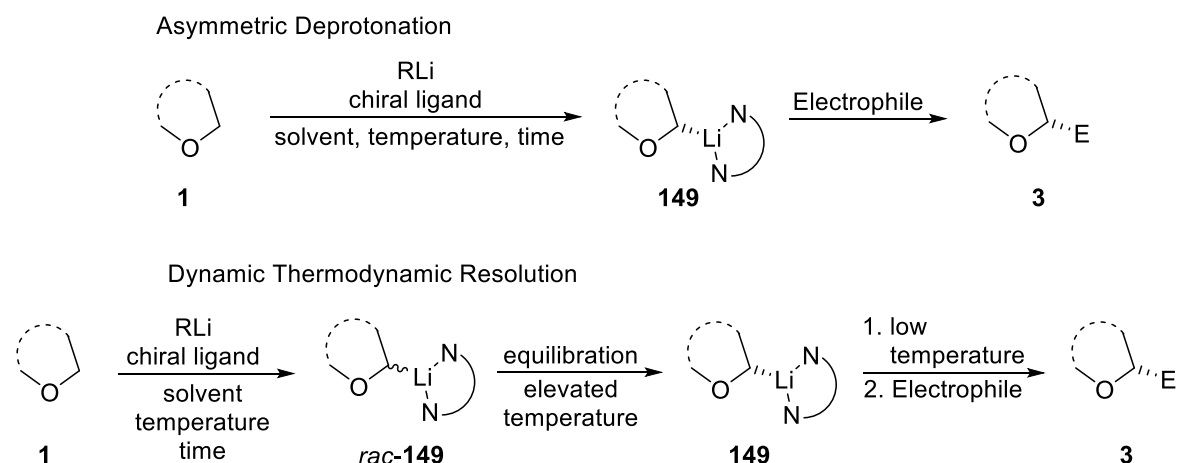
Scheme 3.7 Ni-Catalysed, Light-Mediated Asymmetric C-H Activation of THF.

The previously reported carbene insertion examples are limited to the introduction of aryl acetates using the corresponding aryldiazoacetates. Martin et al. showed that coupling of THF to aryl bromides is possible but presented only one example. A widely applicable method to enantioenriched α -substituted saturated oxygen heterocycles starting from the parent oxygen heterocycle has not been reported.

3.2 Asymmetric Deprotonation of THF, THP and N-Methyl Morpholine

In this section, an approach towards the synthesis of enantioenriched α -substituted oxygen heterocycles using lithiation and subsequent trapping is described. As the synthesis of enantioenriched saturated oxygen heterocycles using organolithium reagents has not been reported previously, it was planned to adapt well-explored lithiation conditions for the preparation of enantioenriched saturated *N*-Boc heterocycles as our starting point. Based on the literature,⁷⁴ two main strategies are established for the generation of enantioenriched α -substituted *N*-heterocycles: asymmetric deprotonation (see Scheme 1.33) and dynamic thermodynamic resolution, see Scheme 1.51. Dynamic kinetic resolution is also possible but is often only successful for limited electrophiles (see Scheme 1.53).

In the case of asymmetric deprotonation, the lithiation would be carried out at low temperatures using an organolithium source and a chiral diamine ligand (Scheme 3.8). During the lithiation, due to the configurational stability of the lithiated species at low temperatures, the abstraction of a proton would be the enantioselective step and a configurationally stable intermediate would be formed which would subsequently be trapped with an electrophile. The lithiation conditions for an asymmetric deprotonation of oxygen heterocycles would need to be carefully chosen to find a compromise between the reactivity of the oxygen heterocycle to generate a lithiated species and high enantioselectivity during the lithiation process.



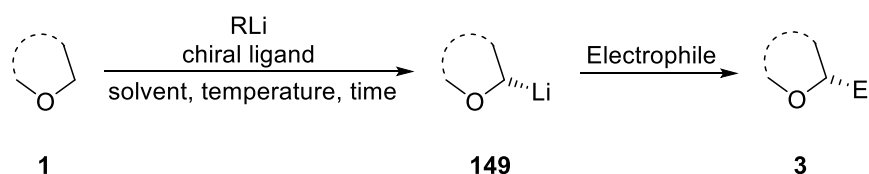
Scheme 3.8 Asymmetric Deprotonation and Dynamic Thermodynamic Resolution Strategies for the α -Functionalisation of Oxygen Heterocycles.

For the synthesis of α -substituted enantioenriched oxygen heterocycles *via* dynamic thermodynamic resolution, the lithiated intermediate would need to be warmed up until it is configurationally labile (Scheme 3.8). The two possible configurations of the lithiated

intermediate would then be in a rapid equilibrium and the addition of a chiral ligand could generate a higher population of a certain lithiated species. This population would then be kept, due to a subsequent cooling process to a temperature where the lithiated species is configurationally stable, and the enantioenriched lithiated species would finally be trapped with an electrophile.

Depending on the oxygen heterocycle, a different strategy might be preferred to obtain the enantioenriched α -substituted products. Based on the chemical stability of the lithiated species, the dynamic thermodynamic resolution strategy should be possible for *N*-methyl morpholine **125**. However, since equilibration would need to be typically carried out at high temperatures (*e.g.* above $-20\text{ }^{\circ}\text{C}$), THF and THP may present problems. This is because of the known retro [3+2] decomposition pathway of lithiated THF (see section 1.3.2) and the observation by a co-worker of the chemical instability of lithiated THP due to its carbenoid character.¹⁰⁷ For all oxygen heterocycles, THF, THP and *N*-methyl morpholine **125**, it should be possible to explore the asymmetric deprotonation pathway. However, as the temperature should be as low as possible for high enantioselectivity, the reactivity of the oxygen heterocycles towards lithiation is the key issue that needed to be considered and explored.

With the O'Brien group's experience in the use of organolithium reagents and chiral diamines in the asymmetric deprotonation of *N*-Boc heterocycles,^{78, 91, 108} it was decided to adapt the same approach for the synthesis of enantioenriched α -substituted oxygen heterocycles. In addition, it was believed that the mentioned decomposition side-reactions of lithiated THF and THP could be suppressed by using a temperature below $-40\text{ }^{\circ}\text{C}$ for the asymmetric deprotonation. Using an organolithium source and a chiral diamine should generate a configurationally stable, enantioenriched lithiated species **149**, which would subsequently be trapped to give α -substituted oxygen heterocycles **3** (Scheme 3.9).



Scheme 3.9 Asymmetric Deprotonation of THF.

As presented in section 2.1, diamines have a significant influence on the reactivity of organolithium / diamine complexes and the formation of the lithiated species. Diamines such as TMEDA and (–)-sparteine were frequently used with *s*-BuLi in racemic and

enantioenriched lithiation-trapping reactions of *N*-heterocycles respectively. However, the *s*-BuLi / (+)-sparteine surrogate complex is known to be more reactive than *s*-BuLi / TMEDA or *s*-BuLi / (–)-sparteine (Figure 3.1).^{108, 118, 145}

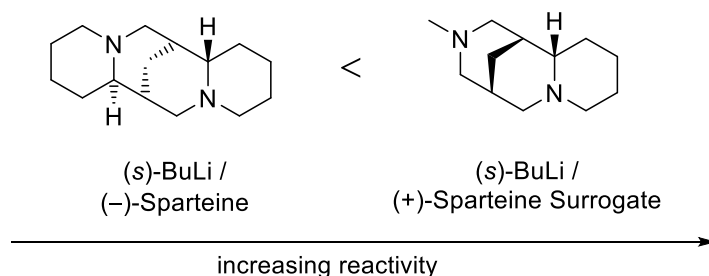
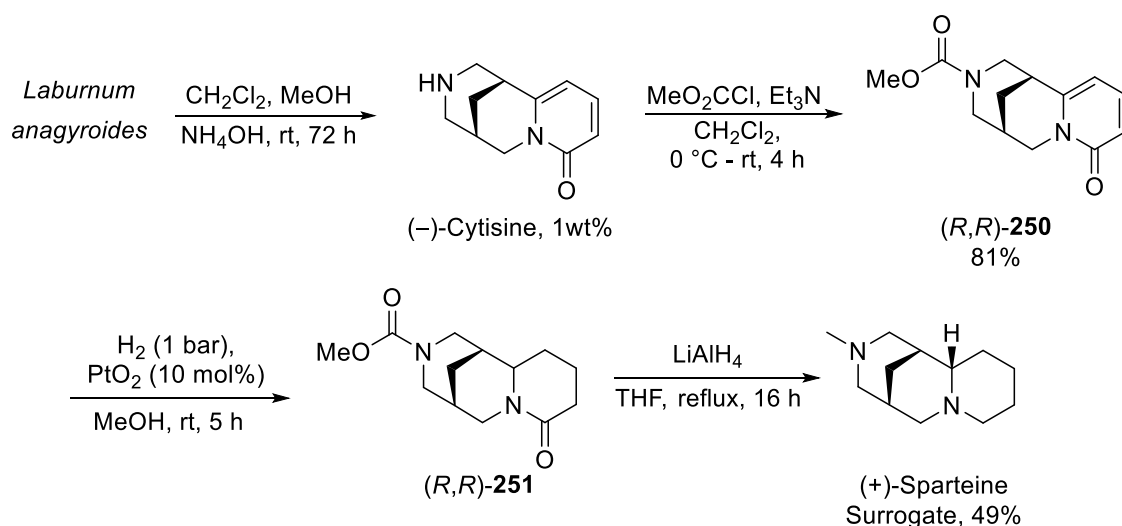


Figure 3.1 Reactivity of Selected *s*-BuLi / Diamine Complexes.

The high reactivity of the *s*-BuLi / (+)-sparteine surrogate complex in the lithiation of *N*-Boc heterocycles encouraged us to use this complex to investigate the asymmetric deprotonation of THF. Therefore, the (+)-sparteine surrogate was synthesised according to the method reported in the O'Brien group.^{71, 146} In the first step, *Laburnum Anagyroides* seeds were extracted using a protocol developed in the O'Brien group. Then, methyl carbamate (*R,R*)-**250** was obtained in 81% yield by reaction of (–)-cytisine with methyl chloroformate and Et₃N. Subsequent diastereoselective hydrogenation using PtO₂/H₂ generated carbamate **251** and reduction using LiAlH₄ gave the (+)-sparteine surrogate in 49% yield over both steps after purification by distillation (Scheme 3.10). This synthesis produced 1.17 g (600 g of seeds used in the extraction step) of the (+)-sparteine surrogate.



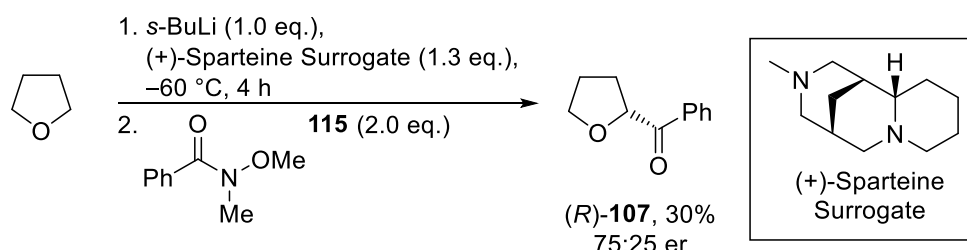
Scheme 3.10 Synthesis of (+)-Sparteine Surrogate.

To start with, reaction conditions for the asymmetric deprotonation of THF and subsequent trapping with an electrophile were designed. Previous investigations in the racemic

lithiation-trapping of THF revealed that use of THF (substrate and solvent) and lithiation at $-60\text{ }^{\circ}\text{C}$ for 4 h gave α -substituted THFs in moderate yields.

Based on the known complexation of *s*-BuLi to the (+)-sparteine surrogate in THF,⁷⁸ it was decided to explore the same reaction with the (+)-sparteine surrogate. It was assumed that the generated lithiated THF would be chemically stable at $-60\text{ }^{\circ}\text{C}$ for 4 h based on a Sn-Li exchange experiment (at $-60\text{ }^{\circ}\text{C}$ for 1 h) reported by Macdonald et al.¹²⁵ In addition, Weinreb amide **115** was chosen as a suitable electrophile because it generates only one stereogenic centre after trapping of the lithiated species.

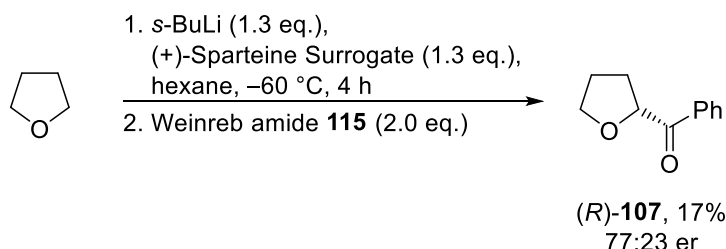
Thus, reaction of THF (solvent and substrate) with *s*-BuLi / (+) sparteine surrogate at $-60\text{ }^{\circ}\text{C}$ for 4 h was followed by trapping with Weinreb amide **115**. Under these conditions, to our delight, ketone **107** was isolated in 30% yield and 75:25 er (Scheme 3.11). The er was determined using CSP-HPLC and compared with a racemic standard that was also prepared and analysed. The absolute configuration of the major enantiomer was assigned by analogy with α -substituted THF (*R*)-**107** as discussed later (see Scheme 3.16). It is assumed that the asymmetric induction by the *s*-BuLi / (+)-sparteine surrogate complex led to the (*R*)-enantiomer as the major enantiomer. The exact induction pathway could be investigated by obtaining solution structures at low temperatures using NMR spectroscopy. This initial result is very promising and suggests that the *s*-BuLi / (+)-sparteine surrogate complex is faster at lithiating THF than *s*-BuLi / THF. In addition, it is possible that due to excess of THF in the reaction, in a background reaction THF could be deprotonated under the previously presented racemic lithiation conditions using the *s*-BuLi / THF complex and result in a decreased er of ketone **107**.



Scheme 3.11 Asymmetric Deprotonation of THF Using *s*-BuLi / (+)-Sparteine Surrogate and Trapping with Weinreb Amide **115.**

Based on this initial result, it was decided to try to reduce the amount of THF with the aim to use only a stoichiometric amount of THF as a substrate. This would also allow us to remove the potential background lithiation by the *s*-BuLi / THF complex. Changing to a

stoichiometric amount of THF and using hexane as solvent under the same conditions gave ketone (*R*)-**107** in 17% yield and 77:23 er (Scheme 3.12). This result is particularly interesting as none of ketone **107** was isolated when TMEDA was used under the same conditions.¹⁰⁶ Thus, this result clearly shows the higher reactivity of *s*-BuLi / (+)-sparteine surrogate compared to the use of *s*-BuLi / TMEDA.

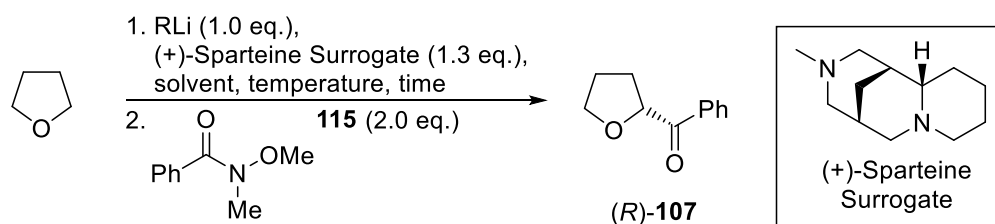


Scheme 3.12 Asymmetric Deprotonation of THF Using *s*-BuLi / (+)-Sparteine Surrogate in Hexane and Trapping with Weinreb Amide **115.**

At this point, it was decided to explore improving the yield and er by investigating different solvents, temperatures and organolithium reagent. The results are shown in Table 3.1, with entries 1 and 2 showing the initial results previously presented. Using Et₂O as a solvent at -60 °C, ketone (*R*)-**107** was obtained in only 10% yield and 78:22 er (entry 3).

Recently, Aggarwal et al.¹⁴⁷ reported higher yields in the lithiation-trapping of a saturated *N*-Boc nitrogen heterocycle using *s*-BuLi / (+)-sparteine surrogate in CPME. This also worked well in our case, since use of CPME increased the yield of ketone (*R*)-**107** to 47% (80:20 er) (entry 4). To try to improve the enantioselectivity, a reaction temperature of -78 °C with a longer lithiation time (8 h) was attempted. This gave a 17% yield of ketone (*R*)-**107** and similar enantioselectivity (81:19 er) (entry 5). The asymmetric deprotonation of THF with *t*-BuLi / (+)-sparteine surrogate was also explored. After lithiation at -60 °C for 4 h and trapping with Weinreb amide **115**, no ketone **107** was obtained (entry 6).

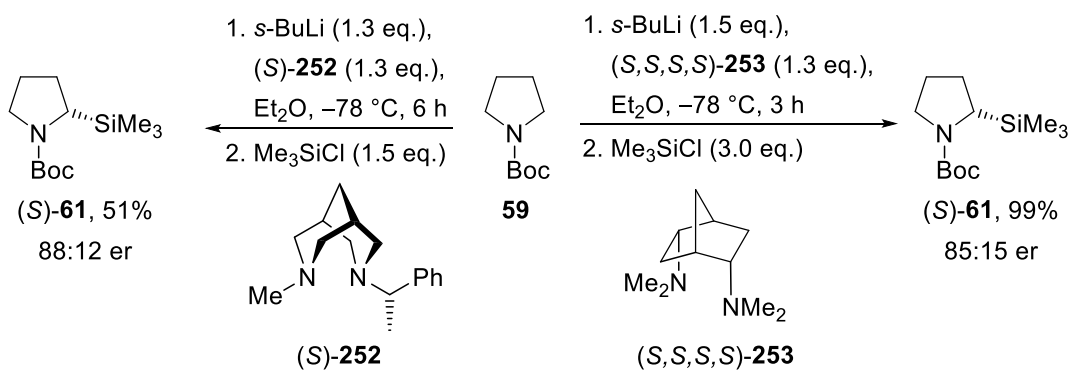
Table 3.1: Asymmetric Lithiation-Trapping of THF.



Entry	RLi	Solvent	Temperature / °C	Lithiation- time / h	Yield (R)- 107 / % ^a	er ^b
1	<i>s</i> -BuLi	THF ^c	−60	4	30	75:25
2	<i>s</i> -BuLi	hexane	−60	4	17	77:23
3	<i>s</i> -BuLi	Et ₂ O	−60	4	10	78:22
4	<i>s</i> -BuLi	CPME	−60	4	47	80:20
5	<i>s</i> -BuLi	CPME	−78	8	17	81:19
6	<i>t</i> -BuLi	CPME	−60	4	0	-

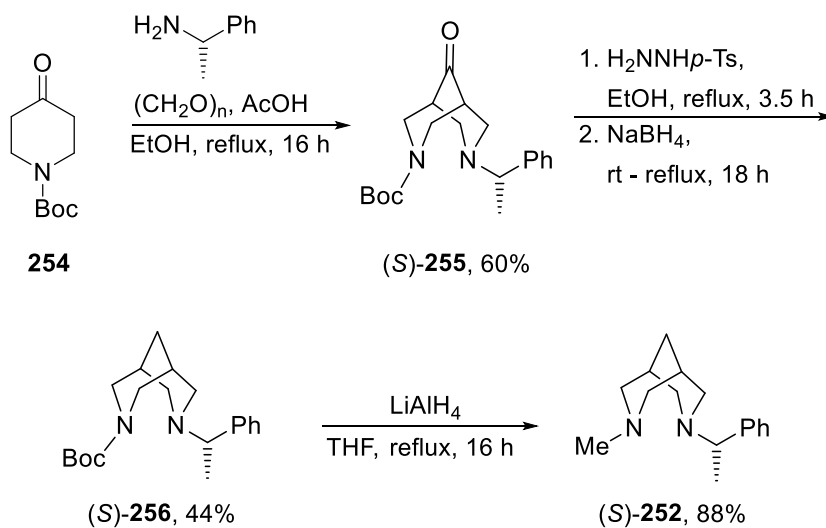
^a Yield after purification by chromatography, ^b er determined by CSP-HPLC, ^c THF as substrate and solvent.

To increase the yield and/or er using the asymmetric deprotonation approach, new ligands were considered which might give a more reactive complex and/or react with higher enantioselectivity. Based on the success with bispidine ligand **157** in the racemic deprotonation of THF (see section 2.1) it was wondered if chiral bispidine (S)-**252** could be used in the asymmetric deprotonation of THF. Beak reported the use of bispidine (S)-**252** in the asymmetric deprotonation of *N*-Boc pyrrolidine **59**. Thus, use of *s*-BuLi and (S)-**252** at −78 °C for 6 h generated the lithiated species which was subsequently trapped with Me₃SiCl to give (S)-**61** in 51% yield and 88:12 er (Scheme 3.13).¹⁴⁸⁻¹⁴⁹ Another ligand which has been used in the asymmetric deprotonation of *N*-Boc pyrrolidine **59** is bicyclic diamine (S,S,S,S)-**253**. Asymmetric deprotonation of *N*-Boc pyrrolidine **59** using *s*-BuLi and ligand (S,S,S,S)-**253** at −78 °C in Et₂O for 3 h and trapping with Me₃SiCl gave silane (S)-**61** in 99% yield and 85:15 er (Scheme 3.13).^{72, 87}



Scheme 3.13 Asymmetric Deprotonation of *N*-Boc Pyrrolidine Using *s*-BuLi / Diamine (S)-252 and *s*-BuLi / Diamine (S,S,S,S)-253.

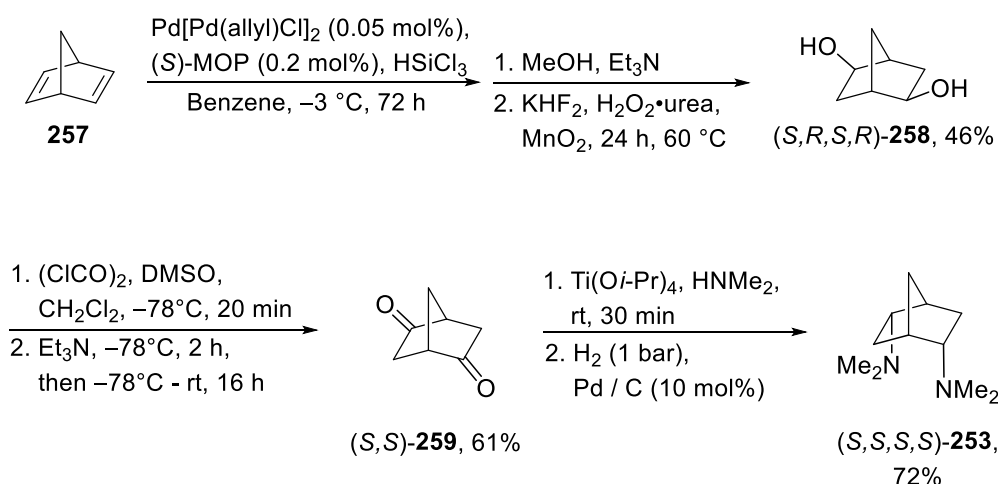
Both ligands (S)-**252** and (S,S,S,S)-**253** were prepared using the literature procedures.^{148, 150-151} Bispidine ligand (S)-**252** was synthesised in three steps starting from *N*-Boc piperidin-4-one **254**. Double Mannich reaction using α -methylbenzylamine and paraformaldehyde gave ketone (S)-**255** in 60% yield. Subsequent reduction gave bispidine (S)-**256** in 44% yield. Finally, reduction with LiAlH_4 gave ligand (S)-**252** in 88% yield (Scheme 3.14).



Scheme 3.14 Synthesis of Diamine (S)-252.

Ligand (S,S,S,S)-**253** was synthesised in five steps starting from norbornadiene (S,S)-**257**. Hayashi-type hydrosilylation of norbornadiene (S,S)-**257** and subsequent Tamao-Fleming oxidation using KHF_2 and urea $\cdot\text{H}_2\text{O}_2$ generated diol (S,R,S,R)-**258** in 46% yield. Subsequent Swern oxidation gave ketone (S,S)-**259** in 61% yield. Finally, reductive amination using $\text{Ti}(\text{O}i\text{-Pr})_4$ and H_2 and Pd / C produced amine (S,S,S,S)-**253** in 72% yield (Scheme 3.15).

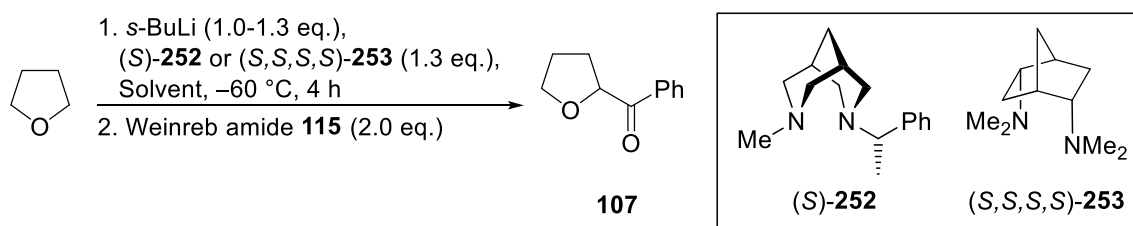
The optical rotation of ligands (S)-**252** and (S,S,S,S)-**253** and of the (+)-sparteine surrogate matched the reported literature values.^{146, 150} Determination of the er of the ligands by CSP-HPLC was not attempted.



Scheme 3.15 Synthesis of Diamine (S,S,S,S)-253.

Diamines (S)-252 and (S,S,S,S)-253 were then used in different experiments for the asymmetric deprotonation of THF and trapping with Weinreb amide **115**. The disappointing results are summarised in Table 3.2.

Table 3.2: Asymmetric Lithiation-Trapping of THF. New Ligands.



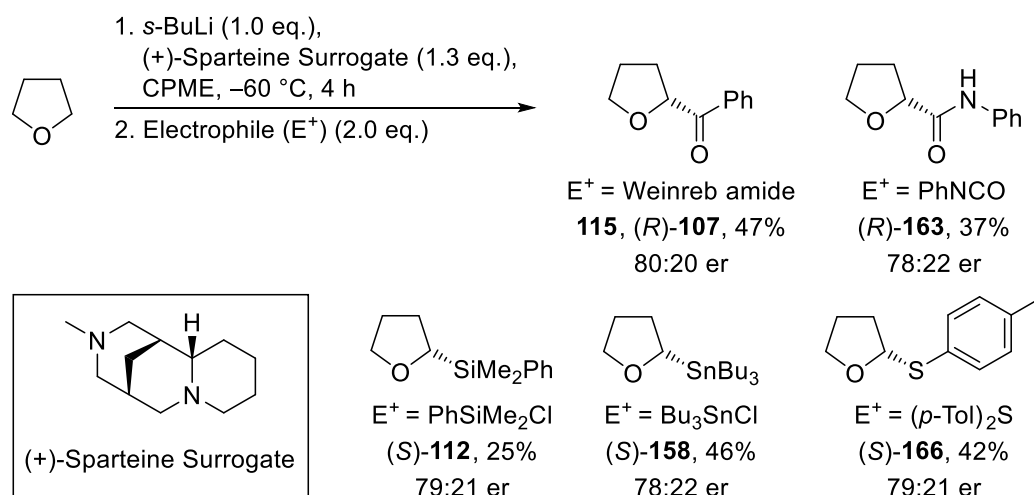
Entry	Ligand	s-BuLi (eq.)	Solvent	Yield 107/ % ^a	er ^b
1	(S)-252	1.0	THF ^c	0	n.d. ^d
2	(S)-252	1.3	CPME	0	n.d. ^d
3	(S,S,S,S)-253	1.0	THF ^c	31	50:50
4	(S,S,S,S)-253	1.3	CPME	0	n.d. ^d

^aYield after purification by column chromatography, ^ber determined by CSP-HPLC, ^cTHF as substrate and as solvent and yields based on the amount of s-BuLi added, ^der not determined.

Unfortunately, the s-BuLi complexes of both of the new ligands (S)-252 and (S,S,S,S)-253 seemed to be inactive in the asymmetric deprotonation of THF. Lithiation of THF using s-BuLi and ligand (S)-252 at -60 °C for 4 h and trapping with Weinreb amide **115** did not result in the formation of the desired ketone **107** (entry 1). Similarly, when CPME was used, no product was isolated (entry 2). Using ligand (S,S,S,S)-253 in the asymmetric deprotonation of THF as a substrate and as a solvent gave α -substituted THF **107** in 31%

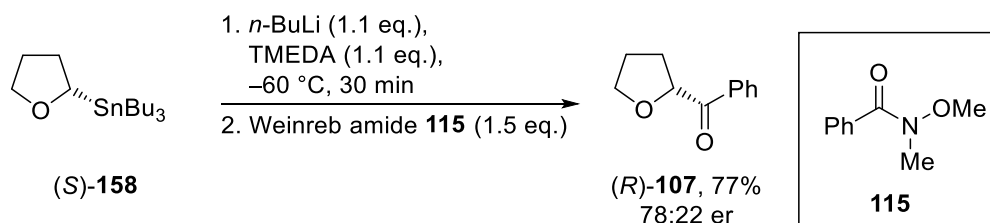
yield (entry 3). However, the product was racemic suggesting that the *s*-BuLi / ligand complex (if formed) is less reactive compared to the *s*-BuLi / THF complex. When CPME was used as a solvent with only a stoichiometric amount of THF, no product was isolated (entry 4).

Thus, the best asymmetric lithiation conditions involved the use of *s*-BuLi / (+)-sparteine surrogate in CPME at $-60\text{ }^{\circ}\text{C}$ for 4 h. Using these conditions, trapping with other electrophiles was investigated (Scheme 3.16). For example, lithiation and subsequent trapping with phenyl isocyanate gave amide (*R*)-**163** in 37% yield and 78:22 er (by CSP-HPLC). Trapping with PhSiMe₂Cl generated silane (*S*)-**112** in 25% yield and 79:21 er (by CSP-HPLC). Use of Bu₃SnCl as the electrophile gave α -stannyl THF (*S*)-**158** in 46% yield and 78:22 er. In this case, the er was determined by CSP-HPLC of ketone (*R*)-**107**, synthesised via subsequent Sn-Li exchange using *n*-BuLi / TMEDA in CPME at $-60\text{ }^{\circ}\text{C}$ and trapping with Weinreb amide **115** (see Scheme 3.17). Finally, with (*p*-Tol)₂S, sulfide (*S*)-**166** was isolated in 42% yield and 79:21 er (by CSP-HPLC). In these five examples, the products were generated in similar ers (78:22-80:20 er), strongly supporting the asymmetric deprotonation mechanism. The stereochemistry of amide (*R*)-**163** was assigned by comparison of the optical rotation and the CSP-HPLC traces with an authentic sample of amide (*R*)-**163** synthesised by a Ni-catalysed amide bond forming reaction from the methyl ester, as reported by Newman et al.¹⁵² The stereochemistry for the other examples, including ketone (*R*)-**107**, was assigned by analogy.



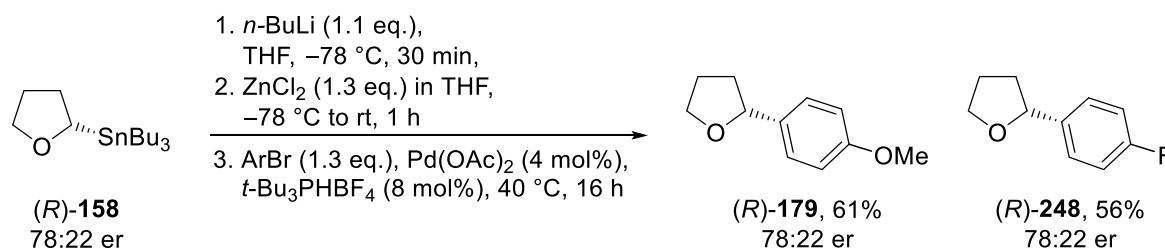
Scheme 3.16 Asymmetric Deprotonation of THF Using *s*-BuLi / (+)-Sparteine Surrogate in CPME and Trapping with Various Electrophiles.

The synthesis of stannane (*S*)-**158** enabled us to explore the configurational stability of the lithiated THF under the asymmetric lithiation conditions (Scheme 3.17). Sn-Li exchange using *n*-BuLi / TMEDA in CPME at $-60\text{ }^{\circ}\text{C}$ for 30 min and subsequent trapping with Weinreb amide **115** gave ketone (*R*)-**107** in 77% yield and 78:22 er which is a similar er to the other four examples (see Scheme 3.16). This allowed us to conclude that the lithiated species is configurationally stable in CPME at $-60\text{ }^{\circ}\text{C}$ for at least 30 min and the asymmetric deprotonation mechanism is operating.



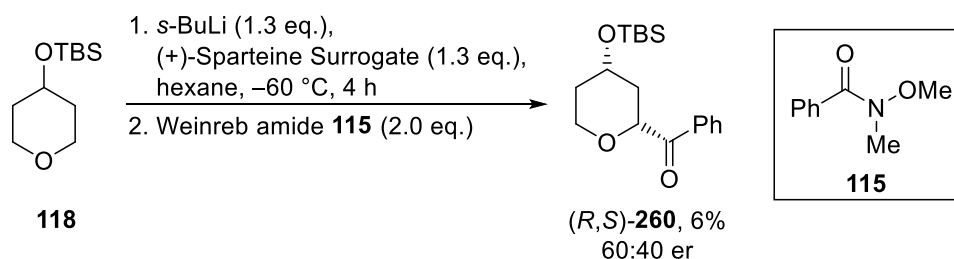
Scheme 3.17 Sn-Li Exchange of Enantioenriched α -Stannyl THF (*S*)-**158** and Trapping with Weinreb Amide **115**.

In addition to the Sn-Li exchange, stannane (*S*)-**158** (78:22 er) was also used as a substrate for the synthesis of α -arylated enantioenriched THFs using the Negishi approach described in chapter 2. Since it has already been shown that Sn-Li exchange, transmetalation and Negishi cross-coupling was stereospecific, it was expected that we could transfer the er of the stannane to the α -arylated THF. Thus, starting from stannane (*S*)-**158**, Sn-Li exchange with *n*-BuLi and transmetalation with ZnCl_2 gave the organozinc species which was subsequently cross-coupled with 4-bromoanisole using $\text{Pd}(\text{OAc})_2$ (4 mol%) and *t*- Bu_3PHBF_4 (8 mol%) to give α -arylated THF (*R*)-**179** in 61% yield and 78:22 er. In addition, Negishi cross-coupling with 4-fluorobromobenzene gave α -arylated THF (*R*)-**248** in 56% yield and 78:22 er. As well as showing that the overall process was stereospecific, these results also demonstrated that the lithiated THF was configurationally stable in THF at $-78\text{ }^{\circ}\text{C}$ for 30 min.



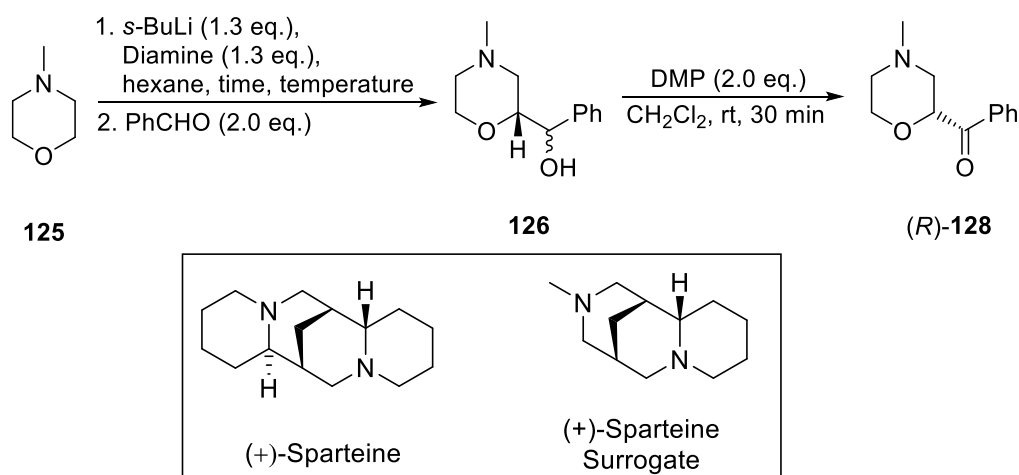
Scheme 3.18 Sn-Li Exchange of Enantioenriched α -Stannyl THF (*S*)-**158**, Transmetalation and Negishi Cross-Coupling with Aryl Bromides.

Having explored the synthesis of enantioenriched α -substituted THFs using asymmetric deprotonation, the asymmetric deprotonation of 4-OTBS-protected THP **118** was investigated. Lithiation-trapping of THP **118** was chosen as this is more easily lithiated than THP as shown by a competition experiment carried out by a co-worker.¹⁰⁷ For comparison reasons, similar reaction conditions as for THF were chosen: *s*-BuLi and (+)-sparteine surrogate in hexane at $-60\text{ }^{\circ}\text{C}$ for 4 h. Subsequent trapping with Weinreb amide **115** resulted in the formation of ketone (*R,S*)-**260** in only 6% yield and 60:40 er (Scheme 3.19). The er was determined using CSP-HPLC compared to a racemic standard. The major enantiomer is unknown but is shown in Scheme 3.19 by analogy with the THF result. The low yield is presumably a result of the low lithiation rate of THP **118** at $-60\text{ }^{\circ}\text{C}$. This is in accordance with the known slower lithiation of *N*-Boc piperidine **54** compared to *N*-Boc pyrrolidine **59**.⁷²



Scheme 3.19 Asymmetric Deprotonation of THP **118 Using *s*-BuLi / (+)-Sparteine Surrogate.**

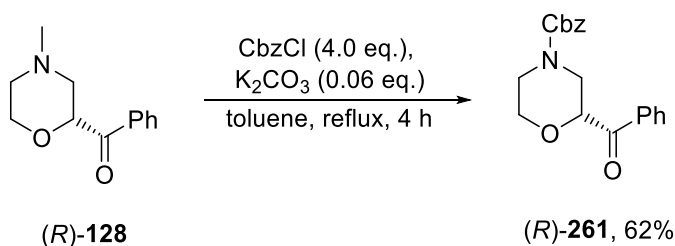
Finally, asymmetric deprotonation of *N*-methyl morpholine **125** using *s*-BuLi / (+)-sparteine surrogate in hexane at $-60\text{ }^{\circ}\text{C}$ and $-78\text{ }^{\circ}\text{C}$ was also explored. Since it has been shown that THF can be lithiated using *s*-BuLi / (+)-sparteine surrogate at $-60\text{ }^{\circ}\text{C}$ in a range of solvents and the racemic lithiation-trapping of *N*-methyl morpholine **125** was explored in hexane (see Table 3.1), it was decided to use hexane as the solvent. In this case, the lithiated species was trapped with benzaldehyde and then the crude alcohols were oxidised using Dess-Martin periodinane (DMP) to give ketone (*R*)-**128**. The results are presented in Table 3.3. Lithiation using *s*-BuLi / (+)-sparteine surrogate in hexane at $-60\text{ }^{\circ}\text{C}$ for 4 h and subsequent trapping with benzaldehyde and oxidation using DMP gave ketone (*R*)-**128** in 53% yield (over both steps) and 63:37 er (entry 1). Due to this good yield in hexane, CPME was not explored. A lower temperature ($-78\text{ }^{\circ}\text{C}$) during the lithiation gave ketone (*R*)-**128** in lower (39%) yield and a slightly higher er (65:35 er) (entry 2).

Table 3.3: Asymmetric Lithiation-Trapping of *N*-Methyl Morpholine 125.


Entry	Diamine	Temperature / °C	Lithiation Time / h	Yield 128 / % ^a	er ^b
1	(+)-Sparteine Surrogate	−60	4	53	63:37
2	(+)-Sparteine Surrogate	−78	4	39	65:35
3	(+)-Sparteine	−60	4	traces	n.d. ^c
4	(+)-Sparteine	−78	4	traces	n.d. ^c

^a Yield over two steps after purification by chromatography, ^ber determined by CSP-HPLC, ^cer not determined. For comparison, lithiation using *s*-BuLi / (+)-sparteine at −60 °C or −78 °C for 4 h followed by trapping with benzaldehyde and DMP oxidation only resulted in traces of ketone (*R*)-128 with an unspecified er (entries 3 and 4). The low yields confirm the known¹¹⁸ lower reactivity of the *s*-BuLi / (+)-sparteine complex compared to the *s*-BuLi / (+)-sparteine surrogate complex.

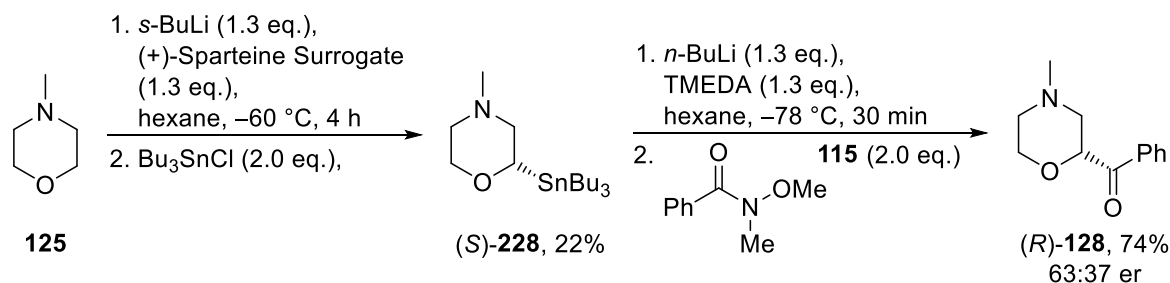
The stereochemistry of the major enantiomer of ketone (*R*)-128 was assigned in the following way. Ketone (*R*)-128 was converted into Cbz-protected ketone (*R*)-261 in 62% yield by reaction with benzyl chloroformate (Scheme 3.20). Comparison of its optical rotation with the enantiomeric ketone (*S*)-261 synthesised from α -stannyl morpholine (*R*)-300 (see section 3.4) allowed the assignment of stereochemistry. This assignment of stereochemistry of ketone (*R*)-261 was also consistent with the same sense of induction obtained in the previously described lithiation of THF using *s*-BuLi / (+)-sparteine surrogate.



Scheme 3.20 Synthesis of Cbz-Protected Ketone (*R*)-**261**.

In similar way to THF, it was decided to prepare a sample of an enantioenriched α -stannyl morpholine (*S*)-**228** and use it to study the configurational stability of the lithiated morpholine at different temperatures. Thus, enantioenriched stannane (*S*)-**228** was synthesised *via* lithiation of *N*-methyl morpholine **125** with *s*-BuLi / (+)-sparteine surrogate at -60 °C for 4 h and trapping with Bu_3SnCl .

The direct determination of the er of α -stannyl morpholine (*S*)-**228** was not possible using CSP-HPLC. Therefore, Sn-Li exchange was performed with *n*-BuLi and TMEDA in hexane at -78 °C for 30 min to recreate the lithiated intermediate. Subsequent trapping with Weinreb amide **115** gave ketone (*R*)-**128** in 74% and 63:37 er (Scheme 3.21), which is the same er, obtained by benzaldehyde trapping and DMP oxidation (see Table 3.3, entry 1). Therefore, it was proposed that lithiated *N*-methyl morpholine is configurationally stable at -78 °C and α -stannyl morpholine (*S*)-**228** must also have been formed in 63:37 er.

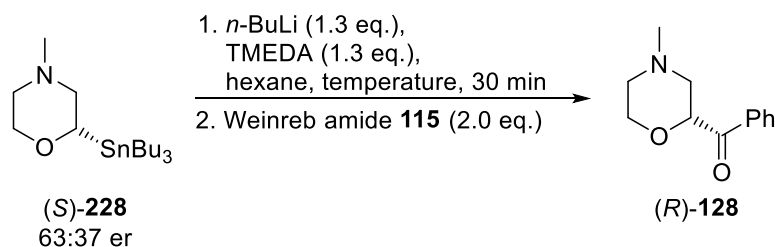


Scheme 3.21 Synthesis of Enantioenriched α -Stannyl Morpholine (*S*)-**228** and Sn-Li Exchange and Trapping with Weinreb Amide **115**.

To investigate the configurational stability, starting from the enantioenriched α -stannyl morpholine (*S*)-**228**, Sn-Li exchange was performed using *n*-BuLi and TMEDA for 30 min at -20 and -40 °C and the lithiated species was subsequently trapped with Weinreb amide **115**. The results are shown in Table 3.4. Sn-Li exchange of α -stannyl morpholine (*S*)-**228** (63:37 er) at -20 °C for 30 min gave racemic ketone **128** (50:50 er) in 89% yield indicating that the lithiated species is configurationally unstable at -20 °C (entry 1). In contrast, performing the Sn-Li exchange at -40 °C generated ketone (*R*)-**128** in 83% yield and 61:39 er (entry 2), which is only slightly lower than the er of the starting stannane (determined by

Sn-Li exchange at $-78\text{ }^{\circ}\text{C}$, entry 3). Based on these results, the configurational instability of this system is assumed to occur between $-20\text{ }^{\circ}\text{C}$ and $-40\text{ }^{\circ}\text{C}$. This temperature range could be used to investigate future dynamic thermodynamic resolution reactions.

Table 3.4: Configurational Stability of the Lithiated Morpholine Species.



Entry	Temperature / $^{\circ}\text{C}$	Yield (<i>R</i>)-128 / % ^a	er ^b
1	-20	89	50:50
2	-40	83	61:39
3	-78	74	63:37

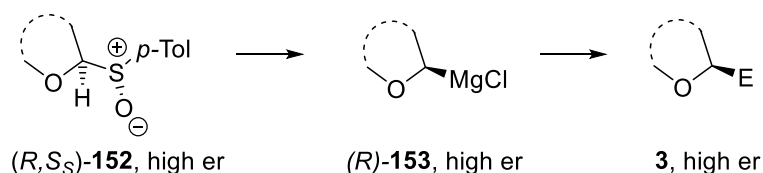
^a Yield after purification by chromatography, ^ber determined by CSP-HPLC.

In this section, the synthesis of enantioenriched α -substituted THF, THP and *N*-methyl morpholines *via* asymmetric deprotonation has been investigated. Among these heterocycles, the asymmetric deprotonation of THF and subsequent trapping with Weinreb amide **115** gave α -substituted ketone **107** in the highest er (80:20 er, 47% yield). For THP **260** (60:40 er) and *N*-methyl morpholine **128** (65:35 er), products with lower ers were obtained.

3.3 Synthesis of α -Substituted Enantioenriched Oxygen Heterocycles via Enantioenriched α -Sulfinyl Oxygen Heterocycles

3.3.1 Outline of the Strategy to Access Enantioenriched α -Sulfinyl Oxygen Heterocycles and Previous Work on α -Sulfinyl Heterocycles

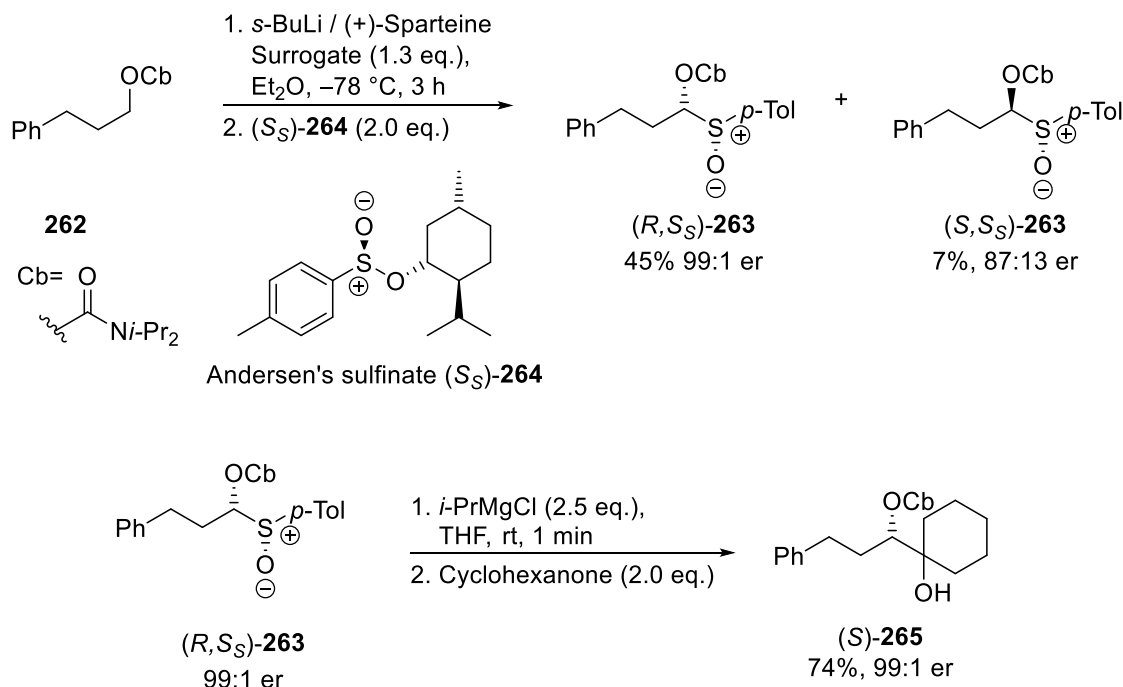
As outlined in the previous section, the best result obtained for the asymmetric deprotonation strategy was the *s*-BuLi / (+)-sparteine surrogate-mediated lithiation of THF and trapping with Weinreb amide **115** to give α -substituted THF **107** in 47% yield and 80:20 er. Since the yield and enantioselectivity were moderate, even with the most reactive *s*-BuLi / diamine complex, it seemed very challenging to try to improve on this result. Therefore, it was focussed on a new approach towards enantioenriched α -substituted saturated oxygen heterocycles *via* enantioenriched oxygen heterocycles containing an α -sulfoxide group such as (*R,S_S*)-**152**. If a synthesis of (*R,S_S*)-**152** in high er was possible, then (*R,S_S*)-**152** could be treated with *i*-PrMgCl to perform sulfoxide-Mg exchange to give the enantioenriched organomagnesium species **153**. The organomagnesium species (*R*)-**153** could subsequently be trapped with an electrophile to give α -substituted oxygen heterocycles **3** in high er (Scheme 3.22). This general strategy is one that the O'Brien group reported in 2013 for an *O*-alkyl carbamate and an *N*-Boc heterocycle and was recently expanded to alkyl-aryl esters by Aggarwal et al.^{117, 153}



Scheme 3.22 Proposed Sulfoxide-Mg Exchange of α -Sulfinyl Oxygen Heterocycles to Access Enantioenriched α -Substituted Oxygen Heterocycles.

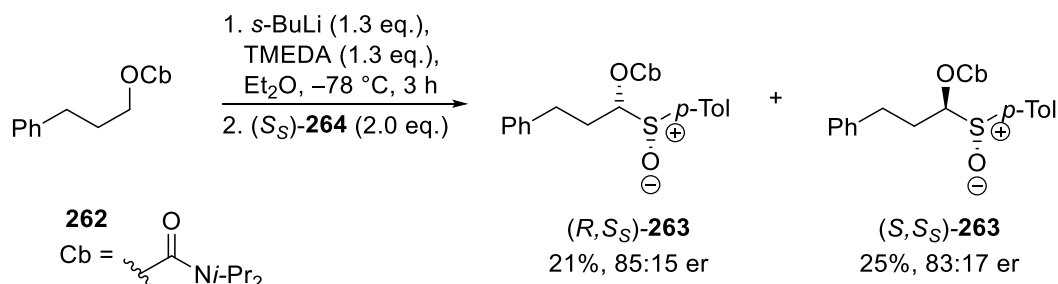
In pioneering work by the O'Brien group, a highly enantioenriched sulfoxide was synthesised as a precursor to α -functionalised *O*-alkyl carbamates.^{117, 153} In the first step, starting from carbamate **262**, enantioenriched α -alkoxy sulfoxides (*R,S_S*)-**263** and (*S,S_S*)-**263** were synthesised *via* asymmetric deprotonation using *s*-BuLi / (+)-sparteine surrogate and trapping with Andersen's sulfinate (*S_S*)-**264**¹¹⁶ in high dr (88:12) (Scheme 3.23). The major diastereomer (*R,S_S*)-**263** was isolated in 45% yield and 99:1 er and then used to generate an enantiopure Grignard reagent *via* sulfoxide-Mg exchange. Addition of *i*-PrMgCl in THF at rt for 1 min gave the organomagnesium species which was then reacted with electrophiles such as cyclohexanone to give α -substituted alcohol (*S*)-**265** in 74% yield and 99:1 er

(Scheme 3.23). Trapping was also explored with aldehydes and allyl bromide resulting in the corresponding alcohols and allyl derivative in high ers (99:1 er).



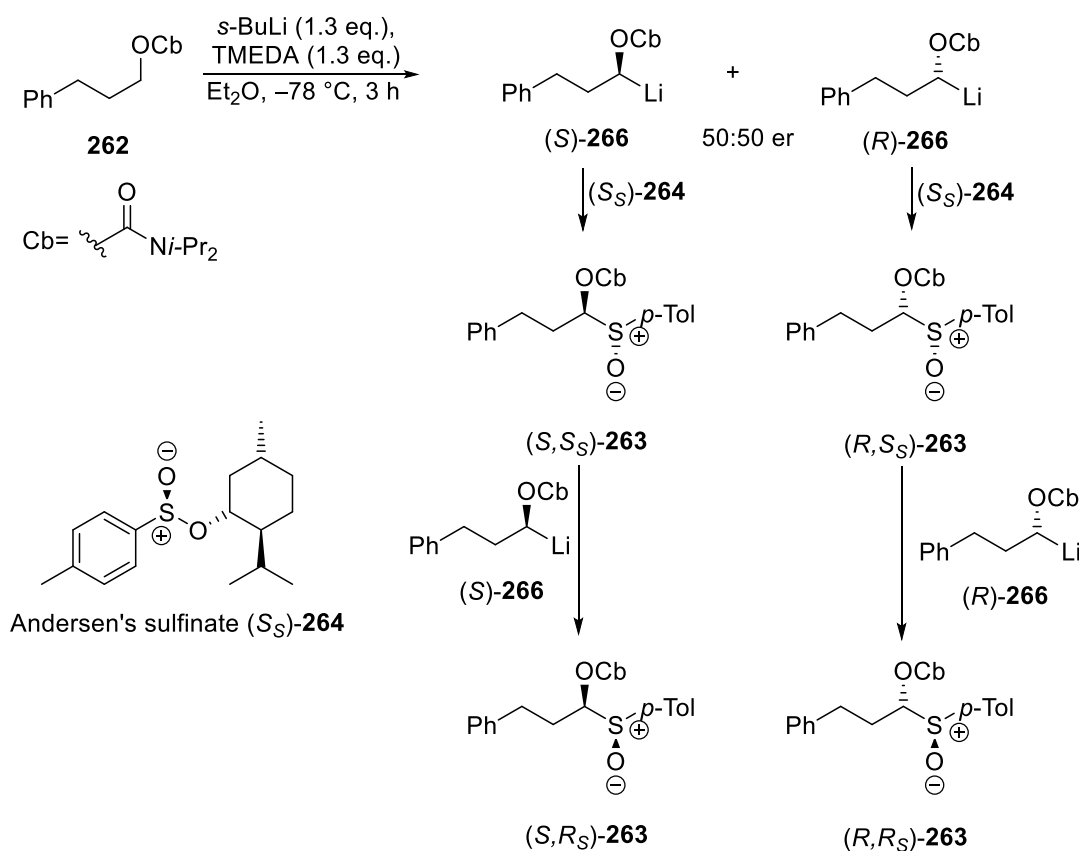
Scheme 3.23 Synthesis of Enantioenriched α -Substituted O-Alkyl Carbamates Using Enantioenriched Sulfoxides (R,S_S)-263** and (S,S_S)-**263**.**

Although it is well reported in the literature that lithiated species react with inversion of configuration at the sulfur atom in chiral sulfinates,¹⁵⁴ the O'Brien group found that racemic lithiation of carbamate **262** or *N*-Boc 4-chloro piperidine **266** and trapping with Andersen's sulfinate (S_S)-**264** resulted in a diastereomeric mixture of sulfoxides with only moderate er.^{117, 155} An example for the racemic lithiation of carbamate **262** and trapping with Andersen's sulfinate (S_S)-**264** is presented in Scheme 3.24. Lithiation of carbamate **262** using $s\text{-BuLi}$ / TMEDA and trapping with Andersen's sulfinate (S_S)-**264** gave sulfoxide (R,S_S)-**263** in 21% yield and 85:15 er and sulfoxide (S,S_S)-**263** in 25% yield and 83:17 er (Scheme 3.24).



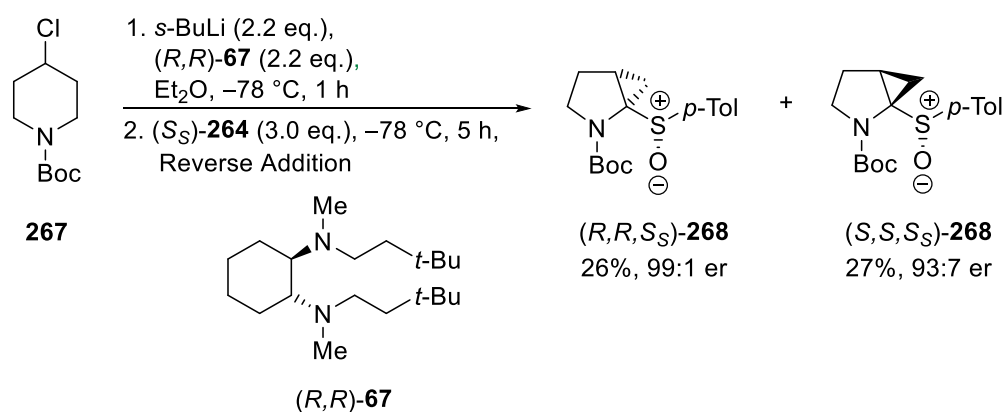
Scheme 3.24 Lithiation of Carbamates using $s\text{-BuLi}$ / TMEDA Leading to Moderate Enantiomeric Ratios.

It was assumed that the reduction in er compared to the enantiopure starting sulfinate (S_S)-**264** is a result of a competing double inversion pathway. Racemic lithiation of carbamate **262** would give a 50:50 ratio of lithiated species (S)-**266** and (R)-**266**. Subsequent trapping with Andersen's sulfinate (S_S)-**264** should result in the formation of (S,S_S)-**263** and in (R,S_S)-**263**. Any remaining lithiated species (S)-**265** and (R)-**265** could then perform a nucleophilic attack on the initially formed sulfoxides (S,S_S)-**263** and (R,S_S)-**263**. This addition would occur with inversion of configuration at the sulfur and ultimately lead to sulfoxides (S,R_S)-**263** and (R,R_S)-**263** respectively. As these are enantiomers of the sulfoxides initially formed during the trapping process, they therefore result in a lower er of the sulfoxides (S,S_S)-**263** and (R,S_S)-**263** (Scheme 3.25).¹⁵⁶ To reduce the amount of double inversion, the O'Brien group generated an enantioenriched lithiated species (R)-**266** or (S)-**266** using *s*-BuLi and a chiral diamine ((-)-sparteine or the (+)-sparteine surrogate) and then trapped with Andersen's sulfinate (S_S)-**264** at low temperature which gave the sulfoxides (S,S_S)-**263** and (R,S_S)-**263** in high er presumably due to chiral amplification as a result of the generated enantioenriched lithiated species.¹¹⁷



Scheme 3.25 Proposed Double Inversion Pathway.

A similar approach *via* asymmetric deprotonation and trapping with Andersen's sulfinate (S_S)-**264** to generate enantioenriched azabicyclo[3.1.0]-hexane sulfoxides (R,R,S_S)-**268** and (S,S,S_S)-**268** was also reported by the O'Brien group.¹¹⁷ Lithiation of *N*-Boc 4-chloro piperidine **267** using *s*-BuLi / diamine (R,R)-**67** at -78 °C and trapping with Andersen's sulfinate (S_S)-**264** gave (R,R,S_S)-**268** in 51% yield and 99:1 er and (S,S,S_S)-**268** in 25% yield and 93:7 er (Scheme 3.26). For comparison, lithiation of 4-chloro piperidine using *s*-BuLi / TMEDA and trapping with Andersen's sulfinate (S_S)-**264** gave sulfoxides (R,R,S_S)-**268** and (S,S,S_S)-**268** in lower ers (58:42 er and 70:30 er respectively). The low ers are presumably a result of the competing double inversion pathway as described previously in the racemic lithiation of carbamate **262** and trapping with Andersen's sulfinate (S_S)-**264** (see Scheme 3.25).

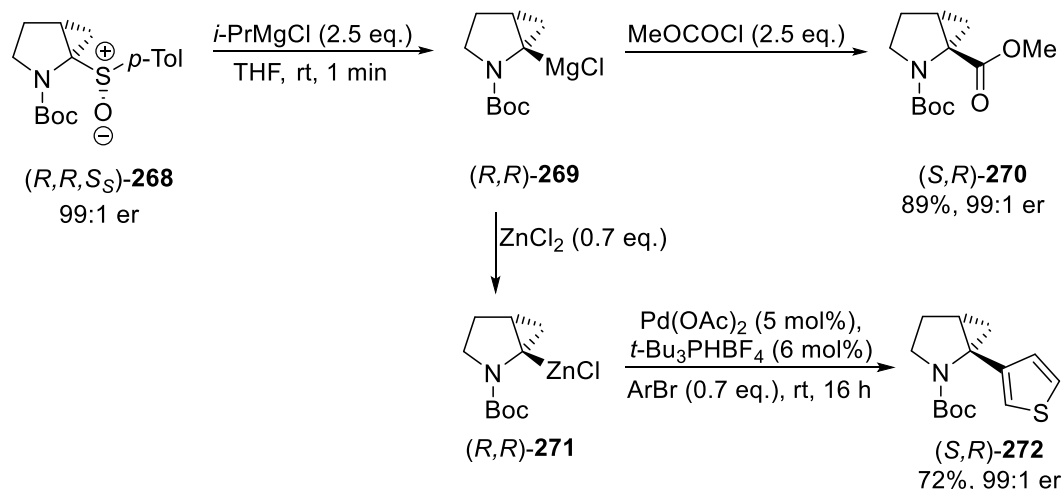


Scheme 3.26 Synthesis of Enantioenriched Azabicyclo[3.1.0]-hexane Sulfoxides (R,R,S_S)-**268** and (S,S,S_S)-**268**.

In the next step, sulfoxide (R,R,S_S)-**268** (99:1 er) was treated with *i*-PrMgCl at rt for 1 min to generate organomagnesium species (R,R)-**269** *via* sulfoxide-Mg exchange. Subsequent trapping with methyl chloroformate gave (S,R)-**270** in 89% yield and 99:1 er (Scheme 3.27). Alternatively, having generated the organomagnesium species (R,R)-**269**, addition of ZnCl_2 gave the organozinc species (R,R)-**271**, which was subsequently used in a Negishi cross-coupling using $\text{Pd}(\text{OAc})_2$, $t\text{-Bu}_3\text{PHBF}_4$ and 3-bromothiophene to give thiophene derivative (S,R)-**272** in 72% yield and 99:1 er (Scheme 3.27). A wide range of electrophiles and other examples of Negishi reactions was also described.

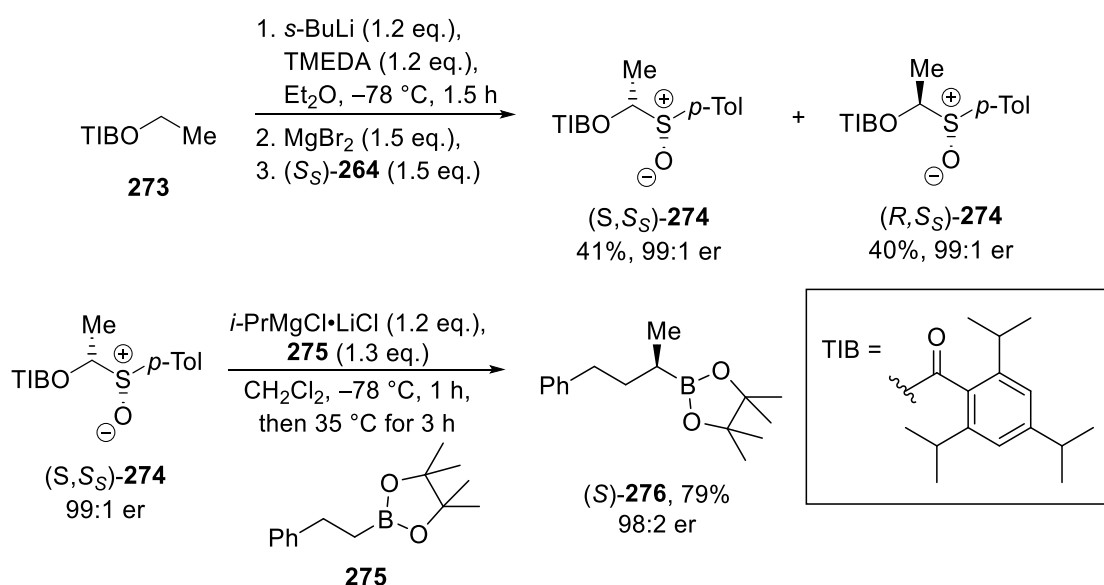
An important aspect for the transfer of the stereochemical information from the enantioenriched sulfoxide precursor to the final enantioenriched product is the configurational stability of the synthesised enantioenriched sulfoxide precursors and

organomagnesium species. In addition, the results showed the stereospecificity of the sulfoxide-Mg exchange and of the trapping process with the electrophile.



Scheme 3.27 Sulfoxide-Mg Exchange of Sulfoxide **(R,R,S_S)-268** and Trapping or Transmetalation and Negishi Cross-Coupling.

Recently, Aggarwal et al. reported the synthesis of enantioenriched boronic esters using α -sulfinyl benzoates **(S,S_S)-274** and **(R,S_S)-274** as precursors.¹⁵³ For example, starting from a sterically hindered TIB ester **273**, racemic lithiation using *s*-BuLi / TMEDA in Et₂O at -78 °C for 1.5 h gave the lithiated species which was then transmetalated using MgBr₂ to give the organomagnesium species. Subsequent addition of Andersen's sulfinates (**S_S)-264**) gave highly enantioenriched α -sulfinyl benzoates in 99:1 er. α -Sulfinyl benzoate **(S,S_S)-274** was isolated in 41% yield and **(R,S_S)-274** was isolated in 40% yield.



Scheme 3.28 Synthesis of α -Sulfinyl Benzoates **(S,S_S)-274** and **(R,S_S)-274** and Subsequent Sulfoxide-Mg Exchange and Addition of Boronic Ester **275**.

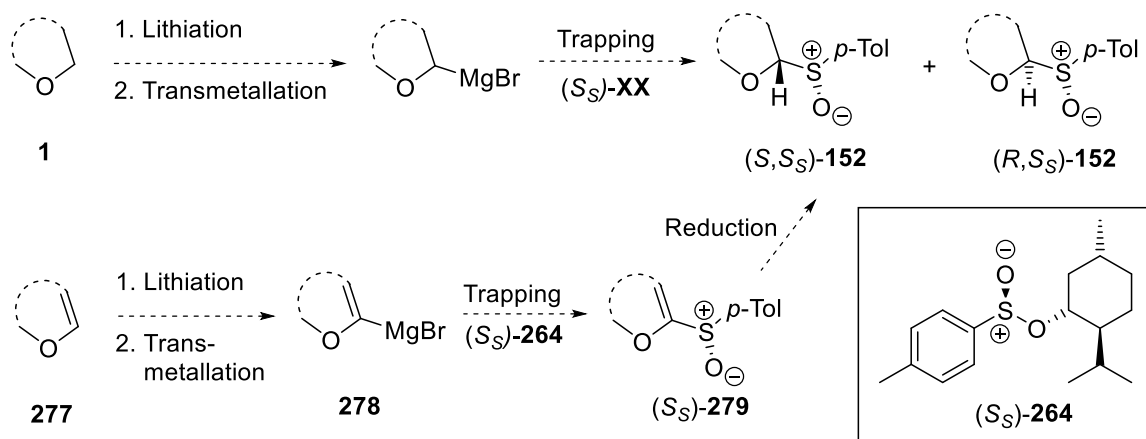
The analogous reaction without Li-Mg exchange gave the sulfoxides in lower yields and er. For example, lithiation of TIB ester **273** and subsequent trapping with Andersen's sulfinate (S_S)-**264** gave α -Sulfinyl benzoates (S,S_S)-**274** in 22% yield (88:12 er) and (R,S_S)-**274** in 25% yield (87:13 er). Clearly, the transmetallation of the organolithium species to the organomagnesium species tempered the nucleophilicity and enabled the trapping with Andersen's sulfinate (S_S)-**264** to occur but not the double-inversion pathway. Therefore, no reduction in er was observed. Treatment of sulfoxide (S,S_S)-**274** with *i*-PrMgCl·LiCl in CH₂Cl₂ at -78 °C to perform the sulfoxide-Mg exchange and trapping with pinacol boronic ester **275** gave boronic ester (S)-**276** in 79% yield and 98:2 er (Scheme 3.26).

The previous results by the O'Brien group and by Aggarwal et al. show that the use of chiral α -sulfinyl heterocycles generated from Andersen's sulfinate allow the synthesis of highly enantioenriched α -substituted carbamates and esters. The main challenge is the generation of the α -sulfinyl heterocycles in high ers. To avoid lower ers, the lithiation of the substrates can be carried out using *s*-BuLi and a chiral diamine or racemic lithiation and then transmetallation of the lithiated species to an organomagnesium species before trapping with Andersen's sulfinate (S_S)-**264**.

Based on this literature precedent, it was considered if the use of enantioenriched α -sulfinyl oxygen heterocycles would allow the synthesis of highly enantioenriched α -substituted saturated oxygen heterocycles such as α -substituted THF, THP and *N*-methyl morpholine derivatives. It was considered two different strategies which are outlined in Scheme 3.29. In the first approach, a direct lithiation of THF, THP or *N*-methyl morpholine **125** would be carried out and the transmetallation and trapping conditions reported by Aggarwal et al. would then be adapted. Transmetallation with MgBr₂ would be carried out at -78 °C and the organomagnesium species would then be trapped with Andersen's sulfinate (S_S)-**264** at -78 °C and the mixture would then be warmed up to rt. This would hopefully result in a diastereomeric mixture of α -substituted THF, THP or *N*-methyl morpholines (S,S_S)-**152** / (R,S_S)-**152** in high er which could hopefully be separated using chromatography.

At the time that this work was initiated, direct lithiation of THF and THP gave products in low yields (for previous lithiation conditions, see Scheme 1.61 and Scheme 1.63) and therefore a second approach was also considered. It was planned to start from the unsaturated dihydrofuran (DHF) or dihydropyran (DHP) derivatives **277** then lithiation at the vinylic position would give the lithiated species; transmetallation using MgBr₂ would then generate vinylic organomagnesium species **278**. The transmetallation was assumed to be important

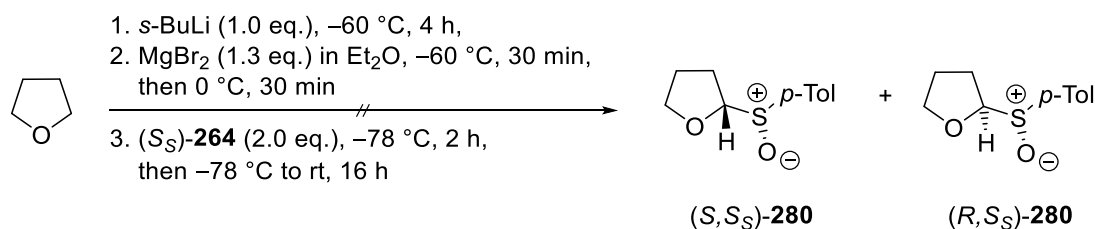
for the retention in configuration in the subsequent trapping with Andersen's sulfinate (S_S)-**264** to give α -sulfinyl-substituted oxygen heterocycles (S_S)-**279** in high er. Reduction of the unsaturated ring systems should then result in a diastereomeric mixture of α -substituted THF and THP derivatives (S,S_S)-**152** / (R,S_S)-**152** in high er, which could hopefully be separable. With access to sulfoxides (S,S_S)-**152** and (R,S_S)-**152**, the sulfoxide-Mg exchange and trapping could be explored to give the enantioenriched THF, THP and *N*-methyl morpholine derivatives.



Scheme 3.29 Strategy for the Synthesis of α -Sulfinyl THFs and α -Sulfinyl THPs.

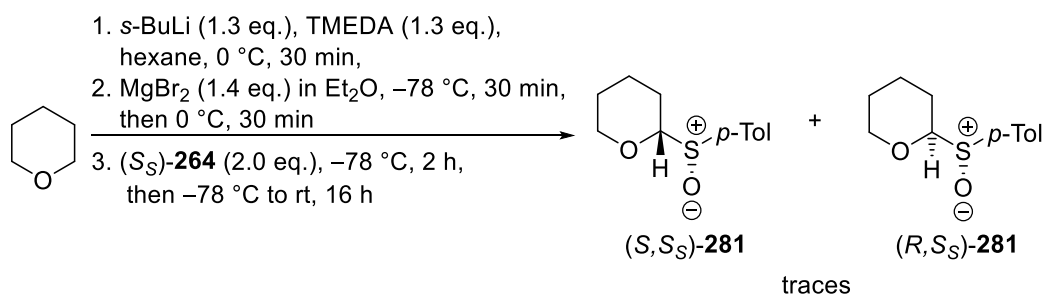
3.3.2 Attempted Synthesis of α -Sulfinyl THF and α -Sulfinyl THP

Initially, the synthesis of α -sulfinyl THFs was explored. At that time the best lithiation conditions for THF used THF as the substrate and as the solvent and *s*-BuLi at $-60\text{ }^{\circ}\text{C}$ for 4 h. After the lithiation, MgBr_2 would be added to the lithiated species at $-60\text{ }^{\circ}\text{C}$. Following the procedure by Aggarwal et al., the reaction mixture would be warmed to $0\text{ }^{\circ}\text{C}$ for 30 min to ensure complete transmetalation to the organomagnesium species. Addition of Andersen's sulfinate (S_S)-**264** would hopefully give α -sulfinyl THFs (S,S_S)-**280** / (R,S_S)-**280**. Unfortunately, lithiation, addition of a freshly prepared solution of MgBr_2 in Et_2O (made from Mg turnings and 1,2-dibromoethane in Et_2O) and subsequent trapping with Andersen's sulfinate (S_S)-**264** did not generate the desired α -sulfinyl THFs (S,S_S)-**280** and (R,S_S)-**280** and mainly Andersen's sulfinate (S_S)-**264** was recovered (Scheme 3.30).



Scheme 3.30 Attempted Synthesis of α -Sulfinyl THFs (S,S_S) -281 and (R,S_S) -281 Starting from THF.

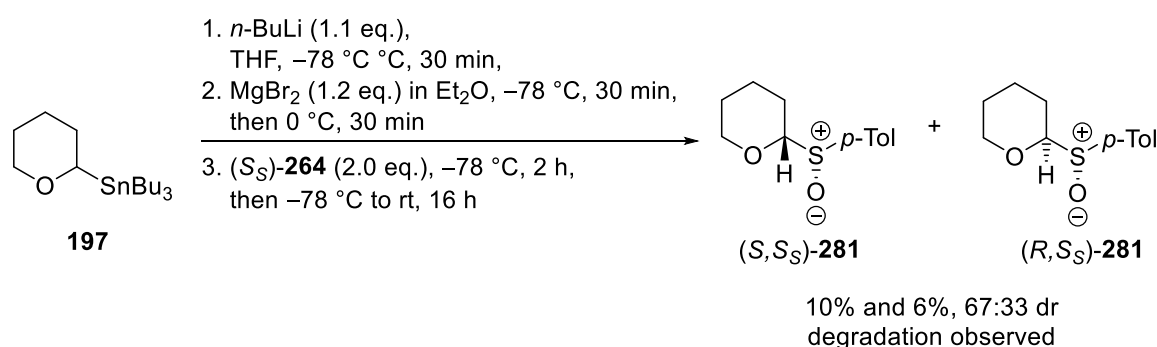
Next, the synthesis of α -sulfinyl THPs using direct lithiation under the previously developed lithiation conditions (*s*-BuLi / TMEDA in hexane at $0\text{ }^{\circ}\text{C}$ for 30 min) was explored. After cooling to $-78\text{ }^{\circ}\text{C}$, MgBr_2 was added and precipitation of a white solid was observed leading to insufficient stirring, probably as a result of insolubility of the organomagnesium species in hexane. Nevertheless, after 30 min at $0\text{ }^{\circ}\text{C}$, the mixture was cooled to $-78\text{ }^{\circ}\text{C}$ before addition of Andersen's sulfinate (S_S) -**264**. The reaction was left to warm up slowly over 16 h. Disappointingly, lithiation, transmetalation to the organomagnesium species and trapping using sulfinate (S_S) -**264** resulted in only traces of the desired α -sulfinyl THFs (S,S_S) -**281** and (R,S_S) -**281** (Scheme 3.31).



Scheme 3.31 Attempted Synthesis of α -Sulfinyl THPs (S,S_S) -281 and (R,S_S) -281 Starting from THP.

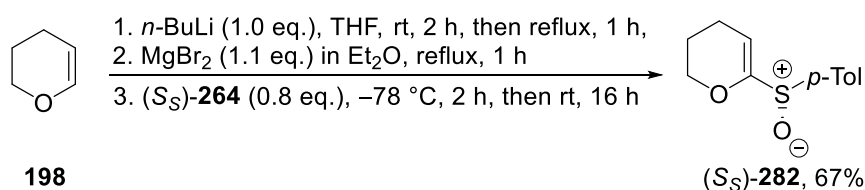
With the direct lithiation approach proving to be unsuccessful, it was decided to generate the lithiated THP from α -stannyl THP **197** using a reliable Sn-Li exchange in THF, as previously shown in section 2.2. Sn-Li exchange starting from α -stannyl THP **197** using *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ in THF gave the lithiated species. Addition of MgBr_2 generated the organomagnesium species which was soluble in THF and trapping was carried out with Andersen's sulfinate (S_S) -**264**. Fortunately, the formation of a diastereomeric mixture of (S,S_S) -**281** and (R,S_S) -**281** (65:35 dr by ^1H NMR spectroscopy of the crude product) could clearly be observed and the diastereomers could be separated using chromatography (Scheme 3.32). The major diastereomer was isolated in 10% yield and the minor diastereomer was isolated in 6% yield. For the α -proton of the major diastereomer, a signal at 4.22 ppm in the ^1H NMR spectrum was observed and showed ^3J coupling constants of 7.5

and 3.0 Hz. For the α -proton of the minor diastereomer a signal at 4.37 ppm in the ^1H NMR spectrum was observed and ^3J coupling values of 8.5 and 3.5 Hz were measured. After recording the ^1H NMR spectra of both α -sulfinyl THPs (*S,S*)-**281** and (*R,S*)-**281**, the last traces of solvent were removed under reduced pressure. Unfortunately, significant degradation of the product (which turned into a brown solid) was observed by subsequent ^1H NMR spectroscopy after 2 h. It was hypothesised that the sulfoxide group could be readily lost via α -elimination and oxonium formation. A similar fragmentation mechanism was proposed in the attempted synthesis of α -sulfinyl pyrrolidine and piperidine reported by the O'Brien group.¹⁵⁵



Scheme 3.32 Synthesis of α -Sulfinyl THPs (*S,S*)-281** and (*R,S*)-**281** Starting from α -Stannyl THP **197**.**

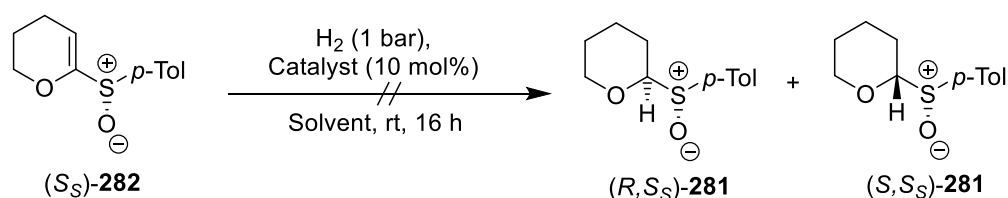
Parallel to the first route to the α -sulfinyl THFs and THPs, the synthesis of the α -sulfinyl THPs starting from DHP **198** was also explored. Montana and Grima have previously explored the lithiation of furan using *n*-BuLi in THF, transmetallation with MgBr_2 and trapping with Andersen's sulfinate (*S,S*)-**264** which gave α -sulfinyl furan in 78% yield.¹⁵⁷ The plan was to adapt these conditions to the lithiation-trapping of DHP with (*S,S*)-**264**. Based on the conditions reported by Montana and Grima, DHP **198** was lithiated using *n*-BuLi in THF at rt for 2 h and then at reflux for 1 h. Then a freshly prepared solution of MgBr_2 in Et_2O was added and the mixture was refluxed for 1 h. Trapping with (*S,S*)-**264** at $-78\text{ }^{\circ}\text{C}$ for 2 h and at rt for 16 h gave α -sulfinyl DHP (*S*)-**282** in 67% yield (Scheme 3.33). The er of (*S,S*)-**264** was not determined.



Scheme 3.33 Synthesis of α -Sulfinyl DHP (*S*)-282**.**

Next, reaction conditions for the reduction of α -sulfinyl DHP (S_S)-**282** were explored. There is no literature precedent for the alkene reduction in sulfoxide ethers such as α -sulfinyl DHP (S_S)-**282**. Lukevics et al. reported the use of Pd/alumina and H_2 for reduction of α -silyl-dihydropyrans, the closest substrate that could be found to (S_S)-**282**.¹⁵⁸ Thus, hydrogenation using Pd/alumina in MeOH and H_2 (1 bar) for 16 h was attempted. This gave only starting material (S_S)-**282** (Table 3.5, entry 1). Changing the solvent to EtOAc under the same conditions also resulted in the recovery of starting material (S_S)-**282** (entry 2). Hydrogenation in MeOH using Pd on alumina at 10 bar in MeOH at rt for 16 h gave only starting material (S_S)-**282** (entry 3). In a final attempt, use of Rh on alumina as a catalyst in EtOAc at rt for 16 h and 1 bar H_2 was similarly unsuccessful (entry 4).

Table 3.5 Investigation of Hydrogenation Conditions using Heterogenous Supported Metals.



Entry	Catalyst	Solvent	Pressure / bar	Yield (R,S_S)- 281 / %	Yield (S,S_S)- 281 / %
1	Pd/alumina	MeOH	1	0	0
2	Pd/alumina	EtOAc	1	0	0
3	Pd/alumina	MeOH	10	0	0
4	Rh/alumina	EtOAc	1	0	0

Further attempts for the alkene reduction of α -sulfinyl DHP (S_S)-**282** performed by another member of the O'Brien group were also unsuccessful.¹⁰⁷ For example, the use of Stryker's reagent as a hydride source and transfer hydrogenation using $Pd(OAc)_2/Et_3SiH$ gave only recovered starting material. Luche reduction gave a complex mixture (by ^1H NMR spectroscopy of the crude product) and no purification was attempted. Of course, some of the reduction reactions may have worked but the instability of the α -sulfinyl THP meant that they decomposed before isolation.

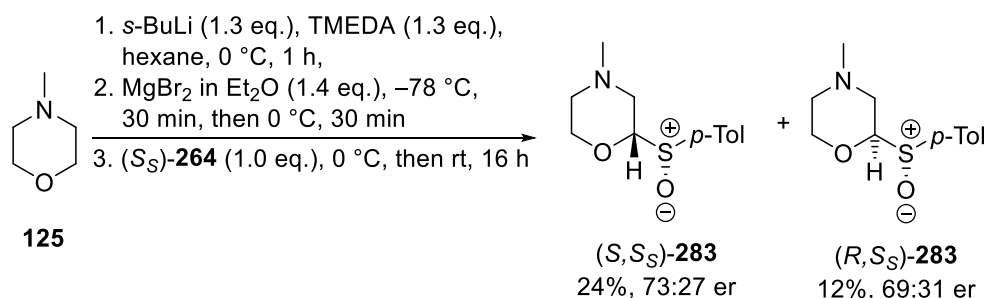
In summary, it was not possible to isolate the α -sulfinyl substituted THFs (S,S_S)-**280** and (R,S_S)-**280**. For THP only traces of the corresponding α -sulfinyl THPs (S,S_S)-**281** and (R,S_S)-**281** were isolated. Synthesis from α -stannyl THP **197** via Sn-Li exchange, transmetallation

and trapping with Andersen's sulfinatate (S_S)-**264** gave access to α -sulfinyl THPs (S,S_S)-**281** and (R,S_S)-**281** but they were unstable and sulfoxide-Mg exchange could not be explored.

3.3.3 Synthesis of α -Sulfinyl Morpholines

With little success with the synthesis of the α -sulfinyl THFs and THPs, the synthesis of α -sulfinyl morpholines (S,S_S)-**283** and (R,S_S)-**283** was attempted next. For the synthesis of the *N*-methyl morpholine derivatives the direct lithiation, transmetallation and trapping with Andersen's sulfinatate (S_S)-**264** was considered since the lithiation-trapping of *N*-methyl morpholine **125** proceeds in high yield (see Scheme 1.65).

Thus, lithiation of *N*-methyl morpholine **125** under standard conditions using *s*-BuLi and TMEDA (1.0 eq.) in hexane at 0 °C for 1 h gave the lithiated species. Transmetallation using MgBr₂ at -78 °C and subsequent trapping with Andersen's sulfinatate (S_S)-**264** initially at 0 °C and then at rt gave a mixture of two diastereomeric sulfoxides. Separation of the mixture by chromatography gave α -sulfinyl morpholine (S,S_S)-**283** in 24% yield (73:27 er) and α -sulfinyl morpholine (R,S_S)-**283** in 12% yield (69:31 er) (Scheme 3.34). The ers were determined by CSP-HPLC in comparison with racemic standards prepared *via* trapping with racemic Andersen's sulfinatate **264**. In contrast to the α -sulfinyl THPs, the two α -sulfinyl morpholines (S,S_S)-**283** and (R,S_S)-**283** were stable for at least a week. Given that the starting Andersen's sulfinatate (S_S)-**264** is of 99:1 er, the relatively low er of both diastereomers (S,S_S)-**283** and (R,S_S)-**283** is believed to be a result of some of the double inversion pathway occurring. It is suggested that the high temperature during the trapping process (0 °C, then rt) means that an amount of the corresponding enantiomers are generated *via* this pathway. Alternatively, α -elimination and regeneration of the α -sulfinyl morpholines could lead to the formation of (R,R_S)-**283** and (S,R_S)-**283** and reduce the er.



Scheme 3.34 Synthesis of α -Sulfinyl Morpholines (S,S_S)-**283** and (R,S_S)-**283**.

The configuration was assigned by an X-ray structure of (*S,S*)-**283** by a co-worker in the O'Brien group (Flack Parameter -0.06).¹⁰⁷ As shown in Figure 3.2, the X-ray structure of (*S,S*)-**283** showed that the sulfinyl substituent sits in the axial position, presumably due to the anomeric effect. This conformation also exists in solution as shown by the ^1H NMR spectrum of (*S,S*)-**283**. A signal at 4.22 ppm assigned to proton H_A adjacent to sulfur showed ^3J couplings of 3.0 Hz to the protons H_B and H_C . In the ^1H NMR spectrum of α -sulfinyl morpholine (*R,S*)-**283**, a signal for proton H_A adjacent to sulfur was observed at 4.37 ppm and showed $^3J_{\text{ax-eq}}$ and $^3J_{\text{eq-eq}}$ coupling of 5.0, 3.0 Hz to H_B and H_C respectively, indicating that H_A is equatorial and the sulfinyl substituent is axial.

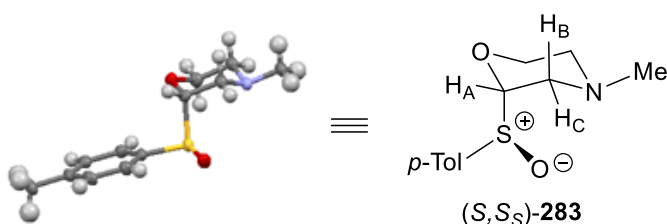


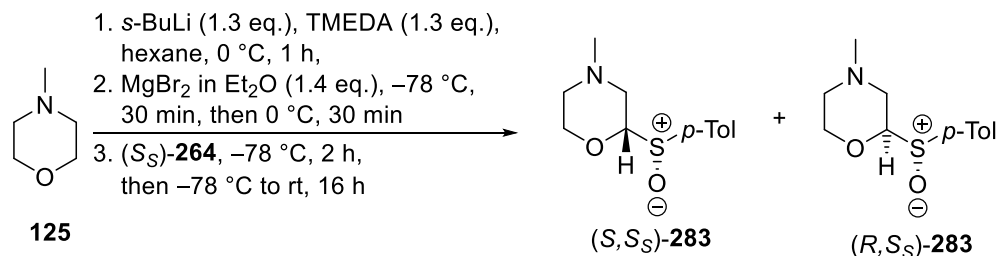
Figure 3.2: X-Ray Structure of Morpholine (*S,S*)-**283**.

To minimise or hopefully prevent the double-inversion pathway, changes to the reaction conditions were explored. For example, the amount of Andersen's sulfinate (*S*)-**264** was increased to 2.0 equivalents. Furthermore, it was decided to follow Aggarwal et al.'s procedure for the trapping of organomagnesium intermediate with Andersen's sulfinate (*S*)-**264** and carried out the initial trapping at low temperatures ($-78\text{ }^\circ\text{C}$) for 2 h before allowing the reaction mixture to warm to rt over 16 h.¹⁵³

Lithiation, transmetallation of *N*-methyl morpholine **125** and subsequent addition of an excess of the sulfinate (*S*)-**264** (2.0 eq.) to the organomagnesium species at $-78\text{ }^\circ\text{C}$ and stirring for 2 h at that temperature before warming up to rt gave an improved result. α -sulfinyl morpholine (*S,S*)-**283** was obtained in 32% yield and 87:13 er and α -sulfinyl morpholine (*R,S*)-**283** was isolated in 10% yield and 88:12 er (Table 3.6, entry 1). Encouragingly, both overall yield and the er of each α -sulfinyl morpholine improved but they were still lower than the 99:1 er obtained by Aggarwal et al. Reverse addition of the transmetallated organomagnesium species to an excess of the sulfinate (*S*)-**264** (2.0 eq.) at low temperature ($-78\text{ }^\circ\text{C}$) was also tried. In this case, α -sulfinyl morpholine (*S,S*)-**283** was isolated in 23% and 96:4 er and α -sulfinyl morpholine (*R,S*)-**283** was formed in 11% yield and 88:12 er (entry 2). Addition of Et_2O to the organomagnesium species in order to better solubilise it and reverse addition to Andersen's sulfinate (*S*)-**264** gave α -sulfinyl

morpholines (*S,S*)-**283** (39% yield, 95:5 er) and α -sulfinyl morpholine (*R,S*)-**283** (29% yield, 95:5 er) (entry 3).

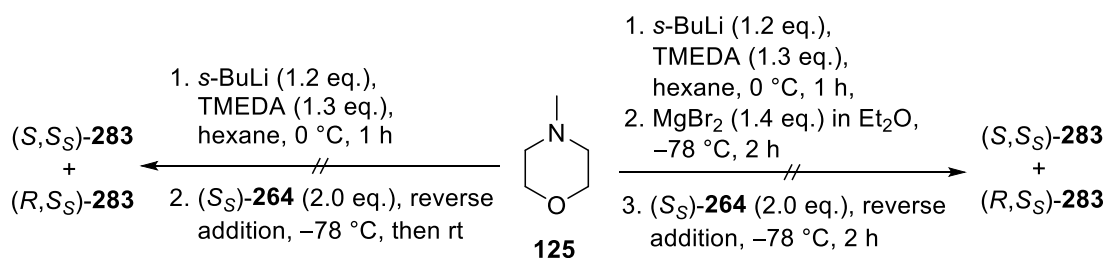
Table 3.6: Optimisation of the Lithiation of N-Me Morpholine **125 and Trapping with Andersen's Sulfinates (*S_S*)-**264**.**



Entry	(<i>S_S</i>)- 264 Addition	(<i>S_S</i>)- 264 / eq.	(<i>S,S</i>)- 283 ^{a,b}	(<i>R,S</i>)- 283 ^{a,b}
1	normal	1.0	32%, 87:13 er	10%, 88:12 er
2	reverse	2.0	23%, 96:4 er	11%, 88:12 er
3 ^c	reverse	2.0	39%, 95:5 er	29%, 95:5 er

^aYield after purification by column chromatography, ^ber determined by CSP-HPLC, ^caddition of Et₂O before addition of Andersen's sulfinates (*S_S*)-**264**.

Alongside these trapping reactions, control reactions were performed to obtain additional understanding of the trapping process using Andersen's sulfinates (*S_S*)-**264** (Scheme 3.35). Lithiation of *N*-methyl morpholine **125** under standard conditions (*s*-BuLi, TMEDA in hexane at 0 °C for 1 h) and direct trapping with sulfinates (*S_S*)-**264** without transmetallation to the organomagnesium species gave a complex mixture by ¹H NMR spectroscopy which did not contain the desired α -sulfinyl morpholines (*R,S*)-**283** and (*S,S*)-**283**. Trapping with sulfinates (*S_S*)-**264** at -78 °C without warming up to rt was also investigated. Lithiation of *N*-methyl morpholine **125** under standard conditions and transmetallation gave the organomagnesium species which was then trapped with sulfinates (*S_S*)-**264** at -78 °C and stirred at that temperature for 2 h before quenching with NH₄Cl_(aq). Unfortunately, only *N*-methyl morpholine **125** and sulfinates (*S_S*)-**283** were recovered from this experiment (Scheme 3.35). Clearly, transmetallation to the organomagnesium species and temperatures above -78 °C are needed for good yields of the α -sulfinyl morpholines.



Scheme 3.35 Attempted Synthesis of α -Sulfinyl Morpholines $(R,S_S)\text{-283}$ and $(S,S_S)\text{-283}$ without Mg Transmetallation and Attempted Trapping Process at Low Temperatures.

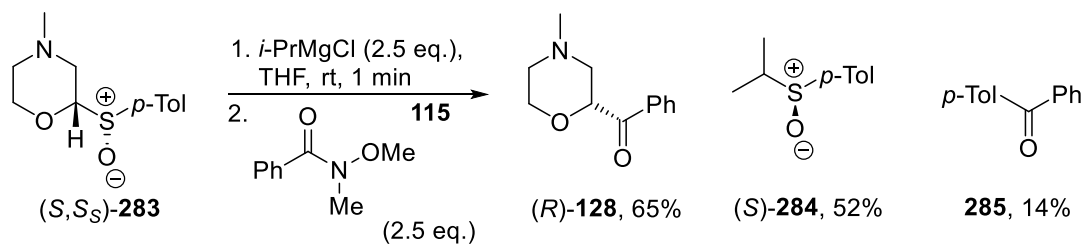
The lithiation of *N*-methyl morpholine **125**, transmetallation to an organomagnesium species and subsequent trapping with Andersen's sulfinate $(S_S)\text{-264}$ gave the desired α -sulfinyl morpholines $(R,S_S)\text{-283}$ in high *ers* and $(S,S_S)\text{-283}$ in moderate to high *ers* and they were separable using chromatography.

3.3.4 Sulfoxide-Mg Exchange and Trapping of α -Sulfinyl Morpholines

Having found a route to synthesise the α -sulfinyl morpholines in high *ers* (95:5-96:4 *er*), sulfoxide-Mg exchange and trapping with electrophiles was explored. To begin with, conditions for the sulfoxide-Mg exchange were investigated. α -Stannyl morpholine $(S,S_S)\text{-283}$ (96:4 *er*) was used as the starting material to attempt to generate the organomagnesium reagent using sulfoxide-Mg exchange. Subsequent trapping with an electrophile should then give the enantioenriched α -substituted *N*-methyl morpholine.

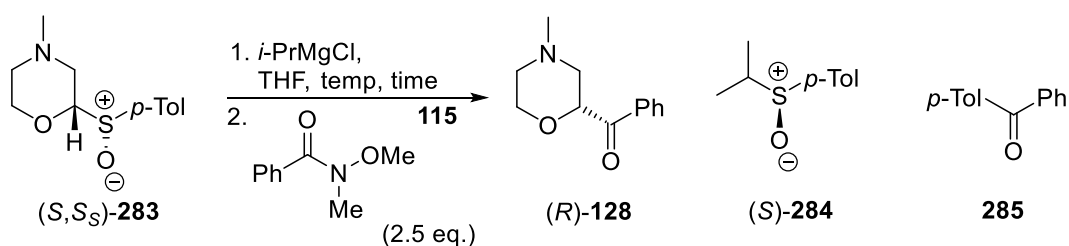
Initial reaction conditions for the sulfoxide-Mg exchange were adapted from the O'Brien group's synthesis of enantioenriched azabicyclo[3.1.0]hexanes (see Scheme 3.26).³⁸ The first attempt for the sulfoxide-Mg exchange used *i*-PrMgCl (2.5 eq.) in THF at rt for 1 min followed by trapping with Weinreb amide **115**. This resulted in the formation of the desired ketone $(R)\text{-128}$ in 65% yield. In addition, sulfoxide $(S)\text{-284}$ (52% yield) was formed as a by-product from the attack of *i*-PrMgCl at the sulfur atom of sulfoxide $(S,S_S)\text{-283}$. The optical rotation value of sulfoxide $(S)\text{-284}$ (in comparison with the literature) from a similar experiment (see Table 3.7, entry 3) confirmed that sulfoxide $(S)\text{-284}$ had formed. As there was initially more interest in the reactivity rather than the stereospecificity, the *ers* were not measured during the explorations of suitable conditions for the sulfoxide-Mg exchange. A small amount (14% yield) of ketone **285** was also isolated. Ketone **285** is formed as a by-

product of a different sulfoxide-Mg exchange whereby a tolyl Grignard reagent is formed and then this is trapped with Weinreb amide **115**.



Scheme 3.36 Sulfoxide-Mg Exchange of (S,S_S) -**283** at rt for 1 min and Trapping with Weinreb Amide **115**.

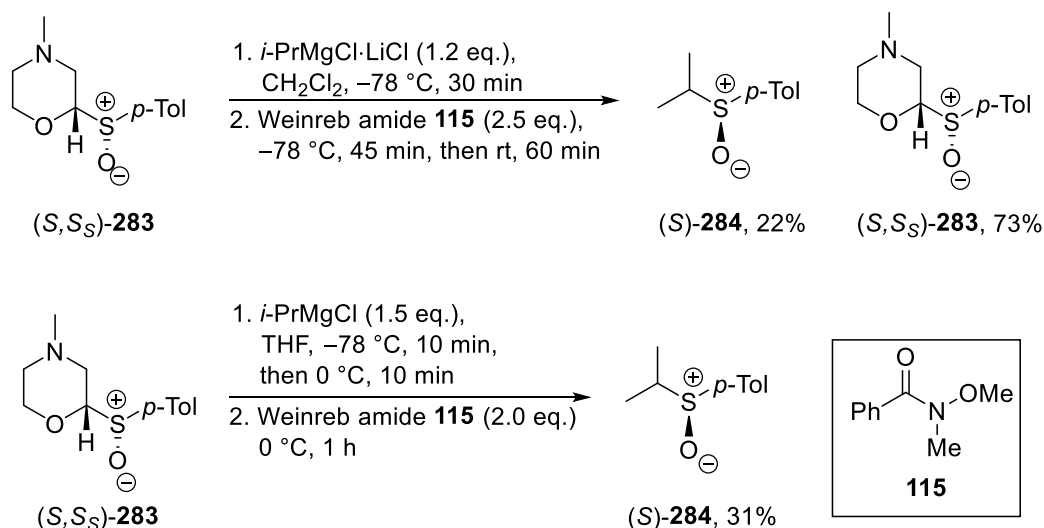
Further studies on the sulfoxide-Mg exchange are summarised in Table 3.7, with the previously described initial result in entry 1. Treatment of α -sulfinyl morpholine (S,S_S) -**283** with *i*-PrMgCl at 0 °C for 1 min and trapping with Weinreb amide **115** gave ketone (R) -**128** in 46% yield and sulfoxide (S) -**284** in 49% yield (entry 2). Increasing the reaction time of the sulfoxide-Mg exchange at rt to 5 min gave ketone (R) -**128** in 69% yield, sulfoxide (S) -**284** in 73% yield and ketone (R) -**128** in 16% yield (entry 3). When the same reaction was performed at 0 °C for 5 min ketone (R) -**128** (37% yield), sulfoxide (S) -**284** (70% yield) and ketone **285** (12% yield) were obtained (entry 4). When the equivalents of *i*-PrMgCl were reduced to 1.3 eq. in the sulfoxide-Mg exchange of (S,S_S) -**283** at rt and at 0 °C, ketone (R) -**128** was isolated in 29% yield (entry 5) and only in traces (entry 6) respectively.

Table 3.7: Optimisation of the Sulfoxide-Mg Exchange of (S,S_s)-**283**.


Entry	<i>i</i> -PrMgCl / eq.	Time / min	Temp. / °C	Yield of (R)- 128 / % ^{a,b}	Yield of (S)- 284 / % ^a	Yield of 285 / % ^a
1	2.5	1	rt	65	52	14
2	2.5	1	0	46	49	10
3	2.5	5	rt	69	73	16
4	2.5	5	0	37	70	12
5	1.3	5	rt	29	49	2
6	1.3	5	0	traces	41	13

^aYields after purification by chromatography, ^bers not determined.

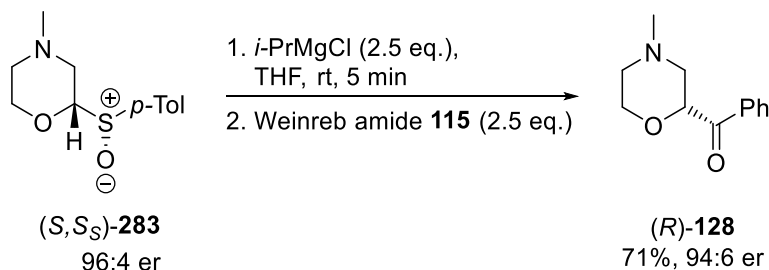
For comparison, conditions for sulfoxide-Mg exchange reported by Aggarwal and by Bull were also attempted. Aggarwal reported that treatment of TIB ester derived sulfoxides (S,S_s)-**273** with *i*-PrMgCl·LiCl in CH₂Cl₂ at −78 °C for 30 min generated an organomagnesium species which was subsequently trapped with various electrophiles (see Scheme 3.28).¹⁵³ Adapting their conditions, sulfoxide-Mg exchange of (S,S_s)-**283** using 1.5 eq. of *i*-PrMgCl·LiCl was carried out at −78 °C for 30 min and, after trapping, sulfoxide (S)-**284** was isolated in 22% yield with a 73% yield of recovered starting material (S,S_s)-**283** (Scheme 3.37). This suggests that the sulfoxide-Mg exchange of α -sulfinyl morpholine (S,S_s)-**283** with *i*-PrMgCl·LiCl at −78 °C is slow. Bull et al. explored the sulfoxide-Mg exchange of sulfinyl cyclopropanes, carrying out the sulfoxide-Mg exchange with *i*-PrMgCl (1.5 eq.) in THF at −78 °C for 10 min and then at 0 °C for 10 min before addition of the electrophile.¹⁵⁹ Use of these conditions in the sulfoxide-Mg exchange of α -sulfinyl morpholine (S,S_s)-**283** gave sulfoxide (S)-**284** in 31% yield (Scheme 3.37) but formation of ketone (R)-**128** was not observed, which is in accordance with our previous result (see Table 3.7, entry 6). Our overall conclusion was that the sulfoxide-Mg exchange of α -sulfinyl morpholine (S,S_s)-**283** is most efficient using an excess of *i*-PrMgCl (2.5 eq.) in THF at rt.



Scheme 3.37 Attempted Sulfoxide-Mg Exchange of (S,S_s)-283 Using Literature Conditions.

The conditions for the sulfoxide-Mg exchange using *i*-PrMgCl 2.5 eq. at rt for 5 min (Table 3.7, entry 3) gave the highest yield and were used to explore the scope of the reaction. Addition of *i*-PrMgCl to the enantioenriched α -sulfinyl morpholine (S,S_s)-**283** (96:4 er) at rt and subsequent trapping with Weinreb amide **115** gave the enantioenriched *N*-methyl morpholine ketone (*R*)-**128** in 71% yield and 94:6 er (by CSP-HPLC) (Scheme 3.38). The er after sulfoxide-Mg exchange and trapping is very similar to the er of the starting α -sulfinyl morpholine (S,S_s)-**283** and the reaction thus shows a high degree of stereospecificity.

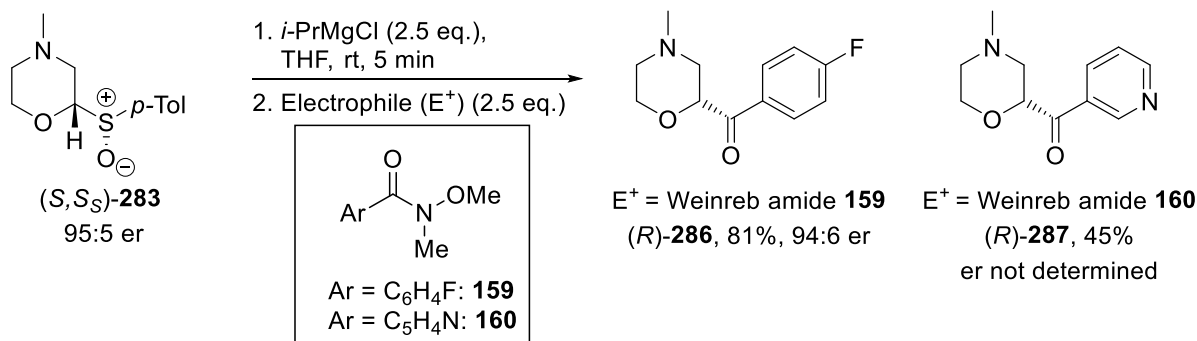
To determine the absolute configuration, the optical rotation of ketone (*R*)-**128** was compared with the optical rotation of the ketone synthesised *via* asymmetric deprotonation of *N*-methyl morpholine using (+)-*s*-BuLi / (+)-sparteine surrogate (see section 1.3.1). The retention of stereochemistry after sulfoxide-Mg exchange and subsequent trapping with electrophiles is well preceded in literature.^{117, 160-161}



Scheme 3.38 Sulfoxide-Mg Exchange of (S,S_s)-283 at rt for 5 min and Trapping with Weinreb Amide 115.

Further electrophiles were explored and the results are presented in Scheme 3.39. Sulfoxide-Mg exchange and addition of Weinreb amide **159** generated ketone (*R*)-**286** in 81% yield

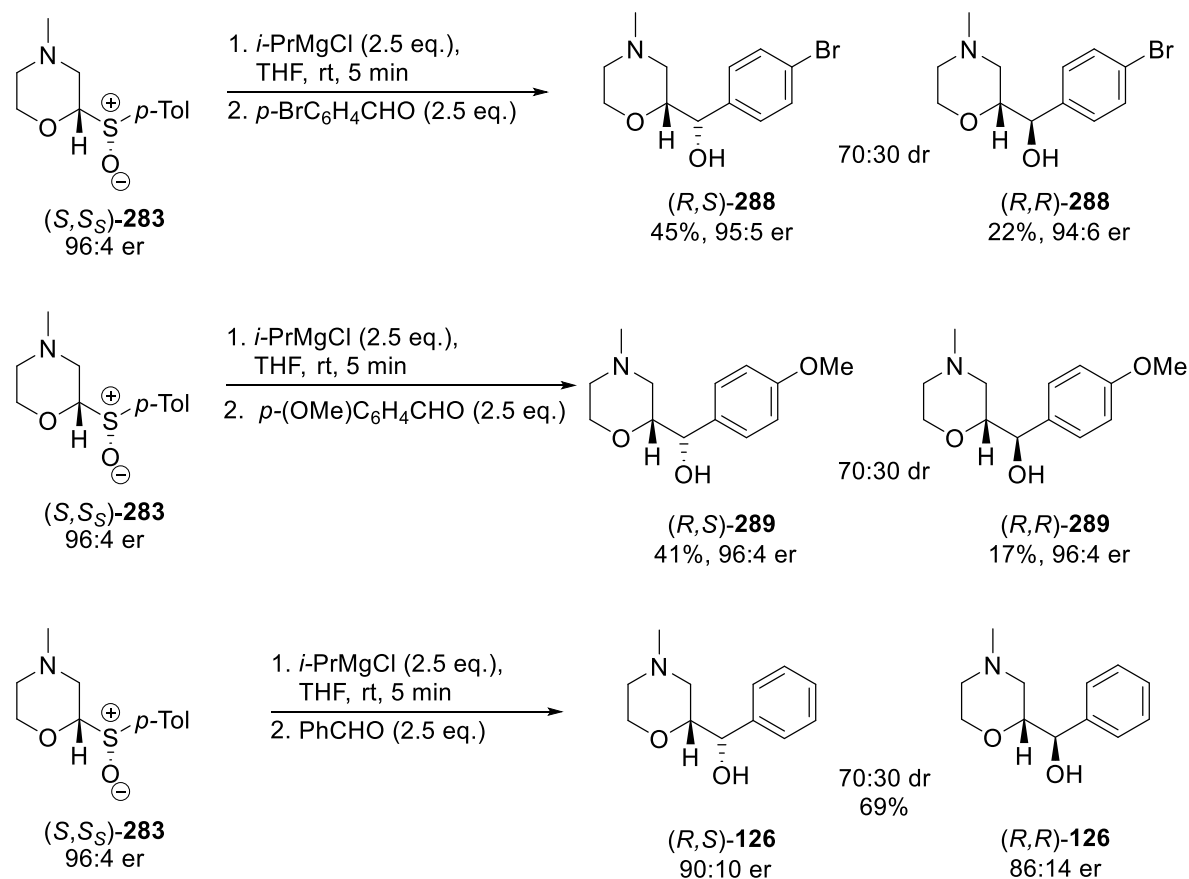
and 94:6 er. In addition, trapping with Weinreb amide **160** gave ketone (*R*)-**287** in 45% yield (er not determined). The stereochemistry for both examples was assigned by analogy with the previous example (Scheme 3.38).



Scheme 3.39 Sulfoxide-Mg Exchange of (*S,S*)-**283** and Trapping with Weinreb Amides.

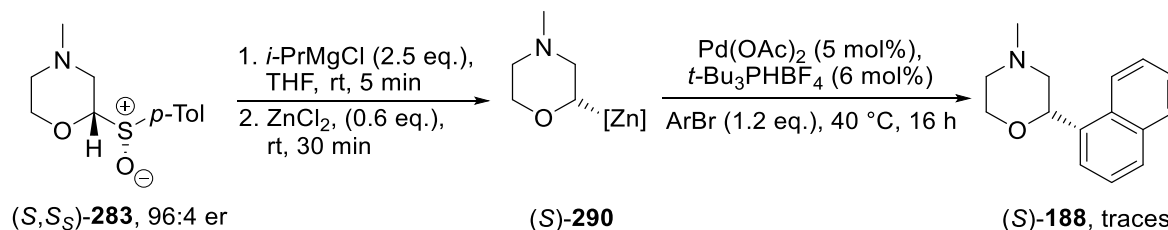
In addition to the trapping with Weinreb amides, the trapping with aldehydes was investigated (Scheme 3.40). Sulfoxide-Mg exchange of α -sulfinyl morpholine (*S,S*)-**283** (96:4 er) under the optimised conditions and trapping with 4-bromo benzaldehyde gave a 70:30 mixture of alcohols (*R,S*)-**288** and (*R,R*)-**288** which were isolated in 45% yield (95:5 er) and 22% yield (94:6 er) respectively. A similar result was obtained with 4-methoxy benzaldehyde, with the reaction giving alcohol (*R,S*)-**289** in 41% yield (96:4 er) and alcohol (*R,R*)-**289** in 17% yield (96:4 er). Both reactions showed a high stereospecificity and the er of the α -sulfinyl morpholine almost matched the ers of the products. Finally, sulfoxide-Mg exchange of α -sulfinyl morpholine (*S,S*)-**283** and subsequent addition of benzaldehyde gave a 70:30 mixture of alcohols (*R,S*)-**126** and (*R,R*)-**126** in 51% yield (90:10 er) and 18% yield (86:14 er) respectively. It is not obvious why benzaldehyde gave products with slightly lower ers. The relative stereochemistry of alcohols (*R,S*)-**126** and (*R,R*)-**126** was assigned by comparison of their ¹H NMR spectra with that of racemic alcohol (*R**,*S**)-**126** synthesised by a co-worker in the O'Brien group (and for which the relative stereochemistry was determined by X-ray crystallography).¹⁰⁶ The other two pairs of diastereomers (from the reactions with 4-bromobenzaldehyde and 4-methoxybenzaldehyde) were assigned by analogy since all three reactions showed the same 70:30 diastereoselectivity and similar trends in their ¹H NMR spectroscopic data. The absolute configuration was assigned by analogy with the previous examples, assuming that the sulfoxide-Mg exchange and trapping occurred with retention of stereochemistry. It is of note that the addition of the organomagnesium species to aldehydes showed some diastereoselectivity since the

corresponding reactions with the lithiated morpholine (to prepare racemic standards for CSP-HPLC) proceed with lower diastereoselectivity (55:45 dr).



Scheme 3.40 Sulfoxide-Mg Exchange of (S,S_S) -**283** and Trapping with Benzaldehydes.

For the synthesis of enantioenriched α -arylated morpholines, conditions based on those from the O'Brien group for the synthesis of azabicyclo[3.1.0]hexane analogues starting from sulfoxide pyrrolidine analogues were initially used (see Scheme 3.27).¹¹⁷ α -Sulfinyl morpholine (S,S_S) -**283** was treated with *i*-PrMgCl for sulfoxide-Mg exchange and then transmetallated using ZnCl₂ to give an organozinc species **290** which was reacted with Pd(OAc)₂ (5 mol%), *t*-Bu₃PHBF₄ (6 mol%) and 1-bromonaphthalene. Disappointingly, only traces of the desired α -aryl morpholine (S) -**188** were obtained (Scheme 3.41).



Scheme 3.41 Sulfoxide-Mg Exchange of (S,S_S) -**283**, Transmetallation and Attempted Negishi Cross Coupling.

Analysis of the ^1H NMR spectrum of the crude product revealed that sulfoxide-Mg exchange had occurred as shown by formation of *i*-Pr-tolyl sulfoxide (S)-**284**. However, the signals corresponding to isopropyl-substituted naphthalene could be identified. Therefore, it is assumed that the remaining *i*-PrMgCl was mainly transmetallated to an organozinc species and underwent Negishi cross-coupling with 1-bromonaphthalene. As only 0.6 eq. of 1-bromonaphthalene was used, the coupling with the *i*-Pr-zinc species could have outcompeted the coupling with the organozinc species **290** derived from the morpholine organomagnesium species. In any future experiments, increasing the amount of ArBr to 2.5 eq. should be explored.

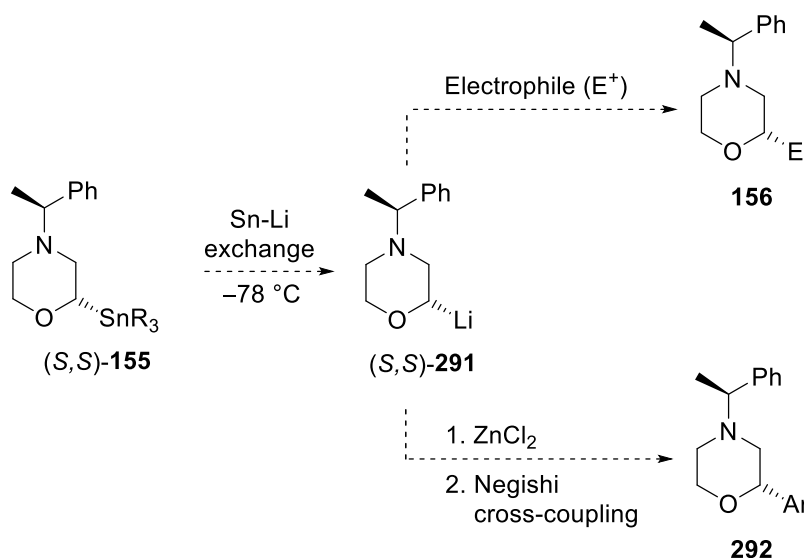
In summary, the synthesis of α -sulfinyl THF and THP was attempted *via* several different approaches. Unfortunately, the synthesis of α -sulfinyl THF was unsuccessful. α -Sulfinyl THP could be synthesised *via* Sn-Li exchange from α -stannyl THP **197** and subsequent trapping with Andersen's sulfinatate (S_S)-**264** but proved to be unstable and therefore it was not possible to study the subsequent sulfoxide-Mg exchange. For the synthesis of α -sulfinyl morpholines, lithiation, transmetallation to an organomagnesium species before trapping with Andersen's sulfinatate (S_S)-**264** was successful and gave α -sulfinyl morpholines (S,S_S)-**283** and (R,S_S)-**283** in up to 96:4 er. In addition, conditions for the sulfoxide-Mg exchange were explored. Good transmetallation was achieved using *i*-PrMgCl. Subsequent trapping with aldehydes and Weinreb amides resulted in the desired enantioenriched α -substituted morpholines in high yields and 86:14-95:5 er.

3.4 Synthesis of α -Substituted Enantioenriched Morpholines via Enantioenriched α -Stannyl Morpholines

3.4.1 Outline of the Strategy to Access Enantioenriched α -Stannyl Morpholines and Previous Work on Enantioenriched Stannanes as Synthetic Building Blocks

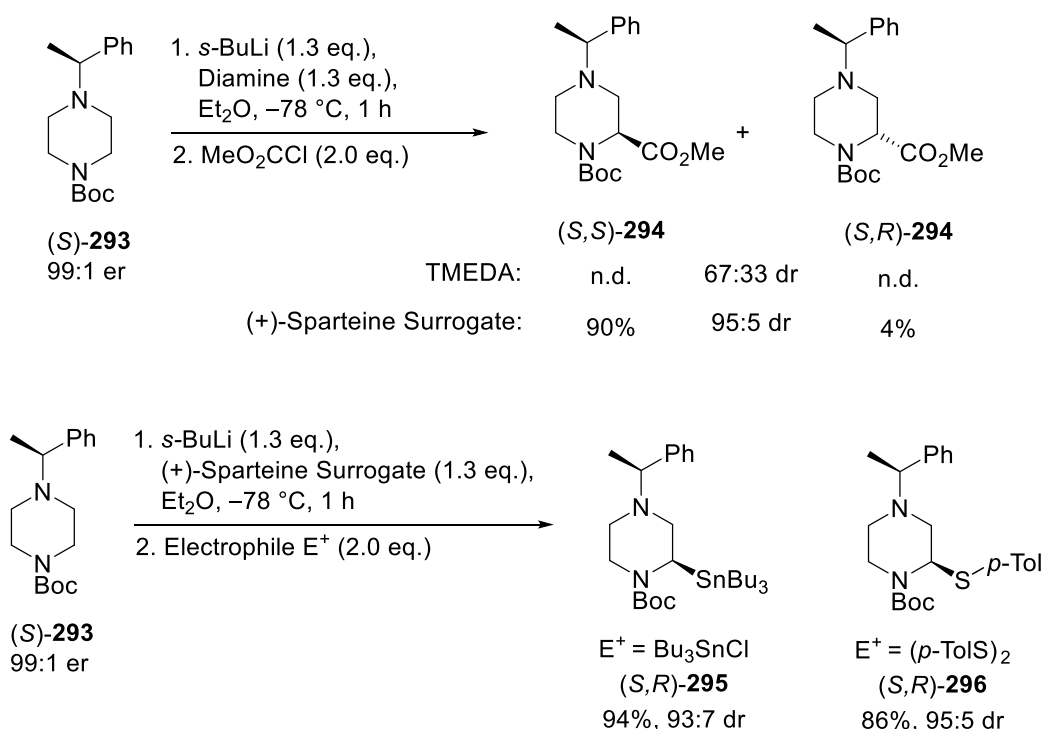
The synthesis of enantioenriched morpholines *via* α -sulfinyl morpholines had two major drawbacks. The synthesis of the sulfoxides did not allow *ers* higher than 96:4-95:5 *er*. In addition, attempts to install aryl substituents using sulfoxide-Mg exchange, transmetallation and Negishi cross-coupling were unsuccessful.

Therefore, there was interest in the synthesis of enantioenriched α -substituted morpholines using enantioenriched α -stannyl morpholines. If it was possible to synthesise stannane (S,S)-**155**, it was expected that stereospecific Sn-Li exchange at low temperatures would generate the lithiated species (S,S)-**291** which could then be trapped with various electrophiles to give α -substituted morpholines **156**. In addition, transmetallation to an organozinc species and subsequent Negishi cross-coupling should allow access to enantioenriched α -aryl morpholines **292**. For the Negishi reaction, it would be possible to use the previously developed Negishi cross-coupling conditions (see chapter 2). Based on the previous results in the synthesis of 2,4-*cis* and 2,6-*cis* configured THPs (see Scheme 1.67 and Scheme 1.68), it is established that Sn-Li exchange, transmetallation to an organozinc species and Negishi cross-coupling are stereospecific.



Scheme 3.42 Postulated Sn-Li Exchange of α -Methyl Benzyl Substituted Morpholine (S,S)-**155** and Electrophile Trapping or Transmetallation and Negishi Cross-Coupling.

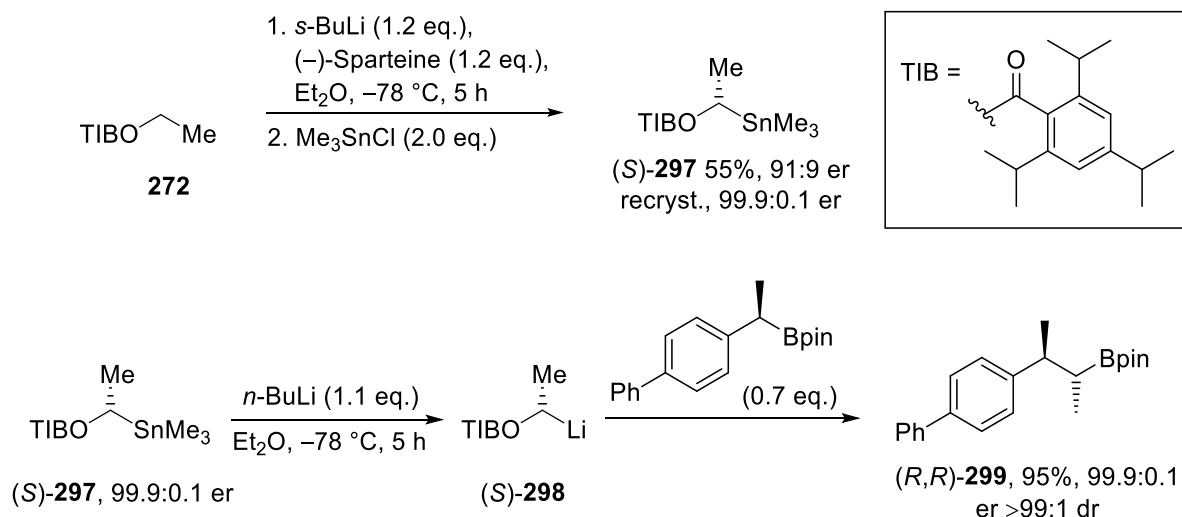
In 2016, a substrate-controlled diastereoselective deprotonation of an α -methylbenzyl-substituted *N*-Boc piperazine and subsequent trapping was reported by the O'Brien group.⁹⁰ In an initial result, deprotonation of *N*-Boc-*N'*- α -methylbenzyl-substituted piperazine (*S*)-**293** with *s*-BuLi / TMEDA at -78 °C for 1 h and trapping with MeO₂CCl gave a 67:33 mixture of diastereomeric piperazines (*S,S*)-**294** and (*S,R*)-**294**. Hence, the deprotonation process was substrate-controlled by the α -methylbenzyl group. Carrying out the deprotonation of piperazine (*S*)-**293** with *s*-BuLi / (+)-sparteine surrogate gave a 95:5 mixture of diastereomeric piperazines (*S,S*)-**294** (90% yield) and (*S,R*)-**294** (4% yield) (Scheme 3.43). The high diastereomeric ratio was the result of a matched case in which the α -methylbenzyl substituent and the *s*-BuLi / (+)-sparteine surrogate complex would favour the deprotonation of the pro-(*R*) proton. Further asymmetric deprotonation of piperazine (*S*)-**293** using *s*-BuLi / (+)-sparteine surrogate and trapping with Bu₃SnCl and (*p*-TolS)₂ led to the formation of (*S,R*)-**295** (94% yield, 93:7 dr) and (*S,R*)-**296** (86% yield, 95:5 dr) respectively (Scheme 3.43). Other examples were also explored.



Scheme 3.43 Diastereoselective Asymmetric Deprotonation of *N*-Boc-*N'*- α -Methylbenzyl-Substituted Piperazine (*S*)-293.

The synthesis and application of highly enantioenriched stannanes has been investigated by Aggarwal et al.¹⁶² The group reported the synthesis of stannyl ester (*S*)-**297** in high er. Alkyl TIB ester **272** was lithiated using *s*-BuLi / (–)-sparteine at -78 °C and then trapped with Me₃SnCl to give stannane (*S*)-**297** in 91:9 er (55% yield). The use of trimethylstannane

substituent was key as it was a crystalline solid and could be recrystallised to increase the er to 99.9:0.1. Stannane (S)-**297** was then treated with *n*-BuLi to carry out Sn-Li exchange resulting in the lithiated species (S)-**298** and subsequent reaction with a boronic ester gave homologated boronic ester (R,R)-**299** in 95% yield and 99.9:0.1 er (Scheme 3.44). In related work, Aggarwal et al. used stannane (S)-**297** in the total synthesis of the natural products (+)-kalkitoxin and (+)-hydroxyphthioceranic acid.¹⁶³

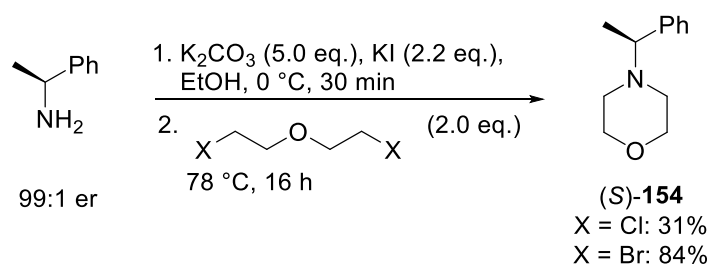


Scheme 3.44 Synthesis of Highly Enantioenriched Stannanes and Boronic Ester Homologation by Aggarwal.

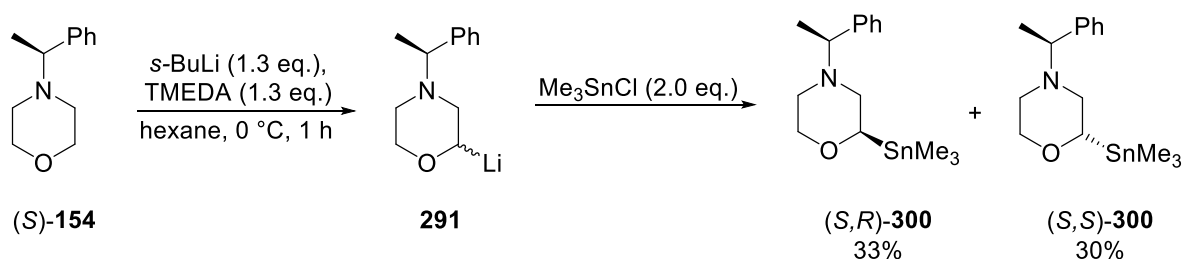
With the precedent for the substrate-controlled lithiation-trapping of *N*-Boc-*N'*- α -methylbenzyl-substituted piperazines and the stereospecific Sn-Li exchange of stannyl esters, our plan was to synthesise α -methylbenzyl-substituted α -stannyl morpholines and explore the Sn-Li exchange and subsequent trapping as well as the Negishi cross-coupling. This would provide a novel route to enantioenriched α -substituted morpholines.

3.4.2 Synthesis of Highly Enantioenriched Stannanes

To begin, the synthesis of the α -methylbenzyl-substituted morpholine and subsequent lithiation-trapping to give α -stannyl morpholines was investigated. The α -methylbenzyl-substituted morpholine (S)-**154** was synthesised using commercially available α -methylbenzylamine (99:1 er) and bis(2-chloroethyl)ether. This gave α -methyl benzyl-substituted morpholine (S)-**154** in 31% yield.¹⁰⁵ However, when bis(2-bromoethyl)-ether was used, the yield of (S)-**154** increased to 84% yield (Scheme 3.45).


 Scheme 3.45 Synthesis of α -Methylbenzyl Substituted Morpholine (S)-154.

With α -methylbenzyl morpholine (S)-154 in hand, the lithiation-trapping of (S)-154 was investigated (Scheme 3.46). Lithiation using *s*-BuLi / TMEDA, in hexane at 0 °C for 1 h gave the lithiated species **291** which was then trapped with Me₃SnCl. This gave a 50:50 mixture of diastereomeric α -stannyl morpholines (S,S)-**300** and (S,R)-**300** which were isolated in 33% and 30% yield respectively after chromatography. The trimethylstannanes were prepared since trapping with Bu₃SnCl led to two diastereomers which were not separable using chromatography. In comparison to the lithiation-trapping of α -methylbenzyl-substituted piperazine (S)-293 (see Scheme 3.43), no substrate control was observed probably due to the high temperature (0 °C) for the lithiation. However, the synthesis of α -stannyl morpholines (S,S)-**300** and (S,R)-**300** using *s*-BuLi / TMEDA allowed access to both diastereomers and on a gram-scale. The reaction shown in Scheme 3.46 was carried out using 1.91 g of α -methylbenzyl morpholine (S)-154 and gave stannanes (S,R)-**300** (1.13 g, 32%) and (S,S)-**300** (1.06 g, 29%). The ers of stannanes (S,R)-**300** and (S,S)-**300** could not be determined *via* CSP-HPLC but they were determined by CSP-HPLC of products obtained after Sn-Li exchange and trapping (see Scheme 3.49 and Scheme 3.50).


 Scheme 3.46 Lithiation of (S)-154 and Trapping with Me₃SnCl.

Starting from *rac*-154, lithiation (*s*-BuLi / TMEDA) and trapping with Me₃SnCl gave access to α -stannyl morpholines (S*,R*)-**300** and (S*,S*)-**300** in 33% and 36% yield respectively. These were used to synthesise racemic samples for the determination of the ers. To our surprise, stannane (S*,S*)-**300** was a crystalline solid (stannanes (S,S)-**300**, (S,R)-**300** and (S*,R*)-**300** were oils) and this allowed assignment of the relative stereochemistry using X-

ray crystallography (Figure 3.3). In the X-ray structure, the α -stannyl group was in the equatorial position. This is in contrast to the X-ray structure of α -sulfinyl morpholine (*S,S*)-**300** (see Figure 3.3), where the sulfoxide group was in the anomeric axial orientation.

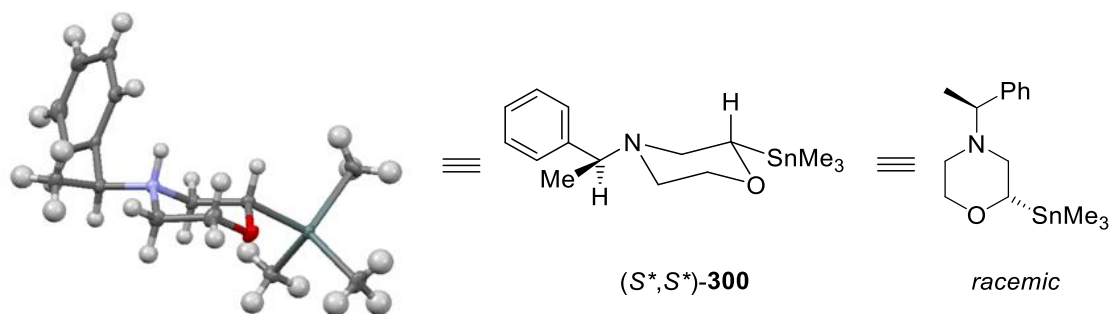
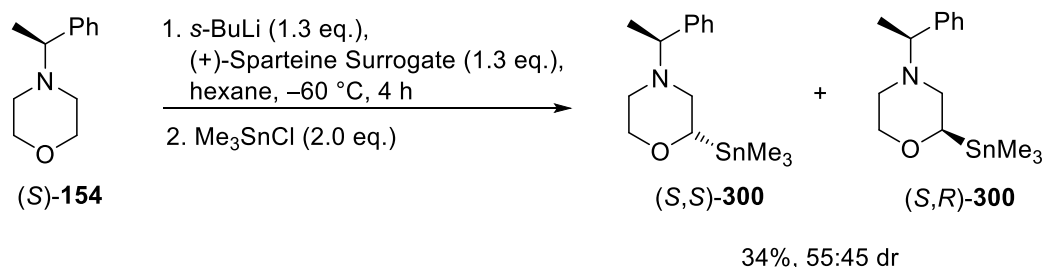


Figure 3.3: Relative Configuration of Stannyl Morpholine (*S*,S)-**300**.**

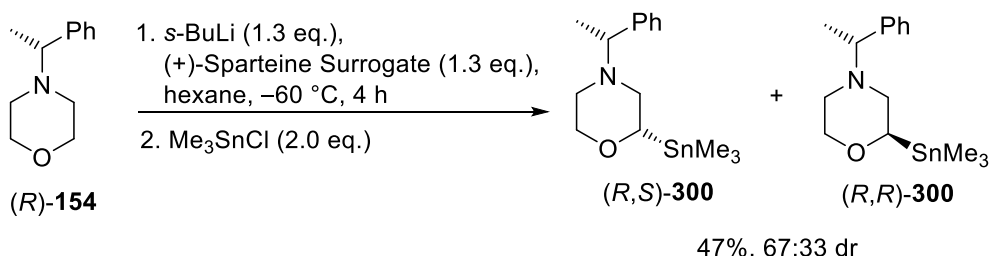
The lithiation of α -methylbenzyl morpholine (*S*)-**154** using *s*-BuLi and TMEDA at 0 °C for 1 h led to the formation of essentially equal amounts of stannanes (*S,R*)-**300** and (*S,S*)-**300** in 63% combined yield. Based on the results on the asymmetric deprotonation of *N*-methyl morpholine **125** (see section 3.1), lithiation of α -methylbenzyl-substituted morpholines (*S*)-**154** or (*R*)-**154** using *s*-BuLi / (+)-sparteine surrogate at –60 °C or lower would be expected to induce some diastereoselectivity. In addition, it was hoped that the α -methylbenzyl group could lead to a preference in the deprotonation of the pro-(*R*) proton or pro-(*S*) proton at these lower temperatures. This could potentially lead to a matched or a mismatched deprotonation reaction as observed in the lithiation-trapping of α -methylbenzyl substituted piperazine (see Scheme 3.43). For the matched case, trapping of the diastereomer-enriched lithiated species with Me₃SnCl could result in useful diastereoselectivity.

Previously, the highest er (63:37 er) in the asymmetric deprotonation and trapping of *N*-methyl morpholine **125** was obtained using *s*-BuLi / (+)-sparteine surrogate in hexane at –60 °C for 4 h (see section 3.1). It was planned to use these asymmetric deprotonation conditions in the lithiation of α -methylbenzyl substituted morpholines (*S*)-**154** and (*R*)-**154** to identify if one would give a matched case with the complex *s*-BuLi / (+)-sparteine surrogate and ultimately a high diastereomeric ratio. Thus, lithiation of morpholine (*S*)-**154** using *s*-BuLi / (+)-sparteine surrogate in hexane at –60 °C for 4 h and trapping with Me₃SnCl was carried out. This resulted in the formation of a 55:45 mixture of α -stannyl morpholines (*S,S*)-**300** and (*S,R*)-**300** (by ¹H NMR spectroscopy of the crude product). The products were isolated in 34% combined yield (Scheme 3.47). Since the diastereomeric ratio is lower than 63:37, it was assumed that this is the mismatched case.



Scheme 3.47 Mismatch Effect Between the (S)- α -Methyl Benzyl Group and the *s*-BuLi / (+)-Sparteine Surrogate Complex.

In contrast, lithiation of morpholine **(R)-154** using the same reaction conditions and trapping with Me_3SnCl gave a 67:33 mixture of α -stannyl morpholines **(R,S)-300** and **(R,R)-300** (47% yield) (Scheme 3.48). A diastereomeric ratio above 63:37 suggests a slight match effect between the (*R*)- α -methyl benzyl group and the *s*-BuLi / (+)-sparteine surrogate complex.

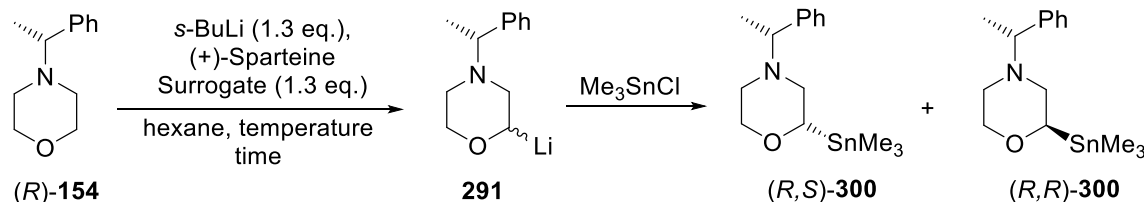


Scheme 3.48 Match Effect Between the (R)- α -Methyl Benzyl Group and the *s*-BuLi / (+)-Sparteine Surrogate Complex.

Having identified a slight matched case using morpholine **(R)-154** and the *s*-BuLi / (+)-sparteine surrogate it was investigated the asymmetric deprotonation conditions in more detail (Table 3.8). With the previous result in hand (entry 1), the temperature during the asymmetric deprotonation was decreased to $-78\text{ }^{\circ}\text{C}$ in the hope that it would increase the diastereomeric ratio. Lithiation of morpholine **(R)-154** using *s*-BuLi / (+)-sparteine surrogate at $-78\text{ }^{\circ}\text{C}$ for 4 h led to an 80:20 mixture of α -stannyl morpholines **(R,S)-300** and **(R,R)-300** in a combined 38% yield (entry 2). A longer lithiation time of 6 h at that temperature and trapping with Me_3SnCl gave an 82:18 mixture of α -stannyl morpholines **(R,S)-300** and **(R,R)-300** (combined yield of 61%) (entry 3). A further increase of the lithiation time to 8 h resulted in an 80:20 mixture of α -stannyl morpholines **(R,S)-300** and **(R,R)-300** and the combined yield increased to 65% yield (entry 4). In an attempt to increase the conversion in the lithiation step, the use of 2.0 eq. of *s*-BuLi / (+)-sparteine surrogate was explored. Lithiation at $-78\text{ }^{\circ}\text{C}$ for 8 h and subsequent trapping with 3.0 eq. of Me_3SnCl gave an 80:20 mixture of α -stannyl morpholines **(R,S)-300** and **(R,R)-300** in a combined yield of 82%. From this

experiment, α -stannyl morpholines (*R,S*)-**300** was isolated in 59% yield and (*R,R*)-**300** was isolated in 23% yield (entry 5).

Table 3.8: Optimisation of the Asymmetric Deprotonation of α -Methylbenzyl-Substituted Morpholine (*R*)-154** and Trapping with Me₃SnCl.**



Entry	Temperature / °C	Time / h	dr (crude) ^a	Yield of (<i>R,S</i>)- 300 and (<i>R,R</i>)- 300 / % ^b	dr ^c
1	-60	4	67:33	47	67:33
2	-78	4	81:19	38	80:20
3	-78	6	80:20	61	82:18
4	-78	8	81:19	65	80:20
5 ^d	-78	8	80:20	82 ^e	80:20

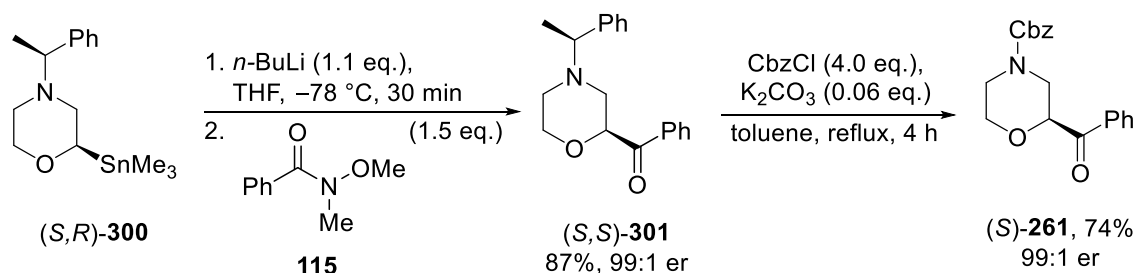
^aby ¹H NMR spectroscopy of the crude product, ^byield after purification by chromatography, ^c¹H NMR spectroscopy of the product after chromatography, ^d2.0 eq. of *s*-BuLi / (+)-sparteine surrogate and 3.0 eq. of Me₃SnCl, ^ediastereomers separated by chromatography gave (*R,S*)-**300** (59%) and (*R,R*)-**300** (23%).

In summary, two different routes to α -stannyl morpholines (*R,S*)-**300** and (*R,R*)-**300** were explored. Lithiation using *s*-BuLi / TMEDA and trapping with Me₃SnCl gave approximately equal amounts of stannanes (*R,S*)-**300** and (*R,R*)-**300** and allowed access to each on a gram-scale. Alternatively, asymmetric deprotonation of α -methylbenzyl morpholine (*R*)-**154** using *s*-BuLi / (+)-sparteine surrogate at -78 °C for 8 h and trapping with Me₃SnCl gave access to an 80:20 mixture of stannanes (*R,S*)-**300** and (*R,R*)-**300** and thus provided a diastereoselective route to stannane (*R,S*)-**300** (isolated in 59% yield).

3.4.3 Sn-Li Exchange of α -Stannyl Morpholines and Subsequent Trapping

With routes to α -stannyl morpholines (*S,R*)-**300** and (*S,S*)-**300** established, the Sn-Li exchange and trapping with electrophiles was investigated. Stannane (*S,R*)-**300** was used in

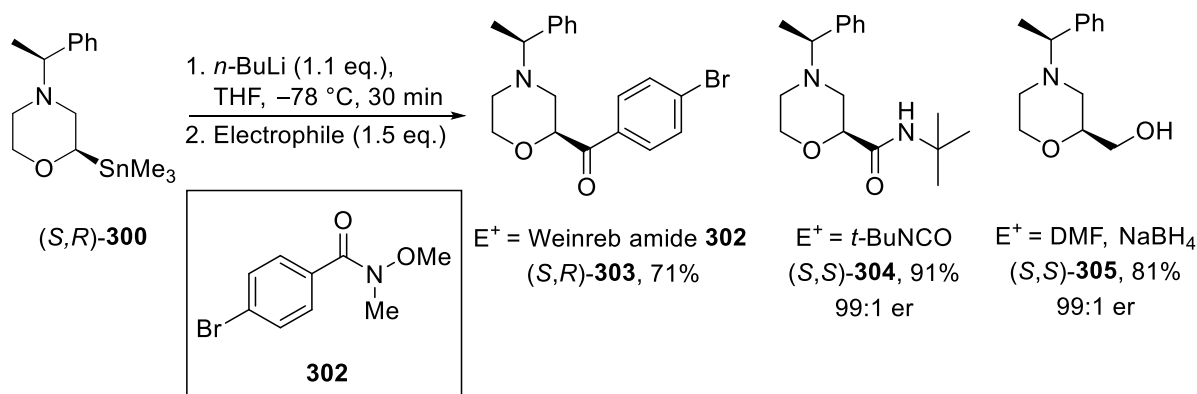
a Sn-Li exchange using 1.1 eq. *n*-BuLi in THF at $-78\text{ }^{\circ}\text{C}$ to generate the lithiated species. Trapping with Weinreb amide **115** gave ketone (*S,S*)-**301** in 87% yield (Scheme 3.49). Ketone (*S,S*)-**301** was isolated as a single diastereomer and in 99:1 er (by CSP-HPLC). The relative stereochemistry of (*S,S*)-**301** was assigned by comparison of its ^1H NMR spectrum with that of an authentic sample of its enantiomer reported in a patent.¹⁶⁴ This result confirmed that the Sn-Li exchange led to a configurationally stable lithiated species and trapping exclusively with retention gave ketone (*S,S*)-**301**.



Scheme 3.49 Sn-Li Exchange of (*S,R*)-**300**, Trapping with Weinreb Amide **115** and CbzCl Addition.

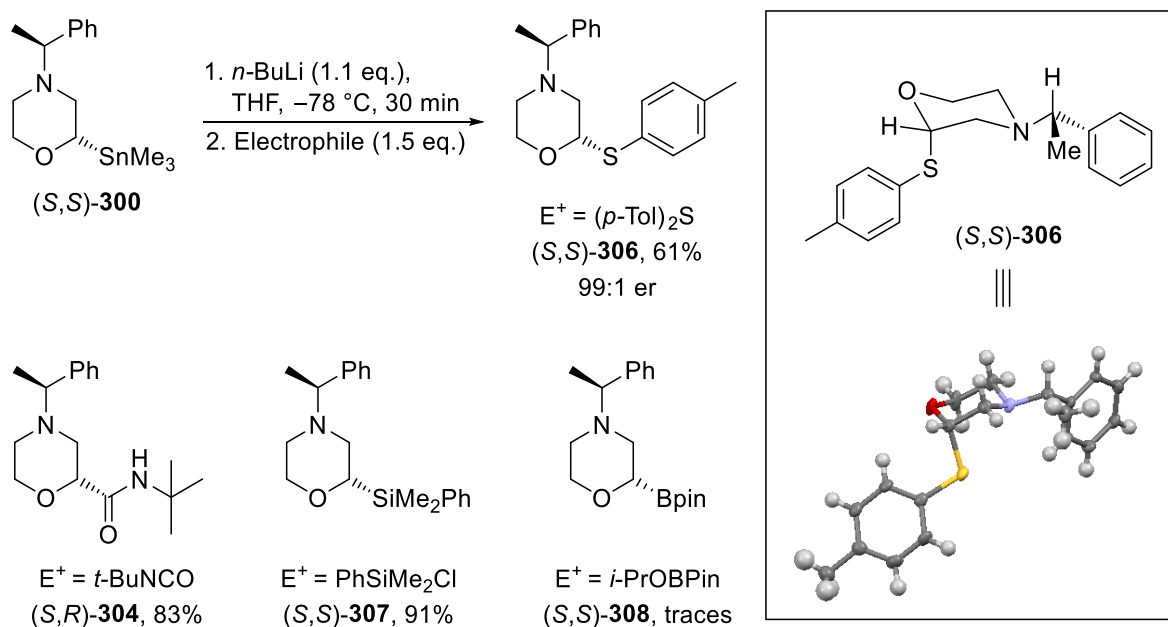
To show that the α -methylbenzyl group could be removed without epimerisation, α -methylbenzyl substituted morpholine (*S,S*)-**301** was reacted with CbzCl and K_2CO_3 to give Cbz-protected morpholine (*S*)-**261** in 74% yield and 99:1 er (by CSP-HPLC) (Scheme 3.49). The stereochemistry was assigned assuming that the Sn-Li exchange and trapping proceeds with retention.¹⁶⁵

With established conditions for the Sn-Li exchange, trapping with other electrophiles was explored (Scheme 3.50). Trapping with Weinreb amide **302** gave ketone (*S,R*)-**303** in 71% yield. When *t*-BuNCO was used as an electrophile, amide (*S,S*)-**304** was isolated in 81% yield and 99:1 er. Trapping of the lithiated species with DMF and subsequent reduction with NaBH_4 gave alcohol (*S,S*)-**305** in 81% yield and 99:1 er. Trapping with paraformaldehyde only gave protonated α -methylbenzyl-substituted morpholine (*S*)-**154**. The racemic standards for CSP-HPLC were synthesised starting from α -stannyl morpholine (*S**,*R**)-**300** via Sn-Li exchange and subsequent trapping with *t*-BuNCO and DMF / NaBH_4 respectively.



Scheme 3.50 Sn-Li Exchange of (S,R)-300 and Trapping with Various Electrophiles.

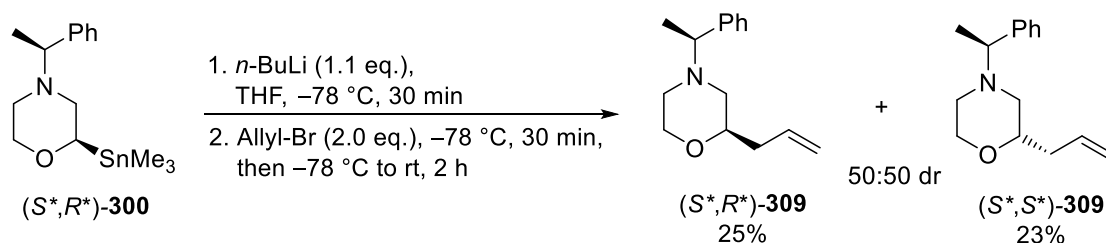
Next, starting from the diastereomeric α -stannyl morpholine (S,S)-300, Sn-Li exchange and trapping with electrophiles was explored (Scheme 3.51). Trapping with (*p*-Tol)₂S gave sulfide (S,S)-306 in 61% and 99:1 er. The absolute configuration of sulfide (S,S)-306 was identified by X-ray crystallography (Flack Parameter 0.005). Trapping with *t*-BuNCO gave amide (S,R)-304 in 60% yield. The ¹H NMR spectrum of amide (S,R)-304 is as expected different to that of the diastereomeric amide (S,S)-304. Addition of PhSiMe₂Cl after Sn-Li exchange resulted in silane (S,S)-307 in 91% yield and 99:1 er. Disappointingly, trapping with *i*-PrOBpin gave only traces of morpholine (S,S)-308. Presumably, the Lewis basic amine lone pair and the Lewis acidic boronic ester are incompatible with each other.



Scheme 3.51 Sn-Li Exchange of (S,S)-300 and Trapping with Various Electrophiles.

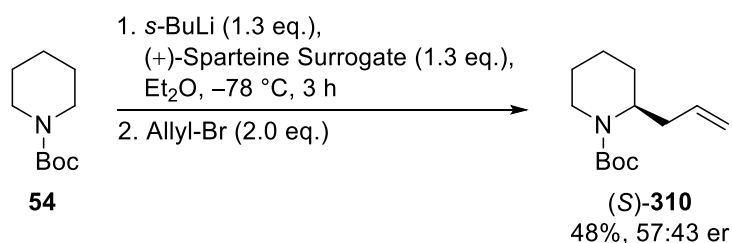
There was an interest in exploring Sn-Li exchange and subsequent introduction of allyl groups in the position α to oxygen. As a model substrate, the allylation of racemic α -stannyl

morpholine (S^*,R^*)-**300** using allyl bromide was investigated first. Sn-Li exchange (THF, $-78\text{ }^\circ\text{C}$) and direct trapping with allyl bromide resulted in a 50:50 mixture of α -allyl morpholines (S^*,R^*)-**309** and (S^*,S^*)-**309** which were isolated in 25% and 23% yield respectively (Scheme 3.52).



Scheme 3.52 Sn-Li Exchange of (S^*,R^*)-**300** and Trapping with Allyl Bromide.

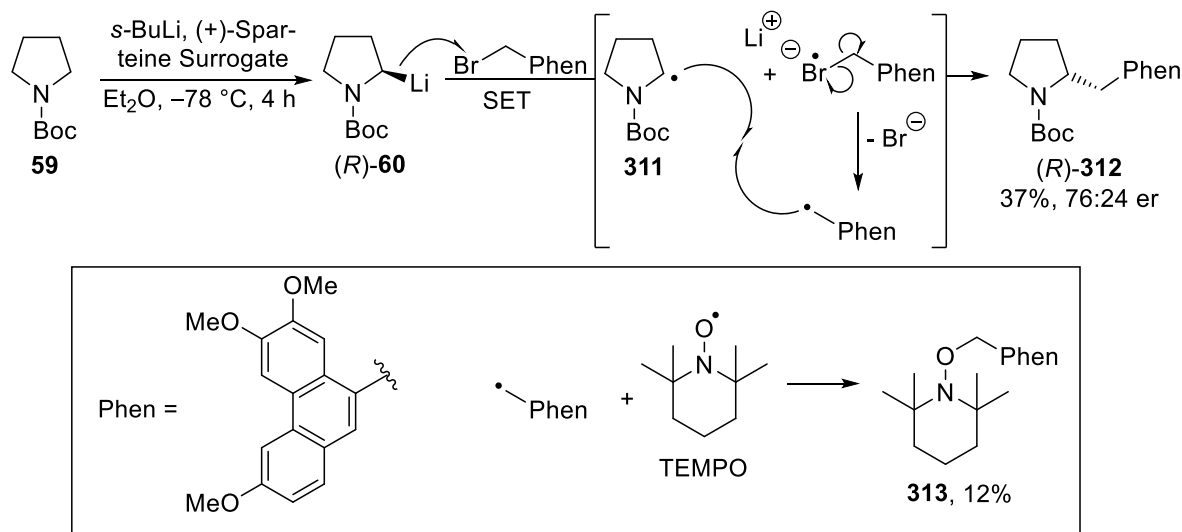
The trapping of an enantioenriched lithiated species using allyl and benzyl bromides can result in allylated and benzylated products in lower er compared to the enantioenriched lithiated species. For example, in the O'Brien group the asymmetric deprotonation of *N*-Boc piperidine **54** using *s*-BuLi / (+)-sparteine surrogate gave an enantioenriched lithiated species in 88:12 er (as shown by trapping with other electrophiles). However, trapping with allyl bromide led to the formation of allylated piperidine in (*S*)-**310** in 57:43 er (48% yield) (Scheme 3.53).⁹¹



Scheme 3.53 Asymmetric Deprotonation of *N*-Boc Piperidine **54** and Trapping With Allyl Bromide.

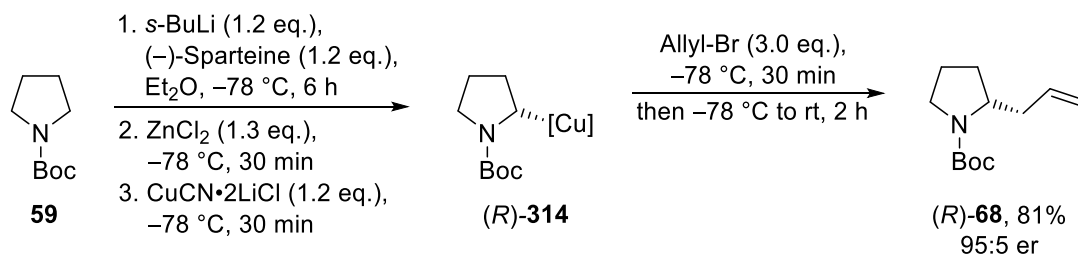
In 2014, Wang et al. reported the lithiation of *N*-Boc pyrrolidine **59** using *s*-BuLi and (+)-sparteine surrogate and trapping with bromomethyl phenanthrene.¹⁶⁶ The desired α -substituted pyrrolidine (*S*)-**312** was isolated in 37% yield and only 76:24 er (Scheme 3.54). In contrast, the O'Brien group reported the generation of an α -substituted *N*-Boc pyrrolidine in 95:5 er in the lithiation- Me_3SiCl trapping of *N*-Boc pyrrolidine **59** under similar conditions.⁷¹ Wang et al. suggested that apart from the direct trapping of α -lithio-*N*-Boc-pyrrolidine **60** with bromomethyl phenanthrene, the lithiated species **60** reacts with the benzyl bromide derivative to give radical **311** and a bromo-containing radical anion which collapses to give the methyl phenanthrene radical. The α -lithio-*N*-Boc-pyrrolidine radical

311 undergoes racemisation and then recombines with the phenanthrene radical to give α -substituted *N*-Boc pyrrolidine (*S*)-**312**. In a separate experiment, addition of radical scavenger TEMPO after lithiation-trapping with bromomethyl phenanthrene gave **313** in 12% yield suggesting the formation of the bromomethyl phenanthrene radical.



Scheme 3.54 Proposed Competing Radical Reaction in the Trapping of α -Lithio Pyrrolidine (*R*)-**60** with Bromomethyl Phenanthrene.

Organocuprates are often used to overcome the fact that trapping of enantioenriched lithiated species with allyl and benzyl bromides can lead to products with low ers. For example, Coldham et al. reported the addition of CuCN·2LiCl before trapping with allyl bromide or benzyl bromide. The best results were achieved when the lithiated species was transmetallated to an organozinc species before addition of the CuCN·2LiCl.¹²⁶ Addition of ZnCl₂ and CuCN·2LiCl to an enantioenriched *N*-Boc- α -lithiopyrrolidine gave cuprate (*R*)-**314** and subsequent addition of allyl bromide gave *N*-Boc- α -allylpyrrolidine (*R*)-**68** (81% yield) in high er (95:5 er).

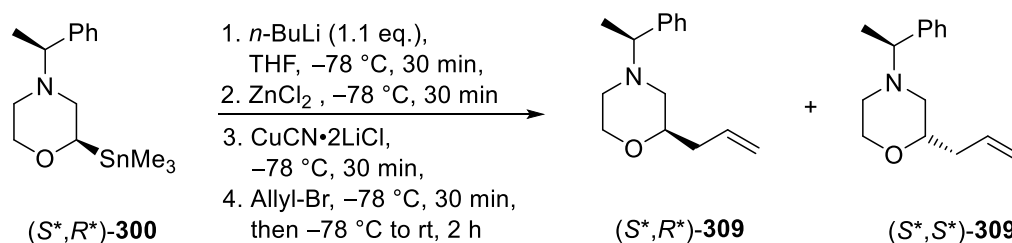


Scheme 3.55 Asymmetric Deprotonation of *N*-Boc Pyrrolidine **59**, Transmetalation and Allyl Bromide Addition.

With the literature in mind the use of organocuprates was explored to try to improve on the direct allylation result shown in Scheme 3.52. Sn-Li exchange of stannane (*S**,*R**)-**300** and

subsequent transmetallation to an organocopper species and trapping with allyl bromide gave an 87:13 mixture of α -allyl substituted morpholines (S^*,R^*)-**309** and (S^*,S^*)-**309** which were isolated in 69% and 9% yield (Table 3.9, entry 2). A further improvement was obtained when proceeding from Li to Cu. Thus, Sn-Li exchange, transmetallation using ZnCl_2 and subsequent transmetallation using $\text{CuCN}\cdot 2\text{LiCl}$ and trapping with allyl bromide was attempted. Trapping of the cuprate with allyl bromide after two transmetallations gave a 95:5 mixture of allyl morpholines (S^*,R^*)-**309** (71% yield) and (S^*,S^*)-**309** (2% yield) (entry 3). After chromatography, the major allyl morpholine (S^*,S^*)-**309** was obtained in 71% yield. It was proposed that the transmetallation to an organocuprate before trapping with allyl bromide inhibits the postulated radical pathway and the overall trapping process is assumed to proceed with retention of stereochemistry for the major product.

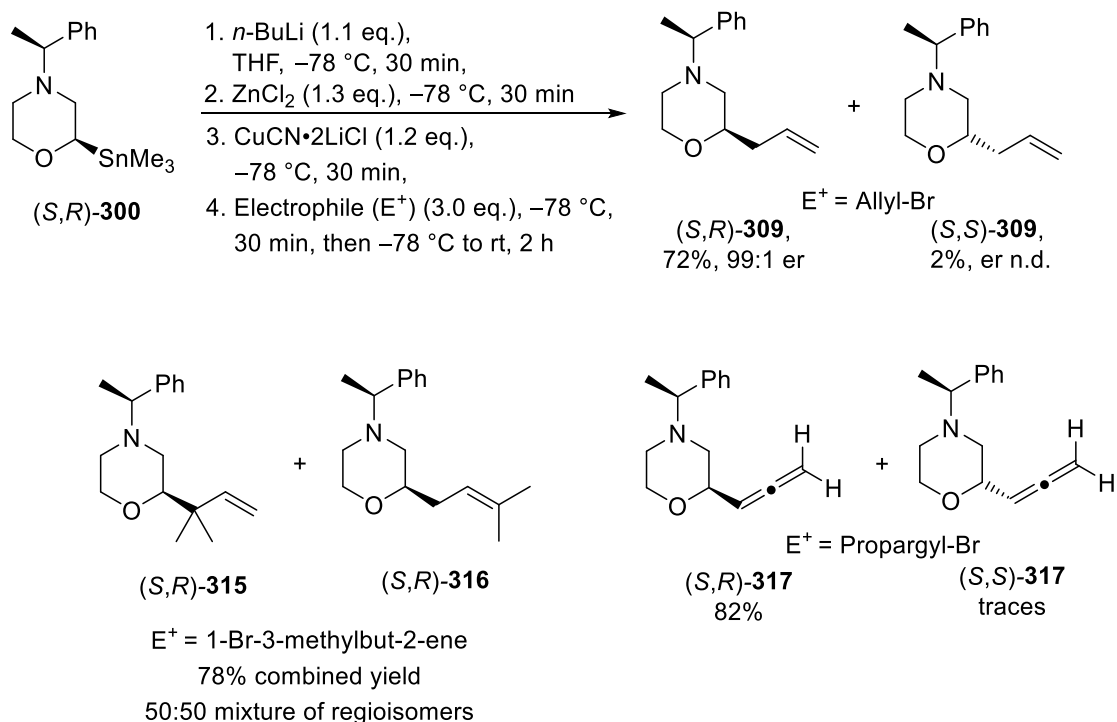
Table 3.9: Trapping with Allyl Bromide.



Entry	ZnCl_2 / eq.	$\text{CuCN}\cdot 2\text{LiCl}$ / eq.	dr ^a	Yield (S^*,R^*)- 309 / % ^b	Yield (S^*,S^*)- 309 / % ^b
1	-	-	50:50	25	23
2	-	1.2	87:13	69	9
3	1.3	1.2	95:5	71	2

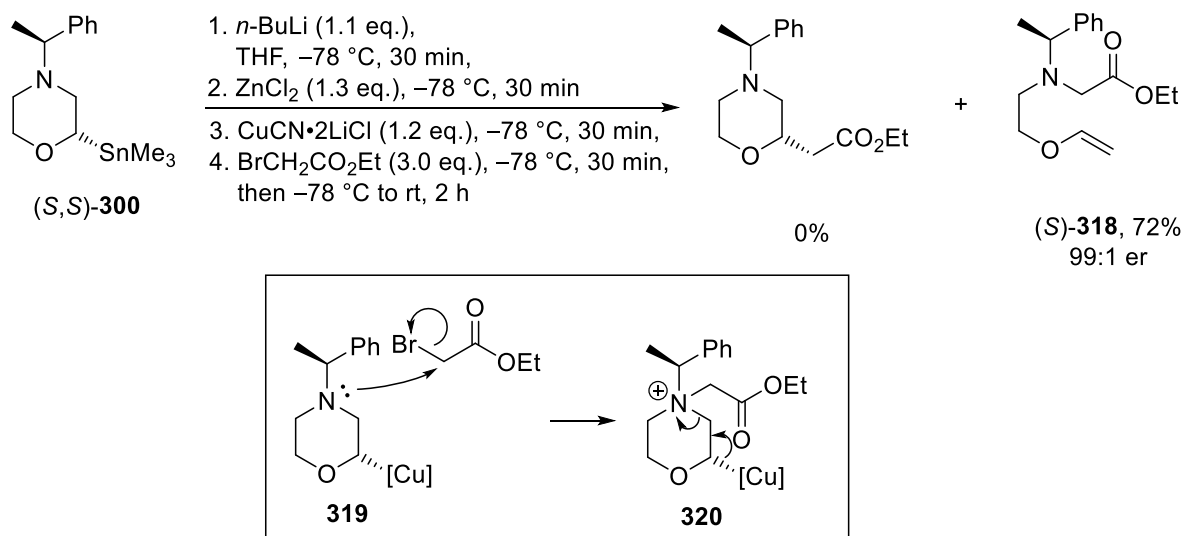
^aby ^1H NMR spectroscopy of the crude product, ^byield after purification by chromatography.

With the allylation reaction improved, the Sn-Li exchange of stannane (S,R)-**300**, transmetallation to an organocopper species (*via* an organozinc species) and trapping with allyl bromide gave the desired allyl morpholine (S,R)-**309** in >95:5 dr (by ^1H NMR spectroscopy of the crude product) (Scheme 3.56). Morpholine (S,R)-**309** was isolated in 72% yield and 99:1 er. Only a 2% yield of morpholine (R,R)-**309** was isolated and the er was not determined. Two other related reaction were explored (Scheme 3.56). Trapping of the organocopper species with 1-bromo-3-methylbut-2-ene gave a 50:50 mixture of regioisomeric morpholines (S,R)-**315** and (S,R)-**316** in a combined yield of 78%. Finally, trapping with propargyl bromide gave morpholine allene (S,R)-**317** in 82% yield. In addition, only traces of allene (S,S)-**317** were obtained.



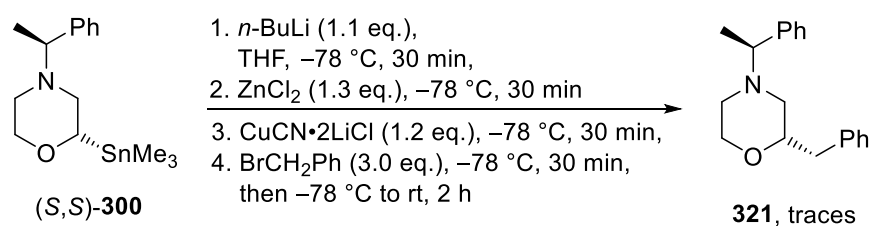
Scheme 3.56 Sn-Li Exchange of (S,S)-300, Transmetallation and Electrophile Addition.

Next, trapping with ethyl 2-bromoacetate was explored. The enantioenriched stannane (S,S)-**300** underwent Sn-Li exchange, subsequent transmetallation using ZnCl₂ and CuCN·2LiCl to the organocuprate and trapping with ethyl 2-bromoacetate to give, unexpectedly, the ring-opened morpholine (S)-**318** in 72% yield and 99:1 er (Scheme 3.57). It is assumed that organocuprate **319** is formed. However, instead of the expected S_N2 reaction on the ethyl 2-bromoacetate, a different process occurred. To account for the formation of the ring-opened product, it was proposed that nucleophilic attack of the nitrogen lone pair on the ethyl 2-bromoacetate could occur to give ammonium species **320**. Ring-opening *via* β -elimination of the positively charged leaving group would then result in vinyl ether (S)-**318**. A similar fragmentation pathway was proposed to explain a similar ring-opening in the lithiation-trapping of *N*-Boc piperazines with methyl chloroformate.¹⁰⁸



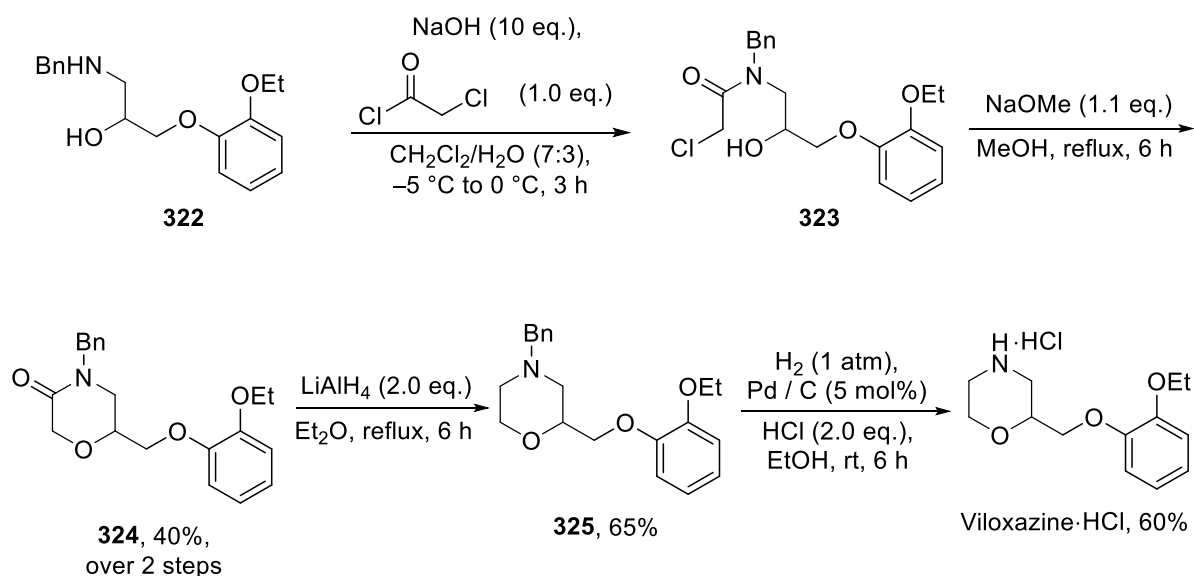
Scheme 3.57 Sn-Li Exchange of (S,S)-300, Transmetalation and Trapping with Ethyl 2-Bromoacetate.

Trapping with benzyl bromide was also explored. Sn-Li exchange of the enantioenriched stannane (S,S)-**300**, subsequent transmetalation using ZnCl_2 and $\text{CuCN}\cdot 2\text{LiCl}$ to the organocuprate and trapping with benzyl bromide resulted in only traces of the corresponding product (S,S)-**321** (Scheme 3.58).



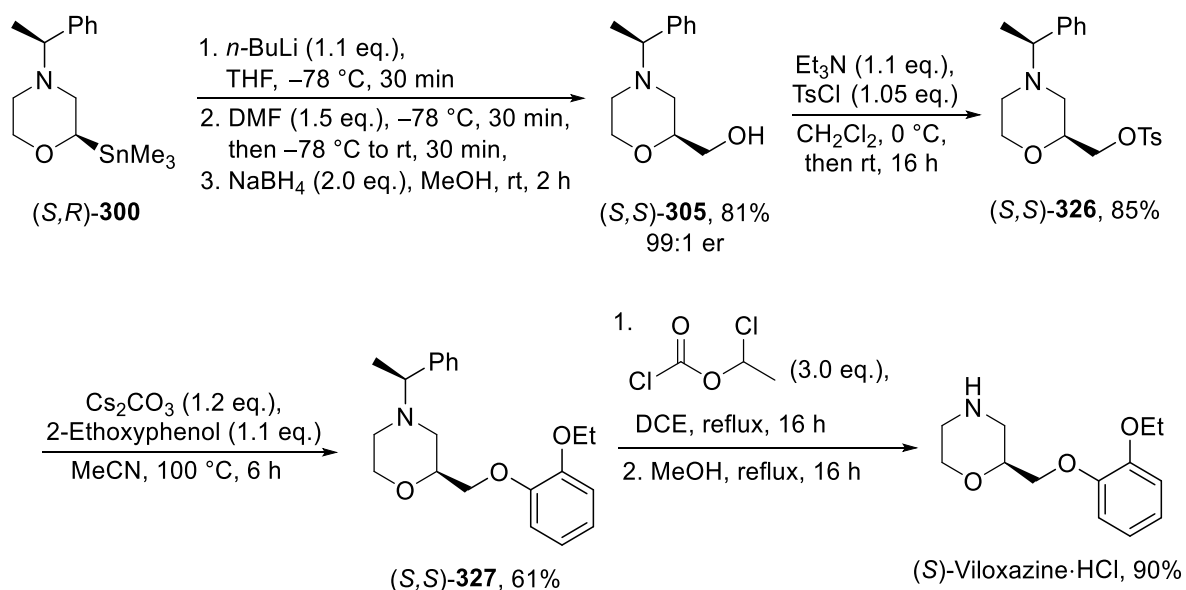
Scheme 3.58 Sn-Li Exchange, Transmetalation and Attempted Trapping with BnBr.

Finally, to show the usefulness of our methodology, it was applied to the synthesis of a drug molecule. In 1976, ICI developed viloxazine (trade name Vivalan[®]), a morpholine derivative that was used as an antidepressant.¹⁶⁷ In the reported synthesis by Turner, viloxazine was synthesised in four steps (Scheme 3.59). In the first step, propranolol derivative **322** underwent amide formation to give alcohol **323**. Subsequent base-mediated ring closure gave morpholinone **324** in 40% yield over two steps. Reduction using LiAlH_4 gave morpholine derivative **325** in 65% yield. Finally, hydrogenation using Pd / C gave viloxazine·HCl in 60% yield.¹⁶⁸



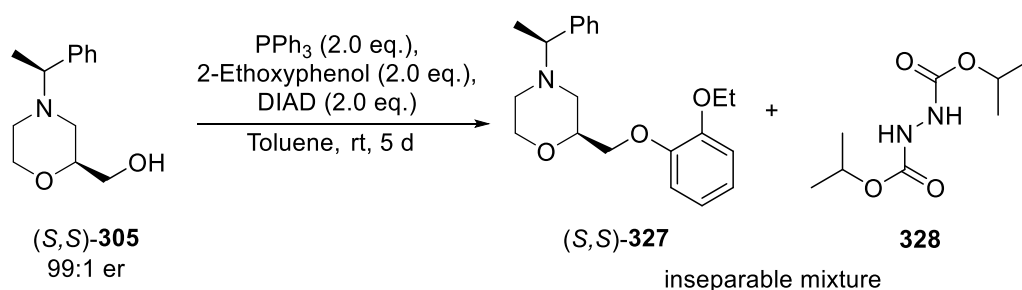
Scheme 3.59 Viloxazine·HCl Synthesis by ICI.

Although marketed as a racemate, in early studies it was discovered that the (*S*)-enantiomer of viloxazine is five times more potent than the (*R*)-enantiomer.¹⁶⁹ Therefore, there was interest in the synthesis of the (*S*)-enantiomer starting from the enantioenriched α -stannyl morpholine (*S,R*)-**300** (Scheme 3.60). Using the previously explored Sn-Li exchange (see Scheme 3.50) starting from α -stannyl morpholine (*S,R*)-**300**, trapping with DMF and subsequent reduction using NaBH₄ gave the alcohol (*S,S*)-**305** in 81% yield and 99:1 er by CSP-HPLC. Tosylation using Et₃N and TsCl gave morpholine (*S,S*)-**326** in 85% yield. Subsequent treatment with Cs₂CO₃ and 2-ethoxyphenol resulted in ether (*S,S*)-**327** in 61% yield. Finally, removal of the α -methylbenzyl substituent was achieved by the procedure by Olofson et al., previously used in the O'Brien group in the removal of the *N*-methyl substituent in the synthesis of reboxetine (see Scheme 1.69).¹¹¹ Reaction of α -chloroethyl chloroformate with morpholine (*S,S*)-**326** resulted in formation of a carbamate species. Addition of MeOH led to carbamate break-down and gave the desired (*S*)-viloxazine·HCl in 90% yield.



Scheme 3.60 Synthesis of (S)-Viloxazine·HCl Starting from (S,R)-300.

An attempt to synthesise morpholine (S,S)-326 via a Mitsunobu reaction starting from alcohol (S,S)-305 was also explored (Scheme 3.61). Treatment of alcohol (S,S)-305 with 2-ethoxyphenol in the presence of PPh₃ and DIAD resulted in a mixture of the desired morpholine (S,S)-326 and a hydrazine by-product. Separation of the by-product using chromatography was not successful.

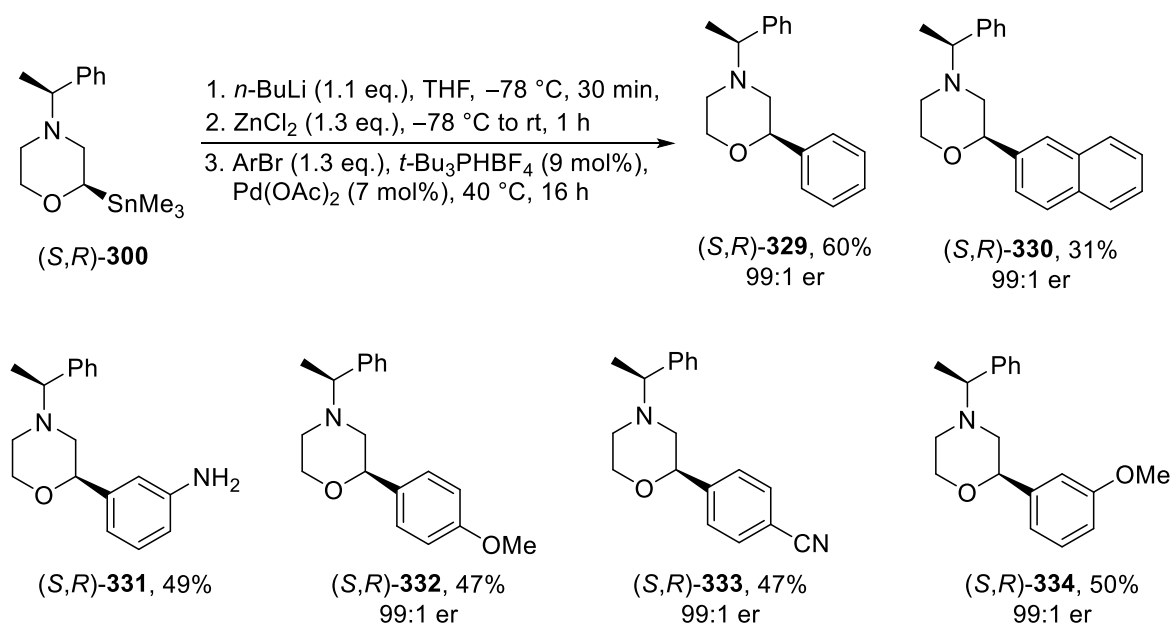


Scheme 3.61 Attempted Mitsunobu Reaction for the Synthesis of Morpholine (S,S)-327.

The Sn-Li exchange of α -stannyl morpholines (S,R)-300 and (S,S)-300 and subsequent trapping was successful with a broad range of electrophiles resulting in α -substituted morpholines as single diastereomers in high ers. For the trapping with allyl bromide and propargyl bromide, transmetallation to an organozinc and organocopper species allowed a stereospecific reaction. In addition, the new method was used in the synthesis of (S)-viloxazine.

3.4.4 Sn-Li Exchange, Transmetallation and Negishi Cross-Coupling of α -Stannyl Morpholines

In addition to the presented Sn-Li exchange and trapping with electrophiles, the introduction of aryl substituents was investigated using Negishi cross-coupling. In section 2.2, eight examples of cross-coupling with α -stannyl morpholines were demonstrated. It was envisaged using the same approach with α -stannyl morpholines (*S,R*)-**300** and (*S,S*)-**300**. For the coupling step, the same coupling conditions as for those of α -stannyl morpholine **228** would be used: ArBr, 7 mol% Pd(OAc)₂, 9 mol% *t*-Bu₃PHBF₄, 40 °C for 16 h (see section 2.2). Starting from stannane (*S,R*)-**300**, Negishi cross-coupling with aryl bromides bearing a primary amine, nitrile and methoxy groups was possible and gave α -aryl morpholines (*S,R*)-**329-334** in yields of 31-60% yield and 99:1 er (Scheme 3.62).



Scheme 3.62 Sn-Li Exchange of (*S,R*)-300**, Transmetallation and Negishi Cross-Coupling.**

The absolute configuration of nitrile (*S,R*)-**333** was determined using X-ray analysis (Figure 3.3). The X-ray structure clearly shows the (*S*)-configuration at the α -methylbenzyl substituent and the (*R*)-configuration at the carbon α to oxygen (Flack Parameter 0.1). This confirmed that, the Sn-Li exchange, transmetallation and Negishi cross-coupling all proceeded with retention of stereochemistry.

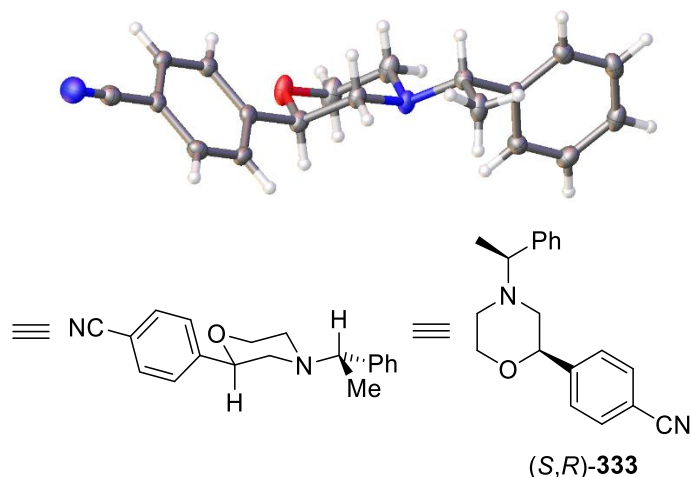
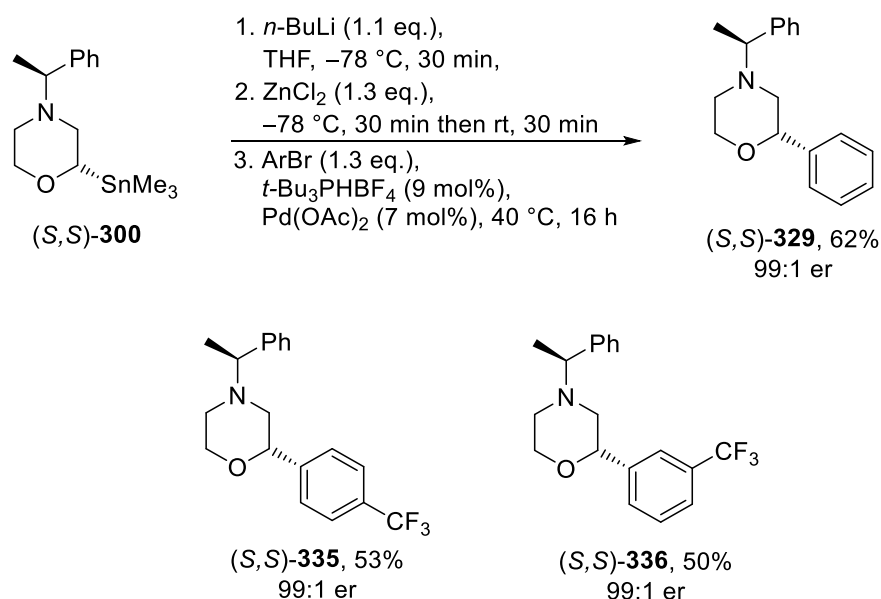


Figure 3.4: X-ray Crystal Structure of α -Aryl Morpholine (S,R)-333.

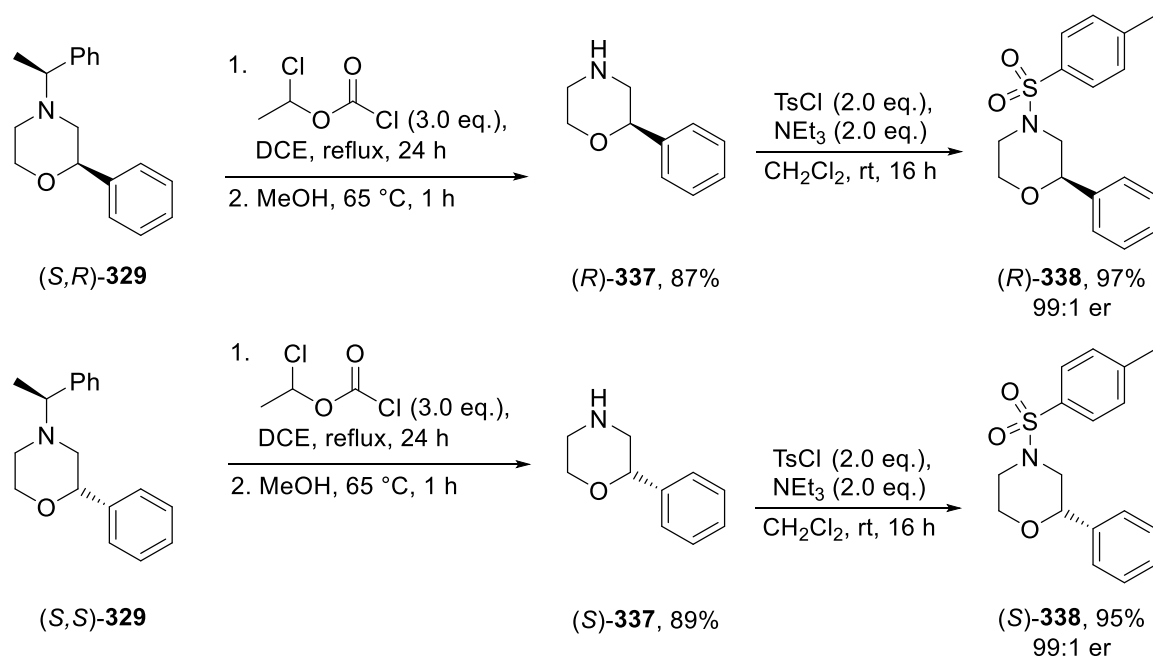
Morpholine stannane (S,S)-300 was also used as a starting material for other Negishi reactions. Sn-Li exchange, transmetallation and Negishi cross-coupling with three aryl bromides generated α -arylated morpholines (S,S)-329, (S,S)-335 and (S,S)-336 in 50-62% yield and 99:1 er (Scheme 3.63).



Scheme 3.63 Sn-Li Exchange of (S,S)-300, Transmetallation and Negishi Cross-Coupling.

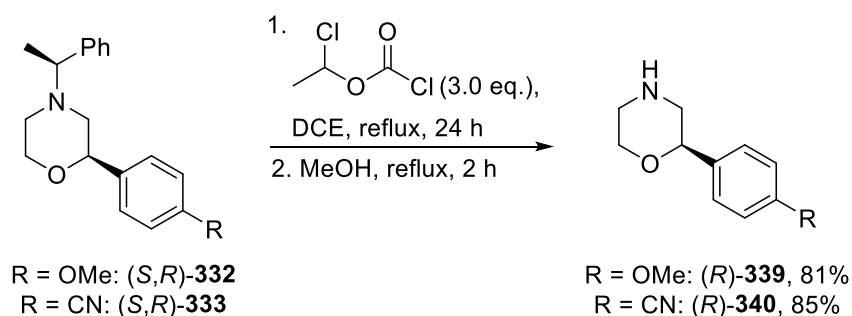
To show that the α -methylbenzyl substituent could be removed from the Negishi products and to confirm the absolute configuration of another arylated morpholine, the α -methylbenzyl substituent of α -aryl substituted morpholines (S,R)-329 and (S,S)-329 was removed. For the removal of the α -methylbenzyl substituent, the previously explored conditions (see Scheme 3.60) were applied.¹¹¹ α -Aryl morpholines (S,R)-329 and (S,S)-329 were treated with chloroethyl chloroformate and MeOH to give morpholines (R)-337 (87%

yield) and (*S*)-**337** (89% yield) (Scheme 3.64). The absolute configuration was determined by comparison of the optical rotation to that in the literature.¹⁷⁰ Subsequent tosylation was possible in high yields to give morpholines (*R*)-**338** and (*S*)-**338** each in 99:1 er as shown by CSP-HPLC analysis. The CSP-HPLC retention times of the morpholines matched the literature values.¹⁷¹



Scheme 3.64 Removal of the α -Methylbenzyl Substituent and Tosylation.

Under the same conditions, using α -chloroethyl chloroformate and subsequent addition of MeOH, the α -methylbenzyl group in α -aryl morpholines (*S,R*)-**332** and (*S,R*)-**333** bearing methoxy and nitrile groups was removed. This resulted in morpholines (*R*)-**339** and (*R*)-**340** in 81% and 85% yield respectively (Scheme 3.65).

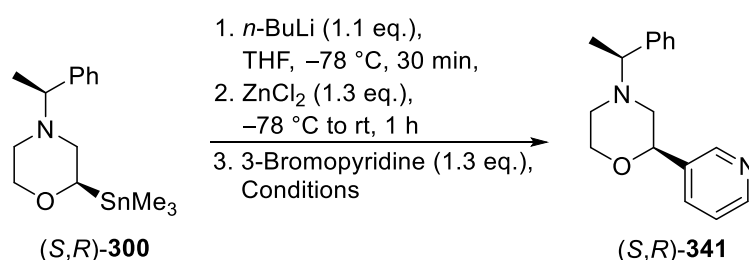


Scheme 3.65 Removal of the α -Methylbenzyl Substituent Using α -Chloroethyl Chloroformate.

Next, Negishi cross-coupling with heteroaromatic bromides was investigated. Starting with stannane (*S,R*)-**300**, after Sn-Li exchange and transmetallation, the Negishi cross-coupling was performed using Pd(OAc)₂ and *t*-Bu₃PHBF₄ and 3-bromopyridine. This gave α -aryl

morpholine (S,R)-**341** in only 33% yield (Table 3.10, entry 1). Therefore, further reaction conditions were explored. Negishi cross-coupling using $\text{Pd}_2(\text{dba})_3$ and S-Phos resulted in the desired α -aryl morpholine (S,R)-**341** in 63% yield (entry 2). Cross-coupling using $\text{Pd}_2(\text{dba})_3$ and X-Phos at 60 °C for 16 h did not result in the desired product (entry 3). A solvent switch to toluene and cross-coupling at 110 °C resulted in only traces of morpholine (S,R)-**341** (entry 4). Finally, Negishi cross-coupling using $\text{Pd}_2(\text{dba})_3$ and Q-Phos did not result in the desired product (entry 5). For subsequent reactions with heteroaromatic systems, cross-coupling reactions were carried out using $\text{Pd}_2(\text{dba})_3$ and S-Phos at 60 °C for 16 h.

Table 3.10: α -Arylation of Morpholines Using Heteroaryl Bromides.

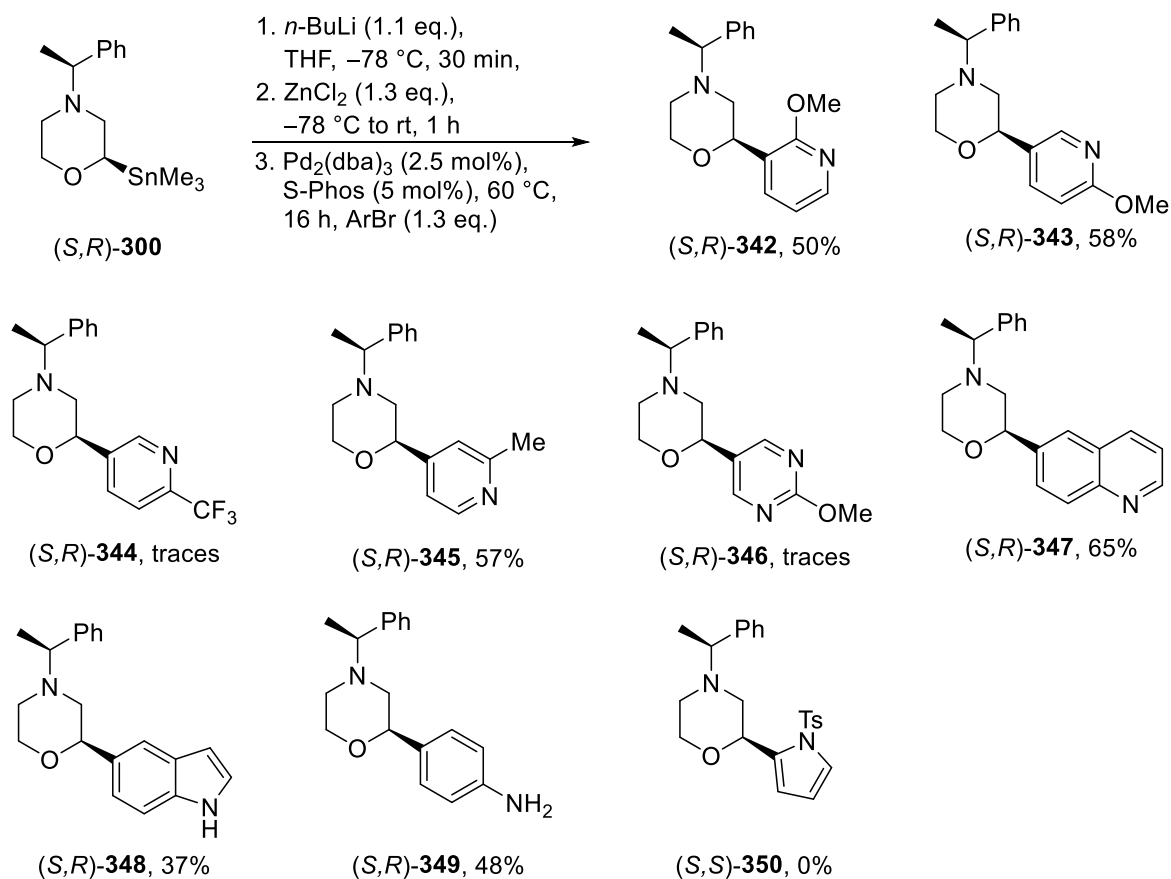


Entry	Catalyst	mol% ^a	Ligand	mol% ^b	Temp. / °C	Time / h	Yield (S,R)- 341 / % ^c
1	$\text{Pd}(\text{OAc})_2$	7	<i>t</i> -Bu ₃ PHBF ₄	9	60	16	33
2	$\text{Pd}_2(\text{dba})_3$	2.5	S-Phos	5	60	16	63
3	$\text{Pd}_2(\text{dba})_3$	2.5	X-Phos	5	60	16	0
4 ^d	$\text{Pd}_2(\text{dba})_3$	2.5	X-Phos	5	110	16	traces
5	$\text{Pd}_2(\text{dba})_3$	2.5	Q-Phos	5	60	16	0

^amol% of the catalyst, ^bmol% of the ligand, ^cyield after purification by chromatography, ^dsolvent switch to toluene for the cross-coupling step.

With the new conditions, coupling with a range of heteroaryl bromides was investigated (Scheme 3.66). Coupling with electron rich 2-methoxy and 4-methoxy pyridines resulted in α -aryl morpholines (S,R)-**342** and (S,R)-**343** in 50% and 58% yield respectively. In contrast, coupling using electron poor CF₃-substituted pyridine gave only traces of α -aryl morpholine (S,R)-**344**. When 4-bromo-2-methylpyridine was used, the corresponding α -aryl morpholine (S,R)-**345** was isolated in 57% yield. Unfortunately, coupling with 4-bromo-2-methoxy-pyrimidine resulted in only traces of the morpholine (S,R)-**346**. Addition of 6-bromoquinoline gave α -aryl morpholine (S,R)-**347** in 65% yield. Coupling with 5-bromo indole and 4-bromoaniline generated α -aryl morpholines (S,R)-**348** and (S,R)-**349** in 37% and 48% yield respectively. Unfortunately, coupling with 2-bromo-1-tosyl-1*H*-pyrrole was

unsuccessful and did not give α -aryl morpholine (*S,S*)-**350**. All of these α -aryl morpholines were generated as single diastereomers as a result of the stereospecific nature of this reaction. The stereochemistry is assigned by analogy with the other examples.



Scheme 3.66 Sn-Li Exchange of (*S,R*)-**300**, Transmetallation and Negishi Cross-Coupling with Heteroaryl Bromides.

The α -stannyl morpholines (*S,R*)-**300** and (*S,S*)-**300** successfully underwent Sn-Li exchange, transmetallation and stereospecific Negishi cross-coupling. Coupling with various aryl bromides was possible in moderate to high yields using $\text{Pd}(\text{OAc})_2$ / *t*-Bu₃PHBF₄. In addition, coupling with heteroaryl bromides was explored and the cross-coupling conditions were slightly modified. The best results for the synthesis of α -heteroaryl morpholines were achieved using $\text{Pd}_2(\text{dba})_3$ and S-Phos.

3.4.5 Synthesis of Flumexadol, Oxflozane and PF219,061

Having established methods for the α -substitution of α -methylbenzyl-substituted morpholine (*S*)-**154** and the cleavage of the α -methylbenzyl substituent, there was interest in applying

the methodology in the synthesis of the pharmaceutically-relevant compounds flumexadol, the related oxaflozane and PF219,061 (Figure 3.5). Flumexadol is a drug which acts as a serotonin 5-HT agonist and has non-opioid analgesic properties.¹⁷² The prodrug oxaflozane was initially marketed by Solvay and is an anxiolytic and antidepressant.¹⁷³ In 2007, Pfizer reported the synthesis of an α -aryl morpholine PF-219,061, which is a potent agonist for the dopamine D₃ receptor.¹⁵

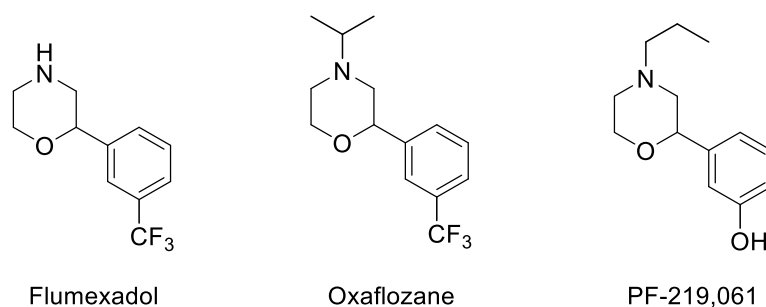
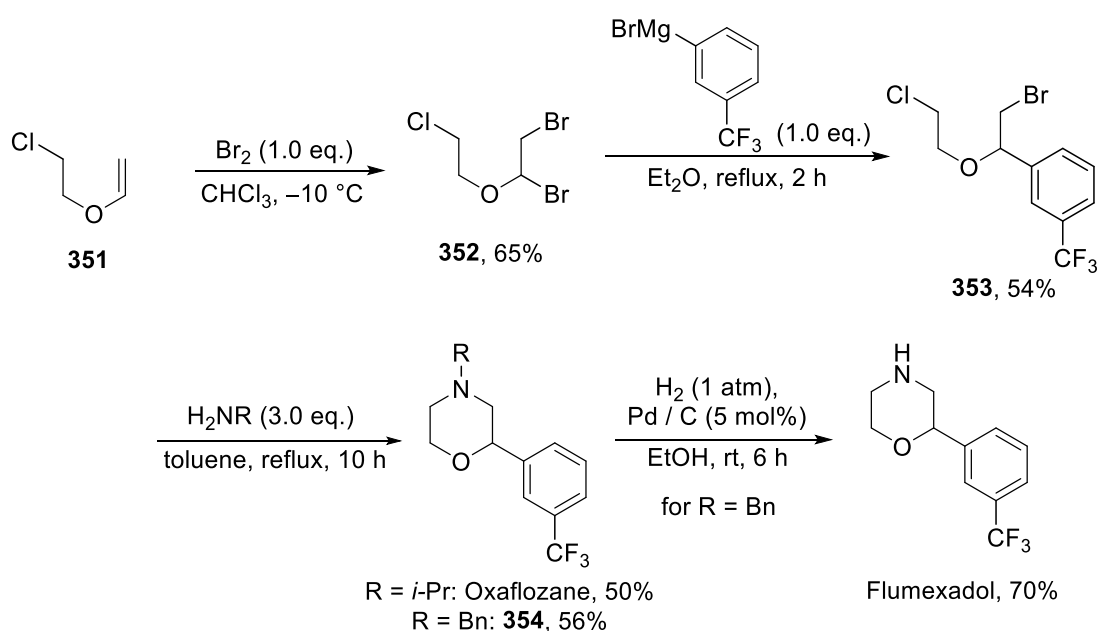


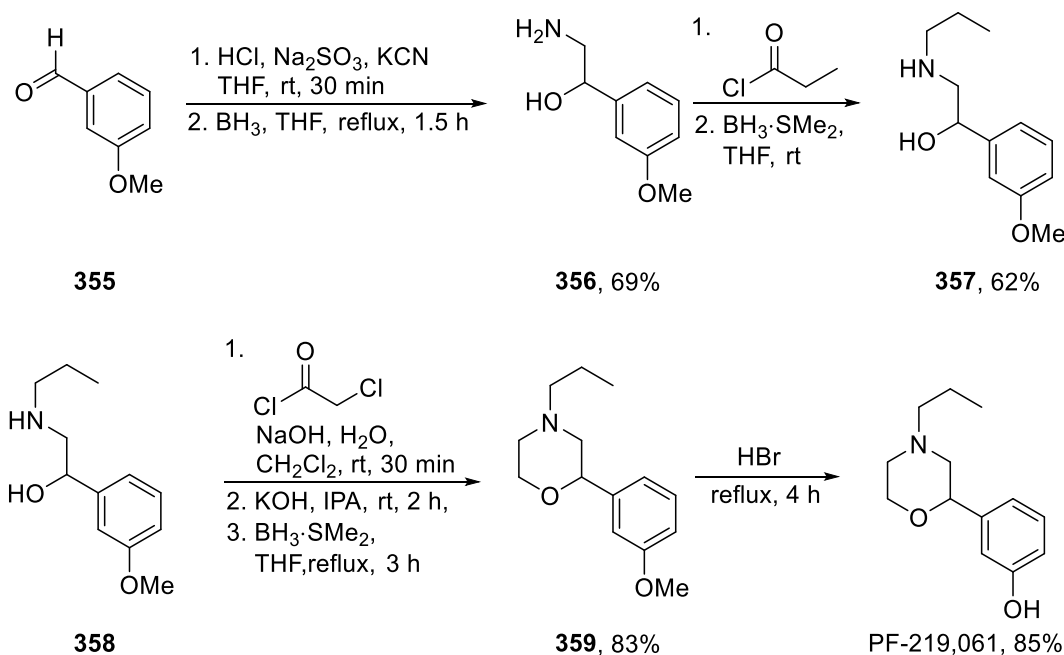
Figure 3.5: Structures of Flumexadol, Oxaflozane and PF219,061.

A previously reported synthesis of flumexadol and oxaflozane by Mauvernay et al. is presented in Scheme 3.67.¹⁷⁴ Starting from 2-chloroethyl vinyl ether **351**, dibromoether **352** was prepared in 65% yield by bromination. Subsequent Grignard reaction with an aryl Grignard reagent gave α -aryl ether **353** in 54% yield. Ring-closure with *i*-PrNH₂ gave oxaflozane in 50% yield. For the synthesis of flumexadol, benzylamine was used to give *N*-benzyl morpholine **354** in 56% yield. Finally, hydrogenation using H₂ and Pd / C (5 mol%) resulted in flumexadol in 70% yield.



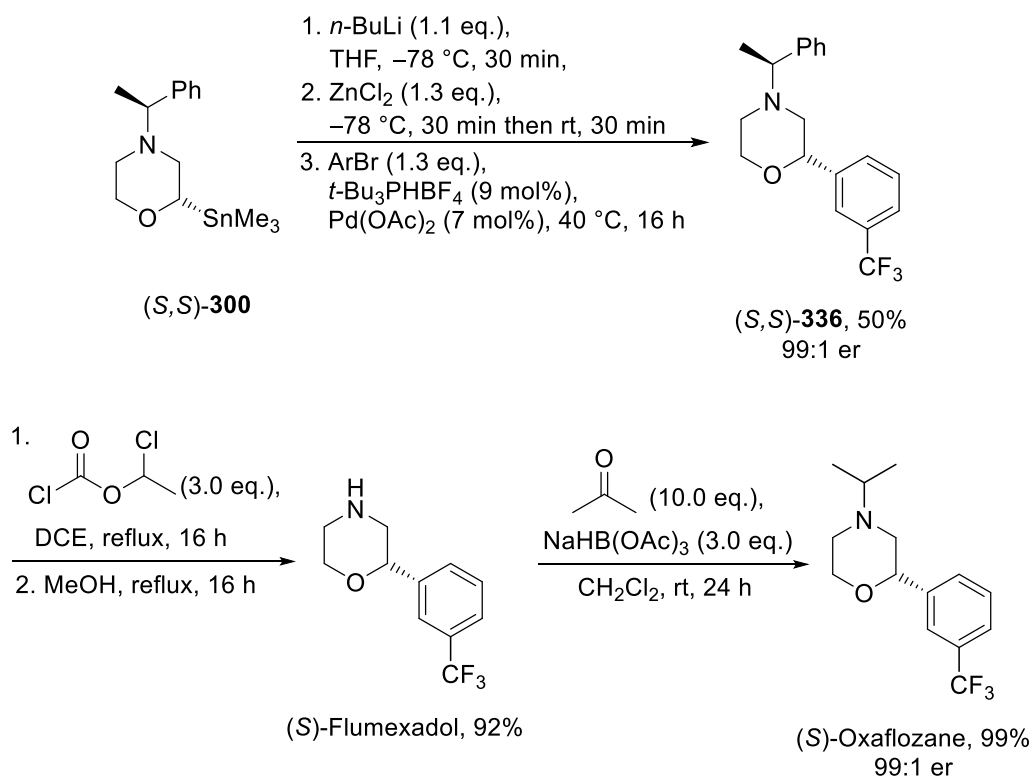
Scheme 3.67 Synthesis of Oxaflozane and Flumexadol by Mauvernay.

The eight-step synthesis of PF219,061 reported by Pfizer is shown in Scheme 3.68. Starting with aldehyde **355**, addition of cyanide and subsequent reduction with BH_3 gave amine **356** in 69% yield. Then, amide formation with propanoyl chloride and reduction led to amino alcohol **357** (62% yield). Subsequent acylation, base-mediated cyclisation and reduction with BH_3 gave morpholine **359** in 83% yield over three steps. Finally, the phenol substituent was revealed by cleavage of the methyl ether using HBr to give PF-219,061 in 85% yield.



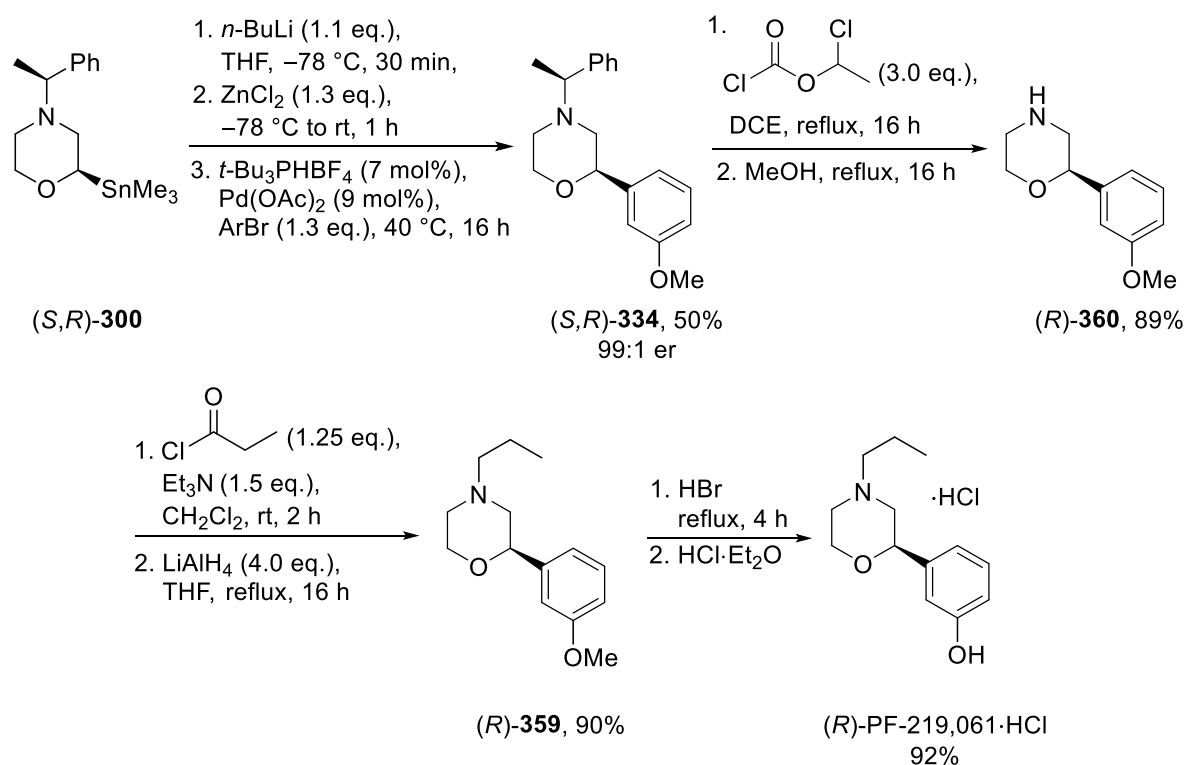
Scheme 3.68 Synthesis of PF-219,061 by Pfizer.

To the best of our knowledge, flumexadol and oxaflozane have only been synthesised as racemates. Our methodology would allow the synthesis of highly enantioenriched derivatives and both enantiomers could be accessed starting from α -stannyl morpholine (*S,S*)-**300** or (*S,R*)-**300**. Both (*S*)-flumexadol and (*S*)-oxaflozane were selected as targets for our new methodology and the synthesis starting from stannane (*S,S*)-**300** is shown in Scheme 3.69. As described previously, α -stannyl morpholine (*S,S*)-**300** was converted into α -aryl morpholine (*S,S*)-**336** in 50% yield. Treatment of morpholine (*S,R*)-**336** with α -chloroethyl chloroformate and MeOH gave (*S*)-flumexadol in 92% yield. Finally, reductive amination using acetone gave the desired (*S*)-oxaflozane in 99% yield and 99:1 er.



Scheme 3.69 Synthesis of (S)-Oxaflozane Starting from Stannane (S,S)-300.

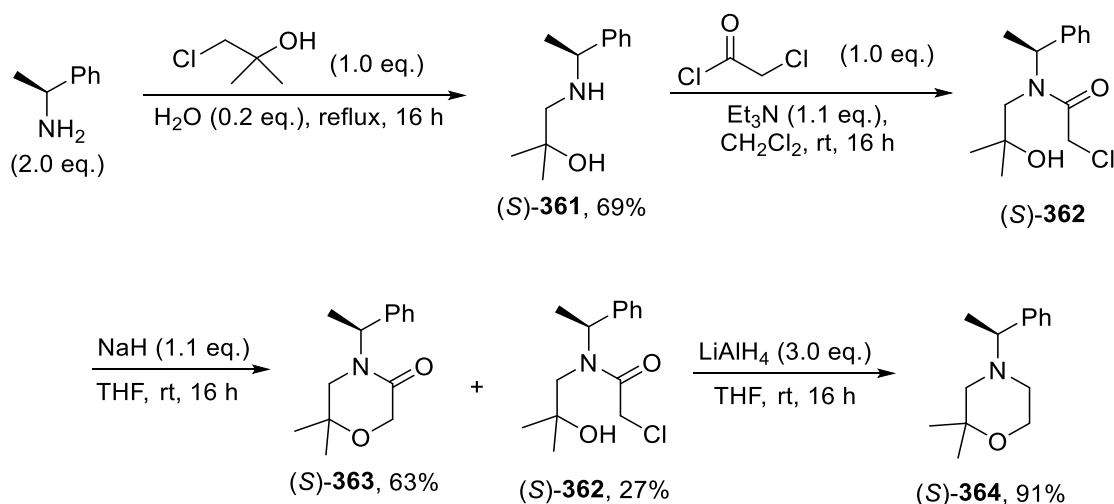
The previously synthesised α -stannyl morpholine (S,R)-**334** (see Scheme 3.62) was reacted with α -chloroethyl chloroformate and MeOH to give α -aryl morpholine (R)-**360** in 89% yield (Scheme 3.70). Then, acylation with propanoyl chloride gave a morpholine amide, which was immediately treated with LiAlH_4 to give *N*-propyl morpholine (R)-**359** in 90% yield. Finally, removal of the methyl group in the methyl ether using Pfizer's procedure with HBr gave (R)-PF-219,061 in 92% yield.¹⁵


 Scheme 3.70 Synthesis of (*R*)-PF-219,061·HCl Starting from Stannane (*S,R*)-300.

Starting from α -stannyl morpholines (*S,S*)-**300**, the synthesis of flumexadol and oxaflozane was accomplished in two and three steps respectively. The synthesis of PF219,061 was successful using α -stannyl morpholine (*S,R*)-**300** as the starting material and in five steps.

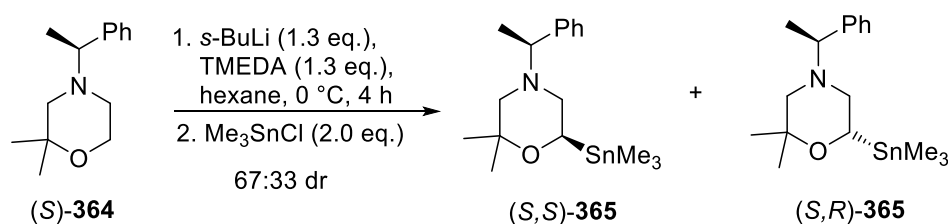
3.4.6 Attempted Synthesis of other α -Stannyl Morpholines and Analogues

It was briefly explored whether this strategy for the synthesis of enantioenriched morpholines could be extended to other morpholines and a homomorpholine. With this in mind, dimethylmorpholine (*S*)-**364** was prepared as outlined in Scheme 3.71. In the first step, following a procedure by Musker et al.,¹⁷⁵ starting from α -methylbenzylamine, addition of 1-chloro-2-methylpropan-2-ol led to the formation of secondary amine (*S*)-**361** in 69% yield. Amide formation *via* an acylation protocol from the synthesis of morpholine derivatives reported by Dugar et al.¹⁷⁶ and subsequent cyclisation gave a 70:30 mixture (by ¹H NMR spectroscopy) of morpholinone (*S*)-**363** (63%) and amide (*S*)-**362** (27%). Finally, reduction of the mixture of morpholinone (*S*)-**363** and amide (*S*)-**362** using LiAlH₄ gave morpholine (*S*)-**364** in 91% yield.



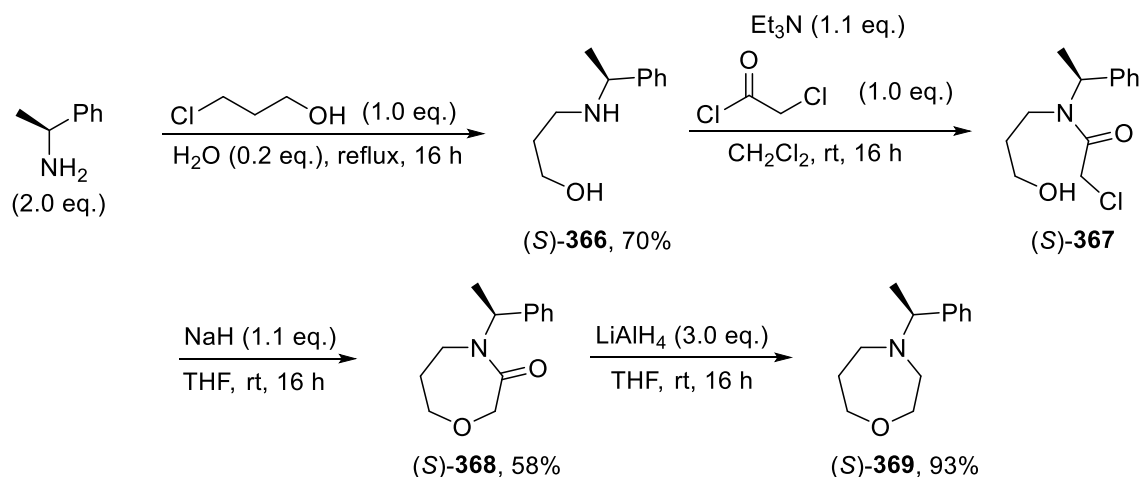
Scheme 3.71 Synthesis of Morpholine (S)-364.

Next, the lithiation-trapping of morpholine (S)-364 was investigated (Scheme 3.72). In previous studies in the O'Brien group, the lithiation of α -substituted morpholines was explored and longer lithiation times (4 h, 0 °C) were needed due to a slower lithiation rate (see section 1.3.2). Therefore, the lithiation of dimethyl morpholine (S)-364 was investigated using *s*-BuLi/TMEDA in hexane at 0 °C for 4 h. Subsequent trapping with Me₃SnCl gave a mixture of starting morpholine (S)-364 and α -stannyl morpholines (S,R)-365 and (S,S)-365. Based on ¹H NMR spectroscopy of the crude product, the reaction gave a 58:28:14 inseparable mixture of starting morpholine (S)-364, α -stannyl morpholine (S,S)-365 and α -stannyl morpholine (S,R)-365 i.e. a 67:33 ratio of α -stannyl morpholines (S,S)-365 and (S,R)-365 was generated. As a result subsequent Sn-Li exchange was not attempted.



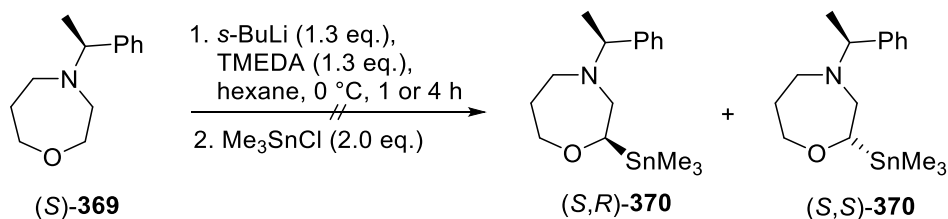
Scheme 3.72 Lithiation-Trapping of Morpholine (S)-364.

The synthesis of the 7-membered homomorpholine (S)-369 (Scheme 3.73) was also carried out. Addition of 3-chloropropanol to α -methylbenzylamine gave alcohol (S)-366 in 70% yield. In the next step, acylation using 2-chloroacetyl chloride furnished alcohol (S)-367 which was immediately cyclised to give homomorpholine (S)-368 in 58% over both steps. Subsequent reduction generated the desired morpholine (S)-369 in 93% yield.



Scheme 3.73 Synthesis of Homomorpholine (S)-369.

Lithiation of homomorpholine (S)-369 using *s*-BuLi / TMEDA in hexane at 0 °C for 1 h and trapping with Me₃SnCl did not result in any of the desired α -stannyl homomorpholine (S,R)-370 and (S,S)-370 being formed and only starting morpholine (S)-369 was recovered. A longer lithiation time of 4 h and trapping with Me₃SnCl gave the same result (Scheme 3.74). The low reactivity of homomorpholine (S)-369 is in accordance with observations in the lithiation of *N*-Boc azepane. *In situ* IR spectroscopic analysis using ReactIR in the lithiation of the corresponding *N*-Boc azepane in the O'Brien group showed a very slow rate of lithiation for the 7-membered *N*-Boc heterocycle.¹⁰⁹



Scheme 3.74 Attempted Lithiation-Trapping of Homomorpholine (S)-369.

Unfortunately, the synthesis of further morpholine stannane derivatives was unsuccessful. In future work, the lithiation-trapping conditions for the homomorpholine could be investigated in more detail. It is possible that the lithiation can be performed at temperatures greater than 0 °C as starting material was recovered in our initial reactions.

3.5 Conclusions and Future Work

In summary, new approaches for the synthesis of enantioenriched α -substituted oxygen heterocycles *via* asymmetric deprotonation were explored. With the asymmetric deprotonation approach, the best results were obtained for the lithiation of THF using *s*-BuLi / (+)-sparteine surrogate in CPME at $-60\text{ }^{\circ}\text{C}$ for 4 h. Trapping was accomplished with five different electrophiles to give α -substituted THFs in 25-47% yield and 79:21-81:19 er (Figure 3.6). In addition, the enantioenriched α -stannyl THF (*S*)-**158** was used as a substrate in stereospecific Sn-Li exchange, transmetallation and Negishi cross-coupling and two enantioenriched α -aryl THFs were synthesised in 78:22 er. Unfortunately, the asymmetric deprotonation of THP and *N*-methyl morpholine and trapping with electrophiles gave α -substituted THPs and morpholines with lower enantioselectivity (up to 63:37 er).

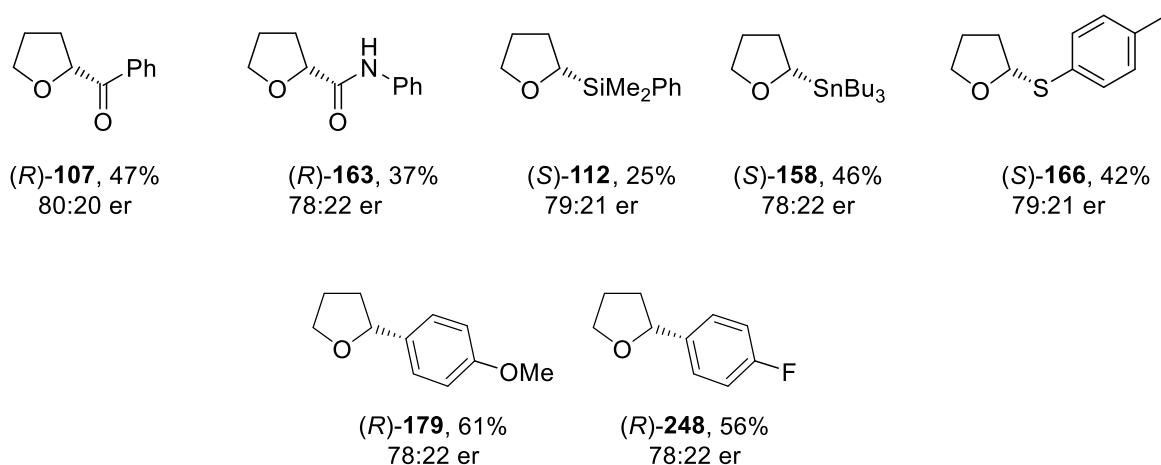
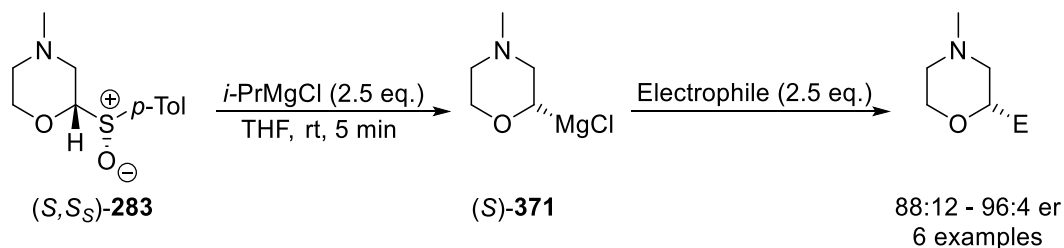


Figure 3.6: Scope in the Enantioenriched α -Substituted THFs.

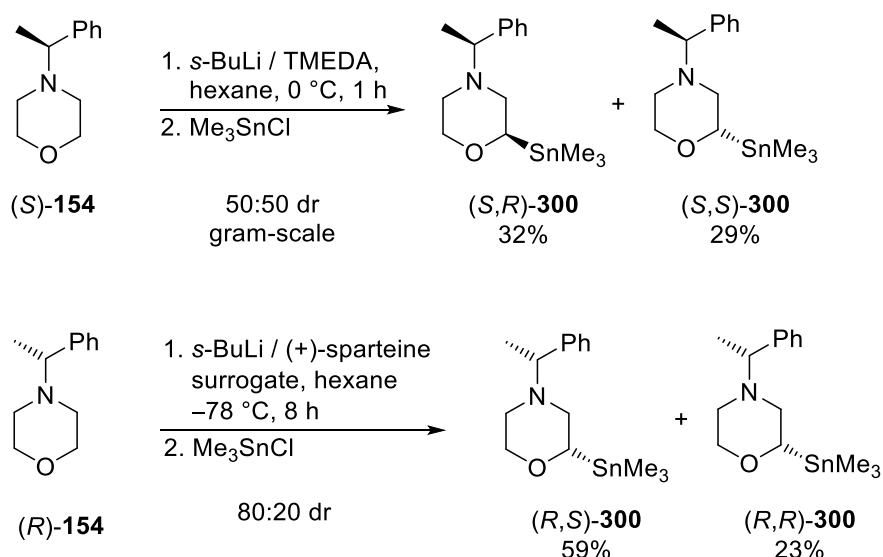
It was then focussed on the synthesis of enantioenriched α -sulfinyl oxygen heterocycles to develop conditions for a subsequent sulfoxide-Mg exchange and trapping with electrophiles. The α -sulfinyl THFs and THPs were found to be unstable. The α -sulfinyl THP could be synthesised in modest yields but rapid fragmentation was observed. It is believed that oxonium ion formation can lead to the elimination of the α -sulfinyl substituent. However, the α -sulfinyl morpholine (*S,S*)-**283** and (*R,S*)-**283** were successfully synthesised *via* lithiation, transmetallation to an organomagnesium species and subsequent trapping with Andersen's sulfinate in good yields and in high ers (up to 96:4). The transmetallation to an organomagnesium species was essential to generate the α -sulfinyl morpholines (*S,S*)-**283** and (*R,S*)-**283** in high ers. Subsequent sulfoxide-Mg exchange of the major α -sulfinyl morpholine (*S,S*)-**283** using *i*-PrMgCl was also studied. Trapping with Weinreb amides and

aldehydes was explored and gave six enantioenriched α -substituted morpholines in high yields (Scheme 3.75).



Scheme 3.75 Sulfoxide-Mg Exchange of (S,S) -**283** and Subsequent Trapping.

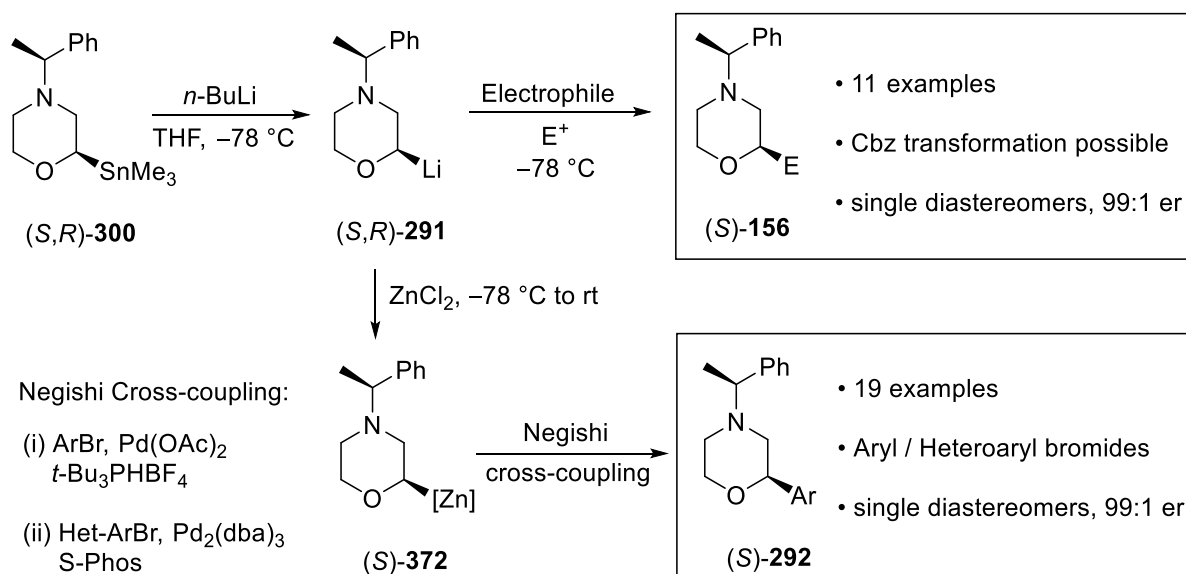
Finally, a protocol to access highly enantioenriched α -substituted morpholines using organostannanes was developed. The key intermediates were the α -methylbenzyl-substituted α -stannyl morpholines (S,R) -**300** and (S,S) -**300** which were separable using chromatography. For the synthesis of the α -stannyl morpholines, two different strategies were studied. Lithiation of morpholine (S) -**154** using *s*-BuLi / TMEDA allowed access to both α -stannyl morpholines (S,R) -**300** and (S,S) -**300** in equal amounts and, in addition, allowed their gram-scale synthesis. Alternatively, an asymmetric lithiation-trapping methodology was developed in which the morpholine (R) -**154** showed a moderate matched case with the induced diastereoselectivity by the *s*-BuLi / (+)-sparteine surrogate complex (80:20 dr). This route allowed the synthesis of α -stannyl morpholine (R,S) -**300** in good yield (Scheme 3.76).



Scheme 3.76 Strategies to Access α -Stannyl Morpholines (S,R) -**300** and (S,S) -**300**.

The enantiopure α -stannyl morpholine (S,R) -**300** and (S,S) -**300** were then used to explore Sn-Li exchange and trapping with a range of electrophiles. In addition, after Sn-Li exchange,

the lithiated species was transmetalated to an organozinc species and Negishi cross-coupling gave access to highly enantioenriched α -aryl morpholines. Selected examples, starting from α -stannyl morpholine (*S,R*)-**300** are depicted in Scheme 3.77. The Sn-Li exchange and trapping or Negishi cross-coupling were stereospecific and α -substituted morpholines were obtained as single diastereomers and in high ers.



Scheme 3.77 Overview of Sn-Li Exchange and Subsequent Trapping or Negishi Cross-Coupling.

Further use of the new methodology was demonstrated by the synthesis of four pharmaceutically relevant compounds. α -Stannyl morpholines (*S,R*)-**300** and (*S,S*)-**300** were used in the synthesis of highly enantioenriched (*R*)-flumexadol (99:1 er), (*R*)-oxaflozane (99:1 er), (*S*)-viloxazine (99:1 er assumed) and (*S*)-PF219,061 (99:1 er assumed) which are shown in Figure 3.7.

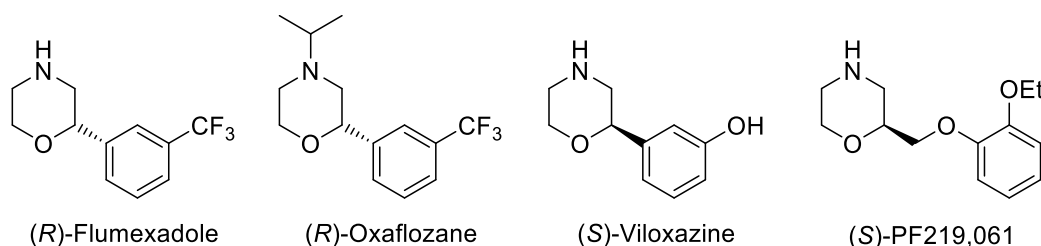
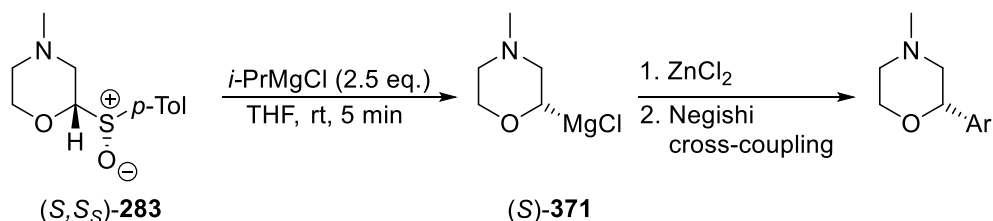


Figure 3.7: Pharmaceutically Relevant Morpholines Accessed via Enantioenriched Stannanes.

In future work, the sulfoxide-Mg exchange of α -sulfinyl morpholines (*S,S*)-**283** and subsequent transmetalation and Negishi cross-coupling could be explored in detail (Scheme 3.78). In particular, the equivalents of aryl bromide should be increased to the same amount of *i*-PrMgCl used in the sulfoxide-Mg exchange to avoid complete consumption of aryl

bromide by coupling with *i*-PrZnCl. This method would be a complementary strategy to the Sn-Li exchange and Negishi protocol of α -stannyl morpholines and would give access to enantioenriched α -aryl morpholines. In addition, this route would allow us to avoid using organotin reagents.



Scheme 3.78 Sulfoxide-Mg Exchange of (S,S)-283 and Negishi Cross-Coupling.

One other proposal for future work would be to identify lithiation-trapping conditions for the synthesis of other α -methylbenzyl-substituted stannanes and three potential targets are shown in Figure 3.8. The lithiation of homomorpholine (S)-369 to give α -stannyl homomorpholine (S,R)-370 could be explored at higher temperatures as the lithiation at 0 °C resulted in the recovery of starting material. In addition, the synthesis of α -stannyl morpholine (S,R)-373 and the α -stannyl thiomorpholine (S,R)-374 could be studied.

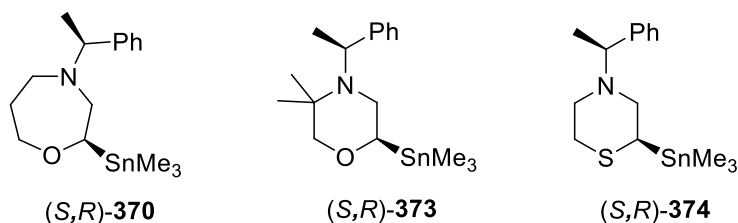
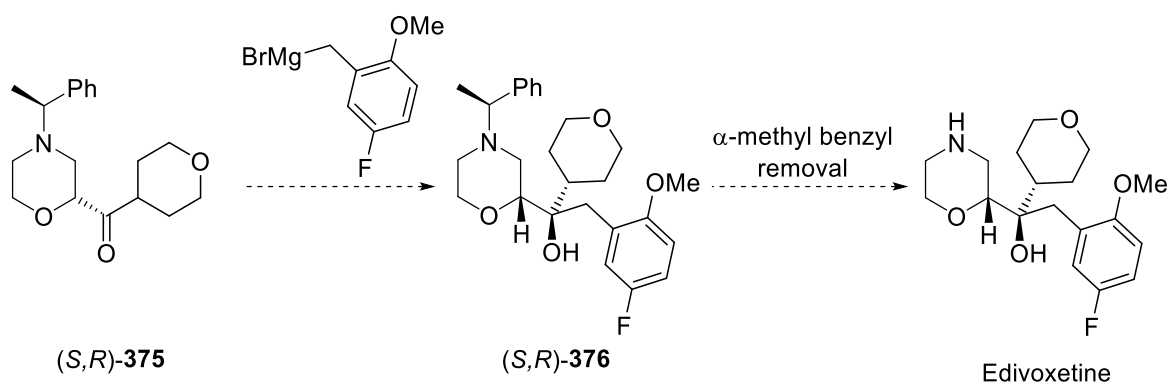


Figure 3.8: α -Methylbenzyl-Substituted Stannanes for Future Sn-Li Exchange Reactions.

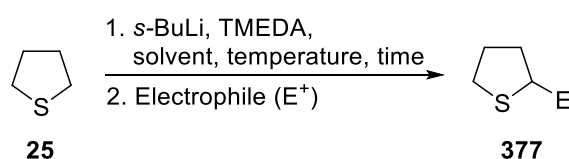
In future, the synthesis of the antidepressant edivoxetine, developed by Eli Lilly could be attempted and a potential route is depicted in Scheme 3.79.¹⁷⁷ α -Stannyl morpholine (S,R)-300 would be used to give ketone (S,R)-375. Subsequent diastereoselective, chelate-controlled Grignard reaction would generate alcohol (S,R)-376.¹⁵⁹ Finally, removal of the α -methylbenzyl substituent would give access to highly enantioenriched edivoxetine in a short synthesis.



Scheme 3.79 Proposed Synthesis of Edivoxetine.

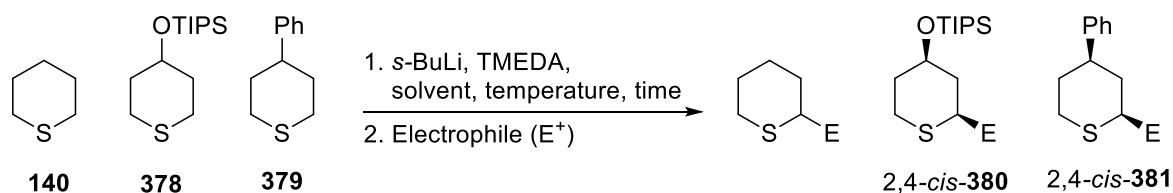
Chapter 4: Lithiation-Trapping of Saturated Sulfur Heterocycles

In Chapter four, the optimisation of methodology for the racemic α -lithiation of saturated sulfur heterocycles and subsequent trapping with electrophiles is presented. To start with, it was planned to study the lithiation of 5-membered tetrahydrothiophene **25** (Scheme 4.1), based on previous results in the α -lithiation of saturated α -substituted oxygen heterocycles. The results in the lithiation-trapping of tetrahydrothiophene **25** to give α -substituted cyclic sulfides **377** are presented in section 4.1.



Scheme 4.1 Proposed Lithiation-Trapping of Tetrahydrothiophene 25.

In addition, it was proposed to expand the lithiation-trapping methodology to 6-membered ring tetrahydrothiopyrans **140**, **378** and **379** (Scheme 4.2). The 4-substituted tetrahydrothiopyrans **378** and **379** would allow us to explore the regio- and stereoselectivity of lithiation-trapping. The results are summarised in section 4.2 and demonstrate that the lithiation-trapping of 4-substituted tetrahydrothiopyrans gave 2,4-*cis*-configured products **380** and **381** (Scheme 4.2).

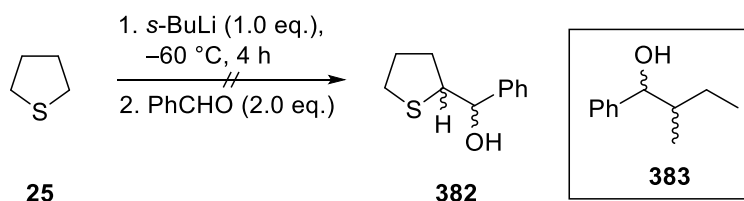


Scheme 4.2 Proposed Lithiation-Trapping of Tetrahydrothiopyran Derivatives.

It was envisaged that other substrates such as 4-membered ring thietanes and thiomorpholines could also undergo lithiation-trapping as described in sections 4.3 and 4.4. In section 4.5, our attempts at α -arylation of saturated sulfur heterocycles are presented.

4.1 Lithiation-Trapping of Tetrahydrothiophenes

Based on our successes with oxygen heterocycles described in the previous chapters, it was decided to explore the lithiation-trapping of saturated sulfur heterocycles using similar reaction conditions. Initially, the 5-membered ring tetrahydrothiophene **25** was investigated. Using one of the conditions for lithiation of THF (*s*-BuLi, $-60\text{ }^{\circ}\text{C}$, 4 h) with tetrahydrothiophene **25** (as solvent and substrate) and benzaldehyde as the electrophile, the formation of the desired alcohols **382** was not observed. Instead, the exclusive formation of direct trapped product **383** was observed (by analysis of the ^1H NMR spectrum of the crude product) (Scheme 4.3). Deprotonation of tetrahydrothiophene **25** was not observed, indicating that the reactivity of tetrahydrothiophene **25** towards lithiation is lower than that of THF.

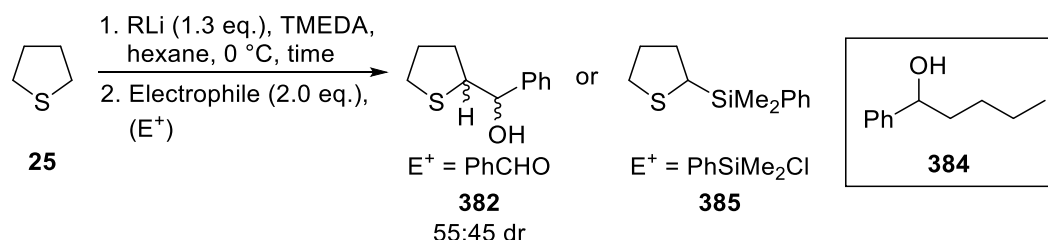


Scheme 4.3 Attempted Lithiation-Trapping of Tetrahydrothiophene 25.

Therefore, reactions at $0\text{ }^{\circ}\text{C}$ were explored and the conditions were modified significantly. Thus, the *s*-BuLi / TMEDA complex in hexane was used to lithiate 1 eq. of tetrahydrothiophene **25**. A study of different reaction conditions is presented in Table 4.1. Using 1.3 eq. of *s*-BuLi / TMEDA in hexane at $0\text{ }^{\circ}\text{C}$ for 1 h and trapping with benzaldehyde a 55:45 mixture of unassigned diastereomeric alcohols **382** (based on ^1H NMR spectroscopy of the crude product) was generated. After chromatography, alcohols **382** were isolated in 87% yield (entry 1). To try to reduce the amount of TMEDA used, a catalytic approach was explored. Use of 0.1 eq. or 0.3 eq. of TMEDA (3 h lithiation time) gave a 9% yield and a 31% yield of alcohols **382** respectively (entries 2 and 3). Since the yields essentially matched the amount of TMEDA used, no catalytic effect was observed and it can be concluded that a stoichiometric amount of TMEDA is essential to obtain trapped products in high yield. The use of *n*-BuLi instead of *s*-BuLi gave direct trapped product **384**, as shown by ^1H NMR spectroscopy of the crude product (entry 4). Presumably, *n*-BuLi is not reactive enough to deprotonate α to sulfur. For further optimisation, PhSiMe_2Cl was used as the product was easier to purify by chromatography. Lithiation times of 2 min, 20 min and 1 h were compared (entries 5-7). After a lithiation time of 2 min or 20 min and trapping with

PhSiMe₂Cl, silane **385** was obtained in 29% and 66% yield respectively (entries 5 and 6). Direct trapped product was observed in the crude product but was not isolated. A lithiation time of 60 min followed by trapping with PhSiMe₂Cl gave the highest yield of silanes **385** (86%, entry 7).

Table 4.1: Investigation of the Lithiation-Trapping Conditions for Tetrahydrothiophene 25.



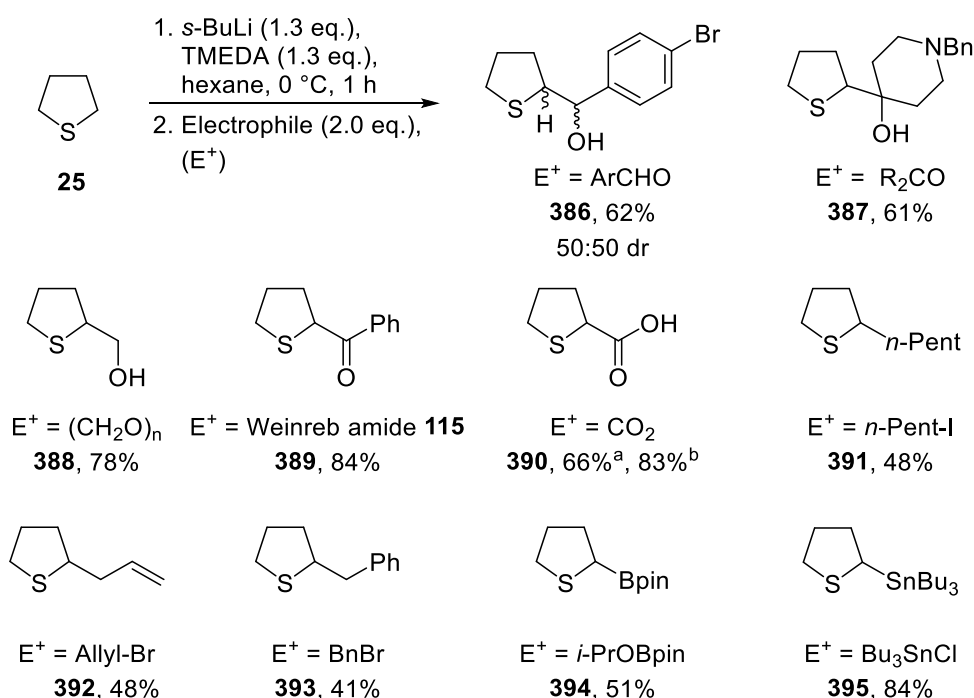
Entry	RLi	TMEDA / eq.	Lithiation time / min	E ⁺	Product	Yield / % ^a
1	<i>s</i> -BuLi	1.3	60	PhCHO	382^b	87
2	<i>s</i> -BuLi	0.1	180	PhCHO	382^b	9
3	<i>s</i> -BuLi	0.3	180	PhCHO	382^b	31
4	<i>n</i> -BuLi	1.3	60	PhCHO	382^b	n.d. ^c
5	<i>s</i> -BuLi	1.3	2	PhSiMe ₂ Cl	385	29
6	<i>s</i> -BuLi	1.3	20	PhSiMe ₂ Cl	385	66
7	<i>s</i> -BuLi	1.3	60	PhSiMe ₂ Cl	385	86
8	<i>s</i> -BuLi	1.3	120	PhSiMe ₂ Cl	385	84
9	<i>s</i> -BuLi	1.3	240	PhSiMe ₂ Cl	385	77

^aYield after purification by chromatography, ^b55:45 dr by ¹H NMR spectroscopy of the crude product, ^cdirect trapped addition product **384** formed but yield not determined.

Longer lithiation times (2 h and 4 h) at 0 °C and trapping with PhSiMe₂Cl gave the desired product **385** in high yields (84% and 77%) suggesting a high stability of the lithiated species at 0 °C (Table 4.1, entries 8-9). Interestingly, the lithiated tetrahydrothiophene **25** in the presence of TMEDA in hexane has a much higher stability than the metallated tetrahydrothiophene that was generated using a Schlosser base, as reported by Glass.¹¹² Under Glass' reaction conditions, metallation using the *n*-BuLi / KO*t*-Bu Schlosser base in THF at 5 °C for 1 h led to complete fragmentation of the metallated species (Scheme 1.71). It is possible that the lithiated species is stabilised by the TMEDA ligand or it may be that the presence of the potassium counterion is the source of instability in Glass' conditions. The

lithiation of tetrahydrothiophene **25** using 1.3 eq. of *s*-BuLi / TMEDA in hexane at 0 °C for 1 h will be referred to as the standard conditions.

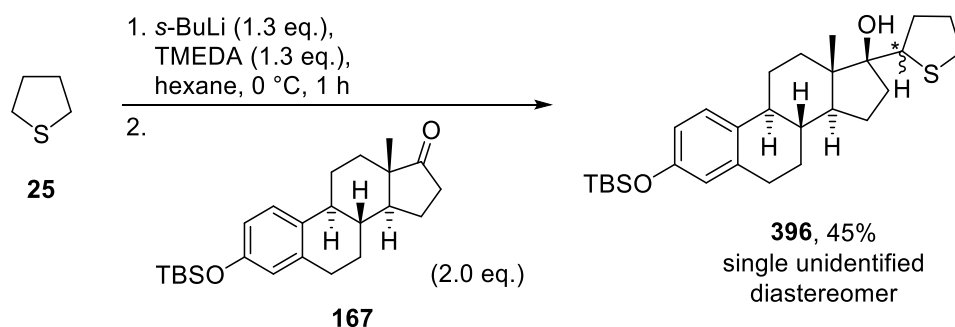
Using the standard lithiation conditions, the trapping of tetrahydrothiophene **25** with several electrophiles was investigated (Scheme 4.4). The lithiated species was trapped with aldehydes and ketones to give the corresponding alcohols **386-388** in 61-78% yield. However, trapping with DMF resulted in only traces of an aldehyde. In contrast, trapping with Weinreb amide **115** gave ketone **389** in 84% yield. For the trapping with CO₂, two different protocols were used. To avoid the formation of the direct trapped product when trapping with CO₂, tetrahydrothiophene **25** was used in excess (3.3 eq.) and the yield was based on the amount of *s*-BuLi. This gave acid **390** in 66% yield. For a gram-scale synthesis of acid **390**, the lithiation was carried out under standard conditions using 20 mmol of the tetrahydrothiophene **25**. Also, the temperature during the trapping process was reduced to -78 °C in case of an exothermic process. Using this method, 2.19 g of acid **390** was obtained (83% yield). Using *n*-pentyl iodine and allyl bromide, trapped products **391** and **392** were each isolated in 48% yield. Trapping with benzyl bromide gave 2-benzyl tetrahydrothiophene **393** in 41% yield whereas trapping with *i*-PrOBpin and Bu₃SnCl gave boronic ester **394** and stannane **395** in 51% and 84% yield respectively.



^aExcess of tetrahydrothiophene used, yield based on *s*-BuLi, ^b20 mmol scale, trapping at -78 °C, then at rt.

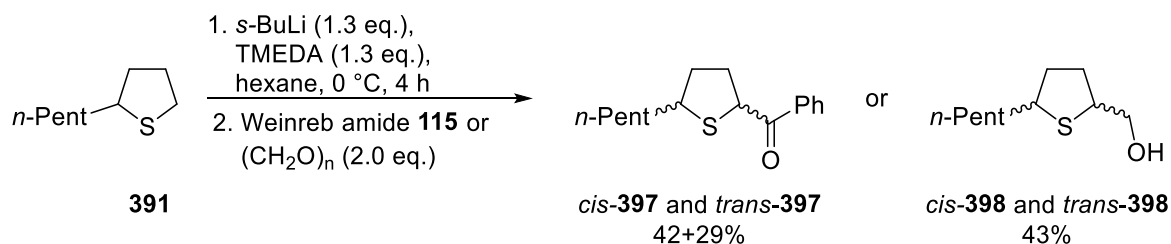
Scheme 4.4 Lithiation of Tetrahydrothiophene **25** and Trapping with Various Electrophiles.

To show further application of this lithiation-trapping methodology, a late-stage style functionalisation of an estrone derivative was performed. Tetrahydrothiophene **25** was lithiated under the standard conditions and then trapped with TBS-protected estrone **167** to give estrone derivative **396** as a single diastereomer in 41% yield (Scheme 4.5). It is assumed that the methyl group of the estrone derivative directs the trapping which presumably occurs from the *Re*-face. However, the stereochemistry α to sulfur is currently unknown.



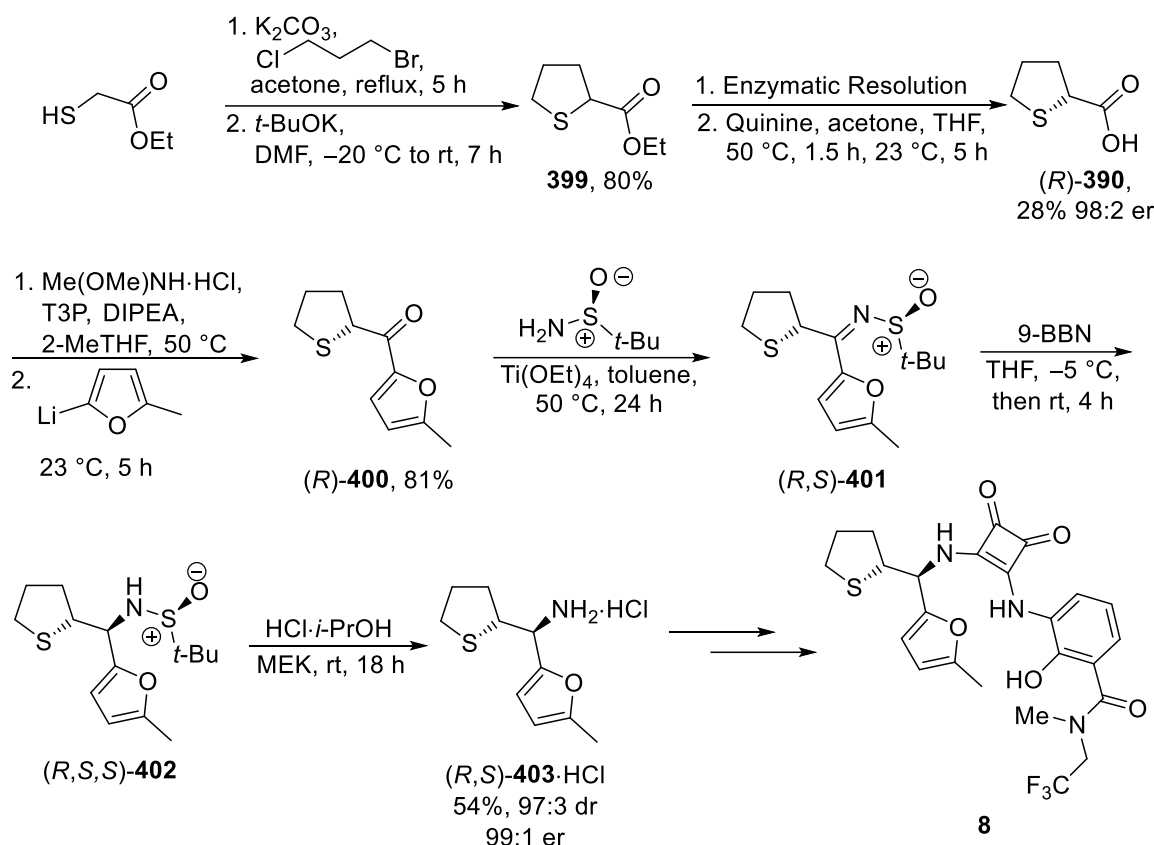
Scheme 4.5 Lithiation of Tetrahydrothiophene **25** and Trapping with TBS-Protected Estrone **167**.

In further experiments, a second trapping of an α -substituted tetrahydrothiophene was investigated. The α -*n*-pentyl substituted tetrahydrothiophene **391** was chosen as the starting material as the *n*-pentyl substituent should be compatible with the relatively harsh lithiation conditions. The lithiation was performed under the established standard conditions (*s*-BuLi / TMEDA in hexane, 0 °C) but the lithiation time was increased to 4 h as it was suspected that the additional substituent would slow down the lithiation (see Scheme 1.68 and Scheme 3.72). Subsequent trapping with Weinreb amide **115** resulted in a mixture of 2,5-substituted tetrahydrothiophenes *cis*-**397** and *trans*-**397** which were separable by chromatography and isolated in 42% and 29% yield (60:40 dr based on ^1H NMR spectroscopy of the crude product) (Scheme 4.6). It was not possible to assign the relative stereochemistry in these two products. The low diastereoselectivity is assumed to be a result of the conformational flexibility of the 5-membered ring. The lack of diastereoselectivity contrasts with the synthesis of 2,4-disubstituted tetrahydrothiopyran ring systems described later (see section 4.2). In a second example, *n*-pentyl tetrahydrothiophene **391** was lithiated under the same conditions and trapped with paraformaldehyde to give a mixture of 2,5-substituted alcohols *cis*-**398** and *trans*-**398** in a combined 43% yield. Due to overlapping signals in the ^1H NMR spectrum, an accurate ratio could not be assigned but the ^{13}C NMR spectrum showed the presence of two diastereomers in approximately equal amounts (Scheme 4.6).



Scheme 4.6 Lithiation-Trapping of α -Pentyl Tetrahydrothiophene **391**.

In order to demonstrate the usefulness of our methodology, there was a particular interest in applying it to the synthesis of amine (*S,R*)-**403** which was a key intermediate in the synthesis of the CXCR antagonist **8** developed by Gerfraud et al. at Nestlé. Gerfraud et al. reported an enantioselective approach towards (*S,R*)-**8** (Scheme 4.7).⁴ Tetrahydrothiopyran ester *rac*-**399** was synthesised in two steps. Subsequent enzymatic resolution *via* ester hydrolysis resulted in carboxylic acid **390** in 93% yield and 98:2 er. Then, acid (*R*)-**390** was converted into a Weinreb amide and reacted with lithiated 2-methyl furan to give ketone (*R*)-**400**. Addition of Ellman's auxiliary generated sulfinyl imine (*R,S*)-**401**. Diastereoselective reduction of the sulfinyl imine (*R,S*)-**401** using 9-BBN gave sulfinamide (*R,S,S*)-**402** in 54% yield after three steps. Final cleavage of the sulfinamide substituent gave amine (*S,R*)-**403** in 97:3 dr and 99:1 er.



Scheme 4.7 Synthesis of Key Intermediate Amine (*S,R*)-403 in the Synthesis of CXCR Antagonist 8.

One of the key steps in this synthesis is the diastereoselective reduction of sulfinyl imine (*R,S*)-401 using 9-BBN. Although not stated in their paper, in order to explain the diastereoselectivity, it was proposed the transition states shown in Figure 4.1 based on work by Chelucci et al.¹⁷⁸ It is assumed that the boron atom of 9-BBN coordinates to the sulfinyl imine resulting in the 6-membered transition state **404**. The tetrahydrothiophenyl substituent is assumed to be higher in steric demand than the planar furanyl substituent and is therefore in the equatorial position in six-membered transition state **404**. Hydride transfer from the boron to the *Re*-face of the imine leads to the diastereoselective formation of the desired sulfinamide (*R,S,S*)-402.

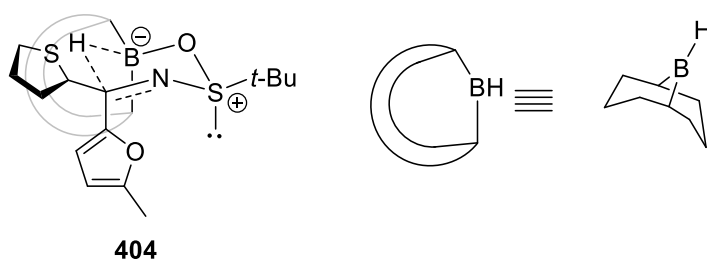
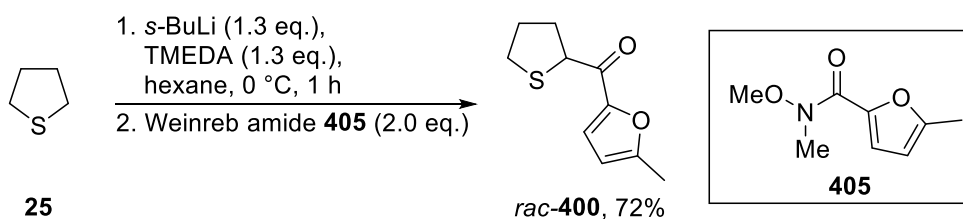


Figure 4.1 Suggested Transition State in the Diastereoselective Reduction Using 9-BBN.

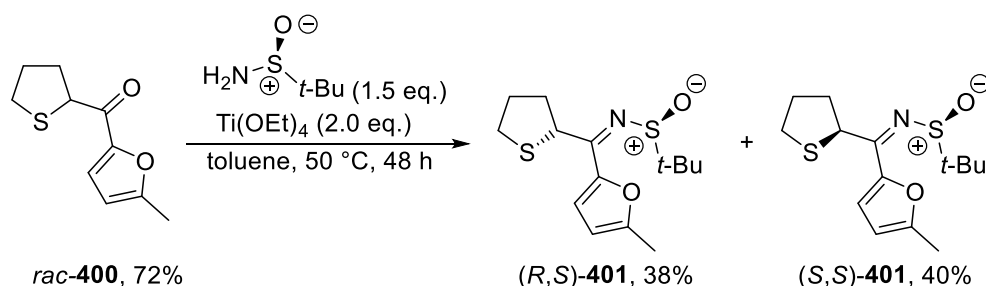
Considering Gerfraud et al.'s synthesis of amine (*R,S*)-**403**, three ways in which our developed lithiation-trapping methodology could provide alternatives were identified. First, as shown in Scheme 4.4, the gram-scale synthesis of acid *rac*-**390** was already carried out *via* lithiation of tetrahydrothiophene and trapping with CO₂. Second, it was proposed to develop a short synthesis of ketone *rac*-**400** *via* lithiation of tetrahydrothiophene **25** and trapping with Weinreb amide **405**. Ketone *rac*-**400** could then be used to synthesise amine (*R,S*)-**403**. Third, we wondered whether the addition of lithiated tetrahydrothiophene to an aldehyde-derived sulfinyl imine could provide a concise, diastereoselective route to amine (*R,S*)-**403** (after removal of the sulfinyl group).

With the second proposed approach in mind, Weinreb amide **405** was synthesised starting from 5-methylfuran-2-carbonyl chloride and methoxymethyl amine in one step in 89% yield. Next, tetrahydrothiophene **25** was lithiated under the standard conditions and trapped with Weinreb amide **405** to give ketone *rac*-**400** in 72% yield (Scheme 4.8). The two-step synthesis compares favourably with Gerfraud et al.'s approach which required five steps but did produce ketone (*R*)-**400** in 98:2 er.



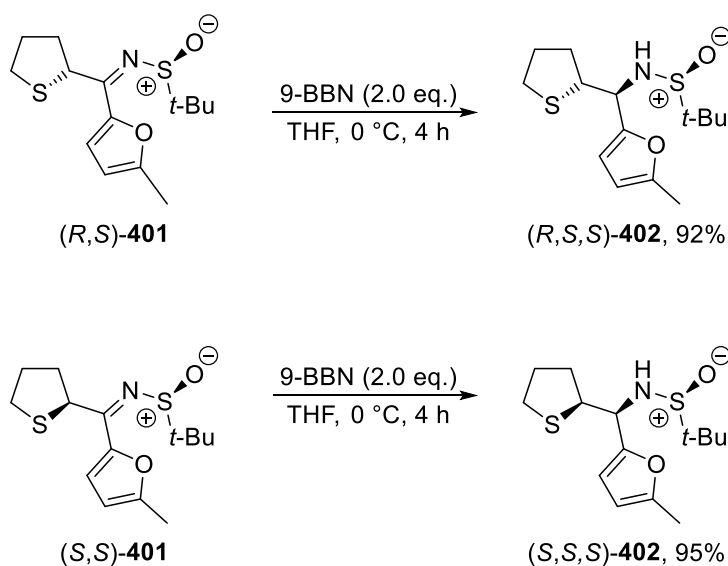
Scheme 4.8 Lithiation of Tetrahydrothiophene and Trapping with Weinreb Amide **405**.

The synthesis of amine (*R,S*)-**403** was then continued *via* the route reported by Gerfraud et al.⁴ Ketone (*R*)-**400** was treated with Ti(OEt)₄ and Ellman's sulfinamide at 50 °C for 48 h to give a 50:50 mixture of sulfinyl imines (*R,S*)-**401** and (*S,S*)-**401**, which were separable and isolated in 38% and 40% yield respectively (Scheme 4.9). Using Ti(Oi-Pr)₄ and Ellman's sulfinamide at a shorter reaction time of 16 h gave the sulfinamides (*R,S*)-**401** and (*S,S*)-**401** in lower yields of 21% and 20% respectively. Sulfinyl imines (*R,S*)-**401** and (*S,S*)-**401** were identified by their subsequent reduction and removal of the sulfinyl substituent, as outlined below. Disappointingly, the condensation reaction was not diastereoselective. However, the chiral sulfinamide auxiliary allowed separation of the two sulfinyl imines using chromatography.



Scheme 4.9 Synthesis of Sulfinyl Imines (*R,S*)-401 and (*S,S*)-401.

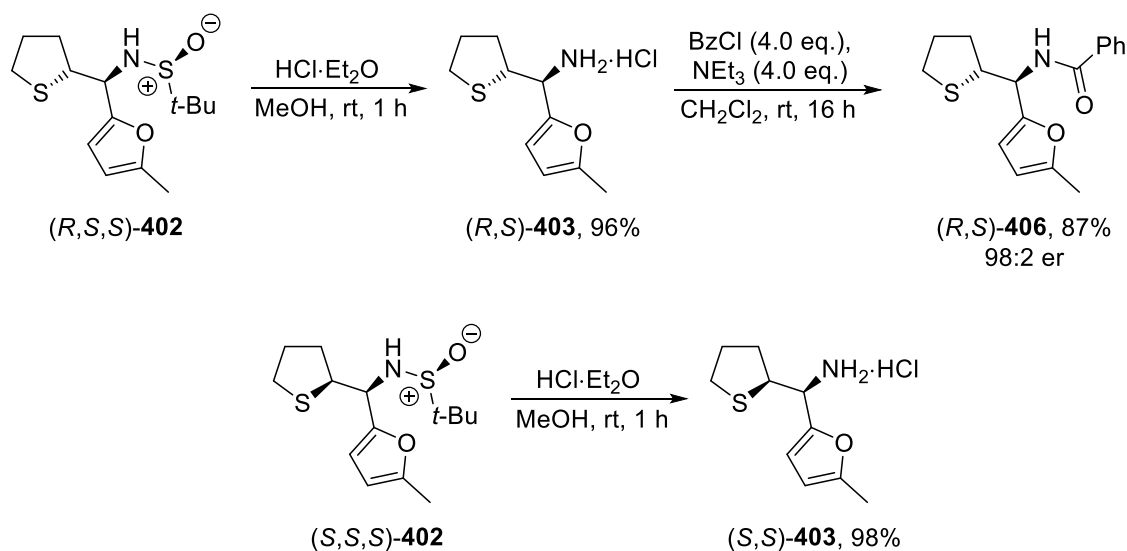
Both diastereomeric sulfinyl imines (*R,S*)-401 and (*S,S*)-401 were independently reduced using 9-BBN. Reduction of the sulfinyl imine (*R,S*)-401 with 9-BBN gave sulfinamide (*R,S,S*)-402 in 92% yield. Under the same reaction conditions, sulfinyl imine (*S,S*)-401 was reduced to give sulfinamide (*S,S,S*)-402 in 95% yield (Scheme 4.10). The stereochemistry of sulfinamides (*R,S,S*)-402 and (*S,S,S*)-402 were assigned based on the removal of the sulfinyl group from each of the sulfinamides (*R,S,S*)-402 and (*S,S,S*)-402 (see Scheme 4.11). Thus, reduction with 9-BBN led in both reactions to the formation of a stereogenic centre with (*S*)-configuration indicating that the reduction is directed by the sulfinamide substituent and in accordance with the transition state model by Chelucci et al. (see Figure 4.1).¹⁷⁸



Scheme 4.10 Reduction of Sulfinamides (*R,S*)-401 and (*S,S*)-401 Using 9-BBN.

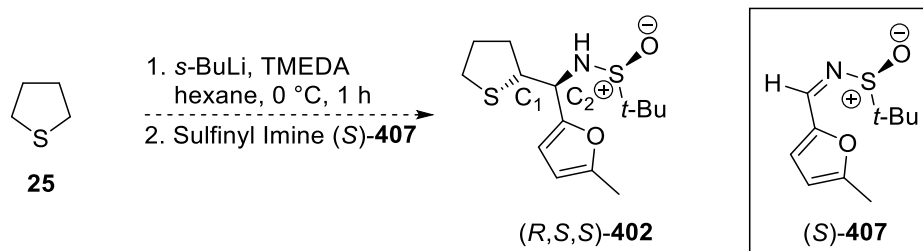
Removal of the sulfinyl substituent in sulfinamide (*R,S,S*)-402 using HCl in Et₂O gave amine (*R,S*)-403·HCl in 96% yield (Scheme 4.11). Comparison of the ¹H NMR spectrum of amine (*R,S*)-403·HCl with that reported by Gerfraud et al. allowed assignment of the relative stereochemistry.⁴ For determination of the *er*, amine (*R,S*)-403·HCl was derivatised to give amide (*R,S*)-406 using benzoyl chloride and Et₃N in 87% yield which allowed the analysis

of the er using CSP-HPLC. Amide (*R,S*)-**406** was shown to be of 98:2 er. For confirmation of the relative stereochemistry, sulfinamide (*S,S,S*)-**402** was converted into amine (*S,S*)-**403**·HCl in 98% yield (Scheme 4.11). Amine (*S,S*)-**403**·HCl was different to amine (*R,S*)-**403**·HCl by ^1H and ^{13}C NMR spectroscopy.



Scheme 4.11 Synthesis of Amines (*R,S*)-**403**·HCl and (*S,S*)-**403**·HCl.

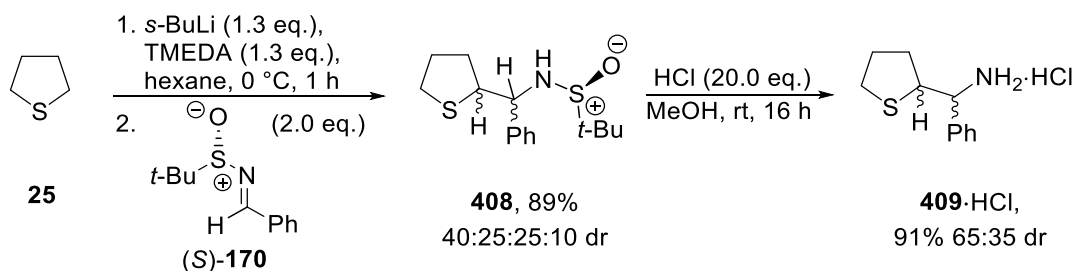
Having explored routes to acid **390** and ketone *rac*-**400**, a direct approach to sulfinamide (*R,S,S*)-**402** was considered *via* lithiation of tetrahydrothiophene **25** and subsequent trapping using sulfinyl imine (*S*)-**407** (Scheme 4.12). This concise, high risk strategy would require a good stereocontrol during the trapping process: (i) the Ellman auxiliary of sulfinyl imine (*S*)-**407** would need to control the attack at the imine carbon by the lithiated tetrahydrothiophene; (ii) stereocontrol at carbon C1 during the trapping process would also be required.



Scheme 4.12 Proposed Route for the Synthesis of (*R,S,S*)-**402**.

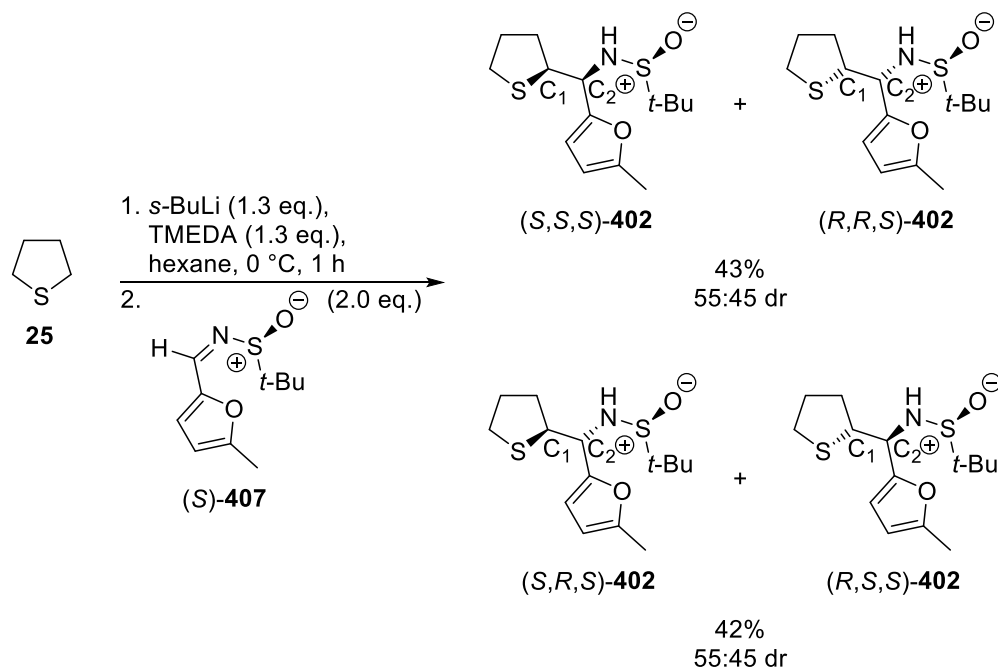
To test the direct lithiation-trapping approach, phenyl-substituted sulfinyl imine (*S*)-**170**, derived from benzaldehyde was used in a model reaction. Lithiation of tetrahydrothiophene **25** under standard conditions and trapping with sulfinyl imine (*S*)-**170** gave an inseparable 40:25:20:15 mixture of all four diastereomeric sulfinamides **408** in 89% yield (by ^1H NMR spectroscopy). Subsequent treatment with HCl in MeOH gave a 65:35 mixture of amines **409**·HCl in 91% yield (^1H NMR spectroscopy) (Scheme 4.13). The exact stereochemistry is

unknown but a 65:35 diastereoselectivity was encouraging enough to explore the reaction on the real system.



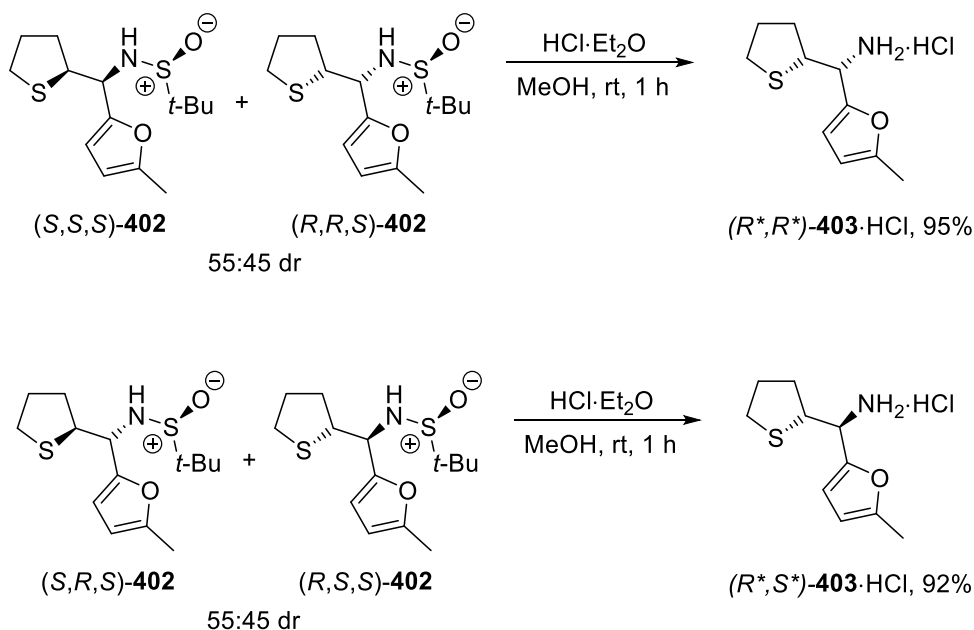
Scheme 4.13 Lithiation of Tetrahydrothiophene **25** and Trapping with Sulfinyl Imine (S)-**170**.

Lithiation of tetrahydrothiophene **25** and trapping with sulfinyl imine (S)-**407** resulted in the formation of a 25:25:25:25 mixture of sulfinamides **402** in (by ^1H NMR spectroscopy of the crude product). Disappointingly, no control of the stereocentres at the C1 and C2 positions was observed. Chromatography allowed the separation of two sets of diastereomers. A 55:45 mixture of sulfinamides (S,S,S)-**402** and (R,R,S)-**402** (43% combined yield) and a 55:45 mixture of sulfinamides (S,R,S)-**402** and (R,S,S)-**402** (42% combined yield) were isolated after chromatography (Scheme 4.13). The relative stereochemistry of the products was assigned by comparison of the ^1H NMR spectra of the sulfinamide mixtures with those of the sulfinamides (R,S,S)-**402** and (S,S,S)-**402** synthesised from ketone *rac*-**400** (see Scheme 4.10) and by removal of the sulfinyl group (see Scheme 4.11).



Scheme 4.14 Lithiation of Tetrahydrothiophene **25** and Trapping with Sulfinyl Imine (S)-**407**.

Sulfinamides (*R,R,S*)-**402** and (*S,S,S*)-**402** were not separable using chromatography. However, treatment of a 55:45 mixture of sulfinamides (*S,S,S*)-**402** and (*R,R,S*)-**402** with HCl·Et₂O gave the racemic amine (*R*,R**)-**403**·HCl as a single diastereomer in 95% yield (Scheme 4.15). The configuration of amine (*R*,R**)-**403**·HCl was assigned by comparison of the ¹H NMR spectrum of the product with that reported by Gerfraud et al.⁴ Similarly, a 55:45 mixture of sulfinamides (*S,R,S*)-**402** and (*R,S,S*)-**402** gave racemic amine (*S*,R**)-**403**·HCl (Scheme 4.15)



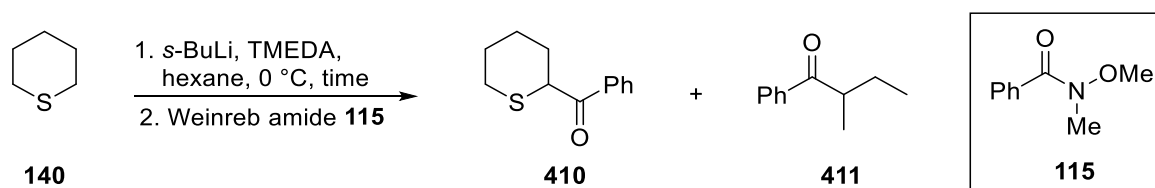
Scheme 4.15 Synthesis of (*R*,R**)-**403**·HCl and (*R*,S**)-**403**·HCl.

In summary, enantioenriched amine (*R,S*)-**403** (98:2 er) was synthesised *via* formation of ketone *rac*-**400**, sulfinyl imine formation and separation of diastereomers, diastereoselective reduction and removal of the sulfinyl substituent in four steps. The direct lithiation of tetrahydrothiophene **25** and trapping with sulfinyl imine (*S*)-**407** allowed the synthesis of racemic amine (*R*,R**)-**403**·HCl in two steps. Unfortunately, no diastereoselectivity was induced during the trapping process with sulfinyl imine (*S*)-**407**.

4.2 Lithiation-Trapping of Tetrahydrothiopyrans

The lithiation-trapping of tetrahydrothiopyran **140** was explored next and optimisation included varying the amount of *s*-BuLi / TMEDA as well as the lithiation time and temperature (Table 4.2). Use of *s*-BuLi / TMEDA in hexane at 0 °C for 1 h and trapping with a Weinreb amide **115** gave ketone **410** in 45% yield and direct trapped product **411** in 50% yield (entry 1). The large amount of direct trapped product **411** suggested that lithiation of tetrahydrothiopyran was incomplete under the conditions used for tetrahydrothiophene **25**. Use of a longer lithiation time (2 h) gave only a slight improvement (58% yield of **410**, entry 2). In contrast, increasing the equivalents of *s*-BuLi / TMEDA to 2.0 eq. (1 h lithiation time) was more successful and ketone **410** was obtained in 85% yield (entry 3). Under the same conditions and a lithiation time of 2 h, ketone **410** was isolated in 91% yield (entry 4). Lithiation-trapping at –10 °C for 2 h resulted in ketone **410** in a lower yield (61%) and direct trapped product **411** in 32% yield (entry 5).

Table 4.2: Investigation of the Lithiation-Trapping Conditions for Tetrahydrothiophene **140**.



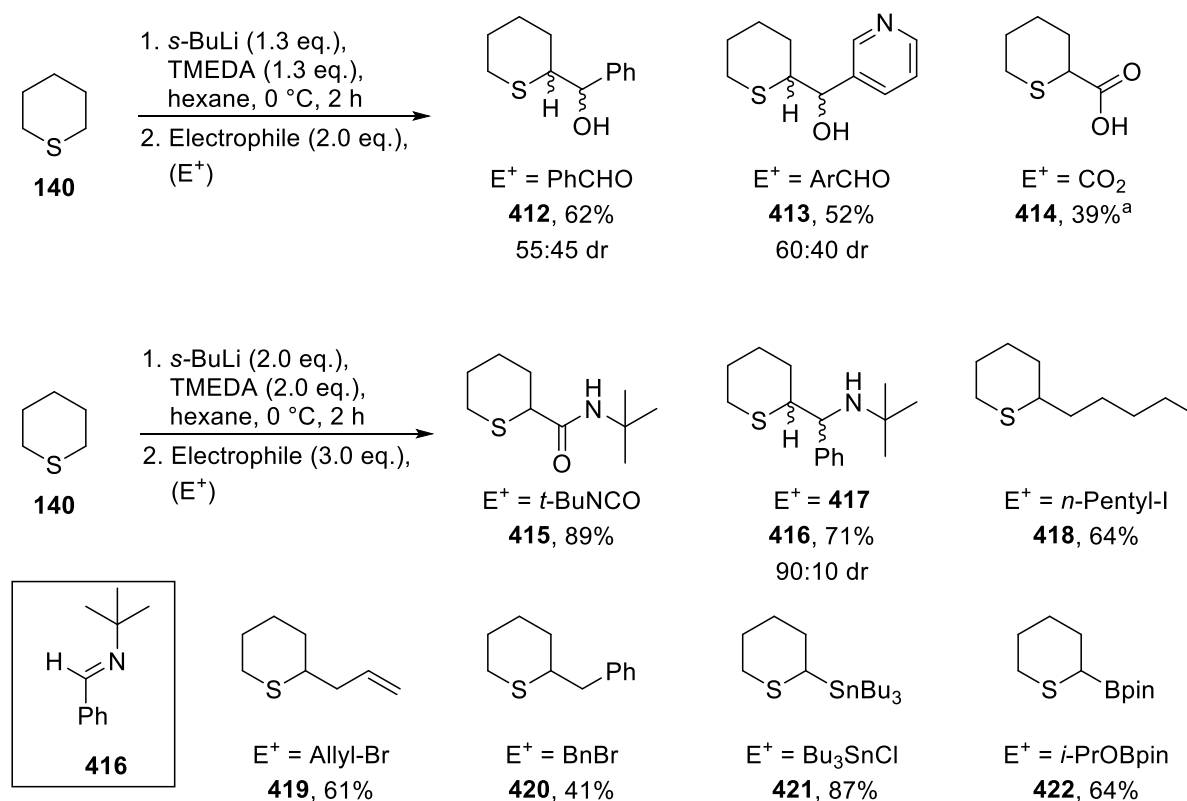
Entry	<i>s</i> -BuLi TMEDA / eq.	Lithiation time/ h	Weinreb amide / eq.	Yield of 410 /% ^a	Yield of 411 /% ^a
1	1.3	1	2.0	45	50
2	1.3	2	2.0	58	n.d. ^b
3	2.0	1	3.0	85	n.d. ^b
4	2.0	2	3.0	91	n.d. ^b
5 ^c	2.0	2	3.0	61	32

^aYield after purification by chromatography, ^bdirect trapped addition product **411** formed but % yield not determined, ^clithiation-trapping at –10 °C.

Comparing the results for tetrahydrothiophene **25** (see Table 4.1) with those for tetrahydrothiopyran **140** (Table 4.2), it appears that the 6-membered tetrahydrothiopyran **140** is slower to be lithiated. This lower reactivity is in accordance with the results for 5- and 6-membered oxygen heterocycles in the O'Brien group and known in the literature for the corresponding *N*-Boc heterocycles.^{91, 108} Investigation of the rate of lithiation of

tetrahydrothiophene **25** using *in situ* ReactIR spectroscopy by a group member was unfortunately unsuccessful.¹⁰⁷ Due to the low intensity of the signals, a characteristic signal accounting for the formation of a lithiated species during the lithiation could not be identified.

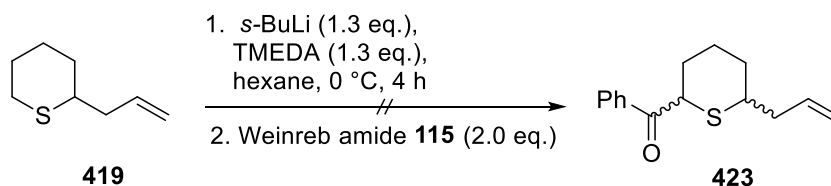
The lithiation-trapping of tetrahydrothiopyran **140** worked well with range of electrophiles (Scheme 4.16). For purification reasons, when trapping with aldehydes, 1.3 equivalents of *s*-BuLi / TMEDA and 2.0 eq. of electrophile were used. In this way, benzaldehyde and nicotinaldehyde gave alcohols **412** (55:45 dr) in 62% yield and **413** (55:45 dr) in 52% yield respectively. Trapping with CO₂ gave carboxylic acid **414** in 37% yield. Lithiation of tetrahydrothiopyran **140** using 2.0 eq. of *s*-BuLi / TMEDA 0 °C for 2 h and trapping with *t*-BuNCO gave amide **415** in 89% yield. Reaction of imine **416** with the lithiated species gave amine **417** in 71% yield and a high diastereomeric ratio of 90:10. The trapping with *n*-pentyl iodide resulted in 2-pentyl substituted tetrahydrothiopyran **418** in 64% yield. A yield of 61% of allyl tetrahydrothiopyran **419** was obtained with allyl bromide. Using 1.3 eq. of *s*-BuLi / TMEDA in the lithiation step gave pentyl substituted tetrahydrothiopyran **418** and allyl tetrahydrothiopyran **419** in 33% and 32% respectively. Trapping with benzyl bromide resulted in 2-benzyl tetrahydrothiopyran **420** in 41% yield. The results with *n*-pentyl iodide and benzyl bromide are notable since alkyl halides do not always react satisfactorily with organolithium intermediates. Trapping with Bu₃SnCl was successful to give stannane **421** (87% yield). With *i*-PrOBpin boronic ester **422** was isolated in 64% yield.



^aExcess of tetrahydrothiopyran used, yield based on *s*-BuLi, trapping at -78 °C, then at rt.

Scheme 4.16 Lithiation-Trapping of Tetrahydrothiopyran **140** with Various Electrophiles.

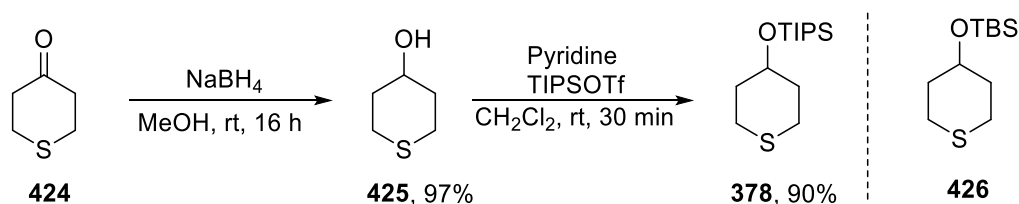
To investigate if an allylic group was compatible with the lithiation-trapping protocol, 2-allyl tetrahydrothiopyran **419** was lithiated using *s*-BuLi and TMEDA in hexane at 0 °C for 4 h and then trapped with Weinreb amide **115** (Scheme 4.17). Disappointingly, the desired 2,6-disubstituted tetrahydrothiopyran **423**, was not formed. Instead, an inseparable mixture of several products was formed (as shown by ¹H NMR spectroscopy). Allylic lithiation or alkene carbolithiation are postulated side-reactions. A successful synthesis of 2,6-*cis,cis*-disubstituted tetrahydrothiopyran **2,4,6-cis,cis-440** is presented in Scheme 4.23. The introduced allyl group was reduced to the corresponding alkyl group before the second lithiation-trapping was attempted.



Scheme 4.17 Attempted Lithiation-Trapping of 2-Allyl Tetrahydrothiopyran **419**.

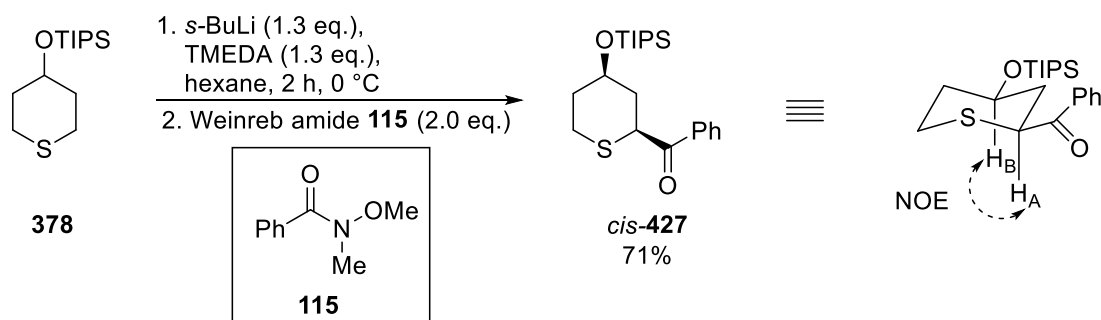
The lithiation-trapping of 4-substituted tetrahydrothiopyrans, was investigated next to gain information on the diastereoselectivity of the lithiation. Previous results in the lithiation-trapping of 4-substituted THP revealed that equatorial lithiation is favoured over axial lithiation leading to 2,4-*cis* configured products (see section 2.3).

TIPS-protected tetrahydrothiopyran **378** was synthesised starting from ketone **424** via reduction to the alcohol **425** and subsequent protection (Scheme 4.18). The TBS-protected tetrahydrothiopyran **426** was synthesised by a co-worker using the same reaction sequence.¹⁰⁶ Due to side-reactions in lithiation-trapping reactions observed when TBS-protected 4-hydroxytetrahydro-thiopyran was used, the sterically more hindered TIPS protecting group was preferred for our studies.



Scheme 4.18 Synthesis of TIPS-Protected 4-Hydroxy Tetrahydrothiopyran **378**.

TIPS-protected 4-hydroxy tetrahydrothiopyran **378** was lithiated under the optimised conditions for tetrahydrothiopyran **140**, namely *s*-BuLi / TMEDA in hexane at 0 °C for 2 h. Subsequent trapping with Weinreb amide **115** gave ketone *cis*-**427** as a single diastereomer in 71% yield (Scheme 4.19).



Scheme 4.19 Lithiation of Tetrahydrothiopyran **378** and Trapping with Weinreb Amide **115**.

Detailed analysis of the HMBC and ¹H, ¹H COSY spectra gave evidence for a 2,4-substituted 6-membered ring system. It was also possible to confirm the stereochemistry of ketone *cis*-**427** by ¹H NMR spectroscopy using ³*J* values. If it has 2,4-*cis* stereochemistry, the 6-membered sulfur ring is expected to have a chair conformation with both groups in equatorial positions. The ¹H NMR spectrum of ketone *cis*-**427** is shown in Figure 4.3. In the case of

ketone *cis*-**427**, proton H_A showed a 2.5 Hz $^3J_{\text{ax-eq}}$ coupling to H_E and an 11.5 Hz $^3J_{\text{ax-ax}}$ coupling to H_G, which indicate that H_A is in an axial position. The $^3J_{\text{ax-ax}}$ couplings between H_B and H_G/H_H of 11.5 Hz and the $^3J_{\text{ax-eq}}$ couplings of H_B and H_E/H_F in the range of 3.5 Hz are evidence for the equatorial position of the OTIPS substituent in the 4-position. Combining all of these ^3J values, the substituents in the 2- and 4-position must be *cis*.

In addition, the relative stereochemistry of ketone *cis*-**427** was assigned using NOESY experiments. The protons H_A and H_B show a NOE interaction and hence both protons can be assigned to be axial (Figure 4.2).

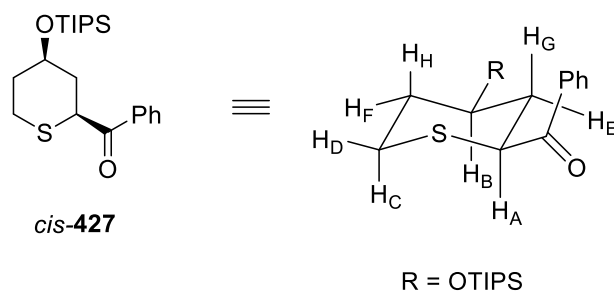


Figure 4.2 Assignment of 2,4-*cis*-Configured Tetrahydrothiopyrans.

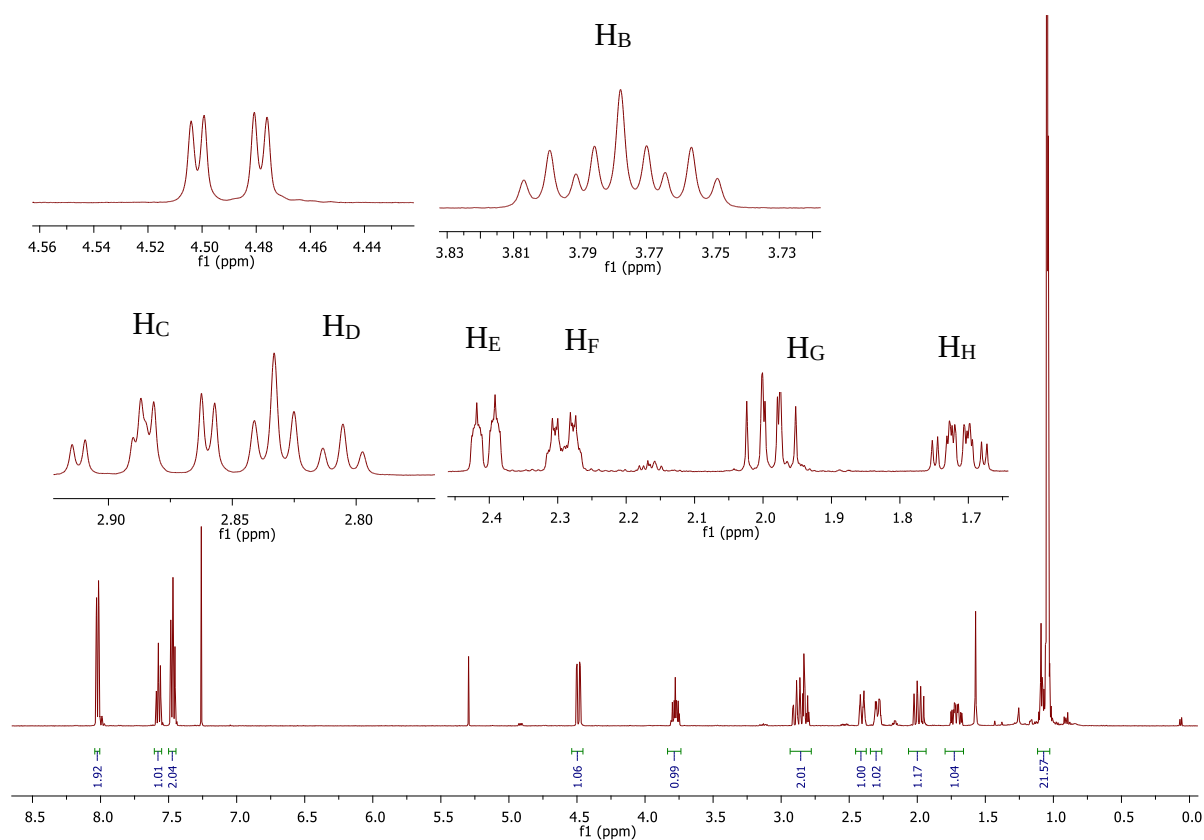
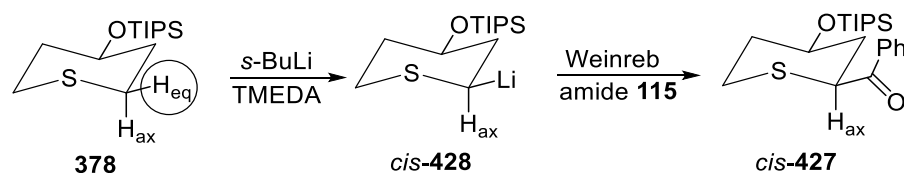


Figure 4.3 ^1H NMR Spectrum of Ketone *cis*-**427**.

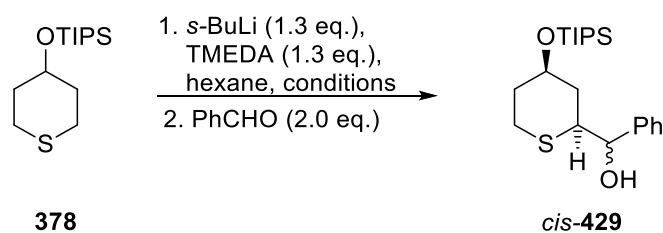
A potential lithiation and trapping pathway is depicted in Scheme 4.20. Preferential lithiation of the equatorial C-2 proton from a tetrahydrothiopyran conformation where the OTIPS group is equatorial would lead to the formation of the lithiated species *cis*-**428**. Subsequent trapping with retention would result in the 2,4-*cis* configured product *cis*-**427**. However, as the lithiation is carried out at 0 °C, an axial deprotonation and immediate equilibration to an equatorial lithiated species *cis*-**428** as the result of a configurationally unstable lithiated species cannot be excluded.



Scheme 4.20 Postulated Equatorial Lithiation of **378** and Trapping with Retention.

Having explored the selectivity of the lithiation-trapping of TIPS-protected 4-hydroxy tetrahydrothiopyran **378** with Weinreb amide **115**, a brief optimisation study on the lithiation-trapping of TIPS-protected 4-hydroxy tetrahydrothiopyran **378** was carried out (Table 4.3). Using benzaldehyde as the electrophile, two diastereomeric alcohols *cis*-**429** (with 2,4-*cis* stereochemistry) were obtained. The stereochemistry could not be proven using ^3J values but the 2,4-*cis* stereochemistry was assigned by analogy with other examples. A lithiation time of 2 h at –20 °C gave alcohols **429** in 66% yield (55:45 dr) and 28% recovered starting material **378** (entry 1). Increasing the temperature to –10 °C (2 h reaction time) resulted in alcohols **429** in 75% yield and starting material **378** (19%) (entry 2). The highest yield (87%) of alcohols **429** and only traces of starting material **378** were obtained after a lithiation time of 2 h at 0 °C (entry 3). Reducing the lithiation-time to 1 h gave a slightly lower yield of **429** (82%, 55:45 dr) and 13% of starting material **378** was recovered (entry 4).

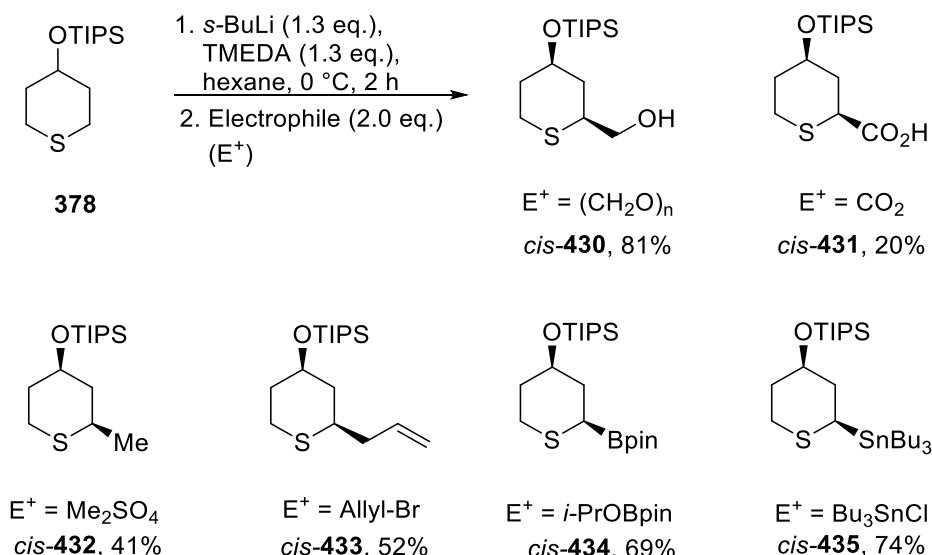
Table 4.3: Optimisation of the Lithiation-Trapping Conditions of THP 378.



Entry	Time / h	T / °C	<i>cis</i> -429 / % ^{a,b}	378 / % ^c
1	2	−20	66	28
2	2	−10	75	19
3	2	0	87	traces
4	1	0	82	13

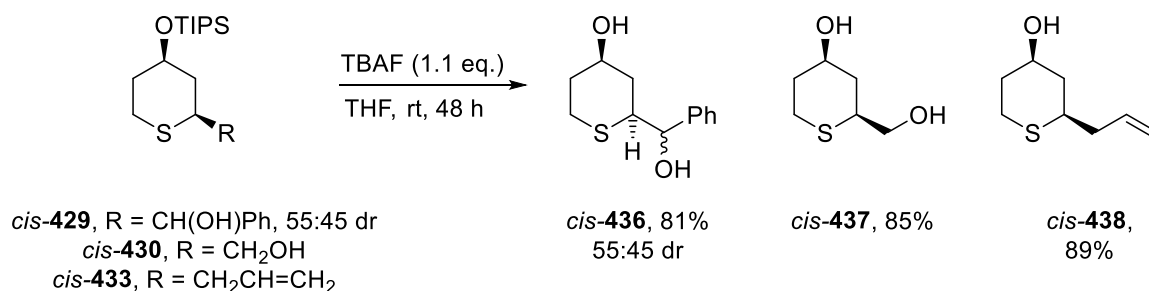
^aYield after purification by chromatography, ^b55:45 dr based on ¹H NMR spectroscopy of the crude product, ^cyield of starting material **378** after purification by chromatography.

Using the optimised lithiation-trapping conditions (s-BuLi / TMEDA, 0 °C, 2 h), the lithiated species derived from TIPS-protected tetrahydrothiopyran **378** was trapped with several electrophiles and the full results are summarised in Scheme 4.21. For example, paraformaldehyde gave alcohol *cis*-**430** in 81% yield. Using DMF, only traces of aldehyde were obtained. Trapping with CO₂ resulted in carboxylic acid *cis*-**431** in 20% yield. The trapping with ethyl chloroformate gave only traces of the corresponding ester. 2-Methyl tetrahydrothiopyran *cis*-**432** was synthesised in 41% yield when Me₂SO₄ was used as the electrophile. An allyl substituent was introduced in the 2-position in 52% yield when trapping with allyl bromide. Use of *i*-PrOBPin gave the boronic ester *cis*-**434** in 69% yield whereas trapping with Bu₃SnCl gave stannane *cis*-**435** in 74% yield. The 2,4-*cis* stereoselectivity was assigned by ³J values for the 2-methyl substituted tetrahydrothiopyran *cis*-**432**, boronic ester *cis*-**434** and stannane *cis*-**435**. For allyl-substituted tetrahydrothiopyran *cis*-**433** and carboxylic acid *cis*-**431**, the ³J values of the axial proton in the 4-position could not be obtained, however the width of the signal of 24.0 Hz for both compounds in combination with the ³J values of the protons in α-position to sulfur gave evidence for the *cis*-configuration. The 2,4-*cis* configuration of alcohol *cis*-**430** was assigned by analogy with the other results.



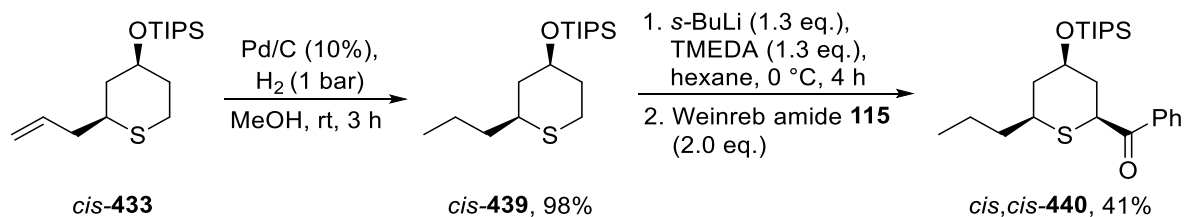
Scheme 4.21 Further Examples in the Lithiation-Trapping of Tetrahydrothiopyran 378.

Next, removal of the TIPS group in some of the products was investigated. It was envisaged that removal could be achieved using TBAF. Indeed, reaction with TBAF in THF at rt for 48 h resulted in the deprotection of the TIPS-protected substrates in high yields to give 4-hydroxy tetrahydrothiopyrans *cis*-**436**, *cis*-**437** and *cis*-**438** in 79–89% yield (Scheme 4.22).



Scheme 4.22 TIPS-Removal of Selected 2,4-*cis* Configured Tetrahydrothiopyrans.

In the next part, it was investigated if 2,4,6-tri-substituted tetrahydrothiopyrans could be prepared starting from 2,4-*cis*-substituted tetrahydrothiopyran *cis*-**433** via a second lithiation-trapping reaction. However, due to the potential acidity of the allylic protons of substrate *cis*-**433** (see Scheme 4.17 for an attempted lithiation in the presence of an allyl substituent), the alkene in the substituent was hydrogenated. The resulting 2-propyl tetrahydrothiopyran *cis*-**439** was obtained in an excellent 98% yield. For the second lithiation-trapping, the lithiation time was increased to 4 h and trapping with Weinreb amide **115** gave trisubstituted tetrahydrothiopyran 2,4,6-*cis,cis*-**440** in 41% yield (Scheme 4.23).



Scheme 4.23 Synthesis of 2,4,6-*cis* Substituted Tetrahydrothiopyran *cis,cis*-440.

The ^3J values in the ^1H NMR spectrum of *cis,cis*-440 were consistent with the *cis,cis*-stereochemistry (Figure 4.4). The 6-membered sulfur ring is expected to have a chair conformation with the benzoyl group, the *n*-propyl group and the TIPS-protected hydroxyl group in equatorial positions. For ketone *cis,cis*-440, proton H_A showed a 2.5 Hz $^3J_{\text{ax-eq}}$ coupling to H_E and a 12.5 Hz $^3J_{\text{ax-ax}}$ coupling to H_G , indicating that the *n*-propyl-substituent at the C-6 carbon is in an equatorial orientation. The $^3J_{\text{ax-ax}}$ couplings between H_B and $\text{H}_\text{H}/\text{H}_\text{G}$ of 12.5 Hz each and the $^3J_{\text{ax-eq}}$ couplings of H_B and $\text{H}_\text{F}/\text{H}_\text{E}$ in the range of 2.5 Hz are evidence for the equatorial position of the TIPS-protected hydroxyl group in the 4-position. Furthermore, the $^3J_{\text{ax-ax}}$ coupling of proton H_C to H_H and $^3J_{\text{ax-eq}}$ coupling of proton H_C to H_F give evidence for the equatorial position of the benzoyl group at the C-2 carbon. Combining the results, the substituents in the 2-, and 4- and 6-positions are confirmed to be *cis*.

The 2,4,6-*cis* configuration of *cis,cis*-440 was also established using NOESY experiments. The NOESY spectrum showed NOE interactions between protons H_A , H_B and H_C which must all be in axial positions.

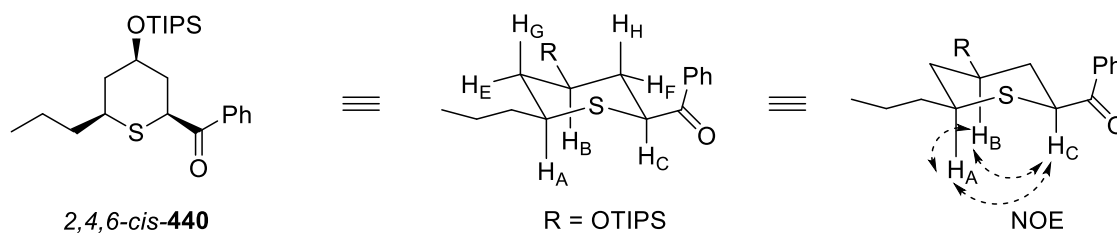
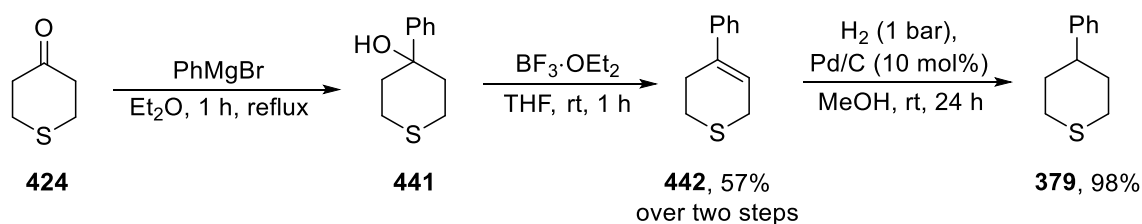
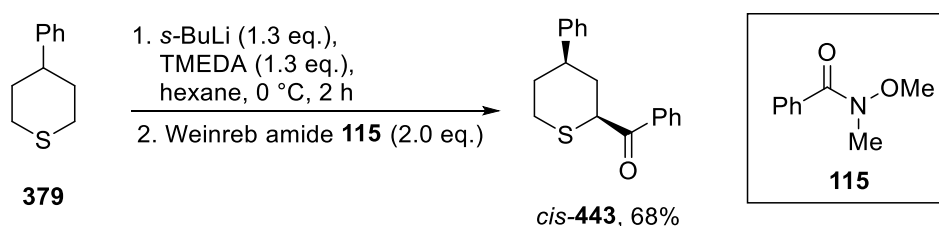


Figure 4.4 Assignment of the *cis* Configuration of *cis,cis*-440.

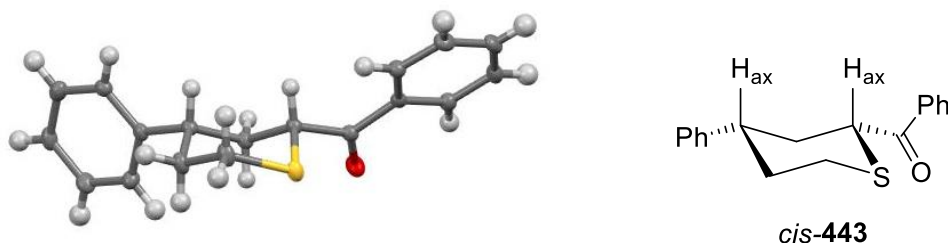
Another substrate for the investigation of the stereochemistry of 4-substituted tetrahydrothiopyran derivatives is 4-phenyl substituted tetrahydrothiopyran **379**. The synthesis route is presented in Scheme 4.24. The first two steps were performed according to a procedure reported by Chang et al.⁴ In the first step, Grignard reaction of phenylmagnesium bromide with tetrahydropyran-4-one **424** gave tertiary alcohol **441** which was subsequently dehydrated using $\text{BF}_3 \cdot \text{OEt}_2$ to give alkene **442** in 57% yield over two steps. Finally, hydrogenation gave 4-phenyl tetrahydrothiopyran **379** in 98% yield.

Scheme 4.24 Synthesis of 4-Phenyl Tetrahydrothiopyran **379**.

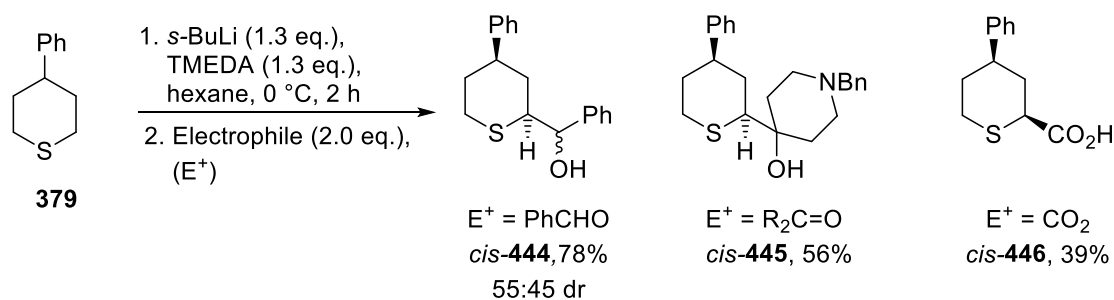
The lithiation-trapping of 4-phenyl tetrahydrothiopyran **379** was performed using standard lithiation conditions (*s*-BuLi / TMEDA, 0 °C, 2 h). Trapping with Weinreb amide **115** led to ketone *cis*-**443** in 68% yield (Scheme 4.25).

Scheme 4.25 Lithiation of 4-Phenyl Tetrahydrothiopyran **379** and Trapping with Weinreb Amide **115**.

A single diastereomeric ketone *cis*-**443** was obtained and its stereochemistry was proven by X-ray crystallography (Figure 4.5). Clearly, the benzoyl substituent at C-2 and the phenyl group at C-4 are *cis* to each other and in equatorial positions.

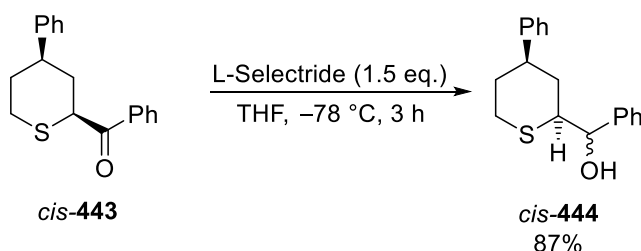
Figure 4.5: X-Ray Structure of Ketone *cis*-**443**.

4-Phenyl tetrahydrothiopyran **379** was also trapped with other electrophiles (Scheme 4.26). Trapping with benzaldehyde gave a mixture of two alcohols *cis*-**444** in 78% yield and 55:45 dr (by ^1H NMR spectroscopy of the crude product). The trapping with *N*-benzyl piperidin-4-one gave alcohol *cis*-**445** in 56% yield. When CO_2 was used as an electrophile, carboxylic acid *cis*-**446** was obtained in 39% yield. The 2,4-*cis* stereoselectivity for ketone *cis*-**443**, alcohol *cis*-**445** and carboxylic acid *cis*-**446** was assigned by ^3J values in their ^1H NMR spectra.



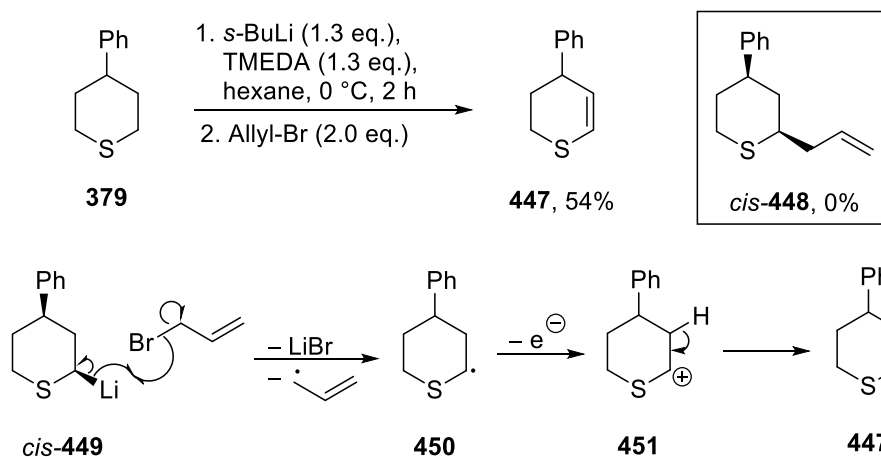
Scheme 4.26 Lithiation-Trapping of 4-Phenyl Tetrahydrothiopyran **379** with Various Electrophiles.

The 2,4-*cis* stereochemistry for diastereomeric alcohols *cis*-**444** could not be assigned by ^3J values in the ^1H NMR spectrum. Therefore, it was planned to reduce ketone *cis*-**443**, with assigned *cis*-configuration, to alcohols *cis*-**444**. Comparison of the ^1H NMR spectrum of the alcohols *cis*-**444** obtained *via* lithiation-trapping with benzaldehyde and the reduction of ketone *cis*-**443** would enable assignment of 2,4-*cis* stereochemistry. Reduction of ketone *cis*-**443** using L-selectride[®] in THF at -78°C for 3 h resulted in a 98:2 diastereomeric mixture of alcohols *cis*-**444** (87% yield) (Scheme 4.27). Comparison of the ^1H NMR spectra revealed that alcohols *cis*-**444** obtained *via* direct lithiation of tetrahydrothiopyran **379** and trapping with benzaldehyde were, as expected, 2,4-*cis* configured.



Scheme 4.27 L-Selectride Reduction of Ketone *cis*-**443**.

Surprisingly, when allyl bromide was used as an electrophile for the lithiation-trapping of tetrahydrothiopyran **379**, vinyl sulfide **447** was obtained in 54% yield and the desired 2,4-*cis* configured allyl tetrahydrothiopyran *cis*-**448** was not observed (Scheme 4.28). A potential pathway for the formation of vinyl sulfide **447** is shown in Scheme 4.28. The lithiated species *cis*-**449** could undergo a SET processes with allyl bromide to give radical **450**, LiBr and the allyl radical. Radical **450** could then undergo another SET to give sulfur stabilised cation **451** from which deprotonation would result in vinyl sulfide **447**.

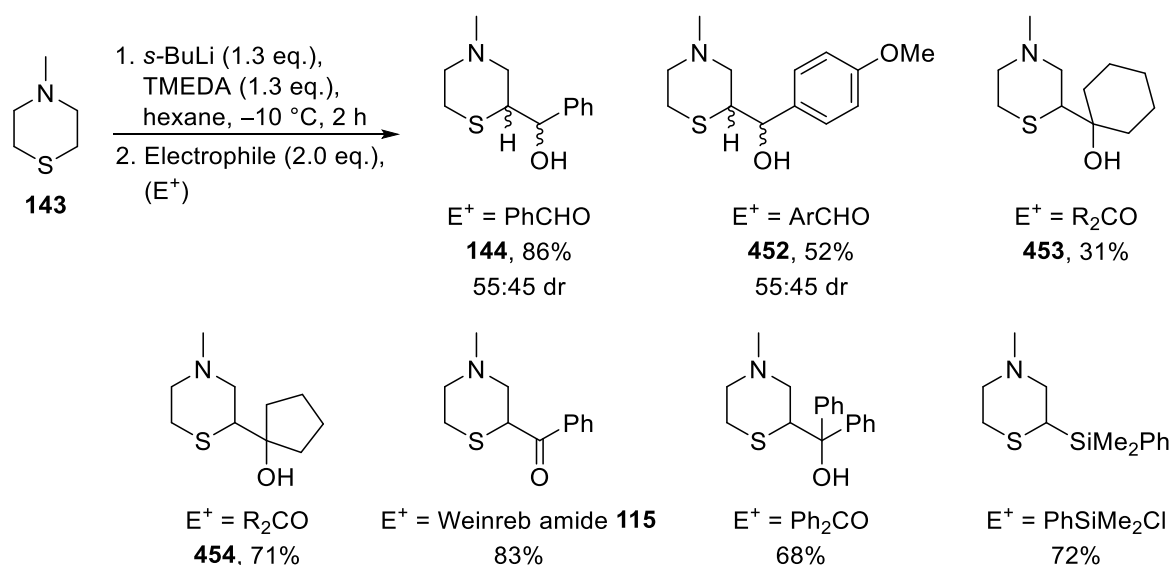


Scheme 4.28 Lithiation of 4-Phenyl Tetrahydrothiopyran **379** and Trapping with Allyl Bromide.

The lithiation-trapping of tetrahydrothiopyrans **378** and **379** resulted in the formation of 2,4-*cis* configured tetrahydrothiopyrans. These results are consistent with previous results in the O'Brien group in the lithiation trapping of THP where 2,4-*cis* configured THPs were obtained (see Scheme 1.64).

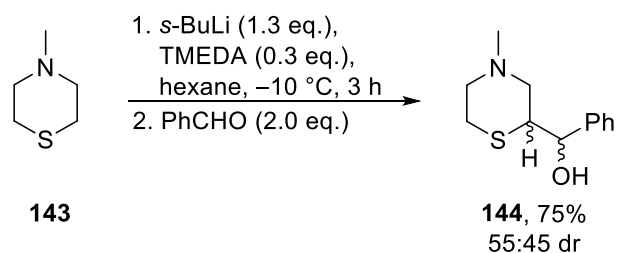
4.3 Lithiation-Trapping of Thiomorpholines, Dithianes and Oxathianes

The lithiation-trapping of thiomorpholines has been investigated by another group member.¹⁰⁶ Under the optimised reaction conditions, *N*-methyl thiomorpholine **143** was lithiated using *s*-BuLi / TMEDA in hexane at $-10\text{ }^{\circ}\text{C}$ for 2 h and subsequently trapped with a range of electrophiles to give α -substituted thiomorpholines (Scheme 4.29). Trapping with aldehydes gave alcohols **144** and **452** in 52-86% and 55:45 dr. Addition of ketones was explored resulting in the corresponding alcohols **453** and **454** in 31-71% yield respectively.



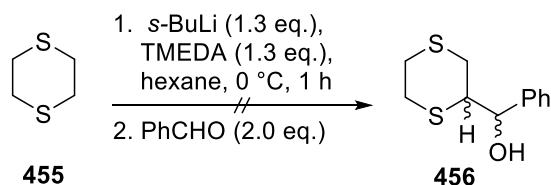
Scheme 4.29 Previously Explored Scope in the Lithiation-Trapping of Thiomorpholine **143**.

In previous work from the O'Brien group, the lithiation-trapping of *N*-methyl morpholine **125** using *s*-BuLi in hexane and substoichiometric amounts of TMEDA was successfully carried out (see section 1.3.2). It was questioned if the same catalytic effect could be observed with *N*-methyl thiomorpholine **143**. *N*-Methyl thiomorpholine **143** was synthesised starting from thiomorpholine *via* reductive amination using $\text{NaBH}(\text{OAc})_3$ and paraformaldehyde to give *N*-methyl thiomorpholine **143** in 69% yield. Then, the established lithiation-trapping conditions for *N*-methyl thiomorpholine **143** (1.3 eq. *s*-BuLi / TMEDA at $-10\text{ }^{\circ}\text{C}$ for 2 h in hexane) were modified. The amount of TMEDA was reduced to 0.3 eq. and the lithiation time was increased to 3 h. Trapping with benzaldehyde gave a mixture of diastereomeric alcohols **144** (55:45 dr based on ^1H NMR spectroscopy of the crude product) in 75% yield, clearly showing that catalytic lithiation-trapping was possible (Scheme 4.30). Having developed this catalytic lithiation-trapping procedure, a co-worker in the group has explored the scope of the reaction and seven additional examples were developed.¹⁰⁷



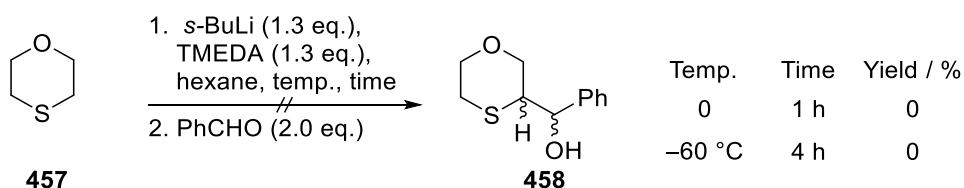
Scheme 4.30 Lithiation-Trapping of Thiomorpholine **143** Using Substoichiometric TMEDA.

In addition, the lithiation of 1,4-dithiane **455** and 1,4-oxathiane **457** were briefly investigated. 1,4-Dithiane **455** was treated with *s*-BuLi / TMEDA in hexane at 0 °C for 1 h and then trapped with benzaldehyde. Unfortunately, only starting material was identified in the ^1H NMR spectrum of the crude product (Scheme 4.31).



Scheme 4.31 Attempted Lithiation of 1,4-Dithiane **457** and Trapping with PhCHO.

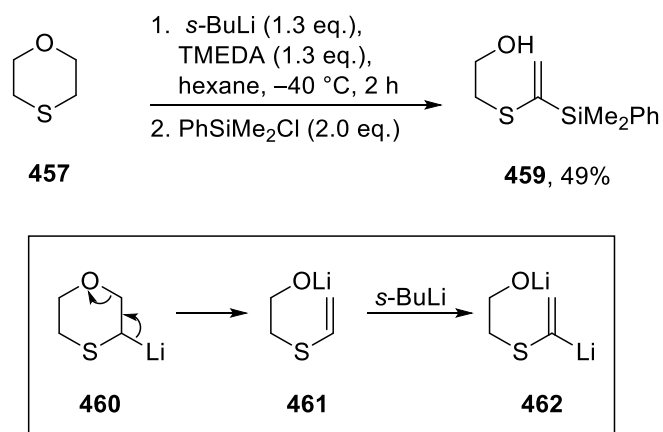
The lithiation of 1,4-oxathiane **457** using *s*-BuLi / TMEDA in hexane for at 0 °C for 1 h and trapping with benzaldehyde gave a complex mixture (by ^1H NMR spectroscopy) which did not contain the desired alcohols **458**. Lithiation at -60 °C for 4 h and trapping with benzaldehyde did not result in the desired α -substituted oxathianes **458** and a complex mixture was obtained (Scheme 4.32).



Scheme 4.32 Attempted Lithiation of 1,4-Oxathiane **457** and Trapping with PhCHO.

The lithiation of 1,4-oxathiane **457** and trapping with a different electrophile, PhSiMe_2Cl , was also explored. Lithiation was carried out using *s*-BuLi and TMEDA in hexane at -40 °C for 2 h. Subsequent trapping with PhSiMe_2Cl did not lead to any of the hoped for substituted oxathiane. Instead, ring-opened product **459** was the only product in 49% yield (Scheme 4.34). To explain its formation, it was proposed that ring-opening of lithiated 1,4-oxathiane **460** occurred to give lithium alkoxide **461**. Vinylic lithiation of **461** with a second equivalent of *s*-BuLi would result in vinylic thioether **462** which could then be trapped with PhSiMe_2Cl

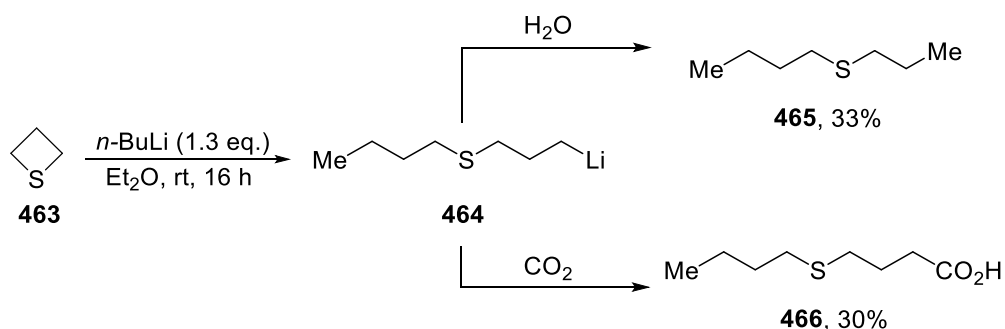
to give ring-opened product **459**. The lithiation and alkoxide elimination steps were reported by Lautens et al. on a structurally related bicyclic oxathiane upon treatment with the chiral lithium amide based popularised by Simpkins et al.¹⁷⁹



Scheme 4.33 Lithiation of 1,4-Oxathiane **457** and Trapping with PhSiMe₂Cl.

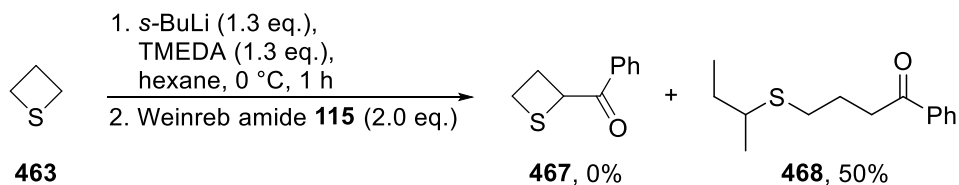
4.4 Lithiation-Trapping of Thietane

Given the success of the lithiation-trapping of saturated 5- and 6-membered ring systems, it was decided to explore the functionalisation of 4-membered ring thietane **463**. In 1954, Pitt et al. reported the ring-opening of thietanes upon reaction with nucleophilic reagents. For example, reaction of *n*-BuLi with thietane **463** at rt for 16 h generated lithiated species **464** due to nucleophilic attack. Subsequent protonation of lithiated species **464** using water gave sulfide **465** in 33% yield. Alternatively, treatment with CO₂ led to the formation of carboxylic acid **466** 30% yield (Scheme 4.34).¹⁸⁰



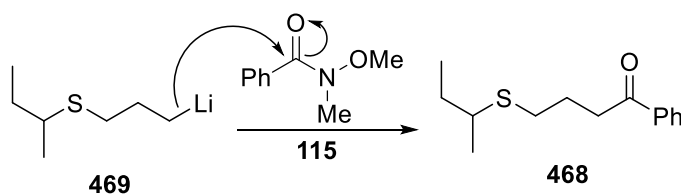
Scheme 4.34 Synthesis of Acyclic Thioethers Starting from Thietane **463**.

Despite the precedence for ring-opening, we wondered if it could be possible to develop suitable conditions for the lithiation-trapping of thietane **463**. In an initial reaction, the conditions for the lithiation-trapping of tetrahydrothiophene **25** (*s*-BuLi / TMEDA, hexane, 0 °C, 1 h) were explored. Disappointingly, after trapping with Weinreb amide **115**, the desired ketone **467** was not observed in the crude product (by analysis of the ¹H NMR spectrum). Instead, the ring-opened keto-sulfide **468** was isolated in 50% yield (Scheme 4.35).



Scheme 4.35 Attempted Lithiation-Trapping of Thietane **463**.

Clearly, treatment of thietane **463** with *s*-BuLi / TMEDA did not lead to deprotonation at the α-position to sulfur. Instead, it is assumed that *s*-BuLi reacts with thietane **463** via nucleophilic attack on sulfur leading to ring-opening of the four-membered ring and the formation of organolithium **469**. Subsequent trapping with Weinreb amide **115** would then give keto-sulfide **468** (Scheme 4.36).



Scheme 4.36 Trapping of Ring-Opened Thietane **469** with Weinreb Amide **115**.

The formation of keto-sulfide **468** was confirmed by analysis of the ^1H NMR, ^{13}C NMR and 2D NMR spectra. The ^1H NMR spectrum showed a signal at 2.71 ppm (sextett, $J = 7.0$ Hz), which is connected to a primary carbon atom with a chemical shift of 41.3 ppm in the ^{13}C NMR spectrum based on the HMBC and DEPT spectra. ^1H , ^1H -COSY gave evidence of a coupling of that proton to protons of an adjacent methyl group and two diastereotopic protons H_8/H_9 (part of the *s*-butyl group) and the signal was therefore assigned to H_7 (Figure 4.6). Furthermore, the signal at 24.0 ppm in the ^{13}C NMR spectrum was assigned to the carbon atom C_2 next to the carbonyl group based on the HMBC spectrum. The signals for the two protons H_1/H_2 connected to that carbon appeared at 3.12 ppm. These two protons couple to protons H_3/H_4 of the adjacent CH_2 group (2.01 ppm), which showed another coupling in the ^1H , ^1H -COSY spectrum to the protons H_5/H_6 CH_2 group next to sulfur (2.60 ppm) in the ^1H NMR spectrum.

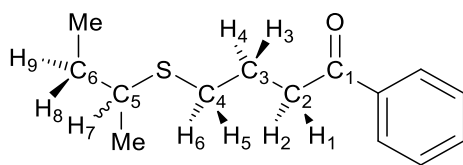
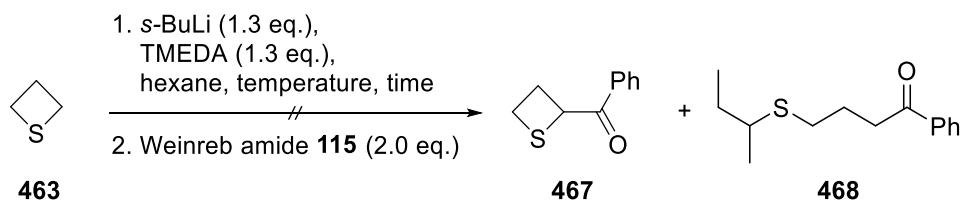


Figure 4.6 Assignment of Sulfide **468**.

Other reaction conditions for the lithiation-trapping of thietane **463** were then explored. A shorter lithiation (2 min lithiation time) of thietane **463** using *s*-BuLi / TMEDA in hexane at 0 °C and trapping with Weinreb amide **115** did not result in the formation of α -substituted thietane **463**, but keto-sulfide **468** was observed in the crude mixture. Isolation was not attempted (Table 4.4, entry 2). The lithiation of thietane **463** using *s*-BuLi / TMEDA in hexane at -40 °C for 40 min and subsequent trapping with Weinreb amide **115** did not give α -substituted thietane **467**, but keto-sulfide **468** was observed in the crude mixture (entry 3). Finally, lithiation of thietane **463** (*s*-BuLi / TMEDA) at -78 °C for 1 h and trapping with Weinreb amide **115** was attempted but disappointingly, it gave exclusively keto-sulfide **468** (entry 4).

Table 4.4: Lithiation-Trapping of Thietane 463.

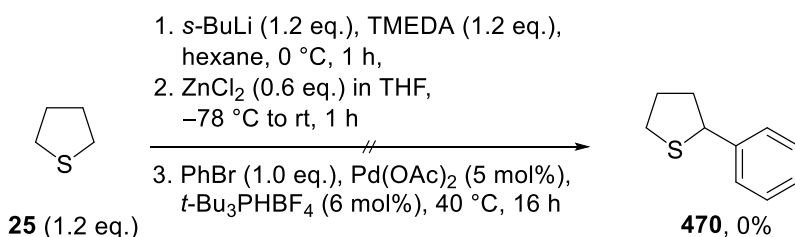


Entry	Temperature / °C	Time	467 / % ^a	468 / % ^a
1	0	1 h	0	50
2	0	2 min	0	n.d. ^b
3	−40	40 min	0	n.d. ^b
4	−78	1 h	0	n.d. ^b

^aYield after purification by chromatography, ^byield not determined.

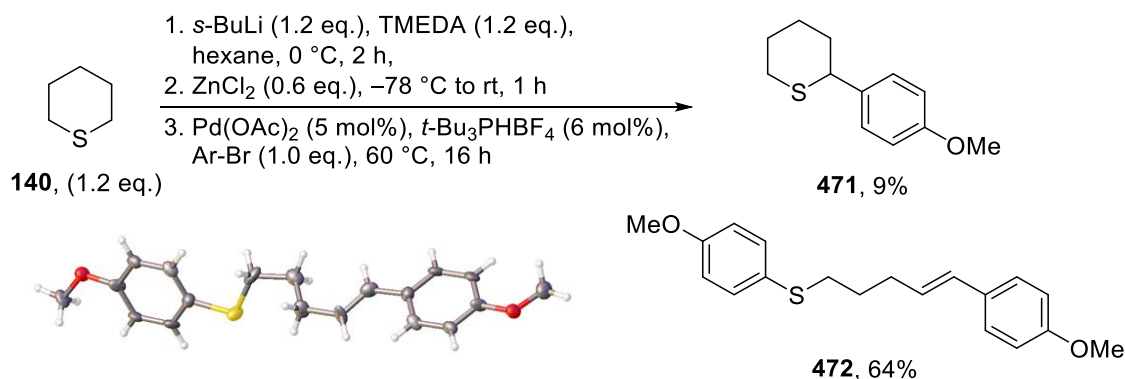
4.5 Arylation of Sulfur Heterocycles

The synthesis of α -arylated sulfur heterocycles *via* lithiation, transmetallation and Negishi coupling has not been reported. Therefore, building on our successful reactions with oxygen heterocycles (see section 2.2.2 and section 3.4.4), it was obvious to try to extend the methodology to sulfur heterocycles. Based on our previously developed conditions with oxygen heterocycles, tetrahydrothiophene **25** (1.2 eq.) was lithiated using *s*-BuLi and TMEDA (1.2 eq.) in hexane at 0 °C for 1 h and then transmetallated with ZnCl₂ (0.6 eq.) in THF. Subsequent reaction with bromobenzene (1.0 eq.) as the limiting reagent and coupling partner in the presence of Pd(OAc)₂ (5 mol%) and *t*-Bu₃PHBF₄ (6 mol%) did not result in the desired α -substituted tetrahydrothiophene derivative **470** and a complex mixture was obtained (Scheme 4.37). The use of other aryl bromides such as 2-bromo pyridine and 4-bromo acetophenone gave the same result. It is not clear why these reactions were unsuccessful.

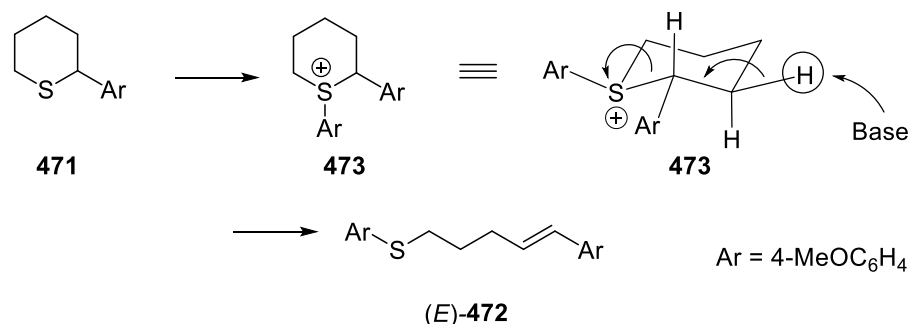


Scheme 4.37 Negishi Cross-Coupling of Tetrahydrothiophene 25.

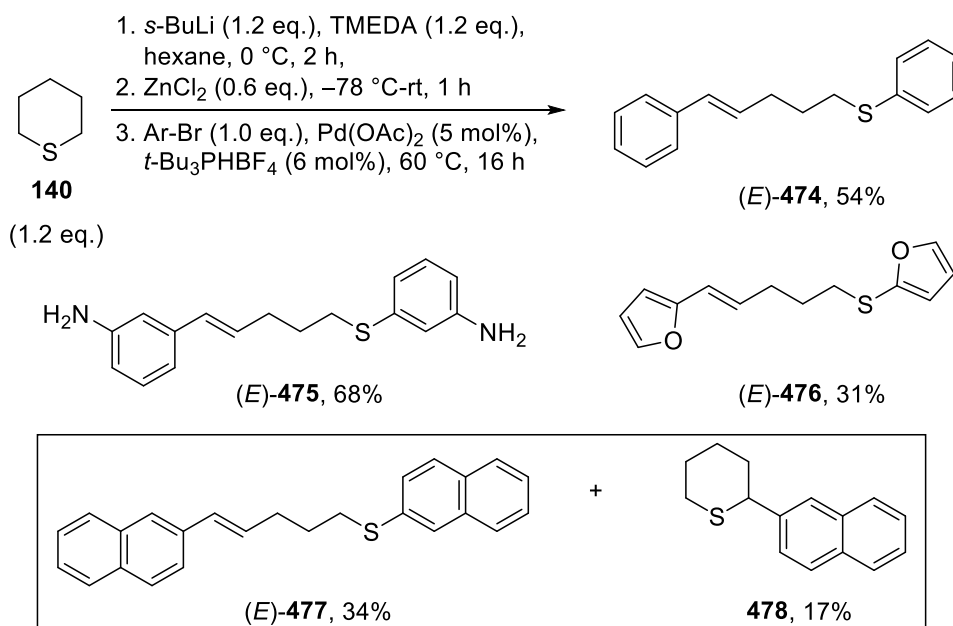
Next, the lithiation of tetrahydrothiopyran **140**, subsequent transmetallation to an organozinc species and Negishi cross-coupling was investigated (Scheme 4.38). However, using 4-methoxy bromobenzene the desired α -arylated sulfide **471** was obtained in only 9% yield. Interestingly, the ring-opened diarylated product (*E*)-**472** was isolated in 64% yield. The yield of (*E*)-**472** is based on aryl bromide as the limiting reagent and being used twice to generate the diarylated product. The structure of diarylated product (*E*)-**472** was established using X-ray crystallography.

Scheme 4.38 Negishi Cross-Coupling of Tetrahydrothiopyran **140**.

Our tentative proposed mechanism to explain the formation of diarylated product **472** is shown in Scheme 4.39. It is assumed that arylation occurs in the position α to sulfur to give the desired α -aryl sulfide **471**. Then, arylation at the sulfur could occur to give sulfonium salt **473**. Subsequent deprotonation at the β -position and cleavage of the C-S bond could lead to the formation of the *trans*-alkene in ring-opened diarylated product (*E*)-**472**.

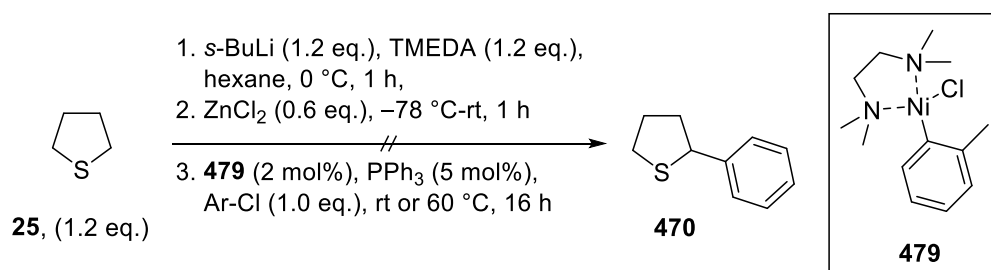
Scheme 4.39 Proposed Pathway for Arylation and Ring-Opening of Tetrahydrothiopyran **140**.

Under the same conditions, a range of aryl bromides was used in the Negishi cross-coupling (Scheme 4.40). Use of bromobenzene in the Negishi cross-coupling step gave diarylated sulfide (*E*)-**474** in 54% yield and traces of the desired α -arylated product. Diamine (*E*)-**475** was isolated in 68% yield after Negishi-cross-coupling using 3-bromo aniline. Sulfide (*E*)-**476** was obtained in 31% yield after cross-coupling using 2-bromofuran. Finally, Negishi cross-coupling with 2-bromonaphthalene gave an inseparable mixture of diarylated sulfide (*E*)-**477** (34% yield) and α -aryl sulfide **478** (17% yield).



Scheme 4.40 Scope of Ring-Opened Arylated Tetrahydrothiopyrans.

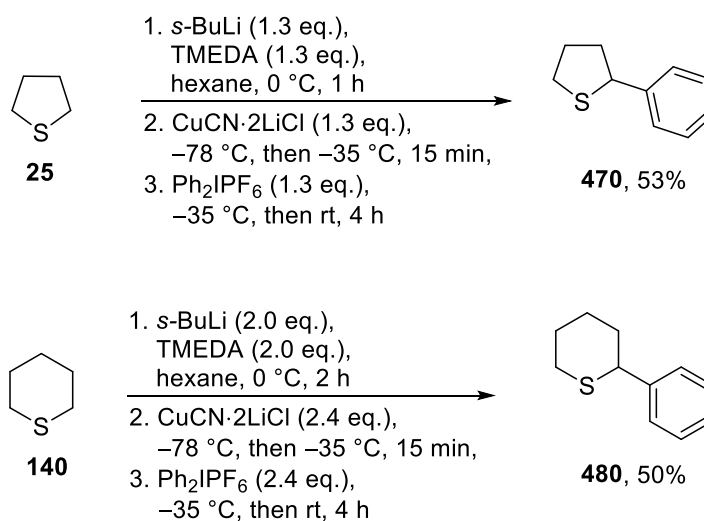
The Negishi cross-coupling of zincated tetrahydrothiophene was also attempted using a Ni catalyst and reaction conditions reported by Magano and Monfette.¹⁸¹ Thus, lithiation of tetrahydrothiophene **25** under standard conditions and transmetalation gave the organozinc species which was then treated with Ni catalyst **479** (2 mol%), PPh₃ (5 mol%) and chlorobenzene at rt or 60 °C. Unfortunately, in both cases, ¹H NMR spectroscopy of the crude product revealed that only traces of α -aryl sulfide **470** were formed (Scheme 4.41).



Scheme 4.41 Attempted Ni-Catalysed Negishi Cross-Coupling.

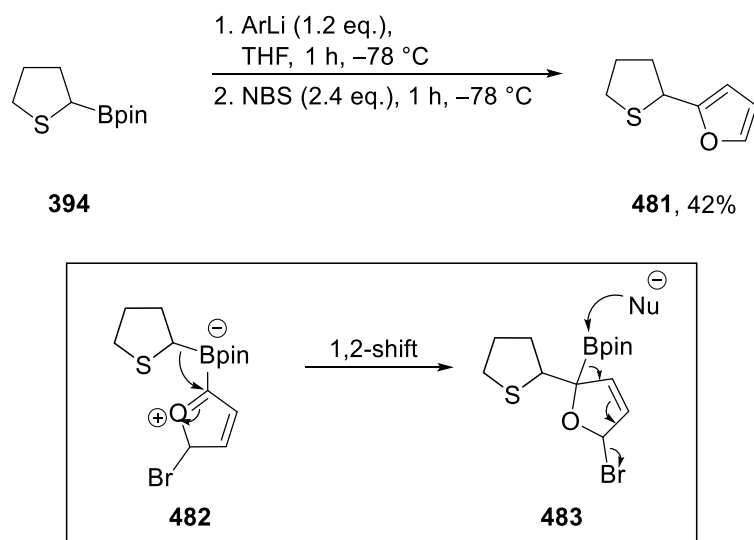
Due to the lack of success with the Negishi cross-coupling approach to α -aryl substituted sulfur heterocycles, other approaches to introduce an aryl group in the α -position were considered. Luisi et al. reported the arylation of a cyclic sulfone using an organocopper species and an iodonium salt. The sulfone was lithiated using *n*-HexLi and then transmetalated to an organocopper species. Reaction with an iodonium salt then gave the α -arylated sulfone in 60% yield.¹⁸²

Adapting the conditions by Luisi, tetrahydrothiophene **25** was lithiated under our standard conditions and then cooled to $-78\text{ }^{\circ}\text{C}$ and $\text{CuCN}\cdot 2\text{LiCl}$ was added and the solution was kept at $-35\text{ }^{\circ}\text{C}$. Subsequent addition of Ph_2IPF_6 gave α -aryl tetrahydrothiophene **470** in 53% yield. The same reaction conditions were used in the α -arylation of tetrahydrothiopyran **140**: lithiation under optimised conditions, transmetalation using $\text{CuCN}\cdot 2\text{LiCl}$ and Ph_2IPF_6 addition gave α -aryl tetrahydrothiopyran **480** in 50% yield (Scheme 4.42). Unfortunately, the lack of a range of readily available iodonium salts limits this methodology and so other α -arylation methods were considered.

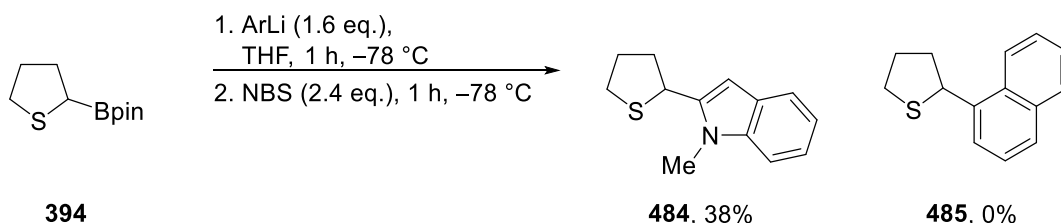


Scheme 4.42 Generation of Organocuprates and Subsequent Arylation Using Iodonium Salts.

In 2015, Aggarwal and Leonori described a transition-metal free stereospecific cross-coupling of boronic esters with aryl organolithiums *via* the formation of boronates and subsequent NBS-mediated rearomatisation.¹⁸³⁻¹⁸⁴ The developed method allowed the synthesis of α -alkylated furans and indoles in high yields. We wondered if boronic ester **394** could be considered as a starting material for this methodology as boronic ester **394** was readily accessible using our established lithiation-trapping methodology (see Scheme 4.4). Lithiation of furan with *n*-BuLi (THF, $-78\text{ }^{\circ}\text{C}$ to rt, 1 h) and subsequent treatment with boronic ester **394** gave a presumed intermediate boronate complex. Addition of NBS and quenching with $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ gave 2-furanyl cyclic sulfide **481** in 42% yield (Scheme 4.43). The key step in this coupling reaction is the 1,2-shift in which the C–B bond of boronate **482** migrates to the furan ring resulting in intermediate **483** bearing a quaternary carbon atom. Work-up of the reaction led to the rearomatisation of the furan ring to give α -furanyl cyclic sulfide **481**.

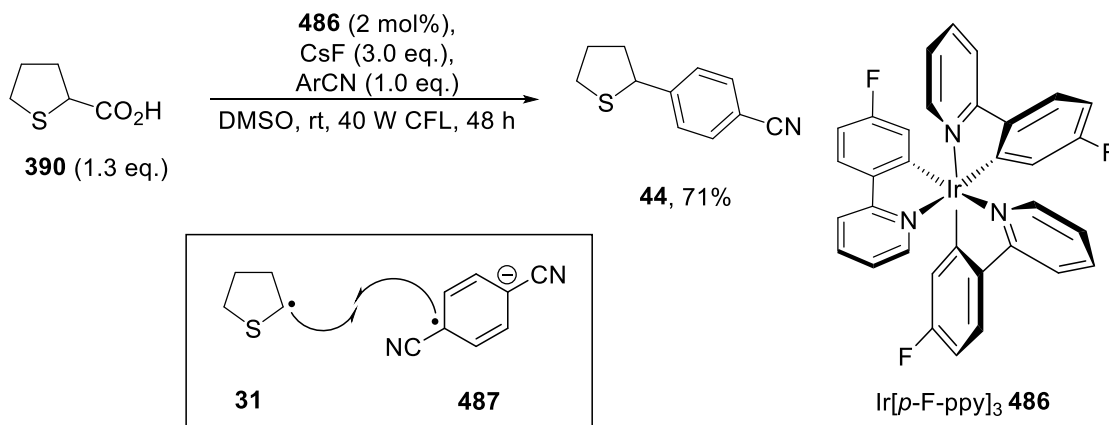
Scheme 4.43 Metal-Free Coupling of Boronic Ester **394** and Furan.

Coupling with *N*-methyl indole was also explored. *N*-Methyl indole was lithiated using *n*-BuLi (THF, rt, then reflux, 3 h). Then, reaction with boronic ester **394** and addition of NBS led to the desired *N*-methyl indole derivative **484** in 38% yield (Scheme 4.44). An attempt to introduce less electron-rich aromatic heterocycles such as 1-bromonaphthalene did not give the desired product **485**. Br-Li exchange of 1-bromonaphthalene using *n*-BuLi (THF, rt, 3 h), subsequent addition of boronic ester **394** and NBS gave only naphthalene (presumably formed by protonation of the lithiated naphthalene during the work-up of the reaction).

Scheme 4.44 Metal-Free Coupling of Boronic Ester **394** and Indole and Naphthalene Derivatives.

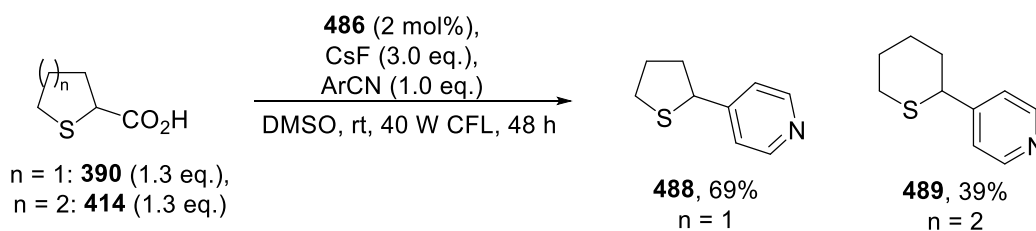
Another method for α -arylation was also investigated. In 2014, Zuo and MacMillan reported a direct decarboxylative arylation of α -amino acids *via* photoredox catalysis using visible light and an Ir-based photocatalyst under basic conditions.¹⁸⁵ It was anticipated extending this decarboxylative arylation method to acid **390** which was synthesised *via* our lithiation-trapping methodology (see Scheme 4.4). Reaction of carboxylic acid **390** with 1,4-dicyano benzene using CsF, Ir(*p*-F-(*t*-Bu)-ppy)₃ **486** and a compact fluorescent light source gave the corresponding nitrile **44** in 71% yield (Scheme 4.45). The decarboxylation of acid **390** promoted by Ir(*p*-F-(*t*-Bu)-ppy)₃ **486** resulted in radical **31** and aryl radical anion **487** in a

SET transfer which could then undergo radical-radical-coupling to give α -aryl tetrahydrothiophene **44**.



Scheme 4.45 Ir-Catalysed Decarboxylative Arylation of Carboxylic Acid **390**.

Using 4-cyanopyridine as the coupling reagent and Ir-catalyst **486**, decarboxylative arylation of acid **390** gave α -pyridyl tetrahydrothiophene **488** in 69% yield. Coupling with 6-membered tetrahydrothiopyran carboxylic acid **414** was also successful. Using 4-cyanopyridine as the aryl coupling partner, α -pyridyl tetrahydrothiopyran **489** was isolated in 39% yield (Scheme 4.46). Unfortunately, attempts to extend this approach to 4-substituted tetrahydrothiopyran acids *cis*-**431** and *cis*-**446** were unsuccessful. Thus, the decarboxylative arylation allowed the synthesis of α -arylated tetrahydrothiophenes and tetrahydrothiopyrans starting from carboxylic acids **390** and **414** in good to high yields.

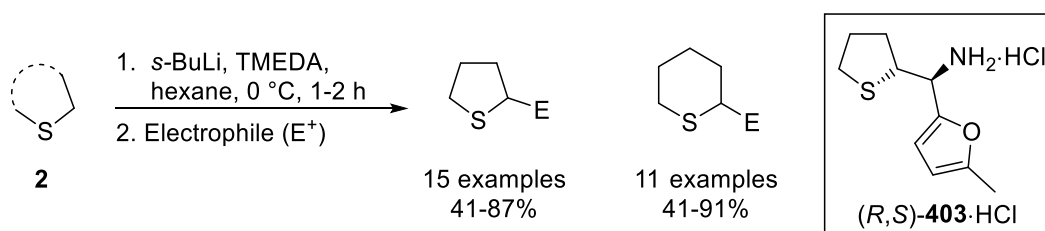


Scheme 4.46 Decarboxylative Arylation of Carboxylic Acids **390** and **414**.

The α -arylation of saturated sulfur heterocycles using direct lithiation, transmetalation and cross-coupling was not successful. Starting from tetrahydrothiopyran **140** it was revealed that diarylated ring-opened sulfides were formed. In contrast, arylation of tetrahydrothiophene **25** and tetrahydrothiopyran **140** using lithiation, organocuprate formation and addition of an iodonium salt was successful and gave α -aryl cyclic sulfides **470** and **480**. Finally, boronic ester **394** and acids **390** and **414** were valuable products that allowed the introduction of heteroaromatic substituents α to sulfur using boronate migration and decarboxylative arylation methodology.

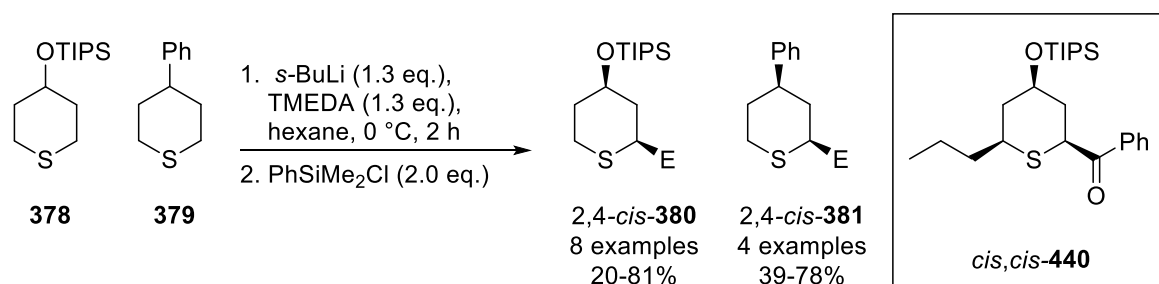
4.6 Conclusions and Future Work

In summary, lithiation conditions for the synthesis of α -substituted tetrahydrothiophenes and tetrahydropyrans were explored and the best results were obtained using *s*-BuLi / TMEDA at 0 °C for 1-2 h for the lithiation step (Scheme 4.47). In total, the trapping of lithiated tetrahydrothiophenes was explored with 15 electrophiles to give α -substituted tetrahydrothiophene in 41-87% yield. In addition, 11 examples (41-91% yield) of α -substituted tetrahydrothiopyrans were synthesised. The usefulness of this new method was also demonstrated in the synthesis of tetrahydrothiophene (*R,S*)-**403**·HCl a key building block in the synthesis of CXCR antagonist **8**.



Scheme 4.47 Lithiation-Trapping of Tetrahydrothiophene and Tetrahydropyran.

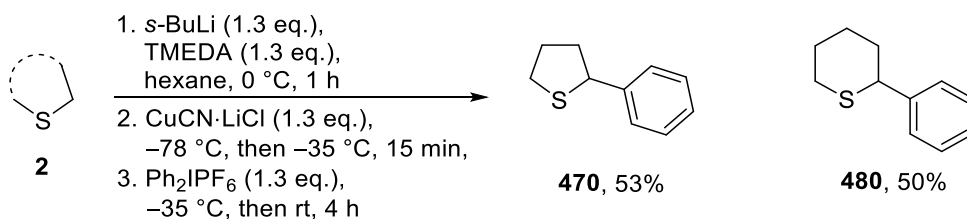
In addition, an important aspect was the study of the stereoselectivity of the lithiation-trapping. It has been shown that the lithiation-trapping of 4-substituted tetrahydropyrans resulted in 2,4-*cis* configured tetrahydropyrans with high diastereoselectivity and 12 examples were synthesised in moderate to high yields. In a final example, it was also discovered that a second lithiation of a 2,4-*cis* configured product gave a *cis,cis*-configured product *cis,cis*-**440** (Scheme 4.48).



Scheme 4.48 Synthesis of 2,4-*cis* Substituted Sulfur Analogues.

Finally, reaction conditions for the introduction of aryl substituents α to sulfur have been explored. Disappointingly, an approach using lithiation, subsequent transmetallation and Negishi cross-coupling was not very successful and, with tetrahydrothiopyran **140**, diarylated ring-opened products were obtained predominantly. Instead, a methodology using lithiation, subsequent transmetallation to an organocopper species and iodonium salt

addition that gave access to α -aryl sulfur heterocycles **470** and **480** in 53% and 50% yield respectively was developed (Scheme 4.49).



Scheme 4.49 Arylation Using Iodonium Salts.

For the introduction of heteroaryl groups α to sulfur, carboxylic acid **390** and boronic ester **394** proved to be valuable products (Figure 4.7). Decarboxylative arylation using light-mediated photoredox chemistry¹⁸⁵ gave access to α -aryl tetrahydrothiophenes **44** and **488** whereas boronic ester coupling¹⁸³ was used to access heteroaryl-substituted tetrahydrothiophenes **481** and **484**.

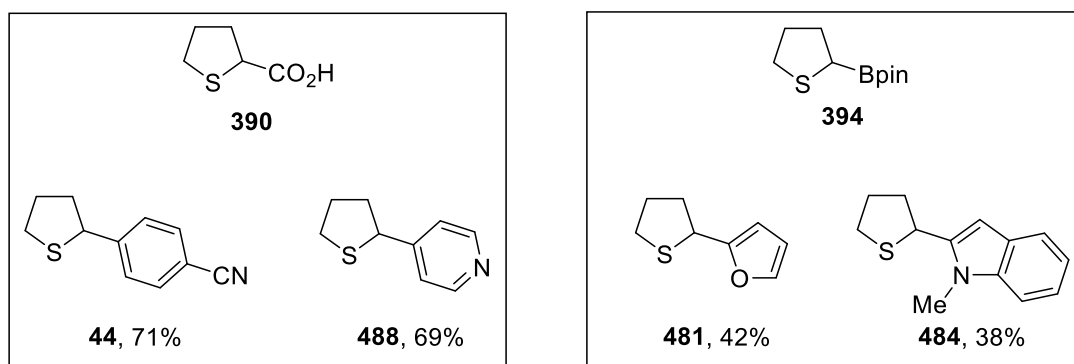
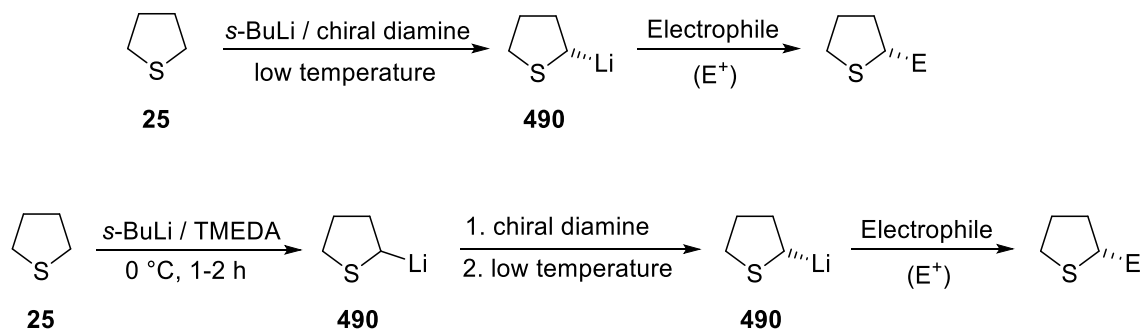


Figure 4.7: Syntheses α -Arylated Tetrahydrothiophenes.

In the future, the synthesis of enantioenriched α -substituted sulfur heterocycles could be attempted. In comparison to oxygen heterocycles, the chemical stability of lithiated sulfur heterocycles appears to be higher. Therefore, asymmetric deprotonation using *s*-BuLi / diamine and the dynamic thermodynamic resolution approaches could be explored to generate the enantioenriched lithiated species **490** (Scheme 4.50).

In the asymmetric deprotonation pathway, *s*-BuLi and diamines such as (–)-sparteine and the (+)-sparteine surrogate could be explored as they show good enantioselectivity with *N*-Boc and oxygen heterocycles.^{75, 108} For the dynamic thermodynamic resolution, conditions by Coldham et al. using proline-derived diamines could be employed after the initial racemic lithiation (see Scheme 1.51).⁹⁹ An important study for both routes would be the determination of the configurational stability of the lithiated cyclic sulfides at different

temperatures. It is envisaged that the configurational stability could be studied starting from enantioenriched stannanes *via* Sn-Li exchange and trapping at various temperatures.



Scheme 4.50 Suggested Pathways to Access Enantioenriched α -Substituted Sulfur Heterocycles.

Chapter 5: Experimental

5.1 General Methods

All-non aqueous reactions were carried out under oxygen free Ar or N₂ using flame-dried glassware. Hexane was freshly distilled over CaH₂. Et₂O and THF were freshly distilled from sodium and benzophenone. Alkylolithiums were titrated against *N*-benzylbenzamide before use. Electrophiles (DMF, Me₂SO₄, ArCHO, ArC(O)N(OMe)Me) and all diamines used in lithiation reactions were distilled over CaH₂ before use. Electrophiles (allyl bromide, benzyl bromide, *N*-Boc piperidine-(4)-one, Bu₃SnCl, (CH₂O)_n, *i*-PrOB(pin), Me₃SnCl, Me₂SO₄, pentyl iodide, propargyl bromide, PhSiMe₂Cl, PhNCO, (*p*-TolS)₂, *t*-BuNCO were used without further purification. When CO₂ was used as an electrophile, dry ice was added to a flame-dried flask and the gas, which evolved due to sublimation was transferred through a flask containing CaCl₂ by cannula and then added into the reaction flask by cannula. Hexane boiling in the range 60-70 °C and was purchased in Winchester quantities (2.5 L quantities purchased from VWR). Brine refers to a saturated solution. Water is distilled water. ZnCl₂ was either used as a commercially available solution (0.7 M in THF) or a solution was prepared from dried ZnCl₂ (heated with a heat gun under high vacuum 3 x 30 s) and dry THF (1.0 M solution in THF). A solution of CuCN·2LiCl was prepared either from commercially available CuCN and a LiCl solution (0.5 M in THF) or was prepared according to general procedure L from commercially available LiCl, CuCN and dry THF. Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F254 aluminium backed silica plates.

Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in CDCl₃, chemical shifts are quoted in parts per million relative to CHCl₃ (δ_H 7.26 ppm) and CDCl₃ (δ_C 77.16 ppm, central line of triplet). For samples recorded in CD₃OD, chemical shifts are quoted in parts per million relative to CD₃OD (δ_H 3.31 ppm, central line of quintet) and CD₃OD (δ_C 49.0 ppm, central line of heptet). For samples recorded in d⁶-acetone, chemical shifts are quoted in parts per million relative to d⁶-acetone (δ_H 2.05 ppm, central line of quintet) and d⁶-acetone (δ_C 29.8 ppm, central line of septet). For samples recorded in d⁶-DMSO, chemical shifts are quoted in parts per million relative to DMSO-d⁶ (δ_H 2.50 ppm, central line of quintet) and d⁶-DMSO (δ_C 39.5 ppm, central line of quintet). In the ¹H NMR spectroscopic data, for

protons which couple to two non-equivalent protons with the same J value and so would appear in the spectrum as a triplet, we prefer to report them as a double doublet (apparent triplet) since this reflects the fact that the proton is coupling to non-equivalent protons (but also emphasises that it actually appears as a triplet). The layout in the data will, for example, be: dd, $J = 7.0, 7.0$ Hz (app t). For the same reason, layout in the data for other signals will, for example, be: ddd, $J = 11.5, 11.5, 2.5$ Hz (app td); ddd, $J = 11.5, 2.0, 2.0$ Hz (app dt); dddd, $J = 12.5, 12.5, 2.5, 2.5$ Hz (app tt); dddd, $J = 13.0, 3.0, 3.0, 3.0$ Hz (app dq). Thus, triplet (t) and quartet (q) will only be used in the primary data for protons which are coupled to two equivalent or three equivalent protons respectively. For Proton NMR spectra 16,384 points (number of data points of the acquisition parameter) were acquired in the FID, giving a total acquisition time of 1.3 s. Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (J) are quoted in Hertz.

Melting points were carried out on a Gallenkamp melting point apparatus. Boiling points given for compounds purified by Kugelrohr distillation correspond to the oven temperature during distillation. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltonics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line, 589 nm) and $[\alpha]_D$ values are given in units of 10^{-1} deg cm³ g⁻¹. Chiral stationary phase HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector.

5.2 General Procedures

General Procedure A: Lithiation-trapping of THF using *s*-BuLi / diamine.

s-BuLi (384 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) was added dropwise to a stirred solution of THF (1.0-10.0 eq.) and bispidine **157** or TMEDA (1.3 eq.) in hexane (2.5 mL) at $-45\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-45\text{ }^{\circ}\text{C}$ for 30 min-2 h. Then, the electrophile (2.0 eq.) was added. The resulting solution was stirred at $-45\text{ }^{\circ}\text{C}$ for 1 h and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

General Procedure B: Lithiation, Transmetallation and Negishi Coupling of THF.

s-BuLi (0.77 mL of 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of THF (5 mL) at $-60\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-60\text{ }^{\circ}\text{C}$ for 4 h. Then, a freshly prepared solution of ZnCl_2 (1.00 mL of a 1.0 M solution in THF, 1.0 mmol, 1.0 eq.) was added. After stirring at $-78\text{ }^{\circ}\text{C}$ for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, $\text{Pd}(\text{OAc})_2$ (8 mg, 8 mol%), *t*-Bu₃PHBF₄ (13 mg, 10 mol%) and aryl bromide (0.5 eq.) were added and the reaction mixture was stirred and heated at $40\text{ }^{\circ}\text{C}$ for 16 h. After being allowed to cool to rt, the solids were removed by filtration through Celite[®] and washed with Et_2O (20 mL). The filtrate was washed with brine (15 mL) and water ($2 \times 15\text{ mL}$), dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

General Procedure C: Sn-Li Exchange, Transmetallation and Negishi Coupling of Stannanes with Aryl Bromides.

n-BuLi (231 μ L of a 1.3 M solution in hexane, 0.310 mmol, 1.1 eq.) was added dropwise to a stirred solution of the stannane (0.282 mmol, 1.0 eq.) in THF (2.5 mL) at $-78\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Then, a commercial solution of ZnCl_2 (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.) was added. After stirring at $-78\text{ }^{\circ}\text{C}$ for 30 min, the mixture was allowed to warm to rt and stirred at rt for 30 min. Then, $\text{Pd}(\text{OAc})_2$ (4 or 7 mol%), *t*-Bu₃PHBF₄ (8 or 9 mol%) and aryl bromide (1.3 eq.) were added and the reaction mixture was stirred and heated at $40\text{--}60\text{ }^{\circ}\text{C}$ for 16 h. After being allowed to cool to rt, the solids were removed by filtration through Celite[®] and washed with Et_2O

(20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure D: Lithiation-Trapping of Morpholines and Isochroman 235 using *s*-BuLi / TMEDA at 0 °C.

s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 eq.) was added dropwise to a stirred solution of the *N*-methyl morpholine **125**, α -methylbenzyl morpholines (*R*)- or (*S*)-**154** or isochroman **235** (1.0 mmol, 1.0 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the electrophile (2.0 eq.) was added. The resulting solution was stirred at 0 °C for 1 h and then allowed to warm to rt. Then, saturated NH₄Cl_(aq) (10 mL) and 10% NaHCO_{3(aq)} (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure E: Asymmetric Diamine-Mediated Lithiation-Trapping of Cyclic Ethers.

s-BuLi (1.00 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of the cyclic ether (1.0 mmol, 1.0 eq.) and chiral diamine (1.3 eq.) in solvent (5 mL) at the specified temperature under Ar. The resulting solution was stirred at the specified temperature for the specified time (4–8 h). Then, the electrophile (1.5–2.0 eq.) was added. The resulting solution was stirred at the specified temperature for the specified time. Then MeOH (1 mL) was added and the solution was allowed to warm to rt over 30 min. Then, saturated NH₄Cl_(aq) (10 mL) and 10% NaHCO_{3(aq)} (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure F: Sulfoxide-Mg Exchange and Trapping of α -Sulfinyl Morpholines.

i-PrMgCl (2.0 M solution in THF, 1.3–2.5 eq.) was added dropwise to a stirred solution of the α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq.) in THF (5 mL) at a certain temperature under Ar. The resulting solution was stirred at the specified temperature for the specified time. Then, the electrophile (2.5 eq.) was added dropwise and the resulting solution

was stirred at the specified temperature for 30 min. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

General Procedure G: Preparation of MgBr_2 in THF.

1,2-Dibromoethane (347 μL , 752 mg, 4.0 mmol, 1.0 eq.) was added dropwise to a stirred suspension of Mg (146 mg, 6.0 mmol, 1.5 eq.) in Et_2O (4 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred and heated at reflux for 3 h. After being allowed to cool to rt, a solution of MgBr_2 in Et_2O was obtained.

General Procedure H: Sn-Li Exchange and Electrophile Trapping.

n-BuLi (0.33 mL of a 1.5 M solution in THF, 0.50 mmol, 1.1 eq.) was added dropwise to a stirred solution of the stannane (*S,S*)-**300** or (*S,R*)-**300** (160 mg, 0.452 mmol, 1.0 eq.) in THF (5 mL) at -78 °C under Ar and the resulting solution was stirred at -78 °C for 30 min. Then, the electrophile (1.5-2.0 eq.) was added. The resulting solution was stirred at -78 °C for 1 h and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

General Procedure I: Removal of the α -Methylbenzyl Group.

α -Chloroethyl chloroformate (121 μL , 1.12 mmol, 3.0 eq.) was added dropwise to a stirred solution of the α -methylbenzyl-substituted morpholine (0.37 mmol, 1.0 eq.) in DCE (4 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. Then, the solvent was evaporated under reduced pressure. MeOH (3 mL) was added to the crude product and the resulting solution was stirred and heated at 65 °C for 16 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (10 mL) and the solution was washed with 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL). The organic layer was dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

General Procedure J: Sn-Li Exchange, Transmetallation to an Organozinc Species, Organocuprate Species and Electrophile Trapping.

n-BuLi (103 μ L of a 1.5 M solution in THF, 0.16 mmol, 1.1 eq.) was added dropwise to a stirred solution of the stannane (50 mg, 0.14 mmol, 1.0 eq.) in THF (5 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 30 min. Then, a commercial solution of ZnCl₂ (261 μ L of a 0.7 M solution in THF, 0.18 mmol, 1.3 eq.) was added and the resulting solution was stirred at -78 °C for 30 min. Then, CuCN·2LiCl (676 μ L of a 0.25 M solution in THF, 0.17 mmol, 1.2 eq. prepared using procedure L) was added and the resulting solution was stirred at -78 °C for 30 min. Then, the electrophile (3.0 eq.) was added. The resulting solution was stirred at -78 °C for 1 h and then allowed to warm to rt. Saturated NH₄Cl_(aq) (10 mL) and 10% NaHCO_{3(aq)} (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure K: Sn-Li Exchange, Transmetallation and Negishi Coupling of Morpholines Stannanes with Heteroaryl Bromides.

n-BuLi (205 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) was added dropwise to a stirred solution of the stannane (100 mg, 0.28 mmol, 1.0 eq.) in THF (3 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 30 min. Then, a commercial solution of ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.) was added. After stirring at -78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for 30 min. Then, Pd₂dba₃ (6.5 mg, 2.5 mol%), S-Phos (8.7 mg, 5 mol%) and heteroaryl bromide (1.3 eq.) were added and the reaction mixture was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, the solids were removed by filtration through Celite[®] and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 $\times$ 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure L: Preparation of CuCN·2LiCl in THF.

LiCl (126 mg, 3.0 mmol, 2.0 eq.) was stirred and heated at 200 °C for 5 h under Ar. After being allowed to cool to rt, THF (3 mL) was added and the mixture was stirred at rt for 30 min to give a clear solution. Then, CuCN (267 mg, 1.50 mmol, 1.0 eq.) was added and the resulting solution was stirred at rt for 30 min. This gave a 0.5 M solution of CuCN·2LiCl in THF.

General Procedure M: Lithiation-Trapping of Sulfur Heterocycles using *s*-BuLi / TMEDA.

s-BuLi (1.3 M solution in hexane, 1.3-2.0 eq.) was added dropwise to a stirred solution of the cyclic thioether (1.0 mmol, 1.0 eq.) and TMEDA (1.3-2.0 eq.) in hexane (5 mL) at a specified temperature under Ar. The resulting solution was stirred at the specified temperature for the specified time (2 min-4 h). Then, the electrophile (2.0-3.0 eq.) was added. The resulting solution was stirred at the specified temperature for 1-2 h and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

General Procedure N: Diamine-mediated Lithiation-Trapping of Sulfur Heterocycles using *s*-BuLi / TMEDA and CO_2 .

s-BuLi (1.3 M solution in hexane, 1.3 eq.) was added dropwise to a stirred solution of the cyclic thioether (1.0 mmol, 1.0 eq.) and TMEDA (1.3 eq.) in hexane (5 mL) at a specified temperature under Ar. The resulting solution was stirred at specified temperature for the specified time (2 min-4 h). Then, a stream of dry CO_2 was bubbled into the solution for 1 h and the resulting solution was allowed to warm up to rt. Then, 1 M $\text{HCl}_{(\text{aq})}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

General Procedure O: Attempted Negishi Coupling of Sulfur Heterocycles.

s-BuLi (1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) was added dropwise to a stirred solution of the cyclic thioether (1.7 mmol, 1.2 eq.) and TMEDA (1.7 mmol, 1.2 eq.) in hexane (3 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the resulting mixture was cooled to -78 °C and a solution of ZnCl_2 (1.0 mL of a freshly prepared 1.0 M solution in THF, 1.0 mmol, 0.6 eq.), was added. After stirring at -78 °C for 30 min, the mixture was allowed warmed to rt and stirred at rt for additional 30 min. Then $\text{Pd}(\text{OAc})_2$ (16 mg, 5 mol%), *t*-Bu₃PHBF₄ (25 mg, 6 mol%), and aryl bromide (1.5 mmol, 1.0 eq.) were added in THF (3 mL) and the reaction mixture was stirred and heated at 40-60 °C for 16 h. After being allowed to cool to rt, the solids were removed by filtration through Celite® and

washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure P: Coupling of Sulfur Heterocycles with Iodonium Salts.

s-BuLi (1.3 M solution in hexane, 1.3-2.0 eq.) was added dropwise to a stirred solution of the cyclic thioether (1.0 mmol, 1.0 eq.) and TMEDA (1.3-2.0 eq.) in hexane at 0 °C under Ar. The resulting solution was stirred at 0 °C for the specified time. Then, the solution was cooled to -78 °C and CuCN·2LiCl (0.5 M solution in THF, 1.3-2.4 eq. prepared using procedure L) was added. The resulting solution was allowed to warm to -35 °C and stirred at -35 °C for 15 min. Then, Ph₂IPF₆ (1.3-2.4 eq.) was added in one portion and the resulting solution was stirred at -35 °C for 15 min and then allowed to warm to rt over 4 h. Saturated NH₄OH_(aq) (20 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure Q: Decarboxylative Arylation of Thioether 2-Carboxylic Acid.

1,4-Dicyano benzene (17.3 mg, 0.12 mmol, 1.0 eq.) was added to a stirred solution of Ir(*p*-F(*t*-Bu)-ppy)₃ (2.1 mg, 2.4 μmol, 0.02 eq.), thioether-2-carboxylic acid (0.36 mmol, 3.0 eq.) and CsF (55 mg, 0.4 mmol, 3.0 eq.) in DMSO (6 mL) at rt. The solution was degassed with Ar for 10 min and then irradiated with a 40 W fluorescent lamp (approximately 2 cm away from the light source) at rt for 48 h. Then, saturated NaHCO_{3(aq)} (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

5.3 Experimental for Chapter Two

Dimethyl(phenyl)(tetrahydrofuran-2-yl)silane **112**

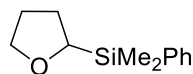
**112**

Table 2.1, entry 3:

Using general procedure A, THF (406 μ L, 361 mg, 5.00 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at $-45\text{ }^{\circ}\text{C}$ for 1 h and PhSiMe₂Cl (168 μ L, 171 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-Et₂O to 95:5 hexane-Et₂O as eluent gave α -substituted THF **112** (68 mg, 66%) as a colourless oil, R_F (90:10 hexane -Et₂O) 0.3; IR (ATR) 3069, 2959, 2866, 1427, 1247, 1041, 830, 810, 775, 730, 698, 651, 466 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 7.62-7.53 (m, 2H, Ph), 7.40-7.32 (m, 3H, Ph), 3.79 (dd, $J = 7.0, 7.0$ Hz (app t), 1H, OCH), 3.69 (dd, $J = 7.0, 7.0$ Hz (app t), 1H, OCH), 3.47 (dd, $J = 11.0, 7.0$ Hz, 1H, OCH), 1.97 (ddd, $J = 12.0, 11.0, 7.0$ Hz, 1H, CH), 1.89-1.75 (m, 1H, CH), 1.71-1.52 (m, 2H, CH), 0.35 (s, 3H, SiMe), 0.33 (s, 3H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 137.3 (*ipso*-Ph), 134.2 (Ph), 129.3 (Ph), 127.9 (Ph), 71.7 (OCH), 69.5 (OCH₂), 28.2 (CH₂), 27.1 (CH₂), -5.2 (SiMe), -5.3 (SiMe); MS (APCI) m/z 207 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₂H₁₈OSi (M + H)⁺ 207.1191, found 207.1199 (-4.1 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁸⁶

Lab Book Reference: **NS11-13**

Table 2.1, entry 1:

s-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) was added dropwise to a stirred solution of bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in THF (2.5 mL) at $-45\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-45\text{ }^{\circ}\text{C}$ for 1 h. PhSiMe₂Cl (168 μ L, 171 mg, 1.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at $-45\text{ }^{\circ}\text{C}$ for 1 h and then allowed to warm to rt. Then, saturated NH₄Cl_(aq) (10 mL) and 10% NaHCO_{3(aq)} (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on

silica with 98:2 hexane-Et₂O to 95:5 hexane-Et₂O as eluent gave α -substituted THF **112** (30 mg, 29%) as a colourless oil.

Lab Book Reference: **NS11-15**

Table 2.1, entry 2:

Using general procedure A, THF (41 μ L, 36 mg, 0.50 mmol, 1.0 eq.), *s*-BuLi (500 μ L of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and PhSiMe₂Cl (168 μ L, 171 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-Et₂O to 95:5 hexane-Et₂O as eluent gave α -substituted THF **112** (4 mg, 4%) as a colourless oil.

Lab Book Reference: **NS11-12**

Table 2.1, entry 4:

Using general procedure A, THF (406 μ L, 361 mg, 5.00 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 30 min and PhSiMe₂Cl (168 μ L, 171 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-Et₂O to 95:5 hexane-Et₂O as eluent gave α -substituted THF **112** (51 mg, 49%) as a colourless oil.

Lab Book Reference: **NS11-14**

Table 2.1, entry 5:

Using general procedure A, THF (406 μ L, 361 mg, 5.00 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 2 h and PhSiMe₂Cl (168 μ L, 171 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-Et₂O to 95:5 hexane-Et₂O as eluent gave α -substituted THF **112** (41 mg, 41%) as a colourless oil.

Lab Book Reference: **NS11-15**

Table 2.1, entry 6:

Using general procedure A, THF (203 μ L, 180 mg, 2.50 mmol, 5.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol,

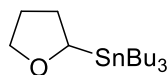
1.3 eq.) in hexane (2.5 mL) 1 h and PhSiMe₂Cl (168 μ L, 171 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-Et₂O to 95:5 hexane-Et₂O as eluent gave α -substituted THF **112** (29 mg, 28%) as a colourless oil.

Lab Book Reference: **NS11-17**

Using general procedure A, THF (406 μ L, 360 mg, 5.00 mmol, 1.0 eq.), *s*-BuLi (384 μ L of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and TMEDA (97.5 μ L, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and PhSiMe₂Cl (168 μ L, 171 mg, 1.0 mmol, 2.0 eq.) gave the crude product which contained only traces of α -substituted THF **112** by ¹H NMR spectroscopy.

Lab Book Reference: **NS11-47**

Tributyl(tetrahydrofuran-2-yl)stannane **158**



158

Using general procedure A, THF (203 μ L, 180 mg, 2.50 mmol, 5.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and Bu₃SnCl (271 μ L, 325 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1 hexane-Et₂O to 95:5 hexane-Et₂O as eluent gave stannane **158** (125 mg, 69%) as a colourless oil; *R*_F (95:5 hexane-Et₂O) 0.5; IR (ATR) 2956, 2924, 2854, 1463, 1377, 1034, 875, 689, 597, 506 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.81-3.69 (m, 2H, OCH), 3.65-3.54 (m, 1H, OCH), 2.24-2.06 (m, 1H, CH), 1.96-1.73 (m, 3H, CH), 1.60-1.39 (m, 6H, CH), 1.37-1.25 (m, 6H, CH), 1.01-0.79 (m, 15H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 72.5 (OCH₂), 68.6 (OCH), 31.4 (CH₂), 29.4 (CH₂), 27.9 (CH₂), 27.6 (CH₂), 13.8 (Me), 8.6 (CH₂); MS (ESI) *m/z* 289 [(¹¹⁸SnBu₃)⁺, 74], 291 [(¹²⁰SnBu₃)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₂₇¹²⁰Sn (¹²⁰M + H)⁺ 291.1135, found 291.1122 (+0.4 ppm error). Spectroscopic data consistent with those reported in the literature.¹²⁵

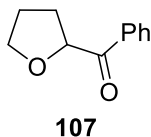
Lab Book Reference: **NS11-18**

HCl (15 mL of a 2.0 M solution in Et₂O, 30 mmol, 1.8 eq.) was added to a stirred solution of dihydropyran (2.27 mL, 2.10 g, 30 mmol, 1.8 eq.) in THF (20 mL) at 0 °C under Ar. The

resulting solution was stirred at 0 °C for 2 h to give a solution of 2-chlorotetrahydrofuran **158** in THF. In a separate flask, *n*-BuLi (11.3 mL, 1.5 M in hexane, 17.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of *i*-Pr₂NH (4.70 mL, 3.39 g, 33.5 mmol) in THF (30 mL) at 0 °C under Ar. The solution was stirred at 0 °C for 5 min. Then, Bu₃SnH (4.63 mL, 5.09 g, 17.5 mmol, 1.03 eq.) was added and the solution was stirred at 0 °C for 15 min to give a solution of Bu₃SnLi in THF. The solution of Bu₃SnLi in THF was added dropwise to the stirred solution of solution of 2-chlorotetrahydrofuran **190** in THF at –78 °C. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt over 16 h. Then, saturated NH₄Cl_(aq) (30 mL) and saturated NaHCO_{3(aq)} (30 mL) were added and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-CH₂Cl₂ then 90:10 hexane-CH₂Cl₂ as eluent gave THP stannane **158** (3.80 g, 62%) as a colourless oil.

Lab Book Reference: **NS12-24**

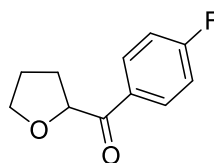
Phenyl(tetrahydrofuran-2-yl)methanone **107**



Using general procedure A, THF (406 µL, 361 mg, 5.00 mmol, 10.0 eq.), *s*-BuLi (385 µL of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and Weinreb amide **115** (149 µL, 168 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1 CH₂Cl₂-acetone to 98:2 CH₂Cl₂-acetone as eluent gave α-substituted THF **107** (51 mg, 58%) as a colourless oil, *R*_F (98:2 CH₂Cl₂-acetone) 0.3; *R*_F (98:2 CH₂Cl₂-acetone) 0.6; IR (ATR) 2873, 1687 (C=O), 1597, 1580, 1448, 1224, 1178, 1224, 1099, 1057, 1003, 923, 888, 730, 690, 657 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.01-7.95 (m, 2H, Ph), 7.57 (t, *J* = 7.5, Hz, 1H, Ph), 7.46 (dd, *J* = 7.5, 7.5 Hz (app t), 2H, Ph), 5.26 (dd, *J* = 8.5, 6.0 Hz, 1H, OCH), 4.08-3.93 (m, 2H, OCH), 2.35-2.23 (m, 2H, CH), 2.18-2.09 (m, 1H, CH), 1.97 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 198.9 (C=O), 135.2 (*ipso*-Ph), 133.4 (Ph), 128.8 (Ph), 128.7 (Ph), 80.1 (OCH), 69.5 (OCH₂), 29.4 (CH₂), 25.7 (CH₂); MS (ESI) *m/z* 177 [(*M* + *H*)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₂O₂ (*M* + *H*)⁺ 177.0910, found 177.0913 (–1.5 ppm error).

Lab Book Reference: **NS11-16**

(4-Fluorophenyl)(tetrahydrofuran-2-yl)methanone 161

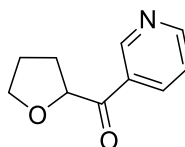


161

Using general procedure A, THF (406 μ L, 361 mg, 5.00 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and Weinreb amide **159** (1 $^{\circ}$ mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99.5:0.5 CH₂Cl₂-acetone as eluent gave α -substituted THF **161** (60 mg, 62%) as a colourless oil; *R*_F (98:2 CH₂Cl₂-acetone) 0.4; IR (ATR) 2978, 2876, 1692 (C=O), 1598, 1227, 1158, 1101, 891, 847, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.07-8.01 (m, 2H, Ar), 7.17-7.10 (m, 2H, Ar), 5.18 (dd, *J* = 8.5, 6.0 Hz, 1H, OCH), 4.08-3.89 (m, 2H, OCH), 2.33-2.09 (m, 2H, CH), 2.05-1.91 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 197.3 (C=O), 165.9 (d, *J* = 255.0 Hz, *ipso*-Ar), 131.70 (d, *J* = 9.5 Hz, Ar), 131.67 (*ipso*-Ar), 115.9 (d, *J* = 22.0 Hz, Ar), 80.2 (OCH), 69.5 (OCH₂), 29.1 (CH₂), 25.8 (CH₂); ¹⁹F NMR (376 MHz, CDCl₃) δ -104.6 (s); MS (ESI) *m/z* 217 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₁FNO₂ (M + Na)⁺ 217.0635, found 217.0638 (-1.1 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁸⁷

Lab Book Reference: **NS11-33**

Pyridin-3-yl(tetrahydrofuran-2-yl)methanone 162



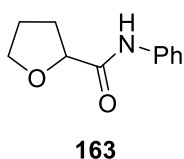
162

Using general procedure A, THF (406 μ L, 361 mg, 5.00 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and Weinreb amide **160** (166 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1 CH₂Cl₂-acetone to 95:5 CH₂Cl₂-acetone as eluent gave α -substituted THF **162** (43 mg, 49%) as a colourless oil; *R*_F (95:5 CH₂Cl₂-acetone) 0.3; IR (ATR) 2977, 2875, 1694 (C=O), 1586,

1419, 1239, 1044, 1001, 926, 890, 704, 677 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 9.23 (s, 1H, Ar), 8.85-8.75 (m, 1H, Ar), 8.35-8.29 (m, 1H, Ar), 7.48-7.41 (m, 1H, Ar), 5.15 (dd, $J = 8.0$, 6.0 Hz, 1H, OCH), 4.03-3.94 (m, 2H, OCH), 2.37-2.15 (m, 2H, CH), 2.07-1.86 (m, 2H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 198.0 (C=O), 153.3 (Ar), 150.1 (Ar), 136.8 (Ar), 130.9 (*ipso*- Ar), 123.9 (Ar), 80.7 (OCH), 69.6 (OCH_2), 28.8 (CH_2), 25.7 (CH_2); MS (ESI) m/z 178 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_2$ ($\text{M} + \text{H})^+$ 178.0863, found 178.0861 (+0.6 ppm error).

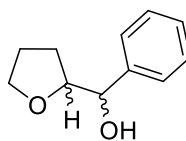
Lab Book Reference: **NS11-38**

N*-Phenyltetrahydrofuran-2-carboxamide **163*



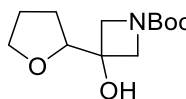
Using general procedure A, THF (406 μL , 361 mg, 5.00 mmol, 10.0 eq.), *s*-BuLi (385 μL of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and PhNCO (109 μL , 119 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane- Et_2O to 80:20 hexane- Et_2O as eluent gave α -substituted THF **163** (49 mg, 51%) as a colourless oil; R_F (80:20 hexane- Et_2O) 0.3; R_F (80:20 hexane- Et_2O) 0.3; IR (ATR) 3318 (NH), 2954, 2876, 1673 (C=O), 1600, 1523, 1442, 1312, 1238, 1070, 940, 754, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.46 (s, 1H, NH), 7.63-7.52 (m, 2H, Ph), 7.40-7.30 (m, 2H, Ph), 7.16-7.08 (m, 1H, Ph), 4.47 (dd, $J = 8.5$, 6.0 Hz, 1H, OCH), 4.05 (ddd, $J = 8.5$, 7.0, 6.0 Hz, 1H, OCH), 3.96 (ddd, $J = 8.5$, 7.0, 7.0 Hz (app dt), 1H, OCH), 2.37 (ddd, $J = 8.5$, 7.5, 7.0, 7.0 Hz, 1H, CH), 2.19 (ddd, $J = 7.0$, 6.0, 6.0 Hz (app dt), 1H, CH), 2.03-1.85 (m, 2H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 171.4 (C=O), 137.4 (*ipso*-Ph), 129.2 (Ph), 124.5 (Ph), 119.7 (Ph), 78.8 (OCH), 69.8 (OCH_2), 30.3 (CH_2), 25.7 (CH_2); MS (ESI) m/z 214 $[(\text{M} + \text{Na})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ ($\text{M} + \text{Na})^+$ 214.0838, found 214.0834 (+2.2 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁵²

Lab Book Reference: **NS11-20**

Phenyl(tetrahydrofuran-2-yl)methanol 113**113**

Using general procedure A, THF (203 μ L, 180 mg, 2.5 mmol, 5.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and benzaldehyde (102 μ L, 106 mg, 1.0 mmol, 2.0 eq.) gave the crude product which contained a 50:50 mixture (by ^1H NMR spectroscopy) of alcohols **113**. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2 -acetone to 90:10 CH_2Cl_2 -acetone as eluent gave a 50:50 mixture of alcohols **113** (53 mg, 60%) as a colourless oil; R_F (95:5 hexane-Et₂O) 0.5; IR (ATR) 3421 (OH), 3030, 2975, 2872, 1494, 1452, 1198, 1055, 1027, 760, 700, 624 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.41-7.22 (m, 5H, Ph), 4.92 (d, J = 4.0 Hz, 0.5H, HOCH), 4.44 (d, J = 7.5 Hz, 0.5H, HOCH), 4.10-4.04 (m, 0.5H, OCH), 4.00 (ddd, J = 7.0, 7.0, 7.0 Hz (app q), 0.5H, OCH), 3.94-3.76 (m, 2H, OCH), 2.61 (s, 1H, OH), 2.00-1.75 (m, 2.5H, CH), 1.74-1.54 (m, 1.5H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 140.8 (*ipso*-Ph), 140.7 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.1 (Ph), 127.5 (Ph), 127.1 (Ph), 126.1 (Ph), 83.6 (HOCH), 83.3 (HOCH), 77.1 (OCH), 74.1 (OCH), 69.1 (OCH₂), 68.5 (OCH₂), 28.0 (CH₂), 26.2 (CH₂), 26.1 (CH₂), 24.9 (CH₂); MS (ESI) m/z 201 [(C₁₁H₁₄O₂+Na)⁺, 100]; HRMS (ESI) m/z calcd for C₁₁H₁₄O₂ (M + Na)⁺ 201.0886, found 201.0886 (+0.1 ppm error). Spectroscopic data consistent with those reported in the literature.¹²⁵

Lab Book Reference: **NS11-19**

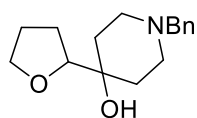
***tert*-Butyl 3-hydroxy-3-(tetrahydrofuran-2-yl)azetidine-1-carboxylate 164****164**

Using general procedure A, THF (406 μ L, 361 mg, 5.0 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and *tert*-butyl 3-oxoazetidine-1-carboxylate (172 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 CH_2Cl_2 -acetone to 70:30 CH_2Cl_2 -acetone as eluent gave α -substituted THF **164** (37 mg, 27%) as a colourless oil; R_F (70:30 CH_2Cl_2 -acetone) 0.4; IR (ATR) 3384 (OH),

2977, 2878, 1674 (C=O), 1416, 1392, 1366, 1161, 1066, 919, 771, 729 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 4.06 (dd, $J = 8.0, 7.0$ Hz, 1H, OCH), 3.98-3.89 (m, 2H, OCH), 3.87-3.76 (m, 4H, NCH), 2.70 (s, 1H, OH), 2.01-1.90 (m, 3H, CH), 1.80-1.69 (m, 1H, CH), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 156.6 (C=O), 82.5 (OCH), 79.8 (HOC), 70.7 (OCMe_3), 69.5 (OCH_2), 60.6 (NCH_2), 58.1 (NCH_2), 28.5 (CMe_3), 26.4 (CH_2), 25.8 (CH_2); MS (ESI) m/z 266 $[(\text{M} + \text{Na})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_4$ ($\text{M} + \text{Na})^+$ 266.1363, found 266.1361 (+0.5 ppm error).

Lab Book Reference: **NS11-40**

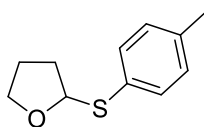
1-Benzyl-4-(tetrahydrofuran-2-yl)piperidin-4-ol **165**



165

Using general procedure A, THF (406 μL , 361 mg, 5.0 mmol, 10.0 eq.), *s*-BuLi (385 μL of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and 1-benzylpiperidin-4-one (185 μL , 189 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 80:20 CH_2Cl_2 -acetone to 60:40 CH_2Cl_2 -acetone as eluent gave α -substituted THF **165** (59 mg, 45%) as a colourless oil, R_F (60:40 CH_2Cl_2 -acetone) 0.2; IR (ATR) 3431 (OH), 2944, 2869, 2813, 1495, 1454, 1367, 1300, 1189, 1061, 1022, 740, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.21 (m, 5H, Ph), 3.88-3.74 (m, 2H, OCH), 3.63 (dd, $J = 7.5, 7.5$ Hz (app t), 1H, OCH), 3.57 (s, 2H, NCH_2Ph), 2.83-2.68 (m, 2H, NCH), 2.48-2.35 (m, 2H, NCH), 1.93-1.57 (m, 7H, CH), 1.52-1.43 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 149.8 (*ipso*-Ph), 129.5 (Ph), 128.4 (Ph), 127.3 (Ph), 85.6 (OCH), 69.8 (HOC), 68.8 (OCH_2), 63.1 (NCH_2Ph), 49.1 (NCH_2), 48.9 (NCH_2), 35.5 (CH_2), 32.1 (CH_2), 26.3 (CH_2), 25.3 (CH_2); MS (ESI) m/z 262 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2$ ($\text{M} + \text{H})^+$ 262.1802, found 262.1797 (+1.8 ppm error).

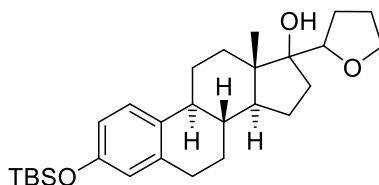
Lab Book Reference: **NS11-32**

2-(*p*-Tolylthio)tetrahydrofuran 166**166**

Using general procedure A, THF (406 μ L, 361 mg, 5.0 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and *p*-tolyl disulfide (246 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂ to 70:30 hexane-CH₂Cl₂ as eluent gave α -substituted THF **166** (63 mg, 65%) as a colourless oil; *R*_F (80:20 hexane-CH₂Cl₂) 0.2; IR (ATR) 2976, 2868, 1492, 1443, 1179, 1044, 906, 806, 754, 493 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.37 (m, 2H, Ar), 7.11-7.08 (m, 2H, Ar), 5.56 (dd, *J* = 7.0, 4.0 Hz, 1H, OCH), 4.04-3.97 (m, 1H, OCH), 3.96-3.89 (m, 1H, OCH), 2.38-2.32 (m, 1H, CH), 2.31 (s, 3H, Me), 2.06-1.78 (m, 3H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 137.1 (*ipso*-Ar), 131.9 (*ipso*-Ar), 131.8 (Ar), 129.7 (Ar), 87.7 (OCH), 67.3 (OCH₂), 32.7 (CH₂), 24.9 (CH₂), 21.2 (Me); MS (APCI) *m/z* 195 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₁₁H₁₄OS (M + H)⁺ 195.0838, found 195.0847 (−4.3 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁸⁸

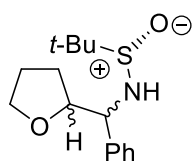
Lab Book Reference: **NS11-34**

Attempted Synthesis of 3-((*tert*-Butyldimethylsilyl)oxy)-13-methyl-17-(tetrahydrofuran-2-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol 168

**168**

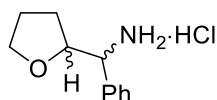
Using general procedure A, THF (406 μ L, 361 mg, 5.0 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and TBS-estrone (288 mg, 0.75 mmol, 1.5 eq.) in THF (2 mL) gave the crude product which contained only traces of the desired product **168** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS11-36**

2-Methyl-N-(phenyl(tetrahydrofuran-2-yl)methyl)propane-2-sulfinamide 172**172**

Using general procedure A, THF (406 μ L, 361 mg, 5.0 mmol, 10.0 eq.), *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) for 1 h and sulfinamide (*S*)-**170** (209 mg, 1.0 mmol, 2.0 eq.) gave the crude product which contained a 50:35:10:5 mixture (by ^1H NMR spectroscopy) of sulfinamides **172**. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave a 60:40 mixture of diastereomeric α -substituted THFs **172** (75 mg, 53%) as a colourless oil, R_F (50:50 hexane-EtOAc) 0.4; IR (ATR) 3224 (NH), 2954, 2868, 1495, 1455, 1363, 1182, 1057, 939, 881, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.45-7.19 (m, 5H, Ph), 4.35 (dd, $J = 6.0, 5.5$ Hz, 0.6H, OCH), 4.31-4.24 (m, 1H, OCH), 4.17 (dd, $J = 6.0, 6.0$ Hz, 0.4H (app t), OCH), 4.14-4.08 (m, 0.4H, OCH), 3.91-3.75 (m, 1.4H, CH), 3.74-3.67 (m, 1.2H, CH), 2.02-1.89 (m, 0.6H, CH), 1.89-1.51 (m, 3.4H), 1.21 (s, 5.4H, CMe_3), 1.20 (s, 3.6H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 140.5 (*ipso*-Ph), 139.7 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.4 (Ph), 128.0 (Ph), 127.9 (Ph), 82.8 (OCH), 81.8 (OCH), 68.81 (OCH₂), 68.79 (OCH₂), 62.5 (NCH), 62.4 (NCH), 56.6 (CMe_3), 56.4 (CMe_3), 28.9 (CH₂), 28.4 (CH₂), 26.0 (CH₂), 25.8 (CH₂), 22.8 (CMe_3), 22.7 (CMe_3) (one Ph and one CMe_3 resonance not resolved); MS (ESI) m/z 304 [$(\text{M} + \text{Na})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_2\text{S}$ ($\text{M} + \text{Na})^+$ 304.1342, found 304.1335 (+2.4 ppm error) and a 90:10 mixture of diastereomeric α -substituted THFs **172** (13 mg, 9%) as a colourless oil; R_F (50:50 hexane-EtOAc) 0.3; IR (ATR) 3270 (NH), 2957, 1873, 1455, 1364, 1059, 946, 702 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.37-7.27 (m, 5H, Ph), 4.67-4.65 (m, 0.1H, OCH), 4.59 (dd, $J = 4.0, 3.0$ Hz, 0.9H, OCH), 4.18-4.12 (m, 1H, OCH), 3.92-3.85 (m, 1H, NCH), 3.82-3.74 (m, 2H, OCH), 1.84-1.65 (m, 4H, CH), 1.23 (s, 8.1H, CMe_3), 1.20 (s, 0.9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) for major diastereomer δ 138.5 (*ipso*-Ph), 128.7 (Ph), 128.4 (Ph), 127.9 (Ph), 82.7 (OCH), 68.9 (OCH₂), 60.8 (NCH), 55.8 (CMe_3), 26.8 (CH₂), 25.9 (CH₂), 22.8 (CMe_3); MS (ESI) m/z 304 [$(\text{M} + \text{Na})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_2\text{S}$ ($\text{M} + \text{Na})^+$ 304.1342, found 304.1341 (+0.4 ppm error).

Lab Book Reference: **NS11-41**

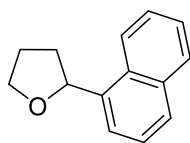
Phenyl(tetrahydrofuran-2-yl)methanamine Hydrochloride 173·HCl**173·HCl**

HCl (400 μ L of a 2.0 M solution in Et₂O, 0.80 mmol, 3.0 eq.) was added to a stirred solution of a 60:40 mixture of diastereomeric sulfinamides **172** (75 mg, 0.27 mmol, 1.0 eq.) in MeOH (2 mL) at rt. After stirring at rt for 1 h, the solvent was evaporated under reduced pressure to give the crude solid. Et₂O (3 mL) was added, the mixture was swirled to dissolve impurities and then the Et₂O was decanted. Addition of Et₂O (3 mL) and decanting was repeated a second time. The residual Et₂O was evaporated under reduced pressure to give a 60:40 mixture of diastereomeric α -substituted THF **173·HCl** (50 mg, 88%) as a colourless oil, IR (ATR) 3399 (NH), 2873, 1600, 1498, 1457, 1189, 1062, 761, 731, 699, 542 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 8.65 (s, 1.8H, NH), 8.51 (s, 1.2H, NH), 7.58-7.48 (m, 0.8H, Ph), 7.51-7.42 (m, 1.2H, Ph), 7.42-7.30 (m, 3H, Ph), 4.31-4.21 (m, 1.2H, OCH), 4.20-4.04 (m, 0.8H, OCH), 3.91-3.79 (m, 0.4H, OCH), 3.81-3.70 (m, 0.4H, OCH), 3.63-3.53 (m, 1.2H, OCH), 1.92-1.33 (m, 4H, CH); ¹³C NMR (100.6 MHz, CD₃OD) δ 144.9 (*ipso*-Ph), 144.4 (*ipso*-Ph), 138.4 (Ph), 138.3 (Ph), 138.1 (Ph), 137.9 (Ph), 137.8 (Ph), 137.6 (Ph), 88.9 (OCH), 88.1 (OCH), 77.6 (OCH₂), 77.5 (OCH₂), 67.5 (NCH), 66.3 (NCH), 37.8 (CH₂), 36.8 (CH₂), 34.7 (CH₂), 34.5 (CH₂); MS (ESI) *m/z* 178 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₅NO (M + H)⁺ 178.1226, found 178.1224 (+1.4 ppm error).

Lab Book Reference: **NS11-45**

HCl (70 μ L of a 2.0 M solution in Et₂O, 0.14 mmol, 3.0 eq.) was added to a stirred solution of a 90:10 mixture of diastereomeric sulfinamides **172** (13 mg, 0.046 mmol, 1.0 eq., 90:10 dr) in MeOH (2 mL) at rt. After stirring at rt for 1 h, the solvent was evaporated under reduced pressure to give the crude solid. Et₂O (3 mL) was added, the mixture was swirled to dissolve impurities and then the Et₂O was decanted. Addition of Et₂O (3 mL) and decanting was repeated a second time. The residual Et₂O was evaporated under reduced pressure to give a 95:5 mixture of diastereomeric α -substituted THFs **173·HCl** (9 mg, 90%) as a colourless oil.

Lab Book Reference: **NS11-46**

2-(Naphthalen-1-yl)tetrahydrofuran 183**183**

Using general procedure C, THF stannane **158** (180 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 1-bromonaphthalene (91 µL, 135 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 67:33 hexane-CH₂Cl₂ to 50:50 hexane-CH₂Cl₂ as eluent gave α -aryl THF **183** (59.5 mg, 60%) as a colourless oil, *R*_F (67:33 hexane-CH₂Cl₂) 0.2; IR (ATR) 3049, 2973, 2865, 1509, 1237, 1071, 1013, 798, 776, 557, 497 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00-7.96 (m, 1H, Ar), 7.90-7.86 (m, 1H, Ar), 7.76 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar), 7.65 (dd, *J* = 7.0, 1.0 Hz, 1H, Ar), 7.56-7.43 (m, 3H, Ar), 5.66 (dd, *J* = 7.0, 7.0 Hz (app t), 1H, OCH), 4.25 (ddd, *J* = 8.5, 7.0, 5.5 Hz, 1H, OCH), 4.04 (ddd, *J* = 8.5, 7.0, 7.0 Hz (app dt), 1H, OCH), 2.63-2.52 (m, 1H, CH), 2.14-1.86 (m, 3H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 139.1 (*ipso*-Ar), 133.5 (*ipso*-Ar), 130.1 (*ipso*-Ar), 128.6 (Ar), 127.2 (Ar), 125.6 (Ar), 125.3 (Ar), 125.2 (Ar), 123.2 (Ar), 121.6 (Ar), 77.7 (OCH), 68.6 (OCH₂), 33.6 (CH₂), 25.8 (CH₂); MS (ESI) *m/z* 199 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₄H₁₄O (M + H)⁺ 199.1117, found 199.1116 (+0.6 ppm error). Spectroscopic data consistent with those reported in the literature.⁵⁸

Lab Book Reference: **NS7-69-A**

Using general procedure B, *s*-BuLi (0.77 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) in THF (5 mL), ZnCl₂ (1.0 mL of a 1.0 M solution in THF, 1.0 mmol, 1.0 eq.), *t*-Bu₃PHBF₄ (13 mg, 10 mol%), Pd(OAc)₂ (7.9 mg, 8 mol%) and 1-bromonaphthalene (104 mg, 79 µL, 0.5 mmol, 0.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ as eluent gave α -aryl THF **183** (20 mg, 20%) as a colourless oil.

Lab Book Reference: **NS6-3**

s-BuLi (0.77 mL of 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of THF (5 mL) at -60 °C under Ar. The resulting solution was stirred at -60 °C for 4 h. Then, a freshly prepared solution of ZnCl₂ (1.00 mL of a 1.0 M solution in

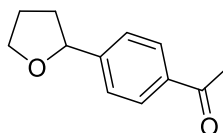
THF, 1.0 mmol, 1.0 eq.) was added. After stirring at $-78\text{ }^{\circ}\text{C}$ for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, $\text{Pd}(\text{OAc})_2$ (7.9 mg, 8 mol%), $t\text{-Bu}_3\text{PHBF}_4$ (13 mg, 10 mol%) and 1-bromonaphthalene (104 mg, 79 μL , 0.5 mmol, 0.5 eq.) were added and the reaction mixture was stirred and heated at $40\text{ }^{\circ}\text{C}$ for 16 h. The solids were removed by filtration through Celite[®] and washed with Et_2O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product which contained only traces of **183** by ^1H NMR spectroscopy.

Lab Book Reference: **NS6-3**

$s\text{-BuLi}$ (385 μL of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) was added dropwise to a stirred solution of THF (406 μL , 361 mg, 5.0 mmol, 10.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at $-45\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-45\text{ }^{\circ}\text{C}$ for 1 h. Then, a commercial solution of ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added. After stirring at $-45\text{ }^{\circ}\text{C}$ for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, $\text{Pd}(\text{OAc})_2$ (4.5 mg, 4 mol%), $t\text{-Bu}_3\text{PHBF}_4$ (11.6 mg, 8 mol%) and 1-bromo-naphthalene (135 mg, 91 μL , 0.65 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at $40\text{ }^{\circ}\text{C}$ for 16 h. The solids were removed by filtration through Celite[®] and washed with Et_2O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane- CH_2Cl_2 as eluent gave α -aryl THF **183** (32 mg, 32%) as a colourless oil.

Lab Book Reference: **NS11-37**

1-(4-(Tetrahydrofuran-2-yl)phenyl)ethan-1-one **178**



178

Using general procedure C, THF stannane **158** (180 mg, 0.50 mmol, 1.0 eq.), $n\text{-BuLi}$ (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 4 mol%), $t\text{-Bu}_3\text{PHBF}_4$ (11.6 mg, 8 mol%) and 1-(4-bromophenyl)ethan-1-one (129 mg, 0.65 mmol,

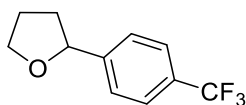
1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave α -aryl THF **178** (59.5 mg, 63%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.3; IR (ATR) 2974, 2870, 1679 (C=O), 1607, 1411, 1358, 1267, 1062, 831, 596 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.97-7.88 (m, 2H, Ar), 7.48-7.36 (m, 2H, Ar), 4.95 (dd, $J = 7.5, 7.5$ Hz (app t), 1H, OCH), 4.11 (ddd, $J = 7.5, 7.0, 7.0$ Hz, 1H (app dt), OCH), 3.96 (ddd, $J = 8.5, 7.5, 7.0$ Hz, 1H, OCH), 2.59 (s, 3H, Me), 2.42-2.31 (m, 1H, CH), 2.06-1.96 (m, 2H, CH), 1.84-1.71 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 198.0 (C=O), 149.3 (*ipso*-Ar), 136.2 (*ipso*-Ar), 128.6 (Ar), 125.7 (Ar), 80.3 (OCH), 69.0 (OCH_2), 34.8 (CH_2), 26.8 (Me), 26.1 (CH_2); MS (ESI) m/z 191 [$(\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$ ($\text{M} + \text{H})^+$ 191.1067, found 191.1067 (-0.1 ppm error). Spectroscopic data consistent with those reported in the literature.⁵⁸

Lab Book Reference: **NS7-69-B**

Using general procedure B, *s*-BuLi (0.77 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) in THF (5 mL), ZnCl_2 (1.0 mL of a 1.0 M solution in THF, 1.0 mmol, 1.0 eq.), $\text{Pd}(\text{OAc})_2$ (7.9 mg, 8 mol%), *t*-Bu₃PHBF₄ (13 mg, 10 mol%) and 1-(4-bromophenyl)ethan-1-one (100 mg, 0.5 mmol, 0.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-Et₂O as eluent gave α -aryl THF **178** (20 mg, 20%).

Lab Book Reference: **NS6-26**

2-(4-(Trifluoromethyl)phenyl)tetrahydrofuran **184**



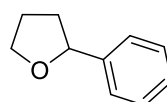
184

Using general procedure B, *s*-BuLi (0.77 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) in THF (5 mL), ZnCl_2 (1.0 mL of a 1.0 M solution in THF, 1.0 mmol, 1.0 eq.), $\text{Pd}(\text{OAc})_2$ (7.9 mg, 8 mol%), *t*-Bu₃PHBF₄ (13 mg, 10 mol%) and 1-bromo-4-(trifluoromethyl)benzene (215 mg, 140 μL , 1.0 mmol, 0.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane- CH_2Cl_2 and then 50:50 hexane- CH_2Cl_2 as eluent gave α -aryl THF **184** (45 mg, 21%) as a colourless oil, R_F (50:50 hexane- CH_2Cl_2) 0.5; IR (ATR) 2978, 2873, 1417, 1322, 1161, 1118, 1064, 836, 601

cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 8.0 Hz, 2H, Ar), 7.44 (d, J = 8.0 Hz, 2H, Ar), 4.95 (dd, J = 7.0, 7.0 Hz (app t), 1H, OCH), 4.11 (ddd, J = 7.0, 7.0, 7.0 Hz (app q), 1H, OCH), 3.96 (ddd, J = 7.0, 7.0, 7.0 Hz (app q), 1H, OCH), 2.37 (dddd, J = 12.5, 7.0, 7.0, 7.0 Hz (app dq), 1H, CH), 2.05-1.96 (m, 2H, CH), 1.77 (dddd, J = 12.5, 7.0, 7.0, 7.0 Hz (app dq), 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 147.9 (br s, *ipso*-Ar), 129.6 (q, J = 32.0 Hz, CCF₃), 125.9 (br s, Ar), 125.4 (q, J = 4.0 Hz, Ar), 124.5 (q, J = 267.0 Hz, CF₃), 80.1 (OCH), 69.0 (OCH₂), 34.9 (CH₂), 26.1 (CH₂); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.3 (s); MS (APCI) m/z 217 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₁H₁₁F₃O (M + H)⁺ 217.0835, found 217.0827 (-3.4 ppm error). Spectroscopic data consistent with those reported in the literature.⁶³

Lab Book Reference: **NS7-44**

2-Phenyltetrahydrofuran **177**

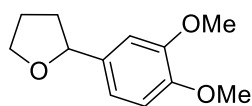


177

Using general procedure B, *s*-BuLi (1.54 mL of a 1.3 M solution in hexane, 2.0 mmol, 1.0 eq.) in THF (10 mL), ZnCl₂ (2.0 mL of a 1.0 M solution in THF, 1.0 mmol, 1.0 eq.), Pd(OAc)₂ (15.8 mg, 8 mol%), *t*-Bu₃PHBF₄ (26 mg, 10 mol%) and bromobenzene (157 mg, 105 μ L, 1.0 mmol, 0.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂, then 50:50 hexane-CH₂Cl₂ as eluent gave α -aryl THF **177** (34 mg of a 50:50 mixture of **177** and CH₂Cl₂ i.e. 22 mg (15%) of **177**) as a yellow oil, R_F (50:50 hexane-CH₂Cl₂) 0.5; ¹H NMR (400 MHz, CDCl₃) δ 7.27-7.14 (m, 5H, Ph), 4.82 (dd, J = 7.0, 7.0 Hz (app t), 1H, OCH), 4.02 (ddd, J = 9.5, 7.5, 7.0 Hz, 1H, OCH), 3.87 (ddd, J = 9.5, 8.0, 7.0 Hz, 1H, OCH), 2.33-2.18 (m, 1H, CH), 2.00-1.86 (m, 2H, CH), 1.73 (dddd, J = 12.0, 8.0, 8.0, 7.5 Hz, 1H (app dtd), CH). Compound **177** was found to be volatile and evaporated completely during the final drying process. Therefore, full characterisation was not possible. ¹H NMR spectroscopic data consistent with those reported in the literature.¹⁸⁹

Lab Book Reference: **NS7-40**

Attempted Synthesis of 2-(3,4-Dimethoxyphenyl)tetrahydrofuran **185**

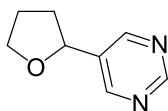


185

Using general procedure B, *s*-BuLi (1.54 mL of a 1.3 M solution in hexane, 2.0 mmol, 1.0 eq.) in THF (10 mL), ZnCl₂ (2.0 mL of a 1.0 M solution in THF, 1.0 mmol, 1.0 eq.), *t*-Bu₃PHBF₄ (26 mg, 10 mol%), Pd(OAc)₂ (15.8 mg, 8 mol%) and 4-bromoveratrol (219 mg, 1.0 mmol, 0.5 eq.) gave the crude product. The ¹H NMR spectrum of the crude product which did not contain the desired product **185** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-40**

Attempted Synthesis of 5-(Tetrahydrofuran-2-yl)pyrimidine **186**

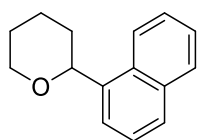


186

Using general procedure B, *s*-BuLi (1.54 mL of a 1.3 M solution in hexane, 2.0 mmol, 1.0 eq.) in THF (10 mL), ZnCl₂ (2.0 mL of a 1.0 M solution in THF, 1.0 mmol, 1.0 eq.), *t*-Bu₃PHBF₄ (26 mg, 10 mol%), Pd(OAc)₂ (15.8 mg, 8 mol%) and 5-bromopyrimidine (158 mg, 1.0 mmol, 0.5 eq.) at 40 °C gave the crude product. The ¹H NMR spectrum of the crude product which did not contain the desired product **186** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-41**

2-(Naphthalen-1-yl)tetrahydropyran **187**



187

s-BuLi (500 µL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of THP (49 µL, 43.1 mg, 0.50 mmol, 1.0 eq.) and bispidine **157** (118 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at 0 °C under Ar. The resulting solution was stirred

at 0 °C for 1 h. Then, a commercial solution of ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added at –78 °C. After stirring at –78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 1-bromonaphthalene (135 mg, 91 µL, 0.65 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at 40 °C for 16 h. The solids were removed by filtration through Celite® and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-CH₂Cl₂ as eluent gave α-aryl THP **187** (65 mg, 55%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.6; IR (ATR) 3050, 2934, 2849, 1510, 1341, 1204, 1086, 1048, 798, 776, 646, 480 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 8.0 Hz, 1H, Ar), 7.86 (d, *J* = 8.0 Hz, 1H, Ar), 7.77 (d, *J* = 8.0 Hz, 1H, Ar), 7.64 (d, *J* = 8.0 Hz, 1H, Ar), 7.54-7.41 (m, 3H, Ar), 5.10-4.98 (m, 1H, OCH), 4.25 (br dd, *J* = 11.0, 3.5 Hz, 1H, OCH), 3.79 (ddd, *J* = 11.0, 11.0, 2.5 Hz (app td), 1H, OCH), 2.10-1.97 (m, 2H, CH), 1.87-1.73 (m, 3H, CH), 1.73-1.63 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 139.0 (*ipso*-Ar), 133.8 (*ipso*-Ar), 130.5 (*ipso*-Ar), 128.9 (Ar), 127.8 (Ar), 125.9 (Ar), 125.7 (Ar), 125.4 (Ar), 123.4 (Ar), 123.1 (Ar), 77.3 (OCH), 69.5 (OCH₂), 33.3 (CH₂), 26.2 (CH₂), 24.4 (CH₂); MS (APCI) *m/z* 213 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₁₅H₁₆O (M + H)⁺ 213.1274, found 213.1272 (–0.9 ppm error). Spectroscopic data consistent with those reported in the literature.⁴⁷

Lab Book Reference: **NS11-43**

s-BuLi (1.08 mL, of a 1.2 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of THP (99 µL, 86 mg, 1.0 mmol, 1.0 eq.) and TMEDA (195 µL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Then, a freshly prepared solution of ZnCl₂ (1.3 mL of a 1.0 M solution in THF, 1.3 mmol, 1.3 eq.) was added at –78 °C. After stirring at –78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, Pd(OAc)₂ (9 mg, 4 mol%), *t*-Bu₃PHBF₄ (23.2 mg, 8 mol%) and 1-bromonaphthalene (181 µL, 269 mg, 1.3 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at 40 °C for 16 h. The solids were removed by filtration through Celite® and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on

silica with 80:20 hexane-CH₂Cl₂ then 80:20 hexane-CH₂Cl₂ as eluent gave α -aryl THP **187** (28 mg, 13%) as a colourless oil.

Lab Book Reference: **NS7-45**

4-Methyl-2-(naphthalen-1-yl)morpholine **188**

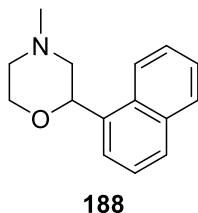


Table 2.2, entry 3:

Using general procedure C, α -stannyl morpholine **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13 mg, 9 mol%), and 1-bromonaphthalene (91 μ L, 135 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH as eluent gave α -aryl morpholine **188** (51.1 mg, 45%) as a colourless oil, *R*_F (96:3:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.5; IR (ATR) 3050, 2936, 2853, 2790, 1449, 1290, 1202, 1141, 1106, 1080, 798, 776, 639, 562 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar), 7.88-7.84 (m, 1H, Ar), 7.79 (ddd, *J* = 8.0, 1.0, 1.0 Hz (app dt), 1H, Ar), 7.67 (ddd, *J* = 7.0, 1.0, 1.0 Hz (app dt), 1H, Ar), 7.55-7.45 (m, 3H, Ar), 5.33 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 4.15 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 4.00 (ddd, *J* = 11.5, 11.5, 2.0 Hz (app td), 1H, OCH), 3.11 (ddd, *J* = 11.5, 2.0, 2.0 Hz (app dt), 1H, NCH), 2.86-2.80 (m, 1H, NCH), 2.35 (s, 3H, NMe), 2.34-2.29 (m, 1H, NCH), 2.18 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 136.2 (*ipso*-Ar), 133.8 (*ipso*-Ar), 130.5 (*ipso*-Ar), 129.0 (Ar), 128.3 (Ar), 126.2 (Ar), 125.61 (Ar), 125.59 (Ar), 123.7 (Ar), 123.1 (Ar), 75.3 (OCH), 67.5 (OCH₂), 61.8 (NCH₂), 55.2 (NCH₂), 46.3 (NMe); MS (ESI) *m/z* 228 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₅H₁₇NO (M + H)⁺ 228.1383, found 228.1383 (−0.1 ppm error).

Lab Book Reference: **NS8-91-A**

s-BuLi (1.00 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of morpholine **125** (110 μ L, 101 mg, 1.0 mmol, 1.0 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C under Ar. The resulting solution was

stirred at 0 °C for 30 min. Then, a freshly prepared solution of ZnCl₂ (1.3 mL of a 1.0 M solution in THF, 1.3 mmol, 1.3 eq.) was added at –78 °C. After stirring at –78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, Pd(OAc)₂ (9 mg, 4 mol%), *t*-Bu₃PHBF₄ (23.2 mg, 8 mol%) and 1-bromonaphthalene (181 µL, 269 mg, 1.3 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at 40 °C for 16 h. The solids were removed by filtration through Celite® and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) then 96:3:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α-aryl morpholine **188** (70.5 mg, 31%) as a colourless oil. Lab Book Reference: **NS7-48**

s-BuLi (1.00 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of morpholine **125** (110 µL, 101 mg, 1.0 mmol, 1.0 eq.) and TMEDA (195 µL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Then, a freshly prepared solution of ZnCl₂ (1.3 mL of a 1.0 M solution in THF, 1.3 mmol, 1.3 eq.) was added at –78 °C. After stirring at –78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, Pd(OAc)₂ (9 mg, 4 mol%), *t*-Bu₃PHBF₄ (23.2 mg, 8 mol%) and 1-bromonaphthalene (181 µL, 269 mg, 1.3 mmol, 1.3 eq.) were added and the reaction mixture was stirred at rt for 16 h. The solids were removed by filtration through Celite® and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) then 96:3:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α-aryl morpholine **188** (29.6 mg, 13%) as a colourless oil.

Lab Book Reference: **NS7-46**

Table 2.2, entry 1:

Using general procedure C, α-stannyl morpholine **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%), and 1-bromonaphthalene (91 µL, 135 mg, 0.65 mmol, 1.3 eq.) at rt gave the crude product. Purification by flash column chromatography on silica

with 90:10 CH₂Cl₂-acetone then 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -aryl morpholine **188** (36 mg, 32%) as a colourless oil.

Lab Book Reference: **NS8-91-D**

Table 2.2, entry 2:

Using general procedure C, α -stannyl morpholine **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PBHF₄ (11.6 mg, 8 mol%), and 1-bromonaphthalene (91 μ L, 135 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -aryl morpholine **188** (46 mg, 40%) as a colourless oil.

Lab Book Reference: **NS8-96-2**

Table 2.2, entry 4:

Using general procedure C, α -stannyl morpholine **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PBHF₄ (11.6 mg, 9 mol%), and 1-bromonaphthalene (91 μ L, 135 mg, 0.65 mmol, 1.3 eq.) at 60 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -aryl morpholine **188** (53 mg, 47%) as a colourless oil.

Lab Book Reference: **NS8-96-1**

Table 2.2, entry 5:

n-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of α -stannyl morpholine **228** (195 mg, 0.50 mmol, 1.0 eq.) in THF (2.5 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 30 min. Then, a commercial solution of ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added at -78 °C. After stirring at -78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, PEPPSI-*i*-Pr (17 mg, 5 mol%) and 1-bromonaphthalene (91 μ L, 135 mg, 0.65 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at 40 °C for 16 h. The solids were removed by filtration through Celite[®] and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and

water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -aryl morpholine **188** (5 mg, 4%) as a colourless oil.

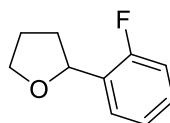
Lab Book Reference: **NS8-91-B**

Table 2.2, entry 6:

n-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of α -stannyl morpholine **228** (195 mg, 0.50 mmol, 1.0 eq.) in THF (2.5 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 30 min. Then, a commercial solution of ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added at -78 °C. After stirring at -78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, X-Phos (12.1 mg, 5 mol%), Pd(dba)₂ (8 mg, 5 mol%) and 1-bromonaphthalene (91 μ L, 135 mg, 0.65 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at 40 °C for 16 h. The solids were removed by filtration through Celite[®] and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -aryl morpholine **188** (27 mg, 24%) as a colourless oil.

Lab Book Reference: **NS8-91-C**

2-(2-Fluorophenyl)tetrahydrofuran **191**



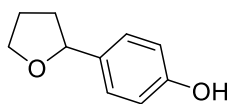
191

Using general procedure C, α -stannyl THF **158** (180 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 1-bromo-2-fluorobenzene (71.1 μ L, 114 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ as eluent gave α -aryl THF **191** (39.1 mg, 47%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.3; IR (ATR) 2977, 2872,

1589, 1486, 1456, 1364, 1230, 1104, 756, 517 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.44 (dddd, $J = 7.5, 7.5, 2.0, 1.0$ Hz (app tdd), 1H, Ar), 7.24-7.17 (m, 1H, Ar), 7.11 (ddd, $J = 7.5, 7.5, 1.0$ Hz (app td), 1H, Ar), 6.99 (ddd, $J = 11.0, 7.5, 1.0$ Hz, 1H, Ar), 5.13 (dd, $J = 7.0, 7.0$ Hz (app t), 1H, OCH), 4.09 (ddd, $J = 8.0, 7.0, 7.0$ Hz (app dt), 1H, OCH), 3.93 (ddd, $J = 8.0, 7.0, 7.0$ Hz (app dt), 1H, OCH), 2.39 (dddd, $J = 12.0, 7.0, 7.0, 7.0$ Hz (app dq), 1H, CH), 2.03-1.94 (m, 2H, CH), 1.84-1.72 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 159.9 (d, $J = 245.5$ Hz, *ipso*-Ar), 131.0 (d, $J = 13.5$ Hz, *ipso*-Ar), 128.5 (d, $J = 8.0$ Hz, Ar), 126.9 (d, $J = 4.5$ Hz, Ar), 124.1 (d, $J = 3.5$ Hz, Ar), 115.2 (d, $J = 21.0$ Hz, Ar), 75.2 (OCH), 68.8 (OCH₂), 33.6 (CH₂), 26.1 (CH₂); ^{19}F NMR (376 MHz, CDCl_3) δ -118.6 (s); MS (APCI) m/z 167 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for $\text{C}_{10}\text{H}_{11}\text{FO}$ (M + H)⁺ 167.0867, found 167.0862 (-2.7 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁹⁰

Lab Book Reference: **NS9-14-B**

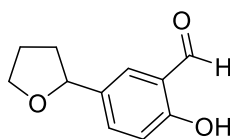
4-(Tetrahydrofuran-2-yl)phenol **192**



192

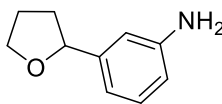
Using general procedure C, α -stannyl THF **158** (180 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 4-bromophenol (113 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc then 80:20 hexane-EtOAc as eluent gave α -aryl THF **192** (52.5 mg, 64%) as a white solid, mp 111-114 °C, R_F (60:40 hexane-EtOAc) 0.4; IR (ATR) 3272 (OH), 2975, 2875, 1615, 1515, 1449, 1266, 1228, 1170, 1038, 923, 830, 537 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.23-7.16 (m, 2H, Ar), 6.80-6.72 (m, 2H, Ar), 5.21 (br s, 1H, OH), 4.82 (dd, $J = 7.0, 7.0$ Hz (app t), 1H, OCH), 4.08 (ddd, $J = 7.5, 7.5, 7.0$ Hz (app td), 1H, OCH), 3.91 (ddd, $J = 8.5, 7.5, 7.0$ Hz, 1H, OCH), 2.34-2.22 (m, 1H, CH), 2.08-1.94 (m, 2H, CH), 1.86-1.75 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 155.1 (*ipso*-Ar), 135.1 (*ipso*-Ar), 127.4 (Ar), 115.3 (Ar), 80.7 (OCH), 68.6 (OCH₂), 34.5 (CH₂), 26.2 (CH₂); MS (ESI) m/z 187 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2$ (M + Na)⁺ 187.0730, found 187.0726 (-0.9 ppm error). Spectroscopic data consistent with those reported in the literature.⁶²

Lab Book Reference: **NS9-16-A**

2-Hydroxy-5-(tetrahydrofuran-2-yl)benzaldehyde 193**193**

Using general procedure C, α -stannyl THF **158** (180 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 5-bromo-2-hydroxybenzaldehyde (102 mg, 68 μ L, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc to 80:20 hexane-EtOAc as eluent gave α -aryl THF **193** (33.6 mg, 35%) as a colourless oil, *R*_F (80:20 hexane-EtOAc) 0.3; IR (ATR) 2973, 2867, 1653 (C=O), 1626, 1592, 1485, 1278, 1206, 1150, 1061, 837, 770, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.95 (s, 1H, (CHO)), 9.89 (s, 1H, OH), 7.55 (d, *J* = 2.5 Hz, 1H, Ar), 7.48 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 6.97 (d, *J* = 8.5 Hz, 1H, Ar), 4.85 (dd, *J* = 7.0, 7.0 Hz (app t), 1H, OCH), 4.10 (ddd, *J* = 8.5, 7.0, 7.0 Hz (app dt), 1H, OCH), 3.94 (ddd, *J* = 8.5, 7.0, 7.0 Hz (app dt), 1H, OCH), 2.39-2.27 (m, 1H, CH), 2.08-1.99 (m, 2H, CH), 1.82-1.70 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.8 (C=O), 160.9 (*ipso*-Ar), 135.2 (*ipso*-Ar), 134.9 (*ipso*-Ar), 130.7 (Ar), 120.4 (Ar), 117.7 (Ar), 79.8 (OCH), 68.8 (OCH₂), 34.6 (CH₂), 26.1 (CH₂); MS (ESI) *m/z* 215 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₂O₃ (M + Na)⁺ 215.0679, found 215.0679 (+0.0 ppm error).

Lab Book Reference: **NS9-14-C**

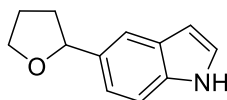
3-(Tetrahydrofuran-2-yl)aniline 194**194**

Using general procedure C, α -stannyl THF **158** (180 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 3-bromoaniline (71 μ L, 112 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 69.5:29.5:1 hexane-EtOAc-Et₃N as eluent gave α -aryl THF **194** (47.3 mg, 58%) as a colourless oil, *R*_F (69.5:29.5:1 hexane-EtOAc-Et₃N) 0.2; IR (ATR) 3353 (NH), 3227 (NH),

2972, 2869, 1606, 1590, 1493, 1461, 1052, 995, 923, 783, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.11 (dd, $J = 7.5, 7.5$ Hz (app t), 1H, Ar), 6.78-6.66 (m, 2H, Ar), 6.57 (ddd, $J = 7.5, 2.0, 1.0$ Hz, 1H, Ar), 4.81 (dd, $J = 7.0, 7.0$ Hz (app t), 1H, OCH), 4.07 (ddd, $J = 8.5, 7.0, 7.0$ Hz (app dt), 1H, OCH), 3.92 (ddd, $J = 8.5, 7.0, 7.0$ Hz (app dt), 1H, OCH), 3.66 (s, 2H, NH_2), 2.38-2.22 (m, 1H, CH), 2.05-1.92 (m, 2H, CH), 1.87-1.71 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 146.5 (*ipso*-Ar), 145.0 (*ipso*-Ar), 129.3 (Ar), 116.1 (Ar), 114.0 (Ar), 112.4 (Ar), 80.7 (OCH), 68.8 (OCH_2), 34.6 (CH_2), 26.1 (CH_2); MS (ESI) m/z 164 $[(\text{M} + \text{H})^+]$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{13}\text{NO}$ ($\text{M} + \text{H})^+$ 164.1070, found 164.1068 (+1.4 ppm error).

Lab Book Reference: **NS9-14-A**

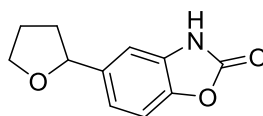
5-(Tetrahydrofuran-2-yl)-1H-indole **195**



195

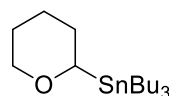
Using general procedure C, α -stannyl THF **158** (180 mg, 0.50 mmol, 1.0 eq.), $n\text{-BuLi}$ (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 4 mol%), $t\text{-Bu}_3\text{PHBF}_4$ (11.6 mg, 8 mol%) and 5-bromoindole (127 mg, 0.65 mmol, 1.3 eq.) at 40 $^\circ\text{C}$ gave the crude product. Purification by flash column chromatography on silica with 79.5:19.5:1 hexane-EtOAc- Et_3N as eluent gave α -aryl THF **195** (42.1 mg, 45%) as a colourless oil, R_F (79.5:19.5:1 hexane-EtOAc- Et_3N) 0.2; IR (ATR) 3408, 3273, 2972, 2870, 1479, 1418, 1367, 1345, 1094, 1045, 875, 805, 767, 727, 568 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.23 (s, 1H, NH), 7.65-7.61 (m, 1H, Ar), 7.36-7.31 (m, 1H, Ar), 7.23-7.13 (m, 2H, Ar), 6.59-6.44 (m, 1H, Ar), 5.01 (dd, $J = 7.0, 7.0$ Hz (app t), 1H, OCH), 4.20-4.11 (m, 1H, OCH), 3.97 (ddd, $J = 8.0, 8.0, 6.0$ Hz (app td), 1H, OCH), 2.39-2.28 (m, 1H, CH), 2.17-1.99 (m, 2H, CH), 1.99-1.84 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 135.4 (*ipso*-Ar), 134.7 (*ipso*-Ar), 127.9 (*ipso*-Ar), 124.6 (Ar), 120.4 (Ar), 117.9 (Ar), 111.1 (Ar), 102.8 (Ar), 81.7 (OCH), 68.7 (OCH_2), 35.0 (CH_2), 26.3 (CH_2); MS (ESI) m/z 210 $[(\text{M} + \text{Na})^+]$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{13}\text{NO}$ ($\text{M} + \text{Na})^+$ 210.0889, found 210.0888 (+0.5ppm error). Spectroscopic data consistent with those reported in the literature.⁶²

Lab Book Reference: **NS9-14-D**

5-(Tetrahydrofuran-2-yl)benzo[d]oxazol-2(3H)-one 196**196**

Using general procedure C, α -stannyl THF **158** (180 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 5-bromobenzo[d]oxazol-2(3H)-one (139 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone as eluent gave α -aryl THF **196** (48.2 mg, 47%) as a colourless oil, *R*_F (90:10 CH₂Cl₂-acetone) 0.3; IR (ATR) 3196 (NH), 2975, 2873, 1765 (C=O), 1498, 1467, 1262, 1060, 921, 814, 708, 589 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.74 (s, 1H, NH), 7.15-7.03 (m, 3H, Ar), 4.89 (dd, *J* = 7.5, 7.0 Hz, 1H, OCH), 4.11 (ddd, *J* = 8.5, 7.0, 7.0 Hz (app dt), 1H, OCH), 3.96 (ddd, *J* = 8.5, 7.0, 7.0 Hz (app dt), 1H, OCH), 2.33 (ddd, *J* = 12.5, 7.0, 6.0 Hz, 1H, CH), 2.10-1.95 (m, 2H, CH), 1.88-1.65 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.3 (C=O), 143.2 (*ipso*-Ar), 140.0 (*ipso*-Ar), 129.7 (*ipso*-Ar), 120.2 (Ar), 109.8 (Ar), 107.6 (Ar), 80.6 (OCH), 68.9 (OCH₂), 35.1 (CH₂), 26.1 (CH₂); MS (ESI) *m/z* 206 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₁NO₃ (M + H)⁺ 206.0812, found 206.0814 (−0.9 ppm error).

Lab Book Reference: **NS9-16-B**

Tributyl(tetrahydro-2H-pyran-2-yl)stannane 197**197**

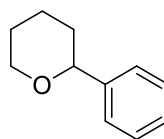
HCl (15 mL of a 2.0 M solution in Et₂O, 30 mmol, 1.8 eq.) was added to a stirred solution of dihydropyran **198** (2.70 mL, 2.52 g, 30 mmol, 1.8 eq.) in THF (20 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h to give a solution of 2-chlorotetrahydropyran in THF. In a separate flask, *n*-BuLi (11.3 mL, 1.5 M in hexane, 17.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of *i*-Pr₂NH (4.70 mL, 3.39 g, 34 mmol) in THF (30 mL) at 0 °C under Ar. The solution was stirred at 0 °C for 5 min. Then, Bu₃SnH (4.63 mL, 5.09 g, 18 mmol, 1.03 eq.) was added and the solution was stirred at 0 °C for 15 min to give a solution of Bu₃SnLi in THF. The solution of Bu₃SnLi in THF was

added dropwise to the stirred solution of solution of 2-chlorotetrahydropyran in THF at -78°C . The resulting solution was stirred at -78°C for 1 h and then allowed to warm to rt over 16 h. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (30 mL) and saturated $\text{NaHCO}_{3(\text{aq})}$ (30 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 70:30 hexane- CH_2Cl_2 then 50:50 hexane- CH_2Cl_2 as eluent gave α -stannyl THP **197** (1.74 g, 43%) as a colourless oil, R_F (50:50 hexane- CH_2Cl_2) 0.5; IR (ATR) 2954, 2924, 2852, 2871, 1460, 1376, 1193, 1168, 1071, 1040, 1004, 914, 874, 690 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.89-3.79 (m, 2H, OCH), 3.35 (ddd, $J = 11.0, 11.0, 2.5$ Hz (app td), 1H, OCH), 1.91-1.40 (m, 12H, CH), 1.37-1.25 (m, 6H, CH), 0.98-0.78 (m, 15H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 75.5 (OCH), 71.0 (OCH_2), 32.4 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 27.3 (CH_2), 25.7 (CH_2), 13.9 (CH_2), 8.47 (Me); MS (ESI) m/z 317 [$((^{118}\text{M}-\text{Bu}) + \text{H})^+$, 73], 319 [$((^{120}\text{M}-\text{Bu}) + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{36}\text{O}^{120}\text{Sn} ((\text{M}-\text{Bu}) + \text{H})^+$ 319.1078, found 319.1025 (+4.7 ppm error). Spectroscopic data consistent with those reported in the literature.¹²⁵

Lab Book Reference: **NS9-25**

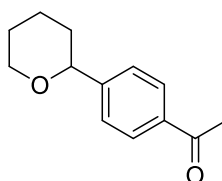
$s\text{-BuLi}$ (15 mL of a 1.3 M solution in hexane, 20.0 mmol, 1.3 eq.) was added dropwise to a solution of THP (1.29 g, 1.47 mL, 15 mmol, 1.0 eq.) and TMEDA (2.93 μL , 20 mmol, 1.3 eq.) in hexane (50.0 mL) at 0°C under Ar. The resulting solution was stirred at 0°C for 30 min. Then, Bu_3SnCl (7.32 g, 6.10 mL, 23 mmol, 1.5 eq.) was added. The resulting solution was stirred at 0°C for 1 h and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (30 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (45 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 85:15 to 50:50 hexane- CH_2Cl_2 as eluent gave α -stannyl THP **197** (1.26 g, 22%) as a colourless oil.

Lab Book Reference: **NS7-64**

2-Phenyltetrahydro-2H-pyran 199**199**

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 1-bromobenzene (102 mg, 68 μ L, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 67:33 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ as eluent gave α -aryl THP **199** (60 mg, 74%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.4; IR (ATR) 3030, 2935, 2845, 1452, 1264, 1204, 1087, 1052, 1040, 907, 749, 697, 547 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.21 (m, 5H, Ph), 4.33 (br d, *J* = 11.5 Hz, 1H, OCH), 4.24-4.07 (m, 1H, OCH), 3.63 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 2.00-1.92 (m, 1H, CH), 1.88-1.80 (m, 1H, CH), 1.75-1.54 (m, 4H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.5 (*ipso*-Ph), 128.4 (Ph), 127.4 (Ph), 126.0 (Ph), 80.3 (OCH), 69.1 (OCH₂), 34.2 (CH₂), 26.0 (CH₂), 24.2 (CH₂); MS (APCI) *m/z* 163 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₁₁H₁₅O (M + H)⁺ 163.1117, found 163.1116 (−1.2 ppm error). Spectroscopic data consistent with those reported in the literature.⁴⁷

Lab Book Reference: **NS6-64A**

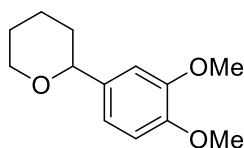
1-(4-(Tetrahydro-2H-pyran-2-yl)phenyl)ethan-1-one 200**200**

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 4-bromoacetophenone (129 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc then 80:20 hexane-EtOAc as eluent gave α -aryl THP **200** (64 mg, 62%)

as a white solid, mp 57-58 °C; R_F (80:20 hexane-EtOAc) 0.3; IR (ATR) 2937, 2847, 1681 (C=O), 1608, 1411, 1359, 1267, 1088, 1046, 824, 598 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 8.0 Hz, 2H, Ar), 7.42 (d, J = 8.0 Hz, 2H, Ar), 4.37 (dd, J = 11.5, 2.5 Hz, 1H, OCH), 4.18-4.11 (m, 1H, OCH), 3.60 (ddd, J = 12.0, 11.5, 2.5 Hz, 1H, OCH), 2.58 (s, 3H, Me), 2.00-1.88 (m, 1H, CH), 1.84 (ddd, J = 12.0, 2.5, 2.5 Hz (app dt), 1H, CH), 1.74-1.47 (m, 4H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 198.0 (C=O), 148.9 (*ipso*-Ar), 136.2 (*ipso*-Ar), 128.5 (Ar), 125.9 (Ar), 79.6 (OCH), 69.0 (OCH_2), 34.2 (CH_2), 26.7 (Me), 25.8 (CH_2), 23.9 (CH_2); MS (ESI) m/z 205 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ ($\text{M} + \text{H})^+$ 205.1223, found 205.1226 (−1.4 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁸⁹

Lab Book Reference: **NS6-64B**

2-(3,4-Dimethoxyphenyl)tetrahydro-2H-pyran **201**

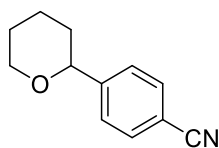


201

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 4-bromo-1,2-dimethoxybenzene (129 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc then 80:20 hexane-EtOAc as eluent gave α -aryl THP **201** (56 mg, 63%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.2; IR (ATR) 2934, 2836, 1592, 1516, 1463, 1266, 1232, 1139, 1084, 1028, 808 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.92 (d, J = 2.0 Hz, 1H, Ar), 6.87 (dd, J = 8.0, 2.0 Hz, 1H, Ar), 6.82 (d, J = 8.0 Hz, 1H, Ar), 4.30-4.24 (m, 1H, OCH), 4.13 (ddd, J = 11.5, 2.5, 2.5 Hz (app dt), 1H, OCH), 3.90 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.61 (ddd, J = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 2.05-1.90 (m, 1H, CH), 1.85-1.77 (m, 1H, CH), 1.71-1.53 (m, 4H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 149.0 (*ipso*-Ar), 148.3 (*ipso*-Ar), 136.2 (*ipso*-Ar), 118.2 (Ar), 110.9 (Ar), 109.3 (Ar), 80.1 (OCH), 69.2 (OCH_2), 56.0 (OMe), 55.9 (OMe), 34.0 (CH_2), 26.0 (CH_2), 24.1 (CH_2); MS (APCI) m/z 223 $[(\text{M} + \text{H})^+, 100]$; HRMS (APCI) m/z calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$ ($\text{M} + \text{H})^+$ 223.1329, found 223.1323 (+2.2 ppm error).

Lab Book Reference: **NS6-65-B**

4-(Tetrahydro-2H-pyran-2-yl)benzonitrile 181

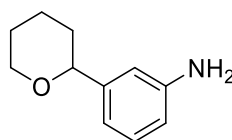


181

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 4-bromobenzonitrile (118 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -aryl THP **181** (49 mg, 53%) as a colourless oil, *R*_F (80:20 hexane-EtOAc) 0.4; IR (ATR) 2938, 2849, 2227 (CN), 1610, 1363, 1087, 1047, 910, 826, 563 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.64-7.59 (m, 2H, Ar), 7.47-7.42 (m, 2H, Ar), 4.37 (dd, *J* = 11.5, 2.5 Hz, 1H, OCH), 4.15 (ddd, *J* = 11.5, 4.0, 2.0 Hz, 1H, OCH), 3.61 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 2.01-1.92 (m, 1H, CH), 1.89-1.80 (m, 1H, CH), 1.75-1.43 (m, 4H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 148.8 (*ipso*-Ar), 132.3 (*ipso*-Ar), 126.5 (Ar), 119.1 (Ar), 111.0 (CN), 79.2 (OCH), 69.0 (OCH₂), 34.2 (CH₂), 25.8 (CH₂), 23.9 (CH₂); MS (ESI) *m/z* 210 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₃NO (M + Na)⁺ 210.0889, found 210.0893 (−1.7 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁸⁹

Lab Book Reference: **NS9-8-B**

3-(Tetrahydro-2H-pyran-2-yl)aniline 202



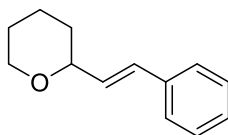
202

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 3-bromoaniline (71 μ L, 112 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with

95:4.5:0.5 CH₂Cl₂-MeOH-NH₄OH as eluent gave α -aryl THP **202** (48 mg, 56%) as a yellow oil, *R*_F (95:4.5:0.5 CH₂Cl₂-MeOH-NH₄OH) 0.2; IR (ATR) 3355 (NH), 2935, 2847, 1495, 1459, 1315, 1364, 1204, 1081, 1037, 996, 903, 729, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.11 (dd, *J* = 8.0, 8.0 Hz (app t), 1H, Ar), 6.74-6.70 (m, 2H, Ar), 6.58 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar), 4.24 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.13 (ddd, *J* = 11.5, 4.0, 2.0 Hz, 1H, OCH), 3.65 (s, 2H, NH), 3.60 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 1.96-1.90 (m, 1H, CH), 1.84-1.77 (m, 1H, CH), 1.72-1.52 (m, 4H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 146.5 (*ipso*-Ar), 144.7 (*ipso*-Ar), 129.3 (Ar), 116.4 (Ar), 114.3 (Ar), 112.7 (Ar), 80.3 (OCH), 69.1 (OCH₂), 34.1 (CH₂), 26.1 (CH₂), 24.2 (CH₂); MS (ESI) *m/z* 178 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₅NO (M + H)⁺ 178.1226, found 178.1228 (−0.8 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁹¹

Lab Book Reference: **NS9-8A**

(*E*)-2-Styryltetrahydro-2H-pyran **203**



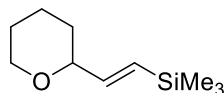
203

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PBHF₄ (11.6 mg, 8 mol%) and (*E*)-(2-bromovinyl)benzene (83 μ L, 119 mg, 68 μ L, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 67:33 hexane-CH₂Cl₂ to 50:50 hexane-CH₂Cl₂ as eluent gave α -aryl THP **203** (63.1 mg, 67%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.3; IR (ATR) 3026, 2934, 2844, 1495, 1448, 1359, 1202, 1081, 1050, 1035, 963, 899, 743, 692, 556 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.35 (m, 2H, Ph), 7.34-7.17 (m, 3H, Ph), 6.59 (d, *J* = 16.0 Hz, 1H, CH=CHPh), 6.22 (dd, *J* = 16.0, 5.5 Hz, 1H, CH=CHPh), 4.13-4.02 (m, 1H, OCH), 3.98 (ddd, *J* = 11.0, 6.0, 2.0 Hz, 1H, OCH), 3.55 (ddd, *J* = 11.5, 11.0, 2.5 Hz, 1H, OCH), 1.89 (ddd, *J* = 11.0, 5.5, 3.0 Hz, 1H, CH), 1.80-1.71 (m, 1H, CH), 1.67-1.42 (m, 4H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 137.1 (*ipso*-Ph), 131.0 (CH=CHPh), 129.9 (CH=CHPh), 128.6 (Ph), 127.6 (Ph), 126.5 (Ph), 78.2 (OCH), 68.6 (OCH₂), 32.4 (CH₂), 26.0 (CH₂), 23.6 (CH₂); MS (ESI) *m/z* 189 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₃H₁₆O

(M + H)⁺ 189.1274, found 189.1274 (−0.2 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁹²

Lab Book Reference: **NS9-28-A**

(E)-Trimethyl(2-(tetrahydro-2H-pyran-2-yl)vinyl)silane 204

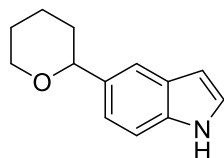


204

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and (*E*)-(2-bromovinyl)trimethylsilane (116 mg, 100 μL, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 67:33 hexane-CH₂Cl₂ as eluent gave α-aryl THP **204** (54.7 mg, 59%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.4; IR (ATR) 2937, 2844, 1623, 1440, 1247, 1194, 1089, 989, 866, 837, 722 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 6.01 (dd, *J* = 19.0, 5.0, 1H, CH=CHSiMe₃), 5.84 (dd, *J* = 19.0, 1.5, 1H, CH=CHSiMe₃), 4.08–4.00 (m, 1H, OCH), 3.82–3.73 (m, 1H, OCH), 3.49 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 1.88–1.80 (m, 1H, CH), 1.71–1.63 (m, 1H, CH), 1.62–1.46 (m, 3H, CH), 1.43–1.27 (m, 1H, CH), 0.05 (s, 9H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 146.9 (CH=CHSiMe₃), 129.4 (CH=CHSiMe₃), 79.9 (OCH), 68.6 (OCH₂), 31.8 (CH₂), 26.0 (CH₂), 23.6 (CH₂), −1.2 (SiMe₃); MS (ESI) *m/z* 185 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₀H₂₀OSi (M + H)⁺ 185.1356, found 185.1359 (+1.6 ppm error).

Lab Book Reference: **NS9-28-B**

5-(Tetrahydro-2H-pyran-2-yl)-1H-indole 205



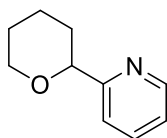
205

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 5-bromoindole (127 mg, 0.65 mmol, 1.3 eq.) at 40 °C

gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc to 50:50 hexane-EtOAc as eluent gave α -aryl THP **205** (45.3 mg, 45%) as a white solid, mp 96-98 °C, R_F (80:20 hexane-EtOAc) 0.1; IR (ATR) 3408 (NH), 3286 (NH), 2934, 2847, 1372, 1346, 1321, 1264, 1202, 1177, 1079, 1032, 766, 806 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 1H, NH), 7.67-7.59 (m, 1H, Ar), 7.42-7.31 (m, 1H, Ar), 7.28-7.14 (m, 2H, Ar), 6.57-6.46 (m, 1H, Ar), 4.47-4.38 (m, 1H, OCH), 4.22-4.12 (m, 1H, OCH), 3.67 (ddd, $J = 13.5, 10.0, 2.5$ Hz, 1H, OCH), 1.96 (ddd, $J = 8.5, 4.5, 2.0$ Hz, 1H, CH), 1.91-1.84 (m, 1H, CH), 1.81-1.66 (m, 3H, CH), 1.64-1.57 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 135.4 (*ipso*-Ar), 135.1 (*ipso*-Ar), 127.9 (*ipso*-Ar), 124.5 (Ar), 120.7 (Ar), 118.2 (Ar), 110.9 (Ar), 102.9 (Ar), 81.1 (OCH), 69.3 (OCH_2), 34.5 (CH_2), 26.2 (CH_2), 24.4 (CH_2); MS (ESI) m/z 202 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{15}\text{NO}$ ($M + H$) $^+$ 202.1226, found 202.1226 (+0.1 ppm error).

Lab Book Reference: **NS9-9-A**

2-(Tetrahydro-2H-pyran-2-yl)pyridine **206**

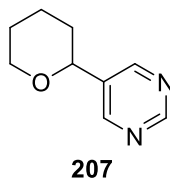


206

Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), $n\text{-BuLi}$ (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 4 mol%), $t\text{-Bu}_3\text{PHBF}_4$ (11.6 mg, 8 mol%) and 2-bromopyridine (93 μL , 140 mg, 0.65 mmol, 1.3 eq.) at 60 °C gave the crude product. Purification by flash column chromatography on silica with EtOAc then 95:5 EtOAc-MeOH as eluent gave α -aryl THP **206** (65 mg of an 85:15 mixture of **206** and EtOAc i.e. 55 mg (58%) of **206**) as a yellow oil, R_F (95:5 EtOAc-MeOH) 0.4; ^1H NMR (400 MHz, CDCl_3) δ 8.56-8.51 (m, 1H, Ar), 7.68 (ddd, $J = 7.5, 7.5, 2.0$ Hz (app td), 1H, Ar), 7.43 (d, $J = 7.5$ Hz, 1H, Ar), 7.18-7.15 (m, 1H, Ar), 4.45 (dd, $J = 11.5, 2.5$ Hz, 1H, OCH), 4.19-4.14 (m, 1H, OCH), 3.65 (ddd, $J = 11.5, 11.5, 2.5$ Hz (app td), 1H, OCH), 2.07-2.02 (m, 1H, CH), 1.97-1.92 (m, 1H, CH), 1.76-1.48 (m, 4H, CH). Compound **206** was found to be volatile and evaporated completely during the final drying process. Therefore, full characterisation was not possible. ^1H NMR spectroscopic data consistent with those reported in the literature.⁵¹

Lab Book Reference: **NS6-65-A**

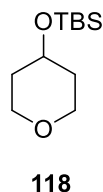
2-(Tetrahydro-2H-pyran-2-yl)pyrimidine 207



Using general procedure C, THP stannane **197** (187 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (4.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (11.6 mg, 8 mol%) and 5-bromopyridine (103 mg, 0.65 mmol, 1.3 eq.) at 60 °C gave the crude product which contained only traces of the product **207** by ¹H NMR spectroscopy.

Lab Book Reference: **NS9-9-B**

***tert*-Butyldimethyl((tetrahydro-2H-pyran-4-yl)oxy)silane 118**

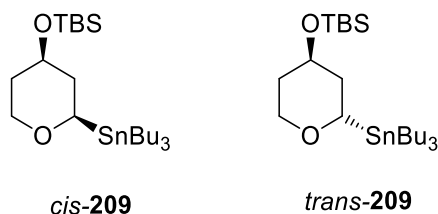


NaBH₄ (2.27 g, 60 mmol, 2.0 eq.) was added to a stirred solution of 4-oxotetrahydropyran **208** (3.00 g, 30 mmol, 1.0 eq.) in MeOH (100 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 2 h. 37% NH₄Cl_(aq) (100 mL) and then EtOAc (100 mL) were added. The two layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude alcohol which was used in the next step. TBSCl (5.90 g, 40 mmol, 2.0 eq.) was added to a stirred solution of the crude alcohol and imidazole (2.66 g, 40 mmol, 2.0 eq) in CH₂Cl₂ (100 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Saturated NH₄Cl_(aq) (50 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 hexane-Et₂O as eluent gave 4-OTBS-substituted THP **118** (4.99 g, 77%) as a colourless oil, *R*_F (50:50 hexane-EtOAc)

0.6; IR (ATR) 2951, 2857, 1471, 1361, 1129, 1105, 1067, 1051, 879, 834, 813, 772, 670 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.95-3.89 (m, 2H, OCH), 3.85 (tt, J = 8.0, 4.0 Hz, 1H, OCH), 3.46 (ddd, J = 11.5, 8.5, 3.0 Hz, 2H, OCH), 1.85-1.70 (m, 2H, CH), 1.54 (dddd, J = 12.5, 8.5, 8.0, 4.0 Hz, 2H, CH), 0.89 (s, 9H, CMe_3), 0.06 (s, 6H, SiMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 67.0 (OCH), 65.4 (OCH_2), 35.9 (CH_2), 25.9 (CMe_3), 18.3 (CMe_3), -4.5 (SiMe); MS (APCI) m/z 210 [$(\text{M} + \text{H})^+$, 100]; HRMS (APCI) m/z calcd for $\text{C}_{11}\text{H}_{24}\text{O}_2\text{Si}$ ($\text{M} + \text{H})^+$ 217.1618, found 217.1612 (+2.8 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁹³

Lab Book Reference: **NS9-10**

***tert*-Butyldimethyl((2-(tributylstannyl)tetrahydro-2*H*-pyran-4-yl)oxy)silane *cis*- and *trans*-209**

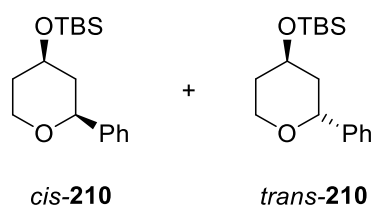


s-BuLi (6.0 mL of a 1.3 M solution in hexane, 7.8 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBS THP **208** (1.30 g, 6.0 mmol, 1.0 eq.) and TMEDA (1.17 mL, 7.8 mmol, 1.3 eq.) in hexane (30.0 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, Bu_3SnCl (3.91 g, 3.30 mL, 12 mmol, 2.0 eq.) was added. The resulting solution was stirred at 0 °C for 1 h and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (30 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (45 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 $\times$ 30 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product which contained a 95:5 mixture (by ^1H NMR spectroscopy) of stannanes *cis*-**209** and *trans*-**209**. Purification by flash column chromatography on silica- K_2CO_3 (90:10) with 75:25 hexane- CH_2Cl_2 as eluent gave a 95:5 mixture of stannanes *cis*-**209** and *trans*-**209** (1.12 g, 37%) as a colourless oil, R_F (50:50 hexane- CH_2Cl_2) 0.4; IR (ATR) 2954, 2927, 2855, 1363, 1252, 1153, 1101, 1071, 998, 882, 836, 809 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.36 (dd, J = 11.5, 2.5 Hz, 0.05H, OCH), 3.99-3.90 (m, 1H, OCH), 3.80 (ddd, J = 11.0, 11.0, 2.5 Hz (app td), 0.05H, OCH), 3.73-3.53 (m, 1.95H, OCH), 3.26 (ddd, J = 12.0, 12.0, 2.0 Hz (app td), 0.95H, OCH), 2.05 (ddd, J = 14.0, 11.0, 2.5 Hz, 0.05H, CH), 1.86-1.70 (m, 2.95H, CH), 1.68-1.37 (m, 7H, CH, 3 $\times$ CH_2), 1.39-1.21 (m, 6H, CH), 1.08-0.71 (m, 24H, CH, Si CMe_3), 0.14-0.00 (m, 6H, SiMe); ^{13}C NMR (100.6 MHz, CDCl_3) for *cis*-**209** δ 72.3 (OCH), 70.4 (OCH), 69.7 (OCH_2),

42.1 (CH₂), 37.2 (CH₂), 29.3 (CH₂), 27.6 (CH₂), 26.1 (CMe₃), 18.4 (CMe₃), 13.9 (Me), 8.4 (CH₂), -4.3 (SiMe), -4.4 (SiMe); MS (ESI) m/z 490 [$^{120}\text{M-Me}^+$, 10]; HRMS (ESI) m/z calcd for C₂₂H₄₆O₂Si¹²⁰Sn(¹²⁰M-Me)⁺ 490.2171, found 490.2289 (+2.4 ppm error).

Lab Book Reference: **NS9-15**

***tert*-Butyldimethyl((2-phenyltetrahydro-2H-pyran-4-yl)oxy)silane *cis*- and *trans*-210**



Using general procedure C, a 95:5 mixture of THP stannanes *cis*-**209** and *trans*-**209** (192 mg, 0.38 mmol, 1.0 eq.), *n*-BuLi (0.28 mL of a 1.5 M solution in hexanes, 0.42 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.71 mL of a 0.7 M solution in THF, 0.49 mmol, 1.3 eq.), Pd(OAc)₂ (3.4 mg, 4 mol%), *t*-Bu₃PHBF₄ (8.8 mg, 8 mol%) and bromobenzene (51.9 μ L, 77.6 mg, 0.49 mmol, 1.3 eq.) at 40 °C gave the crude product which contained a 95:5 mixture of α -aryl THPs *cis*-**209** and *trans*-**209** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 50:50 hexane-CH₂Cl₂ as eluent gave α -aryl THP *cis*-**210** (119 mg, 81%) as a colourless oil, R_F (50:50 hexane-CH₂Cl₂) 0.2; IR (ATR) 2952, 2927, 2858, 1462, 1359, 1252, 1072, 1047, 891, 776, 698, 682 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.24 (m, 5H, Ph), 4.30 (dd, J = 11.5, 2.0 Hz, 1H, OCH), 4.14 (ddd, J = 11.5, 5.0, 2.0 Hz, 1H, OCH), 3.91 (dddd, J = 10.5, 10.5, 4.5, 4.5 Hz (app tt), 1H, OCH), 3.57 (ddd, J = 12.0, 12.0, 2.0 Hz (app td), 1H, OCH), 2.08-2.01 (m, 1H, CH), 1.84 (ddd, J = 11.5, 4.5, 2.0 Hz, 1H, CH), 1.75-1.57 (m, 2H, CH), 0.89 (s, 9H, CMe₃), 0.09 (s, 3H, SiMe), 0.08 (s, 3H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 142.3 (*ipso*-Ph), 128.5 (Ph), 127.7 (Ph), 126.2 (Ph), 78.8 (OCH), 69.2 (OCH), 66.7 (OCH₂), 44.0 (CH₂), 36.2 (CH₂), 26.0 (CMe₃), 18.3 (CMe₃), -4.4 (SiMe), -4.4 (SiMe); MS (APCI) m/z 293 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₇H₂₈O₂Si (M + H)⁺ 293.1931, found 293.1922 (-3.1 ppm error) and α -aryl THP *trans*-**210** (5 mg, 4%) as a colourless oil, R_F (50:50 hexane-CH₂Cl₂) 0.2; IR (ATR) 2952, 2928, 2855, 1472, 1371, 1252, 1150, 1112, 1087, 996, 900, 832, 775, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.29 (m, 4H, Ph), 7.27-7.19 (m, 1H, Ph), 4.81 (dd, J = 13.5, 6.0 Hz, 1H, OCH), 4.24 (dddd, J = 3.5, 3.5, 3.5, 3.5 Hz (app tt), 1H, OCH), 4.07 (ddd, J = 13.5, 11.0, 2.0 Hz, 1H, OCH), 3.89 (ddd, J = 11.0, 5.0, 2.0 Hz, 1H, OCH), 1.88 (dddd, J = 13.5, 12.5, 5.5, 2.5 Hz, 1H, CH), 1.81-1.73 (m, 2H, CH), 1.54-1.48 (m, 1H, CH), 0.93 (s, 9H, CMe₃), 0.08 (s, 3H, SiMe), 0.07 (s, 3H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.3 (*ipso*-

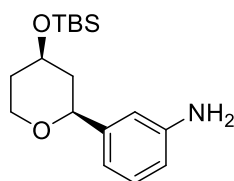
Ph), 128.5 (Ph), 127.4 (Ph), 126.0 (Ph), 74.1 (OCH), 64.8 (OCH), 63.4 (OCH₂), 41.8 (CH₂), 33.7 (CH₂), 26.0 (CMe₃), 18.2 (CMe₃), -4.70 (SiMe), -4.72 (SiMe); MS (APCI) *m/z* 293 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₁₇H₂₈O₂Si (M + H)⁺ 293.1931, found 293.1921 (+3.7 ppm error).

Lab Book Reference: **NS9-17-A**

s-BuLi (385 μ L of a 1.3 M solution in hexane, 0.50 mmol, 1.0 eq.) was added dropwise to a stirred solution of a 95:5 mixture of THP stannanes *cis*-**209** and *trans*-**209** (126 mg, 0.25 mmol, 1.0 eq.) and TMEDA (165 μ L, 0.28 mmol, 1.1 eq.) in hexane (2.5 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 30 min. Then, a freshly prepared solution of ZnCl₂ (335 μ L of a 1.0 M solution in THF, 0.33 mmol, 1.3 eq.) was added. After stirring at -78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for 30 min. Then, Pd(OAc)₂ (2.25 mg, 4 mol%), *t*-Bu₃PHBF₄ (5.8 mg, 8 mol%) and bromobenzene (34 μ L, 0.33 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at 40 °C for 16 h. The solids were removed by filtration through Celite® and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained only 4-OTBS THP **118** and bromobenzene (by ¹H NMR spectroscopy).

Lab Book Reference: **NS9-68**

3-(4-((*tert*-Butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)aniline *cis*-**213**



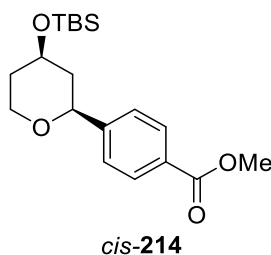
cis-**213**

Using general procedure C, a 95:5 mixture of THP stannanes *cis*-**209** and *trans*-**209** (192 mg, 0.38 mmol, 1.0 eq.), *n*-BuLi (0.28 mL of a 1.5 M solution in hexanes, 0.42 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.71 mL of a 0.7 M solution in THF, 0.49 mmol, 1.3 eq.), Pd(OAc)₂ (3.4 mg, 4 mol%), *t*-Bu₃PHBF₄ (8.8 mg, 8 mol%) and 3-bromoaniline (85 mg, 53.8 μ L, 0.49 mmol, 1.3 eq.) at 40 °C gave the crude product which contained only α -aryl THP *cis*-**213** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 80:19.5:0.5 hexane-EtOAc-Et₃N as eluent gave α -aryl THP *cis*-**213** (60 mg, 77%) as a yellow oil, *R*_F (80:19.5:0.5 hexane-EtOAc-Et₃N) 0.3; IR (ATR) 3360 (NH), 2951, 2927,

2855, 1610, 1462, 1251, 1148, 1111, 1082, 901, 834, 774, 697, 669 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.16-7.06 (m, 1H, Ar), 6.76-6.69 (m, 2H, Ar), 6.63-6.55 (m, 1H, Ar), 4.21 (dd, J = 11.5, 2.0 Hz, 1H, OCH), 4.12 (ddd, J = 11.5, 4.5, 2.0 Hz, 1H, OCH), 3.88 (dddd, J = 11.0, 11.0, 4.5, 4.5 Hz (app tt), 1H, OCH), 3.66 (s, 2H, NH), 3.54 (ddd, J = 13.0, 11.5, 2.0 Hz, 1H, OCH), 2.02 (dddd, J = 13.0, 4.5, 2.0, 2.0 Hz (app ddt), 1H, CH), 1.82 (dddd, J = 13.0, 4.5, 2.0, 2.0 Hz (app ddt), 1H, CH), 1.73-1.54 (m, 2H, CH), 0.88 (s, 9H, CMe_3), 0.082 (s, 3H, SiMe), 0.080 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 146.6 (*ipso*-Ar), 143.6 (*ipso*-Ar), 129.4 (Ar), 116.5 (Ar), 114.5 (Ar), 112.9 (Ar), 78.8 (OCH), 69.2 (OCH), 66.6 (OCH_2), 43.9 (CH_2), 36.2 (CH_2), 26.0 (CMe_3), 18.3 (CMe_3), -4.40 (SiMe), -4.38 (SiMe); MS (ESI) m/z 330 [$(\text{M} + \text{Na})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{29}\text{NNaO}_2\text{Si}$ ($\text{M} + \text{Na})^+$ 330.1860, found 330.1861 (-0.4 ppm error).

Lab Book Reference: **NS9-17-B**

Methyl 4-(4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)benzoate *cis*-214

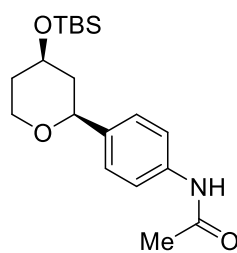


Using general procedure C, a 95:5 mixture of THP stannanes *cis*-209 and *trans*-209 (192 mg, 0.38 mmol, 1.0 eq.), *n*-BuLi (0.28 mL of a 1.5 M solution in hexanes, 0.42 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl_2 (0.71 mL of a 0.7 M solution in THF, 0.49 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (3.4 mg, 4 mol%), *t*-Bu₃PHBF₄ (8.8 mg, 8 mol%) and methyl 4-bromobenzoate (106 mg, 0.49 mmol, 1.3 eq.) at 40 °C gave the crude product which contained only α -aryl THP *cis*-214 (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 90:10 hexane-EtOAc then 50:50 hexane- CH_2Cl_2 as eluent gave α -aryl THP *cis*-214 (97 mg, 73%) as a white solid, mp 60-62 °C, R_F (90:10 hexane-EtOAc) 0.2; IR (ATR) 2951, 2928, 2855, 1723 (C=O), 1435, 1276, 1251, 1150, 1103, 1086, 997, 772, 705 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.04-7.96 (m, 2H, Ar), 7.45-7.39 (m, 2H, Ar), 4.36 (dd, J = 11.5, 2.0 Hz, 1H, OCH), 4.15 (ddd, J = 11.5, 4.5, 2.0 Hz, 1H, OCH), 3.97-3.87 (m, 1H, OCH), 3.91 (s, 3H, OMe), 3.57 (ddd, J = 12.5, 12.5, 2.0 Hz (app td), 1H, OCH), 2.04 (dddd, J = 12.5, 4.5, 2.0, 2.0 Hz (app ddt), 1H, CH), 1.85 (dddd, J = 11.0, 4.5, 2.0, 2.0 Hz (app ddt), 1H, CH), 1.68 (dddd, J = 12.5, 12.5, 11.0, 4.5 Hz (app tdd), 1H, CH), 1.55 (ddd, J = 12.5, 11.5, 11.0 Hz, 1H, CH), 0.88 (s, 9H, CMe_3), 0.09 (s, 3H, SiMe), 0.08 (s, 1H, SiMe); ^{13}C NMR (100.6

MHz, CDCl₃) δ 167.1 (C=O), 147.5 (*ipso*-Ar), 129.9 (Ar), 129.4 (*ipso*-Ar), 125.9 (Ar), 78.2 (OCH), 69.0 (OCH), 66.6 (OCH₂), 52.2 (OMe), 44.0 (CH₂), 36.1 (CH₂), 25.9 (CMe₃), 18.2 (CMe₃), -4.36 (SiMe), -4.41 (SiMe); MS (APCI) m/z 351 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₉H₃₀O₄Si (M + H)⁺ 351.1986, found 351.1994 (-2.4 ppm error).

Lab Book Reference: **NS9-17-C**

***N*-(4-(*cis*-4-((*tert*-Butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)phenyl)acetamide**
***cis*-215**

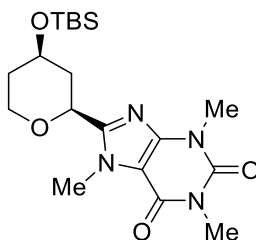


***cis*-215**

Using general procedure C, a 95:5 mixture of THP stannanes *cis*-**209** and *trans*-**209** (167 mg, 0.33 mmol, 1.0 eq.), *n*-BuLi (241 μ L of a 1.5 M solution in hexanes, 0.36 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.71 mL of a 0.7 M solution in THF, 0.43 mmol, 1.3 eq.), Pd(OAc)₂ (3.0 mg, 4 mol%), *t*-Bu₃PHBF₄ (7.7 mg, 8 mol%) and methyl *N*-(4-bromophenyl)acetamide (91.8 mg, 0.43 mmol, 1.3 eq.) at 40 °C gave the crude product which contained only α -aryl THP *cis*-**215** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 95:5 CH₂Cl₂-acetone to 90:10 CH₂Cl₂-acetone as eluent gave α -aryl THP *cis*-**215** (90 mg, 78%) as a colourless oil, *R*_F (90:10 CH₂Cl₂-acetone) 0.2; IR (ATR) 3303 (NH), 2952, 2928, 2855, 1667 (C=O), 1604, 1537, 1517, 1315, 1252, 1106, 1084, 996, 901, 833, 774, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (s, 1H, NH), 7.48-7.42 (m, 2H, Ar), 7.31-7.25 (m, 2H, Ar), 4.26 (dd, *J* = 11.5, 2.0 Hz, 1H, OCH), 4.11 (ddd, *J* = 12.0, 5.0, 2.0 Hz, 1H, OCH), 3.89 (dddd, *J* = 10.0, 10.0, 4.5, 4.5 Hz (app tt), 1H, OCH), 3.55 (ddd, *J* = 12.0, 12.0, 2.0 Hz (app td), 1H, OCH), 2.12 (s, 3H, C(O)Me), 2.05-1.95 (m, 1H, CH), 1.86-1.78 (m, 1H, CH), 1.73-1.51 (m, 2H, CH), 0.88 (s, 9H, CMe₃), 0.08 (s, 3H, SiMe), 0.07 (s, 3H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.6 (C=O), 138.1 (*ipso*-Ar), 137.4 (*ipso*-Ar), 126.8 (Ar), 119.9 (Ar), 78.3 (OCH), 69.1 (OCH), 66.6 (OCH₂), 43.8 (CH₂), 36.1 (CH₂), 25.9 (CMe₃), 24.6 (C(O)Me), 18.2 (CMe₃), -4.39 (SiMe), -4.41 (SiMe); MS (ESI) m/z 327 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₁₉H₃₁NO₃Si (M + Na)⁺ 372.1965, found 372.1962 (+1.0 ppm error).

Lab Book Reference: **NS9-27-C**

Attempted Synthesis of 8-(*cis*-4-((*tert*-Butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-1,3,7-trimethyl-3,4,5,7-tetrahydro-1*H*-purine-2,6-dione *cis*-216

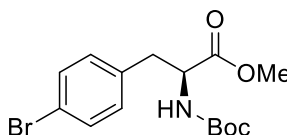


cis-216

Using general procedure C, a 95:5 mixture of THP stannanes *cis*-209 and *trans*-209 (167 mg, 0.33 mmol, 1.0 eq.), *n*-BuLi (241 μ L of a 1.5 M solution in hexanes, 0.36 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.71 mL of a 0.7 M solution in THF, 0.43 mmol, 1.3 eq.), Pd(OAc)₂ (3.0 mg, 4 mol%), *t*-Bu₃PHBF₄ (7.7 mg, 8 mol%) and methyl 8-bromo caffeine (117 mg, 0.43 mmol, 1.3 eq.) at 40 °C gave the crude product which did not contain the desired product *cis*-216 (by ¹H spectroscopy).

Lab Book Reference: **NS9-27-A**

Methyl (*S*)-3-(4-Bromophenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (*S*)-217



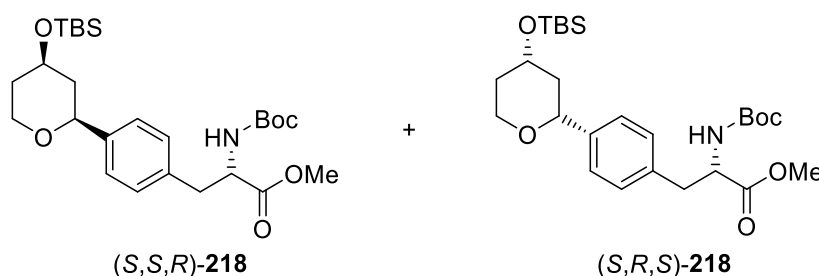
(*S*)-217

Trimethylsilyldiazomethane (2.0 mL of a 1.0 M solution in hexane, 2.0 mmol, 1.0 eq.) was added to a stirred solution of (*S*)-4-bromophenylalanine (531 mg, 2.0 mmol, 1.0 eq.) in MeOH (8 mL) and toluene (12 mL) at 0 °C. The solution was then allowed to warm to rt and stirred at rt for 30 min. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 67:33 hexane-EtOAc as eluent gave phenyl alanine derivative (*S*)-217 (715 mg, 99%) as a colourless oil, [α]_D +31.1 (*c* 1.00 in CHCl₃) (lit.,¹²⁷ +29.6, (*c* 1.35 in CHCl₃)); *R*_F (67:33 hexane-EtOAc) 0.3; IR (ATR) 3363 (NH), 2977, 1745 (C=O, ester), 1713 (C=O, Boc), 1489, 1366, 1164, 1250, 1215, 1071, 1012 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.37 (m, 2H, Ar), 7.05-6.95 (m, 2H, Ar), 4.98 (d, *J* = 8.0 Hz, 1H, NH), 4.57 (ddd, *J* = 8.0, 6.0, 6.0 Hz (app dt), 1H, NCHCH₂), 3.71 (s, 3H, OMe), 3.09 (dd, *J* = 14.0, 6.0 Hz, 1H, ArCH), 2.99 (dd, *J* = 14.0, 6.0 Hz, 1H, ArCH), 1.42 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 172.2 (C=O), 155.1 (C=O), 135.2 (*ipso*-Ar), 131.8 (Ar), 131.2 (Ar), 121.2 (*ipso*-Ar), 80.2 (OCMe₃), 54.3 (NCH),

52.5 (OMe), 37.9 (CH₂), 28.4 (CMe₃); MS (ESI) m/z 380 [(⁷⁹M + Na)⁺, 100], 382 [(⁸¹M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₁₅H₂₀⁷⁹BrNO₄ (⁷⁹M + Na)⁺ 380.0468, found 380.0464 (+1.0 ppm error). Spectroscopic data consistent with those reported in the literature.¹²⁷

Lab Book Reference: NS9-23

Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-(4-((*tert*-butyldimethylsilyl)oxy)-tetrahydro-2*H*-pyran-2-yl)phenyl)propanoate (*S,S,R*)-218 and (*S,R,S*)-218

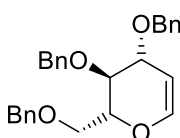


Using general procedure C, a 95:5 mixture of THP stannanes *cis*-**209** and *trans*-**209** (167 mg, 0.33 mmol, 1.0 eq., 95:5 dr), *n*-BuLi (241 μ L of a 1.5 M solution in hexanes, 0.36 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.71 mL of a 0.7 M solution in THF, 0.43 mmol, 1.3 eq.), Pd(OAc)₂ (3.0 mg, 4 mol%), *t*-Bu₃PHBF₄ (7.7 mg, 8 mol%) and phenylalanine derivative (*S*)-**217** (135 mg, 0.43 mmol, 1.3 eq.) at 40 °C gave the crude product which contained a ~50:50 mixture of α -aryl THPs (*S,S,R*)-**218** and (*S,S,R*)-**218** (by ¹³C NMR spectroscopy). Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave a ~50:50 mixture of α -aryl THPs (*S,S,R*)-**218** and (*S,S,R*)-**218** (119 mg, 73%) as a colourless oil, *R*_F (50:50 hexane-EtOAc) 0.6; IR (ATR) 3368 (NH), 2952, 2929, 2856, 1746 (C=O, ester), 1715 (C=O, Boc), 1499, 1366, 1251, 1164, 1085, 997, 902, 775, 858, 733, 669 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.23 (m, 2H, Ar), 7.12-7.08 (m, 2H, Ar), 4.92 (d, *J* = 8.5 Hz, 1H, NH), 4.56 (ddd, *J* = 9.0, 6.0, 3.0 Hz, 1H, NCH), 4.30-4.25 (m, 1H, OCH), 4.12 (ddd, *J* = 12.0, 5.0, 1.5 Hz, 1H, OCH), 3.88 (ddd, *J* = 11.0, 10.5, 5.0, 5.0 Hz (app ddt), 1H, OCH), 3.70 (s, 3H, OMe), 3.55 (ddd, *J* = 12.5, 12.0, 2.5 Hz, 1H, OCH), 3.16-2.98 (m, 2H, ArCH), 2.01 (ddd, *J* = 12.5, 4.5, 2.0 Hz, 1H, CH), 1.82 (ddd, *J* = 12.5, 5.0, 2.5 Hz, 1H, CH), 1.73-1.61 (m, 1H, CH), 1.59 (ddd, *J* = 12.0, 11.5, 11.5 Hz, 1H (app dt), CH), 1.41 (s, 9H, OCMe₃), 0.88 (s, 9H, SiCMe₃), 0.077 (s, 3H, SiMe), 0.073 (s, 3H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 172.4 (C=O), 172.3 (C=O), 155.2 (C=O), 141.0 (*ipso*-Ar), 135.4 (*ipso*-Ar), 129.48 (Ar), 129.45 (Ar), 126.4 (Ar), 80.0 (OCH), 78.51 (OCH), 78.50 (OCH), 69.1 (OCH₂), 66.6 (ArCH₂), 54.4 (NCH), 52.3 (OMe), 43.88 (CH₂), 43.83 (CH₂), 37.9 (CH₂), 36.1 (CH₂), 28.4 (CMe₃), 25.9 (CMe₃), 18.2 (CMe₃), -4.41 (SiMe), -4.44 (SiMe) (10

resonances not resolved); MS (ESI) m/z 516 $[(M + Na)^+, 100]$; HRMS (ESI) m/z calcd for $C_{26}H_{43}NO_6Si$ $(M + Na)^+$ 516.2752, found 516.2756 (-0.7 ppm error).

Lab Book Reference: **NS9-27-B**

(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran (R,S,R)-219

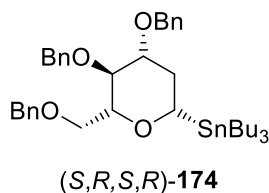


(*R,S,R*)-**219**

NaOH (2.40 g, 60 mmol, 6.0 eq.), TBAI (96 mg, 0.26 mmol, 2.6 mol%) and BnBr (5.35 mL, 7.70 g, 45 mmol, 4.5 eq.) were added to a stirred solution of tri-*O*-acetyl-D-glucal (2.72 g, 10 mmol, 1.0 eq.) in THF (10 mL) at rt. The resulting suspension was stirred at rt for 40 h. Then, the reaction mixture was poured into H₂O (30 mL) and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with H₂O (30 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc then 80:20 hexane-EtOAc as eluent gave 3,4,6-tri-*O*-benzyl-D-glucal (*R,S,R*)-**219** (3.66 g, 88%) as a white solid; mp 55-57 °C (lit.,¹⁹⁴ 54-55 °C), $[\alpha]_D -3.7$ (c 1.00 in CH₂Cl₂) (lit.,¹⁹⁴ -4.9 (c 1.00 in CH₂Cl₂)); R_F (80:20 hexane-EtOAc) 0.2; IR (ATR) 3063, 3030, 2864, 1646 (C=C), 1496, 1453, 1362, 1096, 1068, 1046, 1026, 908, 732, 695 cm⁻¹; ¹H NMR (400 MHz, d⁶-acetone) δ 7.40-7.24 (m, 15H, Ph), 6.42 (dd, J = 6.0, 1.5 Hz, 1H, OCH=CH), 4.95 (dd, J = 6.0, 3.0 Hz, 1H, OCH), 4.85 (d, J = 11.5 Hz, 1H, OCH), 4.71 (dd, J = 6.0, 1.5 Hz, 1H, OCH=CH), 4.68 (d, J = 9.0 Hz, 1H, OCH), 4.61-4.55 (m, 3H, OCH), 4.21-4.17 (m, 1H, OCH), 4.06 (ddd, J = 8.0, 5.0, 3.0 Hz, 1H, OCH), 3.90-3.82 (m, 2H, OCH), 3.78 (dd, J = 11.0, 3.0 Hz, 1H, OCH); ¹³C NMR (100.6 MHz, d⁶-acetone) δ 145.1 (OCH=CH), 139.8 (*ipso*-Ph), 139.7 (*ipso*-Ph), 139.5 (*ipso*-Ph), 129.1 (Ph), 129.0 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.24 (Ph), 128.22 (Ph), 128.19 (Ph), 100.8 (OCH=CH), 77.6 (OCH), 76.2 (OCH), 75.4 (OCH), 74.0 (OCH₂), 73.7 (OCH₂), 70.8 (OCH₂), 69.4 (OCH₂) (one Ph resonance not resolved); MS (ESI) m/z 439 $[(M + Na)^+, 100]$; HRMS (ESI) m/z calcd for $C_{27}H_{28}O_4$ $(M + Na)^+$ 439.1860, found 439.1875 (+1.0 ppm error). Spectroscopic data consistent with those reported in the literature.¹²⁴

Lab Book Reference: **NS9-30**

((2*S*,4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)tributylstannane (*S*,*R*,*S*,*R*)-174

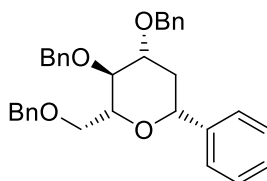


HCl (1.0 mL of a 2.0 M solution in Et₂O, 2.0 mmol, 1.2 eq.) was added to a stirred solution of glucal (*R*,*S*,*R*)-**219** (832 mg, 2.0 mmol, 1.2 eq.) in THF (2.5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h to give a solution of 2-chloroglucal in THF. In a separate flask, *n*-BuLi (1.19 mL, 1.4 M in hexane, 1.7 mmol, 1.0 eq.) was added dropwise to a stirred solution of *i*-Pr₂NH (560 µL, 405 mg, 4.0 mmol, 2.0 eq.) in THF (2.5 mL) at 0 °C under Ar. The solution was stirred at 0 °C for 5 min. Then, Bu₃SnH (484 µL, 533 mg, 1.8 mmol, 1.1 eq.) was added and the solution was stirred at 0 °C for 15 min to give a solution of Bu₃SnLi in THF. The solution of Bu₃SnLi in THF was added dropwise to the stirred solution of solution of 2-chloroglucal in THF at –78 °C. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt over 16 h. Then, saturated NH₄Cl_(aq) (10 mL) and saturated NaHCO_{3(aq)} (10 mL) were added and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with hexane then 95:5 hexane-EtOAc to 90:10 hexane-EtOAc as eluent gave stannane (*S*,*R*,*S*,*R*)-**174** (531 mg, 45%) as a colourless oil, *R*_F (80:20 hexane-EtOAc) 0.6; [α]_D –9.3 (c 1.00 in CHCl₃) (lit.,¹²⁴ –9.1 (c 1.00 in CHCl₃)); IR (ATR) 3030, 2955, 2924, 2852, 1454, 1359, 1100, 1028, 732, 696 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.21 (m, 15H, Ph), 4.91 (d, *J* = 11.0 Hz, 1H, OCH), 4.71 (d, *J* = 11.5 Hz, 1H, OCH), 4.67–4.62 (m, 2H, OCH), 4.61 (d, *J* = 12.0 Hz, 1H, OCH), 4.54 (d, *J* = 12.5 Hz, 1H, OCH), 3.75–3.68 (m, 2H, OCH), 3.62 (dd, *J* = 13.0, 2.0 Hz, 1H, OCH), 3.56 (ddd, *J* = 10.5, 9.0, 5.0 Hz, 1H, OCH), 3.48 (dd, *J* = 9.0, 9.0 Hz (app t), 1H, OCH), 3.23 (ddd, *J* = 9.0, 3.5, 3.0 Hz, 1H, OCH), 2.12 (ddd, *J* = 13.0, 5.0, 2.0 Hz, 1H, CH), 1.83 (ddd, *J* = 13.0, 13.0, 10.5 Hz (app td), 1H, CH), 1.61–1.42 (m, 6H, CH), 1.38–1.22 (m, 6H, CH), 1.02–0.76 (m, 15H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 139.07 (*ipso*-Ph), 139.02 (*ipso*-Ph), 138.9 (*ipso*-Ph), 128.53 (Ph), 128.47 (Ph), 128.39 (Ph), 128.2 (Ph), 127.8 (Ph), 127.69 (Ph), 127.67 (Ph), 127.58 (Ph), 127.43 (Ph), 83.3 (OCH), 82.9 (OCH), 77.4 (OCH), 75.3 (OCH₂), 73.5 (OCH₂), 71.7 (OCH₂), 70.8 (OCH), 70.1 (OCH₂), 37.1 (CH₂), 29.2 (CH₂), 27.5 (CH₂), 13.9 (Me), 8.7

(CH₂); MS (ESI) m/z 729 [(¹¹⁸M + Na)⁺, 74], 731 [(¹²⁰M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₃₉H₅₆O₄¹²⁰Sn (¹²⁰M + Na)⁺ 731.3100, found 731.3093 (+0.2 ppm error). Spectroscopic data consistent with those reported in the literature.¹²⁴

Lab Book Reference: **NS9-35**

(2*R*,3*S*,4*R*,6*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-6-phenyltetrahydro-2*H*-pyran (*R,S,R,R*)-175

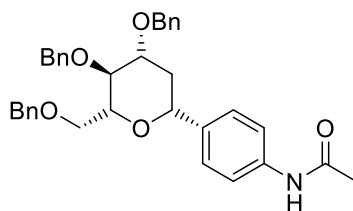


(*R,S,R,R*)-175

Using general procedure C, stannane (*S,R,S,R*)-**174** (106 mg, 0.15 mmol, 1.0 eq.), *n*-BuLi (112 μ L of a 1.5 M solution in hexanes, 0.17 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.28 mL of a 0.7 M solution in THF, 0.20 mmol, 1.3 eq.), Pd(OAc)₂ (1.4 mg, 4 mol%), *t*-Bu₃PHBF₄ (3.5 mg, 8 mol%) and bromobenzene (61.2 mg, 40.8 μ L, 0.39 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 98:2 CH₂Cl₂-acetone as eluent gave α -aryl glucal (*R,S,R,R*)-**175** (61 mg, 82%) as a colourless oil, R_F (95:5 CH₂Cl₂-acetone) 0.6; [α]_D +20.0 (*c* 1.00 in CHCl₃) (lit.,¹³² +21.1 (*c* 0.9 in CHCl₃)); IR (ATR) 3063, 3030, 2861, 1452, 1360, 1090, 1074, 1028, 1001, 734, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.20 (m, 20H, Ph), 4.97 (d, *J* = 11.0 Hz, 1H, OCH), 4.74 (d, *J* = 11.5 Hz, 1H, OCH), 4.69 (d, *J* = 12.0 Hz, 1H, OCH), 4.65 (d, *J* = 11.0 Hz, 1H, OCH), 4.65 (d, *J* = 11.0 Hz, 1H, OCH), 4.60 (d, *J* = 12.0 Hz, 1H, OCH), 4.44 (dd, *J* = 11.5, 2.0 Hz, 1H, OCH), 3.91-3.77 (m, 3H, OCH), 3.67 (dd, *J* = 13.5, 7.5 Hz, 1H, OCH), 3.61 (ddd, *J* = 10.0, 4.5, 2.0 Hz, 1H, OCH), 2.41 (ddd, *J* = 13.0, 4.5, 2.0 Hz, 1H, CH), 1.76 (ddd, *J* = 13.0, 11.5 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 141.6 (*ipso*-Ph), 138.6 (*ipso*-Ph), 138.6 (*ipso*-Ph), 138.6 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 128.5 (Ph), 128.2 (Ph), 127.9 (Ph), 127.8 (Ph), 127.7 (Ph), 127.6 (Ph), 126.1 (Ph), 81.3 (OCH), 79.6 (OCH), 78.5 (OCH), 77.6 (OCH), 75.2 (OCH₂), 73.6 (OCH₂), 71.5 (OCH₂), 69.7 (OCH₂), 39.3 (CH₂) (three resonances not resolved); MS (ESI) m/z 517 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₃₃H₃₄O₄ (M + Na)⁺ 517.2350, found 517.2349 (−0.1 ppm error). Spectroscopic data consistent with those reported in the literature.¹²⁴

Lab Book Reference: **NS9-37-A**

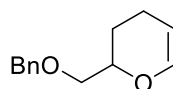
N*-(4-((2*R*,4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2-pyran-2-yl)phenyl)acetamide (*R,R,S,R*)-**221*



(*R,R,S,R*)-**221**

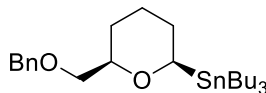
Using general procedure C, stannane (*S,R,S,R*)-**174** (106 mg, 0.15 mmol, 1.0 eq.), *n*-BuLi (112 μ L of a 1.5 M solution in hexanes, 0.17 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.28 mL of a 0.7 M solution in THF, 0.20 mmol, 1.3 eq.), Pd(OAc)₂ (1.4 mg, 4 mol%), *t*-Bu₃PHBF₄ (3.5 mg, 8 mol%) and *N*-(4-bromophenyl)acetamide (84 mg, 0.39 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 95:5 CH₂Cl₂-acetone as eluent gave α -aryl THP (*R,R,S,R*)-**221** (60 mg, 73%) as a white solid, mp 108-109 °C, [α]_D +18.8 (*c* 1.00 in CHCl₃); *R*_F (95:5 CH₂Cl₂-acetone) 0.2; IR (ATR) 3313 (NH), 3063, 3030, 2861, 1603 (C=O), 1536, 1517, 1453, 1367, 1313, 1073, 734, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.51-7.20 (m, 19H, Ar), 4.95 (d, *J* = 11.0 Hz, 1H, OCH), 4.71 (d, *J* = 11.5 Hz, 1H, OCH), 4.67-4.63 (m, 2H, OCH), 4.62 (d, *J* = 10.0 Hz, 1H, OCH), 4.56 (d, *J* = 11.5 Hz, 1H, OCH), 4.38 (d, *J* = 10.0 Hz, 1H, OCH), 3.87-3.76 (m, 3H, OCH), 3.65-3.54 (m, 2H, OCH), 2.35 (ddd, *J* = 11.5, 5.0, 2.0 Hz, 1H, CH), 2.13 (s, 3H, Me), 1.71 (ddd, *J* = 11.5, 11.5, 11.5 Hz (app q), 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.5 (C=O), 138.6 (*ipso*-Ar), 138.6 (*ipso*-Ar), 138.5 (*ipso*-Ar), 137.5 (*ipso*-Ar), 137.4 (*ipso*-Ar), 128.56 (Ar), 128.50 (Ar), 128.47 (Ar), 128.18 (Ar), 127.92 (Ar), 127.79 (Ar), 127.77 (Ar), 127.68 (Ar), 126.8 (Ar), 119.8 (Ar), 81.3 (OCH), 79.5 (OCH), 78.4 (OCH), 77.2 (OCH), 75.2 (OCH₂), 73.6 (OCH₂), 71.5 (OCH₂), 69.7 (OCH₂), 39.1 (CH₂), 24.7 (Me) (2 resonances not resolved); MS (ESI) *m/z* 574 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₃₅H₃₇NO₅ (M + Na)⁺ 574.2564, found 574.2564 (−0.0 ppm error).

Lab Book Reference: **NS9-37-B**

(2-((Benzyloxy)methyl)-3,4-dihydro-2H-pyran 222**222**

(3,4-Dihydro-2H-pyran-2-yl)methanol (2.28 g, 20 mmol, 1.0 eq.) was added to a stirred suspension of NaH (960 mg, 60% in mineral oil, 32 mmol, 1.6 eq.) in THF (20 mL). The resulting suspension was stirred at 0 °C for 30 min. Then, BnBr (4.75 mL, 6.84 g, 40 mmol, 2.0 eq.) was added and the mixture was allowed to warm to rt and stirred at rt for 24 h. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (30 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with hexane then 95:5 hexane- Et_2O as eluent gave dihydropyran **222** (3.82 g, 93%) as a colourless oil, R_F (90:10 hexane- Et_2O) 0.6; IR (ATR) 3062, 2852, 1650 (C=C), 1496, 1453, 1241, 1100, 1070, 1028, 733, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.26 (m, 5H, Ph), 6.41 (d, J = 6.5 Hz, 1H, $\text{OCH}=\text{CH}$), 4.72-4.66 (m, 1H, $\text{OCH}=\text{CH}$), 4.63 (d, J = 12.0 Hz, 1H, OCHPh), 4.58 (d, J = 12.0 Hz, 1H, OCHPh), 4.04 (ddd, J = 10.0, 8.5, 4.5 Hz, 1H, OCH), 3.60 (dd, J = 10.0, 6.5 Hz, 1H, OCH), 3.53 (dd, J = 10.0, 4.5 Hz, 1H, OCH), 2.16-2.05 (m, 1H, CH), 2.04-1.92 (m, 1H, CH), 1.86 (ddd, J = 13.5, 6.5, 3.0 Hz, 1H, CH), 1.77-1.64 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 143.7 ($\text{OCH}=\text{CH}$), 138.2 (Ph), 128.5 (Ph), 127.9 (Ph), 127.8 (Ph), 100.6 ($\text{OCH}=\text{CH}$), 74.2 (OCH), 73.5 (OCH_2), 72.6 (OCH_2), 24.7 (CH_2), 19.5 (CH_2); MS (ESI) m/z 227 [$(\text{M} + \text{Na})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ ($\text{M} + \text{Na})^+$ 227.1043, found 227.1040 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.¹³³

Lab Book Reference: **NS9-34**

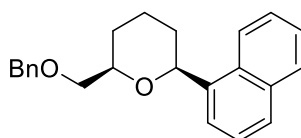
(cis)-6-((Benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)tributylstannane cis-224**cis-224**

HCl (5 mL of a 2.0 M solution in Et_2O , 10 mmol, 1.2 eq.) was added to a stirred solution of 2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran **222** (2.04 g, 10 mmol, 1.2 eq.) in THF (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h to give a solution of *trans*-2-((benzyloxy)methyl)-6-chlorotetrahydro-2H-pyran in THF. In a separate flask, *n*-BuLi (1.19 mL, 1.4 M in hexane, 1.7 mmol, 1.0 eq.) was added dropwise to a stirred solution

of *i*-Pr₂NH (2.80 mL, 2.02 g, 20 mmol, 2.0 eq.) in THF (10 mL) at 0 °C under Ar. The solution was stirred at 0 °C for 5 min. Then, Bu₃SnH (2.43 mL, 2.67 g, 9.2 mmol, 1.1 eq.) was added and the solution was stirred at 0 °C for 15 min to give a solution of Bu₃SnLi in THF. The solution of Bu₃SnLi in THF was added dropwise to the stirred solution of solution of *trans*-2-((benzyloxy)methyl)-6-chlorotetrahydro-2*H*-pyran in THF at -78 °C. The resulting solution was stirred at -78 °C for 1 h and then allowed to warm to rt over 16 h. Then, saturated NH₄Cl_(aq) (30 mL) and saturated NaHCO_{3(aq)} (10 mL) were added and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 hexane-Et₂O as eluent gave stannane *cis*-**224** (916 mg, 23%) as a colourless oil, *R*_F (90:10 hexane-Et₂O) 0.6; IR (ATR) 2954, 2922, 2852, 1454, 1375, 1103, 1029, 874, 732, 696, 595 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.19 (m, 5H, Ph), 4.58 (d, *J* = 12.0 Hz, 1H, OCHAr), 4.56 (d, *J* = 12.0 Hz, 1H, OCHAr), 3.81 (dd, *J* = 13.0, 2.0 Hz, 1H, OCH), 3.47- 3.31 (m, 3H, OCH), 1.91-1.70 (m, 2H, CH), 1.64-1.41 (m, 10H, CH), 1.35-1.23 (m, 6H, CH), 0.97-0.76 (m, 15H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 138.9 (*ipso*-Ph), 128.4 (Ph), 127.6 (Ph), 127.5 (Ph), 79.6 (OCH), 74.6 (OCH), 74.4 (OCH₂), 73.4 (OCH₂), 31.9 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 27.5 (CH₂), 25.7 (CH₂), 13.9 (Me), 8.5 (CH₂); MS (ESI) *m/z* 517 [(¹¹⁸M + Na)⁺, 73], 519 [(¹²⁰M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₅H₄₄O₂¹²⁰Sn (¹²⁰M + Na)⁺ 519.2255, found 519.2258 (+0.4 ppm error).

Lab Book Reference: **NS9-38**

***cis*-2-((Benzyloxy)methyl)-6-(naphthalen-1-yl)tetrahydro-2*H*-pyran *cis*-225**



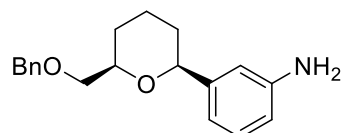
cis-**225**

Using general procedure C, stannane *cis*-**224** (124 mg, 0.25 mmol, 1.0 eq.), *n*-BuLi (0.18 mL of a 1.5 M solution in hexanes, 0.28 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.47 mL of a 0.7 M solution in THF, 0.33 mmol, 1.3 eq.), Pd(OAc)₂ (2.3 mg, 4 mol%), *t*-Bu₃PHBF₄ (5.8 mg, 8 mol%) at 40 °C and 1-bromonaphthalene (68 mg, 46 μL, 0.33 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-Et₂O then 80:20 hexane-Et₂O as eluent gave α-aryl THP *cis*-**225** (62.1 mg, 75%) as a colourless oil, *R*_F (90:10 hexane-Et₂O) 0.2; IR (ATR) 3061, 2934, 2855, 1496, 1453, 1313,

1198, 1081, 1008, 1050, 798, 777, 735, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.14-8.07 (m, 1H, Ar), 7.89-7.83 (m, 1H, Ar), 7.78 (d, J = 8.0 Hz, 1H, Ar), 7.67 (d, J = 7.0 Hz, 1H, Ar), 7.53-7.44 (m, 3H, Ar), 7.41-7.26 (m, 5H, Ar), 5.13 (dd, J = 11.0, 2.0 Hz, 1H, OCHAr), 4.63 (br s, 2H, OCH_2Ph), 3.96 (dddd, J = 11.0, 6.5, 4.5, 2.0 Hz, 1H, OCH), 3.68 (dd, J = 10.0, 6.5 Hz, 1H, OCH), 3.58 (dd, J = 10.0, 4.5 Hz, 1H, OCH), 2.13-2.00 (m, 2H, CH), 1.93-1.66 (m, 3H, CH), 1.63-1.43 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 138.9 (*ipso*-Ar), 138.7 (*ipso*-Ar), 133.9 (*ipso*-Ar), 130.7 (*ipso*-Ar), 128.9 (Ar), 128.5 (Ar), 127.9 (Ar), 127.8 (Ar), 127.6 (Ar), 125.9 (Ar), 125.6 (Ar), 125.4 (Ar), 123.8 (Ar), 123.2 (Ar), 78.2 (OCH), 77.2 (OCH), 73.9 (OCH_2), 73.5 (OCH_2), 32.8 (CH_2), 28.4 (CH_2), 24.0 (CH_2); MS (ESI) m/z 355 $[(\text{M} + \text{Na})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{24}\text{O}_2$ ($\text{M} + \text{Na})^+$ 355.1669, found 355.1669 (-0.2 ppm error).

Lab Book Reference: **NS9-41-A**

***cis*-3-((6-((Benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)aniline *cis*-226**



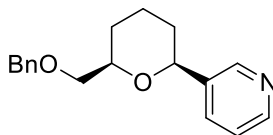
***cis*-226**

Using general procedure C, stannane ***cis*-224** (124 mg, 0.25 mmol, 1.0 eq.), *n*-BuLi (0.18 mL of a 1.5 M solution in hexanes, 0.28 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl_2 (0.47 mL of a 0.7 M solution in THF, 0.33 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (2.3 mg, 4 mol%), *t*-Bu₃PHBF₄ (5.8 mg, 8 mol%) and 3-bromoaniline (56.8 mg, 36.0 μL , 0.33 mmol, 1.3 eq.) at 40 $^\circ\text{C}$ gave the crude product. Purification by flash column chromatography on silica with 90:9.5:0.5 hexane-EtOAc-Et₃N then 80:19.5:0.5 hexane-EtOAc-Et₃N as eluent gave α -aryl THP ***cis*-226** (54.3 mg, 73%) as a yellow oil, R_F (49.8:49.8:0.4 hexane-EtOAc-Et₃N) 0.3; IR (ATR) 3363 (NH), 2933, 2855, 1495, 1454, 1314, 1200, 1081, 1042, 785, 737, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.25 (m, 5H, Ar), 7.09 (dd, J = 8.0, 8.0 Hz (app t), 1H, Ar), 6.74-6.70 (m, 2H, Ar), 6.56 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H, Ar), 4.60 (br s, 2H, OCH_2Ph), 4.31 (dd, J = 11.0, 2.0 Hz, 1H, OCHAr), 3.73 (dddd, J = 11.0, 5.5, 5.0, 2.0 Hz, 1H, OCH), 3.61 (dd, J = 10.0, 5.5 Hz, 1H, OCH), 3.60 (br s, 2H, NH), 3.49 (dd, J = 10.0, 5.0 Hz, 1H, OCH), 1.99-1.90 (m, 1H, CH), 1.84-1.77 (m, 1H, CH), 1.74-1.60 (m, 2H, CH), 1.54-1.29 (m, 2H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 146.5 (*ipso*-Ar), 144.7 (*ipso*-Ar), 138.7 (*ipso*-Ar), 129.2 (Ar), 128.5 (Ar), 127.8 (Ar), 127.6 (Ar), 116.4 (Ar), 114.2 (Ar), 112.8 (Ar), 79.9 (OCH), 77.5 (OCH), 73.9 (OCH_2), 73.5 (OCH_2), 33.9 (CH_2), 28.3 (CH_2), 23.8 (CH_2); MS

(ESI) m/z 298 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $C_{19}H_{23}NO_2$ $(M + H)^+$ 298.1802, found 298.1800 (+0.6 ppm error).

Lab Book Reference: **NS9-41-B**

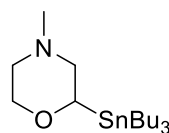
3-((*cis*)-6-((Benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)pyridine *cis*-227



cis-227

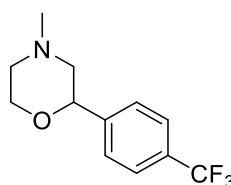
Using general procedure C, stannane *cis*-224 (100 mg, 0.20 mmol, 1.0 eq.), *n*-BuLi (0.15 mL of a 1.5 M solution in hexanes, 0.22 mmol, 1.1 eq.) in THF (2.5 mL), $ZnCl_2$ (0.37 mL of a 0.7 M solution in THF, 0.26 mmol, 1.3 eq.), $Pd(OAc)_2$ (1.8 mg, 4 mol%), $t-Bu_3PHBF_4$ (4.6 mg, 8 mol%) and 3-bromopyridine (41.4 mg, 25.2 μ L, 0.26 mmol, 1.3 eq.) at 60 °C gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave α -aryl THP *cis*-227 (35.0 mg, 61%) as a colourless oil, R_F (50:50 hexane-EtOAc) 0.5; IR (ATR) 3031, 2934, 2856, 1577, 1454, 1424, 1363, 1079, 1048, 1026, 796, 713, 698, 618 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.0 Hz, 1H, Ar), 8.49 (dd, J = 4.5, 1.5 Hz, 1H, Ar), 7.69 (ddd, J = 8.0, 1.5, 1.0 Hz, 1H, Ar), 7.36-7.23 (m, 6H, Ar), 4.60 (d, J = 12.5 Hz, 1H, *OCHPh*), 4.57 (d, J = 12.5 Hz, 1H, *OCHPh*), 4.45 (dd, J = 11.5, 2.5 Hz, 1H, *OCHAr*), 3.77 (dddd, J = 11.5, 6.5, 4.5, 2.0 Hz, 1H, OCH), 3.58 (dd, J = 10.0, 6.5 Hz, 1H, OCH), 3.48 (dd, J = 10.0, 4.5 Hz, 1H, OCH), 2.04-1.93 (m, 1H, CH), 1.88-1.80 (m, 1H, CH), 1.74-1.62 (m, 2H, CH), 1.57-1.46 (m, 1H, CH), 1.43-1.30 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.8 (Ar), 147.9 (Ar), 138.7 (*ipso*-Ar), 138.5 (*ipso*-Ar), 133.7 (Ar), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 123.4 (Ar), 77.7 (OCH), 77.6 (OCH), 73.7 (OCH_2), 73.5 (OCH_2), 33.8 (CH_2), 27.9 (CH_2), 23.6 (CH_2); MS (ESI) m/z 284 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $C_{18}H_{21}NO_2$ $(M + H)^+$ 284.1645, found 284.1642 (+1.2 ppm error).

Lab Book Reference: **NS10-28**

4-Methyl-2-(tributylstannyl)morpholine 228**228**

Using general procedure D, *N*-methyl morpholine **125** (306 mg, 3.0 mmol, 1.0 eq.), *s*-BuLi (3.0 mL of a 1.2 M solution in hexane, 3.9 mmol, 1.3 eq.), TMEDA (585 μ L, 450 mg, 3.3 mmol, 3.3 eq.) in hexane (15 mL) and Bu₃SnCl (1.95 g, 1.63 mL, 6.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98.5:1:0.5 to 97.5:2:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -stannyl morpholine **228** (1.09 g, 91%) as a colourless oil, *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.8; IR (ATR) 2955, 2922, 1456, 1284, 1093, 1078 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.99 (dd, *J* = 11.5, 2.0 Hz, 1H, OCH), 3.81 (ddd, *J* = 11.5, 2.5, 2.5 Hz (app dt), 1H, OCH), 3.56 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 2.70-2.58 (m, 2H, NCH), 2.34 (dd, *J* = 11.5, 11.5 Hz (app t), 1H, NCH), 2.25 (s, 3H, NMe), 2.21 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, NCH), 1.55-1.45 (m, 6H, CH), 1.36-1.25 (m, 6H, CH), 0.93-0.86 (m, 15H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 73.3 (OCH), 69.3 (OCH₂), 60.6 (NCH₂), 56.2 (NCH₂), 46.5 (NMe), 29.2 (CH₂), 27.5 (CH₂), 13.8 (Me), 8.5 (CH₂); MS (ESI) *m/z* 390 [(¹¹⁸M + H)⁺, 74], 392 [(¹²⁰M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₇H₃₇NO¹²⁰Sn (¹²⁰M + H)⁺ 392.1973, found 392.1966 (+1.0 ppm error).

Lab Book Reference: **NS2-23**

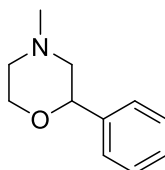
4-Methyl-2-(4-(trifluoromethyl)phenyl)morpholine 229**229**

Using general procedure C, morpholine stannane **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13.0 mg, 9 mol%) and 1-bromo-4-(trifluoromethyl)benzene (146 mg, 91 μ L, 0.65 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with CH₂Cl₂-acetone 90:10 then 96:3:1 CH₂Cl₂-MeOH-NH₄OH as eluent gave α -

aryl morpholine **229** (50 mg, 41%) as a colourless oil, R_F (95:5:1 CH₂Cl₂-MeOH-NH₄OH) 0.3; IR (ATR) 2937, 2857, 2794, 1452, 1323, 1163, 1118, 1103, 1066, 918, 834, 606 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.61-7.58 (m, 2H, Ar), 7.51-7.45 (m, 2H, Ar), 4.61 (dd, J = 10.5, 2.5 Hz, 1H, OCH), 4.05 (ddd, J = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.84 (ddd, J = 11.5, 11.5, 2.0 Hz, 1H, OCH), 2.90 (ddd, J = 11.5, 2.0, 2.0 Hz (app dt), 1H, NCH), 2.75 (dd, J = 11.5, 2.5 Hz, 1H, NCH), 2.33 (s, 3H, NMe), 2.23 (ddd, J = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.99 (dd, J = 11.5, 10.5 Hz, 1H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 144.5 (br s, *ipso*-Ar), 130.2 (q, J = 32.0 Hz, Ar), 126.5 (br s, not resolved, Ar), 125.4 (q, J = 4.0 Hz, Ar), 124.5 (q, J = 270.0 Hz, CF₃), 77.5 (OCH), 67.2 (OCH₂), 62.2 (NCH₂), 54.7 (NCH₂), 46.3 (NMe); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.4 (s); MS (APCI) m/z 246 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₂H₁₄F₃NO (M + H)⁺ 246.1100, found 246.1101 (-0.1 ppm error).

Lab Book Reference: **NS8-99-A**

4-Methyl-2-phenylmorpholine **230**



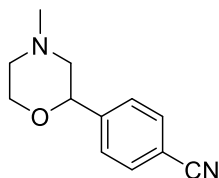
230

Using general procedure C, morpholine stannane **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PBHF₄ (13.0 mg, 9 mol%) and bromobenzene (102 mg, 68 μ L, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with CH₂Cl₂-acetone 90:10 then 96:3:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -aryl morpholine **230** (45 mg, 52%) as a colourless oil, R_F (95:4:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.3; IR (ATR) 2935, 2855, 2790, 1450, 1288, 1142, 1106, 1082, 1029, 752, 697, 588 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.20 (m, 5H, Ph), 4.56 (dd, J = 10.5, 2.5 Hz, 1H, OCH), 4.05 (ddd, J = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.84 (ddd, J = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 2.90 (ddd, J = 11.5, 2.5, 1.5 Hz, 1H, NCH), 2.83-2.69 (m, 1H, NCH), 2.33 (s, 3H, NMe), 2.24 (ddd, J = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 2.05 (dd, J = 11.5, 10.5 Hz, 1H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 140.4 (*ipso*-Ph), 128.5 (*ipso*-Ph), 127.9 (Ph), 126.3 (Ph), 78.3 (OCH), 67.2 (OCH₂), 62.3 (NCH₂), 54.8 (NCH₂), 46.3 (NMe); MS (APCI) m/z

178 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₅NO (M + H)⁺ 178.1226, found 178.1228 (−0.6 ppm error).

Lab Book Reference: **NS8-100-A**

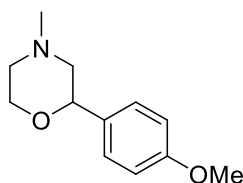
4-(4-Methylmorpholin-2-yl)benzonitrile **231**



231

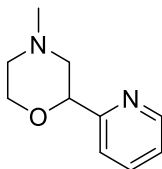
Using general procedure C, morpholine stannane **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13.0 mg, 9 mol%) and 4-bromobenzonitrile (118 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with CH₂Cl₂-acetone 90:10 then 96:3:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α-aryl morpholine **231** (39 mg, 39%) as a colourless oil, *R*_F (95:5:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.3; IR (ATR) 2936, 2856, 2793, 2228 (CN), 1610, 1452, 1288, 1141, 1103, 1082, 918, 866, 831, 597, 562 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.61 (m, 2H, Ar), 7.49-7.45 (m, 2H, Ar), 4.60 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.05 (ddd, *J* = 11.5, 3.5, 2.5 Hz, 1H, OCH), 3.83 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 2.89 (ddd, *J* = 11.5, 2.5, 2.0 Hz, 1H, NCH), 2.82-2.71 (m, 1H, NCH), 2.33 (s, 3H, NMe), 2.22 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.95 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 145.8 (*ipso*-Ar), 132.3 (Ar), 126.8 (Ar), 118.9 (CN), 111.6 (*ipso*-Ar), 77.4 (OCH), 67.2 (OCH₂), 62.0 (NCH₂), 54.7 (NCH₂), 46.3 (NMe); MS (APCI) *m/z* 203 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₄N₂O (M + H)⁺ 203.1181, found 203.1179 (−1.0 ppm error).

Lab Book Reference: **NS8-99-B**

2-(4-Methoxyphenyl)-4-methylmorpholine 232**232**

Using general procedure C, morpholine stannane **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13 mg, 9 mol%) and 4-methoxy-1-bromobenzene (122 mg, 82 µL, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) to 96:3:1 CH₂Cl₂-MeOH-NH₄OH as eluent gave α-aryl morpholine **232** (60 mg, 47%) as a colourless oil, *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.5; IR (ATR) 2933, 2838, 2790, 1613, 1514, 1453, 1289, 1244, 1174, 1082, 1031, 917, 885, 604 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.27 (m, 2H, Ar), 6.90-6.82 (m, 2H, Ar), 4.50 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.02 (ddd, *J* = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.83 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.79 (s, 3H, OMe), 2.85 (ddd, *J* = 11.5, 2.5, 1.5 Hz, 1H, NCH), 2.73 (ddd, *J* = 11.5, 2.5, 1.5 Hz, 1H, NCH), 2.32 (s, 3H, NMe), 2.22 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 2.04 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.3 (*ipso*-Ar), 132.7 (Ar), 127.6 (Ar), 113.8 (*ipso*-Ar), 78.0 (OCH), 67.2 (OCH₂), 62.4 (NCH₂), 55.4 (OMe), 54.9 (NCH₂), 46.3 (NMe); MS (APCI) *m/z* 208 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₁₂H₁₇NO₂ (M + H)⁺ 208.1332, found 208.1333 (−0.5 ppm error).

Lab Book Reference: **NS8-97-C**

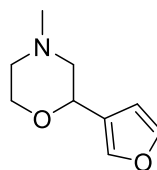
4-Methyl-2-(pyridin-2-yl)morpholine 233**233**

Using general procedure C, morpholine stannane **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13 mg, 9 mol%) and 2-bromopyridine (103 mg, 62 µL, 0.65 mmol, 1.3 eq.) at

60 °C gave the crude. Purification by flash column chromatography on silica with 97:2.0:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -aryl morpholine **233** (14 mg, 8%) as a yellow oil, *R*_F (97:2.0:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.3; IR (ATR) 2923, 2854, 1742, 1593, 1450, 1348, 1269, 1146, 1118, 771, 589 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 8.52-8.49 (m, 1H, Ar), 7.92-7.81 (m, 1H, Ar), 7.57 (ddd, *J* = 8.5, 1.5, 1.0 Hz, 1H, Ar), 7.39-7.33 (m, 1H, Ar), 4.75-4.69 (m, 1H, OCH), 4.17-4.08 (m, 1H, OCH), 3.89 (ddd, *J* = 12.0, 12.0, 2.5 Hz (app td), 1H, OCH), 3.42-3.35 (m, 1H, NCH), 3.09-3.02 (m, 1H, NCH), 2.69-2.58 (m, 1H, NCH), 2.57 (s, 3H, NMe), 2.52-2.39 (m, 1H, NCH); ¹³C NMR (100.6 MHz, CD₃OD) δ 159.3 (Ar), 149.6 (Ar), 138.9 (*ipso*-Ar), 124.6 (Ar), 122.3 (Ar), 78.2 (OCH), 66.6 (OCH₂), 60.0 (NCH₂), 55.0 (NCH₂), 45.5 (NMe); MS (APCI) *m/z* 179 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₀H₁₅N₂O (M + H)⁺ 179.1179, found 179.1178 (+0.5 ppm error).

Lab Book Reference: **NS8-100-B**

Attempted Synthesis of 2-(furan-3-yl)-4-methylmorpholine **234**

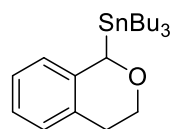


234

Using general procedure C, morpholine stannane **228** (195 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13.0 mg, 9 mol%) and 3-bromofuran (96 mg, 58 μ L, 0.65 mmol, 1.3 eq.) at 60 °C gave the crude product which did not contain the desired product **234** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-97-D**

Tributyl(isochroman-1-yl)stannane **236**



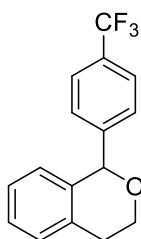
236

Using general procedure D, isochroman **235** (1.34 mg, 124 μ L, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and Bu₃SnCl (651 mg, 543 μ L, 2.0 mmol, 2.0 eq.) at 40 °C gave

the crude product. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ as eluent gave stannane **236** (220 mg, 51%) as a colourless oil, *R*_F (80:20 hexane-CH₂Cl₂) 0.4; IR (ATR) 2955, 2921, 2850, 1488, 1457, 1376, 1209, 1113, 1072, 941, 746, 660, 591 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.12-6.93 (m, 3H, Ar), 6.78-6.71 (m, 1H, Ar), 5.43 (s, 1H, OCH), 3.89-3.80 (m, 2H, OCH), 2.91-2.75 (m, 2H, CH₂), 1.53-1.36 (m, 6H, CH), 1.33-1.21 (m, 6H, CH), 0.99-0.79 (m, 15H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 141.4 (*ipso*-Ar), 130.9 (*ipso*-Ar), 129.1 (Ar), 126.0 (Ar), 123.8 (Ar), 122.3 (Ar), 75.2 (OCH), 65.5 (OCH₂), 29.4 (CH₂), 29.2 (CH₂), 27.5 (CH₂), 13.8 (Me), 10.1 (CH₂); MS (APCI) *m/z* 425 [(¹¹⁸M+H)⁺, 74], 425 [(¹²⁰M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₂₁H₃₆O¹²⁰Sn(¹²⁰M + H)⁺ 425.1865, found 425.1877 (+2.9 ppm error).

Lab Book Reference: **NS9-94**

Attempted Synthesis of 1-(4-(Trifluoromethyl)phenyl)isochromane **237**



237

Using general procedure C, isochromane stannane **236** (150 mg, 0.35 mmol, 1.0 eq.), *n*-BuLi (0.26 mL of a 1.5 M solution in hexanes, 0.39 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.66 mL of a 0.7 M solution in THF, 0.46 mmol, 1.3 eq.), Pd(OAc)₂ (3.2 mg, 4 mol%), *t*-Bu₃PHBF₄ (8.2 mg, 8 mol%) and 1-bromo-4-(trifluoromethyl)benzene (104 mg, 65 μL, 0.46 mmol, 1.3 eq.) gave the crude product which only contained traces of the desired product **237** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS9-95**

5.4 Experimental for Chapter Three

(1*R*,5*S*)-1,2,3,4,5,6-Hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (–)-**cytisine**

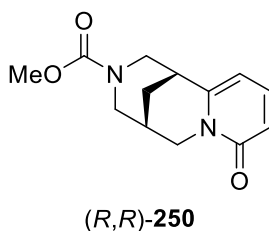


(–)-Cytisine

MeOH (180 mL) and $\text{NH}_4\text{OH}_{(\text{aq})}$ (90 mL) were added to a solution of *Laburnum anagyroides* seeds (600 g, Vilmorin, France, powdered in a food blender) in CH_2Cl_2 (880 mL) and the resulting mixture was stirred with an overhead stirrer at rt for 96 h. Then, the mixture was decanted and the residue was washed with CH_2Cl_2 (3 x 200 mL). The filtrate was then acidified using 3 M $\text{HCl}_{(\text{aq})}$ until pH 1 and the emulsion was allowed to settle at rt for 7 days. Then, the layers were separated and the aqueous layer was basified using $\text{NH}_4\text{OH}_{(\text{aq})}$ until pH 11-12. The aqueous layer was extracted with CH_2Cl_2 (3 x 500 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Recrystallisation from toluene gave (–)-cytisine (6.21 g, 1 wt%) as a white solid, mp 151-154 °C; (lit.,¹⁹⁵ 153-154 °C); $[\alpha]_{\text{D}} -70.3$ (*c* 1.0 in CHCl_3) (lit.,¹⁹⁵ -76.0 (*c* 1.0 in CHCl_3)); IR (ATR) 3316 (NH), 2934, 1645 (C=O), 1543, 1470, 1356, 1143, 1108, 907, 798, 737, 613 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.19 (m, 1H, Ar), 6.50-6.35 (m, 1H, Ar), 5.99-5.92 (m, 1H, Ar), 4.15-4.00 (m, 1H, NCH), 3.95-3.72 (m, 1H, NCH), 3.12-2.91 (m, 4H, NCH), 2.86 (s, 1H, CH), 2.29 (br s, 1H, CH), 1.97-1.86 (m, 2H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 163.8 (C=O), 151.2 (*ipso*-Ar), 138.9 (Ar), 116.8 (Ar), 105.8 (Ar), 54.1 (NCH_2), 53.1 (NCH_2), 49.8 (NCH_2), 35.7 (CH), 27.8 (CH), 26.4 (CH_2); MS (ESI) m/z 191 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$ (M + H)⁺ 191.1179, found 191.1180 (–0.8 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁴⁶

Lab Book Reference: **NS5-56**

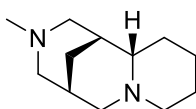
Methyl (1*R*,5*R*)-8-oxo-1,5,6,8-tetrahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine-3(4*H*)-carboxylate (*R,R*)-250



MeO₂CCl (1.70 mL, 22 mmol, 1.1 eq.) was added dropwise over 10 min to a stirred solution of (–)-cytisine (3.80 g, 20 mmol, 1.0 eq.) and Et₃N (3.10 mL, 2.23 g, 22 mmol, 1.1 eq.) in CH₂Cl₂ at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h and then at rt for 3 h. The solvent was evaporated under reduced pressure. EtOAc (50 mL) was added and the solids were removed by filtration and washed with EtOAc (3 x 50 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-MeOH as eluent gave carbamate **250** (4.04 g, 81%) as a white solid, mp 104-106 °C (lit.,¹⁹⁶ 108 °C); [α]_D –206.4 (*c* 1.0 in CHCl₃) (lit.,¹⁴⁶ –207.9 (*c* 0.47 in CHCl₃)); *R*_F (90:10 CH₂Cl₂-MeOH) 0.5; IR (ATR) 2848, 2867, 1693, 1647, 1562, 1544, 1445, 1235, 1124, 801, 768, 599, 523 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.24 (m, 1H, Ar), 6.44 (br d, *J* = 9.0 Hz, 1H, Ar), 6.05 (br s, 1H, Ar), 4.37-4.04 (m, 3H, NCH), 3.85 (dd, *J* = 15.5, 6.5 Hz, 1H, NCH), 3.18-2.92 (m, 3H, NCH, CH), 2.46 (br s, 1H, CH), 2.07-1.87 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 163.6 (C=O), 156.3 (C=O), 148.8 (Ar), 139.1 (*ipso*-Ar), 117.6 (Ar), 105.9 (Ar), 52.9 (OMe), 51.2 (NCH₂), 50.3 (NCH₂), 49.1 (NCH₂), 34.6 (CH), 27.3 (CH), 25.9 (CH₂); MS (ESI) *m/z* 271 [(*M* + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₃H₁₆N₂O₃ (*M* + Na)⁺ 271.1053, found 271.2055 (–0.8 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁴⁶

Lab Book Reference: **NS4-34**

(11*aS*)-3-Methyldecahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine (+)-sparteine surrogate



(+)-Sparteine Surrogate

PtO₂ (369 mg, 1.7 mmol, 0.1 eq.) was added to a stirred solution of carbamate **250** in MeOH (60 mL) at rt under Ar. Then, the reaction flask was evacuated under reduced pressure and

back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred under a H₂ balloon at rt for 16 h. The solids were removed by filtration through Celite[®] and washed with 9:1 CH₂Cl₂-MeOH (50 mL). The filtrate was evaporated under reduced pressure to give the crude hydrogenation product. Then, the crude product was dissolved in THF (100 mL) and added to a stirred suspension of LiAlH₄ (3.31 g, 87 mmol, 5.5 eq.) in THF (100 mL) at 0 °C under Ar. The mixture was allowed to warm to rt and then stirred and heated at reflux for 16 h. After cooling to 0 °C, Et₂O (100 mL) was added, followed by addition of Na₂SO₄ x 10 H₂O until a white solid precipitated. The resulting mixture was stirred for 30 min until gas evolution had ceased and the solids were removed by filtration through Celite[®] and washed with 90:10 CH₂Cl₂-MeOH (100 mL). The filtrate was dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by distillation (160 °C, full vacuum) gave (+)-sparteine surrogate (1.17 g, 49%) as a colourless oil, [α]_D +26.8 (c 1.0 in EtOH) (lit.¹⁴⁶ +29.7 (c 1.10 in EtOH)); *R*_F (90:10 Et₂O-MeOH) 0.5 IR (ATR) 2931, 2856, 2778, 1446, 1272, 1107, 1044, 1001, 988, 729, 590 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.99 (dd, *J* = 10.5, 10.5 Hz (app t), 2H, NCH), 2.92-2.83 (m, 2H, NCH), 2.24 (ddd, *J* = 10.5, 3.5, 1.5 Hz, 1H, NCH), 2.18-2.11 (m, 3H, NMe), 1.97 (dd, *J* = 10.5, 3.5 Hz, 1H, NCH), 1.90 (d, *J* = 10.5 Hz, 1H, NCH), 1.85-1.45 (m, 10H, NCH, CH), 1.37-1.22 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 66.6 (NCH), 60.61 (NCH₂), 60.59 (NCH₂), 57.8 (NCH₂), 56.5 (NCH₂), 47.6 (NMe), 35.4 (CH), 34.1 (CH₂), 31.0 (CH₂), 30.8 (CH), 25.8 (CH₂), 25.3 (CH₂); MS (ESI) *m/z* 195 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₂₂N₂ (M + H)⁺ 195.1856, found 195.1856 (–0.3 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁴⁶

Lab Book Reference: **NS4-39**

(*R*)-Phenyl(tetrahydrofuran-2-yl)methanone (*R*)-107

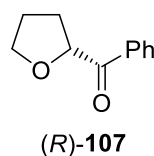


Table 3.1, entry 1:

s-BuLi (0.77 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in THF (5 mL) at –60 °C under Ar. The resulting solution was stirred at –60 °C for 4 h. Then, Weinreb amide **115** (330 mg, 304 μ L, 2.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at –

60 °C for 1 h. MeOH (1 mL) was added and the resulting solution was allowed to warm to rt over 30 min. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone then 98:2 CH_2Cl_2 -acetone as eluent gave ketone (*R*)-**107** (53 mg, 30%, 75:25 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +3.0$ (*c* 0.5 in CHCl_3); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min⁻¹) 11.4 min (minor), 14.2 min (major). Spectroscopic data consistent with those reported in the literature.¹⁸⁷

Lab Book Reference: **NS4-22**

Table 3.1, entry 2:

Using general procedure E, THF (72 mg, 81 μL , 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at -60 °C for 4 h and Weinreb amide **115** (330 mg, 304 μL , 2.0 mmol, 2.0 eq.) at -60 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone then 98:2 CH_2Cl_2 -acetone as eluent gave ketone (*R*)-**107** (30 mg, 17%, 77:23 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +3.0$ (*c* 0.5 in CHCl_3); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min⁻¹) 15.3 min (minor), 19.4 min (major).

Lab Book Reference: **NS4-24**

Table 3.1, entry 3:

Using general procedure E, THF (72 mg, 81 μL , 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (5 mL) at -60 °C for 4 h and Weinreb amide **115** (330 mg, 304 μL , 2.0 mmol, 2.0 eq.) at -60 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone then 98:2 CH_2Cl_2 -acetone as eluent gave ketone (*R*)-**107** (17 mg, 10%, 78:22 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +3.2$ (*c* 0.5 in CHCl_3); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min⁻¹) 16.7 min (minor), 20.0 min (major).

Lab Book Reference: **NS4-25**

Table 3.1, entry 4:

Using general procedure E, THF (72 mg, 81 μ L, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in CPME (5 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and Weinreb amide **115** (330 mg, 304 μ L, 2.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone then 98:2 CH_2Cl_2 -acetone as eluent gave ketone (*R*)-**107** (82 mg, 47%, 80:20 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +3.7$ (*c* 0.5 in CHCl_3); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min $^{-1}$) 10.7 min (minor), 13.1 min (major).

Lab Book Reference: **NS4-40**

Table 3.1, entry 5:

Using general procedure E, THF (72 mg, 81 μ L, 1.0 mmol, 1.0 eq.), *s*-BuLi (0.7 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in CPME (5 mL) at $-78\text{ }^{\circ}\text{C}$ for 8 h and Weinreb amide **115** (330 mg, 304 μ L, 2.0 mmol, 2.0 eq.) at $-78\text{ }^{\circ}\text{C}$ for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone then 98:2 CH_2Cl_2 -acetone as eluent gave ketone (*R*)-**107** (30 mg, 17%, 81:19 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +5.0$ (*c* 0.5 in CHCl_3); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min $^{-1}$) 14.7 min (minor), 17.5 min (major).

Lab Book Reference: **NS4-43**

Table 3.1, entry 6:

t-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of THF (72 mg, 81 μ L, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in CPME (5 mL) at $-60\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-60\text{ }^{\circ}\text{C}$ for 4 h. Then, Weinreb amide **115** (330 mg, 304 μ L, 2.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at $-60\text{ }^{\circ}\text{C}$ for 1 h. Then MeOH (1 mL) was added and the resulting solution was allowed to warm to rt over 30 min. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product which contained none of ketones **107** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS4-45**

Table 3.2 entry 3:

Using general procedure E, *s*-BuLi (770 μ L of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) and (*S,S,S,S*)-**253** (236 mg, 1.3 mmol, 1.3 eq.) in THF (5 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and Weinreb amide **115** (330 mg, 304 μ L, 2.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone then 98:2 CH_2Cl_2 -acetone as eluent gave ketone **207** (42 mg, 31%, 50:50 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +0.0$ (*c* 0.5 in CHCl_3); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) 11.9 min, 14.9 min.

Lab Book Reference: **NS5-23**

Table 3.2 entry 1:

Using general procedure E, *s*-BuLi (385 μ L of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) and (*S*)-**252** (159 mg, 0.65 mmol, 1.3 eq.) in THF (5 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and Weinreb amide **115** (165 mg, 152 μ L, 1.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product which was added. The resulting solution was stirred $-60\text{ }^{\circ}\text{C}$ for 1 h. Then MeOH (1 mL) was added and the resulting solution was allowed to warm to rt over 30 min. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure gave the crude product which did not contain the desired product **107** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS5-44**

Table 3.2 entry 2:

Using general procedure E, THF (40 μ L, 36 mg, 1.0 eq.), *s*-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and diamine (*S*)-**252** (159 mg, 0.65 mmol, 1.3 eq.) in CPME (5 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and Weinreb amide **115** (165 mg, 152 μ L, 1.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product which did not contain the desired product **107** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS5-50**

Table 3.2 entry 4:

Using general procedure E, THF (80 μ L, 72 mg, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and diamine (*S,S,S,S*)-**253** (236 mg, 1.3 mmol, 1.3 eq.) in CPME at $-60\text{ }^{\circ}\text{C}$ for 4 h and Weinreb amide **115** (330 mg, 304 μ L, 2.0 mmol, 2.0 eq.) at

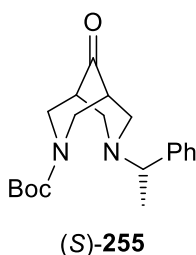
–60 °C for 1 h gave the crude product which did not contain the desired product **107** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS5-24**

n-BuLi (135 μL of a 2.3 M solution in hexane, 0.31 mmol, 1.1 eq.) was added dropwise to a stirred solution of enantioenriched stannane (*S*)-**158** (100 mg, 0.28 mmol, 1.0 eq.) and TMEDA (46 μL , 0.31 mmol, 1.1 eq.) in CPME (2.5 mL) at –60 °C under Ar. The resulting solution was stirred at –60 °C for 30 min. Then, Weinreb amide **115** (70 mg, 65 μL , 0.42 mmol, 1.5 eq.) was added. The resulting solution was stirred at –60 °C for 30 min. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Mg_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone as eluent gave ketone (*R*)-**107** (38 mg, 77%, 78:22 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +7.2$ (*c* 1.0 in CHCl_3); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) 15.0 min (minor), 18.3 min (major).

Lab Book Reference: **NS12-29**

***tert*-Butyl 9-oxo-7-((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (*S*)-255**

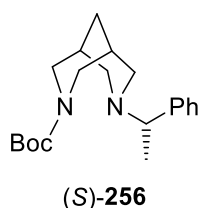


Acetic acid (0.45 g, 0.45 mL, 7.5 mmol, 1.5 eq.) was added to a stirred solution of (*S*)-1-phenylethan-1-amine (2.57 mL, 20 mmol, 1.0 eq.) and paraformaldehyde (1.20 g, 40 mmol, 8.0 eq.) in MeOH (20 mL) at 0 °C. Then, *N*-Boc piperidinone **254** (581 mg, 5.0 mmol, 1.0 eq.) was added and the mixture was stirred and heated at reflux for 21 h. The solvent was evaporated under reduced pressure to give a red oil. H_2O (50 mL) was added and the mixture was extracted with Et_2O (3×50 mL). The aqueous layer was basified to pH = 12 using 2 M $\text{NaOH}_{(\text{aq})}$ and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by

flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave ketone (S)-**255** (4.15 g, 60%) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.3; IR (ATR) 2974, 2934, 1734 (C=O, ester), 1691 (C=O, Boc), 1422, 1365, 1250, 1167, 1121, 985, 703 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 50:50 mixture of rotamers δ 7.39-7.16 (m, 5H, Ph), 4.54-4.47 (m, 1.5H, CH), 4.29 (br d, $J = 13.5$ Hz, 0.5H, CH), 3.50-2.96 (m, 5H, CH), 2.80-2.24 (m, 4H, CH), 1.54 (s, 9H, CMe_3), 1.40-1.36 (m, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 214.54 (C=O), 214.52 (C=O), 155.12 (C=O), 155.10 (C=O), 143.6 (*ipso*-Ph), 143.1 (*ipso*-Ph), 128.8 (Ph), 127.8 (Ph), 127.8 (Ph), 127.6 (Ph), 80.6 (CMe_3), 80.4 (CMe_3), 64.7 (NCHMe), 64.3 (NCHMe), 57.5 (NCH_2), 57.0 (NCH_2), 57.0 (NCH_2), 56.6 (NCH_2), 51.1 (NCH_2), 50.6 (NCH_2), 50.4 (NCH_2), 50.0 (NCH_2), 48.3 (CH), 48.2 (CH), 47.9 (CH), 47.8 (CH), 29.1 (CMe_3), 29.0 (CMe_3), 20.9 (NCHMe), 20.5 (NCHMe) (two Ph resonances not resolved); MS (ESI) m/z 345 $[(M + H)^+]$, 100; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_3$ ($M + H$) $^+$ 345.2173, found 345.2180 (−2.0 ppm error).

Lab Book Reference: NS5-33

***tert*-Butyl-7-((S)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (S)-256**

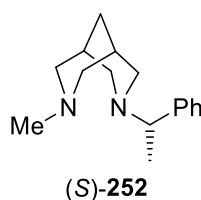


p-Toluenesulfonyl hydrazine (2.70 g, 15 mmol, 1.2 eq.) was added to a stirred solution of bispidone (S)-**255** (4.00 g, 12. mmol, 1.0 eq.) in EtOH (100 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3.5 h. After cooling to rt, the solvent was evaporated under reduced pressure. The residue was dissolved in 80:20 THF-H₂O (70 mL) and cooled to 0 °C. NaBH₄ (3.83 g, 60 mmol, 8.4 eq.) was added portion-wise over 20 min. The resulting mixture was stirred at rt for 18 h and then stirred and heated at reflux for 4 h. The solution was allowed to cool to rt and H₂O (50 mL) was added. The layers were separated and the aqueous layer was extracted with Et₂O (4 x 50 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave *N*-Boc bispidine (S)-**256** (1.75 g, 44%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.2; $[\alpha]_D^{25} +12.3$ (c 0.2 in CHCl_3); IR (ATR) 2974, 2914, 2859, 1688 (C=O), 1451, 1364, 1424, 1241, 1176, 1130, 996, 873, 763, 702 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 50:50 mixture

of rotamers δ 7.33-7.27 (m, 4H, Ph), 7.27-7.15 (m, 1H, Ph), 4.17-3.96 (m, 1.5H, CH), 3.87 (d, J = 12.5 Hz, 0.5H, CH), 3.22-3.05 (m, 3H, CH, NCHMe), 3.02-2.96 (ddd, J = 13.0, 4.0, 2.0 Hz, 0.5H, CH), 2.87 (br d, J = 12.0 Hz, 0.5H, CH), 2.80 (br d, J = 12.0 Hz, 0.5H, CH), 2.26-2.14 (m, 1H, CH), 2.09-1.97 (m, 1 H, CH), 1.96-1.89 (m, 0.5H, CH), 1.86-1.81 (m, 0.5H, CH), 1.79-1.70 (m, 1H, CH), 1.68-1.52 (m, 2.5H, CH), 1.54 (s, 4.5H, CMe₃), 1.53 (s, 4.5H, CMe₃), 1.28 (d, J = 6.5 Hz, 1.5H, NCHMe), 1.26 (d, J = 6.5 Hz, 1.5H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 155.2 (C=O), 155.1 (C=O), 145.5 (*ipso*-Ph), 144.8 (*ipso*-Ph), 128.3 (Ph), 128.2 (Ph), 127.7 (Ph), 127.6 (Ph), 126.6 (Ph), 78.9 (CMe₃), 78.7 (CMe₃), 65.6 (NCHMe), 65.5 (NCHMe), 57.3 (NCH₂), 56.6 (NCH₂), 55.9 (NCH₂), 55.9 (NCH₂), 48.9 (NCH₂), 48.3 (NCH₂), 48.0 (NCH₂), 47.6 (NCH₂), 31.6 (CH₂), 31.0 (CH₂), 29.4 (CH), 29.14 (CH), 29.13 (CH), 29.11 (CH), 28.9 (CMe₃), 28.9 (CMe₃), 20.7 (NCHMe), 20.4 (NCHMe) (one Ph resonance not resolved); MS (ESI) m/z 331 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₂₀H₃₀N₂O₂ (M + H)⁺ 331.2380, found 331.2377 (+0.8 ppm error).

Lab Book Reference: **NS5-38**

3-Methyl-7-((S)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane (S)-252

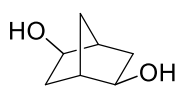


LiAlH₄ (1.00 g, 27 mmol, 5.0 eq.) was added portion-wise over 20 min to a stirred solution of *N*-Boc bispidine **256** (1.60 g, 5.3 mmol, 1.0 eq.) in THF (40 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and stirred and heated at reflux for 16 h. After cooling to 0 °C, Et₂O (100 mL) was added, followed by the addition of Na₂SO₄ x 10 H₂O until a white solid precipitated. The resulting mixture was stirred for 30 min until gas evolution had ceased. The solids were removed by filtration through Celite[®] and washed with 9:1 CH₂Cl₂-MeOH (100 mL). The filtrate was dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by distillation (160 °C, full vacuum) gave bispidine (S)-**252** (1.16 g, 88%) as a colourless oil, [α]_D +16.8 (c 0.1 in CHCl₃); IR (ATR) 2919, 2774, 1450, 1258, 1231, 1052, 922, 762, 699, 542 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, J = 7.5 Hz, 2H, Ph), 7.30 (dd, J = 7.5, 7.5 Hz (app t), 2H, Ph), 7.21 (dd, J = 7.5, 7.5 Hz (app t), 1H, Ph), 3.40 (q, J = 6.5 Hz, 1H, NCHMe), 2.75 (d, J = 9.5 Hz, 1H, CH), 2.66-2.39 (m, 5H, CH), 2.29-2.21 (m, 2H, CH), 2.23 (s, 3H, NMe), 1.99-1.85 (m, 2H,

CH), 1.66-1.53 (m, 1H, CH), 1.32 (d, $J = 6.5$ Hz, 3H, NCHMe), 1.30-1.27 (m, 1 H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 145.3 (*ipso*-Ph), 128.0 (Ph), 127.9 (Ph), 126.5 (Ph), 64.5 (NCHMe), 59.1 (NCH₂), 59.0 (NCH₂), 55.8 (NCH₂), 54.7 (NCH₂), 46.3 (NMe), 29.1 (CH), 29.0 (CH), 28.9 (CH₂), 19.2 (NCHMe); MS (ESI) m/z 245 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2$ $(\text{M} + \text{H})^+$ 245.2012, found 245.2015 (-1.2 ppm error). Spectroscopic data consistent with those reported in the literature.²

Lab Book Reference: NS5-43

(1*S*,2*R*,4*S*,5*R*)-Bicyclo[2.2.1]heptane-2,5-diol (*S*,*R*,*S*,*R*)-258

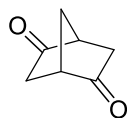


(*S*,*R*,*S*,*R*)-**258**

HSiCl_3 (10.0 mL, 99 mmol, 2.4 eq.) was added to a stirred solution of $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (7.3 mg, 20.0 μmol , 0.05 mol%) and (*S*)-MOP (39.4 mg, 80.0 μmol , 0.20 mol%) in benzene (1 mL) at rt under Ar. After cooling to -3°C , norbornadiene **257** (4.17 mL, 41 mmol, 1.0 eq.) was added dropwise and the reaction mixture was stirred at -3°C for 72 h. Then, the solvent was evaporated under reduced pressure and the crude mixture was dissolved in Et_2O (25 mL). A mixture of dry MeOH (30 mL), dry Et_3N (40 mL) and Et_2O (25 mL) was added dropwise and the mixture was stirred at rt for 16 h. The solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product. The crude product was dissolved in THF (40 mL) and MeOH (40 mL). Then, KHF_2 (16.0 g, 204 mmol, 5.0 eq.) and $\text{H}_2\text{O}_2\cdot\text{urea}$ (29.9 g, 318 mmol, 7.8 eq.) were added and the resulting white suspension was stirred and heated at 60°C for 16 h. Then, MnO_2 (356 mg, 4.1 mmol, 0.1 eq.) was added and the mixture was stirred at rt for 4 h. The solids were removed by filtration and washed with MeOH. The filtrates were combined and evaporated under reduced pressure. The residue was dissolved in H_2O (50 mL) and extracted with 75:25 v/v CHCl_3 -*i*-PrOH (5 x 50 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product as a white solid. Recrystallisation from 10:90 v/v CHCl_3 -hexane gave diol (*S*,*R*,*S*,*R*)-**258** (2.46 g, 46%) as a white solid, mp $152\text{--}154^\circ\text{C}$ (lit.,¹⁵¹ 158°C), IR (ATR) 3271 (OH), 2960, 1349, 1088, 992, 931 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.75-3.67 (m, 2H, OCH), 2.21-2.13 (m, 2H, CH), 1.59-1.36 (m, 6H, CH, OH), 1.31-1.21 (m, 2H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 73.7 (OCH), 43.5 (CH), 37.0 (CH_2), 30.5 (CH_2). Spectroscopic data consistent with those reported in the literature.¹⁵¹

Lab Book Reference: **NS5-10**

(1*S*,4*S*)-Bicyclo[2.2.1]heptane-2,5-dionemethanol (*S,S*)-259

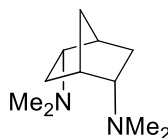


(*S,S*)-259

DMSO (9.75 mL, 137 mmol, 8.8 eq.) was added dropwise to a stirred solution of oxalyl chloride (6.54 mL, 69 mmol, 4.4 eq.) in CH₂Cl₂ (180 mL) at $-78\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 5 min. Then, a solution of diol (*S,R,S,R*)-258 (2.00 g, 15.6 mmol, 1.0 eq.) in CH₂Cl₂ (350 mL) was added and stirred at $-78\text{ }^{\circ}\text{C}$ for 20 min. Et₃N (37.0 mL, 25 mmol, 16 eq.) was added and the solution was stirred and allowed to warm to rt over 16 h. 1 M HCl_(aq) (50 mL) was added and the two layers were separated. The aqueous layer was extracted with 1:1 v/v CH₂Cl₂-Et₂O (4 x 100 mL). The combined organic layers washed with saturated NaHCO_{3(aq)} (100 mL) and brine (100 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 Et₂O-hexane then 67:33 Et₂O-hexane as eluent gave diketone (*S,S*)-259 (1.20 g, 61%) as an off-white solid, mp 117-119 $^{\circ}\text{C}$ (lit.,¹⁵¹ 115-133 $^{\circ}\text{C}$), $[\alpha]_{\text{D}} -3.8$ (c 1.0 in CHCl₃) (lit.,¹⁵¹ -4.2 (c 1.00 in CHCl₃)); *R*_F (67:33 Et₂O-hexane) 0.3; IR (ATR) 2962, 2923, 1752 (C=O), 1736 (C=O), 1406, 1188, 1001, 963, 895 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.02-2.97 (m, 2H, CH), 2.45-2.35 (m, 1H, CH), 2.38-2.34 (m, 1H, CH), 2.23-2.17 (m, 1H, CH), 2.14-2.12 (m, 1H, CH), 2.11-2.09 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 212.5 (C=O), 48.7 (CH), 39.1 (CH₂), 36.5 (CH₂). Spectroscopic data consistent with those reported in the literature.¹⁵¹

Lab Book Reference: **NS5-18**

(1*S*,2*S*,4*S*,5*S*)-*N,N,N,N*-Tetramethylbicyclo[2.2.1]heptane-2,5-diamine (*S,S,S,S*)-253



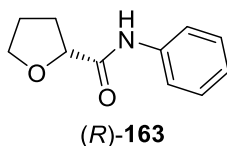
(*S,S,S,S*)-253

HNMe₂ (8.0 mL of a 2.0 M solution in THF, 16 mmol, 2.0 eq.) was added to a stirred solution of Ti(O*i*-Pr)₄ (9.1 g, 9.5 mL, 32 mmol, 4.0 eq.) and diketone (*S,S*)-259 (1.06 g, 8.1 mmol,

1.0 eq.) at rt. The resulting solution was stirred at rt for 20 min. Then, 10% Pd/C (900 mg, 0.85 mmol, 10 mol%) was added. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred vigorously under a balloon of H₂ at rt for 16 h. Then, 1 M NaOH_(aq) (20 mL) was added and the reaction mixture was stirred at rt for 10 min. Then, the two layers were separated and the aqueous layer was extracted with EtOAc (5 x 30 mL). The combined organic layers were flushed through a plug of Celite[®], dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave amine (S,S,S,S)-**253** (1.06 g, 72%) as a colourless oil, [α]_D +38.0 (c 1.0 in CHCl₃) (lit.,¹⁵⁰ +40.6 (c 1.08 in CHCl₃)); IR (ATR) 2976, 2947, 2811, 2762, 1457, 1354, 1214, 1149, 1064, 1034, 911, 805 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.16-2.05 (m, 2H, CH), 2.09-2.07 (m, 12H, NMe), 2.07-1.96 (m, 2H, CH), 1.53-1.38 (m, 4H, CH), 1.35 (s, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 70.2 (NCH), 45.3 (NMe), 40.2 (CH), 37.6 (CH₂), 27.5 (CH₂); MS (ESI) *m/z* 183 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₂₂N₂ (M + H)⁺ 183.1856, found 183.1855 (+0.7 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁵⁰

Lab Book Reference: **NS5-21**

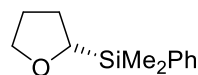
(*R*)-*N*-Phenyltetrahydrofuran-2-carboxamide (*R*)-**163**



Using general procedure E, THF (80 μ L, 72 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in CPME (5 mL) –60 °C for 4 h and PhNCO (238 mg, 219 μ L, 2.0 mmol, 2.0 eq.) at –60 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-Et₂O as eluent gave amide (*R*)-**163** (71 mg, 37%, 78:22 er by CSP-HPLC) as a colourless oil, [α]_D –14.4 (c 0.25 in MeCN) (lit.,¹⁵² +7.41 (c 0.0005 in MeCN) for (*S*)-**163** of 97:3 er); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min⁻¹) 30.0 min (major), 53.5 min (minor). Spectroscopic data consistent with those reported in the literature.¹⁵²

Lab Book Reference: **NS10-62**

(S)-Dimethyl(phenyl)(tetrahydrofuran-2-yl)silane (S)-112

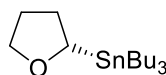


(S)-112

Using general procedure E, THF (80 μ L, 72 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) at $-60\text{ }^{\circ}\text{C}$ for 4 h and PhSiMe_2Cl (341 mg, 336 μ L, 2.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane- CH_2Cl_2 as eluent gave silane (S)-112 (52 mg, 25%, 79:21 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} -11.1$ (c 0.4 in CHCl_3); CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 1.0 mL min^{-1}) 4.2 min (minor), 4.4 min (major).

Lab Book Reference: **NS5-69**

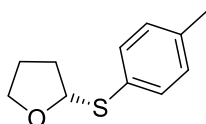
(S)-Tributyl(tetrahydrofuran-2-yl)stannane (S)-158



(S)-158

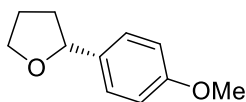
Using general procedure E, THF (160 μ L, 144 mg, 2.0 mmol, 1.0 eq.), *s*-BuLi (2.2 mL of a 1.2 M solution in hexane, 2.6 mmol, 1.3 eq.) and (+)-sparteine surrogate (504 mg, 2.6 mmol, 1.3 eq.) in CPME (10 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and Bu_3SnCl (1.30 g, 1.09 mL, 4.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product. Purification by flash column chromatography on silica with 75:25 hexane- CH_2Cl_2 then 50:50 hexane- CH_2Cl_2 as eluent gave α -stannyl THF (S)-158 (326 mg, 46%, 78:22 er determined by conversion into ketone (R)-107 using Sn-Li exchange and trapping with Weinreb amide 115 and analysis by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +4.4$ (c 0.50 in CHCl_3).

Lab Book Reference: **NS12-27**

(S)-2-(*p*-Tolylthio)tetrahydrofuran (S)-166**(S)-166**

Using general procedure E, THF (80 μ L, 72 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in CPME (5 mL) -60 $^{\circ}$ C for 4 h and *p*-tolylidysulfide (492 mg, 2.0 mmol, 2.0 eq.) at -60 $^{\circ}$ C for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 hexane-CH₂Cl₂ then 90:10 hexane-CH₂Cl₂ as eluent gave sulfide (S)-**166** (81 mg, 42%, 79:21 er by CSP-HPLC) as a colourless oil, $[\alpha]_D +140.8$ (*c* 0.25 in CHCl₃); CSP-HPLC: Chiralcel AD-H (97:3 hexane-*i*-PrOH, 1.0 mL min⁻¹) 8.4 min (major), 10.9 min (minor).

Lab Book Reference: **NS10-63**

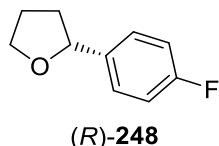
(R)-2-(4-Methoxyphenyl)tetrahydrofuran (R)-179**(R)-179**

Using general procedure C, THF stannane (S)-**158** (100 mg, 0.28 mmol, 1.0 eq., 78:22 er), *n*-BuLi (135 μ L of a 2.3 M solution in hexanes, 0.31 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.36 mmol, 1.3 eq.), Pd(OAc)₂ (2.5 mg, 4 mol%), *t*-Bu₃PHBF₄ (6.4 mg, 8 mol%) and 4-bromomethoxybenzene (68 mg, 0.36 mmol, 1.3 eq.) at 40 $^{\circ}$ C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc then 95:5 hexane-EtOAc as eluent gave α -aryl THF (R)-**179** (53 mg, 61%, 78:22 er by CSP-HPLC) as a colourless oil, $[\alpha]_D -7.6$ (*c* 0.2 in CHCl₃), *R*_F (90:10 hexane-EtOAc) 0.3; IR (ATR) 2956, 2899, 1613, 1513, 1462, 1301, 1174, 1060, 1035, 829, 540 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.26 (m, 2H, Ar), 6.91-6.86 (m, 2H, Ar), 4.84 (dd, *J* = 7.5, 6.5 Hz, 1H, OCH), 4.09 (ddd, *J* = 8.0, 7.5, 6.5 Hz, 1H, OCH), 3.92 (ddd, *J* = 8.0, 8.0, 6.0 Hz, 1H (app td), OCH), 3.80 (s, 3H, OMe), 2.28 (dddd, *J* = 12.0, 8.0, 6.5, 5.0 Hz, 1H, CH), 2.10-1.93 (m, 2H, CH), 1.80 (dddd, *J* = 12.0, 8.5, 8.0, 7.5 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.9 (*ipso*-Ar), 135.4 (*ipso*-Ar), 127.1 (Ar), 113.8 (Ar), 80.6 (OCH), 68.6 (OCH₂), 55.4 (OMe), 34.6 (CH₂), 26.2 (CH₂); MS (ESI) *m/z* 179 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₄O₂ (M + H)⁺ 179.1067, found 179.1066 (+0.3 ppm

error). Chiralcel OD-H (95:5 hexane-*i*-PrOH, 0.5 mL min⁻¹) 19.4 min (minor), 20.0 min (major).

Lab Book Reference: **NS12-30**

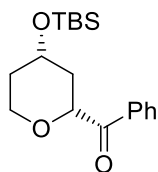
(*R*)-2-(4-Fluorophenyl)tetrahydrofuran (*R*)-248



Using general procedure C, THF stannane (*S*)-**158** (98 mg, 0.27 mmol, 1.0 eq., 78:22 er), *n*-BuLi (130 μ L of a 2.3 M solution in hexanes, 0.30 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (506 μ L of a 0.7 M solution in THF, 0.36 mmol, 1.3 eq.), Pd(OAc)₂ (2.4 mg, 4 mol%), *t*-Bu₃PBHF₄ (6.1 mg, 8 mol%) and 4-fluorobromobenzene (40 mg, 0.36 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 75:25 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ as eluent gave α -aryl THF (*R*)-**248** (25 mg, 56%, 78:22 er by CSP-HPLC) as a colourless oil, [α]_D +19.0 (*c* 0.5 in CH₂Cl₂) (lit.,¹⁹⁷ +37.9 (*c* 0.75 in CH₂Cl₂) for (*R*)-**248** of 98:2 er), *R*_F (50:50 hexane-CH₂Cl₂) 0.3; IR (ATR) 2975, 2870, 1605, 1508, 1460, 1358, 1222, 1156, 1015, 831, 556, 531 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.21 (m, 2H, Ar), 7.06-6.93 (m, 2H, Ar), 4.84 (dd, *J* = 7.0, 7.0 Hz (app t), 1H, OCH), 4.07 (ddd, *J* = 8.5, 7.0, 7.0 Hz (app dt), 1H, OCH), 3.97-3.86 (m, 1H, OCH), 2.29 (dddd, *J* = 7.0, 7.0, 7.0, 6.0 Hz (app qd), 1H, CH), 2.05-1.94 (m, 2H, CH), 1.82-1.65 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 162.1 (d, *J* = 245.0 Hz, *ipso*-Ar), 139.2 (d, *J* = 3.0 Hz, Ar), 127.4 (d, *J* = 8.0 Hz, Ar), 115.2 (d, *J* = 21.5 Hz, Ar), 80.2 (OCH), 68.7 (OCH₂), 34.8 (CH₂), 26.1 (CH₂); ¹⁹F NMR (376 MHz, CDCl₃) δ -115.8 (s); MS (APCI) *m/z* 167 [(*M* + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₁₀H₁₁FO (*M* + H)⁺ 167.0867, found 167.0866 (-0.3 ppm error); Chiralcel AD-H (99:1 hexane-*i*-PrOH, 1.0 mL min⁻¹) 9.2 min (major), 10.7 min (minor). Spectroscopic data consistent with those reported in the literature.¹⁹⁷

Lab Book Reference: **NS12-32**

(4-((*tert*-Butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)(phenyl)methanone (R,S)-260



(R,S)-260

Using general procedure E, TBS-protected THP **118** (108 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) and in hexane (5 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and Weinreb amide **115** (330 mg, 304 μL , 2.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone as eluent gave ketone (R,S)-**260** (20 mg, 6%, 60:40 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +0.8$ (*c* 0.5 in CHCl_3); R_{F} (98:2 CH_2Cl_2 -acetone) 0.5; IR (ATR) 2954, 2928, 2856, 1693 (C=O), 1463, 1449, 1251, 1087, 971, 900, 835, 774, 692, 670, 642, 565 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 7.5$ Hz, 2H, Ph), 7.57 (dd, $J = 7.5, 7.5$ Hz (app t), 1H, Ph), 7.46 (dd, $J = 7.5, 7.5$ Hz (app t), 2H, Ph), 4.63 (dd, $J = 12.0, 2.0$ Hz, 1H, OCH), 4.20 (ddd, $J = 12.0, 4.5, 2.0$ Hz, 1H, OCH), 3.98-3.89 (m, 1H, OCH), 3.58 (ddd, $J = 12.0, 12.0, 2.0$ Hz (app td), 1H, OCH), 2.19-2.10 (m, 1H, CH), 1.90-1.81 (m, 1H, CH), 1.75-1.61 (m, 2H, CH), 0.88 (s, 9H, CMe_3), 0.08 (s, 3H, SiMe), 0.06 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 197.5 (C=O), 135.1 (*ipso*-Ph), 133.5 (Ph), 129.1 (Ph), 128.7 (Ph), 79.2 (OCH), 68.7 (OCH), 66.7 (OCH₂), 38.7 (CH₂), 35.9 (CH₂), 25.9 (CMe_3), 18.2 (CMe_3), -4.4 (SiMe) (one SiMe resonance not resolved); MS (ESI) m/z 321 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{28}\text{O}_3\text{Si}$ ($\text{M} + \text{H})^+$ 321.1882, found 321.1888 (-2.3 ppm error); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) 3.1 min (major), 5.5 min (minor). The stereochemistry of the major product is only tentatively assigned.

Lab Book Reference: **NS4-21**

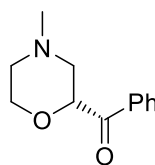
(R)-(4-Methylmorpholin-2-yl)(phenyl)methanone (R)-128**(R)-128**

Table 3.3, entry 1:

Using general procedure E, *N*-methyl morpholine **125** (102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and benzaldehyde (201 mg, 210 μL , 2.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude alcohols. Then, DMP (848 mg, 2.0 mmol, 2.0 eq.) was added to the crude alcohols in CH_2Cl_2 (2 mL) and the solution was stirred at rt for 1 h. Saturated NaHCO_3 (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98.5:1.4:0.1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave morpholine (R)-**128** (109 mg, 53%, 63:37 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}}^{25} +9.1$ (c 1.0 in CHCl_3); R_{F} (90:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.8; IR (ATR) 2939, 2795, 1689 (C=O), 1448, 1118, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.02-7.94 (m, 2H, Ph), 7.61-7.55 (m, 1H, Ph), 7.51-7.42 (m, 2H, Ph), 4.93 (dd, $J = 11.5, 2.5$ Hz, 1H, OCH), 4.09 (ddd, $J = 11.5, 2.5, 2.5$ Hz (app dt), 1H, OCH), 3.84 (ddd, $J = 11.5, 11.5, 2.5$ Hz (app td), 1H, OCH), 3.01 (dd, $J = 11.5, 2.5$ Hz, 1H, NCH), 2.69 (dd, $J = 11.5, 2.5$ Hz, 1H, NCH), 2.33 (s, 3H, NMe), 2.26 (ddd, $J = 11.5, 11.5, 2.5$ Hz (app td), 1H, NCH), 2.21 (dd, $J = 11.5, 11.5$ Hz (app t), 1H, NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 196.9 (C=O), 135.1 (*ipso*-Ph), 133.6 (Ph), 129.0 (Ph), 128.8 (Ph), 78.1 (OCH), 67.1 (OCH_2), 56.9 (NCH_2), 54.7 (NCH_2), 46.4 (NMe); MS (ESI) m/z 206 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_2$ ($\text{M} + \text{H})^+$ 206.1176, found 206.1171 (+2.4 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) 7.5 min (major), 19.5 min (major).

Lab Book Reference: **NS2-21**

Table 3.3, entry 2:

Using general procedure E, *N*-methyl morpholine **125** (102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) at $-78\text{ }^{\circ}\text{C}$ for 4 h and benzaldehyde (201 mg, 210 μL ,

2.0 mmol, 2.0 eq.) at $-78\text{ }^{\circ}\text{C}$ for 1 h gave the crude alcohols. Then, DMP (848 mg, 2.0 mmol, 2.0 eq.) was added to the crude alcohols in CH_2Cl_2 (2 mL) and the solution was stirred at rt for 1 h. Saturated NaHCO_3 (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98.5:1.4:0.1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave morpholine (*R*)-**128** (80 mg, 39%, 65:35 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +10.6$ (*c* 1.0 in CHCl_3); CSP-HPLC: Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) 7.5 min (major), 19.5 min (major).

Lab Book Reference: **NS2-22**

Table 3.3, entry 3:

Using general procedure E, *N*-methyl morpholine **125** (102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and (+)-sparteine (304 mg, 1.3 mmol, 1.3 eq.) at $-60\text{ }^{\circ}\text{C}$ for 4 h and benzaldehyde (201 mg, 210 μL , 2.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude alcohols. Then, DMP (848 mg, 2.0 mmol, 2.0 eq.) was added to the crude alcohols in CH_2Cl_2 (2 mL) and the solution was stirred at rt for 1 h. Saturated NaHCO_3 (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98.5:1.4:0.1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ gave the crude product which did not contain any desired product (*R*)-**128** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS2-29**

Table 3.3, entry 4:

Using general procedure E, *N*-methyl morpholine **125** (102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and (+)-sparteine (304 mg, 1.3 mmol, 1.3 eq.) at $-78\text{ }^{\circ}\text{C}$ for 4 h and benzaldehyde (201 mg, 210 μL , 2.0 mmol, 2.0 eq.) at $-78\text{ }^{\circ}\text{C}$ for 1 h gave the crude alcohols. Then, DMP (848 mg, 2.0 mmol, 2.0 eq.) was added to the crude alcohols in CH_2Cl_2 (2 mL) and the solution was stirred at rt for 1 h. Saturated NaHCO_3 (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98.5:1.4:0.1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave the

crude product which did not contain any desired product (*R*)-**128** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS2-30**

Table 3.4, entry 1:

n-BuLi (50 μL of a 2.0 M solution in hexane, 0.22 mmol, 1.0 eq.) was added dropwise to a stirred solution of enantioenriched stannane (*S*)-**228** (45 mg, 0.22 mmol, 1.0 eq.) and TMEDA (18 μL , 1.0 mmol, 0.22 eq.) in hexane (0.6 mL) at $-78\text{ }^\circ\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 30 min. Then, Weinreb amide **115** (20 mg, 22 μL , 0.22 mmol, 1.0 eq.) was added. The resulting solution was stirred at $-20\text{ }^\circ\text{C}$ for 10 min and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic layers were dried (Mg_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:1.5:0.5 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave ketone (*R*)-**128** (40 mg, 74%, 63:37 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +7.2$ (*c* 1.0 in CHCl_3); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) 9.6 min (major), 25.9 min (minor).

Lab Book Reference: **NS4-20**

Table 3.4, entry 2:

n-BuLi (95 μL of a 2.0 M solution in hexane, 0.45 mmol, 1.0 eq.) was added dropwise to a stirred solution of enantioenriched stannane (*S*)-**228** (96 mg, 0.45 mmol, 1.0 eq., 63:37 er) and TMEDA (95 μL , 0.45 mmol, 1.0 eq.) in hexane (1.2 mL) at $-40\text{ }^\circ\text{C}$ under Ar. The resulting solution was stirred at $-40\text{ }^\circ\text{C}$ for 30 min. Then, Weinreb amide **115** (59 mg, 58 μL , 0.45 mmol, 1.0 eq.) was added. The resulting solution was stirred at $-40\text{ }^\circ\text{C}$ for 10 min and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic layers were dried (Mg_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:1.5:0.5 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave ketone (*R*)-**128** (77 mg, 83%, 61:39 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +6.0$ (*c* 1.0 in CHCl_3); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) 9.4 min (major), 24.9 min (minor).

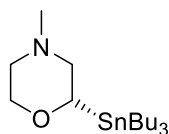
Lab Book Reference: **NS4-19**

Table 3.4, entry 3:

n-BuLi (164 μ L of a 2.0 M solution in hexane, 0.41 mmol, 1.0 eq.) was added dropwise to a stirred solution of enantioenriched stannane (*S*)-**228** (160 mg, 0.41 mmol, 1.0 eq., 63:37 er) and TMEDA (62 μ L, 0.41 mmol, 1.0 eq.) in hexane (2 mL) at $-20\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-20\text{ }^{\circ}\text{C}$ for 30 min. Then, Weinreb amide **115** (70 mg, 74 μ L, 0.41 mmol, 1.0 eq.) was added. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic layers were dried (Mg_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98.4:1.5:0.1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave ketone *rac*-**128** (74 mg, 89%, 50:50 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} 0.0$ (*c* 1.0 in CHCl_3); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) 8.4 min, 21.4 min.

Lab Book Reference: **NS4-15**

(*S*)-4-Methyl-2-(tributylstannyl)morpholine (*S*)-228

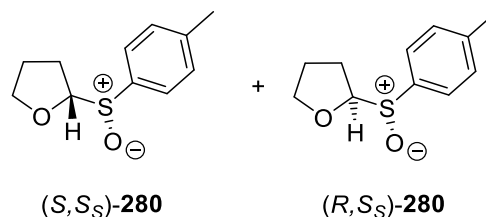


(*S*)-228

Using general procedure E, *N*-methyl morpholine **125** (220 mg, 2.0 mmol, 1.0 eq.), *s*-BuLi (2 mL of a 1.3 M solution in hexane, 2.6 mmol, 1.3 eq.) and (+)-sparteine surrogate (504 mg, 2.6 mmol, 1.3 eq.) in hexane (10 mL) at $-60\text{ }^{\circ}\text{C}$ for 1 h and Bu_3SnCl (1.95 g, 1.62 mL, 4.0 mmol) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:0.9:0.1 to 97.5:2:0.5 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave α -stannyl morpholine (*S*)-**228** (164 mg, 22%, 67:33 er determined by conversion into ketone (*R*)-**128** using Sn-Li exchange and trapping with Weinreb amide **115** and analysis by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} +3.5$ (*c* 1.0 in CHCl_3).

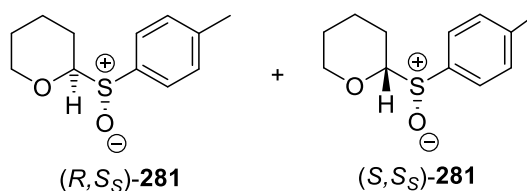
Lab Book Reference: **NS4-14**

Attempted Synthesis of 2-(*p*-Tolylsulfinyl)tetrahydrofuran (*S,S*)-**280** and (*R,S*)-**280**



s-BuLi (1.42 mL of a 1.4 M solution in hexane, 2.0 mmol, 1.0 eq.) was added to a stirred solution of THF (10 mL) at $-60\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-60\text{ }^{\circ}\text{C}$ for 4 h. Then, a freshly prepared solution of MgBr_2 in Et_2O (prepared using general procedure G from 1,2-dibromoethane (242 μL , 2.6 mmol) and Mg turnings (116 mg, 4.8 mmol) in Et_2O (5 mL)) was added and stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and then allowed to warm to $0\text{ }^{\circ}\text{C}$ and stirred at $0\text{ }^{\circ}\text{C}$ for 30 min. Then, a solution of Andersen's sulfinate (*S_S*)-**264** (1.18 g, 4.0 mmol, 2.0 eq.) in Et_2O (10 mL) was added at $-78\text{ }^{\circ}\text{C}$. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (20 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O ($3 \times 30\text{ mL}$). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which did not contain α -sulfinyl THFs (*S,S*)-**280** and (*R,S*)-**280** (by ^1H NMR spectroscopy). Lab Book Reference: **NS7-17**

2-(*p*-Tolylsulfinyl)tetrahydro-2*H*-pyran (*R,S*)-**281** and (*S,S*)-**281**



n-BuLi (0.43 mL of a 2.3 M solution in hexane, 1.1 mmol, 1.1 eq.) was added to a stirred solution of α -stannyl THP **197** (375 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Then, a freshly prepared solution of MgBr_2 in Et_2O (prepared using general procedure G from 1,2-dibromoethane (103 μL , 1.2 mmol) and Mg turnings (39 mg, 1.6 mmol) in Et_2O (2.5 mL)) was added and stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and then allowed to warm to $0\text{ }^{\circ}\text{C}$ and stirred at $0\text{ }^{\circ}\text{C}$ for 30 min. Then, a solution of Andersen's sulfinate (*S_S*)-**264** (1.18 g, 4.0 mmol, 2.0 eq.) in Et_2O (10 mL) was added. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h and then allowed to warm to rt

and stirred at rt for 16 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (20 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained a 65:35 mixture (by ^1H NMR spectroscopy) of α -sulfinyl THPs (*S,S*)-**281** and (*R,S*)-**281**. Purification by flash column chromatography on silica with 99:1 to 90:10 CH_2Cl_2 -acetone as eluent gave α -sulfinyl THPs (*S,S*)-**281** (46 mg, 10%) as a yellow oil, R_F (90:10 CH_2Cl_2 -acetone) 0.2; ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.49 (m, 2H, Ar), 7.33-7.24 (m, 2H, Ar), 4.16 (dd, $J = 7.5, 3.5$ Hz, 1H, OCH), 4.01 (ddd, $J = 11.5, 5.5, 3.5$ Hz, 1H, OCH), 3.56 (ddd, $J = 11.5, 8.0, 3.5$ Hz, 1H, OCH), 2.39 (s, 3H, Me), 2.13-2.00 (m, 1H, CH), 2.02-1.90 (m, 1H, CH), 1.86-1.76 (m, 1H, CH), 1.70-1.53 (m, 3H, CH) and α -sulfinyl THP (*R,S*)-**281** (26 mg, 6%) as a yellow oil, R_F (90:10 CH_2Cl_2 -acetone) 0.2; ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.50 (m, 2H, Ar), 7.32-7.28 (m, 2H, Ar), 4.28 (dd, $J = 8.5, 3.0$ Hz, 1H, OCH), 4.12 (ddd, $J = 12.0, 4.0, 4.0$ Hz (app dt), 1H, OCH), 3.60 (ddd, $J = 12.0, 8.5, 4.0$ Hz, 1H, OCH), 2.40 (s, 3H, CMe), 1.92-1.38 (m, 6H, CH). No further characterisation was possible due to degradation of the products. The stereochemistry of the products is only tentatively assigned.

Lab Book Reference: **NS7-65**

s-BuLi (1.85 mL of a 1.4 M solution in hexane, 2.6 mmol, 1.3 eq.) was added to a stirred solution of THP (172 mg, 196 μmol , 2.0 mmol, 1.0 eq.) and TMEDA (380 μL , 1.3 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the solution was cooled to -78 °C and a freshly prepared solution of MgBr_2 in Et_2O (prepared using general procedure G from 1,2-dibromoethane (242 μL , 2.8 mmol) and Mg turnings (116 mg, 4.8 mmol) in Et_2O (10 mL)) was added and stirred at -78 °C for 30 min and then allowed to warm to 0 °C and stirred at 0 °C for 30 min. Then, a solution of Andersen's sulfinate (*S_S*)-**264** (1.18 g, 4.0 mmol, 2.0 eq.) in Et_2O (10 mL) was added. The resulting solution was stirred at -78 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (20 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained only traces of the desired products (by ^1H NMR spectroscopy).

Lab Book Reference: **NS7-18**

Table 2.3 entry 1:

10% Pd/alumina (70 mg, 0.05 mmol, 10 mol%) was added to a stirred solution of α -sulfinyl DHP (*S_S*)-**282** (112 mg, 0.50 mmol, 1.0 eq.) in MeOH (4 mL) at rt. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred vigorously under a balloon of H₂ at rt for 3 h. The solids were removed by filtration through Celite[®] and washed with MeOH (10 mL). The filtrate was evaporated under reduced pressure to give the crude product which contained only starting α -sulfinyl DHP (*S_S*)-**282** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-81a**

Table 2.3 entry 2:

10% Pd/alumina (70 mg, 0.05 mmol, 10 mol%) was added to a stirred solution of α -sulfinyl DHP (*S_S*)-**282** (112 mg, 0.50 mmol, 1.0 eq.) in EtOAc (4 mL) at rt. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred vigorously under a balloon of H₂ at rt for 3 h. The solids were removed by filtration through Celite[®] and washed with MeOH (10 mL). The filtrate was evaporated under reduced pressure to give the crude product which contained only starting α -sulfinyl DHP (*S_S*)-**282** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-82**

Table 2.3 entry 3:

10% Pd/alumina (70 mg, 0.05 mmol, 10 mol%) was added to a stirred solution of α -sulfinyl DHP (*S_S*)-**282** (112 mg, 0.50 mmol, 1.0 eq.) in EtOAc (4 mL) at rt. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred vigorously under a balloon of H₂ at rt for 3 h. The solids were removed by filtration through Celite[®] and washed with MeOH (10 mL). The filtrate was evaporated under reduced pressure to give the crude product which contained only starting α -sulfinyl DHP (*S_S*)-**282** (by ¹H NMR spectroscopy).

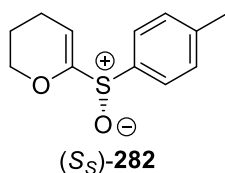
Lab Book Reference: **NS6-81b**

Table 2.3 entry 4:

10% Rh/alumina (70 mg, 0.05 mmol, 10 mol%) was added to a stirred solution of α -sulfinyl DHP (*S_S*)-**282** (112 mg, 0.50 mmol, 1.0 eq.) in EtOAc (4 mL) at rt. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred vigorously under a balloon of H₂ at rt for 3 h. The solids were removed by filtration through Celite® and washed with MeOH (10 mL). The filtrate was evaporated under reduced pressure to give the crude product which contained only starting α -sulfinyl DHP (*S_S*)-**282** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-84**

(*S*)-5-(*p*-Tolylsulfinyl)-2,3-dihydropyran (*S_S*)-282****



n-BuLi (3.51 mL of a 2.3 M solution in hexane, 8.1 mmol, 1.2 eq.) was added dropwise to a stirred solution of dihydrofuran **198** (734 μ L, 679 mg, 8.1 mmol, 1.2 eq.) in Et₂O (10 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h and then stirred and heated at 35 °C for 1 h. Then, a freshly prepared solution of MgBr₂ (prepared using general procedure G from 1,2-dibromoethane (762 μ L, 8.9 mmol, 1.3 eq.) and Mg turnings (430 mg, 18 mmol, 2.6 eq.) in Et₂O (5 mL)) was added at 35 °C and the reaction mixture was stirred and heated at 35 °C for 1 h. After cooling to -78 °C, a solution of Andersen's sulfinat (*S_S*)-**264** (2.00 g, 1.8 mmol, 1.0 eq.) in Et₂O (10 mL) was added and the resulting solution was stirred at -78 °C for 2 h and then at rt for 16 h. Then, saturated NH₄Cl_(aq) (20 mL) and 10% NaHCO_{3(aq)} (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 CH₂Cl₂-acetone as eluent gave vinyl sulfoxide (*S_S*)-**282** (276 mg, 67%, er not determined) as a white solid, mp 93-95 °C; *R_F* (90:10 hexane-EtOAc) 0.1; [α]_D +84.6 (*c* 0.5 in CHCl₃); IR (ATR) 2928, 1651 (C=C), 1345, 1275, 1091, 1076, 1049, 907, 842, 811, 625 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.0 Hz, 2H, Ar), 7.28 (d, *J* = 8.0 Hz, 2H, Ar), 5.68 (dd, *J* = 4.0, 4.0 Hz (app t), 1H, OC=CH), 4.05 (ddd, *J* = 10.5, 6.0, 4.0 Hz, 1H, OCH), 3.97 (ddd, *J* = 10.5, 7.0, 4.0 Hz, 1H, OCH), 2.38 (s, 3H, Me), 2.25-2.17 (m, 2H, CH), 1.87-1.74 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.0

(OC=CH), 141.6 (*ipso*-Ar), 138.9 (*ipso*-Ar), 129.8 (Ar), 125.3 (Ar), 104.9 (OC=CH), 68.6 (OCH₂), 22.0 (CH₂), 21.5 (Me), 20.6 (CH₂); MS (ESI) *m/z* 223 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₄O₂S (M + H)⁺ 223.0787, found 223.0784 (+1.4 ppm error).

Lab Book Reference: **NS6-77**

4-Methyl-2-(*p*-tolylsulfinyl)morpholine (*S,S*)-**283** and (*R,S*)-**283**

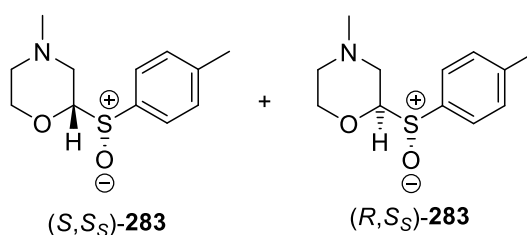


Table 2.4 entry 3:

s-BuLi (2.84 mL of a 1.3 M solution in hexane, 3.6 mmol, 1.2 eq.) was added to a solution of *N*-methyl morpholine **125** (300 mg, 330 μmol, 3.0 mmol, 1.0 eq.) and TMEDA (540 μL, 3.6 mmol, 1.2 eq.) in hexane (15 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the solution was cooled to −78 °C and a freshly prepared solution of MgBr₂ in Et₂O (prepared using general procedure G from 1,2-dibromoethane (0.76 mL, 4.2 mmol) and Mg turnings (174 mg, 7.2 mmol) in Et₂O (5 mL)) was added and stirred at −78 °C for 30 min and then allowed to warm to 0 °C and stirred at 0 °C for 30 min. Then, the organomagnesium species was added dropwise to a precooled solution of Andersen's sulfinate (*S*)-**264** (1.77 g, 6.0 mmol, 2.0 eq.) in Et₂O (10 mL) at −78 °C. The resulting solution was stirred at −78 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Saturated NH₄Cl_(aq) (20 mL) and 10% NaHCO_{3(aq)} (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product which contained a 60:40 mixture (by ¹H NMR spectroscopy) of α-sulfinyl morpholines (*S,S*)-**283** and (*R,S*)-**283**. Purification by flash column chromatography on silica with 98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) and then 97.5:2:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α-sulfinyl morpholine (*S,S*)-**283** (281 mg, 39%, 95:5 er by CSP-HPLC) as a white solid, mp 70-72 °C; *R*_F (97.5:2:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.3; [α]_D +70.1 (*c* 0.5 in CHCl₃); IR (ATR) 2940, 2874, 2792, 1633, 1493, 1453, 1281, 1207, 1142, 1113, 1082, 1032, 1016, 846, 809, 619 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 8.0 Hz, 2H, Ar), 7.33 (d, *J* = 8.0 Hz, 2H, Ar), 4.37 (dd, *J* = 5.0, 3.0 Hz, 1H, OCH), 4.25 (ddd, *J*

= 11.5, 8.0, 3.0 Hz, 1H, OCH), 3.84 (ddd, J = 11.5, 5.5, 3.0 Hz, 1H, OCH), 2.54 (dddd, J = 12.0, 5.5, 3.0, 1.5 Hz, 1H, NCH), 2.42 (s, 3H, NMe), 2.46-2.38 (m, 2H, NCH), 2.27 (ddd, J = 12.0, 5.0, 1.5 Hz, 1H, NCH), 2.21 (s, 3H, Me); ^{13}C NMR (100.6 MHz, CDCl_3) δ 142.3 (*ipso*-Ar), 137.8 (*ipso*-Ar), 130.1 (Ar), 125.6 (Ar), 95.5 (OCH), 65.5 (OCH_2), 54.5 (NCH_2), 53.5 (NCH_2), 46.4 (NMe), 21.7 (Me); MS (ESI) m/z 262 $[(\text{M} + \text{Na})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{S}$ ($\text{M} + \text{Na})^+$ 262.0872, found 262.0873 (−0.2 ppm error); CSP-HPLC: Chiralcel OD-H (90:10 hexane-*i*-PrOH, 1.0 mL min $^{-1}$) 22.8 min (minor), 26.4 min (major), and α -sulfinyl morpholine (*R,S*)-**283** (208 mg, 29%, 95:5 er by CSP-HPLC) as a white solid, mp 49-51 °C; R_F (97.5:2:0.5 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.25; $[\alpha]_D^{+184.3}$ (c 0.5 in CHCl_3); IR (ATR) 2939, 2872, 2794, 1454, 1280, 1143, 1110, 1035, 907, 849, 812, 625 cm $^{-1}$; ^1H NMR (400 MHz, CDCl_3) δ 7.56 (d, J = 8.0 Hz, 2H, Ar), 7.32 (d, J = 8.0 Hz, 2H, Ar), 4.22 (dd, J = 35, 3.5 Hz (app t), 1H, OCH), 4.12 (ddd, J = 11.5, 9.0, 3.5 Hz, 1H, OCH), 3.73 (ddd, J = 11.5, 3.5, 3.5 Hz (app td), 1H, OCH), 3.26 (ddd, J = 12.5, 3.5, 1.5 Hz, 1H, NCH), 2.70-2.59 (m, 1H, NCH), 2.53 (dd, J = 12.5, 3.5 Hz, 1H, NCH), 2.46-2.31 (m, 7 H, NMe, Me, NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 141.8 (*ipso*-Ar), 139.4 (*ipso*-Ar), 129.9 (Ar), 125.0 (Ar), 94.3 (OCH), 65.7 (OCH_2), 54.3 (NCH_2), 52.3 (NCH_2), 46.4 (NMe), 21.6 (Me); MS (ESI) m/z 262 $[(\text{M} + \text{Na})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{S}$ ($\text{M} + \text{Na})^+$ 262.0872, found 262.0872 (+0.1 ppm error), CSP-HPLC: CSP-HPLC: Chiralcel OD-H (85:15 hexane-*i*-PrOH, 1.0 mL min $^{-1}$) 18.3 min (major), 21.4 min (minor).

Lab Book Reference: **NS8-67**

s-BuLi (8.1 mL of a 1.3 M solution in hexane, 11 mmol, 1.3 eq.) was added to a stirred solution of *N*-methyl morpholine **125** (817 mg, 890 μmol , 8.1 mmol, 1.0 eq.) and TMEDA (1.57 mL, 11 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the solution was cooled to −78 °C and a freshly prepared solution of MgBr_2 in Et_2O (prepared using general procedure G from 1,2-dibromoethane (0.98 mL, 11 mmol) and Mg turnings (324 mg, 13 mmol) in Et_2O (10 mL)) was added and stirred at −78 °C for 30 min and then allowed to warm to 0 °C and stirred at 0 °C for 30 min. Then, a solution of Andersen's sulfinate (*S*)-**264** (2.40 g, 8.1 mmol, 1.0 eq.) in Et_2O (10 mL) was added. The resulting solution was stirred at −78 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (20 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 $\times$ 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained a 67:33 mixture (by ^1H

NMR spectroscopy) of α -sulfinyl morpholines (*S,S*)-**283** and (*R,S*)-**283**. Purification by flash column chromatography on silica with 98:1.7:0.3 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -sulfinyl morpholine (*S,S*)-**283** (465 mg, 24%, 69:31 er by CSP-HPLC) as a white solid, $[\alpha]_D +34.4$ (c 0.5 in CHCl₃); CSP-HPLC: Chiralcel OD-H (90:10 hexane-*i*-PrOH, 1.0 mL min⁻¹) 19.3 min (minor), 21.1 min (major) and α -sulfinyl morpholine (*R,S*)-**283** (226 mg, 12%, 68:32 er by CSP-HPLC) as a white solid, $[\alpha]_D +77.9$ (c 0.5 in CHCl₃); CSP-HPLC: Chiralcel OD-H (85:15 hexane-*i*-PrOH, 1.0 mL min⁻¹) 18.9 min (major), 21.9 min (minor).

Lab Book Reference: **NS6-83**

Table 2.4 entry 1:

s-BuLi (8.1 mL of a 1.3 M solution in hexane, 11 mmol, 1.3 eq.) was added to a stirred solution of *N*-methyl morpholine **125** (817 mg, 890 μ mol, 8.1 mmol, 1.0 eq.) and TMEDA (1.57 mL, 11 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the solution was cooled to -78 °C and a freshly prepared solution of MgBr₂ in Et₂O (prepared using general procedure G from 1,2-dibromoethane (0.98 mL, 11 mmol) and Mg turnings (324 mg, 13 mmol) in Et₂O (10 mL)) was added and stirred at -78 °C for 30 min and then allowed to warm to 0 °C and stirred at 0 °C for 30 min. After cooling to -78 °C, a solution of Andersen's sulfinat (*S*)-**264** (2.40 g, 8.1 mmol, 1.0 eq.) in Et₂O (10 mL) was added. The resulting solution was stirred at -78 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Saturated NH₄Cl_(aq) (20 mL) and 10% NaHCO_{3(aq)} (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product which contained a 67:33 mixture (by ¹H NMR spectroscopy) of α -sulfinyl morpholines (*S,S*)-**283** and (*R,S*)-**283**. Purification by flash column chromatography on silica with 98:1.8:0.2 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -sulfinyl morpholine (*S,S*)-**283** (619 mg, 32%, 87:13 er by CSP-HPLC) as a white solid, $[\alpha]_D +40.0$ (c 0.5 in CHCl₃); CSP-HPLC: Chiralcel OD-H (90:10 hexane-*i*-PrOH, 1.0 mL min⁻¹) 23.1 min (minor), 25.5 min (major), and α -sulfinyl morpholine (*R,S*)-**283** (187 mg, 10%, 88:12 er by CSP-HPLC) as a white solid, $[\alpha]_D +148.0$ (c 1.0 in CHCl₃); CSP-HPLC: Chiralcel OD-H (85:15 hexane-*i*-PrOH, 1.0 mL min⁻¹) 22.1 min (major), 26.2 min (minor).

Lab Book Reference: **NS6-88**

Table 2.4 entry 2:

s-BuLi (1.84 mL of a 1.3 M solution in hexane, 2.4 mmol, 1.2 eq.) was added to a solution of *N*-methyl morpholine **125** (200 mg, 220 μ mol, 2.0 mmol, 1.2 eq.) and TMEDA (360 μ L, 2.4 mmol, 1.2 eq.) in hexane (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the solution was cooled to –78 °C and a freshly prepared solution of MgBr₂ in Et₂O (prepared using general procedure G from 1,2-dibromoethane (242 μ L, 2.8 mmol) and Mg turnings (116 mg, 4.7 mmol) in Et₂O (5 mL)) was added and stirred at –78 °C for 30 min and then allowed to warm to 0 °C and stirred at 0 °C for 30 min to give the organomagnesium species.

Half of the organomagnesium species from above was added dropwise to a precooled solution of Andersen's sulfinate (*S_S*)-**264** (589 mg, 2.0 mmol, 2.0 eq.) in Et₂O (5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Saturated NH₄Cl_(aq) (20 mL) and 10% NaHCO_{3(aq)} (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product which contained a 63:37 mixture (by ¹H NMR spectroscopy) of diastereomeric α -sulfinyl morpholines (*S,S_S*)-**283** and (*R,S_S*)-**283**. Purification by flash column chromatography on silica with 98:1.8:0.2 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave α -sulfinyl morpholine (*S,S_S*)-**283** (37 mg, 15%, 96:4 er by CSP-HPLC) as a white solid, [α]_D +57.0 (*c* 0.5 in CHCl₃); CSP-HPLC: Chiralcel OD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{–1}) 23.1 min (minor), 25.1 min (major) and α -sulfinyl morpholine (*R,S_S*)-**283** (19 mg, 8%, 88:12 er by CSP-HPLC) as a white solid, [α]_D +169.3 (*c* 0.5 in CHCl₃); CSP-HPLC: Chiralcel OD-H (85:15 hexane-*i*-PrOH, 1.0 mL min^{–1}) 24.2 min (minor), 27.2 min (major).

Lab Book Reference: **NS6-94**

Half of the organomagnesium species from above was added dropwise to a precooled solution of a racemic mixture of Andersen's sulfinate *rac*-**264** (589 mg, 2.0 mmol, 2.0 eq.) in Et₂O (5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Saturated NH₄Cl_(aq) (20 mL) and 10% NaHCO_{3(aq)} (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product which contained a 65:35

mixture (by ^1H NMR spectroscopy) of α -sulfinyl morpholines (S^*,S_S^*)-**283** and R^*,S_S^*)-**283**. Purification by flash column chromatography on silica with 98:1.8:0.2 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave α -sulfinyl morpholine (S^*,S_S^*)-**283** (54 mg, 32%) as a white solid and α -sulfinyl morpholine (R^*,S_S^*)-**283** (27 mg, 11%) as a white solid.

Lab Book Reference: **NS6-94**

s-BuLi (6.21 mL of a 1.3 M solution in hexane, 8.1 mmol, 1.2 eq.) was added to a stirred solution of *N*-methyl morpholine **125** (817 mg, 890 μmol , 8.1 mmol, 1.2 eq.) and TMEDA (1.21 mL, 8.1 mmol, 1.2 eq.) in hexane (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the solution was cooled to -78 °C and a freshly prepared solution of MgBr_2 in Et_2O (prepared using general procedure G from 1,2-dibromoethane (0.76 mL, 8.8 mmol) and Mg turnings (324 mg, 13 mmol) in Et_2O (10 mL)) was added and stirred at -78 °C for 30 min and then allowed to warm to 0 °C and stirred at 0 °C for 30 min. After cooling to -78 °C, the solution was added to a precooled solution of Andersen's sulfinate (S_S)-**264** (2.00 g, 6.7 mmol, 1.0 eq.) in Et_2O (10 mL) at -78 °C. After stirring for 5 min at -78 °C, MeOH (2 mL) were added and the mixture was allowed to warm to rt. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (20 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 $\times$ 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained a complex mixture of products and no evidence of the desired products (by ^1H NMR spectroscopy).

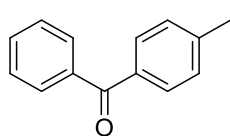
Lab Book Reference: **NS6-91**

s-BuLi (0.92 mL of a 1.3 M solution in hexane, 1.2 mmol, 1.2 eq.) was added to a stirred solution of *N*-methyl morpholine **125** (101 mg, 110 μmol , 1.0 mmol, 1.0 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the solution was cooled to -78 °C and a freshly prepared solution of MgBr_2 in Et_2O (prepared using general procedure G from 1,2-dibromoethane (121 μL , 262 mg, 1.4 mmol) and Mg turnings (58 mg, 2.4 mmol) in Et_2O (2 mL)) was added and stirred at -78 °C for 30 min and then allowed to warm to 0 °C and stirred at 0 °C for 30 min. Then, the organomagnesium species was added dropwise to a precooled solution of Andersen's sulfinate (S_S)-**264** (589 mg, 2.0 mmol, 2.0 eq.) in Et_2O (6 mL) at -78 °C. The resulting solution was stirred at -78 °C for 2 h. Then, MeOH (2 mL) was added and the solution was allowed to warm to rt. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (20 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$

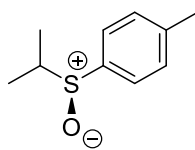
(20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. The ¹H NMR spectrum of the crude product showed which contained a complex mixture of products and no evidence of the desired products (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-93**

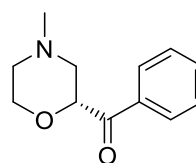
Phenyl(*p*-tolyl)methanone **285, 1-(*i*-Propylsulfinyl)-4-methylbenzene (*S*)-**284** and (*R*)-4-Methylmorpholin-2-yl(phenyl)methanol (*R*)-**128****



285



(*S*)-**284**



(*R*)-**128**

Table 3.7, entry 3:

Using general procedure F, α-sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (250 μL, of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at rt for 5 min and Weinreb amide **115** (76 μL, 83 mg, 0.50 mmol, 2.5 eq.) at rt gave the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave ketone **285** (6 mg, 16%) as a colourless oil, *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.6; IR (ATR) 2935, 1637 (C=O), 1577, 1447, 1377, 1212, 1180, 977, 787, 703, 558 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.80-7.74 (m, 2H, Ar), 7.74-7.68 (m, 2H, Ar), 7.60-7.53 (m, 1H, Ar), 7.50-7.42 (m, 2H, Ar), 7.31-7.26 (m, 2H, Ar), 3.51 (s, 3H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.7 (C=O), 143.4 (*ipso*-Ar), 138.1 (*ipso*-Ar), 135.0 (*ipso*-Ar), 132.3 (Ar), 130.5 (Ar), 130.1 (Ar), 129.1 (Ar), 128.4 (Ar), 21.8 (Me); MS (ESI) *m/z* 197 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₄H₁₂O (M + H)⁺ 197.0961, found 197.0962 (−0.3 ppm error), sulfoxide (*S*)-**284** (27 mg, 73%), as a colourless oil, [α]_D −165.2 (c 1.00 in acetone) (lit.,¹⁹⁸ −178.0 (c 1.00 in acetone) for (*S*)-**284** of 99:1 er), *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.3; IR (ATR) 2968, 2928, 1545, 1493, 1463, 1085, 1039, 1022, 923, 810, 728, 624, 532 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.34 (m, 2H, Ar), 7.34-7.27 (m, 2H, Ar), 2.79 (septet, *J* = 7.0 Hz, 1H, CHMe), 2.40 (s, 3H, ArMe), 1.18 (d, *J* = 7.0 Hz, 3H, CHMe), 1.13 (d, *J* = 7.0 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 141.5 (*ipso*-Ar), 138.5 (*ipso*-Ar), 129.7 (Ar), 125.1 (Ar), 54.6 (ArMe), 21.52 (CHMe), 15.8 (CHMe), 14.2 (CHMe); MS (ESI) *m/z* 183 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for

$C_{10}H_{14}OS$ ($M + H$)⁺ 183.0838, found 183.0835 (+1.9 ppm error), and morpholine (*R*)-**128** (28 mg, 69%, er not determined) as a colourless oil, $[\alpha]_D +14.3$ (*c* 1.00 in $CHCl_3$); R_F (90:9:1 CH_2Cl_2 -MeOH-NH₄OH_(aq)) 0.2. Spectroscopic data for ketone **285**¹⁹⁹ and (*S*)-**284**²⁰⁰ are consistent with those reported in the literature.

Lab Book Reference: **NS9-1**

Table 3.7, entry 1:

Using general procedure F, α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (250 μ L, of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at rt for 1 min and Weinreb amide **115** (76 μ L, 83 mg, 0.50 mmol, 2.5 eq.) at rt gave the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH_2Cl_2 -MeOH-NH₄OH_(aq) as eluent gave ketone **285** (5.5 mg, 14%) as a colourless oil, sulfoxide (*S*)-**284** (18.9 mg, 52%) as a colourless oil and morpholine (*R*)-**128** (27 mg, 65%, er not determined) as a colourless oil, $[\alpha]_D +14.9$ (*c* 1.00 in $CHCl_3$).

Lab Book Reference: **NS9-11**

Table 3.7, entry 2:

Using general procedure F, α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (250 μ L, of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at 0 °C for 1 min and Weinreb amide **115** (76 μ L, 83 mg, 0.50 mmol, 2.5 eq.) at 0 °C gave the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH_2Cl_2 -MeOH-NH₄OH_(aq) as eluent gave ketone **285** (4.0 mg, 10%) as a colourless oil, sulfoxide (*S*)-**284** (25.5 mg, 70%) as a colourless oil and morpholine (*R*)-**128** (19 mg, 46%, er not determined) as a colourless oil, $[\alpha]_D +14.0$ (*c* 1.00 in $CHCl_3$).

Lab Book Reference: **NS9-3**

Table 3.7, entry 4:

Using general procedure F, α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (250 μ L, of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at 0 °C for 5 min and Weinreb amide **115** (76 μ L, 83 mg, 0.50 mmol, 2.5 eq.) at 0 °C gave the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH_2Cl_2 -MeOH-NH₄OH_(aq) as eluent gave ketone **285** (7 mg, 12%) as a colourless

oil, sulfoxide (S)-**284** (17.9 mg, 70%) as a colourless oil and morpholine (R)-**283** (15.2 mg, 37%, er not determined) as a colourless oil, $[\alpha]_D +14.3$ (c 1.00 in CHCl₃).

Lab Book Reference: **NS9-2**

Table 3.7, entry 5:

Using general procedure F, α -sulfinyl morpholine (S,S_s)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (130 μ L, of a 2.0 M solution in THF, 0.26 mmol, 1.3 eq.) in THF (5 mL) at rt for 5 min and Weinreb amide **115** (76 μ L, 83 mg, 0.50 mmol, 2.5 eq.) at 0 °C gave the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave ketone **285** (7.8 mg, 2%) as a colourless oil, sulfoxide (S)-**284** (18 mg, 49%) as a colourless oil and morpholine (R)-**128** (12 mg, 29%, er not determined) as a colourless oil.

Lab Book Reference: **NS9-12**

Table 3.7, entry 6:

Using general procedure F, α -sulfinyl morpholine (S,S_s)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (130 μ L, of a 2.0 M solution in THF, 0.26 mmol, 1.3 eq.) in THF (5 mL) at rt for 5 min and Weinreb amide **115** (76 μ L, 83 mg, 0.50 mmol, 2.5 eq.) at rt gave the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave ketone **285** (5 mg, 13%) as a colourless oil, (S)-sulfoxide (S)-**284** (15 mg, 41%) as a colourless oil and morpholine (R)-**128** (traces, er not determined) as a colourless oil, $[\alpha]_D +14.3$ (c 1.00 in CHCl₃).

Lab Book Reference: **NS9-4**

i-PrMgCl·LiCl (153 μ L, of a 1.6 M solution in THF, 0.24 mmol, 1.2 eq.) was added dropwise to a stirred solution of α -sulfinyl morpholine (S,S_s)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) in CH₂Cl₂ (2 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 30 min. Then, Weinreb amide **115** (76 mg, 0.50 mmol, 2.5 eq.) was added and the resulting mixture was stirred at -78 °C for 30 min and then at rt for 1 h. Then, saturated NH₄Cl_(aq) (15 mL) and Et₂O (15 mL) were added and the two layers were separated. The aqueous layer was extracted Et₂O (3 x 20 mL). The combined organic phases were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave

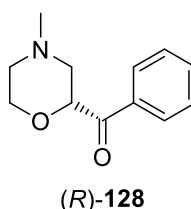
sulfoxide (S)-**284** (8.0 mg, 22%) as a colourless oil and recovered starting morpholine (S,S₅)-**283** (34 mg, 73%) as a colourless oil.

Lab Book Reference: **NS9-5**

i-PrMgCl (191 μ L, of a 1.6 M solution in THF, 0.30 mmol, 1.5 eq.) was added dropwise to a stirred solution of α -sulfinyl morpholine (S,S₅)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) in THF (5 mL) at -78 °C under Ar. The resulting mixture was stirred at -78 °C for 15 min and then at to 0 °C for 10 min. Then, Weinreb amide **115** (76 mg, 0.50 mmol, 2.5 eq.) was added and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was warmed to rt and saturated NH₄Cl_(aq) (5 mL) and water (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave sulfoxide (S)-**284** (11 mg, 31%) as a colourless oil.

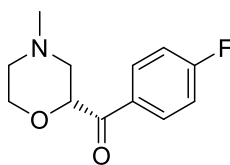
Lab Book Reference: **NS9-6**

(R)-(4-Methylmorpholin-2-yl)(phenyl)methanone (R)-128



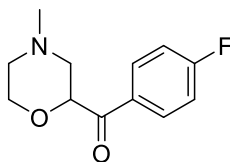
Using general procedure F, α -sulfinyl morpholine (S,S₅)-**283** (31 mg, 130 μ mol, 1.0 eq., 96:4 er) and *i*-PrMgCl (162 μ L, of a 2.0 M solution in THF, 324 μ mol, 2.5 eq.) in THF (5 mL) at rt for 5 min and Weinreb amide **115** (54 mg, 49 μ L, 324 μ mol 2.5 eq.) at rt gave the crude product. Purification by flash column chromatography on silica with 98.5:1.4:0.1 CH₂Cl₂-MeOH-NH₄OH_(aq) then 97.5:2:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave ketone (R)-**128** (19 mg, 71%, 94:6 er by CSP-HPLC) as a white solid, $[\alpha]_D +15.2$ (*c* 0.5 in CHCl₃); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min⁻¹) 8.1 min (major), 22.7 min (minor).

Lab Book Reference: **NS7-1**

(*R*)-(4-Fluorophenyl)(4-methylmorpholin-2-yl)methanone (*R*)-286**(*R*)-286**

Using general procedure F, α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (318 μ L, of a 1.6 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at rt for 5 min and Weinreb amide **159** (92 mg, 0.50 mmol, 2.5 eq.) at rt gave the crude product. Purification by flash column chromatography on silica with 98:1.8:0.2 CH₂Cl₂-MeOH-NH₄OH_(aq) then 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave ketone (*R*)-**286** (36 mg, 81%, 94:6 er by CSP-HPLC) as a white solid, mp 47-49 °C; [α]_D +38.2 (*c* 0.25 in CHCl₃); *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.3; IR (ATR) 2940, 2849, 2796, 1687 (C=O), 1595, 1215, 1147, 1118, 1086, 910, 851, 614 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.06-7.93 (m, 2H, Ar), 7.17-6.99 (m, 2H, Ar), 4.85-4.77 (m, 1H, OCH), 4.07-3.95 (m, 1H, OCH), 3.85-3.74 (m, 1H, OCH), 3.02-2.91 (m, 1H, NCH), 2.70-2.61 (m, 1H, NCH), 2.36-2.28 (m, 3H, NMe), 2.28-2.15 (m, 2H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 195.3 (C=O), 165.9 (d, *J* = 255.5 Hz, *ipso*-Ar), 131.9 (d, *J* = 9.5 Hz, Ar), 131.4 (d, *J* = 3.0 Hz, *ipso*-Ar), 115.8 (d, *J* = 21.5 Hz, Ar), 78.0 (OCH), 67.1 (OCH₂), 56.6 (NCH₂), 54.6 (NCH₂), 46.4 (NMe); ¹⁹F NMR (376 MHz, CDCl₃) δ -104.1 (s); MS (ESI) *m/z* 224 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₄FNO₂ (M + H)⁺ 224.1081, found 224.1082 (-0.4 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min⁻¹) 5.4 min (major), 23.0 min (minor).

Lab Book Reference: **NS8-73**

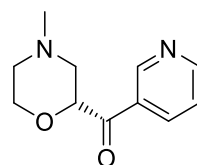
(4-Fluorophenyl)(4-methylmorpholin-2-yl)methanone *rac*-286***rac*-286**

Using general procedure D, morpholine **128** (110 μ L, 101 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (0.73 mL of a 1.5 M solution in hexane, 1.1 mmol, 1.0 eq.), TMEDA (150 mg, 195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and Weinreb amide **159** (275 mg, 2.0 mmol, 2.0 eq.)

gave the crude product. Purification by flash column chromatography on silica with 98:1.7:0.3 CH₂Cl₂-MeOH-NH₄OH_(aq) then 97.5:2:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave ketone *rac*-**286** (53 mg, 30%) as a yellow solid.

Lab Book Reference: **NS8-66**

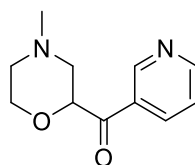
(4-Methylmorpholin-2-yl)(pyridin-3-yl)methanone (*R*)-287



(*R*)-287

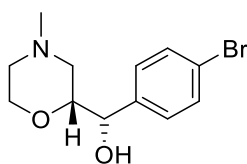
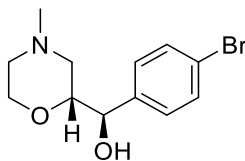
Using general procedure F, α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 95:5 er) and *i*-PrMgCl (318 μ L, of a 1.6 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at rt for 5 min and Weinreb amide **160** (84 mg, 0.50 mmol, 2.5 eq.) at rt gave the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) then 95:4:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave morpholine (*R*)-**287** (26 mg, 45%, er not determined) as a yellow oil, $[\alpha]_D^{25} +23.6$ (*c* 0.17 in CHCl₃); *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.5; IR (ATR) 2943, 2858, 2902, 1693 (C=O), 1486, 1543, 1291, 1116, 1068, 1010, 909, 823, 726, 542 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.21 (s, 1H, Ar), 8.77 (d, *J* = 4.5 Hz, 1H, Ar), 8.26 (d, *J* = 8.0 Hz, 1H, Ar), 7.41 (dd, *J* = 8.0, 4.5 Hz, 1H, Ar), 4.79 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 4.02 (d, *J* = 11.5 Hz, 1H, OCH), 3.85 (ddd, *J* = 11.5, 10.5, 2.5 Hz, 1H, OCH), 3.02 (br d, *J* = 11.5 Hz, 1H, NCH), 2.69 (br d, *J* = 12.0 Hz, 1H, NCH), 2.35 (s, 3H, NMe), 2.33-2.21 (m, 2H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.3 (C=O), 153.8 (Ar), 150.7 (Ar), 136.6 (Ar), 130.7 (*ipso*-Ar), 123.7 (Ar), 78.4 (OCH), 67.2 (OCH₂), 56.2 (NCH₂), 54.6 (NCH₂), 46.4 (NMe); MS (ESI) *m/z* 207 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₄N₂O₂ (M + H)⁺ 207.1128, found 207.1128 (+0.1 ppm error).

Lab Book Reference: **NS8-79**

(4-Methylmorpholin-2-yl)(pyridin-3-yl)methanone *rac*-287*rac*-287

Using general procedure D, *N*-methyl morpholine **125** (101 mg, 110 μ L, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.06 mL of a 1.2 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and Weinreb amide **160** (233 mg, 1.4 mmol, 1.4 eq.) gave the crude product. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) then 95:4.5:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave ketone *rac*-**287** (138 mg, 67%) as a yellow oil.

Lab Book Reference: **NS8-77**

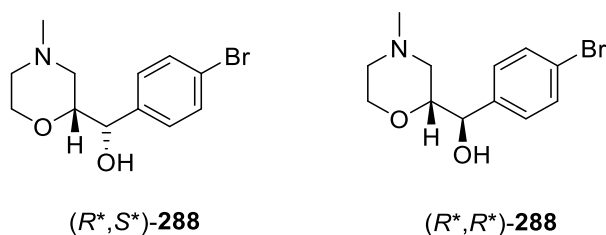
(4-Bromophenyl)(4-methylmorpholin-2-yl)methanol (*R,S*)-288 and (*R,R*)-288*(R,S)*-288*(R,R)*-288

Using general procedure F, α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (318 μ L, of a 1.6 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at rt for 5 min and 4-bromobenzaldehyde (93 mg, 0.50 mmol, 2.5 eq.) at rt gave the crude product which contained a 70:30 mixture (by ¹H NMR spectroscopy) of morpholines (*R,S*)-**288** and (*R,R*)-**288**. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) then 95:4:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave morpholine (*R,S*)-**288** (26 mg, 45%, 95:5 er by CSP-HPLC) as a white solid, mp 113-115 °C; *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.30; [α]_D +23.4 (*c* 0.50 in CHCl₃); IR (ATR) 2943, 2858, 2902, 1486, 1543, 1291, 1116, 1068, 1010, 909, 823, 726, 542 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.43 (m, 2H, Ar), 7.21-7.17 (m, 2H, Ar), 4.44 (d, *J* = 7.5 Hz, 1H, HOCH), 3.91 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.65 (ddd, *J* = 11.5, 11.5, 2.0 Hz (app td), 1H, OCH), 3.64 (br s, 1H, OH), 3.52 (ddd, *J* = 10.0, 7.5, 2.0 Hz, 1H, OCH), 2.57 (dd, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.27 (ddd, *J* = 11.5, 2.0, 2.0 Hz (app dt), 1H, NCH), 2.15 (s, 3H, NMe), 2.09 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.80 (dd, *J* = 11.5, 10.0 Hz, 1H,

NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 139.0 (*ipso*-Ar), 131.7 (Ar), 128.9 (Ar), 122.1 (*ipso*-Ar), 79.4 (HOCH), 75.1 (OCH), 66.7 (OCH_2), 56.4 (NCH_2), 54.6 (NCH_2), 46.3 (NMe); MS (ESI) m/z 286 [$(^{79}\text{M} + \text{H})^+$, 100], 288 [$(^{81}\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{16}^{79}\text{BrNO}_2$ ($^{79}\text{M} + \text{H})^+$ 286.0437, found 286.0435 (+0.8 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min $^{-1}$) 5.4 min (major), 23.0 min (minor) and morpholine (*R,R*)-**288** (12.6 mg, 22%, 94:6 er by CSP-HPLC) as a white solid, mp 142–144 °C; R_F (90:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.25; $[\alpha]_D^{25} +37.5$ (*c* 1.00 in CHCl_3); IR 2855, 2803, 1487, 1453, 1142, 1109, 1070, 1029, 822, 752, 724, 545 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, J = 8.5 Hz, 2H, Ar), 7.24 (d, J = 8.5 Hz, 2H, Ar), 4.85 (d, J = 4.0 Hz, 1H, HOCH), 3.95 (dd, J = 11.5, 3.0 Hz, 1H, OCH), 3.77–3.65 (m, 2H, OCH), 2.85 (br s, 1H, OH), 2.60 (dd, J = 11.5, 2.5 Hz, 1H, NCH), 2.42 (ddd, J = 11.5, 2.5, 2.5 Hz (app dt), 1H, NCH), 2.22 (s, 3H, NMe), 2.12 (ddd, J = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 2.01 (dd, J = 11.5, 11.5 Hz (app t), 1H, NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 139.1 (*ipso*-Ar), 131.6 (Ar), 128.0 (Ar), 121.6 (*ipso*-Ar), 78.5 (HOCH), 74.3 (OCH), 66.9 (OCH_2), 54.9 (NCH_2), 54.1 (NCH_2), 46.5 (NMe); MS (ESI) m/z 286 [$(^{79}\text{M} + \text{H})^+$, 100], 288 [$(^{81}\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{16}^{79}\text{BrNO}_2$ ($^{79}\text{M} + \text{H})^+$ 286.0437, found 286.0433 (+1.6 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min $^{-1}$) 5.4 min (major), 23.0 min (minor).

Lab Book Reference: **NS8-78**

(4-Bromophenyl)(4-methylmorpholin-2-yl)methanol (*R*,S)-288 and (*R*,R**)-288**

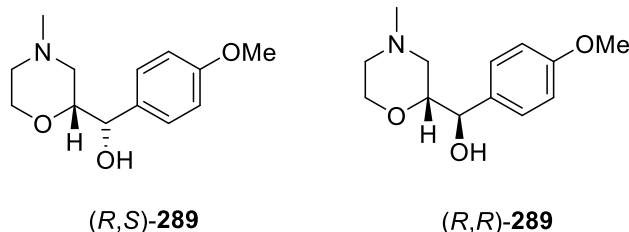


Using general procedure D, *N*-methyl morpholine **125** (101 mg, 110 μL , 1.0 mmol, 1.0 eq.), *s*-BuLi (1.06 mL of a 1.2 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) and 4-bromobenzaldehyde (278 mg, 1.5 mmol, 1.5 eq.) gave the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of morpholines (*R*,R**)-**288** and (*R*,S**)-**288**. Purification by flash column chromatography on silica with 98:1.8:0.2 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ then 90:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as

eluent gave morpholine (*R*,R**)-**288** (115 mg, 40%) as a white solid and morpholine (*R*,S**)-**288** (140 mg, 49%) as a white solid.

Lab Book Reference: **NS8-74**

(4-Methoxyphenyl)(4-methylmorpholin-2-yl)methanol (*R,S*)-289** and (*R,R*)-**289****

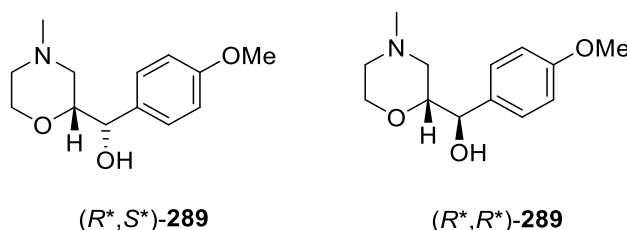


Using general procedure F, α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (250 μ L, of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at rt for 5 min and 4-methoxybenzaldehyde (61 μ L, 68 mg, 0.50 mmol, 2.5 eq.) at rt gave the crude product which contained a 70:30 mixture (by ^1H NMR spectroscopy) of morpholines (*R,S*)-**289** and (*R,R*)-**289**. Purification by flash column chromatography on silica with 96.5:3:0.5 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ then 95:4:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave morpholine (*R,R*)-**289** (8 mg, 17%, 96:4 er by CSP-HPLC) as a white solid, $[\alpha]_{\text{D}}^{25} +60.4$ (*c* 0.13 in CHCl_3); mp 118-120 $^\circ\text{C}$; R_{F} (90:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.15; IR (ATR) 2855, 2795, 1611, 1454, 1513, 1245, 1174, 1115, 1032, 835, 818 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.28-7.21 (m, 2H, Ar), 6.90-6.85 (m, 2H, Ar), 4.46 (d, J = 8.0 Hz, 1H, HOCH), 4.02-3.92 (m, 1H, OCH), 3.80 (s, 3H, OMe), 3.72 (ddd, J = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.61 (ddd, J = 10.0, 8.0, 2.5 Hz, 1H, OCH), 3.15 (s, 1H, OH), 2.63 (br d, J = 11.5 Hz, 1H, NCH), 2.32 (br d, J = 11.5 Hz, 1H, NCH), 2.19 (s, 3H, NMe), 2.13 (ddd, J = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.81 (dd, J = 11.5, 11.5 Hz (app t), 1H, NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 159.7 (*ipso*-Ar), 131.7 (*ipso*-Ar), 128.5 (Ar), 114.0 (Ar), 79.7 (OCH), 75.4 (HOCH), 66.7 (OCH_2), 56.5 (NCH_2), 55.4 (OMe), 54.7 (NCH_2), 46.3 (NMe); MS (ESI) m/z 238 [$(\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_3$ ($\text{M} + \text{H})^+$ 238.1438, found 238.1438 (+0.0 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) 14.4 min (major), 17.0 min (minor) and morpholine (*R,S*)-**289** (19.5 mg, 41%, 96:4 er by CSP-HPLC) as a white solid, $[\alpha]_{\text{D}}^{25} +101.6$ (*c* 0.17 in CHCl_3); mp 105-107 $^\circ\text{C}$; R_{F} (90:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.10; IR (ATR) 2959, 2836, 2802, 1612, 1511, 1455, 1301, 1243, 1116, 1027, 825, 731 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.25 (m, 2H, Ar), 6.92-6.84 (m, 2H, Ar), 4.83-4.76 (m, 1H, HOCH), 3.97-3.90 (m, 1H, OCH), 3.80 (s, 3H, OMe), 3.75-3.65 (m, 2H, OCH), 2.75 (s, 1H, OH), 2.60 (dd, J = 11.5,

2.0 Hz, 1H, NCH), 2.53 (br d, $J = 11.5$ Hz, 1H, NCH), 2.22 (s, 3H, NMe), 2.16-2.07 (m, 1H, NCH), 2.02 (dd, $J = 11.0, 11.0$ Hz (app t), 1H, NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 159.2 (*ipso*-Ar), 132.3 (*ipso*-Ar), 127.5 (Ar), 113.8 (Ar), 78.8 (OCH), 74.5 (HOCH), 66.9 (OCH₂), 55.4 (NCH₂), 54.9 (OMe), 54.5 (NCH₂), 46.5 (NMe); MS (ESI) m/z 238 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_3$ (M + H)⁺ 238.1438, found 238.1439 (−0.7 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{−1}) 18.2 min (major), 24.6 min (minor).

Lab Book Reference: **NS8-87**

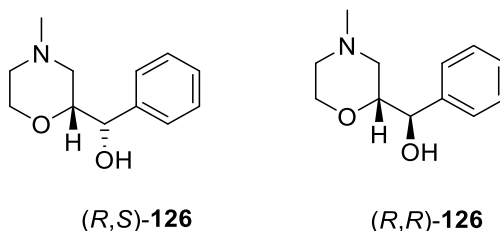
(4-Methoxyphenyl)(4-methylmorpholin-2-yl)methanol (*R*,S)-289 and (*R*,R**)-289**



Using general procedure D, *N*-methyl morpholine **125** (101 mg, 110 μL , 1.0 mmol, 1.0 eq.), *s*-BuLi (1.06 mL of a 1.2 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) and 4-methoxybenzaldehyde (183 μL , 204 mg, 1.5 mmol, 1.5 eq.) gave the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of morpholines (*R*,R**)-**289** and (*R*,S**)-**289**. Purification by flash column chromatography on silica with 96:5:3:0.5 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ then 90:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave morpholine (*R*,R**)-**289** (78 mg, 33%) as a white solid, and morpholine (*R*,S**)-**289** (85 mg, 36%) as a white solid.

Lab Book Reference: **NS8-86**

(4-Methylmorpholin-2-yl)(phenyl)methanol (*R,S*)-126 and (*R,R*)-126

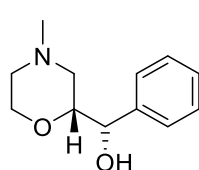


Using general procedure F, α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er) and *i*-PrMgCl (318 μL , of a 1.6 M solution in THF, 0.50 mmol, 2.5 eq.) in THF (5 mL) at rt for 5 min and benzaldehyde (51 μL , 53 mg, 0.50 mmol, 2.5 eq.) at rt gave the crude product which contained a 70:30 mixture (by ^1H NMR spectroscopy) of morpholines

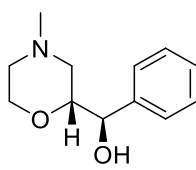
(*R,S*)-**126** and (*R,R*)-**126**. Purification by flash column chromatography on silica with 96.5:3:0.5 CH₂Cl₂-MeOH-NH₄OH_(aq) then 95:4:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave a 70:30 mixture of morpholines (*R,S*)-**126** and (*R,R*)-**126** (29 mg, 69%) as a white solid (morpholine (*R,S*)-**126** was formed in 90:10 er by CSP-HPLC and morpholine (*R,R*)-**126** was formed in 86:14 er by CSP-HPLC); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min⁻¹) 9.5 min ((*R,S*)-**126**), 12.9 min ((*R,R*)-**126**), 14.6 min ((*S,R*)-**126**), 23.6 min ((*S,S*)-**126**).

Lab Book Reference: **NS8-80**

(4-Methylmorpholin-2-yl)(phenyl)methanol (*R*,S**)-**126** and (*R*,R**)-**126**



(*R*,S**)-**126**



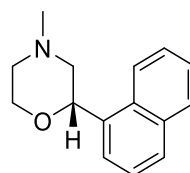
(*R*,R**)-**126**

Using general procedure D, morpholine **125** (110 μ L, 101 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (0.73 mL of a 1.5 M solution in hexane, 1.1 mmol, 1.0 eq.), TMEDA (150 mg, 195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and benzaldehyde (151 μ L, 159 mg, 1.5 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:1.7:0.3 CH₂Cl₂-MeOH-NH₄OH_(aq) then 90:9:1 CH₂Cl₂-MeOH-NH₄OH as eluent gave alcohol (*R*,S**)-**126** (52 mg, 25%) as a yellow oil, *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.5; IR (ATR) 3346 (OH), 2940, 2866, 2800, 1495, 1453, 1292, 1150, 1115, 1031, 765, 703, 629 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.26 (m, 5H, Ph), 4.50 (d, *J* = 8.0 Hz, 1H, HOCH), 3.96 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.69 (ddd, *J* = 11.5, 11.5, 2.0 Hz (app td), 1H, OCH), 3.60 (ddd, *J* = 10.0, 8.0, 2.0 Hz, 1H, OCH), 3.20 (s, 1H, OH), 2.60 (dd, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.30 (ddd, 11.5, 2.0, 2.0 Hz (app dt), 1H, NCH), 2.17 (s, 3H, NMe), 2.11 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.83 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 140.3 (*ipso*-Ph), 128.4 (Ph), 127.7 (Ph), 126.3 (Ph), 78.8 (HOCH), 74.8 (OCH), 66.8 (OCH₂), 54.9 (NCH₂), 54.3 (NCH₂), 46.4 (NMe); MS (ESI) *m/z* 208 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₇NO₂ (M + H)⁺ 208.1332, found 208.1332 (−0.0 ppm error), a mixture of 50:50 mixture of diastereomeric alcohols (*R*,S**)-**126** and (*R*,R**)-**126** (61 mg, 29%) and alcohol (*R*,R**)-**126** (45 mg, 22%) as a yellow oil, *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.5; IR (ATR) 3062 (OH), 2942, 2859, 2802, 1494, 1453, 1146, 1289, 1110, 1064, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.17 (m, 5H,

Ph), 4.89 (d, $J = 4.5$ Hz, 1H, HOCH), 3.95 (ddd, $J = 11.5, 3.5, 2.0$ Hz, 1H, OCH), 3.77-3.68 (m, 2H, OCH), 2.85 (s, 1H, OH), 2.59 (dd, $J = 11.5, 2.0$ Hz, 1H, NCH), 2.46 (ddd, $J = 11.5, 2.0, 2.0$ Hz (app dt), 1H, NCH), 2.21 (s, 3H, NMe), 2.13 (ddd, $J = 11.5, 11.0, 3.5$ Hz, 1H, NCH), 2.05 (dd, $J = 11.0, 10.5$ Hz, 1H, NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 139.7 (*ipso*-Ph), 128.6 (Ph), 127.9 (Ph), 126.3 (Ph), 78.5 (HOCH), 74.7 (OCH), 66.5 (OCH_2), 54.7 (NCH_2), 53.9 (NCH_2), 46.2 (NMe); MS (ESI) m/z 208 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2$ ($\text{M} + \text{H})^+$ 208.1332, found 208.1329 (+1.5 ppm error).

Lab Book Reference: **NS8-67**

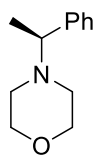
Attempted Synthesis of (S)-4-Methyl-2-(naphthalen-1-yl)morpholine (S)-188



(S)-188

i-PrMgCl (318 μL , of a 1.6 M solution in THF, 0.50 mmol, 2.5 eq.) was added dropwise to a stirred solution of α -sulfinyl morpholine (*S,S*)-**283** (48 mg, 0.20 mmol, 1.0 eq., 96:4 er), in THF (5 mL) at rt under Ar. The resulting solution was stirred at rt for 5 min. Then, a freshly prepared solution of ZnCl_2 (240 μL of a 1.0 M solution in THF, 0.24 mmol, 1.2 eq.) was added and the solution was stirred for 30 min at rt. Then, $\text{Pd}(\text{OAc})_2$ (3.0 mg, 5 mol%), *t*-Bu₃PHBF₄ (3.5 mg, 6 mol%) and 1-bromonaphthalene (49 mg, 0.24 mmol, 1.2 eq.) were added and the solution was stirred and heated at 40 °C for 16 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 $\times$ 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained traces of morpholine (S)-**188** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS8-84**

(S)-4-(1-Phenylethyl)morpholine (S)-154**(S)-154**

K_2CO_3 (21.0 g, 152 mmol, 5.0 eq.) and KI (11.1 g, 67 mmol, 2.2 eq.) were added to a stirred solution of (S)- α -methylbenzylamine (3.68 g, 3.91 mL, 30 mmol, 1.0 eq., 99:1 er) in EtOH (120 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min. Then, 2,2-dibromodiethyl ether (14.1 g, 7.64 mL, 61 mmol, 2.0 eq.) was added and the reaction mixture was stirred and heated at 78 °C for 16 h. The reaction mixture was allowed to cool to rt and the solids were removed by filtration. CH_2Cl_2 (100 mL) was added to the filtrate and the solution was washed with H_2O (2 $\times$ 100 mL) and brine (100 mL). The organic layer was dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave morpholine (S)-**154** (4.92 g, 84%) as a colourless oil, $[\alpha]_{\text{D}} -25.5$ (c 0.5 in CHCl_3) (lit.,²⁰¹ -36.5 (c 2.5 in CHCl_3)); R_{F} (50:50 hexane-EtOAc) 0.4; IR (ATR) 2852, 2804, 1450, 1116, 947, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.32 (m, 4H, Ph), 7.29-7.24 (m, 1H, Ph), 3.74-3.69 (m, 4H, OCH), 3.32 (q, $J = 7.0$ Hz, 1H, NCHMe), 2.59-2.46 (m, 2H, NCH), 2.45-2.34 (m, 2H, NCH), 1.37 (d, $J = 7.0$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 144.1 (*ipso*-Ph), 128.4 (Ph), 127.8 (Ph), 127.1 (Ph), 67.4 (OCH₂), 65.6 (NCHMe), 51.5 (NCH₂), 20.0 (NCHMe); MS (ESI) m/z 192 $[(\text{M} + \text{H})^+]$, 100; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$ ($\text{M} + \text{H})^+$ 192.1383, found 192.1382 (+0.7 ppm error). Spectroscopic data consistent with those reported in the literature.²⁰¹

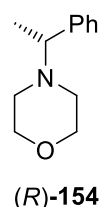
Lab Book Reference: **NS9-47**

K_2CO_3 (21.0 g, 152 mmol, 5.0 eq.) and KI (11.1 g, 67 mmol, 2.2 eq.) were added to a stirred solution of (S)- α -methylbenzylamine (3.68 g, 3.91 mL, 30 mmol, 1.0 eq., 99:1 er) in EtOH (120 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min. Then, 2,2-dichlorodiethyl ether (8.69 g, 7.13 mL, 61 mmol, 2.0 eq.) was added and the reaction mixture was stirred and heated at 78 °C for 16 h. The reaction mixture was allowed to cool to rt and the solids were removed by filtration. CH_2Cl_2 (100 mL) was added to the filtrate and the solution was washed with H_2O (2 $\times$ 100 mL) and brine (100 mL). The organic layer was dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave morpholine (S)-**154** (1.80 g, 31%) as a pale yellow oil, Spectroscopic data consistent with those reported in the literature.

Lab Book Reference: **NS9-18**

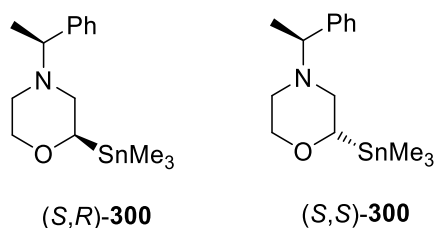
(R)-4-(1-Phenylethyl)morpholine (R)-154



K₂CO₃ (21.0 g, 152 mmol, 5.0 eq.) and KI (11.1 g, 67 mmol, 2.2 eq.) were added to a stirred solution of (R)- α -methylbenzylamine (3.68 g, 3.91 mL, 30 mmol, 1.0 eq., 99:1 er) in EtOH (120 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min. Then, 2,2-dibromodiethyl ether (8.69 g, 7.13 mL, 61 mmol, 2.0 eq.) was added and the reaction mixture was stirred at 78 °C for 16 h. The reaction mixture was allowed to cool to rt and the solids were removed by filtration. CH₂Cl₂ (100 mL) was added to the filtrate and the solution was washed with H₂O (2 × 100 mL) and brine (100 mL). The organic layer was dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave morpholine (R)-**154** (4.70 g, 81%) as a pale yellow oil, [α]_D +26.3 (c 0.5 in CHCl₃) (lit.,²⁰¹ -36.5 (c 2.5 in CHCl₃) for (S)-**154**).

Lab Book Reference: **NS9-54**

4-(1-Phenylethyl)-2-(trimethylstannyl)morpholine (S,R)-300 and (S,S)-300



Using general procedure D, morpholine (S)-**154** (202 mg, 2.0 mmol, 1.0 eq.), *s*-BuLi (2 mL of a 1.3 M solution in hexane, 2.6 mmol, 1.3 eq.) and TMEDA (390 μ L, 2.6 mmol, 1.3 eq.) in hexane (5 mL) and Me₃SnCl (4.0 mL of a 1.0 M solution in hexane, 4.0 mmol, 2.0 eq.) gave the crude product which contained a 50:50 mixture (by ¹H NMR spectroscopy) of α -

stannyl morpholines (*S,R*)-**300** and (*S,S*)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave morpholine (*S,R*)-**300** (233 mg, 33%) as a colourless oil, $[\alpha]_D -11.3$ (*c* 0.25 in CHCl_3); R_F (90:10 hexane-EtOAc) 0.4; IR (ATR) 3027, 2974, 2949, 2902, 2848, 2796, 1491, 1451, 1370, 1343, 1317, 1088, 971, 764, 701, 528 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.16 (m, 5H, Ph), 4.00 (dd, $J = 10.5, 2.5$ Hz, 1H, OCH), 3.68 (ddd, $J = 11.0, 3.0$ Hz, 1H, OCH), 3.53 (ddd, $J = 11.0, 10.5, 2.5$ Hz, 1H, OCH), 3.23 (q, $J = 6.5$ Hz, 1H, NCHMe), 2.96-2.85 (m, 1H, NCH), 2.48-2.42 (m, 1H, NCH), 2.38 (dd, $J = 11.5, 10.5$ Hz, 1H, NCH), 2.23-2.10 (m, 1H, NCH), 1.34 (d, $J = 6.5$ Hz, 3H, NCHMe), 0.12 (s, 9H, SnMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 144.2 (*ipso*-Ph), 128.4 (Ph), 127.8 (Ph), 127.1 (Ph), 73.3 (OCH), 69.3 (OCH_2), 65.8 (NCHMe), 55.8 (NCH_2), 52.4 (NCH_2), 20.3 (NCHMe), -10.6 (SnMe_3); MS (ESI) m/z 354 [$(^{118}\text{M} + \text{H})^+$, 74], 356 [$(^{120}\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{25}\text{NO}^{120}\text{Sn}$ ($^{120}\text{M} + \text{H})^+$ 356.1031, found 356.1029 (+1.3 ppm error) and morpholine (*S,S*)-**300** (212 mg, 30%) as a colourless oil, $[\alpha]_D -40.0$ (*c* 1.00 in CHCl_3); R_F (90:10 hexane-EtOAc) 0.5; IR (ATR) 3027, 2974, 2949, 2902, 2796, 1492, 1451, 1371, 1345, 1132, 1096, 1088, 950, 762, 701, 528 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.19 (m, 5H, Ph), 3.95 (dd, $J = 9.5, 2.5$ Hz, 1H, OCH), 3.75 (ddd, $J = 11.5, 3.5, 3.5$ Hz, 1H, OCH), 3.62 (ddd, $J = 11.5, 9.0, 3.0$ Hz, 1H, OCH), 3.27 (q, $J = 6.5$ Hz, 1H, NCHMe), 2.76-2.63 (m, 1H, NCH), 2.57-2.50 (m, 1H, NCH), 2.47-2.36 (m, 1H, NCH), 2.30 (ddd, $J = 11.5, 9.0, 3.5$ Hz, 1H, NCH), 1.32 (d, $J = 6.5$ Hz, 3H, NCHMe), 0.06 (s, 9H, SnMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 144.2 (*ipso*-Ph), 128.4 (Ph), 127.8 (Ph), 127.0 (Ph), 73.6 (OCH), 69.0 (OCH_2), 65.4 (NCHMe), 56.1 (NCH_2), 51.7 (NCH_2), 19.9 (NCHMe), -10.4 (SnMe_3); MS (ESI) m/z 354 [$(^{118}\text{M} + \text{H})^+$, 74], 356 [$(^{120}\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{25}\text{NO}^{120}\text{Sn}$ ($^{120}\text{M} + \text{H})^+$ 356.1031, found 356.1030 (+0.9 ppm error).

Lab Book Reference: **NS9-43**

Using general procedure D, morpholine (*S*)-**154** (1.91 g, 10 mmol, 1.0 eq.), *s*-BuLi (10.0 mL of a 1.3 M solution in hexane, 13 mmol, 1.3 eq.) and TMEDA (1.95 mL, 13.0 mmol, 1.3 eq.) in hexane (100 mL) and Me_3SnCl (20 mL of a 1.0 M solution in hexane, 20 mmol, 2.0 eq.) gave the crude product which contained a 50:50 mixture (by ^1H NMR spectroscopy) of α -stannyl morpholines (*S,R*)-**300** and (*S,S*)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -aryl morpholine (*S,R*)-**300** (1.13 g, 32%) as a colourless oil and morpholine (*S,S*)-**300** (1.06 g, 29%) as a colourless oil.

Lab Book Reference: **NS11-75**

Using general procedure E, morpholine (*S*)-**154** (95 mg, 0.50 mmol, 1.0 eq.), *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and Me_3SnCl (1.0 mL of a 1.0 M solution in hexane, 2.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of α -stannyl morpholines (*S,R*)-**300** and (*S,S*)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave a 55:45 mixture of morpholines (*S,R*)-**300** and (*S,S*)-**300** (60 mg, 34%) as a colourless oil.

Lab Book Reference: **NS10-38**

4-(1-Phenylethyl)-2-(trimethylstannyl)morpholine (*R,S*)-**300** and (*R,R*)-**300**

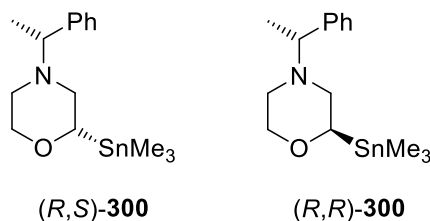


Table 3.8, entry 1:

Using general procedure E, morpholine (*R*)-**154** (95 mg, 0.50 mmol, 1.0 eq.), *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at $-60\text{ }^{\circ}\text{C}$ for 4 h and Me_3SnCl (1.0 mL of a 1.0 M solution in hexane, 2.0 mmol, 2.0 eq.) at $-60\text{ }^{\circ}\text{C}$ for 1 h gave the crude product which contained a 67:33 mixture (by ^1H NMR spectroscopy) of α -stannyl morpholines (*R,S*)-**300** and (*R,R*)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave a 67:33 mixture of α -stannyl morpholines (*R,S*)-**300** and (*R,R*)-**300** (83 mg, 47%) as a colourless oil.

Lab Book Reference: **NS10-37**

Table 3.8, entry 2:

Using general procedure E, morpholine (*R*)-**154** (95 mg, 0.50 mmol, 1.0 eq.), *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at $-78\text{ }^{\circ}\text{C}$ for 4 h and Me_3SnCl (1.0 mL of a 1.0 M solution in hexane, 2.0 mmol, 2.0 eq.) at $-78\text{ }^{\circ}\text{C}$ for 1 h gave the crude product which contained a 81:19 mixture (by ^1H NMR spectroscopy) of α -stannyl morpholines (*R,S*)-**300** and (*R,R*)-**300**. Purification by flash column chromatography on silica with 90:10

hexane-EtOAc as eluent gave an 80:20 mixture of morpholines (*R,S*)-**300** and (*R,R*)-**300** (67 mg, 38%) as a colourless oil.

Lab Book Reference: **NS10-54**

Table 3.8, entry 3:

Using general procedure E, morpholine (*R*)-**154** (95 mg, 0.50 mmol, 1.0 eq.), *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at $-78\text{ }^{\circ}\text{C}$ for 6 h and Me_3SnCl (1.0 mL of a 1.0 M solution in hexane, 2.0 mmol, 2.0 eq.) at $-78\text{ }^{\circ}\text{C}$ for 1 h gave the crude product which contained an 80:20 mixture (by ^1H NMR spectroscopy) of α -stannyl morpholines (*R,S*)-**300** and (*R,R*)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave an 82:18 mixture of morpholines (*R,S*)-**300** and (*R,R*)-**300** (107 mg, 61%) as a colourless oil.

Lab Book Reference: **NS10-55**

Table 3.8, entry 4:

Using general procedure E, morpholine (*R*)-**154** (95 mg, 0.50 mmol, 1.0 eq.), *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at $-78\text{ }^{\circ}\text{C}$ for 8 h and Me_3SnCl (1.0 mL of a 1.0 M solution in hexane, 2.0 mmol, 2.0 eq.) at $-78\text{ }^{\circ}\text{C}$ for 1 h gave the crude product which contained an 81:19 mixture (by ^1H NMR spectroscopy) of α -stannyl morpholines (*R,S*)-**300** and (*R,R*)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave an 80:20 mixture of morpholines (*R,S*)-**300** and (*R,R*)-**300** (115 mg, 65%) as a colourless oil.

Lab Book Reference: **NS10-56**

Table 3.8, entry 5:

Using general procedure E, morpholine (*R*)-**154** (95 mg, 0.50 mmol, 1.0 eq.), *s*-BuLi (0.77 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.5 eq.) and (+)-sparteine surrogate (194 mg, 1.5 mmol, 1.5 eq.) in hexane (5 mL) at $-78\text{ }^{\circ}\text{C}$ for 8 h and Me_3SnCl (2.0 mL of a 1.0 M solution in hexane, 2.0 mmol, 3.0 eq.) at $-78\text{ }^{\circ}\text{C}$ for 1 h gave the crude product which contained a 80:20 mixture (by ^1H NMR spectroscopy) of α -stannyl morpholines (*R,S*)-**300** and (*R,R*)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave morpholine (*R,S*)-**300** (105 mg, 59%) as a colourless oil, $[\alpha]_{\text{D}} +7.2$ (*c*

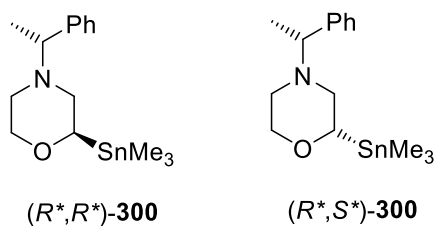
1.00 in CHCl₃) and morpholine (*R,R*)-**300** (41 mg, 23%) as a colourless oil, [α]_D +44.2 (c 1.00 in CHCl₃).

Lab Book Reference: **NS10-59**

Using general procedure D, morpholine (*R*)-**154** (765 mg, 4.0 mmol, 1.0 eq.), *s*-BuLi (5.2 mL of a 1.3 M solution in hexane, 5.2 mmol, 1.3 eq.) and TMEDA (780 μ L, 5.2 mmol, 1.3 eq.) in hexane (20 mL) and Me₃SnCl (8.0 mL of a 1.0 M solution in hexane, 8.0 mmol, 2.0 eq.) gave the crude product which contained a 50:50 mixture (by ¹H NMR spectroscopy) of α -stannyl morpholines (*R,S*)-**300** and (*R,R*)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave morpholine (*R,S*)-**300** (496 mg, 35%) as a colourless oil, [α]_D +5.9 (c 0.50 in CHCl₃) and morpholine (*R,R*)-**300** (453 mg, 32%) as a colourless oil, [α]_D +46.6 (c 1.00 in CHCl₃).

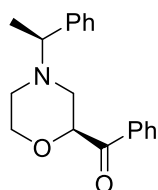
Lab Book Reference: **NS9-56**

4-(1-Phenylethyl)-2-(trimethylstannyl)morpholine (*R*,S**)-**300** and (*R*,R**)-**300**



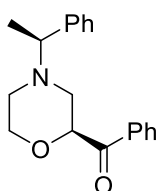
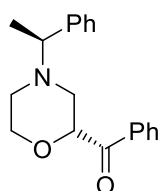
Using general procedure D, morpholine (*rac*)-**154** (1.91 g, 10 mmol, 1.0 eq.), *s*-BuLi (10.0 mL of a 1.3 M solution in hexane, 13 mmol, 1.3 eq.) and TMEDA (1.95 mL, 13.0 mmol, 1.3 eq.) in hexane (100 mL) and Me₃SnCl (20 mL of a 1.0 M solution in hexane, 20 mmol, 2.0 eq.) gave the crude product which contained a 50:50 mixture (by ¹H NMR spectroscopy) of α -stannyl morpholines (*R*,R**)-**300** and (*S*,S**)-**300**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave morpholine (*R*,R**)-**300** (1.17 g, 33%) as a colourless oil and morpholine (*R*,S**)-**300** (1.27 g, 36%) as a white solid, mp 76-78 °C.

Lab Book Reference: **NS10-67**

Phenyl((S)-4-((S)-1-phenylethyl)morpholin-2-yl)methanone (S,S)-301**(S,S)-301**

Using general procedure H, stannane (*S,R*)-**300** (177 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (103 μ L of a 1.5 M solution in hexane, 0.16 mmol, 1.1 eq.) in THF (2.5 mL) and Weinreb amide **115** (152 μ L, 165 mg, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -substituted morpholine (*S,S*)-**301** (129 mg, 87%, 99:1 er by CSP-HPLC) as a colourless oil, $[\alpha]_D -13.9$ (c 1.00 in CHCl_3); R_F (90:10 hexane-EtOAc) 0.3; IR (ATR) 2972, 2814, 1690 (C=O), 1598, 1449, 1206, 1122, 955, 762, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.02-7.95 (m, 2H, Ph), 7.60-7.53 (m, 1H, Ph), 7.50-7.40 (m, 2H, Ph), 7.33-7.20 (m, 5H, Ph), 4.93 (dd, $J = 10.0, 2.5$ Hz, 1H, OCH), 3.96 (ddd, $J = 11.5, 3.5, 2.5$ Hz, 1H, OCH), 3.75 (ddd, $J = 11.5, 11.5, 2.5$ Hz (app td), 1H, OCH), 3.38 (q, $J = 6.5$ Hz, 1H, NCHMe), 3.29-3.19 (m, 1H, NCH), 2.56 (dd, $J = 11.5, 2.5$ Hz, 1H, NCH), 2.29 (dd, $J = 11.5, 10.0$ Hz, 1H, NCH), 2.19 (ddd, $J = 11.5, 11.5, 3.5$ Hz (app td), 1H, NCH), 1.35 (d, $J = 6.5$ Hz, 1H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 197.3 (C=O), 143.5 (*ipso*-Ph), 135.2 (*ipso*-Ph), 133.6 (Ph), 129.1 (Ph), 128.7 (Ph), 128.5 (Ph), 127.7 (Ph), 127.3 (Ph), 78.4 (OCH), 67.4 (OCH₂), 65.2 (NCHMe), 52.4 (NCH₂), 50.8 (NCH₂), 19.7 (NCHMe); MS (ESI) m/z 296 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$ ($M + H$)⁺ 296.1645, found 296.1644 (+0.3 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min⁻¹) 6.8 min (minor), 9.9 min (major). Spectroscopic data consistent with those reported in the literature.¹⁶⁴

Lab Book Reference: **NS9-87**

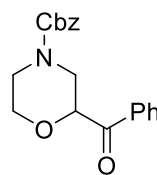
Phenyl(4-(1-phenylethyl)morpholin-2-yl)methanones (*S*,S)-301 and (*S*,R**)-301****(*S*,S**)-301****(*S*,R**)-301**

Using general procedure D, α -methyl benzyl morpholine *rac*-**125** (191.3 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA

(195 μ L, 150 mg, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and Weinreb amide **115** (304 μ L, 330 mg, 2.0 mmol, 2.0 eq.) gave the crude product which contained a 50:50 mixture (by ^1H NMR spectroscopy) of α -substituted morpholines (S^*,S^*)-**301** and (S^*,R^*)-**301**. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave α -substituted morpholine (S^*,S^*)-**301** (109 mg, 37%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.3 and a 60:40 mixture of morpholine (S^*,R^*)-**301** and Weinreb amide **115** (141 mg, i.e. 95 mg (32%) of (S^*,R^*)-**301**) and as a colourless oil R_F (80:20 hexane-EtOAc) 0.25; ^1H NMR (400 MHz, CDCl_3) for (S^*,R^*)-**301**: δ 7.94-7.86 (m, 2H, Ph), 7.70-7.64 (m, 1H, Ph), 7.56-7.49 (m, 2H, Ph), 7.34-7.20 (m, 5H, Ph), 4.84 (br d, $J = 10.0$ Hz, 1H, OCH), 4.09 (ddd, $J = 11.5, 3.0, 1.5$ Hz, 1H, OCH), 3.86 (dd, $J = 10.5, 10.5$ Hz (app t), 1H, OCH), 3.48-3.38 (m, 1H, NCHMe), 3.03-2.84 (m, 2H, NCH), 2.33 (dd, $J = 11.5, 11.5$ Hz (app t), 1H, NCH), 2.19 (dd, $J = 10.5, 10.0$ Hz, 1H, NCH), 1.37 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) for (S^*,R^*)-**301**: δ 197.3 (C=O), 143.5 (*ipso*- Ph), 134.3 (*ipso*- Ph), 133.5 (Ph), 129.0 (Ph), 128.6 (Ph), 128.5 (Ph), 127.7 (Ph), 127.3 (Ph), 78.6 (OCH), 67.5 (OCH₂), 65.0 (NCHMe), 53.1 (NCH₂), 49.8 (NCH₂), 19.5 (NCHMe); MS (ESI) for (S^*,R^*)-**301**: m/z 296 [$(\text{M} + \text{H})^+$, 100]; HRMS (ESI) for (S^*,R^*)-**301**: m/z calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$ ($\text{M} + \text{H})^+$ 296.1645, found 296.1643 (+0.8 ppm error); Spectroscopic data for (S^*,S^*)-**301** and (S^*,R^*)-**301** consistent with those reported in the literature.¹⁶⁴

Lab Book Reference: **NS9-89**

Benzyl (S)-2-benzoylmorpholine-4-carboxylate (S)-**261**



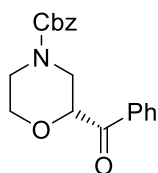
rac-**261**

Benzylchloroformate (257 mg, 1.5 mmol, 4.0 eq.) was added to a stirred solution of morpholine (S,S)-**301** (111 mg, 0.38 mmol, 1.0 eq.) and K_2CO_3 (1.4 mg, 22.6 μ mol, 0.06 eq.) in toluene (3 mL) at rt. The resulting mixture was stirred and heated at reflux for 16 h. Then, H_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 hexane-acetone then 90:10 hexane-acetone as eluent gave α -substituted morpholine (S)-**261** (94 mg, 74%, 99:1 er by CSP-HPLC) as a colourless

oil, $[\alpha]_D -24.9$ (c 0.50 in CHCl_3); R_F (90:10 hexane-acetone) 0.2; IR (ATR) 2859, 1690 (C=O), 1448, 1425, 1233, 1213, 1110, 1087, 1002, 911, 763, 694, 625 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.05-7.90 (m, 2H, Ph), 7.63-7.53 (m, 1H, Ph), 7.51-7.28 (m, 7H, Ph), 5.23-5.12 (m, 2H, OCHPh), 4.94-4.64 (m, 1H, OCH), 4.45-4.20 (m, 1H, OCH), 4.13-3.90 (m, 2H, OCH, NCH), 3.79-3.63 (m, 1H, NCH), 3.31-3.02 (m, 2H, NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 155.3 (C=O), 136.4 (*ipso*-Ph), 134.7 (*ipso*-Ph), 133.9 (Ph), 129.1 (Ph), 128.9 (Ph), 128.7 (Ph), 128.4 (Ph), 128.2 (Ph), 77.1 (OCH), 67.7 (OCH_2Ph), 66.8 (OCH_2), 45.8 (NCH_2), 43.7 (NCH_2); MS (ESI) m/z 348 $[(\text{M} + \text{H})^+]$, 100; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4$ ($\text{M} + \text{Na})^+$ 348.1206, found 348.1207 (-0.3 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) 27.0 min (minor), 35.3 min (major).

Lab Book Reference: **NS9-90**

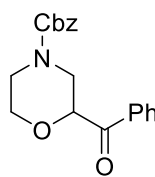
Benzyl (*R*)-2-benzoylmorpholine-4-carboxylate (*R*)-261



(*R*)-261

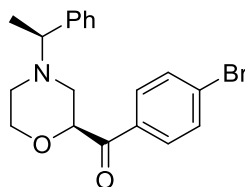
Benzylchloroformate (102 mg, 0.60 mmol, 4.0 eq.) was added to a stirred solution of morpholine (*R*)-128 (30 mg, 0.15 mmol, 1.0 eq., 63:37 er) and K_2CO_3 (0.50 mg, 7.3 μmol , 0.02 eq.) in toluene (2.5 mL) at rt. The resulting mixture was stirred and heated at reflux for 16 h. Then, H_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 hexane-acetone then 90:10 hexane-acetone as eluent gave α -substituted morpholine (*R*)-261 (35 mg, 62%) as a colourless oil, $[\alpha]_D +14.7$ (c 0.50 in CHCl_3).

Lab Book Reference: **NS12-33**

Benzyl (S)-2-benzoylmorpholine-4-carboxylate *rac*-261*rac*-261

Benzylchloroformate (162 mg, 0.95 mmol, 4.0 eq.) was added dropwise to a stirred solution of morpholine (*S*,R**)-**301** (70 mg, 0.24 mmol, 1.0 eq.) and K₂CO₃ (0.9 mg, 14.2 μmol, 0.06 eq.) in toluene (3 mL) at rt. The resulting mixture was stirred and heated at reflux for 16 h. Then, H₂O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 hexane-acetone then 90:10 hexane-acetone as eluent gave α -substituted morpholine *rac*-**261** (59 mg, 77%) as a colourless oil.

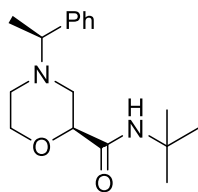
Lab Book Reference: **NS9-91**

(4-Bromophenyl)((S)-4-((S)-1-phenylethyl)morpholin-2-yl)methanone (S,S)-303(S,S)-**303**

Using general procedure H, stannane (*S,R*)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (233 μL of a 1.3 M solution in hexane, 0.30 mmol, 1.1 eq.) in THF (2.5 mL) and Weinreb amide **302** (103 μL, 0.42 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -substituted morpholine (*S,S*)-**303** (75 mg, 71%) as a colourless oil, [α]_D -6.7 (*c* 1.00 in CHCl₃); *R*_F (90:10 hexane-EtOAc) 0.3; IR (ATR) 2971, 2855, 2814, 1692 (C=O), 1585, 1450, 1203, 1121, 1069, 999, 955, 753, 701, 545 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.87-7.82 (m, 2H, Ar), 7.61-7.55 (m, 2H, Ar), 7.33-7.20 (m, 5H, Ar), 4.83 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 3.94 (ddd, *J* = 11.0, 3.5, 2.0 Hz, 1H, OCH), 3.73 (ddd, *J* = 11.0, 11.0, 2.0 Hz (app td), 1H, OCH), 3.38 (q, *J* = 6.5 Hz, 1H, NCHMe), 3.20 (ddd, *J* = 11.5, 2.0, 2.0 Hz (app dt), 1H, NCH), 2.56 (dd, *J* = 11.5, 2.5 Hz, 1H, NCH), 2.29 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH), 2.19 (ddd, *J* = 11.5, 11.0, 3.5 Hz, 1H, NCH), 1.35 (d, *J* = 6.5 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ

196.4 (C=O), 143.4 (*ipso*-Ar), 133.9 (*ipso*-Ar), 131.9 (Ar), 130.7 (Ar), 128.7 (Ar), 128.5 (Ar), 127.7 (Ar), 127.3 (Ar), 78.4 (OCH), 67.3 (OCH₂), 65.1 (NCHMe), 52.1 (NCH₂), 50.8 (NCH₂), 19.6 (NCHMe); MS (ESI) m/z 374 [$(^{79}\text{M} + \text{H})^+$, 100], 376 [$(^{81}\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for C₁₉H₂₀⁷⁹BrNO₂ ($(^{79}\text{M} + \text{H})^+$) 374.0750, found 372.0749 (+0.2 ppm error).
Lab Book Reference: **NS9-48**

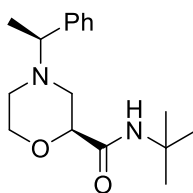
(S)-N-(*tert*-Butyl)-4-((S)-1-phenylethyl)morpholine-2-carboxamide (S,S)-304



(S,S)-304

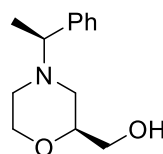
Using general procedure H, stannane (*S,R*)-**300** (160 mg, 0.45 mmol, 1.0 eq.), *n*-BuLi (0.33 mL of a 1.5 M solution in hexane, 0.50 mmol, 1.1 eq.) in THF (5 mL) and *t*-butyl isocyanate (77 μL , 0.68 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 75:25 hexane-EtOAc as eluent gave α -substituted morpholine (*S,S*)-**304** (119 mg, 91%, 99:1 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} -33.0$ (c 0.5 in CHCl₃); R_{F} (75:25 hexane-EtOAc) 0.3; IR (ATR) 3410 (NH), 2972, 2871, 1670 (C=O), 1526, 1452, 1365, 1215, 1122, 1083, 953, 749, 701, 542 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.18 (m, 5H, Ph), 6.37 (br s, 1H, NH), 3.93 (dd, $J = 11.0, 3.0$ Hz, 1H, OCH), 3.79 (ddd, $J = 11.0, 3.0, 1.5$ Hz, 1H, OCH), 3.57 (ddd, $J = 11.5, 11.0, 2.5$ Hz, 1H, OCH), 3.45 (dd, $J = 11.5, 3.0$ Hz, 1H, NCH), 3.31 (q, $J = 6.5$ Hz, 1H, NCHMe), 2.50 (ddd, $J = 11.5, 2.5, 1.5$ Hz, 1H, NCH), 1.97 (ddd, $J = 11.5, 11.5, 3.0$ Hz (app td), 1H, NCH), 1.89 (dd, $J = 11.0, 11.0$ Hz (app t), 1H, NCH), 1.36 (d, $J = 6.5$ Hz, 3H, NCHMe), 1.35 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 169.5 (C=O), 143.8 (*ipso*-Ph), 128.5 (Ph), 127.8 (Ph), 127.2 (Ph), 76.3 (OCH), 67.0 (OCH₂), 65.3 (NCHMe), 53.0 (NCH₂), 50.9 (NCH₂), 50.8 (NCMe₃), 28.9 (CMe₃), 20.0 (NCHMe); MS (ESI) m/z 291 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₇H₂₆N₂O₂ (M + H)⁺ 291.2067, found 291.2068 (−0.2 ppm error); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min⁻¹) 6.0 min (major), 7.9 min (minor).

Lab Book Reference: **NS10-31**

***N*-(*tert*-Butyl)-4-(1-phenylethyl)morpholine-2-carboxamide (*S**,*S**)-304****(*S**,*S**)-304**

Using general procedure H, stannane (*S**,*R**)-**300** (66 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (137 μ L of a 1.5 M solution in hexane, 0.21 mmol, 1.1 eq.) in THF (3 mL) and *t*-butyl isocyanate (32.1 μ L, 28.0 mg, 0.28 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 75:25 hexane-EtOAc as eluent gave α -substituted morpholine (*S**,*S**)-**304** (50 mg, 93%) as a colourless oil.

Lab Book Reference: **NS10-32**

((*S*)-4-((*S*)-1-Phenylethyl)morpholin-2-yl)methanol (*S*,*S*)-305**(*S*,*S*)-305**

Using general procedure H, stannane (*S*,*R*)-**300** (354 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.73 mL of a 1.5 M solution in hexane, 1.1 mmol, 1.1 eq.) in THF (5 mL) and DMF (115 μ L, 110 mg, 1.5 mmol, 1.5 eq.) gave the crude aldehyde product. The crude aldehyde product was diluted in MeOH (5 mL) and NaBH₄ (76 mg, 2.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at rt for 1 h. The solvent was evaporated under reduced pressure. Then, H₂O (20 mL) and Et₂O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 20 mL) and the combined organic layers were dried (MgSO₄) and evaporated to give the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 50:50 CH₂Cl₂-acetone as eluent gave α -substituted morpholine (*S*,*S*)-**305** (179 mg, 81%, 99:1 er by CSP-HPLC) as a colourless oil, [α]_D -15.9 (*c* 0.50 in CHCl₃); *R*_F (50:50 hexane-EtOAc) 0.3; IR (ATR) 3428 (OH), 2971, 2870, 2814, 1451, 1119, 1077, 1051, 981, 763, 702, 546 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.20 (m, 5H, Ph), 3.80 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.73-3.52 (m, 4H, OCH), 3.32 (q, *J* = 6.5 Hz, 1H, NCHMe), 2.90 (br d, *J* = 11.0 Hz, 1H, NCH), 2.55-2.48 (m, 1H, NCH), 2.13-1.97 (m, 3H, NCH, OH), 1.35 (d, *J* = 6.5 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.7 (*ipso*-Ph), 128.5 (Ph), 127.7 (Ph), 127.2

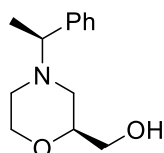
(Ph), 76.2 (OCH₂), 66.9 (OCH), 65.4 (OCH₂), 64.5 (NCHMe), 52.0 (NCH₂), 51.1 (NCH₂), 19.7 (NCHMe); MS (ESI) m/z 222 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₃H₁₉NO₂ (M + H)⁺ 222.1489, found 222.1488 (+0.5 ppm error); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 0.5 mL min⁻¹) 23.4 min (major), 26.0 min (minor).

Lab Book Reference: **NS11-51**

Using general procedure H, stannane (*S,R*)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (0.205 mL of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (2.5 mL) and paraformaldehyde (25 mg, 0.85 mmol, 3.0 eq.) gave the crude product which did not contain any desired alcohol (by ¹H NMR spectroscopy).

Lab Book Reference: **NS10-71**

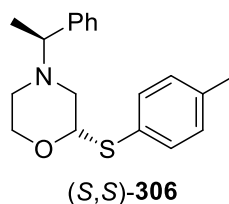
(4-(1-Phenylethyl)morpholin-2-yl)methanol (*S*,S**)-**305**



(*S*,S**)-**305**

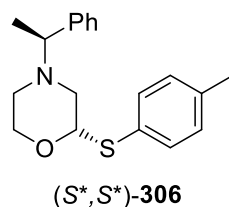
Using general procedure H, stannane (*S*,R**)-**300** (248 mg, 0.70 mmol, 1.0 eq.), *n*-BuLi (513 µL of a 1.5 M solution in hexane, 0.77 mmol, 1.1 eq.) in THF (4 mL) and DMF (89 µL, 85 mg, 1.2 mmol, 1.5 eq.) gave the crude aldehyde product. The crude aldehyde product was diluted in MeOH (5 mL) and NaBH₄ (58 mg, 1.5 mmol, 2.0 eq.) was added and the resulting solution was stirred at rt for 1 h. The solvent was evaporated under reduced pressure. Then, H₂O (20 mL) and Et₂O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 20 mL) and the combined organic layers were dried (MgSO₄) and evaporated to give the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 50:50 CH₂Cl₂-acetone as eluent gave α-substituted morpholine (*S*,S**)-**305** (126 mg, 83%) as a colourless oil.

Lab Book Reference: **NS11-52**

(S)-4-((S)-1-Phenylethyl)-2-(p-tolylthio)morpholine (S,S)-306

Using general procedure H, stannane (S,S)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (207 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL) and *p*-tolyl disulfide (104 mg, 0.42 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc then 90:10 hexane-EtOAc as eluent gave α -substituted morpholine (S,S)-**306** (54 mg, 61%, 99:1 er by CSP-HPLC) as a white solid, mp 65-67 °C; R_F (90:10 hexane-EtOAc) 0.3; $[\alpha]_D -104.3$ (*c* 1.00 in CHCl₃); IR (ATR) 2970, 2869, 2803, 1492, 1450, 1278, 1136, 1081, 917, 806, 767, 700, 501 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.28 (m, 6H, Ar), 7.28-7.24 (m, 1H, Ar), 7.14-7.05 (m, 2H, Ar), 5.18-5.13 (m, 1H, OCH), 4.25 (ddd, *J* = 13.0, 6.0, 4.0 Hz, 1H, OCH), 3.67-3.55 (m, 1H, OCH), 3.35 (q, *J* = 6.5 Hz, 1H, NCHMe), 2.81-2.69 (m, 2H, NCH), 2.47-2.42 (m, 2H, NCH), 2.31 (s, 3H, ArMe), 1.34 (d, *J* = 6.5 Hz, 1H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.7 (*ipso*-Ar), 137.0 (*ipso*-Ar), 132.1 (*ipso*-Ar), 131.5 (Ar), 129.7 (Ar), 128.5 (Ar), 127.7 (Ar), 127.2 (Ar), 85.3 (OCH), 64.7 (NCHMe), 63.6 (OCH₂), 55.4 (NCH₂), 50.7 (NCH₂), 21.2 (ArMe), 19.6 (NCHMe); MS (ESI) *m/z* 314 [(*M* + *H*)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₉H₂₃NOS (*M* + *H*)⁺ 314.1573, found 314.1569 (+1.4 ppm error); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min⁻¹) 8.3 min (minor), 11.2 min (major).

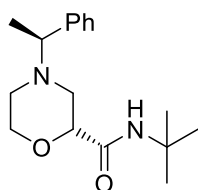
Lab Book Reference: **NS10-12**

4-((-1-Phenylethyl)-2-(p-tolylthio)morpholine (S*,S*)-306

Using general procedure H, stannane (S*,S*)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (207 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL) and *p*-tolyl disulfide (104 mg, 0.42 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc then 90:10 hexane-EtOAc as eluent gave α -substituted morpholine (S*,S*)-**306** (54 mg, 61%) as a white solid.

Lab Book Reference: **NS10-8**

(*R*)-*N*-(*tert*-Butyl)-4-((*S*)-1-phenylethyl)morpholine-2-carboxamide (*S,R*)-304

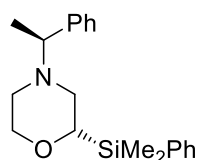


(*S,R*)-304

Using general procedure H, stannane (*S,R*)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (206 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL) and *t*-butyl isocyanate (48 μ L, 0.42 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on basic silica (pre-washed with 99:1 hexane: Et₃N) with 60:40 hexane-EtOAc as eluent gave an 85:15 mixture (by ¹H NMR spectroscopy) of α -substituted morpholine (*S,R*)-**304** and α -methyl benzyl morpholine (*S*)-**154** (76 mg, i.e. 68 mg (83%) of (*S,R*)-**304**, 8 mg of (*S*)-**154** (14%)) as a colourless oil, *R*_F (50:50 hexane-EtOAc) 0.2; *R*_F (50:50 hexane-EtOAc) 0.3; IR (ATR) 3412 (NH), 2969, 2869, 1678 (C=O), 1522, 1452, 1464, 1284, 1227, 1122, 960, 762, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) for (*S,R*)-**304** δ 7.34-7.16 (m, 5H, Ph), 6.33 (br s, 1H, NH), 3.91 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.85 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 3.69 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.44 (q, *J* = 7.0 Hz, 1H, NCHMe), 3.13 (dd, *J* = 11.5, 2.5 Hz, 1H, NCH), 2.78 (ddd, *J* = 11.5, 2.5, 2.0 Hz, 1H, NCH), 2.15 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.83 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH), 1.36 (d, *J* = 7.0 Hz, 3H, NCHMe), 1.31 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) for (*S,R*)-**304** δ 169.0 (C=O), 142.4 (*ipso*-Ph), 128.1 (Ph), 127.5 (Ph), 126.9 (Ph), 75.9 (OCH), 66.7 (OCH₂), 64.5 (NCHMe), 52.6 (NCH₂), 50.5 (NCMe₃), 49.5 (NCH₂), 28.5 (CMe₃), 18.9 (NCHMe); MS (ESI) *m/z* 291 [(*M* + *H*)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₇H₂₆N₂O₂ (*M* + *H*)⁺ 291.2067, found 291.2067 (+0.1 ppm error).

Lab Book Reference: **NS10-9**

(*S*)-2-(Dimethyl(phenyl)silyl)-4-((*S*)-1-phenylethyl)morpholine (*S,S*)-307



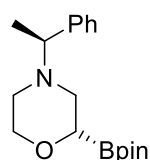
(*S,S*)-307

Using general procedure H, stannane (*S,S*)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (207 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL) and PhSiMe₂Cl (71 μ L, 72 mg, 0.41 mmol, 1.5 eq.) gave the crude product. Purification by flash column

chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -substituted morpholine (S,S)-**307** (84 mg, 91%) as a colourless oil, $[\alpha]_D -33.7$ (c 0.50 in CHCl₃); R_F (90:10 hexane-EtOAc) 0.4; IR (ATR) 3069, 2955, 2900, 2849, 2802, 1451, 1428, 1116, 1098, 872, 832, 814, 731, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.44 (m, 3H, Ph), 7.36-7.18 (m, 7H, Ph), 3.91 (ddd, $J = 11.5, 3.0, 2.0$ Hz, 1H, OCH), 3.65 (ddd, $J = 11.5, 11.5, 2.5$ Hz (app td), 1H, OCH), 3.48 (dd, $J = 11.5, 2.0$ Hz, 1H, OCH), 3.30 (q, $J = 6.5$ Hz, 1H, NCHMe), 2.87 (dd, $J = 11.5, 2.0$ Hz, 1H, NCH), 2.50 (ddd, $J = 11.5, 2.5, 2.0$ Hz, 1H, NCH), 2.22 (ddd, $J = 11.5, 11.5, 3.0$ Hz (app td), 1H, NCH), 2.05 (dd, $J = 11.5, 11.5$ Hz (app t), 1H, NCH), 1.33 (d, $J = 6.5$ Hz, 3H, NCHMe), 0.26 (s, 3H, SiMe), 0.22 (s, 3H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.9 (*ipso*-Ph), 136.8 (*ipso*-Ph), 134.1 (Ph), 129.3 (Ph), 128.3 (Ph), 127.8 (Ph), 127.7 (Ph), 127.0 (Ph), 71.3 (OCH), 69.2 (OCH₂), 65.2 (NCHMe), 53.0 (NCH₂), 50.9 (NCH₂), 19.2 (NCHMe), -5.1 (br, SiMe) (one SiMe resonance not resolved); MS (ESI) m/z 326 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₂₀H₂₇NOSi (M + H)⁺ 326.1935, found 326.1935 (-0.1 ppm error).

Lab Book Reference: **NS11-68**

Attempted Synthesis of (S)-4-((S)-1-Phenylethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)morpholine (S,S)-**308**

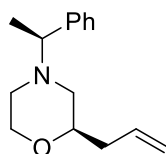


(S,S)-**308**

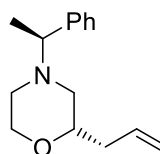
Using general procedure H, stannane (S,S)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (207 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL) and *i*-PrOBpin (86 μ L, 78.7 mg, 0.42 mmol, 1.5 eq.) gave the crude product which did not contain the desired α -substituted morpholine (S,S)-**308** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS12-11**

2-Allyl-4-(1-phenylethyl)morpholine (S*,R*)-**309** and (S*,S*)-**309**



(S*,R*)-**309**



(S*,S*)-**309**

Table 3.1, entry 2:

n-BuLi (103 μ L of a 1.5 M solution in hexane, 0.16 mmol, 1.1 eq.) was added dropwise to a stirred solution of stannane (*S**,*R**)-**300** (50 mg, 0.14 mmol, 1.0 eq.) in THF (3 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 30 min. Then, CuCN $\cdot$ 2LiCl (676 μ L of a 0.25 M solution in THF, 0.17 mmol, 1.2 eq.) was added. After stirring at -78 °C for 30 min, allyl bromide (36 μ L, 0.42 mmol, 3.0 eq.) was added. The resulting solution was stirred at -78 °C for 1 h and allowed to warm to rt. Saturated NH₄Cl_(aq) (10 mL) and 10% NaHCO_{3(aq)} (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained an 87:13 mixture of α -substituted morpholines (*S**,*R**)-**309** and (*S**,*S**)-**309** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave α -substituted morpholine (*S**,*R**)-**309** (20 mg, 69%) as a colourless oil, *R*_F (95:5 hexane-EtOAc) 0.2; IR (ATR) 2875, 2853, 2806, 1492, 1449, 1346, 1115, 989, 912, 763, 702, 546 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.20 (m, 5H, Ph), 5.83 (dddd, *J* = 17.0, 10.5, 7.0, 7.0 Hz (app ddt), 1H, CH=CH₂), 5.12-5.03 (m, 2H, CH=CH₂), 3.76 (ddd, *J* = 11.5, 3.0, 2.0 Hz, 1H, OCH), 3.64-3.57 (m, 1H, OCH), 3.56 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.28 (q, *J* = 6.5 Hz, 1H, NCHMe), 2.95 (ddd, *J* = 11.5, 2.5, 2.5 Hz (app dt), 1H, NCH), 2.48 (ddd, *J* = 11.5, 2.0, 2.0 Hz (app dt), 1H, NCH), 2.29 (ddd, *J* = 14.0, 7.0, 2.0 Hz, 1H, CH), 2.24-2.15 (m, 1H, CH), 2.00 (ddd, *J* = 11.5, 11.5, 3.0 Hz (app td), 1H, NCH), 1.85 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH), 1.34 (d, *J* = 7.0 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 144.0 (*ipso*-Ph), 134.6 (CH=CH₂), 128.4 (Ph), 127.8 (Ph), 127.1 (Ph), 117.1 (CH=CH₂), 75.4 (OCH), 67.2 (OCH₂), 65.4 (NCHMe), 55.5 (NCH₂), 51.2 (NCH₂), 38.6 (CH₂), 19.9 (NCHMe); MS (ESI) *m/z* 232 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₅H₂₁NO (M + H)⁺ 232.1696, found 232.1697 (-0.6 ppm error) and α -substituted morpholine (*S**,*S**)-**309** (3 mg, 9%) as a colourless oil, *R*_F (95:5 hexane-EtOAc) 0.2; IR (ATR) 2875, 2853, 2807, 1450, 1140, 1116, 961, 912, 762, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.19 (m, 5H, Ph), 5.74 (dddd, *J* = 17.0, 10.5, 7.0, 7.0 Hz (app ddt), 1H, CH=CH₂), 5.06-4.93 (m, 2H, CH=CH₂), 3.90 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.68 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.48 (dddd, *J* = 10.5, 7.5, 5.5, 2.5 Hz, 1H, OCH), 3.30 (q, *J* = 6.5 Hz, 1H, NCHMe), 2.84 (dd, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.56 (ddd, *J* = 11.5, 2.0, 2.0 Hz (app td), 1H, NCH), 2.22-2.11 (m, 2H, CH), 2.11-1.99 (m, 1H, NCH), 1.73 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH), 1.33 (d, *J* = 6.5 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 144.0 (*ipso*-Ph), 134.7 (CH=CH₂), 128.4 (Ph), 127.8 (Ph), 127.1 (Ph), 116.9

(CH=CH₂), 75.5 (OCH), 67.3 (OCH₂), 65.2 (NCHMe), 56.4 (NCH₂), 50.2 (NCH₂), 38.3 (CH₂), 19.8 (NCHMe); MS (ESI) *m/z* 232 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₅H₂₁NO (M + H)⁺ 232.1696, found 232.1697 (−0.4 ppm error).

Lab Book Reference: **NS10-22**

Table 3.1, entry 1:

Using general procedure H, stannane (*S*,R**)-**300** (50 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (103 µL of a 1.5 M solution in hexane, 0.16 mmol, 1.1 eq.) in THF (3 mL) and allyl bromide (18 µL, 0.21 mmol, 1.5 eq.) gave the crude product which contained a 50:50 mixture of α-substituted morpholine (*S*,R**)-**309** and (*S*,S**)-**309** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave α-substituted morpholine (*S*,R**)-**309** (8 mg, 25%) as a colourless oil and α-substituted morpholine (*S*,S**)-**309** (7 mg, 23%) as a colourless oil.

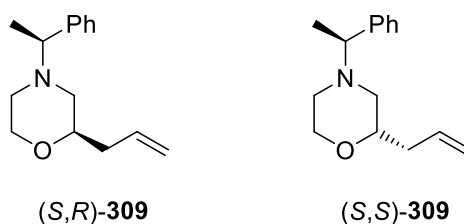
Lab Book Reference: **NS10-23**

Table 3.1, entry 3:

Using general procedure J, stannane (*S*,R**)-**300** (50 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (103 µL of a 1.5 M solution in hexane, 0.16 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (261 µL of a 0.7 M solution in THF, 0.18 mmol, 1.3 eq.), CuCN·2LiCl (676 µL of a 0.25 M solution in THF, 0.17 mmol, 1.2 eq.) and allyl bromide (36 µL, 0.42 mmol, 3.0 eq.) gave the crude product which contained a 95:5 mixture of α-substituted morpholines (*S*,R**)-**309** and (*S*,S**)-**309** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave α-substituted morpholine (*S*,R**)-**309** (24 mg, 71%) as a colourless oil and α-substituted morpholine (*S*,S**)-**309** (2 mg, 2%) as a colourless oil.

Lab Book Reference: **NS10-24**

2-Allyl-4-(1-phenylethyl)morpholine (*S,R*)-**309** and (*S,S*)-**309**

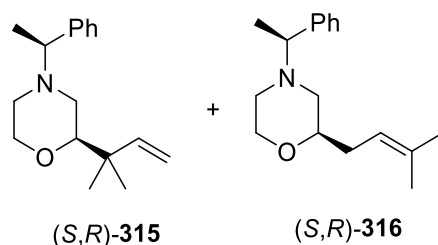


Using general procedure J, stannane (*S,R*)-**300** (50 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (103 µL of a 1.5 M solution in hexane, 0.16 mmol, 1.1 eq.) in THF (3 mL) ZnCl₂ (261 µL of a 0.7 M

solution in THF, 0.18 mmol 1.3 eq.), CuCN·2LiCl (676 µL of a 0.25 M solution in THF, 0.17 mmol, 1.2 eq.) and allyl bromide (36 µL, 0.42 mmol, 3.0 eq.) gave the crude product which contained a 95:5 mixture of α -substituted morpholines (*S,R*)-**309** and (*S,S*)-**309** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave α -substituted morpholine (*S,R*)-**309** (46 mg, 72%, 99:1 er by CSP-HPLC) as a colourless oil, $[\alpha]_{\text{D}} -20.8$ (c 0.50 in CHCl_3); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 0.7 mL min $^{-1}$) 5.7 min (major), 6.6 min (minor) and α -substituted morpholine (*S,S*)-**309** (1 mg, 2%) as a colourless oil.

Lab Book Reference: NS10-25

(*R*)-2-(2-Methylbut-3-en-2-yl)-4-((*S*)-1-phenylethyl)morpholine (*S,R*)-315** and (*R*)-2-(3-Methylbut-2-en-1-yl)-4-((*S*)-1-phenylethyl)morpholine (*S,R*)-**316****

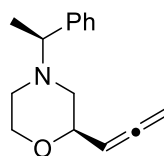


Using general procedure J, stannane (*S,R*)-**300** (100 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (150 µL of a 2.08 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL) ZnCl₂ (523 µL of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.), CuCN·2LiCl (1.35 mL of a 0.25 M solution in THF, 0.34 mmol, 1.2 eq.) and 1-bromo-3-methylbut-2-ene (98 µL, 0.85 mmol, 3.0 eq.) gave the crude product which contained a 50:50 mixture of α -substituted morpholines (*S,R*)-**315** and (*S,R*)-**316** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 90:10 hexane-EtOAc to 80:20 hexane-EtOAc as eluent gave a 50:50 mixture of α -substituted morpholines (*S,R*)-**315** and (*S,R*)-**316** (57 mg, 78%) as a colourless oil, R_{F} (80:20 hexane-EtOAc) 0.4; IR (ATR) 2968, 2853, 2809, 1492, 1450, 1321, 1137, 1117, 1087, 947, 913, 763, 701, 548 cm $^{-1}$; ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.16 (m, 5H, Ph), 5.90 (dd, J = 18.0, 10.5 Hz, 0.5H, $\text{CH}=\text{CH}_2$), 5.19-5.13 (m, 0.5H, $\text{CH}_2\text{CH}=\text{C}(\text{Me}_2)$), 5.02-4.96 (m, 1H, $\text{CH}=\text{CH}_2$), 3.79-3.69 (m, 1H, OCH), 3.60-3.47 (m, 1.5H, OCH), 3.34-3.21 (m, 1.5H, OCH, 2 x NCHMe), 3.03-2.92 (m, 1H, NCH), 2.51-2.42 (m, 1H, NCH), 2.22 (ddd, J = 14.0, 7.0, 7.0 Hz (app dt), 0.5H, CH), 2.13 (ddd, J = 14.0, 7.0, 7.0 Hz (app dt), 0.5H, CH), 1.98 (ddd, J = 11.5, 11.5, 3.0 Hz (app td), 0.5H, NCH), 1.90 (ddd, J = 12.0, 11.5, 3.0 Hz, 0.5H, NCH), 1.85-1.79 (m, 1H, NCH), 1.71 (s, 1.5H, $\text{CH}=\text{CMe}$), 1.61 (s, 1.5H, $\text{CH}=\text{CMe}$), 1.34 (d, J = 6.5 Hz, 1.5H, NCHMe), 1.33 (d, J = 6.5 Hz, 1.5H, NCHMe), 1.03 (s, 3H,

$\text{CMe}_2\text{CH}=\text{CH}_2$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 145.5 ($\text{CH}=\text{CMe}_2$), 144.1 (*ipso*-Ph), 144.0 (*ipso*-Ph), 133.9 ($\text{CH}=\text{CMe}_2$), 128.4 (Ph), 127.77 (Ph), 127.76 (Ph), 127.10 (Ph), 127.07 (Ph), 119.9 ($\text{CH}=\text{CH}_2$), 111.9 ($\text{CH}=\text{CH}_2$), 82.8 (OCH), 76.3 (OCH), 67.5 (OCH_2), 67.2 (OCH_2), 65.8 (NCHMe), 65.5 (NCHMe), 55.8 (NCH_2), 51.4 (NCH_2), 51.4 (NCH_2), 51.3 (NCH_2), 39.9 ($\text{CMe}_2\text{CH}=\text{CH}_2$), 32.9 ($\text{CH}_2\text{CH}=\text{CMe}_2$), 25.9 ($\text{CH}=\text{CMe}_2$), 23.9 ($\text{CMe}_2\text{CH}=\text{CH}_2$), 23.4 ($\text{CMe}_2\text{CH}=\text{CH}_2$), 20.2 (NCHMe), 20.1 (NCHMe), 18.1 ($\text{CH}=\text{CMe}_2$) (one Ph resonance not resolved); MS (ESI) m/z 260 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{25}\text{NO}$ (M + H)⁺ 260.2009, found 260.2008 (+0.2 ppm error).

Lab Book Reference: **NS12-3**

(R)-4-((S)-1-Phenylethyl)-2-(propa-1,2-dien-1-yl)morpholine (S,R)-317

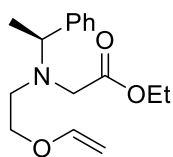


(S,R)-317

Using general procedure J, stannane (S,R)-**300** (100 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (150 μL of a 2.08 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL), ZnCl_2 (523 μL of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.), $\text{CuCN}\cdot 2\text{LiCl}$ (1.35 mL of a 0.25 M solution in THF, 0.34 mmol, 1.2 eq.) and propargyl bromide (76 μL , 101 mg, 0.85 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc to 80:20 hexane-EtOAc as eluent gave α -allenyl morpholine (S,R)-**317** (53 mg, 82%) as a colourless oil, $[\alpha]_{\text{D}} -39.9$ (c 0.50 in CHCl_3); R_{F} (80:20 hexane-EtOAc) 0.4; IR (ATR) 2970, 2854, 2807, 1958 (C=C), 1450, 1344, 1214, 1110, 1095, 944, 848, 763, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.15 (m, 5H, Ph), 5.22 (dd, $J = 6.5, 6.5$ Hz (app t), 1H, $\text{HC}=\text{C}=\text{CH}_2$), 4.87 (dd, $J = 6.5, 2.5$ Hz, 1H, $\text{HC}=\text{C}=\text{CH}_2$), 4.82 (dd, $J = 6.5, 2.5$ Hz, 1H, $\text{HC}=\text{C}=\text{CH}_2$), 4.17-4.06 (m, 1H, OCH), 3.80 (ddd, $J = 11.5, 3.0, 2.0$ Hz, 1H, OCH), 3.61 (ddd, $J = 11.5, 11.0, 2.5$ Hz, 1H, OCH), 3.32 (q, $J = 6.5$ Hz, 1H, NCHMe), 2.98 (ddd, $J = 11.0, 2.5, 2.0$ Hz, 1H, NCH), 2.48 (dd, $J = 11.5, 2.0$ Hz, 1H, NCH), 2.08 (ddd, $J = 11.5, 11.0, 3.5$ Hz, 1H, NCH), 2.01 (dd, $J = 11.5, 11.5$ Hz (app t), 1H, NCH), 1.35 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 208.3 ($\text{CH}=\text{C}=\text{CH}_2$), 143.9 (*ipso*-Ph), 128.4 (Ph), 127.7 (Ph), 127.1 (Ph), 90.7 ($\text{CH}=\text{C}=\text{CH}_2$), 77.0 ($\text{CH}=\text{C}=\text{CH}_2$), 73.7 (OCH), 67.1 (OCH_2), 65.2 (NCHMe), 55.5 (NCH_2), 50.9 (NCH_2), 19.8 (NCHMe); MS (ESI) m/z 230 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{NO}$ (M + H)⁺ 230.1539, found 230.1537 (+0.9 ppm error).

Lab Book Reference: **NS12-4**

(S)-Ethyl *N*-(1-phenylethyl)-*N*-(2-(vinylloxy)vinyl)glycinate (S)-318

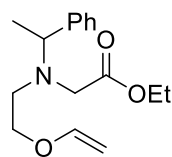


(S)-318

Using general procedure J, stannane (*S,S*)-**300** (50 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (103 μ L of a 1.5 M solution in hexane, 0.16 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (262 μ L of a 0.7 M solution in THF, 0.18 mmol, 1.3 eq.), CuCN·2LiCl (680 μ L of a 0.25 M solution in THF, 0.17 mmol, 1.2 eq.) and ethyl 2-bromoacetate (47 μ L, 0.42 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave enol ether (*S*)-**318** (28 mg, 72%, 99:1 er by CSP-HPLC) as a colourless oil, $[\alpha]_D -13.6$ (c 0.25 in CHCl₃); R_F (90:10 hexane-EtOAc) 0.4; IR (ATR) 2975, 2930, 1737 (C=O), 1615, 1371, 1320, 1199, 1080, 1030, 968, 819, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.32 (m, 2H, Ph), 7.34-7.24 (m, 2H, Ph), 7.24-7.19 (m, 1H, Ph), 6.40 (dd, J = 14.5, 7.0 Hz, 1H, OCH=CH₂), 4.14 (br q, J = 7.0 Hz, 2H, OCHMe), 4.15-4.10 (m, 1H, OCH=CH₂), 4.09 (q, J = 7.0 Hz, 1H, NCHMe), 3.94 (dd, J = 7.0, 2.0 Hz, 1H, OCH=CH₂), 3.69 (br d, J = 6.0 Hz, 1H, OCH), 3.68 (br d, J = 6.0 Hz, 1H, OCH), 3.53 (d, J = 17.0 Hz, 1H, CHC(O)), 3.39 (d, J = 17.0 Hz, 1H, CHC(O)), 2.95 (ddd, J = 14.0, 6.0, 6.0 Hz (app dt), 1H, NCH), 2.87 (ddd, J = 14.0, 6.0, 6.0 Hz (app dt), 1H, NCH), 1.34 (d, J = 7.0 Hz, 3H, NCHMe), 1.24 (t, J = 7.0 Hz, 3H, CH₂Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 172.3 (C=O), 151.8 (OCH=CH₂), 144.7 (*ipso*-Ph), 128.5 (Ph), 127.7 (Ph), 127.2 (Ph), 86.6 (OCH=CH₂), 67.7 (OCH₂), 61.1 (NCHMe), 60.4 (OCH₂), 52.6 (NCH₂), 50.4 (NCH₂), 19.8 (NCHMe), 14.4 (CH₂Me); MS (ESI) m/z 278 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₆H₂₃NO₃ (M + H)⁺ 278.1751, found 278.1748 (+1.1 ppm error); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min⁻¹) 4.8 min (major), 5.3 min (minor).

Lab Book Reference: **NS10-26**

Ethyl *N*-(1-phenylethyl)-*N*-(2-(vinylloxy)vinyl)glycinate *rac*-318

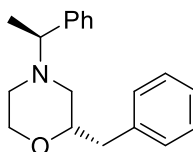


rac-318

Using general procedure J, stannane (*S,S*)-**300** (50 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (103 μ L of a 1.5 M solution in hexane, 0.16 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (262 μ L of a 0.7 M solution in THF, 0.18 mmol, 1.3 eq.), CuCN·2LiCl (680 μ L of a 0.25 M solution in THF, 0.17 mmol, 1.2 eq.) and ethyl 2-bromoacetate (47 μ L, 0.42 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave enol ether *rac*-**318** (27 mg, 69%) as a colourless oil.

Lab Book Reference: **NS10-27**

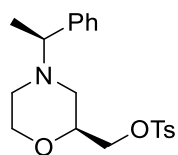
Attempted Synthesis of Ethyl 2-((*S*)-4-((*S*)-1-phenylethyl)morpholin-2-yl)acetate (*S,S*)-321



(*S,S*)-321

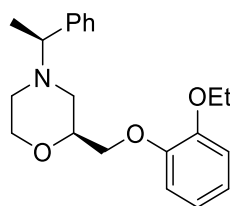
Using general procedure J, stannane (*S,S*)-**300** (50 mg, 0.14 mmol, 1.0 eq.), *n*-BuLi (103 μ L of a 1.5 M solution in hexane, 0.16 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (262 μ L of a 0.7 M solution in THF, 0.18 mmol, 1.3 eq.), CuCN·2LiCl (680 μ L of a 0.25 M solution in THF, 0.17 mmol, 1.2 eq.) and benzyl bromide (47 μ L, 0.42 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave only traces of α -substituted morpholine as a colourless oil.

Lab Book Reference: **NS10-30**

(S)-4-((S)-1-Phenylethyl)morpholin-2-yl)methyl 4-methylbenzenesulfonate (S,S)-326**(S,S)-326**

4-Toluenesulfonyl chloride (191 mg, 1.0 mmol, 1.05 eq.) was added to a stirred solution of alcohol (S,S)-**305** (211 mg, 0.95 mmol, 1.0 eq.) and Et₃N (146 μ L, 106 mg, 235 mg, 1.1 mmol, 1.1 eq.) in CH₂Cl₂ (5 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure and EtOAc (20 mL) was added. The EtOAc solution was washed with H₂O (20 mL) and brine (20 mL), dried MgSO₄ and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc then EtOAc as eluent gave tosylate (S,S)-**326** (303 mg, 85%) as a colourless oil [α]_D –12.8 (*c* 0.8 in CHCl₃); *R*_F (80:20 hexane-EtOAc) 0.1; IR (ATR) 2971, 2860, 1493, 1451, 1370, 1189, 1175, 1122, 995, 814, 703, 666, 554 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.82-7.77 (m, 2H, Ar), 7.37-7.20 (m, 7H, Ar), 4.05 (dd, *J* = 10.5, 5.0 Hz, 1H, OCH), 3.99 (dd, *J* = 10.5, 5.0 Hz, 1H, OCH), 3.82-3.73 (m, 1H, OCH), 3.71 (ddd, *J* = 11.5, 3.5, 2.5 Hz, 1H, OCH), 3.52 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.30 (q, *J* = 6.5 Hz, 1H, NCHMe), 2.88 (br d, *J* = 11.0 Hz, 1H, NCH), 2.52-2.45 (m, 1H, NCH), 2.45 (s, 3H, ArMe), 2.02 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.92 (dd, *J* = 10.5, 10.5 Hz (app t), 1H, NCH), 1.31 (d, *J* = 6.5 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 145.0 (*ipso*-Ar), 143.6 (*ipso*-Ar), 132.9 (*ipso*-Ar), 129.9 (Ar), 128.5 (Ar), 128.2 (Ar), 127.7 (Ar), 127.2 (Ar), 73.2 (OCH), 70.5 (OCH₂), 66.9 (OCH₂), 65.1 (NCHMe), 51.9 (NCH₂), 50.7 (NCH₂), 21.8 (ArMe), 19.6 (NCHMe); MS (ESI) *m/z* 376 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₀H₂₅NO₄S (M + H)⁺ 376.1577, found 376.1572 (+1.3 ppm error).

Lab Book Reference: **NS11-84**

(S)-2-((2-Ethoxyphenoxy)methyl)-4-((S)-1-phenylethyl)morpholine (S,S)-327**(S,S)-327**

2-Ethoxyphenol (84 μ L, 91 mg, 0.66 mmol, 1.1 eq.) was added dropwise to a stirred solution of tosylate (S,S)-**326** (226 mg, 0.60 mmol, 1.0 eq.) and Cs_2CO_3 (235 mg, 0.72 mmol, 1.2 eq.) in MeCN (5 mL) at rt. The resulting mixture was stirred and heated at 100 $^\circ\text{C}$ for 6 h. After cooling to rt, the solids were removed by filtration through Celite[®] and washed with EtOAc (30 mL). The filtrate was dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc then EtOAc as eluent gave morpholine (S,S)-**327** (130 mg, 61%) as a colourless oil, $[\alpha]_D -25.4$ (c 0.33 in CHCl_3); R_F (80:20 hexane-EtOAc) 0.3; IR (ATR) 2974, 2928, 2871, 2810, 1592, 1501, 1451, 1253, 1218, 1123, 1040, 763, 749, 701, 546 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.41-7.22 (m, 5H, Ar), 7.03-6.87 (m, 4H, Ar), 4.20-3.96 (m, 5H, OCH), 3.86 (ddd, $J = 11.0, 3.5, 2.0$ Hz, 1H, OCH), 3.69 (ddd, $J = 11.0, 11.0, 2.5$ Hz (app td), 1H, OCH), 3.40 (q, $J = 6.5$ Hz, 1H, NCHMe), 3.24 (ddd, $J = 11.0, 2.0, 2.0$ Hz (app dt), 1H, NCH), 2.57 (ddd, $J = 11.5, 2.0, 2.0$ Hz (app dt), 1H, NCH), 2.20-2.05 (m, 2H, NCH), 1.47 (t, $J = 7.0$ Hz, 3H, CH_2Me), 1.42 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 149.4 (*ipso*-Ar), 148.9 (*ipso*-Ar), 143.9 (*ipso*-Ar), 128.4 (Ar), 127.7 (Ar), 127.1 (Ar), 122.0 (Ar), 121.2 (Ar), 115.4 (Ar), 114.2 (Ar), 74.4 (OCH), 71.1 (OCH_2), 67.1 (OCH_2), 65.3 (NCHMe), 64.7 (OCH_2), 53.1 (NCH₂), 51.2 (NCH₂), 19.8 (NCHMe), 15.1 (CH_2Me); MS (ESI) m/z 342 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_3$ ($M + H$)⁺ 342.2064, found 342.2060 (+1.0 ppm error).

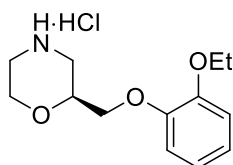
Lab Book Reference: **NS11-86**

DIAD (267 μ L, 275 mg, 1.4 mmol, 2.0 eq.) was added to a stirred solution of 2-ethoxyphenol (172 μ L, 88 mg, 1.4, 2.0 eq.), morpholine (S,S)-**305** (150 mg, 0.68 mmol, 1.0 eq.) and PPh_3 (325 μ L, 356 mg, 1.4 mmol, 2.0 eq.) in toluene (5 mL) at rt. The resulting mixture was stirred at rt for 5 days. After cooling to rt, the solvent was evaporated to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave a 50:50 mixture (by ^1H NMR spectroscopy) of α -substituted morpholine (S,S)-**327** and reduced DIAD **328** (204 mg, i.e. 130 mg (53%) of (S,S)-**327**) as a yellow oil. Further

chromatographic purification could not separate morpholine (S,S)-**327** from the reduced DIAD **328**.

Lab Book Reference: **NS11-66**

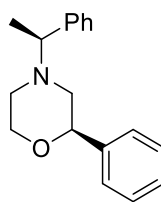
(S)-2-((2-Ethoxyphenoxy)methyl)morpholine hydrochloride (S)-Viloxazine·HCl



(S)-Viloxazine·HCl

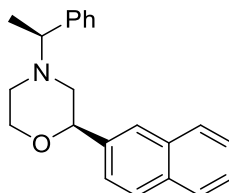
α -Chloroethyl chloroformate (108 μ L, 143 mg, 1.0 mmol, 4.0 eq.) was added dropwise to a stirred solution of the morpholine (S)-**327** (85 mg, 0.25 mmol, 1.0 eq.) in DCE (3 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. Then, the solvent was evaporated under reduced pressure. MeOH (3 mL) was added to the crude product and the resulting solution was stirred and heated at 65 $^{\circ}$ C for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 CH_2Cl_2 -EtOAc then 90:10 CH_2Cl_2 -MeOH then 80:20 CH_2Cl_2 -MeOH as eluent gave (S)-Viloxazine·HCl (62 mg, 90%) as a white solid, mp 151-153 $^{\circ}$ C (lit.,²⁰² 166-167 $^{\circ}$ C), $[\alpha]_{\text{D}} -4.6$ (c 0.9 in MeOH) (lit.,²⁰² -4.5 (c 1.0 in MeOH)); R_{F} (67:33 CH_2Cl_2 -MeOH) 0.4; IR (ATR) 3397 (NH), 2927, 2770, 2469, 1592, 1504, 1453, 1254, 1216, 1114, 1087, 1039, 746 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 7.01-6.79 (m, 4H, Ar), 4.17-3.98 (m, 6H, OCH), 3.87 (ddd, $J = 12.5, 12.5, 2.5$ Hz (app td), 1H, OCH), 3.47 (br d, $J = 12.5$ Hz, 1H, NCH), 3.36-3.25 (m, 2H, NCH, NH), 3.25-3.08 (m, 2H, NCH), 1.37 (t, $J = 7.0$ Hz, 3H, CH_2Me); ^{13}C NMR (100.6 MHz, CD_3OD) δ 150.6 (*ipso*-Ar), 149.6 (*ipso*-Ar), 123.7 (Ar), 122.3 (Ar), 116.9 (Ar), 115.2 (Ar), 73.2 (OCH), 71.2 (OCH_2), 65.6 (OCH_2), 64.7 (OCH_2), 45.9 (NCH_2), 44.1 (NCH_2), 15.3 (CH_2Me); MS (ESI) m/z 238 $[(\text{M})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_3$ M^+ 238.1438, found 238.1437 (+0.1 ppm error).

Lab Book Reference: **NS11-90**

(R)-2-Phenyl-4-((S)-1-phenylethyl)morpholine (S,R)-329**(S,R)-329**

Using general procedure C, stannane (S,R)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (231 μ L of a 1.3 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.37 mL of a 1.0 M solution in THF, 0.37 mmol, 1.3 eq.), Pd(OAc)₂ (4.4 mg, 7 mol%), *t*-Bu₃PHBF₄ (7.3 mg, 9 mol%) and bromobenzene (38 μ L, 0.37 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave α -aryl morpholine (S,R)-**329** (45 mg, 60%, 99:1 er by CSP-HPLC of *N*-Ts morpholine (R)-**338**) as a colourless oil, [α]_D -32.5 (c 1.00 in CHCl₃); *R*_F (80:20 hexane-EtOAc) 0.3; IR (ATR) 2975, 3028, 2969, 2854, 2806, 1450, 1290, 1257, 1223, 1118, 1097, 956, 919, 762, 699, 551 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.19 (m, 10H, Ph), 4.60 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 3.93 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.75 (ddd, *J* = 12.0, 11.5, 2.5 Hz, 1H, OCH), 3.36 (q, *J* = 6.5 Hz, 1H, NCHMe), 3.12 (ddd, *J* = 11.5, 2.5, 2.5 Hz (app dt), 1H, NCH), 2.60 (dd, *J* = 11.5, 2.5 Hz, 1H, NCH), 2.14 (ddd, *J* = 12.0, 11.5, 3.5 Hz, 1H, NCH), 2.16-2.04 (m, 1H, NCH), 1.36 (d, *J* = 6.5 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.8 (*ipso*-Ph), 140.9 (*ipso*-Ph), 128.47 (Ph), 128.45 (Ph), 127.9 (Ph), 127.8 (Ph), 127.2 (Ph), 126.4 (Ph), 78.6 (OCH), 67.5 (OCH₂), 65.4 (NCHMe), 57.9 (NCH₂), 51.0 (NCH₂), 19.9 (NCHMe); MS (ESI) *m/z* 268 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₈H₂₁NO (M + H)⁺ 268.1696, found 268.1691 (+1.8 ppm error).

Lab Book Reference: **NS9-44**

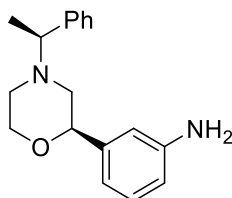
(R)-2-(Naphthalen-2-yl)-4-((S)-1-phenylethyl)morpholine (S,R)-330**(S,R)-330**

Using general procedure C, stannane (S,R)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (205 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.), Pd(OAc)₂ (4.4 mg, 7 mol%), *t*-Bu₃PHBF₄

(7.4 mg, 9 mol%) and 2-bromonaphthalene (76 mg, 0.37 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc to 90:10 hexane-EtOAc as eluent gave α -aryl morpholine (*S,R*)-**330** (28 mg, 31%) as a colourless oil, $[\alpha]_D -32.6$ (*c* 1.00 in CHCl₃); R_F (80:20 hexane-EtOAc) 0.4; IR (ATR) 3058, 2969, 2854, 2807, 1492, 1450, 1116, 1097, 821, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.93-7.75 (m, 4H, Ar), 7.56-7.20 (m, 8H, Ar), 4.77 (br d, *J* = 10.0 Hz, 1H, OCH), 3.98 (br d, *J* = 11.5 Hz, 1H, OCH), 3.87-3.72 (m, 1H, OCH), 3.45-3.31 (m, 1H, NCHMe), 3.20 (br d, *J* = 11.0 Hz, 1H, NCH), 2.63 (br d, *J* = 11.0 Hz, 1H, NCH), 2.29-2.10 (m, 2H, NCH), 1.40-1.32 (m, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.8 (*ipso*-Ar), 138.4 (*ipso*-Ar), 133.4 (*ipso*-Ar), 133.2 (*ipso*-Ar), 128.5 (Ar), 128.2 (Ar), 127.8 (Ar), 127.2 (Ar), 126.2 (Ar), 125.9 (Ar), 125.2 (Ar), 124.5 (Ar), 78.6 (OCH), 67.5 (OCH₂), 65.4 (NCHMe), 57.9 (NCH₂), 51.0 (NCH₂), 19.8 (NCHMe) (two Ar resonances not resolved); MS (ESI) *m/z* 318 [(*M* + *H*)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₂H₂₃NO (*M* + *H*)⁺ 318.1852, found 318.1854 (−0.5 ppm error).

Lab Book Reference: **NS11-63**

3-((*R*)-4-((*S*)-1-Phenylethyl)morpholin-2-yl)aniline (*S,R*)-**331**



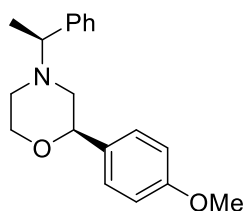
(*S,R*)-**331**

Using general procedure C, stannane (*S,R*)-**300** (200 mg, 0.57 mmol, 1.0 eq.), *n*-BuLi (467 μ L of a 1.3 M solution in hexane, 0.62 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (734 μ L of a 1.0 M solution in THF, 0.73 mmol, 1.3 eq.), Pd(OAc)₂ (8.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (14.7 mg, 9 mol%) and 3-bromo-aniline (80 μ L, 0.73 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 49.5:49.5:1 hexane-EtOAc-Et₃N as eluent gave α -aryl morpholine (*S,R*)-**331** (78 mg, 49%) as a colourless oil, $[\alpha]_D -36.7$ (*c* 1.00 in CHCl₃); R_F (49.5:49.5:1 hexane-EtOAc-Et₃N) 0.4; IR (ATR) 3364 (NH), 2970, 2856, 2807, 1608, 1492, 1450, 1289, 1105, 1083, 1029, 955, 752, 698, 543 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.28 (m, 3H, Ar), 7.28-7.21 (m, 1H, Ar), 7.23-7.18 (m, 1H, Ar), 7.09-6.99 (m, 1H, Ar), 6.65-6.60 (m, 2H, Ar), 6.59-6.50 (m, 1H, Ar), 4.38 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.04 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.84 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.60 (s, 2H, NH), 3.36 (q, *J* = 6.5 Hz, 1H, NCHMe), 2.93

(br dd, $J = 11.5, 2.0$ Hz, 1H, NCH), 2.73 (dd, $J = 11.5, 2.0$ Hz, 1H, NCH), 2.27 (ddd, $J = 11.5, 11.5, 3.5$ Hz (app td), 1H, NCH), 1.95 (dd, $J = 11.5, 10.5$ Hz, 1H, NCH), 1.37 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 146.5 (*ipso*-Ar), 143.6 (*ipso*-Ar), 141.9 (*ipso*-Ar), 129.3 (Ar), 128.5 (Ar), 127.8 (Ar), 127.1 (Ar), 116.7 (Ar), 114.6 (Ar), 113.1 (Ar), 78.7 (OCH), 67.4 (OCH_2), 65.2 (NCHMe), 58.2 (NCH_2), 50.2 (NCH_2), 19.8 (NCHMe); MS (ESI) m/z 283 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$ ($\text{M} + \text{H})^+$ 283.1805, found 283.1799 (+1.9 ppm error).

Lab Book Reference: **NS9-51**

(*R*)-2-(4-Methoxyphenyl)-4-((*S*)-1-phenylethyl)morpholine (*S,R*)-332

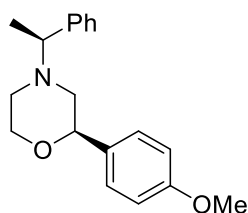


(*S,R*)-332

Using general procedure C, stannane (*S,R*)-**300** (177 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.37 mL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (3 mL), ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (7.9 mg, 7 mol%), $t\text{-Bu}_3\text{PHBF}_4$ (13.1 mg, 9 mol%) and 4-bromoanisole (81 μL , 122 mg, 0.65 mmol, 1.3 eq.) at 40 $^\circ\text{C}$ gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -aryl morpholine (*S,R*)-**332** (70 mg, 47%, 99:1 er by CSP-HPLC) as a white solid, mp 72-74 $^\circ\text{C}$, $[\alpha]_{\text{D}} -33.1$ (c 1.00 in CHCl_3); R_{F} (80:20 hexane-EtOAc) 0.2; IR (ATR) 2960, 2853, 1612, 1515, 1301, 1246, 1107, 1033, 956, 830, 702, 552 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.23 (m, 7H, Ar), 6.92-6.86 (m, 2H, Ar), 4.54 (dd, $J = 10.5, 2.5$ Hz, 1H, OCH), 3.90 (ddd, $J = 11.0, 3.5, 1.5$ Hz, 1H, OCH), 3.80 (s, 3H, OMe), 3.73 (ddd, $J = 12.5, 11.0, 2.5$ Hz, 1H, OCH), 3.35 (d, $J = 6.5$ Hz, 1H, NCHMe), 3.08 (ddd, $J = 11.5, 2.5, 2.0$ Hz, 1H, NCH), 2.59 (ddd, $J = 11.5, 2.0, 2.0$ Hz (app dt), 1H, NCH), 2.17-2.06 (m, 2H, NCH), 1.36 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 159.3 (*ipso*-Ar), 143.5 (*ipso*-Ar), 133.1 (*ipso*-Ar), 128.5 (Ar), 127.9 (Ar), 127.7 (Ar), 127.3 (Ar), 113.8 (Ar), 78.1 (OCH), 67.3 (OCH_2), 65.5 (NCHMe), 57.9 (NCH_2), 55.4 (OMe), 50.9 (NCH_2), 19.8 (NCHMe); MS (ESI) m/z 298 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_2$ ($\text{M} + \text{H})^+$ 298.1802, found 298.1799 (+0.8 ppm error); CSP-HPLC: Chiralcel OD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) 13.5 min (minor), 34.3 min (major).

Lab Book Reference: **NS10-6**

(*R)-2-(4-Methoxyphenyl)-4-((*S**)-1-phenylethyl)morpholine (*S**,*R**)-332**

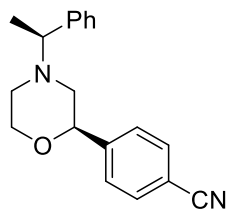


(*S**,*R**)-332

Using general procedure C, stannane (*S**,*R**)-**300** (177 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (367 μ L of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13.1 mg, 9 mol%) and 4-bromoanisole (81 μ L, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -aryl morpholine (*S**,*R**)-**332** (63 mg, 43%) as a white solid.

Lab Book Reference: **NS10-7**

4-((*R*)-4-((*S*)-1-Phenylethyl)morpholin-2-yl)benzonitrile (*S*,*R*)-333



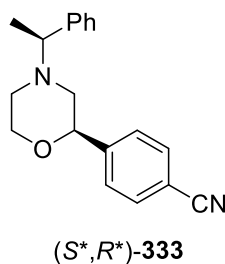
(*S*,*R*)-333

Using general procedure C, stannane (*S*,*R*)-**300** (177 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (367 μ L of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13.1 mg, 9 mol%) and 4-bromo benzonitrile (120 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave α -aryl morpholine (*S*,*R*)-**333** (69 mg, 47%, 99:1 er by CSP-HPLC) as white solid, mp 82-84 °C (lit.,¹⁶ 83.6 °C); [α]_D -45.2 (*c* 1.00 in CHCl₃) (lit.,²⁰³ +50.7 (*c* 2.36 in CHCl₃) for (*R*,*S*)-**333** of 99:1 er); *R*_F (80:20 hexane-EtOAc) 0.3; IR (ATR) 2972, 2857, 2809, 2228 (CN), 1611, 1492, 1450, 1290, 1257, 1120, 957, 833, 766, 702, 565 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.66-7.60 (m, 2H, Ar), 7.51-7.43 (m, 2H, Ar), 7.35-7.22 (m, 5H, Ar), 4.64 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 3.97-3.88 (m, 1H, OCH), 3.73 (ddd, *J* = 11.5,

11.5, 2.5 Hz (app td), 1H, NCH), 3.37 (q, $J = 6.5$ Hz, 1H, NCHMe), 3.08 (ddd, $J = 11.5, 2.5, 2.5$ Hz (app dt), 1H, NCH), 2.61 (dd, $J = 11.5, 2.5$ Hz, 1H, NCH), 2.13 (ddd, $J = 11.5, 11.5, 2.5$ Hz (app td), 1H, NCH), 2.00 (dd, $J = 11.5, 10.0$ Hz, 1H, NCH), 1.36 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 146.1 (*ipso*-Ar), 143.3 (*ipso*-Ar), 132.3 (Ar), 128.5 (Ar), 127.8 (Ar), 127.3 (Ar), 127.0 (Ar), 119.0 (CN), 111.6 (*ipso*-Ar), 77.7 (OCH), 67.3 (OCH₂), 65.2 (NCHMe), 57.5 (NCH₂), 50.7 (NCH₂), 19.6 (NCHMe); MS (ESI) m/z 293 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$ (M + H)⁺ 293.1648, found 293.1648 (+0.1 ppm error). CSP-HPLC: Chiralcel OD-H (98:2 hexane-*i*-PrOH, 1.0 mL min⁻¹) 12.9 min (major), 14.5 min (minor). Spectroscopic data consistent with those reported in the literature.²⁰³

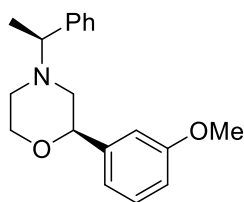
Lab Book Reference: **NS10-13**

4-((*R*^{*})-4-((*S*^{*})-1-Phenylethyl)morpholin-2-yl)benzonitrile (*S*^{*},*R*^{*})-333



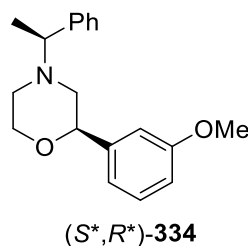
Using general procedure C, stannane (*S*^{*},*R*^{*})-**300** (177 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (367 μL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (3 mL), ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13.1 mg, 9 mol%) and 4-bromobenzonitrile (120 mg, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave α -aryl morpholine (*S*^{*},*R*^{*})-**333** (66 mg, 45%) as a white solid.

Lab Book Reference: **NS10-10**

(R)-2-(3-Methoxyphenyl)-4-((S)-1-phenylethyl)morpholine (S,R)-334**(S,R)-334**

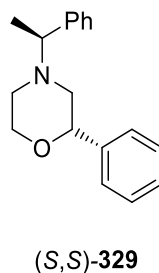
Using general procedure C, stannane (S,R)-**300** (354 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.73 mL of a 1.5 M solution in hexane, 1.1 mmol, 1.1 eq.) in THF (5 mL), ZnCl₂ (1.86 mL of a 0.7 M solution in THF, 1.3 mmol, 1.3 eq.), Pd(OAc)₂ (15.7 mg, 7 mol%), *t*-Bu₃PHBF₄ (26 mg, 9 mol%) and 3-bromoanisole (165 μ L, 1.3 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc gave morpholine (S,R)-**334** (148 mg, 50%, 99:1 er by CSP-HPLC) as a colourless oil, [α]_D –41.1 (*c* 0.33 in CHCl₃); *R*_F (90:10 hexane-EtOAc) 0.4; IR (ATR) 2959, 2854, 1603, 1586, 1451, 1288, 1266, 1118, 1097, 1045, 942, 864, 780, 699, 545 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.29 (m, 4H, Ar), 7.27-7.21 (m, 2H, Ar), 6.97-6.92 (m, 2H, Ar), 6.85-6.79 (m, 1H, Ar), 4.57 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 3.91 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.81 (s, 3H, OMe), 3.73 (ddd, *J* = 11.5, 11.5, 2.0 Hz (app td), 1H, OCH), 3.34 (q, *J* = 6.5 Hz, 1H, NCHMe), 3.11 (ddd, *J* = 11.5, 2.0, 2.0 Hz (app dt), 1H, NCH), 2.59 (dd, *J* = 11.5, 2.5 Hz, 1H, NCH), 2.13 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 2.08 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH), 1.35 (d, *J* = 6.5 Hz, 1H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.8 (*ipso*-Ar), 143.8 (*ipso*-Ar), 142.6 (*ipso*-Ar), 129.5 (Ar), 128.5 (Ar), 127.8 (Ar), 127.2 (Ar), 118.8 (Ar), 113.5 (Ar), 111.9 (Ar), 78.5 (OCH), 67.4 (OCH₂), 65.4 (NCHMe), 57.9 (NCH₂), 55.4 (OMe), 51.0 (NCH₂), 19.9 (NCHMe); MS (ESI) *m/z* 298 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₉H₂₃NO₂ (M + H)⁺ 298.1802, found 298.1799 (+1.0 ppm error); CSP-HPLC: Chiralcel OD-H (95:5 hexane-*i*-PrOH, 1.0 mL min⁻¹) 14.0 min (minor), 55.2 min (major).

Lab Book Reference: **NS10-72**

(*R)-2-(3-Methoxyphenyl)-4-((*S**)-1-phenylethyl)morpholine (*S**,*R**)-334**

Using general procedure C, stannane (*S**,*R**)-**300** (354 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.73 mL of a 1.5 M solution in hexane, 1.1 mmol, 1.1 eq.) in THF (5 mL), ZnCl₂ (1.86 mL of a 0.7 M solution in THF, 1.3 mmol, 1.3 eq.), Pd(OAc)₂ (15.7 mg, 7 mol%), *t*-Bu₃PHBF₄ (26.2 mg, 9 mol%) and 3-bromoanisole (165 μL, 1.3 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc gave morpholine (*S**,*R**)-**334** (155 mg, 52%) as a colourless oil.

Lab Book Reference: **NS10-73 / NS11-92**

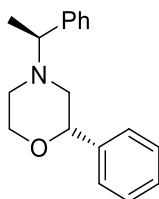
(*S*)-2-Phenyl-4-((*S*)-1-phenylethyl)morpholine (*S*,*S*)-329

Using general procedure C, stannane (*S*,*S*)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (231 μL of a 1.3 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (2.5 mL), ZnCl₂ (0.36 mL of a 1.0 M solution in THF, 0.37 mmol, 1.3 eq.), Pd(OAc)₂ (4.4 mg, 7 mol%), *t*-Bu₃PHBF₄ (7.4 mg, 9 mol%) and bromobenzene (38.4 μL, 0.37 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave α-aryl morpholine (*S*,*S*)-**329** (47 mg, 62%, 99:1 er by CSP-HPLC of *N*-Ts morpholine (*R*)-**338**) as a colourless oil, [α]_D −27.9 (*c* 1.00 in CHCl₃); *R*_F (80:20 hexane-EtOAc) 0.3; IR (ATR) 3028, 2970, 2853, 2805, 1450, 1344, 1259, 1223, 1107, 1084, 1057, 1029, 960, 758, 698, 543 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.17 (m, 10H, Ph), 4.48 (dd, *J* = 10.0, 2.0 Hz, 1H, OCH), 4.07 (ddd, *J* = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.87 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.39 (q, *J* = 6.5 Hz, 1H, NCHMe), 3.01-2.91 (m, 1H, NCH), 2.81-2.72 (m, 1H, NCH), 2.31 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.99 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH), 1.39 (d, *J* = 6.5 Hz, 1H, NCHMe); ¹³C NMR (100.6 MHz,

CDCl₃) δ 143.7 (*ipso*-Ph), 140.7 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 127.80 (Ph), 127.75 (Ph), 127.1 (Ph), 126.4 (Ph), 78.6 (OCH), 67.4 (OCH₂), 65.2 (NCHMe), 58.3 (NCH₂), 50.2 (NCH₂), 19.8 (NCHMe); MS (ESI) m/z 268 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₈H₂₁NO (M + H)⁺ 268.1696, found 268.1690 (+2.1 ppm error).

Lab Book Reference: **NS9-45**

(S*)-2-Phenyl-4-((S*)-1-phenylethyl)morpholine (S*,S*)-329

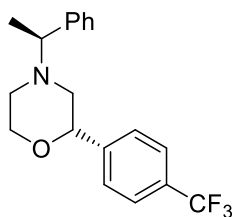


(S*,S*)-329

Using general procedure C, stannane (S*,S*)-**300** (354 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.85 mL of a 1.3 M solution in hexane, 1.1 mmol, 1.1 eq.) in THF (5 mL), ZnCl₂ (1.30 mL of a 1.0 M solution in THF, 1.3 mmol, 1.3 eq.), Pd(OAc)₂ (15.8 mg, 7 mol%), *t*-Bu₃PHBF₄ (26.2 mg, 9 mol%) and bromobenzene (136 μ L, 204 mg, 1.3 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -aryl morpholine (S*,S*)-**329** (166 mg, 62%) as a colourless oil.

Lab Book Reference: **NS9-64**

(S)-4-((S)-1-Phenylethyl)-2-(4-(trifluoromethyl)phenyl)morpholine (S,S)-335



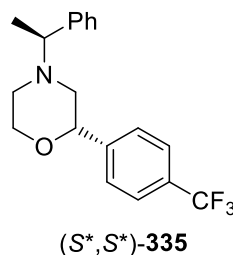
(S,S)-335

Using general procedure C, stannane (S,S)-**300** (177 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (367 μ L of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), Pd(OAc)₂ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13.1 mg, 9 mol%) and 1-bromo-4-(trifluoromethyl)benzene (91 μ L, 0.65 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -aryl morpholine (S,S)-**335** (87 mg, 53%, 99:1 er by CSP-HPLC) as a colourless oil, [α]_D -33.9 (*c* 0.50 in CHCl₃); *R*_F (90:10 hexane-EtOAc) 0.3;

IR (ATR) 2973, 2807, 1492, 1451, 1323, 1163, 1120, 1105, 1067, 1017, 835, 756, 701, 604, 542 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.50 (m, 2H, Ar), 7.39-7.35 (m, 2H, Ar), 7.32-7.27 (m, 4H, Ar), 7.25-7.19 (m, 1H, Ar), 4.52 (dd, $J = 10.5, 2.5$ Hz, 1H, OCH), 4.07 (ddd, $J = 11.5, 3.5, 2.0$ Hz, 1H, OCH), 3.86 (ddd, $J = 11.5, 11.5, 2.5$ Hz (app td), 1H, OCH), 3.37 (q, $J = 6.5$ Hz, 1H, NCHMe), 2.96 (dd, $J = 11.5, 2.0$ Hz, 1H, NCH), 2.74 (ddd, $J = 11.5, 2.5, 2.0$ Hz, 1H, NCH), 2.29 (ddd, $J = 11.5, 11.5, 3.5$ Hz (app td), 1H, NCH), 1.92 (dd, $J = 11.5, 10.5$ Hz, 1H, NCH), 1.38 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 144.6 (br s, *ipso*-Ar), 143.5 (*ipso*-Ar), 129.9 (q, $J = 32.5$ Hz, *ipso*-Ar), 128.5 (Ar), 127.7 (Ar), 127.2 (Ar), 126.6 (Ar), 125.23 (q, $J = 4.0$ Hz, Ar), 124.1 (q, $J = 272.0$ Hz, CF_3), 77.8 (OCH), 67.4 (OCH_2), 65.1 (NCHMe), 58.2 (NCH_2), 50.0 (NCH_2), 19.7 (NCHMe); ^{19}F NMR (376 MHz, CDCl_3) δ -62.4 (s); MS (ESI) m/z 336 [$(\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{20}\text{F}_3\text{NO}$ ($\text{M} + \text{H})^+$ 336.1570, found 336.1566 (+1.1 ppm error); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 0.8 mL min^{-1}) 4.2 min (major), 4.7 min (minor).

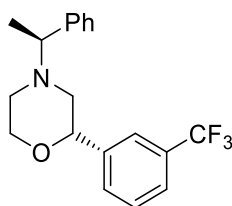
Lab Book Reference: **NS10-15**

(*S^)-4-((*S^**)-1-Phenylethyl)-2-(4-(trifluoromethyl)phenyl)morpholine (*S^*,S^**)-335**



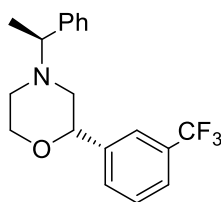
Using general procedure C, stannane (*S,S*)-**300** (177 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (367 μL of a 1.5 M solution in hexane, 0.55 mmol, 1.1 eq.) in THF (3 mL), ZnCl_2 (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.), $\text{Pd}(\text{OAc})_2$ (7.9 mg, 7 mol%), *t*-Bu₃PHBF₄ (13.1 mg, 9 mol%) and 1-bromo-4-(trifluoromethyl)benzene (91 μL , 0.65 mmol, 1.3 eq.) at 40 $^\circ\text{C}$ gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -aryl morpholine (*S^*,S^**)-**335** (88 mg, 53%) as a colourless oil.

Lab Book Reference: **NS10-14**

(S)-4-((S)-1-Phenylethyl)-2-(3-(trifluoromethyl)phenyl)morpholine (S,R)-336**(S,S)-336**

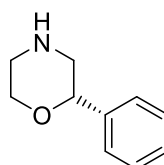
Using general procedure C, stannane (S,S)-**300** (354 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.73 mL of a 1.5 M solution in hexane, 1.1 mmol, 1.1 eq.) in THF (5 mL), ZnCl₂ (1.86 mL of a 0.7 M solution in THF, 1.3 mmol, 1.3 eq.), Pd(OAc)₂ (15.7 mg, 7 mol%), *t*-Bu₃PHBF₄ (26.2 mg, 9 mol%) and 1-bromo-3-(trifluoromethyl)benzene (181 μ L, 1.3 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α -aryl morpholine (S,S)-**336** (168 mg, 50%, 99:1 er by CSP-HPLC) as a colourless oil, [α]_D -43.6 (*c* 0.33 in CHCl₃); *R*_F (90:10 hexane-EtOAc) 0.3; IR (ATR) 2972, 2858, 2808, 1450, 1328, 1222, 1164, 1073, 898, 801, 701, 673 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.55 (m, 1H, Ar), 7.53-7.44 (m, 1H, Ar), 7.44-7.35 (m, 2H, Ar), 7.33-7.28 (m, 4H, Ar), 7.26-7.20 (m, 1H, Ar), 4.52 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.07 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.86 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.39 (q, *J* = 6.5 Hz, 1H, NCHMe), 2.95 (br dd, *J* = 11.5, 2.5 Hz, 1H, NCH), 2.75 (br d, *J* = 11.5 Hz, 1H, NCH), 2.31 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 1.96 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH), 1.38 (d, *J* = 6.5 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.5 (*ipso*-Ar), 141.7 (*ipso*-Ar), 130.7 (q, *J* = 32.0 Hz, *ipso*-Ar), 129.8 (Ar), 128.7 (Ar), 128.5 (Ar), 127.7 (Ar), 127.3 (Ar), 124.6 (q, *J* = 4.0 Hz, Ar), 124.0 (q, *J* = 275.0 Hz, CF₃), 123.3 (q, *J* = 4.0 Hz, Ar), 77.9 (OCH), 67.4 (OCH₂), 65.1 (NCHMe), 58.2 (NCH₂), 50.0 (NCH₂), 19.7 (NCHMe); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.4 (s); MS (ESI) *m/z* 336 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₉H₂₀F₃NO (M + H)⁺ 336.1570, found 336.1573 (-0.8 ppm error); CSP-HPLC: Chiralcel OD-H (99:1 hexane-*i*-PrOH, 1.0 mL min⁻¹) 15.4 min (major), 30.8 min (minor).

Lab Book Reference: **NS10-69**

(S*)-4-((S*)-1-Phenylethyl)-2-(3-(trifluoromethyl)phenyl)morpholine (S*,S*)-336**(S*,S*)-336**

Using general procedure C, stannane (S*,S*)-**300** (354 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.73 mL of a 1.5 M solution in hexane, 1.1 mmol, 1.1 eq.) in THF (5 mL), ZnCl₂ (1.86 mL of a 0.7 M solution in THF, 1.3 mmol, 1.3 eq.), Pd(OAc)₂ (15.7 mg, 7 mol%), *t*-Bu₃PHBF₄ (26.2 mg, 9 mol%) and 1-bromo-3-(trifluoromethyl)benzene (181 µL, 1.3 mmol, 1.3 eq.) at 40 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave α-aryl morpholine (S*,S*)-**336** (168 mg, 53%) as a colourless oil.

Lab Book Reference: **NS10-68**

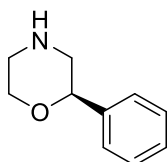
(S)-2-Phenylmorpholine (S)-337**(S)-337**

Using general procedure I, morpholine (S,S)-**329** (100 mg, 0.38 mmol, 1.0 eq.), α-chloroethyl chloroformate (121 µL, 161 mg, 1.1 mmol, 3.0 eq.) in DCE (4 mL) and then MeOH (3 mL) gave the crude hydrochloride product. Purification by flash column chromatography on silica with 60:40 CH₂Cl₂-EtOAc then 90:10 CH₂Cl₂-MeOH then 70:30 CH₂Cl₂-MeOH as eluent gave α-aryl morpholine (S)-**337** (55 mg, 89%) as a colourless oil, [α]_D +39.3 (c 0.4 in MeOH) (lit.,¹⁷⁰ +19.8 (c 0.4 in MeOH)); *R*_F (90:10 hexane-EtOAc) 0.4; IR (ATR) 2975 (NH), 2930, 1371, 1320, 1199, 1080, 1030, 968, 819, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.22 (m, 5H, Ph), 4.48 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.03 (ddd, *J* = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.77 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.08-2.95 (m, 2H, NCH), 2.94-2.83 (m, 1H, NCH), 2.79 (dd, *J* = 12.5, 10.5 Hz, 1H, NCH), 1.93 (br s, 1H, NH); ¹³C NMR (100.6 MHz, CDCl₃) δ 140.3 (*ipso*-Ph), 128.2 (Ph), 127.5 (Ph), 125.9 (Ph), 79.2 (OCH), 68.2 (OCH₂), 53.1 (NCH₂), 45.5 (NCH₂); MS (ESI) *m/z* 164 [(M +

H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₀H₁₃NO (M + H)⁺ 164.1070, found 164.1068 (+1.4 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁷⁰

Lab Book Reference: NS9-67

(R)-2-Phenylmorpholine (R)-337

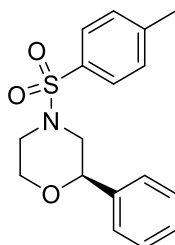


(R)-337

Using general procedure I, morpholine (S,R)-329 (100 mg, 0.38 mmol, 1.0 eq.), α -chloroethyl chloroformate (121 μ L, 161 mg, 1.1 mmol, 3.0 eq.) in DCE (4 mL) and then MeOH (3 mL) gave the crude product. Purification by flash column chromatography on silica with 60:40 CH₂Cl₂-EtOAc then 90:10 CH₂Cl₂-MeOH then 70:30 CH₂Cl₂-MeOH as eluent gave α -aryl morpholine (R)-337 (53 mg, 87%) as a colourless oil, $[\alpha]_D$ -38.3 (c 0.4 in MeOH) (lit.,¹⁷⁰ +19.8 (c 0.4 in MeOH) for (S)-337).

Lab Book Reference: NS9-66

(R)-2-Phenyl-4-tosylmorpholine (R)-338



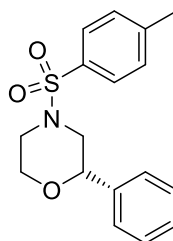
(R)-338

4-Toluenesulfonyl chloride (23.4 mg, 0.12 mmol, 2.0 eq.) was added to a stirred solution of morpholine (R)-337 (10 mg, 61.3 μ mol, 1.0 eq.) and Et₃N (17.0 μ L, 12.4 mg, 0.12 mmol, 2.0 eq.) in CH₂Cl₂ (1.0 mL) at rt. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave morpholine (R)-338 (19 mg, 97%, 99:1 er by CSP-HPLC) as a white solid, mp 114-116 °C (lit.,²⁰⁴ 105-107 °C), $[\alpha]_D$ -120.2 (c 1.00 in CH₂Cl₂) (lit.,²⁰⁵ -106.7 (c 1.11 in CH₂Cl₂)); R_F (50:50 hexane-EtOAc) 0.2; IR (ATR) 2923, 2855, 1450, 1350, 1282, 1165, 1103, 965, 764, 700, 660, 555, 547 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.62-7.58 (m, 2H, Ar), 7.36-7.26 (m, 7H, Ar), 4.59 (dd, J = 10.5, 2.5 Hz, 1H, OCH), 4.06 (ddd, J = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.85

(ddd, $J = 11.5, 2.5, 2.5$ Hz (app dt), 1H, OCH), 3.75 (dd, $J = 11.5, 2.5$ Hz, 1H, NCH), 3.62 (ddd, $J = 11.5, 2.5, 1.5$ Hz, 1H, NCH), 2.48 (ddd, $J = 11.5, 11.5, 3.5$ Hz (app td), 1H, NCH), 2.42 (s, 3H, Me), 2.22 (dd, $J = 11.5, 10.5$ Hz, 1H, NCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 144.1 (*ipso*-Ar), 138.8 (*ipso*-Ar), 132.2 (*ipso*-Ar), 129.9 (Ar), 128.7 (Ar), 128.5 (Ar), 128.0 (Ar), 126.2 (Ar), 77.6 (OCH), 66.4 (OCH₂), 52.1 (NCH₂), 45.6 (NCH₂), 21.7 (Me); MS (ESI) m/z 340 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_3\text{S}$ (M + Na)⁺ 340.0978, found 340.0978 (+0.1 ppm error); CSP-HPLC: Chiralcel OD-H (90:10 hexane-*i*-PrOH, 1.0 mL min⁻¹) 21.3 min (minor), 48.4 min (major). Spectroscopic data consistent with those reported in the literature.²⁰⁵

Lab Book Reference: **NS9-70**

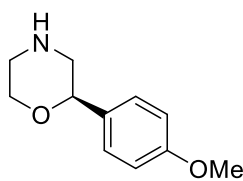
(S)-2-Phenyl-4-tosylmorpholine (S)-338



(S)-338

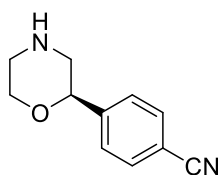
4-Toluenesulfonyl chloride (46.8 mg, 0.25 mmol, 2.0 eq.) was added to a stirred solution of morpholine (S)-337 (20 mg, 123 μmol , 1.0 eq.) and Et_3N (34.0 μL , 24.8 mg, 0.25 mmol, 2.0 eq.) in CH_2Cl_2 (2 mL) at rt. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave α -aryl morpholine (S)-338 (37 mg, 95%, 99:1 er by CSP-HPLC) as a white solid, mp 114-116 °C (lit.,²⁰⁴ 105-107 °C), $[\alpha]_{\text{D}} +122.6$ (c 1.00 in CH_2Cl_2) (lit.,²⁰⁵ -106.7 (c 1.11 in CH_2Cl_2) for (R)-338); R_{F} (50:50 hexane-EtOAc) 0.2; CSP-HPLC: Chiralcel OD-H (90:10 hexane-*i*-PrOH, 1.0 mL min⁻¹) 20.7 min (major), 48.7 min (minor). Spectroscopic data consistent with those reported in the literature.²⁰⁵

Lab Book Reference: **NS9-71**

(R)-2-(4-Methoxyphenyl)morpholine (R)-339**(R)-339**

Using general procedure I, morpholine (*S,R*)-**332** (30 mg, 0.10 mmol, 1.0 eq.), α -chloroethyl chloroformate (33 μ l, 0.30 mmol, 3.0 eq.) in DCE (2 mL) and then MeOH (2 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 CH₂Cl₂-MeOH then 70:30 CH₂Cl₂-MeOH as eluent gave α -aryl morpholine (*R*)-**339** (16 mg, 81%) as a colourless oil, $[\alpha]_D -13.6$ (*c* 0.5 in CHCl₃); R_F (90:10 CH₂Cl₂-MeOH) 0.3; IR (ATR) 3495 (NH), 2936, 2837, 1612, 1515, 1455, 1247, 1177, 1090, 1031, 831, 776 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.23 (m, 2H, Ar), 6.90-6.84 (m, 2H, Ar), 4.53 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.27 (br s, 1H, NH), 4.09-3.99 (m, 1H, OCH), 3.87 (ddd, *J* = 12.0, 10.0, 4.5 Hz, 1H, OCH), 3.78 (s, 3H, OMe), 3.16-3.07 (m, 1H, NCH), 3.05-2.94 (m, 2H, NCH), 2.84 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.5 (*ipso*-Ar), 131.9 (*ipso*-Ar), 127.6 (Ar), 114.0 (Ar), 78.1 (OCH), 67.4 (OCH₂), 55.4 (OMe), 52.0 (NCH₂), 45.0 (NCH₂); MS (ESI) *m/z* 194 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₅NO₂ (M + H)⁺ 194.1176, found 194.1173 (+1.5 ppm error).

Lab Book Reference: **NS9-80**

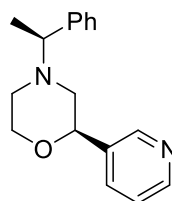
(R)-4-(Morpholin-2-yl)benzonitrile (R)-340**(R)-340**

Using general procedure I, morpholine (*S,R*)-**333** (40 mg, 0.14 mmol, 1.0 eq.), α -chloroethyl chloroformate (59 μ l, 0.41 mmol, 3.0 eq.) in DCE (2 mL) and then MeOH (2 mL) gave the crude product. Then, EtOAc (10 mL) were added and the solution was washed with 2 M NaOH(aq) (10 mL). The organic layer was dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 CH₂Cl₂-MeOH then 70:30 CH₂Cl₂-MeOH as eluent gave α -aryl morpholine (*R*)-**340** (22 mg, 85%) as a colourless oil, $[\alpha]_D -42.5$ (*c* 0.5 in MeOH); R_F (70:30 CH₂Cl₂-MeOH) 0.3; IR (ATR) 3212 (NH), 2971, 2945, 1890, 1851, 2231 (CN), 1608, 1506, 1413, 1126,

1084, 1035, 902, 872, 565 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, J = 8.5 Hz, 2H, Ar), 7.45 (d, J = 8.5 Hz, 2H, Ar), 4.52 (dd, J = 10.5, 2.5 Hz, 1H, OCH), 4.03 (br dd, J = 11.5, 2.5 Hz, 1H, OCH), 3.76 (ddd, J = 11.5, 11.5, 3.5 Hz (app td), 1H, OCH), 3.05 (dd, J = 12.5, 2.5 Hz, 1H, NCH), 2.96 (ddd, J = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 2.92-2.86 (m, 1H, NCH), 2.68 (dd, J = 12.5, 10.5 Hz, 1H, NCH), 1.86 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 145.9 (*ipso*-Ar), 132.3 (Ar), 126.7 (Ar), 118.9 (*ipso*-Ar), 111.5 (CN), 78.5 (OCH), 68.4 (OCH_2), 53.2 (NCH_2), 45.6 (NCH_2); MS (ESI) m/z 189 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$ ($\text{M} + \text{H})^+$ 189.1022, found 189.1024 (-0.7 ppm error).

Lab Book Reference: **NS9-81**

(*R*)-4-((*S*)-1-Phenylethyl)-2-(pyridin-3-yl)morpholine (*S,R*)-341



(*S,R*)-341

Table 3.10, entry 2:

Using general procedure K, stannane (*S,R*)-300 (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (205 μL of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL), ZnCl_2 (523 μL of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.), Pd_2dba_3 (6.5 mg, 2.5 mol%), S-Phos (5.7 mg, 5 mol%) and 3-bromopyridine (35 μL , 38 mg, 0.37 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc to EtOAc as eluent gave α -aryl morpholine (*S,R*)-341 (48 mg, 63%) as a colourless oil, $[\alpha]_{\text{D}}^{25} +5.6$ (c 0.33 in CHCl_3); R_{F} (EtOAc) 0.4; IR (ATR) 2965, 1637, 1337, 1163, 1127, 1085, 1023, 753, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.52-8.44 (m, 2H, Ar), 7.60 (ddd, J = 8.0, 2.0, 2.0 Hz (app dt), 1H, Ar), 7.33-7.16 (m, 6H, Ar), 4.52 (br d, J = 10.0 Hz, 1H, OCH), 4.05 (ddd, J = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.95-3.82 (m, 1H, OCH), 3.44-3.35 (m, 1H, NCHMe), 2.97 (br d, J = 11.5 Hz, 1H, NCH), 2.74 (br d, J = 11.5 Hz, 1H, NCH), 2.31 (ddd, J = 12.0, 11.5, 3.0 Hz, 1H, NCH), 1.97 (dd, J = 11.0, 11.0 Hz (app t), 1H, NCH), 1.39 (d, J = 6.5 Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 149.3 (Ar), 148.2 (Ar), 136.1 (*ipso*-Ar), 134.0 (Ar), 128.6 (Ar), 127.7 (Ar), 127.4 (Ar), 123.4 (Ar), 76.3 (OCH), 67.4 (OCH_2), 65.2 (NCHMe), 58.0 (NCH_2), 50.0 (NCH_2), 19.7 (NCHMe) (one *ipso*-Ar not resolved); MS (ESI) m/z 269 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$ ($\text{M} + \text{H})^+$ 269.1648, found 299.1647 ($+1.0$ ppm error).

Lab Book Reference: **NS11-71**

Table 3.10, entry 1:

Using general procedure C, stannane (*S,R*)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (205 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.), Pd(OAc)₂ (4.2 mg, 7 mol%), *t*-Bu₃PHBF₄ (7.3 mg, 9 mol%) and 3-bromopyridine (35 μ L, 38 mg, 0.37 mmol, 1.3 eq.) at 60 °C gave the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc to EtOAc as eluent gave α -aryl morpholine (*S,R*)-**341** (48 mg, 33%) as a colourless oil.

Lab Book Reference: **NS11-60**

Table 3.10, entry 3:

n-BuLi (215 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) was added dropwise to a stirred solution of stannane (*S,R*)-**300** (100 mg, 0.28 mmol, 1.0 eq.) in THF (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 30 min. Then, a commercial solution of ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.) was added. After stirring at –78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for 30 min. Then, Pd₂dba₃ (6.5 mg, 14.1 μ mol, 2.5 mol%), X-Phos (6.7 mg, 14.1 μ mol, 5 mol%) and 3-bromopyridine (35 μ L, 58 mg, 0.37 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at 60 °C for 16 h. The solids were removed by filtration through Celite[®] and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which did not contain the desired product by ¹H NMR spectroscopy.

Lab Book Reference: **NS11-70**

Table 3.10, entry 4:

n-BuLi (205 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) was added dropwise to a stirred solution of stannane (*S,R*)-**300** (100 mg, 0.28 mmol, 1.0 eq.) in THF (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 30 min. Then, a commercial solution of ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.) was added. After stirring at –78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for 30 min. The solvent was evaporated under reduced pressure and toluene (5 mL) was added. Then, Pd₂dba₃ (6.5 mg, 14.1 μ mol, 2.5 mol%), X-Phos (6.7 mg, 14.1 μ mol, 5 mol%) and 3-

bromopyridine (35 μ L, 58 mg, 0.366 mmol, 1.3 eq.) were added and the mixture was stirred and heated at 110 $^{\circ}$ C for 16 h. After cooling to rt, the solvent was evaporated under reduced pressure. Et₂O (10 mL) and H₂O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were combined, dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained only traces of the desired product (by ¹H NMR spectroscopy).

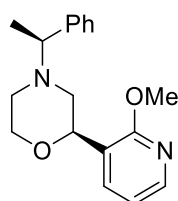
Lab Book Reference: **NS11-69**

Table 3.10, entry 5:

n-BuLi (215 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) was added dropwise to a stirred solution of stannane (*S,R*)-**300** (100 mg, 0.28 mmol, 1.0 eq.) in THF (3 mL) at -78° C under Ar. The resulting solution was stirred at -78° C for 30 min. Then, a commercial solution of ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.) was added. After stirring at -78° C for 30 min, the mixture was allowed to warm to rt and stirred at rt for 30 min. Then, Pd₂dba₃ (6.5 mg, 2.5 mol%), Q-Phos (10.0 mg, 5 mol%) and 3-bromopyridine (35 μ L, 58 mg, 0.37 mmol, 1.3 eq.) were added and the reaction mixture was stirred and heated at 60 $^{\circ}$ C for 16 h. The solids were removed by filtration through Celite[®] and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which did not contain the desired product by ¹H NMR spectroscopy.

Lab Book Reference: **NS11-72**

(*R*)-2-(2-Methoxypyridin-3-yl)-4-((*S*)-1-phenylethyl)morpholine (*S,R*)-342



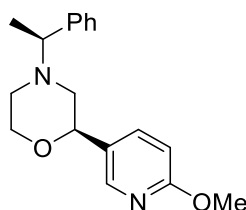
(*S,R*)-342

Using general procedure K, stannane (*S,R*)-**300** (150 mg, 0.42 mmol, 1.0 eq.), *n*-BuLi (310 μ L of a 1.5 M solution in hexane, 0.34 mmol, 1.1 eq.) in THF (5 mL), ZnCl₂ (784 μ L of a 0.7 M solution in THF, 0.55 mmol, 1.3 eq.), Pd₂dba₃ (9.7 mg, 14.1 μ mol, 2.5 mol%), S-Phos (8.7 mg, 21.2 μ mol, 5 mol%) and 3-bromo-2-methoxypyridine (65 μ L, 103 mg, 0.55 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc to 90:10 hexane-EtOAc as eluent gave α -aryl morpholine

(*S,R*)-**342** (62 mg, 50%) as a colourless oil, $[\alpha]_D -65.1$ (*c* 0.50 in CHCl_3); R_F (80:20 hexane-EtOAc) 0.4; IR (ATR) 2952, 2855, 2805, 1589, 1464, 1250, 1099, 1019, 794, 775, 702, 546 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.02 (dd, $J = 5.0, 2.0$ Hz, 1H, Ar), 7.66 (dd, $J = 7.5, 2.0$ Hz, 1H, Ar), 7.36-7.19 (m, 5H, Ar), 6.84 (dd, $J = 7.5, 5.0$ Hz, 1H, Ar), 4.75 (br d, $J = 10.0$ Hz, 1H, OCH), 4.06 (ddd, $J = 11.5, 3.5, 1.5$ Hz, 1H, OCH), 3.94-3.84 (m, 1H, OCH), 3.82 (s, 3H, OMe), 3.49-3.36 (m, 1H, NCH), 3.02-2.89 (m, 2H, NCH, NCHMe), 2.30 (dd, $J = 12.0, 12.0$ Hz (app t), 1H, NCH), 1.76 (dd, $J = 10.5, 10.0$ Hz, 1H, NCH), 1.40 (d, $J = 7.0$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 160.5 (Ar), 145.6 (Ar), 143.4 (*ipso*-Ar), 135.3 (Ar), 128.4 (Ar), 127.9 (Ar), 127.2 (*ipso*-Ar), 123.5 (*ipso*-Ar), 116.9 (Ar), 72.8 (OCH), 67.5 (OCH₂), 64.9 (NCHMe), 56.3 (NCH₂), 53.2 (OMe), 50.2 (NCH₂), 19.5 (NCHMe); MS (ESI) m/z 299 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$ ($M + H$)⁺ 299.1754, found 299.1751 (+1.0 ppm error).

Lab Book Reference: **NS11-79**

(*R*)-2-(6-Methoxypyridin-3-yl)-4-((*S*)-1-phenylethyl)morpholine (*S,R*)-343



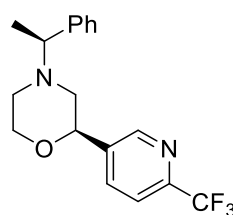
(*S,R*)-**343**

Using general procedure K, stannane (*S,R*)-**300** (150 mg, 0.42 mmol, 1.0 eq.), *n*-BuLi (310 μL of a 1.5 M solution in hexane, 0.46 mmol, 1.1 eq.) in THF (3 mL), ZnCl_2 (785 μL of a 0.7 M solution in THF, 0.55 mmol, 1.3 eq.), Pd_2dba_3 (9.7 mg, 10.6 μmol , 2.5 mol%), S-Phos (8.7 mg, 21.2 μmol , 5 mol%) and 5-bromo-2-methoxypyridine (71.0 μL , 103 mg, 0.55 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 49.5:49.5:1 hexane-EtOAc: Et_3N as eluent gave α -aryl morpholine (*S,R*)-**343** (66 mg, 58%) as a colourless oil, $[\alpha]_D -33.6$ (*c* 1.00 in CHCl_3); R_F (70:30 hexane-EtOAc) 0.2; IR (ATR) 2972, 2854, 2807, 1610, 1493, 1451, 1286, 1250, 1111, 1026, 959, 831, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 2.5$ Hz, 1H, Ar), 7.51 (dd, $J = 8.5, 2.5$ Hz, 1H, Ar), 7.34-7.18 (m, 5H, Ar), 6.65 (d, $J = 8.5$ Hz, 1H, Ar), 4.48-4.37 (m, 1H, OCH), 4.02 (ddd, $J = 11.5, 3.5, 1.5$ Hz, 1H, OCH), 3.87 (s, 3H, OMe), 3.86-3.77 (m, 1H, OCH), 3.44-3.32 (m, 1H, NCHMe), 2.99-2.92 (m, 1H, NCH), 2.73-2.65 (m, 1H, NCH), 2.37-2.23 (m, 1H, NCH), 1.97 (dd, $J = 11.0, 11.0$ Hz (app t), 1H, NCH), 1.38 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 164.0 (*ipso*-Ar), 145.2 (Ar), 143.5 (*ipso*-Ar), 137.2 (Ar),

129.0 (*ipso*-Ar), 128.5 (Ar), 127.8 (Ar), 127.3 (Ar), 110.7 (Ar), 76.0 (OCH), 67.4 (OCH₂), 65.3 (NCHMe), 58.0 (NCH₂), 53.5 (OMe), 50.1 (NCH₂), 19.8 (NCHMe); MS (ESI) *m/z* 299 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₈H₂₂N₂O₂ (M + H)⁺ 299.1754, found 299.1750 (+1.5 ppm error).

Lab Book Reference: **NS11-83**

Attempted Synthesis of (R)-4-((S)-1-Phenylethyl)-2-(6-(trifluoromethyl)pyridin-3-yl)morpholine (S,R)-344

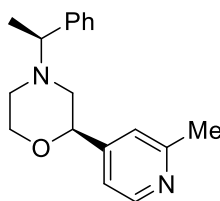


(S,R)-344

Using general procedure K, stannane (S,R)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (205 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.), Pd(OAc)₂ (4.2 mg, 7 mol%), *t*-Bu₃PHBF₄ (7.8 mg, 9 mol%) and 5-bromo-2-(trifluoromethyl)pyridine (83 mg, 0.37 mmol, 1.3 eq.) gave the crude product which contained only traces of the desired product by ¹H NMR spectroscopy.

Lab Book Reference: **NS11-61**

(R)-2-(2-Methylpyridin-4-yl)-4-((S)-1-phenylethyl)morpholine (S,R)-345



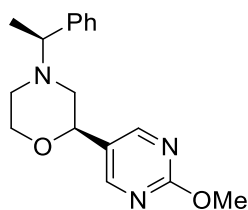
(S,R)-345

Using general procedure K, stannane (S,R)-**300** (150 mg, 0.42 mmol, 1.0 eq.), *n*-BuLi (310 μ L of a 1.5 M solution in hexane, 0.465 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (785 μ L of a 0.7 M solution in THF, 0.55 mmol, 1.3 eq.), Pd₂dba₃ (9.7 mg, 2.5 mol%), S-Phos (8.7 mg, 5 mol%) and 4-bromo-2-methylpyridine (65 μ L, 94 mg, 0.55 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 49.5:49.5:1 hexane-EtOAc: Et₃N as eluent gave α -aryl morpholine (S,R)-**345** (68 mg, 57%) as a colourless oil, [α]_D -28.6 (c 1.00 in CHCl₃); *R*_F (EtOAc) 0.3; IR (ATR) 2961, 2924, 2857,

1504, 1452, 1256, 1218, 1119, 1046, 703 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.40-8.36 (d, $J = 5.0$ Hz, 1H, Ar), 7.36-7.24 (m, 5H, Ar), 7.07 (s, 1H, Ar), 6.97 (d, $J = 5.0$ Hz, 1H, Ar), 4.54 (br d, $J = 10.0$ Hz, 1H, OCH), 4.07 (ddd, $J = 11.5, 3.5, 1.5$ Hz, 1H, OCH), 3.95 (dd, $J = 11.5, 11.5$ Hz (app t), 1H, OCH), 3.47 (q, $J = 6.5$ Hz, 1H, NCHMe), 3.02 (br d, $J = 11.5$ Hz, 1H, NCH), 2.80 (br d, $J = 11.5$ Hz, 1H, NCH), 2.51 (s, 3H, ArMe), 2.34 (ddd, $J = 11.5, 11.5, 3.5$ Hz (app td), 1H, NCH), 1.95 (dd, $J = 11.5, 10.0$ Hz, 1H, NCH), 1.44 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 158.6 (*ipso*-Ar), 149.4 (*ipso*-Ar), 149.0 (Ar), 142.2 (*ipso*-Ar), 128.7 (Ar), 127.9 (Ar), 127.6 (Ar), 120.6 (Ar), 118.3 (Ar), 76.7 (OCH), 66.9 (OCH_2), 65.4 (NCHPh), 57.1 (NCH_2), 49.9 (NCH_2), 24.5 (ArMe), 19.3 (NCHMe); MS (ESI) m/z 283 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$ ($M + H$) $^+$ 283.1805, found 283.1808 (-0.9 ppm error).

Lab Book Reference: **NS11-87**

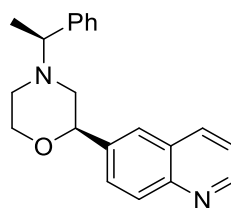
Attempted Synthesis of (*R*)-2-(2-Methoxypyrimidin-5-yl)-4-((*S*)-1-phenylethyl)-morpholine (*S,R*)-346



(*S,R*)-346

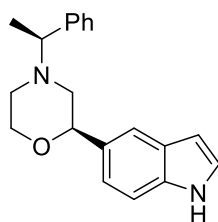
Using general procedure K, stannane (*S,R*)-300 (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (215 μL of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL), ZnCl_2 (784 μL of a 0.7 M solution in THF, 0.55 mmol, 1.3 eq.), Pd_2dba_3 (6.5 mg, 2.5 mol%), S-Phos (5.8 mg, 5 mol%) and 5-bromo-2-methoxypyrimidine (69 mg, 0.37 mmol, 1.3 eq.) gave the crude product which did not contain the desired product (by ^1H NMR spectroscopy).

Lab Book Reference: **NS11-74**

(R)-2-(Quinolin-6-yl)-4-((S)-1-phenylethyl)morpholine (S,R)-347**(S,R)-347**

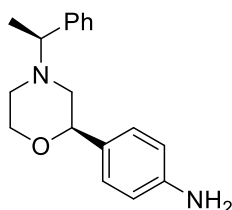
Using general procedure K, stannane (S,R)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (215 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.), Pd₂dba₃ (6.5 mg, 2.5 mol%), S-Phos (5.8 mg, 5 mol%) and 6-bromoquinoline (50 μ L, 76 mg, 0.37 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc to 70:30 hexane-EtOAc as eluent gave α -aryl morpholine (S,R)-**347** (58 mg, 65%) as a colourless oil, $[\alpha]_D -32.6$ (c 0.50 in CHCl₃); *R*_F (50:50 hexane-EtOAc) 0.3; IR (ATR) 2958, 2925, 2854, 2807, 1572, 1501, 1450, 1112, 1085, 907, 837, 764, 731, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.87 (dd, *J* = 4.5, 1.5 Hz, 1H, Ar), 8.12-8.07 (m, 1H, Ar), 8.02 (d, *J* = 8.5 Hz, 1H, Ar), 7.75 (d, *J* = 2.0 Hz, 1H, Ar), 7.60 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 7.38-7.19 (m, 6H, Ar), 4.69 (br d, *J* = 10.0 Hz, 1H, OCH), 4.13 (ddd, *J* = 11.5, 3.5, 1.5 Hz, 1H, OCH), 4.01-3.90 (m, 1H, OCH), 3.43 (q, *J* = 6.5 Hz, 1H, NCHMe), 3.01 (d, *J* = 11.5 Hz, 1H, NCH), 2.90-2.82 (m, 1H, NCH), 2.36 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 2.05 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH), 1.41 (d, *J* = 6.5 Hz, 1H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 150.5 (Ar), 148.0 (*ipso*-Ar), 143.3 (*ipso*-Ar), 138.93 (*ipso*-Ar), 138.91 (*ipso*-Ar), 136.2 (Ar), 129.5 (Ar), 128.5 (Ar), 128.1 (Ar), 127.7 (Ar), 127.3 (Ar), 124.9 (Ar), 121.3 (Ar), 78.1 (OCH), 67.4 (OCH₂), 65.2 (NCHMe), 58.2 (NCH₂), 50.1 (NCH₂), 19.6 (NCHMe); MS (ESI) *m/z* 319 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₁H₂₂N₂O (M + H)⁺ 319.1805, found 319.1805 (+0.1 ppm error).

Lab Book Reference: **NS11-81**

(R)-2-(1*H*-Indol-5-yl)-4-((S)-1-phenylethyl)morpholine (S,R)-348**(S,R)-348**

Using general procedure K, stannane (S,R)-**300** (100 mg, 0.28 mmol, 1.0 eq.), *n*-BuLi (205 μ L of a 1.5 M solution in hexane, 0.31 mmol, 1.1 eq.) in THF (3 mL) ZnCl₂ (523 μ L of a 0.7 M solution in THF, 0.37 mmol, 1.3 eq.), Pd₂dba₃ (6.5 mg, 2.5 mol%), S-Phos (5.7 mg, 5 mol%) and 5-bromoindole (72 mg, 0.37 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc to EtOAc as eluent gave α -aryl morpholine (S,R)-**348** (57 mg, 37%) as a colourless oil, $[\alpha]_D -23.8$ (*c* 0.33 in CHCl₃); *R*_F (EtOAc) 0.4; IR (ATR) 3414 (NH), 3028, 2971, 2855, 1492, 1451, 1323, 1113, 1091, 767, 729, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H, NH), 7.66 (d, *J* = 1.0 Hz, 1H, Ar), 7.37-7.17 (m, 8H, Ar), 6.56-6.49 (m, 1H, Ar), 4.75-4.66 (m, 1H, OCH), 3.95 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.79 (dd, *J* = 11.5, 11.5 Hz (app t), 1H, OCH), 3.45-3.31 (m, 1H, NCHMe), 3.17 (br d, *J* = 11.5 Hz, 1H, NCH), 2.62 (br d, *J* = 11.5 Hz, 1H, NCH), 2.25-2.11 (m, 2H, NCH), 1.37 (d, *J* = 6.0 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 144.0 (*ipso*-Ar), 135.7 (Ar), 132.4 (*ipso*-Ar), 128.5 (Ar), 127.9 (Ar), 127.27 (*ipso*-Ar), 127.21 (*ipso*-Ar), 124.8 (Ar), 120.9 (Ar), 118.8 (Ar), 111.0 (Ar), 102.9 (Ar), 79.3 (OCH), 67.5 (OCH₂), 65.6 (NCHMe), 58.4 (NCH₂), 51.1 (NCH₂), 20.0 (NCHMe); MS (ESI) *m/z* 307 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₀H₂₂N₂O (M + H)⁺ 307.1805, found 307.1805 (−0.1 ppm error).

Lab Book Reference: **NS11-62**

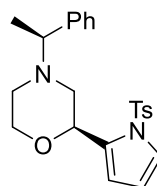
4-((R)-4-((S)-1-Phenylethyl)morpholin-2-yl)aniline (S,R)-349**(S,R)-349**

Using general procedure K, stannane (S,R)-**300** (150 mg, 0.42 mmol, 1.0 eq.), *n*-BuLi (310 μ L of a 1.5 M solution in hexane, 0.46 mmol, 1.1 eq.) in THF (3 mL), ZnCl₂ (785 μ L

of a 0.7 M solution in THF, 0.55 mmol, 1.3 eq.), Pd₂dba₃ (9.7 mg, 2.5 mol%), S-Phos (8.7 mg, 5 mol%) and 4-bromoaniline (94 mg, 0.55 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-EtOAc to 70:30 CH₂Cl₂-EtOAc as eluent gave α -aryl morpholine (*S,R*)-**349** (57 mg, 48%) as a colourless oil, [α]_D -41.6 (c 1.00 in CHCl₃); *R*_F (50:50 hexane-EtOAc) 0.5; IR (ATR) 3361 (NH), 2969, 2852, 2808, 1623, 1520, 1450, 1289, 1257, 1113, 1094, 1016, 829, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.20 (m, 5H, Ar), 7.18-7.13 (m, 2H, Ar), 6.69-6.60 (m, 2H, Ar), 4.56-4.44 (m, 1H, OCH), 3.88 (ddd, *J* = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.80-3.55 (m, 3H, OCH, NH), 3.42-3.30 (m, 1H, NCH), 3.14-3.03 (m, 1H, NCHMe), 2.58 (br d, *J* = 11.5 Hz, 1H, NCH), 2.18-2.04 (m, 2H, NCH), 1.36 (d, *J* = 6.5 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 146.2 (*ipso*-Ar), 143.8 (*ipso*-Ar), 130.9 (*ipso*-Ar), 128.5 (Ar), 127.9 (Ar), 127.7 (Ar), 127.2 (Ar), 115.1 (Ar), 78.4 (OCH), 67.3 (OCH₂), 65.5 (NCHMe), 57.8 (NCH₂), 51.0 (NCH₂), 19.8 (NCHMe); MS (ESI) *m/z* 283 [(*M* + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₈H₂₂N₂O (*M* + H)⁺ 283.1805, found 283.1804 (+0.4 ppm error).

Lab Book Reference: **NS11-82**

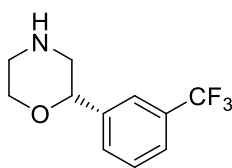
Attempted Synthesis of (*S*)-4-((*S*)-1-Phenylethyl)-2-(1-tosyl-1*H*-pyrrol-2-yl)morpholine (*S,S*)-**350**



(*S,S*)-**350**

Using general procedure K, stannane (*S,R*)-**300** (150 mg, 0.42 mmol, 1.0 eq.), *n*-BuLi (310 μ L of a 1.5 M solution in hexane, 0.47 mmol, 1.1 eq.) in THF (3. mL), ZnCl₂ (785 μ L of a 0.7 M solution in THF, 0.55 mmol, 1.3 eq.), Pd₂dba₃ (9.7 mg, 2.5 mol%), S-Phos (8.7 mg, 5 mol%) and 2-bromo-1-tosyl-1*H*-pyrrole (165 mg, 0.55 mmol, 1.3 eq.) gave the crude product which did not contain the desired product (by ¹H spectroscopy).

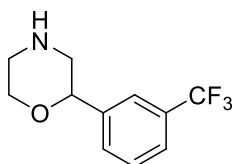
Lab Book Reference: **NS11-88**

(S)-2-(3-(Trifluoromethyl)phenyl)morpholine (S)-Flumexadol

(S)-Flumexadol

Using general procedure I, morpholine (*S,S*)-**336** (92 mg, 0.27 mmol, 1.0 eq.), α -chloroethyl chloroformate (88 μ l, 116 mg, 0.82 mmol, 3.0 eq.) in DCE (2 mL) and then MeOH (2 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 90:10 CH₂Cl₂-MeOH as eluent gave morpholine (*S*)-flumexadol (57 mg, 90%) as a colourless oil, $[\alpha]_D^{25} +28.5$ (*c* 0.1 in CHCl₃); *R*_F (90:10 CH₂Cl₂-MeOH) 0.4; IR (ATR) 2949 (NH), 2852, 1448, 1326, 1256, 1162, 1072, 873, 801, 703, 673, 560 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.26-7.20 (m, 1H, Ar), 6.95-6.88 (m, 2H, Ar), 6.85-6.76 (m, 1H, Ar), 4.45 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.02 (br dd, *J* = 11.5, 2.5 Hz, 1H, OCH), 3.80 (s, 3H, OMe), 3.75 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.04 (dd, *J* = 12.5, 2.5 Hz, 1H, NCH), 2.98 (ddd, *J* = 12.0, 11.5, 3.5 Hz, 1H, NCH), 2.92-2.82 (m, 1H, NCH), 2.77 (dd, *J* = 12.5, 10.5 Hz, 1H, NCH), 1.92 (br s, 1H, NH); ¹³C NMR (100.6 MHz, CDCl₃) δ 141.6 (*ipso*-Ar), 130.9 (q, *J* = 32.5 Hz, *ipso*-Ar), 129.5 (br s, Ar), 128.9 (Ar), 125.6 (q, *J* = 273.0 Hz, CF₃), 124.6 (Ar), 123.0 (Ar), 78.7 (OCH), 68.5 (OCH₂), 55.4 (NCH₂), 45.7 (NCH₂), ¹⁹F NMR (376 MHz, CDCl₃) δ -62.5 (s); MS (ESI) *m/z* 232 [(*M* + *H*)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₂F₃NO (*M* + *H*)⁺ 232.0944, found 232.0941 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.²⁰⁶

Lab Book Reference: **NS10-75**

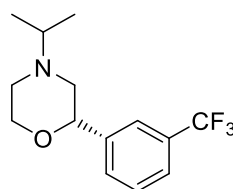
2-(3-(Trifluoromethyl)phenyl)morpholine *rac*-Flumexadol*rac*-Flumexadol

Using general procedure I, morpholine (*S*^{*},*S*^{*})-**336** (62 mg, 0.19 mmol, 1.0 eq.), α -chloroethyl chloroformate (60 μ l, 79 mg, 0.56 mmol, 3.0 eq.) in DCE (2 mL) and then MeOH (2 mL) gave the crude hydrochloride product. Then, EtOAc (10 mL) were added and the solution was washed with 2 M NaOH_(aq) (10 mL). The organic layer was dried (MgSO₄)

and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 90:10 CH₂Cl₂-MeOH as eluent gave *rac*-flumexadol (39 mg, 92%) as a colourless oil.

Lab Book Reference: **NS10-74**

(S)-4-Isopropyl-2-(3-(trifluoromethyl)phenyl)morpholine (S)-Oxaflozane

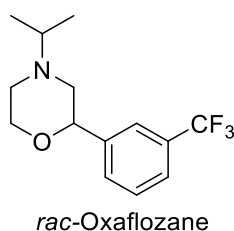


(S)-Oxaflozane

Acetone (250 μ L, 3.3 mmol, 20 eq.) was added to a stirred solution of (S)-flumexadol (39 mg, 0.16 mmol, 1.0 eq.) in CH₂Cl₂ (2 mL) at rt. The resulting solution was stirred at rt for 2 h. Then, sodium triacetoxyborohydride (108 mg, 0.50 mmol, 3.0 eq.) was added and the mixture was stirred at rt for 48 h. The reaction mixture was poured into 2 M NaOH_(aq) solution (15 mL) and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 CH₂Cl₂-acetone then 95:5 CH₂Cl₂-MeOH as eluent gave (S)-oxaflozane (46 mg, 99% , 99:1 er by CSP-HPLC) as a colourless oil, $[\alpha]_D -5.9$ (c 0.5 in CHCl₃); *R_F* (95:5 CH₂Cl₂-MeOH) 0.3; IR (ATR) 2966, 2858, 1449, 1327, 1163, 1118, 1000, 894, 803, 702, 670 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.63 (m, 1H, Ar), 7.57-7.48 (m, 2H, Ar), 7.49-7.39 (m, 1H, Ar), 4.59 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.06 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.81 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 2.90 (ddd, *J* = 11.5, 2.5, 2.5 Hz (app dt), 1H, NCH), 2.75 (br d, *J* = 11.5 Hz, 1H, NCH), 2.67 (sept, *J* = 6.5 Hz, 1H, NCHMe₂), 2.41 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, NCH), 2.17 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH), 1.06 (d, *J* = 6.5 Hz, 6H, NCHMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 141.9 (*ipso*-Ar), 130.8 (q, *J* = 32.5 Hz, *ipso*-Ar), 129.7 (Ar), 128.8 (Ar), 124.6 (q, *J* = 4.0 Hz, Ar), 124.3 (q, *J* = 272.5 Hz, CF₃), 123.1 (q, *J* = 4.0 Hz, Ar), 78.0 (OCH), 67.6 (OCH₂), 56.6 (NCH₂), 54.9 (NCH), 48.5 (NCH₂), 18.7 (NCHMe), 18.4 (NCHMe); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.4 (s); MS (ESI) *m/z* 274 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₄H₁₈F₃NO (M + H)⁺ 274.1413, found 274.1408 (+1.8 ppm error); CSP-HPLC: Chiralcel OD-H (99:1 hexane-*i*-PrOH, 1.0 mL min⁻¹) 10.1 min (major), 12.0 min (minor). Spectroscopic data consistent with those reported in the literature.²⁰⁷

Lab Book Reference: **NS10-80**

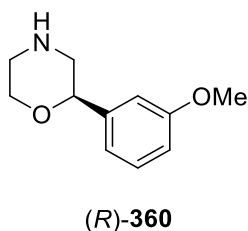
4-Isopropyl-2-(3-(trifluoromethyl)phenyl)morpholine *rac*-Oxaflozane



Acetone (242 μ L, 3.3 mmol, 20 eq.) was added dropwise to a stirred solution of *rac*-flumexadol (38.2 mg, 0.17 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at rt. The resulting solution was stirred at rt for 2 h. Then, sodium triacetoxyborohydride (105 mg, 0.50 mmol, 3.0 eq.) was added and the mixture was stirred at rt for 48 h. The reaction mixture was poured into 2 M $\text{NaOH}_{(\text{aq})}$ solution (15 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 CH_2Cl_2 -acetone then 95:5 CH_2Cl_2 -MeOH as eluent gave *rac*-oxaflozane (45 mg, quant.) as a colourless oil.

Lab Book Reference: **NS10-81**

(*R*)-2-(3-Methoxyphenyl)morpholine (*R*)-360

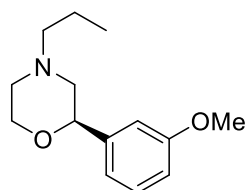


Using general procedure I, morpholine (*S,R*)-**334** (112 mg, 0.38 mmol, 1.0 eq.), α -chloroethyl chloroformate (122 μ L, 1.1 mmol, 3.0 eq.) in DCE (2 mL) and then MeOH (2 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 CH_2Cl_2 -acetone then 95:5 CH_2Cl_2 -MeOH as eluent gave morpholine (*R*)-**360** (64 mg, 89%) as a colourless oil, $[\alpha]_{\text{D}} -48.5$ (*c* 0.1 in CHCl_3); R_{F} (90:10 CH_2Cl_2 -MeOH) 0.4; IR (ATR) 3248 (NH), 2944, 2837, 1603, 1585, 1454, 1267, 1087, 1039, 879, 785, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.20 (m, 1H, Ar), 6.95-6.88 (m, 2H, Ar), 6.85-6.76 (m, 1H, Ar), 4.45 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.02 (br dd, *J* = 11.5, 2.5 Hz, 1H, OCH), 3.80 (s, 3H, OMe), 3.75 (ddd, *J* = 11.5, 11.5, 2.5 Hz (app td), 1H, OCH), 3.04 (dd, *J* = 12.5, 2.5 Hz,

1H, NCH), 2.98 (ddd, $J = 12.0, 11.5, 2.5$ Hz, 1H, NCH), 2.87 (dd, $J = 12.0, 2.5$ Hz, 1H, NCH), 2.77 (dd, $J = 12.5, 10.5$ Hz, 1H, NCH), 1.92 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 159.8 (*ipso*-Ar), 142.3 (*ipso*-Ar), 129.5 (Ar), 118.5 (Ar), 113.5 (Ar), 111.6 (Ar), 79.4 (OCH_2), 68.5 (OCH), 55.4 (OMe), 53.4 (NCH_2), 45.8 (NCH_2); MS (ESI) m/z 194 [(M + H) $^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2$ (M + H) $^+$ 194.1176, found 194.1172 (+1.6 ppm error).

Lab Book Reference: **NS11-93**

(R)-2-(3-Methoxyphenyl)-4-propylmorpholine (R)-359



(R)-359

Propionyl chloride (30 μL , 31 mg, 0.34 mmol, 1.25 eq.) was added to a stirred solution of morpholine (R)-**360** (52 mg, 0.27 mmol, 1.0 eq.) and Et_3N (56 μL , 41 mg, 0.41 mmol, 1.5 eq.) in CH_2Cl_2 (3 mL) at 0 $^\circ\text{C}$ under Ar. The resulting solution was allowed to warm to rt and stirred for 2 h. Then, H_2O (10 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The organic layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude amide product A solution of the crude amide (60 mg, 0.24 mmol, 1.0 eq.) in THF (5 mL) was added dropwise to a stirred suspension of LiAlH_4 (37 mg, 0.96 mmol, 4.0 eq.) in THF (5 mL) at 0 $^\circ\text{C}$ under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 16 h. After cooling to 0 $^\circ\text{C}$, Et_2O (10 mL) was added, followed by addition of $\text{Na}_2\text{SO}_4 \times 10 \text{ H}_2\text{O}$ until a white solid precipitated. The resulting mixture was stirred for 30 min until gas evolution had ceased and the solids were removed by filtration through Celite[®] and washed with EtOAc (3 x 10 mL). The filtrate was dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc then 50:50 hexane-EtOAc as eluent gave α -aryl morpholine (R)-**359** (52 mg, 90%, over two steps) as a colourless oil, $[\alpha]_{\text{D}} +5.6$ (c 0.1 in MeOH); R_{F} (50:50 hexane-EtOAc) 0.3; IR (ATR) 2958, 2933, 2871, 2808, 1587, 1488, 1456, 1270, 1112, 1043, 784, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.27-7.21 (m, 1H, Ar), 6.95-6.90 (m, 2H, Ar), 6.86-6.77 (m, 1H, Ar), 4.58 (br d, $J = 10.5$ Hz, 1H, OCH), 4.03 (ddd, $J = 11.5, 3.5, 1.5$ Hz, 1H, OCH), 3.86 (ddd, $J = 11.5, 10.5, 2.0$ Hz, 1H, OCH),

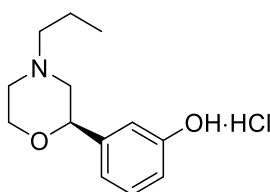
3.80 (s, 3H, OMe), 2.95 (br d, $J = 11.5$ Hz, 1H, NCH), 2.82 (br d, $J = 11.5$ Hz, 1H, NCH), 2.40-2.30 (m, 2H, NCH), 2.24 (ddd, $J = 11.5, 11.5, 3.5$ Hz (app td), 1H, NCH), 2.06 (dd, $J = 11.5, 10.5$ Hz, 1H, NCH), 1.61-1.49 (m, 2H, CH_2Me), 0.94-0.88 (m, 3H, CH_2Me); ^{13}C NMR (100.6 MHz, CDCl_3) δ 159.8 (*ipso*-Ar), 142.1 (*ipso*-Ar), 129.5 (Ar), 118.6 (Ar), 113.6 (Ar), 111.7 (Ar), 78.1 (OCH), 67.1 (OCH_2), 60.9 (NCH_2), 60.6 (OMe), 55.4 (NCH_2), 53.0 (NCH_2), 19.7 (CH_2Me), 12.0 (CH_2Me); MS (ESI) m/z 236 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2$ $(\text{M} + \text{H})^+$ 236.1645, found 236.1643 (+0.8 ppm error). Spectroscopic data consistent with those reported in the literature.²⁰⁸

Lab Book Reference: **NS11-94/95**

Propanal (64 μL , 52 mg, 0.89 mmol, 6.0 eq.) was added dropwise to a stirred solution of morpholine (*R*)-**360** (35 mg, 0.15 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at rt. The resulting solution was stirred at rt for 2 h. Then, sodium triacetoxyborohydride (95 mg, 0.47 mmol, 3.0 eq.) was added and the mixture was stirred at rt for 48 h. The reaction mixture was poured into 2 M $\text{NaOH}_{(\text{aq})}$ (15 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 CH_2Cl_2 -acetone then 95:5 CH_2Cl_2 -MeOH as eluent gave a complex mixture containing morpholine (*R*)-**359** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS10-83**

(*R*)-3-(4-Propylmorpholin-2-yl)phenol hydrochloride (*R*)-PF-219,061·HCl



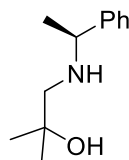
(*R*)-PF216,061·HCl

HBr (10 mL of a 48% solution in H_2O) was added dropwise to a stirred solution of morpholine (*R*)-**359** (40 mg, 0.17 mmol, 1.0 eq.) in H_2O (2 mL) at rt. The resulting solution was stirred and heated at reflux for 3 h. After cooling to rt, water (10 mL) was added followed by addition of $\text{NH}_4\text{OH}_{(\text{aq})}$ until pH 7 was reached. The solution was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude amine. HCl (130 μL of a 2.0 M solution in Et_2O , 0.26 mmol, 1.5 eq.) was added to a stirred solution of the crude amine in Et_2O (2 mL) at rt. After

stirring at rt for 30 min, the solvent was evaporated under reduced pressure to give the crude product as a solid. Et₂O (2 mL) was added, the mixture was swirled to dissolve impurities and then the Et₂O was decanted. Addition of Et₂O (2 mL) and decanting was repeated a second time. The residual Et₂O was evaporated under reduced pressure to give morpholine (*R*)-PF219,061·HCl (46 mg, 92%) as a white solid, mp 80-82 °C, [α]_D -5.8 (*c* 1.00 in MeOH) (lit.,²⁰⁸ -5.66 (*c* 1.06 in MeOH); IR (ATR) 3178 (OH), 2938, 2595, 1603, 1591, 1455, 1281, 1097, 1052, 999, 791, 700 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.20 (dd, *J* = 8.0, 8.0 Hz (app t), 1H, Ar), 6.89-6.85 (m, 2H, Ar), 6.80-6.76 (m, 1H, Ar), 4.90 (s, 1 H, OH), 4.82-4.73 (m, 1H, OCH), 4.24 (dd, *J* = 13.5, 3.5 Hz, 1H, OCH), 4.04 (ddd, *J* = 13.5, 12.5, 2.5 Hz, 1H, OCH), 3.65-3.53 (m, 2H, NCH), 3.24-3.09 (m, 3H, NCH), 3.03 (dd, *J* = 12.5, 11.0 Hz, 1H, NCH), 1.92-1.75 (m, 2H, CH₂Me), 1.02 (t, *J* = 7.5 Hz, 3H, CH₂Me); ¹³C NMR (100.6 MHz, CD₃OD) δ 158.9 (*ipso*-Ar), 139.9 (*ipso*-Ar), 130.8 (Ar), 118.3 (Ar), 116.7 (Ar), 114.2 (Ar), 76.8 (OCH), 65.1 (OCH₂), 60.2 (NCH₂), 57.9 (NCH₂), 52.2 (NCH₂), 18.2 (CH₂Me), 11.2 (CH₂Me); MS (ESI) *m/z* 222 [*M*⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₃H₂₀NO₂ *M*⁺ 222.1489, found 222.1487 (+0.9 ppm error). Spectroscopic data consistent with those reported in the literature.²⁰⁸

Lab Book Reference: **NS11-96**

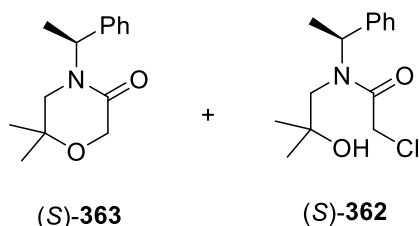
(*S*)-2-Methyl-1-((1-phenylethyl)amino)propan-2-ol (*S*)-361



(*S*)-361

α -Chloro-2-methylpropan-2-ol (4.34 g, 4.10 mL, 40 mmol, 1.0 eq.) was added to a stirred solution of (*S*)- α -methylbenzylamine (9.70 g, 10.3 mL, 80 mmol, 2.0 eq.) and H₂O (1.20 mL, 80 mmol, 2.0 eq.) at rt. The resulting solution was stirred and heated at reflux for 16 h. After cooling to rt, 20% NaOH_(aq) (50 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation (106 °C-108 °C / 0.6 mmHg) gave alcohol (*S*)-**361** (5.34 g, 69%) as a yellow oil, [α]_D -40.7 (*c* 0.5 in MeOH) (lit.,²⁰⁹ +49.7 (*c* 10.0 in MeOH) for (*R*)-**361**); IR (ATR) 3411 (NH / OH), 2970, 1493, 1451, 1372, 1121, 910, 761, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.22 (m, 5H, Ph), 3.76 (q, *J* = 6.5 Hz, 1H, NCHMe), 3.10 (s, 1H, NH),

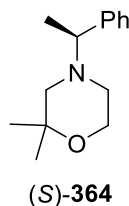
(S)-6,6-Dimethyl-4-(1-phenylethyl)morpholin-3-one (S)-363



356

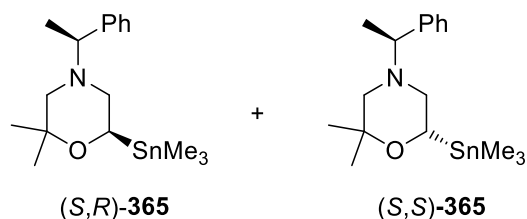
NMR (100.6 MHz, CDCl₃) for (S)-**363** δ 166.4 (C=O) 139.3 (*ipso*-Ph), 128.5 (Ph), 127.7 (Ph), 127.2 (Ph), 77.3 (OCMe₂), 63.5 (OCH₂), 57.4 (NCHMe), 41.9 (NCH₂), 28.0 (CMe), 24.7 (CMe), 18.4 (NCHMe); MS (ESI) for (S)-**363** m/z 256 [(M + Na)⁺, 100]; HRMS (ESI) for (S)-**363** m/z calcd for C₁₄H₁₉NO₂ (M + Na)⁺ 256.1308, found 256.1307 (−0.1 ppm error).
Lab Book Reference: **NS10-64**

(S)-2,2-Dimethyl-4-(1-phenylethyl)morpholine (S)-364

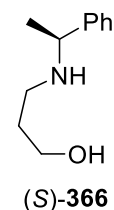


A solution of a 70:30 mixture of morpholinone (S)-**363** and alcohol (S)-**362** (5.74 g, i.e. 3.85 g, 22 mol, 1.0 eq. of morpholinone (S)-**363**) in THF (100 mL) was added dropwise to a stirred suspension of LiAlH₄ (2.54 g, 67 mmol, 3.0 eq.) in THF (50 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 16 h. After cooling to 0 °C, Et₂O (100 mL) was added, followed by addition of Na₂SO₄ x 10 H₂O until a white solid precipitated. The resulting mixture was stirred for 30 min until gas evolution had ceased and the solids were removed by filtration through Celite[®] and washed with EtOAc (3 x 50 mL). The filtrate was dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave morpholine (S)-**364** (4.45 g, 91%) as a colourless oil, [α]_D −29.6 (*c* 0.25 in CHCl₃); *R*_F (90:10 hexane-EtOAc) 0.3; IR (ATR) 2972, 2869, 1492, 1451, 1361, 1122, 1093, 1021, 915, 864, 762, 700, 546 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.27 (m, 4H, Ph), 7.25-7.19 (m, 1H, Ph), 3.83-3.65 (m, 2H, OCH), 3.24 (q, *J* = 6.5 Hz, 1H, NCHMe), 2.51 (ddd, *J* = 10.0, 4.5, 4.0 Hz, 1H, NCH), 2.26 (ddd, *J* = 10.0, 7.0, 4.0 Hz, 1H, NCH), 2.18 (d, *J* = 11.0 Hz, 1H, NCH), 2.14 (d, *J* = 11.0 Hz, 1H, NCH), 1.23 (s, 3H, CMe), 1.18 (s, 3H, CMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 144.9 (*ipso*-Ph), 128.4 (Ph), 127.6 (Ph), 126.9 (Ph), 71.7 (OCMe₂), 64.9 (NCHMe), 61.9 (OCH₂), 60.8 (NCH₂), 51.0 (NCH₂), 25.8 (CMe), 24.6 (CMe), 20.0 (NCHMe); MS (ESI) m/z 220 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₄H₂₁NO (M + H)⁺ 220.1696, found 220.1694 (+0.9 ppm error).

Lab Book Reference: **NS10-70**

Lab Book Reference: **NS10-78**

(S)-3-((1-Phenylethyl)amino)propan-1-ol (S)-366

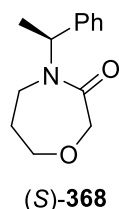


358

colourless oil, $[\alpha]_D +52.4$ (c 1.2 in CHCl_3) (lit.,²¹⁰ $+51.6$ (c 1.2 in CHCl_3)); IR (ATR) 3276 (NH), 2927, 1493, 1451, 1370, 1117, 1074, 1057, 761, 735, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.19 (m, 5H, Ph), 3.84-3.68 (m, 3H, OCH, NCHMe), 2.90 (br s, 1H, NH), 2.82-2.70 (m, 1H, NCH), 2.70-2.58 (m, 1H, NCH), 1.77-1.62 (m, 1H, CH), 1.65-1.54 (m, 1H, CH), 1.35 (d, $J = 6.5$ Hz, 3H, NCHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 144.9 (*ipso*-Ph), 128.7 (Ph), 127.3 (Ph), 126.6 (Ph), 64.6 (OCH_2), 58.8 (NCHMe), 48.0 (NCH_2), 31.3 (NCHMe), 24.4 ($\text{CH}_2\text{CH}_2\text{OH}$); MS (ESI) m/z 180 $[(M + H)^+]$, 100; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{17}\text{NO}$ ($M + H$)⁺ 180.1383, found 180.1382 (+0.3 ppm error). Spectroscopic data consistent with those reported in the literature.¹⁷⁵

Lab Book Reference: **NS10-48**

(S)-4-(1-Phenylethyl)-1,4-oxazepan-3-one (S)-368

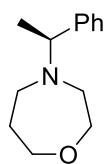


α -Chloroacetyl chloride (887 μL , 1.26 g, 11 mmol, 1.0 eq.) was added to a stirred solution of alcohol (S)-**366** (2.00 g, 11 mmol, 1.0 eq.) and Et_3N (1.70 mL, 1.24 g, 12 mmol, 1.1 eq.) in CH_2Cl_2 (40 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure. EtOAc (50 mL) and H_2O (50 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude amide. A solution of the crude amide (S)-**367** (2.86 g, 11 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a suspension of NaH (480 mg of a 60wt% suspension in mineral oil, 12 mmol, 1.1 eq.) in THF (100 mL) at 0 °C under Ar. The resulting suspension was allowed to warm to rt and stirred at rt for 16 h. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (50 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave morpholinone (S)-**368** (1.42 g, 58%) as a colourless oil, $[\alpha]_D -104.7$ (c 0.5 in CHCl_3); R_F (50:50 hexane-EtOAc) 0.2; IR (ATR) 3500 (NH), 2972, 1638 (C=O), 1480, 1420, 1322, 1130, 1105, 973, 942,

702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.24 (m, 5H, Ph), 5.97 (q, J = 7.0 Hz, 1H, NCHMe), 4.29 (br s, 2H, OCHC(O)), 3.84-3.68 (m, 2H, OCH), 3.32-3.15 (m, 2H, NCH), 1.49 (d, J = 7.0 Hz, 3H, NCHMe), 1.53-1.20 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 172.4 (C=O), 140.3 (*ipso*-Ph), 128.6 (Ph), 127.67 (Ph), 127.63 (Ph), 73.7 (OCH₂), 71.5 (OCH₂), 51.4 (NCHMe), 41.4 (NCH₂), 30.4 (CH₂), 15.8 (NCHMe); MS (ESI) m/z 242 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₁₃H₁₇NO₂ (M + Na)⁺ 242.1151, found 242.1148 (+1.3 ppm error).

Lab Book Reference: **NS10-51**

(S)-4-(1-Phenylethyl)-1,4-oxazepane (S)-369

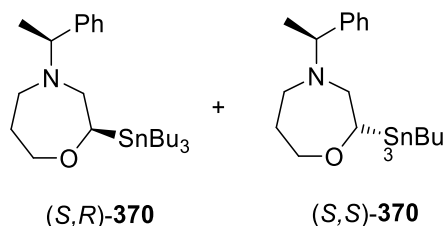


(S)-369

A solution of morpholinone (S)-**368** (1.30 g, 5.9 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a stirred suspension of LiAlH₄ (675 mg, 18 mmol, 3.0 eq.) in THF (50 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 16 h. After cooling to 0 °C, Et₂O (100 mL) was added, followed by addition of Na₂SO₄ x 10 H₂O until a white solid precipitated. The resulting mixture was stirred for 30 min until gas evolution had ceased and the solids were removed by filtration through Celite® and washed with EtOAc (3 x 50 mL). The filtrate was dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave morpholine (S)-**369** (1.21 g, 93%) as a colourless oil, [α]_D +3.25 (c 0.5 in CHCl₃); R_F (80:20 hexane-EtOAc) 0.4; IR (ATR) 2936, 2857, 1453, 1368, 1146, 1116, 913, 768, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.16 (m, 5H, Ph), 3.81-3.76 (m, 3H, NCHMe, OCH), 3.70-3.63 (m, 2H, OCH), 2.79-2.61 (m, 4H, NCH), 1.87-1.78 (m, 2H, CH), 1.36 (d, J = 6.5 Hz, 3H, NCHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 144.4 (*ipso*-Ph), 128.3 (Ph), 127.7 (Ph), 126.9 (Ph), 70.4 (OCH₂), 68.8 (OCH₂), 63.1 (NCHMe), 54.3 (NCH₂), 50.8 (NCH₂), 30.6 (CH₂), 18.3 (NCHMe); MS (ESI) m/z 206 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₃H₁₉NO (M + H)⁺ 206.1539, found 206.1537 (+1.0 ppm error).

Lab Book Reference: **NS10-53**

Attempted Synthesis of 4-(1-Phenylethyl)-2-(trimethylstannyl)morpholine (S,R)-370 and (S,S)-370



Using general procedure D, morpholine (S)-**369** (205 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and Me₃SnCl (2.0 mL of a 1.0 M solution in hexane, 2.0 mmol, 2.0 eq.) gave the crude product which did not contain the desired product (by ¹H spectroscopy).

Lab Book Reference: **NS10-57**

s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 eq.) was added dropwise to a stirred solution of the morpholine (S)-**369** (205 mg, 1.0 mmol, 1.0 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 4 h. Then, Me₃SnCl (2.0 mL of a 1.0 M solution in hexane, 4.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at 0 °C for 1 h and then allowed to warm to rt. Then, saturated NH₄Cl_(aq) (10 mL) and 10% NaHCO_{3(aq)} (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which did not contain the desired products (by ¹H spectroscopy).

Lab Book Reference: **NS10-61**

5.5 Experimental for Chapter Four

Phenyl(tetrahydrothiophen-2-yl)methanol **382**

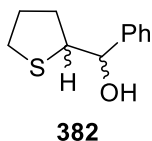


Table 4.1, entry 1:

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and benzaldehyde (210 mg, 201 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of alcohols **382**. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2 -acetone then 80:20 CH_2Cl_2 -acetone as eluent gave a 55:45 mixture of alcohols **382** (168 mg, 87%) as a colourless oil, R_F (90:10 CH_2Cl_2 -acetone) 0.3; IR (ATR) 3402 (OH), 2932, 2860, 1452, 1020, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.23 (m, 5H, Ph), 4.72 (dd, J = 12.5, 5.5 Hz, 0.55H, HOCH), 4.54 (dd, J = 5.5, 5.5 Hz (app t), 0.45H, HOCH), 3.86-3.72 (m, 1H, SCH), 2.94-2.83 (m, 2H, CH), 2.81 (br d, J = 5.5 Hz, 0.55H, OH), 2.71 (br s, 0.45H, OH), 2.16-2.02 (m, 1H, CH), 2.01-1.74 (m, 3H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 143.0 (*ipso*-Ph), 142.1 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 128.0 (Ph), 127.8 (Ph), 126.3 (Ph), 126.2 (Ph), 76.8 (HOCH), 74.8 (HOCH), 57.9 (SCH), 56.5 (SCH), 34.2 (CH_2), 33.3 (CH_2), 32.7 (CH_2), 31.4 (CH_2), 31.1 (CH_2), 30.9 (CH_2); MS (ESI) m/z 217 [(M + H) $^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{OS}$ (M + Na) $^+$ 217.0658, found 217.0653 (+2.1 ppm error).

Lab Book Reference: **NS3-24**

Table 4.1, entry 2:

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (15 μ L, 0.11 mmol, 0.1 eq.) in hexane (5 mL) at 0 °C for 3 h and benzaldehyde (210 mg, 201 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of alcohols **382**. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2 -acetone then 80:20 CH_2Cl_2 -acetone as eluent gave a 55:45 mixture of alcohols **382** (18 mg, 9%) as a colourless oil.

Lab Book Reference: **NS3-33**

Table 4.1, entry 3:

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (45 μ L, 0.33 mmol, 0.3 eq.) in hexane (5 mL) at 0 °C for 3 h and benzaldehyde (210 mg, 201 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of alcohols **382**. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2 -acetone then 80:20 CH_2Cl_2 -acetone as eluent gave a 55:45 mixture of alcohols **382** (60 mg, 31%) as a colourless oil.

Lab Book Reference: **NS3-37**

Table 4.1, entry 4

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.65 mL of a 1.7 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and benzaldehyde (210 mg, 201 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which did not contain the desired alcohols **382** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS3-32**

s-BuLi (0.77 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of tetrahydrothiophene **25** (5 mL) at –60 °C under Ar. The resulting solution was stirred at –60 °C for 4 h. Then, benzaldehyde (210 mg, 201 μ L, 2.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at –60 °C for 1 h and then allowed to warm to rt. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 10% $\text{NaHCO}_{3(\text{aq})}$ (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 $\times$ 10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of direct trapped alcohols **383**, tetrahydrothiophene **25** and benzaldehyde (by ^1H NMR spectroscopy). Diagnostic signals for the direct trapped products **383**: ^1H NMR (400 MHz, CDCl_3) 4.72 (d, J = 5.0 Hz, 0.45H, HOCH), 4.53 (d, J = 6.5 Hz, 0.55H, HOCH).

Lab Book Reference: **N3-15**

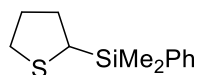
Dimethyl(phenyl)(tetrahydrothiophen-2-yl)silane 385**385**

Table 4.1, entry 7:

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and PhSiMe₂Cl (340 mg, 355 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ as eluent gave silane **385** (191 mg, 86%) as a colourless oil, *R*_F (75:25 hexane-CH₂Cl₂) 0.4; IR (ATR) 2932, 2860, 1452, 1441, 1263, 1189, 1020, 762, 734, 698, 529, 556 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.55 (m, 2H, Ph), 7.39-7.33 (m, 3H, Ph), 2.91 (ddd, *J* = 11.0, 8.0, 2.5 Hz, 1H, SCH), 2.69 (ddd, *J* = 11.0, 11.0, 6.0 Hz (app td), 1H, SCH), 2.59 (dd, *J* = 11.5, 6.0 Hz, 1H, SCH), 2.24-2.15 (m, 2H, CH), 1.74-1.60 (m, 1H, CH), 1.49 (dddd, *J* = 11.5, 11.5, 11.5, 6.0 Hz (app qd), 1H, CH), 0.37 (s, 3H, SiMe), 0.36 (s, 3H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 138.2 (*ipso*-Ph), 134.4 (Ph), 129.7 (Ph), 128.2 (Ph), 34.1 (CH₂), 33.6 (SCH), 33.0 (CH₂), 32.9 (CH₂), -3.6 (SiMe), -4.3 (SiMe); MS (ESI) *m/z* 217 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₄OS (M + Na)⁺ 217.0658, found 217.0653 (+2.1 ppm error).

Lab Book Reference: **NS3-21**

Table 4.1, entry 5:

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 20 min and PhSiMe₂Cl (340 mg, 355 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ as eluent gave silane **385** (145 mg, 66%) as a colourless oil.

Lab Book Reference: **NS3-20**

Table 4.1, entry 6:

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol,

1.3 eq.) in hexane (5 mL) at 0 °C for 2 min and PhSiMe₂Cl (340 mg, 355 µL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ as eluent gave silane **385** (64 mg, 29%) as a colourless oil.

Lab Book Reference: **NS3-19**

Table 4.1, entry 8:

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 µL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and PhSiMe₂Cl (340 mg, 355 µL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ as eluent gave silane **385** (187 mg, 84%) as a colourless oil.

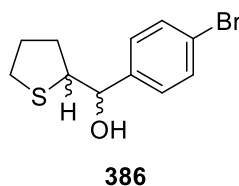
Lab Book Reference: **NS10-89**

Table 4.1, entry 9:

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 µL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 4 h and PhSiMe₂Cl (340 mg, 355 µL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ as eluent gave silane **385** (171 mg, 77%) as a colourless oil.

Lab Book Reference: **NS10-90**

(4-Bromophenyl)(tetrahydrothiophen-2-yl)methanol **386**

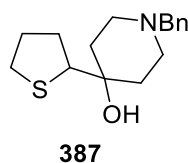


Using general procedure M, tetrahydrothiophene **25** (191 mg, 1.0 mmol, 1.0 eq.), s-BuLi (0.77 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.0 eq.) and TMEDA (195 µL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and *p*-bromobenzaldehyde (270 mg, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 50:50 mixture (by ¹H NMR spectroscopy) of alcohols **386**. Purification by flash column chromatography on silica with 99:1 to 98:2 CH₂Cl₂-acetone as eluent gave a 50:50 mixture of alcohols **386** (168 mg, 62%)

as a colourless oil, R_F (98:2 CH_2Cl_2 -acetone) 0.6; IR (ATR) 3402 (OH), 2946, 2859, 1487, 1263, 1184, 1070, 1008, 818, 736, 531, 506 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.50-7.44 (m, 2H, Ar), 7.28-7.19 (m, 2H, Ar), 4.73 (dd, $J = 7.0, 4.5$ Hz, 0.5H, HOCH), 4.51 (dd, $J = 6.0, 6.0$ Hz (app t), 0.5H, HOCH), 3.78-3.67 (m, 1H, SCH), 2.98-2.87 (m, 2.5H, CH, OH), 2.78-2.75 (m, 0.5H, CH), 2.65-2.57 (m, 1H, CH), 2.28-2.19 (m, 1H, CH), 2.18-2.10 (m, 1H, CH), 2.02-1.93 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 142.0 (*ipso*-Ar), 141.0 (*ipso*-Ar), 131.7 (*ipso*-Ar), 131.6 (*ipso*-Ar), 128.0 (Ar), 127.9 (Ar), 121.8 (Ar), 121.5 (Ar), 75.9 (OCH), 74.0 (OCH), 57.8 (SCH), 56.3 (SCH), 34.1 (CH_2), 33.3 (CH_2), 32.7 (CH_2), 31.4 (CH_2), 30.92 (CH_2), 30.91 (CH_2); MS (ESI) m/z 294 [$^{79}\text{M} + \text{Na}$] $^+$, 100], 296 [$^{81}\text{M} + \text{Na}$] $^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{13}^{79}\text{BrOS}$ ($^{79}\text{M} + \text{Na}$) $^+$ 294.9763, found 294.9764 (–0.6 ppm error).

Lab Book Reference: **NS5-83**

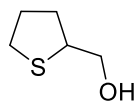
1-Benzyl-4-(tetrahydrothiophen-2-yl)piperidin-4-ol **387**



Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and 1-benzylpiperidin-4-one (378 mg, 371 μL , 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 500:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ then 100:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave alcohol **387** (198 mg, 61%) as a red oil, R_F (500:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.3; IR (ATR) 3468 (OH), 2932, 2859, 2810, 1453, 1316, 1185, 1145, 1063, 1047, 811, 735, 697, 466 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.22 (m, 5H, Ph), 3.52 (s, 2H, NCH_2Ph), 3.47 (dd, $J = 9.5, 5.5$ Hz, 1H, SCH), 2.86-2.79 (m, 1H, SCH), 2.75 (ddd, $J = 9.5, 5.5, 5.5$ Hz (app dt), 1H, SCH), 2.72-2.59 (m, 2H, CH), 2.40-2.30 (m, 2H, CH), 2.24 (br s, 1H, OH), 2.22-2.18 (m, 1H, CH), 2.05-1.99 (m, 1H, CH), 1.87-1.55 (m, 5H, CH), 1.50 (dddd, $J = 13.5, 3.0, 3.0, 3.0$ Hz (app dq), 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 138.6 (*ipso*-Ph), 129.3 (Ph), 128.3 (Ph), 127.1 (Ph), 69.2 (OC), 63.3 (NCH_2Ph), 61.7 (SCH), 49.7 (NCH_2), 49.4 (NCH_2), 39.6 (CH_2), 34.8 (CH_2), 32.3 (SCH_2), 31.9 (CH_2), 30.5 (CH_2); MS (ESI) m/z 278 [(M + H) $^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{23}\text{NOS}$ (M + H) $^+$ 278.1573, found 278.1572 (–0.3 ppm error).

Lab Book Reference: **NS3-48**

(Tetrahydrothiophan-2-yl)methanol 388

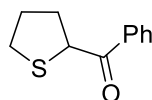


388

Using general procedure M, tetrahydrothiophene **25** (88 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and paraformaldehyde (60 mg, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 500:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq) then 300:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave alcohol **388** (92 mg, 78%) as a colourless oil, *R*_F (500:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.3; IR (ATR) 3351 (OH), 2934, 2861, 1441, 1019, 732 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.66-3.56 (m, 2H, OCH, SCH), 3.52 (dd, *J* = 10.0, 5.0 Hz, 1H, OCH), 2.89-2.81 (m, 2H, SCH), 2.09 (br s, 1H, OH), 2.05-1.95 (m, 3H, CH), 1.88-1.77 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 65.7 (OCH₂), 51.1 (SCH), 33.2 (CH₂), 32.6 (CH₂), 30.7 (CH₂); MS (ESI) *m/z* 141 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₅H₁₀OS (M + Na)⁺ 141.0345, found 141.0351 (+4.6 ppm error).

Lab Book Reference: **NS3-25**

Phenyl(tetrahydrothiophan-2-yl)methanone 389



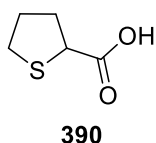
389

Using general procedure M, tetrahydrothiophene **25** (191 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and Weinreb amide **115** (330 mg, 304 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica 50:50 hexane-CH₂Cl₂ as eluent gave ketone **389** (162 mg, 84%) as a white solid, mp 55-56 °C; *R*_F (50:50 hexane-CH₂Cl₂) 0.3; IR (ATR) 3059, 2934, 2861, 1679 (C=O), 1596, 1447, 1219, 688 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.97-7.92 (m, 2H, Ph), 7.58-7.53 (m, 1H, Ph), 7.49-7.44 (m, 2H, Ph), 4.73 (dd, *J* = 7.0, 4.5 Hz, 1H, SCH), 2.98-

2.87 (m, 2H, SCH), 2.65-2.57 (m, 1H, CH), 2.28-2.19 (m, 1H, CH), 2.18-2.10 (m, 1H, CH), 2.02-1.93 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 196.5 (C=O), 136.0 (*ipso*-Ph), 133.2 (Ph), 128.7 (Ph), 128.7 (Ph), 49.4 (SCH), 34.1 (SCH_2), 31.4 (CH_2), 31.3 (CH_2); MS (ESI) m/z 193 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{12}\text{OS}$ ($\text{M} + \text{H})^+$ 193.0682, found 193.0685 (−0.6 ppm error). Spectroscopic data consistent with those reported in the literature.²¹¹

Lab Book Reference: **NS3-26**

Tetrahydrothiophene-2-carboxylic acid **390**

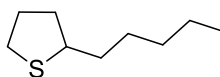


Using general procedure N, tetrahydrothiophene **25** (1.76 g, 20 mmol, 1.0 eq.), *s*-BuLi (20 mL of a 1.3 M solution in hexane, 26 mmol, 1.3 eq.) and TMEDA (3.90 mL, 26 mmol, 1.3 eq.) in hexane (100 mL) at 0 °C for 1 h and CO_2 at −78 °C for 30 min and then at rt for 30 min gave the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 then 99:1 CH_2Cl_2 -AcOH gave acid **390** (2.19 g, 83%) as a viscous oil, R_F (CH_2Cl_2) 0.1, IR (ATR) 2935, 1698 (C=O), 1440, 1416, 1225, 925, 798, 680, 537, 501 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.94 (br s, 1H, CO_2H), 3.95 (dd, $J = 7.0, 4.5$ Hz, 1H, SCH), 3.00 (ddd, $J = 10.0, 7.0, 7.0$ Hz (app dt), 1H, SCH), 2.89 (ddd, $J = 10.0, 7.0, 7.0$ Hz (app dt), 1H, SCH), 2.35-2.27 (m, 1H, 1H, CH), 2.24-1.95 (m, 3H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 179.9 (C=O), 47.6 (SCH), 33.5 (CH_2), 33.3 (SCH_2), 30.9 (CH_2); MS (ESI) m/z 155 $[(\text{M} + \text{Na})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_5\text{H}_8\text{O}_2\text{S}$ ($\text{M} + \text{Na})^+$ 155.0137, found 155.0138 (−0.8 ppm error). Spectroscopic data consistent with those reported in the literature.²¹²

Lab Book Reference: **NS11-72**

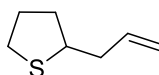
Using general procedure N, tetrahydrothiophene **25** (880 mg, 10 mmol, 3.3 eq.), *s*-BuLi (2.4 mL of a 1.3 M solution in hexane, 3.0 mmol, 1.0 eq.) and TMEDA (1.17 mL, 6.0 mmol, 2.0 eq.) in hexane (15 mL) at 0 °C for 1 h and CO_2 at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 then 99:1 CH_2Cl_2 -AcOH gave acid **390** (270 mg, 66%) as a viscous oil.

Lab Book Reference: **NS4-69**

2-Pentyltetrahydrothiophene 391**391**

Using general procedure M, tetrahydrothiophene **25** (176 mg, 2.0 mmol, 1.0 eq.), *s*-BuLi (2.0 mL of a 1.3 M solution in hexane, 2.6 mmol, 1.3 eq.) and TMEDA (390 μ L, 2.6 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C for 1 h and *n*-pentyl iodide (792 mg, 522 μ L, 4.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂ gave pentyl tetrahydrothiophene **391** (158 mg, 48%) as a colourless oil, *R*_F (90:10 hexane-CH₂Cl₂) 0.4; IR (ATR) 2926, 2857, 1442, 1260 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.32 (ddd, *J* = 14.0, 7.5, 6.0 Hz, 1H, SCH), 2.91-2.80 (m, 2H, CH), 2.14-2.01 (m, 2H, CH), 1.93-1.81 (m, 1H, CH), 1.70-1.44 (m, 3H, CH), 1.41-1.23 (m, 6H, CH), 0.88 (t, *J* = 7.0 Hz, 3H, CH₂Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 49.6 (SCH), 37.9 (CH₂), 37.5 (CH₂), 32.2 (CH₂), 31.9 (CH₂), 30.5 (CH₂), 29.0 (CH₂), 22.7 (CH₂), 14.2 (Me); MS (APCI) *m/z* 159 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₉H₁₈S (M + H)⁺ 159.1202, found 159.1197 (−2.9 ppm error). Spectroscopic data consistent with those reported in the literature.²¹³

Lab Book Reference: **NS3-75**

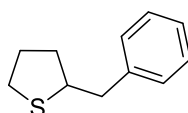
2-Allyltetrahydrothiophene 392**392**

Using general procedure M, tetrahydrothiophene **25** (176 mg, 2.0 mmol, 1.0 eq.), *s*-BuLi (2.0 mL of a 1.3 M solution in hexane, 2.6 mmol, 1.3 eq.) and TMEDA (390 μ L, 2.6 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C for 1 h and allyl bromide (484 mg, 346 μ L, 4.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂ as eluent gave allyl tetrahydrothiophene **392** (124 mg, 48%) as a colourless oil, *R*_F (90:10 hexane-CH₂Cl₂) 0.2; IR (ATR) 2958, 2925, 1461, 1381, 1259, 916 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.81 (dddd, *J* = 17.0, 10.5, 7.0, 7.0 Hz (app ddt), 1H, CH=CH₂), 5.12-5.01 (m, 2H, CH=CH₂), 3.46-3.36 (m, 1H, SCH), 2.95-2.81 (m, 2H, CH), 2.44-2.26 (m, 2H, CH), 2.13-2.01 (m, 2H, CH), 1.97-1.82 (m, 1H, CH), 1.65-1.56

(m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 136.9 (CH=CH₂), 116.4 (CH=CH₂), 48.4 (SCH), 41.8 (CH₂), 36.9 (CH₂), 32.5 (CH₂), 30.4 (CH₂). Spectroscopic data consistent with those reported in the literature.²¹⁴

Lab Book Reference: **NS3-76**

2-Benzyltetrahydrothiophene 393

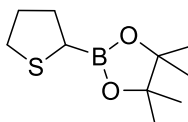


393

Using general procedure M, tetrahydrothiophene **25** (176 mg, 2.0 mmol, 1.0 eq.), *s*-BuLi (2.0 mL of a 1.3 M solution in hexane, 2.6 mmol, 1.3 eq.) and TMEDA (390 μL , 2.6 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C for 1 h and benzyl bromide (695 mg, 486 μL , 4.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂ as eluent gave benzyl tetrahydrothiophene **393** (137 mg, 41%) as a colourless oil, R_F (90:10 hexane-CH₂Cl₂) 0.3; IR (ATR) 3061, 3026, 2941, 2859, 1495, 1453, 1441, 749, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.49-7.25 (m, 5H, Ph), 3.82-3.70 (m, 1H, CH), 3.10-2.96 (m, 4H, SCH, CH), 2.29-2.13 (m, 2H, CH), 2.13-1.96 (m, 1H, CH), 1.86-1.73 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 140.6 (*ipso*-Ph), 129.0 (Ph), 128.5 (Ph), 126.4 (Ph), 50.4 (SCH), 43.8 (CH₂), 36.9 (CH₂), 32.6 (CH₂), 30.2 (CH₂); MS (ESI) m/z 178 [(M)⁺, 100]; HRMS (ESI) m/z calcd for C₁₁H₁₄S (M)⁺ 178.8016, found 178.0821 (+0.5 ppm error).

Lab Book Reference: **NS3-62**

4,4,5,5-Tetramethyl-2-(tetrahydrothiophen-2-yl)-1,3,2-dioxaborolane 394



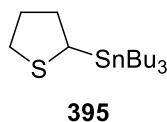
394

Using general procedure M, tetrahydrothiophene **25** (261 mg, 3.0 mmol, 1.0 eq.), *s*-BuLi (3.0 mL of a 1.3 M solution in hexane, 3.9 mmol, 1.3 eq.) and TMEDA (585 μL , 3.9 mmol, 1.3 eq.) in hexane (15 mL) at 0 °C for 1 h and *i*-PrOBpin (1.11 g, 1.22 mL, 6.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography

on silica with 95:5 hexane-Et₂O then 90:10 hexane-Et₂O as eluent gave boronate **394** (200 mg, 51%) as a colourless oil, *R*_F (90:10 hexane-Et₂O) 0.4; IR (ATR) 2977, 1407, 1372, 1327, 1215, 1142, 972, 851, 678 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.92-2.78 (m, 2H, SCH), 2.61 (dd, *J* = 9.0, 6.5 Hz, 1H, SCH), 2.23-2.11 (m, 2H, CH), 1.84-1.74 (m, 2H, CH), 1.26 (s, 12H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 83.8 (OCMe₂), 33.6 (CH₂), 32.6 (CH₂), 32.5 (CH₂), 24.8 (Me), 24.7 (Me); MS (ESI) *m/z* 237 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₀H₁₉BO₂S (M + Na)⁺ 237.1093, found 237.1083 (+4.1 ppm error).

Lab Book Reference: **NS3-40**

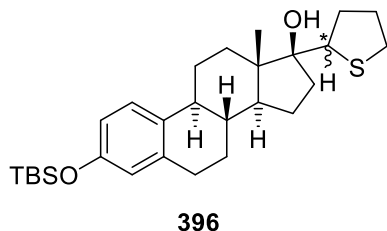
Tributyl(tetrahydrothiophen-2-yl)stannane **395**



Using general procedure M, tetrahydrothiophene **25** (264 mg, 3.0 mmol, 1.0 eq.), *s*-BuLi (3.0 mL of a 1.3 M solution in hexane, 3.9 mmol, 1.3 eq.) and TMEDA (585 μL, 3.9 mmol, 1.3 eq.) in hexane (15 mL) at 0 °C for 1 h and Bu₃SnCl (1.95 g, 1.63 mL, 6.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 50:50 hexane-CH₂Cl₂ as eluent gave stannane **395** (949 mg, 84%) as a colourless oil, *R*_F (hexane) 0.3; IR (ATR) 2954, 2924, 2870, 2853, 1463, 1073, 873, 688, 662, 596, 506 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.89 (ddd, *J* = 10.5, 8.0, 2.5 Hz, 1H, SCH), 2.70 (ddd, *J* = 10.5, 10.0, 7.0 Hz, 1H, SCH), 2.48-2.34 (m, 2H, CH), 2.29-2.15 (m, 1H, CH), 1.67-1.41 (m, 8H, CH), 1.36-1.25 (m, 6H, CH), 1.02-0.78 (m, 15H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 37.1 (CH₂), 32.0 (CH₂), 31.5 (CH₂), 29.3 (CH₂), 28.0 (SCH), 27.5 (CH₂), 13.8 (Me), 9.1 (CH₂); MS (ESI) *m/z* 377 [(¹¹⁸M + H)⁺, 74], 379 [(¹²⁰M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₆H₃₄S¹²⁰Sn (¹²⁰M + H)⁺ 379.1477, found 379.1469 (+2.1 ppm error).

Lab Book Reference: **NS5-91**

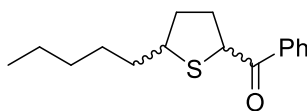
(13S,17S)-3-((*tert*-Butyldimethylsilyl)oxy)-13-methyl-17-(tetrahydrothiophen-2-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol 396



Using general procedure M, tetrahydrothiophene **25** (44 mg, 0.5 mmol, 1.0 eq.), *s*-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and TMEDA (98 μ L, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at 0 °C for 1 h and TBS-estrone **167** (385 mg, 1.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 CH₂Cl₂-acetone then 95:5 CH₂Cl₂-acetone gave a single diastereomeric alcohol **396** (103 mg, 45%) as a colourless oil, *R*_F (CH₂Cl₂) 0.6; IR (ATR) 3410 (OH), 2929, 2857, 1496, 1285, 1254, 953, 837, 817, 779 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.10 (d, *J* = 8.5 Hz, 1H, Ar), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 6.54 (d, *J* = 2.5 Hz, 1H, Ar), 3.81 (dd, *J* = 10.0, 6.5 Hz, 1H, CH), 2.84-2.69 (m, 3H, CH), 2.36-2.19 (m, 3H, CH), 2.12 (ddd, *J* = 10.0, 10.0, 4.0 Hz (app td), 1H, CH), 2.03-1.59 (m, 7H, CH, OH), 1.53-1.12 (m, 8H, CH), 0.97 (s, 9H, CMe₃), 0.91-0.86 (m, 3H, Me), 0.18 (s, 6H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 153.5 (*ipso*-Ar), 137.9 (*ipso*-Ar), 133.1 (*ipso*-Ar), 126.3 (Ar), 120.0 (Ar), 117.3 (Ar), 84.2 (HOC), 57.7 (CH), 50.9 (CH), 47.9 (C), 43.7 (CH), 39.7 (CH), 34.6 (CH₂), 33.9 (CH₂), 33.6 (CH₂), 31.4 (CH₂), 29.8 (CH₂), 27.7 (CH₂), 26.7 (CH₂), 25.9 (CMe₃), 23.4 (CH₂), 18.3 (CMe₃), 15.0 (CH₂), -4.24 (SiMe); MS (ESI) *m/z* 495 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₈H₄₄O₂SSi (M + Na)⁺ 495.272349, found 495.271406 (-1.9 ppm error).

Lab Book Reference: **NS3-74**

(5-Pentyltetrahydrothiophen-2-yl)(phenyl)methanone *cis*-397 and *trans*-398



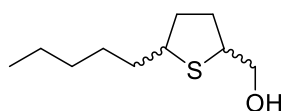
cis-**397** and *trans*-**397**

Using general procedure M, pentyl tetrahydrothiophene **391** (50 mg, 0.31 mmol, 1.0 eq.), *s*-BuLi (400 μ L of a 1.3 M solution in hexane, 0.40 mmol, 1.3 eq.) and TMEDA (78 μ L, 0.40 mmol, 1.3 eq.) in hexane (1.6 mL) at 0 °C for 4 h and Weinreb amide **115** (110 mg,

100 μ L, 0.61 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 67:33 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ as eluent gave ketone **397a** (22 mg, 42%) as a colourless oil, R_F (50:50 hexane-CH₂Cl₂) 0.4; IR (ATR) 2855, 2926, 1683 (C=O), 1448, 1208, 990, 731, 688 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.97-7.91 (m, 2H, Ph), 7.60-7.52 (m, 1H, Ph), 7.46 (dd, J = 7.5, 7.5 Hz (app t), 2H, Ph), 4.70 (dd, J = 7.0, 3.0 Hz, 1H, SCHC(O)), 3.51-3.39 (m, 1H, SCH), 2.76-2.66 (m, 1H, CH), 2.29-2.18 (m, 1H, CH), 2.05-1.82 (m, 2H, CH), 1.72-1.45 (m, 2H, CH), 1.36-1.20 (m, 6H, CH), 0.93-0.79 (m, 3H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.7 (C=O), 135.9 (*ipso*-Ph), 133.2 (Ph), 128.8 (Ph), 128.7 (Ph), 52.5 (SCH), 49.5 (SCH), 37.2 (CH₂), 36.7 (CH₂), 31.8 (CH₂), 31.0 (CH₂), 29.1 (CH₂), 22.7 (CH₂), 14.1 (Me); MS (ESI) m/z 263 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₆H₂₂OS (M + H)⁺ 263.1464, found 263.1465 (+0.5 ppm error) and ketone **397b** (35 mg, 29%) as a colourless oil, R_F (50:50 hexane-CH₂Cl₂) 0.3; IR (ATR) 2927, 2855, 1682 (C=O), 1448, 1222, 899, 720, 688, 666 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00-7.91 (m, 2H, Ph), 7.55 (dd, J = 7.5 Hz (app t), 1H, Ph), 7.46 (dd, J = 7.5, 7.5 Hz (app t), 2H, Ph), 4.78 (dd, J = 6.5, 6.5 Hz (app t), 1H, SCHC(O)), 3.52-3.36 (m, 1H, SCH), 2.62-2.51 (m, 1H, CH), 2.36 (dddd, J = 12.0, 12.0, 6.5, 6.5 Hz (app tt), 1H, CH), 2.19-2.08 (m, 1H, CH), 1.86-1.74 (m, 1H, CH), 1.71-1.63 (m, 1H, CH), 1.59-1.51 (m, 1H, CH), 1.42-1.23 (m, 6H, CH), 0.87 (t, J = 6.5 Hz, 3H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.5 (C=O), 136.2 (*ipso*-Ph), 133.3 (Ph), 128.7 (Ph), 128.4 (Ph), 51.6 (SCH), 49.9 (SCH), 37.6 (CH₂), 36.9 (CH₂), 31.8 (CH₂), 30.3 (CH₂), 28.9 (CH₂), 22.7 (CH₂), 14.1 (Me); MS (ESI) m/z 263 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₆H₂₂OS (M + Na)⁺ 285.1284, found 285.1275 (−3.1 ppm error).

Lab Book Reference: **NS3-67**

(5-Pentyltetrahydrothiophen-2-yl)methanol **398**



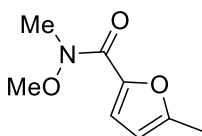
398

Using general procedure M, tetrahydrothiophene **25** (155 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.0 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 4 h and paraformaldehyde (60 mg, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with CH₂Cl₂ then 95:5 CH₂Cl₂-acetone gave a non-quantifiable mixture (by ¹³C NMR

spectroscopy) of alcohols **398** (81 mg, 43%) as a colourless oil, R_F (CH_2Cl_2) 0.3; IR (ATR) 3351 (OH), 2925, 2855, 1457, 1378, 1023, 728 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.69-3.59 (m, 1H, OCH), 3.57-3.50 (m, 1H, OCH), 3.39-3.30 (m, 1H, SCH), 2.20-1.94 (m, 3H, CH), 1.83-1.45 (m, 4H, CH), 1.39-1.22 (m, 6H, CH), 0.88 (t, $J = 7.0$ Hz, 3H, CH_2Me); ^{13}C NMR (100.6 MHz, CDCl_3) δ 66.1 (OCH₂), 65.4 (OCH₂), 51.5 (SCH), 51.2 (SCH), 50.5 (SCH), 50.3 (SCH), 37.9 (CH₂), 37.5 (CH₂), 37.3 (CH₂), 36.3 (CH₂), 32.5 (CH₂), 32.5 (CH₂), 31.8 (CH₂), 29.0 (CH₂), 22.7 (CH₂), 14.2 (Me) (one Me and three CH₂ resonances not resolved); MS (ESI) m/z 211 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{20}\text{OS}$ (M + H)⁺ 211.1127, found 211.1122 (−2.2 ppm error).

Lab Book Reference: **NS3-89**

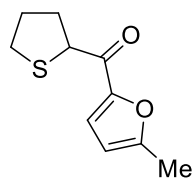
N*-Methoxy-*N*-methyl-5-methylfuran-2-carboxamide **405*



405

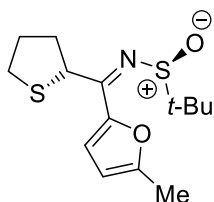
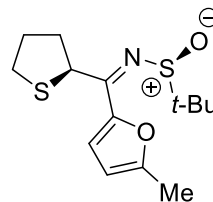
5-Methylfuran-2-carbonyl chloride (2.00 g, 14 mmol, 1.0 eq.) was added to a stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (1.35 g, 14 mmol, 1.0 eq.) and pyridine (2.46 mL, 2.41 g, 31 mmol, 2.2 eq.) in CH_2Cl_2 (50 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, H_2O (50 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave Weinreb amide **405** (2.08 g, 89%) as a colourless oil, R_F (50:50 hexane-EtOAc) 0.3; IR (ATR) 3505, 2976, 1937, 1638 (C=O), 1516, 1413, 1378, 1029, 1007, 961, 861, 798, 742, 551 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.10-6.98 (m, 1H, Ar), 6.17-5.85 (m, 1H, Ar), 3.71 (s, 3H, OMe), 3.30 (s, 3H, NMe), 2.35 (s, 3H, Me); ^{13}C NMR (100.6 MHz, CDCl_3) δ 159.4 (C=O), 156.1 (*ipso*-Ar), 144.2 (*ipso*-Ar), 118.9 (Ar), 108.3 (Ar), 61.3 (OMe), 33.3 (NMe), 14.0 (Me); MS (ESI) m/z 192 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_8\text{H}_{11}\text{NO}_3$ (M + Na)⁺ 192.0631, found 192.0629 (+1.1 ppm error). Spectroscopic data consistent with those reported in the literature.²¹⁵

Lab Book Reference: **NS10-95**

(5-Methylfuran-2-yl)(tetrahydrothiophen-2-yl)methanone *rac*-400**400**

Using general procedure M, tetrahydrothiophene **25** (587 μ L, 587 mg, 6.7 mmol, 1.0 eq.), *s*-BuLi (6.66 mL of a 1.3 M solution in hexane, 8.7 mmol, 1.3 eq.) in hexane (33 mL) at 0 °C for 1 h and Weinreb amide **405** (1.69 g, 10 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-Et₂O then 80:20 hexane-Et₂O as eluent gave ketone *rac*-**400** (941 mg, 72%) as a colourless oil, *R*_F (90:10 hexane-Et₂O) 0.2; IR (ATR) 2935, 2862, 1667 (C=O), 1513, 1440, 1370, 1266, 1207, 1065, 1027, 850, 803 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.10 (d, *J* = 3.5 Hz, 1H, Ar), 6.16-6.14 (m, 1H, Ar), 4.53 (dd, *J* = 7.0, 4.5 Hz, 1H, SCH), 3.00-2.85 (m, 2H, SCH), 2.51 (dddd, *J* = 12.5, 6.0, 6.0, 4.5 Hz (app dtd), 1H, CH), 2.39 (s, 3H, Me), 2.31-2.18 (m, 1H, CH), 2.11 (dddd, *J* = 12.5, 6.5, 6.5, 1.5 Hz (app dtd), 1H, CH), 1.95 (dddd, *J* = 12.5, 8.0, 6.5, 6.0 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 185.9 (C=O), 158.2 (*ipso*-Ar), 150.7 (*ipso*-Ar), 119.9 (Ar), 109.2 (Ar), 49.3 (SCH), 33.9 (SCH₂), 31.41 (CH₂), 31.39 (CH₂), 14.3 (Me); MS (ESI) *m/z* 219 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₀H₁₂O₂S (M + Na)⁺ 219.0450, found 219.0448 (+0.9 ppm error). Spectroscopic data consistent with those reported in the literature.⁴

Lab Book Reference: **NS10-100**

2-Methyl-*N*-((*E*)-(5-methylfuran-2-yl)(tetrahydrothiophen-2-yl)methylene)-propane-2-sulfinamides (*R,S*)-401 and (*S,S*)-401**(*R,S*)-401****(*S,S*)-401**

Ti(OEt)₄ (218 μ L, 233 mg, 1.0 mmol, 2.0 eq.) was added to a stirred solution of (*S*)-2-methylpropane-2-sulfinamide (93 mg, 0.51 mmol, 1.0 eq.) and ketone *rac*-**400** (100 mg, 0.51 mmol, 1.0 eq.) in toluene (5 mL) at rt under Ar. The resulting solution was stirred and heated at 50 °C for 48 h. Then, the solvent was evaporated under reduced pressure. CH₂Cl₂

(20 mL) and water (20 mL) were added and the solids were removed by filtration through Celite®. The filtercake was washed with CH₂Cl₂ (50 mL). The two layers were separated and the organic layer was dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained a 50:50 mixture of sulfinyl imines (*R,S*)-**401** and (*S,S*)-**401** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave sulfinyl imine (*R,S*)-**401** (58 mg, 38%) as a colourless oil, [α]_D +90.9 (c 0.25 in CHCl₃); *R*_F (50:50 hexane-EtOAc) 0.5; IR (ATR) 2955, 2862, 1564, 1505, 1248, 1212, 1069, 1031, 793, 621 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.44 (br s, 1H, Ar), 6.17 (d, *J* = 3.5 Hz, 1H, Ar), 4.92-4.73 (m, 1H, SCH), 3.08-2.83 (m, 2H, SCH), 2.62-2.50 (m, 1H, CH), 2.37 (s, 3H, Me), 2.33-2.19 (m, 1H, CH), 2.13-1.94 (m, 2H, CH), 1.26 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 169.1 (C=N), 156.9 (2 x *ipso*-Ar), 122.6 (Ar), 109.8 (Ar), 57.1 (SCH), 51.0 (CMe₃), 33.7 (CH₂), 30.97 (SCH₂), 30.95 (CH₂), 22.5 (CMe₃), 14.2 (Me) (one *ipso*-Ar not resolved); MS (ESI) *m/z* 322 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₄H₂₁NO₂S₂ (M + Na)⁺ 322.0906, found 322.0900 (+1.8 ppm error) and sulfinamide (*S,S*)-**401** (61.1 g, 40%) as a colourless oil, [α]_D +140.8 (c 0.50 in CHCl₃); *R*_F (50:50 hexane-EtOAc) 0.4; IR (ATR) 2926, 2862, 1596, 1564, 1503, 1360, 1248, 1212, 1070, 1032, 793, 613 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 3.5 Hz, 1H, Ar), 6.20-6.16 (m, 1H, Ar), 4.88-4.73 (m, 1H, SCH), 3.01-2.85 (m, 2H, SCH), 2.72-2.59 (m, 1H, CH), 2.39 (s, 3H, Me), 2.31-2.18 (m, 1H, CH), 2.17-1.93 (m, 2H, CH), 1.28 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.0 (C=N), 157.3 (*ipso*-Ar), 131.0 (*ipso*-Ar), 122.5 (Ar), 109.7 (Ar), 57.4 (SCH), 50.9 (CMe₃), 33.9 (CH₂), 32.9 (SCH₂), 31.3 (CH₂), 22.4 (CMe₃), 14.2 (Me); MS (ESI) *m/z* 322 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₄H₂₁NO₂S₂ (M + Na)⁺ 322.0906, found 322.0902 (+1.2 ppm error).

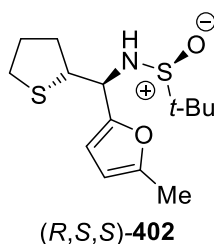
Lab Book Reference: **NS11-23**

Ti(Oi-Pr)₄ (2.36 mL, 2.26 g, 7.9 mmol, 2.0 eq.) was added to a stirred solution of (*S*)-2-methylpropane-2-sulfinamide (1.21 g, 10 mmol, 1.0 eq.) and ketone *rac*-**400** (780 mg, 4.0 mmol, 1.0 eq.) in toluene (10 mL) at rt under Ar. The resulting solution was stirred and heated at 50 °C for 16 h. Then, the solvent was evaporated under reduced pressure, CH₂Cl₂ (20 mL) and water (20 mL) were added and the solids were removed by filtration through Celite® and washed with CH₂Cl₂ (50 mL). The two layers were separated and the organic layer was dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained a 50:50 mixture of sulfinyl imines (*R,S*)-**401** and (*S,S*)-**401** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 70:30 hexane-

EtOAc as eluent gave sulfinyl imine (*R,S*)-**401** (250 mg, 21%) as a colourless oil, and sulfinyl imine (*S,S*)-**401** (243 g, 20%) as a colourless oil.

Lab Book Reference: **NS11-3**

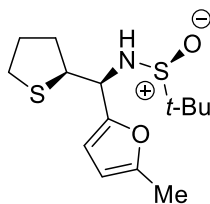
(*S*)-2-Methyl-*N*-((*S*)-(5-methylfuran-2-yl)((*R*)-tetrahydrothiophen-2-yl)methyl)-propane-2-sulfinamide (*R,S,S*)-402****



9-BBN (1.0 mL of a 0.5 M solution in THF, 0.50 mmol, 2.0 eq.) was added to stirred a solution of sulfinyl imine (*R,S*)-**401** (75 mg, 0.25 mmol, 1.0 eq.) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 4 h. Then, MeOH (5 mL) was added and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc to 70:30 hexane-EtOAc as eluent gave sulfinamide (*R,S,S*)-**402** (69 mg, 92%) as a colourless oil, $[\alpha]_D^{25} +54.2$ (*c* 1.00 in CHCl₃); *R*_F (70:30 hexane-EtOAc) 0.3; IR (ATR) 3222 (NH), 2950, 2863, 1561, 1442, 1364, 1222, 1051, 1021, 903, 784, 685, 594 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.16-6.12 (m, 1H, Ar), 5.93-5.85 (m, 1H, Ar), 4.47-4.40 (m, 1H, NCH), 3.91 (d, *J* = 4.5 Hz, 1H, NH), 3.90 -3.78 (m, 1H, SCH), 2.89-2.77 (m, 2H, SCH), 2.25 (s, 3H, Me), 2.16-1.83 (m, 4H, CH), 1.19 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 152.0 (*ipso*-Ar), 151.4 (*ipso*-Ar), 109.3 (Ar), 106.3 (Ar), 56.8 (NCH), 56.2 (CMe₃), 53.0 (SCH), 33.2 (CH₂), 33.1 (SCH₂), 31.1 (CH₂), 22.6 (CMe₃), 13.7 (Me); MS (ESI) *m/z* 324 [(*M* + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₄H₂₃NO₂S₂ (*M* + Na)⁺ 324.1062, found 324.1062 (+0.2 ppm error).

Lab Book Reference: **NS11-21**

(S)-2-Methyl-N-((S)-(5-methylfuran-2-yl)((S)-tetrahydrothiophen-2-yl)methyl)propane-2-sulfinamide (S,S,S)-402

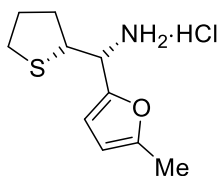


(S,S,S)-402

9-BBN (1.33 mL of a 0.5 M solution in THF, 0.67 mmol, 2.0 eq.) was added to a stirred solution of sulfinyl imine (S,S)-**401** (100 mg, 0.33 mmol, 1.0 eq.) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 4 h. Then, MeOH (5 mL) was added and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc to 70:30 hexane-EtOAc as eluent gave sulfinamide (S,S,S)-**402** (95 mg, 95%) as a colourless oil, $[\alpha]_D^{25} +162.7$ (c 1.00 in CHCl₃); R_F (70:30 hexane-EtOAc) 0.4; IR (ATR) 3255 (NH), 2950, 2864, 1565, 1443, 1385, 1364, 1220, 1072, 1020, 905, 786, 594 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.16-6.08 (m, 1H, Ar), 5.92-5.84 (m, 1H, Ar), 4.35-4.24 (m, 2H, NCH, NH), 3.89 (dd, $J = 5.5, 5.5$ Hz (app td), 1H, SCH), 2.88-2.77 (m, 2H, SCH), 2.24 (s, 3H, Me), 2.13-1.85 (m, 4H, CH), 1.21 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 152.2 (*ipso*-Ar), 151.7 (*ipso*-Ar), 109.3 (Ar), 106.2 (Ar), 57.1 (NCH), 56.1 (CMe₃), 53.3 (SCH), 33.8 (CH₂), 32.7 (SCH₂), 30.4 (CH₂), 22.8 (CMe₃), 13.7 (Me); MS (ESI) m/z 324 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₁₄H₂₃NO₂S₂ (M + Na)⁺ 324.1062, found 324.1061 (+0.5 ppm error).

Lab Book Reference: **NS11-22**

(5-Methylfuran-2-yl)(tetrahydrothiophen-2-yl)methan ammonium chloride (R*,R*)-403·HCl



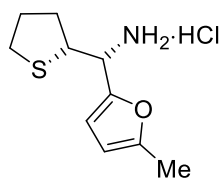
(R*,R*)-403·HCl

HCl (1.10 mL of a 2.0 M solution in Et₂O, 2.2 mmol, 3.0 eq.) was added to a stirred solution of a 55:45 mixture of sulfinamides (S,R,S)-**402** and (R,S,S)-**402** (221 mg, 0.73 mmol, 1.0 eq.) in MeOH (2 mL) at rt. After stirring at rt for 1 h, the solvent was evaporated under reduced pressure to give the crude solid. Et₂O (3 mL) was added, the mixture was swirled to dissolve impurities and then the Et₂O was decanted. Addition of Et₂O (3 mL) and decanting was

repeated a second time. The residual Et₂O was evaporated under reduced pressure to give amine (*R*,R**)-**403**·HCl (215 mg, 92%) as a colourless oil, IR (ATR) 3400 (NH), 2928, 2862, 1601, 1563, 1505, 1443, 1227, 1102, 1023, 793 cm⁻¹; ¹H NMR (400 MHz, d⁶-DMSO) δ 8.68 (m, 3H, NH), 6.48 (d, *J* = 3.0 Hz, 1H, Ar), 6.17-6.05 (m, 1H, Ar), 4.28 (d, *J* = 8.0 Hz, 1H, NCH), 3.86 (ddd, *J* = 8.0, 6.0, 6.0 Hz (app dt), 1H, SCH), 2.87-2.78 (m, 2H, SCH), 2.26 (s, 3H, Me), 1.97-1.79 (m, 3H, CH), 1.76-1.65 (m, 1H, CH); ¹³C NMR (100.6 MHz, d⁶-DMSO) δ 152.1 (*ipso*-Ar), 147.6 (*ipso*-Ar), 110.6 (Ar), 106.9 (Ar), 52.4 (NCH), 49.7 (SCH), 33.3 (CH₂), 32.2 (SCH₂), 29.6 (CH₂), 13.3 (Me); MS (ESI) *m/z* 220.0763 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₀H₁₅NOS (M + Na)⁺ 220.0767, found 220.0763 (+1.4 ppm error). Spectroscopic data consistent with those reported in the literature.⁴

Lab Book Reference: **NS10-98**

(5-Methylfuran-2-yl)(tetrahydrothiophen-2-yl)methan ammonium chloride (*R,R*)-403**·HCl**

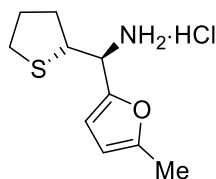


(*R,R*)-**403**·HCl

HCl (175 μL of a 2.0 M solution in Et₂O, 0.35 mmol, 3.0 eq.) was added to a stirred solution of sulfinamide (*R,S,S*)-**402** (35 mg, 0.12 mmol, 1.0 eq.) in MeOH (2 mL) at rt. After stirring at rt for 1 h, the solvent was evaporated under reduced pressure to give the crude solid. Et₂O (3 mL) was added, the mixture was swirled to dissolve impurities and then the Et₂O was decanted. Addition of Et₂O (3 mL) and decanting was repeated a second time. The residual Et₂O was evaporated under reduced pressure to give amine (*R,R*)-**403**·HCl (28 mg, 98%) as a white solid; mp 166-167 °C, [α]_D +74.3 (*c* 1.00 in CHCl₃).

Lab Book Reference: **NS11-26**

(5-Methylfuran-2-yl)(tetrahydrothiophen-2-yl)methan ammonium chloride (*R*,S)-403·HCl**

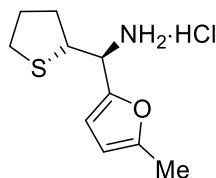


(*R*,S)-403·HCl**

HCl (1.10 mL of a 2.0 M solution in Et₂O, 2.2 mmol, 3.0 eq.) was added to a stirred solution of a 55:45 mixture of diastereomeric sulfinamide (*S,S,S*)-**402** and (*R,R,S*)-**402** (218 mg, 0.72 mmol, 1.0 eq.) in MeOH (2 mL) at rt. After stirring at rt for 1 h, the solvent was evaporated under reduced pressure to give the crude solid. Et₂O (3 mL) was added, the mixture was swirled to dissolve impurities and then the Et₂O was decanted. Addition of Et₂O (3 mL) and decanting was repeated a second time. The residual Et₂O was evaporated under reduced pressure to give amine (*R*,S**)-**403**·HCl (222 mg, 95%) as a white solid, mp 160–162 °C; IR (ATR) 3400 (NH), 2863, 2599, 1601, 1561, 1508, 1444, 1229, 1022, 788 cm⁻¹; ¹H NMR (400 MHz, d⁶-DMSO) δ 8.68 (s, 3H, NH), 6.42 (d, *J* = 3.5 Hz, 1H, Ar), 6.23–5.92 (m, 1H, Ar), 4.26 (dd, *J* = 9.5, 4.5 Hz, 1H, SCH), 3.89 (ddd, *J* = 9.5, 6.0, 6.0 Hz (app dt), 1H, NCH), 2.82–2.69 (m, 1H, SCH), 2.26 (s, 3H, Me), 2.15–2.05 (m, 2H, SCH), 2.04–1.83 (m, 4H, CH); ¹³C NMR (100.6 MHz, d⁶-DMSO) δ 151.9 (*ipso*-Ar), 148.5 (*ipso*-Ar), 110.6 (Ar), 106.9 (Ar), 52.2 (NCH), 49.4 (SCH), 33.4 (CH₂), 31.9 (SCH₂), 30.1 (CH₂), 13.3 (Me); MS (ESI) *m/z* 220 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₀H₁₅NOS (M + Na)⁺ 220.0767, found 220.0768 (–0.9 ppm error).

Lab Book Reference: **NS10-99**

(5-Methylfuran-2-yl)(tetrahydrothiophen-2-yl)methan ammonium chloride (*R,S*)-403·HCl



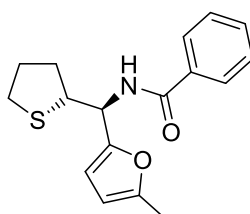
(*R,S*)-403·HCl

HCl (175 μL of a 2.0 M solution in Et₂O, 0.35 mmol, 3.0 eq.) was added to a stirred solution of sulfinamide (*R,S,S*)-**402** (35 mg, 0.12 mmol, 1.0 eq.) in MeOH (2 mL) at rt. After stirring at rt for 1 h, the solvent was evaporated under reduced pressure to give the crude solid. Et₂O (3 mL) was added, the mixture was swirled to dissolve impurities and then the Et₂O was

decanted. Addition of Et₂O (3 mL) and decanting was repeated a second time. The residual Et₂O was evaporated under reduced pressure to give amine (*R,S*)-**403**·HCl (27 mg, 96%) as a white solid, [α]_D −34.6 (*c* 1.00 in CHCl₃).

Lab Book Reference: **NS11-25**

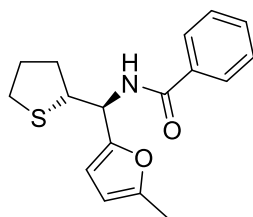
N*-((5-Methyl-furan-2-yl)(tetrahydrothiophen-2-yl)methyl)benzamide (*R,S*)-**406*



(*R,S*)-**406**

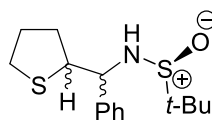
Benzoyl chloride (54 μ L, 65 mg, 0.46 mmol, 4.0 eq.) was added to a stirred solution of amine (*R,R*)-**403**·HCl (54 mg, 0.23 mmol, 1.0 eq.) and Et₃N (64 μ L, 46 mg, 0.46 mmol, 4.0 eq.) in CH₂Cl₂ (2 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 24 h. Then, CH₂Cl₂ (10 mL) and water (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with 1 M HCl_(aq) (30 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc then 70:30 hexane-EtOAc as eluent gave amide (*R,S*)-**406** (29 mg, 87%) as a white solid, mp 118-120 °C, [α]_D +14.7 (*c* 0.25 in CHCl₃); *R*_F (70:30 hexane-EtOAc) 0.5; IR (ATR) 3301 (NH), 2949, 1635 (C=O), 1530, 1489, 1444, 1326, 1222, 1025, 786, 695 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.80-7.74 (m, 2H, Ph), 7.54-7.46 (m, 1H, Ph), 7.45-7.39 (m, 2H, Ph), 6.52 (d, *J* = 9.0 Hz, 1H, NH), 6.19 (d, *J* = 3.0 Hz, 1H, Ar), 5.90-5.88 (m, 1H, Ar), 5.31 (dd, *J* = 9.0, 9.0 Hz (app t), 1H, NCH), 3.91-3.80 (m, 1H, SCH), 2.91-2.77 (m, 2H, SCH), 2.26 (s, 3H, Me), 2.12-1.90 (m, 4H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 166.7 (C=O), 151.9 (*ipso*-Ar), 151.4 (*ipso*-Ar), 134.4 (*ipso*-Ph), 131.8 (Ph), 128.7 (Ph), 127.2 (Ph), 108.6 (Ar), 106.4 (Ar), 52.3 (NCH), 52.2 (SCH), 33.9 (CH₂), 32.9 (SCH₂), 30.2 (CH₂), 13.7 (Me); MS (ESI) *m/z* 324 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₇H₁₉NO₂S (M + H)⁺ 324.1029, found 324.1025 (+1.2 ppm error); CSP-HPLC: Chiralcel AD-H (90:10 hexane-*i*-PrOH, 1.0 mL min^{−1}) *t*_R = 15.1 min (major), 20.4 min (minor).

Lab Book Reference: **NS11-28**

***N*-((5-Methyl-furan-2-yl)(tetrahydrothiophen-2-yl)methyl)benzamide (*R**,*R**)-406****(*R**,*R**)-406**

Benzoyl chloride (107 μ L, 129 mg, 0.92 mmol, 4.0 eq.) was added to a stirred solution of amine (*R**,*R**)-**403**·HCl (54 mg, 0.23 mmol, 1.0 eq.) and Et₃N (129 μ L, 93 mg, 0.92 mmol, 4.0 eq.) in CH₂Cl₂ (2 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 24 h. Then, CH₂Cl₂ (10 mL) and water (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with 1 M HCl_(aq) (30 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc then 70:30 hexane-EtOAc as eluent gave amide (*R**,*R**)-**406** (59 mg, 84%) as a white solid.

Lab Book Reference: NS11-27

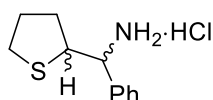
2-Methyl-*N*-(phenyl(tetrahydrothiophen-2-yl)methyl)propane-2-sulfinamide 408**408**

Using general procedure M, tetrahydrothiophene **25** (176 mg, 2.0 mmol, 1.0 eq.), *s*-BuLi (2.0 mL of a 1.3 M solution in hexane, 2.6 mmol, 1.3 eq.) and TMEDA (390 μ L, 2.6 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C for 1 h and (*R*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (*S*)-**170** (836 mg, 4.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 40:25:25:10 mixture (by ¹H NMR spectroscopy) of sulfinamides **408**. Purification by flash column chromatography on silica with 98:2 CH₂Cl₂-acetone then 400:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave a 40:25:25:10 mixture of sulfinamides **408** (529 mg, 89%) as a yellow oil, *R*_F (98:2 CH₂Cl₂-acetone) 0.4; IR (ATR) 3221 (NH), 2952, 2863, 1454, 1363, 1055, 909, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.16 (m, 5H, Ph), 4.50 (dd, *J* = 6.0, 2.5 Hz, 0.10H, NCH), 4.42 (dd, *J* = 8.0, 5.0 Hz, 0.25H, NCH), 4.39 (d, *J* = 2.5 Hz, 0.25H, NCH), 4.34 (dd, *J* = 7.5, 7.0 Hz, 0.40H, NCH), 4.19 (dd, *J* = 8.5,

3.0 Hz, 0.25H, SCH), 4.13-4.10 (m, 0.10H, SCH), 4.10-4.05 (m, 0.40H, SCH), 3.99 (dd, $J = 7.0, 7.0$ Hz (app t), 0.25H, SCH), 3.89-3.75 (m, 0.50H, NH), 3.69-3.63 (m, 0.40H, NH), 3.39-3.34 (m, 0.10H, NH), 2.98-2.59 (m, 2H, SCH), 2.21-1.58 (m, 4H, CH), 1.25-1.18 (m, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 145.8 (*ipso*-Ph), 144.2 (*ipso*-Ph), 142.1 (*ipso*-Ph), 128.8 (Ph), 128.71 (Ph), 128.69 (Ph), 128.4 (Ph), 128.35 (Ph), 128.33 (Ph), 128.2 (Ph), 128.15 (Ph), 128.12 (Ph), 128.0 (Ph), 127.1 (Ph), 64.3 (NCH), 63.8 (NCH), 62.7 (NCH), 60.6 (NCH), 56.94 (CMe₃), 56.92 (CMe₃), 56.8 (CMe₃), 56.53 (SCH), 56.52 (SCH), 54.1 (SCH), 34.8 (SCH₂), 34.13 (SCH₂), 34.11 (SCH₂), 32.7 (SCH₂), 32.5 (CH₂), 31.03 (CH₂), 31.00 (CH₂), 30.6 (CH₂), 29.81 (CH₂), 22.88 (CMe₃), 22.80 (CMe₃), 22.78 (CMe₃) (nine resonances not resolved); MS (ESI) m/z 320 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₅H₂₃NOS₂ (M + H)⁺ 320.1113, found 320.1112 (+0.5 ppm error).

Lab Book Reference: **NS5-82**

Phenyl(tetrahydrothiophen-2-yl)methanamine hydrochloride **409**·HCl

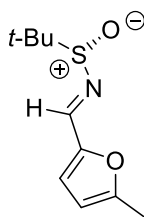


409·HCl

Concentrated HCl_(aq) (2.0 mL, 24 mmol, 24 eq.) was added to a stirred solution of a 40:25:25:10 mixture of sulfinamides **408** (297 mg, 1.0 mmol, 1.0 eq.) in MeOH (3 mL) at rt. The resulting solution was stirred at rt for 14 h. Then, the solvent was evaporated under reduced pressure to give the crude product which contained a 65:35 mixture (by ¹H NMR spectroscopy) of amines **409**·HCl. Purification by flash column chromatography on silica with 75:25 hexane-Et₂O as eluent gave a 65:35 mixture of amines **409**·HCl (175 mg, 91%) as a colourless oil, R_F (75:25 hexane-Et₂O) 0.2; IR (ATR) 3026, 2943, 2859, 1661, 1451, 1440, 1295, 1178, 887, 848, 762, 699, 599 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.04 (m, 5H, Ph), 4.02 (d, $J = 7.0$ Hz, 0.35H, NCH), 3.81 (d, $J = 8.0$ Hz, 0.65H, NCH), 3.76-3.72 (m, 0.35H, SCH), 3.68-3.63 (m, 0.65H, SCH), 2.96-2.77 (m, 2H, SCH), 2.52-2.30 (br s, 3H, NH₃), 2.13-1.99 (m, 1.35H, CH), 1.95-1.81 (m, 1.30H, CH), 1.81-1.67 (m, 0.70H, CH), 1.66-1.52 (m, 0.65H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 144.7 (*ipso*-Ph), 144.3 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 127.6 (Ph), 127.5 (Ph), 127.0 (Ph), 126.9 (Ph), 62.0 (NCH), 59.9 (NCH), 57.9 (SCH), 56.3 (SCH), 34.8 (SCH₂), 32.9 (SCH₂), 32.7 (CH₂), 31.3 (CH₂), 31.1 (CH₂), 30.8 (CH₂); MS (ESI) m/z 194 [M⁺, 100]; HRMS (ESI) m/z calcd for C₁₁H₁₆N M⁺ 194.0998, found 194.0998 (−0.1 ppm error).

Lab Book Reference: **NS5-85**

(S)-2-Methyl-N-((5-methylfuran-2-yl)methylene)propane-2-sulfinamide (S)-407

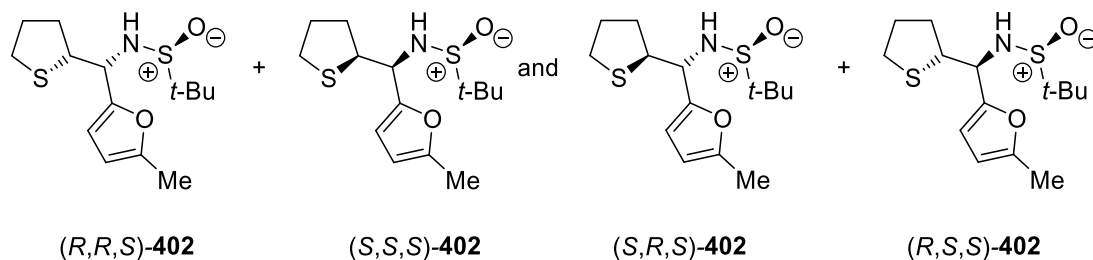


(S)-407

Ti(Oi-Pr)₄ (5.92 mL, 5.68 g, 20 mmol, 2.0 eq.) was added to a stirred solution of (S)-2-methylpropane-2-sulfinamide (1.21 g, 10 mmol, 1.0 eq.) and 5-methylfuran-2-carbaldehyde (995 μ L, 1.10 g, 10 mmol, 1.0 eq.) in toluene (20 mL) at rt under Ar. The resulting solution was stirred at rt for 4 h. Then, the solvent was evaporated under reduced pressure. CH₂Cl₂ (20 mL) and water (20 mL) were added and the solids were removed by filtration through Celite[®] and washed with CH₂Cl₂ (50 mL). The two layers were separated and the organic layer was dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave sulfinyl imine (S)-407 (2.12 g, 99%) as a colourless oil, [α]_D +32.5 (*c* 1.00 in CHCl₃); *R*_F (80:20 hexane-EtOAc) 0.3; IR (ATR) 2960, 2925, 1614, 1569, 1525, 1370, 1080, 1023, 800, 581 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H, HC=N), 6.89 (d, *J* = 3.0 Hz, 1H, Ar), 6.21-6.14 (m, 1H, Ar), 2.40 (s, 3H, Me), 1.23 (s, 9H, CMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.3 (*ipso*-Ar), 149.7 (*ipso*-Ar), 149.4 (HC=N), 121.2 (Ar), 109.4 (Ar), 57.9 (CMe₃), 22.6 (CMe₃), 14.2 (Me); MS (ESI) *m/z* 236 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₀H₁₅NO₂S (M + Na)⁺ 236.0716, found 236.0711 (+1.9 ppm error). Spectroscopic data consistent with those reported in the literature.²¹⁶

Lab Book Reference: **NS10-93**

2-Methyl-N-((5-methylfuran-2-yl)(tetrahydrothiophen-2-yl)methyl)propane-2-sulfonamide (*(R,R,S)*-402**, (*(S,S,S)*-**402**, (*(S,R,S)*-**402** and (*(R,S,S)*-**402****

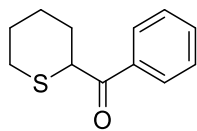


Using general procedure M, tetrahydrothiophene **25** (176 mg, 2.0 mmol, 1.0 eq.), *s*-BuLi (2.0 mL of a 1.3 M solution in hexane, 2.6 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C for 1 h and sulfinyl imine (*(S)*-**407** (640 mg, 3.0 mmol, 1.5 eq.) gave the crude product which contained a 25:25:25:25 mixture of sulfonamides (*(R,R,S)*-**402**, (*(S,S,S)*-**402**, (*(S,R,S)*-**402** and (*(R,S,S)*-**402** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave a 55:45 mixture of sulfonamides (*(R,R,S)*-**402** and (*(S,S,S)*-**402** (269 mg, 43%) as a colourless oil; R_F (50:50 hexane-EtOAc) 0.3; IR (ATR) 3235 (NH), 2950, 2863, 1442, 1388, 1363, 1220, 1070, 1020, 786 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.21 (d, $J = 3.0$ Hz, 0.55H, Ar), 6.14 (d, $J = 3.0$ Hz, 0.45H, Ar), 5.92-5.82 (m, 1H, Ar), 4.37-4.23 (m, 1.45H, NCH, SCH, NH), 3.98-3.84 (m, 1.55H, NCH, SCH, NH), 2.90-2.75 (m, 2H, SCH), 2.25 (s, 3H, CMe), 2.16-2.04 (m, 1H, CH), 2.05-1.82 (m, 2.55H, CH), 1.73-1.58 (m, 0.45H, CH), 1.23 (s, 4.95H, CMe₃), 1.21 (s, 4.05H, CMe₃); ^{13}C NMR (100.6 MHz, CDCl_3) δ 152.6 (*ipso*-Ar), 152.2 (*ipso*-Ar), 151.9 (*ipso*-Ar), 151.8 (*ipso*-Ar), 109.2 (Ar), 108.5 (Ar), 106.5 (Ar), 106.2 (Ar), 59.2 (NCH), 57.1 (NCH), 56.9 (CMe₃), 56.1 (CMe₃), 54.3 (SCH), 53.3 (SCH), 34.1 (CH₂), 33.8 (CH₂), 32.71 (SCH₂), 32.69 (SCH₂), 31.2 (CH₂), 30.4 (CH₂), 22.9 (CMe₃), 22.8 (CMe₃), 13.71 (Me), 13.70 (Me); MS (ESI) m/z 324 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₁₄H₂₃NO₂S₂ (M + Na)⁺ 324.1062, found 324.1059 (+1.0 ppm error) and a 55:45 mixture of sulfonamides (*(S,R,S)*-**402** and (*(R,S,S)*-**402** (265 mg, 42%) as a colourless oil; R_F (50:50 hexane-EtOAc) 0.2; IR (ATR) 3217 (NH), 2950, 2863, 1562, 1443, 1363, 1222, 1051, 1021, 895, 784, 597 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.21 (d, $J = 3.0$ Hz, 0.55H, Ar), 6.14 (d, $J = 3.0$ Hz, 0.45H, Ar), 5.97-5.85 (m, 1H, Ar), 4.44 (dd, $J = 7.0, 4.5$ Hz, 0.45H, NCH), 4.30 (dd, $J = 8.5, 7.0$ Hz, 0.55H, NCH), 3.92-3.81 (m, 1.45H, SCH, NH), 3.62 (d, $J = 7.0$ Hz, 0.55H, NH), 2.88-2.77 (m, 2H, CH), 2.25 (s, 3H, Me), 2.23-1.77 (m, 4H, CH), 1.21 (s, 4.95H, CMe₃), 1.19 (s, 4.05H, CMe₃); ^{13}C NMR (100.6 MHz, CDCl_3) δ 152.2 (*ipso*-Ar), 152.0 (*ipso*-Ar), 151.9 (*ipso*-Ar), 151.4 (*ipso*-Ar), 109.3 (Ar), 108.9 (Ar), 106.5 (Ar), 106.3 (Ar), 59.2 (NCH), 56.8 (NCH), 56.6 (CMe₃), 56.1 (CMe₃), 53.0 (SCH), 52.8 (SCH), 34.2 (CH₂), 33.14 (CH₂), 33.08 (CH₂), 32.8 (CH₂), 31.1

(SCH₂), 30.6 (SCH₂), 22.8 (CMe₃), 22.6 (CMe₃), 13.73 (Me), 13.72 (Me); MS (ESI) *m/z* 324 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₄H₂₃NO₂S₂ (M + Na)⁺ 324.1062, found 324.1053 (+2.8 ppm error).

Lab Book Reference: **NS10-94**

Phenyl(tetrahydro-2H-thiopyran-2-yl)methanone **410**



410

Table 4.2, entry 4:

Using general procedure M, tetrahydrothiopyran **140** (101 μ L, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 μ L, 2.0 mmol, 2.0 eq.) in hexane (5 mL) at 0 °C for 2 h and Weinreb amide **115** (456 μ L, 3.0 mmol, 3.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 67:33 hexane-CH₂Cl₂ as eluent gave ketone **411** (yield not determined) as a white solid; *R*_F (50:50 hexane-CH₂Cl₂) 0.4 and ketone **410** (188 mg, 91%) as a white solid; *R*_F (50:50 hexane-CH₂Cl₂) 0.3 mp 68-70 °C (lit.⁴⁰ 69-70 °C); *R*_F (90:10 hexane-CH₂Cl₂) 0.4; IR (ATR) 3059, 2927, 2848, 1678 (C=O), 1596, 1448, 1246, 1222, 1198, 1006, 927, 721, 688 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00-7.95 (m, 2H, Ph), 7.59-7.53 (m, 1H, Ph), 7.50-7.43 (m, 2H, Ph), 4.39 (dd, *J* = 7.5, 3.5 Hz, 1H, SCH), 2.81-2.66 (m, 2H, SCH), 2.16-2.02 (m, 3H, CH), 1.96-1.74 (m, 2H, CH), 1.62-1.51 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 197.7 (C=O), 135.6 (*ipso*-Ph), 133.3 (Ph), 128.8 (Ph), 128.7 (Ph), 45.1 (SCH), 29.1 (CH₂), 28.6 (CH₂), 26.8 (CH₂), 24.3 (CH₂); MS (ESI) *m/z* 229 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₄OS (M + Na)⁺ 229.0658, found 229.0648 (−4.0 ppm error). Spectroscopic data for ketone **410** consistent with those reported in the literature.²¹⁷

Lab Book Reference: **NS10-35**

Table 4.2, entry 1:

Using general procedure M, tetrahydrothiopyran **140** (101 μ L, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and Weinreb amide **115** (304 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column

chromatography on silica with 67:33 hexane-CH₂Cl₂ as eluent gave ketone **411** (81 mg, 50%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.4; IR (ATR) 2966, 2933, 2875, 1681 (C=O), 1596, 1449, 1217, 1001, 972, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.99-7.90 (m, 2H, Ph), 7.59-7.49 (m, 1H, Ph), 7.48-7.42 (m, 2H, Ph), 3.39 (dq, *J* = 7.0, 6.5 Hz, 1H, CH), 1.82 (dq, *J* = 14.0, 7.5, 6.5 Hz, 1H, CH), 1.55-1.42 (m, 1H, CH), 1.18 (d, *J* = 7.0 Hz, 1H, CH), 0.91 (t, *J* = 7.5 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 204.7 (C=O), 136.9 (*ipso*-Ph), 132.9 (Ph), 128.7 (Ph), 128.4 (Ph), 42.3 (CH), 26.8 (CH₂), 16.9 (CHMe), 11.9 (CH₂Me); MS (ESI) *m/z* 163 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₆H₂₃NO₃ (M + H)⁺ 163.1117, found 163.1120 (+1.4 ppm error) and ketone **410** (92 mg, 45%) as a white solid.

Lab Book Reference: **NS10-33**

Table 4.2, entry 2:

Using general procedure M, tetrahydrothiopyran **140** (102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 µL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and Weinreb amide **115** (330 mg, 304 µL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 85:15 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ as eluent gave ketone **410** (120 mg, 58%) as a white solid.

Lab Book Reference: **NS3-14**

Table 4.2, entry 3:

Using general procedure M, tetrahydrothiopyran **140** (101 µL, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 µL, 2.0 mmol, 2.0 eq.) in hexane (5 mL) at 0 °C for 1 h and Weinreb amide **115** (456 µL, 3.0 mmol, 3.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 67:33 hexane-CH₂Cl₂ as eluent gave ketone **411** (yield not determined) as a colourless oil and ketone **410** (175 mg, 85%) as a white solid.

Lab Book Reference: **NS10-34**

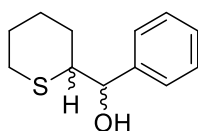
Table 4.2, entry 5:

Using general procedure M, tetrahydrothiopyran **140** (101 µL, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 µL, 2.0 mmol, 2.0 eq.) in hexane (5 mL) at -10 °C for 2 h and Weinreb amide **115** (456 µL,

3.0 mmol, 3.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 67:33 hexane-CH₂Cl₂ as eluent gave ketone **411** (52 mg, 32%) as a colourless oil and ketone **410** (188 mg, 61%) as a white solid.

Lab Book Reference: **NS10-36**

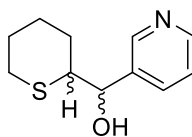
Phenyl(tetrahydro-2H-thiopyran-2-yl)methanol **412**



412

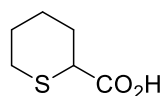
Using general procedure M, tetrahydrothiopyran **140** (101 µL, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 µL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and benzaldehyde (201 mg, 210 µL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 55:45 mixture (by ¹H NMR spectroscopy) of alcohols **412**. Purification by flash column chromatography on silica with 85:15 hexane-CH₂Cl₂ then 55:45 hexane-CH₂Cl₂ then 300:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave a 50:50 mixture of alcohols **412** (129 mg, 62%) as a colourless oil, *R*_F (200:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.2; IR (ATR) 3409 (OH), 3061, 3029, 2925, 2848, 1492, 1452, 1439, 1257, 1062, 1021, 761, 699, 611 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.46-7.18 (m, 5H, Ph), 4.80-4.56 (m, 1H, HOCH), 3.08 (ddd, *J* = 8.5, 5.5, 2.5 Hz, 0.5H, SCH), 2.95 (ddd, *J* = 8.5, 8.5, 2.5 Hz (app dt), 0.5H, SCH), 2.91 (s, 0.5H, OH), 2.78 (ddd, *J* = 10.5, 7.5, 2.5 Hz, 0.5H, CH), 2.73-2.68 (m, 0.5H, CH), 2.67-2.59 (m, 0.5H, CH), 2.59-2.52 (m, 0.5H, CH), 2.32-2.18 (m, 0.5H, OH), 2.04 (ddd, *J* = 13.5, 3.5, 3.5 Hz (app dt), 0.5H, CH), 1.95-1.66 (m, 3H, CH), 1.64-1.21 (m, 2.5H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 141.6 (*ipso*-Ph), 141.4 (*ipso*-Ph), 128.6 (Ph), 128.4 (Ph), 128.2 (Ph), 128.0 (Ph), 126.9 (Ph), 126.5 (Ph), 76.7 (OCH), 75.2 (OCH), 49.7 (SCH), 49.4 (SCH), 29.4 (CH₂), 28.5 (CH₂), 27.1 (CH₂), 27.0 (CH₂), 26.9 (CH₂), 25.9 (CH₂), 24.0 (CH₂) (one CH₂ resonance not resolved); MS (ESI) *m/z* 231 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₆OS (M + Na)⁺ 231.0814, found 231.0814 (−0.2 ppm error). Spectroscopic data consistent with those reported in the literature.²¹⁸

Lab Book Reference: **NS3-9**

Pyridin-3-yl(tetrahydro-2H-thiopyran-2-yl)methanol 413**413**

Using general procedure M, tetrahydrothiopyran **140** (101 μ L, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and nicotine aldehyde (214 mg, 200 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 60:40 mixture (by ^1H NMR spectroscopy) of alcohols **413**. Purification by flash column chromatography on silica with 500:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ as eluent gave a 70:30 mixture of alcohols **413** (105 mg, 52%) as a colourless oil, R_F (500:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.2; IR (ATR) 3340 (OH), 2970, 2930, 1466, 1427, 1379, 1161, 1128, 950, 816, 713, 628 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.54-8.44 (m, 2H, Ar), 7.78-7.73 (m, 1H, Ar), 7.34-7.27 (m, 1H, Ar), 4.74-4.70 (m, 1H, OCH), 4.14-3.74 (m, 1H, OH), 3.07 (ddd, J = 11.0, 6.0, 2.5 Hz, 0.7H, SCH), 2.96 (ddd, J = 7.5, 7.5, 2.5 Hz (app td), 0.3H, SCH), 2.86-2.54 (m, 2H, CH), 2.13-2.04 (m, 0.7H, CH), 1.98-1.84 (m, 1.7H, CH), 1.83-1.67 (m, 1H, CH), 1.66-1.25 (m, 2.6H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 149.2 (Ar), 148.8 (Ar), 148.5 (Ar), 148.2 (Ar), 137.6 (*ipso*-Ar), 137.4 (*ipso*-Ar), 134.6 (Ar), 134.5 (Ar), 123.6 (Ar), 123.4 (Ar), 74.3 (OCH), 73.0 (OCH), 49.6 (SCH), 49.1 (SCH), 29.36 (CH_2), 29.32 (CH_2), 28.7 (CH_2), 27.1 (CH_2), 27.04 (CH_2), 27.02 (CH_2), 25.7 (CH_2), 24.1 (CH_2); MS (ESI) m/z 210 [(M + H) $^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{16}\text{NOS}$ (M + H) $^+$ 210.0947, found 210.0943 (+2.2 ppm error).

Lab Book Reference: **NS3-54**

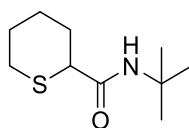
Tetrahydro-2H-thiopyran-2-carboxylic acid 414**414**

Using general procedure N, tetrahydrothiopyran **140** (500 mg, 5.0 mmol, 2.5 eq.), *s*-BuLi (1.54 mL of a 1.3 M solution in hexane, 2.0 mmol, 1.0 eq.) and TMEDA (975 μ L, 5.0 mmol, 2.5 eq.) in hexane (10 mL) at 0 °C for 2 h and CO_2 at -78 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2 -acetone as eluent

gave acid **414** (102 mg, 39%) as a colourless oil; IR (ATR) 2929, 2850, 1698 (C=O), 1439, 1419, 1250, 1190, 931, 897, 841, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 10.93 (br s, 1H, CO_2H), 3.52 (dd, $J = 8.0, 3.5$ Hz, 1H, SCH), 2.79 (ddd, $J = 13.5, 8.0, 3.5$ Hz, 1H, SCH), 2.57 (ddd, $J = 13.5, 8.0, 3.5$ Hz, 1H, SCH), 2.16-2.06 (m, 1H, CH), 2.03-1.66 (m, 4H, CH), 1.56-1.44 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 178.5 (C=O), 42.9 (SCH), 29.4 (CH_2), 27.9 (CH_2), 26.5 (CH_2), 23.8 (CH_2); MS (ESI) m/z 169 $[(\text{M} + \text{Na})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_6\text{H}_{10}\text{O}_2\text{S}$ ($\text{M} + \text{Na})^+$ 169.0294, found 169.0297 (−1.7 ppm error).

Lab Book Reference: **NS5-22**

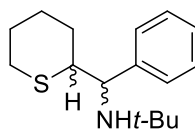
N*-(*tert*-Butyl)tetrahydro-2*H*-thiopyran-2-carboxamide **415*



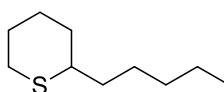
415

Using general procedure M, tetrahydrothiopyran **140** (101 μL , 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 μL , 2.0 mmol, 2.0 eq.) in hexane (5 mL) at 0 °C for 2 h and *tert*-butyl isocyanate (343 μL , 297 mg, 3.0 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane- Et_2O as eluent gave amide **415** (179 mg, 89%) as a white solid; mp 106-108 °C, R_F (90:10 hexane- Et_2O) 0.3; R_F (90:10 hexane- Et_2O) 0.3; IR (ATR) 3289 (NH), 2966, 2927, 1643 (CO), 1549, 1508, 1455, 1363, 1223, 917, 735, 655 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 85:15 mixture of rotamers δ 7.09 (br s, 0.15H, NH), 6.78 (s, 0.85H, NH), 3.24 (dd, $J = 6.5, 4.0$ Hz, 0.85H, CH), 2.63 (ddd, $J = 12.5, 8.5, 4.0$ Hz, 0.85H, CH), 2.56-2.47 (m, 1.30H, CH), 2.33-2.19 (m, 1.0H, CH), 1.97-1.87 (m, 0.85H, CH), 1.84-1.67 (m, 2.15H, CH), 1.62-1.48 (m, 2.0H, CH), 1.35 (s, 7.65H, CMe_3), 1.30 (s, 1.35H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) rotamers δ 169.8 (C=O), 168.7 (C=O), 63.3 (SCH), 51.6 (CMe), 51.3 (CMe), 44.7 (SCH), 35.5 (CH_2), 29.1 (CH_2), 28.7 (CMe_3), 28.5 (CMe_3), 28.2 (CH_2), 28.0 (CH_2), 26.7 (CH_2), 25.8 (CH_2), 23.9 (CH_2), 23.6 (CH_2); MS (ESI) m/z 224 $[(\text{M} + \text{Na})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{19}\text{NOS}$ ($\text{M} + \text{Na})^+$ 224.1080, found 224.1079 (+0.3 ppm error).

Lab Book Reference: **NS10-39**

2-Methyl-N-(phenyl(tetrahydro-2H-thiopyran-2-yl)methyl)propan-2-amine 417**417**

Using general procedure M, tetrahydrothiopyran **140** (101 μ L, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 μ L, 2.0 mmol, 2.0 eq.) in hexane (5 mL) at 0 °C for 2 h and imine **416** (534 μ L, 483 mg, 3.0 mmol, 3.0 eq.) gave the crude product which contained a 90:10 mixture of diastereomers (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 90:10 hexane-Et₂O then 80:20 hexane-CH₂Cl₂ as eluent gave a 90:10 mixture of diastereomeric amines **417** (187 mg, 71%) as a colourless oil; *R*_F (80:20 hexane-Et₂O) 0.5; IR (ATR) 2960, 2928, 1451, 1364, 1225, 1107, 1027, 756, 703, 592, 496 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 7.41-7.14 (m, 5H, Ph), 3.81 (d, *J* = 5.5 Hz, 0.90H, NCH), 3.60 (d, *J* = 5.5 Hz, 0.10H, NCH), 2.93-2.84 (m, 1H, CH), 2.71-2.51 (m, 2H, CH), 2.04-1.76 (m, 3H, CH, NH), 1.59-1.08 (m, 3H, CH), 0.97-0.93 (m, 9H, CMe), 0.89-0.79 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl₃) δ for major diastereomer 145.4 (*ipso*-Ph), 127.88 (Ph), 127.86 (Ph), 126.8 (Ph), 60.9 (NCH), 51.3 (CMe), 50.8 (SCH), 30.2 (CMe), 29.9 (CH₂), 29.5 (CH₂), 27.3 (CH₂), 26.8 (CH₂); MS (ESI) *m/z* 264 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₆H₂₅NS (M + H)⁺ 264.1780, found 264.1778 (+1.0 ppm error).

Lab Book Reference: **NS10-42****2-Pentyltetrahydro-2H-thiopyran 418****418**

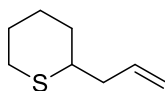
Using general procedure M, tetrahydrothiopyran **140** (101 μ L, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 μ L, 2.0 mmol, 2.0 eq.) in hexane (5 mL) at 0 °C for 2 h and *n*-pentyl iodide (392 μ L, 594 mg, 3.0 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂ then as eluent gave pentyl tetrahydrothiopyran **418** (110 mg, 64%) as a colourless oil, *R*_F (hexane) 0.2; IR (ATR) 2955, 2924, 2854, 1454, 1424, 1439, 1274, 1259, 726 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 2.73-2.53 (m, 3H, SCH, CH),

2.02-1.79 (m, 3H, CH), 1.63-1.20 (m, 11H, CH), 0.88 (t, $J = 7.0$ Hz, 3H, CH_2Me); ^{13}C NMR (100.6 MHz, CDCl_3) δ 42.9 (SCH), 36.4 (CH_2), 35.0 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 22.7 (CH_2), 14.2 (Me); MS (APCI) m/z 173 [$(\text{M} + \text{H})^+$, 100]; HRMS (APCI) m/z calcd for $\text{C}_{10}\text{H}_{21}\text{S}$ ($\text{M} + \text{H})^+$ 173.1359, found 173.1354 (+2.7 ppm error).
Lab Book Reference: **NS10-44**

Using general procedure M, tetrahydrothiopyran **140** (103 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and *n*-pentyl iodide (396 mg, 261 μL , 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane- CH_2Cl_2 as eluent gave pentyl tetrahydrothiopyran **418** (57 mg, 33%) as a colourless oil.

Lab Book Reference: **NS3-57**

2-Allyltetrahydro-2H-thiopyran **419**



419

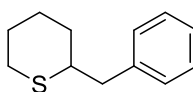
Using general procedure M, tetrahydrothiopyran **140** (101 μL , 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 μL , 2.0 mmol, 2.0 eq.) in hexane (5 mL) at 0 °C for 2 h and allyl bromide (363 mg, 259 μL , 3.0 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with hexane then 95:5 to 85:15 hexane- CH_2Cl_2 as eluent gave allyl tetrahydrothiopyran **419** (87 mg, 61%) as a colourless oil; R_F (85:15 hexane- CH_2Cl_2) 0.3; R_F (85:15 hexane- CH_2Cl_2) 0.3; IR (ATR) 3076, 2977, 2924, 2846, 1438, 1272, 991, 912, 805, 682, 653, 619 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.90-5.73 (m, 1H, $\text{CH}=\text{CH}_2$), 5.16-4.97 (m, 2H, $\text{CH}=\text{CH}_2$), 2.80-2.55 (m, 3H, CH, SCH), 2.26-2.20 (m, 2H, CH), 2.04-1.81 (m, 3H, CH), 1.64-1.50 (m, 1H, CH), 1.46-1.28 (m, 2H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 135.6 ($\text{CH}=\text{CH}_2$), 116.9 ($\text{CH}=\text{CH}_2$), 42.3 (SCH), 40.7 (CH_2), 34.3 (CH_2), 29.4 (CH_2), 27.3 (CH_2), 26.3 (CH_2). Attempted characterisation by MS was unsuccessful.

Lab Book Reference: **NS10-40**

Using general procedure M, tetrahydrothiopyran **140** (101 μ L, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and allyl bromide (242 mg, 173 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-CH₂Cl₂ then 85:15 hexane-CH₂Cl₂ as eluent gave allyl tetrahydrothiopyran **419** (46 mg, 32%) as a colourless oil.

Lab Book Reference: **NS3-10**

2-Benzyltetrahydro-2H-thiopyran **420**

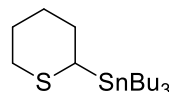


420

Using general procedure M, tetrahydrothiopyran **140** (101 μ L, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and benzyl bromide (347 mg, 243 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with hexane then 95:5 hexane-CH₂Cl₂ as eluent gave benzyl tetrahydrothiopyran **420** (78 mg, 41%) as a colourless oil, *R*_F (95:5 hexane-CH₂Cl₂) 0.8; IR (ATR) 3026, 2924, 2849, 1495, 1438, 1453, 1258, 1046, 750, 700, 541 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.08 (m, 5H, Ph), 3.02-2.89 (m, 1H, SCH), 2.87-2.57 (m, 4H, CH), 2.05-1.82 (m, 3H, CH), 1.70-1.54 (m, 1H, CH), 1.53-1.25 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 139.2 (*ipso*-Ph), 129.3 (Ph), 128.4 (Ph), 126.5 (Ph), 44.1 (SCH), 42.7 (CH₂), 34.1 (CH₂), 29.5 (CH₂), 27.3 (CH₂), 26.2 (CH₂); MS (ESI) *m/z* 209 [(M + OH)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₇S (M + OH)⁺ 209.0995, found 209.0998 (−1.8 ppm error).

Lab Book Reference: **NS3-56**

Tributyl(tetrahydro-2H-thiopyran-2-yl)stannane **421**



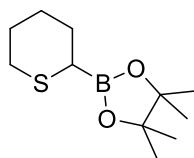
421

Using general procedure M, tetrahydrothiopyran **140** (101 μ L, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 μ L, 2.0 mmol, 2.0 eq.) in hexane (5 mL) at 0 °C for 2 h and Bu₃SnCl (814 μ L, 977 mg, 3.0 mmol,

3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with hexane then 90:10 hexane-CH₂Cl₂ as eluent gave stannane **421** (340 mg, 87%) as a colourless oil; *R*_F (hexane) 0.3; IR (ATR) 2955, 2846, 2919, 1463, 1376, 1264, 1072, 1034, 875, 689, 665, 596, 504 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.67 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, SCH), 2.58 (dd, *J* = 12.0, 2.5 Hz, 1H, SCH), 2.41 (ddd, *J* = 13.0, 3.5, 3.5 Hz (app dt), 1H, SCH), 2.05-1.90 (m, 2H, CH), 1.85-1.69 (m, 3H, CH), 1.56-1.41 (m, 7H, CH), 1.35-1.25 (m, 6H, CH), 0.98-0.79 (m, 15H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 32.7 (CH₂), 31.8 (SCH₂), 29.3 (CH₂), 28.8 (CH₂), 28.2 (CH₂), 27.6 (CH₂), 26.1 (SCH), 13.8 (Me), 8.6 (CH₂); MS (APCI) *m/z* 391 [(¹¹⁸M + H)⁺, 74], 393 [(¹²⁰M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₇H₃₆S¹²⁰Sn (¹²⁰M + H)⁺ 393.1634, found 393.1654 (+4.0 ppm error).

Lab Book Reference: **NS10-41**

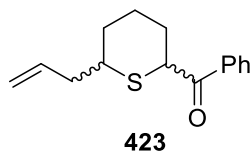
4,4,5,5-Tetramethyl-2-(tetrahydro-2H-thiopyran-2-yl)-1,3,2-dioxaborolane **422**



422

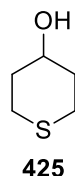
Using general procedure M, tetrahydrothiopyran **140** (101 μL, 102 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.53 mL of a 1.3 M solution in hexane, 2.0 mmol, 2.0 eq.) and TMEDA (300 μL, 2.0 mmol, 2.0 eq.) in hexane (5 mL) at 0 °C for 2 h and boronic ester (612 μL, 558 mg, 3.0 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-Et₂O then 90:10 hexane-Et₂O as eluent gave boronic ester **422** (146 mg, 64%) as a colourless oil, *R*_F (90:10 hexane-Et₂O) 0.3; IR (ATR) 2977, 2924, 1367, 1324, 1250, 1135, 973, 875, 846 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.69-2.52 (m, 2H, SCH), 2.43-2.32 (m, 1H, SCH), 2.05-1.93 (m, 1H, CH), 1.93-1.83 (m, 1H, CH), 1.82-1.65 (m, 3H, CH), 1.43-1.34 (m, 1H, CH), 1.25 (s, 6H, Me), 1.25 (s, 6H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 83.9 (CO), 29.4 (CH₂), 29.1 (CH₂), 27.5 (CH₂), 26.6 (CH₂), 24.8 (Me), (SCH resonance not resolved); MS (ESI) *m/z* 229 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₂₁BO₂S (M + H)⁺ 229.1430, found 229.1427 (+1.6 ppm error).

Lab Book Reference: **NS10-43**

Attempted Synthesis of (6-allyltetrahydro-2H-thiopyran-2-yl)(phenyl)methanone 423

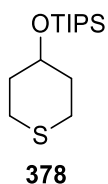
Using general procedure M, allyl tetrahydrothiopyran **419** (71 mg, 0.50 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (2.5 mL) at 0 °C for 4 h and Weinreb amide **115** (165 mg, 152 μ L, 1.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which did not contain the desired product (by ^1H NMR spectroscopy).

Lab Book Reference: **NS3-80**

4-Hydroxytetrahydrothiopyran 425

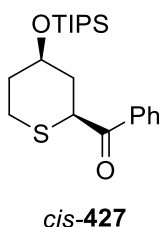
NaBH_4 (1.51 g, 40 mmol, 2.0 eq.) was added to a stirred solution of tetrahydro-4H-thiopyran-4-one **424** (2.52 g, 20 mmol, 1.0 eq.) in MeOH (100 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave alcohol **425** (2.16 g, 97%) as a white solid, mp 48-49 °C (lit.,²¹⁹ 48-50 °C), R_F (50:50 hexane-EtOAc) 0.2; ^1H NMR (400 MHz, CDCl_3) δ 3.68-3.59 (m, 1H, OCH), 2.75 (br d, J = 13.5 Hz, 2H, SCH), 2.57 (ddd, J = 13.5, 13.5, 2.5 Hz (app td), 2H, SCH), 2.20-2.10 (m, 2H, CH), 1.83-1.63 (m, 3H, OH, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 68.9 (OCH), 36.2 (SCH₂), 26.6 (CH₂). Spectroscopic data consistent with those reported in the literature.²¹⁹

Lab Book Reference: **NS2-44**

Triisopropyl((tetrahydro-2H-thiopyran-4-yl)oxy)silane 378

Pyridine (1.36 mL, 17 mmol, 2.0 eq.) and TIPSOTf (4.56 mL, 17 mmol, 2.0 eq.) were added to a stirred solution of alcohol **425** (1.0 g, 8.5 mmol, 1.0 eq.) in CH₂Cl₂ (50 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, saturated NH₄Cl_(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with 15% CuSO_{4(aq)} (30 mL) and with saturated EDTA_(aq) (30 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 hexane-Et₂O as eluent gave TIPS-protected tetrahydrothiopyran **378** (2.26 g, 90%) as a colourless oil, *R*_F (95:5 hexane-Et₂O) 0.2; IR (ATR) 2940, 2865, 2892, 1463, 1425, 1105, 1083, 1067, 996, 824, 788, 678, 657, 627 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.90 (tt, *J* = 8.5, 3.0 Hz, 1H, OCH), 2.99-2.87 (m, 2H, SCH), 2.43 (ddd, *J* = 12.5, 8.5, 3.0 Hz, 2H, SCH), 2.00 (dddd, *J* = 12.5, 8.5, 3.0, 3.0 Hz (app ddt), 2H, CH), 1.84 (dddd, *J* = 10.5, 8.5, 8.5, 3.0 Hz (app dtd), 2H, CH), 1.08-1.03 (m, 21H, CHMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 67.9 (OCH), 36.2 (SCH₂), 25.1 (CH₂), 18.2 (CHMe₂), 12.4 (CHMe₂); MS (ESI) *m/z* 297 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₄H₃₀OSSi (M + Na)⁺ 297.1679, found 297.1674 (+1.7 ppm error).

Lab Book Reference: **NS2-46**

Phenyl(4-((triisopropylsilyl)oxy)tetrahydro-2H-thiopyran-2-yl)methanone *cis*-427

Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (275 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) in hexane (5 mL) and TMEDA (195 μL, 1.3 mmol, 1.3 eq.) at 0 °C for 2 h and Weinreb amide **115** (330 mg, 304 μL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash

column chromatography on silica with 85:15 hexane-CH₂Cl₂ as eluent gave ketone *cis*-**427** (268 mg, 71%) as a white solid, mp 89-91 °C, *R*_F (75:25 hexane-CH₂Cl₂) 0.2; IR (ATR) 2942, 2864, 1681 (C=O), 1462, 1448, 1267, 1102, 684 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.04-8.00 (m, 2H, Ph), 7.61-7.55 (m, 1H, Ph), 7.47 (dd, *J* = 7.5, 7.5 Hz (app t), 2H, Ph), 4.49 (dd, *J* = 11.5, 2.5 Hz, 1H, SCHC(O)), 3.77 (dddd, *J* = 11.5, 11.5, 3.5, 3.5 Hz (app tt), 1H, OCH), 2.89 (ddd, *J* = 11.5, 3.5, 3.5 Hz (app dt), 1H, SCH), 2.82 (ddd, *J* = 11.5, 3.5, 3.5 Hz (app dt), 1H, SCH), 2.44-2.37 (m, 1H, CH), 2.33-2.25 (m, 1H, CH), 1.99 (dd, *J* = 11.5, 11.5 Hz (app t), 1H, CH), 1.71 (ddd, *J* = 11.5, 11.5, 3.5 Hz (app td), 1H, CH), 1.08-1.02 (m, 21H, CHMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.4 (C=O), 135.2 (*ipso*-Ph), 133.6 (Ph), 129.0 (Ph), 128.8 (Ph), 71.0 (OCH), 48.4 (SCH), 40.0 (CH₂), 37.1 (CH₂), 28.5 (SCH₂), 18.2 (CHMe₂), 12.5 (CHMe₂); MS (ESI) *m/z* 401 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₁H₃₄O₂SSi (M + Na)⁺ 401.1937, found 401.1941 (-1.1 ppm error).

Lab Book Reference: **NS2-50**

Phenyl(4-((triisopropylsilyl)oxy)tetrahydro-2*H*-thiopyran-2-yl)methanol *cis*-429

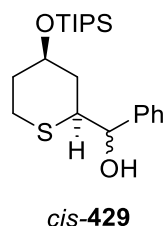


Table 4.3, entry 3:

Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (273 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and benzaldehyde (201 mg, 210 μL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 55:45 mixture (by ¹H NMR spectroscopy) of alcohols *cis*-**428**. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ then 90:10 CH₂Cl₂-MeOH as eluent gave a 55:45 mixture of alcohols *cis*-**429** (331 mg, 87%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.2; IR (ATR) 2942, 2891, 2865, 1462, 1454, 1263, 1100, 1067, 881, 699, 679 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.26 (m, 5H, Ph), 4.79 (dd, *J* = 5.5, 3.0 Hz, 0.6H, HOCH), 4.68 (dd, *J* = 7.5, 3.0 Hz, 0.4H, HOCH), 3.64-3.53 (m, 1H, SCH), 3.14-3.03 (m, 1H, OCH), 2.85 (ddd, *J* = 13.5, 5.0, 3.5 Hz, 0.4H, CH), 2.81-2.76 (m, 0.4H, OH), 2.76-2.72 (m, 0.6H, CH), 2.68-2.55 (m, 1H, CH), 2.42 (br d, *J* = 3.0 Hz, 0.6H, OH), 2.29-2.22

(m, 0.6H, CH), 2.17-2.10 (m, 1H, CH), 1.91 (ddd, $J = 13.0, 3.5, 3.5$ Hz (app dt), 0.4H, CH), 1.73-1.52 (m, 2H, CH), 1.06-0.92 (m, 21H, CHMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 141.6 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.2 (Ph), 128.0 (Ph), 126.8 (Ph), 126.4 (Ph), 77.6 (HOCH), 76.4 (HOCH), 70.7 (OCH), 70.3 (OCH), 50.0 (SCH), 49.0 (SCH), 40.5 (CH₂), 38.2 (CH₂), 36.8 (CH₂), 36.6 (CH₂), 26.8 (CH₂), 26.2 (CH₂), 18.2 (CHMe₂), 18.1 (CHMe₂), 12.4 (CHMe₂), 12.3 (CHMe₂) (one *ipso*-Ar resonance not resolved); MS (ESI) m/z 403 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₂₁H₃₆O₂SSi (M + Na)⁺ 403.2097, found 403.2084 (−3.2 ppm error).

Lab Book Reference: **NS2-47**

Table 4.3, entry 1:

Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (273 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at −20 °C for 2 h and benzaldehyde (201 mg, 210 μ L, 2.0 mmol, 2.0 eq.) at −10 °C for 1 h gave the crude product which contained a 55:45 mixture (by ¹H NMR spectroscopy) of alcohols *cis*-**429**. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ then 90:10 CH₂Cl₂-MeOH as eluent gave recovered TIPS-protected tetrahydrothiopyran **378** (76 mg, 28%) as a colourless oil and a 55:45 mixture of alcohols *cis*-**429** (251 mg, 66%) as a colourless oil.

Lab Book Reference: **NS2-47**

Table 4.3, entry 2:

Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (273 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at −10 °C for 2 h and benzaldehyde (201 mg, 210 μ L, 2.0 mmol, 2.0 eq.) at −20 °C for 1 h gave the crude product which contained a 55:45 mixture (by ¹H NMR spectroscopy) of alcohols *cis*-**429**. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ then 90:10 CH₂Cl₂-MeOH as eluent gave recovered TIPS-protected tetrahydrothiopyran **378** (52 mg, 19%) as a colourless oil and a 55:45 mixture of alcohols *cis*-**429** (285 mg, 75%) as a colourless oil.

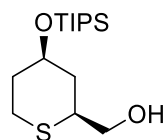
Lab Book Reference: **NS2-48**

Table 4.3, entry 4:

Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (273 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 1 h and benzaldehyde (201 mg, 210 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of alcohols *cis*-**429**. Purification by flash column chromatography on silica with 80:20 hexane- CH_2Cl_2 then 90:10 CH_2Cl_2 -MeOH as eluent gave recovered TIPS-protected tetrahydrothiopyran **378** (36 mg, 13%) as a colourless oil and a 55:45 mixture of alcohols *cis*-**429** (312 mg, 82%) as a colourless oil.

Lab Book Reference: **NS2-50**

(4-((Triisopropylsilyl)oxy)tetrahydro-2H-thiopyran-2-yl)methanol *cis*-430

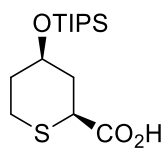


cis-**430**

Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (273 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and paraformaldehyde (60 mg, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane- CH_2Cl_2 then 47.5:47.5:5 hexane- CH_2Cl_2 -MeOH as eluent gave alcohol *cis*-**430** (247 mg, 81%) as a colourless oil, R_F (90:10 hexane- CH_2Cl_2) 0.3; IR (ATR) 3392 (OH), 2940, 2865, 1463, 1368, 1255, 1104, 1067, 1013, 881, 827, 789, 678, 656 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.86-3.65 (m, 3H, OCH), 2.99-2.91 (m, 1H, CH), 2.89-2.79 (m, 1H, CH), 2.49 (ddd, J = 10.0, 10.0, 2.5 Hz (app td), 1H, CH), 2.21-2.08 (m, 3H, OH, CH), 1.78-1.60 (m, 2H, CH), 1.05 (br s, 21H, CHMe_2); ^{13}C NMR (100.6 MHz, CDCl_3) δ 69.3 (OCH), 66.2 (OCH₂), 44.0 (SCH), 39.4 (CH₂), 36.5 (CH₂), 24.7 (CH₂), 18.23 (CHMe_2), 18.21 (CHMe_2), 12.4 (CHMe_2); MS (ESI) m/z 327 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{32}\text{O}_2\text{SSi}$ (M + Na)⁺ 327.1784, found 327.1795 (+3.2 ppm error).

Lab Book Reference: **NS2-65**

4-((Triisopropylsilyl)oxy)tetrahydro-2H-thiopyran-2-carboxylic acid *cis*-431

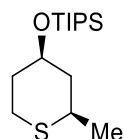


cis-431

Using general procedure N, TIPS-protected tetrahydrothiopyran **378** (273 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and CO₂ at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 85:15 hexane-EtOAc then 75:25 hexane-EtOAc as eluent gave acid *cis*-431 (63 mg, 20%) as a colourless oil, *R*_F (85:15 hexane-CH₂Cl₂) 0.2; IR (ATR) 2941, 2866, 1706 (C=O), 1463, 1261, 1197, 1083, 1065, 881, 734, 658, 679 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 10.04 (br s, 1H, CO₂H), 4.31-4.23 (m, 1H, OCH), 4.02 (dd, *J* = 9.0, 4.0 Hz, 1H, SCH), 3.06 (ddd, *J* = 9.0, 9.0, 6.0 Hz (app td), 1H, CH), 2.54 (ddd, *J* = 13.5, 4.0, 4.0 Hz (app dt), 1H, CH), 2.21 (ddd, *J* = 13.5, 6.0, 4.0 Hz, 1H, CH), 2.12-2.03 (m, 1H, CH), 1.94-1.85 (m, 2H, CH), 1.11-1.00 (m, 21H, CHMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 178.4 (C=O), 65.6 (OCH), 40.2 (SCH), 37.8 (CH₂), 34.6 (CH₂), 24.0 (CH₂), 18.2 (CHMe₂), 12.4 (CHMe₂); MS (ESI) *m/z* 341 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₅H₃₀O₃SSi (M + Na)⁺ 341.1577, found 341.1572 (−1.4 ppm error).

Lab Book Reference: NS2-69

Triisopropyl((2-methyltetrahydro-2H-thiopyran-4-yl)oxy)silane *cis*-432



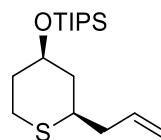
cis-432

Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (275 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and Me₂SO₄ (252 mg, 189 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 95:5 then 85:15 hexane-CH₂Cl₂ as eluent gave methyl

tetrahydrothiopyran *cis*-**432** (118 mg, 41%) as a colourless oil, R_F (95:5 hexane-CH₂Cl₂) 0.4; IR (ATR) 2941, 2866, 1464, 1366, 1350, 1330, 1136, 1098, 847, 677 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.57 (dddd, J = 11.5, 11.5, 4.0, 4.0 Hz (app tt), 1H, OCH), 2.84 (dq, J = 11.5, 7.0, 3.0 Hz, 1H, SCHMe), 2.72-2.58 (m, 2H, CH), 2.24-2.18 (m, 2H, CH), 1.60-1.49 (m, 1H, CH), 1.46-1.35 (m, 1H, CH), 1.22 (d, J = 7.0 Hz, 3H, CHMe), 1.10-1.02 (m, 21H, CHMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 71.2 (OCH), 46.9 (CH₂), 37.4 (SCH), 37.0 (CH₂), 28.0 (SCH₂), 21.7 (CHMe), 18.3 (CHMe₂), 12.5 (CHMe₂); MS (APCI) m/z 275 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₅H₃₂OSSi (M + H)⁺ 275.1859, found 275.1862 (+1.1 ppm error).

Lab Book Reference: **NS2-57**

((2-Allyltetrahydro-2H-thiopyran-4-yl)oxy)triisopropylsilane *cis*-433

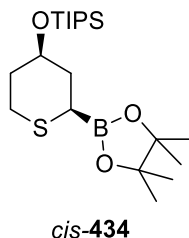


cis-**433**

Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (275 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and allyl bromide 242 mg, 173 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-CH₂Cl₂ as eluent gave allyl tetrahydrothiopyran *cis*-**433** (163 mg, 52%) as a colourless oil, R_F (90:10 hexane-CH₂Cl₂) 0.3; IR (ATR) 2940, 2865, 1463, 1078, 1062, 995, 881, 679, 663 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.88-5.73 (m, 1H, CH=CH₂), 5.10-5.03 (m, 2H, CH=CH₂), 4.24 (br s, 1H, OCH), 3.33-3.25 (m, 1H, SCH), 3.18 (ddd, J = 13.5, 13.5, 2.0 Hz (app td), 1H, CH), 2.33 (ddd, J = 13.5, 3.5, 3.5 Hz (app dt), 1H, CH), 2.26-2.18 (m, 2H, CH), 2.00 (br d, J = 13.5 Hz, 1H, CH), 2.01-1.95 (m, 1H, CH), 1.78-1.68 (m, 1H, CH), 1.58-1.50 (m, 1H, CH), 1.08-1.03 (m, 21H, CHMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 135.4 (CH=CH₂), 117.0 (CH=CH₂), 66.2 (OCH), 41.5 (CH₂CH=CH₂), 40.4 (CH₂), 35.8 (SCH), 34.6 (CH₂), 23.2 (SCH₂), 18.3 (CHMe₂), 12.4 (CHMe₂); MS (ESI) m/z 337 [(M + Na)⁺, 100]; HRMS (ESI) m/z calcd for C₁₇H₃₄OSSi (M + Na)⁺ 337.1985, found 337.1992 (-2.0 ppm error).

Lab Book Reference: **NS2-54**

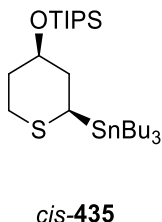
Triisopropyl((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)tetrahydro-2H-thiopyran-4-yl)oxy)silane *cis*-434



Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (273 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and *i*-PrOBpin (372 mg, 408 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂ then 67:33 hexane-CH₂Cl₂ as eluent gave boronate *cis*-434 (270 mg, 69%) as a colourless oil, *R*_F (85:15 hexane-CH₂Cl₂) 0.3; IR (ATR) 2941, 2865, 1463, 1368, 1106, 1083, 1068, 996, 881, 824, 787, 678, 656, 517 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.51 (dddd, *J* = 10.5, 10.5, 4.0, 4.0 Hz (app tt), 1H, OCH), 2.75-2.62 (m, 2H, CH), 2.46 (dd, *J* = 13.5, 2.5 Hz, 1H, CH), 2.24-2.17 (m, 2H, CH), 1.69-1.57 (m, 2H, SCH, CH), 1.28-1.22 (m, 12H, CMe₂), 1.10-1.02 (m, 21H, CHMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 84.1 (OC), 71.9 (OCH), 39.0 (CH₂), 37.7 (CH₂), 29.8 (CH₂), 24.84 (OCMe), 24.76 (OCMe), 18.3 (TIPS-CHMe₂), 12.6 (CHMe₂); MS (ESI) *m/z* 401 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₀H₄₂BO₃SSi (M + Na)⁺ 401.2716, found 401.2712 (+0.9 ppm error).

Lab Book Reference: NS2-58

Triisopropyl((2-(tributylstannyl)tetrahydro-2H-thiopyran-4-yl)oxy)silane *cis*-435

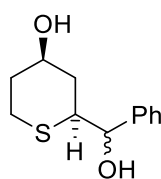


Using general procedure M, TIPS-protected tetrahydrothiopyran **378** (275 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and Bu₃SnCl (651 mg, 542 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column

chromatography on silica with hexane then CH₂Cl₂ as eluent gave stannane *cis*-**435** (414 mg, 74%) as a colourless oil, *R*_F (90:10 hexane-CH₂Cl₂) 0.5; IR (ATR) 2955, 2924, 2865, 1463, 1098, 1068, 881, 828, 791, 679, 656 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.45 (dddd, *J* = 11.5, 11.5, 3.0, 3.0 Hz (app tt), 1H, OCH), 2.72 (ddd, *J* = 11.5, 11.5, 3.0 Hz (app td), 1H, SCH), 2.59 (ddd, *J* = 11.5, 3.0, 3.0 Hz (app dt), 1H, SCH), 2.53 (dd, *J* = 11.5, 3.0 Hz, 1H, SCH), 2.29-2.19 (m, 2H, CH), 1.80-1.68 (m, 2H, CH), 1.58-1.47 (m, 6H, CH), 1.38-1.27 (m, 6H, CH), 1.08-1.04 (m, 21H, CH), 0.90 (m, 15H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 72.7 (OCH), 42.6 (CH₂), 38.3 (CH₂), 32.2 (SCH₂), 29.3 (CH₂), 27.6 (CH₂), 24.3 (SCH), 18.2 (CHMe₂), 13.8 (CH₂Me), 12.5 (CHMe₂), 8.8 (CH₂); MS (ESI) *m/z* 585 [(¹¹⁸M + Na)⁺, 75], 587 [(¹²⁰M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₆H₅₆OSSi¹²⁰Sn (¹²⁰M + Na)⁺ 587.2738, found 587.2726 (+2.1 ppm error).

Lab Book Reference: **NS2-59**

2-(Hydroxy(phenyl)methyl)tetrahydro-2*H*-thiopyran-4-ol *cis*-**436**



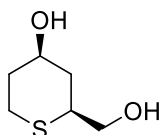
cis-**436**

TBAF (0.55 mL of a 1.0 M solution in THF, 0.55 mmol, 1.1 eq.) was added to a stirred solution of a 55:45 mixture of alcohols *cis*-**429** (190 mg, 0.50 mmol, 1.0 eq.) in THF (2 mL) at rt. The resulting solution was stirred at rt for 48 h. Then, the solvent was evaporated under reduced pressure to give the crude product which contained a 55:45 mixture (by ¹H NMR spectroscopy) of diols *cis*-**436**. Purification by flash column chromatography on silica with 95:4:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave a 55:45 mixture of diols *cis*-**436** (90 mg, 81%) as a colourless oil, *R*_F (200:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.3; IR (ATR) 3341 (OH), 2967, 2927, 1452, 1261, 1068, 1048, 1023, 950, 764, 699, 599, 534 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) 7.56-7.10 (m, 5H, Ph), 4.93-4.83 (m, 2H, OCH, OH), 4.56 (d, *J* = 7.0 Hz, 0.6H, HOCH), 4.52 (d, *J* = 7.0 Hz, 0.4H, HOCH), 3.48-3.26 (m, 1.2H, CH, OH), 3.23-3.04 (m, 0.8H, CH), 2.78-2.57 (m, 2H, CH), 2.51-2.34 (m, 0.4H, CH), 2.29-2.14 (m, 1H, CH), 1.98-1.81 (m, 0.6H, CH), 1.54-1.19 (m, 2H, CH); ¹³C NMR (100.6 MHz, CD₃OD) δ 143.8 (*ipso*-Ph), 143.6 (*ipso*-Ph), 129.2 (Ph), 129.0 (Ph), 128.8 (Ph), 128.6 (Ph), 128.0 (Ph), 127.8 (Ph), 78.5 (HOCH), 77.5 (HOCH), 71.0 (OCH), 70.9 (OCH), 51.0 (SCH), 50.4 (SCH), 41.2

(CH₂), 40.0 (CH₂), 37.4 (CH₂), 37.4 (CH₂), 28.1 (CH₂), 27.8 (CH₂); MS (ESI) *m/z* 247 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₆O₂S (M + Na)⁺ 247.0763, found 247.0757 (+2.6 ppm error).

Lab Book Reference: **NS2-80**

2-(Hydroxymethyl)tetrahydro-2H-thiopyran-4-ol *cis*-437

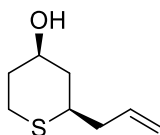


cis-437

TBAF (1.8 mL of a 1.0 M solution in THF, 1.8 mmol, 1.1 eq.) was added to a stirred solution of alcohol *cis*-430 (500 mg, 1.6 mmol, 1.0 eq.) in THF (5 mL) at rt. The resulting solution was stirred at rt for 72 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 200:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave diol *cis*-437 (125 mg, 85%) as a colourless oil, *R*_F (200:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.2; IR (ATR) 3383 (OH), 2941, 2866, 1463, 1368, 1255, 1107, 1068, 1014, 997, 882, 827, 790, 680 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.76-3.70 (m, 2H, OCH), 3.70-3.61 (m, 1H, OCH), 3.06-2.97 (m, 1H, CH), 2.82 (ddd, *J* = 14.0, 5.0, 3.0 Hz, 1H, CH), 2.66 (ddd, *J* = 14.0, 11.0, 3.0 Hz, 1H, CH), 2.29-2.18 (m, 2H, CH), 2.08-1.81 (m, 2H, OH), 1.68-1.59 (m, 1H, CH), 1.59-1.49 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 69.3 (OCH), 66.3 (OCH₂), 44.2 (SCH), 39.4 (CH₂), 36.1 (CH₂), 26.0 (CH₂). Attempted characterisation by MS was unsuccessful.

Lab Book Reference: **NS2-88**

2-Allyltetrahydro-2H-thiopyran-4-ol *cis*-438



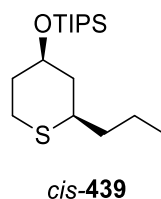
cis-438

TBAF (1.1 mL of a 1.0 M solution in THF, 1.1 mmol) was added to a stirred solution of allyl tetrahydrothiopyran *cis*-433 (309 mg, 1.0 mmol, 1.0 eq.) in THF (4 mL) at rt. The resulting

solution was stirred at rt for 48 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 600:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq) as eluent gave alcohol *cis*-**438** (142 mg, 89%) as a colourless oil, *R*_F (600:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq)) 0.5; IR (ATR) 3358 (OH), 2970, 2912, 1427, 1275, 1043, 992, 950, 916, 816, 651, 611, 489 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.87-5.74 (m, 1H, CH=CH₂), 5.13-5.04 (m, 2H, CH=CH₂), 4.15 (br s, 1H, OCH), 3.19 (dddd, *J* = 13.5, 13.5, 13.5, 3.5 Hz (app qd), 1H, CH), 3.04 (ddd, *J* = 13.5, 11.0, 3.5 Hz, 1H, CH), 2.42 (ddd, *J* = 13.5, 3.5, 3.5 Hz (app dt), 1H, CH), 2.32-2.19 (m, 2H, CH), 2.03 (ddd, *J* = 13.5, 5.0, 3.5 Hz, 1H, CH), 1.99-1.82 (m, 2H, CH), 1.69 (ddd, *J* = 13.5, 11.0, 3.5 Hz, 1H, CH), 1.36 (br s, 1H, OH); ¹³C NMR (100.6 MHz, CDCl₃) δ 135.4 (CH=CH₂), 117.2 (CH=CH₂), 65.7 (OCH), 40.6 (CH₂), 40.1 (CH₂), 36.2 (SCH), 34.1 (CH₂), 23.1 (CH₂). Attempted characterisation by MS was unsuccessful.

Lab Book Reference: **NS2-89**

Triisopropyl((2-propyltetrahydro-2*H*-thiopyran-4-yl)oxy)silane *cis*-**439**

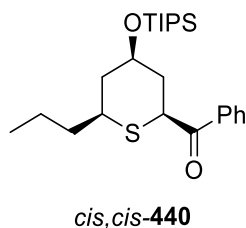


10% Pd/C (75 mg, 0.10 mmol, 10 mol%) was added to a stirred solution of allyl tetrahydrothiopyran *cis*-**433** (320 mg, 1.0 mmol, 1.0 eq.) in MeOH (5 mL) at rt. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred vigorously under a balloon of H₂ at rt for 3 h. The solids were removed by filtration through Celite[®] and washed with MeOH (10 mL). The filtrate was evaporated under reduced pressure to give propyl tetrahydrothiopyran *cis*-**439** (318 mg, 98%) as a colourless oil, *R*_F (90:10 hexane-CH₂Cl₂) 0.5; IR (ATR) 2957, 2931, 2865, 1463, 1207, 1078, 1063, 881, 679, 662 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.27-4.20 (m, 1H, OCH), 3.27-3.20 (m, 1H, CH), 3.16 (ddd, *J* = 13.0, 13.0, 2.5 Hz (app td), 1H, CH), 2.32 (ddd *J* = 13.0, 4.0, 4.0 Hz (app dt), 1H, CH), 2.08-1.94 (m, 2H, CH), 1.81-1.69 (m, 1H, CH), 1.54 (ddd, *J* = 13.0, 11.5, 2.5 Hz, 1H, SCH), 1.45-1.37 (m, 4H, CH), 1.07-1.03 (m, 21H, CHMe₂), 0.90 (t, *J* = 7.0 Hz, 3H, CH₂Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 66.3 (OCH), 42.2 (CH₂), 38.3 (CH₂), 35.9 (SCH), 34.9 (CH₂), 23.2 (CH₂), 20.0 (CH₂), 18.3 (CHMe₂), 14.1 (CH₂Me), 12.4 (CHMe₂); MS (ESI) *m/z* 317 [(M +

Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₇H₃₆OSSi (M + H)⁺ 317.2329, found 317.2326 (–0.8 ppm error).

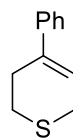
Lab Book Reference: NS2-73

Phenyl(6-propyl-4-((triisopropylsilyl)oxy)tetrahydro-2H-thiopyran-2-yl)methanone
***cis,cis*-440**



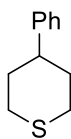
Using general procedure M, propyl tetrahydrothiopyran *cis*-439 (314 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 µL, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 4 h and Weinreb amide **115** (330 mg, 304 µL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 75:25 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ as eluent gave ketone *cis,cis*-440 (173 mg, 41%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.2; IR (ATR) 2941, 2865, 1683, 1463, 1448, 1271, 1077, 1059, 996, 980, 882, 684 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 8.04 (dd, *J* = 7.5, 1.0 Hz, 2H, Ph), 7.60–7.54 (m, 1H, Ph), 7.46 (dd, *J* = 7.5, 7.5 Hz (app t), 2H, Ph), 5.10 (dd, *J* = 12.5, 2.5 Hz, 1H, SCHC(O)), 4.49–4.41 (m, 1H, OCH), 3.55–3.44 (m, 1H, CH), 2.26 (ddd, *J* = 12.5, 2.5, 2.5 Hz (app dt), 1H, SCH), 2.12 (ddd, *J* = 12.5, 2.5, 2.5 Hz (app dt), 1H, CH), 1.98 (ddd, *J* = 12.5, 12.5, 2.5 Hz (app td), 1H, CH), 1.59–1.51 (m, 1H, CH), 1.51–1.40 (m, 4H, CH), 1.11–1.07 (m, 21H, CHMe₂), 0.92 (t, *J* = 7.0 Hz, 3H, CH₂Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 198.5 (C=O), 135.3 (*ipso*-Ph), 133.5 (Ph), 129.0 (Ph), 128.7 (Ph), 66.8 (SCHC(O)), 43.3 (CH₂), 41.4 (SCHCH₂), 37.9 (CH₂), 37.1 (CH₂), 20.0 (CH₂), 18.3 (CHMe₂), 14.1 (CH₂Me), 12.4 (CHMe₂); MS (ESI) *m/z* 421 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₂₄H₄₀O₂SSi (M + H)⁺ 421.2591, found 421.2589 (–0.4 ppm error).

Lab Book Reference: NS2-77

4-Phenyl-3,6-dihydro-2H-thiopyran 442**442**

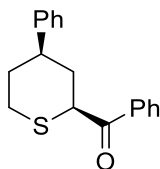
PhMgBr (10.0 mL of a 3.0 M solution in Et₂O, 30 mmol, 1.5 eq.) was added dropwise to a stirred solution of tetrahydro-4*H*-thiopyran-4-one **424** (2.34 g, 20 mmol, 1.0 eq.) in Et₂O (60 mL) at 0 °C under Ar. After being allowed to warm to rt, the resulting solution was stirred and heated at reflux for 1 h. Then, the mixture was cooled to 0 °C and ice-water (100 mL) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (2 x 80 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give crude alcohol **441**. Crude alcohol **441** was dissolved in THF (40 mL) and the solution was cooled to 0 °C. Then, BF₃•OEt₂ (10 mL, 81 mmol, 2.7 eq.) was added and the solution was allowed to warm to rt and stirred at rt for 2 h. Then, the solvent was evaporated under reduced pressure and saturated NaHCO_{3(aq)} (20 mL) and EtOAc (40 mL) were added. The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 80 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave 4-phenyl-3,6-dihydro-2*H*-thiopyran **442** (2.01 mg, 57%) as a colourless oil, *R*_F (50:50 hexane-EtOAc) 0.5; IR (ATR) 3057, 2919, 1661 (C=C), 1495, 1446, 1138, 1034, 871, 767, 743, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.23 (m, 5H, Ph), 6.20-6.15 (m, 1H, C=CH), 3.34 (dt, *J* = 4.5, 2.5 Hz, 2H, SCH₂), 2.89 (t, *J* = 5.5, Hz, 2H, SCH₂), 2.74-2.68 (m, 2H, CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.0 (*ipso*-Ph), 138.3 (C=CH), 128.4 (Ph), 127.3 (Ph), 125.6 (Ph), 121.7 (C=CH), 28.7 (CH₂), 26.3 (CH₂), 25.5 (CH₂); MS (APCI) *m/z* 177 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₁₁H₁₂S (M + H)⁺ 177.0732, found 177.0728 (−2.4 ppm error). Spectroscopic data consistent with those reported in the literature.²²⁰⁻²²¹

Lab Book Reference: **NS2-100 / 4-42**

4-Phenyltetrahydro-2H-thiopyran 379**379**

10% Pd/C (1.11 g, 1.1 mmol, 10 mol%) was added to a stirred solution of 4-phenyl-3,6-dihydro-2H-thiopyran **442** (1.83 g, 11 mmol, 1.0 eq.) in MeOH (80 mL). Then, the reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred vigorously under a balloon of H₂ at rt for 24 h. The solids were removed by filtration through Celite® and washed with 10:1 CH₂Cl₂-MeOH (50 mL). The filtrate was evaporated under reduced pressure to give 4-phenyltetrahydro-2H-thiopyran **379** (1.83 g, 98%) as a yellow oil, *R*_F (95:5 hexane-CH₂Cl₂) 0.4; IR (ATR) 3032, 2907, 2892, 2924, 1494, 1425, 1269, 948, 759, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (dd, *J* = 7.5, 7.5 Hz (app t), 2H, Ph), 7.30-7.25 (m, 3H, Ph), 2.91 (ddd, *J* = 12.5, 12.5, 3.5 Hz (app td), 2H, SCH), 2.77 (br d, *J* = 12.5 Hz, 2H, SCH), 2.59 (tt, *J* = 12.5, 3.5 Hz, 1H, CHPh), 2.25-2.17 (m, 2H, CH), 1.93 (dddd, *J* = 12.5, 12.5, 12.5, 3.5 Hz (app qd), 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 147.0 (*ipso*-Ph), 128.6 (Ph), 126.9 (Ph), 126.4 (Ph), 44.4 (CHPh), 35.2 (CH₂), 29.4 (SCH₂); MS (APCI) *m/z* 179 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₁₁H₁₄S (M + H)⁺ 179.0889, found 179.0886 (+1.6 ppm error). Spectroscopic data consistent with those reported in the literature.²²²

Lab Book Reference: NS3-4 / NS4-44

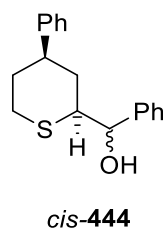
Phenyl(4-phenyltetrahydro-2H-thiopyran-2-yl)methanone *cis*-443*cis*-**443**

Using general procedure M, 4-phenyltetrahydro-2H-thiopyran **379** (191 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and Weinreb amide **115**

(330 mg, 304 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 85:15 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ gave ketone *cis*-**443** (192 mg, 68%) as a white solid, mp 73 °C, *R*_F (50:50 hexane-CH₂Cl₂) 0.4; IR (ATR) 3059, 3027, 2906, 2842, 1679 (C=O), 1597, 1448, 1281, 1258, 1226, 1004, 987, 759, 722, 699, 688 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 7.5 Hz, 2H, Ph), 7.60-7.55 (m, 1H, Ph), 7.47 (dd, *J* = 7.5, 7.5 Hz (app t), 2H, Ph), 7.34-7.29 (m, 2H, Ph), 7.25-7.19 (m, 3H, Ph), 4.66 (dd, *J* = 12.5, 3.0 Hz, 1H, SCHC(O)), 3.07 (ddd, *J* = 12.0, 12.0, 3.0 Hz (app td), 1H, CH), 2.91 (ddd, *J* = 12.0, 3.0, 3.0 Hz (app dt), 1H, CH), 2.73 (dddd, *J* = 12.5, 12.5, 3.0, 3.0 Hz (app tt), 1H, CHPh), 2.38-2.23 (m, 2H, CH), 2.23-2.12 (m, 1H, CH), 1.89 (dddd, *J* = 12.5, 12.5, 12.5, 3.0 Hz (app qd), 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 197.5 (C=O), 146.0 (*ipso*-Ph), 135.3 (Ph), 133.6 (*ipso*-Ph), 129.0 (Ph), 128.8 (Ph), 128.8 (Ph), 127.0 (Ph), 126.8 (Ph), 49.3 (SCH), 44.4 (CHPh), 37.5 (CH₂), 34.8 (CH₂), 30.4 (CH₂); MS (ESI) *m/z* 305 [(M + Na)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₈H₁₈OS (M + Na)⁺ 305.0971, found 305.0965 (+1.7 ppm error).

Lab Book Reference: **NS3-13**

Phenyl(4-phenyltetrahydro-2*H*-thiopyran-2-yl)methanol *cis*-**444**



Using general procedure M, 4-phenyltetrahydro-2*H*-thiopyran **379** (191 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and benzaldehyde (210 mg, 201 μ L, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 55:45 mixture (by ¹H NMR spectroscopy) of alcohols *cis*-**444**. Purification by flash column chromatography on silica with 85:15 hexane-CH₂Cl₂ then 50:50 hexane-CH₂Cl₂ then 90:9:1 CH₂Cl₂-MeOH-NH₄OH_(aq) gave a 55:45 mixture of alcohols *cis*-**444** (221 mg, 78%) as a colourless oil, *R*_F (50:50 hexane-CH₂Cl₂) 0.1; IR (ATR) 3403 (OH), 3060, 3027, 2925, 2903, 1493, 1452, 1024, 760, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.12 (m, 10H, Ph), 4.78 (d, *J* = 5.0 Hz, 0.4H, HOCH), 4.65 (d, *J* = 7.5 Hz, 0.6H, HOCH), 3.38-3.25 (m, 1H, SCH), 2.95-2.77 (m, 2H, CH), 2.51-2.42 (m, 1.6H, CH, OH), 2.26 (br d, *J* = 13.5 Hz, 0.6H,

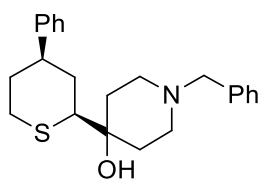
CH), 2.18-2.10 (m, 1H, CH), 1.93-1.67 (m, 2.8H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 146.6 (*ipso*-Ph), 146.5 (*ipso*-Ph), 141.4 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.3 (Ph), 128.1 (Ph), 127.0 (Ph), 126.8 (Ph), 126.5 (Ph), 77.9 (HOCH), 76.7 (HOCH), 51.3 (SCH), 50.3 (SCH), 44.5 (CHPh), 44.4 (CHPh), 38.2 (CH_2), 36.2 (CH_2), 34.9 (CH_2), 34.8 (CH_2), 29.7 (CH_2), 29.3 (CH_2) (one Ph resonance not resolved); MS (ESI) m/z 307 [(M + Na) $^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{20}\text{OSS}$ (M + Na) $^+$ 307.1127, found 307.1113 (–4.5 ppm error).

Lab Book Reference: **NS3-5**

L-Selectride[®] (160 μL of a 1.0 M solution in THF, 0.16 mmol, 1.5 eq.) was added to a stirred solution of ketone *cis*-**443** (30.1 mg, 0.11 mmol, 1.0 eq.) in THF (5 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 3 h. Then MeOH (1 mL), 20% Rochelle's salt_(aq) (10 mL) and Et₂O (10 mL) were added and the resulting mixture was allowed to warm to rt and stirred vigorously at rt for 30 min. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude product which contained a 98:2 mixture (by ^1H NMR spectroscopy) of alcohols *cis*-**444**. Purification by flash column chromatography on silica with 50:50 hexane- CH_2Cl_2 then 95:5 CH_2Cl_2 -MeOH as eluent gave a 98:2 mixture of alcohols *cis*-**444** (26.2 mg, 87%) as a colourless oil

Lab Book Reference: **NS12-19**

1-Benzyl-4-(4-phenyltetrahydro-2*H*-thiopyran-2-yl)piperidin-4-ol *cis*-**445**



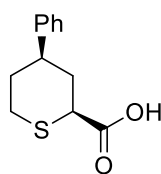
cis-**445**

Using general procedure M, 4-phenyltetrahydro-2*H*-thiopyran **379** (178 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0°C for 2 h and 1-benzylpiperidin-4-one (378 mg, 371 μL , 2.0 mmol, 2.0 eq.) at 0°C for 1 h gave the crude product. Purification by flash column chromatography on silica with 98.5:1.4:0.1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ then 97.5:2:0.5 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ gave alcohol *cis*-**445** (205 mg, 56%) as a colourless

oil, R_F (98.5:1.4:0.1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.2; IR (ATR) 3445 (OH), 3027, 2919, 2813, 1467, 1494, 1453, 1366, 1109, 1074, 1028, 762, 735, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.47-7.17 (m, 10H, Ph), 3.55 (s, 2H, NCH_2Ph), 3.01 (dd, $J = 12.5, 2.5$ Hz, 1H, SCH), 2.92-2.85 (m, 2H, CH), 2.76-2.69 (m, 2H, CH), 2.56 (dddd, $J = 12.5, 12.5, 2.5, 2.5$ Hz (app tt), 1H, CH), 2.41-2.31 (m, 2H, CH), 2.28 (br d, $J = 13.0$ Hz, 1H, CH), 2.16 (dddd, $J = 13.0, 3.0, 3.0, 3.0$ Hz (app dq), 1H, CH), 1.93-1.68 (m, 6H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 146.7 (*ipso*-Ph), 138.6 (*ipso*-Ph), 129.2 (Ph), 128.7 (Ph), 128.3 (Ph), 127.1 (Ph), 126.9 (Ph), 126.6 (Ph), 71.2 (HOC), 63.2 (NCH_2Ph), 55.0 (SCH), 49.3 (CH_2), 44.9 (CHPh), 35.8 (CH_2), 35.4 (CH_2), 34.8 (CH_2), 34.3 (CH_2), 29.4 (CH_2); MS (ESI) m/z 368 [$(\text{M} + \text{H})^+$, 100]; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{29}\text{NOS}$ ($\text{M} + \text{H})^+$ 368.2043, found 368.2043 (+0.2 ppm error).

Lab Book Reference: **NS4-48**

4-Phenyltetrahydro-2*H*-thiopyran-2-carboxylic acid *cis*-446



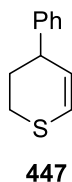
cis-446

Using general procedure N, 4-phenyltetrahydro-2*H*-thiopyran **379** (178 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 h and CO_2 at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$ gave acid *cis*-446 (86 mg, 39%) as a colourless oil, R_F (90:9:1 CH_2Cl_2 -MeOH- $\text{NH}_4\text{OH}_{(\text{aq})}$) 0.1; IR (ATR) 3443 (OH), 3027, 2923, 2811, 1717 (C=O), 1494, 1454, 1349, 1118, 1072, 1028, 811, 738, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.92 (br s, 1H, CO_2H), 7.50-7.16 (m, 5H, Ph), 3.82 (dd, $J = 13.0, 3.0$ Hz, 1H, SCH), 2.96-2.88 (m, 1H, CH), 2.83 (ddd, $J = 13.0, 3.0, 3.0$ Hz (app dt), 1H, CH), 2.59 (dddd, $J = 13.0, 13.0, 3.0, 3.0$ Hz (app tt), 1H, CH), 2.48 (br d, $J = 13.0$ Hz, 1H, CH), 2.16 (br d, $J = 13.0$ Hz, 1H, CH), 2.00 (ddd, $J = 13.0, 13.0, 13.0$ Hz (app q), 1H, CH), 1.84 (dddd, $J = 13.0, 13.0, 13.0, 3.0$ Hz (app qd), 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 177.5 (C=O), 145.6 (*ipso*-Ph), 128.8 (Ph), 126.9 (Ph), 126.8 (Ph), 46.2 (SCH), 44.2 (CHPh), 37.9 (CH_2), 34.2 (CH_2), 29.7 (CH_2);

MS (ESI) m/z 223 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $C_{12}H_{14}O_2S$ $(M + H)^+$ 223.0787, found 223.0790 (+1.3 ppm error).

Lab Book Reference: **NS4-47**

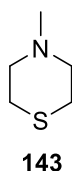
4-Phenyl-3,4-dihydro-2H-thiopyran **447**



Using general procedure M, 4-phenyltetrahydro-2H-thiopyran **379** (382 mg, 1.0 mmol, 2.0 eq.), *s*-BuLi (2.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 2.6 eq.) and TMEDA (390 μ L, 2.6 mmol, 1.3 eq.) in hexane (10 mL) at 0 °C for 2 h and allyl bromide (484 mg, 346 μ L, 2.0 mmol, 4.0 eq.) at 0 °C for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-CH₂Cl₂ then 85:15 hexane-CH₂Cl₂ as eluent gave vinyl sulfide **447** (73 mg, 43%) as a colourless oil, R_F (50:50 hexane-CH₂Cl₂) 0.5; IR (ATR) 3025, 2916, 1602 (C=C), 1491, 1451, 1279, 927, 803, 764, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.29 (m, 2H, Ph), 7.26-7.21 (m, 3H, Ph), 6.27 (dd, J = 10.0, 2.0 Hz, 1H, CH=CHS), 5.81 (dd, J = 10.0, 4.0 Hz, 1H, CH=CHS), 3.55 (ddd, J = 10.0, 7.0, 2.0 Hz, 1H, CHPh), 2.95-2.77 (m, 2H, CH₂), 2.28 (dddd, J = 13.5, 7.0, 4.0, 2.0 Hz, 1H, CH), 2.11-1.99 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 145.3 (*ipso*-Ph), 128.6 (Ph), 128.1 (Ph), 126.6 (CH=CHS), 123.6 (Ph), 120.9 (CH=CHS), 39.7 (CHPh), 31.3 (CH₂), 23.9 (CH₂); MS (ESI) m/z 177 $[(M + H)^+, 100]$; HRMS (ESI) m/z calcd for $C_{11}H_{12}S$ $(M + H)^+$ 177.0733, found 177.0735 (+1.4 ppm error).

Lab Book Reference: **NS4-46**

N-Methyl thiomorpholine **143**

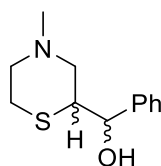


NaBH(OAc)₃ (9.23 g, 44 mmol, 1.5 eq.) was added to a stirred solution of thiomorpholine (3.00 g, 29 mmol, 1.0 eq.), 37% aqueous formaldehyde (23.6 mL, 29 mmol, 10.0 eq.) and MgSO₄ (9.75 g) in 4:1 CH₂Cl₂-AcOH (142 mL) at rt under Ar. The resulting mixture was

stirred at rt for 14 h. Then, 37% NH₄OH(aq) (150 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 200 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure (care, product is volatile) to give the crude product. Purification by flash column chromatography on silica with 300:9:1 CH₂Cl₂-MeOH-NH₄OH(aq) as eluent gave *N*-methyl thiomorpholine **143** (2.36 g, 69%) as a colourless oil, *R*_F (90:9:1 CH₂Cl₂-MeOH-NH₄OH(aq)) 0.7; IR (ATR) 2911, 2841, 2790, 2678, 1456, 1285, 1132, 1120, 1069, 1000, 956, 763, 667 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.72-2.53 (m, 8H, CH₂), 2.25 (s, 3H, NMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 56.7 (NCH₂), 47.4 (NMe), 28.1 (SCH₂). Spectroscopic data consistent with those reported previously in the group.²²

Lab Book Reference: **NS2-71**

2-(Hydroxy(phenyl)methyl)tetrahydro-2*H*-thiopyran-4-ol **144**



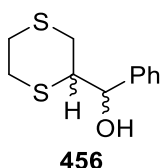
144

Using general procedure M, *N*-methyl thiomorpholine **143** (117 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (45 µL, 0.3 mmol, 0.3 eq.) in hexane (5 mL) at 0 °C for 3 h and benzaldehyde (201 mg, 210 µL, 2.0 mmol, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained a 55:45 mixture (by ¹H NMR spectroscopy) of alcohols **144**. Purification by flash column chromatography on silica with 98:1.5:0.5 to 95:4:1 CH₂Cl₂-MeOH-NH₄OH(aq) as eluent gave alcohol **144a** (103 mg, 41%) as a white solid, mp 67-69 °C; *R*_F (98:1.5:0.5 CH₂Cl₂-MeOH-NH₄OH(aq)) 0.4; IR (ATR) 3381 (OH), 2801, 1453, 1290, 1119, 1064, 978, 791, 767, 699, 601, 535 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.46-7.29 (m, 5H, Ph), 5.09 (d, *J* = 6.5 Hz, 1H, HOCH), 4.55 (br s, 1H, OH), 3.24-3.15 (m, 1H, CH), 2.93-2.85 (m, 2H, CH), 2.76 (dd, *J* = 12.0, 4.5 Hz, 1H, CH), 2.62 (dd, *J* = 12.0, 3.0 Hz, 1H, CH), 2.55-2.46 (m, 2H, CH), 2.24 (s, 3H, NMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 142.0 (*ipso*-Ph), 128.3 (Ph), 127.7 (Ph), 126.7 (Ph), 76.2 (HOCH), 59.7 (SCH₂), 56.3 (NCH₂), 47.2 (NMe), 47.1 (SCH), 26.9 (NCH₂); MS (ESI) *m/z* 224 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₂H₁₇NOS (M + H)⁺ 224.1104, found 224.1106 (−1.0 ppm error) and alcohol **144b** (82 mg, 34%) as a colourless oil, *R*_F (98:1.5:0.5 CH₂Cl₂:MeOH:NH₄OH) 0.3; mp 67-70 °C, IR (ATR) 3354 (OH), 3061, 2801, 1454, 1289,

1119, 1054, 978, 791, 764, 699, 592, 534 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.28 (m, 5H, Ph), 5.09 (d, $J = 4.5$ Hz, 1H, HOCH), 3.30-3.18 (m, 1H, CH), 2.99-2.90 (m, 1H, CH), 2.82-2.74 (m, 2H, CH), 2.70 (dd, $J = 12.5, 3.0$ Hz, 1H, CH), 2.67-2.62 (m, 1H, CH), 2.58 (ddd, $J = 12.0, 9.0, 3.0$ Hz, 1H, CH), 2.25 (s, 3H, NMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 143.6 (*ipso*-Ph), 128.4 (Ph), 127.6 (Ph), 125.9 (Ph), 79.7 (HOCH), 57.2 (SCH_2), 56.2 (NCH_2), 47.1 (NMe), 44.5 (SCH), 27.0 (NCH_2); MS (ESI) m/z 224 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{NOS}$ ($\text{M} + \text{H})^+$ 224.1104, found 224.1107 (-1.7 ppm error).

Lab Book Reference: **NS3-78**

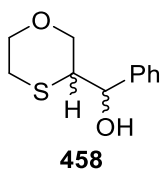
Attempted Synthesis of (1,4-Dithian-3-yl)(phenyl)methanol **456**



Using general procedure M, 1,4-dithian **455** (120 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 $^\circ\text{C}$ for 1 h and benzaldehyde (201 mg, 210 μL , 2.0 mmol, 2.0 eq.) at 0 $^\circ\text{C}$ for 1 h gave the crude product which did not contain the desired product (by ^1H NMR spectroscopy).

Lab Book Reference: **NS4-23**

Attempted Synthesis of (1,4-Oxathian-3-yl)(phenyl)methanol **458**



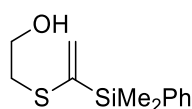
Using general procedure M, 1,4-oxathiane **457** (104 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 $^\circ\text{C}$ for 1 h and benzaldehyde (201 mg, 210 μL , 2.0 mmol, 2.0 eq.) at 0 $^\circ\text{C}$ for 1 h gave the crude product which did not contain the desired product (by ^1H NMR spectroscopy).

Lab Book Reference: **NS6-15**

Using general procedure M, 1,4-oxathiane **457** (104 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at -60 $^{\circ}$ C for 4 h and benzaldehyde (201 mg, 210 μ L, 2.0 mmol, 2.0 eq.) at -60 $^{\circ}$ C for 1 h gave the crude product which did not contain the desired product (by ^{1} H NMR spectroscopy).

Lab Book Reference: **NS6-16**

2-((1-(Dimethyl(phenyl)silyl)vinyl)thio)ethan-1-ol **459**

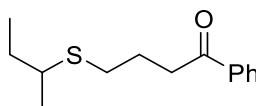


459

Using general procedure M, 1,4-oxathiane **457** (104 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at -40 $^{\circ}$ C for 2 h and PhSiMe₂Cl (340 mg, 331 μ L, 2.0 mmol, 2.0 eq.) at -40 $^{\circ}$ C for 1 h gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-CH₂Cl₂ as eluent gave silane **459** (76 mg, 49%) as a colourless oil, *R*_F (80:20 hexane-CH₂Cl₂) 0.2; IR (ATR) 3069, 2959, 2864, 1585, 1428, 1249, 1212, 1112, 835, 820, 780, 700 cm^{-1} ; ^{1} H NMR (400 MHz, CDCl₃) δ 7.59-7.54 (m, 2H, Ph), 7.38-7.31 (m, 3H, Ph), 4.67 (d, *J* = 2.5 Hz, 1H, C=CH₂), 4.37 (d, *J* = 2.5 Hz, 1H, C=CH₂), 3.80 (t, *J* = 6.0 Hz, 2H, CH₂OH), 2.79-2.72 (m, 2H, SCH₂), 0.40 (s, 6H, SiMe); ^{13} C NMR (100.6 MHz, CDCl₃) δ 167.8 (C=CH₂), 137.1 (*ipso*-Ph), 134.1 (Ph), 129.4 (Ph), 127.9 (Ph), 96.3 (C=CH₂), 68.3 (OCH₂), 24.0 (SCH₂), -3.5 (SiMe).

Lab Book Reference: **NS6-27**

4-(*sec*-Butylthio)-1-phenylbutan-1-one **468**



468

Table 4.4, entry 1:

Using general procedure M, thietane **463** (72 μ L, 74 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μ L, 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 $^{\circ}$ C for 1 h and Weinreb amide **115** (304 μ L, 330 mg, 2.0 eq.) at 0 $^{\circ}$ C

for 1 h gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave keto-sulfide **468** (119 mg, 50%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.4; IR (ATR) 2962, 2924, 2869, 1685 (C=O), 1448, 1222, 1001, 745, 689, 568; ^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, J = 7.5 Hz, 2H, Ph), 7.55 (t, J = 7.5 Hz, 1H, Ph), 7.46 (t, J = 7.5, Hz, 2H, Ph), 3.12 (t, J = 7.0 Hz, 2H, (CH_2CO)), 2.71 (ddq, J = 7.0, 7.0, 7.0 Hz (app sextet), 1H, CHMe), 2.63 (t, J = 7.0 Hz, 2H, SCH_2), 2.07-1.99 (m, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 1.60 (ddq, J = 14.5, 7.0, 7.0 Hz (app septet), 1H, CHHMe), 1.50 (ddq, J = 14.5, 7.0, 7.0 Hz (app septet), 1H, CHHMe), 1.26 (d, J = 7.0 Hz, 3H, CHMe), 0.97 (t, J = 7.0 Hz, 3H, CH_2Me); ^{13}C NMR (100.6 MHz, CDCl_3) δ 199.9 (C=O), 137.0 (*ipso*-Ph), 133.2 (Ph), 128.7 (Ph), 128.2 (Ph), 41.6 (SCH), 37.4 (SCH_2), 29.96 (CH_2), 29.92 (Me), 24.2 (CH_2CO), 20.9 (CH_2), 11.6 (Me); MS (APCI) m/z 259 [$(\text{M} + \text{Na})^+$, 100]; HRMS (APCI) m/z calcd for $\text{C}_{14}\text{H}_{20}\text{OS}$ ($\text{M} + \text{Na})^+$ 259.1127, found 259.1125 (+0.8 ppm error).

Lab Book Reference: **NS6-68**

Table 4.4, entry 2:

Using general procedure M, thietane **463** (72 μL , 74 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at 0 °C for 2 min and Weinreb amide **115** (304 μL , 330 mg, 2.0 eq.) at 0 °C for 1 h gave the crude product which contained keto-sulfide **468** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS6-67**

Table 4.4, entry 3:

Using general procedure M, thietane **463** (72 μL , 74 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at -40 °C for 40 min and Weinreb amide **115** (304 μL , 330 mg, 2.0 eq.) at -40 °C for 1 h gave the crude product which contained keto-sulfide **468** (by ^1H NMR spectroscopy).

Lab Book Reference: **NS6-69**

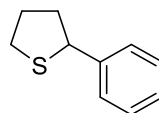
Table 4.4, entry 4:

Using general procedure M, thietane **463** (72 μL , 74 mg, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) and TMEDA (195 μL , 1.3 mmol, 1.3 eq.) in hexane (5 mL) at -78 °C for 1 h and Weinreb amide **115** (304 μL , 330 mg, 2.0 eq.) at

−78 °C for 1 h gave the crude product which contained keto-sulfide **468** (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-70**

Attempted Synthesis of α -Phenyltetrahydrothiophene **470**



470

Using general procedure O, tetrahydrothiophene **25** (154 mg, 1.7 mmol, 1.2 eq.), *s*-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL), ZnCl₂ (1.0 mL of a 1.0 M solution in THF, 1.0 mmol, 0.6 eq.), Pd(OAc)₂ (16 mg, 5 mol%), *t*-Bu₃PHBF₄ (25 mg, 6 mol%), and bromobenzene (153 μ L, 229 mg, 1.5 mmol, 1.0 eq.) in THF (3 mL) at 60 °C gave the crude product which did not contain the desired product (by ¹H NMR spectroscopy).

Lab Book Reference: **NS5-96**

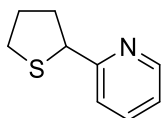
s-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) was added dropwise to a stirred solution of the tetrahydrothiophene **25** (175 μ L, 175 mg, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the resulting solution was cooled to −78 °C and a freshly prepared solution of ZnCl₂ (1.0 mL of a freshly prepared 1.0 M solution in THF, 1.0 mmol, 0.6 eq.) was added. After stirring at −78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, a solution of PPh₃ (23 mg, 5 mol%), Ni-catalyst **479** (10.5 mg, 2 mol%) and 4-chlorobenzene (164 mg, 148 μ L, 1.5 mmol, 1.0 eq.) in THF (3 mL) was added and the mixture was stirred at rt for 16 h. The solids were removed by filtration through Celite[®] and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which did not contain the desired product (by ¹H NMR spectroscopy).

Lab Book Reference: **NS8-9**

s-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) was added dropwise to a stirred solution of the tetrahydrothiophene **25** (175 μ L, 175 mg, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, the resulting solution was cooled to –78 °C and a freshly prepared solution of ZnCl₂ (1.0 mL of a freshly prepared 1.0 M solution in THF, 1.2 mmol, 0.6 eq.) was added. After stirring at –78 °C for 30 min, the mixture was allowed to warm to rt and stirred at rt for additional 30 min. Then, a solution of PPh₃ (23 mg, 5 mol%), Ni-catalyst **479** (10.5 mg, 2 mol%) and 4-chlorobenzene (164 mg, 148 μ L, 1.5 mmol, 1.0 eq.) in THF (3 mL) was added and the mixture was stirred and heated at 60 °C for 16 h. After allowing to cool to rt, the solids were removed by filtration through Celite® and washed with Et₂O (20 mL). The filtrate was washed with brine (15 mL) and water (2 x 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which did not contain the desired product (by ¹H NMR spectroscopy).

Lab Book Reference: **NS8-10**

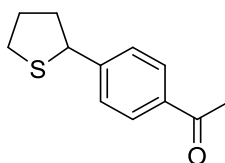
Attempted Synthesis of 2-(tetrahydrothiophen-2-yl)pyridine



Using general procedure O, tetrahydrothiophene **25** (154 mg, 1.7 mmol, 1.2 eq.), *s*-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL), ZnCl₂ (1.0 mL of a 1.0 M solution in THF, 1.0 mmol, 0.6 eq.), Pd(OAc)₂ (16 mg, 5 mol%), *t*-Bu₃PHBF₄ (25 mg, 6 mol%) and 2-bromopyridine (143 μ L, 237 mg, 1.5 mmol, 1.0 eq.) in THF (3 mL) at 60 °C gave the crude product which did not contain the desired product (by ¹H NMR spectroscopy).

Lab Book Reference: **NS5-91**

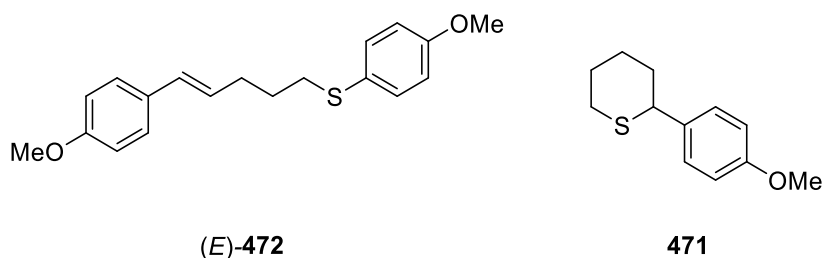
Attempted Synthesis of 1-(4-(tetrahydrothiophen-2-yl)phenyl)ethan-1-one



Using general procedure O, tetrahydrothiophene **25** (154 mg, 1.7 mmol, 1.2 eq.), *s*-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL), ZnCl₂ (1.0 mL of a 1.0 M solution in THF, 1.0 mmol, 0.6 eq.), Pd(OAc)₂ (16 mg, 5 mol%), *t*-Bu₃PHBF₄ (25 mg, 6 mol%) and 4-bromoacetophenone (299 mg, 1.5 mmol, 1.0 eq.) in THF (3 mL) at 60 °C gave the crude product which did not contain the desired product (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-2**

2-(4-Methoxyphenyl)tetrahydro-2*H*-thiopyran **471** and (*E*)-(4-Methoxyphenyl)(4-(4-methoxyphenyl)but-3-en-1-yl)sulfane (*E*)-**472**

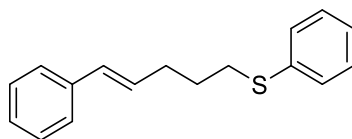


Using general procedure O, tetrahydrothiopyran **25** (175 μ L, 175 mg, 1.7 mmol, 1.2 eq.), *s*-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL), ZnCl₂ (1.0 mL of a freshly prepared 1.0 M solution in THF, 1.0 mmol, 0.6 eq.), Pd(OAc)₂ (16 mg, 5 mol%), *t*-Bu₃PHBF₄ (25 mg, 6 mol%) and 4-bromomethoxybenzene (184 μ L, 275 mg, 1.5 mmol, 1.0 eq.) in THF (3 mL) at 60 °C gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-Et₂O as eluent gave diarylated sulfide (*E*)-**472** (148 mg, 64%) as a white solid, mp 92-94 °C; *R*_F (80:20 hexane-Et₂O) 0.5; IR (ATR) 2935, 2837, 1605, 1510, 1494, 1440, 1244, 1176, 905, 727 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.32 (m, 2H, Ar), 7.29-7.20 (m, 2H, Ar), 6.88-6.78 (m, 4H, Ar), 6.31 (br d, *J* = 16.0 Hz, 1H, CH=CHAr), 6.00 (dt, *J* = 16.0, 7.0 Hz, 1H, CH=CHAr), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.85 (t, *J* = 7.0 Hz, 2H, CH₂), 2.29 (tdd, *J* = 7.0, 7.0, 1.5 Hz (app qd), 2H, CH₂), 1.73 (tt, *J* = 7.0, 7.0 Hz (app p), 2H, CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.9 (*ipso*-Ar), 158.8 (*ipso*-Ar), 133.3 (Ar), 130.6 (*ipso*-Ar),

130.1 (Ar), 127.5 (Ar), 127.2 (Ar), 126.7 (*ipso*-Ar), 114.6 (=CH), 114.0 (=CH), 55.45 (OMe), 55.41 (OMe), 35.4 (SCH₂), 31.9 (CH₂), 29.2 (CH₂); MS (APCI) m/z 315 [(M + H)⁺, 100]; HRMS (ESI) m/z calcd for C₁₉H₂₂O₂S (M + H)⁺ 315.1413, found 315.1415 (−0.6 ppm error) and α -aryl sulfide **471** (27 mg, 9%) as a colourless oil, R_F (80:20 hexane-Et₂O) 0.2; IR (ATR) 2924, 2893, 2837, 1611, 1512, 1249, 1030, 1176, 811, 733, 532 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.21 (m, 2H, Ar), 6.86–6.81 (m, 2H, Ar), 3.80 (dd, J = 11.5, 2.5 Hz, 1H, SCH), 3.78 (s, 3H, OMe), 2.86 (ddd, J = 13.5, 12.5, 2.5 Hz, 1H, CH, SCH), 2.64 (ddd, J = 13.5, 5.0, 3.0 Hz, 1H, SCH), 2.10 (ddd, J = 13.0, 6.5, 3.0 Hz, 1H, CH), 2.04–1.85 (m, 1H, CH), 1.72–1.60 (m, 2H, CH), 1.53–1.39 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.8 (*ipso*-Ar), 135.2 (*ipso*-Ar), 128.6 (Ar), 113.9 (Ar), 55.4 (OMe), 46.8 (SCH), 35.5 (SCH₂), 31.0 (CH₂), 27.2 (CH₂), 26.9 (CH₂); MS (APCI) m/z 209 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₂H₁₆OS (M + H)⁺ 209.0995, found 209.0999 (−2.4 ppm error).

Lab Book Reference: **NS8-1**

(*E*)-Phenyl(5-phenylpent-4-en-1-yl)sulfane (*E*)-474

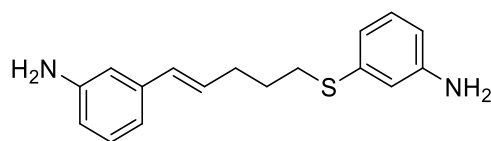


(*E*)-474

Using general procedure O, tetrahydrothiopyran **25** (175 μ L, 175 mg, 1.7 mmol, 1.2 eq.), *s*-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL), ZnCl₂ (1.0 mL of a freshly prepared 1.0 M solution in THF, 1.0 mmol, 0.6 eq.), Pd(OAc)₂ (16 mg, 5 mol%), *t*-Bu₃PHBF₄ (25 mg, 6 mol%) and bromobenzene (153 μ L, 231 mg, 1.5 mmol, 1.0 eq.) in THF (3 mL) at 60 °C gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-toluene as eluent gave diarylated sulfide (*E*)-**474** (100 mg, 54%) as a colourless oil, R_F (70:30 hexane-toluene) 0.5; IR (ATR) 3057, 3024, 2928, 2847, 1492, 1480, 1267, 1180, 1025, 963, 735, 689, 473 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.23 (m, 8H, Ph), 7.22–7.10 (m, 2H, Ph), 6.39 (d, J = 16.0 Hz, 1H, PhCH=CH), 6.17 (dt, J = 16.0, 7.0 Hz, 1H, PhCH=CH), 2.96 (t, J = 7.5 Hz, 2H, SCH₂), 2.35 (dt, J = 7.0, 7.0 Hz (app q), 2H, CH₂), 1.82 (tt, J = 7.5, 7.5 Hz (app p), 2H, CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 137.7 (*ipso*-Ph), 136.8 (*ipso*-Ph), 130.9 (=CH), 129.5 (Ph), 129.3 (=CH), 129.0 (Ph), 128.7 (Ph), 127.2 (Ph), 126.1 (Ph), 126.0 (Ph), 33.2 (SCH₂), 32.1 (CH₂), 28.9 (CH₂); MS (APCI) m/z 255 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₇H₁₈S (M + H)⁺ 255.1202, found 255.1214 (+4.9 ppm error).

Lab Book Reference: **NS7-84**

(*E*)-3-((5-(3-Aminophenyl)pent-4-en-1-yl)thio)aniline (*E*)-475

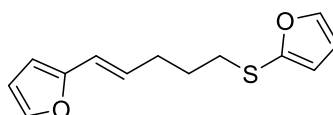


(*E*)-475

Using general procedure O, tetrahydrothiopyran **25** (175 μ L, 175 mg, 1.7 mmol, 1.2 eq.), *s*-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL), ZnCl₂ (1.0 mL of a freshly prepared 1.0 M solution in THF, 1.0 mmol, 0.6 eq.), Pd(OAc)₂ (16 mg, 5 mol%), *t*-Bu₃PHBF₄ (25 mg, 6 mol%) and 3-bromoaniline (159 μ L, 251 mg, 1.5 mmol, 1.0 eq.) in THF (3 mL) at 60 °C gave the crude product. Purification by flash column chromatography on silica with 75:25 hexane-EtOAc as eluent gave diarylated sulfide (*E*)-**475** (141 mg, 68%) as a colourless oil, *R*_F (50:50 hexane-EtOAc) 0.3; IR (ATR) 3429 (NH), 3348 (NH), 3213 (NH), 3023, 2926, 2849, 1616, 1588, 1481, 1439, 1299, 1267, 1165, 968, 770, 686 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.09 (t, *J* = 8.0 Hz, 1H, Ar), 7.06 (t, *J* = 8.0 Hz, 1H, Ar), 6.78-6.71 (m, 2H, Ar), 6.68-6.65 (m, 2H, Ar), 6.55 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar), 6.49 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar), 6.32 (d, *J* = 16.0 Hz, 1H, ArCH=CH), 6.14 (dt, *J* = 16.0, 7.0 Hz, 1H, ArCH=CH), 3.64 (s, 4H, NH₂), 2.93 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.33 (dt, *J* = 7.0, 7.0 Hz (app q), 2H, CH₂), 1.82 (tt, *J* = 7.0, 7.0 Hz (app p), 1H, CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 146.9 (*ipso*-Ar), 146.6 (*ipso*-Ar), 138.8 (*ipso*-Ar), 137.6 (*ipso*-Ar), 130.9 (=CH), 129.8 (=CH), 129.5 (Ar), 129.4 (Ar), 119.1 (Ar), 116.8 (Ar), 115.3 (Ar), 114.1 (Ar), 112.9 (Ar), 112.6 (Ar), 32.8 (SCH₂), 31.9 (CH₂), 28.9 CH₂; MS (ESI) *m/z* 285 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₇H₂₀N₂S (M + H)⁺ 285.1416, found 285.1420 (+1.3 ppm error).

Lab Book Reference: **NS7-85**

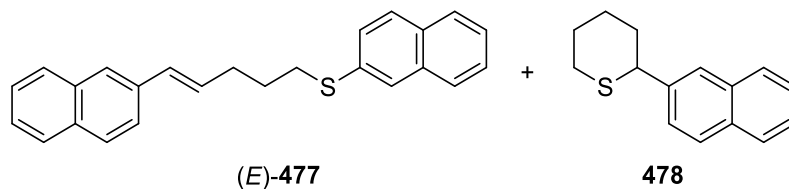
(*E*)-2-((5-(Furan-2-yl)pent-4-en-1-yl)thio)furan (*E*)-476



(*E*)-476

Using general procedure O, tetrahydrothiopyran **25** (175 μ L, 175 mg, 1.7 mmol, 1.2 eq.), *s*-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 21.2eq.) and TMEDA (263 μ L,

(E)-Naphthalen-2-yl(5-(naphthalen-2-yl)pent-4-en-1-yl)sulfane (E)-477 and 2-(Naphthalen-2-yl)tetrahydro-2H-thiopyran 478

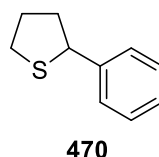


Using general procedure O, tetrahydrothiopyran **140** (175 μ L, 175 mg, 1.7 mmol, 1.2 eq.), *s*-BuLi (1.35 mL of a 1.3 M solution in hexane, 1.7 mmol, 1.2 eq.) and TMEDA (263 μ L, 1.7 mmol, 1.2 eq.) in hexane (3 mL), ZnCl₂ (1.0 mL of a freshly prepared 1.0 M solution in THF, 1.0 mmol, 0.6 eq.), Pd(OAc)₂ (16 mg, 5 mol%), *t*-Bu₃PHBF₄ (25 mg, 6 mol%) and 2-bromonaphthalene (304 mg, 1.5 mmol, 1.0 eq.) in THF (3 mL) at 60 °C gave the crude product which contained a 50:50 mixture (by ¹H NMR spectroscopy) of diarylated sulfide (*E*)-**477** and α -arylated sulfide **478**. Purification by flash column chromatography on silica with 80:20 toluene-hexane as eluent gave a 50:50 mixture of diarylated sulfide (*E*)-**477** and α -aryl sulfide **478** (144 mg, i.e. 56 mg, (17%) of **477** and 88 mg (34%) of (*E*)-**478**) as a white solid mp 92-94 °C; *R*_F (80:20 toluene-hexane) 0.5; ¹H NMR (400 MHz, CDCl₃): δ 7.84-7.71 (m, 5.5H, Ar), 7.66 (d, *J* = 1.5 Hz, 0.5H, Ar), 7.57 (dd, *J* = 8.5, 1.5 Hz, 0.5H, Ar), 7.51 (dd, *J* = 8.5, 1.5 Hz, 0.5H, Ar), 7.50-7.40 (m, 3.5H, Ar), 6.58 (d, *J* = 16.0 Hz, 0.5H, =CH), 6.33 (d, *J* = 16.0, 7.0 Hz, 0.5H, =CH), 4.04 (dd, *J* = 11.5, 2.5 Hz, 0.5H, SCH), 3.11 (t, *J* = 7.5 Hz,

1H, CH₂), 2.94 (ddd, $J = 13.5, 12.5, 2.5$ Hz, 0.5H, SCH), 2.78-2.69 (m, 0.5H, SCH), 2.46 (dt, $J = 7.5, 7.0$ Hz, 1H, CH₂), 2.30-2.19 (m, 0.5H, CH), 2.12-2.03 (m, 1.5H, CH), 1.93 (tt, $J = 7.5, 7.0$ Hz, 1H, CH₂), 1.81-1.67 (m, 0.5H, CH), 1.59-1.51 (m, 0.5H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 140.5 (*ipso*-Ar), 135.1 (*ipso*-Ar), 134.3 (*ipso*-Ar), 133.9 (*ipso*-Ar), 133.8 (*ipso*-Ar), 133.6 (*ipso*-Ar), 132.92 (*ipso*-Ar), 132.90 (*ipso*-Ar), 131.8 (*ipso*-Ar), 131.1 (=CH), 129.9 (=CH), 128.5 (Ar), 128.3 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.75 (Ar), 127.73 (Ar), 127.5 (Ar), 127.2 (Ar), 126.9 (Ar), 126.6 (Ar), 126.3 (Ar), 126.2 (Ar), 126.1 (Ar), 126.0 (Ar), 125.9 (Ar), 125.7 (Ar), 125.7 (Ar), 123.6 (Ar), 47.6 (SCH), 35.3 (SCH₂), 33.0 (SCH₂), 32.1 (CH₂), 31.0 (CH₂), 28.9 (CH₂), 27.1 (CH₂), 26.9 (CH₂) (two Ar resonances not resolved); MS for **478** (APCI) m/z 229 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₅H₁₆S (M + H)⁺ 229.1045, found 274.1408 (+1.3 ppm error); MS for **477** (APCI) m/z 355 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₂₅H₂₂S (M + H)⁺ 355.1498, found 355.1514 (+4.9 ppm error).

Lab Book Reference: **NS8-4**

α -Phenyltetrahydrothiophene 470

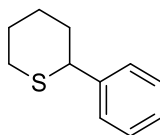


Using general procedure P, tetrahydrothiophene **25** (50 μ L, 0.50 mmol, 1.0 eq.), *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) and TMEDA (97 μ L, 0.65 mmol, 1.3 eq.) in hexane (2.5 mL) at 0 °C for 1 h, CuCN·2LiCl (1.30 mL of a 0.5 M solution in THF, 0.65 mmol, 1.3 eq.) and Ph₂IPF₆ (277 mg, 0.65 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with hexane then 90:10 hexane-CH₂Cl₂ gave α -phenyl sulfide **470** (44 mg, 53%) as a colourless oil, R_F (80:20 hexane-CH₂Cl₂) 0.5; IR (ATR) 3026, 2945, 2859, 1490, 1451, 1440, 1260, 1156, 1099, 758, 697, 521 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.39 (m, 2H, Ph), 7.33-7.28 (m, 2H, Ph), 7.25-7.18 (m, 1H, Ph), 4.52 (dd, $J = 8.5, 6.0$ Hz, 1H, SCH), 3.16 (ddd, $J = 10.5, 8.5, 6.5$ Hz, 1H, SCH), 3.02 (ddd, $J = 10.5, 6.5, 4.0$ Hz, 1H, SCH), 2.43-2.35 (m, 1H, CH), 2.32-2.24 (m, 1H, CH), 2.07-1.88 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.1 (*ipso*-Ph), 128.5 (Ph), 127.8 (Ph), 127.1 (Ph), 52.9 (SCH), 40.7 (SCH₂), 33.6 (CH₂), 31.2 (CH₂); MS (APCI) m/z 165 [(M + H)⁺, 100]; HRMS (APCI) m/z calcd for C₁₀H₁₂S (M + H)⁺ 165.0732,

found 165.0729 (−2.3 ppm error). Spectroscopic data consistent with those reported in the literature.²²³

Lab Book Reference: **NS7-18**

2-Phenyltetrahydro-2H-thiopyran **480**

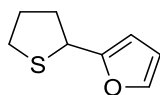


480

Using general procedure P, tetrahydrothiopyran **25** (50 μ L, 0.50 mmol, 1.0 eq.), *s*-BuLi (0.76 mL of a 1.3 M solution in hexane, 1.0 mmol, 2.0 eq.) and TMEDA (150 μ L, 1.0 mmol, 2.0 eq.) in hexane (2.5 mL) at 0 °C for 2 h, CuCN·2LiCl (2.40 mL of a 0.5 M solution in THF, 1.2 mmol, 2.4 eq.) and Ph₂IPF₆ (511 mg, 1.2 mmol, 2.4 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-CH₂Cl₂ as eluent gave α -phenyl sulfide **480** (45 mg, 50%) as a colourless oil, *R*_F (90:10 hexane-CH₂Cl₂) 0.2; IR (ATR) 3028, 2926, 2847, 1491, 1451, 1439, 1260, 886, 756, 697, 607, 517 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.27 (m, 4H, Ph), 7.24-7.20 (m, 1H, Ph), 3.84 (dd, *J* = 11.5, 2.5 Hz, 1H, SCH), 2.87 (ddd, *J* = 13.5, 12.5, 2.5 Hz, 1H, SCH), 2.66 (ddd, *J* = 13.5, 3.5, 2.5 Hz, 1H, SCH), 2.19-2.07 (m, 1H, CH), 2.04-1.88 (m, 3H, CH), 1.73-1.61 (m, 1H, CH), 1.52-1.41 (m, 1H, CH).; ¹³C NMR (100.6 MHz, CDCl₃) δ 143.1 (*ipso*-Ph), 128.7 (Ph), 127.6 (Ph), 127.4 (Ph), 47.6 (SCH), 35.3 (SCH₂), 31.0 (CH₂), 27.2 (CH₂), 26.9 (CH₂); MS (ESI) *m/z* 179 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₄ (M + H)⁺ 179.0889, found 179.0888 (−0.7 ppm error). Spectroscopic data consistent with those reported in the literature.²²⁴

Lab Book Reference: **NS10-49**

2-(Tetrahydrothiophen-2-yl)furan **481**



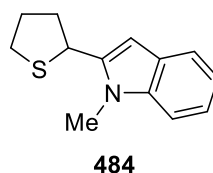
481

n-BuLi (261 μ L of a 2.3 M solution in hexane, 0.60 mmol, 1.2 eq.) was added dropwise to a stirred solution of furan (44 μ L, 41 mg, 0.60 mmol, 1.2 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 1 h. Then, the solution was cooled to −78 °C and a solution of boronic ester **394** (1.0 mL of a 0.5 M solution in THF, 0.50 mmol, 1.0 eq.) was added dropwise. The resulting solution was stirred at

–78 °C for 1 h. Then, a solution of NBS (2.0 mL of a 0.6 M solution in THF, 1.2 mmol, 2.4 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 1 h. Saturated Na₂S₂O_{3(aq)} (2 mL) was added and the mixture was stirred at –78 °C for 5 min and then allowed to warm to rt. Et₂O (10 mL) and H₂O (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (2 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 hexane-CH₂Cl₂ as eluent gave α-furanyl sulfide **481** (32 mg, 42%) as a colourless oil, *R*_F (95:5 hexane-CH₂Cl₂) 0.4; IR (ATR) 2925, 2855, 1739, 1504, 1442, 1262, 1073, 1009, 804, 733 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.30 (m, 1H, Ar), 6.28 (dd, *J* = 3.5, 2.0 Hz, 1H, Ar), 6.17 (d, *J* = 3.5 Hz, 1H, Ar), 4.55 (dd, *J* = 6.0, 6.0 Hz (app t), 1H, SCH), 3.08 (ddd, *J* = 10.0, 7.0, 6.5 Hz, 1H, SCH), 3.08 (ddd, *J* = 10.0, 5.5, 5.5 Hz (app dt), 1H, SCH), 2.31-2.12 (m, 3H, CH), 2.11-1.97 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.3 (*ipso*-Ar), 142.0 (Ar), 110.3 (Ar), 105.8 (Ar), 44.6 (SCH), 36.6 (CH₂), 33.2 (CH₂), 30.8 (CH₂); MS (APCI) *m/z* 155 [(M + H)⁺, 100]; HRMS (APCI) *m/z* calcd for C₈H₁₀OS (M + H)⁺ 155.0525, found 155.0519 (+3.9 ppm error). Spectroscopic data consistent with those reported in the literature.²²⁵

Lab Book Reference: **NS5-84**

1-Methyl-2-(tetrahydrothiophen-2-yl)-1*H*-indole **484**

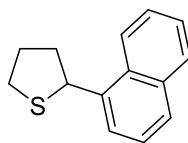


n-BuLi (173 μL of a 2.3 M solution in hexane, 0.40 mmol, 1.6 eq.) was added dropwise to a stirred solution of *N*-methyl indole (50 μL, 52 mg, 0.40 mmol, 1.6 eq.) in THF (2 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3 h. Then, the solution was cooled to –78 °C and a solution of boronic ester **394** (1 mL of a 0.25 M solution in THF, 0.25 mmol, 1.0 eq.) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of NBS (1 mL of a 0.6 M solution in THF, 0.60 mmol, 2.4 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 1 h. Saturated Na₂S₂O_{3(aq)} (2 mL) was added and the mixture was stirred at –78 °C for 5 min and then allowed to warm to rt. EtOAc (10 mL) and H₂O (15 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were

dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 hexane-Et₂O as eluent gave 2-indolyl sulfide **484** (21 mg, 38%) as a colourless oil, *R*_F (50:50 hexane-EtOAc) 0.8; IR (ATR) 3050, 2925, 2855, 1548, 1471, 1329, 1233, 1013, 761, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 7.5 Hz, 1H, Ar), 7.28 (d, *J* = 7.5 Hz, 1H, Ar), 7.22 (dd, *J* = 7.5, 7.5 Hz (app t), 1H, Ar), 7.12 (dd, *J* = 7.5, 7.5 Hz (app t), 1H, Ar), 7.06 (s, 1H, Ar), 4.85 (dd, *J* = 7.5, 7.5 Hz (app t), 1H, SCH), 3.74 (s, 3H, NMe), 3.15 (ddd, *J* = 10.5, 7.5, 6.5 Hz, 1H, SCH), 3.01 (ddd, *J* = 10.5, 7.5, 5.0 Hz, 1H, SCH), 2.44-2.34 (m, 1H, CH), 2.30-1.99 (m, 3H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 137.6 (*ipso*-Ar), 126.9 (*ipso*-Ar), 126.6 (Ar), 121.9 (Ar), 119.6 (Ar), 119.0 (Ar), 116.7 (*ipso*-Ar), 109.5 (Ar), 44.5 (SCH₂), 38.7 (SCH), 33.0 (NMe), 32.8 (CH₂), 30.8 (CH₂); MS (ESI) *m/z* 218 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₃H₁₅NS (M + H)⁺ 218.0998, found 218.1005 (−3.3 ppm error). Spectroscopic data consistent with those reported in the literature.²²⁵

Lab Book Reference: **NS6-48**

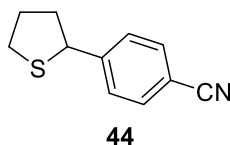
Attempted Synthesis of 2-(Naphthalen-1-yl)tetrahydrothiophene **485**



485

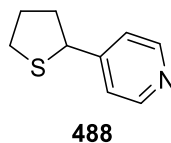
n-BuLi (139 μL of a 2.3 M solution in hexane, 0.30 mmol, 1.2 eq.) was added dropwise to a stirred solution of 1-bromonaphthalene (57 μL, 83 mg, 0.30 mmol, 1.2 eq.) in THF (2 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3 h. Then, the solution was cooled to −78 °C and a solution of boronic ester **394** (1 mL of a 0.25 M solution in THF, 0.25 mmol, 1.0 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 1 h. Then, a solution of NBS (1 mL of a 0.6 M solution in THF, 0.60 mmol, 2.4 eq.) was added dropwise and the resulting solution was stirred at −78 °C for 1 h. Saturated Na₂S₂O_{3(aq)} (2 mL) was added and the mixture was stirred at −78 °C for 5 min and then allowed to warm to rt. EtOAc (10 mL) and H₂O (15 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which did not contain the desired product (by ¹H NMR spectroscopy).

Lab Book Reference: **NS6-49**

4-(Tetrahydrothiophen-2-yl)benzonitrile 44

Using general procedure Q, Ir(*p*-F-ppy)₃ **486** (2.1 mg, 2.4 μmol, 0.02 eq.), carboxylic acid **390** (48 mg, 0.36 mmol, 3.0 eq.), CsF (55 mg, 0.4 mmol, 3.0 eq.) and 1,4-dicyanobenzene (17 mg, 0.12 mmol, 1.0 eq.) in DMSO (6 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave α-aryl sulfide **44** (16 mg, 71%) as a colourless oil, *R*_F (95:5 hexane-EtOAc) 0.2; IR (ATR) 2949, 2862, 2227 (CN), 1606, 1502, 1414, 1264, 910, 839, 822, 731, 560 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 8.5 Hz, 2H, Ar), 7.52 (d, *J* = 8.5 Hz, 2H, Ar), 4.51 (dd, *J* = 8.0, 6.5 Hz, 1H, SCH), 3.17 (ddd, *J* = 10.0, 8.5, 6.5 Hz, 1H, SCH), 3.03 (ddd, *J* = 10.0, 8.5, 6.5 Hz, 1H, SCH), 2.42 (dddd, *J* = 11.5, 8.5, 8.0, 5.0 Hz, 1H, CH), 2.25 (dddd, *J* = 10.0, 8.5, 8.0, 5.0 Hz, 1H, CH), 2.09-1.96 (m, 1H, CH), 1.94-1.83 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 149.0 (*ipso*-Ar), 132.3 (Ar), 128.6 (Ar), 119.0 (*ipso*-Ar), 110.8 (CN), 52.3 (SCH), 40.6 (CH₂), 33.8 (CH₂), 31.2 (CH₂); MS (ESI) *m/z* 190 [(M + H)⁺, 100]; HRMS (ESI) *m/z* calcd for C₁₁H₁₁NS (M + H)⁺ 190.0685, found 190.0688 (−1.7 ppm error). Spectroscopic data consistent with those reported in the literature.⁵⁷

Lab Book Reference: **NS4-75**

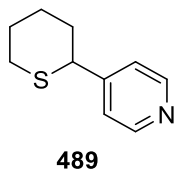
4-(Tetrahydrothiophen-2-yl)pyridine 488

Using general procedure Q, Ir(*p*-F-ppy)₃ **486** (2.1 mg, 2.4 μmol, 0.02 eq.), carboxylic acid **390** (48 mg, 0.36 mmol, 3.0 eq.), CsF (55 mg, 0.40 mmol, 3.0 eq.) and 4-cyanopyridine (12.5 mg, 0.12 mmol, 1.0 eq.) in DMSO (6 mL) gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave α-aryl sulfide **488** (14 mg, 69%) as a colourless oil, *R*_F (70:30 hexane-EtOAc) 0.2; IR (ATR) 2949, 1597, 1441, 1412, 993, 810, 543 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.53-8.50 (m, 2H, Ar), 7.35-7.31 (m, 2H, Ar), 4.44 (dd, *J* = 8.0, 6.0 Hz, 1H, SCH), 3.14 (ddd, *J* = 10.5, 8.5, 6.5 Hz, 1H, SCH), 3.02 (ddd, *J* = 10.5, 6.5, 4.5 Hz, 1H, SCH), 2.41 (dddd, *J* = 11.0, 8.5, 8.0, 5.0 Hz, 1H,

CH), 2.22 (dddd, $J = 11.0, 8.5, 8.0, 6.0$ Hz, 1H, CH), 2.07-1.97 (m, 1H, CH), 1.95-1.85 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 152.7 (*ipso*-Ar), 149.9 (Ar), 123.0 (Ar), 51.5 (SCH), 40.1 (CH_2), 33.7 (CH_2), 31.1 (CH_2); MS (ESI) m/z 166 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_9\text{H}_{11}\text{NS}$ ($\text{M} + \text{H})^+$ 166.0685, found 166.0685 (−0.1 ppm error).

Lab Book Reference: **NS4-83**

4-(Tetrahydro-2H-thiopyran-2-yl)pyridine **489**



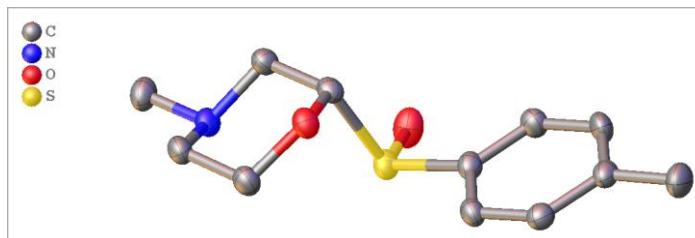
Using general procedure Q, $\text{Ir}(p\text{-F-ppy})_3$ **486** (3 mg, 3.4 μmol , 0.02 eq.), carboxylic acid **414** (75 mg, 0.51 mmol, 3.0 eq.), CsF (78 mg, 0.51 mmol, 3.0 eq.) and 4-cyanopyridine (18 mg, 0.17 mmol, 1.0 eq.) in DMSO (6 mL) gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave α -aryl sulfide **489** (12 mg, 39%) as a white solid, mp 84-86 °C, R_f (70:30 hexane-EtOAc) 0.2; IR (ATR) 2930, 2856, 2812, 2765, 1594, 1438, 1355, 1264, 1150, 1035, 911, 803, 609, 539 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.54 (br d, $J = 3.5$ Hz, 2H, Ar), 7.29-7.24 (m, 2H, Ar), 3.81 (dd, $J = 11.5, 2.5$ Hz, 1H, SCH), 2.87 (ddd, $J = 13.0, 12.5, 3.0$ Hz, 1H, SCH), 2.69 (ddd, $J = 13.0, 3.0, 3.0$ Hz (app dt), 1H, SCH), 2.13 (ddd, $J = 13.0, 7.0, 3.5$ Hz, 1H, CH), 2.07-1.97 (m, 2H, CH), 1.90 (dddd, $J = 13.0, 13.0, 11.5, 3.5$ Hz (app tdd), 1H, CH), 1.75-1.61 (m, 1H, CH), 1.55-1.42 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 151.7 (*ipso*-Ar), 150.1 (Ar), 122.8 (Ar), 46.3 (SCH), 34.4 (CH_2), 30.6 (CH_2), 26.7 (CH_2), 26.6 (CH_2); MS (ESI) m/z 180 $[(\text{M} + \text{H})^+, 100]$; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{13}\text{NS}$ ($\text{M} + \text{H})^+$ 180.0841, found 180.0843 (−0.8 ppm error).

Lab Book Reference: **NS5-26**

Appendix

X-ray Crystallography Data

Compound (S,S₅)-283, paob1816



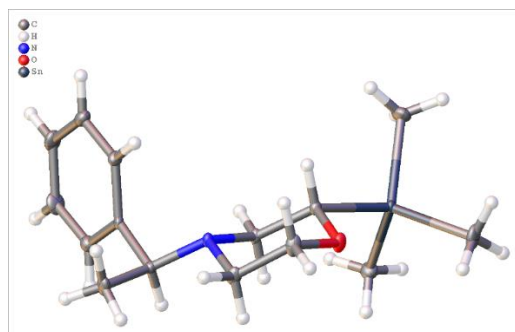
Crystal data and structure refinement for paob1816.

Identification code	paob1816
Empirical formula	C ₁₂ H ₁₇ NO ₂ S
Formula weight	239.32
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	P2 ₁
a/Å	8.9986(3)
b/Å	6.2688(3)
c/Å	10.8971(4)
α/°	90
β/°	102.123(3)
γ/°	90
Volume/Å ³	601.00(4)
Z	2
ρ _{calc} /g/cm ³	1.322
μ/mm ⁻¹	2.277
F(000)	256.0
Crystal size/mm ³	0.211 × 0.066 × 0.031
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	8.3 to 134.078

Index ranges	$-10 \leq h \leq 9, -7 \leq k \leq 7, -12 \leq l \leq 13$
Reflections collected	6406
Independent reflections	2107 [$R_{\text{int}} = 0.0340, R_{\text{sigma}} = 0.0339$]
Data/restraints/parameters	2107/1/147
Goodness-of-fit on F^2	1.055
Final R indexes [$I > 2\sigma(I)$]	$R_1 = 0.0379, wR_2 = 0.0949$
Final R indexes [all data]	$R_1 = 0.0393, wR_2 = 0.0966$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.43/-0.17
Flack parameter	-0.06(2)

Data collected, solved and refined by Adrian C Whitwood

Compound (S,S)-300, paob1922



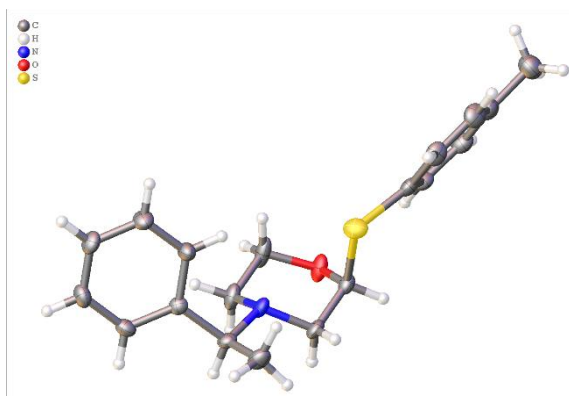
Crystal data and structure refinement for paob1922.

Identification code	paob1922
Empirical formula	$\text{C}_{15}\text{H}_{25}\text{NOSn}$
Formula weight	354.05
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
$a/\text{\AA}$	9.71622(12)
$b/\text{\AA}$	8.99916(12)
$c/\text{\AA}$	18.4738(2)
$\alpha/^\circ$	90
$\beta/^\circ$	104.1085(12)

$\gamma/^{\circ}$	90
Volume/ $\text{\AA}^3$	1566.59(3)
Z	4
$\rho_{\text{calc}}/\text{g/cm}^3$	1.501
μ/mm^{-1}	12.879
F(000)	720.0
Crystal size/ mm^3	$0.309 \times 0.252 \times 0.153$
Radiation	$\text{CuK}\alpha$ ($\lambda = 1.54184$)
2Θ range for data collection/ $^{\circ}$	9.386 to 142.18
Index ranges	$-11 \leq h \leq 11, -9 \leq k \leq 10, -22 \leq l \leq 22$
Reflections collected	12593
Independent reflections	2995 [$R_{\text{int}} = 0.0258, R_{\text{sigma}} = 0.0188$]
Data/restraints/parameters	2995/0/167
Goodness-of-fit on F^2	1.103
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0265, wR_2 = 0.0702$
Final R indexes [all data]	$R_1 = 0.0269, wR_2 = 0.0705$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.83/-1.66

Data collected and refined by Theo Tanner

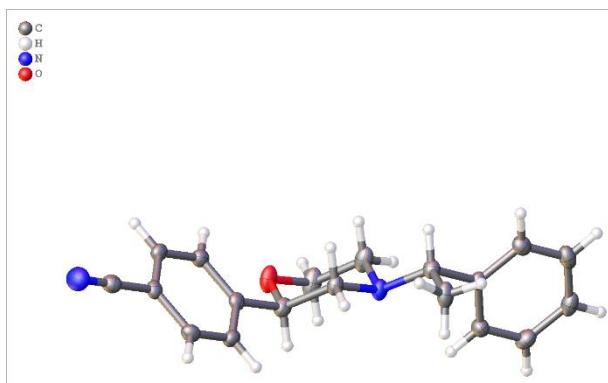
Compound (S,Ss)-306, paob2002a



Crystal data and structure refinement for paob2002a.

Identification code	paob2002a
Empirical formula	$\text{C}_{19}\text{H}_{23}\text{NOS}$

Formula weight	313.44
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	P2 ₁
a/Å	10.6657(4)
b/Å	6.1824(3)
c/Å	13.0383(5)
$\alpha/^\circ$	90
$\beta/^\circ$	100.563(4)
$\gamma/^\circ$	90
Volume/Å ³	845.18(6)
Z	2
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.232
μ/mm^{-1}	1.697
F(000)	336.0
Crystal size/mm ³	0.273 × 0.19 × 0.102
Radiation	CuK α (λ = 1.54184)
2 Θ range for data collection/ $^\circ$	8.434 to 141.92
Index ranges	-12 ≤ h ≤ 12, -7 ≤ k ≤ 6, -15 ≤ l ≤ 15
Reflections collected	6748
Independent reflections	2957 [R_{int} = 0.0257, R_{sigma} = 0.0316]
Data/restraints/parameters	2957/1/201
Goodness-of-fit on F ²	1.040
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0302, wR_2 = 0.0745
Final R indexes [all data]	R_1 = 0.0323, wR_2 = 0.0760
Largest diff. peak/hole / e Å ⁻³	0.17/-0.20
Flack parameter	0.005(14)
Data collected and refined by Theo Tanner	

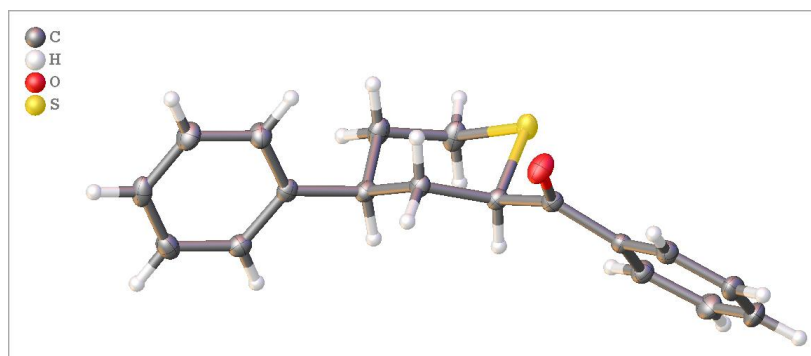
Compound (S,R)-333, paob1925**Crystal data and structure refinement for paob1925.**

Identification code	paob1925
Empirical formula	C ₁₉ H ₂₀ N ₂ O
Formula weight	292.37
Temperature/K	110.00(10)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	5.31585(17)
b/Å	8.1969(2)
c/Å	37.2525(12)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/Å ³	1623.21(9)
Z	4
$\rho_{\text{calc}}/\text{g cm}^{-3}$	1.196
μ/mm^{-1}	0.584
F(000)	624.0
Crystal size/mm ³	0.26 × 0.132 × 0.119
Radiation	CuK α (λ = 1.54184)
2 θ range for data collection/ $^\circ$	9.496 to 142.382
Index ranges	-6 ≤ h ≤ 6, -7 ≤ k ≤ 9, -45 ≤ l ≤ 31
Reflections collected	5801
Independent reflections	3050 [R_{int} = 0.0261, R_{sigma} = 0.0360]

Data/restraints/parameters	3050/0/200
Goodness-of-fit on F^2	1.086
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0360$, $wR_2 = 0.0893$
Final R indexes [all data]	$R_1 = 0.0410$, $wR_2 = 0.0933$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.12/-0.18
Flack parameter	0.1(2)

Data Collected and refined by Theo Tanner

Compound *cis*-443 paob1707



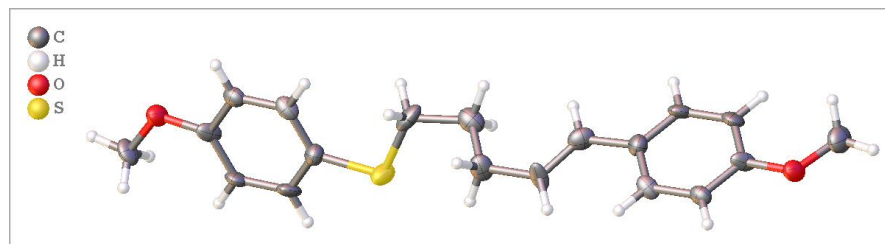
Crystal data and structure refinement for paob1707.

Identification code	paob1707
Empirical formula	$C_{18}H_{18}OS$
Formula weight	282.38
Temperature/K	110.05(10)
Crystal system	triclinic
Space group	P-1
$a/\text{\AA}$	5.7160(3)
$b/\text{\AA}$	10.3831(6)
$c/\text{\AA}$	12.6364(6)
$\alpha/^\circ$	99.392(4)
$\beta/^\circ$	92.292(4)
$\gamma/^\circ$	98.711(4)
Volume/ $\text{\AA}^3$	729.76(7)
Z	2

$\rho_{\text{calc}}/\text{cm}^3$	1.285
μ/mm^{-1}	1.892
F(000)	300.0
Crystal size/ mm^3	$0.302 \times 0.255 \times 0.059$
Radiation	$\text{CuK}\alpha$ ($\lambda = 1.54184$)
2 Θ range for data collection/ $^\circ$	7.106 to 134.11
Index ranges	$-6 \leq h \leq 6, -12 \leq k \leq 12, -14 \leq l \leq 15$
Reflections collected	10400
Independent reflections	2594 [$R_{\text{int}} = 0.0188, R_{\text{sigma}} = 0.0151$]
Data/restraints/parameters	2594/0/182
Goodness-of-fit on F^2	1.036
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0274, wR_2 = 0.0693$
Final R indexes [all data]	$R_1 = 0.0292, wR_2 = 0.0707$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.25/-0.18

Data collected, solved and refined by Adrian C Whitwood

Compound 472, paob1810



Crystal data and structure refinement for paob1810.

Identification code	paob1810
Empirical formula	$\text{C}_{19}\text{H}_{22}\text{O}_2\text{S}$
Formula weight	314.42
Temperature/K	110.00(10)
Crystal system	orthorhombic
Space group	Pbcn
$a/\text{\AA}$	35.4840(11)
$b/\text{\AA}$	7.46090(19)

$c/\text{\AA}$	6.23047(14)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/ $\text{\AA}^3$	1649.47(8)
Z	4
$\rho_{\text{calc}}/\text{g/cm}^3$	1.266
μ/mm^{-1}	1.770
F(000)	672.0
Crystal size/ mm^3	$0.238 \times 0.149 \times 0.036$
Radiation	CuK α ($\lambda = 1.54184$)
2 Θ range for data collection/ $^\circ$	9.97 to 134.154
Index ranges	$-42 \leq h \leq 42, -8 \leq k \leq 6, -7 \leq l \leq 5$
Reflections collected	9877
Independent reflections	1474 [$R_{\text{int}} = 0.0683, R_{\text{sigma}} = 0.0295$]
Data/restraints/parameters	1474/15/135
Goodness-of-fit on F^2	1.170
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0891, wR_2 = 0.1704$
Final R indexes [all data]	$R_1 = 0.0912, wR_2 = 0.1712$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.36/-0.35

Data collected, solved and refined by Adrian C Whitwood

The crystal was disordered by a 180 degree rotation about an axis parallel to b. The aromatic rings were constrained to be regular hexagons with C-C bond lengths of 1.39 angstroms. The O-Me bond lengths were restrained to be equal as were the O-C(Ar) bond lengths and the C(Ar)-O-CH₃ distances.

Abbreviations

Ac	Acetyl
acac	Acetylacetone
AIBN	Azobisisobutronitrile
app	apparent
aq.	Aqueous
Ar	Aryl
BHT	Butylhydroxytoluene
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
bp	Boiling point
br	Broad
Bu	Butyl
Cb	Carbamate
Cbz	Benzyl chloroformate
CFL	compact fluorescent lamp
cm ⁻¹	Wave length
CPME	Cyclopentyl methyl ether
CSP-HPLC	Chiral Stationary Phase High Performance Liquid Chromatography
CzIPN	2,4,5,6-Tetra(9 <i>H</i> -carbazol-9- yl)isophthalonitrile
δ	Chemical shift

d	Doublet
DABCO	1,4-Diazabicyclo(2,2,2)octane
DCE	1,2-Dichloroethane
DFT	Density Functional Theory
DHF	2,3-Dihydrofuran
DHP	2,3-Dihdropyran
DIAD	Di- <i>iso</i> -propyl azodicarboxylate
DMAP	Dimethylaminopyridine
DMBP	2,4-dimethylbenzoyl peroxide
DMBS	<i>N,N'</i> -dimethyl bispidine
DMF	Dimethyl formamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyl
DTBP	Di- <i>tert</i> -butylperoxide
E ⁺	Electrophile
ESI	Electrospray Ionisation
eq.	Equivalents
er	Enantiomeric ratio
FDA	Food and Drug Administration
g	Gram(s)
h	Hour(s)
HAT	Hydrogen Atom Transfer

HRMS	High resolution mass
Hz	Hertz
<i>i</i> -Pr	<i>iso</i> -Propyl
IR	Infra-red
<i>J</i>	Coupling constant in Hertz
LED	Light
M	molar
M ⁺	Molecular ion
m	Multiplet
<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrams
min	Minutes
mL	Millilitre
mmol	Millimole
mol	Mole
MOP	2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
mp	Melting point
MS	Mass Spectrometry
<i>m/z</i>	Mass to charge ratio
NCS	<i>N</i> -Chlorosuccinimide
NMR	Nuclear Magnetic Resonance

NOE	Nuclear Overhauser Effect
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
ppm	Parts per million
q	Quartet
R	Alkyl or aryl group
R _F	Retention factor
rt	Room temperature
Ru-Phos	2-Dicyclohexylphosphino-2',6'-di- <i>iso</i> -propoxybiphenyl
s	Singlet
<i>s</i> -Bu	<i>sec</i> -Butyl
S-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SET	Single Electron Transfer
t	Triplet
TBADT	Tetrabutylammonium decatungstate
TBS	<i>tert</i> -Butyldimethylsilyl
Tol	Tolyl
TBHP	<i>tert</i> -Butyl Hydrogen Peroxide
<i>t</i> -Bu	<i>tert</i> -Butyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoro acetic acid

THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Tri- <i>iso</i> -propyl-silane
TLC	Thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylenediamine
Ts	<i>para</i> -Toluenesulfonyl
UV	Ultraviolet
X-Phos	2-(Dicyclohexylphosphino)2',4',6'-tri- <i>iso</i> -propylbiphenyl

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