2,2,5,5-Tetramethyloxolane (TMO): A Green Solvent for Buchwald-Hartwig Aminations and Lithiation-Trapping Reactions of *N*- and *O*-Heterocycles

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Abstract

This thesis describes the application of 2,2,5,5-tetramethyloxolane (TMO), a solvent with a similar property profile to toluene, in Buchwald-Hartwig aminations and lithiation-trapping reactions of *N*- and *O*-heterocycles.

Chapter 2 involves a comparative reaction performance study between TMO and toluene in the synthesis of *N*-arylamines *via* Buchwald-Hartwig cross-coupling. The cross-coupling of aryl bromides with primary and secondary amines with NaO*t*-Bu and Cs_2CO_3 as the base in TMO is demonstrated and the synthesis of a medicinally-relevant molecule is included.

Chapter 3 describes the use of TMO as solvent for lithiation-trapping reactions of *N*-Boc heterocycles. The stability of TMO in the presence of *s*-BuLi is determined and compared against established ether solvent 2-MeTHF. The effect of TMO in enantioselective lithiation-trapping reactions with two chiral ligands is of particular note. Additionally, an exploration into the use of chiral auxiliaries for the diastereoselective lithiation-trapping of *N*-Boc piperazines is carried out.

The use of TMO in the lithiation-transmetallation-arylation of *O*-heterocycles is presented in chapter 4. New lithiation-trapping and Negishi cross-coupling conditions are developed culminating in the one-pot synthesis of α-aryl *O*-heterocycles.

The work contained within this thesis demonstrates the significant promise that TMO offers to replace problematic solvents such as toluene and peroxide forming ether solvents in synthetic organic chemistry.

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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. Part of the work disclosed herein has been published in the following article.

2,2,5,5-Tetramethyloxolane (TMO) as a Solvent for Buchwald-Hartwig Aminations

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Chapter 1: Introduction

1.1 Green Chemistry, Solvent Selection Guides and Green Metrics

The current reliance on petroleum-based resources by the chemical industry is not sustainable considering the diminishing supplies of crude oil[1] and the environmental damage and effects on human health from the usage and disposal of petroleum-based resources. In a typical synthetic reaction, organic solvents are used in considerable excess compared to reactants and reagents. Following the reaction, organic solvents may be required for extraction processes and purification of the products *via* recrystallisation and column chromatography. In turn, this generates significant quantities of solvent waste in the synthesis of fine chemicals and pharmaceutically-relevant compounds. It has been estimated by researchers at GlaxoSmithKline (GSK) that around 85% of the total mass that is used in the synthesis of pharmaceutical products is accounted for by solvents.[2] In many cases solvents are essential for the success of a reaction. Solvents are able to dissolves reactants and reagents generating a homogenous environment to facilitate reactions. Furthermore, solvents can influence reaction rates and stereo- and regioselectivity. Solvents also provide a safety barrier to users by acting as a heat sink and improving the ease of transfers of potentially harmful chemicals.[3] However, many traditional (petroleum-derived) solvents often possess toxic and environmentally damaging traits. The use of solvents on a large scale has driven increased legislation and regulation to limit their detrimental impact on both health and the environment. One example of such solvent is toluene, a non-polar, aprotic, aromatic hydrocarbon solvent which is commonly used in both academia and industry.[4] Toluene was recently added to the REACH (Registration, Evaluation, Authorisation and Restriction of Chemical Substances) restricted substances list as a result of the health hazards it poses. These include reprotoxicity and organ damage.[5,6] Toluene is a petroleum-derived resource as it is synthesised from crude oil *via* the benzene, toluene and xylenes (BTX) process.[7]

With increasing legislation and regulation surrounding the use of traditional solvents, interest in the development of environmentally-friendly solvents with low toxicity profiles has increased considerably. Principle 5 (Safer Solvents and Auxiliaries) of the 12 Principles of Green Chemistry developed by Anastas and Warner introduces the concept of green/safer solvents.[8] It can be further deduced from the 12 Principles that green/safer alternative solvents will ideally be used sparingly (Principle 1: Waste Prevention), improve the safety of a chemical process (Principle 3: Less Hazardous Chemical Synthesis, Principle 4: Designing Safer Chemicals and Principle 12: Inherently Safer Chemistry) and be made from renewable resources (Principle 7: Use of Renewable Feedstocks) .

Solvent selection guides have been developed by Pfizer,[9] GSK,[10,11] Sofani[12] and AstraZeneca (unpublished). These guides help the user in selecting a solvent for a process based on environmental, health and safety impact factors. These guides represent attempts made by the chemical industry to move from using potential harmful solvents to safer and environmentally benign solvents. Pfizer assessed solvents using three general areas; worker safety which took into account carcinogenicity, mutagenicity, reprotoxicity, skin absorption and toxicity; process safety which included flammability, potential for high emissions, potential peroxide formation and odour. Finally, environmental and regulatory considerations were taken into account which included environmental toxicity, regulatory restrictions, effects on ozone depletion and photoreactive potential. After assessment, solvents are then categorised into three distinct groups: Preferred, Usable or Undesirable. Some examples of solvents in these categories are shown in Table 1.1.

Preferred	Usable	Undesirable
water	toluene	Et_2O
ethanol	acetonitrile	chlorinated solvents
ethyl acetate	THF	dioxane
2-propanol	2-MeTHF	NMP

Table 1.1: Solvents in Pfizer solvent selection guide.[9]

GSK developed solvent guides in 2011 and 2016.[10,11] The considerations taken into account included: waste, environmental impact, effect on health, flammability and explosion potential, reactivity and stability, life cycle, regulatory flags and melting and boiling points. Each consideration was then given a score from 1 (major issues) to 10 (few/no issues). Average scores based on all the considerations were not determined as the average score could hide major issues associated with the solvent. Sofani's solvent selection guide[12] ranks solvents based on limits set by the International council for Harmonisation (ICH), health, safety and environmental hazards as well as industrial and legal constraints. These individual considerations are then scored and combined to give a colour coded overall ranking: green (recommended), yellow (substitution advised), red (substitution requested) and brown (banned). These solvent selection guides are useful for chemists in both industry and academia. However, in some cases contradicting results for the same solvent can arise as a result of different criteria being used to formulate each individual guide. For example, acetonitrile is considered recommended in Sofani's guide and usable in Pfizer's guide[9,12] whereas, in GSK's guide, acetonitrile is considered problematic.[10,11] This has the potential to cause confusion when choosing a solvent from a solvent selection guide. Furthermore, neoteric solvents are not added to these guides as they are not updated regularly. This means that the use of potentially safer and more environmentally friendly alternative solvents can be overlooked. The CHEM21 solvent selection guide is an exception to this.[13] The results from the previous guides were compared[14] and the data was compiled to develop a consistent solvent selection guide.[13] Solvents were grouped into four categories: Recommended, Problematic, Hazardous and Highly hazardous. Solvents were scored from 1 to 10, where 10 is the highest hazard, in three criterion: Safety (based on flammability, auto-ignition temperatures, electrostatic charges and potential to form explosive peroxides), Health (based on the hazard statements of individual solvents) and Environment (based on ozone layer depletion, ecotoxicity, bio-accumulation, volatility and recyclability). If a solvent exhibits one score of ≥ 8 or two scores between $7-10$, it is ranked as hazardous; if one score is equal to 7 or two scores from $4-6$, the solvent will be ranked as problematic, otherwise it will be ranked as recommended. Examples of some solvents presented in this guide and relevant to this work are shown in Table 1.2. Water scored 1 in all three of the criteria, ranking it as recommended. On the other hand, Et_2O was ranked as highly hazardous as the solvent scored 10 in safety as a result of its potential to form explosive peroxides, low auto-ignition temperature and high flammability. A score of 3 was given in the health category and 7 in environment. THF scored 6 in safety, 7 in health as it is a potential carcinogen and 5 in environment ranking it as problematic. 2-MeTHF, a bio-derived alternative solvent to THF and Et_2O (*vide infra*) is also classed as problematic scoring 6 in safety, 5 in health and 3 in environment. Finally, toluene scored 5 in safety, 6 in health and 3 in environment ranking the solvent as problematic. Although only a few neoteric solvents have been displayed in the CHEM21 solvent selection guide, the authors have provided a spreadsheet for readers to add newly developed solvents to the guide.[13]

Solvent selection guides are tools that raise awareness for safer solvent use in the chemical industry and help guide chemists to choose alternative solvents over potentially harmful solvents. However, these guides have limitations and can be over-simplified. As such, the user must be observant when using one. For a successful solvent substitution, it is important to consider other factors which may affect a reaction's performance. These include the solubility of reagents in the solvent, physical properties, such as boiling and freezing points (for when reactions are carried out at high or low temperatures), the stability of the solvent under the reaction conditions, how the solvent affects the kinetics and selectivity of a reaction and removal and recyclability of the solvent after use.

Solvent	Safety Score	Health Score	Env. Score	Ranking
Water	1	1	1	Recommended
Et_2O	10	3	7	Highly Hazardous
THF	6	7	5	Problematic
2-MeTHF	6	5	3	Problematic
Toluene	5	6	3	Problematic

Table 1.2: CHEM21 solvent selection guide of select solvents.[13]

Green metrics are often used to look beyond the reaction yield to ascertain the greenness of a synthetic process. Atom economy, a metric developed by Trost in 1991, measures the molar mass of the product(s) over the total molar mass of the starting materials expressed as a percentage (Equation 1.1).[15]

$$AE = \frac{molar\ mass\ of\ product}{\sum molar\ mass\ of\ reactants} \times 100\% \qquad \text{(Equation 1.1)}$$

Atom economy does not consider solvents and auxiliary chemicals, molar excesses or reaction yields. As such, is not a true representation of the wastefulness of a process.

Researchers at GSK provided an alternative metric, Reaction Mass Efficiency (RME), which incorporates the reaction yield into the calculation.[16] RME measures the mass obtained of the desired product over the mass of the all reactants expressed as a percentage (Equation 1.2).

$$RME = \frac{mass\ of\ product}{\sum mass\ of\ reactants} \times 100\% \qquad \text{(Equation 1.2)}$$

Although more insightful than AE, RME does not address the use of solvents used in a process or consider the waste generated in the work-up and purification of the desired product. Environmental factor (E-Factor), developed by Sheldon, is a metric which evaluates the amount of waste produced in a process.[17] E-factor is defined as the total waste produced in the process over total mass of the product (Equation 1.3). Hence, incorporating yield, molar excesses, the amount of solvent that is used and the waste generated *via* work-up and purification.

$$E - Factor = \frac{mass\ of\ waste\ produced}{mass\ of\ product} \qquad \text{(Equation 1.3)}$$

Process mass intensity (PMI) is defined as the total mass of all materials used in a process, including solvents, auxiliaries, work-up and purification materials, over the total mass of the product (Equation 1.4).[18] In a similar way to E-Factor (PMI = E-Factor + 1), this metric takes into account the yield, molar excesses and solvent usage, providing a more accurate insight into the greenness of a reaction.

$$PMI = \frac{\sum mass\ of\ all\ materials}{mass\ of\ product} \qquad \text{(Equation 1.4)}$$

A significant limitation of the metrics described above is their failure to consider the health, safety and environmental concerns of a process. The EcoScale, a metric developed by Van Aken and co-workers, attempts to incorporate ecological and economical parameters in order to ascertain the greenness of a process.[19] Six parameters are taken into account: yield, price of reaction components, safety of materials used, technical set-up, reaction temperature and time and work-up and purification. Depending on the severity of each parameter, penalty points are accrued. For example, crystallisation and filtration is 1 penalty point whereas, flash column chromatography adds 10 penalty points. The sum of all penalties is then taken away from 100 giving the final EcoScale score (Equation 1.5).

$$EcoScale = 100 - sum\ of\ individual\ penalties \qquad \text{(Equation 1.5)}$$

When assessing a chemical process, mass metrics provide a good insight into the greenness of the process. However, there are limitations when just mass metrics are considered. When an alternative solvent is used as a direct replacement for traditional solvents in a reaction, resulting in similar yields from the same amount of solvent, mass metrics do not change, overlooking the health, safety and environment impact of the solvent. However, if the alternative solvent improves solubility of the substrates in the reaction and less is required or a higher yield has been obtained mass metrics will be improved compared to the conventional solvent. In this case, there is merit in using mass metrics. For a clearer understanding of the relative greenness of a process, a combination of mass metrics and the use of solvent selection guides would be favourable.

1.2 Green Solvents

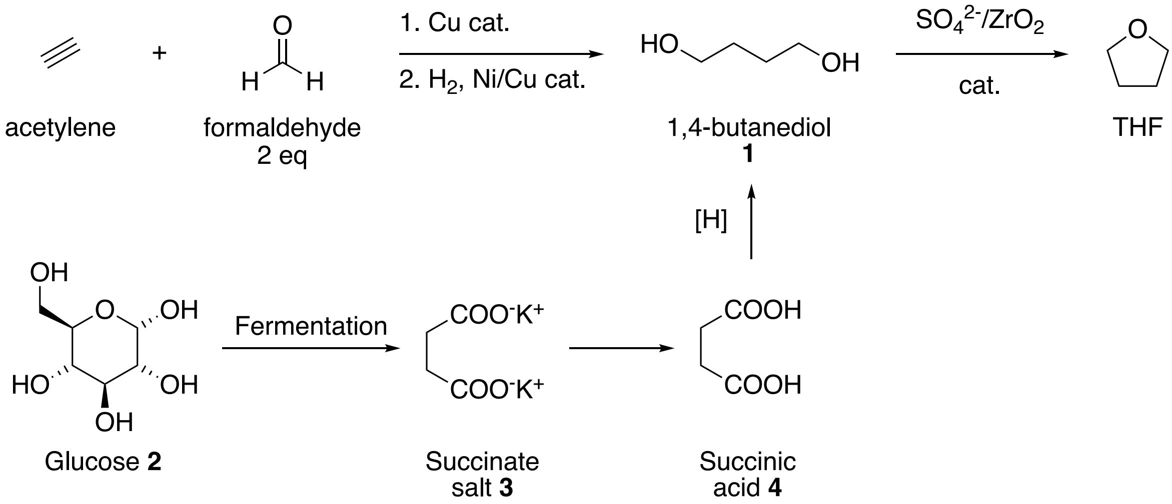
Solvents are an important component in the majority of chemical reactions. As such, performing reactions in the absence of solvents, although possible in some cases, cannot be considered as a sensible solution to the concerns surrounding solvent use in industry and academia. With legislative constraints and restrictions on traditional solvent usage, the development and use of sustainable and safer solvents has increased considerably in recent times with a number of reviews detailing their development and applications.[2,20–22] Gu and Jérôme defined a Green Solvent as a solvent which follows the following 12 criteria. It is unlikely and unrealistic for an alternative solvent to adhere to all of these criteria, as such, these principles are better viewed as a guide for the development of new alternative solvents[23]:

1. Availability: The solvent needs to be consistently available on a large scale.
2. Price: The solvent price must not be volatile and must be competitive with traditional solvents to ensure sustainability of a chemical process.
3. Recyclability: The solvent must be recycled using eco-efficient processes.
4. Grade: Technical grade solvent are preferred so that time and energy consuming purification processes are not required.
5. Synthesis: Preparation of the solvent must be highly atom economic and not involve energy demanding processes.
6. Toxicity: The solvent should exhibit minimal toxicity so that potential risks are limited when used by humans or released into environment.
7. Biodegradability: The solvent should be biodegradable and not produce toxic metabolites.

8. Performance: The solvent must perform similarly or better than conventional solvents in a chemical process.
9. Stability: The solvent must exhibit thermo- and chemical stability.
10. Flammability: A green solvent should not be flammable.
11. Storage: The solvent should be easy to store and follow legislation so that it can be safely transported.
12. Renewability: Renewable resources should preferentially be used for the production of the solvent.

Et_2O and THF are solvents which are routinely used in lithiation-trapping methodologies, a reaction of particular relevance to the work described in this thesis, and many other reactions and applications. These ether solvents possess undesirable and harmful characteristics; hence, their replacement is of particular interest. Et_2O exhibits a low boiling point, is exceedingly volatile, has a low flash point, is very flammable and has the potential to form explosive peroxides.[24] Furthermore, the CHEM21 solvent selection guide considers Et_2O as highly hazardous.[13] As such, Et_2O is generally avoided in an industrial setting but is commonly used in laboratories in academia. Et_2O can be prepared from petroleum-based resources using the Barbet process whereby ethanol is treated with catalytic H_2SO_4.[25] The more common process for Et_2O production is as a by-product of the vapour phase hydration of ethylene to give ethanol.[26] Although not as hazardous as Et_2O, THF exhibits a number of health and safety concerns including flammability, peroxide formation and is also a suspected carcinogen. Moreover, THF exhibits high water solubility, as such, its separation from aqueous waste is poor, thus effecting some practical aspects of its use to chemists.[27] THF is manufactured *via* acid-catalysed ring closure of 1,4-butanediol **1** which can be accessed from the copper-catalysed condensation of acetylene with formaldehyde.

Hydrogenation using a Ni/Cu catalyst provides diol **1** (Scheme 1.1).[28,29] Alternative bio-based methods to access THF and 1,4-butandiol precursor **1** have been achieved on a laboratory scale. However, these processes are yet to become economically viable on an industrial scale.[30] One example of the bio-based synthesis of THF precursor diol **1** involved the production of succinic acid **4** from the fermentation of glucose **2**. The fermentation step requires neutral/mildly acidic conditions; hence, succinic acid **4** must first be neutralised and isolated as succinate salt **3**. Reduction of succinic acid **4** then affords precursor diol **1** (Scheme 1.1).[31]



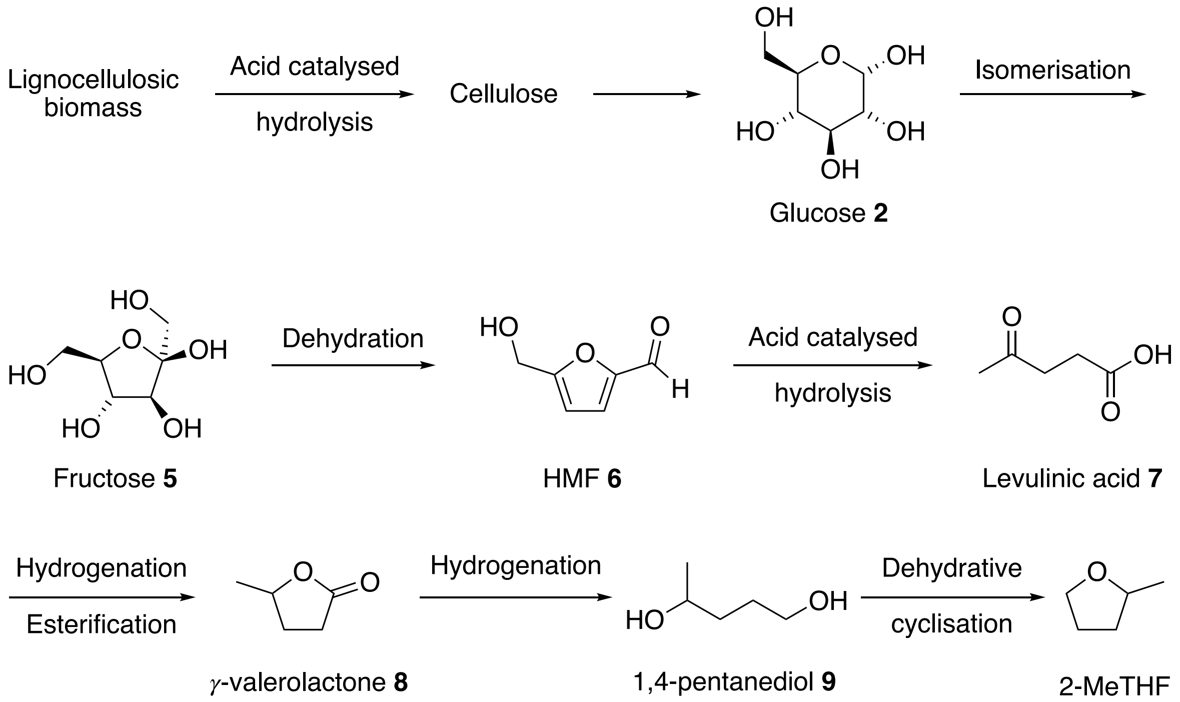
Scheme 1.1: Petroleum- and bio-based routes to THF

Analysis of THF in regard to the 12 criteria of green solvents developed by Gu and Jérôme[23] highlights the concerns associated with this solvent:

- Water solubility of THF means that recyclability (criteria 3) of the solvent can be challenging;
- THF is potentially carcinogenic, and therefore toxicity of the solvent is high (criteria 6);

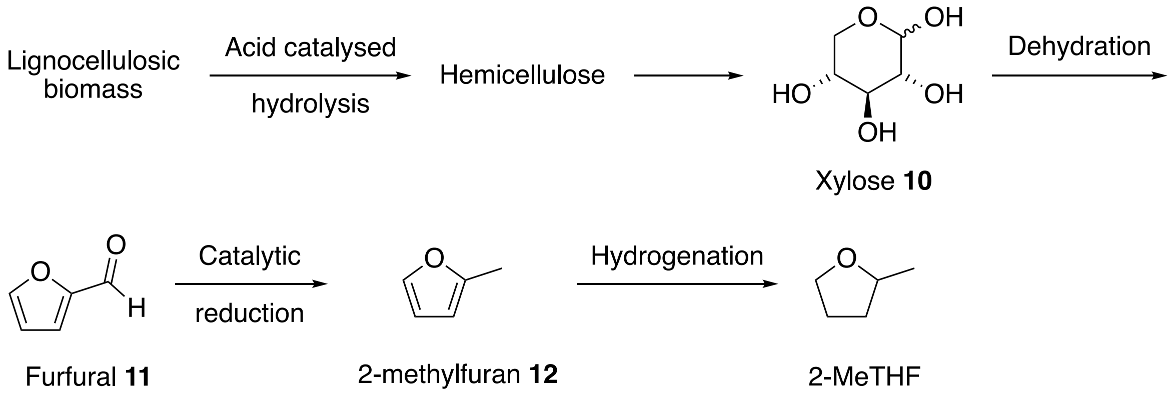
- THF is highly flammable and therefore does not meet the conditions for criteria 10;
- The potential of THF to form explosive peroxides is high and thus peroxide inhibitor, 2,6-di-*tert*-butyl-methyl phenol (BHT), must be added for the long-term storage and transport of THF (criteria 11);
- Although potential bio-based routes to THF are achievable, they are not yet economically viable compared to the petroleum-derived synthesis; as such, presently, THF does not follow criteria 12.

2-MeTHF is a well-established bio-based solvent and is seen as a sustainable and safer alternative to Et_2O and THF.[32] 2-MeTHF can be produced from well-known platform molecules, 5-(hydroxymethyl)furfural **6** (HMF) or furfural **11**, which are derived from lignocellulosic biomass.[33] Lignocellulosic biomass can be converted into glucose **2** (from cellulose), xylose **10** (from hemicellulose) and lignin by acid-catalysed hydrolysis. Conversion of glucose **2** into HMF **6** first requires isomerisation to fructose **5**. Subsequent dehydration of fructose **5** constructs HMF **6**.[34,35] HMF **6** is then converted into levulinic acid **7** by acid-catalysed hydrolysis.[36] Hydrogenation and subsequent esterification converted levulinic acid **7** to γ-valerolactone **8**.[37] Ring opening of γ-valerolactone **8** formed 1,4-pentanediol **9**. Then, dehydrative ring closure furnished 2-MeTHF (Scheme 1.2).[38,39]



Scheme 1.2: Bio-based route to 2-MeTHF from glucose **2**

Alternatively, a more atom economic process to produce 2-MeTHF from xylose **10** is possible. Dehydration of xylose **10** with the use of solid acid catalysts formed furfural **11**.[40,41] Catalytic reduction of furfural **11** furnished 2-methylfuran **12**. Subsequent catalytic hydrogenation of 2-methylfuran **12** gives 2-MeTHF (Scheme 1.3).



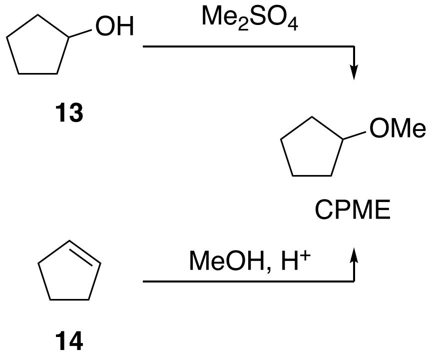
Scheme 1.3: Bio-based route to 2-MeTHF from xylose **10**

A comparison of 2-MeTHF and THF in the 12 criteria of green solvents[23] reveals its improved green credentials:

- The increased hydrophobicity of 2-MeTHF means that the solvent is more easily separated from aqueous waste thus improving the recyclability of the solvent (criteria 3);
- 2-MeTHF does not exhibit carcinogenic properties resulting in a lower toxicity profile (criteria 6);
- 2-MeTHF is a bio-based molecule (criteria 12);
- However, 2-MeTHF is able to form explosive peroxide and thus must be stored with peroxide inhibitor and is highly flammable (criteria 10 and 11).

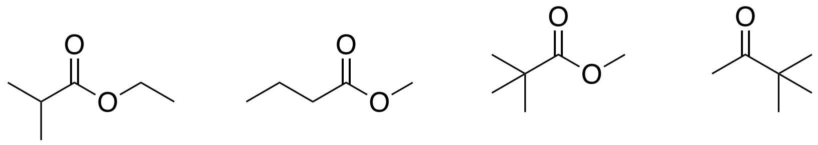
Hence, in terms of the greenness of the solvent, 2-MeTHF is an improvement compared to THF but there are still significant hazards associated with this alternative solvent.

Another alternative ether solvent is cyclopentyl methyl ether (CPME).[42] There are two practical syntheses of CPME. The first involves the methylation of cyclopentanol **13** with Me_2SO_4. However, production of by-products and the use of a highly toxic methylating agent means that this process is not favourable. Alternatively, addition of MeOH to cyclopentene **14** forms CPME (Scheme 1.4). This route does not produce waste and avoids the use of particularly toxic reagents. A bio-based route to cyclopentanol **13** from furfural **11** *via* a Ru-Mo-carbon nanotube-catalysed hydrogenation-rearrangement reaction has recently been reported. However, this process has not yet been commercialised.[43] The authors state that CPME exhibits greater hydrophobicity compared to traditional ether solvents, and this is advantageous when carrying out reactions that require anhydrous conditions. It is also beneficial for when the solvent is used in aqueous work-up procedures. Sluggish peroxide formation over a 30-day period compared to THF and Et_2O was also a characteristic of CPME.[42] However, commercial CPME is supplied with peroxide inhibitor. Contrary to this, studies of peroxide formation in ether solvents by Byrne and co-workers have reported notable peroxide formation in CPME (*vide infra*).[44] CPME is stable under both acidic and basic conditions and exhibits a narrow explosion range. These characteristics make the alternative solvent desirable in both academia and industry from a green chemistry perspective. That being said, CPME is considered problematic in the CHEM21 solvent selection guide as a result of its low auto-ignition temperature (AIT) of 180 °C.[13]



Scheme 1.4: Synthetic routes to cyclopentyl methyl ether (CPME)

The addition of toluene to the REACH restricted substances list[6] and the limited examples of bio-based aromatic solvents (*p*-cymene is an example of a bio-based aromatic solvent derived from limonene[45]) has led researchers to suggest non-aromatic solvents as replacements for toluene. Byrne and co-workers proposed that bio-based ketones and esters could be potential replacements for toluene.[46] A methodical approach was taken when selecting potential candidates. First, solvent boiling point was taken into account and an upper limit equal to toluene's boiling point was chosen (111 °C). It is suggested in the CHEM21 solvent selection guide that the preferred boiling point of solvents is in the range of 70−139 °C.[13] Next, a solubility test was carried out, which involved the dissolution of natural rubber. Hydrocarbon solvents such as toluene, due to their low polarity, are effective at solubilising natural rubber. The four best candidates following these tests were ethyl isobutyrate **15**, methyl butyrate **16**, methyl pivalate **17** and pinacolone **18** (Figure 1.1).[46] Experimentally, each of the four candidate solvents performed similarly to toluene in the radical-initiated polymerisation of butyl acrylate, showcasing the potential of the solvents as toluene replacements. This publication did not highlight the issues regarding pinacolone's **18** toxicity. Considering the toxicity, it should not be considered as a safe alternative solvent for toluene.[47] Methyl butyrate **16** exhibits a particularly unpleasant odour which has the potential to hamper its use within academia and industry. Furthermore, the inherent structural features present in ester and ketone solvents may also interfere with and hinder synthetic reactions. As such, the use of esters and ketones have limited use in the replacement of toluene.



Ethyl isobutyrate **15**

Methyl butyrate **16**

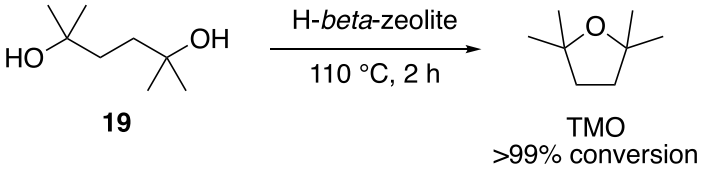
Methyl pivalate **17**

Pinacolone **18**

Figure 1.1: Ketones and esters as potential replacements for toluene

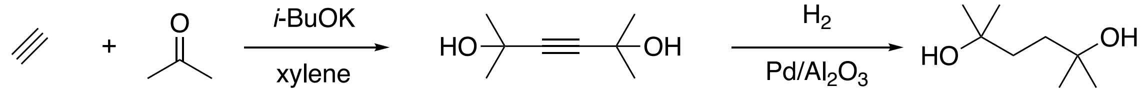
1.3 2,2,5,5-Tetramethyloxolane (TMO)

In the search for greener and more sustainable solvents researchers at the Green Chemistry Centre of Excellence (GCCE) at the University of York developed the non-polar, non-peroxide forming ether solvent 2,2,5,5-tetramethyloxolane (TMO) as a suitable candidate as a replacement for toluene.[44] TMO has a characteristic menthol-like odour and low toxicity as indicated from Ames mutagenicity testing. It was synthesised on the multi-kg scale *via* the cyclisation of the commercially available diol **19** using a heterogenous acid catalyst (H-*beta*-zeolite, 1 wt%) at 110 °C with near perfect selectivity (>99%, Scheme 1.5). Notably, the only waste product from this reaction was water, which could be removed simply *via* extraction. Furthermore, the solid acid catalyst could be reused, without loss of performance, by filtering the reaction residue and calcination at 600 °C for 4 h. This catalytic method for the synthesis of TMO uses reagents which possess low toxicity and has a high AE of 96% and RME of 93% thus following criteria 5 for green solvents (atom economic synthesis). Initial studies have predicted TMO to have low toxicity and be non-peroxide forming. Therefore, TMO would not require the addition of peroxide inhibitor for long-term storage, as such, TMO adheres to criteria 6 (low toxicity) and 11 (ease of storage). TMO has also been found to be stable under acidic conditions and high temperatures thus following criteria 9 (stability). These green characteristics give promise to TMO as being a potentially useful green alternative solvent.



Scheme 1.5: Synthesis of TMO

Although TMO exhibits promising green characteristics, namely, its non-peroxide forming nature and low-toxicity profile, it currently has no commercially-viable synthetic routes from biomass. Precursor diol **19** is currently derived from petroleum-based acetone and acetylene, a process patented by BASF (Scheme 1.6).[48] However, both acetylene and acetone can be accessed from biomass. Partial combustion of methane, formed from anaerobic digestion, generates acetylene[49] whereas, acetone can be accessed through acetone-butanol-ethanol (ABE) fermentation.[50] The increased costs of these processes compared to petroleum-based acetone and acetylene means that these routes are not yet commercially competitive. However, with improving technologies and increasing legislation, this may soon change.

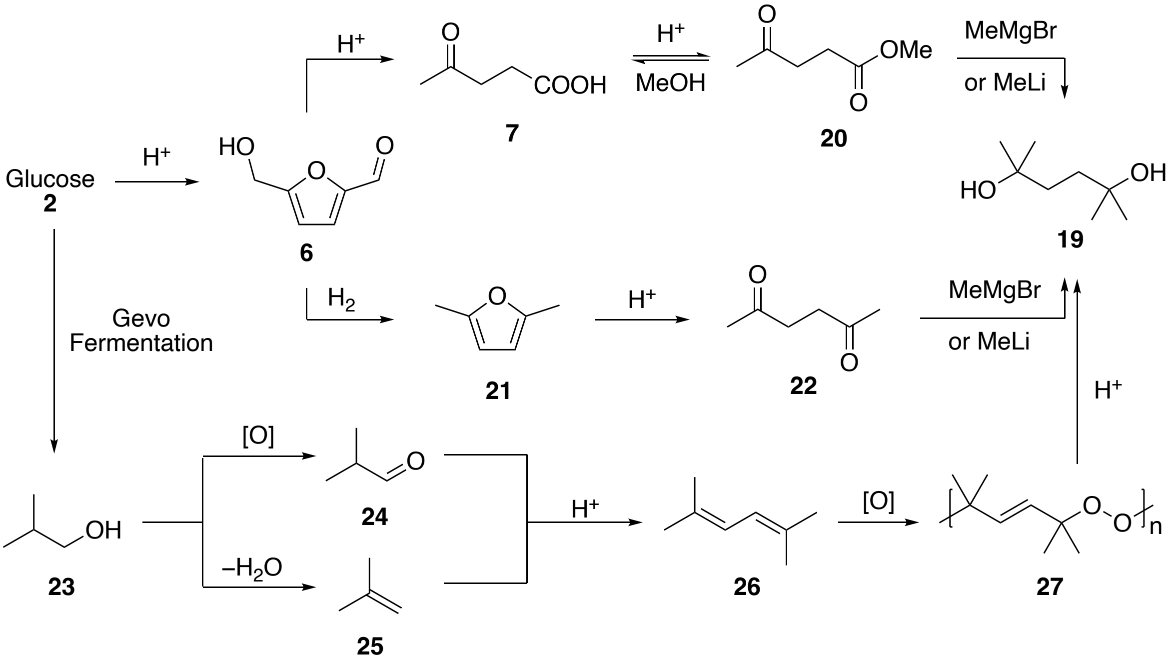


acetylene acetone 2 eq 2,5-dimethyl-3-yne-2,5-diol **19**

Scheme 1.6: Synthesis of diol **19** from acetylene and acetone

Byrne and co-workers reported on potential bio-based routes to precursor diol **19** and thus in turn TMO.[51] The first route involved the isolation of HMF **6** from glucose **2**.[33,35] Acid-catalysed hydrolysis of HMF **6** affords levulinic acid **7**.[36] Esterification of levulinic acid **7** gave methyl levulinate **20** which can be converted into precursor diol **19** by reaction with MeMgBr or MeLi. This leads to the formation of TMO with 64% bio-based carbon. Alternatively, hydrogenation of HMF **6** forms 2,5-dimethylfuran **21**. Acid-catalysed hydrolysis then converts 2,5-dimethylfuran **21** into dione **22**.[52] Addition of MeMgBr or MeLi yields the diol precursor **19**. This route gives access to TMO with 75% bio-based carbon. The final route involves the conversion of glucose **2** to isobutanol **23** *via* fermentation, a process patented by Gevo.[53] Isobutanol **23** is then converted into aldehyde

24 by oxidation and alkene **25** by dehydration. A Prins reaction with alkene **25** and aldehyde **24** gives diene **26**.[54] Diene **26** is oxidised in air at room temperature to form polyperoxide oligomers **27**; hydrogenation of polyperoxide **27** generates precursor diol **19**. This process would afford TMO with 100% bio-based carbon (Scheme 1.7). These processes offer alternative bio-based routes to TMO. However, the routes starting from HMF **6** require the use of at least 2 equivalents of MeMgBr or MeLi. This generates considerable quantities of Mg- or Li-based waste meaning that these processes are unlikely to be commercialisible. The other alternative method starting from isobutanol **23** required the most synthetic steps to TMO but is a less wasteful route. However, diene **26** is no longer advertised by Gevo. Hence, the most ecological and scalable route to TMO would be from bio-based acetone and acetylene as described in Scheme 1.6.



Scheme 1.7: Potential bio-based routes to diol **19**

Byrne and co-workers analysed peroxide formation in TMO by bubbling air through the solvent with irradiation by UV light (254 nm) for 3 h.[44] The formation of peroxides in the solvent was determined through the use of peroxide test strips and compared against ether solvents THF, 2-MeTHF and CPME (Table 1.3). Under these conditions, THF was found to have >100 ppm levels of peroxide formation whereas 2-MeTHF contained >30 ppm and CPME had 3−10 ppm. TMO exhibited no peroxide formation under these conditions, and the same result was obtained at reflux. Peroxide formation arises from the abstraction of a hydrogen atom adjacent to oxygen in ether solvents by a radical species (e.g. peroxy radical) generated by low energy visible light. This then gives an ether radical that is subsequently trapped with oxygen. The ether peroxy radical can then abstract another α-hydrogen atom to form the hydroperoxide and another ether radical.[55] The replacement of the α-hydrogen atoms in THF with methyl groups in TMO inhibits this process from occurring.

Solvent	**Peroxide Formation (ppm)**
THF	>100
2-MethylTHF	>30
CPME	10−30
TMO	0[a]

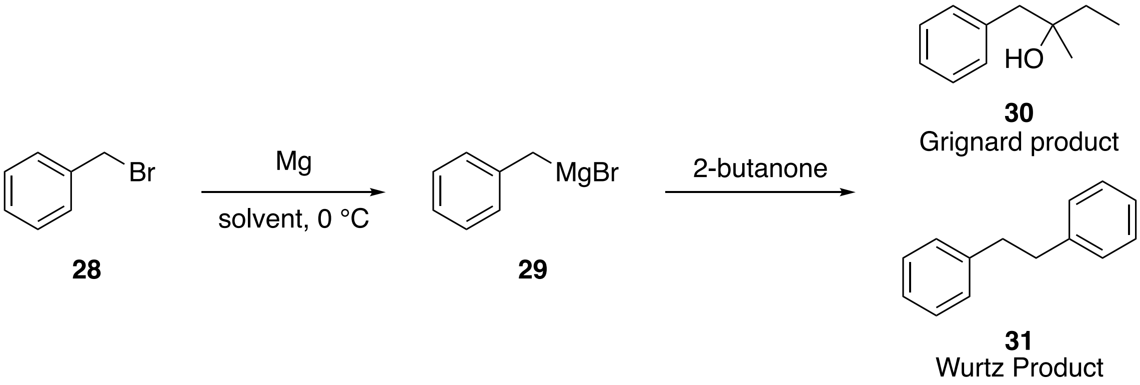
Table 1.3: Peroxide formation in ether solvents. [a]Peroxide tests carried out at both room temperature and reflux

The physical and solubility properties of TMO were found to be more similar to toluene than with the structurally similar THF. TMO shares a very similar boiling point to toluene (112 °C for TMO compared to 111 °C for toluene). Furthering its green credentials, TMO has been found to have a high AIT of 417 °C; this is lower than toluene (552 °C) but higher than THF (321 °C), 2-MeTHF (270 °C) and Et_2O (180 °C).[44] Hansen Solubility Parameters (HSP)[56] indicate that the intermolecular interactions of TMO are more akin to toluene than traditional ether solvents. Thus, it is expected that TMO and toluene will be suitable solvents for the same substrates. The physical and solubility properties of TMO, toluene and THF are displayed in Table 1.4. HSP uses three parameters to predict if a solvent is able to dissolve another material. These parameters are dispersion forces (δ_D), polarity (δ_P) and hydrogen bonding ability (δ_H). A three-dimensional map is then plotted using these parameters and, following the principle 'like-dissolves-like', solvents within a similar vicinity of each other on the map will exhibit a similar solvation power. The hydrogen bonding ability of ether solvents is expected to be high as a consequence of the oxygen present in the solvents. This is evident in THF, where $\delta_H = 8.0$. In contrast, $\delta_H = 2.1$ for TMO. A low δ_H is characteristic of hydrocarbon solvents such as toluene ($\delta_H = 2.0$). This difference between the ether solvents can be explained by their molecular structure. The four methyl groups present in TMO sterically hinder the lone pairs on the oxygen thus inhibiting its hydrogen-bonding ability.[44]

Solvent Properties	**TMO**	**Toluene**	**THF**
Boiling point (°C)	112	111	66
AIT (°C)	417	552	321
δ_D (MPa$^{0.5}$)	18.0	15.4	16.8
δ_P (MPa$^{0.5}$)	2.4	1.4	5.7
δ_H (MPa$^{0.5}$)	2.1	2.0	8.0

Table 1.4: Physical and solubility properties of TMO, toluene and THF

This divergence from ether solvents was further demonstrated experimentally in a reaction using Grignard reagents (Table 1.5).[44] In THF, benzyl bromide **28** was converted into the corresponding Grignard reagent **29** using Mg turnings at 0 °C. Reaction with 2-butanone formed tertiary alcohol **30** and Wurtz product **31** in 99% conversion (entry 1). An analogous result was achieved in 2-MeTHF (100% conversion, entry 2). In contrast, in both toluene and TMO, 0% conversion was observed (entries 3 and 4 respectively). The authors state that this was likely a consequence of the increased steric hindrance compared to THF and 2-MeTHF introduced by the additional methyl groups in TMO inhibiting the formation and solubilisation of the Grignard reagent **29**, hence, prohibiting further reaction. TMO has exhibited similar reaction performance to toluene in radical-initiated polymerisation,[44] amidation reactions,[44] enzyme-catalysed esterification[57] and the biocatalysed synthesis of polyesters.[58]

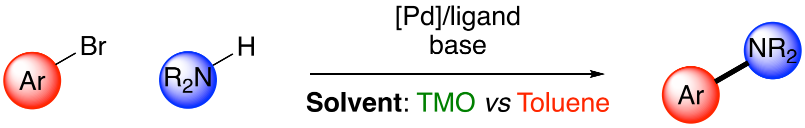


Entry	**Solvent**	**Conversion (%)**	**30:31 ratio**
1	THF	99	18:82
2	2-MeTHF	100	87:13
3	Toluene	0	-
4	TMO	0	-

Table 1.5: Grignard reaction of benzyl bromide **28** with 2-butanone

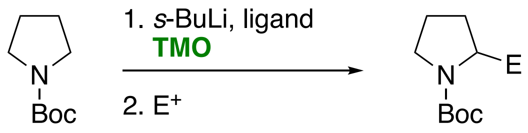
1.4 Project Outline

Since the physical and solubility properties of TMO are similar to those of toluene, the first part of this project (Chapter 2) will involve a comparative reaction performance study between toluene and TMO in Buchwald-Hartwig aminations (Scheme 1.8). Buchwald-Hartwig amination is a palladium-catalysed cross-coupling reaction which forms *N*-arylamines and most commonly employs toluene as the solvent. It was felt that this reaction would further improve TMO's credentials as a safer alternative to toluene in medicinally-relevant synthetic reactions.



Scheme 1.8: Proposed comparative study of TMO and toluene in Buchwald-Hartwig aminations

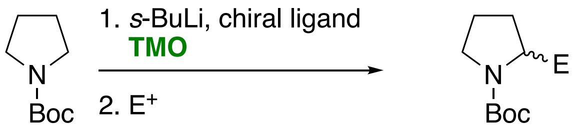
Lithiation-trapping reactions of *N*-heterocycles typically use THF or Et_2O as the solvent. As a result of the high flammability of these solvents and the tendency to form explosive peroxides, the use of these solvents in an industrial environment is avoided as much as possible. An investigation into the use of TMO in lithiation-trapping reactions of *N*-heterocycles, mainly *N*-Boc pyrrolidine **32**, will be undertaken and the results are presented in Chapter 3. Racemic lithiation-trapping of *N*-Boc pyrrolidine **32** will first be explored to ascertain the suitability of the new solvent in this reaction (Scheme 1.9).



32

Scheme 1.9: Proposed use of TMO in racemic lithiation-trapping of *N*-Boc pyrrolidine **32**

The investigation will be extended to enantioselective lithiation-trapping of *N*-heterocycles with the use of chiral diamine ligands (Scheme 1.10). The stereochemical outcome of lithiation-trapping reactions are often solvent dependent. As such, the effect TMO has on the stereoselectivity of this reaction compared with conventional ether solvents would be of interest.

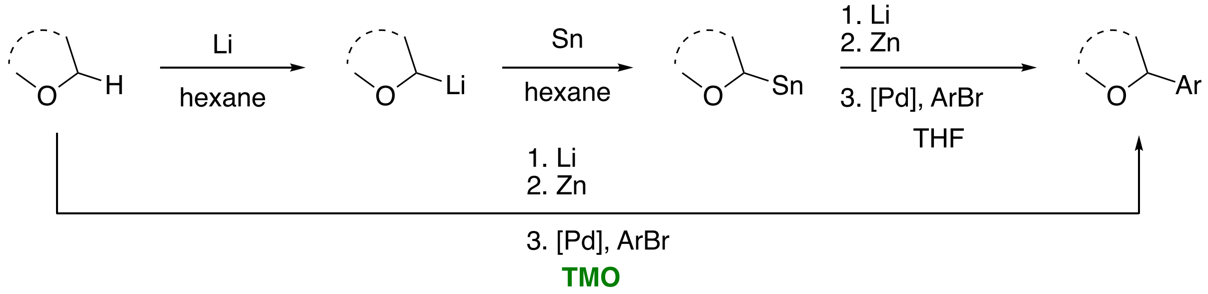


32

Enantioselective?

Scheme 1.10: Proposed use of TMO in enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32**

Finally, the development of lithiation-trapping and Negishi cross-coupling conditions for *O*-heterocycles in TMO will be investigated in Chapter 4. Use of conventional ether solvents in the lithiation-trapping reactions of *O*-heterocycles has previously been unsuccessful. However, hexane has proven to be a suitable solvent for this transformation. Difficulties have been encountered when extending this methodology to the arylation of *O*-heterocycles *via* Negishi cross-coupling due to the insolubility of the organozinc species in hexane. In order to overcome this limitation, formation and isolation of organostannanes has been required. Following this, a solvent switch to THF and regeneration of the lithiated intermediate then transmetallation to zinc was required for the arylation of *O*-heterocycles to be successful. Use of toxic organostannane reagents and the wasteful nature of this process makes this methodology undesirable from a green chemistry perspective. If lithiation-trapping conditions could be found, would the use of TMO provide a solution for the solvent incompatibility issues found in this methodology? Hence, this would facilitate a streamlined synthesis of arylated *O*-heterocycles which avoids the use of toxic organostannane reagents and generates less waste (Scheme 1.11).



Scheme 1.11: Proposed route to α-arylated *O*-heterocycles in TMO

Chapter 2: Use of TMO as Solvent for Buchwald-Hartwig Aminations

2.1: Introduction to *N*-Arylamines

N-Arylamines are prevalent structural motifs found in numerous pharmaceuticals, natural products and agrochemicals. Hence, the construction of the C-N bond to form aniline and aniline derivatives is of significant importance to synthetic chemists. Representative examples of pharmaceutical agents, agrochemicals and natural products featuring a *N*-arylamine motif include Imatanib, a tyrosine kinase inhibitor used for the treatment of chronic myelogenous leukaemia (CML) and gastrointestinal tumours, currently marketed by Novartis;[59] Mepanipyrim, a fungicide that is used to protect fruits and vegetables from grey mould and brown rot;[60] and Mukoline, a tricyclic carbazole alkaloid, isolated from *Murraya koenigii* (Figure 2.1).[61] In each case, the *N*-arylamine bond highlighted in bold has been crafted using Buchwald-Hartwig aminations, a palladium-catalysed cross-coupling reaction between amines and aryl (pseudo)halides.

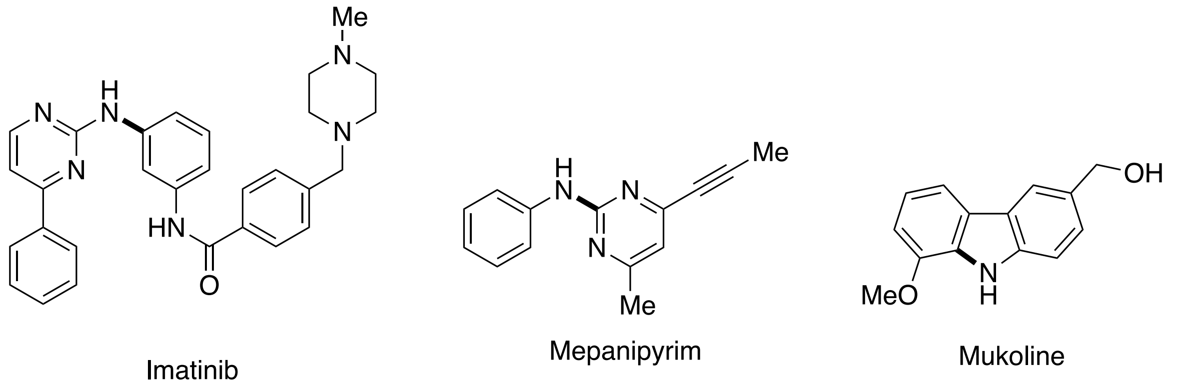
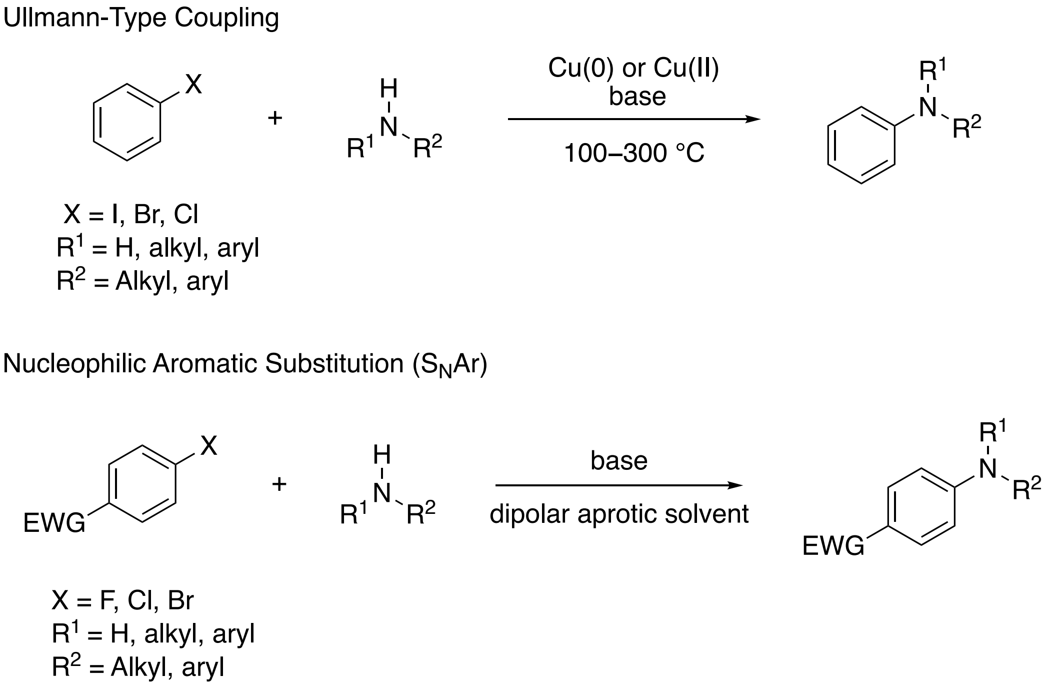


Figure 2.1: Pharmaceuticals, agrochemicals and natural products containing the *N*-arylamine structural motif

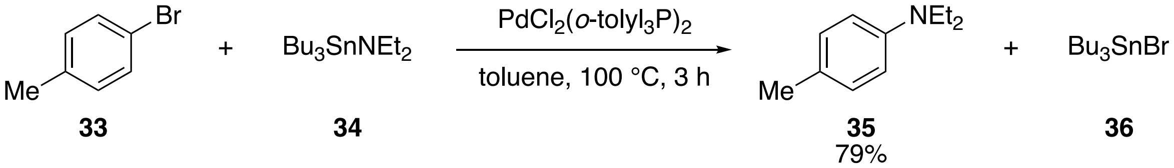
2.2 Introduction to Buchwald-Hartwig Aminations

Historically, *N*-arylamines were synthesised *via* Ullmann-type aryl amination reactions requiring the use of a copper catalyst or copper salts and a base to facilitate the coupling between an aryl halide and an amine (Scheme 2.1). However, it is usually necessary to heat the reaction to high temperatures in order to promote the coupling of the substrates.[62] Nucleophilic aromatic substitution (S_NAr) is also routinely used for the construction of *N*-arylamines through reaction with amines and aryl (pseudo)halides bearing electron-withdrawing substituents *ortho*- or *para*- to the halide (Scheme 2.1). S_NAr reactions typically require high temperatures and also use dipolar aprotic solvents (which are difficult to remove and are toxic).[63] The substrate scope of these reactions is somewhat limited by the use of very high temperatures and the requirement of activating substituents to be present on the aryl ring.



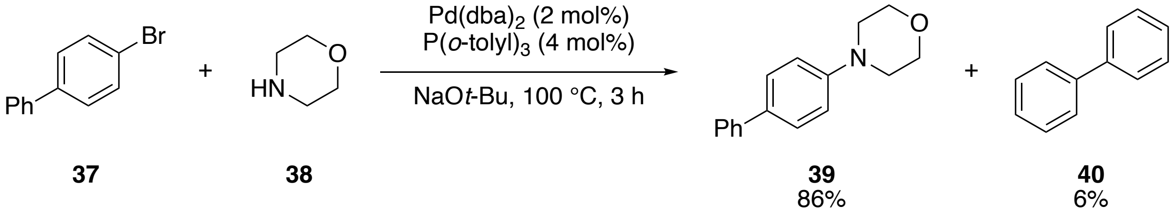
Scheme 2.1: Previous synthetic methods to access *N*-arylamines

An alternative approach to access *N*-arylamines, reported by Kosugi and co-workers in 1983, is the reaction between aminostannanes and aryl bromides in the presence of a palladium catalyst.[64] In a representative example, the reaction between aryl bromide **33** and aminostannane **34** in the presence of pre-catalyst $PdCl_2(o\text{-}tolyl_3P)_2$ in toluene at 100 °C for 3 h formed tertiary amine **35** in 79% yield (Scheme 2.3). However, a limited substrate scope was reported and the functional group tolerance was poor. Furthermore, the protocol required the use of toxic organotin reagents and formed organotin by-product **36** that required a complex work-up procedure for its removal. The use of toxic reagents and poor substrate scope in this methodology highlights the shortcomings of this reaction.



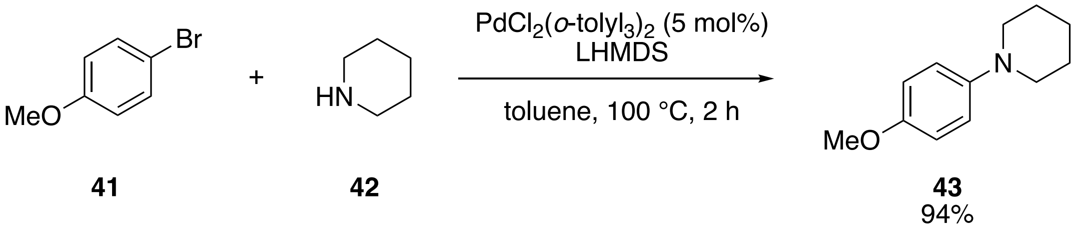
Scheme 2.3: Palladium-catalysed cross-coupling of aryl bromide **33** and aminostannane **34**

Seminal independent reports by the Buchwald and Hartwig groups improved on the method developed by Kosugi and co-workers.[65,66] In efforts to eliminate the need for the toxic aminostannane reagents, Buchwald *et al.* initially reported the successful application of aminoboranes as the amine nucleophile for the palladium-catalysed cross-coupling reaction with aryl bromides. This facilitated the synthesis of *N*-arylamines in good yields. In the same report, the direct use of amines for the cross-coupling with aryl bromides was also found to be possible. For example, biphenyl bromide **37** and morpholine **38** were cross-coupled using $Pd(dba)_2$, $P(o\text{-}tolyl)_3$ and stoichiometric quantities of Na*Ot*-Bu in toluene at 100 °C for 3 h. The resultant tertiary amine **39** was obtained in 86% yield (Scheme 2.4). Hydrodehalogenated side-product **40** was also formed, arising from the reduction of aryl bromide **37** *via* a β-hydride elimination pathway. Greater quantities of the arene side-product were formed when coupling of primary amines was attempted. The cross-coupling of aryl bromides and amines containing base-sensitive functional groups was unsuccessful. This was likely caused by use of strong base, NaO*t*-Bu, which could potentially react with the base-sensitive functional groups.



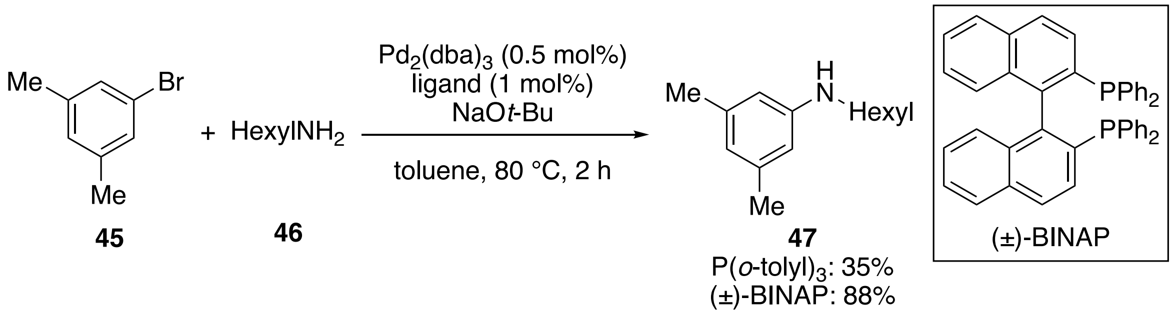
Scheme 2.4: Buchwald-Hartwig amination of biphenyl bromide **37** and morpholine **38**

Using a similar method, Hartwig and co-workers reported the cross-coupling of aryl bromide **41** and piperidine **42** using $PdCl_2(o\text{-tolyl}_3P)_2$ and LHMDS in toluene at 100 °C for 2 h. This gave tertiary amine **43** in 94% yield (Scheme 2.5). THF was also employed as solvent and no change in reaction rate, selectivity or side-product formation was observed compared to toluene. Using this method, the coupling of primary amines and aryl bromides was not successful as only the arene by-product was obtained.[66]



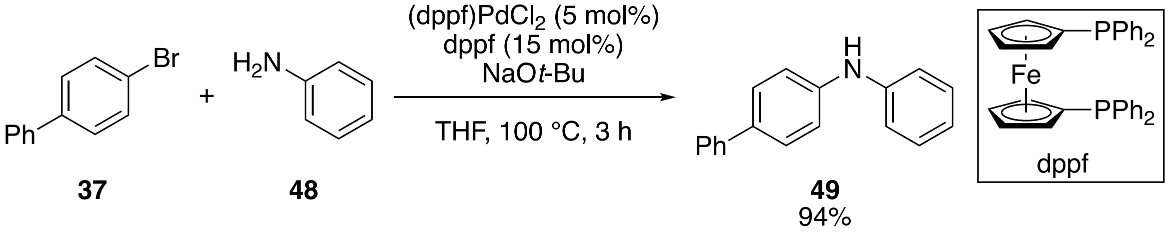
Scheme 2.5: Buchwald-Hartwig amination of 4-bromoanisole **41** and piperidine **42**

The coupling of primary amines with aryl bromides was unsuccessful when the monodentate ligand P(*o*-tolyl)$_3$ was used. Subsequent independent efforts by the Buchwald and Hartwig groups involved the development of a catalytic system which could tolerate the coupling of primary amines and aryl halides. Buchwald and co-workers reported a protocol which utilised the bidentate bis(phosphine), (±)-BINAP, as the supporting ligand for the synthesis of secondary *N*-arylamines.[67] Cross-coupling of aryl bromide **45** and hexylamine **46** with Pd$_2$(dba)$_3$, P(*o*-tolyl)$_3$ and NaO*t*-Bu in toluene at 80 °C for 2 h resulted in only a 35% yield of secondary amine **47** as a consequence of competitive *β*-hydride elimination. In contrast, under otherwise identical conditions, with (±)-BINAP in place of P(*o*-tolyl)$_3$, secondary amine **47** was furnished in a much-improved 88% yield (Scheme 2.6).



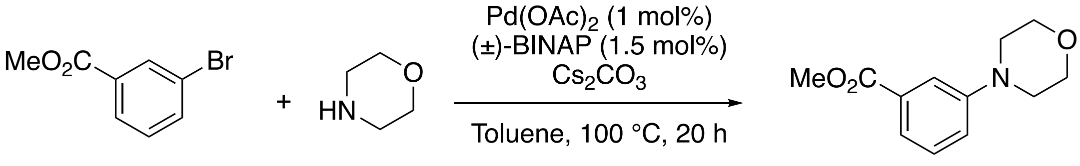
Scheme 2.6: Use of (±)-BINAP as the ligand for the cross-coupling of aryl bromide **45** and primary amine **46**

Hartwig and co-workers concurrently discovered that primary amines could be cross-coupled with aryl bromides using 1,1'bis(diphenylphosphino)ferrocene (dppf)-ligated palladium complexes.[68] Aryl bromide **37** and primary amine **48** were successfully cross-coupled with (dppf)PdCl$_2$, dppf and NaO*t*-Bu in THF at 100 °C for 3 h to give secondary aryl amine **49** in 94% yield (Scheme 2.7). In both reports by Buchwald and Hartwig secondary amines were also shown to be tolerated. Hartwig showed that *β*-hydride elimination occurs from the 14-electron, 3-coordinate amido complex intermediate which forms when monodentate ligands are used.[69] In contrast, reductive elimination can occur from both 3- and 4-coordinate amido-complexes.[70] As such, reductive elimination to form the desired *N*-arylamine is favoured over *β*-hydride elimination with chelating ligands.[71] This explains the improved yields of *N*-arylamines when this class of ligand is used.



Scheme 2.7: Use of dppf as the ligand for the cross-coupling of aryl bromide **37** and primary amine **48**

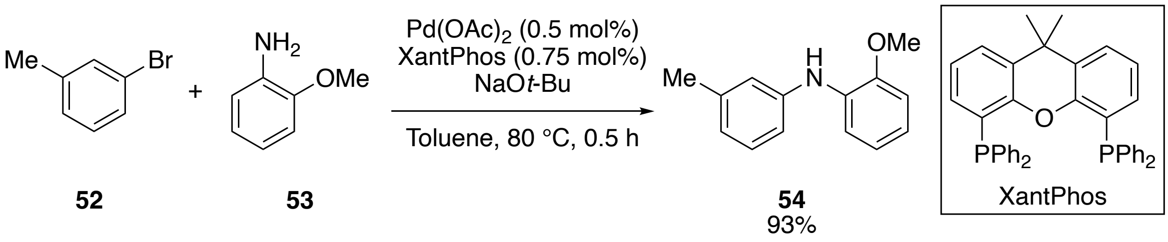
The cross-coupling of aryl bromides and amines exhibiting base-sensitive functionality had been unsuccessful as a consequence of the use of the strong base, NaO*t*-Bu, in excess quantities.[65] In 1997, with a desire to expand the substrate scope to include the coupling of base-sensitive substrates, Buchwald and Wolfe found success using the milder base Cs_2CO_3 in place of NaO*t*-Bu.[72] The coupling of base-sensitive aryl bromide **50** and morpholine **38** with $Pd(OAc)_2$, (±)-BINAP and Cs_2CO_3 in toluene at 100 °C for 20 h facilitated the synthesis of previously inaccessible tertiary amine **51** in a 86% yield (Scheme 2.8). The discovery of this milder base for C-N cross-coupling reactions has drastically expanded the utility of the reaction by allowing the coupling of a wide range of aryl bromides and amines. Other weak inorganic bases, which are more economically-attractive, such as K_3PO_4 and K_2CO_3, have also been successfully used in Buchwald-Hartwig aminations involving base- and nucleophile-sensitive substrates.[73] However, Cs_2CO_3 is often the preferred base since it has slightly higher solubility in organic solvents compared to the other weak inorganic bases.[74]



50 **38** **51** 86%

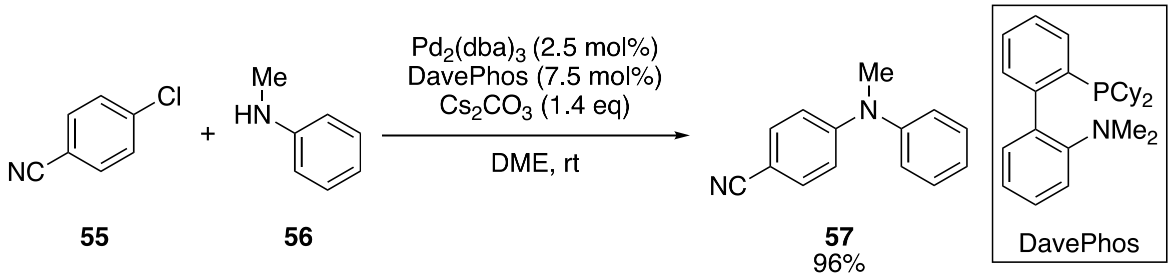
Scheme 2.8: Use of Cs_2CO_3 in Buchwald-Hartwig amination of base-sensitive substrates

Since the inception of Buchwald-Hartwig aminations, a main focus of research has been in the development of new ligands. The use of these ligands has further increased the substrate scope, improved reaction rates at decreased catalyst loadings and facilitated the use of milder reaction conditions.[73,75–77] A POP-type bisphosphine ligand developed by van Leeuwen has been found to be an effective ligand for Buchwald-Hartwig aminations.[78,79] Aryl bromide **52** was cross-coupled with aromatic amine **53** using $Pd(OAc)_2$, XantPhos and NaO*t*-Bu in toluene at 80 °C for 0.5 h to form secondary amine **54** in 92% yield (Scheme 2.9). None of the hydrodehalogenated side product was observed when this chelating ligand was used further highlighting the enhanced selectivity for reductive elimination with bisphosphine ligands. Other structurally related POP-type ligands have proven to be effective for Buchwald-Hartwig amination.[80,81]



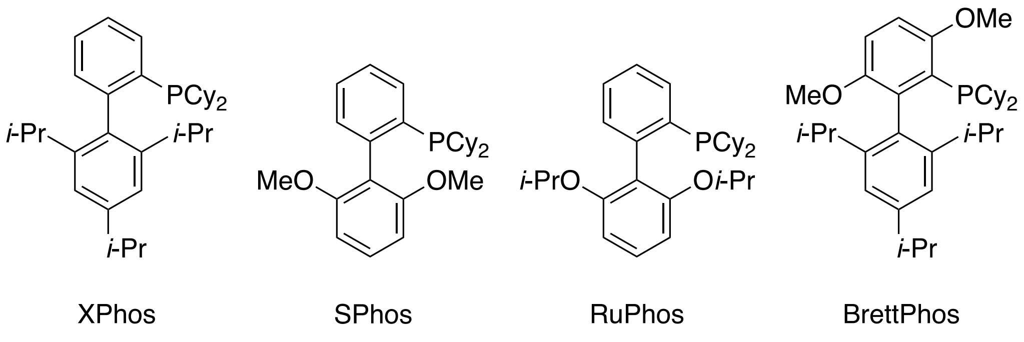
Scheme 2.9: Use of XantPhos as a ligand in Buchwald-Hartwig aminations

Dialkylbiaryl phosphines developed by Buchwald are a class of ligand which has seen considerable use in the amination reaction as well as other palladium-catalysed cross-coupling reactions, for example, Suzuki-Miyaura cross-coupling. Buchwald and co-workers initially reported that the rate limiting step for the amination reactions of aryl bromide and amines with $Pd(OAc)_2$ and (±)-BINAP as the catalyst system was the oxidative addition step.[82] However, the effective rate determining step can change, for example, to the ammonium deprotonation step when a poorly soluble weak base is used.[83] Anticipating that the coupling of aryl chlorides would be slower than aryl bromides, electron-rich ligands capable of facilitating the coupling of such substrates were developed. This led to the first reported use of dialkylbiaryl phosphine ligand, DavePhos.[82] In one example, the first reported coupling of aryl chloride **55** with secondary amine **56** at room temperature using $Pd_2(dba)_3$, DavePhos and NaO*t*-Bu in DME gave tertiary amine **57** in 96% yield (Scheme 2.10).



Scheme 2.10: Use of DavePhos in the Buchwald-Hartwig amination of aryl chlorides

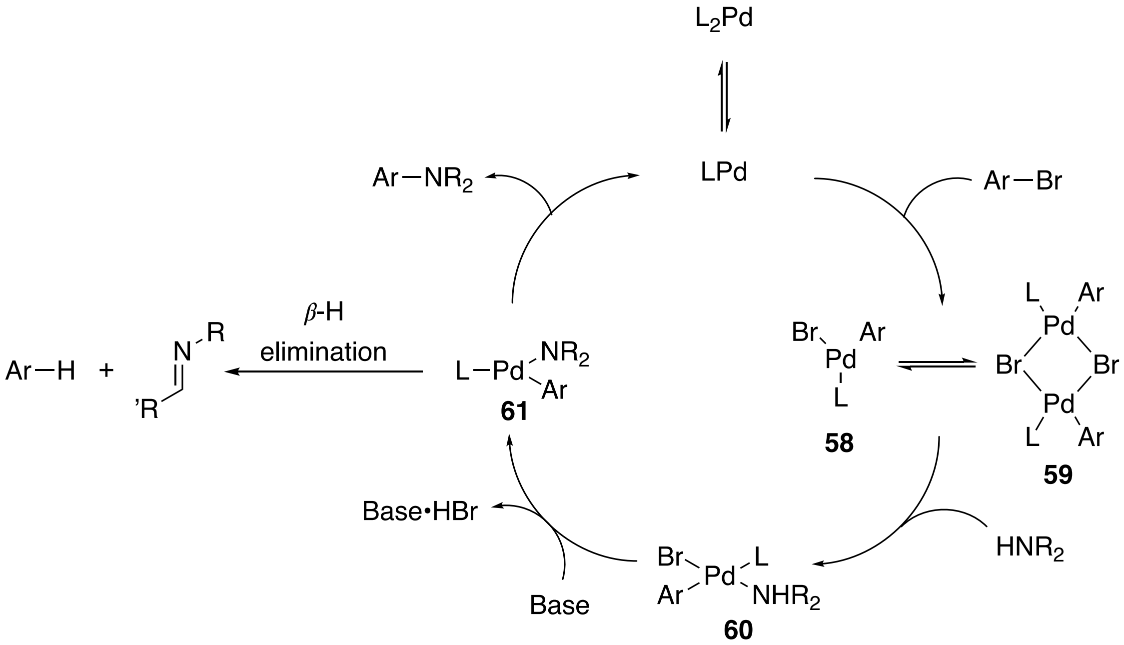
The synthesis of these dialkylbiaryl phosphine Buchwald ligands involves a one-step procedure whereby the addition of an aryl lithium or Grignard reagent to the appropriate aryne and quenching with chlorophosphine constructs the desired ligand.[84,85] This simple procedure has enabled the synthesis of a catalogue of structurally-related ligands which are now widely commercially available (Figure 2.2). Their use within both academia and industry has since become ubiquitous, showcased by their use in the synthesis of numerous pharmaceutically-relevant molecules and natural products. A number of extensive reviews has since been published detailing the best choice of ligand for the specific substrates being studied.[73,75–77]



XPhos SPhos RuPhos BrettPhos

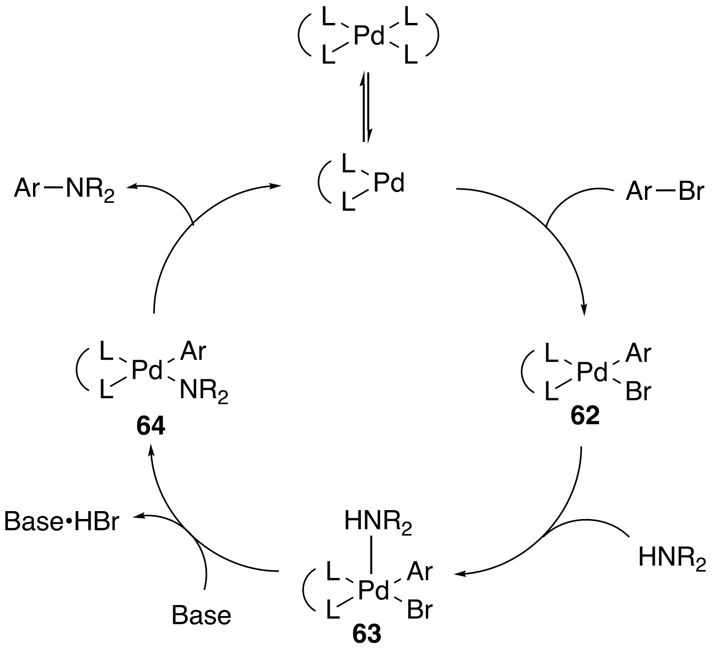
Figure 2.2: Examples of commonly used dialkylbiaryl phosphine Buchwald ligands

Studies to ascertain the mechanism of the catalytic cycle have been performed throughout the development of the Buchwald-Hartwig amination. As a result of these studies, different catalytic cycles have been proposed depending on the nature of the supporting ligand. First, with monophosphine ligands such as $P(o\text{-tolyl})_3$ and the dialkylbiaryl phosphine Buchwald ligands, reduction of the Pd(II) salt precursor gives access to $L_2Pd(0)$ and dissociation of one of the supporting ligand gives rise to the catalytically active LPd(0).[65,66] Oxidative addition of the aryl bromide leads to the formation of 3-coordinatate monomer **58** and dimeric species **59**. Complexation of the amine forms amino-complex **60**. Coordination of the amine to the palladium centre leads to enhanced acidity of the amine resulting in deprotonation with a base affording 3-coordinate amido-complex **61**. Reductive elimination furnishes the desired aryl amine; this is, however, in competition with a β-hydride elimination pathway which results in the formation of arene and imine side-products (Scheme 2.11). Sterically hindered Buchwald ligands are able to circumvent the competing β-hydride elimination pathway. It is reported that reductive elimination is promoted when sterically hindered ligands are used to relieve the steric pressure at the metal centre.[86,87] Furthermore, DFT studies have indicated that interactions between the non-phosphine-containing ring and the palladium centre lowers the activation energy of reductive amination.[88]



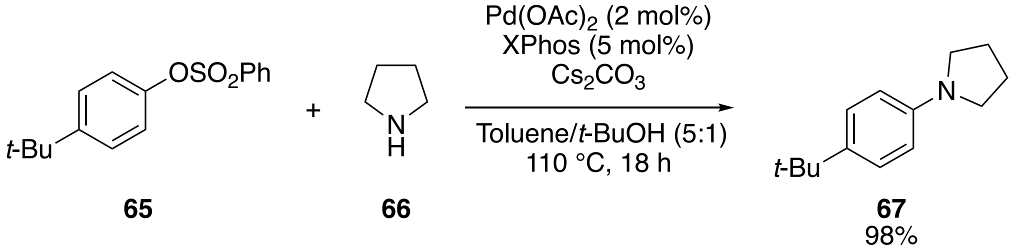
Scheme 2.11: Buchwald-Hartwig catalytic cycle when monodentate ligands are used

On the other hand, with a bidentate ligand, such as (±)-BINAP, a different mechanism has been suggested.[67] Initially, ligand dissociation forms the catalytically active palladium species. Then, oxidative addition of the aryl bromide gives rise to the 4-coordinate complex **62** which then coordinates to the amine to give the 5-coordinate amino-complex **63**. Coordination of the amine to the metal centre enhances the acidity of the amine allowing deprotonation with a base to give the 4-coordinate amido complex **64**. In this case, the chelating effect from the bidentate ligands disfavours the β-hydride elimination pathway resulting in diminished levels of arene and imine side-product formation. Finally, reductive elimination furnished the desired aryl amine and regenerates the catalytically-active palladium species, restarting the cycle (Scheme 2.12).



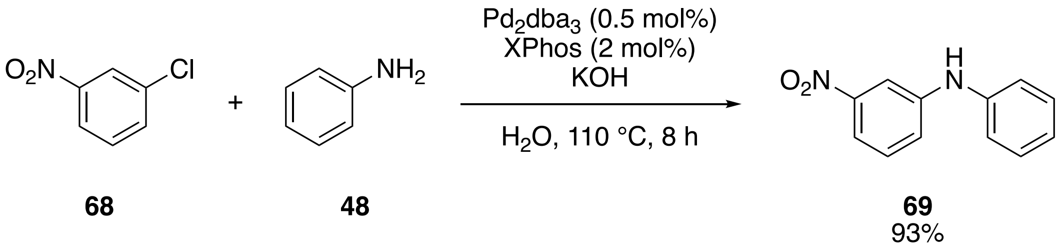
Scheme 2.12: Buchwald-Hartwig catalytic cycle when bidentate ligands are used

A variety of solvents can be used in Buchwald-Hartwig aminations. By far the most commonly used solvents are toluene and 1,4-dioxane the latter of which has notable issues regarding toxicity and peroxide formation associated with it.[89] Other ether solvents have been used including *n*-Bu_2O, THF, DME and bio-derived ether solvent 2-MeTHF. However, these ether solvents still exhibit peroxide forming properties and, in some cases, high toxicity profiles.[27,90,91] Generally, non-polar aprotic solvents are used most in Buchwald-Hartwig aminations. In cases where solubility of the substrates is not possible in non-polar solvents, polar aprotic solvents have occasionally been used.[73] However, formation of arene side-products *via* β-hydride elimination have been found to increase in polar solvents compared to non-polar solvents.[92] The use of toluene has been found to be beneficial in Buchwald-Hartwig aminations of aryl iodides and amines by preventing the solubilisation of by-product iodide salts. Solubilised NaI is found to impede the catalysis by the binding of the halide anion to the palladium centre forming a catalytically-inactive 'palladium-ate' species.[93] *t*-BuOH has also been used in Buchwald-Hartwig aminations as a co-solvent. Addition of this alcohol solvent in toluene has been found to improve solubility of the inorganic base and subsequently increased reaction rates.[94] For example, cross-coupling of aryl sulfonate **65** with pyrrolidine **66** using $Pd(OAc)_2$, XPhos and Cs_2CO_3 in toluene/*t*-BuOH (5:1) at 110 °C for 18 h formed tertiary amine **67** in 98% yield (Scheme 2.13).



Scheme 2.13: Use of *t*-BuOH as co-solvent in Buchwald-Hartwig aminations

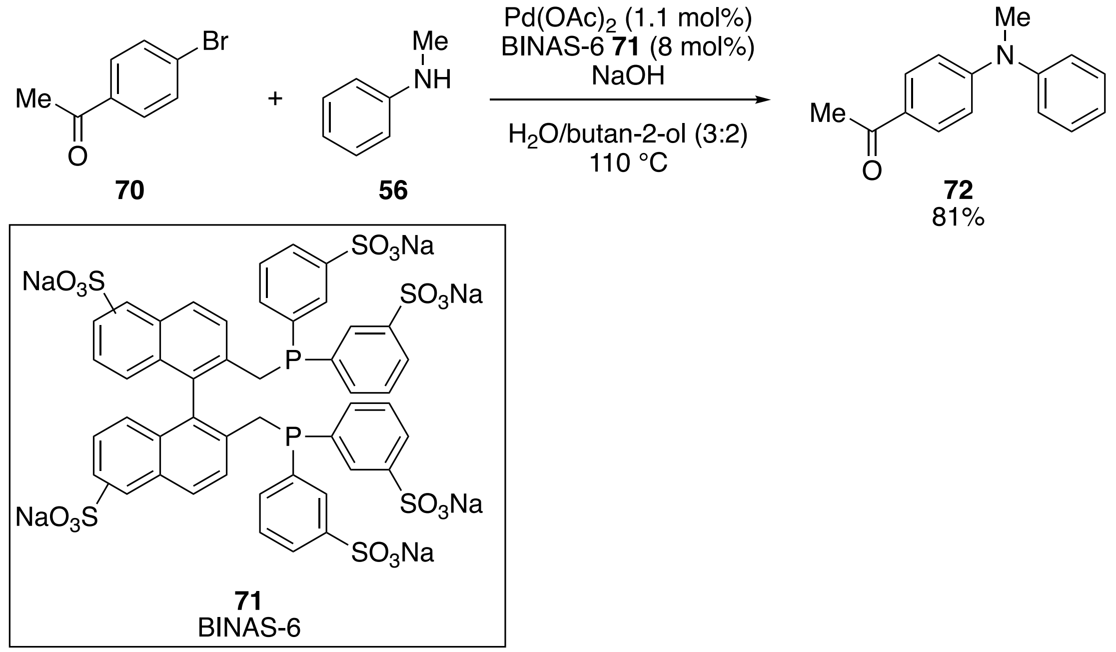
Water is an attractive solvent to use in reactions as it is non-toxic and non-flammable. However, it is rarely used in Buchwald-Hartwig aminations due to poor solubility of the reagents. However, Buchwald and co-worker have reported the cross-coupling of aryl chlorides with amines in water.[94] 1-Chloro-4-nitrobenzene **68** and aniline **48** were successfully cross-coupled with Pd_2dba_3, XPhos and NaOH in water at 110 °C for 8 h to form secondary amine **69** in 93% yield (Scheme 2.14).



Scheme 2.14: Buchwald-Hartwig amination in water

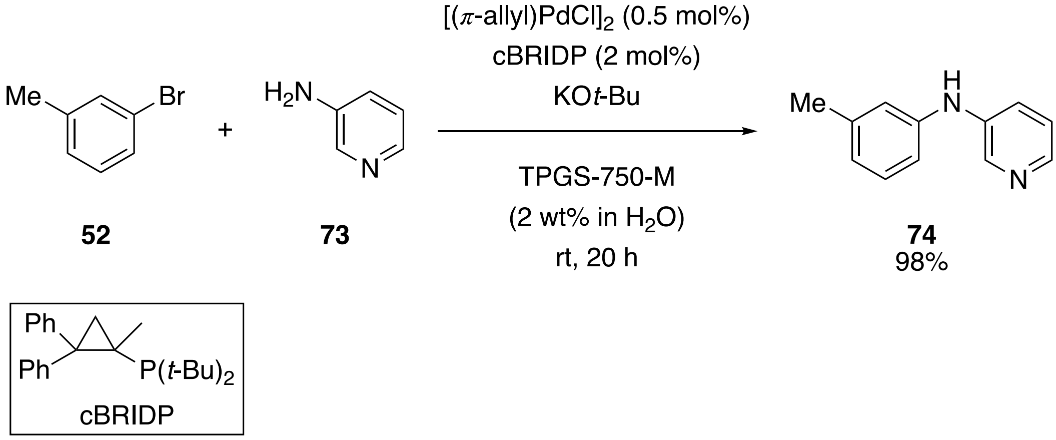
Boche *et al*. reported a Buchwald-Hartwig amination in a biphasic mixture of water/butan-2-ol using a water soluble bidentate phosphine ligand.[95] Cross-coupling of 4-

bromoacetophenone **70** and *N*-methylaniline **56** with Pd(OAc)$_2$, water-soluble phosphine ligand (BINAS-6 **71**) and NaOH gave tertiary amine **72** in 81% yield (Scheme 2.15). When the reaction was exclusively carried out in water, a lower yield of tertiary amine **72** was obtained (36%). A reason for this difference in yields is not provided. However, this is likely a result of the insolubility of the reagents in water. As such, a miscible co-solvent was required to increase the solubility of the reactants and improve reaction performance.



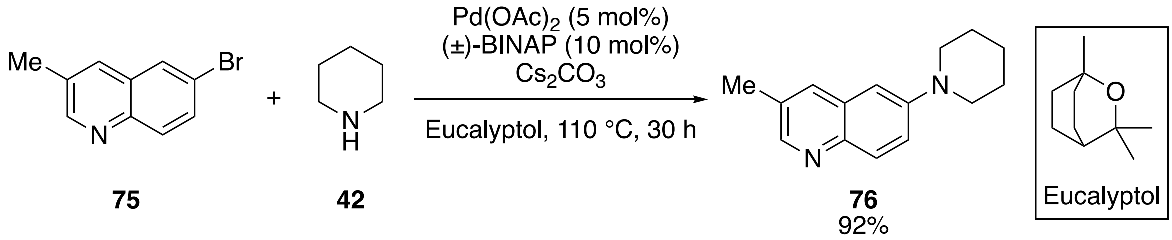
Scheme 2.15: Buchwald-Hartwig amination in H$_2$O/butan-2-ol using a water-soluble phosphine ligand

In 2011, Lipshutz and co-workers reported that the addition of an amphiphile (TPGS-750-G) which aids the solubilisation of reagents in water enabled the Buchwald-Hartwig amination to take place.[96] Addition of this amphiphile to water generates micellar reactors within the aqueous media providing lipophilic pockets where the reaction can take place. As an example, aryl bromide **52** was coupled with heteroaryl amine **73** using [(π-allyl)PdCl]$_2$ and cBRIDP as the catalyst and KO*t*-Bu in water and TPGS-750-G. This gave secondary amine **74** in 98% yield (Scheme 2.16). The scope of the reaction in water was unexplored by Lipshutz with only two examples reported. The Schmitt group independently reported *t*-BuXPhos as a vastly superior ligand to cBRIDP in this reaction in water/micelles. It provided an improved substrate tolerance and higher yields in a comparative study comparing the two ligands.[97]



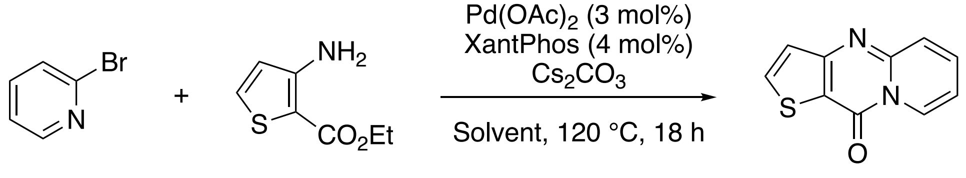
Scheme 2.16: Buchwald-Hartwig amination in water/micelles

Berteina-Raboin and Campos have recently shown that the bioderived monoterpene bicyclic ether molecule, eucalyptol, can be used as a suitable replacement for hydrocarbon-based solvents in Buchwald-Hartwig amination.[98] In one example, heteroaryl bromide **75** was cross-coupled with piperidine **42** using $Pd(OAc)_2$, (±)-BINAP and Cs_2CO_3 in eucalyptol at 110 °C for 30 h which formed tertiary amine **76** in 92% yield (Scheme 2.17). A comparison was made between the reaction performance in eucalyptol and literature yields in commonly used solvents; eucalyptol was found to give comparable and, in some cases, improved yields in the Buchwald-Hartwig aminations reported.



Scheme 2.17: Use of eucalyptol as solvent for Buchwald-Hartwig aminations

A comparative study between toluene and alternative ether solvents eucalyptol, 2-MeTHF and CPME in a Buchwald-Hartwig amination and subsequent pyridine dearomatisation was examined by Berteina-Raboin and co-workers (Table 2.1).[99] In toluene, 2-bromopyridine **77** and aminothiophene **78** was cross-coupled using $Pd(OAc)_2$, XantPhos and Cs_2CO_3 at 120 °C for 18 h; pyridine dearomatisation then formed tricyclic product **79** in 86% yield (entry 1). Using otherwise identical reaction conditions, eucalyptol facilitated the reaction in a comparable 87% yield (entry 2). The cross-coupling reaction was also well tolerated in 2-MeTHF and CPME forming tricyclic product **79** in 89% and 82% yields respectively (entries 3 and 4). From these comparative solvent studies, ether solvents are suitable solvents for Buchwald-Hartwig aminations facilitating the cross-coupling of aryl halides and amine in high yields. The low dipolarity of ethers likely prevent the β-hydride elimination pathway that had been observed in polar aprotic solvents.[92]

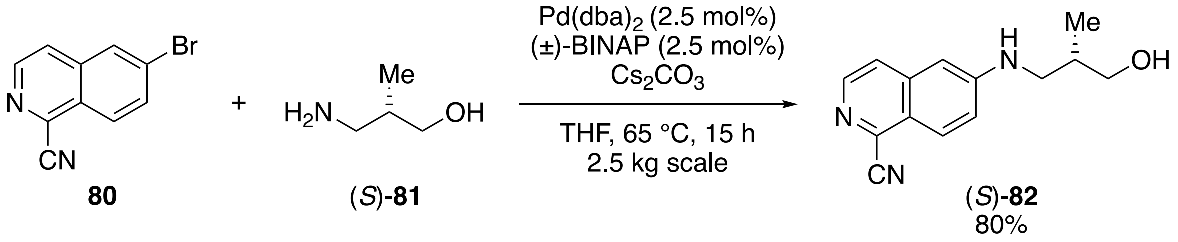


77 **78** **79**

Entry	Solvent	Yield (%)
1	Toluene	86
2	Eucalyptol	87
3	2-MeTHF	89
4	CPME	82

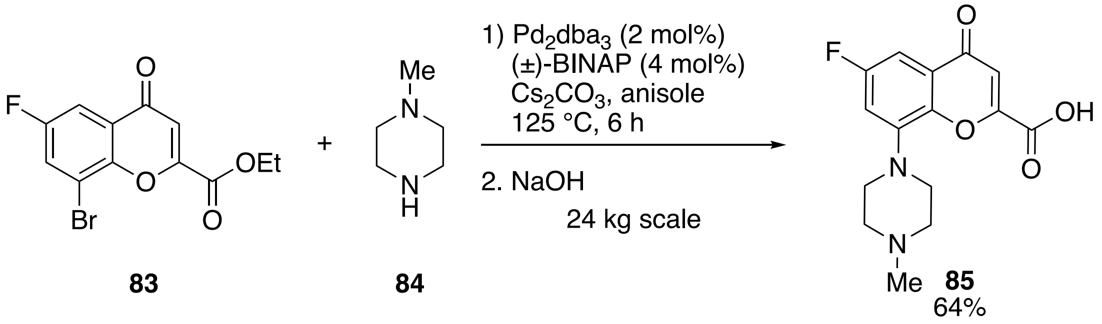
Table 2.1: Comparative study between toluene and alternative ether solvents in Buchwald-Hartwig cross-coupling and pyridine dearomatisation

The versatility of the Buchwald-Hartwig amination has led to its widespread use in the synthesis of *N*-arylamines in pharmaceutical, agrochemicals and natural products in both academia and in industrial settings up to multi-kg scales. A number of extensive reviews detailing such uses of the Buchwald-Hartwig amination has been published.[60,73,75,77,100–103] Researchers at Pfizer reported the scale-up and optimisation of the Buchwald-Hartwig cross-coupling reaction between heteroaryl bromide **80** and chiral amine (*S*)-**81** required for the synthesis of pharmaceutically-active intermediate (*S*)-**82**.[104] Over-arylation of the amine (*S*)-**82** proved to be a significant problem but this was overcome with the use of chelating ligand (±)-BINAP which prevented this undesired reaction. Optimised conditions used Pd(dba)$_2$, (±)-BINAP and Cs_2CO_3 in THF at 65 °C and gave heteroaryl amine (*S*)-**82** in 80% yield on a 2.5 kg scale (Scheme 2.18).



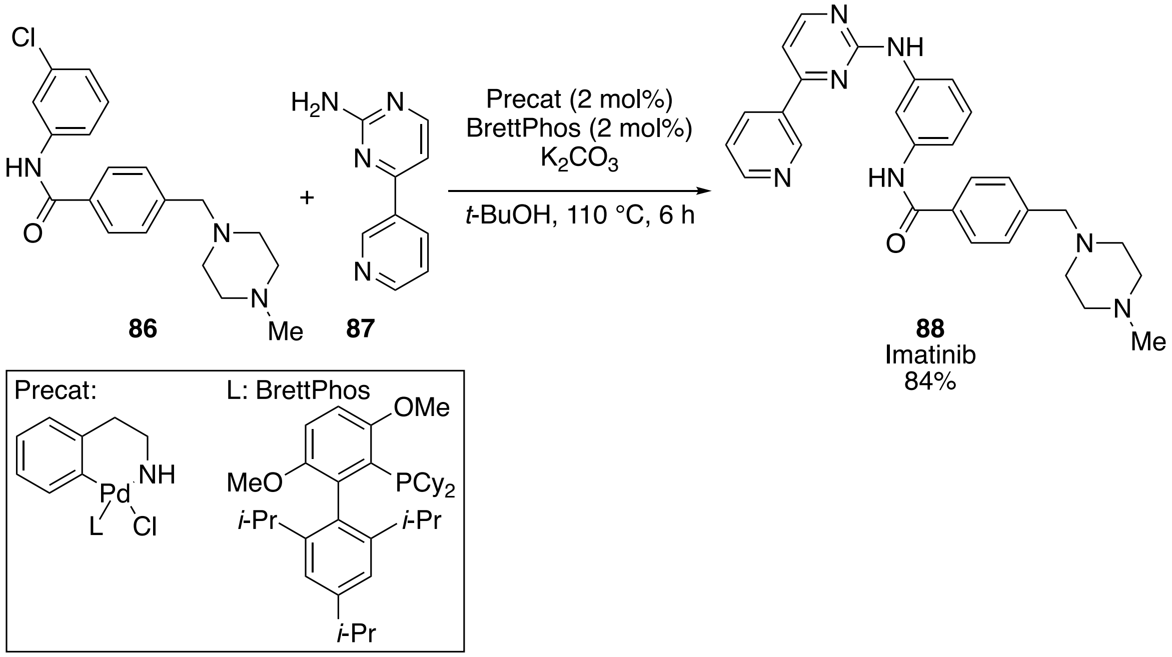
Scheme 2.18: Use of a Buchwald-Hartwig amination in the synthesis of pharmaceutically-active intermediate (*S*)-**82**

In 2004, researchers at AstraZeneca reported a Buchwald-Hartwig amination in the synthesis of an intermediate to the potent 5-HT_{1B} receptor antagonist ZM549865 developed as a potential treatment for depression and anxiety.[105] Coupling between bromoester **83** and *N*-methylpiperazine **84** with Pd_2dba_3, (±)-BINAP and Cs_2CO_3 in anisole provided access to intermediate tertiary amine**.** Subsequent base-catalysed ester hydrolysis with NaOH afforded the desired tertiary amine **85** in 64% yield over two steps on a 24 kg scale (Scheme 2.19).



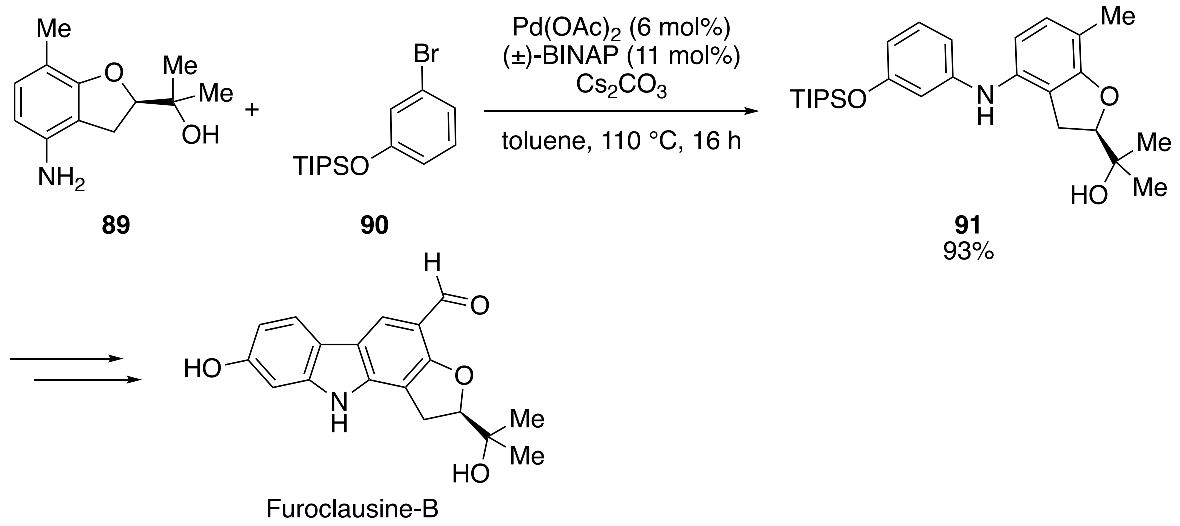
Scheme 2.19: Use of a Buchwald-Hartwig amination in the synthesis of ZM549865 intermediate **85**

The Buchwald group reported the use of a Buchwald-Hartwig amination in the final step of a synthesis of Imatinib **88**, a protein kinase inhibitor used in the treatment of chronic myelogenous leukaemia.[106–109] Coupling of aryl chloride **86** with heteroaryl amine **87** was achieved with BrettPhos pre-catalyst and K_2CO_3 in *t*-BuOH at 110 °C for 6 h constructing Imatinib **88** in 84% yield (Scheme 2.20).



Scheme 2.20: Use of a Buchwald-Hartwig amination in the synthesis of Imatinib **88**.

Knölker employed a Buchwald-Hartwig amination in the synthesis of Furoclausine-B, a furocarbazole alkaloid from the root bark of *Clausena excavate*.[61,110] Enantioenriched arylamine **89** was cross-coupled with aryl bromide **90** using $Pd(OAc)_2$, (±)-BINAP and Cs_2CO_3 in toluene to give secondary amine **91** in 93% yield. Further reactions led to the formation of Furoclausine-B (Scheme 2.21).



Scheme 2.21: Use of a Buchwald-Hartwig amination in the synthesis of natural product Furoclausine-B

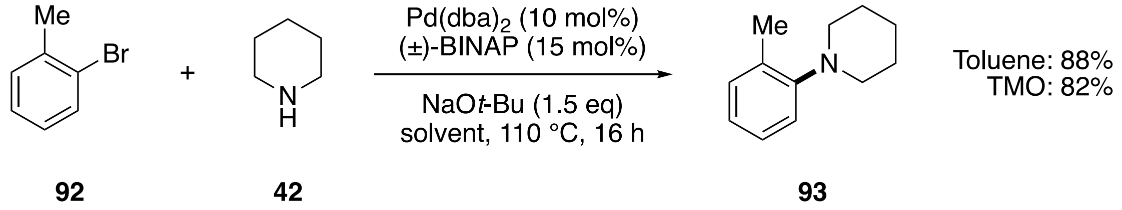
2.3 Buchwald-Hartwig Aminations in TMO

The applications described in the previous section showcased the prevalence of Buchwald-Hartwig aminations in the synthesis of pharmaceutically-active compounds as well as natural products. Its versatility has helped the reaction become one of the most valuable methodologies in the toolkit of a modern synthetic chemist. The main focuses of research involving Buchwald-Hartwig aminations have been the development of new ligands in order to further develop the reaction's substrate scope.[73,75,76,111,112] Solvent choice in the reaction is usually based on the solubility of the substrates and, the use of green solvents in this reaction has, in many cases, been neglected. Buchwald-Hartwig aminations of aryl bromides and primary and secondary amines most commonly employ toluene, 1,4-dioxane and THF as the reaction solvents. In some cases, where solubility issues have arisen with more polar substrates, NMP and DMF have occasionally been utilised.[73,76,77,112,113] There are some reported examples of Buchwald-Hartwig aminations carried out in alternative ether solvents and water.[94–99] The alternative solvents used, namely, eucalyptol, 2-MeTHF and CPME exhibit either peroxide formation or a high boiling point. Furthermore, in water, complex water-soluble phosphine ligands or additives were required to facilitate the cross-coupling reaction. As such, the reaction was chosen to demonstrate the utility of TMO as a prospective alternative to toluene and showcase TMO's potential as a solvent in synthetic applications.

In this chapter, a comparative study detailing the use of toluene and TMO in Buchwald-Hartwig aminations using NaO*t*-Bu as the base is described. Buchwald-Hartwig reactions of aryl bromides and amines featuring nucleophile- and base-sensitive substituents using Cs_2CO_3 as the base in toluene and TMO will also be presented. This includes the synthesis of an intermediate of a pharmaceutically-relevant compound. Lastly, sustainable considerations and a metric assessment of the Buchwald-Hartwig amination in toluene and TMO will be discussed to ascertain the greenness of the process in both solvents.

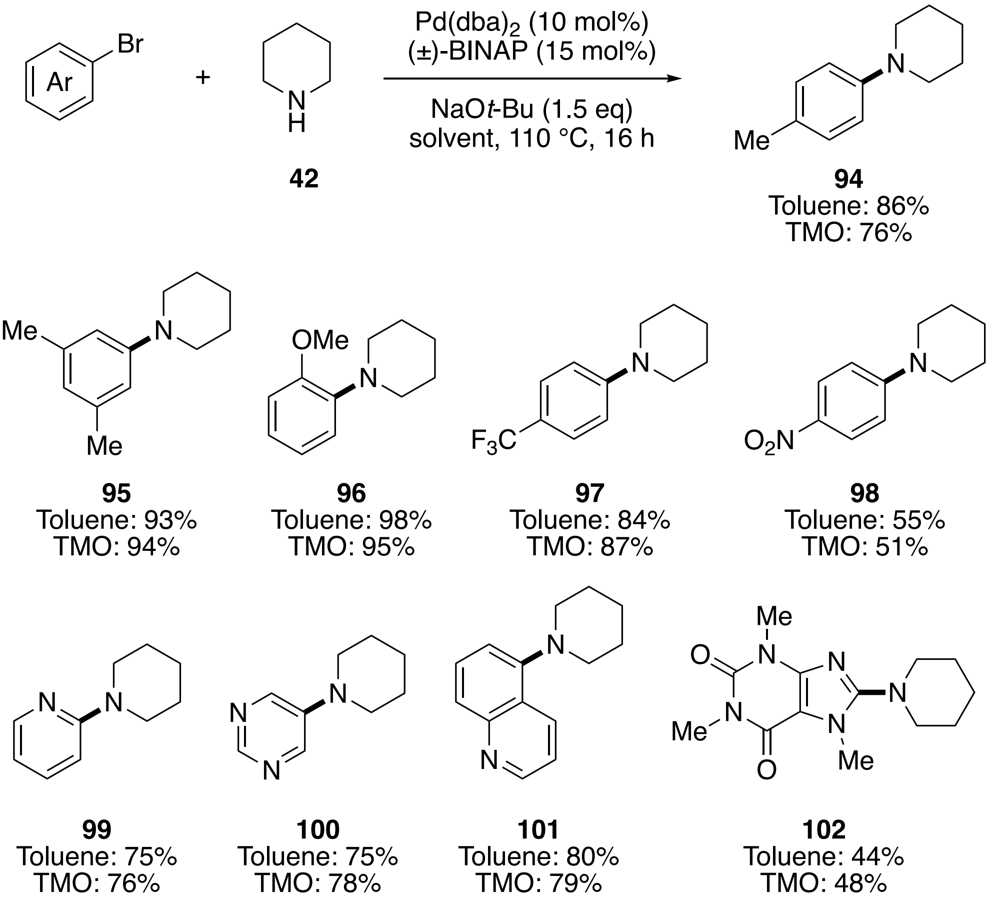
2.3.1 Buchwald-Hartwig Aminations in TMO – NaO*t*-Bu as the Base

First, an investigation into the use of TMO in Buchwald-Hartwig aminations with NaO*t*-Bu employed as the base was carried out and a comparison against toluene was made. The studies described in section 2.2 showed that a combination of $Pd(dba)_2$ and (±)-BINAP is an effective and widely used catalyst system and it was thus chosen as the catalyst and ligand for this investigation.[67,75,111,114] To start, cross-coupling of 2-bromotoluene **92** and piperidine **42** with $Pd(dba)_2$ (10 mol%), (±)-BINAP (15 mol%) and NaO*t*-Bu in toluene at 110 °C gave tertiary amine **93** in 88% yield after chromatography. Pleasingly, when the reaction was run in TMO there was no observable difference compared to toluene and an 82% yield of tertiary amine **93** was obtained (Scheme 2.22).



Scheme 2.22: Comparison of toluene and TMO in the Buchwald-Hartwig amination

Having established effective conditions for the Buchwald-Hartwig amination in toluene and TMO, the aryl bromide scope was explored (Scheme 2.23). First, the coupling of simple aryl bromides bearing substituents in the *ortho*-, *meta*- and *para*-positions with piperidine **42** was investigated. In toluene, the cross-coupling of the aryl bromides with piperidine **42** to form tertiary amines **94**–**97** proceeded without issue and high yields were obtained in all examples (84–98%). Upon switching the solvent to TMO, comparable yields of tertiary amines **94**–**97** were achieved (76−95%). However, for the cross-coupling of an aryl bromide featuring a nitro group and piperidine **42**, only modest yields of tertiary amine **98** were achieved in both solvents (55% for toluene and 51% for TMO). The moderate yield of tertiary amine **98** is presumably a result of the base sensitivity of the aryl bromide.[65,72] The more challenging cross-coupling of heteroaryl bromides with piperidine **42** was then explored. 2-Pyridinyl, 5-pyrimidinyl, and the sterically encumbered 5-quinolinyl-coupled products (**99**−**101** respectively) were all synthesised in good yields in TMO (76−79%). Coupling of complex aryl bromide 8-bromocaffeine with piperidine **42** was also possible, furnishing tertiary amine **102** in 48% yield. In toluene, the coupling of heteroaryl bromides with piperidine **42** was achieved in similar yields compared to TMO (44−80%).



42

94
Toluene: 86%
TMO: 76%

95
Toluene: 93%
TMO: 94%

96
Toluene: 98%
TMO: 95%

97
Toluene: 84%
TMO: 87%

98
Toluene: 55%
TMO: 51%

99
Toluene: 75%
TMO: 76%

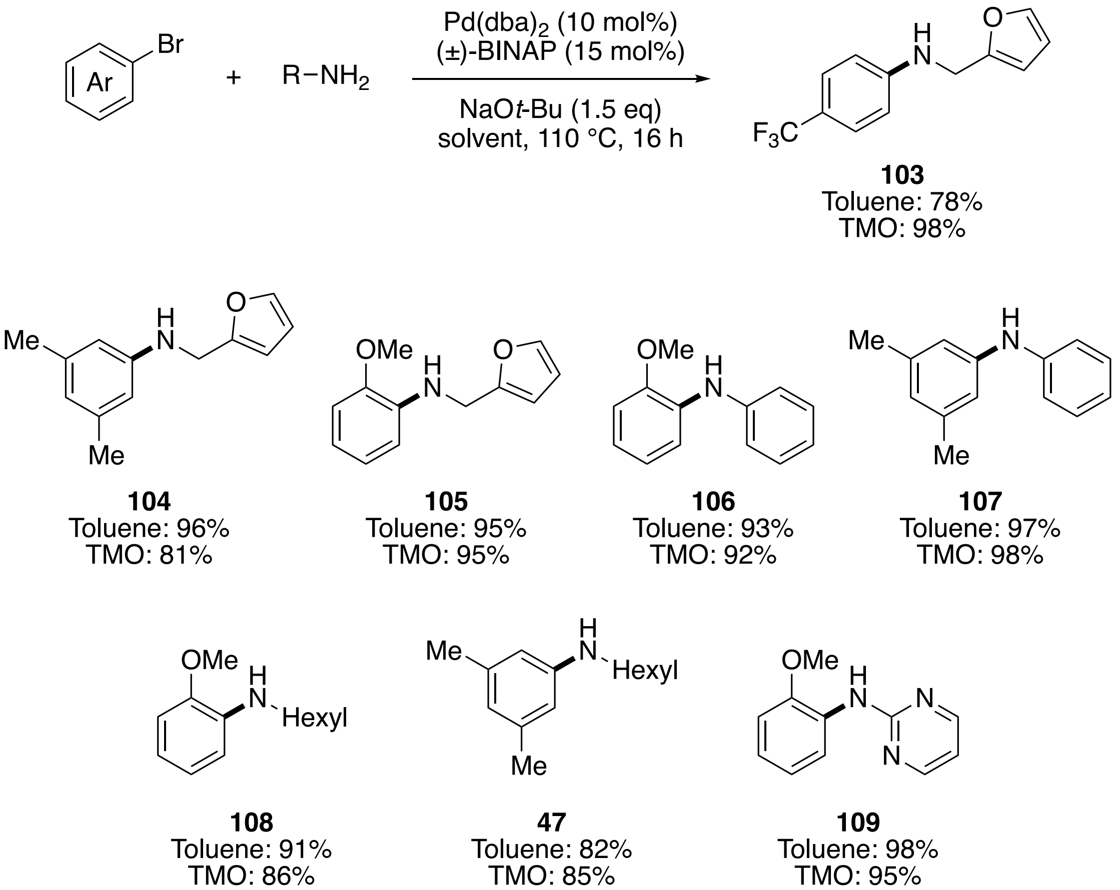
100
Toluene: 75%
TMO: 78%

101
Toluene: 80%
TMO: 79%

102
Toluene: 44%
TMO: 48%

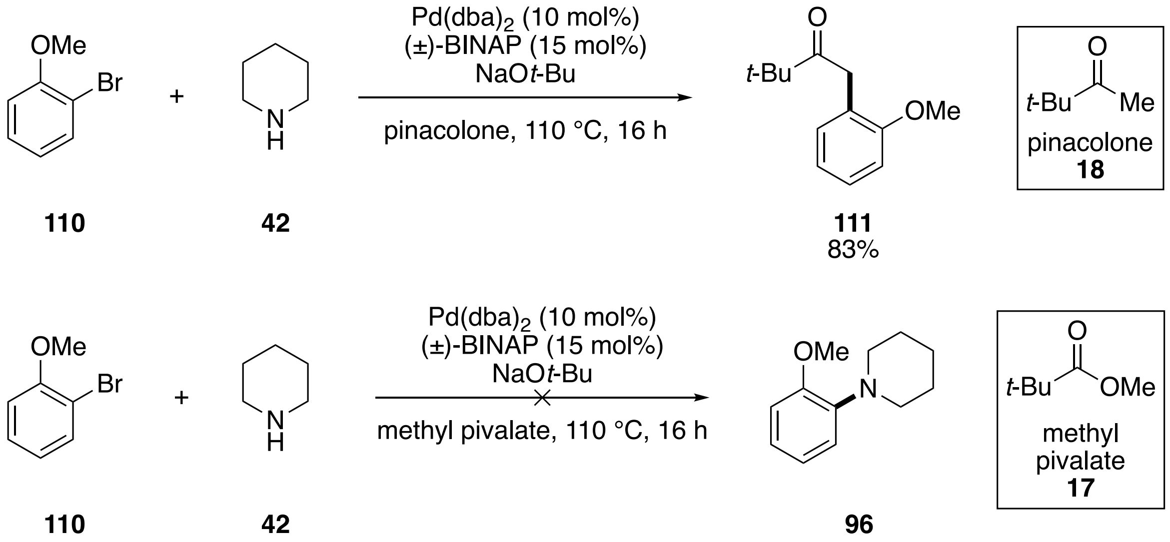
Scheme 2.23: Buchwald-Hartwig amination of aryl bromides and piperidine **42** in toluene and TMO using NaO*t*-Bu as the base

Primary amines were subsequently investigated in the cross-coupling reaction with a range of aryl bromides (Scheme 2.24). (±)-BINAP was chosen as the ligand for this cross-coupling reaction as it has been reported that (±)-BINAP discourages over-arylation of the amine and hydrodehalogenation of the aryl halide.[67,114] Furfurylamine, an amine readily sourced from biomass and a component of the *N*-aryl-furfurylamine moiety present in the diuretic and hypertensive agent furosemide,[115] was cross-coupled with aryl bromides in TMO constructing secondary amines **103−105** in 81−98% yield. Similar yields of **103−105** were achieved in toluene (78−96%). Aniline **48** and *n*-hexylamine **46** were also cross-coupled with aryl bromides in both solvents without issue, constructing secondary amines **47**, **106−108** in 85−98% yield in TMO and 82−97% yield in toluene. The coupling of heteroaryl amine 2-aminopyrimidine with 2-bromoanisole was possible, forming secondary amine **109** in 95% yield in TMO and 98% yield in toluene. It is clear from the results obtained in this substrate scope that, when using NaO*t*-Bu as the base, no significant variation in product yield was observed when comparing the two solvents. TMO is thus promising as a direct replacement for toluene in Buchwald-Hartwig aminations when this base is employed in the reaction.



Scheme 2.24: Buchwald-Hartwig amination of aryl bromides and primary amines in toluene and TMO using NaO*t*-Bu as the base

With the promising results achieved in Buchwald-Hartwig aminations with TMO as the solvent, an investigation into the use of other alternative solvents for this cross-coupling reaction was carried out. The alternative solvents chosen for this investigation were pinacolone **18** and methyl pivalate **17**, both of which have been reported as potential alternative solvents to toluene.[46] The cross-coupling of 2-bromoanisole **110** and piperidine **42** with Pd(dba)$_2$ and (±)-BINAP with NaO*t*-Bu was chosen as the representative example (Scheme 2.25). In pinacolone **18**, none of the desired coupled product **96** was formed; instead, enolate arylation was the preferential reaction pathway forming ketone **111** in 83% yield. Palladium-catalysed arylation of enolisable ketones has previously been reported.[116] This result is presumably due to the large excess of solvent relative to the amine in the reaction. In methyl pivalate, upon heating the reaction mixture, a tar-like substance formed which restricted the stirring of the mixture and no evidence of the coupled product **96** was observed. Evident by the failures of these two reactions, TMO distinguishes itself from other alternative solvents with potential to replace toluene in Buchwald-Hartwig aminations when NaO*t*-Bu is used as the base.

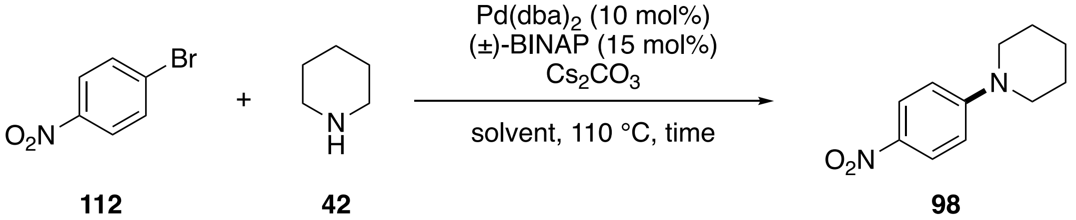


Scheme 2.25: Use of pinacolone **18** and methyl pivalate **17** for Buchwald-Hartwig aminations

In summary, it has been shown that TMO is a suitable direct replacement for toluene in Buchwald-Hartwig cross-coupling when NaO*t*-Bu is employed as the base. The cross-coupling of aryl bromides with primary and secondary amines was achieved in good to excellent yields in TMO. The cross-coupling of challenging heteroaryl bromides and heteroaryl amines was also possible in TMO. In all examples, comparative yields were obtained when the reaction was carried out in toluene. Furthermore, the use of alternative solvents that have the potential to replace toluene, pinacolone and methyl pivalate, was unsuccessful due to undesirable side reactions as a result of the inherent structural features present in these solvents. This distinguishes TMO from these alternative solvents in this amination reaction.

2.3.2 Buchwald-Hartwig Amination – Cs_2CO_3 as the Base

The use of Cs_2CO_3, a milder base compared to NaO*t*-Bu, for the coupling of base- and nucleophile-sensitive aryl bromides and amines such as those containing nitro and nitrile substituents has been advocated by Buchwald and Wolfe.[72,114] This has expanded the substrate scope of the Buchwald-Hartwig amination considerably. In the previous section, only moderate yields for the coupling of 1-bromo-4-nitrobenzene **112** with piperidine **42** were obtained in toluene (51%) and TMO (55%) when NaO*t*-Bu was used as the base. These yields are significantly lower than those achieved in all the other examples (see Scheme 2.23). As such, the cross-coupling of the base-sensitive aryl bromide **112** and piperidine **42** was revisited utilising Cs_2CO_3 as the base in place of NaO*t*-Bu (Table 2.2). Under other identical reaction conditions (110 °C, 16 h), in TMO, tertiary amine **98** was isolated in only 30% yield (entry 1). However, a notable quantity of unreacted aryl bromide **112** was observed in the ^1H NMR spectrum of the crude product. Hence, the reaction time was increased to 72 h in order to allow the reaction to reach completion. Pleasingly, a much-improved yield of tertiary amine **98** was achieved (75%) (entry 2). This is a considerable enhancement on the yield obtained compared to when NaO*t*-Bu was used as the base (51%). A comparison with toluene was then made and, interestingly, after 72 h, only a 50% yield of tertiary amine **98** was obtained (entry 3).



Entry	Time (h)	Solvent	Yield (%)[a]
1	16	TMO	30
2	72	TMO	75
3	72	Toluene	50

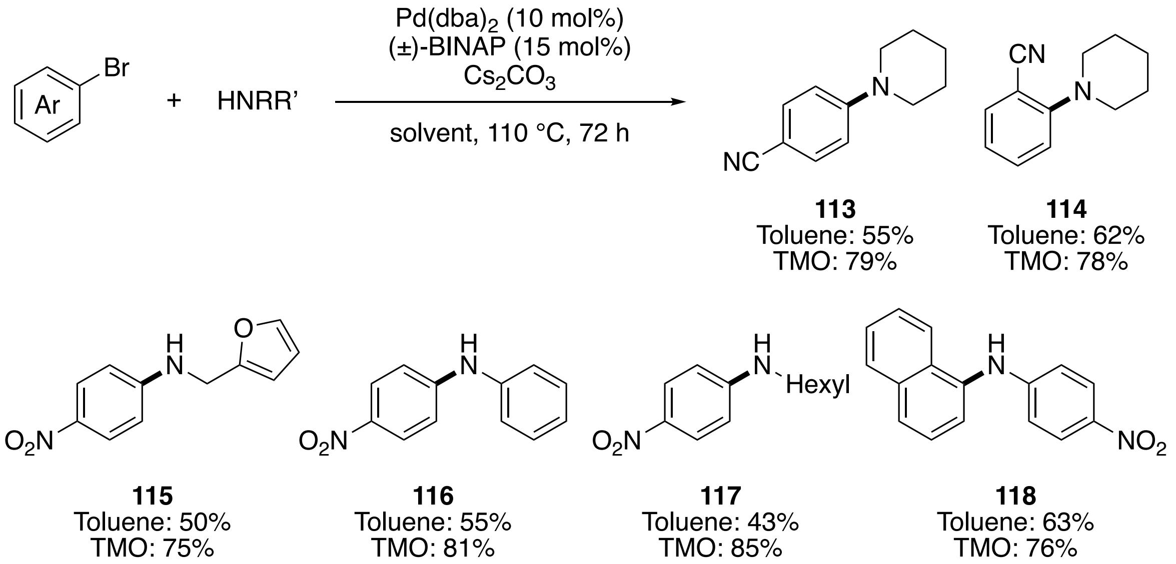
Table 2.2: Buchwald-Hartwig amination of aryl bromide **112** and piperidine **42** using Cs_2CO as base. [a]Yield after chromatography

In order to explore the difference in the yield in TMO compared to toluene, an investigation into the solubility of Cs_2CO_3 in both solvents was carried out. It has been reported that Cs_2CO_3 is virtually insoluble in toluene and that the amine deprotonation step occurs at the solid-liquid phase boundary.[83,117] Furthermore, amine deprotonation is believed to be rate-determining when a poorly soluble weak base is used. This has resulted in the particle size and shape of the insoluble base having a considerable influence on the reaction outcome, with Cs_2CO_3 from different suppliers exhibiting differing reactivities. Use of SEM imaging has supported this claim as a correlation between the base's performance in the cross-coupling reaction and its particle properties have been observed.[73,83] It must also be noted that a number of research groups have reported improved yields when Cs_2CO_3 has been ground to increase the surface area of the base prior to use.[72,118,119] We hypothesised that a small increase in the solubility of Cs_2CO_3 in TMO compared to toluene could account for the higher-yielding reactions observed in TMO as the deprotonation step would not be as reliant on interactions on the solid-liquid phase boundary. To assess this, a simple solubility screen was performed. In separate flasks of each solvent, Cs_2CO_3 was stirred at 110 °C for 72 h to mimic the reaction conditions. The solutions were then cooled to room temperature and filtered to remove excess solids and the solvents were analysed using ICP-MS to determine the concentration of Cs in both solvents (Table 2.3). Cs_2CO_3 was confirmed to be insoluble in toluene as the Cs concentration was below quantifiable levels (<0.6 ppb, entry 1). Contrary to this, the Cs concentration in TMO was quantified at 484 ppb (entry 2), several orders of magnitude higher than that observed in toluene. The results gathered from the ICP-MS analysis logically account for the discrepancy in performance between the two solvents with this base, especially if the amine deprotonation step is rate determining.[83]

Entry	**Solvent**	**Cs concentration (ppb)**
1	Toluene	<0.6
2	TMO	484

Table 2.3: ICP-MS analysis of Cs content in toluene and TMO

The aryl bromide and amine scope with Cs_2CO_3 was investigated in TMO and toluene and the reaction yields were compared (Scheme 2.26). Piperidine **42** was coupled with 4-bromobenzonitrile to form tertiary amine **113** in 55% yield in toluene and 79% yield in TMO. The cross-coupling of 2-bromobenzonitrile and piperidine **42** was also successful in constructing tertiary amine **114** in 62% yield in toluene and 78% yield in TMO. Coupling of furfurylamine, aniline **48** and *n*-hexylamine **46** with 1-bromo-4-nitrobenzene **112** was also tolerated providing access to secondary amines **115−117** in 43−55% yield in toluene and 76−85% yield in TMO. Finally, secondary amine **118** was furnished in 76% yield in TMO. However, consistent with the previous results obtained in toluene, a lower yield was obtained in toluene (63%).



113
Toluene: 55%
TMO: 79%

114
Toluene: 62%
TMO: 78%

115
Toluene: 50%
TMO: 75%

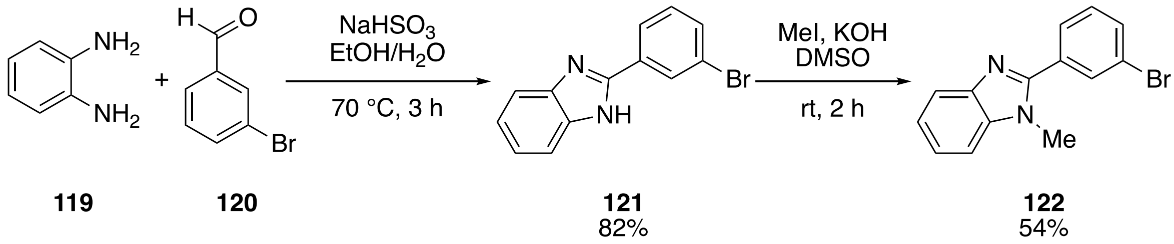
116
Toluene: 55%
TMO: 81%

117
Toluene: 43%
TMO: 85%

118
Toluene: 63%
TMO: 76%

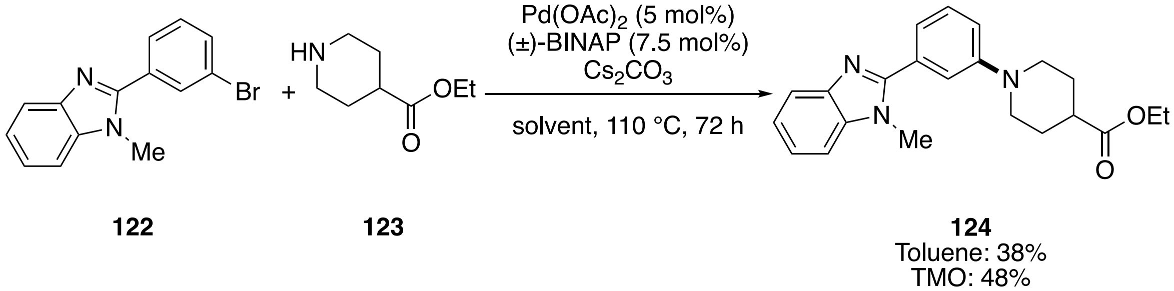
Scheme 2.26: Buchwald-Hartwig amination in toluene and TMO using Cs_2CO_3 as the base

With a desire to further demonstrate the utility of carrying out Buchwald-Hartwig aminations in TMO, our methodology was extended to the synthesis of tertiary amine **124**, an intermediate in the synthesis of drug candidate SEN826 an SMO (smoothened) receptor antagonist. SMO receptor antagonists are a drug class which is critical for the treatment of a number of different cancers, blocking the signalling pathways for cell development, differentiation, growth and migration.[119,120] It was first required to synthesise bromo-benzimidazole **122** prior to the cross-coupling reaction. Following the literature procedure developed by Betti and co-workers, diamine **119** was treated with aryl bromide **120** and $NaHSO_3$ in EtOH at 70 °C for 3 h.[119] Benzimidazole **121** precipitated during the course of the reaction and could be isolated without further purification *via* filtration and an EtOH/H_2O wash in 82% yield. Next, methylation of benzimidazole **121** was carried out using KOH and MeI in DMSO. Bromo-benzimidazole **122** precipitated through the course of the reaction and the crude product was isolated *via* filtration. Recrystallisation from *i*-PrOAc provided bromo-benzimidazole **122** in 54% yield (Scheme 2.27).



Scheme 2.27: Synthesis of bromo-benimidazole **122**

Buchwald-Hartwig amination with bromo-benzimidazole **122** and secondary amine **123** was then carried out. Using the conditions developed by Betti,[119] $Pd(OAc)_2$, (±)-BINAP and Cs_2CO_3 (required to tolerate the nucleophile-sensitive ester group present in the amine substrate **123**) facilitated the coupling and provided tertiary amine **124** in a modest 48% yield in TMO. In toluene, under otherwise identical conditions, tertiary amine **124** was obtained in 38% yield (Scheme 2.28). This further demonstrated the improved yields achieved in TMO compared to toluene when Cs_2CO_3 is employed as the base. However, it must be noted that purification of the tertiary amine **124** in toluene was achieved *via* recrystallisation from the crude residue at −20 °C. This was not possible in TMO and removal of the solvent was required followed by recrystallisation from toluene allowing isolation of the pure tertiary amine **124**.

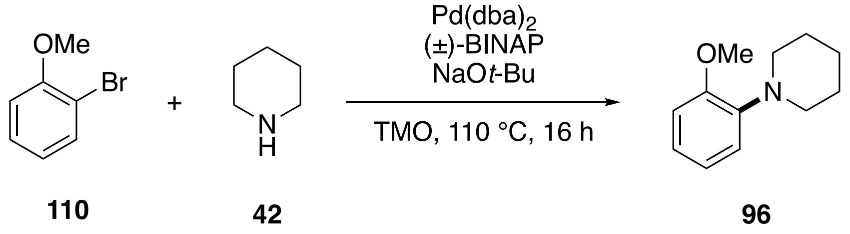


Scheme 2.28: Buchwald-Hartwig amination for the synthesis of SEN826 intermediate **124**

In summary, TMO has been shown to be an excellent solvent for Buchwald-Hartwig aminations when Cs_2CO_3 was used as the base. Significantly higher yields were achieved in TMO compared to when toluene was used as the solvent in the coupling of base- and nucleophile-sensitive substrates. ICP-MS analysis suggests that enhanced performance may be a result of greater solubilisation of the Cs_2CO_3 in TMO compared to toluene. Furthermore, the construction of SEN826 intermediate **124** was accomplished in TMO highlighting the significant potential offered by TMO as a solvent for critical cross-coupling reactions in the synthesis of bioactive compounds, particularly when the coupling of base-sensitive substrates is required.

3.3.3 Sustainability Considerations and Metrics Assessment

Palladium is a metal of wide importance and is utilised in a number of different applications which include catalytic convertors, hydrogenation reactions and an array of cross-coupling reactions, including Buchwald-Hartwig aminations. Palladium is a precious metal and has a low natural abundance. Issues surrounding its medium- to long-term supply are concerning considering that the metal is utilised in the synthesis of numerous pharmaceutical and fine chemicals.[121,122] The usefulness of palladium coupled with its diminishing global supplies means that it is viewed as a critical element and therefore one where a more sustainable approach to its use is necessary.[123,124] In some cases, however, where replacement of the critical element is not trivial and recovery and reuse are currently uneconomical, the next most sustainable method is to develop improved catalytic systems that are effective with low quantities of the critical element. The catalyst loadings used in the previous sections were relatively high (10 mol% Pd) and, therefore, an investigation into Buchwald-Hartwig aminations at lower catalyst loadings in TMO was carried out. The coupling of 2-bromoanisole **110** and piperidine **42** to form tertiary amine **96** was chosen as the model example utilising NaO*t*-Bu as the base (Table 2.4). The $Pd(dba)_2$ and (±)-BINAP molar ratio was maintained at 1:1.5 throughout and thus any changes in palladium loading correspond to an equivalent change in ligand loading. At 10 mol% $Pd(dba)_2$, tertiary amine **96** formed in 95% yield (entry 1, see Scheme 2.23). A ten-fold reduction in the catalyst loading to 1 mol% $Pd(dba)_2$ was used and, pleasingly, an 82% yield of tertiary amine **96** was obtained (entry 2). This is only a small drop in yield compared to when 10 mol% $Pd(dba)_2$ was used. However, further reduction of the catalyst loading to 0.5 mol% resulted in a considerably diminished yield of 50% and only 5% of tertiary amine **96** was isolated when a catalyst loading of 0.25 mol% was used (entry 3 and 4 respectively).



Entry	Pd loading (mol%)	(±)-BINAP loading (mol%)	Yield (%)[a]
1	10	15	95
2	1	1.5	82
3	0.5	0.75	50
4	0.25	0.375	5

Table 2.4: An investigation into decreased catalyst loadings for the Buchwald-Hartwig amination in TMO. [a]Yield after chromatography

With the promising result achieved when catalyst loadings at 1 mol% were utilised, the coupling of four more examples were chosen in order to prove the generality of the reaction at this low catalyst loading (Figure 2.3). First, with examples using NaO*t*-Bu as the base, heteroaryl amine **101** and secondary amine **103** were synthesised in 79% yield and 86% yield respectively. These yields are similar to those obtained when the reaction was carried out using 10 mol% catalyst loading (79% and 98% respectively). Similarly, the coupling of base-sensitive substrates with primary and secondary amines, using Cs_2CO_3 as the base, constructing tertiary amine **98** and secondary amine **115** was possible in 74% and 69% yields respectively. At 10 mol% catalyst loading, tertiary amine **98** was formed in 75% yield whereas secondary amine **115** was also formed in 75% yield. Hence, Buchwald-Hartwig aminations utilising both NaO*t*-Bu and Cs_2CO_3 in TMO, at catalyst loadings as low as 1 mol%, were possible without significant diminishment of the yields compared to when the reaction was performed using 10 mol% catalyst loading.

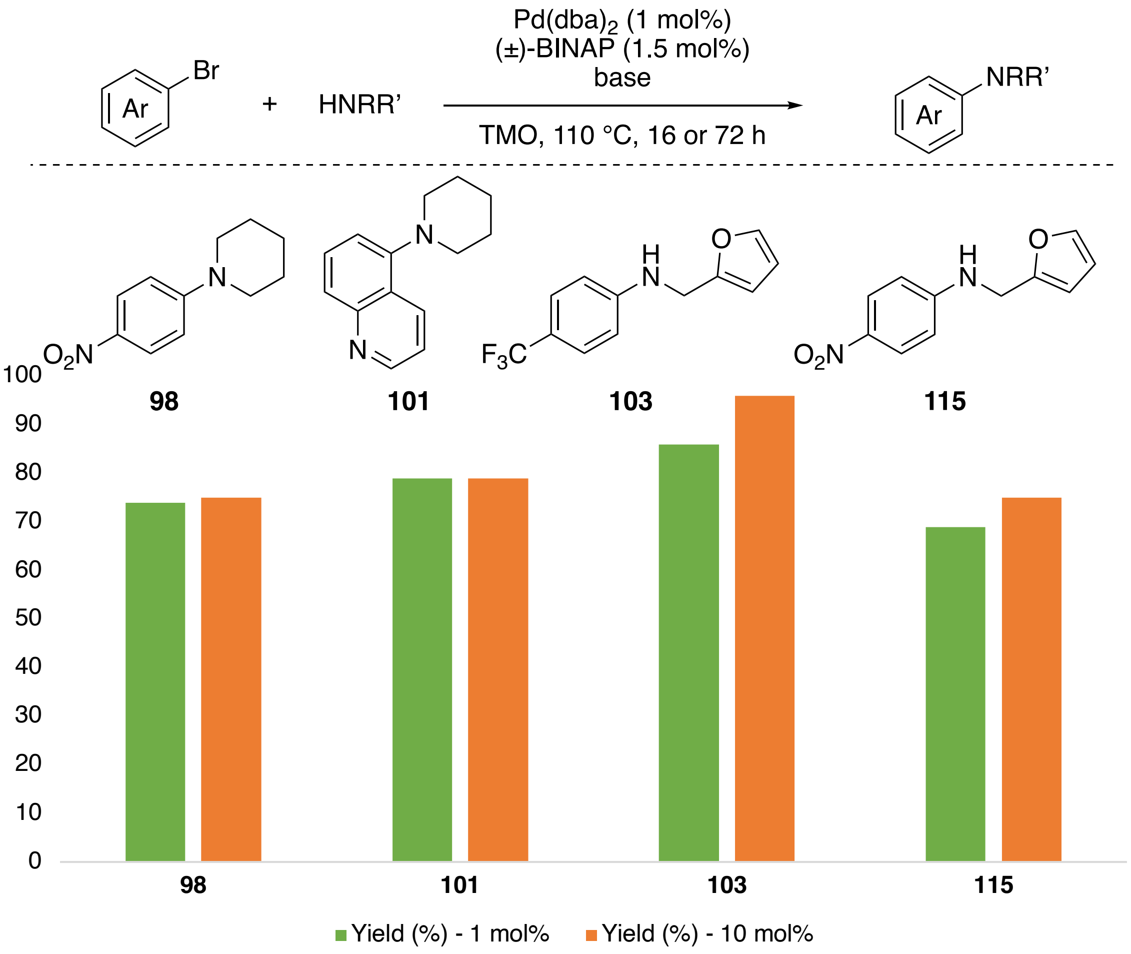


Figure 2.3: Comparison of Buchwald-Hartwig aminations in TMO at 1 mol% and 10 mol% palladium loadings

Residual palladium can be present in the isolated compound even after column chromatography. This can be particularly problematic when the compounds are intended for use in the pharmaceutical industry as extra purification steps are required for the removal of the metal. As such, ICP-MS analysis of isolated samples of amines **106**, **47** and **124** was conducted to establish the residual palladium content in the isolated products and to determine if any difference in palladium content is observed when the reaction was run in either solvent (Table 2.5). In all three of the amines tested, the detected levels of palladium were lower in those synthesised in TMO compared to those using toluene solvent. For amine **106**, palladium content in TMO was 0.7841 ppm whereas in toluene, palladium content was 1.4267 ppm. For amine **47**, slightly higher palladium content were observed: 2.4204 ppm in TMO and 3.6600 ppm in toluene. However, these values are below the pharmaceutical regulatory maximum of 5 ppm in both solvents.[125,126] Residual palladium levels were considerably higher in tertiary amine **124** (38.0947 ppm in TMO and 46.7501 ppm in toluene) and would require further purification before use in a drug development setting. Amines **106** and **47** were purified *via* flash column chromatography whereas amine **124** was purified *via* recrystallisation which could account for the notable differences in palladium content between the samples. Nevertheless, the preliminary data indicates that TMO offers a tangible benefit to the sustainability of Buchwald-Hartwig aminations by allowing both lower catalyst loadings and reducing palladium contamination in the isolated product.

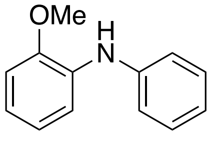
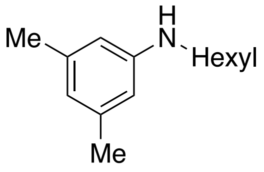
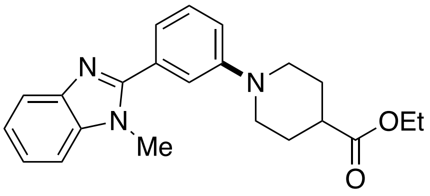
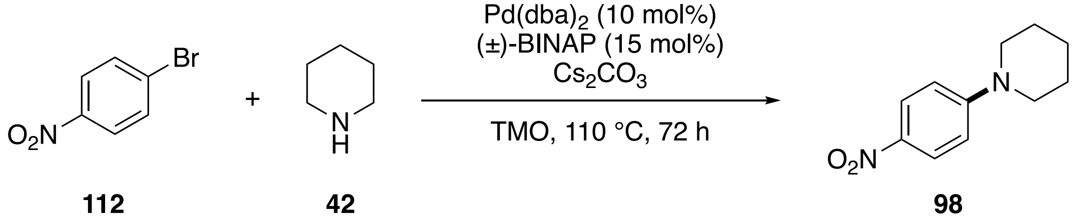
Aryl Amine	**Palladium Content (TMO)**	**Palladium Content (Toluene)**
 **106**	0.7861 ppm	1.4267 ppm
 **47**	2.4204 ppm	3.6600 ppm
 **124**	38.0947 ppm	46.7501 ppm

Table 2.5: Palladium content in aryl amines following purification

In all the reactions carried out in this comparative study, Et_2O was used as the solvent for the work-up. Et_2O presents a number of hazards and its use within an industrial setting is generally avoided.[24] With this in mind, an investigation into alternative solvents to Et_2O in the reaction work-up was carried out and compared with Et_2O. The model reaction chosen for this investigation was the cross-coupling of aryl bromide **112** and piperidine **42** with $Pd(dba)_2$, (±)-BINAP and Cs_2CO_3 in TMO to give tertiary amine **98** (Table 2.6). Following the reaction, the mixture was diluted with the work-up solvent and filtered *via* celite®. Evaporation of the solvent gave the crude product and tertiary amine **98** was isolated following column chromatography. When Et_2O was used for the work-up a 75% yield of tertiary amine **98** was achieved (see Table 2.2). EtOAc was tried as the work-up solvent and a 69% yield was obtained (entry 2). However, the added polarity of EtOAc led to an inseparable dba impurity being isolated with the product following flash column chromatography. Finally, TMO was used as the work-up solvent and tertiary amine **98** was isolated without issue in 69% yield (entry 3). However, due to the considerably higher boiling point of TMO compared to Et_2O, a noticeably longer, more energy intensive evaporation time was required for its removal.



Entry	Work-up Solvent	Yield (%)[a]	Comment
1	Et_2O	75	As in Table 2.2
2	EtOAc	69	Inseparable dba impurity
3	TMO	69	Slow removal of solvent

Table 2.6: Investigation into different work-up solvents for the Buchwald-Hartwig aminations. [a]Yield after chromatography

Finally, an assessment using the CHEM21 Metric Toolkit was performed on a selection of Buchwald-Hartwig reactions to ascertain the relative greenness of the methodology (Figure 2.4).[127] In this study, atom economy (AE), reaction mass efficiency (RME) and process mass intensity (PMI), which was split into $PMI_{overall}$ which considers all the materials used in the reaction and work-up and PMI_{react} which ignores the additional materials used in the work-up, were compared for both the solvents used in this investigation. First, the synthesis of aryl amine **93** was assessed. In toluene, a yield of 87% was achieved resulting in a $PMI_{overall}$ of 102, PMI_{react} of 32 and RME of 58. On the other hand, in TMO, a slightly reduced yield (82%) led to marginally worse $PMI_{overall}$ (107) and RME (54) values and the same PMI_{react} value (32). In these examples, the RME and PMI metrics are predominately dictated by the reaction yield as the reaction is not varied other than the changing of the solvents. As such, in examples where the yields are similar (**93**, **100** and **124**), there is no discernible difference in the $\mathrm{PMI_{overall}}$, $\mathrm{PMI_{react}}$ and RME values. However, in the examples where there was a larger discrepancy in the reaction yields, the difference in PMI and RME values are more obvious. For example, in toluene, tertiary amine **98** was synthesised in 50% yield which led to $\mathrm{PMI_{overall}}$ of 155, $\mathrm{PMI_{react}}$ of 101 and RME of 32. In contrast, in TMO, a much-improved yield of 75% was achieved and this resulted in improved $\mathrm{PMI_{overall}}$, $\mathrm{PMI_{react}}$ and RME values (101, 32 and 52 respectively). The AE, which is a measure of the amount of atoms in the reactants that end up in the product, is unaffected by yield and molar excesses and thus is the same in both solvents. In the Buchwald-Hartwig reactions chosen for this investigation, the AE ranged from 67% to 82% because of the atomic loses due to the bromide salt produced. As a result of this, higher AE were obtained when larger reactants were coupled with the highest observed in the synthesis of SEN826 intermediate **124** (82%).

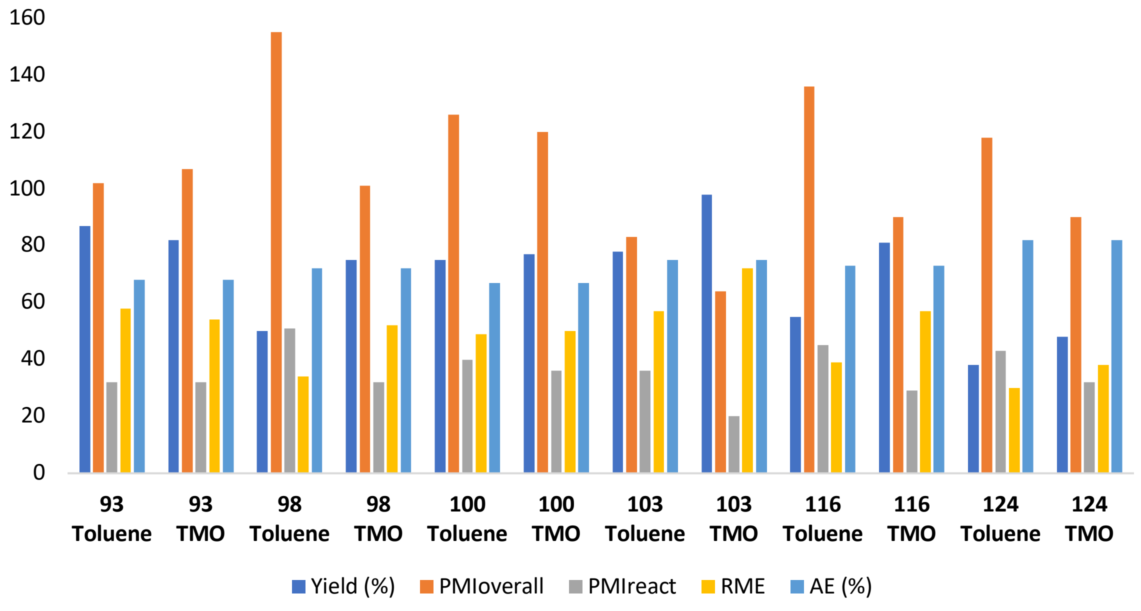
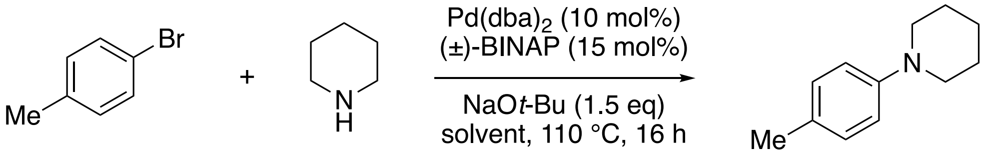


Figure 2.4: Metrics assessment of the Buchwald-Hartwig cross-coupling reactions in toluene and TMO

Unfortunately, these metrics do not consider the health, safety and environmental concerns of reactants/solvents used in the process. As such, an accurate representation of the 'greenness' of the reaction in both solvents cannot be determined when only these metrics are used. The EcoScale is a semi-quantitative tool which considers both economical and ecologic parameters.[128] The six parameters which are taken into account are: yield, price of reagents, safety, technical setup, temperature/time and work-up/purification. Within these parameters, penalty points are accrued based on the perceived hazard or limitation of the reaction and the EcoScale is equal to 100 minus the sum of individual penalties (see Equation 1.5). The synthesis of tertiary amine **94** was chosen as a representative example for this study (Table 2.7). The price of reagents and solvents was not considered as TMO is not yet a commercial product; only the safety of the solvents was considered for the safety parameter for this calculation in order to focus this study on the use of different solvents. For the reaction in toluene, a penalty of 6 points was given for the yield (87%). In terms of safety, a total of 15 points penalty was accumulated due to the solvent's flammability, potential to damage the environment and its toxicity. The use of a nitrogen atmosphere for the reaction added 1 penalty point and heating the reaction at 110 °C for 16 h added a further 3 penalty points. Finally, the use of column chromatography added a final 10 penalty points resulting in a total penalty count of 36 points giving an EcoScale score of 64. In contrast, when the reaction was performed in TMO, a lower 76% yield resulted in a more severe penalty of 12 points. There are no known environmental or toxicity issues with TMO and only a 5 point penalty reduction was included for the flammability of the solvent. The use of an inert atmosphere, heating for 16 h and column chromatography resulted in an additional 14 penalty points, analogous to toluene for these parameters. This culminates in a total penalty count of 31 and EcoScale score of 69. Even with the lower yield of tertiary amine **94** in TMO compared to toluene, the reduced toxicity and environmental impact caused by the solvent results in TMO achieving a better EcoScale score than toluene in Buchwald-Hartwig aminations.



33 **42** **94**

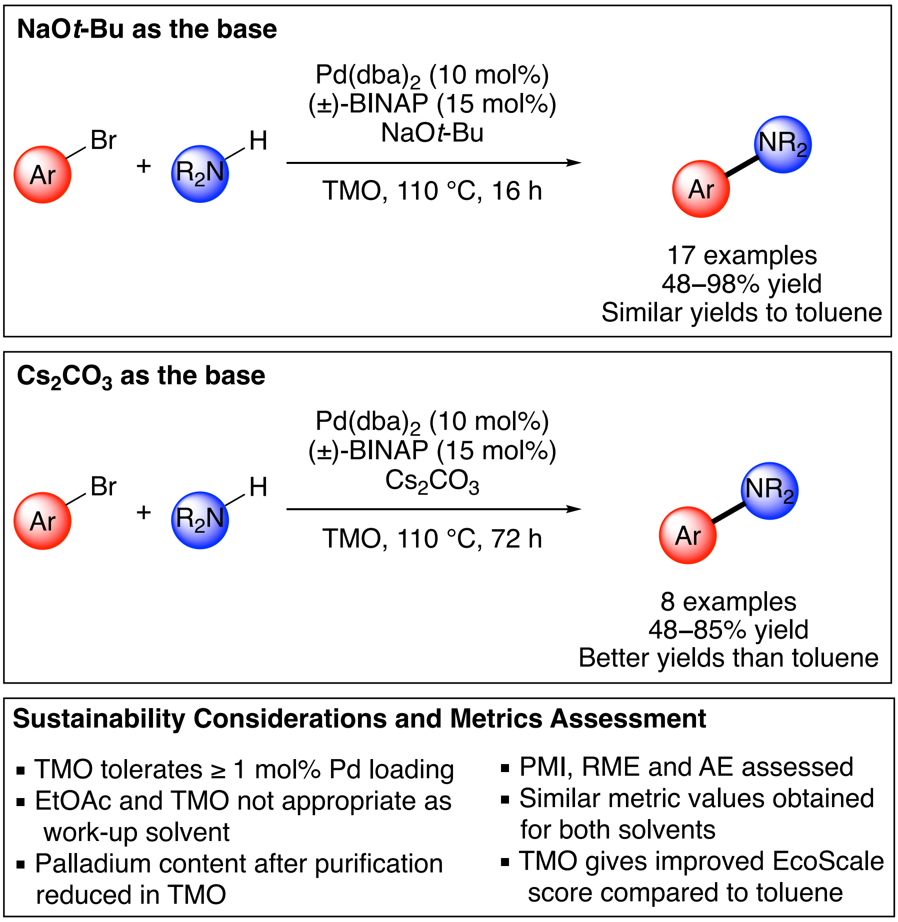
Reaction in Toluene		Reaction in TMO	
Parameter	Penalty	Parameter	Penalty
Yield (86%)	7.0	Yield (76%)	12
Safety	High flammability: 5 Environmental danger: 5 Toxicity: 5	Safety	High flammability: 5
Technical Setup	Inert atmosphere: 1	Technical Setup	Inert Atmosphere: 1
Temp/Time	Heating >1 h: 3	Temp/Time	Heating >1 h: 3
Workup/Purification	Filtration: 0 Chromatography: 10	Workup/Purification	Filtration: 0 Chromatography: 10
Total: 36		Total: 31	
EcoScale: 64		EcoScale: 69	

Table 2.7: EcoScale calculation for the synthesis of tertiary amine **94**

In summary, catalyst loadings as low as 1 mol% Pd(dba)$_2$ were shown to be effective at facilitating the cross-coupling of aryl bromides and amines in TMO without any considerable reductions in the reaction yield. At catalyst loadings lower than 1 mol%, a notable reduction in the yields was observed. Residual palladium content following purification was determined through ICP-MS analysis. The data collected from this investigation indicates a reduction in residual palladium content in the product when the reaction was performed in TMO compared to toluene. In order to ascertain the relative greenness of the reaction, PMI, RME, AE and the EcoScale were calculated for the synthesis of selected aryl amines. The values gathered for PMI, RME and AE are mainly dictated by the yields achieved in the reaction. As such, when the yields were similar in both solvents, the metric values were very similar. The use of the EcoScale parameter gave a more accurate representation of the overall greenness of the reaction in either solvent as safety and reaction set-ups were taken into account.

2.4 Conclusions and Future Work

In this chapter, a comparative investigation into the use of TMO and toluene in Buchwald-Hartwig aminations was carried out. A broad substrate scope was demonstrated by the combination of different (hetero)aryl bromides and amines, including the synthesis of a key intermediate **124** in the route to drug candidate SEN826, highlighting the potential for TMO to be used in the synthesis of biologically active compounds. When NaO*t*-Bu was used as the base, only very marginal differences in reaction yields were observed. In contrast, when Cs_2CO_3 was used as the base, considerable improvements in yield were observed in TMO compared to toluene. Through the use of ICP-MS analysis, the base was discovered to be considerably more soluble in TMO than in toluene. This could account for the differences in yields between the solvents using Cs_2CO_3. Reduction of palladium catalyst loading from 10 mol% down to 1 mol% was possible in TMO with minimal losses in yield. Preliminary ICP-MS results also indicated an added benefit of TMO as the use of this solvent led to reduced residual palladium content in isolated compounds. This is important in the synthesis of compounds used in the pharmaceutical industry. Finally, a greenness assessment was carried out for a number of reactions performed in the substrate scope and this indicated that TMO enhanced RME and PMI for several of the reactions screened. However, these values were primarily dictated by the higher yields obtained in the solvent. As such, a further calculation to determine the EcoScale was performed which resulted in a more accurate representation of the relative greenness of the reaction in either solvent. A summary of the results gathered in this chapter are displayed in Figure 2.5.



- TMO tolerates ≥ 1 mol% Pd loading
- EtOAc and TMO not appropriate as work-up solvent
- Palladium content after purification reduced in TMO
- PMI, RME and AE assessed
- Similar metric values obtained for both solvents
- TMO gives improved EcoScale score compared to toluene

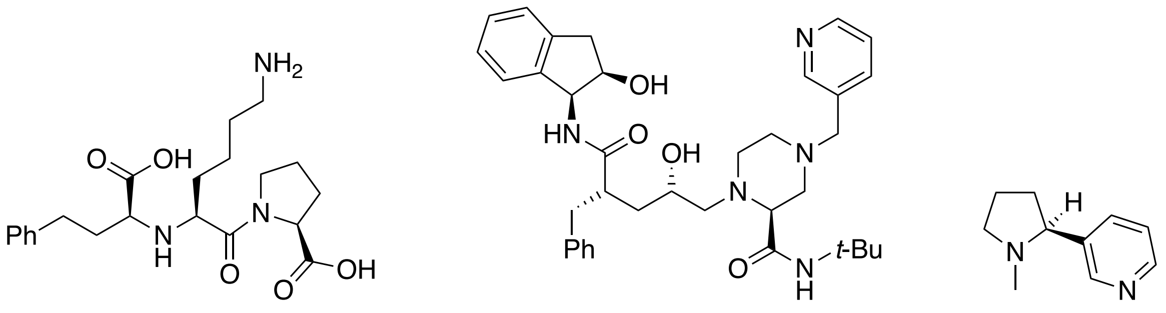
Figure 2.5: Summary of Buchwald-Hartwig aminations in TMO

Given the hazards presented by toluene, TMO can now be considered as an appealing alternative to toluene in Buchwald-Hartwig aminations where other green solvents such as methyl pivalate and pinacolone could not be applied due to their inherent structural features. A number of studies on the use of different ligand for Buchwald-Hartwig aminations have been carried in. In this study, only (±)-BINAP was used for the cross-coupling reactions. Future work may include an investigation into using these different ligands with TMO as the solvent for Buchwald-Hartwig aminations. A bio-derived route to TMO has recently been developed.[129] An investigation into the reaction performance of bio-derived TMO in the Buchwald-Hartwig amination could be carried out in order to ascertain if impurities present in bio-derived TMO negatively affect the reaction outcome. An exploration into the use of other solvents for Buchwald-Hartwig aminations that use Cs_2CO_3 as the base could also be warranted to further establish the effect of solubility of base on the reaction performance.

Chapter 3: Use of TMO as Solvent in the Lithiation-Trapping of *N*-Boc Heterocycles

3.1: Introduction to Saturated *N*-Heterocycles

Non-aromatic nitrogen heterocycles are ubiquitous in natural products, pharmaceutically active compounds and fine chemicals with piperidine, piperazine and pyrrolidine amongst the top 5 most prevalent moieties in the US FDA approved drugs containing nitrogen heterocycles.[130] Examples of these include the pyrrolidine-containing Lisinopril (Merck), an angiotensin-converting enzyme (ACE) inhibitor commonly used for the treatment of hypertension, heart failure and heart attacks;[131] the piperazine containing Indinavir (Merck), a protease inhibitor used in the treatment of HIV and AIDS;[132] and the naturally occurring addictive alkaloid (−)-nicotine found in tobacco products (Figure 3.1).



Lisinopril Indinavir (−)-nicotine

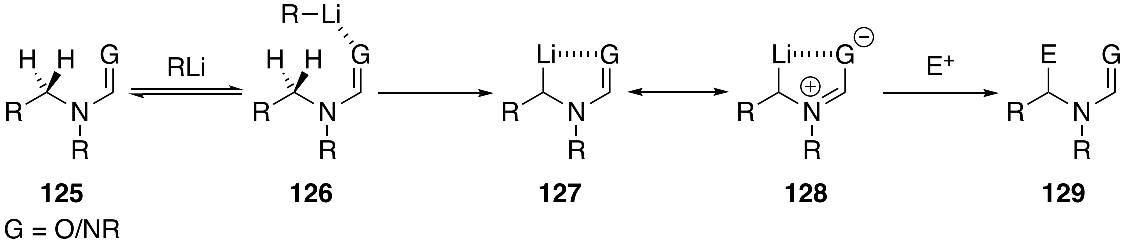
Figure 3.1: Saturated *N*-heterocycle containing drugs and natural products

In all of these examples, the saturated nitrogen heterocycle exhibits functionality α- to the heteroatom. Organolithium reagents have allowed chemists to incorporate α-functionality into nitrogen heterocycles through lithiation-trapping methodologies. Furthermore, use of a chiral ligand in lithiation-trapping reactions has enabled access to highly enantioenriched functionalised nitrogen heterocycles which is important in the synthesis of biologically active compounds and natural products.

3.2: Introduction to the Lithiation-Trapping of *N*-Heterocycles

3.2.1 Racemic Lithiation-Trapping of *N*-Heterocycles

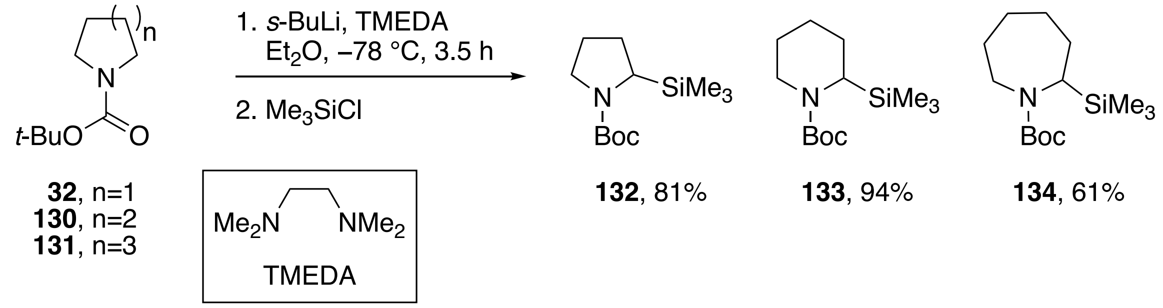
Organolithium reagents are some of the most established reagents used in organic synthesis.[133] Their use in the generation of dipole-stabilised carbanions *α* to nitrogen to form a new carbon-carbon bond, generating a new stereocentre, has received much attention within the synthetic community over the last 30 years.[134] The use of a directing group bound to nitrogen in **125** allows reversible coordination of the organolithium reagent to give pre-lithiation complex **126**. This coordination brings the basic organolithium reagent in close proximity to the acidic *α*-protons facilitating deprotonation and generates a reactive lithiated intermediate **127** which is stabilised through resonance (**128**). The lithiated intermediate (**127** and **128**) can then be trapped with an electrophile giving the desired *α*-functionalised product **129** (Scheme 3.1).



Scheme 3.1: Directed deprotonation

Appropriate directing groups must allow the coordination of the organolithium reagents, be resistant to nucleophilic attack and be both easily incorporated and removed. Pioneering work by Beak and Lee in 1989 introduced the use of *tert*-butoxycarbonyl (Boc) as a directing group for the lithiation-trapping of *N*-heterocycles.[135] Treatment of *N*-Boc pyrrolidine **32**, piperidine **130** and azepane **131** with *s*-BuLi and TMEDA in Et_2O at −78 °C for 3.5 h followed by trapping with Me_3SiCl gave functionalised products **132−134** in high yields

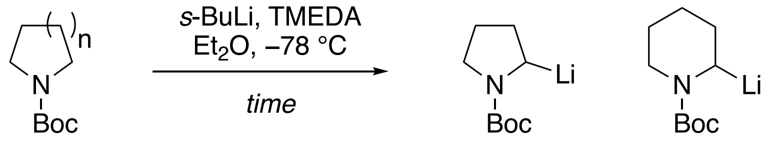
(61−91%, Scheme 3.2). The starting *N*-Boc heterocycles can be synthesised simply by addition of di-*tert*-butyl dicarbonate (Boc_2O) to the corresponding amine. The Boc group can be readily removed by treatment with TFA or HCl. Other directing groups used for lithiation-trapping of *N*-heterocycles include amides, nitrosamines, formamidines, ureas and thioamides.[136–141]



Scheme 3.2: Lithiation-trapping of *N*-Boc heterocycles

More recently, the O'Brien group discovered that the long lithiation time of 3.5 h was not necessary for some *N*-Boc heterocycles.[142,143] *In situ* IR spectroscopy (ReactIR) was used to monitor the time required for complete lithiation to have occurred. ReactIR measures the intensity of the ν_{co} corresponding to the carbonyl on the Boc group over the course of the reaction. During a lithiation event, there are three distinct species: the unfunctionalised *N*-Boc heterocycle **125**, the pre-lithiation complex **126** and the lithiated intermediate **127** and **128** (see Scheme 3.1). The lithiation time (t_{lith}) was determined once the intensity of the ν_{co} corresponding to the lithiated intermediate **127** and **128** had plateaued. The use of ReactIR allowed the O'Brien group to accurately determine the lithiation times for a range of *N*-Boc heterocycles using *s*-BuLi and TMEDA. Of particular interest, the t_{lith} of *N*-Boc pyrrolidine **32** to form lithiated pyrrolidine **135** was only 5 min at −78 °C proving that Beak's original lithiation time of 3.5 h was excessive. In contrast, the rate of lithiation of *N*-Boc piperidine

130 to form lithiated piperidine **136** is considerably slower with a t_{lith} of 6 h at –78 °C (Scheme 3.3).



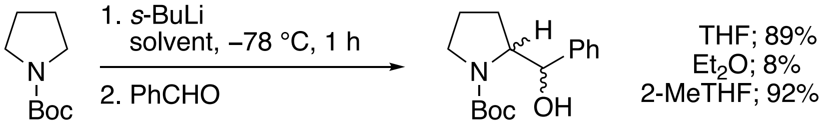
32, n=1
130, n=2

135
t_{lith} = 5 min

136
t_{lith} = 6 h

Scheme 3.3: Use of *in situ* IR spectroscopy to determine accurate lithiation times

Addition of a diamine ligand (*e.g.* TMEDA) is essential for the success of the lithiation reaction in poorly coordinating solvents such as Et_2O. In the absence of TMEDA, the *s*-BuLi/Et_2O complex is not reactive enough to facilitate deprotonation. This led to poor conversion to the lithiated intermediate resulting in poor yields of the functionalised product. However, in 2010, the O'Brien group developed a 'diamine-free' lithiation-trapping protocol.[144] Using THF as the reaction solvent, treatment of *N*-Boc pyrrolidine **32** with *s*-BuLi at −78 °C for 60 min and trapping with PhCHO gave *α*-functionalised pyrrolidine **137** in 89% yield. In contrast, when the reaction was performed in Et_2O, only 8% yield of **137** was isolated, highlighting the distinction in reactivity between the *s*-BuLi/THF complex and *s*-BuLi/Et_2O complex. The green solvent, 2-MeTHF, also facilitated high yields of the desired product (92%) (Scheme 3.4).

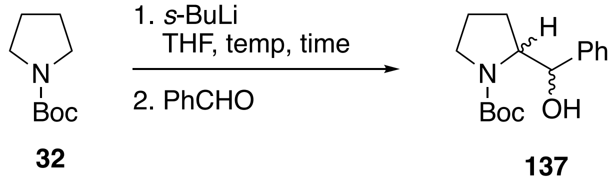


32

syn-**137**:*anti*-**137**
~75:25 *syn*:*anti*

Scheme 3.4: Diamine-free lithiation-trapping protocol

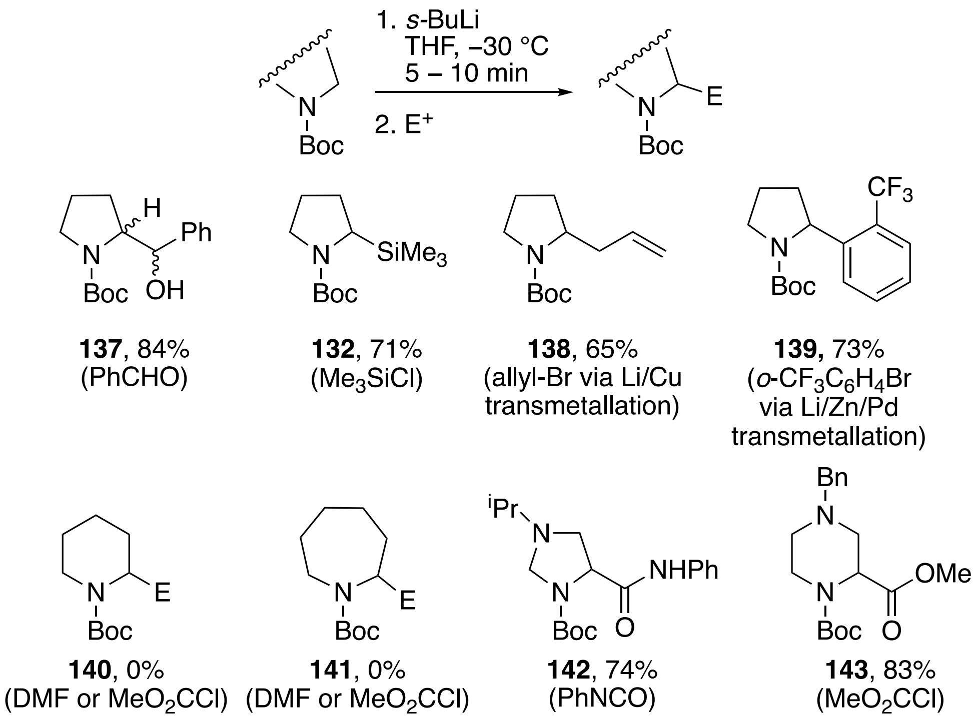
These promising results in THF prompted an investigation into diamine-free lithiation-trapping at temperatures above −78 °C (Table 3.1). At −40 °C, the lithiation-trapping of *N*-Boc pyrrolidine **32** for 1 h and trapping with PhCHO formed amino alcohols **137** in 64% yield (*syn*:*anti* ~75:25) (entry 1). A decrease to 37% yield was observed when the reaction was carried out at −30 °C for 1 h (entry 2). The diminishing yields with increasing temperature can be accounted for by the instability of the lithiated intermediate at these elevated temperatures and also by consumption of the organolithium through reaction with THF. Reducing the reaction time to 5 min addressed these issues providing the α-functionalised product **137** in 84% yield (entry 3). At temperatures above −30 °C, however, mitigation of unwanted side reactions and issues with instability of the lithiated substrate became unavoidable as, at −20 °C for 5 min, the yield of **137** was only 66% (entry 4). The erosion of the yield was further exaggerated when the reaction temperature was increased further. At −10 °C for 5 min, only a 29% yield of **137** was obtained and, at 0 °C, none of the amino alcohols **137** was formed (entries 5 and 6 respectively).



Entry	Temperature (°C)	Time (min)	Yield (%)
1	−40	60	64
2	−30	60	37
3	−30	5	84
4	−20	5	66
5	−10	5	29
6	0	30	0

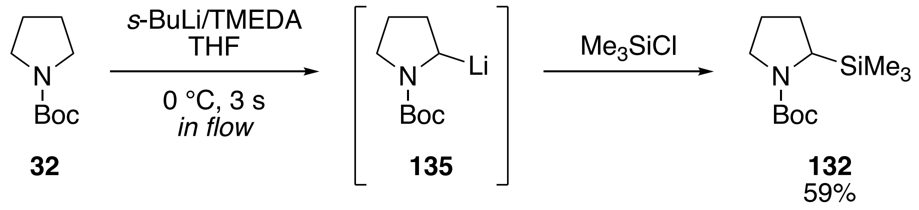
Table 3.1: High-temperature diamine-free lithiation-trapping of *N*-Boc pyrrolidine **32**

The electrophile scope was examined with the newly optimised conditions (−30 °C for 5 min) (Scheme 3.5). Trapped products **132**, **137**−**139** were all isolated in good yields (65−84%), including the product from a Li/Zn/Pd transmetallation and Negishi cross-coupling which enabled the synthesis of *α*-arylated pyrrolidine **139**. Mixed success was found when the *N*-Boc heterocycle scope was explored with *N*-Boc piperidine **130** and azepane **131** not forming the desired adducts **140** and **141**. This is presumably due to the *s*-BuLi/THF complex being considerably less reactive than the *s*-BuLi/TMEDA complex and thus unable to facilitate lithiation of these substrates even at elevated temperatures. However, lithiation-trapping of *N*-Boc imidazolidine and *N*-Boc piperazines, originally described by Coldham *et al.*[145,146] and van den Hoogenband and van Maarseveen[147] respectively, proceeded without issue with a range of electrophiles to give representative examples **142** and **143** (74% and 83% respectively).



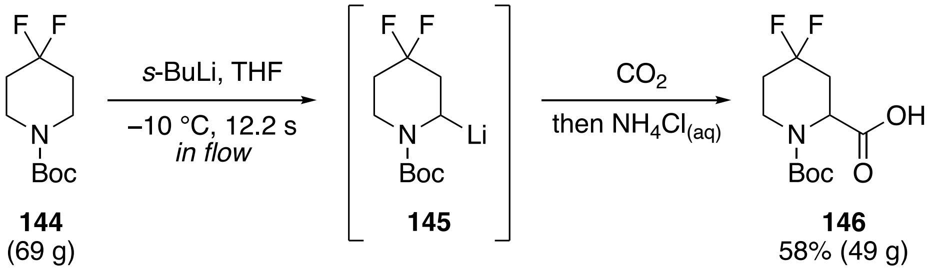
Scheme 3.5: Electrophile and *N*-Boc heterocycle scope of diamine-free 'high-temperature' lithiation-trapping

Use of high-temperature lithiation-trapping reactions of *N*-Boc heterocycles on large-scale using batch conditions is likely to be unsuitable given the instability of the lithiated intermediate, fast addition of the *s*-BuLi and the need for efficient stirring and control of exotherms. Continuous flow processes have enabled lithiation-trapping of *N*-Boc heterocycles at convenient and less energy intensive temperatures and, furthermore, are potentially suitable for scale-up.[148,149] O'Brien and co-workers reported the first example of a lithiation-trapping reaction of a *N*-Boc heterocycles using flow chemistry.[148] Lithiation of *N*-Boc pyrrolidine **32** using *s*-BuLi/TMEDA in THF at 0 °C with a residence time of 3 s formed lithiated intermediate **135**. Trapping with Me_3SiCl gave silyl pyrrolidine **132** in 59% yield (Scheme 3.6).



Scheme 3.6: Lithiation-trapping of *N*-Boc pyrrolidine **32** in flow

Large-scale lithiation-carboxylation of *N*-Boc-4,4-difluoropiperidine **144** using a continuous flow process was recently reported by researchers at UCB Biopharma.[149] Addition of *s*-BuLi to *N*-Boc-4,4-difluoropiperidine **144** at −10 °C for 12.2 s on a 69 g scale formed lithiated intermediate **145**. Subsequent addition of CO_2 afforded carboxylic acid **146** in 58% yield (49 g) (Scheme 3.7). In order to prepare larger quantities of carboxylic acid **146** (177 g scale), the reaction had to be performed at −40 °C in order to control the exotherm.

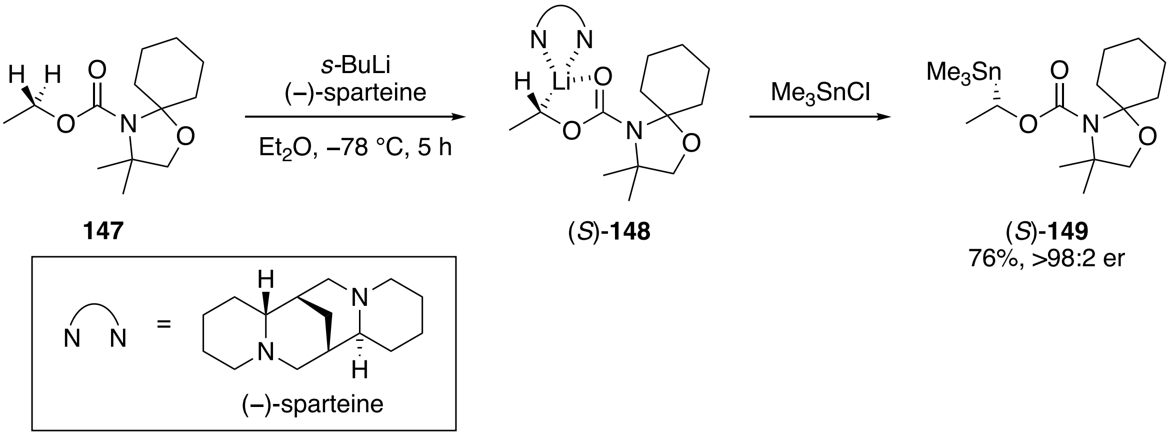


Scheme 3.7: Large-scale lithiation-trapping of *N*-Boc-4,4-difluoropiperidine **144** in flow

From a Green Chemistry perspective, these high temperature conditions developed by O'Brien and co-workers[144,148] are considerably improved compared to the original conditions described by Beak in 1989.[135] For example, the conditions move away from −78 °C to the less energy intensive and more industrially applicable temperature of −30 °C (in batch) or −10 °C to 0 °C (in flow), whilst also decreasing the reaction time from 3.5 h to 5 min. This follows Principle 6 (Design for Energy Efficiency) of the '12 Principles of Green Chemistry'.[150,151] Furthermore, removing the necessity for TMEDA in the reaction makes the lithiation-trapping a less wasteful process. The success of using the green solvent, 2-MeTHF,[152] addresses Principle 7 (Use of Renewable Feedstocks).

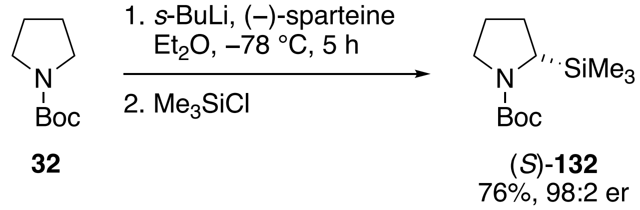
3.2.2 Enantioselective Lithiation-Trapping of *N*-Boc Heterocycles

In 1990, Hoppe reported that directed lithiation-trapping could be performed enantioselectively if a chiral diamine was used in place of TMEDA.[153] *O*-alkyl carbamate **147** was treated with *s*-BuLi and (−)-sparteine in Et_2O at −78 °C for 5 h which gave configurationally-stable, diastereoenriched lithiated intermediate (*S*)-**148**. Trapping with Me_3SnCl occurred with retention of stereochemistry to give the enantioenriched product (*S*)-**149** in a high yield and enantioselectivity (76%, >98:2 er, Scheme 3.8).



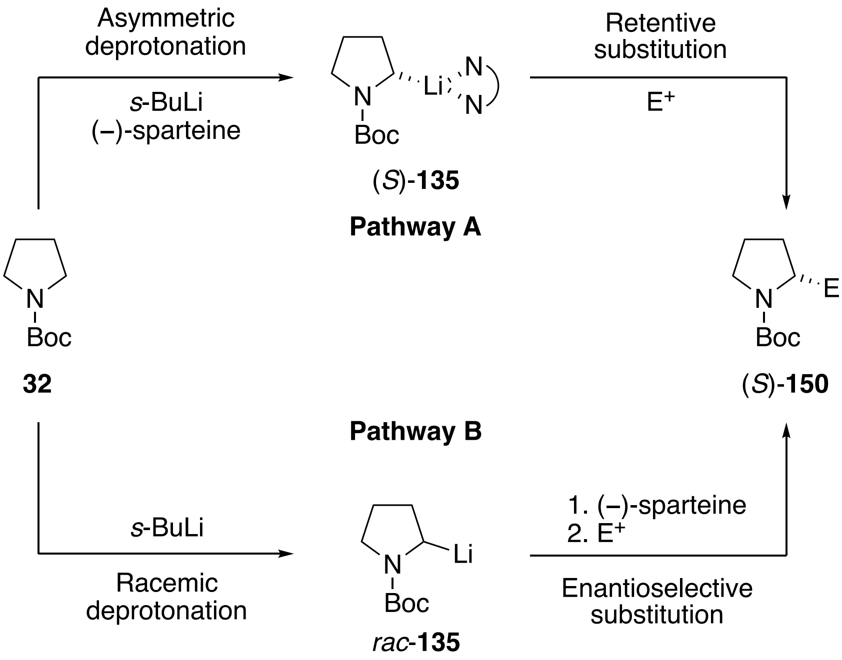
Scheme 3.8: Enantioselective lithiation-trapping of *O*-alkyl carbamate **147**

Beak and Kerrick applied Hoppe's method for the synthesis of enantioenriched *α*-functionalised *N*-Boc pyrrolidine **32** (Scheme 3.9).[154] In one example, deprotonation of **32** with *s*-BuLi and (−)-sparteine at −78 °C for 5 h followed by trapping with Me_3SiCl gave the enantioenriched product (*S*)-**132** in 76% yield and 98:2 er, analogous to the findings reported by Hoppe.[153]



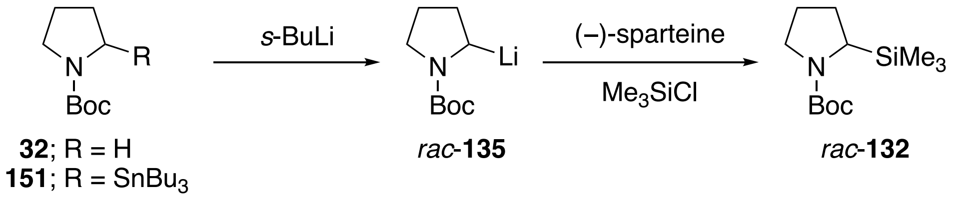
Scheme 3.9: Enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32**

Beak proposed that there are two possible pathways that could be responsible for the enantioselectivity in the lithiation-trapping of *N*-Boc pyrrolidine **32** (Scheme 3.10).[155] Pathway A involves asymmetric deprotonation whereby the organolithium/(−)-sparteine complex selectively deprotonates **32** giving a diastereoenriched, configurationally stable lithiated intermediate (*S*)-**135**. Subsequent trapping with an electrophile occurs with retention of stereochemistry to give enantioenriched product (*S*)-**150**. Pathways B proceeds *via* racemic deprotonation to give lithiated intermediate *rac*-**135**. Complexation of the chiral ligand gives diastereomeric lithiated intermediates which can interconvert if they are configurationally unstable. The rate of epimerisation of the diastereomeric lithiated intermediates and trapping of the electrophile then determines the stereochemical outcome of the reaction.



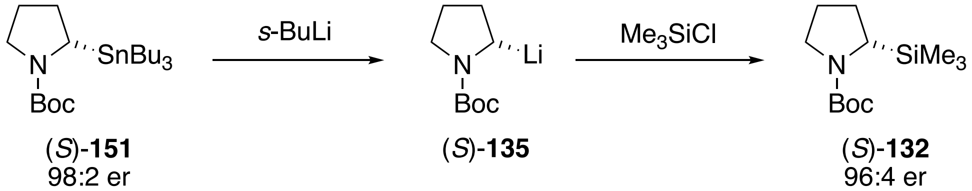
Scheme 3.10: Proposed pathways for enantioenrichment in lithiation-trapping

In order to determine which pathway led to the observed enantioselectivity, Beak conducted two conclusive experiments.[155] First, addition of Me_3SiCl and (−)-sparteine to racemic lithiated intermediate **135**, formed *via* racemic deprotonation of **32** or tin-lithium exchange with the corresponding racemic organostannane **151**, gave the essentially racemic product *rac*-**132** (Scheme 3.11). This experiment ruled out the possibility of enantioselectivity being induced through asymmetric trapping of the electrophile (Pathway B).



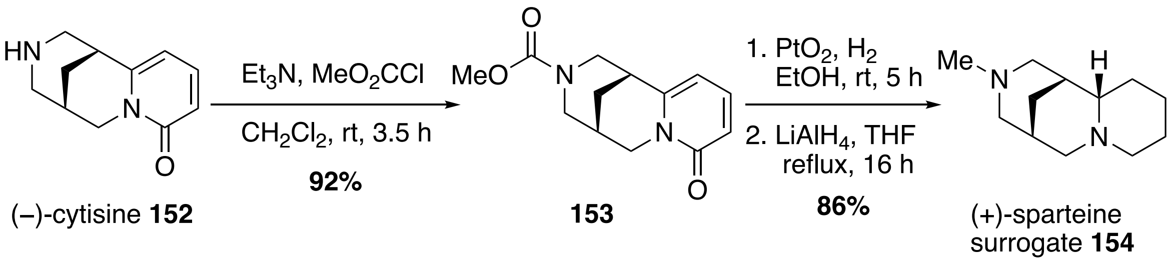
Scheme 3.11: Attempted asymmetric electrophile trapping

The configurational stability of the lithiated intermediate was also determined. Enantiopure stannane (*S*)-**151** (98:2 er) underwent tin-lithium exchange with *s*-BuLi at −78 °C forming the enantioenriched lithiated intermediate (*S*)-**135**. Trapping with Me_3SiCl afforded the trapped product (*S*)-**132** with little erosion of the stereochemistry (96:4 er) (Scheme 3.12). This confirmed that the lithiated intermediate was configurationally stable for at least the time required for electrophile trapping to occur. Therefore, it was concluded that the asymmetric deprotonation (Pathway A, see Scheme 3.10) is the enantio-determining step.



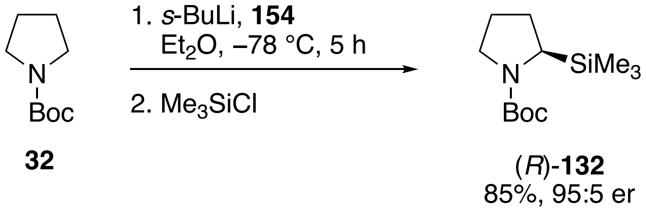
Scheme 3.12: Configurational stability of lithiated intermediate (*S*)-**135**

For a time, sparteine was only commercially available as the (−)-enantiomer, with (+)-sparteine only recently becoming more accessible in bulk quantities. As such, it was only possible to synthesise a single enantiomer in asymmetric lithiation-trapping reactions (that derived from (−)-sparteine). In order to combat this issue, the O'Brien group, in 2002, reported the development of readily accessible (+)-sparteine surrogate **154**, which they had previously reported to be a good candidate to be used in place of (+)-sparteine.[156,157] Naturally occurring alkaloid (−)-cytisine **152** was treated with MeO_2CCl and Et_3N giving pyridone **153** in 92%. Hydrogenation of pyridone **153** followed by conversion of the Boc group into a methyl group using $LiAlH_4$ gave the desired diamine **154** in 86% yield (79% overall yield) and ≥95:5 er (Scheme 3.13).



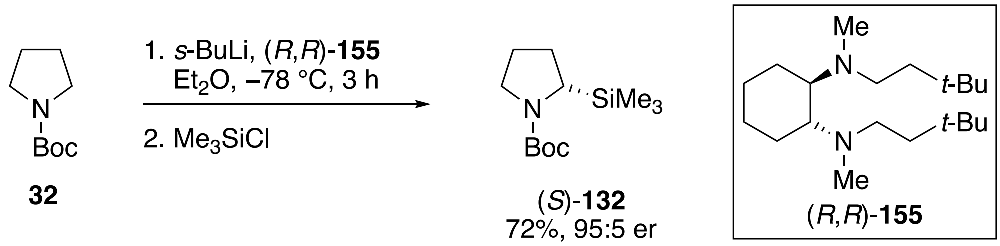
Scheme 3.13: Synthesis of (+)-sparteine surrogate **154**

With ready access to the (+)-sparteine surrogate **154**, the opposite enantiomer from asymmetric lithiation-trapping was now accessible. O'Brien *et al.* demonstrated this with the synthesis of silyl pyrrolidine (*R*)-**132** *via* enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32** using *s*-BuLi and (+)-sparteine surrogate **154** and trapping with Me$_3$SiCl in 84% yield and 95:5 er (Scheme 3.14). This high yield and er (in the opposite sense) is comparable with the results observed when (−)-sparteine is used (see Scheme 3.9).[157]



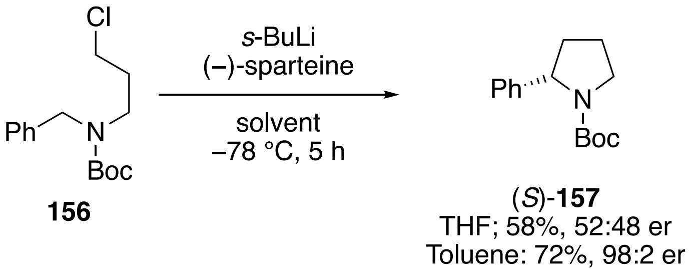
Scheme 3.14: (+)-Sparteine surrogate **154** mediated lithiation-trapping of *N*-Boc pyrrolidine **32**

The O'Brien group also reported the use of cyclohexyl diamine **155** (Alexakis diamine) in the enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32** (Scheme 3.15).[158] Treatment of **32** with *s*-BuLi and (*R,R*)-**155** in Et$_2$O at −78 °C for 3 h followed by addition of Me$_3$SiCl afforded silyl pyrrolidine (*S*)-**132** in 72% yield and 95:5 er. Isolation of the desired enantiomer of diamine **155** requires the resolution of *trans*-cyclohexane-1,2-diamine with tartaric acid. Therefore, both antipodes of the ligand are easily accessible through the use of *d*- or *l*-tartaric acid and, thus, both enantiomers of the α-functionalised pyrrolidine **132** can be obtained with the use of this ligand.



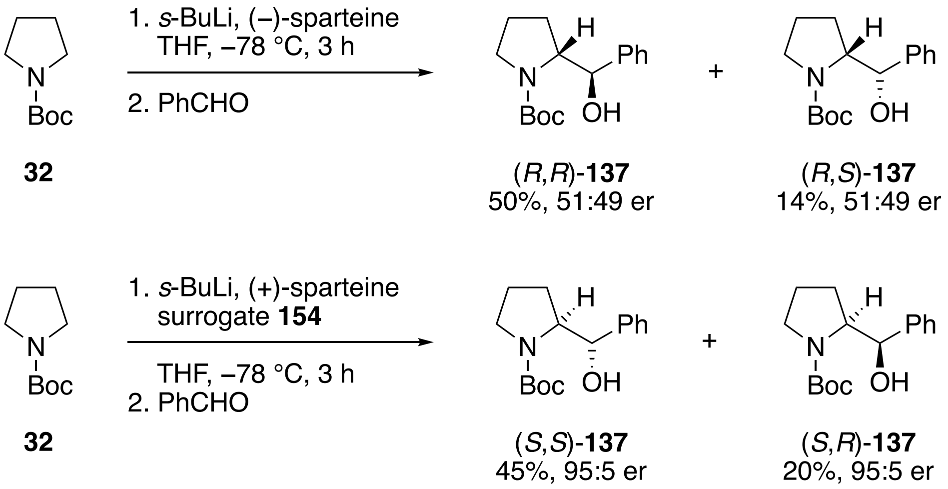
Scheme 3.15: Alexakis diamine (*R*,*R*)-**155** mediated lithiation-trapping of *N*-Boc pyrrolidine **32**

As shown in the previous examples, enantioselective lithiation-trapping reactions using *s*-BuLi/diamines in Et_2O proceed with high yields and er. However, when similar reactions are performed in THF, lithiation-trapping reactions proceed with negligible enantioselectivity giving essentially racemic products (except with (+)-sparteine surrogate, *vide infra*). This was exemplified by Beak *et al.* with the *s*-BuLi/(−)-sparteine-mediated deprotonation-cyclisation of *N*-Boc amino chloride **156** to form the enantioenriched arylated pyrrolidine (*S*)-**157**.[159] With a poorly coordinating solvent, toluene in this case, high enantioenrichment was achieved (98:2 er). In contrast, with THF, an essentially racemic product **157** was obtained (Scheme 3.16). The use of THF in other (−)-sparteine-mediated lithiation-trapping reactions has also led to racemic products whilst other less coordinating solvents proceed with good enantioenrichment.[160–163]



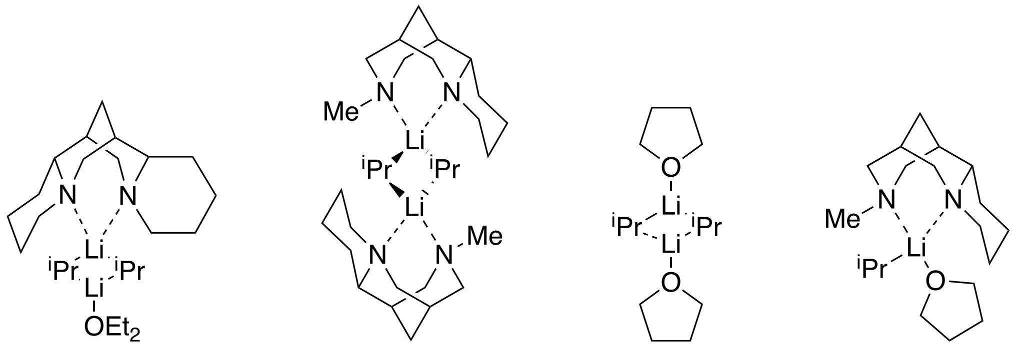
Scheme 3.16: Deprotonation-cyclisation of *N*-Boc amino chloride **156** in THF and toluene

Lithiation-trapping of *N*-Boc pyrrolidine **32** with *s*-BuLi/(−)-sparteine in THF proceeds with negligible enantioselectivity. Contrary to this, the O'Brien group found that the use of (+)-sparteine surrogate **154** could provide high enantioselectivity in lithiation-trapping reactions in THF.[164] Treatment of *N*-Boc pyrrolidine **32** with *s*-BuLi and (−)-sparteine in THF at −78 °C for 3 h and trapping with PhCHO afforded diastereomeric alcohols (*R,R*)-**137** and (*R*,*S*)-**137** in 64% total yield with both diastereomers exhibiting 51:49 er, i.e. deprotonation of **32** is dictated by the *s*-BuLi/THF complex. On the other hand, treatment of *N*-Boc pyrrolidine **32** with *s*-BuLi and (+)-sparteine surrogate **154** under otherwise identical conditions and trapping with PhCHO provided diastereomeric alcohols (*S,S*)-**137** and (*S*,*R*)-**137** in a total yield of 65%, with 95:5 er for each diastereomer (Scheme 3.17).



Scheme 3.17: Enantioselective lithiation-trapping in THF

The stereochemical outcome of these reactions was explained through NMR spectroscopic investigations to determine the solution structures of *i*-PrLi (a model for *s*-BuLi which reduces the complexity of the NMR spectra caused by the presence of diastereomeric complexes with *s*-BuLi) with (−)-sparteine and (+)-sparteine surrogate **154** (Figure 3.2). The use of *i*-PrLi in the lithiation-trapping of *N*-Boc pyrrolidine **32** gave analogous yields and enantiomer ratios to *s*-BuLi in Et_2O and THF with (−)-sparteine and (+)-sparteine surrogate **154**. First, the solution structures of the *i*-PrLi/(−)-sparteine and the *i*-PrLi/(+)-sparteine surrogate complexes in Et_2O-d_{10} using ^{6}Li and ^{13}C NMR spectroscopy were determined. Consistent with the solutions structures determined by Beak *et al.*, the *i*-PrLi/(−)-sparteine complex was found to exist as heterodimer **158**[165] whereas the *i*-PrLi/(+)-sparteine surrogate **154** complex existed as 'head-to-tail' homodimer **159**. Next, the solution structures of the two organolithium/chiral diamine complexes in THF-d_8 were solved. Unsurprisingly, given the reaction result shown in Scheme 3.17, in THF, (−)-sparteine did not complex to the organolithium; instead, the solvated homodimer **160** was formed. Contrary to this, the (+)-sparteine surrogate **154** in THF gave rise to the partially solvated monomer **161**. These solution structures explain why (+)-sparteine surrogate **154** behaves so differently compared to (−)-sparteine in THF and why it is possible for the *s*-BuLi/(+)-sparteine surrogate **154** complex to induce enantioselectivity in the lithiation-trapping products in THF.



158 **159** **160** **161**

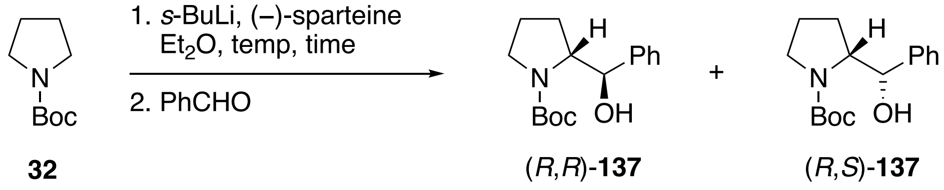
Figure 3.2: Solution structures of (−)-sparteine/*i*-PrLi and (+)-sparteine surrogate **154**/*i*-PrLi complexes in Et_2O-d_{10} and THF-d_8

A detailed investigation into the use of ReactIR monitoring of the enantioselective lithiation-trapping reactions of a number of *N*-Boc heterocycles with a range of chiral ligands has been carried out over the last decade by members of the O'Brien group. This has allowed accurate lithiation times to be determined without the requirement of extensive optimisation.[142,143,166] Of note, lithiation of *N*-Boc pyrrolidine **32** was complete with the *s*-BuLi/(−)-sparteine complex at −78 °C within 45 min. Interestingly, the *s*-BuLi/(+)-sparteine surrogate **154** complex only required 2 min for complete lithiation to have occurred which is considerably shorter than the lithiation time of 5 h which was previously reported.[157] ReactIR is an invaluable tool for the lithiation-trapping reactions of *N*-Boc heterocycles as it is able to provide accurate lithiation times for a multitude of ligands streamlining the development of reaction conditions, avoiding the requirement of optimisation through time consuming trial and error. Using this technique, the O'Brien group has developed an excellent general guide for lithiation- and electrophile-trapping times for *N*-Boc heterocycles.[142,143,166]

Following on from the success of their high-temperature 'diamine-free' lithiation-trapping protocol,[144] the O'Brien group developed a high-temperature enantioselective lithiation-trapping method for *N*-Boc heterocycles, in an attempt to make the asymmetric process more energy efficient and sustainable.[167] First, four points were taken into consideration which could affect the yield and stereochemical outcome of the reactions when reaction temperatures were increased above −78 °C:

1. The time taken for lithiation of the substrate to be complete would likely be reduced at higher temperatures;
2. The chemical stability of the lithiated intermediate may be decreased at increased temperatures;
3. The enantioselectivity (i.e. the kinetic selectivity due to interaction of the *s*-BuLi/chiral ligand complex with the *N*-Boc heterocycles) will be a function of temperature;
4. The configurational stability of the lithiated intermediate will likely be reduced at higher temperatures.

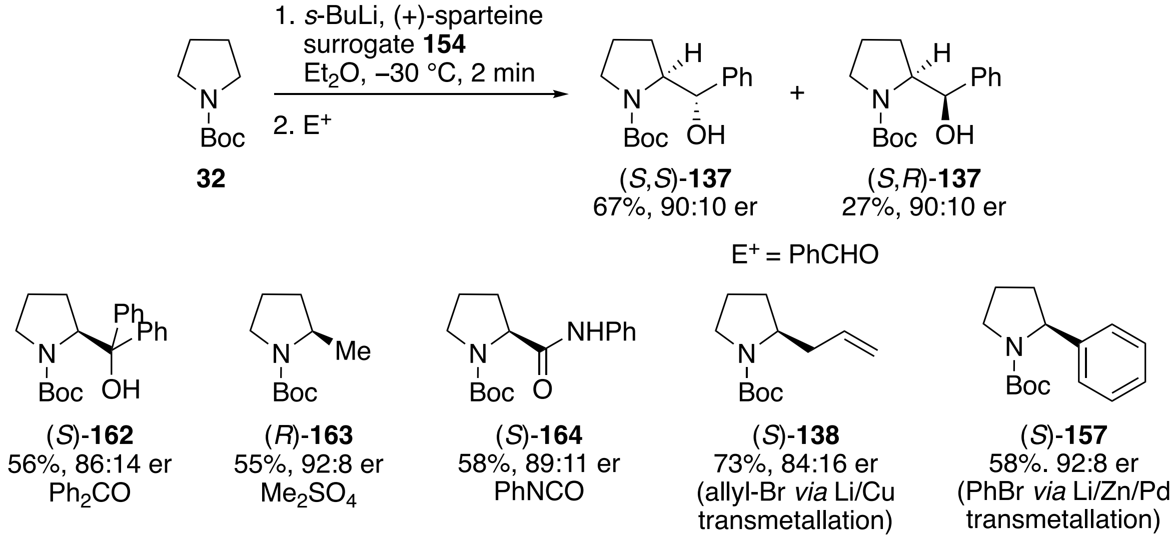
Of these, points 1 and 2 will have an impact on the yield whereas points 3 and 4 will affect the enantioselectivity. An investigation into the effect of temperature, with various lithiation times, on yield and enantioselectivity was carried out. Lithiation of *N*-Boc pyrrolidine **32** with *s*-BuLi and (−)-sparteine and trapping with PhCHO in Et_2O to form diastereomeric alcohols (*R,R*)-**137** and (*R,S*)-**137** was chosen as the model reaction (Table 3.2). Unsurprisingly, a high combined yield (86%) and er of both diastereomers (97:3 er) were obtained when the reaction was carried out at −78 °C (entry 1). Increasing the temperature to –40 °C with a 2 min lithiation time saw negligible change in combined yield (84%) but a marginal drop in er was observed in both diastereomers ((*R,R*)-**137**; 93:7 er, (*R,S*)-**137**; 91:9 er) (entry 2). At –30 °C for 2 min, an excellent combined yield of 92% was achieved albeit accompanied with another small reduction in the enantiomer ratio ((*R,R*)-**137**; 90:10 er, (*R*,*S*)-**137**; 89:11 er) (entry 3). Extending the lithiation time to 1 h saw a considerable reduction in yield (72%), presumably due to decreased chemical stability of the lithiated intermediate at this temperature, and further exaggerated the reduction in enantioselectivity ((*R,R*)-**137**; 87:13 er, (*R*,*S*)-**137**; 84:16 er), suggesting that with longer reaction times the configurational stability of the lithiated intermediate becomes compromised at this temperature (entry 4). Finally, at 0 °C for 1 min, both the yield and enantiomer ratios were significantly eroded with only a combined yield of 60% being achieved and the enantiomeric ratios of (*R*,*R*)-**137** and (*R*,*S*)-**137** being 65:35 er and 62:38 er respectively (entry 5). The conditions described in entry 3 were chosen as optimal furnishing the product in the highest yield with only a small decrease in enantioselectivity compared to conventional conditions (entry 1).



Entry	**Temp (°C)**	**Time (min)**	**Overall Yield (%)**	**er of (*R*,*R*)-137**	**er of (*R*,*S*)-137**
1	−78	180	86	97:3	97:3
2	−40	2	84	93:7	91:9
3	−30	2	92	90:10	89:11
4	−30	60	72	87:13	84:16
5	0	1	60	65:35	62:38

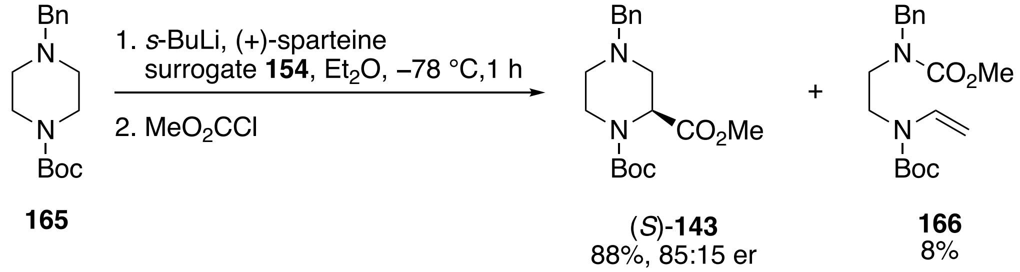
Table 3.2: High-temperature enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32**

With the (+)-sparteine surrogate **154**, under otherwise identical conditions as entry 3 (−30 °C, 2 min), comparable results were achieved when trapping with PhCHO to form diastereomeric alcohols (*S*,*S*)-**137** (67%, 90:10 er) and (*S*,*R*)-**137** (27%, 90:10 er). The electrophile scope was then explored under the newly developed conditions. Trapping with Ph_2CO to give amino alcohol (*S*)-**162**, Me_2SO_4 to give (*R*)-**163** and PhNCO to give amide (*S*)-**164** all proceeded in reasonable yields and good enantiomeric ratios (56%; 86:14 er, 55%; 92:8 er and 58%; 89:11 er respectively). Allylation *via* Li/Cu transmetallation and reaction with allyl bromide and arylation *via* Li/Zn/Pd transmetallation (Negishi cross-coupling) and reaction with bromobenzene worked well, furnishing the α-functionalised products (*S*)-**138** and (*S*)-**157** in 73% and 84:16 er and 58% and 92:8 er respectively (Scheme 3.18). These high-temperature asymmetric lithiation-trapping results represent a more energy efficient process to access enantioenriched α-functionalised *N*-Boc pyrrolidine removing the necessity of exceedingly low, energy intensive temperatures which were previously thought to be required.



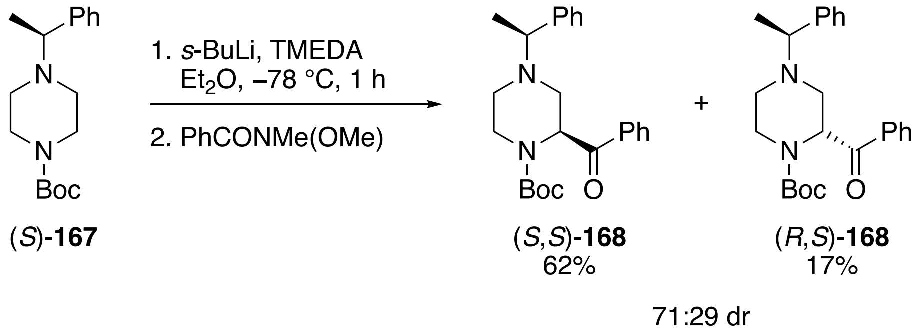
Scheme 3.18: High-temperature enantioselective lithiation-trapping scope

In 2015, the O'Brien group reported a new protocol for the synthesis of enantiopure *α*-functionalised piperazines.[168] Initially, it was found that treatment of *N*-Boc-*N*'-benzylpiperazine **165** with *s*-BuLi and (+)-sparteine surrogate **154** and trapping with MeO_2CCl gave rise to the desired *α*-functionalised piperazine (*S*)-**143** in 88% yield but only 85:15 er (Scheme 3.19). Even lower enantiomeric ratios were recorded with other electrophiles. Formation of side-product **166**, arising from ring fragmentation of the lithiated piperazine, was also a problem that was encountered. Fragmentation side-products akin to **166** formed in varying quantities depending on the electrophile employed.



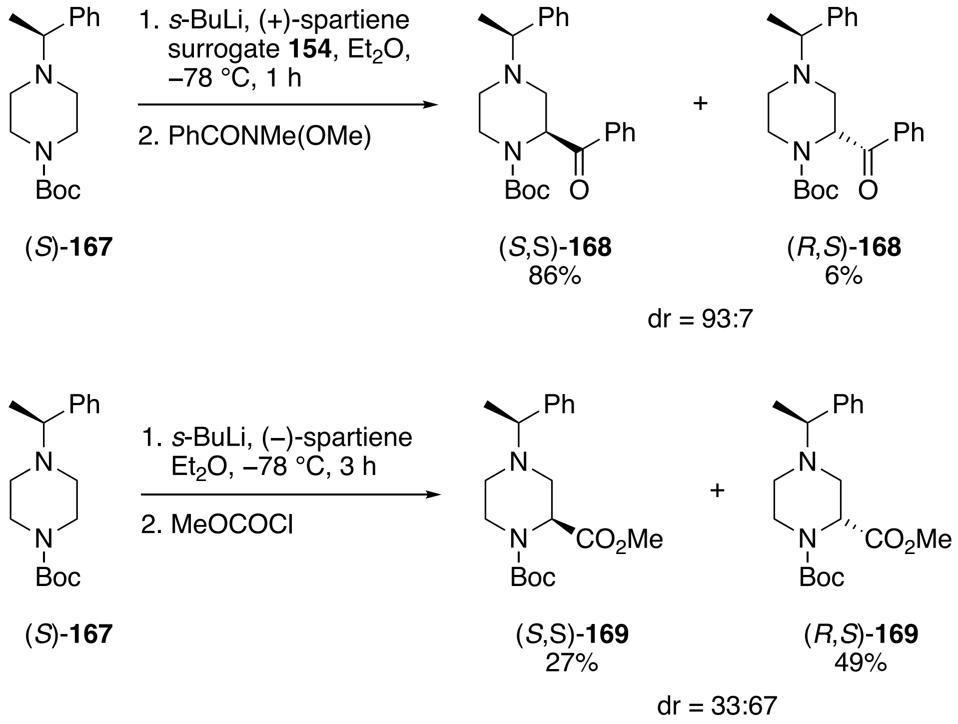
Scheme 3.19: Enantioselective lithiation-trapping of *N*-Boc-*N*'-benzyl piperazine **165**

An interesting result was discovered when the benzyl protecting group on the distal nitrogen was replaced with *α*-methyl benzyl to give *N*-Boc-*N'*-*α*-methyl benzyl piperazine (*S*)-**167**.[143,168] Lithiation of *N*-Boc-*N'*-*α*-methyl benzyl piperazine (*S*)-**167** in Et_2O at −78 °C for 1 h and trapping with a Weinreb amide (PhCONMe(OMe)) furnished diastereomeric adducts (*S*,*S*)-**168** in 62% yield and (*R*,*S*)-**168** in 17% yield (71:29 dr) (Scheme 3.20). This result shows that an inherent diastereoselectivity can be introduced with the addition of a chiral auxiliary. Furthermore, the increased steric hindrance present on the distal nitrogen disfavoured the formation of ring fragmentation side-product as none of it was detected.



Scheme 3.20: Diastereoselective lithiation-trapping of *N*-Boc-*N'*-*α*-methyl benzyl piperazine (*S*)-**167** with TMEDA

An improved diastereoselectivity was achieved when a combination of the chiral auxiliary and a matched chiral ligand was used. Lithiation-trapping of *N*-Boc-*N*-*α*-methyl benzyl piperazine (*S*)-**167** with *s*-BuLi and (+)-sparteine surrogate **154** in Et_2O at −78 °C for 1 h and then PhCONMe(OMe) constructed diastereomeric ketones (*S*,*S*)-**168** (86% yield) and (*R*,*S*)-**168** (6% yield) in a ratio of 93:7. Lithiation-trapping of *N*-Boc-*N*-*α*-methyl benzyl piperazine (*S*)-**167** with a mismatched chiral ligand, (−)-sparteine, resulted in a reversal of the diastereoselectivity. Diastereomeric esters (*S*,*S*)-**169** (27% yield) and (*R*,*S*)-**169** (49%) formed in a 33:67 ratio when trapped with MeOCOCl following lithiation at −78 °C for 3 h in Et_2O (Scheme 3.21).



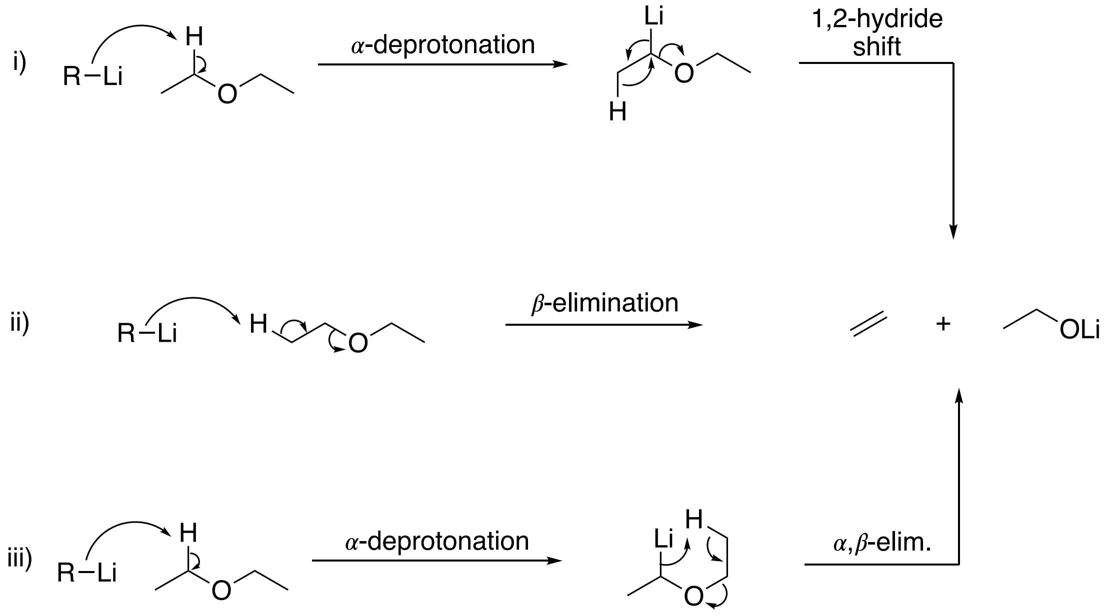
Scheme 3.21: Diastereoselective lithiation-trapping of *N*-Boc-*N*-α-methylbenzyl piperazine (*S*)-**167** with (+)-sparteine surrogate **154** and (−)-sparteine

Some attempts have been made to improve the greenness of enantioselective lithiation-trapping reactions of *N*-Boc heterocycles, namely, the use of a high-temperature enantioselective lithiation-trapping protocol which makes the process less energy intensive (see Scheme 3.18).[167] The green solvent 2-MeTHF has also been shown to be a suitable solvent, when (+)-sparteine surrogate **154** is used as the ligand, in enantioselective-lithiation trapping reactions (*vide infra*). However, as with THF, when (−)-sparteine and other weakly coordinating ligands are used, racemic products are obtained.[164] As such, the common use of Et_2O as the reaction solvent in enantioselective lithiation-trapping still needs addressing as the considerable health and safety hazards it possesses could limit the reaction's use in an industrial setting. Alternatively, the less volatile *tert*-butyl methyl ether (TBME) has been found to be an effective solvent at facilitating enantioselective lithiation-trapping reactions.[169,170]

3.3: Overview of Solvent Considerations for Lithiation-Trapping Reactions

3.3.1 Stability of Ether Solvents in the Presence of Organolithium Reagents

Organolithium chemistries are typically performed in ether solvents such as Et_2O and THF. However, the stability of these solvents in the presence of organolithiums such as *n*-BuLi and *s*-BuLi can be compromised. In 1987, Maercker reviewed the decomposition pathways of Et_2O through reaction with organolithium reagents.[171] Through deuterium labelling studies, three different solvent decomposition pathways were identified. These pathways include: i) α-deprotonation followed by a 1,2-hydride shift, ii) β-elimination and iii) α-deprotonation followed by α, β-elimination, with all three giving ethene and lithium ethoxide (Scheme 3.22).



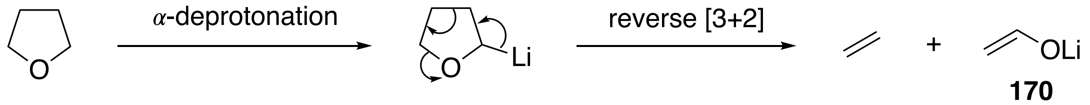
Scheme 3.22: Decomposition pathways of Et_2O

In 1997, Stanetty and Mihovilovic determined the lifetime of organolithium reagents in ether solvents using titration experiments.[172] The half-life ($t_{1/2}$) of commonly used organolithiums in Et_2O at different temperatures was determined, both in the presence and absence of TMEDA (Table 3.3). *s*-BuLi reacted slowly with Et_2O at −20 °C ($t_{1/2}$ = 19.8 h) (entry 1). With introduction of TMEDA into the system, at the same temperature, *s*-BuLi remained stable at 0.65 M concentrations (entry 2). However, increasing the temperature to 0 °C, the organolithium becomes unstable, with a half-life of 2.32 h being recorded (entry 3). On the other hand, *n*-BuLi is considerably more stable in Et_2O. At ambient temperatures in the presence of TMEDA, a half-life of 10.1 h was recorded (entry 4). This was extended to 153 h when TMEDA was excluded (entry 5). However, upon heating to 35 °C the stability was decreased ($t_{1/2}$ = 31 h) (entry 6).

Entry	**RLi**	**Solvent**	**Temp (°C)**	**$t_{1/2}$ (h)**
1	*s*-BuLi	Et_2O	−20	19.8
2	*s*-BuLi	Et_2O + TMEDA	−20	Stable at 0.65 M
3	*s*-BuLi	Et_2O	0	2.32
4	*n*-BuLi	Et_2O + TMEDA	20	10.1
5	*n*-BuLi	Et_2O	20	153
6	*n*-BuLi	Et_2O	35	31

Table 3.3: Stability of organolithiums in Et_2O

THF is also known to decompose in the presence of organolithium reagents.[173] One possible pathway of decomposition was determined through NMR spectroscopic studies by Bates *et al.* whereby, α-deprotonation followed by [3+2] reverse cycloaddition led to formation of ethene and lithium enolate **170** (Scheme 3.23).[174]



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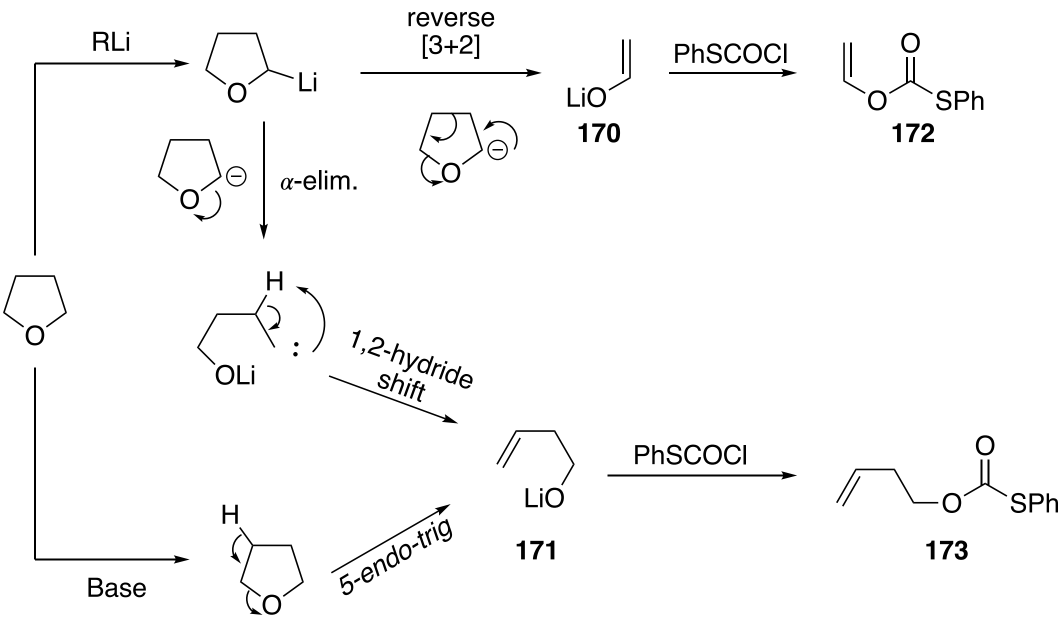
Scheme 3.23: Reverse [3+2] decomposition route for THF

Fleming *et al*. suggested that THF can also decompose to form lithium but-3-ene-oxide **171** as shown by trapping of the lithium alkoxide by dinitrobenzoyl chloride.[175] A more detailed study by Clayden in 2002 reported the formation of this decomposition product.[176] Addition of an organolithium and hexamethylphosphoramide (HMPA) ligand to THF followed by trapping with PhSCOCl formed but-3-en-lyl thiocarbonate **173**. The possible origins of lithium but-3-ene oxide **171** are *via* *β*-elimination followed by 5-*endo*-*trig* ring opening (disfavoured in the Baldwin's rules[177]) or by *via* *α*-deprotonation followed by a 1,2-hydride shift (Scheme 3.24). HMPA was found to promote the 5-*endo*-*trig* decomposition pathway whereas, when other ligands were used such as (−)-sparteine, the lithium enolate trapped product **172** (formed through reverse [3+2] decomposition) preferentially formed.



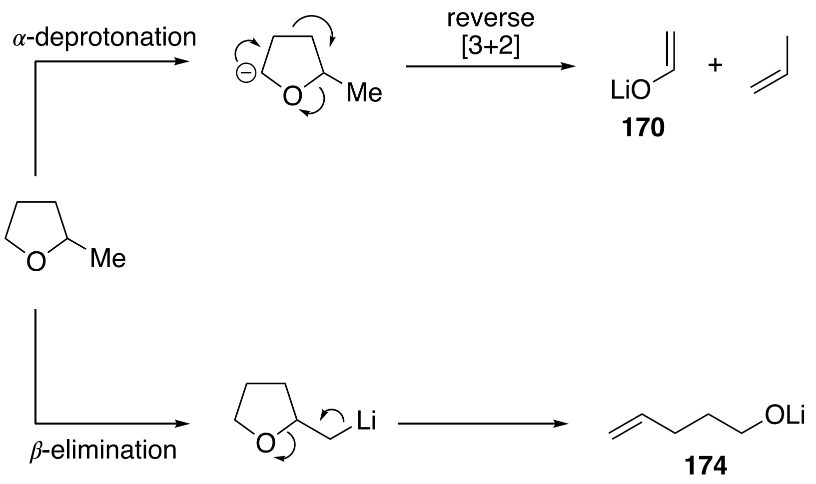
Scheme 3.24: Decomposition pathways for THF followed by trapping with phenyl thiochloroformate

Stanetty and Mihovilovic also measured the lifetime of organolithiums in THF (Table 3.4).[172] At −40 °C, both with and without the addition of TMEDA, *s*-BuLi was stable at 0.52 M concentrations (entries 1 and 2). However, when the temperature was increased to −20 °C, *s*-BuLi exhibited a $t_{1/2}$ of only 1.30 h. This decreased even further to 0.47 h with the addition of TMEDA (entries 3 and 4 respectively). As also observed for Et_2O (see Table 3.3), *n*-BuLi was considerably more stable than *s*-BuLi. Under otherwise identical conditions to those in entry 4, *n*-BuLi exhibited a half-life of 55.2 h (entry 5). At 0 °C, both without and with TMEDA the half-life was reduced to 17.3 and 5.63 h respectively (entries 6 and 7). This was reduced further to 1.78 h when *n*-BuLi was stored at ambient conditions (entry 8) and 0.63 h when TMEDA was present in the system (entry 9). It is clear from the data collected by Stanetty *et al*. that organolithiums are considerably less stable in THF than in Et_2O.

Entry	RLi	Solvent	Temperature (°C)	$t_{1/2}$ (h)
1	*s*-BuLi	THF	−40	Stable at 0.52 M
2	*s*-BuLi	THF + TMEDA	−40	Stable at 0.52 M
3	*s*-BuLi	THF	−20	1.30
4	*s*-BuLi	THF + TMEDA	−20	0.47
5	*n*-BuLi	THF + TMEDA	−20	55.2
6	*n*-BuLi	THF	0	17.3
7	*n*-BuLi	THF+TMEDA	0	5.63
8	*n*-BuLi	THF	20	1.78
9	*n*-BuLi	THF+TMEDA	20	0.63

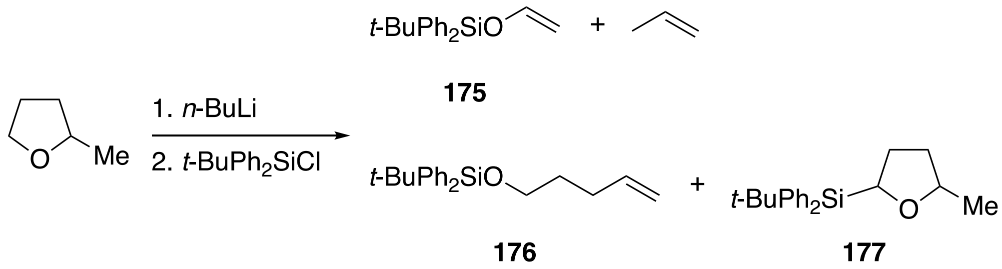
Table 3.4: Stability of organolithiums in THF

2-MeTHF, a bio-derived alternative solvent to THF,[152] has also been shown to be a suitable solvent for lithiation chemistry (*vide infra*).[32,144,148] However, similarly to Et_2O and THF, 2-MeTHF is known to undergo decomposition processes through reaction with organolithium reagents. There are two plausible decomposition routes which are available to 2-MeTHF in the presence of organolithiums: i) α-deprotonation followed by reverse [3+2] cycloaddition (in a similar fashion to THF) to give lithium enolate **170** and propene and ii) β-elimination leading to the formation of lithium pent-4-en-1-oxide **174** (Scheme 3.25).



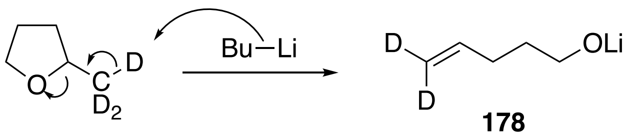
Scheme 3.25: Decomposition pathways for 2-MeTHF

In 1993, Cohen and Stokes performed a number of experiments to gain a better understanding of the decomposition processes available to 2-MeTHF.[178] Addition of *n*-BuLi (10 M in hexane) to 2-MeTHF at ambient temperatures followed by the addition of *t*-$BuPh_2SiCl$ gave rise to a mixture of four products: silyl enol ether **175** and propene formed *via* α-deprotonation then reverse [3+2] cycloaddition, silyl ether **176** resulting from β-elimination and **177**, the direct trapping product from α-lithiated 2-MeTHF (Scheme 3.26).



Scheme 3.26: Electrophile trapped decomposition products of 2-MeTHF

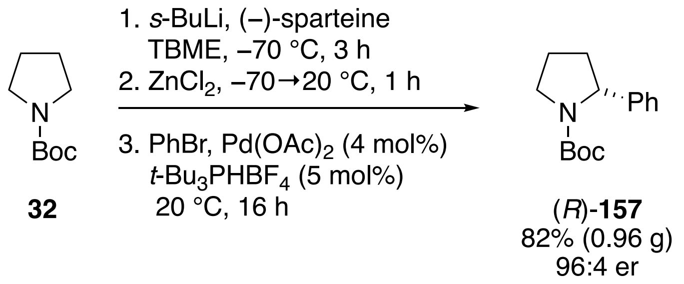
Following on from this, Cohen then performed deuterium labelling experiments to determine if silyl ether **176** was formed *via* β-elimination or α-deprotonation then α, β-elimination. 2-CD_3THF was treated with *n*-BuLi and GC-MS analysis of the crude product showed that two deuterium atoms were still present in product **178**, indicating that the product is a result of *β*-elimination (Scheme 3.27).



Scheme 3.27: *β*-Elimination of 2-CD_3THF

3.3.2 Use of Alternative Solvents for Lithiation-Trapping Methodologies

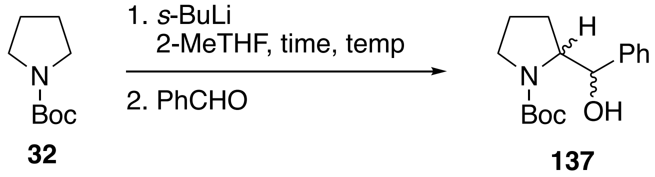
The hazards associated with solvents typically employed in lithiation-trapping methodologies are well-known. Et_2O has a low boiling point of 34.6 °C as well as an exceptionally high vapour pressure at ambient temperatures (440 mmHg at 20 °C) meaning that application of this solvent within an industrial large-scale setting is generally avoided Furthermore, it is also considered to be extremely flammable, can form explosive peroxides when exposed to light and air and is also suspected of causing cancer.[24] In some cases, the less volatile TBME has been used as an alternative to Et_2O. Researchers at Merck in 2006 reported the use of TBME in a gram-scale enantioselective synthesis of *α*-phenyl pyrrolidine (*R*)-**157** *via* Li/Zn/Pd transmetallation and Negishi cross-coupling of *N*-Boc pyrrolidine **32**.[169] Lithiation of *N*-Boc pyrrolidine **32** with *s*-BuLi and (−)-sparteine in TBME at −70 °C for 3 h was carried out; subsequent transmetallation with $ZnCl_2$ formed the organozinc species. Finally, Negishi cross-coupling, using $Pd(OAc)_2$ (4 mol%) and *t*-Bu_3PHBF_4 (5 mol%) with bromobenzene at 20 °C for 16 h constructed *α*-phenyl pyrrolidine (*R*)-**157** in 82% yield and 96:4 er (Scheme 3.28). Although TBME is considered as a safer alternative solvent to Et_2O due to its higher boiling point (55 °C), lower vapor pressure (204 mmHg at 20 °C) and resistance to forming explosive peroxides there are significant concerns regarding its use. Notably, these include its persistence in the environment and bioaccumulation.[179]



Scheme 3.28: Enantioselective lithiation-transmetallation-Negishi cross-coupling of *N*-Boc pyrrolidine **32** in TBME

Similar undesirable characteristics to Et_2O are also associated with THF. THF is highly flammable and capable of forming explosive peroxides as well as being a suspected carcinogen.[27] However, its higher boiling point (66 °C) and lower vapour pressure (132 mmHg at 20 °C) relative to Et_2O means that it finds widespread use in an industrial setting.[180]

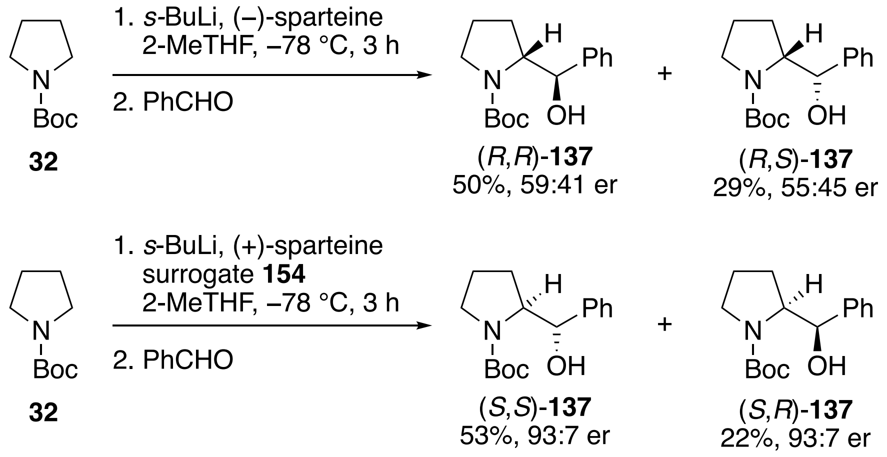
Et_2O, THF and TBME are derived from petroleum-based feedstocks.[25,181,182] The bio-derived solvent 2-MeTHF is an attractive alternative solvent to Et_2O and THF in lithiation chemistry and has already seen application in lithiation and other organometallic reactions.[32,144,148,183] Notably, it was featured as a possible solvent for the high-temperature diamine-free lithiation-trapping of *N*-Boc heterocycles developed by the O'Brien group (Table 3.5). *N*-Boc pyrrolidine **32** was treated with *s*-BuLi in 2-MeTHF at −78 °C for 1 h; PhCHO trapping gave amino alcohol **137** as a mixture of diastereomers in 92% yield (entry 1). 2-MeTHF performed similarly to THF (see Scheme 3.4), proving that the *s*-BuLi/2-MeTHF complex is sufficiently reactive enough to facilitate lithiation of *N*-Boc pyrrolidine **32**. A marginally improved yield of 94% was achieved when the reaction was run at −40 °C for 1 h (entry 2). Product yields were significantly eroded when the reaction temperature was raised to −30 °C (entry 3). A lithiation time of 5 min gave 73% yield and increasing this to 1 h resulted in no conversion to the amino alcohol **137** (entry 4). This was presumably due to a combination of unwanted reaction between the organolithium and the solvent and decreased stability of the lithiated intermediate.



Entry	Temperature (°C)	Time (min)	Yield (%)
1	−78	60	92
2	−40	60	94
3	−30	60	0
4	−30	5	73

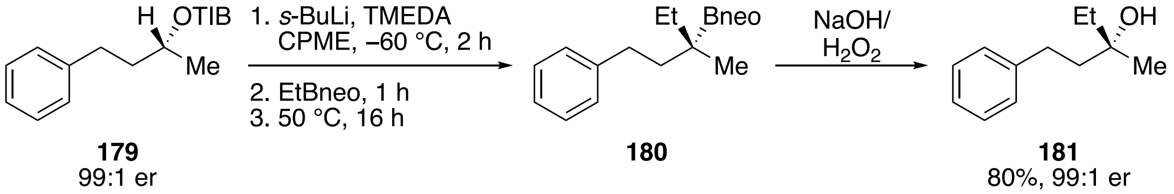
Table 3.5: High temperature diamine-free lithiation-trapping in 2-MeTHF

The highly coordinating nature of 2-MeTHF hinders its use in asymmetric lithiation-trapping of *N*-Boc heterocycles using (−)-sparteine. The O'Brien group reported that high yields but very poor enantiomeric ratios were achieved when *s*-BuLi/(−)-sparteine-mediated lithiation-trapping of *N*-Boc pyrrolidine **32** with PhCHO was attempted in 2-MeTHF. This was due to the preferential coordination of the solvent to the organolithium in place of the ligand. However, analogous to THF, with the use of the (+)-sparteine surrogate **154**, high yields and enantiomeric ratio were obtained (Scheme 3.29), highlighting the similarities of 2-MeTHF to THF in their performance in asymmetric lithiation trapping.[164]



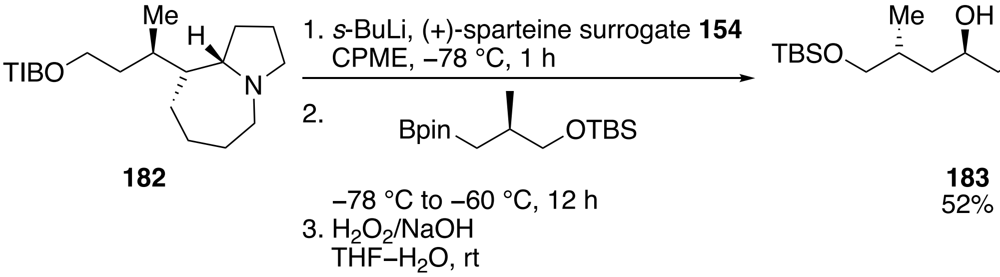
Scheme 3.29: Enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32** in 2-MeTHF

Another solvent which has recently been utilised in lithiation chemistry is cyclopentyl methyl ether (CPME). In 2013, Aggarwal *et al.* reported the use of CPME in the synthesis of enantioenriched tertiary boronic esters through the lithiation-borylation of secondary alkyl benzoates (Scheme 3.30).[184] CPME was the solvent of choice following optimisation studies for the *s*-BuLi/TMEDA-mediated deprotonation of enantiopure benzoate **179** (99:1 er). The lithiated intermediated was subsequently treated with neopentyl boronic ester (EtBneo) furnishing boronic ester **180**. Oxidation of the boronic ester revealed tertiary alcohol **181** in 80% with no erosion of the enantiomeric ratio (99:1 er).



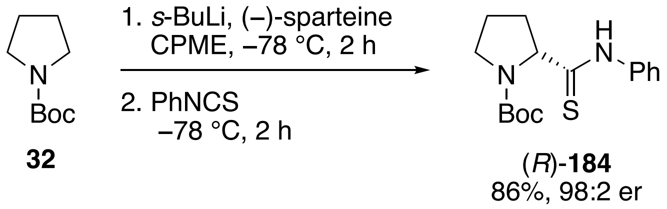
Scheme 3.30: Synthesis of tertiary alcohol **181** *via* lithiation-borylation with CPME as solvent

The Aggarwal group further demonstrated the use of CPME in this field of lithiation methodology in the stereocontrolled synthesis of (−)-stemaphylline (Scheme 3.31).[185] Lithiation-borylation of benzoate **182** in Et_2O and oxidation with NaOH/H_2O to give secondary alcohol **183** was unsuccessful, returning only starting material. Replacement of Et_2O with CPME facilitated the reaction constructing **183** in 52% yield. Further reactions then gave (−)-stemaphylline with full stereocontrol exemplifying CPME's potential in lithiation chemistry for the synthesis of natural products.



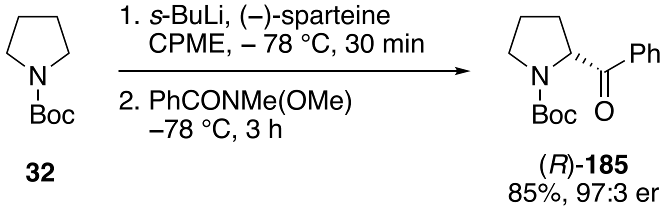
Scheme 3.31: Lithiation-borylation synthetic step in the synthesis of (−)-Stemaphylline

Pace *et al*. described the enantioselective synthesis of secondary thioamides through the use of lithiation-trapping methodologies in CPME (Scheme 3.32).[186] In one such example, treatment of *N*-Boc pyrrolidine **32** with *s*-BuLi and (−)-sparteine at −78 °C for 2 h in CPME followed by addition of isothiocyanate PhNCS furnished enantioenriched thioamide (*R*)-**184** (86% yield, 98:2 er). This highlights CPME as a potential replacement for Et_2O in enantioselective lithiation-trapping reactions with weakly coordinating ligands such as (−)-sparteine. Similarly impressive results were obtained for the lithiation-trapping of a Hoppe-type *O*-alkyl carbamate **147**.



Scheme 3.32: Enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32** with isothiocyanates in CPME

CPME's use in lithiation-trapping reactions was further demonstrated by the Pace group in 2019, reporting the enantioselective synthesis of *α*-pyrrolydinyl ketones *via* lithiation-trapping of *N*-Boc pyrrolidine **32** with Weinreb amides in CPME.[187] Addition of *s*-BuLi and (−)-sparteine to **32** in CPME and subsequent trapping with Weinreb amide PhCONMe(OMe) gave (*R*)-**185** in 85% yield and 97:3 er (Scheme 3.33). Interestingly, only a 30 min lithiation time was required, compared to 45 min in Et_2O determined through ReactIR experiments (*vide supra*), suggesting an increased reactivity of the *s*-BuLi/(−)-sparteine complex when CPME is used for lithiation-trapping reactions. A significant benefit of using CPME in this reaction was the possibility for isolating (*R*)-**185** *via* recrystallisation, as opposed to flash column chromatography, mitigating the generation of large quantities of solvent waste. The valuable chiral ligand was also recycled by firstly extracting in the aqueous layer phase and basification with NaOH. The ligand was then isolated in high purity *via* fractional distillation.



Scheme 3.33: Lithiation-trapping of *N*-Boc pyrrolidine **32** with a Weinreb amide in CPME

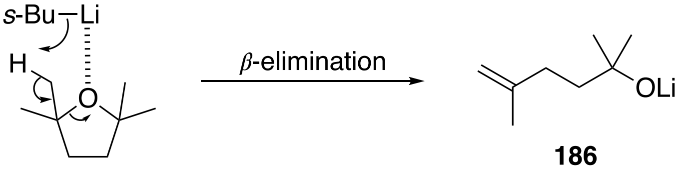
3.4: Lithiation-Trapping of *N*-Boc Heterocycles in TMO

In lithiation-trapping reactions carried out in ether solvents, Et_2O and THF are without doubt the most commonly employed solvents. The requirement for Et_2O to be used in enantioselective lithiation-trapping reaction potentially hinders the reaction use within an industrial setting, although CPME and TBME are potential alternatives. More recently, the green alternative 2-MeTHF has seen use in lithiation-trapping reaction but poor stereoselectivity is typically observed when 2-MeTHF is used in enantioselective lithiation-trapping reactions.

This chapters details the use of TMO in lithiation-trapping reactions of *N*-Boc heterocycles using *s*-BuLi alone or *s*-BuLi in combination with diamines. First, the stability of TMO in the presence of *s*-BuLi at various temperatures will be discussed and a comparison made with the structurally related 2-MeTHF. An investigation into the use of TMO in racemic lithiation-trapping of *N*-Boc pyrrolidine **32**, both in the absence and presence of TMEDA will also be presented and TMO's applicability in enantioselective lithiation-trapping reaction of *N*-Boc pyrrolidine **32** with different chiral ligands will be determined. Finally, a brief investigation into the diastereoselective lithiation-trapping of enantiopure *N*-Boc piperazines bearing chiral auxiliaries in the absence of chiral ligands will be presented.

3.4.1 Determining the Stability of TMO and 2-MeTHF in the Presence of *s*-BuLi

As discussed in Section 3.3.1, ether solvents Et_2O, THF and 2-MeTHF, are all known to undergo decomposition in the presence of organolithium reagents *via* a range of cleavage reaction pathways.[171,176,178] As such, before investigating the possibility of TMO being used as the solvent in lithiation-trapping methodologies, it was first decided to determine at what temperatures TMO undergoes reaction with the organolithium reagents in the absence of any substrate. As TMO lacks any α-protons, only the β-elimination decomposition pathway is available to the solvent forming tertiary lithium alkoxide **186** (Scheme 3.34).



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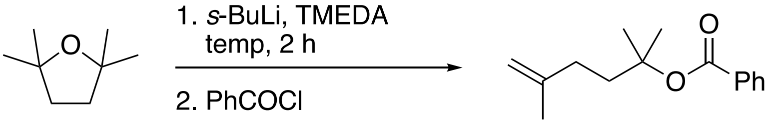
Scheme 3.34: Cleavage of TMO *via* β-elimination

An investigation into the reaction between TMO (as solvent) and *s*-BuLi both in the presence and in the absence of TMEDA for 2 h was carried out. To identify at which temperature any decomposition would potentially occur, the presumed lithium alkoxide **186** was trapped with PhCOCl and the yields of the formed alkyl benzoate **187** at different temperatures were compared (Table 3.6). At 0 °C, without TMEDA, decomposition of the solvent readily occurred with alkyl benzoate **187** being isolated in 54% yield (entry 1). This is unsurprising considering that other conventional ether solvents also readily undergo decomposition in the presence of *s*-BuLi at this temperature.[172] Reducing the temperature to −10 °C, a lower yield of 40% of alkyl benzoate **187** was observed suggesting an improvement in the stability of the solvent (entry 2). This was further illustrated when the temperature was reduced to −20 °C and a yield of 27% was achieved when TMEDA was present (entry 3). Exclusion of TMEDA resulted in a slightly higher yield at this temperature which was unexpected as the *s*-BuLi/TMEDA complex would presumably be more reactive than the *s*-BuLi/TMO complex (37%, entry 4). However, at temperatures below −20 °C, both in the presence and in the absence of ligand (entries 5−8), none of alkyl benzoate **187** was detected in the ^{1}H NMR spectrum of the crude product. This clearly indicated that, at −30 °C or −40 °C, TMO is stable in the presence of *s*-BuLi or *s*-BuLi/TMEDA for at least 2 h. This is a significant finding for any planned lithiation reaction that would use TMO as solvent.



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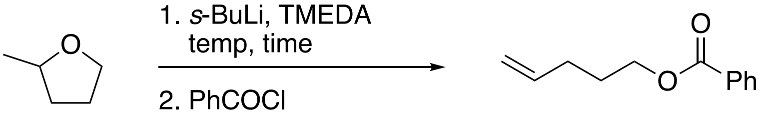
Entry	Ligand	Temperature (°C)	Yield (%)[a]
1	-	0	54
2	-	−10	40
3	TMEDA	−20	27
4	-	−20	37
5	TMEDA	−30	0
6	-	−30	0
7	TMEDA	−40	0
8	-	−40	0

Table 3.6: Ring opening of TMO. [a]Yield after chromatography

The stability of TMO was then compared with the green solvent 2-MeTHF. 2-MeTHF has been used on many occasions in lithiation-trapping reactions.[144,148] However, it is known to undergo a β-elimination decomposition pathway in the presence of *s*-BuLi.[178] As such, like with TMO, 2-MeTHF was treated with *s*-BuLi both in the presence and absence of TMEDA. The lithium alkoxide **174** formed was then trapped with PhCOCl and the yields compared to determine the solvent's stability under these conditions (Table 3.7). At 0 °C for 2 h without TMEDA, alkyl benzoate **188** was formed in 47% yield (entry 1). The yield was increased to 55% with the introduction of TMEDA (entry 2). These results similarly match the findings reported for TMO at this temperature (54% yield, see Table 3.6, entry 1). Extending the reaction time to 4 h, a small increase in yield was observed: 53% without TMEDA (entry 3) and 64% when TMEDA was included in the reaction (entry 4). Unlike TMO, however, when the reaction temperature was reduced to −40 °C and the reaction was run for 2 h, decomposition of 2-MeTHF was still prevalent, with alkyl benzoate **188** forming in 48% yield in the absence of the ligand (entry 5) and in 56% yield when the ligand was present (entry 6). Interestingly, even at temperatures as low as −60 and −78 °C, temperatures which are typically employed in lithiation-trapping reactions, alkyl benzoate **188** was still forming in notable quantities, 36% and 38% respectively (entries 7 and 8).



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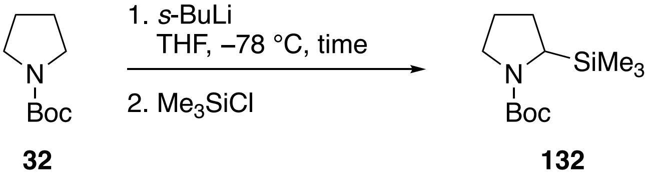
Entry	Ligand	Time (h)	Temperature (°C)	Yield (%)[a]
1	-	2	0	47
2	TMEDA	2	0	55
3	-	4	0	53
4	TMEDA	4	0	64
5	-	2	−40	48
6	TMEDA	2	−40	56
7	TMEDA	2	−60	36
8	TMEDA	2	−78	38

Table 3.7: Ring opening of 2-MeTHF. [a]Yield after chromatography

It is evident from the results presented in Tables 3.6 and 3.7 that TMO is significantly more stable than 2-MeTHF in the presence of *s*-BuLi regardless of the addition of a diamine ligand. 2-MeTHF undergoes decomposition *via* β-elimination to form lithium alkoxide **174**, at temperature even as low at −78 °C. In contrast, only at temperatures above −30 °C, do we observe decomposition of TMO. This difference between rates of decomposition between the two solvents could be explained by the increased steric hindrance in TMO compared to 2-MeTHF. Hence, coordination of *s*-BuLi or *s*-BuLi/TMEDA would be easier with 2-MeTHF, promoting decomposition at lower temperatures. This is not a concern when lithiation-trapping reactions with easy-to-lithiate substrates are performed in 2-MeTHF as the rate of lithiation of the substrate is presumably faster than the rate of decomposition (see Scheme 3.29).[144] However, with substrates that are slower to lithiate, competing decomposition reactions between 2-MeTHF and the organolithium could become problematic.

3.4.2 Racemic Lithiation-Trapping of *N*-Boc Pyrrolidine 32 in TMO

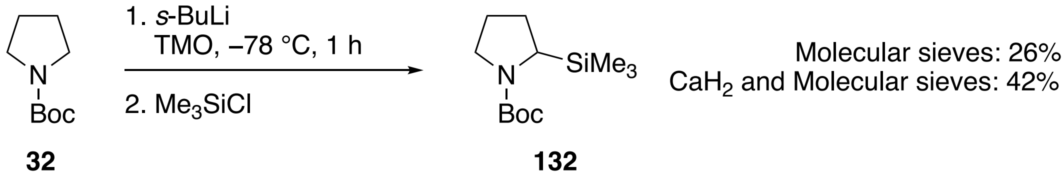
Initially, the diamine-free lithiation-trapping of *N*-Boc pyrrolidine **32** and trapping with Me_3SiCl as the electrophile to form silyl pyrrolidine **132**, first in THF, was carried out in order to corroborate results previously reported in the literature (Table 3.8).[144] *N*-Boc pyrrolidine **32** was treated with *s*-BuLi in THF at −78 °C for 1 h. Me_3SiCl was added to the lithiated intermediate and the reaction mixture was allowed to warm to room temperature over 1 h. Following purification *via* flash column chromatography and drying the purified product to remove residual solvent under a high vacuum line (16 h), silyl pyrrolidine **132** was isolated in an underwhelming 46% yield (entry 1). This is considerably lower than that previously reported in the literature.[144] Disappointed with the result, the lithiation time was extended to 2 h in an attempt to improve the yield (entry 2). However, after leaving the purified product on the high vacuum line over a weekend (60 h), none of the product remained, suggesting that product **132** had an unknown but significant volatility. As a result, excessive drying of the purified product was resulting in inaccurate recordings of the product yields. To avoid this, removal of residual solvent on the high vacuum line was limited to 1 h. Under identical reaction conditions as entry 1 (−78 °C, 1 h), silyl pyrrolidine **132** was isolated in a much-improved yield of 70% fully consistent with yields reported in the literature (entry 3).



Entry	Time (h)	Drying time (h)[a]	Yield (%)[b]
1	1	16	46
2	2	60	0
3	1	1	70

Table 3.8: Diamine-free lithiation-trapping of *N*-Boc pyrrolidine **32** with Me_3SiCl. [a]Time drying on high vacuum line. [b]Yield after chromatography

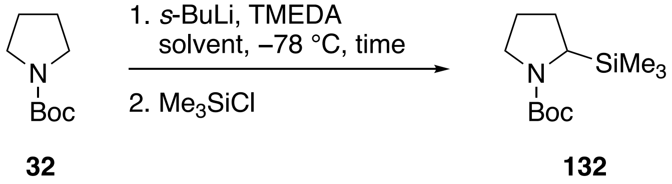
THF used in these reactions was taken from a solvent purification system ensuring that water content was in low ppm levels. This is important in lithiation-trapping methodologies due to the organolithium reagents inherent reactivity towards water. As TMO is synthesised in-house, with its sole by-product being water, efforts needed to be made to ensure that the residual water content in TMO was kept to a minimum. As such, two different solvent drying methods were chosen and the yields of diamine-free lithiation-trapping of *N*-Boc pyrrolidine **32** with Me_3SiCl to form silyl pyrrolidine **132** were compared to determine the appropriate solvent drying technique. First, TMO was stored over 3 Å molecular sieves and purged with N_2 to ensure that the solvent was being held under an inert atmosphere. The solvent was then taken forward for use in the lithiation-trapping reaction and a disappointing 26% yield of silyl pyrrolidine **132** was achieved. The next, more thorough, drying technique involved distillation over ground CaH_2 and storage over 3 Å molecular sieves under an inert atmosphere. This batch of TMO was then used in the lithiation-trapping reaction and an improved, yet still modest, 42% yield of silyl pyrrolidine **132** was achieved. This proves that only storing TMO over molecular sieves is not appropriate in this highly water-sensitive chemistry and more thorough drying of the solvent through distillation over a desiccant is required. As such, TMO was dried using this technique for all further lithiation-trapping reactions (Scheme 3.35).



Scheme 3.35: Diamine-free lithiation-trapping of *N*-Boc pyrrolidine **32** using TMO (dried using different techniques) as solvent.

The modest yields achieved even when the solvent was thoroughly dried in the lithiation-trapping reaction in TMO relative to THF using the diamine-free protocol suggests that the increased steric bulk surrounding the oxygen in TMO affects it ability to coordinate to the organolithium. This steric hindrance presumably leads to the *s*-BuLi/TMO complex being less reactive than the *s*-BuLi/THF complex; this steric hindrance is likely the reason behind the increased stability of TMO in the presence of *s*-BuLi (see Scheme 3.34). However, this results in the *s*-BuLi/TMO complex being less effective in facilitating deprotonation of the substrate, which is similar to the *s*-BuLi/Et_2O complex, albeit not to the same extent.

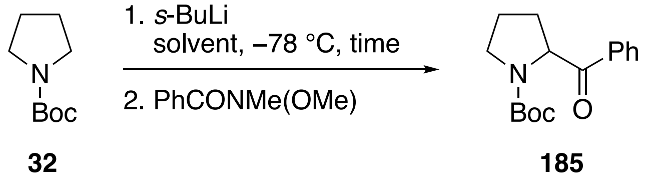
As a result of the above conclusion, lithiation-trapping of *N*-Boc pyrrolidine **32** with the addition of TMEDA in TMO was investigated and compared with the same reaction in Et_2O (Table 3.9). First, *s*-BuLi was added to a solution of **32** and TMEDA in Et_2O at −78 °C and stirred for 5 min. Subsequent addition of Me_3SiCl furnished the α-functionalised product **132** in 85% yield, consistent with the findings reported in the literature (entry 1).[135] The reaction was then performed in TMO with a slightly longer lithiation time of 15 min to ensure that complete lithiation had occurred. Pleasingly, a high yield of 89% of silyl pyrrolidine **132** was achieved. Comparing this with the diamine-free protocol, it is clear that the addition of TMEDA is essential to achieve a high yielding reaction when using TMO as the reaction solvent.



Entry	Solvent	Time (min)	Yield (%)[a]
1	Et_2O	5	85%
2	TMO	15	89%

Table 3.9: TMEDA-mediated lithiation-trapping of *N*-Boc pyrrolidine **32**. [a]Yield after chromatography

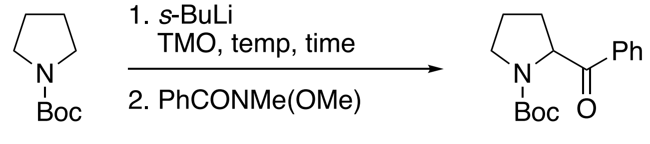
For future reactions, it was decided to use a Weinreb amide, PhCONMe(OMe), as the electrophile while investigating the lithiation-trapping reactions of *N*-Boc pyrrolidine **32** as the volatility of silyl pyrrolidine **132** could potentially negatively affect the accuracy of the yields. Therefore, the diamine-free lithiation-trapping of *N*-Boc pyrrolidine **32** and trapping with PhCONMe(OMe) was investigated (Table 3.10). *N*-Boc pyrrolidine **32** was treated with *s*-BuLi in THF at −78 °C for 1 h. Addition of the electrophile furnished the desired adduct **185** in 81% yield (entry 1). With Et_2O, under otherwise identical conditions, only a 7% yield of adduct **185** was achieved. This is a result of the *s*-BuLi/Et_2O complex being ineffective at promoting deprotonation of the substrate.[144] In a similar way to when Me_3SiCl was used as the electrophile, when switching the solvent to TMO, a 42% yield of ketone **185** was recorded (entry 3). Extending the lithiation time to 2 h resulted in no notable change in yield with only 40% of ketone **185** being isolated (entry 4). These results reinforce the conclusion that the increased steric hindrance present in TMO leads to the *s*-BuLi/TMO complex being only mildly reactive towards lithiation of the substrate.



Entry	Solvent	Time (h)	Yield (%)[a]
1	THF	1	81
2	Et_2O	1	7
3	TMO	1	42
4	TMO	2	40

Table 3.10: Diamine-free lithiation-trapping of *N*-Boc pyrrolidine **32** with PhCONMe(OMe). [a]Yield after chromatography

Unimpressed with the yields achieved using the diamine-free lithiation-trapping protocol of *N*-Boc pyrrolidine **32** in TMO at −78 °C, an investigation into a 'high-temperature' diamine-free lithiation-trapping reaction that could potentially improve the reactivity of the *s*-BuLi/TMO complex was undertaken (Table 3.11). At −60 °C, no improvement of the yield, compared to −78 °C (42%), was observed (33%) (entry 1). Further increasing the temperature to −40 °C also offered no meaningful improvement with 45% yield of the desired adduct **185** being achieved (entry 2). At −30 °C for 1 h, a considerable drop in yield to 14% of ketone **185** was observed (entry 3). This could be a result of the instability of the lithiated intermediate at this temperature as it is unlikely to be caused through consumption of *s*-BuLi through reaction with the solvent as we had previously demonstrated that this is not occurring at −30 °C (see Table 3.6). Reducing the lithiation time to 30 min resulted in a 38% yield (entry 4) which is consistent with our conjecture concerning the stability of the lithiated intermediate. Similar results were obtained when the reaction time was further decreased to 20 min (38% yield, entry 5), 10 min (30% yield, entry 6) and 5 min (37% yield, entry 7). Unfortunately, increasing the reaction temperature in this diamine-free protocol did not result in improved yields. It is likely that the *s*-BuLi/TMO complex is more reactive and so the rate of lithiation is increased at higher temperatures. However, the lithiated intermediate becomes unstable at these temperatures resulting in yields between 14−45%. Furthermore, the stability of the lithiated intermediate could be further compromised by the lack of coordination of the sterically hindered TMO.

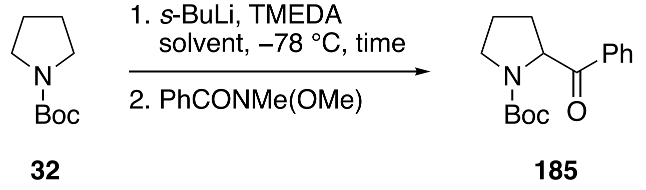


32 **185**

Entry	Temperature (°C)	Time (min)	Yield (%)[a]
1	−60	60	33
2	−40	60	45
3	−30	60	14
4	−30	30	38
5	−30	20	38
6	−30	10	30
7	−30	5	37

Table 3.11: ‘High-temperature’ lithiation-trapping of *N*-Boc pyrrolidine **32**. [a]Yield after chromatography

The *s*-BuLi/TMEDA-mediated lithiation of *N*-Boc pyrrolidine **32** was revisited, this time trapping with PhCONMe(OMe) (Table 3.12). As expected, treatment of a solution of **32** and TMEDA in Et_2O at −78 °C with *s*-BuLi for 5 min followed by the addition of PhCONMe(OMe) furnished the *α*-functionalised product **185** in an excellent yield of 88% (entry 1). Et_2O was then substituted by TMO and the lithiation time was extended to 15 min to ensure lithiation in the new solvent had been completed. Ketone **185** was synthesised in an equally high 89% yield (entry 2). When using a lithiation time of 5 min, a small reduction in the yield (79%) was observed (entry 3).



Entry	Solvent	Time (min)	Yield (%)[a]
1	Et_2O	5	88
2	TMO	15	89
3	TMO	5	79

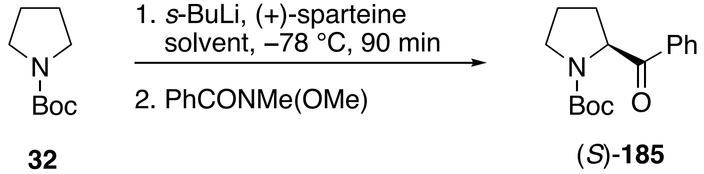
Table 3.12: TMEDA-mediated lithiation-trapping of *N*-Boc pyrrolidine **32** with PhCONMe(OMe). [a]Yield after chromatography

The results presented in this section clearly illustrate the potential of TMO being used in lithiation-trapping methodologies. It is, however, essential for high yields that when TMO is used in racemic lithiation-trapping reactions of *N*-Boc heterocycles an additive diamine ligand, such as TMEDA, is included in the reaction. This is because the *s*-BuLi/TMO complex on its own is not reactive enough to enable complete lithiation of the substrate. At higher temperatures a balance could not be found between the rate of lithiation and the rate of decomposition of the lithiated intermediate. As a result of this, only moderate yields could be achieved using the diamine-free protocol.

3.4.3 Enantioselective Lithiation-Trapping of *N*-Boc Pyrrolidine 32

The results obtained in the racemic lithiation-trapping experiments indicate that the methyl groups present in TMO hinders its ability to coordinate to the organolithium reagent and form a reactive *s*-BuLi/TMO complex. This claim is supported by the modest yields which were acquired when attempting diamine-free lithiation-trapping reactions in TMO (see Table 3.11). It is well established that enantioselective lithiation-trapping reactions when using (+)-

or (−)-sparteine are highly solvent dependant. Poorly coordinating solvents, such as Et_2O, are required to achieve a highly enantioselective reaction.[164] If THF is used as the reaction solvent, an undesirable racemic result is generally realised (see Schemes 3.16 and 3.17).[160–164] As such, we felt that there was an opportunity for TMO to be used in enantioselective lithiation-trapping reactions based on the requirement for the addition of TMEDA to achieve a high yielding racemic lithiation-trapping reaction in TMO. Before carrying out enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32**, the reaction was first performed in Et_2O and THF in order to verify the results reported in the literature (Table 3.13).[164] In Et_2O, *s*-BuLi was added to a solution of *N*-Boc pyrrolidine **32** and (+)-sparteine at −78 °C and the reaction mixture was stirred for 90 min. PhCONMe(OMe) was subsequently added to the reaction mixture which was then allowed to warm to room temperature over 1 h. The resulting α-functionalised product (*S*)-**185** was isolated in 87% yield. The enantiomeric ratio was determined through use of chiral stationary phase (CSP)-HPLC which confirmed that the reaction proceeded with excellent levels of enantioselectivity (96:4 er), consistent with results reported in the literature (entry 1). Comparison of the optical rotation with that reported in the literature[187] confirmed that (*S*)-**185** had formed when using (+)-sparteine as the chiral ligand. Enantioselective lithiation-trapping was then attempted in THF. In agreement with the results reported in the literature,[164] the reaction in THF gave the product (*S*)-**185** in a moderate yield (45%) and near racemic 52:48 er (entry 2). The reason for the difference in enantioselectivity between the reactions in Et_2O and THF has already been discussed (see Figure 3.2) and is a consequence of the preference of THF to coordinate to the organolithium over the chiral ligand leading to racemic deprotonation.[164,188] With the results confirmed in enantioselective lithiation-trapping in conventional ether solvents, the reaction was then performed in TMO. *s*-BuLi was added to a solution of *N*-Boc pyrrolidine **32** and (+)-sparteine in TMO at −78 °C and left for 90 min. Addition of the electrophile furnished (*S*)-**185** in 86% yield and, most importantly, the reaction also proceeded with a high level of enantioselectivity (97:3 er, entry 3). The enantioselectivity achieved in this reaction is presumably a result of the steric hindrance caused by the methyl groups surrounding the oxygen in TMO inhibiting its ability to strongly coordinate to the organolithium. This allows the chiral ligand to preferentially coordinate to the organolithium without interference from the solvent leading to asymmetric deprotonation of the substrate **32**. This result illustrates the potential for TMO to be used in place of hazardous Et_2O for enantioselective lithiation-trapping reactions with no loss of enantioselectivity or yield.

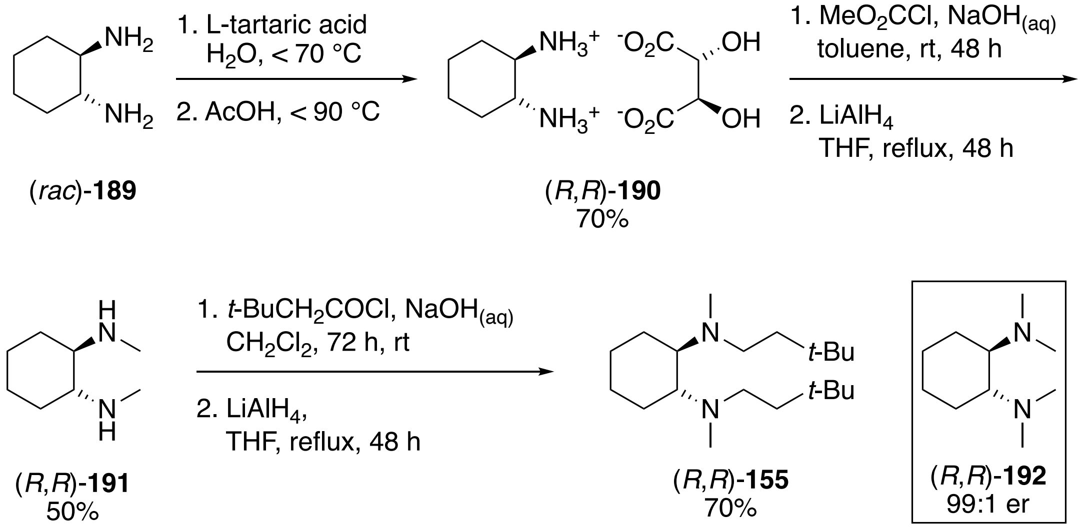


Entry	Solvent	Yield (%)[a]	er[b]
1	Et_2O	87	96:4
2	THF	45	52:48
3	TMO	86	97:3

Table 3.13: (+)-Sparteine-mediated enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32**. [a]Yield after column chromatography. [b]er determined using CSP-HPLC

To further enhance TMO's case as a viable replacement for Et_2O in enantioselective lithiation-trapping reactions, lithiation-trapping using a chiral cyclohexyl diamine ligand (*R*,*R*)-**155** (Alexakis diamine) was investigated in TMO and compared with the reaction performed in Et_2O. (*R*,*R*)-**155** is not commercially available and so had to be synthesised (Scheme 3.36).[158] First, racemic *trans*-cyclohexane-1,2-diamine **189** was resolved using L-(+)-tartaric acid in water ensuring that the reaction temperature did not exceed 70 °C.

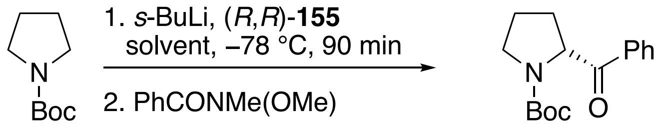
Addition of acetic acid whilst keeping the reaction temperature below 90 °C then incubation at ~5 °C caused (*R*,*R*)-**190** to precipitate and it was isolated *via* vacuum filtration in 70% yield. The enantiomeric ratio was determined through conversion of the salt (*R*,*R*)-**190** into tertiary amine (*R*,*R*)-**192** *via* Eschweiler-Clarke methylation. Chiral shift NMR spectroscopy using Pirkle's alcohol (2,2,2-trifluoro-1-(9-anthryl)-ethanol) confirmed an enantiomeric ratio of ≥99:1. The enantiopure salt (*R*,*R*)-**190** was converted into the carbamate through reaction with MeO_2CCl and $NaOH_{(aq)}$ in toluene. The crude carbamate was then reduced with $LiAlH_4$ forming diamine (*R*,*R*)-**191** in 50% over two steps. (*R*,*R*)-**191** was then reacted with *t*-$BuCH_2COCl$ and $NaOH_{(aq)}$ constructing the crude amide. The crude amide was carried forwarded without further purification and reduced with $LiAlH_4$ to reveal the desired enantiopure tertiary diamine (*R*,*R*)-**155**. Purification *via* short path distillation afforded diamine (*R*,*R*)-**155** in a 70% yield over two steps (overall yield of 25% over 5 steps).



Scheme 3.36: Synthesis of (*R*,*R*)-**155**

With the chiral ligand (*R*,*R*)-**155** in hand, a comparison between Et_2O and TMO in the enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32** was carried out (Scheme 3.37).

In Et_2O, *s*-BuLi was added to a solution of *N*-Boc pyrrolidine **32** and (*R*,*R*)-**155** at −78 °C and stirred for 90 min. Addition of PhCONMe(OMe) and warming to room temperature over 1 h afforded ketone (*R*)-**185** in 74% yield and 93:7 er. In TMO, under otherwise identical conditions, ketone (*R*)-**185** was synthesised in a lower yield of 56%. However, as with (+)-sparteine, high levels of enantioselectivity were obtained (93:7 er).



32

(*R*)-**185**
Et_2O: 74%, 93:7 er
TMO: 56%, 93:7er

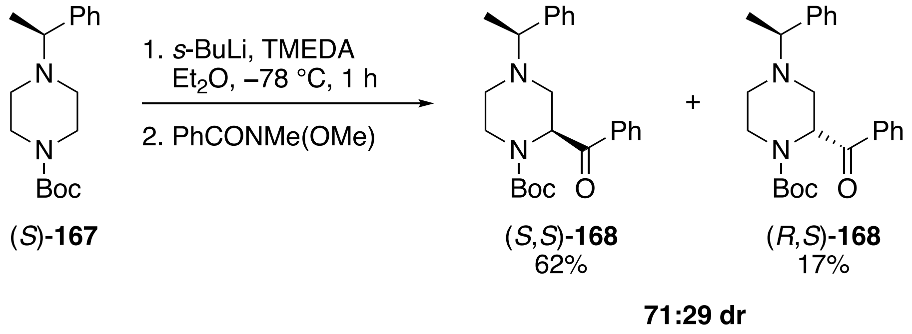
Scheme 3.37: Enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32** with (*R*,*R*)-**155**

In conclusion, TMO has proven to be a suitable solvent for enantioselective lithiation-trapping reactions with *N*-Boc pyrrolidine **32**. When (+)-sparteine was employed as the chiral ligand, lithiation-trapping in TMO facilitated the synthesis α-functionalised pyrrolidine (*S*)-**185** in equally high yields and enantioselectivity as when the reaction was performed in Et_2O. The use of chiral ligand (*R*,*R*)-**155** was also investigated for enantioselective lithiation-trapping of *N*-Boc pyrrolidine **32** in TMO and high levels of enantioselectivity were also achieved. The results displayed in this section demonstrate the potential for TMO to replace conventional ether solvents used in lithiation-trapping reactions. The added benefit of TMO being resistant to forming explosive peroxide and having no known serious health hazards associated with it distinguishes it from harmful solvents such as Et_2O, THF, 2-MeTHF, TBME and CPME which are commonly used in this area of chemistry.

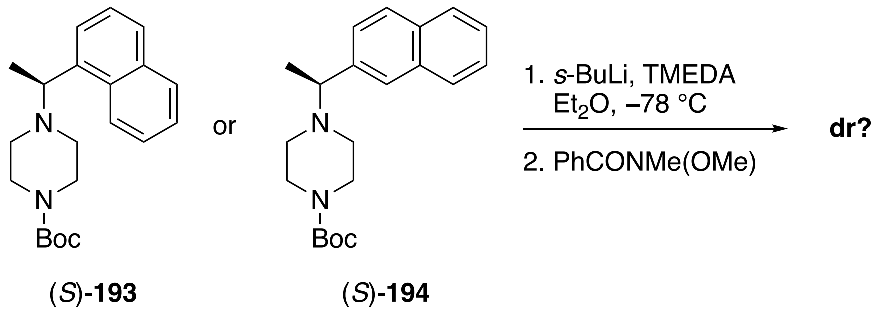
3.4.4 Diastereoselective Lithiation-Trapping of *N*-Boc Piperazine

With a desire to expand the substrate scope of lithiation-trapping reactions in TMO, the lithiation-trapping of *N*-Boc piperazines were investigated. For this work, it was felt that there was also an opportunity to expand on the methodology developed by previous members of the O'Brien group on the diastereoselective synthesis of *α*-substituted *N*-Boc piperazines.[168] Previously, as discussed in Section 3.2.2, for the lithiation-trapping of *N*-Boc piperazine to proceed with high levels of stereoselectivity, a combination of chiral ligand and matched chiral auxiliary must be employed. The addition of this chiral auxiliary also inhibited ring cleavage side reactions. When TMEDA was used as the ligand in this reaction in conjunction with the chiral auxiliary, only moderate levels of diastereoselectivity were obtained (71:29 dr), We therefore planned to investigate the lithiation-trapping of *N*-Boc piperazines bearing chiral auxiliaries (*S*)-**193** and (*S*)-**194** which should present higher degrees of steric hindrance, compared to *α*-methylbenzyl. This was with the hope that the increased steric hindrance would further influence the diastereoselectivity so that the need for expensive and precious chiral ligands, such as (+)-sparteine, would no longer be required (Scheme 3.38). Then, if successful, the reaction in TMO would be investigated.

Previous result

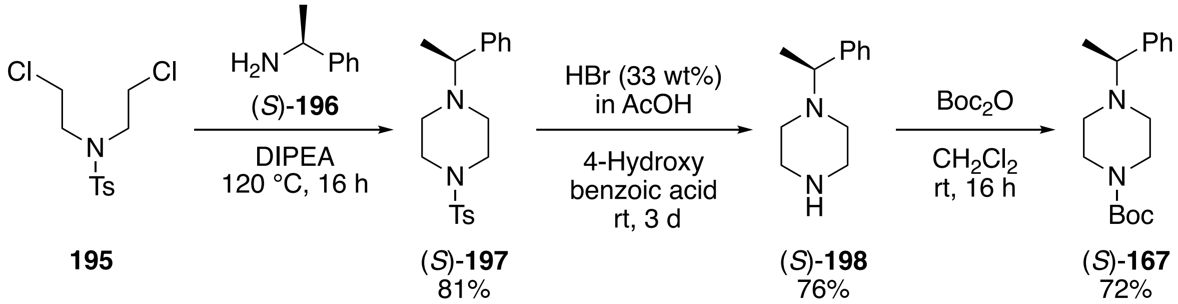


New chiral auxilaries



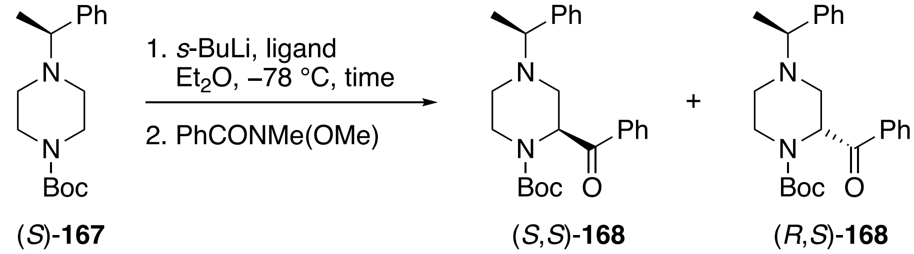
Scheme 3.38: Proposed plan for the diastereoselective lithiation-trapping of *N*-Boc piperazines

Initially, it was decided to use Et$_2$O for this study. In order to corroborate the results previously reported by the O'Brien group[168], lithiation-trapping of *N*-Boc-*N'*-(*S*)-*α*-methyl benzyl piperazine (*S*)-**167** was first performed. The synthesis of (*S*)-**167** followed a literature route and is summarised in Scheme 3.39. Starting with the commercially available *N*-tosyl amide **195**, reaction with enantiopure (*S*)-(−)-*α*-methylbenzylamine (*S*)-**196** in DIPEA at 120 °C facilitated ring closure to form tosyl piperazine (*S*)-**197** in 81% yield on a multi-gram scale without the need for purification *via* flash column chromatography. Tosyl removal was achieved by addition of HBr (33 wt%) in acetic acid and 4-hydroxybenzoic acid which revealed secondary amine (*S*)-**198** in 76% yield. Finally, addition of Boc$_2$O to the secondary amine (*S*)-**198** furnished the enantiopure Boc protected piperazine (*S*)-**167** in 72% yield (overall yield of 44% over 3 steps).



Scheme 3.39: Synthesis of enantiopure piperazine (*S*)-**167**

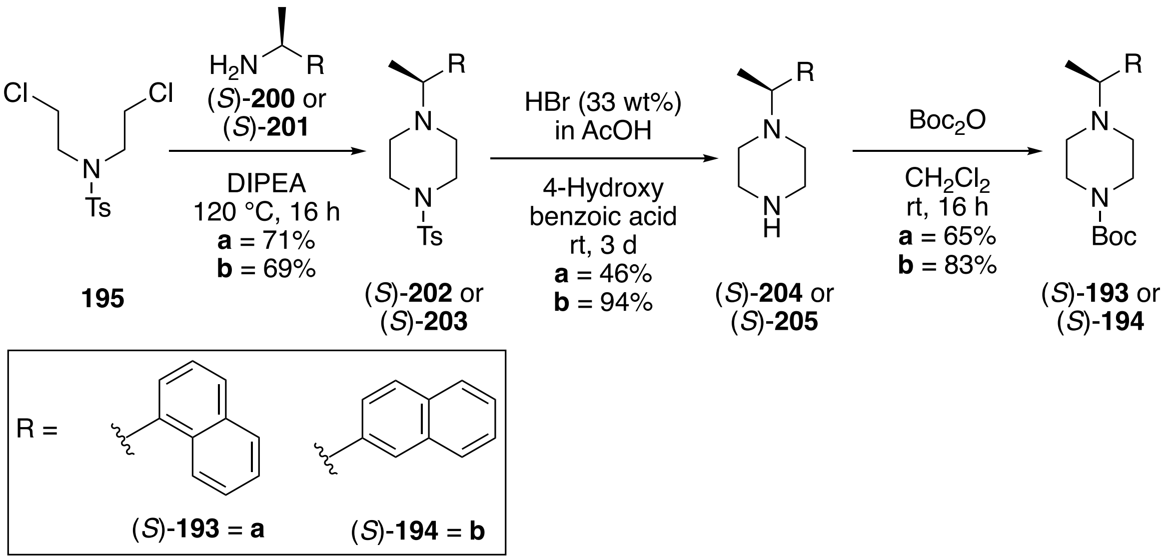
With the enantiopure piperazine (*S*)-**167** now in hand, lithiation-trapping of the piperazine (*S*)-**167** was investigated (Table 3.14). The lithiation time for the deprotonation of (*S*)-**167** has already been established through the use of ReactIR.[168] As such, (*S*)-**167** in Et_2O was treated with *s*-BuLi and TMEDA at −78 °C for 1 h. Addition of PhCONMe(OMe) led to the formation of adducts (*S*,*S*)-**168** and (*R*,*S*)-**168** in a combined yield of 66%; in our hands, the diastereomers could not be separated *via* flash column chromatography. Through analysis of the ^{1}H NMR spectrum of the crude product mixture, a 70:30 mixture of (*S*,*S*)-**168** and (*R*,*S*)-**168** (70:30 dr) was observed confirming the inherent stereoselectivity of the substrate in the lithiation-trapping reaction with the use of an achiral ligand (entry 1). Lithiation-trapping of (*S*)-**167** was performed with (+)-sparteine now utilised in place of TMEDA. The lithiation time was extended to 3 h due to the decreased reactivity of the *s*-BuLi/(+)-sparteine complex and trapping with PhCONMe(OMe) afforded adduct (*S*,*S*)-**168** in 61% yield and none of the opposite diastereomeric adduct (*R*,*S*)-**168** was isolated . Upon analysis of the ^{1}H NMR spectrum of the crude product, the use of matched chiral ligand (+)-sparteine improved the diastereomeric ratio to >98:2 dr (entry 2). These results are consistent with the findings reported by the O'Brien group.[168]



Entry	Ligand	Time (h)	Combined Yield (%)[a]	dr[b]
1	TMEDA	1	66	70:30
2	(+)-sparteine	3	61	>98:2

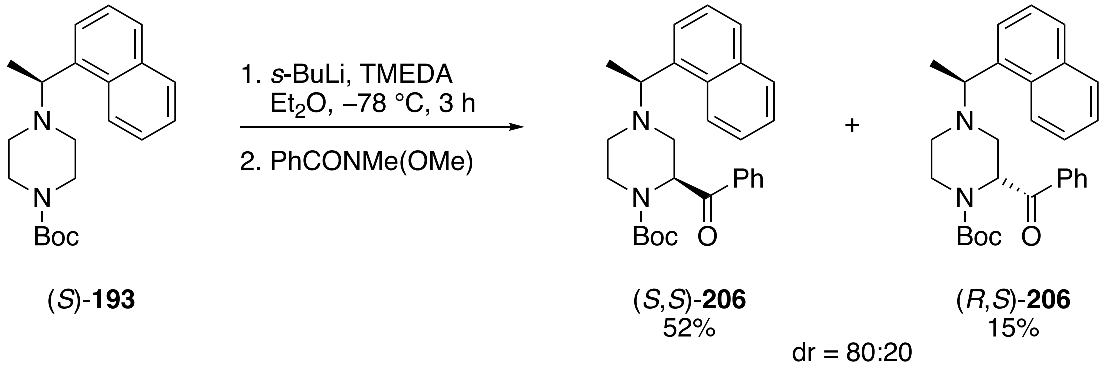
Table 3.14: Diastereoselective lithiation-trapping of *N*-Boc piperazine (*S*)-**167**. [a]Yield after chromatography. [b]dr determined from the ^{1}H NMR spectrum of the crude product

Next, the synthesis of two new chiral *N*-Boc piperazines (*S*)-**193** and (*S*)-**194** was undertaken (see Scheme 3.38). It was planned to use these substrates in lithiation-trapping reactions to ascertain if increasing the steric hindrance provided by the chiral auxiliary would further influence the diastereoselectivity of the reaction. In a similar fashion to the synthesis of (*S*)-**167**, *N*-tosyl amide **195** was reacted with enantiopure amine (*S*)-**200** or (*S*)-**201** facilitating ring closure to form enantioenriched piperazine (*S*)-**202** or (*S*)-**203** in 71% and 69% respectively. In this case, both (*S*)-**202** and (*S*)-**203** required purification *via* flash column chromatography. Tosyl removal with HBr (33 wt%) in acetic acid and 4-hydroxybenzoic acid revealed secondary amines (*S*)-**204** in 46% and (*S*)-**205** in 94% yields. Finally, conventional Boc protection of the amine constructed chiral piperazines (*S*)-**193** in 65% (overall yield of 21% over 3 steps) and (*S*)-**194** 83% yields (overall yield of 54% over 3 steps) respectively (Scheme 3.40).



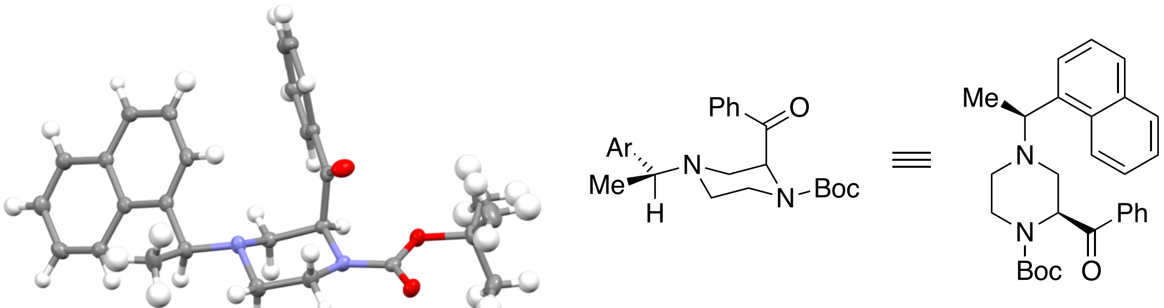
Scheme 3.40: Synthesis of enantiopure *N*-Boc piperazines (*S*)-**193** and (*S*)-**194**

First, lithiation-trapping of piperazine (*S*)-**193** was carried out. Thus, (*S*)-**193** was treated with *s*-BuLi and TMEDA in Et_2O at −78 °C. The time required for full lithiation of (*S*)-**193** is unknown and thus 3 h was chosen in the hope that complete lithiation would have taken place. Addition of PhCONMe(OMe) furnished separable diastereomeric ketones (*S*,*S*)-**206** in 52% yield and (*R*,*S*)-**206** in 15% yield (67% yield overall) (Scheme 3.41). Analysis of the ^{1}H NMR spectrum of the crude product revealed that the diastereomeric ratio of the two products was 80:20 dr. Pleasingly, increasing the steric bulk on the chiral auxiliary did indeed increase the diastereoselectivity of the lithiation event.



Scheme 3.41: Diastereoselective lithiation-trapping of *N*-Boc piperazine (*S*)-**193**

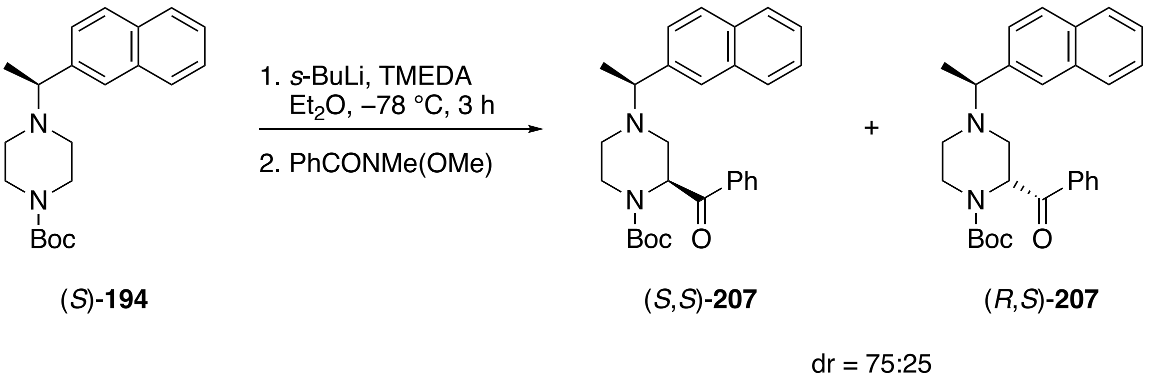
X-ray crystallography was performed on the major diastereomer (*S*,*S*)-**206** to determine it's relative stereochemistry. The X-ray crystal structure in Figure 3.3 clearly shows the (*S*)-configuration at both the *α*-methyl naphthyl auxiliary and at the carbon *α* to the *N*-Boc group. The piperazine ring adopts a chair conformation and the trapped substituent is in the axial position in order to reduce the $A^{1,3}$-type strain between itself and the Boc group.



(*S*,*S*)-**206**

Figure 3.3: X-Ray Structure of (*S*,*S*)-**206**

Next, (*S*)-**194** was likewise treated with *s*-BuLi and TMEDA in Et_2O at −78 °C for 3 h and trapped with PhCONMe(OMe) which gave diastereomeric ketones (*S*,*S*)-**207** and (*R*,*S*)-**207**. Disappointingly, very low quantities of the diastereomeric ketones (*S*,*S*)-**207** and (*R*,*S*)-**207** were formed (based on the ^{1}H NMR spectrum of the crude product) and it was not possible to isolate them following column chromatography. The diastereomeric ratio determined from the ^{1}H NMR spectrum of the crude product was 75:25 dr. This is slightly lower than that obtained from the lithiation-trapping of (*S*)-**193** (Scheme 3.42). However, this is still higher than the dr achieved with the original *N*-Boc-*N*'-(*S*)-*α*-methyl benzyl piperazine (*S*)-**167**. The decreased diastereomeric ratio could be explained by the shifting of the naphthyl group away from piperazine ring reducing the influence it has on the selectivity of the lithiation event.



(*S*)-**194**

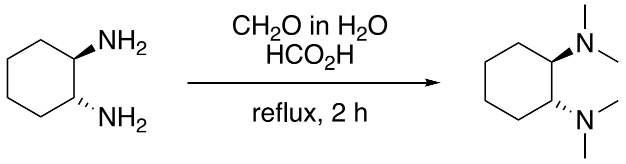
(*S*,*S*)-**207**

(*R*,*S*)-**207**

dr = 75:25

Scheme 3.42: Diastereoselective lithiation-trapping of *N*-Boc piperazine (*S*)-**194**

The encouraging result from the 1-naphthyl derivative (*S*)-**193** led us to explore the effect of bulkier racemic ligands on the diastereoselectivity of the lithiation-trapping of (*S*)-**193**. This was with a view of improving the diastereoselectivity even further. As such, two ligands were chosen for this investigation. The first being *trans* tertiary diamine *rac*-**192**, which was synthesised in one step from cyclohexyl diamine *rac*-**189** *via* an Eschweiler-Clarke methylation with formaldehyde and formic acid. This gave the desired diamine *rac*-**192** in 31% yield (Scheme 3.43).

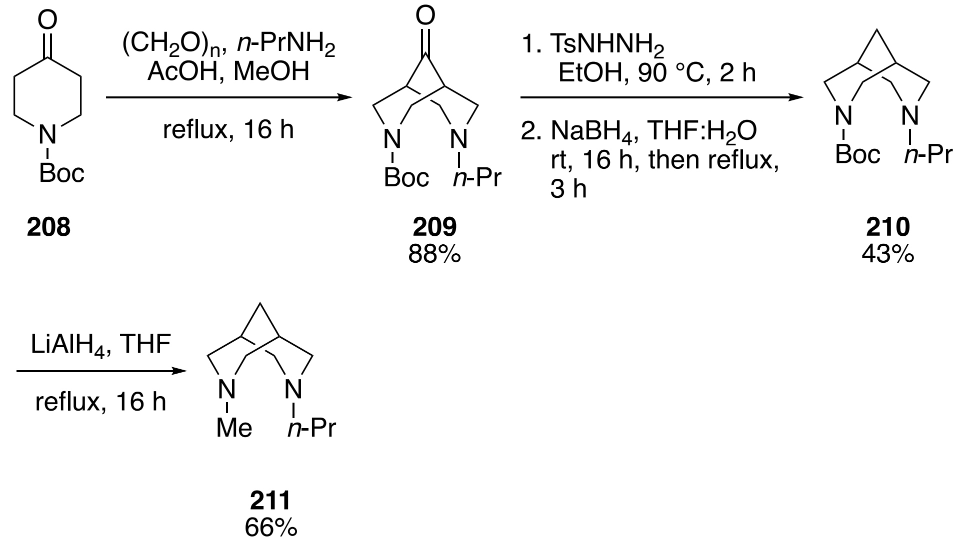


rac-**189**

rac-**192**
31%

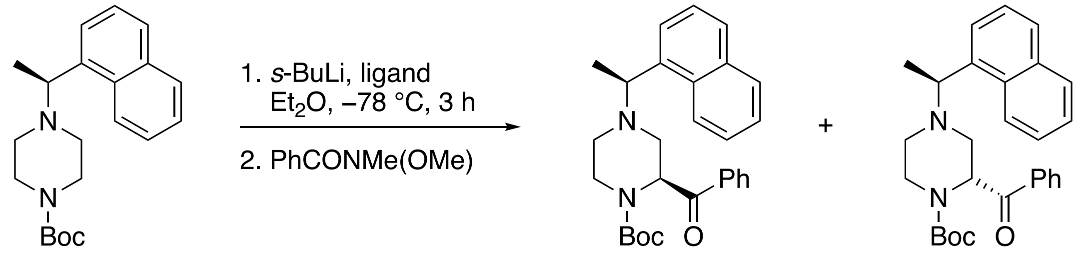
Scheme 3.43: Synthesis of *rac*-TMCDA **192**

The other ligand chosen for this investigation was *N*-methyl-*N*'-*n*-propyl bispidine **211** which also had to be synthesised using a known route in the O'Brien group[189] (Scheme 3.44). *N*-Boc piperidone **208** was subjected to a double Mannich reaction with paraformaldehyde, *n*-PrNH2 and acetic acid in MeOH furnishing bispidone **209** in 88% yield. Bispidone **209** was reduced to bispidine **210** through treatment with tosyl hydrazine to form the corresponding hydrazone *in situ* which was subsequently cleaved with $NaBH_4$. This gave *N*-Boc bispidine **210** in 43% yield. Finally, *N*-Boc bispidine **210** was converted into *N*-methyl-*N*'-*n*-propyl bispidine **211** through reaction with $LiAlH_4$ in 66% yield (25% overall yield over 3 steps). *N*-methyl-*N*'-*n*-propyl bispidine **211** was not stable when stored for extended periods of time even under an inert atmosphere (*ca*. 2 weeks). Hence, the diamine ligand was stored as the *N*-Boc bispidine **210** precursor and reduced to *N*-methyl-*N*'-*n*-propyl bispidine **211** and distilled when required.



Scheme 3.44: Synthesis of *N*-methyl-*N*'-*n*-propyl bispidine **211**

N-Boc piperazine (*S*)-**193** was subjected to lithiation-trapping with these two ligands (Table 3.15). With *rac*-TMCDA **192** and trapping with PhCONMe(OMe), diastereomeric ketones (*S*,*S*)-**206** (40% yield) and (*R*,*S*)-**206** (9% yield) were obtained. These yields are lower than the same reaction with TMEDA. Unfortunately, with *rac*-TMCDA **192**, no improvement of the stereoselectivity was observed with a diastereomeric ratio of 80:20 dr being obtained (entry 1). Disappointingly, with bispidine ligand **211**, the yield of the adducts was significantly reduced with (*S*,*S*)-**206** forming in 10% yield and (*R*,S)-**206** in 3% yield. Even with this more sterically hindered ligand, no change in diastereoselectivity was observed with an 80:20 dr determined through analysis of the ^{1}H NMR spectrum of the crude product (entry 2). It is evident from the ligand investigation that the ligands chosen in this investigation do not have an influence on the diastereoselectivity of the reaction with all three ligands giving 80:20 dr.

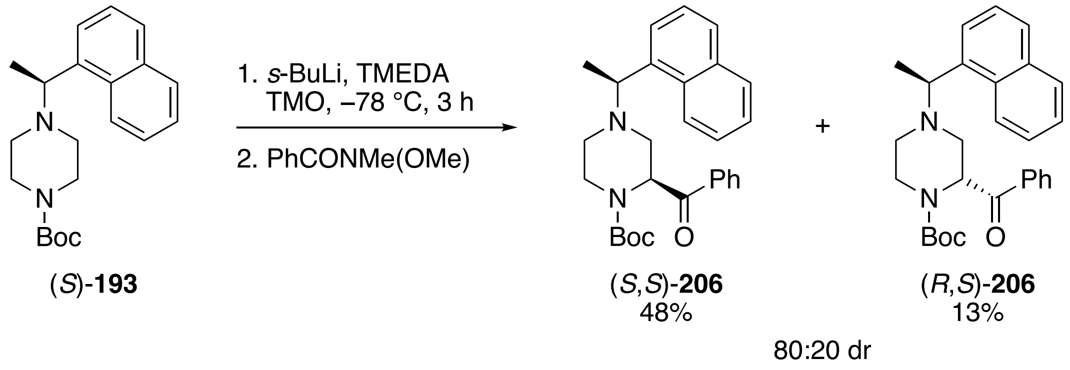


(*S*)-**193** (*S*,*S*)-**206** (*R*,*S*)-**206**

Entry	Ligand	**(*S*,*S*)-206 Yield (%)**[a]	**(*R*,*S*)-206 Yield (%)**[a]	**dr**[b]
1	*rac*-**192**	40	9	80:20
2	**211**	10	3	80:20

Table 3.15: Ligand effects on the lithiation-trapping of *N*-Boc piperazine (*S*)-**193**. [a]Yield after chromatography. [b]dr determine from the ^{1}H NMR spectrum of the crude product.

The best reaction in Et_2O ((*S*)-**193** with *s*-BuLi/TMEDA) was then carried out in TMO. Thus, (*S*)-**193** was first treated with *s*-BuLi/TMEDA in TMO at −78 °C for 3 h. Trapping with PhCONMe(OMe) gave diastereomeric ketones (*S*,*S*)-**206** (48% yield) and (*R*,*S*)-**206** (13% yield). The yields achieved in TMO are comparable with those obtained in Et_2O ((*S*,*S*)-**206** in 52% yield and (*R*,*S*)-**206** in 15% yield, see Scheme 3.41). Furthermore, upon analysis of the ^{1}H NMR spectrum of the crude product, changing the solvent from Et_2O to TMO resulted in no change of the diastereoselectivity (80:20 dr) (Scheme 3.45). This confirms that TMO is a suitable replacement solvent for Et_2O in the diastereoselective lithiation-trapping of *N*-Boc piperazine (*S*)-**206**.



Scheme 3.45: Lithiation-trapping of *N*-Boc piperazine (*S*)-**193** in TMO

In summary, two new chiral *N*-Boc-*N*'-α-methyl naphthyl piperazines (*S*)-**193** and (*S*)-**194** have been synthesised. Lithiation-trapping of *N*-Boc piperazine (*S*)-**193** with TMEDA furnished diastereomeric adducts (*S*,*S*)-**206** and (*R*,*S*)-**206** in 67% yield overall and 80:20 dr. In contrast, it was not possible to isolate (*S*,*S*)-**207** and (*R*,*S*)-**207** and a 75:25 dr was obtained when the lithiation trapping of *N*-Boc piperazine (*S*)-**194** was performed. This suggests that the position of the naphthyl group has an effect on the diastereoselectivity of the reaction. This is a moderate improvement compared to the diastereoselectivity in the lithiation-trapping of *N*-Boc-*N*-α-methyl benzyl piperazine (*S*)-**167** previously employed by the O'Brien group (66% overall yield, 70:30 dr), thus, confirming that increased steric hindrance from the chiral auxiliary does in fact increase the diastereoselectivity of the lithiation-trapping reaction. Disappointingly, the influence of the chiral auxiliary in (*S*)-**193** was not enough to match that of the combination of (+)-sparteine and α-methyl benzyl chiral auxiliary (61% overall yield, >98:2 dr). The use of sterically hindered diamine ligands *rac*-TMCDA **192** and bispidine **211** in the lithiation-trapping of *N*-Boc piperazine (*S*)-**193** did not improve the stereoselectivity (both 80:20 dr) and had a negative effect on the yield in both cases (49% and 13% yields respectively). When lithiation-trapping of (*S*)-**193** with *s*-BuLi and TMEDA was carried out in TMO, similar yields and diastereomeric ratios, compared to when Et_2O was used as solvent, were obtained (61% total yield, 80:20 dr).

3.5 Conclusions and Future Work

In this chapter, an investigation into the stability of TMO in the presence of *s*-BuLi was carried out. TMO was stable in the presence of *s*-BuLi at temperatures below −30 °C. However, above this temperature TMO decomposed *via* *s*-BuLi-mediated lithiation and *β*-elimination to form lithium alkoxide **186** which could be subsequently trapped with PhCOCl to form alkyl benzoate **187**. The stability was compared to 2-MeTHF, a green solvent commonly used in lithiation-trapping reactions. Even at temperatures as low as −78 °C, 2-MeTHF underwent a similar decomposition reaction with *s*-BuLi. The results from this investigation confirm that TMO is considerably more stable than 2-MeTHF in the presence of *s*-BuLi. This is likely caused by the increased steric hindrance from the four methyl groups in TMO inhibiting coordination to the organolithium.

An investigation into the use of TMO in racemic lithiation-trapping reactions of *N*-heterocycles was carried out. With the addition of a ligand in the reaction mixture such as TMEDA, lithiation-trapping proceeded without issue in TMO furnishing *α*-functionalised pyrrolidine **132** and **185** in excellent yields (89% for both **132** and **185**). This is comparable with the results from when the reaction was performed in Et_2O (85% for **132**, 88% for **185**). Disappointingly, the diamine-free lithiation-trapping reaction in TMO did not perform as well, with the yield of **185** not exceeding 45% even when the temperature was increased to above −78 °C in an attempt to increase the reactivity of the *s*-BuLi/TMO complex.

However, the lack of reactivity of the *s*-BuLi/TMO complex in diamine-free lithiation-trapping reactions was beneficial in enantioselective lithiation-trapping. TMO facilitated a highly enantioselective and yielding reaction when (+)-sparteine was used as the chiral ligand (89%, 97:3 er). High enantioselectivity was also obtained when (*R*,*R*)-**155** was employed as the chiral ligand (93:7 er). This confirms that TMO is as a suitable green alternative to Et_2O and other ether solvents in enantioselective lithiation-trapping reactions.

Finally, diastereoselective lithiation-trapping reactions of chiral *N*-Boc piperazines (*S*)-**193** and (*S*)-**194** was investigated. Improved diastereoselectivity (80:20 dr) was achieved with *N*-Boc piperazine (*S*)-**193** compared to the previously used chiral *N*-Boc piperazine (*S*)-**167** (70:30 dr). Disappointingly, this diastereoselectivity achieved with *N*-Boc piperazine (*S*)-**193** was still considerably less than the diastereoselectivity obtained when chiral piperazine (*S*)-**167** was used in conjunction with a chiral ligand (+)-sparteine. Further investigation into the tailoring of chiral auxiliaries for *N*-Boc piperazine should be carried out to determine if high diastereoselectivity (>90:10 dr) can be reached without the need for a chiral ligand. The results of this chapter are summarised in Figure 3.3.

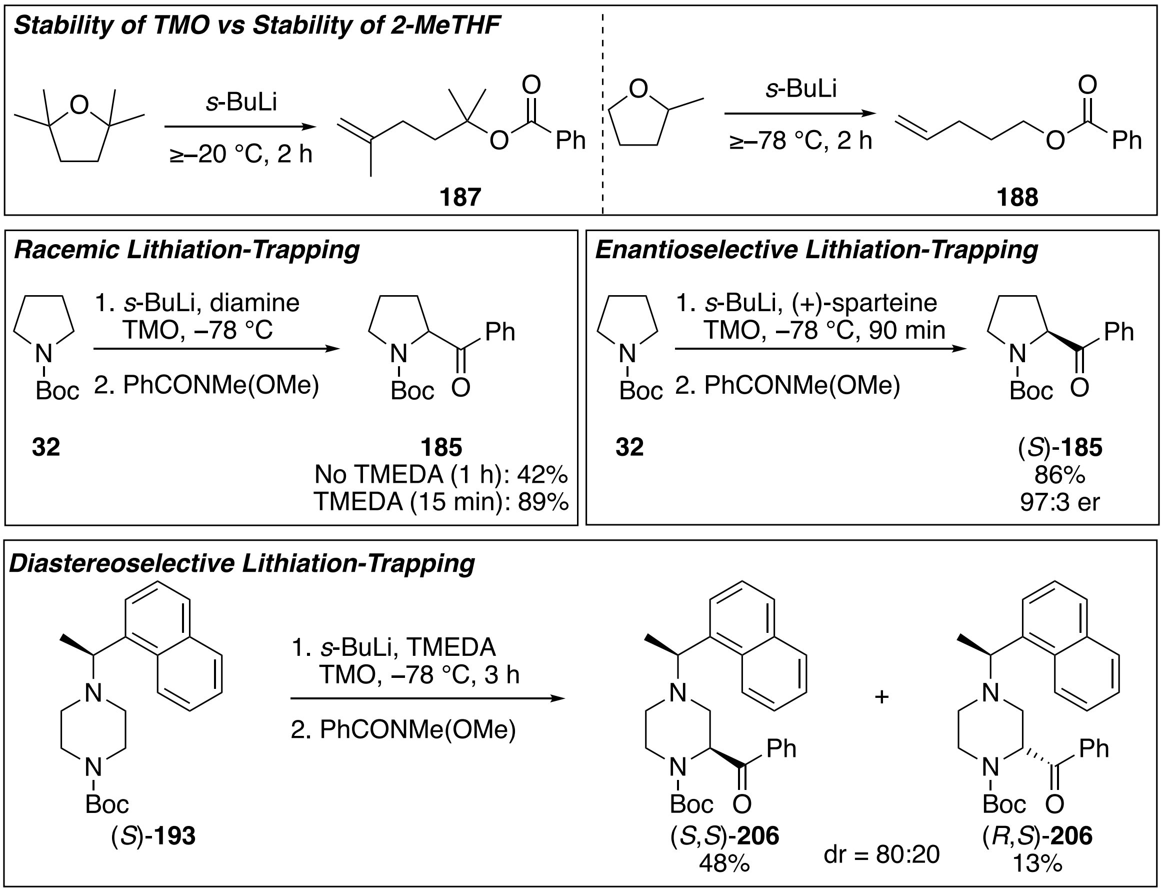
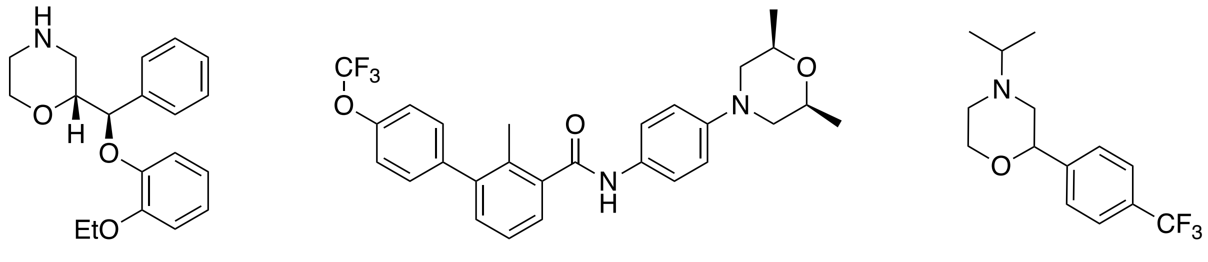


Figure 3.4: Summary of the lithiation-trapping of *N*-Boc heterocycles in TMO

Chapter 4: Use of TMO as Solvent in the Lithiation-Trapping and α-Arylation of *O*-Heterocycles

4.1: An Introduction to Saturated *O*-Heterocycles in Medicinally-Relevant Molecules and Natural Products

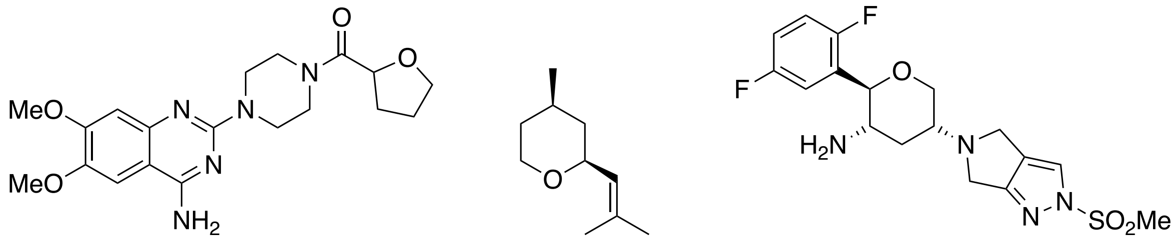
Although not as common as *N*-heterocycles, *O*-heterocycles are prevalent in pharmaceutically-active compounds. A total of 331 FDA approved drugs were reported, in 2018, to contain *O*-heterocycles with the large majority of these being 5- and 6-membered saturated rings.[190] One of the most common *O*-heterocycles in this catalogue of approved drugs is morpholine. Examples of drugs containing morpholine are shown in Figure 4.1. Reboxetine, developed by Pfizer, contains an α-substituted morpholine and is a norepinephrine reuptake inhibitor used in the treatment of depression.[191] Sonidegib, marketed by Novartis, is a smoothened (SMO) receptor antagonist used to treat basal cell carcinoma.[192] Oxaflozane, which contains an α-arylated morpholine scaffold, was developed by Solvay and used to treat depression by acting as an agonist for the serotonin 5-HT$_{1A}$ and 5-HT$_{2C}$ receptors.[193]



Robexetine Sonidegib Oxaflozane

Figure 4.1: Medicinally-relevant molecules featuring morpholine

Tetrahydrofuran (THF) and tetrahydropyran (THP) are also *O*-heterocyclic structural motifs found in both natural products and pharmaceutically-relevant molecules (Figure 4.2). Terazosin, a non-selective alpha-1 adrenoreceptor antagonist developed by Abbott Laboratories used to treat benign prostatic hyperplasia and hypertension, contains an *α*-functionalised THF scaffold.[194] The monoterpene (−)-Rose oxide is a *cis* configured 2,4-substituted THP and has a distinctive smell of roses.[195] Omarigliptin, a DPP-4 inhibitor antidiabetic drug is currently under development by Merck and exhibits an *α*-arylated THP scaffold.[196]



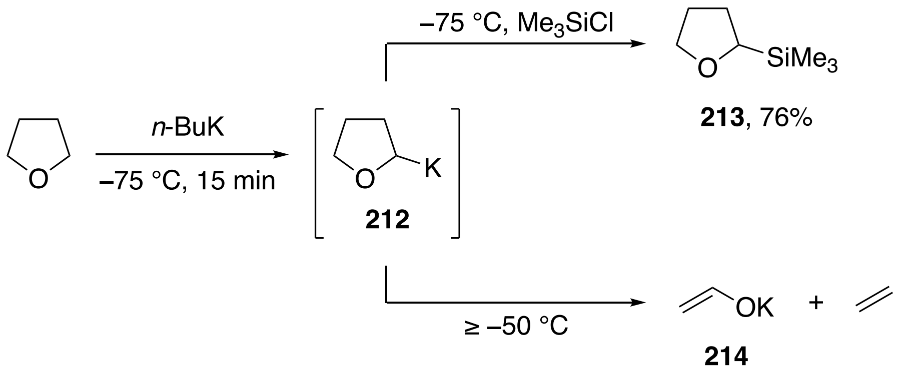
Terazosin (−)-Rose Oxide Omarigliptin

Figure 4.2: Medicinally-relevant molecules and natural products featuring THF and THP

4.2 Introduction to *α*-Functionalisation of *O*-Heterocycles *via* Metallation-Trapping

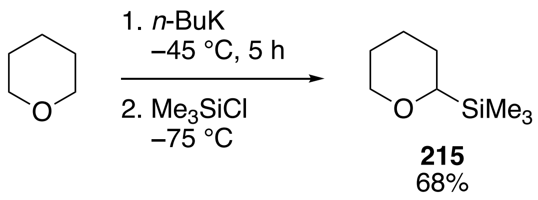
4.2.1 Metallation Routes to *α*-Functionalised *O*-Heterocycles

Metallation routes for the *α*-functionalisation of *O*-heterocycles have been largely under-explored compared to *N*-heterocycles. Most approaches have employed radical-based reaction pathways to access these *α*-functionalised molecules.[197–203] Metallation-based approaches to *α*-functionalised *O*-heterocycles are limited. This presents a specific and unique problem. Lithiation of THF with *n*-BuLi occurs readily but subsequent fragmentation of the lithiated intermediate *via* reverse [3+2] cycloaddition occurs, as reported by Bates and co-workers in 1972.[174] This resulted in the formation of lithium enolate **170** and ethene, highlighting the difficulty in controlling the stability of the lithiated intermediate (see Scheme 3.23). Despite the instability of metallated THF, Lehmann and Schlosser reported the first successful route to *α*-functionalised THF *via* a metallation process in 1984.[204] Addition of *n*-BuK at −75 °C to THF, acting as both the solvent and the substrate, and stirring the reaction mixture for 15 min formed potassiated intermediate **212**. Treatment of intermediate **212** with Me_3SiCl gave silyl THF **213** in 76% yield. When the metallation of THF was attempted at −50 °C, none of silyl THF **213** was isolated. This was a result of the instability of the potassiated intermediate **212** at this temperature, which underwent fragmentation to form potassium enolate **214** and ethene (Scheme 4.1).



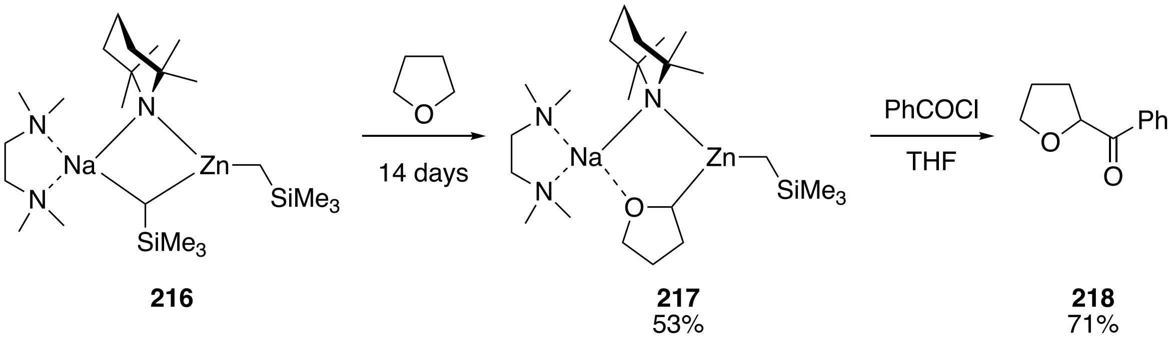
Scheme 4.1: α-Functionalisation of THF using *n*-BuK

The methodology was extended to THP, where silyl THP **215** was furnished in 68% yield (Scheme 4.2). An increased reaction temperature of −45 °C and a longer reaction time of 5 h was required, as the rate of metallation was significantly reduced when moving up to the larger ring system. Similar relative rates of lithiation have been reported with 5- and 6-membered *N*-Boc heterocycles.[142] The pitfall of this methodology for the synthesis of α-functionalised THF and THP is in the synthesis of *n*-BuK which requires the use of the highly toxic $HgCl_2$ and subsequently $HgBu_2$ in stoichiometric quantities as well as the use of a reactive Na/K alloy.



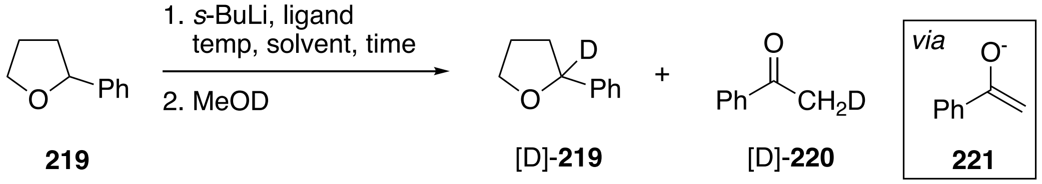
Scheme 4.2: α-Functionalisation of THP using *n*-BuK

Mulvey and co-workers reported the use of bimetallic zincate bases for the successful metallation of THF.[205] Complexation of the bimetallic base, containing Na and Zn, to THF facilitated α-metallation of the substrate. First, bimetallic complex **216** was synthesised and it was then added to THF, acting as both the solvent and substrate. This solution was then stirred for up to 14 days. Removal of excess THF and addition of hexane to the residue at −30 °C formed crystalline *α*-zincated THF complex **217** which could be isolated and stored at room temperature. It was then possible to form ketone **218** by addition of PhCOCl in THF in 71% yield (Scheme 4.3). It was necessary to first crystallise the *α*-zincated THF complex **217** in hexane prior to the addition of PhCOCl as the direct addition of PhCOCl to complex **217** in THF resulted in a lower yield of ketone **218** (38%). Bimetallic THP complex could also be formed but, in this case, reaction with an electrophile did not result in THP trapped adducts.



Scheme 4.3: *α*-Zincation of THF using bimetallalic base **216**

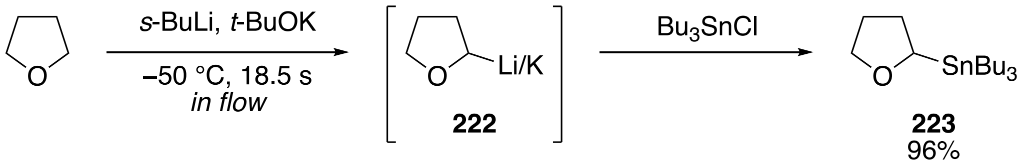
Lithiation-trapping at the benzylic position of 2-PhTHF **219** was shown to be possible by Capriati *et al.* in 2013 (Table 4.1).[206] The increased acidity of the proton provided by the phenyl group makes deprotonation easier than in unsubstituted THF. Hence, 2-PhTHF **219** was deprotonated with *s*-BuLi in THF at −78 °C for 2 min and trapped with MeOD to give [D]-**219** in 50% yield. [D]-**220** was also obtained in 50% yield (entry 1). Ketone [D]-**220** arises from the formation of lithium enolate **221** *via* retro [3+2] cycloaddition. Addition of TMEDA improved the yield of [D]-**219** (80%) by reducing the formation of decomposition product [D]-**220** (20%, entry 2). However, Capriati found that the substrate required a longer lithiation time (10 min). In hexane, with *s*-BuLi/TMEDA at −90 °C for 2 min, [D]-**219** was isolated in 90% yield and none of the decomposition product [D]-**220** was obtained (entry 3). Similarly, in toluene with *s*-BuLi/TMEDA at −78 °C for 2 min, >98% yield of [D]-**219** was achieved (entry 4).



Entry	Solvent	Ligand	Temp (°C)	Time (min)	Yield [D]-219	Yield [D]-220
1	THF	-	−78	2	50	50
2	THF	TMEDA	−78	10	80	20
3	Hexane	TMEDA	−90	2	90	0
4	Toluene	TMEDA	−78	2	>98	0

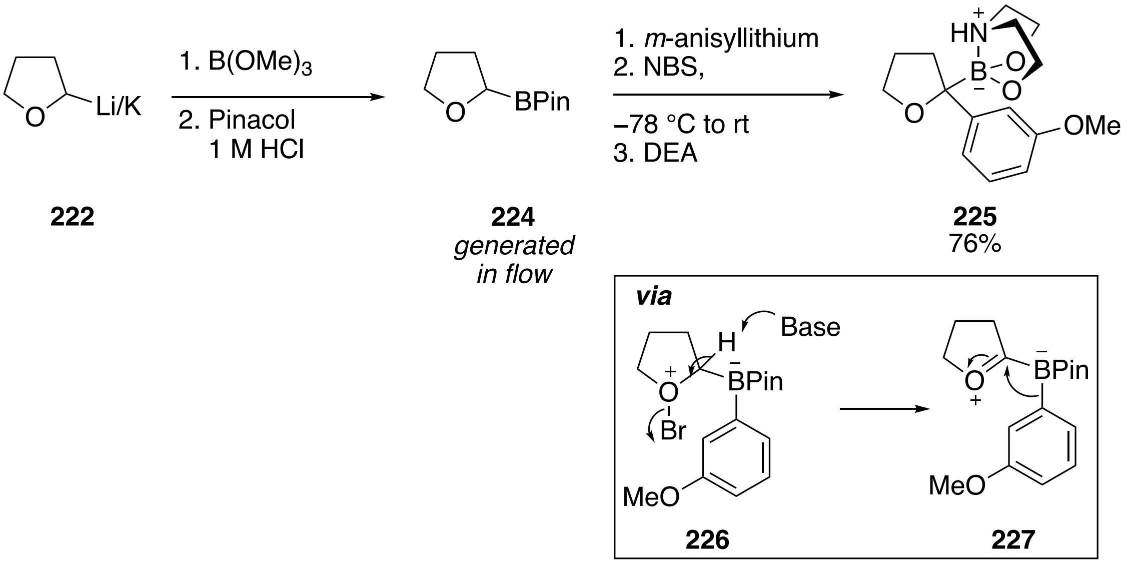
Table 4.1: Lithiation-trapping of 2-PhTHF **219**

In 2022, published after the work described in this chapter was carried out, Kim *et al.* reported a strategy to generate metallated THF **222** using flow conditions and functionalised the substrate by addition of a range of electrophiles.[207] Use of Schlosser's base, a superbase formed from a mixture of *s*-BuLi and *t*-BuOK,[208] with THF, for a residence time of 18.5 s at −50 °C facilitated the metallation of THF forming *α*-metallated THF **222**. This careful control of the residence time and reaction temperature stopped metallated THF **222** from undergoing decomposition pathways (such as retro [3+2] cycloaddition). Intermediate **222**, formed under these flow conditions, was then trapped with Bu_3SnCl to furnish stannane **223** in an excellent 96% yield (Scheme 4.4). The electrophile scope was explored and good to excellent yields were obtained in all examples.



Scheme 4.4: Metallation-trapping of THF using flow conditions and Schlosser's base

Kim and co-workers expanded the synthetic utility of this methodology through arylation *via* Bpin THF **224**. Using their methodology, metallated THF **222** was generated in flow and it was then trapped with $B(OMe)_3$ which was subsequently converted into BPin THF **224** with the addition of pinacol. Treatment of BPin THF **224** with *m*-anisyllithium and NBS resulted in the unprecedented formation of difunctionalised THF **225** in 76% yield (BPin was converted into the more stable boronic ester **225** with diethanolamine (DEA) to isolate the product) (Scheme 4.5). Kim suggested that difunctionalised product **225** arises from the formation of oxonium intermediate **226** which then generates furan-1-ium intermediate **227** instead of the planned 1,2-metallate rearrangement previously described by Aggarwal and co-workers.[209]

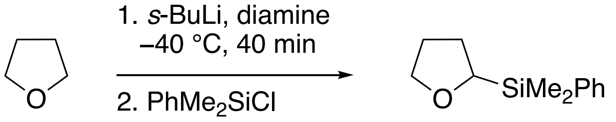


Scheme 4.5: α-Arylation of THF using flow conditions and Schlosser's base

4.2.2 O'Brien Group's Lithiation-Trapping Approach to *α*-Functionalised *O*-Heterocycles

The published work described in the previous section has shown that the metallation of cyclic ethers α to oxygen has been accomplished in good to excellent yields. However, these processes require notably toxic starting materials and intermediates or the use of superbases in complex set-ups and, generally, the *O*-substrate scope has been limited. Furthermore, in many cases, the substrate required to be lithiated must be also used as the reaction solvent. In unpublished reports from the O'Brien group, lithiation-trapping of a range of saturated *O*-heterocycles has been investigated.[189,210,211]

Initial work in the group was carried out on THF and lithiation-trapping conditions using *s*-BuLi in THF were explored. The challenge with this substrate was finding a temperature and lithiation time which provided the best balance between rate of lithiation of THF and the rate of decomposition of the lithiated intermediate. The best result was found when THF was employed as both the solvent and the substrate and lithiation was performed at −40 °C for 40 min. Trapping with $PhMe_2SiCl$ afforded silyl THF **228** in 31% yield (yield based on amount of *s*-BuLi). An analogous yield of silyl THF **228** (30%) was achieved when the reaction was performed in the absence of TMEDA (Scheme 4.6).[210]

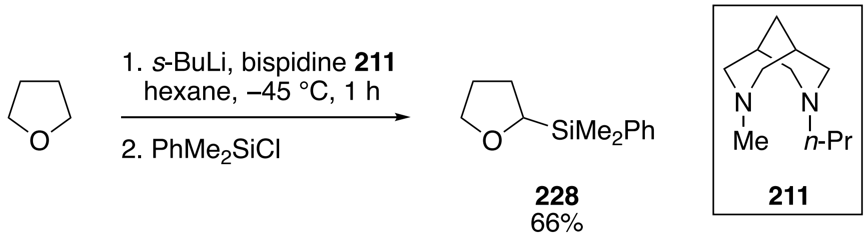


228
31% (TMEDA)
30% (No TMEDA)

Scheme 4.6: Lithiation-trapping of THF with *s*-BuLi and *s*-BuLi/TMEDA

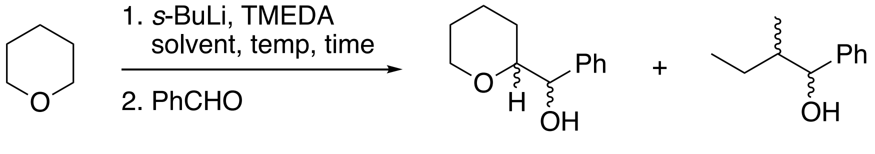
To try and improve on these initial results for the lithiation of THF, the O'Brien group explored the lithiation of THF using bispidine ligand **211** in place of TMEDA.[189,211]

Aggarwal and co-workers have reported improved rates of lithiation with a structurally similar *s*-BuLi/bispidine complex compared to *s*-BuLi/TMEDA complex.[212] Thus, lithiation-trapping of THF was carried out with *s*-BuLi and bispidine **211** (Scheme 4.7). The best result was found using 10 equivalents of THF in hexane, which was treated with *s*-BuLi and bispidine **211** at −45 °C for 1 h. Trapping with $PhMe_2SiCl$ furnished silyl THF **228** in 66% yield, doubling the yield obtained when using TMEDA (31%, see Scheme 4.6). The procedure proved the most reliable and reproducible for the lithiation-trapping of THF. Furthermore, in a modified procedure with 1.0 equivalents of THF in CPME at −60 °C for 4 h, the use of *s*-BuLi and (+)-sparteine surrogate **154** gave trapped products in 25-47% yields and ~80:20 er.[211]



Scheme 4.7: Lithiation-trapping of THF with *s*-BuLi and bispidine **211**

An investigation into lithiation-trapping conditions with THP was also carried out in the O'Brien group (Table 4.2).[210] Lithiation-trapping of 6-membered heterocycles is known to be more difficult than its 5-membered counterpart.[142,213,214] Hence, lithiation was first attempted at −30 °C for 1 h in the inert solvent, hexane. Upon trapping with PhCHO, none of the desired secondary alcohol **229** was formed, with only direct addition product **230** being detected in the ^1H NMR spectrum of the crude product suggesting that lithiation of the substrate was not occurring (entry 1). As such, the temperature was increased to 0 °C. This facilitated the lithiation of THP and secondary alcohol **229** was achieved in 29% yield; addition product **230** was also isolated in 38% yield suggesting that lithiation had not reached completion (entry 2). However, a lower 26% yield of secondary alcohol **229** was obtained when the reaction time was extended to 2 h, and this was accompanied by a lower yield (18%) of addition product **230** (entry 3). When THP was used as both the solvent and the substrate, the reaction gave none of the desired secondary alcohol **229** after lithiation at 0 °C for 2 h (entry 4).



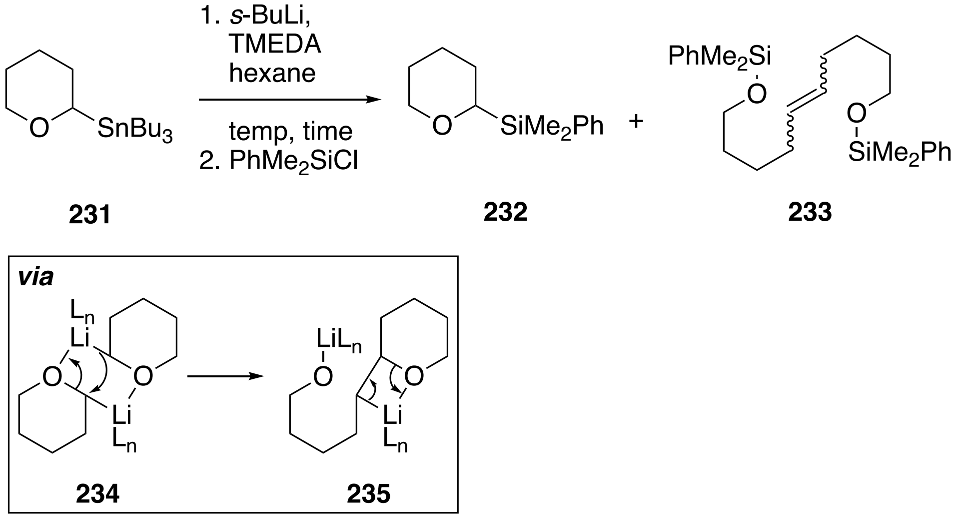
229 **230**

Entry	Solvent	Temp (°C)	Time (h)	Yield 229 (%)	Yield 230 (%)[a]
1	Hexane	−30	1	0	N.D.[b]
2	Hexane	0	1	29	38
3	Hexane	0	2	26	18
4	THP	0	2	0	0

Table 4.2: Lithiation-trapping of THP with s-BuLi and TMEDA. [a]Yield based on amount of s-BuLi; [b]Yield not determined, observed in ^{1}H NMR spectrum of crude product.

The decrease in yield when the lithiation time of THP was extended from 1 h to 2 h at 0 °C (Table 4.2, entries 2 and 3) suggested that the lithiated intermediate was not stable at this temperature for extended periods of time. As such, the O'Brien group investigated the stability of lithiated THP to elucidate its decomposition pathway(s).[189] Sn-Li exchange was performed on stannane **231** at various temperatures for different periods of time. $PhMe_2SiCl$ was then added and the product was isolated (Table 4.3). At −78 °C for 30 min, only silyl THP **232** was isolated in 83% yield (entry 1). In contrast, when the temperature was increased to 0 °C, silyl THP **232** was isolated in 46% yield and alkene **233** was also observed

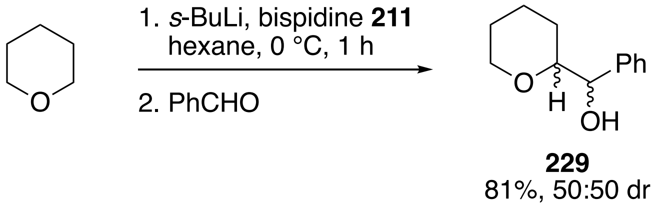
(**232**:**233**, 61:39; entry 2). The yield of silyl THP **232** decreased when the reaction time was increased to 240 min. This was accompanied with an increase in formation of alkene **233** (**232**:**233**, 22:78; entry 3). It was suggested that alkene **233** arises from the dimerisation of lithiated THP forming intermediates **234** then **235** which subsequently breaks down into alkene **233**; this would explain the decrease in yield of secondary alcohol **232** at extended lithiation times in Table 4.2.



Entry	Temp (°C)	Time (min)	Yield (%)	232:233
1	−78	30	83	100:0
2	0	30	46	61:39
3	0	240	15	22:78

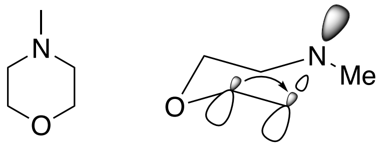
Table 4.3: Stability studies of lithiated THP

An improved yield for the lithiation-trapping of THP was achieved with *s*-BuLi and bispidine **211**.[189] Use of *s*-BuLi and bispidine **211** at 0 °C for 1 h and trapping with PhCHO furnished secondary alcohol **229** in 81% (Scheme 4.8). It is proposed that the increased steric hindrance provided by the bispidine ligand **211** deters the dimerisation of the lithiated intermediate which was responsible for the poor yields achieved when TMEDA was used as the ligand.



Scheme 4.8: Lithiation-trapping of THP with *s*-BuLi and bispidine **211**

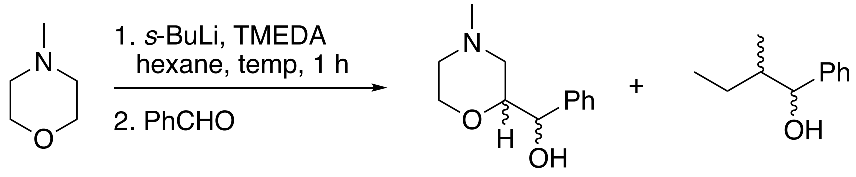
Lithiation-trapping of *N*-methylmorpholine **236** was also investigated.[210] The rate of lithiation of *N*-methylmorpholine *α* to oxygen was expected to be faster than in THP. This is explained by the back donation from the C-H σ-orbital into the C-N σ*-orbital increasing the acidity of the proton (Figure 4.3). Similar increased lithiation reactivity has been observed with the *N*-Boc piperazine system compared to *N*-Boc piperidine.[142]



236

Figure 4.3: Back donation model of *N*-methylmorpholine **236**

Lithiation of *N*-methylmorpholine **236** (1.0 equivalent) at various temperatures and trapping with PhCHO was carried out using *s*-BuLi and TMEDA in hexane (Table 4.4).[210] At −40 °C for 1 h, only a 15% yield of secondary alcohol **237** was obtained; an 81% yield of addition product **230** was isolated, indicating that lithiation had not reached completion (entry 1). Increasing the temperature to −30 °C resulted in an improved yield of secondary alcohol **237** (42%), and less addition product **230** (52%) (entry 2). This trend continued when the reaction temperature was further increased to −20 °C (entry 3). The best result came when the reaction was performed at 0 °C. Secondary alcohol **237** was synthesised in 89% yield and only a 2% yield of the addition product **230** was observed (entry 4).

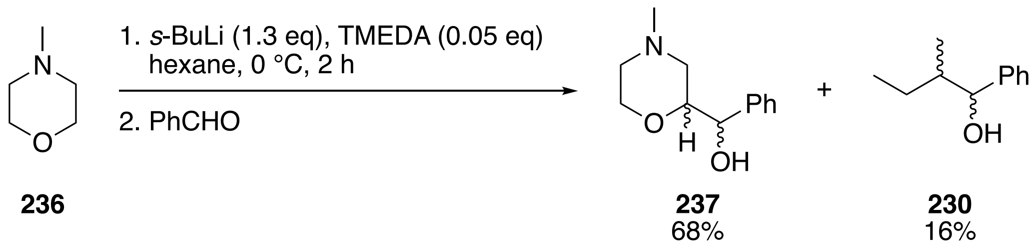


236 **237** **230**

Entry	Temp (°C)	Yield 237 (%)	Yield 230 (%)[a]
1	−40	15	81
2	−30	40	52
3	−20	63	43
4	0	89	2

Table 4.4: Lithiation-trapping of *N*-methylmorpholine **236** [a]Yield based off of amount of *s*-BuLi

Interestingly, it was found that the lithiation-trapping of *N*-methylmorpholine **236** could be performed with substoichiometric quantities of TMEDA.[210] At ligand quantities as low as 0.05 equivalents, the lithiation of *N*-methylmorpholine **236** with *s*-BuLi/TMEDA at 0 °C for 2 h and trapping with PhCHO formed secondary alcohols **237** in 68% yield and 16% yield of addition product **230** (Scheme 4.9). This is only a 21% reduction in yield compared to when the lithiation-trapping was performed with stoichiometric amounts of ligand (Table 4.4, entry 4). Furthermore, the formation of addition product **230** indicates that the lithiation step had not reached completion. Hence, a longer lithiation time may have been necessary for complete lithiation to have occurred. This is a significant discovery as lithiation-trapping of *N*-Boc heterocycles with substoichiometric quantities of ligands is not possible.

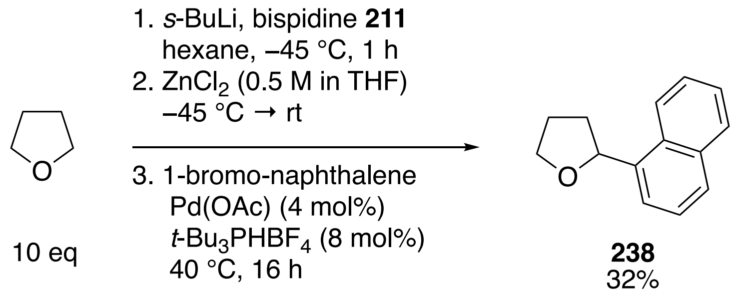


Scheme 4.9: Lithiation-trapping of *N*-methylmorpholine **236** using substoichiometric quantities of TMEDA

The use of *s*-BuLi and bispidine **211** in hexane has facilitated the lithiation-trapping of THF and THP in good yields (see Schemes 4.7 and 4.8). Slightly different lithiation conditions are required for the two ring systems; this is similar to 5- and 6-membered *N*-Boc heterocycles which have different relative rates of lithiation.[142] The increased acidity of the *α*-protons in *N*-methylmorpholine **236** means that the relatively less reactive *s*-BuLi/TMEDA complex in hexane can facilitate deprotonation thus providing access to *α*-functionalised *N*-methylmorpholines in excellent yields (see Table 4.4). Moreover, it was found possible to perform lithiation-trapping of *N*-methylmorpholines using substoichiometric quantities of TMEDA. These lithiation-trapping methods developed by the O'Brien group have extended the substrate scope further than that found in the literature whilst employing easily accessible conditions without the requirement of complex reaction set-ups.

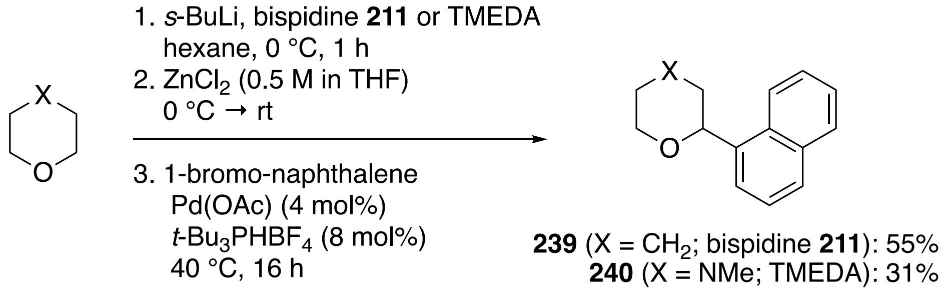
4.2.3 O'Brien Group's *α*-Arylation of *O*-Heterocycles *via* Negishi Cross-Coupling

With effective lithiation-trapping conditions developed, the O'Brien group expanded the methodology to *α*-arylation of *O*-heterocycles *via* Li-Zn transmetallation followed by Negishi cross-coupling.[211] Procedures previously developed by Campos[169] and by Coldham and Leonori[215] on the Li-Zn transmetallation then Negishi cross-coupling for the *α*-arylation of *N*-heterocycles were first applied to the THF system. Hence, 10 equivalents of THF was treated with *s*-BuLi and bispidine **211** in hexane at −45 °C for 1 h. The lithiated intermediate was transmetallated to Zn using $ZnCl_2$ (0.7 M solution in THF). Then, at room temperature, 1-bromonaphthalene, $Pd(OAc)_2$ and *t*-Bu_3PHBF_4 were directly added to the organozinc solution. The resultant solution was stirred at 40 °C for 16 h. This gave a 32% yield of arylated THF **238** (Scheme 4.10). This is a surprisingly low yield considering around 70% of the lithiated intermediate should have been forming (see Scheme 4.7).



Scheme 4.10: Lithiation-transmetallation-Negishi cross-coupling of THF

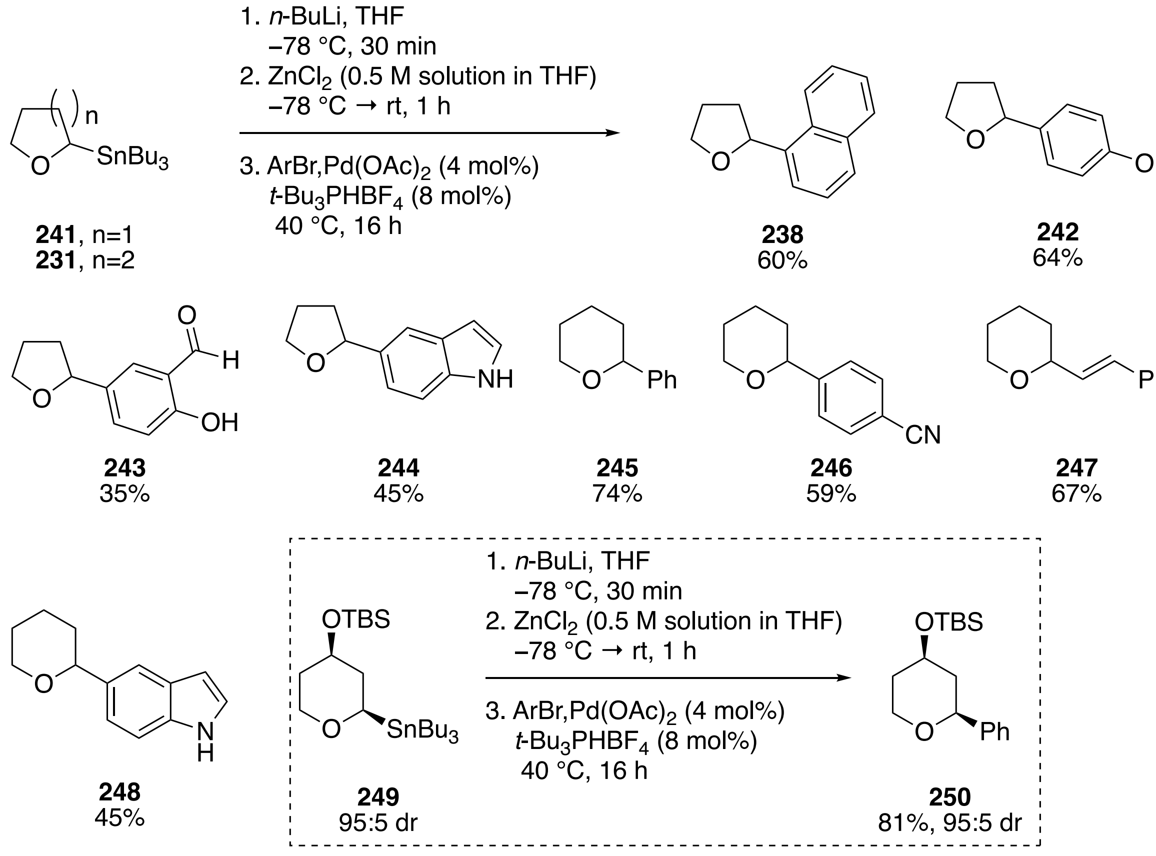
The Negishi cross-coupling method was also attempted with THP and *N*-methylmorpholine **236**.[211] Using the lithiation conditions which were developed for THP (*s*-BuLi, bispidine **211** in hexane at 0 °C for 1 h) and then transmetallation with $ZnCl_2$, the organozinc reagent was formed. Addition of the aryl bromide, $Pd(OAc)_2$ and *t*-Bu_3PHBF_4 gave, after heating at 40 °C for 16 h, arylated THP **239** in 55% yield (Scheme 4.11). Next, the morpholine system was investigated.[211] Lithiation of *N*-methylmorpholine **236** was carried out using *s*-BuLi and TMEDA in hexane at 0 °C for 1h. Transmetallation to Zn using $ZnCl_2$ and Negishi cross-coupling with the aryl bromide, $Pd(OAc)_2$ and *t*-Bu_3PHBF_4 at 40 °C for 16 h gave arylated morpholine **240** in 31% yield (Scheme 4.11).



239 (X = CH_2; bispidine **211**): 55%
240 (X = NMe; TMEDA): 31%

Scheme 4.11: Lithiation-transmetallation-Negishi cross-coupling of THP and *N*-methylmorpholine **236**

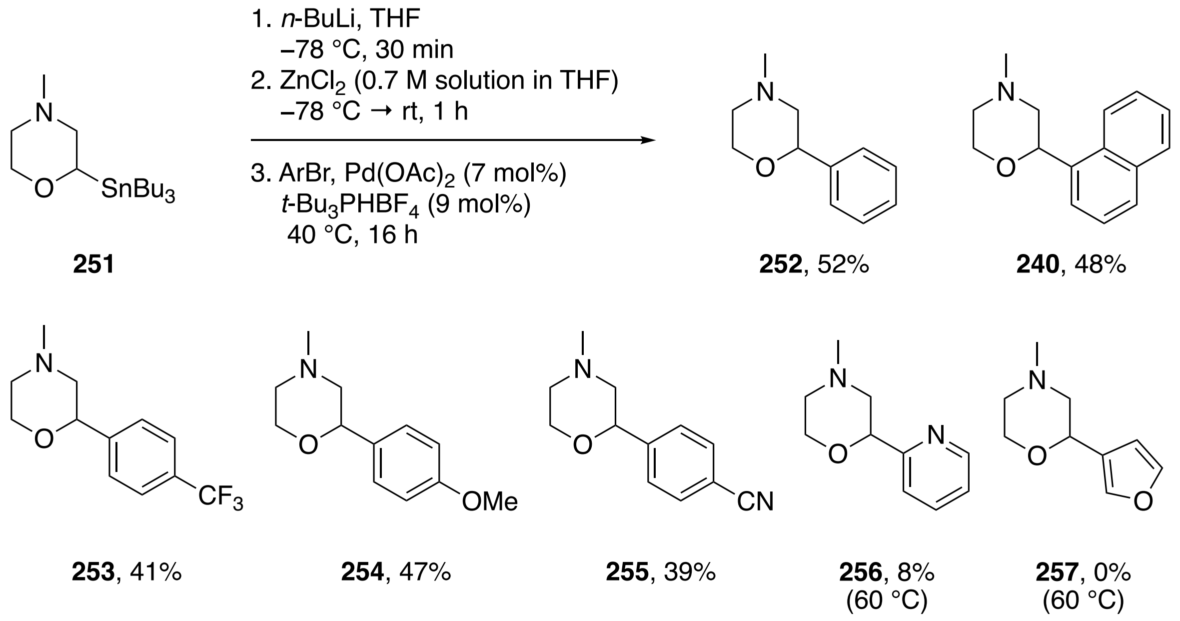
The yields obtained in the direct lithiation, transmetallation and Negishi cross-coupling of the three *O*-heterocycles were all significantly lower than the yields achieved in the direct lithiation-trapping reactions. It was noted that addition of the $ZnCl_2$ to the lithiated intermediate to effect transmetallation resulted in precipitation of the organozinc species in hexane. This caused stirring of the organozinc mixture to become difficult. It was therefore suggested that hexane was responsible for the poor yields achieved in these reactions as a result of poor solubility of the organozinc substrate.[211] Hence, a new method was developed that avoided the use of hexane in the organozinc formation and subsequent Negishi cross-coupling reaction.[211] First, α-stannyl THF **241** was synthesised and isolated using a known procedure.[216] In THF, α-stannyl THF **241** was subjected to Sn–Li exchange using *n*-BuLi at −78 °C for 30 min. The lithiated intermediate was then transmetallated using $ZnCl_2$ and, notably, no precipitation was observed when forming the organozinc species in THF. Negishi cross-coupling was then performed using $Pd(OAc)_2$ (4 mol%), *t*-Bu_3PHBF_4 (8 mol%) and 1-bromonaphthalene at 40 °C for 16 h which gave arylated THF **238** in 60% yield (Scheme 4.12).



Scheme 4.12: Sn-Li exchange-transmetallation-Negishi cross-coupling of α-stannyl THF **241**, THP **231** and 2,4-*cis* THP **249**[211]

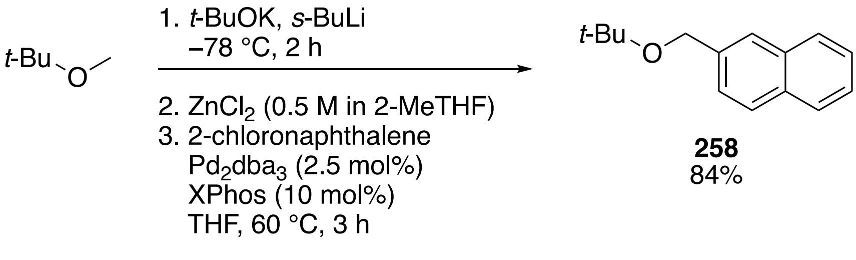
The (hetero)aryl bromide scope was explored by a previous member of the O'Brien group and moderate to good yields of α-arylated THF (**242**−**244**) have been achieved (35−64%).[211] Under otherwise identical conditions, α-stannyl THP **231** was subjected to Sn−Li exchange, transmetallation and Negishi cross-coupling with bromobenzene as the cross-coupling partner. This gave arylated THP **245** in 74% yield (Scheme 4.12). A range of aryl, vinyl and heteroaryl bromides were also well tolerated for this substrate forming α-functionalised THP **246**−**248** in 45−67% yield.[211] Furthermore, the substrate scope was extended to 2,4-*cis* configured disubstituted α-stannyl THP **249** (95:5 dr). Using identical conditions, cross-coupling with bromobenzene formed *cis*-**250** in 81% yield and maintained the diastereomeric ratio (95:5 dr) (Scheme 4.12).[211] This new method has considerably improved the yields compared to direct lithiation-transmetallation-Negishi cross-coupling of THF and THP (see Scheme 4.10 and 4.11) and further expanded both the substrate and aryl bromide scope highlighting the generality and robustness of this procedure. However, this method requires the synthesis and use of organotin reagents that are particularly toxic, this could potentially hinder the method's further use.

Finally, Sn−Li exchange, transmetallation with $ZnCl_2$ and Negishi cross-coupling was performed with α-stannyl morpholine **251** by the O'Brien group.[211] Slightly different Negishi cross-coupling conditions were developed for this system. Sn−Li exchange with *n*-BuLi in THF gave the lithiated intermediate and subsequent transmetallation with $ZnCl_2$ gave the organozinc species. Negishi cross-coupling with $Pd(OAc)_2$ (7 mol%), *t*-Bu_3PHBF_4 (9 mol%) and bromobenzene then gave arylated morpholine **252** in 52% yield (Scheme 4.13). The aryl bromide scope was then explored: 1-bromonaphthalene and aryl bromides containing both electron withdrawing and donating groups were reasonably well tolerated giving arylated morpholines **240, 253−255** in 39−48% yield (Scheme 4.13). However, the coupling of heteroaryl bromides was not well tolerated, even when the Negishi cross-coupling reaction was performed at 60 °C: 2-pyridinyl morpholine **256** was only obtained in 8% yield. None of arylated morpholine **257** was formed when the cross-coupling with 3-bromofuran was attempted.[211]



Scheme 4.13: Lithiation-transmetallation-Negishi cross-coupling of α-stannyl morpholine **251**[211]

Although no examples on cyclic ethers were reported, Newman and co-workers reported an example of arylation α to oxygen using Schlosser's base and Negishi cross-coupling in 2021.[217] *t*-BuOK and *s*-BuLi was added to TBME (substrate and solvent) at −78 °C for 2 h. Dropwise addition of $ZnCl_2$ formed the organozinc solution. The organozinc solution was then subjected to Negishi cross-coupling with 2-chloronaphthalene using Pd_2dba_3 and XPhos as the catalyst system in THF at 60 °C for 3 h. This led to the formation of cross-coupled product **258** in 84% yield (Scheme 4.14).



Scheme 4.14: Metallation-transmetallation-Negishi cross-coupling of TBME

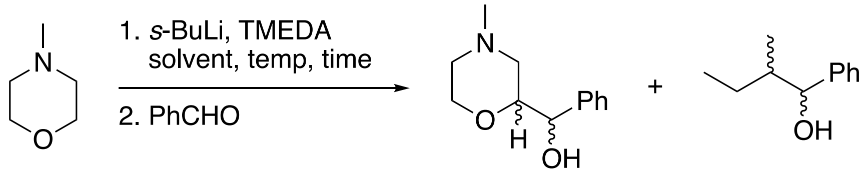
4.3 Lithiation-Trapping and Negishi Cross-Coupling of Saturated *O*-Heterocycles in TMO

As discussed in section 4.2.3 lithiation-trapping and α-arylation by Negishi cross-coupling of *O*-heterocycles has been carried out in the O'Brien group.[189,210,211] However, direct lithiation of the substrates followed by transmetallation with $ZnCl_2$ and Negishi cross-coupling was low yielding (31−55%). This was a result of the necessity to perform the lithiation of THF, THP and *N*-methylmorpholine **236** in hexane. This solvent was problematic for the subsequent transmetallation to Zn and Negishi cross-coupling as the organozinc reagent formed *in situ* was insoluble in hexane. To bypass this solubility problem, a two-step process was required to access α-arylated *O*-heterocycles: first, formation and isolation of the α-stannyl *O*-heterocycles then Sn−Li−Zn exchange in THF followed by Negishi cross-coupling. The use of this two-step process did result in improved yields in the Negishi cross-coupling step. However, toxic organostannane reagents were required. The process was also wasteful, since multiple organometallic reagents were necessary to access the organozinc species (Li−Sn−Li−Zn). Furthermore, purification *via* column chromatography of both the α-stannyl *O*-heterocycles and the desired product was needed.

We therefore sought an alternative approach to improving the overall α-arylation by Negishi cross-coupling. In section 3.4.1, the stability of TMO in the presence of *s*-BuLi at various temperatures was reported (see Table 3.6). Encouraged by these results, it was decided to investigate the lithiation-trapping of *O*-heterocycles in TMO. If successful, we wondered if TMO would be a suitable solvent for the generation of the organozinc species (without precipitating the organozinc species) and subsequent α-arylation of *O*-heterocycles *via* Negishi cross-coupling. The high boiling point of TMO could also be useful for improving the yields of any challenging Negishi cross-coupling reactions that were encountered. Overall, the use of TMO would avoid both the toxic organostannane reagents and should lead to a more streamlined one-step process.

4.3.1 Lithiation-Trapping of *N*-Methylmorpholine 236 using *s*-BuLi/TMEDA in TMO and Negishi Cross-Coupling

To start, lithiation-trapping conditions for *N*-methylmorpholine **236** in TMO were developed. From the investigation in Section 3.4.1 on the stability of TMO at various temperatures in the presence of *s*-BuLi, it was likely that the conditions developed in hexane by the O'Brien group (0 °C, 1 h)[210] would not be appropriate. As such, the lithiation of *N*-methylmorpholine **236** at various temperatures and lithiation times was performed to elucidate the optimised conditions in TMO (Table 4.5). First, the reaction was run in hexane using the conditions developed by the O'Brien group. Thus, *N*-methylmorpholine **236** was treated with *s*-BuLi and TMEDA in hexane at 0 °C for 1 h and subsequently trapped with PhCHO which gave an inseparable mixture of diastereomeric alcohols **237** in 76% yield and 50:50 dr (entry 1). These conditions were now repeated in TMO and, unsurprisingly, only a 24% yield of secondary alcohol **237** was achieved (entry 2). This low yield is likely a consequence of the organolithium reagent being consumed through reaction with the solvent and, as a result, less *s*-BuLi was available to react with *N*-methylmorpholine **236**. The reaction temperature was lowered to −10 °C and, pleasingly, a notable increase in yield of alcohols **237** (58%) was achieved (entry 3). The reduction in temperature clearly reduces the rate at which the organolithium is reacting with the solvent. As this yield was still low compared to when the reaction was run in hexane, lithiation of TMO is likely still occurring at this temperature. As such, the reaction temperature was lowered to −20 °C which gave a further improved 69% yield of alcohols **237**; secondary alcohols **230**, resulting from nucleophilic addition of *s*-BuLi to PhCHO, were also isolated in 26% yield (entry 4). The formation of addition product **230** suggests that lithiation was not complete after 1 h. The lithiation time was therefore increased to 2 h and a 75% yield of alcohols **237** was achieved; none of the addition product **230** was detected indicating that the lithiation was completed within 2 h (entry 5). This result is comparable with the yield obtained when the reaction was run in hexane (entry 1). A further reduction in temperature to −30 °C was then investigated: after 2 h, a 56% yield of alcohols **237** and a 28% yield of the addition product **230** were isolated (entry 6). No improvement in the yield was observed when the lithiation time was extended to 3 h with a 55% yield of alcohols **237** and a 17% yield of addition product **230** being obtained (entry 7). From this investigation, it is clear that the optimised conditions for the lithiation of *N*-methylmorpholine **236** in TMO are *s*-BuLi/TMEDA at −20 °C for 2 h (entry 5). As such, these conditions were chosen to be taken forward for developing the Negishi cross-coupling reaction in TMO.

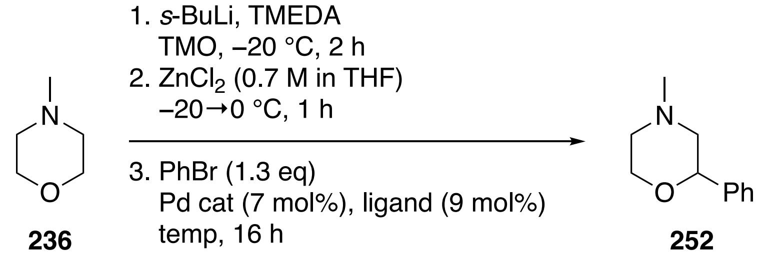


236 **237** **230**

Entry	Solvent	Temp (°C)	Time (h)	Yield 237 (%)[a,b]	Yield 230 (%)[b,c]
1	Hexane	0	1	76	-
2	TMO	0	1	24	-
3	TMO	−10	1	58	-
4	TMO	−20	1	69	26
5	TMO	−20	2	75	-
6	TMO	−30	2	56	28
7	TMO	−30	3	55	17

Table 4.5: Lithiation-trapping of *N*-methylmorpholine **236**. [a]Yield after chromatography. [b]50:50 dr. [c]Yield based on amount of *s*-BuLi, after chromatography

With the newly developed lithiation-trapping conditions in hand, an investigation into the Negishi cross-coupling of an organozinc species in TMO derived from *N*-methylmorpholine **236** was undertaken (Table 4.6). In 2006, Campos reported the *α*-arylation of *N*-Boc pyrrolidine **32** *via* lithiation then transmetallation with $ZnCl_2$ followed by Negishi cross-coupling using $Pd(OAc)_2$ and *t*-Bu_3PHBF_4 (an air-stable phosphonium salt of P(*t*-$Bu)_3$)[218] at 40 °C for 16 h.[169] The O'Brien group subsequently found success when applying these conditions with *O*-heterocycles (see section 4.2.3).[211] As such, these conditions served as a starting point for optimising the Negishi cross-coupling of *N*-methylmorpholine **236** in TMO. *N*-Methylmorpholine **236** was treated with *s*-BuLi and TMEDA in TMO at −20 °C for 2 h which gave the lithiated intermediate. This was transmetallated using $ZnCl_2$ (in THF) and then the solution was allowed to warm to room temperature over 1 h which gave an opaque organozinc solution. A small amount of precipitation occurred with the addition of $ZnCl_2$ to the lithiated intermediate in TMO but this did not affect the stirring of the reaction mixture. Subsequent Negishi cross-coupling was then performed using $Pd(OAc)_2$ (7 mol%), *t*-Bu_3PHBF_4 (9 mol%) and bromobenzene. Unfortunately, only trace amounts of arylated morpholine **252** was detected in the ^{1}H NMR spectrum of the crude product (entry 1). It must be noted that both $Pd(OAc)_2$ and *t*-Bu_3PHBF_4 were not very soluble when added to the organozinc solution and this could account for the lack of reactivity in TMO. The reaction temperature for the Negishi cross-coupling was increased to 80 °C in an attempt to improve the reactivity. Pleasingly, a 30% yield of arylated morpholine **252** was achieved (entry 2). Dialkylbiaryl phosphine ligand, RuPhos, has been shown to be an excellent ligand for Negishi cross-coupling reactions.[219.] As such, RuPhos was tried in this reaction and it resulted in a marginal increase in yield (35%) of arylated morpholine **252** (entry 3). This was further improved upon when the reaction temperature was increased to 100 °C with 50% yield of arylated morpholine **252** being obtained (entry 4). This is a notable result as it essentially matches the yield obtained for the synthesis of arylated morpholine **252** *via* the stannane route (see Scheme 4.13).[211] Pd sources $[Pd(allyl)Cl]_2$ and Pd_2dba_3 were also investigated but, in both cases, only 44% yield of arylated morpholine **252** was achieved (entries 5 and 6 respectively). CPhos and SPhos are other dialkylbiaryl ligands found to be effective in Negishi cross-coupling reactions.[220–222] However, the use of either of these ligands did not result in improved yields compared to RuPhos, as both gave 44% yield of arylated morpholine **252** (entries 7 and 8 respectively).



Entry	Pd cat	Ligand	Temp (°C)	Yield (%)^a
1	Pd(OAc)$_2$	*t*-Bu$_3$PHBF$_4$	40	Traces
2	Pd(OAc)$_2$	*t*-Bu$_3$PHBF$_4$	80	30
3	Pd(OAc)$_2$	RuPhos	80	35
4	Pd(OAc)$_2$	RuPhos	100	50
5	[Pd(allyl)Cl]$_2$	RuPhos	100	44
6	Pd$_2$dba$_3$	RuPhos	100	44
7	Pd(OAc)$_2$	CPhos	100	44
8	Pd(OAc)$_2$	SPhos	100	44

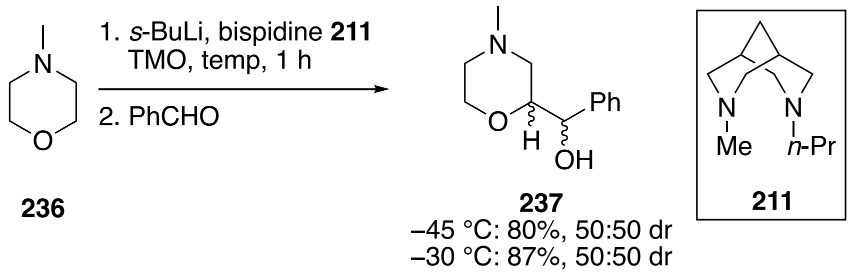
Table 4.6: Optimisation of the Negishi cross-coupling of *N*-methylmorpholine **236** in TMO. ^{a}Yield after chromatography

In summary, when *s*-BuLi/TMEDA were used, the most effective lithiation-trapping conditions in TMO were found to be −20 °C for 2 h, which generated the desired *α*-functionalised morpholine **237** in 75% yield. These lithiation-trapping conditions were taken forward to be used in a Negishi cross-coupling reaction with *N*-methylmorpholine **236**. The use of Pd(OAc)$_2$ and RuPhos at 100 °C facilitated the Negishi cross-coupling with bromobenzene to give arylated morpholine **252** in 50% yield. This is a considerable improvement (20%) when the lithiation step was carried out in hexane.[210] It also matches the yield which was achieved when arylated morpholine **252** was accessed *via* the stannane route.[211] However, the direct lithiation-trapping result suggested that only 75% of the lithiated intermediate is being formed under these conditions. Therefore, it was decided to explore if the use of a different ligand in the lithiation step could increase the amount of lithiated intermediate which would subsequently lead to an increase in yield of the direct trapping products and the Negishi cross-coupled products.

4.3.2 Lithiation-Trapping of *N*-Methylmorpholine using *s*-BuLi/Bispidine 211 in TMO and Negishi Cross-Coupling

Previous members of the O'Brien group have reported enhanced reactivity in the lithiation-trapping reactions of THF and THP when using *s*-BuLi and bispidine ligand **211** compared to TMEDA (see section 4.2.2).[189,211] In the previous section, a lower temperature (−20 °C) was required when developing lithiation-trapping conditions in TMO for *N*-methylmorpholine **236** compared to hexane (0 °C). This was required to mitigate the reaction between *s*-BuLi and TMO making complete lithiation of the *N*-methylmorpholine **236** more challenging. It was therefore decided to revisit the lithiation-trapping of *N*-methylmorpholine **236**. The plan was to utilise the more reactive *s*-BuLi/bispidine **211** complex with a desire to improve the yield that was achieved when TMEDA was used as the ligand.

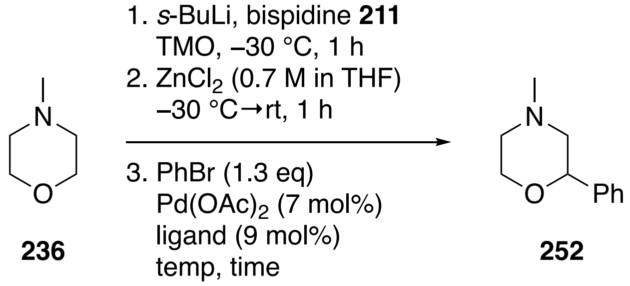
To start, *N*-methylmorpholine **236** was treated with *s*-BuLi and bispidine **211** in TMO at −45 °C for 1 h. Trapping with PhCHO constructed the diastereomeric alcohols **237** in an excellent 80% yield. Increasing the reaction temperature to −30 °C resulted in a further improved yield (87%) of alcohols **237** (Scheme 4.15). These results highlight the considerable increase in reactivity of *s*-BuLi/bispidine **211** compared with *s*-BuLi/TMEDA. Hence, the lithiation conditions, using bispidine **211**, chosen to be taken forward for the Negishi cross-coupling of *N*-methylmorpholine **236** were −30 °C for 1 h.



Scheme 4.15: Lithiation-trapping of *N*-methylmorpholine **236** with *s*-BuLi/bispidine **211**

With these new lithiation-conditions now in hand, the Negishi cross-coupling reaction optimisation was revisited (Table 4.7). The best conditions found when using TMEDA were initially explored, namely $Pd(OAc)_2$ and RuPhos at 100 °C for 16 h. Unfortunately, only a minor increase in yield to 52% of arylated morpholine **252** was observed (entry 1). Increasing the reaction time to 60 h had negligible effect on the yield with 51% of the arylated morpholine **252** being isolated (entry 2). Thus far, temperature has had the largest impact on the yield in this Negishi cross-coupling reaction. Therefore, using a pressure tube, the reaction was heated to 120 °C but this showed no improvement and a 49% yield of arylated morpholine **252** was obtained (entry 3). Organ and co-workers have reported that in non-polar solvents, additives such as LiCl promote the formation of higher order zincate species ($RZnX_3^{2-}$) which are active towards transmetallation, improving the overall efficiency of Negishi reactions.[223] As such, the reaction was repeated with the addition of 1.3 equivalents of LiCl. Unfortunately, the use of this additive resulted in no improvement in yield (47%) of arylated morpholine **252** (entry 4). Use of polar co-solvents have been found to provide an environment that can accelerate the Negishi cross-coupling reaction.[224] Addition of a solvent quantity of dimethyl-2-imidazolidinone (DMI) failed to give any of the arylated morpholine **252** based on the ^1H NMR spectrum of the crude product (entry 5). When the catalyst loading was increased to $Pd(OAc)_2$ (10 mol%) and RuPhos (14 mol%), only a 41% yield of arylated morpholine **252** was obtained (entry 6). Both XPhos[225] and 2-

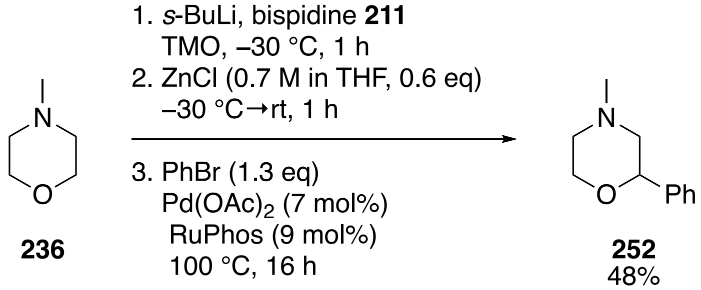
tfp (tri-(2-furyl)phosphine)[226] have previously been successful at facilitating Negishi cross-coupling reactions. However, both ligands gave inferior yields compared to RuPhos with arylated morpholine **252** being isolated in only 40% and 20% yields respectively (entries 7 and 8). PEPPSI-*i*Pr, a ligand advocated by Organ and co-workers in Negishi cross-coupling reactions,[227,228] was also unsuccessful at facilitating the cross-coupling reaction. Only trace quantities of the arylated morpholine **252** were detected in the ^{1}H NMR spectrum of the crude product (entry 9). Interestingly, chlorobenzene was successfully coupled without any variation in yield compared to its bromide counterpart, with arylated morpholine **252** being formed in 52% yield (entry 10). Unfortunately, after significant attempts to optimise this Negishi cross-coupling reaction by increasing temperature, addition of additives, increasing catalyst loadings or the use of different ligands, no improvement on the original conditions could be achieved.



Entry	Ligand	Temp (°C)	Time (h)	Alteration	Yield (%)[a]
1	RuPhos	100	16	-	52
2	RuPhos	100	60	-	51
3	RuPhos	120	16	Pressure tube	49
4	RuPhos	100	16	1.3 eq of LiCl added	47
5	RuPhos	100	16	1 mL of DMI added	0
6	RuPhos	100	16	10/14 mol% [Pd]/ligand	41
7	XPhos	100	16	-	40
8	2-tfp	100	16	14 mol% of ligand	20
9	PEPPSI-*i*Pr	100	16	No $Pd(OAc)_2$	Traces
10	RuPhos	100	16	PhCl used	52

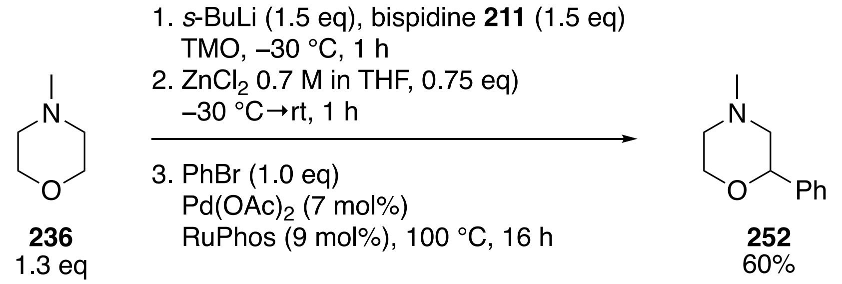
Table 4.7: Lithiation (*s*-BuLi/bispidine **211**)-metallation-Negishi cross-coupling of *N*-methylmorpholine **236**. [a]Yield after chromatography

In an attempt to improve the Negishi cross-coupling step, other factors were considered. Campos *et al*. reported that substoichiometric amounts of $ZnCl_2$ can be used with no detrimental effect on the reaction yield.[169] This is a result of different organozinc species (RZnCl, R_2Zn and R_3ZnLi) being able to form and being competent for Negishi cross-coupling. Hence, the Negishi cross-coupling reaction of *N*-methylmorpholine **236** was performed using 0.6 equivalents of $ZnCl_2$. *N*-methylmorpholine **236** was treated with *s*-BuLi and bispidine **211** in TMO at −30 °C for 1 h. Transmetallation with 0.6 equivalents of $ZnCl_2$ gave the organozinc solution which was allowed to warm to rt over 1 h. Negishi cross-coupling was then performed with $Pd(OAc)_2$ (7 mol%) and RuPhos (9 mol%) at 100 °C for 16 h. No significant reduction in yield (48% yield) of arylated morpholine **252** was observed (Scheme 4.16).



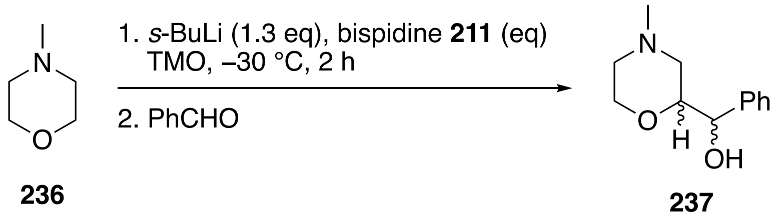
Scheme 4.16: Lithiation-transmetallation-Negishi cross-coupling of *N*-methylmorpholine **236** with substoichiometric quantities of $ZnCl_2$

Thus far, morpholine **236** has been used as the limiting reagent in the cross-coupling reaction, with bromobenzene always being used in excess. It was decided to swap the limiting reagent so that more of the organozinc was available for transmetallation. With the morpholine **236** in excess (1.3 equivalents), arylated morpholine **252** was isolated in an improved 60% yield (Scheme 4.17).



Scheme 4.17: Lithiation-transmetallation-Negishi cross-coupling of *N*-methylmorpholine **236**, with *N*-methylmorpholine **236** in excess

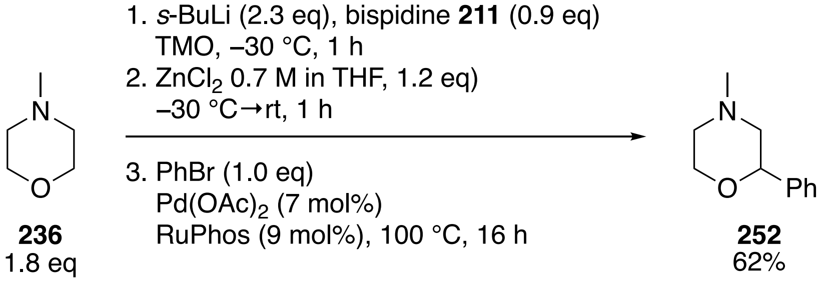
Increasing the amount of morpholine **236** in the reaction meant that more equivalents of *s*-BuLi and bispidine **211** were required for the lithiation step. As outlined earlier, bispidine **211** is not commercially available and requires a slightly time-consuming synthesis (see Scheme 3.44); moreover, bispidine **211** is not stable for extended periods of time. As such, we were reluctant to use considerable excesses of bispidine **211**. A previous member of the O'Brien group reported that lithiation-trapping of *N*-methylmorpholine **236** could be carried out using substoichiometric quantities of TMEDA (see Scheme 4.9).[210] Lithiation-trapping of *N*-methylmorpholine **236** with substoichiometric quantities of bispidine **211** was therefore explored (Table 4.8). *N*-methylmorpholine **236** was treated with *s*-BuLi (1.3 equivalents) and bispidine **211** (0.5 equivalents) in TMO at −30 °C. With this reduction in ligand quantity, we expected that a longer lithiation time would be required. As such, the lithiation time was extended to 2 h. Trapping with PhCHO furnished the desired alcohols **237** in 91% yield (entry 1). Reducing the amount bispidine **211** further to 0.3 equivalents resulted in a reduction in the yield of alcohols **237** to 60% (entry 2). However, it would be expected that with a longer lithiation time this yield could be improved.



Entry	Bispidine 211 (eq)	Yield (%)[a,b]
1	0.5	91
2	0.3	60

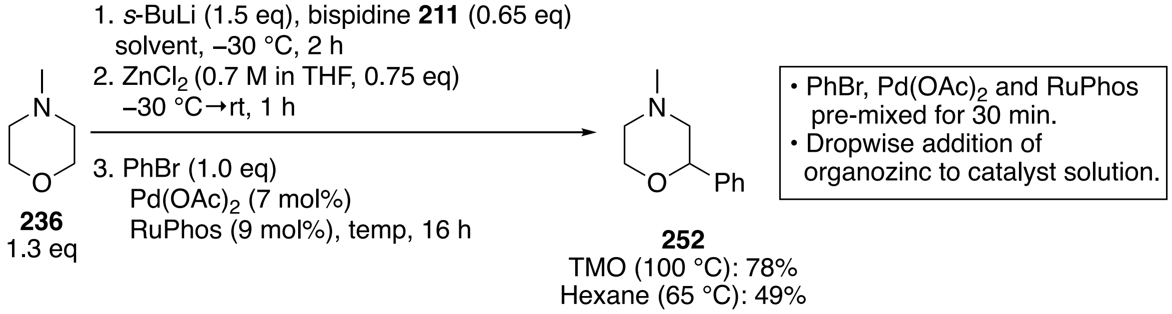
Table 4.8: Lithiation-trapping of *N*-methylmorpholine **236** using substoichiometric quantities of bispidine **211**. [a]Yield after chromatography. [b]50:50 dr

The Negishi cross-coupling reaction of *N*-methylmorpholine **236** was revisited a final time now that we had a suitable lithiation procedure with substoichiometric amounts of the somewhat precious bispidine ligand **211**. For this, a larger excess of *N*-methylmorpholine **236** (1.8 equivalents) was used and the lithiation was performed using 0.9 equivalents of bispidine **211** (0.5 equivalents relative to *N*-methylmorpholine **236**). Transmetallation with $ZnCl_2$ (1.2 equivalents) and Negishi cross-coupling constructed arylated morpholine **252** in a marginally improved 62% yield (Scheme 4.18). Considering the large excesses of other reagents when performing this reaction, it was decided that further reactions would be performed with 1.3 equivalents of *N*-methylmorpholine **236**.



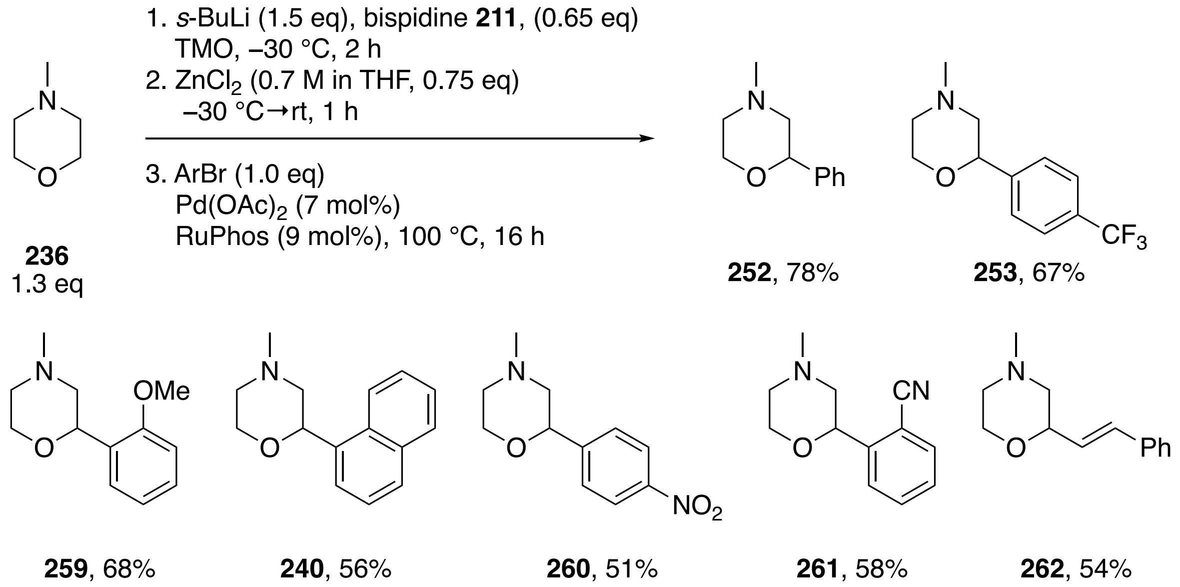
Scheme 4.18: Negishi cross-coupling of *N*-methylmorpholine **236** (1.8 equivalents)

The Negishi cross-coupling reactions described thus far in this section were all performed by first forming the organozinc reagent under an inert atmosphere. This inert atmosphere had to be compromised as the flask was opened for the addition of the palladium catalyst, ligand and bromobenzene before being sealed again. Efforts were made to mitigate the introduction of air and moisture by opening the flask over a flow of N_2. However, it was not possible to confirm that the flask was then under air- and moisture-free conditions. With this in mind, combining the organozinc with the Negishi catalytic reagents was performed in a different manner to ensure that the flask would be free from any of air and moisture. First, *N*-methylmorpholine **236** (1.3 equivalents) was treated with *s*-BuLi (1.5 equivalents) and bispidine **211** (0.65 equivalents) in TMO at −30 °C for 2 h. Transmetallation with $ZnCl_2$ (0.75 equivalents) afforded an opaque organozinc solution which was allowed to warm to room temperature over 1 h. In a separate flame-dried flask, $Pd(OAc_2)$ (7 mol%), RuPhus (9 mol%) and bromobenzene (1.0 equivalent) were pre-stirred in TMO (1 mL) for 30 min. The organozinc solution was then transferred to the flask containing the Negishi catalytic components dropwise over 15 min and then heated at 100 °C for 16 h. Pleasingly, this process afforded the arylated morpholine **252** in a much-improved 78% yield (Scheme 4.19). These conditions became our standard optimised conditions. For comparison, the reaction was repeated in hexane and the Negishi cross-coupling was heated to 65 °C, due to the lower boiling point of hexane. Upon addition of the $ZnCl_2$ to the lithiated intermediate in hexane, the solution became turbid which made stirring and transfer of the organozinc solution difficult. This resulted in a poorer yield of arylated morpholine **252** (49%). These comparative reactions highlight the benefits of using TMO in this Negishi cross-coupling reaction. First, access to higher temperatures enables increased reactivity in the Negishi cross-coupling step. Second, improved solubility of the organozinc reagent in TMO could also improve reactivity as well as making the transfer of the organozinc solution to the catalytic solution easier.



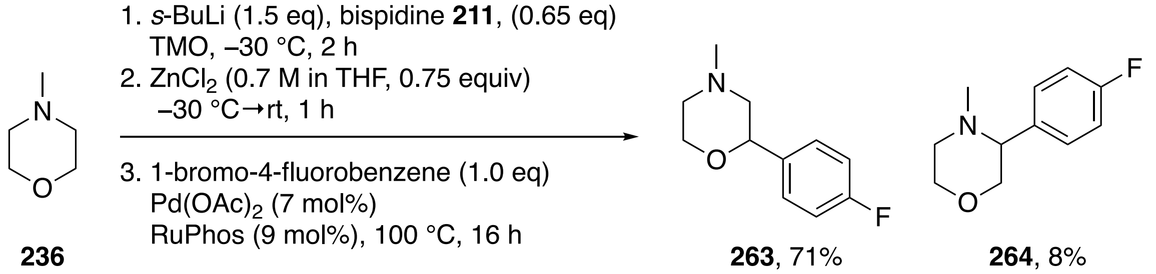
Scheme 4.19: Optimised method for the lithiation-transmetallation-Negishi cross-coupling of *N*-methylmorpholine **236**

Having identified synthetically useful conditions for the Negishi cross-coupling reaction of *N*-methylmorpholine **236**, the aryl bromide scope was explored (Scheme 4.20). A range of aryl bromides were used in the cross-coupling reaction to give arylated morpholines **240**, **252**, **253**, **259**–**262** in yields up to 78%. Aryl bromides containing CF$_3$ and methoxy were well tolerated achieving yields of 67% (**253**) and 68% (**259**) respectively. Unsubstituted naphthyl bromides and aryl bromides containing electron withdrawing nitro and nitrile groups could also be coupled in yields above 50%. Vinylation was also possible with vinyl morpholine **262** being synthesised in 54% yield.



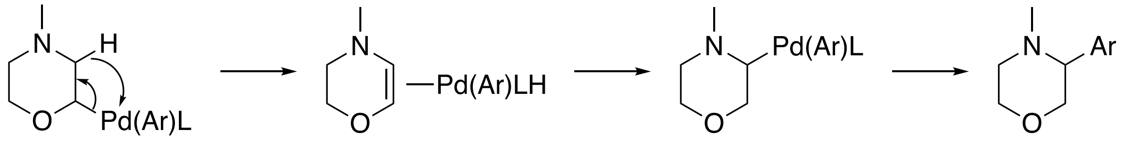
Scheme 4.20: Negishi cross-coupling of *N*-methylmorpholine **236** aryl/vinyl bromide scope

In the cross-coupling of an aryl bromide containing a fluorine substituent with *N*-methylmorpholine **236**, arylated morpholine **263** was obtained in 71% yield. Of note, formation of regioisomeric arylated morpholine **264** was also observed in 8% yield (Scheme 4.21). The O'Brien group have reported the formation of a similar *β*-arylated product in the Negishi cross-coupling of *N*-Boc piperazine.[229]



Scheme 4.21: Synthesis of *α*- and *β*-arylated *N*-methylmorpholine **263** and **264** *via* Negishi cross-coupling

A mechanistic explanation, similar to that reported by Knochel and Baudoin on the synthesis of 2,5-disubstituted *N*-Boc piperidines and ligand controlled *β*-selective arylation of *N*-Boc piperidines respectively, is proposed to account for this observation.[230,231] In our example, *β*-hydride elimination of *α*-palladated *N*-methylmorpholine **265** could form intermediate alkene **266**. Subsequent *syn* hydropalladation of alkene **266** would then give rise to *β*-palladated *N*-methylmorpholine **267** which would then undergo reductive elimination to form the observed *β*-arylated *N*-methylmorpholine **264** (Scheme 4.22). Baudoin *et al.* suggested that the *β*-selectivity was a result of the rate determining reductive elimination step transition state energy being lower for the formation of the *β*-arylated product than that of the *α*-arylated product.[231] If this is indeed the case, further exploration into the ligand choice for this methodology could result in a ligand-controlled site-selective arylation of *N*-methylmorpholine **236**.

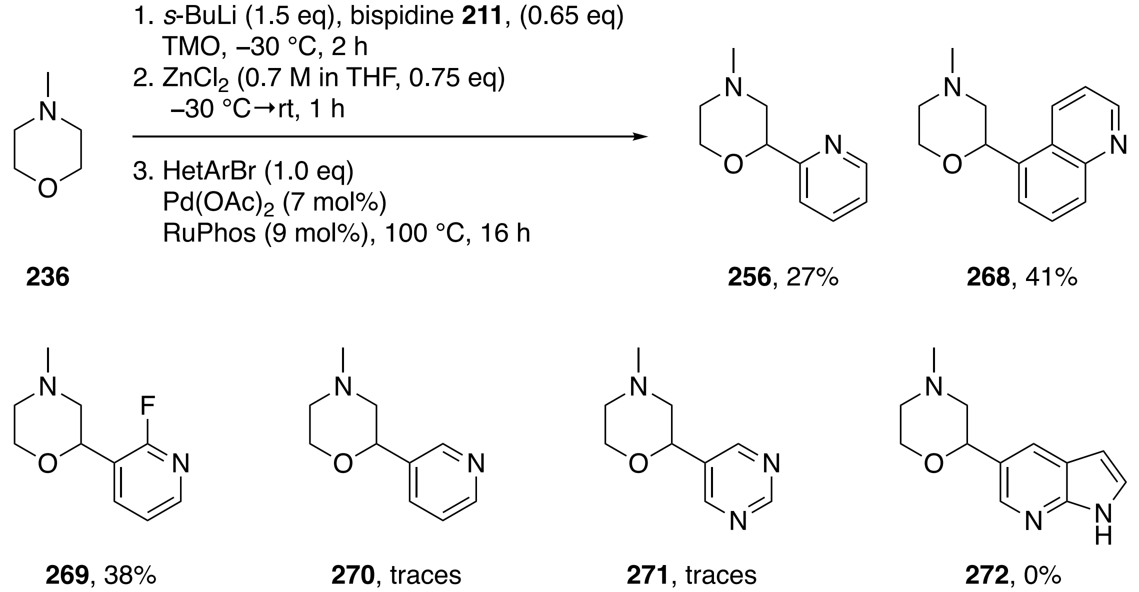


265 **266** **267** **264**

Scheme 4.22: Possible mechanism for the formation of *β*-arylated *N*-methylmorpholine **264**

Heteroaryl bromides were then investigated for the cross-coupling reaction (Scheme 4.23). 2-Pyridinyl and 5-quinolinyl functionalised morpholines **256** and **268** were synthesised in 27% and 41% yield respectively. 2-Fluoropyridine coupled morpholine **269** was furnished in 38% yield. Disappointingly, 3-pyridinyl and 5-pyrimindyl coupled morpholine **270** and **271** were only detected in trace quantities in the ^{1}H NMR spectrum of the crude products.

Finally, the attempted coupling of 5-bromo-7-azaindole to give heteroaryl morpholine **272** was, unfortunately, not successful.



236

256, 27%

268, 41%

269, 38%

270, traces

271, traces

272, 0%

Scheme 4.23: Negishi cross-coupling of *N*-methylmorpholine **236** heteroaryl bromide scope

The aryl group on the morpholine ring in all of the cross-coupled products was established as being positioned in the equatorial position by ^{1}H NMR spectroscopy using ^3J coupling constant values. Figure 4.4 shows part of the ^{1}H NMR spectrum of arylated morpholine **259**. Proton $\mathrm{H_A}$ shows a 10.0 Hz $^3J_{\text{ax-ax}}$ and 2.5 Hz $^3J_{\text{ax-eq}}$ coupling constants, which indicates that $\mathrm{H_A}$ is axial and, hence, the aryl group is in an equatorial position. Furthermore, the positions of the two other protons α to oxygen ($\mathrm{H_B}$ and $\mathrm{H_C}$) can also be determined by analysis of the ^2J and ^3J coupling constant values. $\mathrm{H_B}$ shows 11.5 Hz ^2J coupling, 3.5 Hz $^3J_{\text{eq-ax}}$ coupling and 1.5 Hz $^3J_{\text{eq-eq}}$ coupling constant values indicative of a proton in the equatorial position. In contrast, $\mathrm{H_C}$ exhibits a 11.5 Hz ^2J coupling constant, a 11.5 Hz $^3J_{\text{az-az}}$ coupling and a 2.5 Hz $^3J_{\text{ax-eq}}$ coupling constant value indicating that this proton is in an axial position. The chemical shifts of all three of these protons is in the 3.80−5.00 ppm range which is consistent with protons next to oxygen. Unfortunately, in a number of the examples in the (hetero)aryl bromide scope, the co-elution of small amounts of RuPhos with the products was unavoidable. The ^{1}H NMR spectrum of arylated morpholine **259** in Figure 4.4 shows arylated morpholine **259** after chromatography: it isolated as a mixture with RuPhos (94:6 **259**:RuPhos). Proton H_D is the diagnostic septet signal representative of the two OCH protons present in RuPhos.

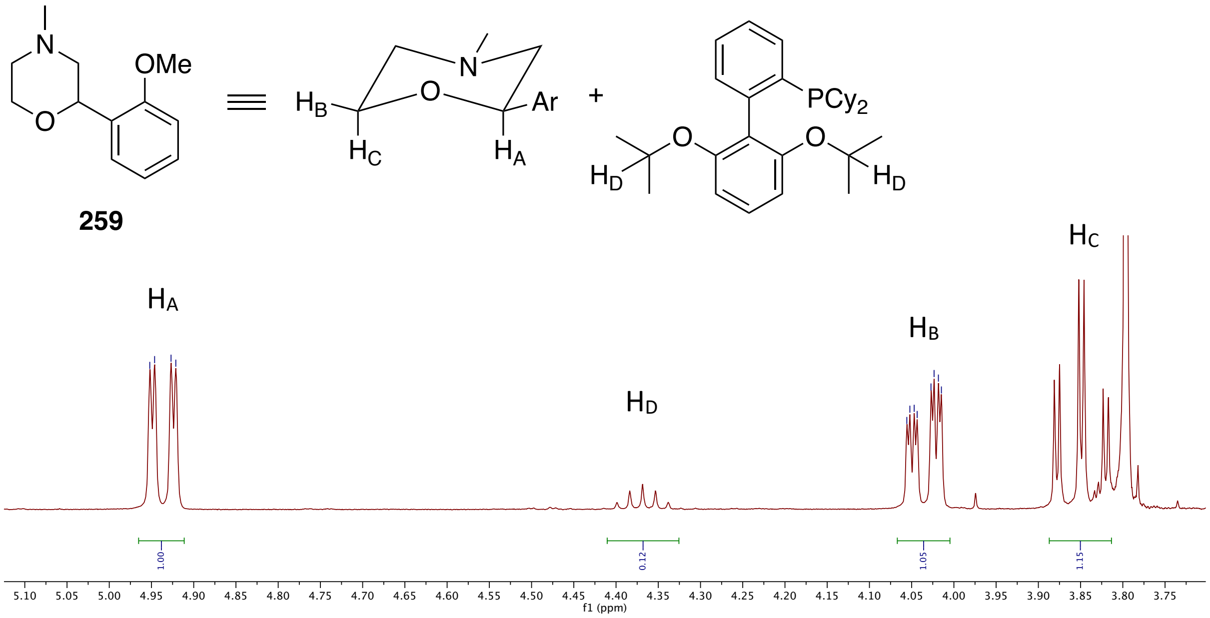


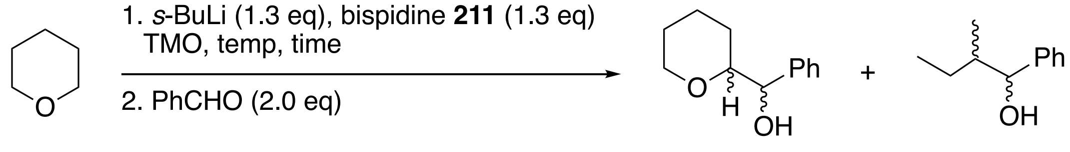
Figure 4.4: ^{1}H NMR spectrum of arylated morpholine **259** isolated as a mixture with RuPhos

In summary, using bispidine ligand **211**, lithiation-trapping conditions for *N*-methylmorpholine **236** have been developed in TMO, which allowed the synthesis of *α*-functionalised morpholine **237** in TMO in an excellent yield (87%). Of note, the lithiation-trapping reaction can be performed with substoichiometric quantities of ligand without detrimental effects on the yield (91%). These lithiation-trapping conditions were then taken forward for use in developing Negishi cross-coupling conditions. Pre-mixing of the

$Pd(OAc)_2$ and RuPhos and the aryl bromide as well as dropwise addition of the organozinc has proven to be essential for high yielding Negishi cross-couplings to be obtained. An aryl bromide and heteroaryl bromide scope was explored and 11 examples were successful in yields in the range of 27−78%.

4.3.3 Preliminary Investigation into the Lithiation-Trapping and Negishi Cross-Coupling of THP in TMO

The lithiation, transmetallation and Negishi cross-coupling methodology developed in TMO was next applied to THP. Lithiation-trapping conditions for THP using *s*-BuLi/bispidine **211** in hexane have previously been developed by the O'Brien group.[189] These conditions used 0 °C for 1 h, and they are likely not applicable with TMO (due to the high temperature). As such, new conditions were developed for the lithiation-trapping of THP with *s*-BuLi and bispidine **211** in TMO. Lithiation at various temperatures and times and trapping with PhCHO to furnish inseparable diastereomeric alcohols **229** was investigated (Table 4.9). To start, lithiation-trapping was performed at −30 °C for 2 h in TMO; addition of PhCHO gave alcohols **229** in 68% yield and 50:50 dr. Addition products **230** were also isolated in 13% yield suggesting that the lithiation of the substrate was not yet complete (entry 1). Therefore, the lithiation time was extended to 3 h: alcohols **229** were isolated in 72% yield and no evidence of addition products **230** was observed confirming that the reaction had reached completion (entry 2). In an attempt to develop more convenient conditions, the reaction temperature was increased to −20 °C and reaction time reduced to 2 h. This resulted in the formation of alcohols **229** in 73% yield with no addition products **230** formed (entry 3). Further increasing the reaction temperature to −15 °C resulted in a reduction in yield (63%) of alcohols **229** (entry 4). This is likely a result of the reaction between the solvent and the organolithium becoming competitive at this temperature. Hence, the optimal conditions chosen to be taken forward for the Negishi cross-coupling reaction were −20 °C for 2 h (entry 3).

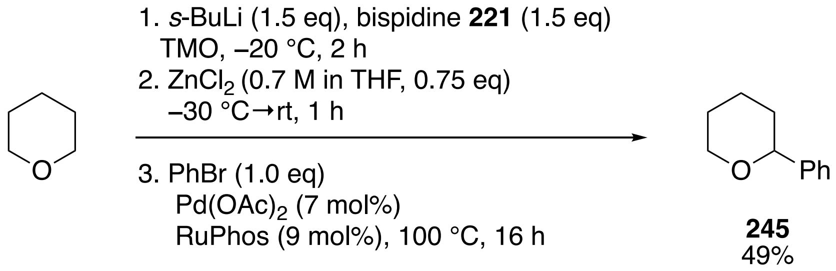


229 **230**

Entry	Temp (°C)	Time (h)	Yield 229 (%)^{a,b}	Yield 230 (%)^{b,c}
1	−30	2	68	13
2	−30	3	72	-
3	−20	2	73	-
4	−15	2	63	-

Table 4.9: Lithiation-trapping of THP in TMO. [a]Yield after chromatography. [b]50:50 dr. [c]Yield based on amount of *s*-BuLi, after chromatography

The Negishi cross-coupling of THP was subsequently investigated. The optimised conditions developed in the Negishi cross-coupling of *N*-methylmorpholine **236** were chosen for this study. First, THP was treated with *s*-BuLi and bispidine **221** at −20 °C for 2 h. Transmetallation to Zn with $ZnCl_2$ gave a slightly opaque organozinc solution. The organozinc solution was then transferred to a pre-mixed solution of $Pd(OAc_2)$ (7 mol%), RuPhos (9 mol%) and bromobenzene in TMO. The resultant solution was heated at 100 °C for 16 h. Disappointingly, only a 49% yield of arylated THP **245** was obtained (Scheme 4.24). Due to time constraints, further exploration and optimisation of the Negishi cross-coupling of THP was not possible.



Scheme 4.24: Lithiation-transmetallation and Negishi cross-coupling of THP in TMO

Overall, lithiation-trapping conditions of THP were developed in TMO and good yields of α-functionalised THP **229** were achieved. Using these lithiation conditions and applying the methodology developed for the Negishi cross-coupling of *N*-methylmorpholine **236** to THP, only a modest yield (49%) of arylated THP **245** could be achieved. Due to time constraints, further optimisation of the Negishi cross-coupling reaction was not investigated.

4.4 Conclusions and Future Work

In summary, new lithiation-trapping conditions for *N*-methylmorpholine **236** in TMO have been developed. A lower temperature, compared to the previously developed conditions by the O'Brien group which employed hexane as the reaction solvent, was required. This was due to an undesired reaction between the solvent and the organolithium. Use of bispidine **211** in substoichiometric quantities (0.5 equivalents) at −30 °C for 2 h facilitated the synthesis of alcohols **237** in 91% yield (Table 4.8, entry 2).

The optimised lithiation-trapping conditions were then applied in the synthesis of arylated morpholines *via* Negishi cross-coupling. The optimal conditions for the α-arylation of *N*-methylmorpholine **236** were found to be $Pd(OAc)_2$ (7 mol%), RuPhos (9 mol%) at 100 °C for 16 h. Pre-mixing of the catalytic components and aryl bromide in TMO prior to the dropwise addition of the organozinc solution was found to be essential for the reaction to be high yielding. These newly developed conditions enabled the synthesis of arylated morpholine **252** in 78% yield. This is a considerable improvement compared to when the reaction is performed in hexane. Furthermore, this protocol is also superior to the stannane route previously developed for the synthesis α-arylated *O*-heterocycles. This improved method avoids the use of toxic organostannane reagents and intermediates whilst improving the overall yield significantly. The (hetero)aryl bromide scope was examined and 11 successful examples **240**, **252**, **253**, **259**−**263**, **268** and **269** were shown in yields in the range of 27−78%. Electron-rich and electron-poor aryl bromides were well tolerated, as were vinyl bromides. In contrast, heteroaryl bromides proved to be more difficult to cross-couple. Finally, lithiation-trapping conditions were developed for THP and the synthesis of alcohols **229** was achieved in 73% yield. α-Arylation of THP was attempted using the conditions developed for *N*-methylmorpholine **236**. However, only a 49% yield of arylated THP **245** was obtained. An overview of these results is presented in Figure 4.5.

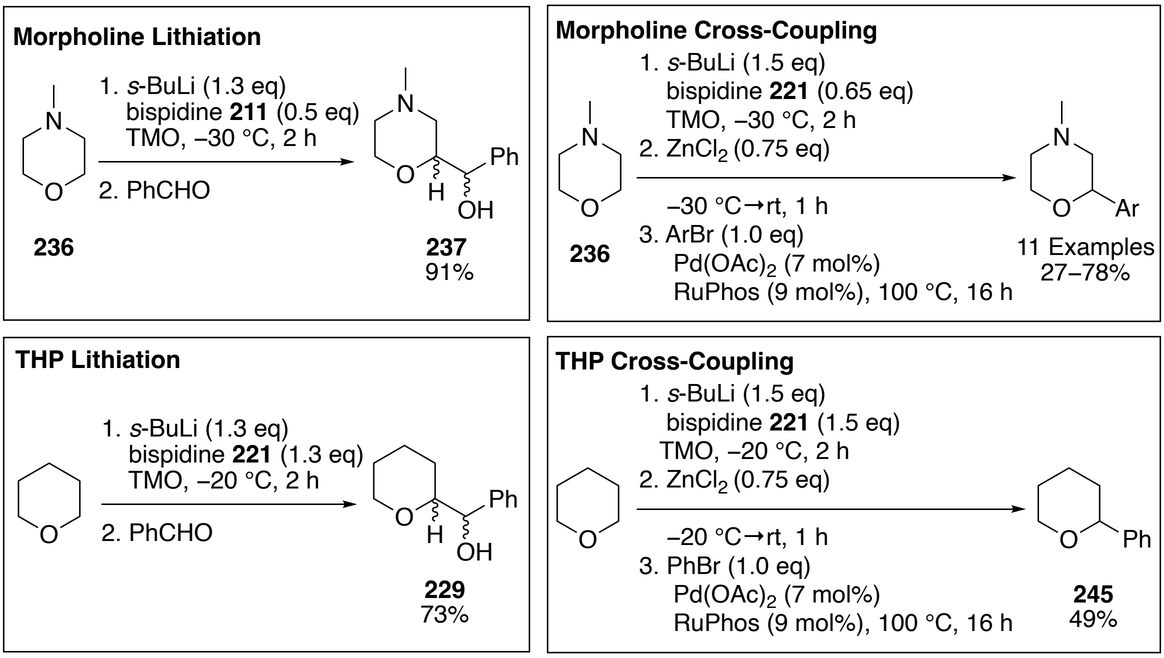


Figure 4.5: Summary of the lithiation-trapping and Negishi cross-coupling of *O*-heterocycles in TMO

Unfortunately, the optimisation of THP Negishi cross-coupling was not possible due to time constraints. It is possible that, with future work, improved conditions from the Negishi cross-coupling reaction can be found. This would enable the synthesis of α-arylated THP in high yields. Additionally, the aryl bromide scope could be investigated. Furthermore, THF is another substrate of interest to the O'Brien group. It is envisaged that TMO can also facilitate the one-pot synthesis of α-arylated THF avoiding the use of stannane intermediates thus further expanding the substrate scope of this methodology in TMO. Lastly, a number of pharmaceutically-active compounds contain *O*-heterocycles. It would be of interest to apply the methodology that has been developed in TMO to the synthesis of these compounds of interest to showcase TMO’s potential to be used as a solvent within a medicinally-relevant process.

Chapter 5: Experimental

5.1 General Methods

All non-aqueous reactions were carried out under oxygen free Ar or N_2 using flame-dried glassware. Et_2O, THF, toluene and hexane were dry and obtained from a PureSolv dispenser. TMO was synthesised in-house following a literature procedure[44] and was distilled over CaH_2 and stored over 3 Å molecular sieves before use unless stated otherwise. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[232] Electrophiles Me_3SiCl, PhCONMe(OMe), PhCHO and all diamines used in lithiation reactions were distilled over CaH_2 before use. Aryl bromides and amines were used without further purification. Petrol ether refers to the fraction of petroleum ether boiling in the range 40−60 °C and was purchased in Winchester quantities. Brine refers to a saturated solution. Water is distilled water. Flash column chromatography was carried out using Sigma-Aldrich silica gel (220−440 mesh). Thin layer chromatography was carried out using Merck F254 aluminium-back silica plates and were visualised by UV (254 nm) or stained using aqueous acidic $KMnO_4$. Celite® 545 used for filtration was purchased from Sigma-Aldrich.

Proton (400 MHz) and carbon (101 MHz) NMR spectra were recorded on a Joel ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CDCl_3$ (δ_H 7.26 ppm) and $CDCl_3$ (δ_C 77.16 ppm, central line of triplet). Carbon NMR spectra were assigned using DEPT experiments. Coupling constants (J) are quoted in Hertz. Melting points were carried out on a Stuart SMP20 melting point apparatus. Boiling points given for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Electrospray low and high resonance mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line; 259 nm) and $[\alpha]_D$ given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph.

5.2 General Procedures

General Procedure A: Buchwald-Hartwig cross-coupling of aryl bromides with amines.

A flask charged with Pd(dba)$_2$, (±)-BINAP and a base (1.50 mmol, 1.50 equiv) was evacuated and placed under an N_2 atmosphere. A solution of aryl bromide (1.00 mmol, 1.00 equiv) in dry toluene or dry TMO (5 mL) was added followed by the amine (1.10 mmol, 1.10 equiv). The resulting mixture was stirred and heated at 110 °C for a specified time (16−72 h). The reaction mixture was then allowed to cool to rt, diluted with Et_2O (5 mL) and the solids removed by filtration through Celite®. The solids were washed with Et_2O (2 × 5 mL) and the filtrate was evaporated under reduced pressure to give the crude product.

General Procedure B: Diamine-free ring-opening/trapping of 2-MeTHF and TMO.

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.00 equiv) was added to the stirred solvent (7 mL) at a specified temperature and was stirred at this temperature for a specified time. PhCOCl (1.3 mmol, 183 mg, 1.00 equiv) was added dropwise to the stirred solution and the solution was allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure C: TMEDA-mediated ring-opening/trapping of 2-MeTHF and TMO.

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.00 equiv) was added to a stirred solution of TMEDA (1.30 mmol, 154 mg, 1.00 equiv) in solvent (7 mL) at a specified temperature and was stirred at this temperature for a specified time.

PhCOCl (1.3 mmol, 183 mg, 1.00 equiv) was added dropwise to the stirred solution and the resulting solution was allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure D: Diamine-free lithiation-trapping of *N*-Boc pyrrolidine 32.

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.3 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.0 equiv) in solvent (7 mL) at a specified temperature and was stirred for a specified time. Electrophile (2.00 mmol, 2.00 equiv) was added dropwise to the stirred solution and the resulting solution was allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure E: Ligand-mediated lithiation-trapping of *N*-Boc pyrrolidine 32.

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexane, 1.3 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **32** (1.0 equiv) and ligand (1.3 equiv) in solvent (5−7 mL) at −78 °C. The resulting solution was stirred for a specified time. Electrophile (2.00 equiv) was added dropwise and the resulting solution was allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure F: Lithiation-trapping of *N*-Boc piperazines.

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexane, 1.3 equiv) was added dropwise to a stirred solution of *N*-Boc piperazine and ligand (1.3 equiv) in solvent (5−7 mL) at −78 °C. The resulting solution was stirred for a specified time. PhCONMe(OMe) (1.30 equiv) was added dropwise and the resulting solution was allowed to warm to rt over 1 h. Saturated $NaHCO_{3(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure G: Lithiation-trapping of *O*-heterocycles.

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexanes, 1.3 equiv) was added dropwise to a stirred solution of *O*-heterocycle (1.0 equiv) and ligand (0.3−1.3 equiv) in solvent (4−7 mL) at a specified temperature and was stirred at this temperature for a specified time. PhCHO (2.0 equiv) was added dropwise to the stirred solution the resulting solution and was allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product.

General Procedure H: Negishi cross-coupling of *N*-methylmorpholine 236 – direct addition of catalyst.

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexanes, 1.3−2.3 equiv) was added dropwise to a stirred solution of *N*-methylmorpholine **236** (1.0−1.8 equiv) and ligand (0.9−1.5 equiv) in TMO (4−7 mL) at a specified temperature and was stirred at this temperature for a specified time. $ZnCl_2$ (0.7 M in THF) (0.6−1.3 equiv) was added to the stirred solution and was allowed to warm to rt over 1 h. Then, palladium precatalyst (7−10 mol%), ligand (9−14 mol%) and bromobenzene (1.0−1.3

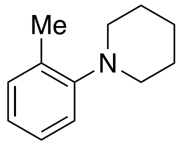
equiv) were added and the reaction mixture was stirred and heated at a specific temperature for a specified time. The resultant solution was allowed to cool to rt and the solids were removed by filtration through Celite® and washed with Et_2O (10 mL). The filtrate was washed with brine (10 mL) and water (2 × 10 mL). The two layers were separated and the organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product.

General Procedure I: Negishi cross-coupling of *N*-methylmorpholine 236 – Pre-mixing catalytic solution.

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv) was added dropwise to a stirred solution of *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv) and bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) at −30 °C and was stirred at this temperature for 2 h. $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 1.5 equiv) was added dropwise to the stirred solution and was allowed to warm to rt over 1 h. Then, the organozinc solution was transferred to stirred solution of $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and aryl bromide (1.0 equiv) in TMO (1 mL) dropwise and the reaction mixture was stirred and heated at 100 °C for 16 h. The resultant solution was allowed to cool to rt and the solids were removed by filtration through Celite® and washed with Et_2O (10 mL). The filtrate was washed with brine (10 mL) and water (2 × 10 mL). The two layers were separated and the organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product.

5.3 Experimental for Chapter 2

1-(2-Methylphenyl)piperidine 93

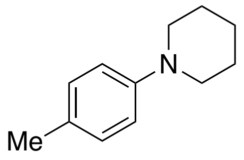


93

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.146 g, 1.50 mmol, 1.50 equiv), 2-bromotoluene (0.171 g, 1.00 mmol, 1.00 equiv) and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave 1-(2-methylphenyl)piperidine **93** (153 mg, 0.88 mmol, 88%, toluene) (143 mg, 0.82 mg, 0.82 mmol, 82%, TMO) as a yellow oil, $R_F = 0.4$ (99:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2931, 2851, 2789, 1599, 1490, 1450, 1378, 1225, 775, 721; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.24−7.20 (m, 2H, Ar), 7.08−7.06 (m, 1H, Ar), 7.04−7.00 (m, 1H, Ar), 2.91 (br t, J = 5.0 Hz, 4H, 2 × NCH$_2$), 2.38 (s, 3H, Me), 1.81−1.75 (m, 4H, NCH$_2$CH_2), 1.67−1.61 (m, 2H, CH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.1 (*ipso*-Ar), 132.8 (*ipso*-Ar), 131.0 (Ar), 126.5 (Ar), 122.7 (Ar), 119.1 (Ar), 53.5 (NCH$_2$), 26.8 (NCH$_2$$CH_2$), 24.6 (Me), 18.0 (CH$_2$); HRMS (ESI) *m*/*z* calc. for $C_{12}H_{17}N$ 176.1436 (M + H)$^+$; found 176.1433 (+0.3 ppm error). Spectroscopic data consistent with those reported in the literature.[233]

Lab Book Reference: BT1/6 and BT1/16

N-(4-Methylphenyl)piperidine 94

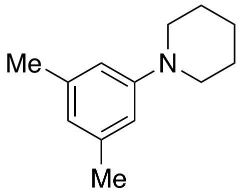


94

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.146 g, 1.50 mmol, 1.50 equiv), 4-bromotoluene (0.171 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave *N*-(4-methylphenyl)piperidine **94** (151 mg, 0.86 mmol, 86%, toluene) (133 mg, 0.76 mmol, 76%, TMO) as a dark yellow oil, $R_F = 0.3$ (99:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2931, 2854, 2804, 1617, 1504, 1451, 1236, 1130, 808, 698; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.08–7.04 (m, 2H, Ar), 6.88–6.85 (m, 2H, Ar), 3.10–3.08 (m, 4H, NCH$_2$), 2.27 (s, 3H, Me), 1.74–1.68 (m, 4H, NCH$_2$C*H*$_2$), 1.59–1.53 (m, 2H, CH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 150.4 (*ipso*-Ar), 129.7 (Ar), 128.9 (*ipso*-Ar), 117.1 (Ar), 51.5 (NCH$_2$), 26.1 (NCH$_2$*C*H$_2$), 24.4 (CH$_2$), 20.6 (Me); HRMS (ESI) *m*/*z* calc. for $C_{12}H_{17}N$ 176.1436 $(M + H)^+$; found 176.1434 (−1.2 ppm error). Spectroscopic data consistent with those reported in the literature.[234]

Lab Book Reference: BT1/2 and BT1/3

N-(3,5-Dimethylphenyl)piperidine 95

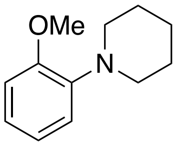


95

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.143 g, 1.50 mmol, 1.50 equiv), 1-bromo-3,5-dimethylbenzene (0.185 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave *N*-(3,5-dimethylphenyl)piperidine **95** (175 mg, 0.93 mmol, 93%, toluene) (179 mg, 0.94 mmol, 94%, TMO) as a pink oil, R_F = 0.8 (99:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2931, 2852, 2789, 1595, 1450, 1257, 1190, 825, 693; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.60–6.58 (m, 2H, Ar), 6.51–6.50 (m, 1H, Ar), 3.15–3.12 (m, 4H, NCH$_2$), 2.28 (s, 6H, Me) 1.74–1.68 (m, 4H, NCH$_2$C*H*$_2$), 1.60–1.54 (m, 2H, CH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 152.6 (*ipso*-Ar), 138.6 (*ipso*-Ar), 121.4 (Ar), 114.7 (Ar), 51.0 (NCH$_2$), 26.1 (NCH$_2$*C*H$_2$), 24.5 (Me), 21.8 (CH$_2$); HRMS (ESI) *m*/*z* calc. for $C_{13}H_{19}N$: 190.1590 $(M + H)^+$; found 190.1587 (+2.0 ppm error). Spectroscopic data consistent with those reported in the literature.[235]

Lab Book Reference: BT1/11 and BT1/25

1-(2-Methoxyphenyl)piperidine 96



96

Scheme 2.23

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave 1-(2-methoxyphenyl)piperidine **96** (188 mg, 0.98 mmol, 98%, toluene) (182 mg, 0.95 mmol, 95%, TMO) as a red oil, R_F = 0.2 (99:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2931, 2850, 2801, 1595, 1497, 1449, 1238, 1126, 1026, 918, 729; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.00−6.95 (m, 2H, Ar), 6.93−6.89 (m, 1H, Ar), 6.86−6.84 (m, 1H, Ar), 3.87 (s, 3H, OMe), 2.98 (br t, *J* = 5.0 Hz, 4H, NCH$_2$), 1.79−1.73 (m, 4H, NCH$_2$C*H*$_2$), 1.60−1.54 (m, 2H, CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.5 (*ipso*-Ar), 142.9 (*ipso*-Ar), 122.6 (Ar), 121.0 (Ar), 118.5 (Ar), 111.1 (Ar), 55.5 (OMe), 52.4 (NCH$_2$), 26.4 (NCH$_2$*C*H$_2$), 24.6 (CH$_2$); HRMS (ESI) *m/z* calc. for $C_{12}H_{17}NO$: 192.1383 (M + H)$^+$; found 192.1387 (−2.3 ppm error). Spectroscopic data consistent with those reported in the literature.[236]

Lab Book Reference: BT1/8 and BT1/12

Table 2.4, entry 1

Following general procedure A, Pd(dba)$_2$ (0.006 g, 0.010 mmol, 0.10 equiv), (±)-BINAP (0.009 g, 0.015 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10

equiv) dry TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave 1-(2-methoxyphenyl)piperidine **96** (155 mg, 0.81 mmol, 81%) as a red oil.

Lab Book Reference: BT1/38

Table 2.4, entry 2

Following general procedure A, Pd(dba)$_2$ (0.003 g, 0.005 mmol, 0.05 equiv), (±)-BINAP (0.005 g, 0.008 mmol, 0.08 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) dry TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave 1-(2-methoxyphenyl)piperidine **96** (96 mg, 0.50 mmol, 50%) as a red oil.

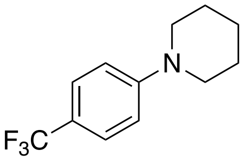
Lab Book Reference: BT1/78

Table 2.4, entry 3

Following general procedure A, Pd(dba)$_2$ (0.0014 g, 0.0025 mmol, 0.025 equiv), (±)-BINAP (0.0024 g, 0.0038 mmol, 0.038 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) dry TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave 1-(2-methoxyphenyl)piperidine **96** (10 mg, 0.05 mmol, 5%) as a red oil.

Lab Book Reference: BT1/74

1-(4-(Trifluoromethyl)phenyl)piperidine 97

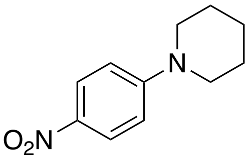


97

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 4-bromobenzotrifluoride (0.225 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave 1-(4-(trifluoromethyl)phenyl)piperidine **97** (193 mg, 0.84 mmol, 84%, toluene) (199 mg, 0.87 mmol, 87%, TMO) as a yellow oil, $R_F = 0.7$ (99:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2938, 2857, 2816, 1614, 1523, 1325, 1237, 1125, 1068, 819, 631; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47–7.44 (m, 2H, Ar), 6.93–6.90 (m, 2H, Ar), 3.27 (br t, J = 5.0 Hz, 4H, NCH$_2$), 1.72–1.67 (m, 4H, NCH$_2$C*H*$_2$), 1.65–1.59 (m, 2H, CH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.9 (*ipso*-Ar), 126.4 (q, J_{C-F} = 4.0 Hz, Ar), 125.0 (q, J_{C-F} = 270.5 Hz, CF$_3$), 119.7 (q, J_{C-F} = 32.5, *ipso*-Ar), 114.7 (Ar), 49.4 (NCH$_2$), 25.6 (NCH$_2$*C*H$_2$), 24.41 (CH$_2$); HRMS (ESI) *m/z* calc. for $C_{12}H_{15}F_3N$: 230.1151 (M + H)$^+$; found 230.1136 (+6.7 ppm error). Spectroscopic data consistent with those reported in the literature.[237]

Lab Book Reference: BT1/9 and BT1/13

1-(4-Nitrophenyl)piperidine 98



98

Scheme 2.23

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 1-(4-nitrophenyl)piperidine **98** (114 mg, 0.55 mmol, 55%, toluene) (105 mg, 0.51 mmol, 51%, TMO) as a yellow crystalline solid, mp 101–103 °C (lit.,[238] 101–103 °C); R_F = 0.4 (9:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2946, 2841, 1593, 1578, 1473, 1448, 1309 (NO$_2$) , 1246, 1200, 1107, 816, 745; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.12–8.08 (m, 2H, Ar), 6.81–6.77 (m, 2H, Ar), 3.45–3.43 (m, 4H, NCH$_2$), 1.70–1.67 (m, 6H, CH$_2$CH$_2$CH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.0 (*ipso*-Ar), 131.9 (*ipso*-Ar), 126.3 (Ar), 112.5 (Ar), 48.5 (NCH$_2$), 25.4 (NCH$_2$*C*H$_2$), 24.4 (CH$_2$); HRMS (ESI) *m/z* calc. for $C_{11}H_{14}N_2O_2$: 207.1128 (M + H)$^+$; found 207.1124 (+1.9 ppm error). Spectroscopic data consistent with those reported in the literature.[238]

Lab Book Reference: BT1/7 and BT1/15

Table 2.2, entry 1

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), Cs$_2$CO$_3$ (0.488 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10

equiv) in dry TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 1-(4-nitrophenyl)piperidine **98** (61 mg, 0.30 mmol, 30%) as a yellow crystalline solid.

Lab Book Reference: BT1/23

Table 2.2, entry 2

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), Cs_2CO_3 (0.488 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry TMO (5 mL) at 110 °C for 72 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 1-(4-nitrophenyl)piperidine **98** (155 mg, 0.75 mmol, 75%) as a yellow crystalline solid.

Lab Book Reference: BT2/1

Table 2.2, entry 3

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), Cs_2CO_3 (0.488 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 1-(4-nitrophenyl)piperidine **98** (103 mg, 0.50 mmol, 50%) as a yellow crystalline solid.

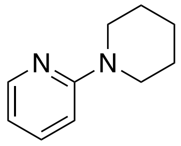
Lab Book Reference: BT1/37

Figure 2.3

Following general procedure A, $Pd(dba)_2$ (0.006 g, 0.010 mmol, 0.10 equiv), (±)-BINAP (0.009 g, 0.015 mmol, 0.15 equiv), Cs_2CO_3 (0.488 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) dry TMO (5 mL) at 110 °C for 72 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 1-(4-nitrophenyl)piperidine **98** (152 mg, 0.74 mmol, 74%) as a yellow crystalline solid.

Lab Book Reference: BT1/64

2-(Piperidin-1-yl)pyridine 99



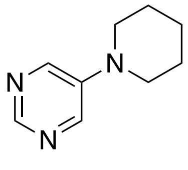
99

Following general procedure A, $Pd(dba)_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromopyridine (0.158 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (49:1 petrol ether:EtOAc) gave 2-(piperidine-1-yl)pyridine **99** (121 mg, 0.75 mmol, 75%, toluene) (123 mg, 0.76 mmol, 76%, TMO) as a yellow oil, R_F = 0.2 (49:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2931, 2852, 1592, 1480, 1334, 1250, 977, 767; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18–8.16 (m, 1H, Ar), 7.46–7.41 (m, 1H, Ar), 6.65–6.63 (m, 1H, Ar), 6.57–6.53 (m, 1H, Ar), 3.53–3.51 (m, 4H, NCH_2), 1.65–1.63 (m, 6H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (*ipso*-Ar), 147.7 (Ar), 137.1 (Ar), 112.2 (Ar), 107.0 (Ar), 46.1 (NCH_2), 25.3 (NCH_2CH_2), 24.5 (CH_2); HRMS (ESI) *m*/*z* calc. for $C_{10}H_{14}N_2$:

163.1230 $(M + H)^+$; found 163.1227 (+1.4 ppm error). Spectroscopic data consistent with those reported in the literature.[239]

Lab Book Reference: BT1/48 and BT1/70

5-(Piperidin-1-yl)pyrimidine 100

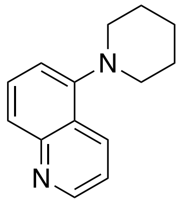


100

Following general procedure A, $Pd(dba)_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 5-bromopyrimidine (0.159 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (EtOAc) gave 5-(piperidin-1-yl)pyrimidine **100** (123 mg, 0.75 mmol, 75%, toluene), (127 mg, 0.78 mmol, 78%. TMO) as a yellow oil, $R_F = 0.3$ (EtOAc); ν_{max}/cm^{-1} 3047, 2934, 2853, 1563, 1436, 1248, 1114, 1022, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H, Ar), 8.34 (s, 2H, Ar), 3.24–3.21 (m, 4H, NCH_2), 1.74–1.68 (m, 4H, NCH_2CH_2), 1.64–1.60 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1 (Ar), 144.9 (*ipso*-Ar), 143.8 (Ar), 48.8 (NCH_2), 25.3 (NCH_2CH_2), 24.0 (CH_2); HRMS (ESI) *m*/*z* calc. for $C_9H_{13}N_3$: 164.1182 $(M + H)^+$; found 164.1182 (−0.6 ppm error). Spectroscopic data consistent with those reported in the literature.[240]

Lab Book Reference: BT2/86 and BT3/4

5-(Piperidin-1-yl)quinoline 101



101

Scheme 2.23

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 5-bromoquinoline (0.208 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (4:1 Pet Ether:EtOAc) gave 5-(piperidin-1-yl)quinoline **101** (171 mg, 0.80 mmol, 80%, toluene) (167 mg, 0.79 mmol, 79%, TMO) as a yellow oil, R_F = 0.2 (4:1 Pet Ether:EtOAc); ν_{max}/cm^{-1} 3062, 2932, 2851, 2802, 1571, 1396, 1243, 1087, 1000, 795; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.87 (dd, *J* = 4.0, 2.0 Hz, 1H, Ar), 8.50 (ddd, *J* = 8.5, 2.0, 1.0 Hz, 1H, Ar), 7.77 (ddd, *J* = 8.5, 1.0, 1.0 Hz, 1H, Ar), 7.61 (dd, *J* = 8.5, 7.5 Hz, 1H, Ar), 7.37 (dd, *J* = 8.5, 4.0 Hz, 1H, Ar), 7.09 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar) 3.09–2.98 (m, 4H, NCH$_2$), 1.84 (quin, *J* = 5.5 Hz, 4H, NCH$_2$C*H*$_2$), 1.69–1.63 (m, 2H, CH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 151.3 (*ipso*-Ar), 150.1 (Ar), 149.6 (*ipso*-Ar), 132.7 (Ar), 129.6 (Ar), 124.4 (*ipso*-Ar), 124.2 (Ar), 120.2 (Ar), 115.0 (Ar), 54.9 (NCH$_2$), 26.7 (NCH$_2$*C*H$_2$), 24.6 (CH$_2$); HRMS (ESI) *m*/*z* calc. for $C_{14}H_{16}N_2$: 213.1386 (M + H)$^+$; found 213.1390 (+2.1 ppm error). Spectroscopic data consistent with those reported in the literature.[241]

Lab Book Reference: BT2/87 and BT3/5

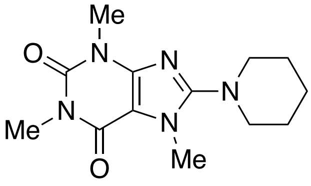
Figure 2.3

Following general procedure A, Pd(dba)$_2$ (0.006 g, 0.010 mmol, 0.10 equiv), (±)-BINAP (0.009 g, 0.015 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 5-

bromoquinoline (0.208 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) dry TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (4:1 petrol ether:EtOAc) gave 5-(piperidin-1-yl)quinoline **101** (169 mg, 0.79 mmol, 79%) as a yellow oil.

Lab Book Reference: BT4/21

1,3,7-Trimethyl-8-(piperidin-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione 102

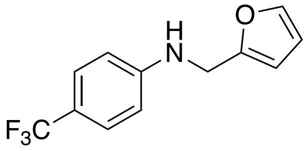


102

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 8-bromocaffeine (0.273 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (1:1 Pet Ether:EtOAc) gave 1,3,7-trimethyl-8-(piperidin-1-yl)-3,7-dihydro-1*H*-purine-2-6-dione **102** (121 mg, 0.44 mmol, 44%, toluene) (134 mg, 0.48 mmol, 48%, TMO) as an off-white solid, mp 134–136 °C; R_F = 0.2 (1:1 Pet Ether:EtOAc); ν_{max}/cm^{-1} 2989, 2941, 2854, 1693 (C=O), 1650 (C=O), 1508, 1435, 1219, 1030, 974, 902, 754; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.72 (s, 3H, NMe), 3.52 (s, 3H, NMe), 3.38 (s, 3H, NMe), 3.22–3.19 (m, 4H, NCH$_2$), 1.74–1.69 (m, 4H, NCH$_2$C*H*$_2$), 1.66–1.62 (m, 2H, CH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.5 (C=O or *ipso*-Ar), 155.1 (C=O or *ipso*-Ar), 152.0 (C=O or *ipso*-Ar), 147.2 (C=O or *ipso*-Ar), 51.0 (NCH$_2$), 32.8 (NMe), 29.8 (NMe), 27.9 (NMe), 25.4 (NCH$_2$*C*H$_2$), 24.2 (CH$_2$) (1 C=O or *ipso*-Ar resonance not resolved); HRMS (ESI) *m*/*z* calc. for $C_{13}H_{19}N_5O_2$: 278.1612 (M + H)$^+$; found 278.1612 (+0.4 ppm error).

Lab Book Reference: BT2/90 and BT3/3

N-(Furan-2-ylmethyl)-4-(trifluoromethyl)aniline 103



103

Scheme 2.24

Following general procedure A, Pd(dba)$_2$ (0.057 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.146 g, 1.50 mmol, 1.50 equiv), 4-bromobenzotrifluoride (0.225 g, 1.00 mmol, 1.00 equiv), and furfurylamine (0.107 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave *N*-(furan-2-ylmethyl)-4-(trifluoromethyl)aniline **103** (189 mg, 0.78 mmol, 78%, toluene) (238 mg, 0.98 mmol, 98%, TMO) as an off-white solid, mp 44–47 °C; R$_f$ = 0.5 (9:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3423 (NH), 2925, 1614, 1530, 1318, 1125, 1061, 819, 724; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, *J* = 9.0 Hz, 2H, Ar), 7.39−7.38 (m, 1H, Ar), 6.68 (d, *J* = 9.0 Hz, 2H, Ar), 6.34 (dd, *J* = 3.0, 2.0 Hz, 1H, Ar), 6.26 (d, *J* = 3.0 Hz, 1H, Ar), 4.36 (br s, 3H, NCH$_2$ and NH); ^{13}C NMR (101 MHz, CDCl$_3$) δ 151.9 (*ipso*-Ar), 150.1 (*ipso*-Ar), 142.3 (Ar), 126.7 (q, $J_{C–F}$ = 4.0 Hz, Ar), 125.0 (q, $J_{C–F}$ = 270.0 Hz, CF$_3$), 119.5 (q, $J_{C–F}$ = 32.5 Hz, *ipso*-Ar), 112.6 (Ar), 110.5 (Ar), 107.5 (Ar), 41.0 (NCH$_2$); HRMS (ESI) *m*/*z* for $C_{12}H_{10}F_3NO$: 242.0787 (M + H)$^+$; found 242.0777 (+4.1 ppm error). Spectroscopic data consistent with those reported in the literature.[242]

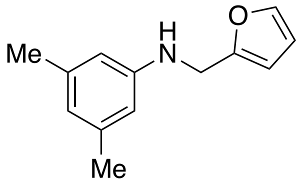
Lab Book Reference: BT1/44 and BT1/50

Figure 2.3

Following general procedure A, $Pd(dba)_2$ (0.006 g, 0.010 mmol, 0.10 equiv), (±)-BINAP (0.009 g, 0.015 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 4-bromobenzotrifluoride (0.225 g, 1.00 mmol, 1.00 equiv), and furfurylamine (0.107 g, 1.10 mmol, 1.10 equiv) dry TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave *N*-(furan-2-ylmethyl)-4-(trifluoromethyl)aniline **103** (208 mg, 0.86 mmol, 86%) as an off-white solid.

Lab Book Reference: BT4/22

N-(Furan-2-ylmethyl)-3,5-dimethylaniline 104



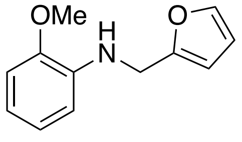
104

Following general procedure A, $Pd(dba)_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.146 g, 1.50 mmol, 1.50 equiv), 1-bromo-3,5-dimethylbenzene (0.185 g, 1.00 mmol, 1.00 equiv), and furfurylamine (0.107 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography on silica gel (99:1 petrol ether:EtOAc) gave *N*-(furan-2-ylmethyl)-3,5-dimethylaniline **104** (194 mg, 0.96 mmol, 96%, toluene) (163 mg, 0.81 mmol, 81%, TMO) as a yellow oil, $R_F = 0.3$ (49:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3409 (NH), 2916, 2857, 1600, 1504, 1331, 1182, 821, 729, 688; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.37 (m, 1H, Ar), 6.43–6.42 (m, 1H, Ar), 6.34–6.33 (m, 3H, Ar), 6.25–6.23 (m, 1H, Ar), 4.31 (s, 2H, NCH_2), 3.91 (br s, 1H, NH), 2.26 (s, 6H, Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (*ipso*-Ar), 147.9 (*ipso*-Ar), 142.0 (Ar), 139.0 (*ipso*-Ar), 120.2 (Ar), 111.2 (Ar), 110.4 (Ar), 107.0 (Ar), 41.6 (NCH_2), 21.6 (Me); HRMS (ESI) *m*/*z* for $C_{12}H_{15}NO$: 202.1226 (M +

H)$^+$; found 202.1226 (+0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[243]

Lab Book Reference: BT1/43 and BT1/51

N-Furfuryl-*o*-anisidine 105

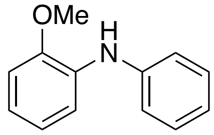


105

Following general procedure A, Pd(dba)$_2$ (0.057 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv), and furfurylamine (0.107 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (99:1 petrol ether:EtOAc) gave *N*-furfuryl-*o*-anisidine **105** (193 mg, 0.95 mmol, 95%, toluene) (194 mg, 0.95 mmol, 95%, TMO) as a yellow oil, R_F = 0.3 (49:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3421 (NH), 2936, 2834, 1601, 1508, 1455, 1246, 1220, 1124, 708; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40–7.49 (m, 1H, Ar), 6.90 (td, *J* = 7.5, 1.0 Hz, 1H, Ar), 6.82–6.80 (m, 1H, Ar), 6.76–6.71 (m, 2H, Ar), 6.35–6.34 (m, 1H, Ar), 6.28–6.27 (m, 1H, Ar), 4.66 (br s, 1H, NH), 4.37 (s, 2H, NCH$_2$), 3.87 (s 3H, OMe); ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.0 (*ipso*-Ar), 147.1 (*ipso*-Ar), 142.0 (Ar), 137.7 (*ipso*-Ar), 121.3 (Ar), 117.2 (Ar), 110.4 (Ar), 110.3 (Ar), 109.6 (Ar), 107.0 (Ar), 55.5 (OMe), 41.2 (NCH$_2$); HRMS (ESI) *m*/*z* calc. for $C_{12}H_{13}NO_2$: 204.1019 (M + H)$^+$; found 204.1019 (+0.2 ppm error).

Lab Book Reference: BT1/45 and BT1/58

2-Methoxy-*N*-phenylaniline 106

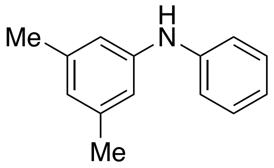


106

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.145 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.188 g, 1.00 mmol, 1.00 equiv), and aniline (0.102 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (49:1 petrol ether:EtOAc) gave 2-methoxy-*N*-phenylaniline **106** (185 mg, 0.93 mmol, 93%, toluene) (183 mg, 0.92 mmol, 92%, TMO) as a pale yellow oil, R_F = 0.2 (49:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3405 (NH), 3046, 2936, 2833, 1589, 1512, 1495, 1230, 114, 743, 691; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32–7.24 (m, 3H, Ar), 7.16–7.14 (m, 2H, Ar), 6.96–6.92 (m, 1H, Ar), 6.90–6.83 (m, 3H, Ar), 6.15 (br s, 1H, NH), 3.89 (s, 3H, OMe); ^{13}C NMR (101 MHz, CDCl$_3$) δ 148.4 (*ipso*-Ar), 142.8 (*ipso*-Ar), 133.1 (*ipso*-Ar), 129.4 (Ar), 121.3 (Ar), 120.9 (Ar), 120.0 (Ar), 118.7 (Ar), 114.7 (Ar), 110.6 (Ar), 55.7 (OMe); HRMS (ESI) *m*/*z* calc. for $C_{13}H_{13}NO$: 200.1070 (M + H)$^+$; found 200.1072 (−0.9 ppm error). Spectroscopic data consistent with those reported in the literature.[244]

Lab Book Reference: BT2/32 and BT2/38

N-(3,5-Dimethylphenyl)aniline 107

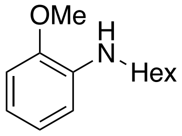


107

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.145 g, 1.50 mmol, 1.50 equiv), 1-bromo-3,5-dimethylbenzene (0.185 g, 1.00 mmol, 1.00 equiv), and aniline (0.102 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (49:1 petrol ether:EtOAc) gave *N*-(3,5-dimethylphenyl)aniline **107** (191 mg, 0.97 mmol, 97%, toluene) (192 mg, 0.98 mmol, 98%, TMO) as a pale brown solid, mp 51−52 °C (lit.,[245] 52−53 °C); R_F = 0.2 (49:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3383 (NH), 3024, 2913, 2853, 1583, 1495, 1326, 1168, 843, 692; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29−7.24 (m, 2H, Ar), 7.08−7.06 (m, 2H, Ar), 6.94−6.90 (m, 1H, Ar), 6.72 (s, 2H, Ar), 6.60 (s, 1H, Ar), 5.62 (br s, 1H, NH), 2.28 (s, 6H, Me); ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.4 (*ipso*-Ar), 143.2 (*ipso*-Ar), 139.2 (*ipso*-Ar), 129.4 (Ar), 123.0 (Ar), 120.9 (Ar), 118.0 (Ar), 115.7 (Ar), 21.6 (Me); HRMS (ESI) *m*/*z* calc. for $C_{14}H_{15}N$: 198.1277 (M + H)$^+$; found 198.1279 (−1.0 ppm error). Spectroscopic data consistent with those reported in the literature.[245]

Lab Book Reference: BT2/33 and BT2/39

N-(2-Methoxyphenyl)hexylamine 108

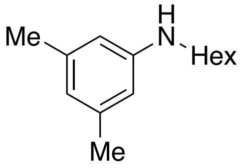


108

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv), and hexylamine (0.101 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (49:1 petrol ether:EtOAc) gave *N*-(2-methoxyphenyl)hexylamine **108** (190 mg, 0.91 mmol, 91%, toluene) (178 mg, 0.86 mmol, 86%, TMO) as a yellow oil, R_F = 0.2 (49:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3425 (NH), 2954, 2926, 2856, 1602, 1511, 1454, 1219, 1029, 734; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.90–6.86 (m, 1H, Ar), 6.78–6.76 (m, 1H, Ar), 6.68–6.64 (m, 1H, Ar), 6.62–6.61 (m, 1H, Ar), 4.17 (br s, 1H, NH), 3.85 (s, 3H, OMe), 3.12 (t, J = 7.0 Hz, 2H, NHCH_2), 1.70–1.62 (m, 2H, CH$_2$), 1.46–1.41 (m, 2H, CH$_2$), 1.35–1.30 (m, 4H, 2 × CH$_2$), 0.91 (t, J = 6.0 Hz, 3H, Me); ^{13}C NMR (101 MHz, CDCl$_3$) δ 146.8 (*ipso*-Ar), 138.6 (*ipso*-Ar), 121.4 (Ar), 116.2 (Ar), 109.9 (Ar), 109.4 (Ar), 55.5 (OMe), 43.9 (NH*C*H$_2$), 31.8 (CH$_2$), 29.6 (CH$_2$), 27.1 (CH$_2$), 22.8 (CH$_2$), 14.2 (Me); HRMS (ESI) *m*/*z* calc. for $C_{13}H_{21}NO$: 208.1696 (M + H)$^+$; found 208.1696 (+0.2 ppm error). Spectroscopic data consistent with those reported in the literature.[246]

Lab Book Reference: BT2/36 and BT2/42

3,5-Dimethyl-*N*-hexylaniline 47

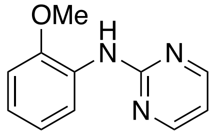


47

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 1-bromo-3,5-dimethylbenzene (0.185 g, 1.00 mmol, 1.00 equiv), and hexylamine (0.101 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (49:1 petrol ether:EtOAc) gave 3,5-dimethyl-*N*-hexylaniline **47** (167 mg, 0.82 mmol, 82%, toluene) (174 mg, 0.85 mmol, 85%, TMO) as a yellow oil, $R_F = 0.2$ (49:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3411 (NH), 2955, 2924, 2855, 1600, 1511, 1336, 1185, 818, 689; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.36 (s, 1H, Ar), 6.25 (s, 2H, Ar), 3.49 (br s, 1H, NH), 3.09 (t, J = 7.0 Hz, 2H, NHCH_2), 2.24 (s, 6H, Me), 1.64–1.57 (m, 2H, CH$_2$), 1.43–1.36 (m, 2H, CH$_2$), 1.34–1.30 (m, 4H, CH$_2$), 0.91 (t, J = 6.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, CDCl$_3$) δ 148.8 (*ipso*-Ar), 139.0 (*ipso*-Ar), 119.2 (Ar), 110.8 (Ar), 44.2 (CH$_2$), 31.8 (CH$_2$), 29.7 (CH$_2$), 27.0 (CH$_2$), 22.8 (CH$_2$), 21.6 (Ar*Me*), 14.2 (Me); HRMS (ESI) *m*/*z* calc. for $C_{14}H_{23}N$: 206.1903 (M + H)$^+$; found 206.1908 (−2.5 ppm error). Spectroscopic data consistent with those reported in the literature.[243]

Lab Book Reference: BT2/37 and BT2/43

(2-Methoxy-phenyl)-pyrimidin-2-yl-amine 109

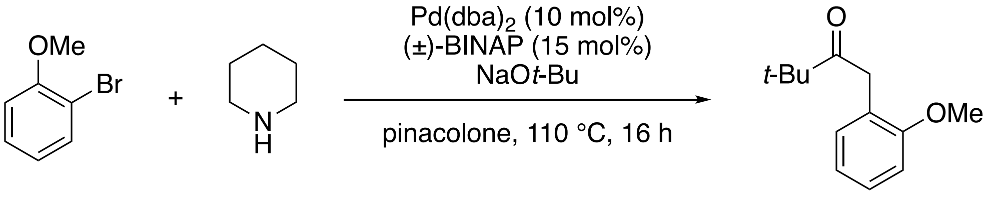


109

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv) and 2-aminopyrimidine (0.105 g, 1.1 mmol, 1.1 equiv) in dry toluene or TMO (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (4:1 petrol ether: EtOAc) gave (2-methoxy-phenyl)-pyrimidin-2-yl-amine **109** (198 mg, 0.98 mmol, 98%, toluene) (192 mg, 0.95 mmol, 95%, TMO) as a pale yellow solid, mp 57−58 °C (lit.,[247] 56.0−57 °C); R_F = 0.4 (4:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3397 (NH), 3038, 2999, 2837, 1595, 1569, 1520, 1429, 1242, 1022, 793, 745; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51–8.48 (m, 1H, Ar), 8.43 (d, *J* = 5.0 Hz, 2H, Ar), 7.77 (br s, 1H, NH), 7.03–6.96 (m, 2H, Ar), 6.91–6.89 (m, 1H, Ar), 6.70 (t, *J* = 5.0 Hz, 1H, Ar), 3.90 (s, 3H, OMe); ^{13}C NMR (101 MHz, CDCl$_3$) δ 160.2 (*ipso*-Ar), 158.0 (Ar), 148.0 (*ipso*-Ar), 129.3 (*ipso*-Ar), 121.9 (Ar), 121.0 (Ar), 118.6 (Ar), 112.5 (Ar), 110.0 (Ar), 55.8 (OMe); HRMS (ESI) *m*/*z* calc. for $C_{11}H_{10}N_3O$: 202.0975 (M + H)$^+$; found 202.0977 (−1.1 ppm error). Spectroscopic data consistent with those reported in the literature.[247]

Lab Book Reference: BT4/82 and BT4/88

Attempted Buchwald-Hartwig Cross-Coupling Using Pinacolone as Solvent

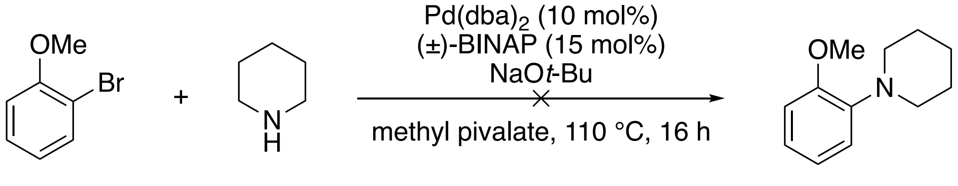


111

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry pinacolone (5 mL) at 110 °C for 16 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 2-methoxyphenylpinacolone **111** (170 mg, 0.83 mmol, 83%, toluene) as a white crystalline solid, mp 38−39 °C (lit.,[116] 34−35 °C); $R_F = 0.5$ (19:1 petrol ether:EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23 (td, J = 7.5. 1.5 Hz, 1H, Ar), 7.08 (dd, J = 7.5, 1.5 Hz, 1H, Ar), 6.93−6.89 (m, 1H, Ar), 6.85 (d, J = 8.0 Hz, 1H, Ar), 3.79 (s, 2H, CH$_2$), 3.76 (s, 3H, OMe), 1.24 (s, 9H, CMe$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 213.4 (C=O), 157.3 (*ipso*-Ar), 131.5 (Ar), 128.2 (Ar), 124.4 (*ipso*-Ar), 120.6 (Ar), 110.4 (Ar), 55.4 (CH$_2$), 44.7 (*C*Me$_3$), 38.4 (OMe), 26.7 (C*Me*$_3$); HRMS (ESI) *m*/*z* calc. for $C_{13}H_{18}O_2$: 207.1381 (M + H)$^+$; found 207.1380 (−0.9 ppm error). Spectroscopic data consistent with those reported in the literature.[116]

Lab Book Reference: BT1/83

Attempted Buchwald-Hartwig Cross-Coupling Using Methyl Pivalate as Solvent

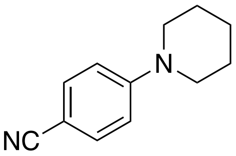


96

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv), 2-bromoanisole (0.187 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry methyl pivalate (5 mL) at 110 °C for 16 h gave the crude product. None of tertiary amine **96** was observed in the ^{1}H NMR spectrum of the crude product and therefore purification was not attempted.

Lab Book Reference: BT1/84

4-(Piperidin-1-yl)benzonitrile 113



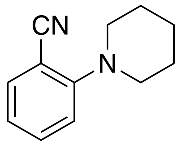
113

Following general procedure A, Pd(dba)$_2$ (0.057 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), Cs$_2$CO$_3$ (0.489 g, 1.50 mmol, 1.50 equiv), 4-bromobenzonitrile (0.182 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 72 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 4-(piperidine-1-yl)benzonitrile **113** (106 mg, 0.57 mmol, 57%, toluene) (147 mg, 0.79 mmol, 79%, TMO) as an off-white solid, mp 57–58 °C (lit.,[248] 57–59 °C); R_F = 0.4 (9:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2938, 2848, 2822, 2215 (CN), 1602, 1512, 1448, 1246, 1179, 1123, 805; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48–7.44 (m, 2H, Ar), 6.85–6.82 (m, 2H, Ar), 3.33–3.31 (m, 4H,

NCH_2), 1.69–1.63 (m, 6H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (*ipso*-Ar), 133.6 (Ar), 120.5 (*ipso*-Ar), 114.2 (Ar), 99.1 (CN), 48.6 (NCH_2), 25.4 (NCH_2CH_2), 24.4 (CH_2); HRMS (ESI) *m*/*z* calc. for $C_{12}H_{14}N_2$: 187.1230 $(M + H)^+$; found 187.1231 (−0.9 ppm error). Spectroscopic data consistent with those reported in the literature.[248]

Lab Book Reference: BT1/20 and BT1/22

2-(Piperidin-1-yl)benzonitrile 114

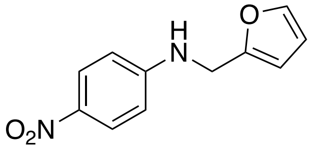


114

Following general procedure A, $Pd(dba)_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv), Cs_2CO_3 (0.489 g, 1.50 mmol, 1.50 equiv), 2-bromobenzonitrile (0.182 g, 1.00 mmol, 1.00 equiv), and piperidine (0.094 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 72 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 2-(piperidine-1-yl)benzonitrile **114** (116 mg, 62 mmol, 62%, toluene) (144 mg, 0.78 mmol, 78%, TMO) as a yellow oil. $R_F = 0.6$ (9:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 2935, 2853, 2811, 2218 (CN), 1594, 1486, 1446, 1233, 924, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.52 (m, 1H, Ar), 7.47–7.42 (m, 1H, Ar), 7.00–6.92 (m, 2H, Ar), 3.16 (br t, $J = 5.0$ Hz, 4H, NCH_2), 1.80–1.75 (m, 4H, NCH_2CH_2), 1.63–1.57 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (*ipso*-Ar), 134.4 (Ar), 133.7 (Ar), 121.1 (Ar), 118.8 (Ar), 106.0 (CN), 53.2 (CH_2), 26.2 (CH_2), 24.2 (CH_2) (1 *ipso*-Ar resonance not resolved); HRMS (ESI) *m*/*z* calc. for $C_{12}H_{14}N_2$: 187.1230 $(M + H)^+$; found 187.1227 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.[249]

Lab Book Reference: BT1/62 and BT1/71

Furan-2-ylmethyl-(-4-nitrophenyl)amine 115



115

Scheme 2.26

Following general procedure A, Pd(dba)$_2$ (0.056 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.097 g, 0.15 mmol, 0.15 equiv), Cs$_2$CO$_3$ (0.489 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and furfurylamine (0.107 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 24 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave furan-2-ylmethyl-(-4-nitrophenyl)amine **115** (108 mg, 0.50 mmol, 50%, toluene) (164 mg, 0.75 mmol, 75%, TMO) as a yellow solid, mp 107–108 °C (lit.,[250] 104–105 °C); *R*$_F$ = 0.5 (19:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3355 (NH), 2934, 1598, 1475, 1297, 1250 (NO$_2$), 1104, 828, 750; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.10 (dd, *J* = 9.0, 2.0 Hz, 2H, Ar), 7.39–7.38 (m, 1H, Ar), 6.62 (dd, *J* = 9.0, 2.0 Hz, 2H, Ar), 6.36–6.34 (m, 1H, Ar), 6.28–6.27 (m, 1H, Ar), 4.84 (br s, 1H, NH), 4.41 (d, *J* = 5.5 Hz, 2H, NCH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 152.7 (*ipso*-Ar), 150.8 (*ipso*-Ar), 142.7 (Ar), 126.5 (Ar), 125.9 (*ipso*-Ar), 111.8 (Ar), 110.7 (Ar), 108.0 (Ar), 40.8 (NCH$_2$); HRMS (ESI) *m/z* calc. for $C_{11}H_{10}N_2O_3$: 219.0764 (M + H)$^+$; found 219.0761 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.[250]

Lab Book Reference: BT1/29 and BT1/34

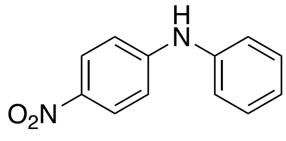
Figure 2.3

Following general procedure A, Pd(dba)$_2$ (0.006 g, 0.010 mmol, 0.10 equiv), (±)-BINAP (0.009 g, 0.015 mmol, 0.15 equiv), Cs$_2$CO$_3$ (0.488 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and furfurylamine (0.107 g, 1.10 mmol, 1.10

equiv) dry TMO (5 mL) at 110 °C for 72 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave furan-2-ylmethyl-(-4-nitrophenyl)amine **115** (151 mg, 0.69 mmol, 69%) as a yellow solid.

Lab Book Reference: BT4/19

4-Nitrophenyl(phenyl)amine 116

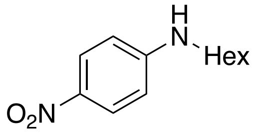


116

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), Cs_2CO_3 (0.488 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and aniline (0.102 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 72 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 4-nitrophenyl(phenyl)amine **116** (117 mg, 0.55 mmol, 55%, toluene) (173 mg, 0.81 mmol, 81%, TMO) as a yellow solid, mp 129–131 °C (lit.,[238] 131–133 °C); R_F = 0.1 (9:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3338 (NH), 3040, 1601, 1579, 1247 (NO_2), 1183, 1097, 775, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.10 (m, 2H, Ar), 7.42–7.37 (m, 2H, Ar), 7.22–7.19 (m, 2H, Ar), 7.18–7.14 (m, 1H, Ar), 6.95−6.92 (m, 2H, Ar), 6.28 (br s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0 (*ipso*-Ar), 139.3 (*ipso*-Ar), 129.6 (Ar), 129.1 (*ipso*-Ar), 126.1 (Ar), 124.5 (Ar), 121.8 (Ar), 113.5 (Ar); HRMS (ESI) *m*/*z* calc. for $C_{12}H_{10}N_2O_2$: 215.0815 $(M + H)^+$; found 215.0818 (−1.4 ppm error). Spectroscopic data consistent with those reported in the literature.[238]

Lab Book Reference: BT2/40 and BT2/48

4-Nitro-*N*-hexylaniline 117

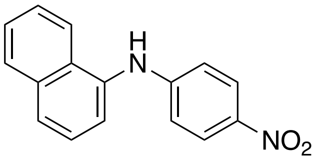


117

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), Cs_2CO_3 (0.489 g, 1.50 mmol, 1.50 equiv), 1-bromo-4-nitrobenzene (0.202 g, 1.00 mmol, 1.00 equiv), and hexylamine (0.101 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 72 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave 4-nitro-*N*-hexylaniline **117** (95 mg, 0.43 mmol, 43%, toluene) (189 mg, 0.85 mmol, 85%, TMO) as a yellow solid, mp 62–64 °C (lit.,[251] 64–67 °C); $R_F = 0.3$ (9:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3345 (NH), 2959, 2933, 2858, 1600, 1461, 1317 (NO_2) , 1107, 843, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.06 (m, 2H, Ar), 6.53–6.49 (m, 2H, Ar), 4.48 (br s, 1H, NH), 3.20 (td, $J = 7.0, 5.5$ Hz, 2H, NHCH_2), 1.65 (quin, $J = 7.0$ Hz, 2H, CH_2), 1.44–1.30 (m, 6H, CH_2), 0.90 (t, $J = 7.0$ Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (*ipso*-Ar), 137.9 (*ipso*-Ar), 126.6 (Ar), 111.0 (Ar), 43.6 (NCH_2), 31.6 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 22.7 (CH_2), 14.2 (Me); HRMS (ESI) *m*/*z* calc. for $C_{12}H_{18}N_2O_2$: 223.1441 $(M + H)^+$; found 223.1441 (−0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[251]

Lab Book Reference: BT2/41 and BT2/49

N-(4-Nitrophenyl)naphthalene-1-amine 118

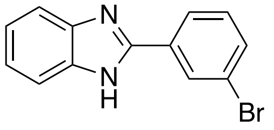


118

Following general procedure A, Pd(dba)$_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.094 g, 0.15 mmol, 0.15 equiv), Cs$_2$CO$_3$ (0.489 g, 1.50 mmol, 1.50 equiv), 1-bromonaphthalene (0.207 g, 1.00 mmol, 1.00 equiv), and 1-amino-4-nitrobenzene (0.152 g, 1.10 mmol, 1.10 equiv) in dry toluene or TMO (5 mL) at 110 °C for 72 h gave the crude product. Purification by flash column chromatography (19:1 petrol ether:EtOAc) gave *N*-(-nitrophenyl)naphthalene-1-amine **118** (167 mg, 0.63 mmol, 63%, toluene) (202 mg, 0.76 mmol, 76%, TMO) as a yellow solid mp 174–175 °C (lit.,[252] 169–172 °C); R_F = 0.3 (19:1 petrol ether:EtOAc); ν_{max}/cm^{-1} 3377 (NH) 3059, 2918, 1595, 1496, 1466, 1300 (NO$_2$), 1110, 803, 777, 746; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.11–8.07 (m, 2H, Ar), 7.94–7.92 (m, 2H, Ar), 7.82–7.80 (m, 1H, Ar), 7.58–7.47 (m, 4H, Ar), 6.79–6.74 (m, 2H, Ar), 6.43 (br s, 1H, NH); ^{13}C NMR (101 MHz, CDCl$_3$) δ 152.2 (*ipso* Ar), 139.7 (*ipso* Ar), 135.3 (*ipso* Ar), 134.9 (*ipso* Ar), 129.7 (*ipso* Ar), 128.9 (Ar), 127.1 (Ar), 126.9 (Ar), 126.8 (Ar), 126.4 (Ar), 126.0 (Ar), 122.5 (Ar), 122.3 (Ar), 113.5 (Ar); HRMS (ESI) *m*/*z* calc. for $C_{16}H_{11}N_2O_2$: 265.0972 (M + H)$^+$; found 265.0978 (−2.5 ppm error). Spectroscopic data consistent with those reported in the literature.[252]

Lab Book Reference: BT4/85 and BT4/86

2-(3-Bromophenyl)-1H-benzimidazole 121

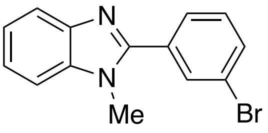


121

A three-neck round bottomed flask charged with $NaHSO_3$ (1.041 g, 10.0 mmol, 1.0 equiv) was evacuated and placed under a N_2 atmosphere. H_2O (12.5 mL) was added and the solution was stirred at room temperature for 5 min. 3-Bromobenzaldehyde **120** (1.850 g, 10.0 mmol, 1.0 equiv) was added dropwise over 5 min and stirred at room temperature for a further 20 min. Then, a solution of 1,2-phenylenediamine **119** (1.081 g, 10.0 mmol, 1.0 equiv) in ethanol (12.5 mL) was added and the resulting solution was stirred and heated at 70 °C for 3 h. During this time, a white precipitate formed. The solution was allowed to cool to room temperature and the solid was collected by filtration. The solid was washed with EtOH:H_2O (1:1) (2 × 10 mL) and dried overnight in a vacuum oven to give 2-(3-bromophenyl)-1H-benzimidazole **121** (2.249 g, 8.2 mmol, 82%) as a white solid, mp 245–248 °C (lit.,[119] 249–251 °C); ν_{max}/cm^{-1} 2800, 2783, 1438, 1399, 728; ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (t, *J* = 1.5 Hz, 1H, Ar), 8.19 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, Ar), 7.69 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar), 7.62 (br s, 2H, Ar), 7.52 (t, *J* = 8.0 Hz, 1H, Ar), 7.26–7.20 (m, 2H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6 (*ipso*-Ar), 132.5 (Ar), 132.4 (*ipso*-Ar), 131.2 (Ar), 128.9 (Ar), 125.4 (Ar), 122.3 (*ipso*-Ar) (two Ar and one *ipso*-Ar resonance not resolved); HRMS (ESI) *m/z* calc. for $C_{13}H_9N_2{}^{79}Br$: 273.0022 (M (^{79}Br) + H)$^+$; found 273.0020 (+0.6 ppm error). Spectroscopic data consistent with those reported in the literature.[119]

Lab Book Reference: BT2/52

2-(3-Bromophenyl)-1-methylbenzimidazole 122

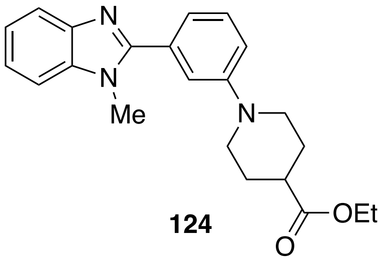


122

A two-necked round bottomed flask (25 mL) charged with KOH pellets (0.531 g, 10.0 mmol, 2.0 equiv) was evacuated and placed under a N_2 atmosphere. Anhydrous DMSO (1.5 mL) was added and the solution was stirred at room temperature for 15 min. 2-(3-Bromophenyl)-1H-benzimidazole **121** (1.366 g, 5.0 mmol, 1.0 equiv) was added portion-wise over 20 min. A solution of MeI (0.780 g, 5.5 mmol, 1.1 equiv) in DMSO (1.0 mL) was added dropwise over 40 min. During this time, a pale yellow precipitate formed. The heterogenous solution was stirred at room temperature for 2 h. Ice (5 g) was added followed by H_2O (2.5 mL). The heterogenous solution was stirred at room temperature for a further 2 h. The solid was collected by filtration and washed with H_2O (2 × 10 mL). Recrystallisation from *i*-PrOAc gave 2-(3-bromophenyl)-1-methylbenzimidazole **122** (778 mg, 2.71 mmol, 54%) as colourless crystals, mp 110–112 °C; ν_{max}/cm^{-1} 3052, 2948, 1459, 1434, 798, 750; ^1H NMR (400 MHz, DMSO-d_6) δ 8.05 (t, *J* = 2.0 Hz, 1H, Ar), 7.87 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, Ar), 7.77 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar), 7.69 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, Ar), 7.65–7.62 (m, 1H, Ar), 7.54 (t, *J* = 8.0 Hz, 1H, Ar), 7.32 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Ar), 7.29–7.24 (m, 1H, Ar), 3.89 (s, 3H, NMe); ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.4 (*ipso*-Ar), 142.4 (*ipso*-Ar), 136.6 (*ipso*-Ar), 132.5 (Ar), 131.8 (Ar), 130.9 (Ar), 128.3 (Ar), 122.7 (Ar), 122.2 (Ar), 121.9 (*ipso*-Ar), 119.2 (Ar), 110.8 (Ar), 31.7 (NMe) (one *ipso*-Ar resonance not resolved); HRMS (ESI) *m*/*z* calc. for $C_{14}H_{11}N_2{}^{79}Br$: 287.0178 (M (^{79}Br) + H)$^+$; found 287.0178 (+0.2 ppm error). Spectroscopic data consistent with those reported in the literature.[119]

Lab Book Reference: BT2/60

Ethyl 1-[3-(1-methyl-benzimidazol-2-yl)phenyl]-piperidine-4-carboxylate 124



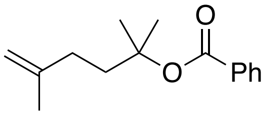
124

A round bottomed flask (25 mL) charged with 2-(3-bromophenyl)-1-methylbenzimidazole **122** (0.287 g, 1.0 mmol, 1.0 equiv), Pd(OAc)$_2$ (0.011 g, 0.05 mmol, 0.05 equiv), (±)-BINAP (0.047 g, 0.075 mmol, 0.075 equiv) and Cs$_2$CO$_3$ (0.978 g, 3.0 mmol, 3.0 equiv) was evacuated and placed under a N$_2$ atmosphere. Dry TMO or toluene (5 mL) was added and the resulting mixture was stirred at room temperature. Ethyl isonipecotate **123** (0.17 g, 1.1 mmol, 1.1 equiv) was added dropwise over 5 min. The resulting mixture was stirred and heated at 110 °C for 72 h. The reaction mixture was then allowed to cool to room temperature and the solids were removed by filtration. The solids were washed with TMO or toluene (2 × 3 mL) and the filtrate was evaporated under reduced pressure to afford the crude product as a viscous orange oil. The crude product was dissolved in a minimum amount of toluene and cooled to −20 °C upon which a solid precipitated. The solid was collected by filtration and washed with toluene (2 × 3 mL) at −20 °C to give ethyl 1-[3-(1-methyl-benzimidazol-2-yl)phenyl]-piperidine-4-carboxylate **124** (173 mg, 0.48 mmol, 48%, TMO) (138 mg, 0.38 mmol, 38%, toluene) as a pale yellow solid, mp 96–98 °C; ν_{max}/cm^{-1} 3048, 2970, 2928, 2895, 2827, 1728 (C=O), 1594, 1444, 1318, 1164, 1045, 740, 683; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.67 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, Ar) , 7.60 (ddd, *J* = 8.0, 1.5, 1.0, 1H, Ar), 7.39 (t, *J* = 8.0 Hz, 1H, Ar), 7.33 (t, *J* = 2.0 Hz, 1H, Ar), 7.31–7.29 (m, 1H, Ar), 7.26–7.22 (m, 1H, Ar), 7.18 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, Ar), 7.17–7.08 (m, 1H, Ar), 4.08 (q, *J* = 7.0 Hz, 2H, OCH$_2$), 3.86 (s, 3H, NMe), 3.75 (dt, *J* = 12.5, 3.0 Hz, 2H, NCH), 2.85 (td, *J* = 12.5, 2.5 Hz, 2H, NCH), 2.57–2.51 (m, 1H, (O)CCH), 1.95−1.90 (m, 2H, CH) 1.73–1.63 (m, 2H, CH), 1.19 (t, *J* = 7.0 Hz, 3H, OCH$_2$*Me*); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 174.3 (C=O), 153.6 (*ipso*-Ar), 151.0 (*ipso*-Ar), 142.5 (*ipso*-Ar), 136.6 (*ipso*-Ar), 130.9 (*ipso*-Ar), 129.3 (Ar), 122.3 (Ar), 121.9 (Ar), 119.3 (Ar), 119.0 (Ar), 117.1 (Ar), 116.5 (Ar), 110.5 (Ar), 60.0 (OCH$_2$), 47.8 (NCH$_2$), 40.1 (CH), 31.7 (NMe), 27.4 (CH$_2$), 14.2 (Me); HRMS (ESI) *m*/*z* calc. for $C_{22}H_{25}N_3O_2$: 363.1947 (M + H)$^+$; found 363.1950 (−0.7 ppm error). Spectroscopic data consistent with those reported in the literature.[119]

Lab Book Reference: BT2/61 and BT2/66

5.4 Experimental for Chapter 3

2,5-Dimethylhex-5-en-2-yl benzoate 187



187

Table 3.6, entry 1

Following general procedure B, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.0 equiv) in TMO (7 mL) at 0 °C for 2 h then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (99:1 Petrol-EtOAc) gave ester **187** (162 mg, 0.70 mmol, 54%) as a colourless oil, $R_F = 0.3$ (99:1 Petrol-EtOAc); ν_{max}/cm^{-1} 3072, 2975, 1710 (C=O), 1450, 1281, 884; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01−7.97 (m, 2H, *o*-Ph), 7.48−7.43 (m, 1H, *p*-Ph), 7.38−7.32 (m, 2H, *m*-Ph), 4.65 (s, 2H, CH_2=C), 2.09−2.02 (m, 2H, CH_2), 1.99−1.92 (m, 2H, CH_2), 1.65 (s, 3H, Me), 1.53 (s, 6H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C=O), 145.8 (CH_2=*C*), 132.6 (Ph), 132.1 (*ipso*-Ph), 129.5 (Ph), 128.4 (Ph), 110.1 (*C*H_2=C), 83.0 (O*C*$(CH_3)_2$), 39.2 (CH_2), 32.3 (CH_2), 26.2 (Me), 22.8 (Me); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}O_2$ $(M + H)^+$ 255.1356 found 255.1356 (0.0 ppm error).

Lab Book Reference: BT3/12

Table 3.6, entry 2

Following general procedure B, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.0 equiv) in TMO (7 mL) at −10 °C for 2 h then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (99:1 Petrol-EtOAc) gave ester **187** (121 mg, 0.52 mmol, 40%) as a colourless oil.

Lab Book Reference: BT3/15

Table 3.6, entry 3

Following general procedure C, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.0 equiv) in TMO (7 mL) at −20 °C for 2 h then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (99:1 Petrol-EtOAc) gave ester **187** (83 mg, 0.35 mmol, 27%) as a colourless oil.

Lab Book Reference: BT3/24

Table 3.6, entry 4

Following general procedure B, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.0 equiv) in TMO (7 mL) at −20 °C for 2 h then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by column chromatography (99:1 Pet Ether-EtOAc) gave ester **187** (110 mg, 0.48 mmol, 37%) as a colourless oil.

Lab Book Reference: BT3/14

Table 3.6, entry 5

Following general procedure C, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.0 equiv) in TMO (7 mL) at −30 °C for 2 h then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: BT3/10

Table 3.6, entry 6

Following general procedure B, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.0 equiv) in TMO (7 mL) at −30 °C for 2 h then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: BT3/11

Table 3.6, entry 7

Following general procedure C, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.0 equiv) in TMO (7 mL) at −40 °C for 2 h then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

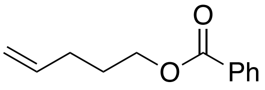
Lab Book Reference: BT3/6

Table 3.6, entry 8

Following general procedure B, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.0 equiv) in TMO (7 mL) at −40 °C for 2 h then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: BT3/7

Pent-4-en-1-yl benzoate 188



188

Table 3.7, entry 1

Following general procedure B, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.0 equiv) in 2-MeTHF (7 mL) for 2 h at 0 °C then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-EtOAc) gave ester **188** (120 mg, 0.61 mmol, 47%) as a colourless oil, R_F = 0.5 (19:1 Petrol-EtOAc); ν_{max}/cm^{-1} 3072, 2956, 1716 (C=O), 1268, 1109, 708; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07−8.03 (m, 2H, *o*-Ph), 7.59−7.53 (m, 1H, *p*-Ph), 7.47−7.42 (m, 2H, *m*-Ph), 5.86 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1 H, $H_2C{=}CH$), 5.13−4.98 (m, 2H, $H_2C{=}CH$), 4.34 (t, *J* = 6.5 Hz, 2H, OCH_2), 2.27−2.19 (m, 2H, $CH_2{=}CHCH_2$), 1.93−1.83 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C=O), 137.6 ($CH{=}CH_2$), 133.0 (Ph), 130.6 (*ipso*-Ph), 129.7 (Ph), 128.5 (Ph), 115.5 ($CH{=}CH_2$), 64.5 (OCH_2), 30.3 (CH_2), 28.1 (CH_2). HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}O_2$ (M + H)$^+$ 213.0886 found 213.0894 (−3.5 ppm error). Spectroscopic data consistent with those reported in the literature.[253]

Lab Book Reference: BT3/39

Table 3.7, entry 2

Following general procedure C, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.0 equiv) and TMEDA (1.30 mmol, 154 mg, 1.0 equiv) in 2-MeTHF (7 mL) for 2 h at 0 °C then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-EtOAc) gave ester **188** (137 mg, 0.72 mmol, 55%) as a colourless oil.

Lab Book Reference: BT3/46

Table 3.7, entry 3

Following general procedure B, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.0 equiv) in 2-MeTHF (7 mL) for 4 h at 0 °C then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-EtOAc) gave ester **188** (132 mg, 0.69 mmol, 53%) as a colourless oil.

Lab Book Reference: BT3/40

Table 3.7, entry 4

Following general procedure C, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.0 equiv) and TMEDA (1.30 mmol, 154 mg, 1.0 equiv) in 2-MeTHF (7 mL) for 4 h at 0 °C then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-EtOAc) gave ester **188** (159 mg, 0.83 mmol, 64%) as a colourless oil.

Lab Book Reference: BT3/41

Table 3.7, entry 5

Following general procedure B, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.0 equiv) in 2-MeTHF (7 mL) for 2 h at −40 °C then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-EtOAc) gave ester **188** (118 mg, 0.62 mmol, 48%) as a colourless oil.

Lab Book Reference: BT3/9

Table 3.7, entry 6

Following general procedure C, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.0 equiv) and TMEDA (1.30 mmol, 154 mg, 1.0 equiv) in 2-MeTHF (7 mL) for 2 h at −40 °C then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-EtOAc) gave ester **188** (138 mg, 0.73 mmol, 55%) as a colourless oil.

Lab Book Reference: BT3/8

Table 3.7, entry 7

Following general procedure C, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.0 equiv) and TMEDA (1.30 mmol, 154 mg, 1.0 equiv) in 2-MeTHF (7 mL) for 2 h at −60 °C then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-EtOAc) gave ester **188** (90 mg, 0.47 mmol, 36%) as a colourless oil.

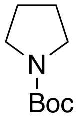
Lab Book Reference: BT3/44

Table 3.7, entry 8

Following general procedure C, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.0 equiv) and TMEDA (1.30 mmol, 154 mg, 1.0 equiv) in 2-MeTHF (7 mL) for 2 h at −78 °C then PhCOCl (1.3 mmol, 183 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-EtOAc) gave ester **188** (94 mg, 0.49 mmol, 38%) as a colourless oil.

Lab Book Reference: BT3/43

N-Boc pyrrolidine 32

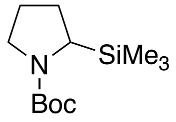


32

Under an inert atmosphere, pyrrolidine (60.0 mmol, 5.01 mL, 1.20 equiv) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (50 mmol, 10.91 g, 1.00 equiv) in dry CH_2Cl_2 (200 mL) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 2 h. $HCl_{(aq)}$ (1 M, 50 mL) was added to the solution and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a pale-yellow oil. Purification by Kugelrohr short path distillation gave *N*-Boc pyrrolidine **32** (7.25 g, 42.5 mmol, 85%) as a colourless oil, bp 80−85 °C/1.0 mmHg (lit.,[144] bp 90−100 °C/0.6 mmHg); ν_{max}/cm^{-1} 2974, 2876, 1692 (C=O), 1391, 1364, 1175, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 3.36−3.23 (m, 4H, NCH_2), 1.85−1.78 (m, 4H, CH_2CH_2), 1.44 (s, 9H, CMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 154.8 (C=O), 79.0 (O*C*Me_3), 46.1 (NCH_2), 45.7 (NCH_2), 28.7 (C*Me*$_3$), 25.9 (CH_2), 25.1 (CH_2). Spectroscopic data consistent with that found in the literature.[144]

Lab Book Reference: BT3/22

N-tert-Butoxycarbonyl-2-trimethylsilylpyrrolidine 132



132

Table 3.8, entry 1

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in dry THF (7 mL) for 1 h at −78 °C then Me_3SiCl (2.00 mmol, 217 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-Et_2O) and drying on high vacuum line for 16 h gave silyl pyrrolidine **132** (112 mg, 0.46 mmol, 46%) as a colourless oil, R_F = 0.3 (19:1 Petrol-Et_2O); ν_{max}/cm^{-1} 2965, 2875, 1687 (C=O), 1390, 1245, 1103, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52−3.46 (m, 1H, NCH), 3.27−3.24 (m, 1H, NCH), 3.18−3.12 (m, 1H, NCH), 2.03−1.95 (m, 1H, CH), 1.81−1.73 (m, 3H, CH), 1.45 (s, 9H, CMe_3), 0.04 (s, 9H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers) δ 155.0 (C=O) 78.9 (O*C*Me_3), 77.4 (O*C*Me_3), 47.8 (NCH), 47.0 (NCH) 46.8 (NCH_2), 28.7 (C*Me*$_3$), 28.1 (CH_2), 28.0 (CH_2), 25.7 (CH_2), −2.0 ($SiMe_3$); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{25}NO_2Si$ $(M + H)^+$ 244.1727 found 244.1733 (−2.4 ppm error). Spectroscopic data consistent with those reported in the literature.[144]

Lab Book Reference: BT2/4

Table 3.8, entry 2

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in dry THF (7 mL) for 1 h at −78 °C then Me_3SiCl (2.00 mmol, 217 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-Et_2O) and drying on high vacuum line for 60 h gave none of silyl pyrrolidine **132** which is likely due to product evaporation.

Lab Book Reference: BT2/6

Table 3.8, entry 3

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in dry THF (7 mL) for 1 h at −78 °C then Me_3SiCl (2.00 mmol, 217 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-Et_2O) and drying on high vacuum line for 1 h gave silyl pyrrolidine **132** (171 mg, 0.70 mmol, 70%) as a colourless oil.

Lab Book Reference: BT2/9

Scheme 3.35, TMO dried with 3 Å molecular sieves

Following general procedure D, *s*-BuLi (1.3 M in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (dried using 3 Å molecular sieves) (7 mL) for 1 h at −78 °C then Me_3SiCl (2.00 mmol, 217 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-Et_2O) and drying on high vacuum line for 1 h gave silyl pyrrolidine **132** (64 mg, 0.26 mmol, 26%) as a colourless oil.

Lab Book Reference: BT2/18

Scheme 3.35, TMO distilled over CaH_2 and stored over 3 Å molecular sieves

Following general procedure D, *s*-BuLi (1.3 M in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (dried by distilling over CaH_2 and storing over 3 Å molecular sieves) (7 mL) for 1 h at −78 °C then Me_3SiCl (2.00

mmol, 217 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-Et_2O) and drying on high vacuum line for 1 h gave silyl pyrrolidine **132** (101 mg, 0.42 mmol, 42%) as a colourless oil.

Lab Book Reference: BT2/24

Table 3.9, entry 1

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) and TMEDA (1.30 mmol, 154 mg, 1.30 equiv) in Et_2O (7 mL) for 5 min at −78 °C then Me_3SiCl (1.00 mmol, 217 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-Et_2O) and drying on high vacuum line for 1 h gave silyl pyrrolidine **132** (208 mg, 0.85 mmol, 85%) as a colourless oil.

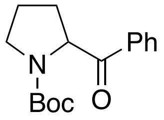
Lab Book Reference: BT2/11

Table 3.9, entry 2

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) and TMEDA (1.30 mmol, 154 mg, 1.30 equiv) in TMO (7 mL) for 15 min at −78 °C then Me_3SiCl (1.00 mmol, 217 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (19:1 Petrol-Et_2O) and drying on high vacuum line for 1 h gave silyl pyrrolidine **132** (217 mg, 0.89 mmol, 89%) as a colourless oil.

Lab Book Reference: BT2/25

2-Benzoylpyrrolidine-1-carboxylic acid *tert*-butyl ester 185



185

Table 3.10, entry 1

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in THF (7 mL) for 1 h at −78 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (223 mg, 0.81 mmol, 81%, 50:50 er by CSP-HPLC) as a white solid, mp 97−98 °C (lit.,[254] mp 96−100 °C); $R_F = 0.2$ (4:1 Petrol-EtOAc); ν_{max}/cm^{-1} 3062, 2967, 2870, 1686 (C=O), 1396, 1228, 989; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture or rotamers) δ 8.00−7.94 (m, 2H, *o*-Ph), 7.61−7.53 (m, 1H, *p*-Ph), 7.50−7.43 (m, 2H, *m*-Ph), 5.33 (dd, $J = 9.0, 3.0$ Hz, 0.4H, NCH), 5.19 (dd, $J = 9.0, 3.0$ Hz, 0.6H, NCH), 3.72−3.60 (m, 1H, NCH), 3.58−3.44 (m, 1H, NCH), 2.38−2.23 (m, 1H, CH), 1.98−1.86 (m, 3H, CH), 1.46 (s, 3.6H, CMe_3), 1.26 (s, 5.4H, CMe_3); ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 199.1 (C=O, ketone), 198.6 (C=O, ketone), 154.6 (C=O, Boc), 154.0 (C=O, Boc), 135.4 (*ipso*-Ph), 135.2 (*ipso*-Ph), 128.84 (Ph), 128.81 (Ph), 128.73 (Ph), 128.67 (Ph), 128.3 (Ph), 79.9 ($\mathit{C}Me_3$), 79.8 ($\mathit{C}Me_3$), 61.5 (NCH), 61.2 (NCH), 46.9 (NCH_2), 46.8 (NCH_2), 31.0 (CH_2), 29.9 (CH_2), 28.6 ($C\mathit{Me}_3$), 28.3 ($C\mathit{Me}_3$), 24.3 (CH_2), 23.7 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{21}NO_3$ $(M + H)^+$ 276.1594 found 276.1595 (−0.3 ppm error); CSP-HPLC (AD-H column, hexane/2-propanol 90/10, flow rate 1.00 mL/min^{-1}, detection UV 250 nm, 25 °C) t_R of isomer A 6.7 min, t_R of isomer B 11.0 min. Spectroscopic data consistent with those reported in the literature.[144]

Lab Book Reference: BT2/67

Table 3.10, entry 2

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in Et_2O (7 mL) for 1 h at −78 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (20 mg, 0.07 mmol, 7%) as a white solid.

Lab Book Reference: BT2/68

Table 3.10, entry 3

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 1 h at −78 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (114 mg, 0.42 mmol, 42%) as a white solid.

Lab Book Reference: BT2/69

Table 3.10, entry 4

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 2 h at −78 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (108 mg, 0.40 mmol, 40%) as a white solid.

Lab Book Reference: BT2/79

Table 3.11, entry 1

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 1 h at −60 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (91 mg, 0.33 mmol, 33%) as a white solid.

Lab Book Reference: BT3/16

Table 3.11, entry 2

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 1 h at −40 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (123 mg, 0.45 mmol, 45%) as a white solid.

Lab Book Reference: BT3/17

Table 3.11, entry 3

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 1 h at −30 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (39 mg, 0.14 mmol, 14%) as a white solid.

Lab Book Reference: BT3/18

Table 3.11, entry 4

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 30 min at −30 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (105 mg, 0.38 mmol, 38%) as a white solid.

Lab Book Reference: BT3/19

Table 3.11, entry 5

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 20 min at −30 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (105 mg, 0.38 mmol, 38%) as a white solid.

Lab Book Reference: BT3/21

Table 3.11, entry 6

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 10 min at −30 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (83 mg, 0.30 mmol, 30%) as a white solid.

Lab Book Reference: BT3/20

Table 3.11, entry 7

Following general procedure D, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) in TMO (7 mL) for 5 min at −30 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone **185** (100 mg, 0.37 mmol, 37%) as a white solid.

Lab Book Reference: BT3/23

Table 3.12, entry 1

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) and TMEDA (1.30 mmol, 154 mg, 1.30 equiv) in Et_2O (7 mL) for 5 min at −78 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-Ether) gave ketone **185** (241 mg, 0.88 mmol, 88%) as a white solid.

Lab Book Reference: BT2/71

Table 3.12, entry 2

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) and TMEDA (1.30 mmol, 154 mg, 1.30 equiv) in TMO (7 mL) for 15 min at −78 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-Ether) gave ketone **185** (245 mg, 0.89 mmol, 89%) as a white solid.

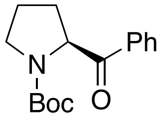
Lab Book Reference: BT2/72

Table 3.12, entry 3

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 1.30 mmol, 1.0 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (1.00 mmol, 171 mg, 1.00 equiv) and TMEDA (1.30 mmol, 154 mg, 1.30 equiv) in TMO (7 mL) for 5 min at −78 °C then PhCONMe(OMe) (2.00 mmol, 330 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-Ether) gave ketone **185** (206 mg, 0.79 mmol, 79%) as a white solid.

Lab Book Reference: BT2/73

(*S*)-2-Benzoylpyrrolidine-1-carboxylic acid-*tert*-butyl ester (*S*)-185



(*S*)-**185**

Table 3.13, entry 1

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (0.50 mmol, 85 mg, 1.00 equiv) and (+)-sparteine (0.65 mmol, 152 mg, 1.30 equiv) in Et_2O (5 mL) for 90 min at −78 °C then PhCONMe(OMe) (1.00 mmol, 165 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone (*S*)-**185** (119 mg, 0.44 mmol, 87%, 96:4 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −30.9 (*c* 1.0 in $CHCl_3$) (lit.,[187] $[\alpha]_D$ −34.9 (*c* 0.5 in $CHCl_3$)); CSP-HPLC (AD-H column, hexane/2-propanol 90/10, flow rate 1.00 mL/min^{-1}, detection UV 250 nm, 25 °C) t_R 5.6 min (minor), t_R 7.7 min (major) (retention times different to racemic sample due to use of a different HPLC machine).

Lab Book Reference: BT2/83

Table 3.13, entry 2

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (0.50 mmol, 85 mg, 1.00 equiv) and (+)-sparteine (0.65 mmol, 152 mg, 1.30 equiv) in THF (5 mL) for 90 min at −78 °C then PhCONMe(OMe) (1.00 mmol, 165 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave (*S*)-**185** (62 mg, 0.23 mmol, 45%, 52:48 er by CSP-HPLC) as a white solid, CSP-HPLC (AD-H column, hexane/2-propanol 90/10, flow rate 1.00 mL/min^{-1}, detection UV 250 nm, 25 °C) t_R 6.1 min (minor), t_R 11.7 min (major).

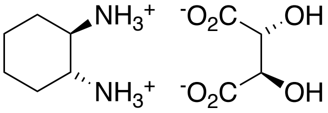
Lab Book Reference: BT3/26

Table 3.13, entry 3

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (0.50 mmol, 85 mg, 1.00 equiv) and (+)-sparteine (0.65 mmol, 152 mg, 1.30 equiv) in TMO (5 mL) for 90 min at −78 °C then PhCONMe(OMe) (1.00 mmol, 165 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave (*S*)-**185** (117 mg, 0.43 mmol, 86%, 97:3 er by CSP-HPLC) as a white solid, CSP-HPLC (AD-H column, hexane/2-propanol 90/10, flow rate 1.00 mL/min^{-1}, detection UV 250 nm, 25 °C) t_R 6.7 min (minor), t_R 11.1 min (major).

Lab Book Reference: BT2/84

(1*R*,2*R*)-Cyclohexane-1,2-diamine 2,3-dihydroxysuccinate salt (*R*,*R*)-190

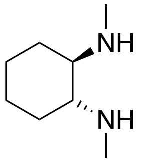


(*R*,*R*)-**190**

trans-(±)-Diaminocyclohexane **189** (166.60 mmol, 19.02 g, 2.00 equiv), was added dropwise to a stirred solution of L-tartaric acid (83.3 mmol, 12.51 g, 1.00 equiv), in water (45 mL) under air such that the temperature of the solution did not exceed 70 °C. A white precipitate formed and the solution was stirred at rt for 1 h, after which the precipitate had disappeared. AcOH (87.3 mmol, 5.0 mL, 1.05 equiv) was added dropwise such that the temperature did not exceed 90 °C. The solution was cooled to *ca* 5 °C and incubated at this temperature for 16 h. The solids were collected from the resulting suspension by filtration and they were washed with cold water (20 mL) and methanol (10 mL) to give salt (*R*,*R*)-**190** (15.58 g, 58.3 mmol, 70%, ≥99:1 er by chiral shift ^{1}H NMR spectroscopy of the TMCDA derivative with 2,2,2 trifluoro-1-(9-anthryl)-ethanol); mp 266−268 °C (lit.,[158] 275−276 °C), ^{1}H NMR (300 MHz, D_2O) δ 4.36 (s, 2H, C(O)$_2$C*H*OH), 3.46−3.33 (m, 2H, NCH), 2.26−2.11 (m, 2H, CH), 1.93−1.77 (m, 2H, CH), 1.63−1.47 (m, 2H, CH), 1.44−1.32 (m, 2H, CH); ^{13}C NMR (75 MHz, D_2O) δ 178.5 (C=O), 73.9 (C(O)$_2$*C*HOH), 52.2 (NCH), 29.4 (CH_2), 22.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[158]

Lab Book Reference: BT3/51

(1*R*,2*R*)-*N*¹,*N*²-Dimethylcyclohexane-1,2-diamine (*R*,*R*)-191

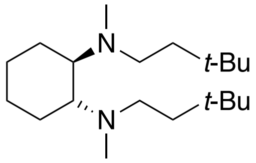


(*R*,*R*)-**191**

MeO_2CCl (125.0 mmol, 9.7 mL, 2.20 equiv) and a solution of NaOH (455.00 mmol, 18.20 g, 8.00 equiv) in H_2O (30 mL) were simultaneously added to a stirred suspension of salt (*R*,*R*)-**190** (56.80 mmol, 15.00 g, 1.00 equiv) in toluene (75 mL) at 0 °C under air. The resulting solution was stirred at rt for 48 h initially forming a gel-like mixture which dissipated over time. $CHCl_3$ (50 mL) was added and the solids were removed by filtration and washed with $CHCl_3$ (2 × 25 mL). H_2O (30 mL) was added to the organic layer. The two layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 × 50 ml). The combined organics were dried (K_2CO_3) and concentrated under reduced pressure to give the crude carbamate (8.01 g, 61%) as a white solid. Without further purification, the crude carbamate (32.60 mmol, 7.50 g, 1.00 equiv) was dissolved in dry THF (60 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (6.19 g, 163.00 mmol, 5.00 equiv) in THF (60 mL) at 0 °C under N_2. The resulting suspension was stirred and heated at reflux for 48 h. The solution was then cooled to 0 °C and diluted with Et_2O (100 mL). H_2O (6 mL) was added dropwise causing evolution of gas. $NaOH_{(aq)}$ (20% w/v, 12 mL) was then added followed by H_2O (6 mL). The solution was dried ($MgSO_4$) filtered through celite® and washed with CH_2Cl_2-MeOH (24:1) (2 × 50 mL). The filtrate was dried (K_2CO_3) and concentrated under reduced pressure to give crude diamine (*R*,*R*)-**191** (3.80 g, 26.7 mmol, 50%) as a yellow oil, ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 6H, NMe), 2.14−2.04 (m, 2H, NCH), 2.03−1.95 (m, 2H, CH), 1.78−1.65 (m, 2H, CH), 1.55 (br s, 2H, NH),1.30−1.16 (m, 2H, CH), 1.02−0.87 (m, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.4 (NCH), 33.8 (NMe), 31.0 (CH_2), 25.2 (CH_2). Spectroscopic data consistent with those reported in the literature.[158]

Lab Book Reference: BT3/54

(1*R*,2*R*)-*N*¹,*N*²-Dimethyl-*N*¹,*N*²-bis(3,3-dimethylbutyl)cyclohexane-1,2-diamine (*R*,*R*)-155

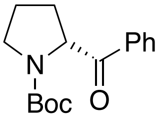


(*R*,*R*)-**155**

A solution of NaOH (163.80 mmol, 6.55 g, 6.66 equiv) in H_2O (25 mL) was added dropwise to a stirred solution of diamine (*R*,*R*)-**191** (24.60 mmol, 3.50 g, 1.00 equiv) in CH_2Cl_2 (50 mL) at 0 °C. A solution of 3,3-dimethylbutyryl chloride (71.30 mmol, 9.59 g, 2.90 equiv) in CH_2Cl_2 (15 mL) was added dropwise to the stirred bisphasic solution at 0 °C. The resulting solution was allowed to warm to rt and stirred for 48 h. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organics were dried (K_2CO_3) and concentrated under reduced pressure to give the crude amide (7.24 g) as a white solid. A solution of the crude amide (20.60 mmol, 7.00 g, 1.00 equiv) in dry THF (50 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (103.0 mmol, 3.91 g, 5.00 equiv) in dry THF (50 mL) at 0 °C. The resulting solution was stirred and heated at reflux for 48 h. The solution was cooled to 0 °C and diluted with Et_2O (75 mL). H_2O (5 mL) was added dropwise causing evolution of gas. $NaOH_{(aq)}$ (20% w/v, 10 mL) was added dropwise followed by H_2O (5 mL). The solution was dried (K_2CO_3), filtered through celite® and washed with CH_2Cl_2-MeOH (24:1) (2 × 50 mL). The filtrate was dried (K_2CO_3) and concentrated under reduced pressure to give the crude product as a yellow oil. Purification by Kugelrohr distillation gave diamine (*R*,*R*)-**151** (5.12 g, 16.5 mmol, 70%) as a colourless oil, bp 160−170 °C/1.0 mmHg (lit.,[158] 180−190 °C/1.5 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56−2.41 (m, 6H, NCH), 2.24 (s, 6H, NMe), 1.85−1.65 (m, 4H, CH), 1.44−1.32 (m, 4H, CH), 1.27−1.05 (m, 4H, CH_2), 0.89 (s, 18H, CMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.9 (NCH) 50.3 (NCH_2), 42.4 (CH_2), 37.2 (NMe), 30.0 (*C*Me_3), 29.8 (C*Me*$_3$), 26.1 (CH_2), 25.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[158]

Lab Book Reference: BT3/56 and BT3/57

(*R*)-2-Benzoylpyrrolidine-1-carboxylic acid-*tert*-butyl ester (*R*)-185



(*R*)-**185**

Scheme 3.37 (Et_2O)

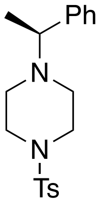
Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (0.50 mmol, 85 mg, 1.00 equiv) and diamine (*R*,*R*)-**155** (0.65 mmol, 202 mg, 1.30 equiv) in Et_2O (5 mL) for 90 min at −78 °C then PhCONMe(OMe) (1.00 mmol, 165 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone (*S*)-**185** (101 mg, 0.37 mmol, 74%, 93:7 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +30.7 (*c* 1.0 in $CHCl_3$) (lit.,[187] $[\alpha]_D$ +26.5 (*c* 0.5 in $CHCl_3$)); CSP-HPLC AD-H column, hexane/2-propanol 90/10, flow rate 1.00 mL/min^{-1}, detection UV 250 nm, 25 °C) t_R 5.6 min (major), t_R 10.4 min (minor).

Lab Book Reference: BT3/59

Scheme 3.37 (TMO)

Following general procedure E, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc pyrrolidine **32** (0.50 mmol, 85 mg, 1.00 equiv) and diamine (*R*,*R*)-**155** (0.65 mmol, 202 mg, 1.30 equiv) in Et_2O (5 mL) for 90 min at −78 °C then PhCONMe(OMe) (1.00 mmol, 165 mg, 2.00 equiv) gave the crude product. Purification by flash column chromatography (4:1 Petrol-EtOAc) gave ketone (*S*)-**185** (78 mg, 0.28 mmol, 56%, 93:7 er by CSP-HPLC) as a white solid, CSP-HPLC AD-H column, hexane/2-propanol 90/10, flow rate 1.00 mL/min^{-1}, detection UV 250 nm, 25 °C) t_R 5.6 min (major), t_R 10.4 min (minor). Lab Book Reference: BT3/62

(*S*)-1-(1-Phenylethyl)-4-methylbenzenesulfonylpiperazine (*S*)-197



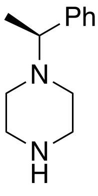
(*S*)-**197**

A mixture of *N*,*N*-bis(2-chloroethyl)-methylbenzenesulfonamide **195** (30.00 mmol, 8.89 g, 1.10 equiv), (*S*)-(−)-*α*-methylbenzylamine (*S*)-**196** (27.25 mmol, 3.30 g, 1.00 equiv, 99:1 er) and DIPEA (60.00 mmol, 7.76 g, 2.00 equiv) were stirred at 120 °C for 16 h. The solution was then allowed to cool to rt. 7:3 H_2O-EtOH (100 mL) was added and the suspension was stirred at rt for a further 16 h. The solids were collected by filtration and washed with 1:1 H_2O-EtOH (2 × 50 mL) and cyclohexane (3 × 25 mL) to give *N*-Ts piperazine (*S*)-**197** (7.65 g, 22.07 mmol, 81%) as a light brown solid, mp 162−164 °C (lit.,[143] 152−153 °C); $[\alpha]_D$ +44.0 (*c* 1.0 in $CHCl_3$) (lit.,[143] $[\alpha]_D$ +48.7 (*c* 1.0 in $CHCl_3$)); ν_{max}/cm^{-1} 2975, 2821, 1597, 1447, 1348, 1167, 1134, 1095, 947, 819, 736; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.57 (m, 2H, Ar), 7.35−7.29 (m, 2H, Ar), 7.28−7.19 (m, 5H, Ar), 3.36 (q, *J* = 6.5 Hz, 1 H, CH), 2.98 (t, *J* = 5.0 Hz, 4H, NCH), 2.61−2.51 (m, 2H, NCH), 2.50−2.43 (m, 2H, NCH), 2.43 (s, 3H, ArC*H*$_3$), 1.31 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7 (*ipso*-Ar), 143.5 (*ipso*-Ar), 132.7 (*ipso*-Ar), 129.8 (Ar), 128.5 (Ar), 128.1 (Ar), 127.6 (Ar), 127.3 (Ar), 64.5 (NCH), 49.7 (NCH_2), 46.5 (NCH_2), 21.6 (Me), 19.6 (Me); HRMS (ESI) *m*/*z* calcd for

$C_{19}H_{24}N_2O_2S$ (M + H)$^+$ 345.1631, found 345.1636 (−1.3 ppm error). Spectroscopic data consistent with those reported in the literature.[143,168]

Lab Book Reference: BT3/42

(*S*)-1-(1-Phenylethyl)piperazine (*S*)-198

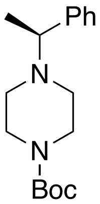


(*S*)-**198**

N-Ts piperazine (*S*)-**197** (18.90 mmol, 6.50 g, 1.00 equiv) and 4-hydroxybenzoic acid (56.70 mmol, 7.83 g, 3.00 equiv) were stirred in HBr (33 wt. % in AcOH, 45 mL) for 3 days at rt. Then, H_2O (55 mL) was added and the resulting mixture was stirred for 2 h forming a white precipitate. The solids were removed *via* filtration and the filtrate was extracted with toluene (3 × 50 mL). The aqueous layer was cooled to 0 °C and basified with solid KOH. The basic solution was then extracted with EtOAc (3 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give piperazine (*S*)-**198** (2.74 g, 14.36 mmol, 76%) as a brown oil, $[\alpha]_D$ −30.4 (*c* 1.0 in $CHCl_3$) (lit.,[168] $[\alpha]_D$ −31.8 (*c* 1.0 in $CHCl_3$)); ν_{max}/cm^{-1} 2971, 2806, 2752, 1491, 1450, 1321, 1265, 1135, 1028, 950, 758, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 5H, Ph), 3,36 (q, *J* = 6.5 Hz, 1H, CH), 2.92 (t, *J* = 5.0 Hz, 4H, NCH), 2.55−2.48 (m, 2H, NCH), 2.44−2.37 (m, 2H, NCH), 1.35 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 143.9 (*ispo*-Ph), 128.4 (Ph), 127.8 (Ph), 127.1 (Ph), 65.3 (CH), 51.1 (NCH_2), 45.9 (NCH_2), 19.6 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{18}N_2$ (M + H)$^+$ 191.1542 found 191.1543 (+0.3 ppm error). Spectroscopic data consistent with those reported in the literature.[168]

Lab Book Reference: BT3/61

(*S*)-*tert*-Butyl 4-(1-phenylethyl)piperazine-1-carboxylate (*S*)-167

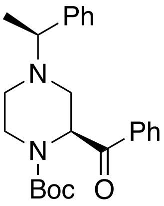


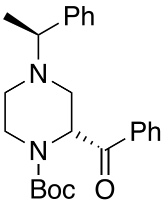
(*S*)-**167**

A solution of di-*tert*-butyl dicarbonate (18.50 mmol, 4.04 g, 1.30 equiv) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of piperazine (*S*)-**198** (14.20 mmol, 2.70 g, 1.0 equiv) in CH_2Cl_2 (30 mL) at 0 °C under N_2. The resulting solution was allowed to warm to rt and stirred for a further 16 h. $NaHCO_{3(aq)}$ (50 mL) was then added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (7:3 hexane-EtOAc) gave *N*-Boc piperazine (*S*)-**167** (2.95 g, 10.22 mmol, 72%) as a yellow oil, R_F = 0.2 (7:3 hexane-EtOAc); $[\alpha]_D$ −35.9 (*c* 1.0 in $CHCl_3$) (lit.,[168] −40.3 (*c* 1.0 in $CHCl_3$)); ν_{max}/cm^{-1} 2974, 2812, 1691 (C=O), 1450, 1418, 1245, 1166, 938, 866, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.15 (m, 5H, Ph), 3.44−3.32 (m, 5H, NCH), 2.45−2.35 (m, 2H, NCH), 2.34−2.25 (m, 2H, NCH), 1.39 (s, 9H, CMe_3), 1.34 (d, *J* = 6.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8 (C=O), 143.7 (*ipso*-Ph), 128.4 (Ph), 127.7 (Ph), 127.1 (Ph), 79.5 ($\mathit{C}Me_3$), 64.8 (NCH), 50.4 (NCH_2), 44.0 (NCH_2), 28.5 ($C\mathit{Me}_3$), 19.7 (Me); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{26}N_2O_2$ $(M + H)^+$ 291.2067 found 291.2074 (−2.4 ppm error). Spectroscopic data consistent with those reported in the literature.[168]

Lab Book Reference: BT3/64

(*S*)-*tert*-Butyl 2-benzoyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*S*,*S*)-168 and (*R*)-*tert*-Butyl 2-benzoyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*R*,*S*)-168

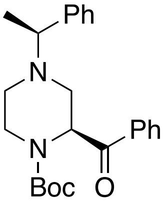

(*S*,*S*)-**168**


(*R*,*S*)-**168**

Following general procedure F, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc piperazine (*S*)-**167** (0.5 mmol, 145 mg, 1.00 equiv), TMEDA (0.65 mmol, 78 mg, 1.30 equiv) in Et$_2$O (5 mL) at −78 °C for 1 h then PhCONMe(OMe) (0.65 mmol, 107 mg, 1.30 equiv) gave the crude product which contained a 70:30 mixture of ketones (*S*,*S*)-**168** and (*R*,*S*)-**168** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography (99:1 CH$_2$Cl$_2$-Et$_2$O) gave a 70:30 mixture of ketones (*S*,*S*)-**168** and (*R*,*S*)-**168** (131 mg, 0.33 mmol, 66%) as a white solid, R_F = 0.1 (99:1 CH$_2$Cl$_2$-Et$_2$O). Diagnostic signals for (*S,S*)-**168**: ^{1}H NMR (400 MHz, CDCl$_3$) (55:45 mixture of rotamers) δ 5.39 (br s, 0.55H, NCH), 5.22 (br s, 0.45H, NCH), 3.91 (br d, *J* = 12.0 Hz, 0.45H, NCH), 3.82 (br d, *J* = 12.0 Hz, 0.55H, NCH), 3.61−3.46 (m, 1H, C*H*Me), 3.23−3.02 (m, 2.45H, NCH), 2.97 (d, *J* = 9.5 Hz, 0.55H, NCH), 2.21 (dd, *J* = 12.0, 5.0 Hz, 1H, NCH), 2.11−1.99 (m, 1H, NCH), 1.46 (s, 5H, CMe$_3$), 1.36 (s, 4H, CMe$_3$), 1.17 (d, *J* = 6.5 Hz, CH*Me*); diagnostic signals for (*R*,*S*)-**168**: ^{1}H NMR (400 MHz, CDCl$_3$) (55:45 mixture of rotamers) δ 5.48 (br s, 0.55H, NCH), 5.30 (br s, 0.45H, NCH), 3.77 (br d, *J* = 11.0 Hz, 0.45H, NCH), 3.68 (br d, *J* = 11.0 Hz, 0.55H, NCH), 3.46−3.24 (m, 3H, NCH + C*H*Me), 2.74−2.57 (m, 1H, NCH), 2.46−2.56 (m, 1H, NCH), 1.46 (s, 5H, CMe$_3$), 1.36 (s, 4H, CMe$_3$), 1.02 (d, *J* = 6.5 Hz, 3H, CH*Me*); HRMS (ESI) *m*/*z* calcd for C$_{24}$H$_{30}$N$_2$O$_3$ (M + H)$^+$ 395.2329 found 395.2329 (+0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[168]

Lab Book Reference: BT3/67

(*S*)-*tert*-Butyl 2-benzoyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*S*,*S*)-168



(*S*,*S*)-**168**

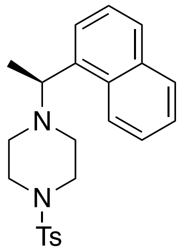
Following general procedure F, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc piperazine (*S*)-**167** (0.5 mmol, 145 mg, 1.00 equiv), (+)-sparteine (0.65 mmol, 152 mg, 1.30 equiv) in Et_2O (5 mL) at −78 °C for 3 h then PhCONMe(OMe) (0.65 mmol, 107 mg, 1.30 equiv) gave the crude product which contained a >98:2 mixture of ketones (*S*,*S*)-**168** and (*R*,*S*)-**168** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography (99:1 CH_2Cl_2-Et_2O) gave ketone (*S*,*S*)-**168** (120 mg, 0.31 mmol, 61%) as a white solid, mp 140−142 °C (lit.,[168] 127−129 °C); $R_F = 0.1$ (98:2 CH_2Cl_2-Et_2O); $[\alpha]_D$ −26.2 (*c* 1.0 in $CHCl_3$) (lit.,[168] −2.6 (*c* 0.8 in $CHCl_3$)); ν_{max}/cm^{-1} 2973, 2851, 1698 (C=O, ketone), 1684 (C=O, Boc), 1597, 1449, 1350, 1166, 1066, 943, 765, 693; ^{1}H NMR (300 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.76−7.62 (m, 2H, Ph), 7.52−7.42 (m, 1H, Ph), 7.40−7.29 (m, 2H, Ph), 7.03−6.90 (m, 5H, Ph), 5.39 (br s, 0.55H, NCH), 5.22 (br s, 0.45H, NCH), 3.92 (br d, *J* = 12.0 Hz, 0.45H, NCH), 3.84 (br d, *J* = 12.0 Hz, 0.55H, NCH), 3.63−3.45 (m, 1H, NCH), 3.25−3.05 (m, 2.45H, NCH), 2.99 (d, *J* = 9.5 Hz, 0.55H, NCH), 2.23 (dd, *J* = 12.0, 5.0 Hz, 1H, NCH), 2.11−2.00 (m, 1H, NCH), 1.47 (s, 5H, CMe_3), 1.37 (s, 4H, CMe_3), 1.18 (d, *J* = 6.5 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 199.0 (C=O, Ketone), 156.3 (C=O, Boc), 156.2 (C=O, Boc), 143.4 (*ipso*-Ph), 143.2 (*ipso*-Ph), 136.3 (*ipso*-Ph), 136.2 (*ipso*-Ph), 132.6 (Ph), 128.6 (Ph) 128.5 (Ph), 128.1 (Ph), 127.8 (Ph), 127.1 (Ph), 126.8 (Ph) 80.2 ($OCMe_3$), 64.5 (NCH), 58.9 (NCH_2), 58.0 (NCH_2), 52.4 (NCH_2), 52.3 (NCH_2), 49.8 (NCH_2), 42.6 (NCH_2), 41.8 (NCH_2), 28.5 (CMe_3), 28.4 (CMe_3), 20.1 (Me), 20.0 (Me);

HRMS (ESI) *m*/*z* calcd for $C_{24}H_{30}N_2O_3$ $(M + H)^+$ 395.2329 found 395.2332 (−0.7 ppm error).

Spectroscopic data consistent with those reported in the literature.[168]

Lab Book Reference: BT3/70

(*S*)-1-(1-(Naphthalen-1-yl)ethyl)-4-tosylpiperazine (*S*)-202

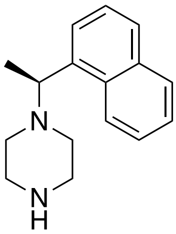


(*S*)-**202**

A mixture of *N*,*N*-bis(2-chloroethyl)-methylbenzenesulfonamide **195** (30.00 mmol, 8.89 g, 1.10 equiv), (*S*)-(−)-1-(1-naphthyl)ethylamine (*S*)-**200** (27.25 mmol, 3.30 g, 1.00 equiv, 99:1 er) and DIPEA (60.00 mmol, 7.76 g, 2.00 equiv) were stirred at 120 °C for 16 h. The solution was then allowed to cool to rt forming a viscous oil. The viscous oil was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (99:1 CH_2Cl_2-Et_2O) gave *N*-Ts piperazine (*S*)-**202** (7.75 g, 19.34 mmol, 71%) as a viscous orange oil. R_F = 0.2 (99:1 CH_2Cl_2-Et_2O); $[\alpha]_D$ +65.5 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2979, 2889, 2853, 2822, 1597, 1344, 1325, 1260, 1162, 1114, 960, 944, 815, 731; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30−8.25 (m, 1H, Ar), 7.87−7.80 (m, 1H, Ar), 7.73 (d, J = 8.0 Hz, 1H, Ar), 7.66−7.58 (m, 2H, Ar), 7.50−7.36 (m, 4H, Ar), 7.35−7.29 (m, 2H, Ar), 4.12 (q, J = 6.5 Hz, 1H, NCH), 2.99 (br t, J = 7.0 Hz, 4H, NCH), 2.74−2.62 (m, 2H, NCH), 2.57−2.51 (m, 2H, NCH), 2.44 (s, 3H, Ar*Me*), 1.43 (d, J = 6.5 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) 147.4 (*ipso*-Ar), 143.7 (*ipso*-Ar), 139.9 (*ipso*-Ar), 134.2 (Ar), 132.8 (*ipso*-Ar), 131.6 (*ipso*-Ar), 129.8 (Ar), 128.9 (Ar), 128.0 (Ar), 127.7 (Ar), 125.8 (Ar), 125.5 (Ar), 124.7 (Ar), 123.9 (Ar) 61.1 (NCH), 50.0 (NCH_2), 46.5 (NCH_2), 21.7 (Ar*Me*), 18.7 (Me); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{26}N_2O_2S$ $(M + H)^+$ 395.1788, found 395.1792 (−1.1 ppm error).

Lab Book Reference: BT3/65

(*S*)-1-(1-(Naphthalen-1-yl)ethyl)piperazine (*S*)-204



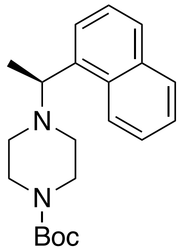
(*S*)-**204**

N-Ts piperazine (*S*)-**202** (19.60 mmol, 7.74 g, 1.00 equiv) and 4-hydroxybenzoic acid (58.80 mmol, 8.12 g, 3.00 equiv) was stirred in HBr (33 wt. % in AcOH, 50 mL) for 3 days at rt. Then, H_2O (55 mL) was added and the resulting mixture was stirred for 2 h forming a white precipitate. The solids were removed *via* filtration and the filtrate was extracted with toluene (3 × 50 mL). The aqueous layer was cooled to 0 °C and basified with solid KOH. The basic solution was then extracted with EtOAc (3 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give piperazine (*S*)-**204** (2.17 g, 9.02 mmol, 46%) as a yellow oil, $[\alpha]_D$ −27.8 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3046, 2972, 2938, 2806, 1508, 1455, 1372, 1322, 1134, 1120, 945, 799, 776; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51−8.43 (m, 1H, Ar), 7.87−7.82 (m, 1H, Ar), 7.77−7.71 (m, 1H, Ar), 7.62−7.55 (m, 1H, Ar), 7.53−7.40 (m, 3H, Ar), 4.08 (q, J = 6.5 Hz, 1H, NCH), 2.95−2.81 (m, 4H, NCH), 2.65−2.53 (m, 2H, NCH), 2.48−2.38 (m, 3H, NCH+NH), 1.47 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6 (*ipso*-Ar), 134.2 (*ipso*-Ar), 131.8 (*ipso*-Ar), 128.8 (Ar), 127.4 (Ar), 125.54 (Ar), 125.52 (Ar), 125.4 (Ar), 124.8 (Ar), 124.3 (Ar), 62.2 (NCH), 52.0

(NCH$_2$), 46.4 (NCH$_2$), 18.8 (Me); HRMS (ESI) *m/z* calcd for $C_{16}H_{20}N_2$ $(M + H)^+$ 241.1699, found 241.1697 (+1.0 ppm error).

Lab Book Reference: BT3/68

tert-Butyl (*S*)-4-(1-(naphthalen-1-yl)ethyl)piperazine-1-carboxylate (*S*)-193

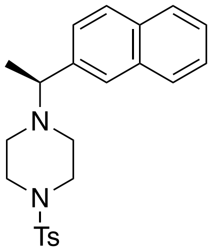


(*S*)-**193**

A solution of di-*tert*-butyl dicarbonate (10.80 mmol, 2.36 g, 1.30 equiv) in CH_2Cl_2 (15 mL) was added dropwise to a stirred solution of piperazine (*S*)-**204** (8.30 mmol, 2.00 g, 1.0 equiv) in CH_2Cl_2 (15 mL) at 0 °C under N_2. The resulting solution was allowed to warm to rt and stirred for a further 16 h. $NaHCO_{3(aq)}$ (50 mL) was then added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (4:1 hexane-EtOAc) gave *N*-Boc piperazine (*S*)-**193** (1.83 g, 5.40 mmol, 65%) as a viscous pale yellow oil, $R_F = 0.2$ (4:1 hexane-EtOAc); $[\alpha]_D$ −21.6 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2923, 2853, 1695 (C=O), 1596, 1450, 1247, 1167, 1121, 1002, 800, 777; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49−8.41 (m, 1H, Ar), 7.93−7.84 (m, 1H, Ar), 7.78 (d, $J = 8.0$ Hz, 1H, Ar), 7.66−7.58 (m, 1H, Ar), 7.55−7.42 (m, 3H, Ar), 4.14 (q, $J = 6.5$ Hz, 1H, NCH), 3.57−3.35 (m, 4H, NCH), 2.64−2.51 (m, 2H, NCH), 2.50−2.37 (m, 2H, NCH), 1.52 (d, $J = 6.5$ Hz, 3H, Me), 1.47 (s, 9H, CMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9 (C=O), 134.2 (*ipso*-Ar), 134.1 (*ipso*-Ar), 131.6 (*ipso*-Ar), 128.9 (Ar), 127.7 (Ar), 125.7 (Ar), 125.6 (Ar), 125.5 (Ar), 124.9 (Ar), 124.2 (Ar) 79.6 (O*C*Me$_3$), 61.7 (NCH), 50.1 (NCH_2), 44.1 (NCH_2), 28.6 (C*Me*$_3$), 18.9 (Me); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{28}N_2O_2$ $(M + H)^+$ 341.2224, found 341.2227 (−1.1 ppm error).

Lab Book Reference: BT3/72

(*S*)-1-(1-(Naphthalen-2-yl)ethyl)piperazine (*S*)-203



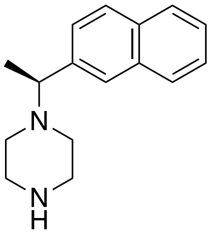
(*S*)-**203**

A mixture of *N*,*N*-bis(2-chloroethyl)-methylbenzenesulfonamide **195** (20.27 mmol, 6.01 g, 1.10 equiv), (*S*)-(−)-1-(2-naphthyl)ethylamine (*S*)-**201** (18.50 mmol, 3.17 g, 1.00 equiv, 99:1 er) and DIPEA (37.00 mmol, 4.80 g, 2.00 equiv) was stirred at 120 °C for 16 h. The solution was then allowed to cool to rt forming a viscous oil. The viscous oil was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The two layers separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (99:1-90:10 CH_2Cl_2-Et_2O) gave *N*-Ts piperazine (*S*)-**203** (5.06 g, 12.77 mmol, 69%) as a light brown solid, mp 159−161 °C; R_F = 0.2 (97:3 CH_2Cl_2-Et_2O); $[\alpha]_D$ +96.2 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2981, 2853, 2826, 1598, 1451, 1340, 1324, 1209, 1162, 1114, 944, 815, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.73 (m, 3H, Ar), 7.67−7.59 (m, 3H, Ar), 7.50−7.39 (m, 3H, Ar), 7.32 (d, *J* = 8.0 Hz, 2H, Ar), 3.51 (q, *J* = 6.5 Hz, 1H, NCH), 3.00 (br s, 4H, NCH), 2.68−2.56 (m, 2H, NCH), 2.55−2.46 (m, 2H, NCH), 2.44 (s, 3H, ArC*H*$_3$), 1.39 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (*ipso*-Ar), 141.2 (*ipso*-Ar), 133.4 (*ipso*-Ar), 132.9 (*ipso*-Ar), 132.6 (*ipso*-Ar), 129.8 (Ar), 128.3 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 126.21 (Ar), 126.19 (Ar), 125.8 (Ar), 125.7 (Ar), 64.7

(CH), 49.9 (NCH_2), 46.5 (NCH_2), 21.7 (Ar*C*H_3), 19.6 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{26}N_2O_2S$ $(M + H)^+$ 395.1788, found 395.1791 (−0.9 ppm error).

Lab Book Reference: BT3/69

(*S*)-1-(1-(Naphthalen-2-yl)ethyl)piperazine (*S*)-205

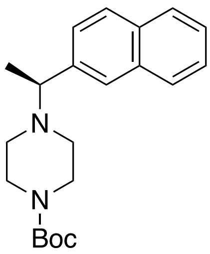


(*S*)-**205**

N-Ts piperazine (*S*)-**203** (12.70 mmol, 5.00 g, 1.00 equiv) and 4-hydroxybenzoic acid (38.10 mmol, 5.26 g, 3.00 equiv) were stirred in HBr (33 wt. % in AcOH, 35 mL) for 3 days at rt. Then, H_2O (30 mL) was added and the resulting mixture was stirred for 2 h forming a white precipitate. The solids were removed *via* filtration and the filtrate was extracted with toluene (3 × 50 mL). The aqueous layer was cooled to 0 °C and basified with solid KOH. The basic solution was then extracted with EtOAc (3 × 50 mL). The combined organics were dried ($MgSO_4$) concentrated under reduced pressure to give piperazine (*S*)-**205** (2.85 g, 11.9 mmol, 94%) as a brown oil, $[\alpha]_D$ 34.1 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3267, 2970, 1937, 2803, 1505, 1455, 1371, 1306, 1242, 1133, 1122, 942, 820, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84−7.77 (m, 3H, Ar), 7.70 (s, 1H, Ar), 7.53−7.42 (m, 3H, Ar), 3.57−3.48 (m, 2H, NCH and NH), 2.95 (t, $J = 5.0$ Hz, 4H, NCH), 2.66−2.54 (m, 2H, NCH), 2.42 (m, 2H, NCH), 1.43 (d, $J = 6.5$ Hz, 3H, Me) ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7 (*ipso*-Ar), 133.5 (*ipso*-Ar), 133.0 (*ipso*-Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 126.3 (Ar), 126.1 (Ar), 126.0 (Ar), 125.7 (Ar), 65.3 (NCH), 50.9 (NCH_2), 45.8 (NCH_2), 19.6 (Me); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{20}N_2$ $(M + H)^+$ 241.1699, found 241.1698 (+0.4 ppm error).

Lab Book Reference: BT3/71

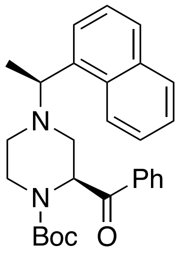
tert-Butyl (*S*)-4-(1-(naphthalen-2-yl)ethyl)piperazine-1-carboxylate (*S*)-194



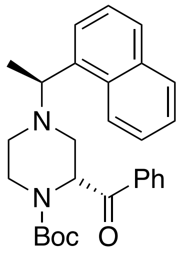
(*S*)-**194**

A solution of di-*tert*-butyl dicarbonate (15.20 mmol, 3.32 g, 1.30 equiv) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of piperazine (*S*)-**205** (11.66 mmol, 2.80 g, 1.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C under N_2. The resulting solution was allowed to warm to rt and stirred for a further 16 h. $NaHCO_{3(aq)}$ (50 mL) was then added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (4:1 hexane-EtOAc) gave *N*-Boc piperazine (*S*)-**194** (3.29 g, 9.68 mmol, 83%) as a viscous pale yellow oil, R_F = 0.2 (4:1 hexane-EtOAc); $[\alpha]_D$ −47.7 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2973, 2809, 1690 (C=O), 1418, 1364, 1245, 1167, 1120, 1002, 933, 820, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87−7.76 (m, 3H, Ar), 7.71 (s, 1H, Ar), 7.58−7.42 (m, 3H, Ar), 3.62−3.51 (m, 1H, NCH), 3.40−3.36 (m, 4H, NCH), 2.61 (m, 2H, NCH), 2.45−2.33 (m, 2H, NCH), 1.47 (d, J = 5.0 Hz, 3H, Me), 1.43 (s, 9H, CMe_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8 (C=O), 141.5 (*ipso*-Ar), 133.4 (*ipso*-Ar), 132.8 (*ipso*-Ar), 128.1 (Ar), 127.8 (Ar), 127.7 (Ar), 126.2 (Ar), 126.0 (Ar), 125.9 (Ar), 125.6 (Ar), 79.5 ($\mathit{C}Me_3$), 64.9 (NCH), 50.5 (NCH_2), 43.8 (NCH_2), 28.5 ($C\mathit{Me}_3$), 19.6 (Me); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{28}N_2O_2$ $(M + H)^+$ 341.2224 found 341.2227 (−1.1 ppm error). Lab Book Reference: BT3/75

*t*ert-Butyl (*S*)-2-benzoyl-4-((*S*)-1-naphthalen-1-yl)ethyl)piperazine-1-carboxylate (*S*,*S*)-206 and *t*ert-Butyl (*R*)-2-benzoyl-4-((*S*)-1-naphthalen-1-yl)ethyl)piperazine-1-carboxylate (*R*,*S*)-206



(*S*,*S*)-**206**



(*R*,*S*)-**206**

Scheme 3.41

Following general procedure F, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc piperazine (*S*)-**193** (0.5 mmol, 170 mg, 1.00 equiv) and TMEDA (0.65 mmol, 78 mg, 1.30 equiv) in Et_2O (5 mL) at −78 °C for 1 h then PhCONMe(OMe) (0.65 mmol, 107 mg, 1.30 equiv) gave the crude product which contained an 80:20 mixture of ketones (*S*,*S*)-**206** and (*R*,*S*)-**206** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography (99:1 CH_2Cl_2-Et_2O) gave ketone (*R*,*S*)-**206** (33 mg, 0.08 mmol, 15%) as an off-white solid, mp 87−89 °C; R_F = 0.2 (98:2 CH_2Cl_2-Et_2O); ν_{max}/cm^{-1} 2973, 2819, 1703 (C=O, ketone), 1683 (C=O, Boc), 1597, 1447, 1362, 1249, 1163, 1049, 960, 773, 695; ^{1}H NMR (300 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 8.23−8.16 (m, 1H, Ar), 7.80−7.71 (m, 1H, Ar), 7.58 (br d, J = 8.0 Hz, 1H, Ar), 7.51−7.43 (m, 2H, Ar), 7.41−7.33 (m, 2H, Ar), 7.25−7.17 (m, 5H, Ar), 5.45 (br s, 0.6H, NCH), 5.26 (br s, 0.4H, NCH), 4.19−4.05 (m, 1H, NCH), 3.81 (br d, J = 12.0 Hz, 0.4H, NCH), 3.71 (br d, J = 12.0 Hz, 0.6H, NCH), 3.54−3.33 (m, 1.60H, NCH), 3.27 (br d, J = 11.0 Hz, 0.4H, NCH), 2.89−2.68 (m, 1H, NCH), 2.51 (dd, J = 12.0, 4.5 Hz, 1H, NCH), 2.40−2.21 (m, 1H, NCH), 1.46 (s, 5.40H, CMe_3), 1.38 (s, 3.60H, CMe_3), 1.20 (d, J = 6.5 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of rotamers) δ 199.5 (C=O, ketone), 156.6 (C=O, Boc), 156.4 (C=O, Boc), 143.8 (*ipso*-Ar), 143.7 (*ipso*-Ar), 136.5 (*ipso*-Ar), 136.4 (*ipso*-Ar), 134.2 (*ipso*-Ar), 134.1 (*ipso*-Ar), 133.8 (*ipso*-Ar), 133.8 (*ipso*-Ar), 132.1 (Ar), 132.0 (Ar), 131.7 (Ar), 131.40 (Ar), 131.37 (Ar), 128.7 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.38 (Ar), 127.35 (Ar), 125.6 (Ar), 125.5 (Ar), 125.0 (Ar), 124.7 (Ar), 124.4 (Ar), 80.2 (*C*Me$_3$), 65.8 (NCH), 60.1 (NCH), 58.4 (NCH), 51.5 (NCH$_2$), 51.5 (NCH$_2$), 49.5 (NCH$_2$), 42.7 (NCH$_2$), 42.7 (NCH$_2$), 28.5 (C*Me*$_3$), 28.3 (C*Me*$_3$), 15.7 (Me), 15.6 (Me); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{32}N_2O_3$ $(M + H)^+$ 445.2486 found 445.2496 (−2.3 ppm error) and ketone (*S*,*S*)-**206** (116 mg, 0.26 mmol, 52%) as a white solid, mp 148−149 °C; $R_F = 0.1$ (98:2 CH_2Cl_2-Et_2O); $[\alpha]_D$ −26.2 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2978, 2806, 1698 (C=O, ketone), 1684 (C=O, Boc), 1598, 1449, 1347, 1220, 1160, 1118, 960, 806, 766; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 8.11−8.03 (m, 1H, Ar), 7.77−7.58 (m, 3H, Ar), 7.51 (br d, *J* = 8.0 Hz, 1H, ar), 7.46−7.37 (m, 3H, Ar), 7.33−7.27 (m, 2H, Ar), 7.19 (br d, *J* = 7.0 Hz, 1H, Ar), 6.99−6.90 (m, 1H, Ar), 5.40 (br s, 0.55H, NCH), 5.22 (s, 0.45H, NCH), 4.05−3.82 (m, 2H, NCH+CH), 3.63−3.47 (m, 1H, NCH), 3.35−3.03 (m, 2H, NCH), 2.45−2.31 (m, 1H, NCH), 2.23−2.11 (m, 1H, NCH), 1.48 (s, 5H, $C(CH_3)_3$), 1.41−1.33 (m, 7H, $C(CH_3)_3$+CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 199.9 (C=O, ketone), 156.2 (C=O, Boc), 155.9 (C=O, Boc), 139.5 (*ipso*-Ar), 139.3 (*ipso*-Ar), 135.9 (*ipso*-Ar), 135.9 (*ipso*-Ar), 133.9 (*ipso*-Ar), 132.6 (Ar), 131.21 (*ipso*-Ar), 131.18 (*ipso*-Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 128.1 (Ar), 127.7 (Ar), 127.2 (Ar), 125.6 (Ar), 125.3 (Ar), 125.19 (Ar), 125.16 (Ar), 124.1 (Ar), 123.7 (Ar), 123.7 (Ar), 60.6 (NCH), 60.5 (NCH), 58.8 (NCH), 57.8 (NCH), 53.4 (NCH$_2$), 53.3 (NCH$_2$), 49.1 (NCH$_2$), 48.8 (NCH$_2$), 42.8 (NCH$_2$), 42.0 (NCH$_2$), 28.5 (C*Me*$_3$), 28.3 (*CMe*$_3$), 19.0 (Me), 18.6 (Me); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{32}N_2O_3$ $(M + H)^+$ 445.2486 found 445.2489 (−0.7 ppm error).

Lab Book Reference: BT3/74

Table 3.15, entry 1

Following general procedure F, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc piperazine (*S*)-**193** (0.5 mmol, 170 mg, 1.00 equiv) and diamine *trans*-**192** (0.65 mmol, 111 mg, 1.30 equiv) in Et_2O (5 mL) at −78 °C for 1 h then PhCONMe(OMe) (0.65 mmol, 107 mg, 1.30 equiv) gave the crude product which contained an 80:20 mixture of ketones (*S*,*S*)-**206** and (*R*,*S*)-**206** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography (99:1 CH_2Cl_2-Et_2O) gave ketone (*R*,*S*)-**206** (20 mg, 0.05 mmol, 9%) as a white solid and ketone (*S*,*S*)-**206** (89 mg, 0.20 mmol, 40%) as a white solid.

Lab Book Reference: BT3/78

Table 3.15, entry 2

Following general procedure F, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc piperazine (*S*)-**193** (0.5 mmol, 170 mg, 1.00 equiv) and bispidine **211** (0.65 mmol, 119 mg, 1.30 equiv) in Et_2O (5 mL) at −78 °C for 1 h then PhCONMe(OMe) (0.65 mmol, 107 mg, 1.30 equiv) gave the crude product which contained a 80:20 mixture of ketones (*S*,*S*)-**206** and (*R*,*S*)-**206** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography (99:1 CH_2Cl_2-Et_2O) gave ketone (*R*,*S*)-**206** (7 mg, 0.02 mmol, 3%) as a white solid and ketone (*S*,*S*)-**206** (22 mg, 0.05 mmol, 10%) as a white solid.

Lab Book Reference: BT4/13

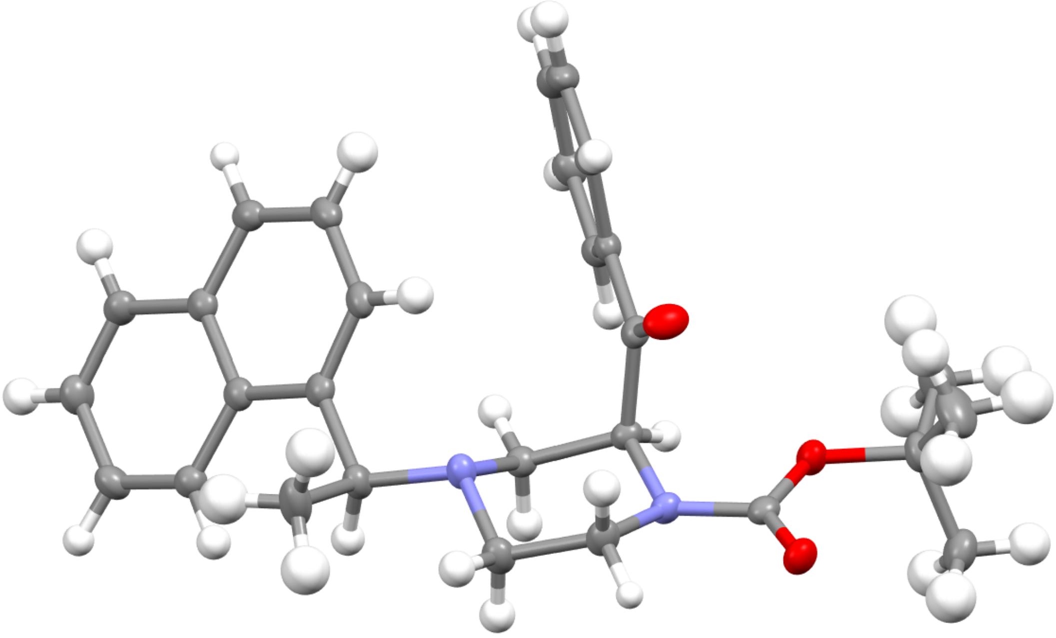
Scheme 3.45

Following general procedure F, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.50 mL, 1.30 equiv), *N*-Boc piperazine (*S*)-**193** (0.5 mmol, 170 mg, 1.00 equiv) and TMEDA (0.65 mmol, 78 mg, 1.30 equiv) in TMO (5 mL) at −78 °C for 1 h then PhCONMe(OMe) (0.65

mmol, 107 mg, 1.30 equiv) gave the crude product which contained an 80:20 mixture of ketones (*S*,*S*)-**206** and (*R*,*S*)-**206** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography (99:1 CH_2Cl_2-Et_2O) gave ketone (*R*,*S*)-**206** (29 mg, 0.07 mmol, 13%) as a white solid and ketone (*S*,*S*)-**206** (107 mg, 0.24 mmol, 48%) as a white solid.

Lab Book Reference: BT5/28

_t_ert-Butyl (_S_)-2-benzoyl-4-((_S_)-1-naphthalen-1-yl)ethyl)piperazine-1-carboxylate (_S_,_S_)-206



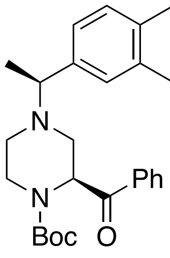
Crystal data and structure refinement for (*S*,*S*)-**206**.

Identification code	paob22009
Empirical formula	$C_{28}H_{32}N_2O_3$
Formula weight	444.55
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.02629(11)

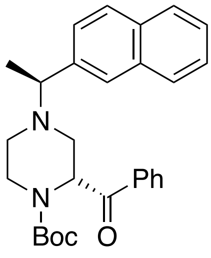
b/Å	10.41163(11)
c/Å	12.02766(13)
α/°	90
β/°	90.7013(10)
γ/°	90
Volume/Å	3 1255.47(2)
Z	2
ρ calc g/cm^3	1.176
μ/mm^1	0.605
F(000)	476.0
Crystal size/mm^3	0.201 × 0.133 × 0.075
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.35 to 134.156
Index ranges	$-11 \leq h \leq 11$, $-12 \leq k \leq 12$, $-10 \leq l \leq 14$
Reflections collected	13151
Independent reflections	4481 [R int = 0.0269, R sigma = 0.0278]
Data/restraints/parameters	4481/1/427
Goodness-of-fit on F^2	1.049
Final R indexes [I>=2σ (I)]	$R_1 = 0.0260$, $wR_2 = 0.0686$
Final R indexes [all data]	$R_1 = 0.0271$, $wR_2 = 0.0693$
Largest diff. peak/hole / e Å^{-3}	0.13/-0.12
Flack parameter	-0.02(9)

Data collected, solved and refined by Adrian C Whitwood

***tert*-Butyl (*S*)-2-benzoyl-4-((*S*)-1-(naphthalen-2-yl)ethyl)piperazine-1-carboxylate (*S*,*S*)-207 and *tert*-Butyl (*R*)-2-benzoyl-4-((*S*)-1-(naphthalen-2-yl)ethyl)piperazine-1-carboxylate (*R*,*S*)-207**



(*S*,*S*)-**207**

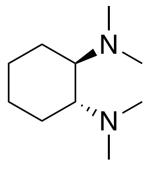


(*R*,*S*)-**207**

Following general procedure F, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.30 equiv), *N*-Boc piperazine (*S*)-**194** (0.5 mmol, 170 mg, 1.00 equiv) and TMEDA (0.65 mmol, 78 mg, 1.3 equiv) in Et_2O (5 mL) at −78 °C for 1 h then PhCONMe(OMe) (0.65 mmol, 107 mg, 1.30 equiv) gave the crude product which contained an 75:25 mixture of ketones (*S*,*S*)-**207** and (*R*,*S*)-**207** (by ^{1}H NMR spectroscopy). Only small quantities of products (*S*,*S*)-**207** and (*R*,*S*)-**207** were observed in the ^{1}H NMR spectrum of the crude product. Purification by flash column chromatography was attempted but (*S*,*S*)-**207** and (*R*,*S*)-**207** could not be isolated.

Lab Book Reference: BT5/33

(*trans*)-(±)-N^1,N^1,N^2,N^2-Tetramethylcyclohexane-1,2-diamine 192

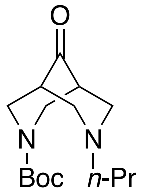


trans-**192**

Formaldehyde (37% w/v solution in water, 128.87 mmol, 9.10 mL, 7.00 equiv) was added dropwise to a stirred solution of *trans*-(±)-diaminocyclohexane **189** (17.51 mmol, 2.00 g, 1.00 equiv), and formic acid (185.53 mmol, 7.00 mL, 10.60 equiv) at 0 °C. The resulting solution was stirred and heated at reflux for 2 h. The solution was then cooled to 0 °C and pellets of $NaOH_{(s)}$ were added until a pH = 12 was reached. The solution was then extracted with Et_2O (3 × 25 mL). The organic extracts were dried (KOH) and concentrated under reduced pressure to give the crude product. The crude product was taken up in EtOAc (25 mL) under N_2 and EtOH (70.04 mmol, 4.10 mL, 4.00 equiv) and acetyl chloride (70.04 mmol, 5.00 mL, 4.00 equiv) were added dropwise to the stirred solution at 0 °C. The resulting suspension was allowed to warm to rt over 1 h. The solids were collected through filtration and washed with EtOAc (2 ×10 mL). Recrystallisation from hot EtOH gave the bis-hydrochloride salt as a white solid. The solid was taken up in EtOH (20 mL) and 20% $NaOH_{(aq)}$ was added. The layers were separated and aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the diamine. Purification by Kugelrohr distillation gave *trans*-**192** (917 mg, 5.43 mmol, 31%) as a colourless oil, bp 55−60 °C/1.0 mmHg (lit.,[255] bp 50 °C/0.1 mmHg); ν_{max}/cm^{-1} 2923, 2855, 2772, 1449, 1271, 1065, 1046, 1024, 950, 876; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47−2.37 (m, 2H, NCH), 2.31 (s, 12H, NMe_2), 1.94−1.83 (m, 2H, CH), 1.77−1.70 (m, 2H, CH), 1.26−1.04 (m, 4H, CH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.1 (NCH), 40.3 (NMe), 25.7 (CH_2), 23.3 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{10}H_{22}N_2$ $(M + H)^+$ 171.1856 found 171.1856 (−0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[256]

Lab Book Reference: BT3/77

***tert*-Butyl 9-oxo-7-propyl-3,7-diazobicyclo[3.3.1]nonane-3-carboxylate 209**

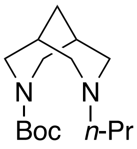


209

A solution of *N*-Boc-piperidin-4-one **208** (50.00 mmol, 9.96 g, 1.00 equiv), *n*-propylamine (50.00 mmol, 4.12 mL, 1.00 equiv) and acetic acid (50.00 mmol, 2.86 mL, 1.00 equiv) in dry MeOH (125 mL) was added dropwise to a stirred suspension of paraformaldehyde (100 mmol, 3.01 g, 2.00 equiv) in dry MeOH (125 mL) at rt under N_2. The resulting suspension was stirred and heated at reflux for 1 h. Paraformaldehyde (100 mmol, 3.01 g, 2.00 equiv) was added to the stirred suspension and heated at reflux for a further 16 h. The now homogenous solution was cooled to rt and concentrated under reduced pressure. The residue was taken up in water (50 mL) and $KOH_{(aq)}$ (1 M, 120 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried (K_2CO_3) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (4:1 → 3:2 Hexane-EtOAc) gave bispidone **209** (12.45 g, 44.00 mmol, 88%) as a yellow oil, $R_F = 0.1{-}0.5$ (3:2 Hexane-EtOAc); ν_{max}/cm^{-1} 2962, 2934, 2873, 1732 (C=O, ketone), 1692 (C=O, Boc), 1418, 1229, 1165, 989, 756; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.60 (br d, *J* = 13.5 Hz, 1H, BocNCH), 4.43 (br d, *J* = 13.5 Hz, 1H, BocNCH), 3.28 (br d, *J* = 13.5 MHz, 1H, BocNCH), 3.22 (d, *J* = 11.0 Hz, 1H, *n*-PrNCH), 3.20−3.15 (m, 1H, *n*-PrNCH), 3.13 (br d, *J* = 13.5 Hz, 1H, BocNCH), 2.65 (dd, *J* = 11.0, 3.0 Hz, 1H, *n*-PrNCH), 2.56 (dd, *J* = 11.0, 3.0 Hz, 1H, *n*-PrNCH), 2.42−2.31 (m, 2H, CH), 2.24 (dt, *J* = 12.0, 7.5 Hz, 1H, $NCH_AH_BCH_2$), 2.15 (dt, *J* = 12.0, 7.5 Hz, 1H, $NCH_AH_BCH_2$), 1.46 (s, 9H, CMe_3), 1.45−1.42 (m, 2H, CH_2Me), 0.84 (t, *J* = 7.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$) (rotamers) δ 214.0 (C=O, ketone), 155.0 (C=O, Boc), 79.9 (O*C*Me$_3$), 59.7 (*n*-PrNCH$_2$), 59.4 (N*C*H$_2$CH$_2$), 58.6 (*n*-PrN*C*H$_2$), 50.8 (BocNCH$_2$), 50.0 (BocNCH$_2$), 48.2 (CH), 48.1 (CH), 28.6 (CMe$_3$), 20.3 (*C*H$_2$Me), 11.9 (Me); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{26}N_2O_3$ $(M + H)^+$ 283.2016 found 283.2022 (−2.1 ppm error).

Lab Book Reference: BT4/39

tert-Butyl 7-propyl-3,7-diazobicyclo[3.3.1]nonane-3-carboxylate 210

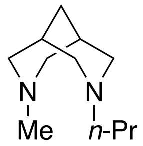


210

Hydrazine tosylate (41.00 mmol, 7.63 g, 1.25 equiv) was added to a stirred solution of bispidone **209** (32.80 mmol, 9.26 g, 1.00 equiv) in EtOH (170 mL) at rt. The resulting solution was stirred and heated at reflux for 2 h. The solution was allowed to cool to rt and was concentrated under reduced pressure. The crude hydrazone was dissolved in 4:1 THF-H_2O (200 mL). The resulting solution was cooled to 0 °C and $NaBH_4$ (344.40 mmol, 13.03 g, 10.50 equiv) was added portion-wise. The resulting solution was allowed to warm to rt over 16 h. The solution was then stirred and heated at reflux for 3 h. The solution was allowed to cool to rt and H_2O (200 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (4 × 50 mL). The combined organics were dried (K_2CO_3) and concentrated under reduced pressure. Purification by flash column chromatography (4:1 Hexane-EtOAc) gave *N*-Boc bispidine **210** (3.77 g, 14.10 mmol, 43%) as a yellow oil, R_F = 0.1−0.3 (4:1 Hexane-EtOAc), ν_{max}/cm^{-1} 2961, 2917, 2761, 1691 (C=O), 1423, 1239, 1176, 1135, 998; ^1H NMR (400 MHz, toluene-d$_8$) (rotamers) δ 4.38 (br d, J = 13.0 Hz, 1H, BocNCH), 4.04 (br d, J = 13.0 Hz, 1H, BocNCH), 2.89 (ddd, J = 13.0, 3.5, 2.0 Hz, 1H, BocNCH), 2.84 (br d, J = 11.0 Hz, 1H, *n*-PrNCH), 2.78 (ddd, J = 13.0, 3.5, 2.0 Hz, 1H, BocNCH), 2.71, (d, J = 11.0 Hz, 1H, *n*-PrNCH), 2.06−2.00 (m, 1H, NCH_AH_BCH$_2$), 1.99−1.96 (m, 1H, NCH$_A$$H_BCH_2$), 1.95−1.91 (m, 1H, CH), 1.85 (br d, J = 11.0 Hz, 1H, CH), 1.50 (s, 9H, CMe$_3$), 1.48−1.39 (m, 2H, CH_2Me), 1.38−1.35 (m, 1H, CH), 1.35−1.31 (m, 1H, CH), 1.30−1.27 (m, 2H, CHCH_2CH), 0.90 (t J = 7.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, toluene-d$_8$) (rotamers) δ 154.7 (C=O), 77.9 (O*C*Me$_3$), 61.2 (N*C*H$_2$CH$_2$), 59.4 (*n*-PrNCH$_2$), 58.4 (*n*-PrNCH$_2$), 48.9 (BocNCH$_2$), 47.9 (BocNCH$_2$), 32.1 (NCH$_2$*C*H$_2$), 29.9 (CH), 29.7 (CH), 28.7 (C*Me*$_3$), 20.2 (CH*C*H$_2$CH), 12.1 (Me); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{28}N_2O_2$ (M + H)$^+$ 269.2224 found 269.2227 (−1.2 ppm error).

Lab Book Reference: BT4/40

3-Methyl-7-propyl-3,7-diazobicyclo[3.3.1]nonane 211



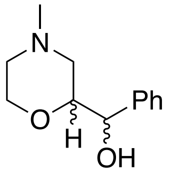
211

A solution of *N*-Boc bispidine **210** (4.47 mmol, 1.20 g, 1.00 equiv) in dry THF (20 mL) was added dropwise to a stirred suspension of LiAlH$_4$ (17.88 mmol, 0.679 g, 4.00 equiv) in dry THF (25 mL) at 0 °C under N$_2$. The resulting suspension was stirred and heated at reflux for 16 h. The solution was then cooled to 0 °C and diluted with Et$_2$O (50 mL) Na$_2$SO$_4$.10H$_2$O was added portion-wise to the stirred solution until gas evolution ceased. The solution was allowed to warm to rt over 1 h. The solids were removed by filtration through celite® and washed with 1:1 EtOH-MeOH (3 × 25 mL). The filtrate was concentrated under reduced pressure. NaOH$_{(aq)}$ (20% w/v, 30 mL) was added to the bispidine/water mixture and the aqueous layer was extracted with Et$_2$O (3 × 25 mL). The combined organics were dried (K$_2$CO$_3$) and concentrated under reduced pressure. Purification *via* Kugelrohr distillation gave product **211** (0.538 g, 2.95 mmol, 66%) as a colourless oil, bp 90−100 °C/1.0 mmHg; ν_{max}/cm^{-1} 2956, 2929, 2759, 1460, 1373, 1275, 1146, 1052, 843; ^{1}H NMR (400 MHz, toluene-d_8) δ 2.63 (br d, J = 11.0 Hz, 2H, *n*-PrNCH), 2.56 (br d, J = 11.0 Hz, 2H, *n*-PrNCH), 2.24 (dd, J = 11.0, 5.0 Hz, 2H, MeNC*H*), 2.21−2.13 (m, 4H, CH_3NC*H* + NC*H*$_2$CH$_2$), 2.12 (s, 3H, NMe), 1.75−1.69 (m, 2H, C*H*CH$_2$C*H*), 1.49−1.37 (m, 4H NCH$_2$C*H*$_2$ + CHC*H*$_2$CH), 0.90 (t, J = 7.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, toluene-d_8) δ 61.3 (N*C*H$_2$CH$_2$), 60.3 (MeN*C*H$_2$), 58.6 (*n*-PrN*C*H$_2$), 46.7 (NMe), 30.3 (CH*C*H$_2$CH), 30.1 (*C*HCH$_2$*C*H), 21.0 (*C*H$_2$Me), 12.6 (Me); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{22}N_2$ $(M + H)^+$ 183.1856 found 183.1849 (+3.8 ppm error).

Lab Book Reference: BT4/36

5.5 Experimental for Chapter 4

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 237



237

Table 4.5, entry 1

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in hexane (7 mL) at 0 °C for 1 h and PhCHO (2.0 mmol, 228 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **237** (158 mg, 0.76 mmol, 76%) as a white solid, mp 76−78 °C; R_F = 0.2 (acetone); ν_{max}/cm^{-1} 3085 (br, OH), 2940, 2855, 2809, 1495, 1449, 1290, 1204, 1140, 1119, 1105, 1029, 914, 767, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H, Ph), 4.84 (d, J = 4.5 Hz, 0.5H, OC*H*Ph), 4.50 (d, J = 7.5 Hz, 0.5H, OC*H*Ph), 3.99−3.89 (m, 1H, OCH), 3.77−3.66 (m, 1.5H, OCH), 3.62 (ddd, J = 10.0, 7.5, 2.5 Hz, 0.5H, OCH), 3.30 (br s, 1H, OH), 2.64−2.55 (m, 1H, NCH), 2.50 (br d, J = 11.5 Hz, 0.5H, NCH), 2.31 (br d, J = 11.5 Hz, 0.5H, NCH), 2.21 (s, 1.5H, NMe), 2.17 (s, 1.5H, NMe), 2.14−2.08 (m, 1H, NCH), 2.05 (dd, J = 11.0, 10.0 Hz, 0.5H, NCH), 1.84 (dd, J = 11.0, 10.0 Hz, 0.5H, NCH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (*ipso*-Ph), 139.9 (*ipso*-Ph), 128.6 (Ph), 128.4 (Ph), 128.4 (Ph), 127.7 (Ph), 127.3 (Ph), 126.4 (Ph), 79.7 (O*C*HPh), 78.8 (O*C*HPh), 75.9 (O*C*H), 74.8 (O*C*H), 66.8 (OCH_2), 66.8 (OCH_2), 56.5 (NCH_2), 54.9 (NCH_2), 54.8 (NCH_2), 54.3 (NCH_2), 46.4 (NMe), 46.3 (NMe); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{17}NO_2$ (M + H)$^+$ 208.1332 found 208.1331 (+0.5 ppm error).

Lab Book Reference: BT4/6

Table 4.5, entry 2

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) at 0 °C for 1 h and PhCHO (2.0 mmol, 228 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **237** (51 mg, 0.24 mmol, 24%) as a white solid.

Lab Book Reference: BT4/7

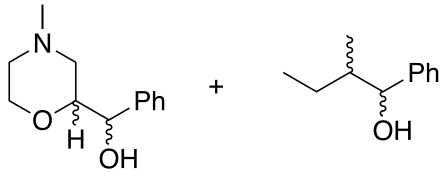
Table 4.5, entry 3

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) at −10 °C for 1 h and PhCHO (2.0 mmol, 228 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **237** (120 mg, 0.58 mmol, 58%) as a white solid.

Lab Book Reference: BT4/16

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 237 and 2-Methyl-1-phenylbutan-1-ol 230

Table 4.5, entry 4



237 **230**

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) at −20 °C for 1 h and PhCHO (2.0 mmol, 228 mg, 2.0

equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **230** (57 mg, 0.34 mmol, 26% with respect to *s*-BuLi) as a colourless oil, $R_F = 0.7$ (acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.21 (m, 5H, Ph), 4.54 (d, J = 6.0 Hz, 0.5H, OCH), 4.44 (d, J = 7.0 Hz, 0.5H, OCH), 1.87−1.62 (m, 2.5H), 1.47−1.30 (m, 0.5H), 1.25−1.01 (m, 1H), 0.96−0.91 (m, 3H, Me), 0.91−0.86 (m, 1.5H, Me), 0.75 (d, J = 7.0 Hz, 1.5H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8 (*ipso*-Ph), 143.3 (*ipso*-Ph), 128.3 (Ph), 127.4 (Ph), 127.1 (Ph), 126.9 (Ph), 126.5 (Ph), 79.0 (OCH), 78.2 (OCH), 42.1 (CH), 41.8 (CH), 26.0 (CH_2), 25.0 (CH_2), 15.3 (Me), 14.1 (Me), 11.8 (Me), 11.5 (Me) (one Ph resonance not resolved) and diastereomeric alcohols **237** as a 50:50 mixture of diastereomers (143 mg, 0.69 mmol, 69%) as a white solid.

Lab Book Reference: BT4/8

Table 4.5, entry 5

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) at −20 °C for 2 h and PhCHO (2.0 mmol, 228 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **237** (155 mg, 0.75 mmol, 75%) as a white solid.

Lab Book Reference: BT4/9

Table 4.5, entry 6

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) at −30 °C for 2 h and PhCHO (2.0 mmol, 228 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **230** (61 mg, 0.36 mmol, 28% with respect to *s*-BuLi) as a colourless oil and a 50:50 mixture of diastereomeric alcohols **237** (115 mg, 0.56 mmol, 56%) as a white solid.

Lab Book Reference: BT4/10

Table 4.5, entry 7

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv) and TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) at −30 °C for 2 h and PhCHO (2.0 mmol, 228 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **230** (36 mg, 0.22 mmol, 17% with respect to *s*-BuLi) as a colourless oil and a 50:50 mixture of diastereomeric alcohols **237** (114 mg, 0.55 mmol, 55%) as a white solid.

Lab Book Reference: BT4/11

Scheme 4.15 (−45 °C)

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv) and bispidine **211** (0. 65 mmol, 119 mg, 1.3 equiv) in TMO (4 mL) at −45 °C for 1 h and PhCHO (1.0 mmol, 106 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **237** (83 mg, 0.40 mmol, 80%) as a white solid.

Lab Book Reference: BT4/37

Scheme 4.15 (−30 °C)

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv) and bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (4 mL) at −30 °C for 1 h and PhCHO (1.0 mmol, 106 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohol **237** (91 mg, 0.44 mmol, 87%) as a white solid.

Lab Book Reference: BT4/38

Table 4.8, entry 1

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv) and bispidine **211** (0.25 mmol, 46 mg, 0.5 equiv) in TMO (4 mL) at −30 °C for 2 h and PhCHO (1.0 mmol, 106 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **237** (95 mg, 0.46 mmol, 91%) as a white solid.

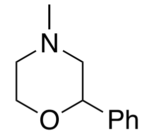
Lab Book Reference: BT4/66

Table 4.8, entry 2

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv) and bispidine **211** (0.15 mmol, 27 mg, 0.3 equiv) in TMO (4 mL) at −30 °C for 2 h and PhCHO (1.0 mmol, 106 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (acetone) gave a 50:50 mixture of diastereomeric alcohols **237** (62 mg, 0.30 mmol, 60%) as a white solid.

Lab Book Reference: BT4/70

4-Methyl-2-phenylmorpholine 252



252

Table 4.6, entry 2

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv), TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) and $ZnCl_2$ (0.7 M solution in THF, 1.3 mmol, 1.85 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.07 mmol, 16 mg, 0.07 equiv), *t*-Bu_3PHBF_4 (0.09 mmol, 26 mg, 0.09 equiv) and bromobenzene (1.3 mmol, 204 mg, 1.3 equiv) at 80 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (61 mg, 0.30 mmol, 30%) as a pale yellow oil, $R_F = 0.2$ (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1); ν_{max}/cm^{-1} 2933, 2853, 2791, 1450, 1353, 1288, 1105, 1082, 916, 883, 752, 697, 587; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H, Ph), 4.56 (dd, J = 10.5, 2.5 Hz, 1H, OCH), 4.04 (ddd, J = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.84 (td, J = 11.5, 2.5 Hz, 1H, OCH), 2.89 (ddd, J = 11.5, 2.5, 1.5 Hz, 1H, NCH), 2.76−2.71 (m, 1H, NCH), 2.32 (s, 3H, NMe), 2.23 (td, J = 11.5, 3.5 Hz, 1H, NCH), 2.04 (dd, J = 11.5, 10.5 Hz, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (*ipso*-Ph), 128.5 (Ph), 127.9 (Ph), 126.3 (Ph), 78.3 (OCH), 67.2 (OCH_2), 62.4 (NCH_2), 54.9 (NCH_2), 46.4 (NMe); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{15}NO$ $(M + H)^+$ 178.1226 found 178.1228 (−0.7 ppm error).

Lab Book Reference: BT4/28

Table 4.6, entry 1

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv), TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) and $ZnCl_2$ (0.7 M solution in THF, 1.3 mmol, 1.85 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.07 mmol, 16 mg, 0.07 equiv), *t*-Bu_3PHBF_4 (0.09 mmol, 26 mg, 0.09 equiv) and bromobenzene (1.3 mmol, 204 mg, 1.3 equiv) at 40 °C for 16 h gave the crude product. Only trace quantities of aryl morpholine **252** were observed in the ^{1}H NMR spectrum of the crude product and therefore purification was not attempted.

Lab Book Reference: BT4/27

Table 4.6, entry 3

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv), TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) and $ZnCl_2$ (0.7 M solution in THF, 1.3 mmol, 1.85 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.07 mmol, 16 mg, 0.07 equiv), RuPhos (0.09 mmol, 42 mg, 0.09 equiv) and bromobenzene (1.3 mmol, 204 mg, 1.3 equiv) at 80 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (61 mg, 0.35 mmol, 35%) as a pale yellow oil.

Lab Book Reference: BT4/29

Table 4.6, entry 4

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv), TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) and $ZnCl_2$ (0.7 M solution in THF, 1.3 mmol, 1.85 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.07 mmol, 16 mg, 0.07 equiv), RuPhos (0.09 mmol, 42 mg, 0.09

equiv) and bromobenzene (1.3 mmol, 204 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (88 mg, 0.50 mmol, 50%) as a pale yellow oil.

Lab Book Reference: BT4/30

Table 4.6, entry 5

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv), TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) and $ZnCl_2$ (0.7 M solution in THF, 1.3 mmol, 1.85 mL, 1.3 equiv) and then $[Pd(allyl)Cl]_2$ (0.07 mmol, 26 mg, 0.07 equiv), RuPhos (0.09 mmol, 42 mg, 0.09 equiv) and bromobenzene (1.3 mmol, 204 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (78 mg, 0.44 mmol, 44%) as a pale yellow oil.

Lab Book Reference: BT4/31

Table 4.6, entry 6

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv), TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) and $ZnCl_2$ (0.7 M solution in THF, 1.3 mmol, 1.85 mL, 1.3 equiv) and then Pd_2dba_3 (0.07 mmol, 64 mg, 0.07 equiv), RuPhos (0.09 mmol, 42 mg, 0.09 equiv) and bromobenzene (1.3 mmol, 204 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (77 mg, 0.44 mmol, 44%) as a pale yellow oil.

Lab Book Reference: BT4/32

Table 4.6, entry 7

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv), TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) and $ZnCl_2$ (0.7 M solution in THF, 1.3 mmol, 1.85 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.07 mmol, 16 mg, 0.07 equiv), CPhos (0.09 mmol, 39 mg, 0.09 equiv) and bromobenzene (1.3 mmol, 204 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (79 mg, 0.44 mmol, 44%) as a pale yellow oil.

Lab Book Reference: BT4/33

Table 4.6, entry 8

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.3 mmol, 1.0 mL, 1.3 equiv), *N*-methylmorpholine **236** (1.0 mmol, 101 mg, 1.0 equiv), TMEDA (1.3 mmol, 154 mg, 1.3 equiv) in TMO (7 mL) and $ZnCl_2$ (0.7 M solution in THF, 1.3 mmol, 1.85 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.07 mmol, 16 mg, 0.07 equiv), SPhos (0.09 mmol, 37 mg, 0.09 equiv) and bromobenzene (1.3 mmol, 204 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (78 mg, 0.44 mmol, 44%) as a pale yellow oil.

Lab Book Reference: BT4/34

Table 4.7, entry 1

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (46 mg, 0.26 mmol, 52%) as a pale yellow oil.

Lab Book Reference: BT4/43

Table 4.7, entry 2

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) at 100 °C for 60 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (45 mg, 0.26 mmol, 51%) as a pale yellow oil.

Lab Book Reference: BT4/46

Table 4.7, entry 3

Following general procedure H, in a pressure tube, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) at 120 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (43 mg, 0.25 mmol, 49%) as a pale yellow oil.

Lab Book Reference: BT4/54

Table 4.7, entry 4

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv), bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) and LiCl (1.3 mmol, 28 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (41 mg, 0.24 mmol, 47%) as a pale yellow oil.

Lab Book Reference: 4/60

Table 4.7, entry 5

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) in DMI (1 mL) at 100 °C for 16 h gave the crude product. None of arylated morpholine **252** was observed in in the ^{1}H NMR spectrum of the crude product and therefore purification was not attempted.

Lab Book Reference: BT4/55

Table 4.7, entry 6

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.05 mmol, 11 mg, 0.10 equiv), RuPhos (0.065 mmol, 30 mg, 0.13 equiv) and bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (37 mg, 0.21 mmol, 41%) as a pale yellow oil.

Lab Book Reference: BT4/53

Table 4.7, entry 7

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (1.3 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), XPhos (0.045 mmol, 22 mg, 0.09 equiv) and bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (36 mg, 0.20 mmol, 40%) as a pale yellow oil.

Lab Book Reference: BT4/61

Table 4.7, entry 8

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.4 mmol, 0.31 mL, 1.2 equiv), *N*-methylmorpholine **236** (0.33 mmol, 34 mg, 1.0 equiv), bispidine **211** (0.4 mmol, 73 mg, 1.2 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.4 mmol, 0.52 mL, 1.2 equiv) and then $Pd(OAc)_2$ (0.023 mmol, 5.2 mg, 0.07 equiv), 2-tfp (0.047 mmol, 11 mg, 0.14 equiv) and bromobenzene (0.4 mmol, 63 mg, 1.2 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (12 mg, 0.10 mmol, 20%) as a pale yellow oil.

Lab Book Reference: BT4/48

Table 4.7, entry 9

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then PEPPSI *i*-Pr (0.035 mmol, 24 mg, 0.07 equiv) and bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Only trace quantities of aryl morpholine **252** were observed in the ^{1}H NMR spectrum of the crude product and therefore purification was not attempted.

Lab Book Reference: BT4/45

Table 4.7, entry 10

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.65 mmol, 0.93 mL, 1.3 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and chlorobenzene (0.65 mmol, 73 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (47 mg, 0.26 mmol, 52%) as a pale yellow oil.

Lab Book Reference: BT4/62

Scheme 4.16

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), *N*-methylmorpholine **236** (0.5 mmol, 51 mg, 1.0 equiv), bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (5 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.325 mmol, 0.46 mL, 0.6 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.65 mmol, 102 mg, 1.3 equiv) at 100 °C for 16 h gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **252** (43 mg, 0.24 mmol, 48%) as a pale yellow oil.

Lab Book Reference: BT4/59

Scheme 4.17

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.75 mmol, 137 mg, 1.5 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.5 mmol, 79 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{aq)}$, 96:3:1) gave aryl morpholine **252** (82 mg, 0.30 mmol, 60%) as a pale-yellow oil.

Lab Book Reference: BT4/64

Scheme 4.18

Following general procedure H, *s*-BuLi (1.3 M solution in hexanes, 1.15 mmol, 0.88 mL, 2.3 equiv), *N*-methylmorpholine **236** (0.9 mmol, 91 mg, 1.8 equiv), bispidine **211** (0.45 mmol, 82 mg, 0.9 equiv) in TMO (6 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.58 mmol, 0.82 mL, 1.15 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.5 mmol, 79 mg, 1.0 equiv) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{aq)}$, 96:3:1) gave aryl morpholine **252** (82 mg, 0.31 mmol, 62%) as a pale-yellow oil.

Lab Book Reference: BT4/69

Scheme 4.19 (TMO)

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.5 mmol, 79 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{aq)}$, 96:3:1) gave aryl morpholine **252** (82 mg, 0.39 mmol, 78%) as a pale-yellow oil.

Lab Book Reference: BT4/71

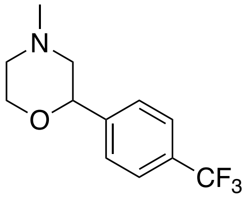
Scheme 4.19 (Hexane)

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv) was added dropwise to a stirred solution of *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv) and bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in hexane (4 mL) at −30 °C and was stirred for 2 h. $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) was added dropwise to the stirred solution and a precipitate formed making stirring difficult. The solution was allowed to warm over 1 h. Then, the organozinc solution was transferred to a stirred solution of $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and bromobenzene (0.5 mmol, 79 mg, 1.0 equiv) in hexane (1 mL) dropwuse and the reaction mixture was stirred and heated at 65 °C for 16 h. The resultant solution was allowed to cool to rt and the solids were removed by filtration through Celite® and washed with Et_2O (10 mL). The filtrate was washed with brine (10 mL) and water (2 × 10 mL). The organics were separated, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (CH_2Cl_2-

MeOH-$NH_4OH_{aq)}$, 96:3:1) gave aryl morpholine **252** (44 mg, 0.25 mmol, 49%) as a pale-yellow oil.

Lab Book Reference: BT4/72

4-Methyl-2-(4-(trifluoromethyl)phenyl)morpholine 253

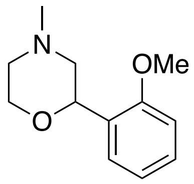


253

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 4-bromobenzotrifluoride (0.5 mmol, 113 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **253** (82 mg, 0.34 mmol, 67%) as a pale-yellow oil, $R_F = 0.1$ (CH_2Cl_2-MeOH-$NH_4OH_{aq)}$, 96:3:1); ν_{max}/cm^{-1} 2928, 2854, 2795, 1456, 1323, 1243, 1323, 1112, 1062, 918, 847, 606; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.57 (m, 2H, Ar), 7.50−7.45 (m, 2H, Ar), 4.61 (dd, *J* = 10.5 Hz, 2.5 Hz, 1H, OCH), 4.05 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.84 (td, *J* = 11.5, 2.0 Hz, 1H, OCH), 2.89 (dt, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.77−2.71 (m, 1H, NCH), 2.33 (s, 3H, NMe), 2.23 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 1.99 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}F_3NO$ $(M + H)^+$ 246.1100 found 246.1099 (+0.6 ppm error).

Lab Book Reference: BT4/73

2-(2-methoxyphenyl)-4-methylmorpholine 259

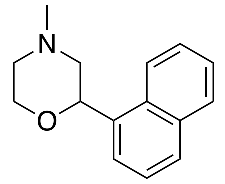


259

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 2-bromoanisole (0.5 mmol, 94 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **259** as a yellow oil, R_F = 0.1 (CH_2Cl_2-MeOH-$NH_4OH_{aq)}$, 96:3:1); ν_{max}/cm^{-1} 2934, 2852, 2789, 1589, 1493, 1455, 1241, 1142, 1110, 1030, 916, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar), 7.25−7.20 (m, 1H, Ar), 6.98−6.93 (m, 1H, Ar), 6.83 (br d, *J* = 8.0 Hz, Ar), 4.94 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 4.04 (ddd, *J* = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.85 (td, *J* = 11.5, 2.5 Hz, 1H, OCH), 3.80 (s, 3H, OMe), 2.98 (ddd, *J* = 11.5, 2.5, 1.5 Hz, 1H, NCH), 2.77−2.70 (m, 1H, NCH), 2.30 (s, 3H, NMe), 2.22 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 1.87 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (*ipso*-Ar), 128.9 (*ipso*-Ar), 128.5 (Ar), 126.7 (Ar), 120.7 (Ar), 110.2 (Ar), 72.7 (OCH), 67.3 (OCH_2), 61.0 (NCH_2), 55.3 (OMe), 55.1 (NCH_2), 46.2 (NMe); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{17}NO_2$ $(M + H)^+$ 208.1332 found 208.1334 (−0.8 ppm error).

Lab Book Reference: BT4/75

4-Methyl-2-(naphthalen-1-yl)morpholine 240

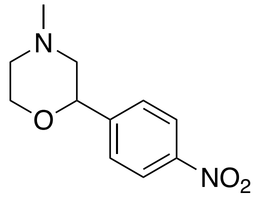


240

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 1-bromonaphthalene (0.5 mmol, 104 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 97:2:1) gave aryl morpholine **240** (64 mg, 0.28 mmol, 56%) as a colourless oil, $R_F = 0.2$ (CH_2Cl_2-MeOH-$NH_4OH_{aq)}$, 97:2:1); ν_{max}/cm^{-1} 3050, 2934, 2851, 2789, 1448, 1289, 1241, 1140, 1105, 1079, 914, 796, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br d, J = 8.5 Hz, 1H, Ar), 7.88−7.84 (m, 1H, Ar), 7.79 (br d, J = 8.0 Hz, 1H, Ar), 7.69−7.66 (m, 1H, Ar), 7.57−7.42 (m, 3H, Ar), 5.32 (dd, J = 10.0, 2.5 Hz, 1H, OCH), 4.16 (ddd, J = 11.5, 3.5, 2.0 Hz, 1H, OCH), 4.00 (td, J = 11.5, 2.0 Hz, 1H, OCH), 3.11 (dt, J = 11.5, 2.0 Hz, 1H, NCH), 2.87−2.77 (m, 1H, NCH), 2.35 (s, 3H, NMe), 2.33 (td, J = 11.5, 3.5 Hz, 1H, NCH), 2.17 (dd, J = 11.5, 10.0 Hz, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2 (*ipso*-Ar), 133.8 (*ipso*-Ar), 130.5 (*ipso*-Ar), 129.0 (Ar), 128.3 (Ar), 126.2 (Ar), 125.6 (Ar), 125.6 (Ar), 123.7 (Ar), 123.1 (Ar), 75.4 (OCH), 67.6 (OCH_2), 61.8 (NCH_2), 55.2 (NCH_2), 46.3 (NCH_3); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{17}NO$ $(M + H)^+$ 228.1383 found 228.1390 (−3.0 ppm error).

Lab Book Reference: BT4/91

2-(4-nitrophenyl)-4-methylmorpholine 260

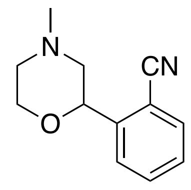


260

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 1-bromo-4-nitrobenzene (0.5 mmol, 101 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **260** (57 mg, 0.26 mmol, 51%) as a yellow solid, mp 93−95 °C; R_F = 0.2 (CH_2Cl_2-MeOH-$NH_4OH_{aq)}$, 96:3:1); ν_{max}/cm^{-1} 3050, 2930, 2846, 2797, 1599, 1509 (NO_2), 1452, 1338 (NO_2), 1289, 1140, 1105, 1081, 857, 749, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22−8.18 (m, 2H, Ar), 7.56−7.51 (m, 2H, Ar), 4.66 (dd, J = 10.5, 2.5 Hz, 1H, OCH), 4.06 (ddd, J = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.84 (td, J = 11.5, 2.0 Hz, 1H, OCH), 2.91 (dt, J = 11.5, 2.5 Hz, 1H, NCH), 2.78−2.72 (m, 1H, NCH), 2.34 (s, 3H, NMe), 2.23 (td, J = 11.5, 3.5 Hz, 1H, NCH), 1.97 (dd, J = 11.5, 10.5 Hz, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8 (*ipso*-Ar), 126.9 (Ar), 123.7 (Ar), 77.4 (OCH), 67.2 (OCH_2), 62.0 (NCH_2), 54.7 (NCH_2), 46.3 (NMe) (one *ipso*-Ar peak not resolved); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}N_2O_3$ (M + H)$^+$ 223.1077 found 223.1076 (+0.6 ppm error).

Lab Book Reference: BT4/74

2-(4-Methylmorpholin-2-yl)benzonitrile 261

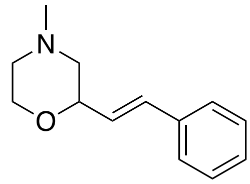


261

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 eq), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 2-bromobenzonitrile (0.5 mmol, 91 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **261** (59 mg, 0.29 mmol, 58%) as a colourless oil, $R_F = 0.2$ (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1); ν_{max}/cm^{-1} 2969, 2933, 2855, 2793, 2224 (CN), 1449, 1288, 1238, 1142, 1109, 1081, 915, 887, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.62 (m, 2H, Ar), 7.61−7.57 (m, 1H, Ar), 7.41−7.35 (m, 1H, Ar), 4.92 (dd, J = 10.5, 2.5 Hz, 1H, OCH), 4.05 (ddd, J = 11.5, 3.5, 2.0 Hz, OCH), 3.88 (td, J = 11.5, 2.0 Hz, 1H, OCH), 2.97 (dt, J = 11.5, 2.0 Hz, 1H, NCH), 2.77−2.72 (m, 1H, NCH), 2.33 (s, 3H, NMe), 2.26 (td, J = 11.5, 3.5 Hz, 1H, NCH), 2.00 (dd, J = 11.5, 10.5 Hz, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (*ipso*-Ar), 133.1 (Ar), 133.0 (Ar), 128.3 (Ar), 127.4 (Ar), 117.4 (CN), 110.7 (*ipso*-Ar), 76.1 (OCH), 67.3 (OCH_2), 61.2 (NCH_2), 54.6 (NCH_2), 46.2 (NMe); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}N_2O$ $(M + H)^+$ 203.1179 found 203.1181 (−0.8 ppm error).

Lab Book Reference: BT5/1

4-Methyl-2-styrylmorpholine

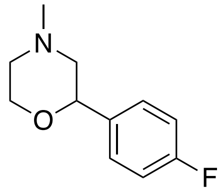


262

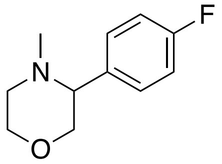
Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and β-bromostyrene (0.5 mmol, 92 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave vinyl morpholine **262** (55 mg, 0.27 mmol, 54%) as a colourless oil, $R_F = 0.3$ (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1); ν_{max}/cm^{-1} 2930, 2852, 2791, 1674, 1596, 1448, 1289, 1117, 1103, 1054, 964, 866, 743, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.35 (m, 2H, Ar), 7.33−7.28 (m, 2H, Ph), 7.26−7.21 (m, 1H, Ph), 6.66 (dd, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*Ph), 6.16 (dd, *J* = 16.0, 6.0 Hz, 1H, C*H*=CHPh), 4.19 (dddd, *J* = 10.0, 6.0, 2.5, 1.5 Hz, 1H, OCH), 3.97 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.76 (td, *J* = 11.5, 2.5 Hz, 1H, OCH), 2.82 (dt, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.71−2.65 (m, 1H, NCH), 2.32 (s, 3H, NMe), 2.17 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 1.98 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (*ipso*-Ph), 131.7 (Ph), 128.6 (Ph), 127.8 *C*H=CH), 127.6 (CH=*C*H), 126.6 (Ph), 76.3 (OCH), 66.8 (OCH_2), 60.5 (NCH_2), 54.8 (NCH_2), 46.3 (NMe); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{17}NO$ $(M + H)^+$ 204.1383 found 204.1387 (−1.9 ppm error).

Lab Book Reference: BT4/79

2-(4-Fluorophenyl)-4-methylmorpholine 263 and 3-(4-fluorophenyl)-4-methylmorpholine 264



263

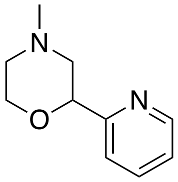


264

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 1-bromo-4-fluorobenzene (0.5 mmol, 88 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 97:2:1) gave aryl morpholine **264** (7.4 mg, 0.04 mmol, 8%) as a colourless oil, R_F = 0.3 (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 97:2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 2H, Ar), 7.05−6.99 (m, 2H, Ar), 3.96−3.86 (m, 1H, OCH), 3.77 (td, J = 11.5, 2.5 Hz, 1H, OCH), 3.68 (dd, J = 11.5, 3.5 Hz, 1H, OCH), 3.35 (dd, J = 11.5, 10.5 Hz, 1H, OCH), 3.05 (dd, J = 10.5, 3.5 Hz, 1H, NCH), 2.88−2.79 (m, 1H, NCH), 2.42 (td, J = 11.5, 3.5 Hz, 1H, NCH), 2.05 (s, 3H, NMe); ^{13}C NMR (101 MHz, $CDCl_3$) δ 115.6 (d, $^2J_{CF}$ = 21.0 Hz, Ar), 73.2 (OCH_2), 68.6 (NCH), 67.5 (NCH_2), 55.6 (OCH_2), 43.7 (NMe) (two *ipso*-Ar peaks and one Ar peak not resolved) and aryl morpholine **263** (69 mg, 0.36 mmol, 71%) as a pale-yellow oil, R_F =0.2 (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 97:2:1), ν_{max}/cm^{-1} 2923, 2852, 1594, 1456, 1382, 1242, 1159, 1100, 1055, 939, 850, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 2H, Ar), 7.08−7.96 (m, 2H, Ar), 4.53 (dd, J = 10.5, 2.5 Hz, 1H, OCH), 4.03 (ddd, J = 11.5, 3.5, 1.5 Hz, 1H, OCH), 3.82 (td, J = 11.5, 2.5 Hz, 1H, OCH), 2.85 (dt, J = 11.5, 2.5 Hz, 1H, NCH), 2.78−2.68 (m, 1H, NCH), 2.32 (s, 3H, NMe), 2.21 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.00 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$) 162.5 (d, $^1J_{CF}$ = 245.5 Hz, *ipso*-Ar), 136.3 (d, $^4J_{CF}$ = 3.0 Hz, *ipso*-Ar), 128.0 (d, $^3J_{CF}$ = 8.0 Hz, Ar), 115.3 (d, $^2J_{CF}$ = 21.5 Hz, Ar), 77.7 (OCH), 67.3 (OCH_3), 62.4 (NCH_2), 54.8 (NCH_2), 46.3 (NMe); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{14}FNO$ $(M + H)^+$ 196.1132 found 196.1138 (−3.1 ppm error).

Lab Book Reference: BT5/5

4-Methyl-2-(pyridin-2-yl)morpholine 256

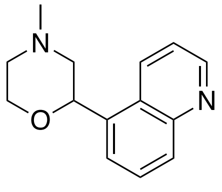


256

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 eq) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 2-bromopyridine (0.5 mmol, 79 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **256** (24 mg, 0.14 mmol, 27%) as a colourless oil, R_F = 0.3 (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Ar), 7.68 (td, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.45 (br d, *J* = 8.0 Hz, 1H, Ar), 7.18 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, Ar), 4.67 (dd, *J* = 10.5, 2.5 Hz, 1H, OCH), 4.07 (ddd, *J* = 11.5, 3.5, 2.0 Hz), 3.87 (td, *J* = 11.5, 2.5 Hz, 1H, OCH), 3.18 (dt, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.77−2.71 (m, 1H, NCH), 2.34 (s, 3H, NMe), 2.24 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.07 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH). Aryl morpholine **256** was found to be volatile and evaporated before full characterisation was carried out. ^{1}H NMR spectroscopic data consistent with those reported by the O'Brien group.[211]

Lab Book Reference: BT4/76

4-Methyl-2-(quinolin-5-yl)morpholine 268



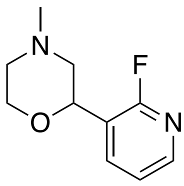
268

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 5-bromoquinoline (0.5 mmol, 104 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **268** (47 mg, 0.21 mmol, 41%) as a colourless oil, $R_F = 0.1$ (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1); ν_{max}/cm^{-1} 2935, 2852, 2792, 1596, 1573, 1503, 1449, 1289, 1267, 1138, 1104, 1032, 914, 800, 659; ^{1}H NMR (400 MHz, $CDCl_3$) 8.91 (dd, *J* = 4.0, 1.5 Hz, 1H, Ar), 8.52−8.48 (m, 1H, Ar), 8.08−8.03 (m, 1H, Ar), 7.71−7.68 (m, 2H, Ar), 7.42 (dd, *J* = 8.5, 4.0 Hz, 1H, Ar), 5.25 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 4.14 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.98 (td, *J* = 11.5, 2.5 Hz, 1H, OCH), 3.03 (dt, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.86−2.78 (m, 1H, NCH), 2.36 (s, 3H, NMe), 2.35 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.23 (dd, *J* = 11.5, 10.0 Hz, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2 (Ar), 148.5 (*ipso*-Ar), 136.5 (*ipso*-Ar), 132.0 (Ar), 129.8 (Ar), 129.2 (Ar), 125.8 (*ipso*-Ar), 124.5

(Ar), 121.1 (Ar), 75.2 (OCH), 67.5 (OCH$_2$), 61.6 (NCH$_2$), 55.0 (NCH$_2$), 46.3 (NMe); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}N_2O$ (M + H)$^+$ 229.1335 found 229.1333 (+1.2 ppm error).

Lab Book Reference: BT4/78

2-(2-Fluoropyridin-3-yl)-4-methylmorpholine



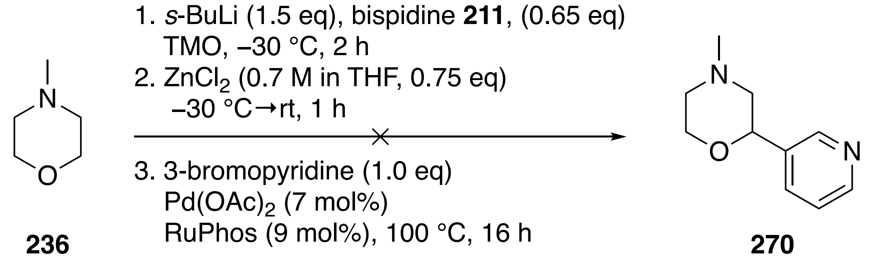
269

Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then Pd(OAc)$_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 3-bromo-2-fluoropyridine (0.5 mmol, 88 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Purification by flash column chromatography (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1) gave aryl morpholine **269** (37 mg, 0.19 mmol, 38%) as a colourless oil, $R_F = 0.2$ (CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$, 96:3:1); ν_{max}/cm^{-1} 2925, 2852, 1594, 1447, 1382, 1242, 1110, 1055, 762, 731; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.13−8.10 (m, 1H, Ar), 7.95−7.90 (m, 1H, Ar), 7.21−7.16 (m, 1H, Ar), 4.78 (dd, J = 10.0, 2.5 Hz, 1H, OCH), 4.03 (ddd, J = 11.5, 3.5, 2.0 Hz, 1H, OCH), 3.84 (td, J = 11.5, 2.5 Hz, 1H, OCH), 3.05−2.91 (m, 1H, NCH), 2.78−2.68 (m, 1H, NCH), 2.31 (s, 3H, NCH$_3$), 2.21 (td, J = 11.5, 3.5 Hz, 1H, NCH), 1.89 (dd, J = 11.5, 10.0 Hz, 1H, NCH); ^{13}C NMR (101 MHz, CDCl$_3$) δ 146.5 (d, $^2J_{CF}$ = 15.0 Hz, *ipso*-Ar), 138.6 (d, $^3J_{CF}$ = 5.0 Hz, Ar), 121.7 (d, $^3J_{CF}$ = 4.5 Hz, Ar) 71.7 (OCH), 67.2 (OCH$_2$), 60.6 (NCH$_2$), 54.4 (NCH$_2$), 46.2 (NMe) (one *ipso*-Ar peak and one Ar peak not resolved);

HRMS (ESI) *m/z* calcd for $C_{10}H_{14}FN_2O$ (M + H)$^+$ 197.1085 found 197.1090 (−2.7 ppm error).

Lab Book Reference: BT5/6

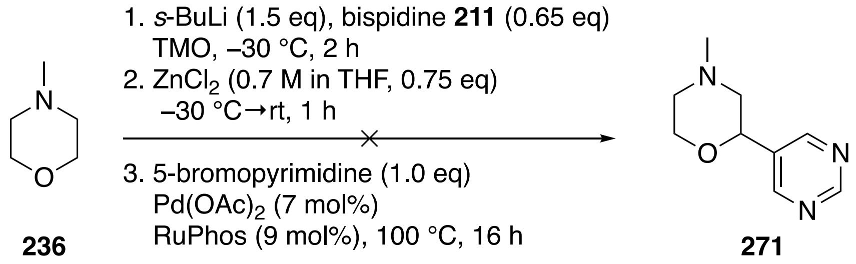
Attempted synthesis of 4-methyl-2-(pyridin-3-yl)morpholine 270



Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and ZnCl$_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then Pd(OAc)$_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 3-bromopyridine (0.5 mmol, 79 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Only trace quantities of aryl morpholine **270** were observed in the ^{1}H NMR spectrum of the crude product and therefore purification was not attempted.

Lab Book Reference: BT5/3

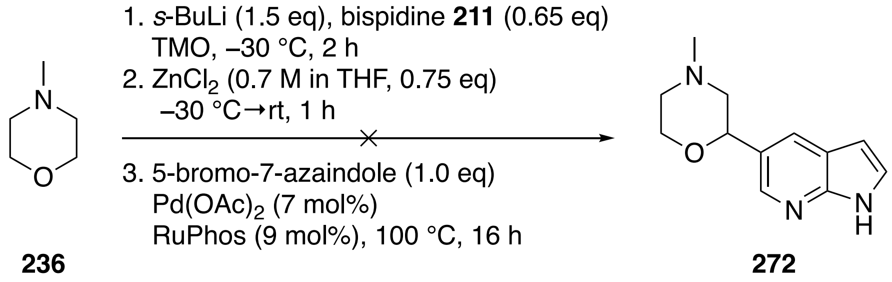
Attempted synthesis of 4-methyl-2-(pyrimidin-5-yl)morpholine



Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and ZnCl$_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then Pd(OAc)$_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 5-bromopyrimidine (0.5 mmol, 80 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. Only trace quantities of aryl morpholine **271** were observed in the ^{1}H NMR spectrum of the crude product and therefore purification was not attempted.

Lab Book Reference: BT4/77

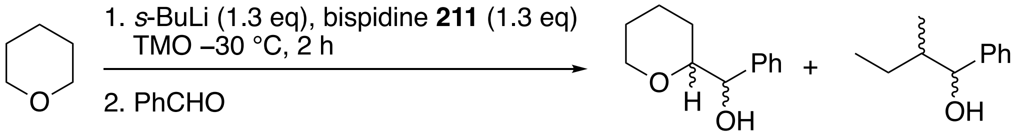
Attempted synthesis of 4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)morpholine



Following general procedure I, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv), *N*-methylmorpholine **236** (0.65 mmol, 66 mg, 1.3 equiv), bispidine **211** (0.325 mmol, 59 mg, 0.65 equiv) in TMO (4 mL) and $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 0.75 equiv) and then $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 0.07 equiv), RuPhos (0.045 mmol, 21 mg, 0.09 equiv) and 5-bromo-7-azaindole (0.5 mmol, 99 mg, 1.0 equiv) in TMO (1 mL) gave the crude product. None of aryl morpholine **272** was observed in the ^{1}H NMR spectrum of the crude product and therefore purification was not attempted.

Lab Book Reference: BT4/80

2-(*α*-Hydroxybenzyl) tetrahydropyran 229 and 2-methyl-1-phenylbutan-1-ol 230



229 **230**

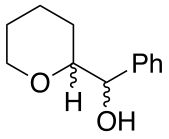
Table 4.9, entry 1

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), tetrahydropyran (0.5 mmol, 43 mg, 1.0 equiv) and bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (4 mL) at −30 °C for 2 h and PhCHO (2.0 mmol, 106 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (hexane-EtOAc, 9:1) gave a mixture of diastereomeric alcohols **230** (14 mg, 0.08 mmol, 13% with respect to *s*-BuLi) as a colourless oil and a 50:50 mixture of diastereomeric alcohols **229** (65 mg, 0.34 mmol, 68%) as a colourless oil, R_F = 0.1 (hexane-EtOAc, 9:1); ν_{max}/cm^{-1} 3433 (br, OH), 2936, 2853, 1451, 1260, 1203, 1087, 1040, 905, 759, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.29 (m, 5H, Ph), 4.83 (d, J = 4.0 Hz, 0.5H, OC*H*Ph), 4.71 (s, 1H, OH), 4.44 (d, J = 8.0 Hz, 0.5H, OC*H*Ph), 4.12−4.02 (m, 1H, OCH), 3.55−3.44 (m, 1.5H, OCH), 3.35−3.28 (m, 0.5H, OCH), 1.65−1.20 (m, 6H, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (*ipso*-Ph), 140.2 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph), 128.1 (Ph), 127.5 (Ph), 127.5 (Ph), 126.6 (Ph), 82.1

(O*C*HPh), 81.2 (O*C*HPh), 78.0 (OCH), 75.9 (OCH), 69.1 (OCH_2), 68.7 (OCH_2), 27.6 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 24.2 (CH_2), 23.1 (CH_2), 23.0 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{16}O_2$ $(M + H)^+$ 215.1043 found 215.1044 (−0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[216]

Lab Book Reference: BT5/15

2-(α-Hydroxybenzyl) tetrahydropyran 229



229

Table 4.9, entry 2

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), tetrahydropyran (0.5 mmol, 43 mg, 1.0 equiv) and bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (4 mL) at −30 °C for 3 h and PhCHO (2.0 mmol, 106 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (hexane-EtOAc, 9:1) gave a 50:50 mixture of diastereomeric alcohols **229** (69 mg, 0.36 mmol, 72%) as a colourless oil.

Lab Book Reference: BT5/17

Table 4.9, entry 3

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), tetrahydropyran (0.5 mmol, 43 mg, 1.0 equiv) and bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (4 mL) at −20 °C for 2 h and PhCHO (2.0 mmol, 106 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (hexane-EtOAc, 9:1) gave a 50:50 mixture of diastereomeric alcohols **229** as a 50:50 (71 mg, 0.37 mmol, 73%) as a colourless oil.

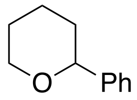
Lab Book Reference: BT5/18

Table 4.9, entry 4

Following general procedure G, *s*-BuLi (1.3 M solution in hexanes, 0.65 mmol, 0.5 mL, 1.3 equiv), tetrahydropyran (0.5 mmol, 43 mg, 1.0 equiv) and bispidine **211** (0.65 mmol, 119 mg, 1.3 equiv) in TMO (4 mL) at −15 °C for 2 h and PhCHO (2.0 mmol, 106 mg, 2.0 equiv) gave the crude product. Purification by flash column chromatography (hexane-EtOAc, 9:1) gave a 50:50 mixture of diastereomeric alcohols **229** (61 mg, 0.32 mmol, 63%) as a colourless oil.

Lab Book Reference: BT5/11

2-Phenyltetrahydro-2*H*-pyran 245



245

Under an inert atmosphere, *s*-BuLi (1.3 M solution in hexanes, 0.75 mmol, 0.58 mL, 1.5 equiv) was added dropwise to a stirred solution of tetrahydropyran (0.65 mmol, 56 mg, 1.3 equiv) and bispidine **211** (0.75 mmol, 137 mg, 1.5 equiv) in TMO (4 mL) at −20 °C and was stirred at this temperature for 2 h. $ZnCl_2$ (0.7 M solution in THF, 0.375 mmol, 0.53 mL, 1.5 equiv) was added dropwise to the stirred solution and was allowed to warm over 1 h. Then, the organozinc solution was transferred to stirred solution of $Pd(OAc)_2$ (0.035 mmol, 7.9 mg, 7 mol%), RuPhos (0.045 mmol, 21 mg, 9 mol%) and bromobenzene (0.5 mmol, 79 mg, 1.0 equiv) in TMO (1 mL) dropwise and the reaction mixture was stirred and heated at 100 °C for 16 h. The resultant solution was allowed to cool to rt and the solids were removed by filtration through Celite® and washed with Et_2O (10 mL). The filtrate was washed with brine (10 mL) and water (2 × 10 mL). The two layers were separated and the organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (hexane-CH_2Cl_2, 3:2) gave aryl THP **245** (40 mg, 0.25 mmol, 49%) as a colourless oil, R_F = 0.2 (Hexane-CH_2Cl_2, 3:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.27 (m, 5H, Ph), 4.33 (dd, J = 10.5, 2.0 Hz, 1H, OCH), 4.18−4.12 (m, 1H, OCH), 3.63 (td, J = 11.5, 2.5 Hz, 1H, OCH), 1.97−1.92 (m, 1H, CH), 1.87−1.80 (m, 1H, CH), 1.74−1.54 (m, 4H, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (*ipso*-Ph), 128.4 (Ph), 127.4 (Ph), 126.0 (Ph), 80.3 (OCH), 69.2 (OCH_2), 34.2 (CH_2), 26.0 (CH_2), 24.2 (CH_2). Spectroscopic data consistent with those found in the literature.[257]

Lab Book Reference: BT5/19

Abbreviations

2-MeTHF	2-methyltetrahydrofuran
ABE	acetone-butanol-ethanol
Ac	acetyl
ACE	angiotensin-converting enzyme
AE	atom economy
AIDS	acquired immune deficiency syndrome
AIT	auto-ignition temperature
aq	aqueous
Ar	aryl
BASF	Badische Anilin und Soda Fabrik
BHT	dibutylhydroxytoluene
BINAP	(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphino)
BINAS	sulfonated 2,2'bis(diphenylphosphinomethyl)-1,1'binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
BrettPhos	2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
BTX	benzene, toluene and xylenes
Bu	butyl
cBRIDP	di-*tert*-butyl(2,2-diphenyl-1-methyl-1cyclopropyl)phosphine

CHEM21	Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries
cm^{-1}	wavenumber
CML	chronic myeloid leukaemia
CPhos	2-dicyclohexylphosphino-2',6'-bis(*N*,*N*-dimethylamino)biphenyl
CPME	cyclopentyl methyl ether
CSP-HPLC	chiral stationary phase high performance liquid chromatography
Cy	cyclohexyl
d	doublet
DavePhos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DEA	diethanolamine
DFT	density functional theory
DIPEA	*N*,*N*-diisoproylethylamine
DME	dimethoxyethane
DMF	dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinono
DMSO	dimethyl sulfoxide
dppf	1,1'bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
E^+	electrophile
eq	equivalent
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl

FDA	Food and Drug Administration
g	grams
GCCE	Green Chemistry Centre of Excellence
GSK	GlaxoSmithKline
h	hours
HIV	human immunodeficiency virus
HMF	5-(hydroxymethyl)furfural
HMPA	hexamethylphosphoramide
HSP	Hanson Solubility parameter
Hz	hertz
ICH	International Council for Harmonisation
ICP-MS	inductively coupled plasma mass spectroscopy
IR	infrared
J	coupling constant in Hz
LHMDS	lithium bis(trimethylsilyl)amide
M	molar
m	multiplet
m/z	mass to charge ratio
M^+	molecular ion
Me	methyl
mg	milligram
min	minutes
mL	millilitre
mmol	millimole
mp	melting point

MS	mass spectroscopy
NBS	*N*-bromosuccinimide
neo	neopentyl
nm	nanometer
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
PEPPSI-*i*Pr	1,3-bis[(2,6-diisopropylphenyl)imidazole-2-ylidene](3-chloropyridyl)palladoim(II) dichloride
Petrol	petroleum ether (fraction which boils at 40−60 °C)
Ph	phenyl
pin	pinacol
PMI	process mass intensity
ppb	parts per billion
ppm	parts per million
Pr	propyl
q	quartet
R	alkyl group
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical Substances
R_F	retention factor
RME	reaction mass efficiency
rt	room temperature
RuPhos	2-dicyclohexylphosphino-2’,6’-diisopropoxybiphenyl
s	singlet
SEM	scanning electron microscopy

SMO	smoothened
S_NAr	nucleophilic aromatic subsitution
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
t	triplet
t-BuXPhos	2-di-*tert*-butylphosphino-2’,4’,6’,triisopropylbiphenyl
TBME	*tert*-butyl methyl ether
TFA	trifluoroacetic acid
tfp	trifurylphosphine
THF	tetrahydrofuran
THP	tetrahydropyran
t_{lith}	lithiation time
TMCDA	*N*,*N*,*N*’,*N*’-tetramethyl-1,2-diaminocyclohexane
TMEDA	*N*,*N*,*N*’,*N*’-tetramethylethylenediamine
TMO	2,2,5,5-tetramethyloxolane
Ts	tosyl
UV	ultraviolet
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

References

1 R. W. Bentley, *Energy Policy*, 2002, **30**, 189–205.

2 R. A. Sheldon, *Green Chem.*, 2005, **7**, 267−278.

3 C. Reichardt and T. Welton, *Solvents and solvent effects in organic chemistry*, Wiley-VCH, Weinheim, Germany, 4th, updated and enl. ed edn., 2011.

4 D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133–137.

5 Toluene - Substance Information - ECHA, https://echa.europa.eu/substance-information/-/substanceinfo/100.003.297, (accessed January 31, 2019).

6 Toluene - Substances restricted under REACH - ECHA, https://echa.europa.eu/substances-restricted-under-reach/-/dislist/details/0b0236e1807e2c14, (accessed May 5, 2020).

7 W. A. Sweeney and P. F. Bryan, in *Kirk-Othmer Encyclopedia of Chemical Technology*, ed. John Wiley & Sons, Inc, Wiley, 1st edn., 2000.

8 P. Anastas and J. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, New York, 2000.

9 K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem*, 2008, **10**, 31–36.

10 R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons, *Green Chem.*, 2011, **13**, 854−862.

11 C. M. Alder, J. D. Hayler, R. K. Henderson, A. M. Redman, L. Shukla, L. E. Shuster and H. F. Sneddon, *Green Chem.*, 2016, **18**, 3879–3890.

12 D. Prat, O. Pardigon, H.-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, *Org. Process Res. Dev.*, 2013, **17**, 1517–1525.

13 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.

14 D. Prat, J. Hayler and A. Wells, *Green Chem*, 2014, **16**, 4546–4551.

15 B. Trost, *Science*, 1991, **254**, 1471–1477.

16 A. D. Curzons, D. N. Mortimer, D. J. C. Constable and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1–6.

17 R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273−1283.

18 C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.

19 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, 1−7.

20 C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl and J. P. Hallett, *Chem. Rev.*, 2018, **118**, 747–800.

21 K. Shanab, C. Neudorfer, E. Schirmer and H. Spreitzer, *Curr. Org. Chem.*, 2013, **17**, 1179–1187.

22 W. Zhang and B. W. Cue, Eds., *Green Techniques for Organic Synthesis and Medicinal Chemistry*, Wiley, 1st edn., 2012.

23 Y. Gu and F. Jérôme, *Chem. Soc. Rev.*, 2013, **42**, 9550−9570.

24 Diethyl ether - Substance Information - ECHA, https://echa.europa.eu/substance-information/-/substanceinfo/100.000.425, (accessed May 13, 2020).

25 E. A. Barbet, U. S. Patent US1328258A, January 20, 1920.

26 L. Karas and W. J. Piel, in *Kirk-Othmer Encyclopedia of Chemical Technology*, American Cancer Society, 2004.

27 Tetrahydrofuran - Substance Information - ECHA, https://echa.europa.eu/substance-information/-/substanceinfo/100.003.389, (accessed May 13, 2020).

28 R. Pinkos, R. E. Lorenz, Y. A. Beste, U.S. Patent US7759531B2, July 20, 2010.

29 E. K. Lee, Y. H. Baek, U.S. Patent US20080161585A1, July 3, 2008.

30 Y. Zhu, J. Yang, F. Mei, X. Li and C. Zhao, *Green Chem.*, 2022, **24**, 6450–6466.

31 C. Delhomme, D. Weuster-Botz and F. E. Kühn, *Green Chem*, 2009, **11**, 13–26.

32 V. Pace, P. Hoyos, L. Castoldi, P. Domínguez de María and A. R. Alcántara, *ChemSusChem*, 2012, **5**, 1369–1379.

33 T. J. Farmer and M. Mascal, in *Introduction to Chemicals from Biomass*, eds. J. Clark and F. Deswarte, Wiley, 1st edn., 2015, pp. 89–155.

34 X. Liu, X. Min, H. Liu, Y. Cao, Y. Liu, M. Han, Z.-M. Sun and S. Ji, *Sustain. Energy Fuels*, 2020, **4**, 5795–5801.

35 Z. Xue, M.-G. Ma, Z. Li and T. Mu, *RSC Adv.*, 2016, **6**, 98874–98892.

36 S. Kang, J. Fu and G. Zhang, *Renew. Sustain. Energy Rev.*, 2018, **94**, 340–362.

37 L. E. Manzer, *Appl. Catal. Gen.*, 2004, **272**, 249–256.

38 F. M. A. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer and W. Leitner, *Angew. Chem. Int. Ed.*, 2010, **49**, 5510–5514.

39 U. Omoruyi, S. Page, J. Hallett and P. W. Miller, *ChemSusChem*, 2016, **9**, 2037–2047.

40 E. I. Gürbüz, J. M. R. Gallo, D. M. Alonso, S. G. Wettstein, W. Y. Lim and J. A. Dumesic, *Angew. Chem. Int. Ed.*, 2013, **52**, 1270–1274.

41 P. L. Dhepe and R. Sahu, *Green Chem.*, 2010, **12**, 2153−2156.

42 K. Watanabe, N. Yamagiwa and Y. Torisawa, *Org. Process Res. Dev.*, 2007, **11**, 251–258.

43 S. Meng, Y. Weng, X. Wang, H. Yin, Z. Wang, Q. Sun, M. Fan and Y. Zhang, *Front. Bioeng. Biotechnol.*, 2020, **8**, 615235.

44 F. Byrne, B. Forier, G. Bossaert, C. Hoebers, T. J. Farmer, J. H. Clark and A. J. Hunt, *Green Chem.*, 2017, **19**, 3671–3678.

45 J. H. Clark, D. J. Macquarrie and J. Sherwood, *Green Chem*, 2012, **14**, 90–93.

46 F. P. Byrne, B. Forier, G. Bossaert, C. Hoebers, T. J. Farmer and A. J. Hunt, *Green Chem.*, 2018, **20**, 4003–4011.

47 3,3-dimethylbutanone - Substance Information - ECHA, https://echa.europa.eu/substance-information/-/substanceinfo/100.000.838, (accessed July 15, 2019).

48 M. Maas-Brunner, J. Henkelmann, G. Kaibel, A. Kindler, C. Knoll, H. Rust, C. Tragut, M. Stroezel, U. Rheude, R. E. Lorenz, J. Aiscar, U.S. Patent US6956141B1, October 18, 2005.

49 H. Kang, D. hoon Lee, K. Kim, S. Jo, S. Pyun, Y. Song and S. Yu, *Fuel Process. Technol.*, 2016, **148**, 209–216.

50 Y. Ni and Z. Sun, *Appl. Microbiol. Biotechnol.*, 2009, **83**, 415–423.

51 F. P. Byrne, J. H. Clark, C. Angelici, E. de Jong and T. J. Farmer, *Sustain. Chem.*, 2021, **2**, 392–406.

52 Y. Li, G. Lv, Y. Wang, T. Deng, Y. Wang, X. Hou and Y. Yang, *ChemistrySelect*, 2016, **1**, 1252–1255.

53 R. M. R. Feldman, U. Gunawardena, J. Urano, P. Meinhold, A. A. Aristidou, C. A. Dundon, C. Smith, U.S. Patent US8017375B2, September 13, 2011.

54 T. J. Taylor, J. D. Taylor, M. W. Peters, D. E. Henton U.S. Patent US8742187B2, June 3, 2014.

55 C. E. Frank, *Chem. Rev.*, 1950, **46**, 155–169.

56 C. M. Hansen, *Hansen Solubility Parameters: A User’s Handbook, Second Edition*, CRC Press, 0 edn., 2007.

57 A. Iemhoff, J. Sherwood, C. R. McElroy and A. J. Hunt, *Green Chem.*, 2018, **20**, 136–140.

58 A. Pellis, F. P. Byrne, J. Sherwood, M. Vastano, J. W. Comerford and T. J. Farmer, *Green Chem.*, 2019, **21**, 1686–1694.

59 R. Morphy, *J. Med. Chem.*, 2010, **53**, 1413–1437.

60 P. Devendar, R.-Y. Qu, W.-M. Kang, B. He and G.-F. Yang, *J. Agric. Food Chem.*, 2018, **66**, 8914–8934.

61 B. Spindler, O. Kataeva and H.-J. Knölker, *J. Org. Chem.*, 2018, **83**, 15136–15143.

62 J. Lindley, *Tetrahedron*, 1984, **40**, 1433–1456.

63 A. J. Belfield, A. J. Foubister and A. Park, *Tetrahedron*, 1999, **55**, 11399–11428.

64 M. Kosugi, M. Kameyama and T. Migita, *Chem. Lett.*, 1983, 927–928.

65 R. A. Rennels and S. L. Buchwald, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 1348–1350.

66 J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609–3612.

67 J. P. Wolfe, S. Wagaw and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215–7216.

68 M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 7217–7218.

69 J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 7010–7011.

70 M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1997, **119**, 8232–8245.

71 B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1998, **120**, 3694–3703.

72 J. P. Wolfe and S. L. Buchwald, *Tetrahedron Lett.*, 1997, **38**, 6359–6362.

73 D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27–50.

74 J. A. Cella and S. W. Bacon, *J. Org. Chem.*, 1984, **49**, 1122–1125.

75 R. Dorel, C. P. Grugel and A. M. Haydl, *Angew. Chem. Int. Ed.*, 2019, **58**, 17118–17129.

76 B. T. Ingoglia, C. C. Wagen and S. L. Buchwald, *Tetrahedron*, 2019, **75**, 4199–4211.

77 B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 1599–1626.

78 Y. Guari, D. S. van Es, J. N. H. Reek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Tetrahedron Lett.*, 1999, **40**, 3789–3790.

79 M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz and J. Fraanje, *Organometallics*, 1995, **14**, 3081–3089.

80 J. P. Sadighi, M. C. Harris and S. L. Buchwald, *Tetrahedron Lett.*, 1998, **39**, 5327–5330.

81 J. Mao, J. Zhang, S. Zhang and P. J. Walsh, *Dalton Trans.*, 2018, **47**, 8690–8696.

82 D. W. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722–9723.

83 C. Meyers, B. U. W. Maes, K. T. J. Loones, G. Bal, G. L. F. Lemie and R. A. Dommisse, *J. Org. Chem.*, 2004, **69**, 6010–6017.

84 H. Tomori, J. M. Fox and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 5334–5341.

85 S. Kaye, J. M. Fox, F. A. Hicks and S. L. Buchwald, *Adv. Synth. Catal.*, 2001, **343**, 789–794.

86 J. F. Hartwig, S. Richards, D. Barañano and F. Paul, *J. Am. Chem. Soc.*, 1996, **118**, 3626–3633.

87 J. F. Hartwig, *Inorg. Chem.*, 2007, **46**, 1936–1947.

88 T. E. Barder and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 12003–12010.

89 1,4-dioxane - Substance Information - ECHA, https://echa.europa.eu/substance-information/-/substanceinfo/100.004.239, (accessed August 29, 2022).

90 1,2-dimethoxyethane - Substance Information - ECHA, https://echa.europa.eu/substance-information/-/substanceinfo/100.003.451, (accessed August 29, 2022).

91 Dibutyl ether - Substance Information - ECHA, https://echa.europa.eu/substance-information/-/substanceinfo/100.005.069, (accessed August 29, 2022).

92 H. Christensen, S. Kiil, K. Dam-Johansen, O. Nielsen and M. B. Sommer, *Org. Process Res. Dev.*, 2006, **10**, 762–769.

93 B. P. Fors, N. R. Davis and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 5766–5768.

94 X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 6653–6655.

95 G. Wüllner, H. Jänsch, F. Schubert and G. Boche, *Chem. Commun.*, 1998, 1509–1510.

96 B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston and R. C. Gadwood, *J. Org. Chem.*, 2011, **76**, 4379–4391.

97 P. Wagner, M. Bollenbach, C. Doebelin, F. Bihel, J.-J. Bourguignon, C. Salomé and M. Schmitt, *Green Chem*, 2014, **16**, 4170–4178.

98 Campos and Berteina-Raboin, *Catalysts*, 2019, **9**, 840.

99 J. F. Campos, M. Cailler, R. Claudel, B. Prot, T. Besson and S. Berteina-Raboin, *Molecules*, 2021, **26**, 1074.

100 C. Torborg and M. Beller, *Adv Synth Catal*, 2009, **351**, 3027–3043.

101 A. O. King and N. Yasuda, *Top. Organomet. Chem.*, 2004, **6**, 205–245.

102 P. A. Forero-Cortés and A. M. Haydl, *Org. Process Res. Dev.*, 2019, **23**, 1478–1483.

103 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564–12649.

104 J. B. Sperry, K. E. Price Wiglesworth, I. Edmonds, P. Fiore, D. C. Boyles, D. B. Damon, R. L. Dorow, E. L. Piatnitski Chekler, J. Langille and J. W. Coe, *Org. Process Res. Dev.*, 2014, **18**, 1752–1758.

105 G. E. Robinson, O. R. Cunningham, M. Dekhane, J. C. McManus, A. O'Kearney-McMullan, A. M. Mirajkar, V. Mishra, A. K. Norton, B. Venugopalan and E. G. Williams, *Org. Process Res. Dev.*, 2004, **8**, 925–930.

106 D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura and S. L. Buchwald, *Chem Sci*, 2011, **2**, 57–68.

107 R. Capdeville, E. Buchdunger, J. Zimmermann and A. Matter, *Nat. Rev. Drug Discov.*, 2002, **1**, 493–502.

108 A. Arora and E. M. Scholar, *J. Pharmacol. Exp. Ther.*, 2005, **315**, 971–979.

109 M. Deininger, E. Buchdunger and B. J. Druker, *Blood*, 2005, **105**, 2640–2653.

110 T.-S. Wu, S.-C. Huang and P.-L. Wu, *Heterocycles*, 1997, **45**, 969−973.

111 A. R. Muci and S. L. Buchwald, in *Cross-Coupling Reactions: A Practical Guide*, ed. N. Miyaura, Springer Berlin Heidelberg, Berlin, Heidelberg, 2002, pp. 131–209.

112 N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott and S. P. Nolan, *J. Am. Chem. Soc.*, 2006, **128**, 4101–4111.

113 M. H. Ali and S. L. Buchwald, *J. Org. Chem.*, 2001, 2560–2565.

114 J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1144–1157.

115 A. Dunbabin, F. Subrizi, J. M. Ward, T. D. Sheppard and H. C. Hailes, *Green Chem.*, 2017, **19**, 397–404.

116 H. N. Nguyen, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11818–11819.

117 G. L. Beutner, J. R. Coombs, R. A. Green, B. Inankur, D. Lin, J. Qiu, F. Roberts, E. M. Simmons and S. R. Wisniewski, *Org. Process Res. Dev.*, 2019, **23**, 1529–1537.

118 B. J. Kotecki, D. P. Fernando, A. R. Haight and K. A. Lukin, *Org. Lett.*, 2009, **11**, 947–950.

119 M. Betti, E. Genesio, G. Marconi, S. Sanna Coccone and P. Wiedenau, *Org. Process Res. Dev.*, 2014, **18**, 699–708.

120 J. Jiang and C. Hui, *Dev. Cell*, 2008, **15**, 801–812.

121 R. M. Izatt, Ed., *Metal Sustainability: Global Challenges, Consequences, and Prospects*, John Wiley & Sons, Ltd, Chichester, UK, 2016.

122 A. J. Hunt, T. J. Farmer and J. H. Clark, in *Green Chemistry Series*, ed. A. Hunt, Royal Society of Chemistry, Cambridge, 2013, pp. 1–28.

123 A. J. Hunt and T. J. Farmer, in *Green Chemistry Series*, ed. M. North, Royal Society of Chemistry, Cambridge, 2015, pp. 1–14.

124 N. Supanchaiyamat and A. J. Hunt, *ChemSusChem*, 2019, **12**, 397–403.

125 G. Strappaveccia, E. Ismalaj, C. Petrucci, D. Lanari, A. Marrocchi, M. Drees, A. Facchetti and L. Vaccaro, *Green Chem.*, 2015, **17**, 365–372.

126 C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889–900.

127 C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111–3121.

128 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, 1−7.

129 F. P. Byrne, J. H. Clark, C. Angelici, E. de Jong and T. J. Farmer, *Sustain. Chem.*, 2021, **2**, 392–406.

130 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.

131 A. A. Patchett, E. Harris, E. W. Tristram, M. J. Wyvratt, M. T. Wu, D. Taub, E. R. Peterson, T. J. Ikeler, J. ten Broeke, L. G. Payne, D. L. Ondeyka, E. D. Thorsett, W. J. Greenlee, N. S. Lohr, R. D. Hoffsommer, H. Joshua, W. V. Ruyle, J. W. Rothrock, S. D. Aster, A. L. Maycock, F. M. Robinson, R. Hirschmann, C. S. Sweet, E. H. Ulm, D. M. Gross, T. C. Vassil and C. A. Stone, *Nature*, 1980, **288**, 280–283.

132 J. P. Vacca, B. D. Dorsey, W. A. Schleif, R. B. Levin, S. L. McDaniel, P. L. Darke, J. Zugay, J. C. Quintero, O. M. Blahy and E. Roth, *Proc. Natl. Acad. Sci.*, 1994, **91**, 4096–4100.

133 J. Clayden, *Organolithiums: Selectivity for Synthesis*, Elsevier, 2002.

134 K. R. Campos, *Chem. Soc. Rev.*, 2007, **36**, 1069–1084.

135 P. Beak and W.-K. Lee, *Tetrahedron Lett.*, 1989, **30**, 1197–1200.

136 Peter. Beak and D. B. Reitz, *Chem. Rev.*, 1978, **78**, 275–316.

137 C. Metallinos, T. Dudding, J. Zaifman, J. L. Chaytor and N. J. Taylor, *J. Org. Chem.*, 2007, **72**, 957–963.

138 D. M. Hodgson and J. Kloesges, *Angew. Chem. Int. Ed.*, 2010, **49**, 2900–2903.

139 D. Seebach and D. Enders, *Angew. Chem. Int. Ed. Engl.*, 1975, **14**, 15–32.

140 A. I. Meyers and S. Hellring, *J. Org. Chem.*, 1982, **47**, 2229–2231.

141 A. I. Meyers, J. Guiles, J. S. Warmus and M. A. Gonzalez, *Tetrahedron Lett.*, 1991, **1**, 5505–5508.

142 A. Islip, phd, University of York, 2017.

143 J. D. Firth, University of York, 2014.

144 G. Barker, P. O'Brien and K. R. Campos, *Org. Lett.*, 2010, **12**, 4176–4179.

145 I. Coldham, R. C. B. Copley, T. F. N. Haxell and S. Howard, *Org. Lett.*, 2001, **3**, 3799–3801.

146 N. J. Ashweek, I. Coldham, T. F. N. Haxell and S. Howard, *Org. Biomol. Chem.*, 2003, **1**, 1532–1544.

147 M. Berkheij, L. van der Sluis, C. Sewing, D. J. den Boer, J. W. Terpstra, H. Hiemstra, W. I. Iwema Bakker, A. van den Hoogenband and J. H. van Maarseveen, *Tetrahedron Lett.*, 2005, **46**, 2369–2371.

148 A. Kwong, J. D. Firth, T. J. Farmer and P. O'Brien, *Tetrahedron*, 2021, **81**, 131899.

149 J.-P. Kestemont, J. R. Frost, J. Jacq, P. Pasau, F. Perl, J. Brown and M. Tissot, *Org. Process Res. Dev.*, 2022, **26**, 635–639.

150 P. Anastas and J. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, New York, 2000.

151 P. Anastas and N. Eghbali, *Chem Soc Rev*, 2010, **39**, 301–312.

152 D. F. Aycock, *Org. Process Res. Dev.*, 2007, **11**, 156–159.

153 B. D. Hoppe, F. Hintze and P. Trhben, *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 107–109.

154 S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 9708–9710.

155 P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552–560.

156 J. R. Harrison, P. O′Brien, D. W. Porter and N. M. Smith, *Chem. Commun.*, 2001, 1202–1203.

157 M. J. Dearden, C. R. Firkin, J.-P. R. Hermet and P. O’Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870–11871.

158 D. Stead, P. O’Brien and A. Sanderson, *Org. Lett.*, 2008, **10**, 1409–1412.

159 S. Wu, S. Lee and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 715–721.

160 K. M. B. Gross, Y. M. Jun and P. Beak, *J. Org. Chem.*, 1997, **62**, 7679–7689.

161 Y. S. Park, M. L. Boys and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 3757–3758.

162 I. Hoppe, M. Marsch, K. Harms, G. Boche and D. Hoppe, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 2158–2160.

163 S. V. Kessar, P. Singh, K. N. Singh, P. Venugopalan, A. Kaur, P. V. Bharatam and A. K. Sharma, *J. Am. Chem. Soc.*, 2007, **129**, 4506–4507.

164 G. Carbone, P. O’Brien and G. Hilmersson, *J. Am. Chem. Soc.*, 2010, **132**, 15445–15450.

165 D. J. Gallagher, S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1992, **114**, 5872–5873.

166 G. Barker, phd, University of York, 2011.

167 G. Gelardi, G. Barker, P. O’Brien and D. C. Blakemore, *Org. Lett.*, 2013, **15**, 5424–5427.

168 J. D. Firth, P. O’Brien and L. Ferris, *J. Am. Chem. Soc.*, 2016, **138**, 651–659.

169 K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer and C. Chen, *J. Am. Chem. Soc.*, 2006, **128**, 3538–3539.

170 A. Klapars, K. R. Campos, J. H. Waldman, D. Zewge, P. G. Dormer and C. Chen, *J. Org. Chem.*, 2008, **73**, 4986–4993.

171 A. Maercker, *Angew. Chem. Int. Ed. Engl.*, 1987, **26**, 972–989.

172 P. Stanetty and M. D. Mihovilovic, *J. Org. Chem.*, 1997, **62**, 1514–1515.

173 H. Gilman and B. J. Gaj, *J. Org. Chem.*, 1957, **22**, 1165–1168.

174 R. B. Bates, L. M. Kroposki and D. E. Potter, *J. Org. Chem.*, 1972, **37**, 560–562.

175 I. Fleming, S. R. Mack, I. Fleming, S. R. Mack and B. P. Clark, *Chem. Commun.*, 1998, **0**, 713–714.

176 J. Clayden and S. A. Yasin, *New J. Chem.*, 2002, **26**, 191–192.

177 J. E. Baldwin, *J. Chem. Soc. Chem. Commun.*, 1976, 734–736.

178 T. Cohen and S. Stokes, *Tetrahedron Lett.*, 1993, **34**, 8023–8024.

179 Tert-butyl methyl ether - Substance Information - ECHA, https://echa.europa.eu/substance-information/-/substanceinfo/100.015.140, (accessed January 10, 2023).

180 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem*, 2007, **9**, 411–420.

181 H. Müller, in *Ullmann's Encyclopedia of Industrial Chemistry*, American Cancer Society, 2011.

182 P. Chu and G. H. Kuhl, *Ind. Eng. Chem. Res.*, 1987, **26**, 365–369.

183 S. Monticelli, L. Castoldi, I. Murgia, R. Senatore, E. Mazzeo, J. Wackerlig, E. Urban, T. Langer and V. Pace, *Monatshefte Für Chem. - Chem. Mon.*, 2017, **148**, 37–48.

184 A. P. Pulis, D. J. Blair, E. Torres and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2013, **135**, 16054–16057.

185 A. Varela, L. K. B. Garve, D. Leonori and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2017, **56**, 2127–2131.

186 V. Pace, L. Castoldi, S. Monticelli, S. Safranek, A. Roller, T. Langer and W. Holzer, *Chem. Eur. J.*, 2015, **21**, 18966–18970.

187 S. Monticelli, W. Holzer, T. Langer, A. Roller, B. Olofsson and V. Pace, *ChemSusChem*, 2019, **12**, 1147−1154.

188 R. Sott, M. Håkansson and G. Hilmersson, *Organometallics*, 2006, **25**, 6047–6053.

189 Kasten, Kevin and O'Brien, Peter, *Unpubl. Results*.

190 M. D. Delost, D. T. Smith, B. J. Anderson and J. T. Njardarson, *J. Med. Chem.*, 2018, **61**, 10996–11020.

191 D. Eyding, M. Lelgemann, U. Grouven, M. Harter, M. Kromp, T. Kaiser, M. F. Kerekes, M. Gerken and B. Wieseler, *BMJ*, 2010, **341**, c4737–c4737.

192 S. Jain, R. Song and J. Xie, *OncoTargets Ther.*, 2017, **10**, 1645–1653.

193 M. Constantin and J. Pognat, *Arzneimittelforschung.*, 1979, **29**, 109−114.

194 H. Lepor, S. Auerbach, A. Puras-Baez, P. Narayan, M. Soloway, F. Lowe, T. Moon, G. Leifer and P. Madsen, *J. Urol.*, 1992, **148**, 1467–1474.

195 P. L. Alsters, W. Jary, V. Nardello-Rataj and J.-M. Aubry, *Org. Process Res. Dev.*, 2010, **14**, 259–262.

196 I. Gantz, M. Chen, S. Suryawanshi, C. Ntabadde, S. Shah, E. A. O'Neill, S. S. Engel, K. D. Kaufman and E. Lai, *Cardiovasc. Diabetol.*, 2017, **16**, 112.

197 J. Li, J. Zhang, H. Tan and D. Z. Wang, *Org. Lett.*, 2015, **17**, 2522–2525.

198 S. Kamijo, G. Takao, K. Kamijo, M. Hirota, K. Tao and T. Murafuji, *Angew. Chem. Int. Ed.*, 2016, **55**, 9695–9699.

199 S. Kamijo, K. Kamijo, K. Maruoka and T. Murafuji, *Org. Lett.*, 2016, **18**, 6516–6519.

200 H.-P. Deng, X.-Z. Fan, Z.-H. Chen, Q.-H. Xu and J. Wu, *J. Am. Chem. Soc.*, 2017, **139**, 13579–13584.

201 X. Fan, J. Rong, H. Wu, Q. Zhou, H. Deng, J. D. Tan, C. Xue, L. Wu, H. Tao and J. Wu, *Angew. Chem. Int. Ed.*, 2018, **57**, 8514–8518.

202 B. Abadie, D. Jardel, G. Pozzi, P. Toullec and J. Vincent, *Chem. – Eur. J.*, 2019, **25**, 16120–16127.

203 P. P. Singh, S. Gudup, H. Aruri, U. Singh, S. Ambala, M. Yadav, S. D. Sawant and R. A. Vishwakarma, *Org. Biomol. Chem.*, 2012, **10**, 1587−1597.

204 R. Lehmann and M. Schlosser, *Tetrahedron Lett.*, 1984, **25**, 745–748.

205 A. R. Kennedy, J. Klett, R. E. Mulvey and D. S. Wright, *Science*, 2009, **326**, 706–708.

206 R. Mansueto, V. Mallardo, F. M. Perna, A. Salomone and V. Capriati, *Chem. Commun.*, 2013, **49**, 10160−10162.

207 D. Kim, H.-J. Lee, Y. Shimizu, J. Yoshida and H. Kim, *Nat. Synth.*, 2022, **1**, 558–564.

208 M. Schlosser and S. Strunk, *Tetrahedron Lett.*, 1984, **25**, 741–744.

209 M. Odachowski, A. Bonet, S. Essafi, P. Conti-Ramsden, J. N. Harvey, D. Leonori and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2016, **138**, 9521–9532.

210 W. S. A. Kwong, University of York, 2016.

211 N. Seling, University of York, 2020.

212 R. C. Mykura, S. Veth, A. Varela, L. Dewis, J. J. Farndon, E. L. Myers and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2018, **140**, 14677–14686.

213 W. F. Bailey, P. Beak, S. T. Kerrick, S. Ma and K. B. Wiberg, *J. Am. Chem. Soc.*, 2002, **124**, 1889–1896.

214 D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham and A. Sanderson, *J. Am. Chem. Soc.*, 2010, **132**, 7260–7261.

215 I. Coldham and D. Leonori, *Org. Lett.*, 2008, **10**, 3923–3925.

216 J. Scott. Sawyer, Andrew. Kucerovy, T. L. Macdonald and G. J. McGarvey, *J. Am. Chem. Soc.*, 1988, **110**, 842–853.

217 G. P. R. Freure, E. A. Skrotzki, J.-D. E. Lavertu and S. G. Newman, *ACS Catal.*, 2021, **11**, 12258–12263.

218 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295–4298.

219 J. E. Milne and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 13028–13032.

220 C. Han and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 7532–7533.

221 G. Manolikakes, M. A. Schade, C. M. Hernandez, H. Mayr and P. Knochel, *Org. Lett.*, 2008, **10**, 2765–2768.

222 G. Manolikakes, C. Muñoz Hernandez, M. A. Schade, A. Metzger and P. Knochel, *J. Org. Chem.*, 2008, **73**, 8422–8436.

223 L. C. McCann and M. G. Organ, *Angew. Chem. Int. Ed.,* 2014, **53**, 4386−4389.

224 L. C. McCann, H. N. Hunter, J. A. C. Clyburne and M. G. Organ, *Angew. Chem. Int. Ed.*, 2012, **51**, 7024–7027.

225 M. R. Luzung, J. S. Patel and J. Yin, *J. Org. Chem.*, 2010, **75**, 8330–8332.

226 R. E. McNamee, M. M. Haugland, J. Nugent, R. Chan, K. E. Christensen and E. A. Anderson, *Chem. Sci.*, 2021, **12**, 7480–7485.

227 C. Valente, M. E. Belowich, N. Hadei and M. G. Organ, *Eur. J. Org. Chem.*, 2010, **23**, 4343–4354.

228 M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien and C. Valente, *Chem. - Eur. J.*, 2006, **12**, 4749–4755.

229 J. D. Firth, P. O'Brien and L. Ferris, *J. Org. Chem.*, 2017, **82**, 7023–7031.

230 S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer and P. Knochel, *J. Am. Chem. Soc.*, 2011, **133**, 4774–4777.

231 A. Millet, P. Larini, E. Clot and O. Baudoin, *Chem. Sci.*, 2013, **4**, 2241−2247.

232 A. F. Burchat, J. M. Chong and N. Nielsen, *J. Organomet. Chem.*, 1997, **542**, 281–283.

233 J. C. Vantourout, R. P. Law, A. Isidro-Llobet, S. J. Atkinson and A. J. B. Watson, *J. Org. Chem.*, 2016, **81**, 3942–3950.

234 J. Shi, P. Yang, Q. Tong and L. Jia, *Dalton Trans.*, 2008, 938–945.

235 T. Hatakeyama, Y. Yoshimoto, S. K. Ghorai and M. Nakamura, *Org. Lett.*, 2010, **12**, 1516–1519.

236 B. de Lange, M. H. Lambers-Verstappen, L. S. de Vondervoort, N. Sereinig, R. de Rijk, A. H. M. de Vries and J. G. de Vries, *Synlett*, 2006, **2006**, 3105–3109.

237 C. Li, Y. Kawamata, H. Nakamura, J. C. Vantourout, Z. Liu, Q. Hou, D. Bao, J. T. Starr, J. Chen, M. Yan and P. S. Baran, *Angew. Chem. Int. Ed.*, 2017, **56**, 13088–13093.

238 C. Yang, F. Zhang, G.-J. Deng and H. Gong, *J. Org. Chem.*, 2019, **84**, 181–190.

239 Y. Zhang, V. César, G. Storch, N. Lugan and G. Lavigne, *Angew. Chem. Int. Ed.*, 2014, **53**, 6482–6486.

240 Z. Zhang, J. Mao, D. Zhu, F. Wu, H. Chen and B. Wan, *Tetrahedron*, 2006, **62**, 4435–4443.

241 T. Wang, D. R. Magnin and L. G. Hamann, *Org. Lett.*, 2003, **5**, 897–900.

242 C.-H. Lim, M. Kudisch, B. Liu and G. M. Miyake, *J. Am. Chem. Soc.*, 2018, **140**, 7667–7673.

243 P. Y. Choy, H. Chung, Q. Yang and M. So, *Asian J. Chem.*, 2018, **13**, 2465–2474.

244 J. Yu, Y. Wang, P. Zhang and J. Wu, *Synlett*, 2013, **24**, 1448–1454.

245 R. R. Jadhav, S. N. Huddar and K. G. Akamanchi, *Eur. J. Org. Chem.*, 2013, **30**, 6779–6783.

246 M. C. Lubinu, L. De Luca, G. Giacomelli and A. Porcheddu, *Chem. Eur. J.*, 2011, **17**, 82–85.

247 J. Yin, M. M. Zhao, M. A. Huffman and J. M. McNamara, *Org. Lett.*, 2002, **4**, 3481–3484.

248 E. Niknam, F. Panahi and A. Khalafi-Nezhad, *Eur. J. Org. Chem.*, 2020, **2020**, 2699–2707.

249 N. B. Shelke, R. Ghorpade, A. Pratap, V. Tak and B. N. Acharya, *RSC Adv.*, 2015, **5**, 31226–31230.

250 K. Okano, H. Tokuyama and T. Fukuyama, *Org. Lett.*, 2003, **5**, 4987–4990.

251 P. Gaur, K. D. B. Yamajala and S. Banerjee, *New J. Chem.*, 2017, **41**, 6523–6529.

252 M. O. Akram, A. Das, I. Chakrabarty and N. T. Patil, *Org. Lett.*, 2019, **21**, 8101–8105.

253 X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 16410–16413.

254 D. Du, K. Zhang, R. Ma, L. Chen, J. Gao, T. Lu, Z. Shi and J. Feng, *Org. Lett.*, 2020, **22**, 6370–6375.

255 N. Cabello, J.-C. Kizirian, S. Gille, A. Alexakis, G. Bernardinelli, L. Pinchard and J.-C. Caille, *Eur. J. Org. Chem.*, 2005, **22**, 4835–4842.

256 J. F. Remenar, B. L. Lucht and D. B. Collum, *J. Am. Chem. Soc.*, 1997, **119**, 5567–5572.

257 L. Ferrand, Y. Tang, C. Aubert, L. Fensterbank, V. Mouriès-Mansuy, M. Petit and M. Amatore, *Org. Lett.*, 2017, **19**, 2062–2065.