"High" Temperature Lithiation-trapping of Nitrogen and Oxygen Heterocycles

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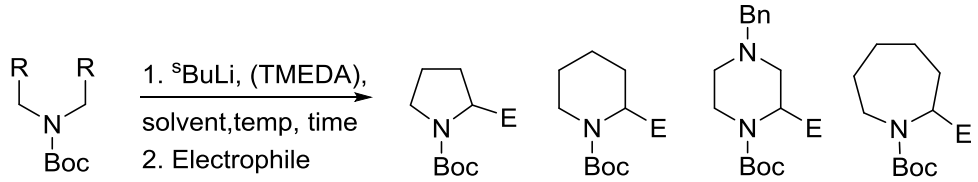
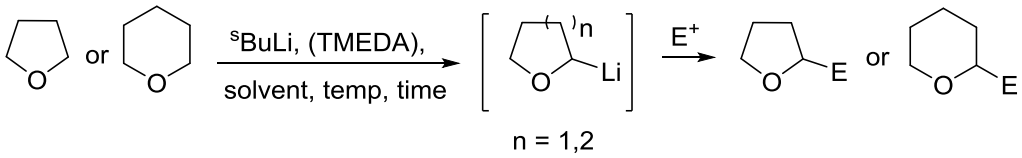
Abstract

This thesis describes some novel aspects of the lithiation-trapping of nitrogen and oxygen heterocycles, including a systematic study of new methodologies at temperature above –78 °C and the use of the sustainable solvent, 2-MeTHF, as an alternative to Et_2O and THF.

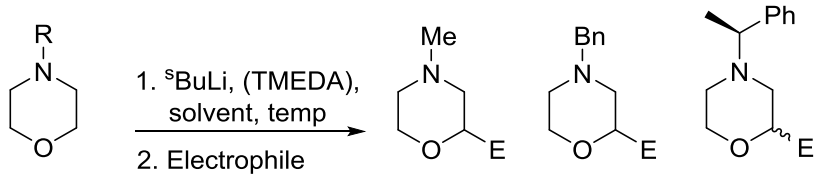
Chapter 2 describes a detailed exploration of the *s*-BuLi-mediated lithiation-trapping of *N*-Boc heterocycles (pyrrolidine, piperidine, piperazine and azepane) using different conditions (diamine, solvent, temperature and time). For *N*-Boc pyrrolidine, two new high temperature lithiation conditions were optimised: (i) 0 °C for 5 sec is best for flow system; (ii) –20 °C for 2 min is best for batch conditions. The stability of the lithiated *N*-Boc pyrrolidine at 0 °C was also investigated.



In Chapter 3, the development of novel methodology for the lithiation-trapping of oxygen heterocycles (THF and THP) is presented. Different conditions were optimised for THF and THP lithiation to give trapped products in 20-32% yield.



The newly developed methodology was extended to the lithiation-trapping of *N*-substituted morpholines. A full study of the reaction conditions and scope of the methodology was carried out for three different *N*-alkyl groups. The best substrate was the *N*-methyl morpholine and the optimised conditions were *s*-BuLi/TMEDA in hexane at 0 °C for 1 h, giving yields of trapped products in 75-90%. A procedure that is catalytic in TMEDA was also discovered.



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Acknowledgments

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Author’s Declaration

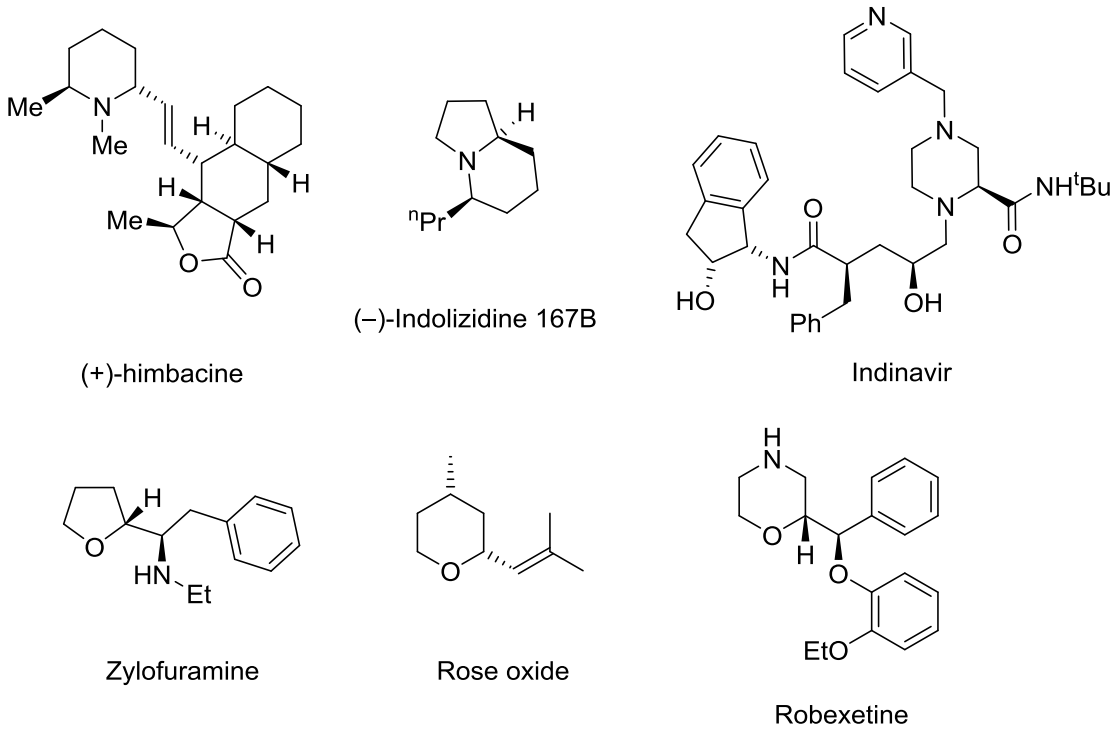
I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Chapter 1: Introduction

Nitrogen and oxygen heterocycles are commonly found as building blocks in a wide range of natural products and drug molecules. Some examples of natural products and drug molecules with substituents α to the nitrogen or oxygen are shown in Figure 1.1.

An example of an α-substituted piperidine is (+)-himbacine, which is a potential drug for the treatment of Alzheimer's disease.[1] (–)-Indolizidine 167B which contains a pyrrolidine ring is one of the simplest indolizidine alkaloids isolated from the skin of a neotropical frog caught on the Isla de Colon, Panama.[2] Compounds containing an α-substituted piperazine ring include Indinavir which is an antiretroviral drug used for the treatment of HIV.[3] In the examples of oxygen heterocycles, Zylofuramine is a stimulant,[4] Rose oxide is a naturally occurring fragrance compound[5] and Reboxetine is an anti-depressant.[6] Due to their useful applications, different synthetic strategies have been employed to construct α-substituted nitrogen and oxygen heterocyclic rings. However, lithiation-trapping is one of the most efficient methodologies to introduce α-functionalities in nitrogen heterocycles, and the investigation of this process, together with its extension to oxygen heterocycles, are the main topics of the research described in this thesis.

Figure 1.1

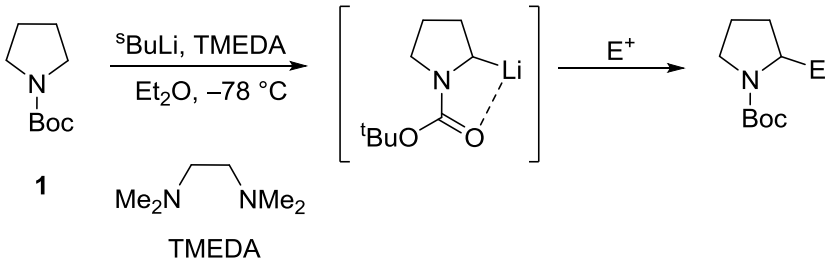


1.1 Brief Overview of Lithiation-trapping of *N*-Boc Heterocycles

1.1.1 Racemic Lithiation-trapping of *N*-Boc Heterocycles

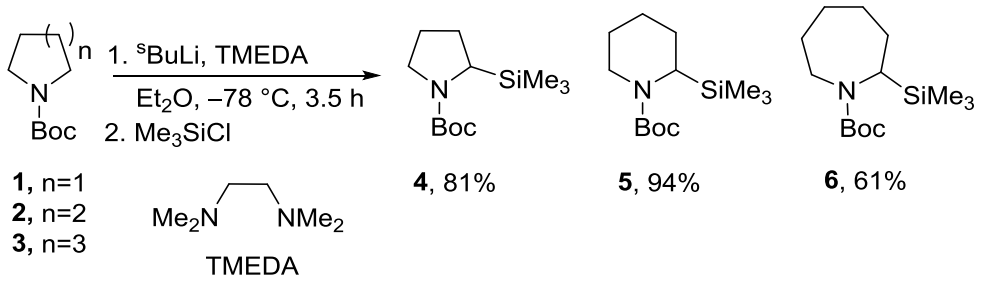
In 1989, Beak and Lee reported a simple protocol for the α-functionalisation of *N*-Boc heterocycles *via* lithiation-trapping.[7] The use of the *tert*-butyl carbamate of the cyclic amines is the key for the α-deprotonation to take place. For example, the lithiation-trapping of *N*-Boc pyrrolidine **1** was achieved by using the strong base *s*-BuLi in the presence of the diamine ligand TMEDA at –78 °C to generate the organolithium intermediate. This was then trapped with a variety of electrophiles to form the desired α-functionalised products (Scheme 1.1).

Scheme 1.1



The presence of a diamine ligand is essential to promote the lithiation in Et_2O. Since Et_2O is a poorly coordinating solvent, the *s*-BuLi/Et_2O complex is not reactive enough to complete the lithiation in high yield at –78 °C. Beak showed that the reactions worked well with *N*-Boc pyrrolidine **1**, *N*-Boc piperidine **2** and *N*-Boc azepane **3**. Trapping with Me_3SiCl gave silylated products **4**-**6** in 61-94% yield (Scheme 1.2).

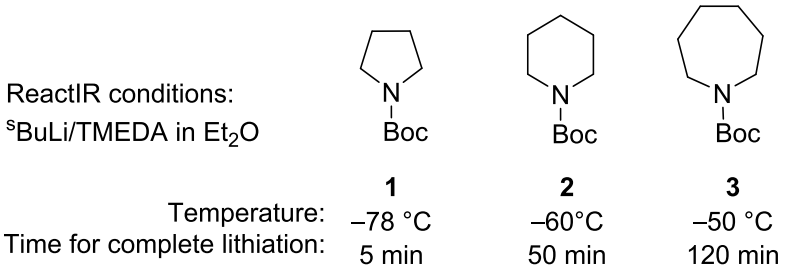
Scheme 1.2



These reaction conditions have been widely used for the α-functionalisation of *N*-Boc heterocycles *via* lithiation–trapping.[8,9,10] Recently, the O'Brien group has applied *in situ* ReactIR spectroscopy to monitor the time required for the lithiation of *N*-Boc heterocycles

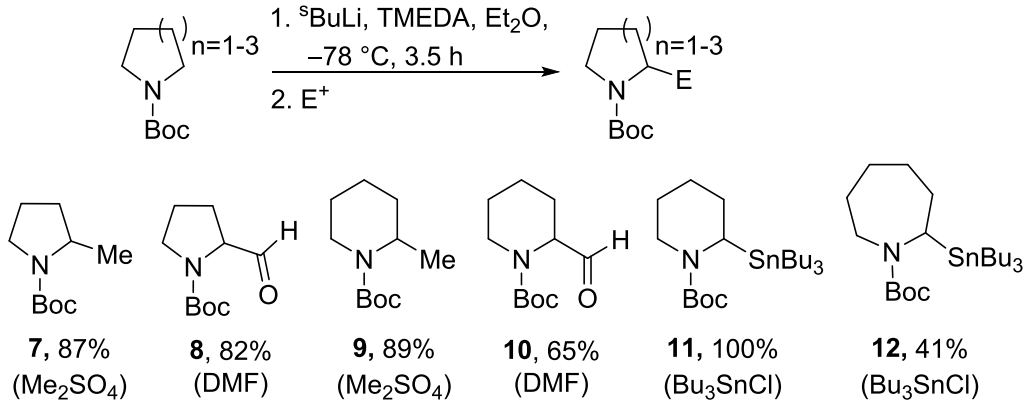
using *s*-BuLi/TMEDA in Et_2O at different temperatures (Figure 1.2).[11] It was shown that the lithiation of *N*-Boc pyrrolidine **1** was completed within 5 min at –78 °C and does not require the long lithiation time (3.5 h) originally reported by Beak.[7] A longer lithiation time of 50 min was, however, required for *N*-Boc piperidine **2** to fully lithiate at a higher temperature (–60 °C). The 7-membered ring system present in *N*-Boc azepane **3** was found to undergo the lithiation extremely slowly: full lithiation was observed after 120 min at a higher temperature (–50 °C). At present, our group does not have an explanation for the difference in reactivity but it could be due to the geometry and conformation of the different cyclic rings making the α-protons more difficult to deprotonate than in *N*-Boc pyrrolidine **1**.

Figure 1.2



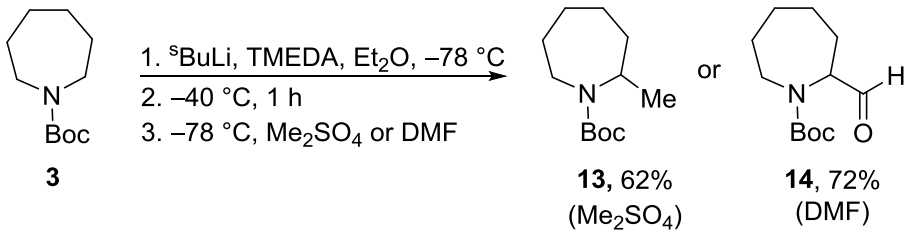
Lithiation-trapping of *N*-Boc heterocycles with a range of electrophiles under the s-BuLi/TMEDA-mediated conditions at –78 °C have been explored by Beak and the results are summarised in Scheme 1.3. As the results show, lithiation of *N*-Boc pyrrolidine **1** and *N*-Boc piperidine **2** gave good yields in general under this period of lithiation time (3.5 h).[7,12]

Scheme 1.3



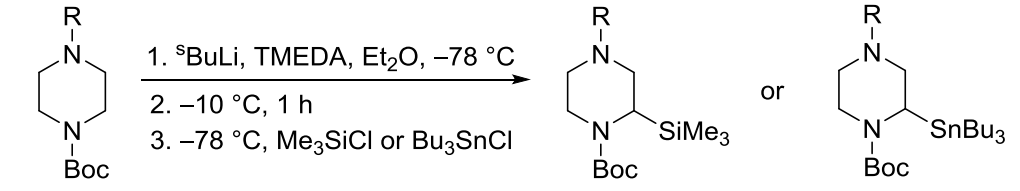
It can be seen from Schemes 1.2 and 1.3 that the yields of the products from the lithiation of *N*-Boc azepane **3** at –78 °C are generally lower than *N*-Boc pyrrolidine **1** and *N*-Boc piperidine **2**. For example, *N*-Boc azepane **3** gave a 61% yield of Me_3Si-trapped product **6** (Scheme 1.2) and a 41% yield of stannane **12** (Scheme 1.3). The *N*-Boc azepane **3** results reported by Beak are consistent with our group's ReactIR study shown in Figure 1.2 suggesting that the lithiation rate of *N*-Boc azepane **3** would be extremely slow at –78 °C and 3.5 h would not be long enough to undergo a full lithiation. Presumably because lithiation at higher temperature would require a shorter lithiation time, Beak carried out the lithiation of *N*-Boc azepane **3** at –40 °C for 1 h.[12] Subsequent methylation of *N*-Boc azepane **3** gave a 62% yield of methylated product **13** and DMF-trapping gave a 72% yield of aldehyde **14** (Scheme 1.4).

Scheme 1.4



In 2005, den Hoogenband and van Maarseveen *et al.* extended Beak's methodology to the lithiation-trapping of *N*-Boc piperazines using similar conditions (Scheme 1.5).[13] *N*-Boc-*N*'-methyl piperazine **15** and *N*-Boc-*N*'-benzyl piperazine **16** were lithiated under the *s*-BuLi/TMEDA-mediated conditions at –78 °C in Et_2O and then at –10 °C for 1 h. Trapping with Me_3SiCl or Bu_3SnCl gave substituted methyl piperazines **17** and **18** in 5% and 82% yields respectively. In contrast, the substituted benzyl piperazines **19** and **20** were isolated in 68% and 71% respectively.

Scheme 1.5



15: R = Me
16: R = Bn

17: R = Me, 5%
19: R = Bn, 68%

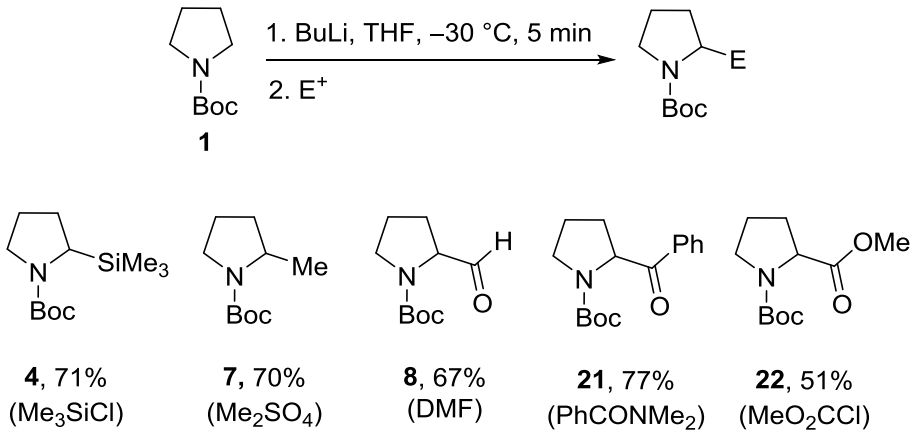
18: R = Me, 82%
20: R = Bn, 71%

There was no explanation from the paper about the low yield of the Me_3Si-substituted methyl piperazine **17**, but work in our group showed that with Me_3SiCl, trapping is slow and a competing ring-fragmentation can occur *via* β-elimination of the organolithium species.[14]

In general, Beak's lithiation conditions of using *s*-BuLi/TMEDA in Et_2O at –78 °C work well for most of the *N*-Boc heterocycles such as *N*-Boc pyrrolidine **1**. However, less reactive substrates such as *N*-Boc azepane **3** require a higher temperature to promote the lithiation and thus to obtain a higher yield.

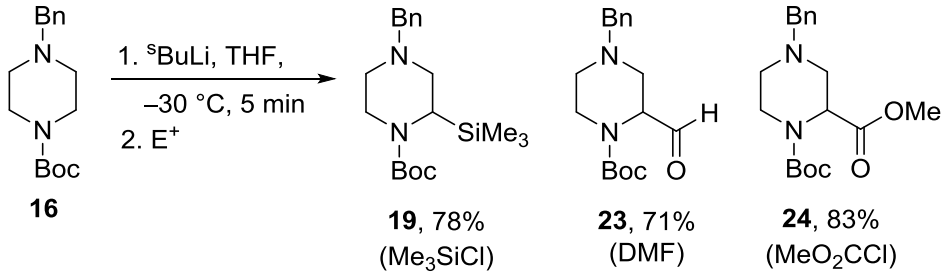
In 2010, our group developed an experimentally simpler, diamine-free protocol for lithiation-trapping of *N*-Boc pyrrolidine **1** which can also be carried out at higher temperatures.[15] For example, *N*-Boc pyrrolidine **1** was lithiated using *s*-BuLi in a more coordinating solvent, THF, at –30 °C for 5 min. The lithiated pyrrolidine was then trapped with a range of electrophiles to give products **4**, **7**-**8**, **21**-**22** with high yields (51-77%) without the use of TMEDA (Scheme 1.6).

Scheme 1.6



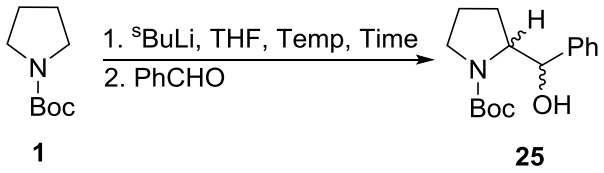
The optimised reaction conditions of the diamine-free lithiation provide a better approach to the principles of Green Chemistry:[16] the atom economy was improved as the TMEDA ligand was not required. In addition, high temperature lithiation can be carried out in a shorter lithiation time while retaining the yield which, if carried out on a process-scale, would reduce the energy consumption. The high temperature *s*-BuLi/THF-mediated lithiation of *N*-Boc-*N*'-benzyl piperazine **16** was also carried out. Using *s*-BuLi in THF at –30 °C for 5 min, substituted piperazines **19**,**23**-**24** were obtained after trapping with a range of electrophiles in high yields (55-83%) (Scheme 1.7).[10]

Scheme 1.7



When the diamine-free lithiation of *N*-Boc pyrrolidine **1** was carried out at temperatures above –30 °C and trapping with benzaldehyde, amino alcohols **25** were obtained with yields in the range of 0-66% (Table 1.1, entries 4-9). Lower yields were generally obtained for longer lithiation times at a particular temperature. For example, lithiation at –20 °C for 30 min gave a low 10% yield (entry 4) whereas a higher yield (66%) was achieved when the lithiation time was reduced to 5 min at the same temperature (entry 5). It was presumed that at high temperature, *s*-BuLi had reacted with THF instead of *N*-Boc pyrrolidine **1** which reduced the yield of amino alcohols **25**. More information on the reaction of organolithiums with THF is discussed in section 1.2.1.

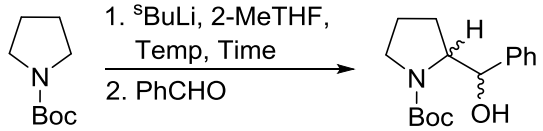
Table 1.1



Entry	Temp (°C)	Time (min)	Yield (%)
1	–30	60	37
2	–30	10	89
3	–30	5	84
4	–20	30	10
5	–20	5	66
6	–20	2	57
7	–10	5	29
8	–10	1	0
9	0	30	0

The diamine-free lithiation protocol was also carried out using the sustainable solvent 2-MeTHF. 2-MeTHF is a bio-derived solvent generated from sustainable biomass such as cellulose and hemicelluloses in lignocelluloses.[17] Since 2-MeTHF has a similar structure to THF, it is considered to be a greener alternative to THF in some organic synthesis applications (see section 1.2.2).[18,19] The results of the lithiation-benzaldehyde trapping of *N*-Boc pyrrolidine **1** in 2-MeTHF are shown in Table 1.2. High yields (92-94%) were obtained when the lithiation was carried out at temperatures below –30 °C (Table 1.2, entries 1-2). Lithiation at –30 °C for 60 min gave no amino alcohol **25** (entry 3) whereas a higher yield (73%) was achieved when the lithiation was reduced to 5 min at the same temperature (entry 4). The results suggested that the *s*-BuLi/2-MeTHF complex has a similar reactivity to the *s*-BuLi/THF complex.

Table 1.2

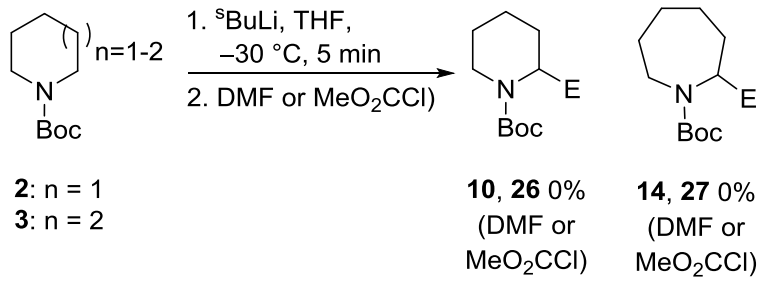


1 **25**

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

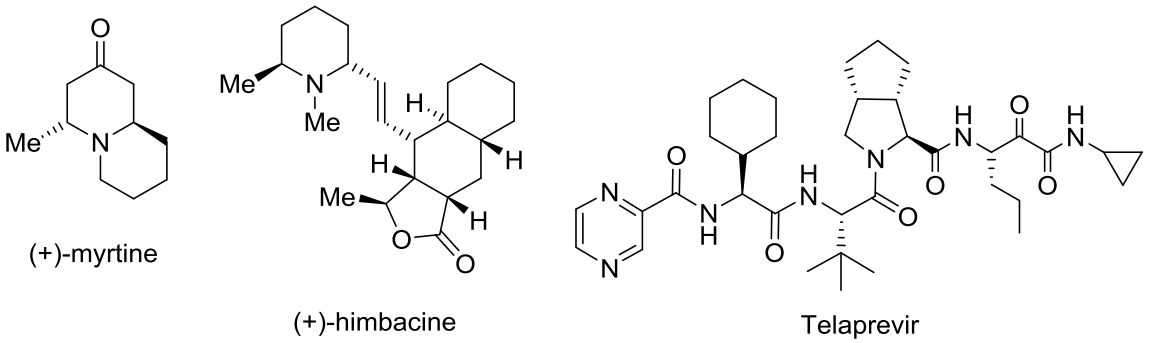
Although the *s*-BuLi/THF-mediated lithiation is a convenient set of conditions for *N*-Boc pyrrolidine **1** and *N*-Boc piperazine **16**, lithiation-trapping of *N*-Boc piperidine **2** and *N*-Boc azepane **3** under the same diamine-free protocol were unsuccessful (Scheme 1.8). Trapped products were not detected with different electrophiles (DMF or MeO_2CCl) and lower temperature conditions (–78 °C for 3 h or 6 h and –40 °C for 1 h or 3 h) were also attempted but were unsuccessful. Presumably, THF is a less coordinating ligand than TMEDA, the *s*-BuLi/THF complex is not reactive enough to complete the lithiation even at high temperature. Hence, the lithiation of the less reactive *N*-Boc heterocycles, *N*-Boc piperidine **2** and *N*-Boc azepane **3**, could not be achieved under diamine-free conditions.

Scheme 1.8



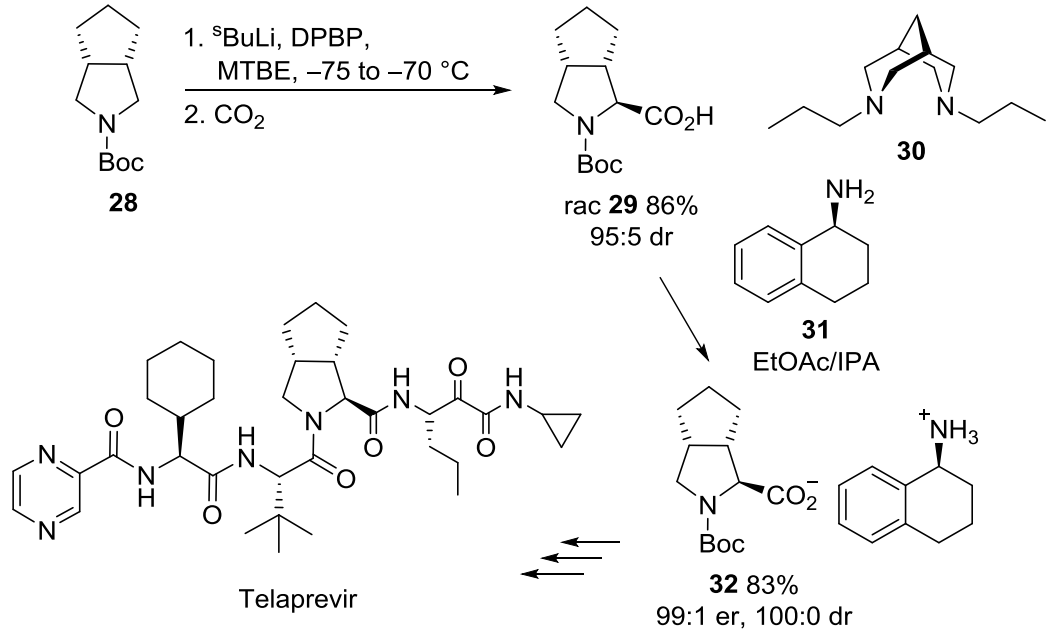
A wide range of examples of biologically active molecules have been synthesised *via* the route of racemic lithiation-trapping of *N*-Boc heterocycles. Examples include (+)-myrtine, (+)-himbacine and Telaprevir (Figure 1.3). (+)-Myrtine is a natural quinolizidine alkloid that can be isolated from *Vaccinium myrtillis* (Ericaceae).[20] Hurvois *et al.* demonstrated that the key piperidine intermediate of (+)-myrtine can be achieved *via* the lithiation-trapping of a substituted *N*-Boc piperidine.[21] Another piperidine derivative example, (+)-himbacine, is a potential drug molecule for the treatment of Alzheimer's disease which was isolated from the bark of Galbulimima baccata, a species that belongs to the magnolia family.[1] Chackalamannil *et al.* applied the racemic lithiation methodology to lithiate 2-methyl *N*-Boc piperidine with *s*-BuLi/TMEDA complex in Et_2O. The resulting disubstituted piperidine was further processed to give (+)-himbacine.[22]

Figure 1.3



Telaprevir is a registered drug for the treatment of hepatitis C virus (HCV) infections. Tanoury *et al.* developed a stereoselective lithiation-trapping sequence for *N*-Boc bicyclopyrrolidine **28** *via* a racemic lithiation-CO_2 trapping followed by classical resolution with a chiral amine (Scheme 1.9).[23]

Scheme 1.9



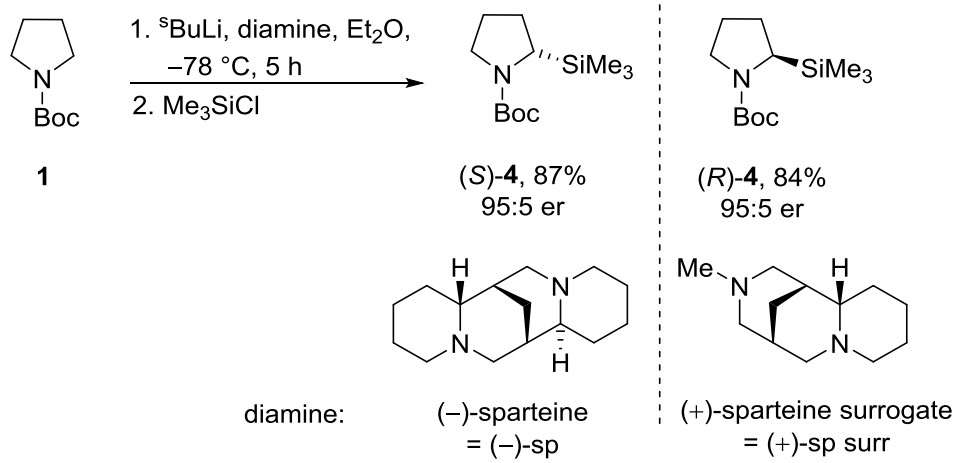
Due to the bicyclopyrrolidine system, lithiation using *s*-BuLi and bispidine ligand **30** provided diastereoselectivity and the intermediate was then trapped with CO_2 to give an 86% yield of acid *rac*-**29** with 95:5 dr. Use of the chiral amine **31** for the resolution followed by recrystallisation gave the salt **32** in 83% yield with 99:1 er and 100:0 dr.

1.1.2 Asymmetric Lithiation-trapping of *N*-Boc Heterocycles

Asymmetric lithiation-trapping of *N*-Boc heterocycles can be achieved using chiral diamine ligands. The first example of the asymmetric lithiation using *s*-BuLi and the chiral diamine, (–)-sparteine, was reported by Beak and Kerrick in 1991.[24,25] In 2002, our group reported the (+)-sparteine surrogate which is able to produce opposite enantioselectivity to (–)-sparteine for the asymmetric lithiation.[26]

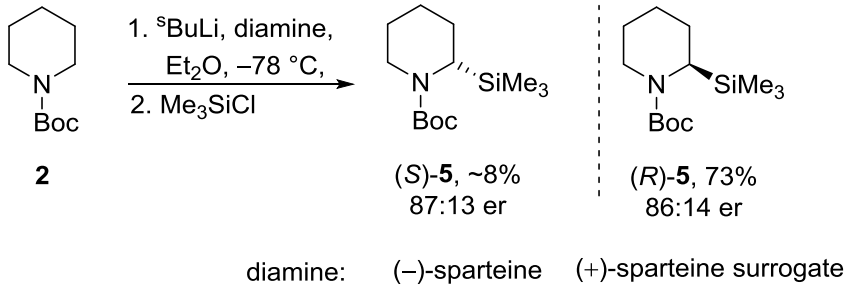
The asymmetric lithiation-trapping of *N*-Boc pyrrolidine **1** is shown in Scheme 1.10. With (–)-sparteine, silyl pyrrolidine (*S*)-**4** was obtained in high yield (87%) with an er of 95:5 whereas in the reaction in the presence of (+)-sparteine surrogate silyl pyrrolidine (*R*)-**4** was obtained in similar yield (84%) with an identical er of 95:5. However, the results from a ReactIR study revealed that there is a different behaviour of the two diamines:[11] with (+)-sparteine surrogate, the lithiation of *N*-Boc pyrrolidine **1** took under 2 min for completion, whereas 60 min was needed for *s*-BuLi/(–)-sparteine to fully lithiate *N*-Boc pyrrolidine **1**.

Scheme 1.10



Similar reactions using these two chiral diamines were carried out for the asymmetric lithiation of *N*-Boc piperidine **2** at –78 °C (Scheme 1.11).[27,28] A poor yield of silyl piperidine (*S*)-**5** (8%) was isolated from the lithiation using *s*-BuLi/(–)-sparteine complex. In contrast, the *s*-BuLi/(+)-sparteine surrogate complex gave a good 73% yield of the silyl piperidine (*R*)-**5**. The results demonstrated that *s*-BuLi/(+)-sparteine surrogate complex is more reactive than the corresponding (–)-sparteine complex for the lithiation of the less reactive substrate, *N*-Boc piperidine **2**. Our group has so far been unable to explain such a large difference in rates of lithiation between the *s*-BuLi/(+)-sparteine surrogate and (–)-sparteine complexes.

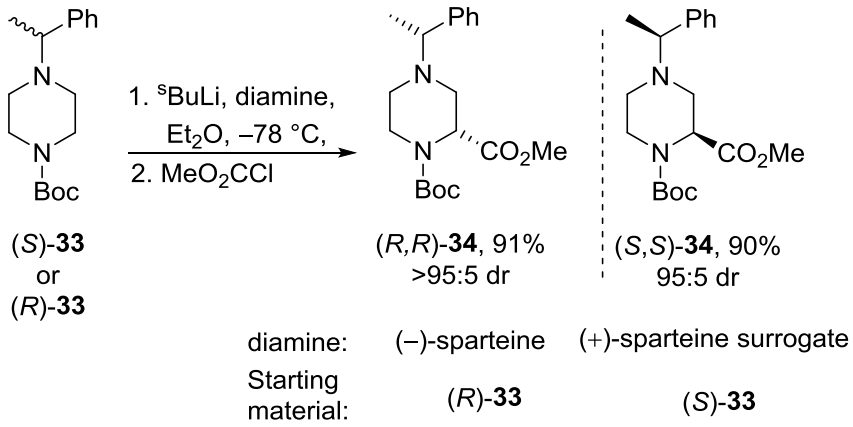
Scheme 1.11



Recently, our group reported a new method to synthesise enantiopure α-substituted piperazines *via* an asymmetric lithiation procedure.[29] A high yield of a single stereoisomer of *N*-Boc piperazine can be obtained by matching the configuration of the stereogenic α-methylbenzyl group with a chiral ligand (Scheme 1.12). Lithiation of (*S*)-**33** using *s*-BuLi/(+)-sparteine surrogate in Et_2O at –78 °C followed by trapping with MeO_2CCl produced a 95:5 mixture of diastereomeric piperazines (*S*,*S*)-**34** and (*R*,*S*)-**34**. The

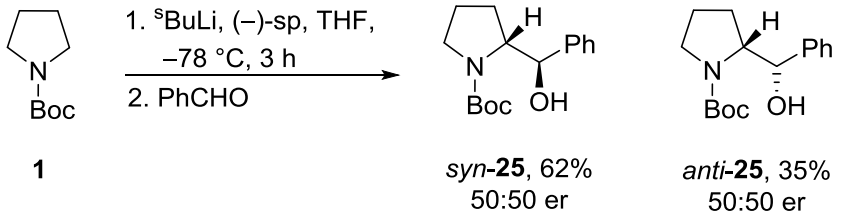
diastereomers were readily separable and after purification, piperazine (*S*,*S*)-**34** was obtained in 90% yield. In addition, lithiation of enantiomeric (*R*)-**33** using the *s*-BuLi/(–)-sparteine complex gave a >95:5 mixture of (*R*,*R*)-**34** and (*S*,*R*)-**34** from which a 91% yield of (*R*,*R*)-**34** was obtained.

Scheme 1.12



Interestingly, when Et_2O was replaced by THF as solvent for *s*-BuLi/(–)-sparteine complex-mediated reactions, a racemic product was formed. For example, lithiation of *N*-Boc pyrrolidine **1** using *s*-BuLi/(–)-sparteine in THF at –78 °C for 3 h and trapping with benzaldehyde gave two separable diastereomers, *syn*-**25** (62%) and *anti*-**25** (35%) (Scheme 1.13). Both *syn*-**25** and *anti*-**25** were produced in 50:50 er.

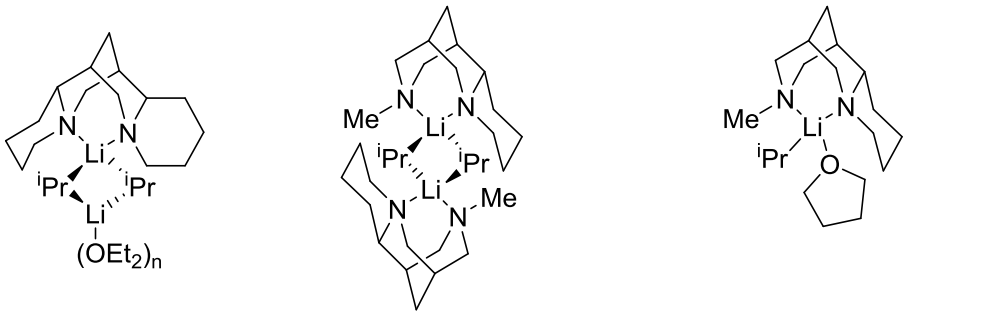
Scheme 1.13



It is known that the coordinating solvent THF can displace (–)-sparteine from the *s*-BuLi/(–)-sparteine complex in solution.[30,31,32] In contrast, in weaker coordinating solvents such as Et_2O or toluene, the (–)-sparteine remains associated with organolithium species. Hence, the *s*-BuLi/THF complex is presumably more reactive than the *s*-BuLi/(–)-sparteine in the solution. A detailed NMR spectroscopic investigation of the behaviour of different chiral diamines was carried out by the O'Brien and Hilmersson groups.[33] The solution structures of *i*-PrLi complexed with (–)-sparteine and (+)-sparteine surrogate under

different conditions were determined using ^{6}Li and ^{13}C NMR spectroscopy. Under conditions in Et_2O-d_{10} at –80 °C, *i*-PrLi/(–)-sparteine exists as Et_2O-complexed heterodimer **35**, whereas *i*-PrLi/(+)-sparteine surrogate complex exists as a head-to-tail homodimer **36** (Figure 1.4). Presumably, the less sterically hindered (+)-sparteine surrogate can more readily complex to *i*-PrLi which allows the homodimer formation in Et_2O. When the corresponding NMR spectroscopic experiments were carried out in THF-d_8 at –80 °C, there was a significant difference in behaviour with the two diamines: a 1:1 mixture of *i*-PrLi and (–)-sparteine did not form a complex, whereas a 1:1 mixture of *i*-PrLi and (+)-sparteine surrogate gave a monomer **37**. The NMR spectroscopy results revealed that (–)-sparteine has a weaker coordination with organolithiums such as *i*-PrLi and *s*-BuLi compared to the (+)-sparteine surrogate in THF.

Figure 1.4



Heterodimer **35** for ^{i}Pr/(–)-sparteine complex in Et_2O

Homodimer **36** for ^{i}Pr/(+)-sparteine surrogate complex in Et_2O

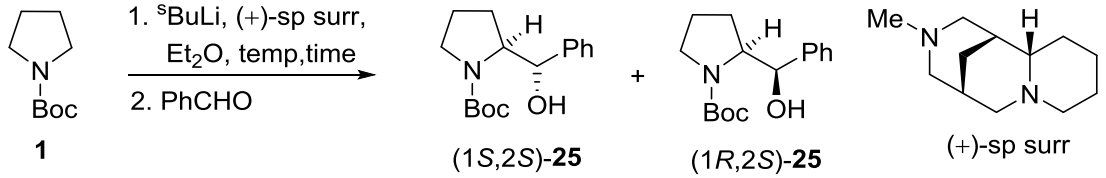
Monomer **37** for ^{i}Pr/(+)-sparteine surrogate complex in THF

The result of the NMR spectroscopic study made it possible to carry out the first examples of asymmetric lithiation-trapping using *s*-BuLi/chiral diamine in THF. The enantioselectivity experiments of lithiation-benzaldehyde trapping of *N*-Boc pyrrolidine **1** at –78 °C showed that there was a poor enantioselectivity when using *s*-BuLi/(–)-sparteine complex in THF or "THF-like" 2-MeTHF, whereas a high enantioselectivity of product was obtained by using *s*-BuLi/(+)-sparteine surrogate complex under the same conditions.

In more recent work, high temperature asymmetric lithiation-trapping of *N*-Boc pyrrolidine **1** in Et_2O was attempted using *s*-BuLi and the (+)-sparteine surrogate (Table 1.3).[34] At –78 °C, both products (1*S*,2*S*)-**25** and (1*R*,2*S*)-**25** were isolated in high er (95:5 and 94:6 respectively) with high yields (81% in total, entry 1). Lithiation was also successful at higher temperatures of –40 °C, –30 °C and –20 °C for 2 min while retaining the yields with high er of both products (entries 2-4). In contrast, at –20 °C for 1 h, products (1*S*,2*S*)-**25**

and (1*R*,2*S*)-**25** were produced with lower er (83:17 and 85:15 respectively) (entry 5). The lower enantioselectivity at higher temperature is presumably due to reduced kinetic selectivity and partial configurational instability.[35,36] The reduction of yields at –20 °C for 1 h is likely due to the chemical instability of the organolithium at this temperature for a prolonged period of time. A similar set of results was obtained for experiments using (–)-sparteine.

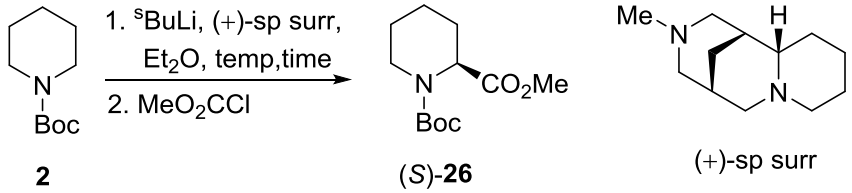
Table 1.3



Entry	Temp (°C)	Time	(1*S*,2*S*)-25 Yield (%), er	(1*R*,2*S*)-25 Yield (%), er	Total yield (%)
1	–78	3 h	58, 95:5	23, 94:6	81
2	–40	2 min	65, 90:10	30, 92:8	95
3	–30	2 min	67, 90:10	27, 90:10	92
4	–20	2 min	50, 89:11	23, 91:9	73
5	–20	1 h	40, 83:17	20, 85:15	60

The investigation of the high temperature asymmetric lithiation protocol using the (+)-sparteine surrogate was further extended to the less reactive substrate, *N*-Boc piperidine **2** (Table 1.4). At –78 °C, 3 h lithiation was required for *N*-Boc piperidine **2** to fully lithiate and give the MeO_2CCl-trapped product (*S*)-**26** in good yield (83%) with 87:13 er (entry 1). Lower yields of product (*S*)-**26** were obtained in the range of 46-64% with lower er for lithiation at temperatures above –50 °C (entries 2-4). There was also some recovered starting material which indicated that the lithiation was not complete using the *s*-BuLi/(+)-sparteine surrogate complex, possibly because reaction with the solvent is competitive at these higher temperatures.

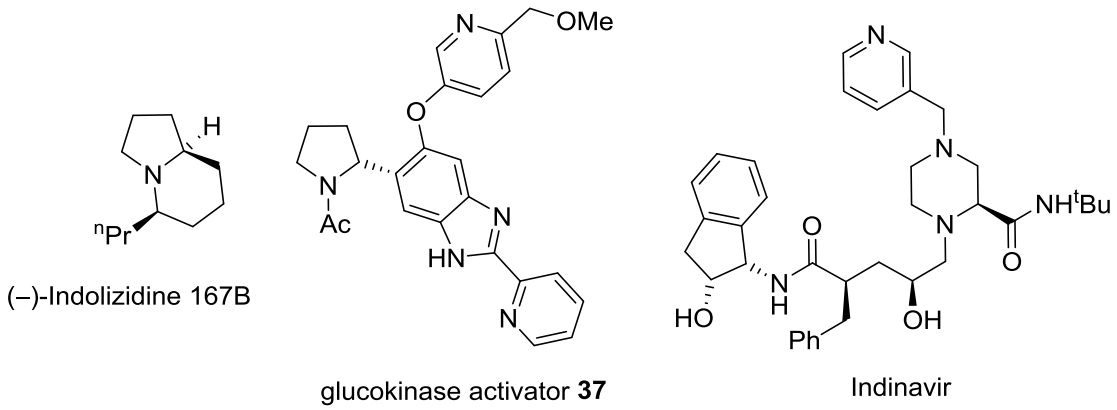
Table 1.4



Entry	Temp (°C)	Time	(*S*)-26 Yield (%)	er of (*S*)-26	2 Yield (%)
1	–78	3 h	83	87:13	0
2	–50	30 min	46	79:21	21
3	–40	20 min	64	80:20	15
4	–30	5 min	47	77:23	26

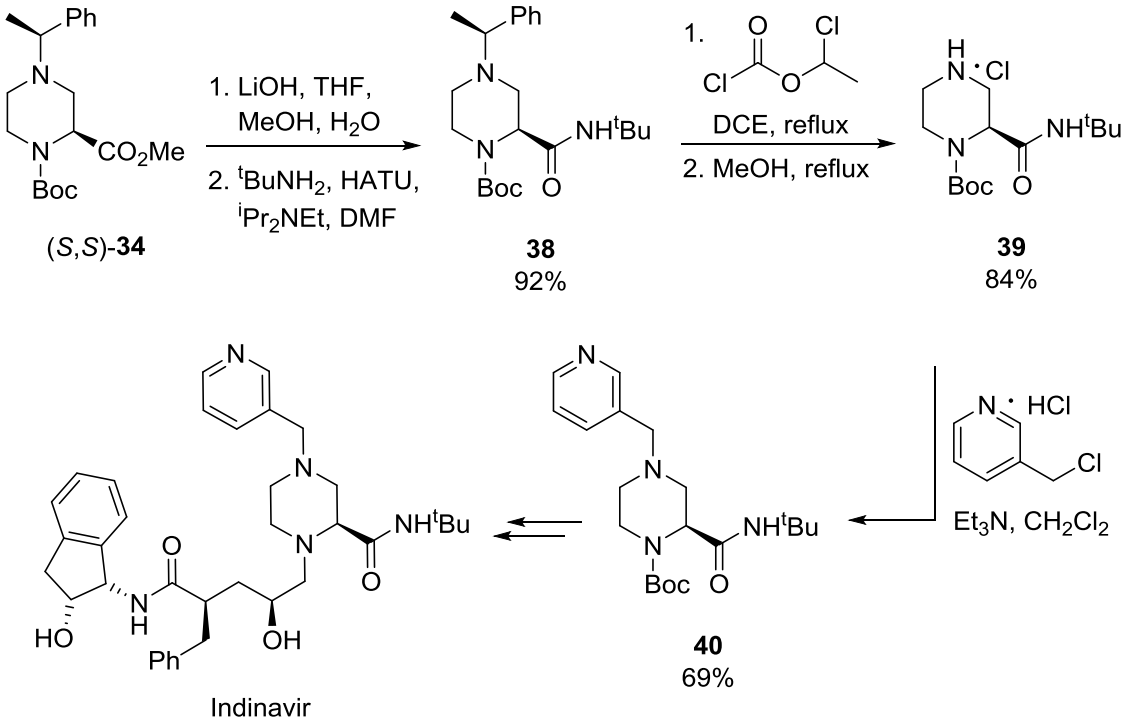
The asymmetric lithiation-trapping of *N*-Boc heterocycles is an effective methodology for synthesis of biologically active molecules. A wide range of examples has been published including (–)-Indolizidine 167B, glucokinase activator **37** and Indinavir (Figure 1.5). Synthesis of (–)-Indolizidine 167B *via* lithiation-allylation of *N*-Boc pyrrolidine **1** was demonstrated by our group in 2008.[37] Lithiation of *N*-Boc pyrrolidine **1** using *s*-BuLi and a chiral diamine followed by lithium-copper transmetallation and allylation generated the enantioenriched intermediate which was further processed to give (–)-Indolizidine 167B. Campos *et al.* applied a lithiation-arylation protocol to the synthesis of glucokinase activator **37** on a large scale *via* the asymmetric lithiation and Negishi methodolgy.[38]

Figure 1.5



Our group demonstrated a formal synthesis of Indinavir by applying the asymmetric lithiation of a single stereoisomeric piperazine (Scheme 1.14).[29] As discussed before, (*S*,*S*)-**34** was prepared using *s*-BuLi/(+)-sparteine surrogate complex and subsequent trapping using MeO_2CCl. Conversion of ester **34** into amide **38** was achieved by ester hydrolysis and amide formation. Deprotection of the α-methylbenzyl group in **38** followed by alkylation gave **40**, the desired fragment of Indinavir.

Scheme 1.14



In summary, the reactivity of *N*-Boc heterocycles towards lithiation-trapping decreases as the size of the ring increases. The less reactive *N*-Boc piperidine **2** and *N*-Boc azepane **3** only undergo high yielding lithiation using *s*-BuLi/TMEDA or *s*-BuLi/(+)-sparteine surrogate complex, and sometimes require temperatures above –78 °C. In contrast, high temperature lithiation-trapping of *N*-Boc pyrrolidine **1** can be completed using *s*-BuLi/THF or 2-MeTHF *via* the diamine-free protocol.

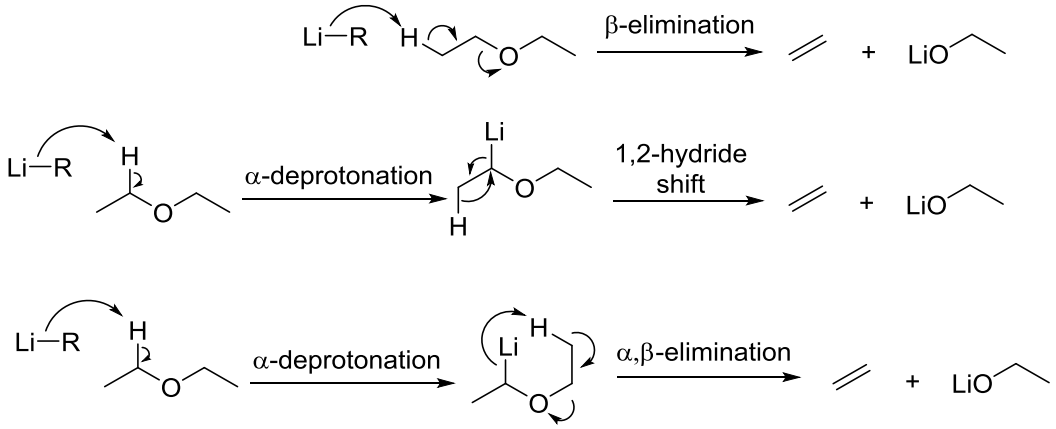
1.2 Overview of Organolithium Reagents in Ether Solvents

Ethers such as Et_2O and THF are the most commonly used solvents in organolithium reactions. They are typically used for the lithiation-trapping of *N*-Boc heterocycles, as discussed in the previous section. Nevertheless, the influence of ether solvents on the reactivity of organolithium species can vary. Many alkyllithium reagents, such as *s*-BuLi and *n*-BuLi, are commercially available as a solution in hydrocarbon solvents (commonly in cyclohexane or mixed hexanes). Although organolithium species are conventionally written as R-Li, they normally exist in a range of aggregates based on the choice of solvents and addition of ligands. For example, *n*-BuLi exists as hexamers, with an octahedral arrangement of Li atoms around the alkyl groups in non-polar hydrocarbons.[39] The more sterically hindered alkyllithiums such as *i*-PrLi, *s*-BuLi and *t*-BuLi aggregate as tetramers in hydrocarbons, with a tetrahedron of Li atoms bridged by the alkyl groups. When a stronger coordinating solvent such as THF is used, it reduces the aggregation state of the organlithium species and the species also become more active. Bauer *et al.* suggested that the *s*-BuLi/THF complex exists as a 78:22 mixture of monomer and dimer.[40] The addition of a diamine, such as TMEDA, can also reduce the degree of aggregation. Diamines are typically used in proportion to the organolithium species which enhances the reactivity. However, organolithium reagents can react with Et_2O and THF at high temperature (above –78 °C) causing cleavage reactions.

1.2.1 Stability of Ethers in the Presence of Organolithium Reagents

The reaction of organolithium compounds with Et_2O to give ethene and lithium ethoxide has been known since 1957.[41] Although β-elimination was considered as the mechanism of this reaction, the details of the decomposition pathway were not studied until 1973 by Maercker.[42,43] The investigation was carried out by studying the kinetic isotope effects of different labelled versions of Et_2O. Three different reaction pathways were identified which would give ethene and lithium ethoxide. The mechanisms are shown in Scheme 1.15. The organolithium could remove the proton at the α- or β-position of Et_2O. For β-elimination, the Et_2O will directly break down into ethene and lithium ethoxide. If the organolithium deprotonates the α-proton, it can then undergo either a 1,2-hydride shift or an intramolecular β-elimination (overall procedure is called α,β-elimination) to give ethene and lithium ethoxide. Using detailed deuterium studies, Maercker confirmed that all three mechanisms were operating with Et_2O.

Scheme 1.15



The decomposition of Et_2O by organolithium reagents depends on the type of organolithium reagent, the presence of ligands and the temperature. In 1997, Stanetty *et al.* published a detailed titration study to investigate the stability of Et_2O under different conditions (Table 1.5).[44] At –20 °C, *s*-BuLi and *t*-BuLi are stable in Et_2O in the presence of TMEDA due to the strong coordination of alkyllithium and TMEDA (entries 1 and 4). Nevertheless, under the same conditions but in the absence of TMEDA, Et_2O reacts slowly in 8-20 h with *s*-BuLi and *t*-BuLi (entries 2 and 6). At 0 °C, *s*-BuLi and *t*-BuLi are relatively unstable without TMEDA (entries 3 and 6). The instability of the *n*-BuLi/TMEDA complex can occur when the temperature is above 0 °C (entry 7). A number of studies concerning the cleavage of cyclic ethers by organolithium species have been reported.

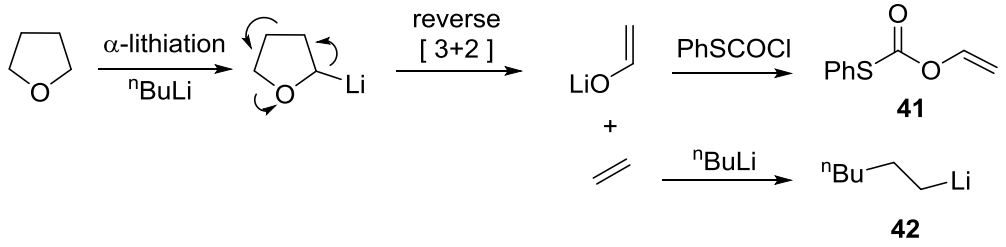
Table 1.5

Entry	Organolithium	Solvent	Temperature (°C)	Half-life
1	*t*-BuLi	Et_2O + TMEDA	–20	Stable at 1.36 M
2	*t*-BuLi	Et_2O	–20	8.05 h
3	*t*-BuLi	Et_2O	0	1.02 h
4	*s*-BuLi	Et_2O + TMEDA	–20	Stable at 0.65 M
5	*s*-BuLi	Et_2O	–20	19.8 h
6	*s*-BuLi	Et_2O	0	2.32 h
7	*n*-BuLi	Et_2O + TMEDA	0	10.1 h
8	*n*-BuLi	Et_2O	20	153 h
9	*n*-BuLi	Et_2O	35	31 h

Since THF is the most commonly used solvent for organolithium reactions among other cyclic ethers, the mechanistic and kinetic studies of THF cleavage by organolithium species were studied by different groups.[45,46] In 1957, Gilman and Gaj compared the stability of some organolithium compounds in THF.[41] Their results showed that MeLi, PhLi and *n*-BuLi are less stable in THF than in Et_2O. They also indicated that the workable temperatures in THF are as follows: 0 °C for MeLi, 0 to –30 °C for PhLi and below –30 °C for *n*-BuLi.

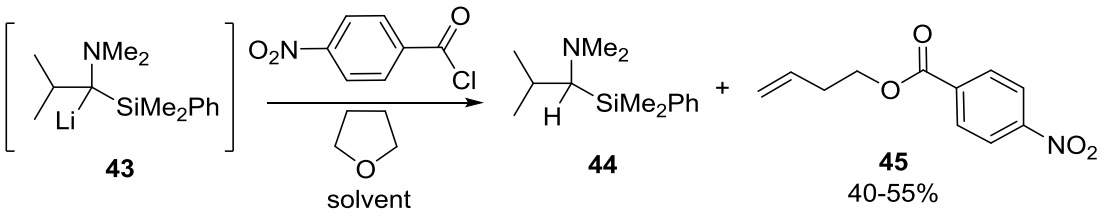
An NMR spectroscopic investigation about the mechanism and half-lives of THF cleavage with *n*-BuLi was carried out by Bates in 1972.[46] The result suggested that THF was deprotonated at the α-position followed by a reverse [3+2] cycloaddition to give ethene and a lithium enolate (Scheme 1.16). The resulting lithium enolate could be trapped by an electrophile, phenyl thiochlorocarbonate in this example, to give enol thiocarbonate **41**. Ethene can also further react with another equivalent of organolithium to give the carbolithiation product **42**.[42]

Scheme 1.16



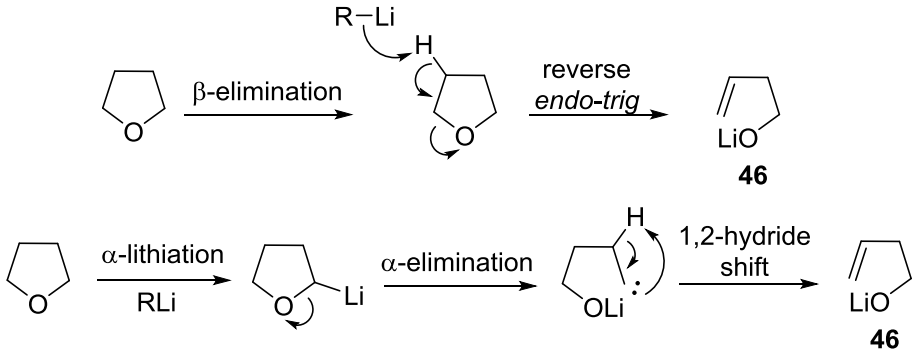
In contrast, Fleming showed an example of THF being broken down into an alkene chain instead of ethene and a lithium enolate.[47] By quenching their lithiated intermediate **43** with *p*-nitrobenzoyl chloride (DNBCl) in THF between –78 °C and –20 °C, the *p*-nitrobenzoate ester **45** of but-en-1-ol was isolated (Scheme 1.17). They suggested that the source of the proton in product **44** is from THF but the mechanism for the deprotonation of THF was not discussed.

Scheme 1.17



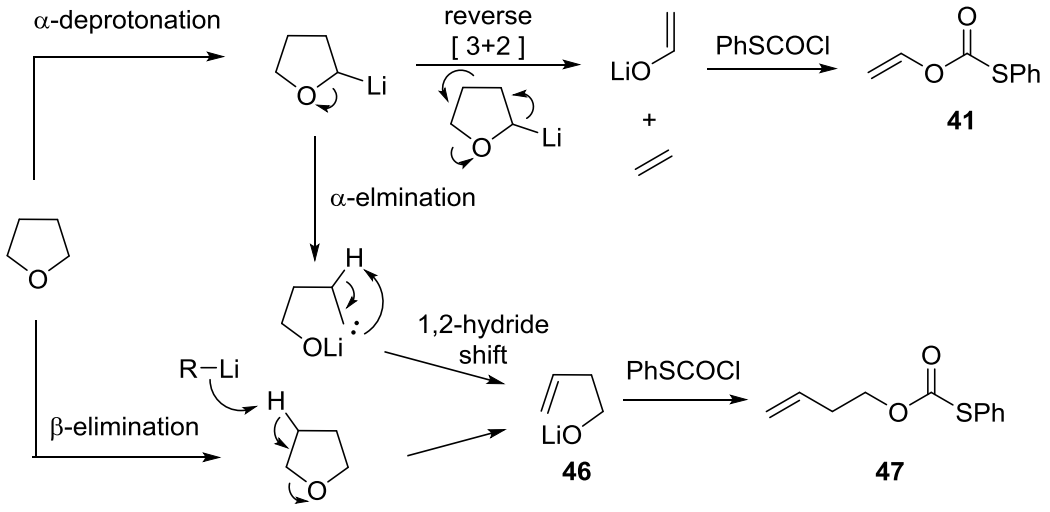
There are two possible pathways for forming lithium but-3-en-1-oxide **46** from THF. The mechanisms are shown in Scheme 1.18. The organolithium could remove a β-proton in a β-elimination pathway. However, it should be noted that the geometry is unfavourable for E2 elimination in these five-membered ring compounds and the reverse 5-*endo-trig* is a Baldwin-disfavoured reaction (Scheme 1.18).[48] The other possible pathway involves the α-lithiation of THF followed by a 1,2-hydride shift.

Scheme 1.18



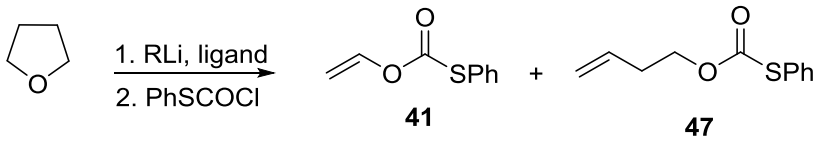
In 2002, Clayden reported the formation of lithium but-3-en-1-oxide **46** from THF.[49] In his paper, the factors that control the decomposition route of THF were investigated. One of the factors focused on was the combination of the ligand and the organolithium and whether the presence of ligand would affect the decomposition route of THF. If the α-deprotonation and reverse [3+2] happens, enol thiocarbonate **41** would be formed (Scheme 1.19). If the reaction favours the formation of lithium but-3-en-1-oxide **46**, but-3-en-1-yl thiocarbonate **47** would be seen.

Scheme 1.19



The results suggested that HMPA has a unique role for the formation of lithium but-3-en-1-oxide **47** compared to the other ligands. However, both α-deprotonation and β-elimination can lead to the formation of lithium but-3-en-1-oxide **46** and the mechanistic pathway that HMPA directs the formation of product **47** has not identified yet (Table 1.6). None of the product **47** formed in the absence of ligand (entries 1 and 2). Excess of HMPA (6 equivalents) with either *n*-BuLi, *s*-BuLi, or *t*-BuLi encouraged the formation of **47** and suppressed the formation of **41** *via* reverse [3+2] cycloaddition (entries 3-5). The yield of **47** was reduced when 1 equivalent of HMPA was used (entry 6) and the reverse [3+2] cycloaddition route was more favourable for other ligands such as TMEDA and (–)-sparteine (entries 9 and 10).

Table 1.6



Entry	Organolithium	Ligand	**41** Yield (%)[a]	**47** Yield (%)[a]
1	*n*-BuLi	nil	26*	0
2	*t*-BuLi	nil	25*	0
3	*t*-BuLi	HMPA (6 eq.)	<1	62
4	*s*-BuLi	HMPA (6 eq.)	<1	42
5	*n*-BuLi	HMPA (6 eq.)	<1	24
6	*t*-BuLi	HMPA (1 eq.)	54	19
7	*s*-BuLi	TMEDA (1 eq.)	0	0
8	*t*-BuLi	TMEDA (1 eq.)	98	2
9	*s*-BuLi	(–)-sparteine (1 eq.)	99	1
10	*t*-BuLi	(–)-sparteine (1 eq.)	98	2

[a]By GC analysis unless otherwise indicated. *Isolated yield.

The titration study from Stanetty also discussed the stability of THF with different organolithium species at different temperatures (Table 1.7). At –20 °C, *t*-BuLi is stable in THF for around 0.7 h and the presence of TMEDA does not have an effect on the result (entries 1 and 2). For *s*-BuLi, THF is stable at –40 °C in the presence of TMEDA (entry 4),

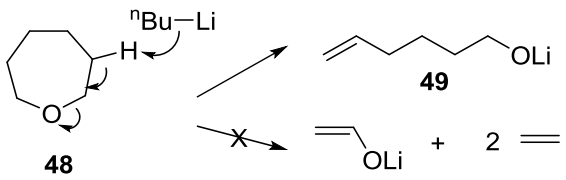
but under the same conditions, the half-life of *s*-BuLi reduced to less than half an hour at –20 °C (entry 5). *n*-BuLi is relatively stable at temperatures above 0 °C (entries 6-9). In general, the half-lives of the organolithium species in THF at –20 °C or above are reduced when TMEDA is present in the reaction mixture.

Table 1.7

Entry	Organolithium	Solvent	Temperature (°C)	Half-life
1	*t*-BuLi	THF	–20	0.70 h
2	*t*-BuLi	THF + TMEDA	–20	0.75 h
3	*s*-BuLi	THF	–20	1.30 h
4	*s*-BuLi	THF + TMEDA	–40	Stable at 0.52 M
5	*s*-BuLi	THF + TMEDA	–20	0.47 h
6	*n*-BuLi	THF	0	17.3 h
7	*n*-BuLi	THF	20	1.78 h
8	*n*-BuLi	THF + TMEDA	0	5.63 h
9	*n*-BuLi	THF + TMEDA	20	0.63 h

Currently there is no evidence to identify the pathway of forming lithium but-3-en-1-oxide **47** from THF from the two possible pathways shown in Scheme 1.19. The β-elimination pathway is unlikely to happen in these five-membered ring compounds due to the unfavourable geometry for E2 elimination. However, as the size of the ring increases to seven, oxepane has the required geometry to access the E2 elimination which is shown in Scheme 1.20. Although oxepane **48** was not used as a solvent, it is useful to compare its results with THF. Bates suggested that oxepane **48** was deprotonated by *n*-BuLi at the β-position to give alkene **49**.

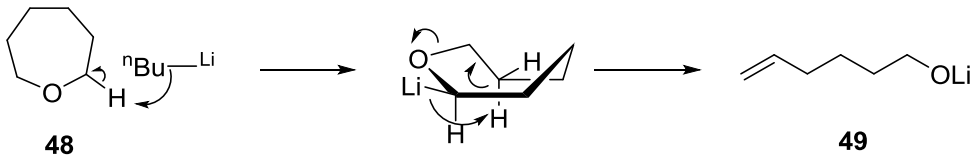
Scheme 1.20



Cohen and Stokes have also studied the β-cleavage of oxepane with *n*-BuLi using kinetic

isotope effect experiments.[50] Surprisingly, their results confirmed that the initial step for cleavage of oxepane **48** takes place *via* lithiation at the α-position followed by a transannular hydrogen shift to form lithium hex-5-en-1-oxide **49**. The mechanism of cleavage of the oxepane is shown in Scheme 1.21.

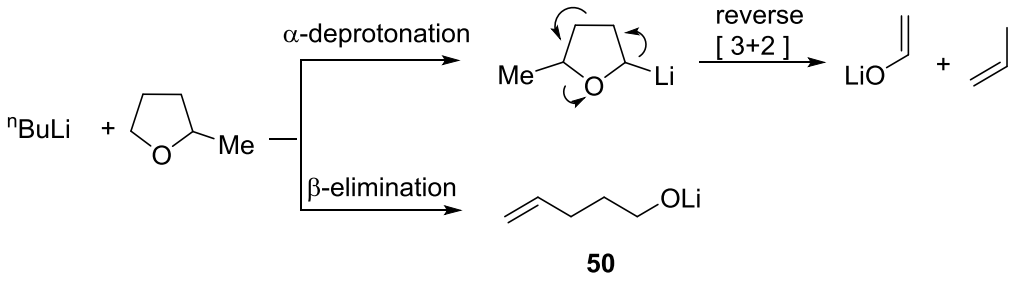
Scheme 1.21



48 **49**

In the last decade, 2-MeTHF has become popular as a greener alternative to THF for use as a solvent.[51,18] Although there is a growing number of examples of the use 2-MeTHF as solvent in a variety of organic synthesis applications, particularly with organolithium reagents, the stability of organolithium reagents in 2-MeTHF has not been reviewed in detail. Cohen and Stokes studied the mechanism of 2-MeTHF cleavage using *n*-BuLi.[50] Although 2-MeTHF can undergo α-deprotonation like THF, the methyl group at the α-position of the five-membered ring favours an alternative β-elimination process (Scheme 1.22).

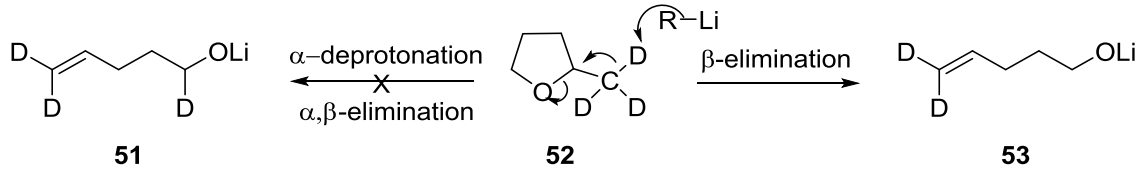
Scheme 1.22



50

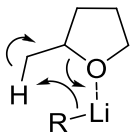
From an isotope labelling experiment shown in Scheme 1.23, the deuterated lithium pent-4-en-1-oxide **53** was isolated and it contained only two deuteriums. This confirmed that the deprotonation of 2-MeTHF occurs at the β-position and that the organolithium preferentially deprotonates the proton from the methyl group instead of the C-3 proton on the ring.

Scheme 1.23



The deprotonation of 2-MeTHF at the β-position on the methyl group is favoured as the organolithium is directed by the oxygen atom of the ring *via* coordination of an oxygen lone pair to the lithium (Figure 1.6). The study did not reveal evidence of the α-deprotonation pathway.

Figure 1.6



In summary, reactions of organolithium reagents with Et_2O and THF can be occur at high temperatures (above –20 °C) and this can then lead to cleavage reactions. The mechanisms of ether cleavage are varied and depend on the ether and the conditions used.

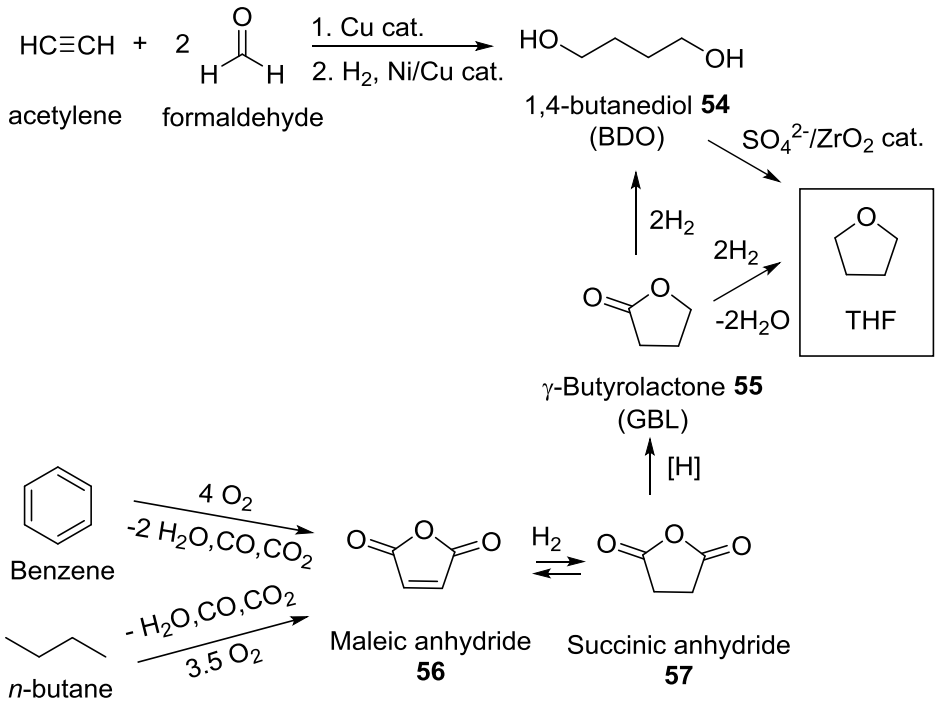
1.2.2 Sustainable Ether Solvents

Solvents are essential for almost all synthetic applications and around 20 million tonnes of solvents are consumed annually across the world. However, driven by environmental and regulatory pressures and concerns of using volatile organic compounds (VOC), the development of solvents that are safer and renewable has increased rapidly in the last fifteen years. The concepts of green (sustainable) solvents are introduced in the 12 principles of Green Chemistry.[52,53,54] The role of a desirable green solvent should be associated with low toxicity, low vapour pressure and minimising environmental impact. More desirably, it should have additional benefits such as assisting the reaction.

As discussed previously, ethers such as Et_2O and THF are the most commonly used solvents for organolithium reactions. However, there are several drawbacks when these two organic solvents are used in commercial production processes: Et_2O has a low boiling point (34.6 °C) and is highly flammable which limits its use in industrial applications; THF has a high water solubility which gives a poor separation from the aqueous waste. This can lead to a difficult or expensive work-up process and waste treatment. In addition, Et_2O and

THF are currently prepared from non-renewable petroleum-based resources. For example, there are several industrial processes for THF production and the most widely used in commercial processes involves the acid-catalyzed dehydration of 1,4-butanediol **54** (BDO) (Scheme 1.24). BDO **54** is a petroleum-derived product which is commercially produced from the condensation of acetylene with formaldehyde using a Cu catalyst followed by high-pressure hydrogenation using a Ni/Cu catalyst.[55] It then undergoes cyclisation using an acid catalyst to form THF.[56] Alternatively, THF can be prepared by reduction of maleic anhydride **56** which is traditionally made from oxidation of benzene or *n*-butane.[57] However, oxidation of benzene or *n*-butane is very exothermic and due to incomplete combustion it generates carbon monoxide and carbon dioxide. This makes THF production *via* maleic anhydride **56** less favourable.

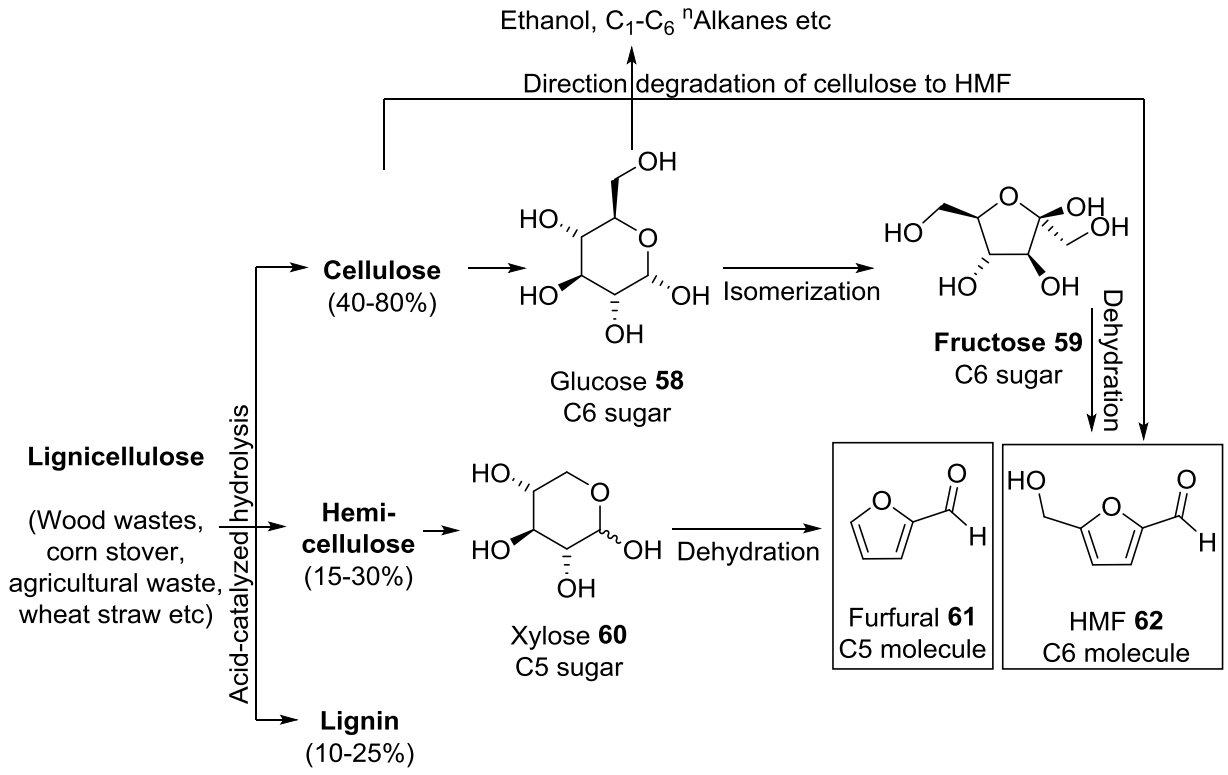
Scheme 1.24



2-Methyltetrahydrofuran (2-MeTHF) is a bio-derived solvent generated from sustainable biomass such as cellulose and hemicelluloses in lignocellulosic waste.[58,59] There are a growing number of examples showing 2-MeTHF can replace THF as a solvent in some organic synthesis applications.[18,19, 60] For example, Pace reported a highly efficient chemoselective preparation of *N*-TBS-arylamines at high temperature (0 °C) using an organolithium reagent in 2-MeTHF where the conventional reaction was carried out in THF at –78 °C.[61]

There are many routes to produce 2-MeTHF from lignocellulose biomass but most of the procedures proceed *via* 5-hydroxymethylfurfural (HMF) or furfural as key bio-derived building blocks, so-called platform molecules.[62] Lignocellulose biomass is converted by depolymerisation (acid-catalyzed hydrolysis/one or more catalytic processes) and/or fermentation (biological enzymes) into lignin (waste), glucose **58** (predominately from cellulose) and xylose **60** (predominately from hemicellulose) and then these are converted into furfural **61** and HMF **62**. The general synthetic routes to furfural **61** and HMF **62** are summarised in Scheme 1.25. HMF **62** can be obtained by the acid-catalysed conversion of carbohydrates based on the C6 sugars, glucose **58** or fructose **59**.[63] As glucose **58** is a 6-ring sugar molecule, isomerization of glucose **58** to form 5-ring fructose **59** is required prior to dehydration of fructose **59** to form 5-ring HMF **62**. HMF **62** can also be obtained directly by degradation of cellulose using various solid acid catalysts and reaction media.[64,65,66,67,68] There is much research that investigates the conversion of HMF **62** from lignocelluloses biomass using greener techniques such as using ionic liquids in biophasic system or using supercritical methanol (scMeOH) as solvent.[58,64] Furfural **61** is a 5-ring molecule that can be prepared by a direct acid-catalysed hydrolysis of hemicelluloses *via* C5 sugar xylose **60** using heterogeneous catalysts.[69,70]

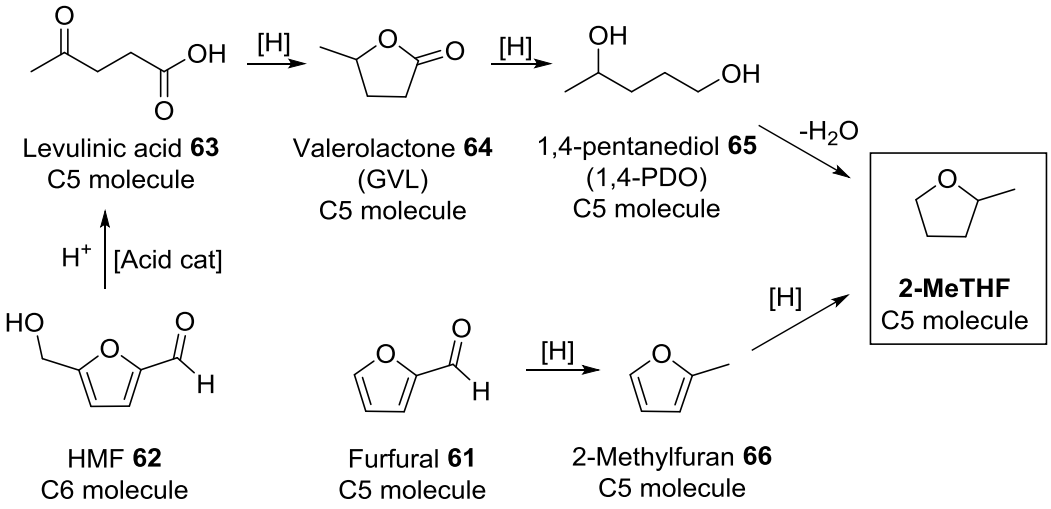
Scheme 1.25



As HMF **62** and furfural **61** are mostly prepared from abundant lignocelluloses biomass with economically and environmentally acceptable processes, they could be scaled up at the industrial level and converted into other useful chemicals. Additionally, most of this lignocellulose can be acquired as waste from other large-scale processes, such as wheat and barley straw and tree toppings from wood production. Other sources of the cellulose or saccharides used for HMF production include poor quality paper following extensive recycling or washings of fruit press cakes.[71]

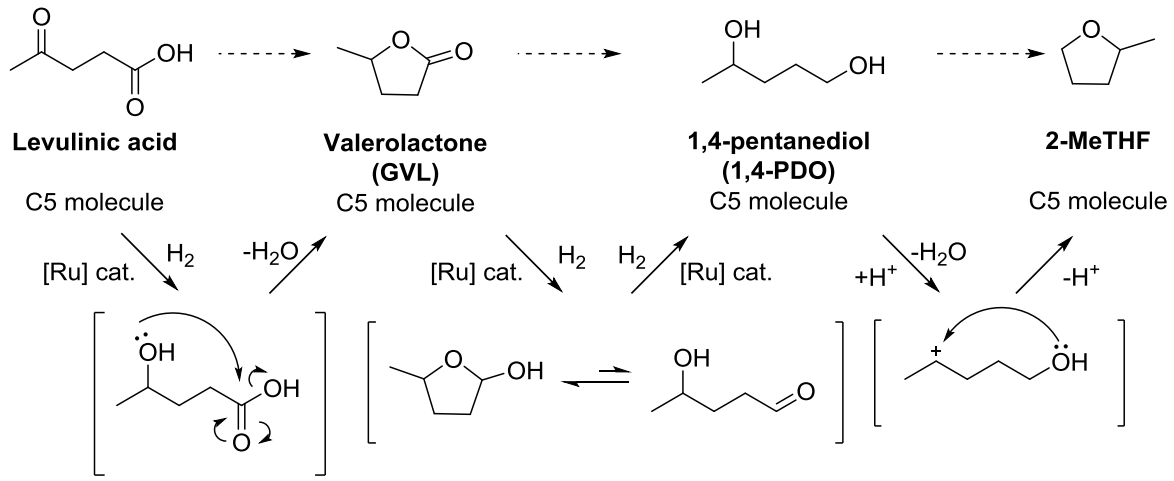
2-MeTHF can be prepared from two main routes: either from furfural **61** or HMF **62** which are summarised in Scheme 1.26. HMF **62** can be hydrolysed and dehydrated by acid catalysis to form levulinic acid **63** and formic acid. Although high conversions from HMF to levulinic acid **63** were reported using different acid catalysts, the mechanism of this transformation is still unknown.[72]

Scheme 1.26



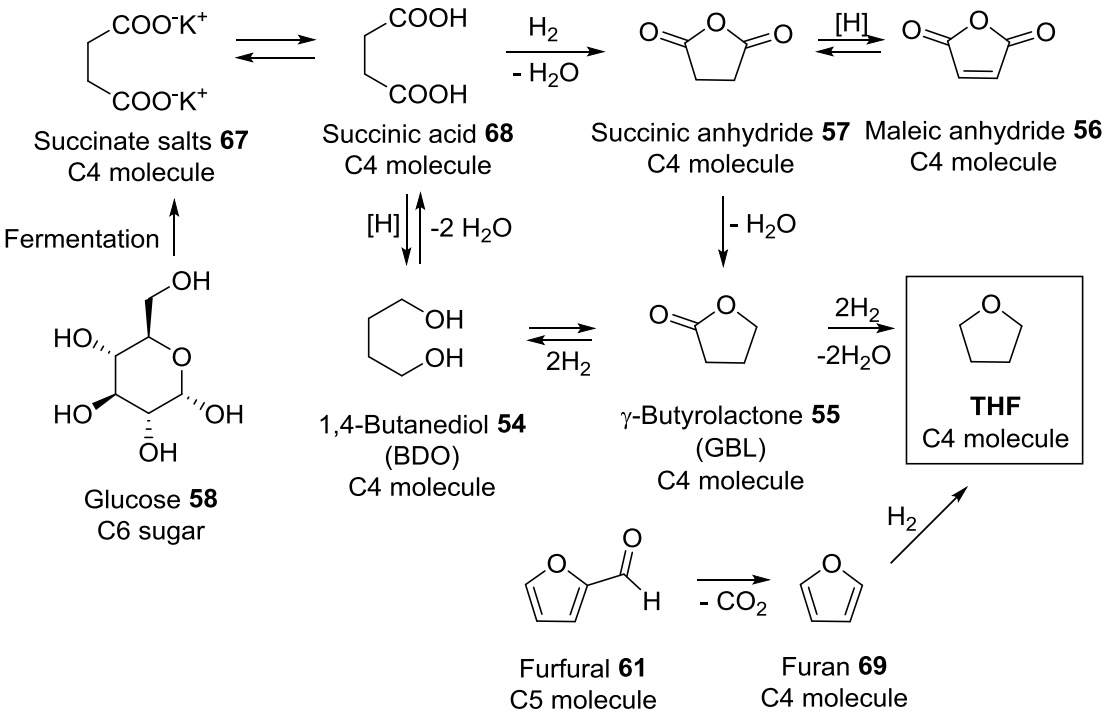
Levulinic acid **63** then undergoes hydrogenation and esterification to give γ-valeroactone **64** (GVL) and 1,4-pentanediol **65** (1,4-PDO) followed by cyclisation to give 2-MeTHF.[73] Leitner reported the production of 2-MeTHF from levulinic acid **63** using ruthenium catalysts and suggested a mechanism (Scheme 1.27).[74] Alternatively, furfural **61** can undergo catalytic reduction to give 2-MeTHF. From a green chemistry point of view, 2-MeTHF production from HMF **62** is less favoured. This is due to the loss of one carbon, as formic acid, throughout the formation of levulinic acid **63** from HMF **62** and the fact that the synthesis requires more steps compared to the direct reduction route from furfural **61**.

Scheme 1.27



Although THF is currently prepared from non-renewable petroleum-based resources, there are examples to show that THF can also be produced in a sustainable manner. As mentioned before, BDO **54** and maleic anhydride **56** are key intermediates for THF synthesis where they are currently obtained either from oxidation of benzene/*n*-butane or condensation of acetylene with formaldehyde. BDO **54** and maleic anhydride **56** can also be generated from a platform molecule, succinic acid **68**. The main route for succinic acid production is the fermentation of cellulose glucose (Scheme 1.28).[75, 76] From the fermentation process, C6 glucose **58** will break down into a C4 succinate fragment. As most fermentation micro-organisms cannot tolerate excessively acidic environments, the fermentation needs to be continually neutralized to give succinate salts, following recovery from the broth. While the fermentation of glucose route provides a greener way for THF synthesis, the purification cost for fermentation-based processes is normally more than 60% of the total production costs.[76] In the case of succinic acid purification, the separation of by-products such as acetic acid, formic acid, lactic acid and pyruvic acid have a crucial effect on process costs as well as consuming energy. Further improvement of the fermentation step to produce purified succinic acid **68** is needed in order to allow the THF production from cellulose/glucose resources to become economically favourable. Mascal *et al.* have also recently reported a route from lignocellulose to succinic acid *via* a wholly chemo-catalytic approach, *via* the oxidation of levulinic acid **63** with H_2O_2 and TFA.[77] Alternatively, THF can be synthesised directly from furfural **61** at high selectivity through catalytic decarbonylation to furan followed by ring hydrogenation. However, this procedure is not favoured due to the loss of one carbon to form CO_2 throughout the reaction, thus offering poor atom economy.

Scheme 1.28



In summary, although there are examples of producing THF from renewable resources, the current fermentation process is not economically favoured to produce THF on an industrial scale. If the technology for the fermentation step is improved, the industrial scale production of THF from sustainable resources could become available, although its cost compared to petroleum-derived THF cannot be predicted at this time. Alternatively, chemo-catalytic routes to succinic acid from biomass could pave the way for bio-derived THF at reduced cost, but this technology is only in its infancy and is as yet un-tested beyond lab-scale.

Apart from the sustainability of 2-MeTHF, its physical and chemical properties offer a safer and better application for organic synthesis compared to other ether solvents such as Et_2O and THF which are summarised in Table 1.8.[78] The lower solubility of 2-MeTHF in water gives a better separation from the aqueous phase (i.e. improved liquid-liquid separations) in the work-up. Also, the higher boiling point and flash point of 2-MeTHF illustrates that they are less volatile; in consequence, 2-MeTHF is safer to handle for large-scale reaction.

Table 1.8

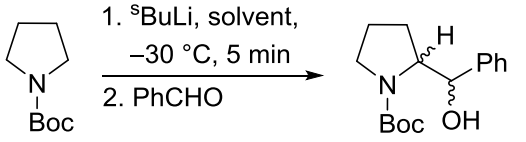
Properties	Et_2O	THF	2-MeTHF
Density (20 °C) [g/cm^3]	0.71	0.89	0.86
Boiling point [°C]	34.6	65	80
Solubility of Solvent in Water (23 °C) [g/100g]	6.5	Infinite	4.1
Azeotropic temp with water (°C)	34	64	89
Flash point (°C)	–40	–17	–12

In summary, Beak's lithiation methodology for the α-functionalisation of *N*-Boc heterocycles is efficient and has been widely used for the synthesis of natural products and drug molecules. However, there are some drawbacks of the typical reaction conditions which are not ideal for process-scale chemistry and against the principles of Green Chemistry: low temperature (–78 °C) and long lithiation time (>3 h) require large energy consumption; addition of a diamine decreases the atom economy and use of non-sustainable solvent (Et_2O). The diamine-free lithiation protocol that was developed by our group gave a better approach with respect to the principles of Green Chemistry, although investigation of using a sustainable solvent is needed further.

1.3 Project Outline

In the first part of the project (Chapter 2), we planned to investigate the racemic lithiation-trapping of *N*-Boc heterocycles at temperatures above –30 °C. In particular, our interest was to optimise the lithiation conditions in terms of the principles of Green Chemistry. The initial investigation was based on the diamine-free lithiation-trapping of *N*-Boc pyrrolidine **1** at –30 °C developed by our group in 2010 (Scheme 1.29). In that work, lithiation of *N*-Boc pyrrolidine **1** was carried out at –30 °C in THF and trapped with benzaldehyde to give an 84% yield of amino alcohols **25** whereas a 73% yield of **25** was obtained in 2-MeTHF.

Scheme 1.29

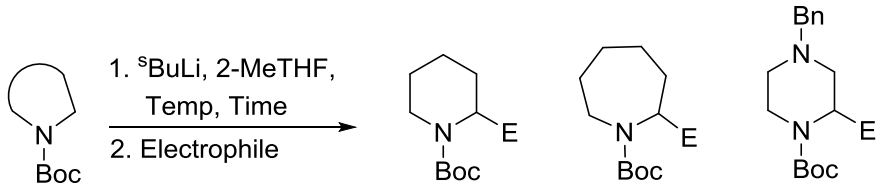


1 **25**
THF: 84%
2-MeTHF: 73%

The results suggested that the renewable solvent 2-MeTHF performs similarly to THF. However, high yields could not be obtained at temperatures above 0 °C in both solvents. Hence, our initial aim was to investigate the reasons for the low yields at temperatures above 0 °C and to explore the highest possible temperature for lithiation of *N*-Boc pyrrolidine **1** using 2-MeTHF.

Subsequently, exploration of the high temperature lithiation protocol was extended to *N*-Boc piperidine **2**, *N*-Boc azepane **3** and *N*-Boc piperazine **16** (Scheme 1.30).

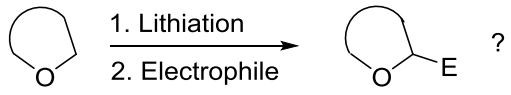
Scheme 1.30



2, **3**, **16**

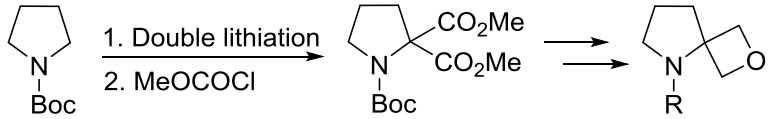
In the second part of the project (Chapter 3), we applied the *N*-Boc α-lithiation-trapping to four different types of oxygen heterocycles: tetrahydrofuran (THF), tetrahydropyran (THP), oxetane and *N*-alkyl morpholines. We hoped to find conditions for successful lithiation-trapping of oxygen heterocycles (Scheme 1.3.1).

Scheme 1.31



As part of the oxygen lithiation project, we wanted to study the lithiation-trapping of oxetane **71**. To prepare oxetane **71**, a route *via* double lithiation-trapping of *N*-Boc pyrrolidine **1** (to give **70**) would be investigated (Scheme 1.32).

Scheme 1.3.2



1 **70** **71**

Chapter 2: Lithiation-trapping of *N*-Boc Heterocycles Above –78 °C

An exploration of the lithiation-trapping of *N*-Boc heterocycles performed at temperatures above –78 °C will be presented in this chapter. As described in Chapter 1, Beak's lithiation methodology for the α-functionalisation of *N*-Boc heterocycles is simple and widely used in the synthesis of natural products and drug molecules. However, two of the major drawbacks of these reaction conditions for process-scale chemistry are the low temperature (–78 °C), and the long lithiation times (>3 h). Therefore, the objective of this part of the project was to optimise the lithiation conditions in terms of temperature and time of lithiation which could lead to a better approach in terms of the principles of Green Chemistry. In addition, an exploration of the use of the sustainable ether solvent, 2-MeTHF will be presented. Section 2.1 describes our investigation of conditions for the lithiation of *N*-Boc pyrrolidine. To try to understand the low yields, a mechanistic investigation was carried out (Section 2.2). In addition, exploration of the high temperature lithiation protocol was extended to *N*-Boc piperidine **2**, *N*-Boc azepane **3** and *N*-Boc piperazine **16** (Sections 2.3 and 2.4).

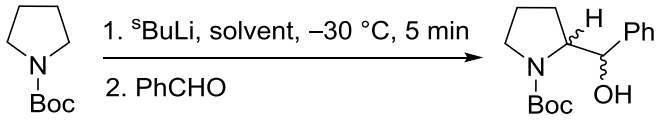
2.1 Optimisation of the Lithiation-trapping of *N*-Boc Pyrrolidine in Different Ether Solvents Above –78 °C

To start the investigation of the high temperature lithiation protocol, we chose *N*-Boc pyrrolidine **1** as the substrate. We know that high temperature lithiation of *N*-Boc pyrrolidine **1** can be carried out. In 2010, our group reported a diamine-free lithiation protocol which can be achieved with *s*-BuLi/THF complex at –30 °C. More recently, asymmetric lithiation of *N*-Boc pyrrolidine **1** can be performed with *s*-BuLi/(+)-sparteine surrogate complex at –20 °C. Thus, we asked ourselves a question: is it possible to use the sustainable solvent, 2-MeTHF, to carry out the lithiation at high temperature, ideally above –20 °C, for the racemic lithiation protocol, If successful, the specialist low temperature set-up for process-scale would not be required. Therefore, two main objectives of this part were to find out whether 2-MeTHF can be a good alternative to Et_2O in the TMEDA-mediated lithiation protocol and THF in the diamine-free lithiation protocol and to identify the highest temperature conditions that can still provide a good yield.

The initial investigation was carried out using the high temperature lithiation protocol developed by our group. In order to examine the potential replacement of Et_2O or THF by the sustainable solvent, 2-MeTHF, the lithiation of *N*-Boc pyrrolidine **1** was carried out using *s*-BuLi at –30 °C for 5 min in various ether solvents: Et_2O, Et_2O with TMEDA (1.3 eq.), THF, 2-MeTHF and 2-MeTHF with TMEDA (1.3 eq.). The lithiated intermediate was then trapped with benzaldehyde to give hydroxyl pyrrolidines **25** (Table 2.1). In all cases, there was an approximately 75:25 mixture of diastereomeric alcohols *syn*-**25** and *anti*-**25** in the ^{1}H NMR spectrum of the crude product. The stereochemistry of these products has previously been assigned (by X-ray crystallography) in our group. To simplify the results, only the combined total yield of *syn*-**25** and *anti*-**25** after purification by column chromatography is shown. Diamine-free lithiation in THF at –30 °C gave the best result of 73% yield (entry 1). Disappointingly, lithiation in 2-MeTHF gave a 47% yield of hydroxyl pyrrolidines **25** (entry 2) although TMEDA-mediated lithiation in 2-MeTHF provided a better result (68% yield of **25**) (entry 3). Lithiation in Et_2O gave a low yield (19% yield) with 13% of starting material recovered from the reaction (entry 4). The low yield indicates that Et_2O is not a very promising solvent for high temperature lithiation. The low 13% yield of starting material perhaps suggests that lithiation occurred but the lithiated intermediate subsequently decomposed before trapping. A better yield was obtained (61%

yield) when using *s*-BuLi/TMEDA in Et_2O (entry 5). The main conclusion from these initial results was that *s*-BuLi in Et_2O should not be further investigated. The other conditions all gave satisfactory yields (>47%).

Table 2.1

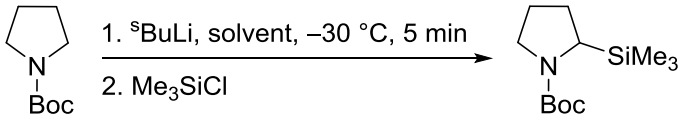


1 **25**

Entry	Solvent	Yield (%)
1	THF	73
2	2-MeTHF	47
3	2-MeTHF + TMEDA (1.3 eq.)	68
4	Et_2O	19
5	Et_2O + TMEDA (1.3 eq.)	61

Since the use of benzaldehyde as the electrophile gives a mixture of diastereomeric products which require more difficult purification by column chromatography, another electrophile which does not create a new stereogenic centre was chosen for the next experiments for comparison. Thus, a similar study of the high temperature lithiation conditions was performed using Me_3SiCl as the electrophile. Lithiation was carried out with *s*-BuLi for 5 min in THF, 2-MeTHF, Et_2O with TMEDA and 2-MeTHF with TMEDA at –30 °C (Table 2.2**)**.

Table 2.2



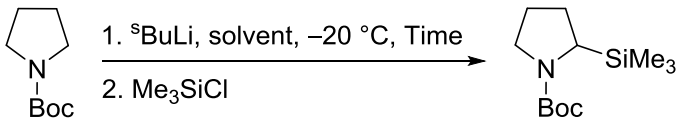
1 **4**

Entry	Solvent	Yield (%)
1	THF	66
2	2-MeTHF	69
3	2-MeTHF + TMEDA (1.3 eq.)	76
4	Et_2O + TMEDA (1.3 eq.)	73

Lithiation in THF and 2-MeTHF at –30 °C gave good 66% and 69% yields of silylated pyrrolidine **4** respectively (entries 1 and 2). To check the reproducibility of the 2-MeTHF diamine-free method, it was repeated and 69% yield was obtained. TMEDA-mediated lithiation in 2-MeTHF and Et_2O under the same conditions gave higher yields of 76% and 73% respectively (entries 3 and 4). Up to this point, similar results were obtained with Me_3SiCl and benzaldehyde as the electrophiles and, in general, all the reaction conditions gave good yields at –30 °C. The results suggested that the sustainable solvent, 2-MeTHF, is a good alternative to THF for diamine-free lithiation and Et_2O for TMEDA-mediated lithiation.

Next, we wanted to know whether high yields of silylated pyrrolidine **4** could be obtained in similar solvent systems when the lithiation was carried out at temperatures above –30 °C. We also wanted to investigate whether lithiation at –20 °C was complete within 5 min and so a shorter lithiation time of 2 min was investigated (Table 2.3). Lithiation at –20 °C for 5 min and 2 min in THF gave yields of 64% and 65% respectively (entries 1 and 2). This clearly indicated that lithiation was completed within 2 min. However, lithiation for 2 min in 2-MeTHF gave a lower yield than for 5 min (52% and 57% respectively; entries 3 and 4). TMEDA-mediated lithiation in 2-MeTHF for 2 and 5 min gave 68-69% yields (entries 5 and 6). Similarly, lithiation in Et_2O with TMEDA for 2 and 5 min gave 70-71% yields (entries 7 and 8).

Table 2.3



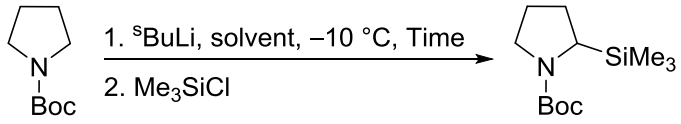
1 **4**

Entry	Solvent	Time (min)	Yield (%)
1	THF	5	64
2	THF	2	65
3	2-MeTHF	5	57
4	2-MeTHF	2	52
5	2-MeTHF + TMEDA (1.3 eq.)	5	69
6	2-MeTHF + TMEDA (1.3 eq.)	2	68
7	Et_2O + TMEDA (1.3 eq.)	5	71
8	Et_2O + TMEDA (1.3 eq.)	2	70

In general, results at –20 °C are consistent with those at –30 °C where most of the reaction conditions provide good yields (>64% yield) except for the use of *s*-BuLi/2-MeTHF complex. Lower yields in the 2-MeTHF diamine-free lithiation may suggest that the steric hindrance of the methyl group could make the *s*-BuLi/2-MeTHF complex less reactive than the *s*-BuLi/THF complex. Consequently, a longer lithiation time (5 min) is required for *s*-BuLi/2-MeTHF to lithiate *N*-Boc pyrrolidine **1**. In addition, lithiation of *N*-Boc pyrrolidine **1** at higher temperatures can still lead to good yields even if only left for a short time (2 min) before trapping. This matched the results from the high temperature asymmetric lithiation (–20 °C for 2 min) using *s*-BuLi and the (+)-sparteine surrogate (see Table 1.3).[34]

Subsequently, lithiation was carried out in similar solvent systems at –10 °C (Table 2.4**)**. Variable lithiation times (2 min, 1 min and 30 sec) were investigated as we expected lithiation would be very fast at such a high temperature. The yields of silylated pyrrolidine **4** after lithiation-trapping in THF at various reaction times were similar (47-53%) (entries 1-3). Lithiation in 2-MeTHF for 30 sec gave 46% (entry 6) whereas lower yields were formed (28% and 35%) when lithiation was carried out for a longer time respectively (1 min and 2 min) (entries 4-5). TMEDA-mediated lithiation in both 2-MeTHF and Et_2O for 30 sec gave good 74% and 69% yields respectively.

Table 2.4



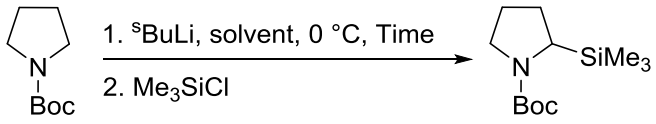
1 **4**

Entry	Solvent	Time	Yield (%)
1	THF	2 min	53
2	THF	1 min	58
3	THF	30 sec	47
4	2-MeTHF	2 min	28
5	2-MeTHF	1 min	35
6	2-MeTHF	30 sec	46
7	2-MeTHF + TMEDA (1.3 eq.)	30 sec	74
8	Et_2O + TMEDA (1.3 eq.)	1 min	67
9	Et_2O + TMEDA (1.3 eq.)	30 sec	69

In general, diamine-free lithiation gave lower yields comparing to the same systems at –30 °C particularly with the use of *s*-BuLi/2-MeTHF complex. As mentioned before, the lower yield might due to the steric hindrance of the methyl group of the 2-MeTHF. However, the result indicated that TMEDA-mediated lithiation still provided good yields (>67% yield) at –10 °C even for shorter reaction times. Two possibilities can explain the lower yields. One is that a slower lithiation was carried out in diamine-free conditions than the TMEDA-mediated protocol thus leading to the lower yields. The other thought is that the lithiated *N*-Boc pyrrolidine was not chemically stable at such a high temperature which would lead to some decomposition of the lithiated *N*-Boc pyrrolidine.

We then explored increasing the lithiation temperature to 0 °C where variable lithiation times were investigated (Table 2.5). Since we suspected that the lithiated *N*-Boc pyrrolidine might be chemically unstable at these higher temperatures, we focused on lithiation times of less than 1 min at 0 °C. Lithiation in THF for 50 sec gave a 39% yield of trapped product (entry 1), 47% yield for 30 sec (entry 2) and 59% yield for only 5 sec (entry 3). This indicated that lithiation at 0 °C gave the best yield in just 5 sec. We therefore tried this optimised lithiation time for other solvents. Diamine-free lithiation in 2-MeTHF gave a 50% yield for 5 sec of the trapped product whereas a lower yield (31%) was obtained when the reaction was carried out for 10 sec (entry 5).

Table 2.5



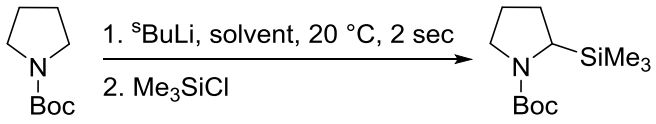
1 **4**

Entry	Solvent	Time (sec)	Yield (%)
1	THF	50	39
2	THF	30	47
3	THF	5	59
4	2-MeTHF	10	31
5	2-MeTHF	5	50
6	2-MeTHF + TMEDA (1.3 eq.)	5	63
7	Et_2O + TMEDA (1.3 eq.)	10	55
8	Et_2O + TMEDA (1.3 eq.)	5	53

At 0 °C, there is the similar trend of using THF and 2-MeTHF in diamine-free lithiation when a shorter lithiation time provides a better yield. The trend matchs our suspicion that the lithiated intermediate is chemically unstable at these higher temperatures over longer lithiation times. TMEDA-mediated lithiation in 2-MeTHF gave a 63% yield of the trapped product (entry 6) and 53% yield in Et_2O (entry 8). In general, TMEDA-mediated lithiation gave a higher yield at 0 °C than the diamine-free conditions, which is consistent with observations at –10 °C. In particular, 2-MeTHF with TMEDA gave the best yield for lithiation at 0 °C for 5 sec, indicating that 2-MeTHF can replace Et_2O for high temperature TMEDA-mediated lithiation, although the use of THF in diamine-free lithiation conditions gave a better yield than in 2-MeTHF.

Finally, the lithiation temperature was then raised to 20 °C and we expected that a very short lithiation time would be required at this high temperature. We knew that 5 sec is sufficient lithiation time at 0 °C and to avoid decomposition of the lithiated *N*-Boc pyrrolidine, we tried to lithiate *N*-Boc pyrrolidine for 2 sec before adding Me_3SiCl (Table 2.6). However, we were disappointed by the low yields in all solvent systems. Diamine-free lithiation in THF gave 22% yield (entry 1) whereas a better yield (33%) was obtained in 2-MeTHF (entry 2). TMEDA-mediated lithiation in 2-MeTHF gave a low 16% yield (entry 3) and 30% yield in Et_2O (entry 4). In summary, diamine-free lithiation using 2-MeTHF as solvent gave the best yield for lithiation at 20 °C, although the yields overall were disappointingly low, suggesting that the lithiated *N*-Boc pyrrolidine was chemically unstable at 20 °C even for a very short period of time.

Table 2.6

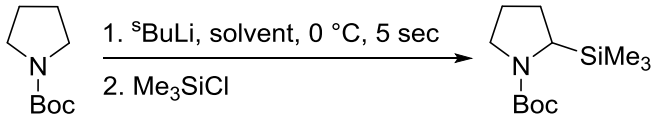


1 **4**

Entry	Solvent	Yield (%)
1	THF	22
2	2-MeTHF	33
3	2-MeTHF + TMEDA (1.3 eq.)	16
4	Et_2O + TMEDA (1.3 eq.)	30

From the optimisation results of high temperature lithiation, lithiation at 0 °C for 5 sec was the highest temperature reaction conditions for lithiation that still provide a synthetically useful yield. Hence, we wanted to explore other ether solvents for the lithiation of *N*-Boc pyrrolidine **1** under the optimised reaction conditions. Diamine-free and TMEDA-mediated lithiation using various ether solvents were investigated and compared: THF, 2-MeTHF, Et_2O, TBME, CPME and TMEDA as solvent and the results are summarised in Table 2.7. In general, TMEDA-mediated lithiation gave a better performance than diamine-free lithiation. TMEDA-mediated lithiation in THF gave a high 66% yield (entry 2) whereas the diamine-free lithiation in THF gave a lower 59% yield (entry 1). TMEDA-mediated lithiation in 2-MeTHF, Et_2O and in TBME gave good yield (63%, 53% and 67% respectively, entries 4, 6 and 8). Lower yields were obtained for diamine-free lithiation in the same solvents under the same reaction conditions (50%, 20%, 14% respectively, entries 3, 5 and 7). It confirms that TMEDA is the best ligand and gave the best performance in lithiation-trapping. However, TMEDA as ligand and solvent gave no product (entry 11). TMEDA-mediated lithiation in CPME surprisingly gave a low yield of 29% (entry 10) and the reason for this is unknown.

Table 2.7

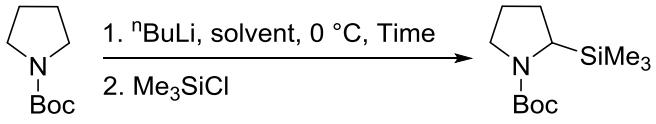


1 **4**

Entry	Solvent	Yield (%)
1	THF	59
2	THF + TMEDA (1.3 eq.)	66
3	2-MeTHF	50
4	2-MeTHF + TMEDA (1.3 eq.)	63
5	Et_2O	20
6	Et_2O + TMEDA (1.3 eq.)	53
7	TBME	14
8	TBME + TMEDA (1.3 eq.)	67
9	CPME	14
10	CPME + TMEDA (1.3 eq.)	29
11	TMEDA	0

Subsequently, we wanted to know whether *s*-BuLi could be substituted by a less strong base, *n*-BuLi, for the high temperature lithiation. The advantages of using *n*-BuLi are that it is more stable, safer to use and cheaper. Lithiation of *N*-Boc pyrrolidine **1** with *n*-BuLi was carried out in THF or 2-MeTHF with TMEDA at 0 °C for 1 or 5 min (Table 2.8). However, after trapping with Me_3SiCl no product was found in all reactions. The ^1H NMR spectrum of the crude product revealed only unreacted starting material **1** present.

Table 2.8

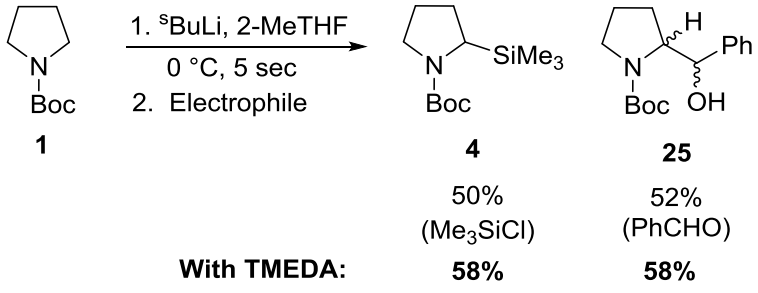


1 **4**

Entry	Solvent	Time (min)	Yield (%)
1	THF	1	0
2	2-MeTHF + TMEDA (1.3 eq.)	5	0
3	2-MeTHF + TMEDA (1.3 eq.)	1	0

Based on the results of the optimisation, we concluded that the highest temperature for the lithiation–trapping of *N*-Boc pyrrolidine **1** that provides good yields is 0 °C for 5 sec for both diamine-free and TMEDA-mediated lithiation in 2-MeTHF. Subsequently, lithiation of *N*-Boc pyrrolidine **1** was carried out at 0 °C for 5 sec using diamine-free or TMEDA-mediated conditions in 2-MeTHF, followed by trapping with benzaldehyde or Me_3SiCl. The results are presented in Scheme 2.1.

Scheme 2.1

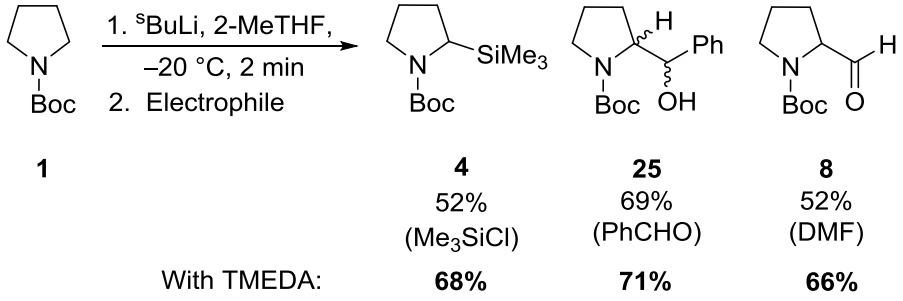


Although TMEDA-mediated lithiation gave a higher 58% yield of both silylated pyrrolidine **4** and hydroxyl pyrrolidines **25**, the yields of silylated pyrrolidine **4** (50%) and hydroxyl pyrrolidines **25** (52%) in the diamine-free protocol were similar. In general, the

diamine-free lithiation at 0 °C for 5 sec in 2-MeTHF provides a better Green chemistry approach for process-scale chemistry, where a temperature of –20 °C or above are preferred; high temperature with a short lithiation time reduces the overall energy consumption and 2-MeTHF is safer to use and is a sustainable solvent.

However, the 5 sec lithiation time is too short to apply in a batch process. Hence, we suggest that the 0 °C for 5 sec reaction conditions are best for a flow chemistry set-up. For the batch process, we recommend that the lithiation is carried out at –20 °C for 2 min. We selected these conditions for the lithiation of *N*-Boc pyrrolidine **1** and trapped with a range of electrophiles (Scheme 2.2). In general, high product yields (52-71%) were obtained. Trapping with Me_3SiCl gave a 68% yield in the TMEDA-mediated protocol and a 52% yield in the diamine-free conditions. When trapping with PhCHO, product **25** was obtained in 71% and 69% yields respectively. Trapping with DMF gave **8** in a 66% and 52% yield correspondingly.

Scheme 2.2



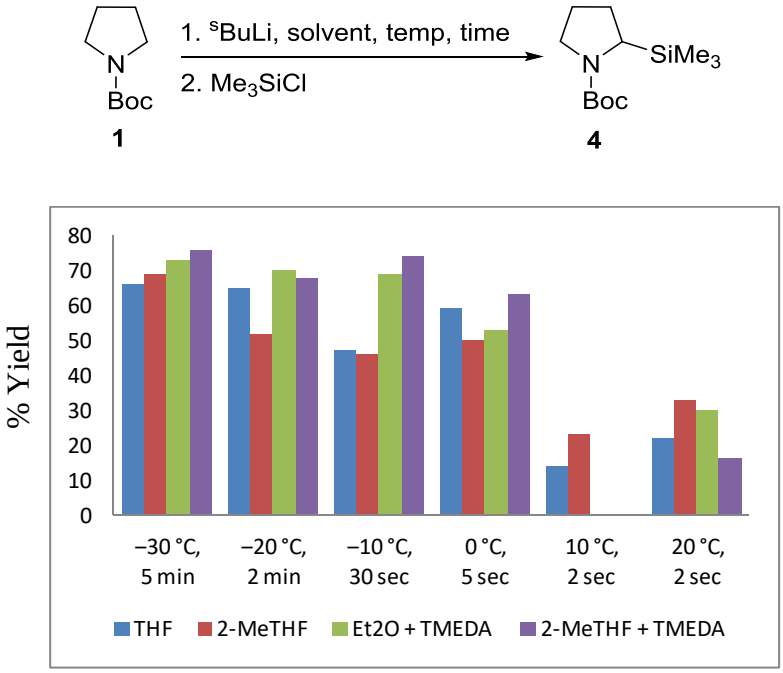
1		**4**	**25**	**8**
		52% (Me_3SiCl)	69% (PhCHO)	52% (DMF)
	With TMEDA:	**68%**	**71%**	**66%**

In summary, by exploring new high temperature conditions for the lithiation of *N*-Boc pyrrolidine **1**, we revealed that the highest temperature for the lithiation–trapping of *N*-Boc pyrrolidine **1** that provides good yields is 0 °C for 5 sec for both diamine-free lithiation in 2-MeTHF and TMEDA-mediated lithiation in 2-MeTHF. However, we suggest that 0 °C for 5 sec is the best conditions for flow chemistry and –20 °C for 2 min is the best conditions for batch scale. In comparison to the original TMEDA-mediated lithiation conditions reported by Beak[7] (–78 °C, 3 h in Et_2O) and the high temperature diamine-free protocol reported by our group recently[15] (–30 °C, 5 min in THF), the newly developed lithiation conditions represent an improvement as they occur at a higher temperature and require a shorter lithiation time. In addition, the use of the sustainable solvent, 2-MeTHF, is a good alternative solvent which is safer to use.

2.2 Investigation of the Reasons for Lower Yields at High Temperatures (≥ 0 °C)

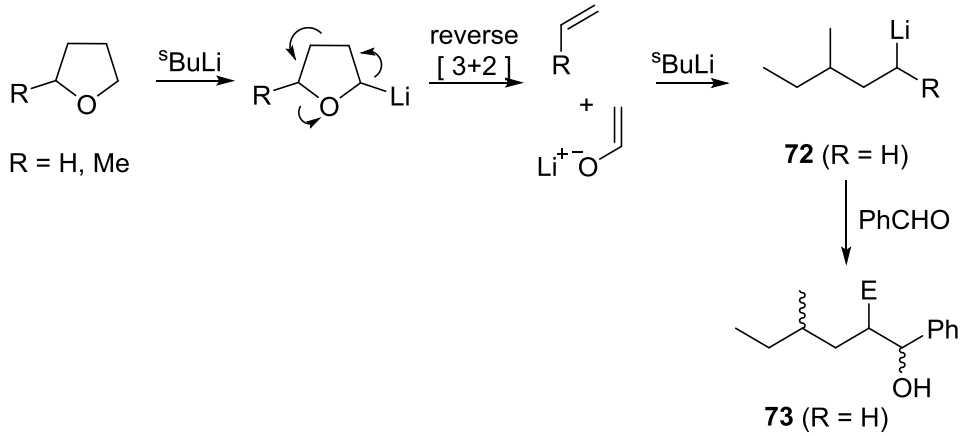
During the optimisation of the high temperature lithiation between –30 °C and 20 °C, there is a significant decrease in the yield of silyl product **4** in all four reaction conditions as the temperature goes higher. This is particularly clear from the plot shown in Figure 2.1. In particular, at 20 °C, yields were in the range of 16-33% whereas 66-76% yields were obtained at –30 °C.

Figure 2.1



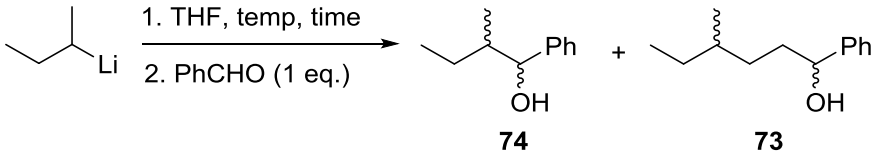
Our two proposals for explaining the lower yield at higher temperatures are as follows. The first suggestion is that, at high temperature, *s*-BuLi started to react with the solvent rather than with *N*-Boc pyrrolidine **1**. The second suggestion is that the higher temperature allows the lithiated *N*-Boc pyrrolidine **1** to decompose (*via* pathways that are discussed later). As mentioned in Chapter 1, lithiation of ethereal solvents, in particular THF, by *s*-BuLi at high temperatures is known.[46] THF can be deprotonated by *s*-BuLi to give lithiated THF, which can then undergo a reverse [3+2] cycloaddition and break down into ethene and a lithium enolate. 2-MeTHF can also undergo a similar decomposition pathway. In both cases, the alkene generated can then be carbolithiated to give **72** and hence **73** after electrophile trapping (Scheme 2.3).

Scheme 2.3



Hence, we wanted to examine the interaction between *s*-BuLi in THF without *N*-Boc pyrrolidine **1** at 0 °C. Our plan was to stir the *s*-BuLi in THF at a specific temperature for a certain time and then trap with benzaldehyde. If the *s*-BuLi did not react with THF, only the direct addition product **74** would be obtained. If the *s*-BuLi did react with the THF, it should lead to the carbolithiation product **73** after trapping with benzaldehyde. In order to prepare a reference sample of the direct addition product **74**, 1 equivalent of *s*-BuLi was added to a stirred solution of benzaldehyde (1 eq.) and THF at –78 °C. This gave the direct addition product **74** which was isolated in 75% yield. Then, we investigated the reactions at 0 °C: *s*-BuLi was stirred in THF for 5 min or 30 min before adding benzaldehyde (Table 2.9, entries 1 and 2). In both of these cases, none of the direct addition product **74** was observed but 48% and 39% yield of the carbolithiated product **73** were isolated respectively. As 2 equivalents of *s*-BuLi are required to form the carbolithiated product **73**, at least 75% and 95% of *s*-BuLi has been consumed in these reactions.

Table 2.9

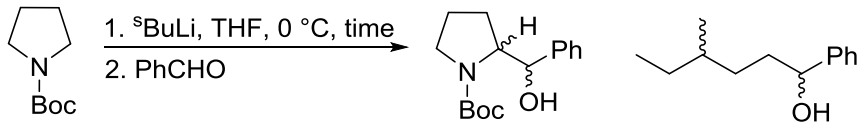


Entry	Temp (°C)	Time (min)	74 Yield (%)	73 Yield (%)
1	0	5	0	48
2	0	30	0	39

Products **73** and **74** can be identified in the ^{1}H NMR spectrum where two different sets of signals are produced, one for each diastereomer. By analysing the proton adjacent to the phenyl and alcohol group, we can recognise different chemical shifts due to different environments between the two compounds. For the mixture of the diastereomic products **74**, the proton adjacent to the phenyl group should give two doublets (one for each diastereomer) as it couples to one proton only. In the ^{1}H NMR spectrum of reference sample **74**, two doublets were obtained at δ 4.53 and δ 4.44. In both of the reactions at 0 °C, neither of the doublets from the direct addition product **74** was observed in the ^{1}H NMR spectra of the crude product. Instead, two double doublets were obtained at δ 4.64 and δ 4.63 which are characteristic of the known diastereomeric carbolithiation product **73**.[15] In each diastereomer, the benzylic proton was coupling to an adjacent CH_2 group to give the double doublet splitting.

We then wanted to see if any of the carbolithiated product **73** would be formed in the high temperature lithiation of *N*-Boc pyrrolidine **1**. For the lithiation, *s*-BuLi in THF for 5 sec and 30 sec at 0 °C was used and trapping with benzaldehyde (Table 2.10). The product(s) obtained from these reactions would indicate whether the *s*-BuLi had reacted with *N*-Boc pyrrolidine **1** and/or THF. In both attempts, only **25** was isolated in good yields (59% and 60%, entries 1 and 2). No carbolithiated product **73** was found in the ^{1}H NMR spectrum of the crude product despite a very careful anaylsis. Hence, the *s*-BuLi preferred to react with the *N*-Boc pyrrolidine **1** rather than THF at 0 °C.

Table 2.10



1 **25** **73**

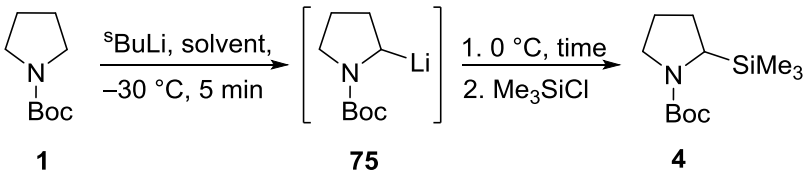
Entry	Time (sec)	25 Yield (%)	73 Yield (%)
1	5	59	0
2	30	60	0

Since there was no direct evidence of *s*-BuLi preferring to react with THF rather than *N*-Boc pyrrolidine **1** at 0 °C, this led us to think of the other possibility for the decrease in

yields at higher temperature, namely the instability of the lithiated *N*-Boc pyrrolidine **75**. We knew that the lithiation of *N*-Boc pyrrolidine **1** using *s*-BuLi at –30 °C for 5 min is sufficient to achieve a high degree of lithiation in all solvent systems. Thus, our plan for examining the stability of lithiated *N*-Boc pyrrolidine **75** was to lithiate *N*-Boc pyrrolidine **1** at –30 °C for 5 min, and then incubate the intermediate **75** at 0 °C for a certain length of time. If the lithiated *N*-Boc pyrrolidine **75** is unstable and decomposed during the incubation at higher temperature, there should be a decrease in the yield of trapped product **4**. Also, we would like to see whether the ligand, TMEDA, THF or 2-MeTHF affects the stability of the lithiated intermediate **75** throughout the period of temperature change.

First, 1.0 eq. of *s*-BuLi was stirred with *N*-Boc pyrrolidine **1** in THF, 2-MeTHF, Et_2O with TMEDA or 2-MeTHF with TMEDA at –30 °C for 5 min. Then, the resulting solution was incubated at 0 °C for 5 min or 30 min before trapping with excess Me_3SiCl (2 eq.) to give the product **4** (Table 2.11).

Table 2.11



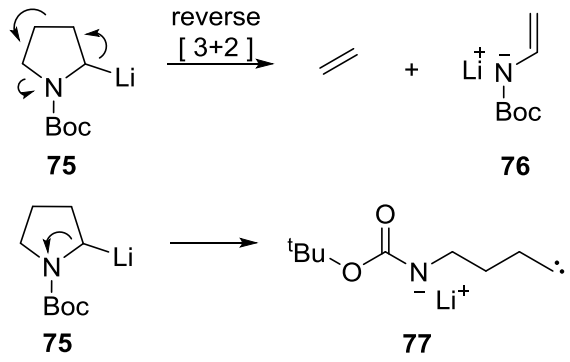
1 **75** **4**

Entry	Solvent	Temp (°C)	Time	Yield (%)
1	THF	–30	5 min	66
2	THF	–30 °C 5 min then 0 °C	5 min	51
3	THF	–30 °C 5 min then 0 °C	30 min	4
4	2-MeTHF	–30	5 min	69
5	2-MeTHF	–30 °C 5 min then 0 °C	5 min	18
6	2-MeTHF	–30 °C 5 min then 0 °C	30 min	2
7	Et_2O with TMEDA (1.3 eq.)	–30	5 min	73
8	Et_2O with TMEDA (1.3 eq.)	–30 °C 5 min then 0 °C	5 min	52
9	Et_2O with TMEDA (1.3 eq.)	–30 °C 5 min then 0 °C	30 min	0
10	2-MeTHF with TMEDA (1.3 eq.)	–30	5 min	76
11	2-MeTHF with TMEDA (1.3 eq.)	–30 °C 5 min then 0 °C	5 min	25
12	2-MeTHF with TMEDA (1.3 eq.)	–30 °C 5 min then 0 °C	30 min	2

The yield for the normal lithiation at –30 °C in THF for 5 min was 66% (entry 1), and it decreased to 51% yield after incubation for 5 min at 0 °C (entry 2). The yield further decreased (to 4%) when the mixture was incubated for 30 min at 0 °C (entry 3). In this case, there is a significant decrease of yield when the lithiated intermediate **75** was held at 0 °C for 30 min. Similar trends were found when the same types of reactions were carried out in other solvents. The yield of product **4** in 2-MeTHF decreased from 69% to 18% and 2% under the same 0 °C incubation conditions for 5 min or 30 min respectively (entries 4-6). Similar results were obtained for the TMEDA-mediated lithiation in Et_2O or 2-MeTHF (entries 7-12). These results suggested that the lithiated *N*-Boc pyrrolidine **75** was chemically stable at –30 °C over 5 min but it started to decompose when the temperature was increased to 0 °C.

Two possibilities for the breakdown of lithiated *N*-Boc pyrrolidine **75** at 0 °C are shown in Scheme 2.4. The first one is a similar route to the breakdown of lithiated THF. Lithiated *N*-Boc pyrrolidine **75** could undergo reverse [3+2] cycloaddition to give ethene and azaenolate **76**. Alternatively, the N-C bond in the ring of lithiated *N*-Boc pyrrolidine **75** could break to form a carbene **77**. However, by analysis of the ^{1}H NMR spectrum of the crude products, we could see no evidence of any decomposition products arsing from **76** or **77**.

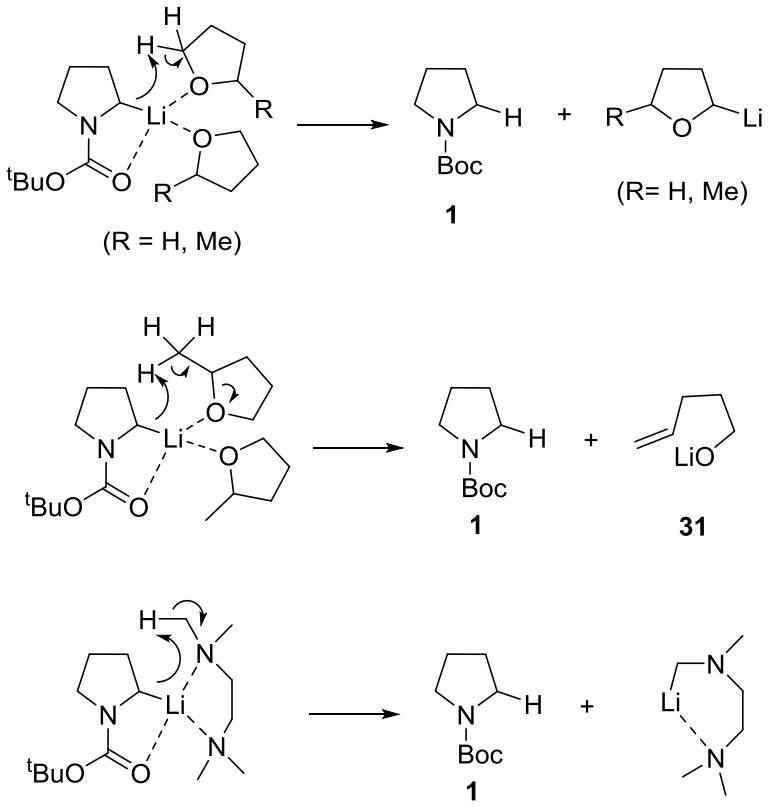
Scheme 2.4



From the lithiation-trapping at –30 °C for 5 min in all solvent systems, none of the *N*-Boc pyrrolidine **1** was recovered. However, *N*-Boc pyrrolidine **1** was recovered by chromatography from two of the incubation reactions of lithiated *N*-Boc pyrrolidine **75**. For example, 20% and 24% of *N*-Boc pyrrolidine **1** was recovered for the incubation in Et_2O with TMEDA and 2-MeTHF at 0 °C for 30 min respectively (entries 6 and 9). In these cases, we speculated that one possibility for the formation of **1** is that the lithiated *N*-

Boc pyrrolidine **75** could be trapped by a proton at 0 °C from the solvents or even TMEDA. For example, lithiated *N*-Boc pyrrolidine **75** could be protonated by α-deprotonation of THF/2-MeTHF, β-elimination of 2-MeTHF or α-deprotonation of TMEDA to give *N*-Boc pyrrolidine **1** (Scheme 2.5). The α-deprotonation of TMEDA has been observed by Strohmann using *t*-BuLi at –78 °C.[79]

Scheme 2.5



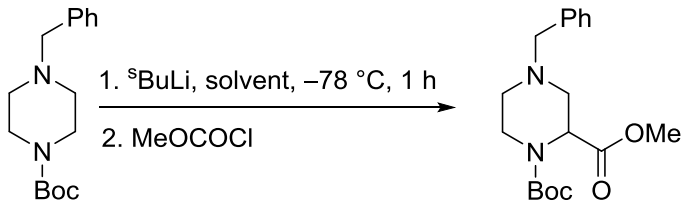
In summary, the cause of the decrease in yields of lithiation-trapping of *N*-Boc pyrrolidine **1** at temperatures above –30 °C was investigated. We initially proposed two possibilities for explaining the lower yield at higher temperatures. However, based on the results of our investigation, it is unlikely that the *s*-BuLi reacts with the solvent during the lithiation of *N*-Boc pyrrolidine **1** at 0 °C. Instead, we suggest that the cause of the decrease in yields of lithiation at temperatures > 0 °C was due to the chemical instability of the lithiated *N*-Boc pyrrolidine **75** leading to the breakdown of the lithiated intermediate. We also believed that the protonation of lithiated *N*-Boc pyrrolidine **75** by THF, 2-MeTHF or TMEDA to give *N*-Boc pyrrolidine **1** is possible in certain cases. These two situations presumably also happen at the moment when normal lithiation takes place.

2.3 High Temperature Lithiation-trapping of *N*-Boc *N*'-benzyl Piperazine

The high temperature (–30 °C) diamine-free lithiation protocol that was developed by our group has also been applied to the lithiation-trapping of *N*-Boc *N*'-benzyl piperazine **16** as mentioned in Chapter 1. *N*-Boc *N*'-benzyl piperazine **16** was lithiated using *s*-BuLi/THF complex at –30 °C for 5 min and trapped with a range of electrophiles in high yields (55-83%) (see Scheme 1.7). With the success of using the sustainable solvent 2-MeTHF for the lithiation of *N*-Boc pyrrolidine **1**, we wanted to explore whether lithiation of *N*-Boc *N*'-benzyl piperazine **16** could be carried out using 2-MeTHF and higher temperatures (above –30 °C). We started the investigation by repeating the diamine-free lithiation at –78 °C (Table 2.12). Methyl chloroformate was chosen as the electrophile as it was known in the group to work well in trapping lithiated *N*-Boc piperazine.[11]

1.3 equivalents of *s*-BuLi was added to *N*-Boc *N*'-benzyl piperazine **16** in THF at –78 °C and the resulting solution was stirred for 1 h. Excess of methyl chloroformate (2 eq.) was added afterwards to give the desired product **24** in 56% yield (entry 1). Under the same conditions, lithiation using 2-MeTHF in place of THF gave a good 69% yield (entry 2).

Table 2.12



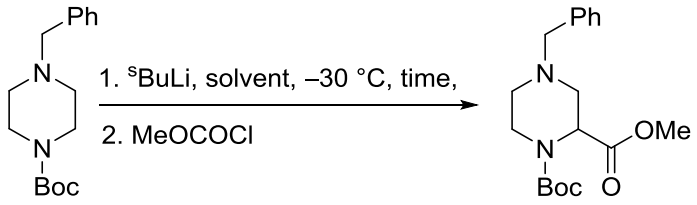
16 **24**

Entry	Solvent	Yield (%)
1	THF	56
2	2-MeTHF	69

The lithiation temperature was then raised to –30 °C (Table 2.13). Lithiation of *N*-Boc *N*'-benzyl piperazine **16** in THF gave a 69% yield (entry 1). Then, we altered the reaction time to see if the lithiation needed as long as 5 min. By reducing the lithiation time from 5 min to 1 min, the yield decreased to 58% (entry 2). However, the yields were slightly better

when compared to the result in THF at –78 °C. In addition, it suggested that *N*-Boc *N*'-benzyl piperazine **16** requires a longer lithiation time (5 min) at –30 °C. Hence, we suspected that 5 min is needed for the lithiation in 2-MeTHF. However, lithiation in 2-MeTHF for 5 min gave a lower yield of product **24** (46%) (entry 3). As discussed in section 2.1, this lower yield may due to the fact that the *s*-BuLi/2-MeTHF complex is less reactive than the *s*-BuLi/THF complex. As a result, a longer lithiation time may be required to fully lithiate *N*-Boc *N*'-benzyl piperazine **16**.

Table 2.13



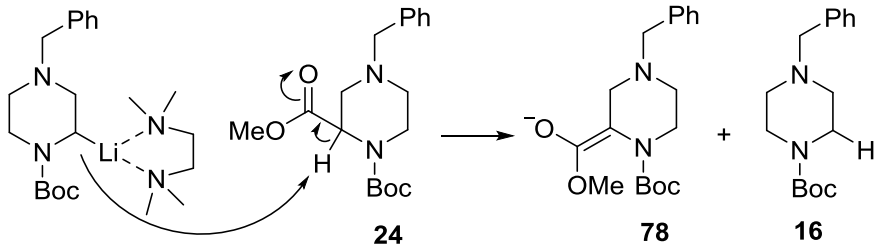
16 **24**

Entry	Solvent	Time (min)	24 Yield (%)	Starting material recovery (%)
1	THF	5	69	0
2	THF	1	58	0
3	2-MeTHF	5	46	0
4	Et_2O + TMEDA (1.3 eq.)	5	25	31
5	Et_2O + TMEDA (1.3 eq.)	1	24	37

Surprisingly, when we tried the TMEDA-mediated lithiation in Et_2O for 5 min at –30 °C, a low yield was obtained (25% yield, entry 4) with 31% of starting material recovered after chromatography. A similar result was achieved when the lithiation time was reduced to 1 min: only 24% of product **24** was obtained and 37% of the starting material was recovered (entry 5). The recovery of the starting material was unexpected, as *s*-BuLi/TMEDA complex is a faster lithiating reagent than the *s*-BuLi/THF complex and it is unlikely to be due to an incomplete lithiation. One of the possibilities to explain both the low yield and recovery of starting material **16** is that the lithiated piperazine could be protonated by the more acidic proton α to the ester in product **24**. The mechanism of the protonation is shown in Scheme 2.6. The protonation of the lithiated piperazine would give starting *N*-Boc *N*'-benzyl piperazine **16** back as well as an enolate **78**. A similar issue was observed

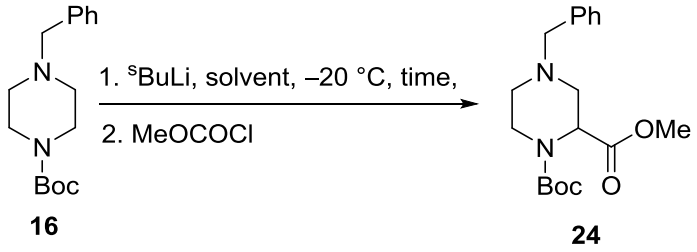
previously in our group: lithiation methyl chloroformate-trapping of *N*-Boc *N*'-benzyl piperazine **16** can sometimes lead to a second trapping with methyl chloroformate due to the more acidic α-proton of the lithiated piperazine.[11] Nevertheless, this issue occurs with methyl chloroformate trapping only. In addition, we suspected that the lithiated piperazine/TMEDA complex is more basic than those with THF or 2-MeTHF and, as a result, the second deprotonation by the lithiated intermediate was not found in those cases.

Scheme 2.6



Subsequently, we raised the lithiation temperature to –20 °C (Table 2.14). As we know from the lithiation-trapping of *N*-Boc pyrrolidine **1**, the lithiation for *N*-Boc *N*'-benzyl piperazine **16** should be completed in less than 5 min at –20 °C. Hence, 5 min and a shorter time of 1 min were investigated. Diamine-free lithiation of *N*-Boc *N*'-benzyl piperazine **16** in THF for 5 min gave 53% yield (entry 1). The same yield was obtained when the lithiation time was reduced to 1 min (entry 2), suggesting that 1 min is enough to promote the lithiation at –20 °C.

Table 2.14

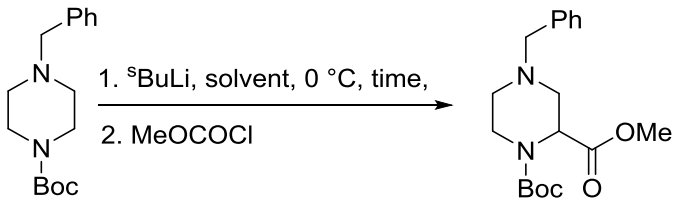


Entry	Solvent	Time (min)	24 Yield (%)	Starting material recovery (%)
1	THF	5	53	0
2	THF	1	53	0
3	Et_2O + TMEDA (1.3 eq.)	5	18	30

When TMEDA-mediated lithiation was carried out in Et_2O at –20 °C, it gave a low 18% yield with 30% starting material recovered (entry 3) as a second deprotonation by the lithiated intermediate took place, leading to the recovery of the starting material. At this point, our results suggest that the TMEDA-mediated lithiation at high temperature is not ideal for *N*-Boc *N*'-benzyl piperazine **16** and therefore we only focused on the diamine-free lithiation for higher temperature conditions.

We finally raised the lithiation temperature to 0 °C with lithiation times less than 1 min (30 and 10 sec) since we believed that a shorter lithiation time would minimise the decomposition of lithiated piperazine. The results are summarised in Table 2.15. Lithiation in THF for 30 sec gave 50% yield (entry 1) whereas a lower yield was obtained when the lithiation time was reduced to 10 sec (33%, entry 2). Lithiation in 2-MeTHF for 30 sec has a lower yield than in THF under the same conditions (28%, entry 3) whereas 31% yield was obtained in 2-MeTHF over 10 sec (entry 4). In general, lithiation in THF for 30 sec provided the highest yield at 0 °C although the yield is lower compared to the same conditions at –78 °C.

Table 2.15



16 **24**

Entry	Solvent	Time (sec)	Yield (%)
1	THF	30	50
2	THF	10	33
3	2-MeTHF	30	28
4	2-MeTHF	10	31

In summary, we revealed that 2-MeTHF can replace THF as solvent for lithiation-trapping of *N*-Boc *N*'-benzyl piperazine **16** at –78 °C, but further work would be needed to see if lithiation using 2-MeTHF could give better yields than in THF at higher temperatures. The new optimised lithiation conditions for *N*-Boc *N*'-benzyl piperazine **16** is 0 °C for 30 sec in

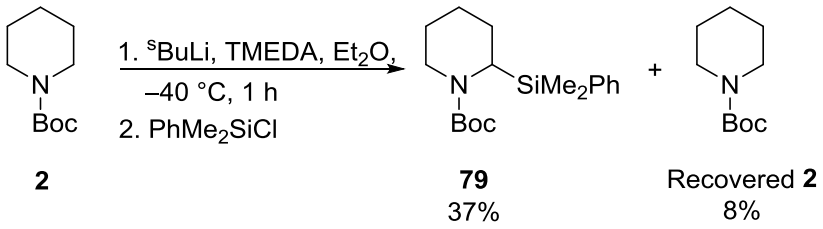
THF for diamine-free lithiation. It appears that the high temperature TMEDA-mediated lithiation is not ideal for *N*-Boc *N*'-benzyl piperazine **16** when trapping with methyl chloroformate. For example, lithiation using Et_2O with TMEDA at –20 °C for 5 min gave a low 18% yield with 30% starting material recovered (Table 2.13, entry 3). The recovery of the starting *N*-Boc *N*'-benzyl piperazine **16** suggested that the lithiated piperazine was protonated by the acidic α-proton of the product **24** as it forms. However, other electrophiles such as Me_3SiCl which do not generate an acidic α-proton should be explored to try and improve the results.

2.4 High Temperature Lithiation-trapping of *N*-Boc Piperidine and *N*-Boc Azepane

As discussed in Chapter 1, *N*-Boc piperidine **2** and *N*-Boc azepane **3** are known to undergo the lithiation incredibly slowly at –78 °C based on the group's ReactIR study (see Figure 1.2). Thus, a potentially long lithiation time at a higher temperature would be required for both substrates to fully lithiate. In addition, from the previous research by our group, the *s*-BuLi/THF complex is not reactive enough to carry out the lithiation of these substrates even at high temperature.[15] Hence, in this part of the project, we focused on the TMEDA-mediated lithiation-trapping of *N*-Boc piperidine **2** and *N*-Boc azepane **3** at temperatures above –78 °C. Our plan was to see if the sustainable solvent 2-MeTHF can replace Et_2O for the reaction.

In 1993, Beak carried out the lithiation of *N*-Boc azepane **3** using *s*-BuLi/TMEDA complex in Et_2O at –78 °C followed by warming up to –40 °C for 1 h before the electrophile was added (see Scheme 1.4). Therefore, we started the investigation of the high temperature lithiation of *N*-Boc piperidine **2** by lithiating it with *s*-BuLi/TMEDA at –40 °C in Et_2O (Scheme 2.7). After trapping with $PhMe_2SiCl$, a moderate yield (37%) of silyl piperidine **79** was obtained with 8% of *N*-Boc piperidine **2** recovered.

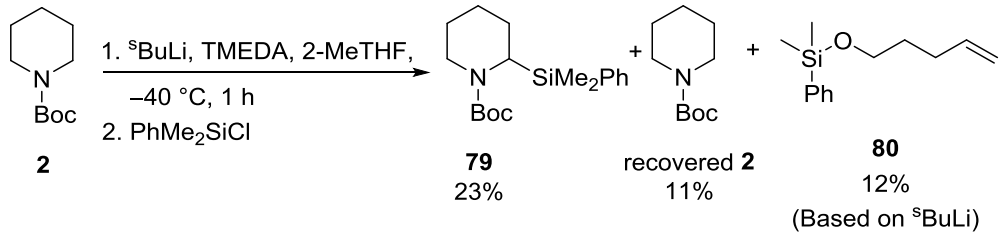
Scheme 2.7



TMEDA-mediated lithiation of *N*-Boc piperidine **2** was then carried out in 2-MeTHF under the same reaction conditions (Scheme 2.8). The yield of silyl product **79** decreased (23% yield) with some *N*-Boc piperidine **2** recovered (11%). Surprisingly, an unexpected product was isolated. The ^{1}H NMR spectrum of this product showed the presence of three alkene protons (including a terminal alkene (δ_H 4.99 and 4.93)) and a triplet (J = 8.0 Hz) of a CH_2 group next to oxygen at δ_H 3.60. The ^{13}C NMR spectrum showed that the compound contained a five carbon chain with one OCH_2 signal (at δ_C 62.5), two alkene signals (at δ_C 138.0 and 114.6, due to $CH{=}CH_2$) and two CH_2 signals which suggested that the

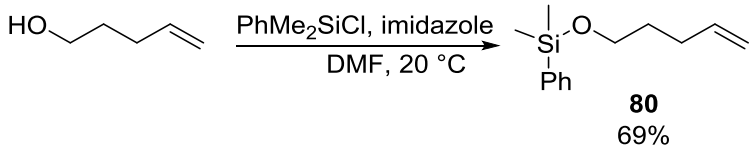
compound was not formed from *N*-Boc piperidine **2**. After consideration of the ^{1}H and ^{13}C NMR spectra, we suspected that the product was alkene **80** which was formed from the solvent 2-MeTHF in 12% yield based on *s*-BuLi (so was isolated together with some $PhMe_2SiCl$).

Scheme 2.8



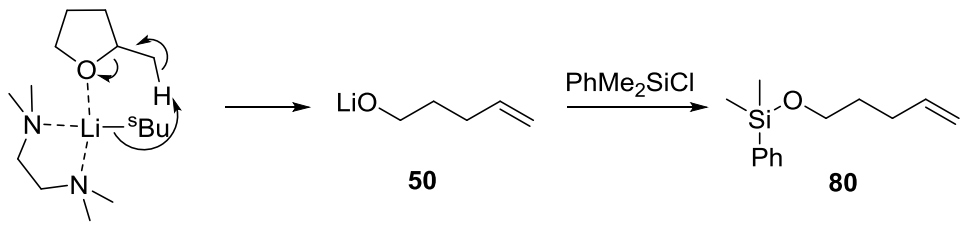
To confirm that alkene **80** was a by-product of the above reaction, an independent synthesis was carried out. Silylation of 4-penten-1-ol using imidazole and $PhMe_2SiCl$ gave silyl alkene **80** in 69% yield (Scheme 2.9). The ^{1}H NMR spectrum of this product was identical to the by-product.

Scheme 2.9



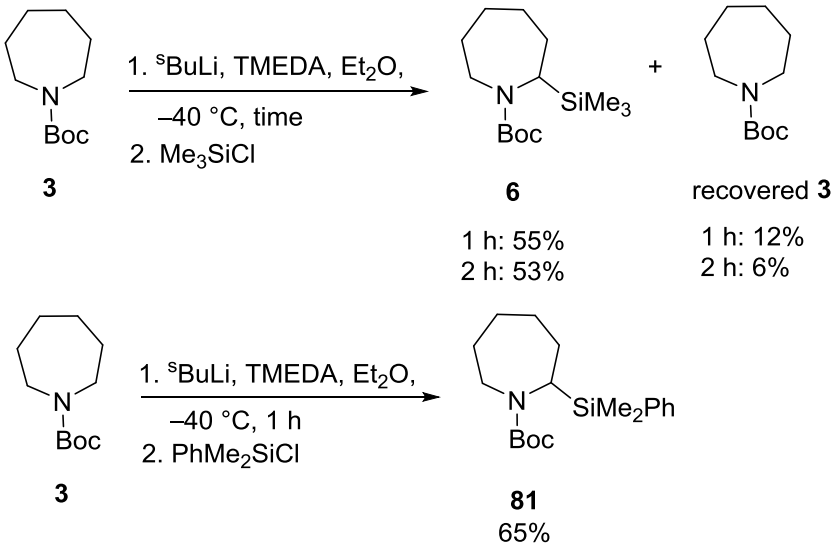
As discussed in Chapter 1, we believe that the alkene product **80** was formed from 2-MeTHF *via* a β-elimination mechanism to give lithium pent-4-en-1-olate **50** which was subsequently trapped by $PhMe_2SiCl$ to give **80** (see Scheme 1.22). Since *N*-Boc piperidine **2** reacts slowly with *s*-BuLi/TMEDA in 2-MeTHF even at –40 °C, some *s*-BuLi has the chance to react with 2-MeTHF *via* the β-elimination mechanism (Scheme 2.10). Given that the β-elimination of 2-MeTHF is a considerably competitive reaction, there is less *s*-BuLi available for the piperidine lithiation. Hence, the yield of the trapped product **79** was lower in 2-MeTHF than in Et_2O.

Scheme 2.10



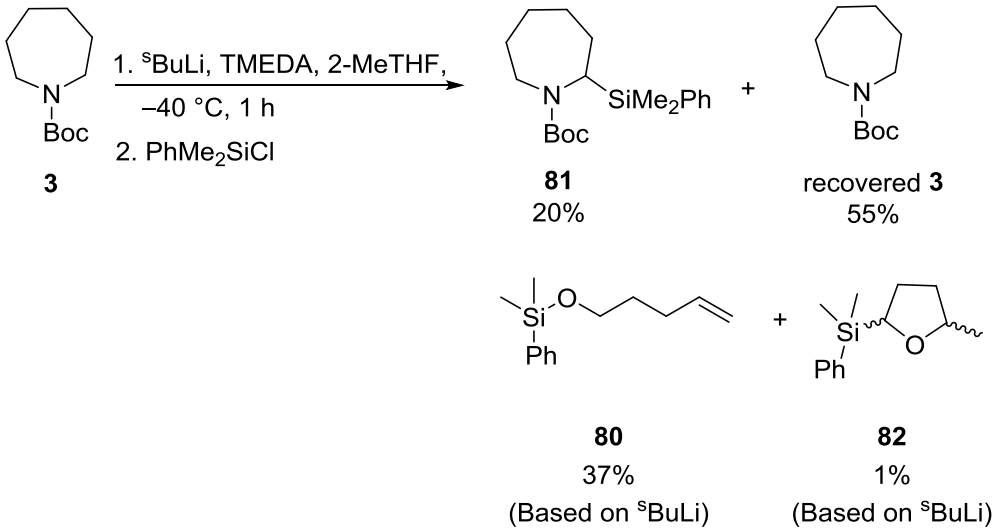
Based on the information of the lithiation time using ReactIR, *N*-Boc piperidine **2** is more reactive than *N*-Boc azepane **3** towards α-deprotonation. This allows us to consider whether a longer lithiation time is needed for *N*-Boc azepane **3** under the –40 °C conditions in Et_2O or 2-MeTHF. Firstly, different lithiation times (1 or 2 h) in Et_2O for lithiation of *N*-Boc azepane **3** were investigated and the results are summarised in Scheme 2.11. The results showed that similar yields (53% and 55%) of silyl product **6** were obtained for 1 h and 2 h lithiation times. Some starting material **3** was recovered (12%) from the 1 h reaction suggesting that a 1 h lithiation time is not long enough to fully lithiate *N*-Boc azepane **3**. However, leaving the lithiation 1 h longer did not lead to an improved yield of **6**, and less **3** was recovered (6%). We also carried out the 1 h lithiation and trapped with $PhMe_2SiCl$. This gave a 65% yield of silyl product **81** (Scheme 2.11).

Scheme 2.11



Since the 1 h and 2 h lithiation times gave similar results, we decided to continue the exploration of high temperature lithiation of *N*-Boc azepane **3** using –40 °C for 1 h and trapping with $PhMe_2SiCl$. We wanted to see if 2-MeTHF can give a similar result for the azepane lithiation. Interestingly, the outcome of the TMEDA-mediated lithiation in 2-MeTHF was very different to that in Et_2O. A low yield of silyl product **81** was obtained (20%) with 55% of recovered staring material **3**. Two side-products were also observed. Alkene **80** was isolated in 37% yield based on *s*-BuLi and forms *via* a β-elimination procedure.

Scheme 2.12



A second side-product was identified as silyl-trapped 2-MeTHF **82**. It was isolated in only 1% yield as a 70:30 mixture of diastereomers from its ^{1}H NMR spectrum. Diagnostic signals for **82** that allowed its identification include: δ_H 4.03-3.89 multiplet (1H integral) for the C*H*Me proton and two OC*H*SiMe$_2$Ph double doublets at δ_H 3.74 and 3.57 (1H integration in total), as well as signals for the PhMe$_2$Si group. The formation of **82** was very surprising, as we expected any lithiated 2-MeTHF to decompose *via* the retro [3+2] pathway (see Scheme 1.16)

Thus, the low yield of silyl azepane **81** (20%) under these conditions (*s*-BuLi/TMEDA, 2-MeTHF, –40 °C, 1 h) can be accounted for by the *s*-BuLi reacting in competition with the solvent, 2-MeTHF. We provide evidence (*via* isolation of **80** and **82**) for two ways in which the *s*-BuLi interacts with the 2-MeTHF: β-elimination (to give **80**) and α-lithiation with the associated likely retro [3+2] decomposition. This has revealed a key limitation of using 2-MeTHF as a solvent in *N*-Boc lithiations, especially when the *N*-Boc hetereocycle is slow to lithiate (*N*-Boc piperidine **2** and *N*-Boc azepane **3**).

However, there is a positive aspect to these results. The formation of silyl 2-MeTHF **82** is very interesting and relatively unprecedented. Therefore, we wondered whether it might be possible to optimise procedures for the α-lithiation-trapping of oxygen heterocycles. This led to our detailed studies which are described in Chapter 3.

In conclusion, the slow lithiation process of the less reactive *N*-Boc heterocycles by *s*-BuLi is the main issue and it allows *s*-BuLi to react with 2-MeTHF. Hence, 2-MeTHF is a not suitable solvent for this chemistry.

2.5 Conclusions and Future Work

The optimisation of high temperature lithiation-trapping of *N*-Boc pyrrolidine **1** was carried out. We concluded that the highest temperature for the lithiation–trapping of *N*-Boc pyrrolidine **1** that provides good yields is 0 °C for 5 sec for both diamine-free lithiation in 2-MeTHF and TMEDA-mediated lithiation in 2-MeTHF. The newly developed lithiation conditions represent an improvement as they occur at a higher temperature and require a shorter lithiation time compared to the original lithiation conditions reported by the Beak and O'Brien groups.

Nevertheless, the lithiation using 0 °C for 5 sec conditions is not appropriate for scaling up to the kg-scale in batch production due to the difficult temperature control of the exothermic reaction. We suggest two possible solutions for this chemistry: (i) use of a flow reactor for the 0 °C for 5 sec conditions and (ii) use of a lower temperature under batch conditions (*e.g.* –20 °C). A range of electrophiles was attempted for both reaction conditions. In general, most of the electrophiles (benzaldehyde, DMF, Me_3SiCl, CO_2 and $PhCONMe_2$) gave good yields of the trapped products in both reaction conditions (–20 °C for 2 min and 0 °C for 5 sec) except Me_2SO_4 which gave a very low yield and is a limitation of this chemistry. In the future work, we would like to apply the 0 °C conditions in a flow chemistry system.

The stability of the lithiated *N*-Boc pyrrolidine **75** at temperatures above –30 °C was studied. The results of the incubation experiments showed that the lithiated *N*-Boc pyrrolidine **75** is chemically unstable when the solution was warmed up from –30 °C. Also, the presence of the ligand did not significantly affect the stability of the intermediate **75**. Two possibilities for the breakdown of lithiated *N*-Boc pyrrolidine **75** at 0 °C were proposed (see Scheme 2.4). In addition, the recovery of starting material from the incubation of lithiated *N*-Boc pyrrolidine **75** could be due to α-deprotonation of THF/2-MeTHF or by β-deprotonation of 2-MeTHF/Et_2O to give *N*-Boc pyrrolidine **1** (see Scheme 2.5).

Lithiation-trapping of *N*-Boc *N*'-benzyl piperazine **16** at higher temperatures was explored. 2-MeTHF can replace THF as solvent for the lithiation-trapping of *N*-Boc *N*'-benzyl piperazine **16** at –78 °C, but further work is needed to show if lithiation using 2-MeTHF gives better yields than in THF at higher temperatures. The new optimised lithiation

conditions for *N*-Boc *N*'-benzyl piperazine **16** are 0 °C for 30 sec in THF for diamine-free lithiation. The recovery of the starting *N*-Boc *N*'-benzyl piperazine **16** suggested that the lithiated piperazine was protonated by the acidic α-proton of the product **78** as it forms. However, other electrophiles such as Me_3SiCl which do not generate an acidic α-proton will be explored to try and improve the results.

The exploration of high temperature lithiation-trapping of *N*-Boc piperidine **2** and *N*-Boc azepane **3** at –40 °C was carried out using *s*-BuLi/TMEDA in Et_2O or in 2-MeTHF. Given that the β-elimination of 2-MeTHF by *s*-BuLi is a competitive reaction due to the slow lithiation of the less reactive *N*-Boc heterocycles, 2-MeTHF is a not suitable solvent for this chemistry. In future work, the lithiation of *N*-Boc piperidine **2** and *N*-Boc azepane **3** using *s*-BuLi/TMEDA in Et_2O at higher temperatures should be explored more fully.

Below is a table that summarises the work undertaken in this Chapter.

Substrate	**Newly Developed Reaction Conditions**
N-Boc pyrrolidine **1**	Flow conditions: 0 °C for 5 sec in 2-MeTHF (TMEDA optional) Batch conditions: –20 °C for 2 min in 2-MeTHF (TMEDA optional)
N-Boc *N*'-benzyl piperazine **16**	0 °C for 30 sec in THF
N-Boc piperidine **2** and *N*-Boc azepane **3**	–40 °C for 1 h in Et_2O (Optimal conditions to be confirmed)

Chapter 3: Lithiation-trapping of Oxygen Heterocycles

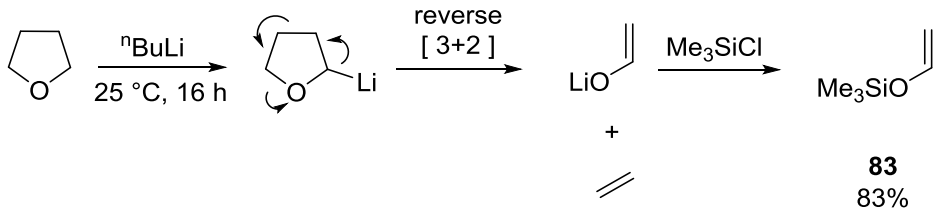
The direct lithiation-trapping of different oxygen heterocycles by *s*-BuLi will be presented in this chapter. As discussed in Chapter 1, organolithium reagents can interact with solvents such as THF *via* α-lithiation. Our plan was to try to discover reaction conditions that would allow high yielding α-lithiation-trapping of oxygen heterocycles to be accomplished. In section 3.1, the current state of the art for the metallation-trapping of cyclic ethers is presented. This highlights some of the limitations. Then, in the next sections, lithiation-trapping of THF and 2-MeTHF (section 3.2), THP (section 3.3), oxetanes (section 3.4) and *N*-alkyl morpholines (sections 3.5) are described.

3.1 Overview of Routes for the Generation and α-Functionalisation of Cyclic Ethers

3.1.1 Direct Metallation-trapping of Cyclic Ethers

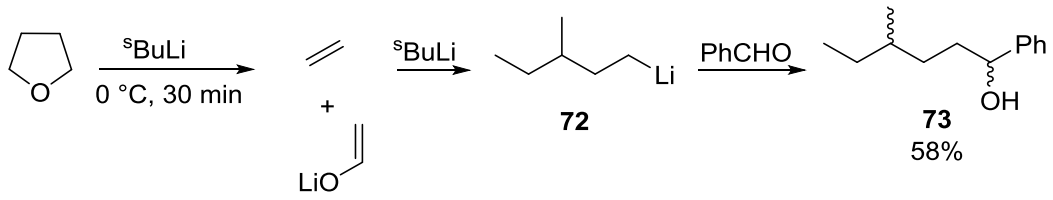
Direct metallation of THF using organolithium reagents has been studied for the past four decades. As discussed in Chapter 1, although α-deprotonation of THF can be carried out by organolithium reagents such as *n*-BuLi at high temperature, it is followed by a rapid decomposition due to the chemical instability of the lithiated intermediate. As the stability of the lithiated THF is key to the metallation taking place, detailed mechanistic and kinetic studies of the decomposition of THF by organolithium species were carried out by different groups. The lithiation of THF using *n*-BuLi was studied by Bates and Jung in the 1970s. Jung showed that when *n*-BuLi was reacted with THF at 25 °C for 16 h, THF was deprotonated at the α-position followed by a reverse [3+2] cycloaddition to give ethene and a lithium enolate (Scheme 3.1).[80] The lithium enolate was trapped with Me_3SiCl to give silyl enol ether **83** in 83% yield. Bates investigated the mechanism and half-lives of THF cleavage with *n*-BuLi by using NMR spectroscopy.[46] Although he attempted to detect the lithiated intermediate by monitoring the reaction in an NMR tube at 35 °C, no signals were detected for the intermediate at this high temperature.

Scheme 3.1



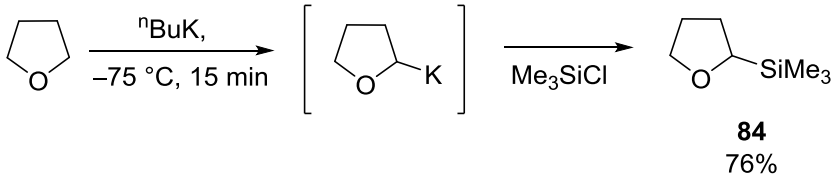
In 2002, Clayden confirmed that organolithium in the presence of diamine ligands such as TMEDA, (–)-sparteine and HMPA can also promote THF decomposition *via* C-2 or C-3 deprotonation depending on the choice of ligand (see Scheme 1.19).[49] Recently, lithiation of THF by a stronger base, *s*-BuLi, at a lower temperature (0 °C) was studied by our group.[15] Although THF was lithiated at a lower temperature and shorter period of time (30 min), the lithiated THF was unstable and broke down into ethene and lithium enolate. In this case, the ethene was further carbolithiated to give **72** and hence **73** in 58% yield after benzaldehyde trapping (Scheme 3.2).

Scheme 3.2



These results suggest that the deprotonation of THF using organolithium reagents can be carried out at high temperature but the trapping process is unlikely to happen as the lithiated THF will preferentially undergo reverse [3+2] cycloaddition as a decomposition pathway. In 1984, Schlosser reported an effective protocol for the metallation-trapping of THF by using a more reactive metallating agent, an organopotassium reagent, which allowed the metallation to be carried out at low temperature.[81] THF as a substrate and solvent was reacted with a solution of *n*-BuK at low temperature (–75 °C) for a short reaction time (15 min). The presumed organopotassium intermediate was trapped with Me_3SiCl to give a 76% yield of silyl THF **84** (Scheme 3.3).

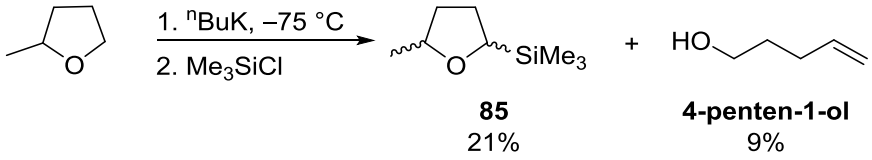
Scheme 3.3



As the result suggested that the organopotassium intermediate is stable at –75 °C, Schlosser further investigated the stability of the organopotassium intermediate at a higher temperature. The metallated intermediate was incubated at –50 °C for an unspecified length of time. It was found that the organopotassium intermediate decomposed into ethene and a potassium enolate.

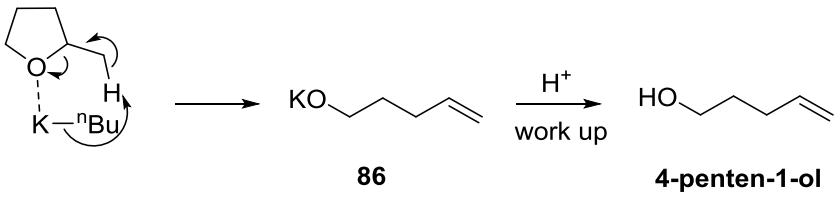
Metallation of 2-MeTHF with *n*-BuK was also carried out at –75 °C (Scheme 3.4). After trapping with Me_3SiCl, a low yield (21%) of a mixture of *cis*/*trans* silyl product **85** and a 9% yield of 4-penten-1-ol were obtained. The ratio of *cis*/*trans* diastereomers was not reported.

Scheme 3.4



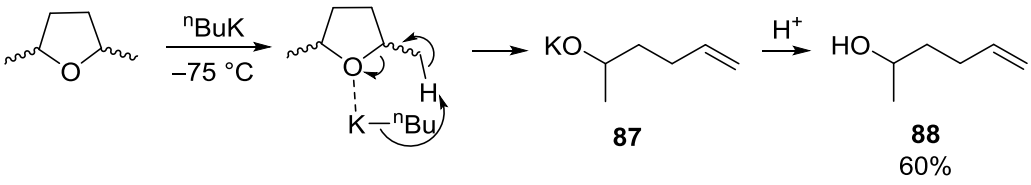
4-penten-1-ol was presumably formed from 2-MeTHF *via* a β-elimination mechanism by the *n*-BuK as shown in Scheme 3.5. This would give potassium pent-4-en-1-olate **86** which would give 4-penten-1-ol after work-up. A similar mechanism for organolithium reagents proposed by Cohen and Stokes[50] was already reviewed in Chapter 1 and we also observed this type of product from attempted lithiation-trapping of *N*-Boc heterocycles as discussed in Chapter 2 (see section 2.4). As the methyl group at the α-position of the five-membered ring allows an alternative β-elimination process, less α-deprotonation occurs even at low temperature which leads to a low yield of the desired product.

Scheme 3.5



The attempted metallation of 2,5-dimethyl THF using *n*-BuK provided a similar result to that with 2-MeTHF. A mixture of *cis*/*trans*-2,5-dimethyl THF was reacted with *n*-BuK at –75 °C. After initial coordination of *n*-BuK, β-elimination occurred to give **87** and hence **88** in 60% yield after trapping by a proton.

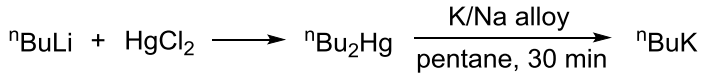
Scheme 3.6



Although metallation of THF using *n*-BuK provided a good methodology for producing α-substituted THF compounds, *n*-BuK is not commercially available and required a highly hazardous chemical synthesis which involved use of toxic mercury(II) chloride and very reactive potassium metal. The preparation of *n*-BuK is shown in Scheme 3.7. The process

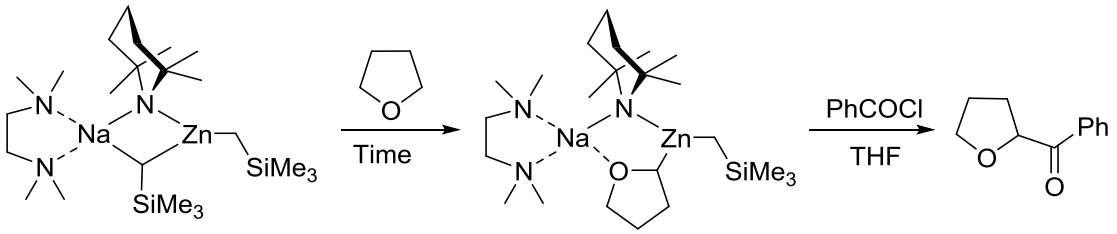
is highly hazardous and against the principles of Green Chemistry and should ideally be avoided. This is presumably why Schlosser's procedure has not attracted any attention from the synthetic organic chemistry community.

Scheme 3.7



In 2009, Mulvey suggested a pathway to stabilise α-metallated THF by using bimetallic bases.[82,83] The strategy involved alkali-metal-mediated zincation (AMMZn). A bimetallic coordination compound containing sodium and zinc was able to direct the α-metallation of cyclic ethers. The Zn/Na complex **89** was prepared first and then THF was added as the substrate and the solvent. The resulting solution was stirred for an extended period (2-14 days!). Then, the THF was removed and hexane was added to the residue at –30 °C to give the crystalline coordinated compound **90**, effectively an α-metallated THF (Scheme 3.8). The structures of Zn/Na complexes **89** and **90** were characterised by X-ray crystallographic and NMR spectroscopic studies. The crystalline compound **90** was isolated and then trapped with benzoyl chloride in THF to give a high yield (71%) of ketone **91** (Scheme 3.8). However, a lower yield (38%) was obtained when the trapping was attempted straight after compound **90** was formed in solution. Although the metallation of THF using a Zn/Na mixed-metal base generates a complex which is stable at 20 °C and gave a good yield of the trapped product, the overall reaction process was extremely slow (taking up to 2 weeks).

Scheme 3.8



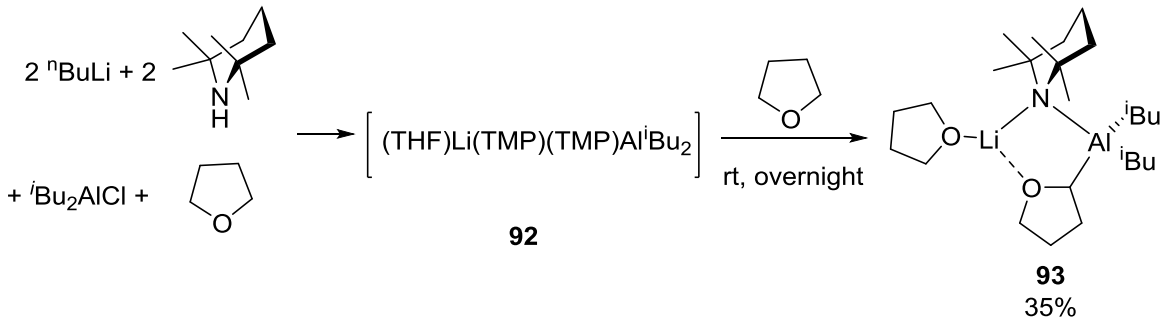
89

90
42% (2 days)
53% (14 days)

91
71%

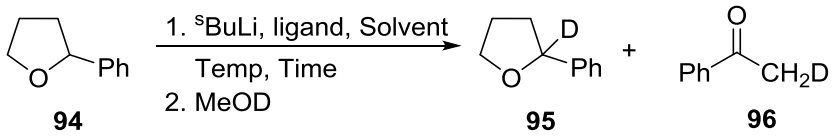
Mulvey reported another bimetallic base, an Al/Li complex, that can also metallate THF. The preparation of the Al/Li complex is more straightforward than the Zn/Na complex. A 2:2:1:1 mixture of *n*-BuLi, TMP, *i*Bu_2AlCl and THF was stirred in hexane to form the Al/Li complex **92** which then reacted with one molar equivalent of THF as substrate at 25 °C overnight to give the crystalline coordinated compound **93** in 35% yield. However, trapping of crystalline compound **93** with electrophiles was not successful.

Scheme 3.9



In 2013, Capriati showed that the direct lithiation-trapping of mono-substituted THF, 2-phenyltetrahydrofuran **94** (2-PhTHF), can be carried out at low temperature.[84] It is presumed that by introducing a phenyl group at the C-2 position of THF, the α–proton becomes more acidic and hence is easier to deprotonate using *s*-BuLi. 2-PhTHF **94** was lithiated in THF at –78 °C for 2 min before trapping with MeOD (Table 3.1, entry 1). The result gave [D]-**95** in 50% yield and 50% of **96** *via* the decomposition of the lithiated intermediate (which initially gives a lithium enolate). A better yield of [D]-**95** (80%) was obtained with 20% of **96** when the *s*-BuLi/TMEDA complex in THF was used (entry 2). Capriati suggested that the presence of TMEDA slowed down the decomposition of the lithiated 2-PhTHF *via* the retro [3+2] pathway but also slowed down the lithiation rate. Hence, a longer lithiation time was needed (10 min). High yields of [D]-**95** (90-98%) were obtained when non-polar solvents such as hexane and toluene were used in the presence of TMEDA and none of **96** was formed (entries 3-4). It is presumed that at –78 °C, the lithiated intermediate coordinating with TMEDA is stable in a non-polar solvent for a short time (2 min). In contrast, no deprotonation occurred in hexane or toluene when TMEDA was absent.

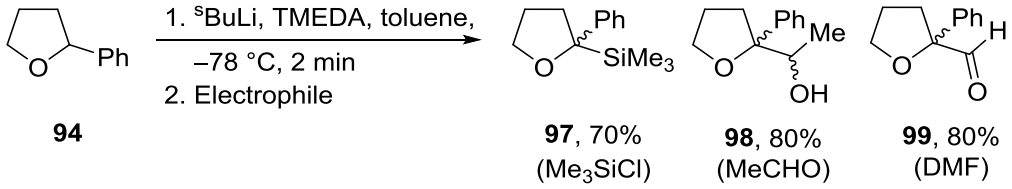
Table 3.1



Entry	Time (min)	Temp (°C)	Solvent	95 Yield (%)	96 Yield (%)
1	2	–78	THF	50	50
2	10	–78	THF + TMEDA	80	20
3	2	–90	Hexane + TMEDA	90	0
4	2	–78	Toluene + TMEDA	>98	0

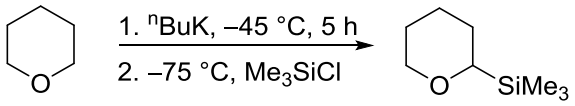
It can be seen that lithiation of 2-PhTHF **94** using *s*-BuLi/TMEDA complex in toluene at –78 °C for 2 min gave the optimised yield. A range of electrophiles were explored and the results are summarised in Scheme 3.10. As the results show, lithiation of 2-PhTHF **94** gave good yields (70-80%) at low temperature and a short lithiation time.

Scheme 3.10



There are a few examples of the metallation-trapping of the 6-membered ring, THP, mostly using the same types of procedures as for THF. For example, metallation-trapping of THP using an organopotassium reagent was studied by Schlosser. Unlike THF, metallated THP cannot undergo the reverse [3+2] cycloaddition. Therefore, metallation-trapping of THP using *n*-BuK was carried out at higher temperature (–45 °C) for longer time (5 h) (Scheme 3.11). The reaction mixture was then cooled back to –75 °C before trapping with Me_3SiCl to give a 68% yield of the silyl THP **100**. Using a competition experiment between THF and THP, Schlosser reported that THP reacted approximately 25 times slower than THF. Hence, a higher temperature and shorter reaction time was needed to promote the deprotonation step.

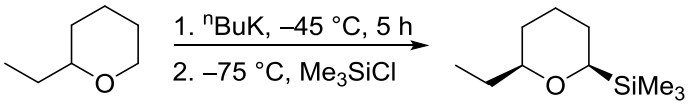
Scheme 3.11



100
68%

Schlosser also studied the metallation of 2-ethyl THP **101**. 2-Ethyl THP **101** was deprotonated using *n*-BuK under the standard THP reaction conditions. This gave a 52% yield of silyl product *cis*-**102**, *via* a regio- and diastereoselective process.

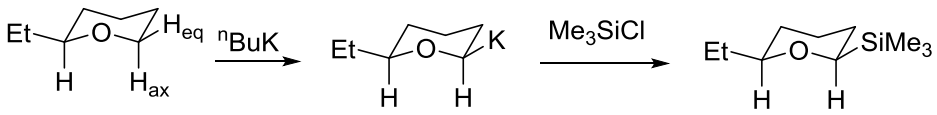
Scheme 3.12



101 *cis*-**102**
52%

Although no explanation was given for the selectivity observed, regioselectivity was presumably a result of removal of a proton from the least sterically hindered side. We also propose the following explanation for the diastereoselectivity. The most stable conformation of 2-ethyl THP **101** will have the ethyl group in the equatorial orientation. Then, preferential equatorial deprotonation could occur to give *cis*-**102** (Scheme 3.13).

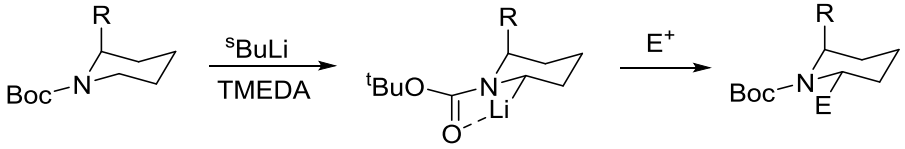
Scheme 3.13



cis-**102**

Equatorial lithiation is well-known in the lithiation-trapping of substituted *N*-Boc piperidines.[29] However, in the case of 2-substituted *N*-Boc piperidine **103**, the substituent favours an axial orientation to avoid the unfavourable $A^{1,3}$-type strain between the Boc group and the substituent (Scheme 3.14). Lithiation of 2-substituted *N*-Boc piperidine **103**, *via* equatorial deprotonation, then gives the trapped product *trans*-**105**.

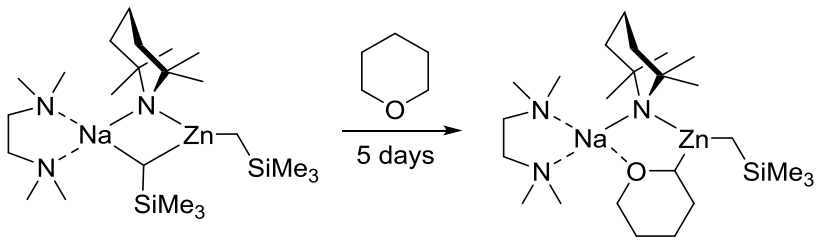
Scheme 3.14



103 **104** *trans*-**105**

Metallation of THP using Zn/Na complex **89** was also investigated by Mulvey.[82] A mixture of THP and the Zn/Na complex **89** was stirred for 5 days and, due to the low reactivity of THP, a 1:1 mixture of **89** and **106** was obtained in 29% yield. However, the attempted trapping of **106** with benzoyl chloride was not successful.

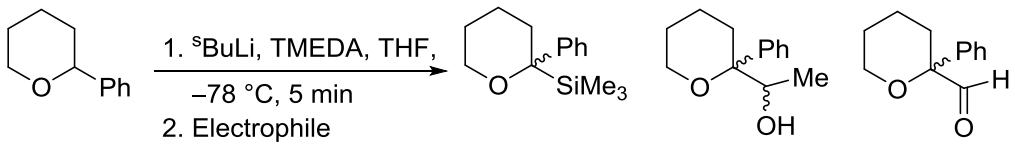
Scheme 3.15



89 **106**

Capriati also studied the direct lithiation-trapping of 2-phenyltetrahydropyran **107** (2-PhTHP) at low temperature.[85] After the investigation of different reaction conditions, the optimised conditions for the lithiation of 2-PhTHP **107** was using *s*-BuLi/TMEDA in THF at –78 °C for 5 min. A range of electrophiles was explored and the results are summarised in Scheme 3.16. As the results show, lithiation of 2-PhTHP **107** gave good yields (47-98%) at low temperature and a short lithiation time.

Scheme 3.16



107

108, 47% (Me_3SiCl)

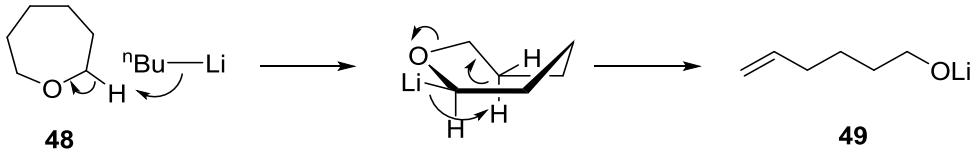
109, 65% (MeCHO)

110, 98% (DMF)

As mentioned in Chapter 1, direct lithiation of a 7-membered ring cyclic ether, oxepane **48**, using *n*-BuLi has been studied by Bates and Cohen.[46,50] When oxepane **48** was lithiated at the α-position, the lithiated intermediate underwent a transannular hydrogen shift to form

lithium hex-5-en-1-oxide **49**. The mechanism of cleavage of the oxepane is shown in Scheme 3.17.

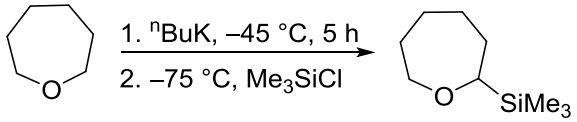
Scheme 3.17



48 **49**

Schlosser tried to deprotonate oxepane **48** using *n*-BuK at –45 °C for 5 h but a low yield (27%) of trapped product **111** was obtained (Scheme 3.18). There was no further information about the low yield or the formation of any side products, but it is known that *N*-Boc azepane **3** is much slower to lithiate than *N*-Boc pyrrolidine **1**.

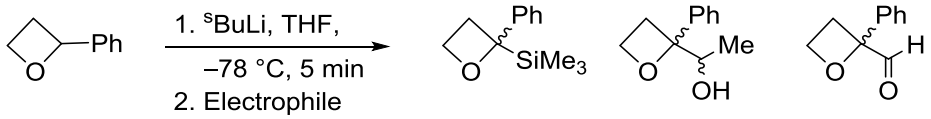
Scheme 3.18



48 **111**
27%

Finally, Capriati has also expanded the direct lithiation-trapping methodology to the substituted 4-membered ring cyclic ether, 2-phenyl oxetane **112**.[86] 2-Phenyl oxetane **112** was successfully lithiated using *s*-BuLi/THF complex in THF at –78 °C for 5 min. In general, a good yield (70-95%) was obtained after the lithiated intermediate was trapped with a range of electrophiles (Scheme 3.19).

Scheme 3.19

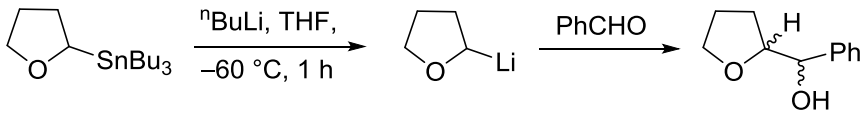


112 **113**, 95% (Me$_3$SiCl) **114**, 70% (MeCHO) **115**, 80% (DMF)

3.1.2 Alternative Routes to α-Lithiated Cyclic Ethers

Apart from direct lithiation of cyclic ethers *via* deprotonation, there are two alternative synthetic pathways that can be used to give the desired α-substituted cyclic ethers *via* lithiated intermediates. One approach is tin-lithium exchange and the other is reductive lithiation of sulfides. Tin-lithium exchange of *N*-Boc heterocycles is often used to access lithiated intermediates particularly when studying mechanistic features.[87] McGarvey showed that α-substituted cyclic ethers can be achieved *via* tin-lithium exchange of stannyl cyclic ethers.[88] As shown in Scheme 3.20, stannyl THF **116** underwent tin-lithium exchange using *n*-BuLi in THF at –60 °C for 1 h to give the lithiated THF **117**, which was then trapped with benzaldehyde to give a 52:48 mixture of diastereomeric alcohols **118** in 71% yield. The high yield suggests that the lithiated THF has good stability at –60 °C and the retro [3+2] decomposition pathway is minimised under these conditions.

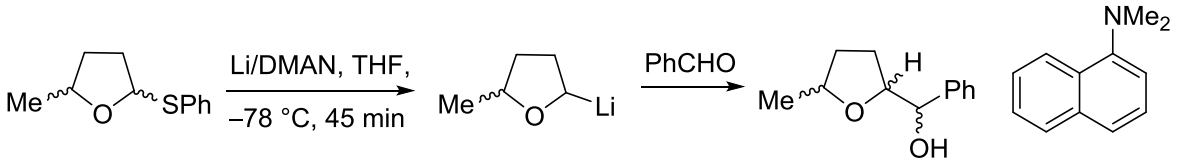
Scheme 3.20



116 **117** **118**, 71%, 52:48 dr

Cohen provided another pathway to α-functionalise 5-membered ring cyclic ethers by reductive lithiation.[89] Reductive lithiation of a mixture of diastereomeric α-phenylthio ethers **119** with Li/DMAN complex at –78 °C followed by trapping with benzaldehyde gave an unknown mixture of diastereomeric alcohols **120** in 51% yield (Scheme 3.21).

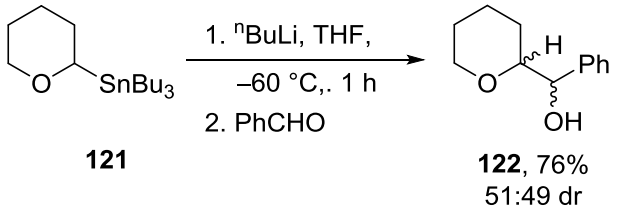
Scheme 3.21



119 **120**, 51% DMAN

A similar reaction using tin-lithium exchange was carried out on the 6-membered cyclic ether, stannyl THP **121**, at –60 °C (Scheme 3.22). In this case, a 51:49 mixture of diastereomeric alcohols **122** was formed in 76% yield.

Scheme 3.22

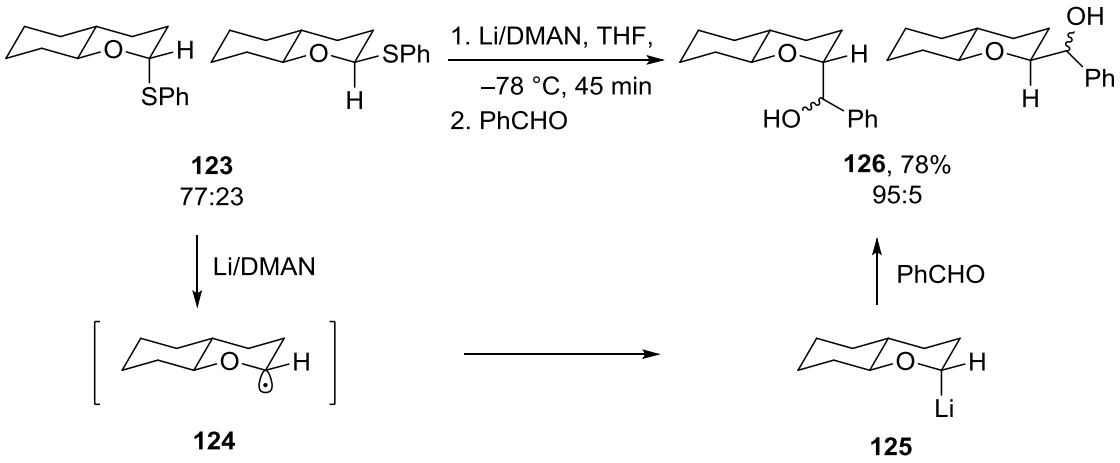


121

122, 76%
51:49 dr

Reductive lithiation of a 77:23 mixture of a diastereomeric bicyclic THPs **123** using Li/DMAN at –78 °C is shown in Scheme 3.23. One electron reduction of the C-S bond generates a radical which can readily interconvert its configuration. However, the axial radical **124** is preferred due to anomeric stabilisation from the axial oxygen lone pair. A second one electron reduction then gives an axial organolithium **125** as the major intermediate. Trapping with benzaldehyde gave a 78% yield of alcohols **126** in total with a 95:5 mixture of axial and equatorial configurations.

Scheme 3.23



123
77:23

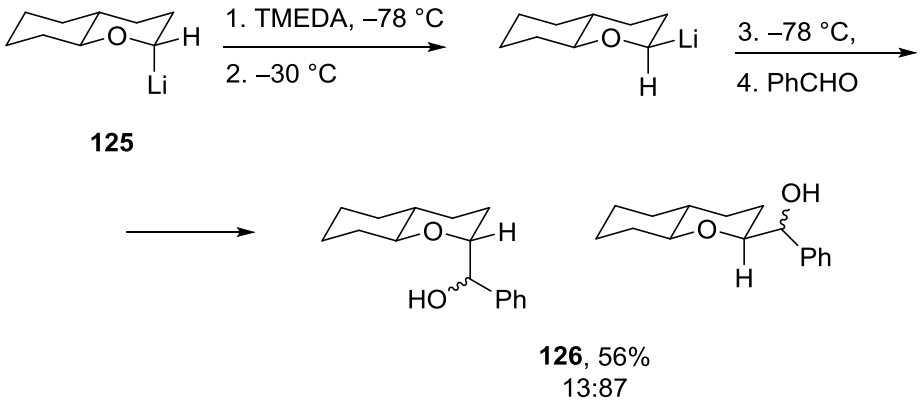
126, 78%
95:5

124

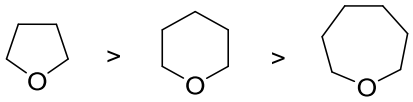
125

As the bicyclic THP **123** is incapable of chair-chair interconversion, Cohen examined the configurational stability of the lithiated intermediate by warming the axial lithiated intermediate from –78 °C to –30 °C. During the incubation at –30 °C, it was found that the lithiated intermediate was configurationally unstable since trapping with benzaldehyde gave the equatorial configuration as the major product (Scheme 3.24).

Scheme 3.24



In summary, the reactivity of oxygen heterocycles towards α-functionalisation decreases as the size of the ring increase. This trend is similar to the reactivity of the ring system in *N*-Boc heterocycles. The most reactive 5-membered ring, THF, can be α-metallated by *n*-BuK at –75 °C whereas the less reactive THP and oxepane **48** require temperatures above –75 °C to promote the metallation.

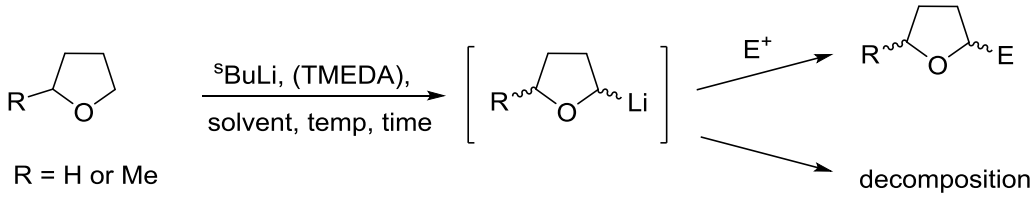


Metallated THF has good chemical stability at –60 °C. When the metallation temperature is above –60 °C, decomposition *via* the retro [3+2] pathway occurs. However, the actual temperature that the retro [3+2] starts to occur is unknown. In contrast, metallated THP and oxepane **48** can not undergo the retro [3+2] pathway like THF. Lithiated THP is configurationally stable at –78 °C but becomes configurationally unstable when the temperature increases to –30 °C.

3.2 Lithiation-trapping of THF and 2-MeTHF

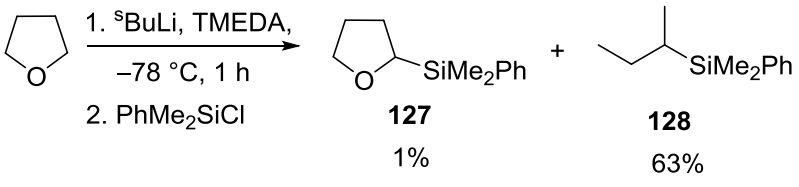
As discussed in Chapter 2, we were able to isolate α-substituted silyl 2-MeTHF **82** as a side product from the lithiation-trapping of *N*-Boc azepane **3** (see Scheme 2.12). This led us to consider whether we could lithiate THF and 2-MeTHF and trap with electrophiles. In order to do this, we needed to investigate lithiation conditions that could stabilise the lithiated intermediate before trapping with electrophiles. With THF and 2-MeTHF, key factors would be the rate of the desired α-lithiation versus the rate of decomposition of the lithiated species *via* the retro [3+2] pathway. Temperature, solvent, and TMEDA were considered to be important factors when trying to identify suitable reaction conditions (Scheme 3.25). In addition, with 2-MeTHF, the β-elimination pathway may also be competitive, as Schlosser found with the *n*-BuK metallation of 2-MeTHF (see Scheme 3.4)

Scheme 3.25



We started the investigation of THF lithiation at low temperature (–78 °C) using THF as both the substrate and the solvent. We presumed that *s*-BuLi is relatively stable in the presence of TMEDA in THF at –78 °C and, therefore, we predicted that THF α-lithiation should be slow. *s*-BuLi was added to a mixture of TMEDA in THF solution at –78 °C. It was stirred for 1 h before adding $PhMe_2SiCl$ as the electrophile and the result is shown in Scheme 3.26.

Scheme 3.26



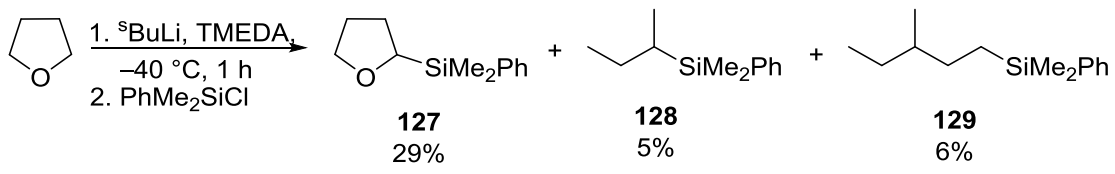
After purification by column chromatography, only a 1% yield of silyl THF **127** was obtained with a 63% yield of the direct trapping product, silane **128**. The % yields of each product are based on the mmol of *s*-BuLi used in the reaction (since THF is in large excess

as it is both the solvent and the substrate). This result suggested that the *s*-BuLi/TMEDA complex is not reactive enough to lithiate THF effectively at –78 °C. Thus, most of the *s*-BuLi was trapped by the electrophile and led to silane **128**.

Characterisation of the two products, **127** and **128**, proved their structures. In the ^{1}H NMR spectrum of silyl THF **127**, there were three 1H signals at δ_H 3.78 (ddd), 3.68 (ddd) and 3.47 (dd) which were assigned to the three protons adjacent to oxygen. The double doublet (J = 11.0, 7.0 Hz) at δ_H 3.47 can be assigned to the α-silyl proton, with ^{3}J coupling to the two diastereotopic ring protons. The presence of a 5H multiplet at δ_H 7.61-7.32 and two 3H singlets at δ_H 0.34 and 0.32 confirmed the presence of the $SiMe_2Ph$ group. The ^{13}C NMR spectrum of the silyl THF **127** had 10 signals with the appropriate δ_C values, including a OCH signal at δ_C 71.6. The ^{1}H NMR spectrum of silane **128** showed there were four 3H signals at δ_H 0.94 (d), 0.90 (t), 0.25 (s) and 0.24 (s) which were assigned to the methyl groups of the *s*-butyl chain and the $SiMe_2Ph$ group. The doublet (J = 7.0 Hz) at δ_H 0.94 and the triplet (J = 7.5 Hz) at δ_H 0.90 are characteristic of the two methyl groups in the *s*-butyl chain. The two singlet signals at δ_H 0.25 and 0.24 can be assigned to the methyl groups in the $SiMe_2Ph$ group. All of signals in the ^{13}C NMR spectrum of silane **128** fitted with the assigned structure.

Since the *s*-BuLi/TMEDA complex was not reactive enough to lithiate THF effectively at –78 °C and gave a poor yield, we decided to lithiate THF at a higher temperature. Lithiation of THF as both the solvent and the substrate using *s*-BuLi/TMEDA was carried out at –40 °C. The resulting solution was stirred for 1 h before trapping with $PhMe_2SiCl$ to give the crude product which contained a 55:20:25 ratio of silyl THF **127**, silane **128** and carbolithiation product **129** (by ^{1}H NMR spectroscopy) (Scheme 3.27). Purification by flash column chromatography gave a very encouraging yield (29%) of silyl **127** and an inseparable 75:25 mixture (by ^{1}H NMR spectroscopy) of silane **128** and carbolithiation product **129**. This corresponds to a 5% yield of silane **128** and a 6% yield of silane **129**.

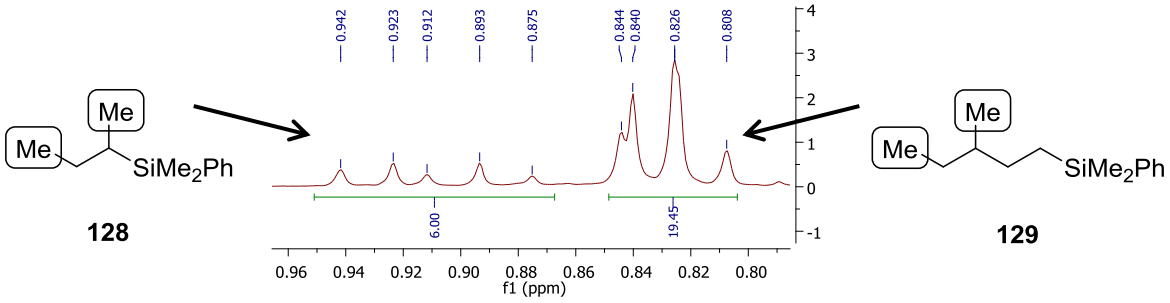
Scheme 3.27



As discussed in Chapter 2, carbolithiation product **129** would be formed by the retro [3+2] cycloaddition of the lithiated THF to give ethene and a lithium enolate, followed by carbolithiation of the ethene with another equivalent of *s*-BuLi (see Scheme 2.3). The diagnostic signals of the carbolithiation product **129** in the ^{1}H NMR spectrum included two 3H signals at δ_H 0.83 (d, J = 5.5 Hz) and 0.82 (t, J = 7.0 Hz) which were assigned to the methyl groups next to the CH and CH_2 groups respectively in the *s*-butyl chain.

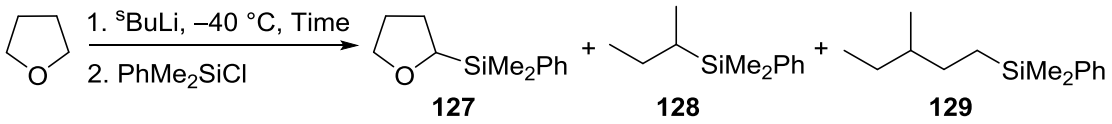
Since silane **128** and carbolithiation product **129** were inseparable, the yields of these two products were calculated from the ratio of specific signals in the ^{1}H NMR spectrum of the mixture which (Figure 3.1). The doublet (δ_H 0.94) and triplet (δ_H 0.90) are assigned to the two methyl groups in silane **128**; the doublet (δ_H 0.83) and triplet (δ_H 0.82) are assigned to the carbolithiation product **129**. Hence, the ratio of the two products was measured according to the integration of these two ranges and the integrations indicated that the mixture contains a 25:75 ratio of the silane **128** and the carbolithiation product **129**.

Figure 3.1



The result of the lithiation at –40 °C for 1 h was very encouraging (29% yield of silyl THF **127**) and it led us to further explore the lithiation conditions at this temperature. We also wanted to investigate whether the TMEDA was needed for the lithiation. Hence, lithiation of THF was carried out using *s*-BuLi/THF or *s*-BuLi/TMEDA complex at –40 °C for various lithiation times (1 h, 40 min, 20 min and 10 min) (Table 3.2). In general, a lower yield of silyl THF **127** was obtained when a shorter lithiation time was carried out, presumably because less THF was lithiated (entries 3-7). The presence of TMEDA did not improve the yield of silyl THF **127** when comparing to the diamine-free protocol under the same lithiation time (compare entries 1/2, 3/4 and 5/6).

Table 3.2



127 **128** **129**

Entry	Diamine	Ratio of 127:128:129[a]	Time	127 Yield (%)	128 Yield (%)[b]	129 Yield (%)[b]
1	TMEDA	55:20:25	1 h	29	5	6
2	–	50:30:20	1 h	29	11	5
3	TMEDA	30:55:15	40 min	31	18	Not recovered
4	–	40:50:10	40 min	30	27	5
5	TMEDA	30:70:0	20 min	14	41	0
6	–	30:70:0	20 min	21	51	0
7	TMEDA	5:95:0	10 min	11	Not recovered	0

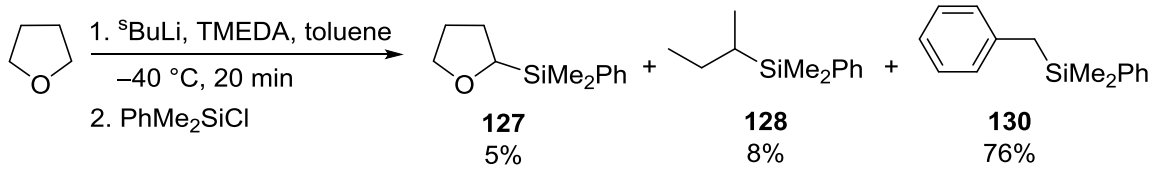
[a] Ratio determined from the ^{1}H NMR spectrum of the crude product.
[b] **128** and **129** inseparable by chromatography. % yield determined by mass of isolated mixture of **128** and **129** and ratio determined from the ^{1}H NMR spectrum of the mixture.

The presence of the carbolithiation product **129** at –40 °C confirmed the breakdown of lithiated THF after the lithiation was carried out for 40 min. Nevertheless, in all the cases, the total yield of the three products **127**, **128** and **129** ranged from 40-72% which suggested some mass was lost during the reaction. In particular, reactions with longer reaction times gave lower mass balances. One of the possibilities was that some of the ethene generated from the breakdown of lithiated THF escaped as a gas (bp –104 °C). Thus, not all of the ethene reacted with another equivalent of *s*-BuLi to give the carbolithiation product **129**. Overall, diamine-free lithiation of THF at –40 °C for 40 min provided the suitable balance of the lithiation rate and decomposition rate *via* the retro [3+2] pathway.

Up to this point, lithiation of THF was carried out in THF as both substrate and solvent. We wanted to investigate whether a higher yield could be obtained in another solvent. Therefore, 1.0 equivalent of THF was lithiated using *s*-BuLi/TMEDA complex in toluene at –40 °C for 20 min (Scheme 3.28). Only a 5% yield of silyl THF **127** was obtained with an 8% yield of silane **128**. Not surprisingly, due to the excess of toluene and high

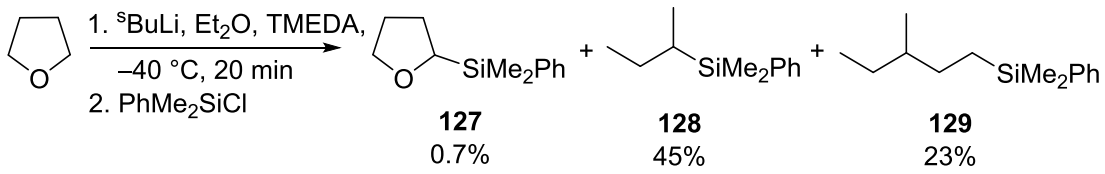
temperature (–40 °C), lithiation of toluene was the major pathway which gave a 76% yield of benzyl silane **130**. The structure of benzyl silane **130** was confirmed by the ^{1}H NMR spectrum. The 2H signal at δ_H 2.31 (s) is characteristic of the benzylic protons adjacent to the $SiMe_2Ph$ group. The data matched with those reported in the literature.[90] The presence of benzyl silane **130** indicated that toluene as solvent is not suitable for this chemistry.

Scheme 3.28



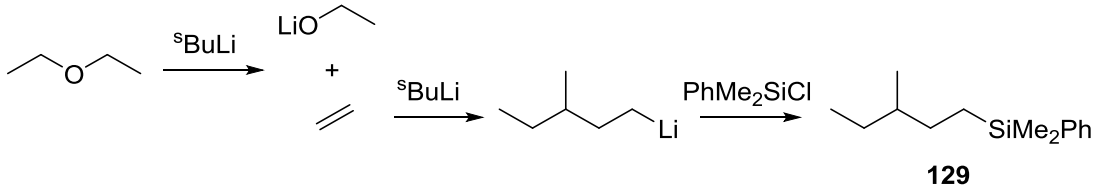
Subsequently, lithiation-trapping in Et_2O was carried out under similar reaction conditions (Scheme 3.29). In this case, less than 1% yield of silyl THF **127** and an inseparable 85:15 mixture (by ^{1}H NMR spectroscopy) of silane **128** and carbolithiation product **129** were isloated. This corresponds to a 45% yield of silane **128** and a 23% yield of silane **129**.

Scheme 3.29



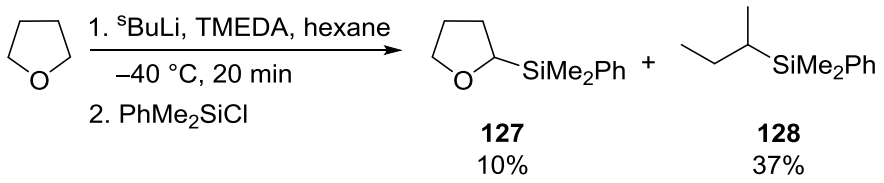
The yield of silane **128** is similar to the lithiation in THF as both substrate and solvent under the same reaction conditions (Table 3.2, entry 5), which suggests that a similar amount of *s*-BuLi reacted with $PhMe_2SiCl$. However, the yield of the desired product is much lower and we suspected the *s*-BuLi was not only reacting with THF but also with Et_2O. As discussed in Chapter 1, deprotonation of Et_2O using organolithiums can be achieved to give ethene and lithium ethoxide (see Scheme 1.15). The carbolithiation of ethene with another equivalent of *s*-BuLi can then be carried out to give the **129** (Scheme 3.30). In this experiment, 23% yield of the carbolithiation product **129** was isolated and we presumed that it could be obtained from THF and Et_2O. Based on the result, Et_2O as solvent is not suitable for THF lithiation.

Scheme 3.30



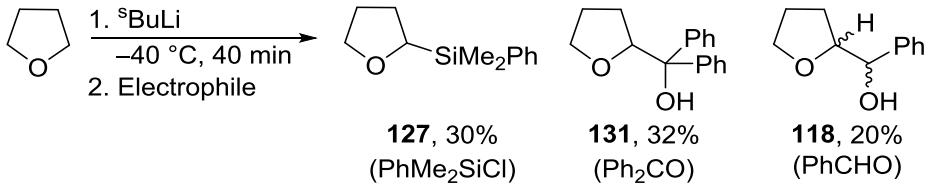
As THF and Et_2O can both potentially react with the *s*-BuLi, we ideally required a non-polar solvent that would not provide an acidic proton for deprotonation which would consume the *s*-BuLi. Hence, lithiation of THF in hexane under similar reaction conditions was carried out. 1.0 equivalent of THF was lithiated using *s*-BuLi/TMEDA complex in hexane at –40 °C for 20 min. This gave a 10% yield of the silyl product **127** together with a 37% yield of silane **128** (Scheme 3.31). This result was very similar to the one in THF under similar conditions (Table 3.2, entry 5).

Scheme 3.31



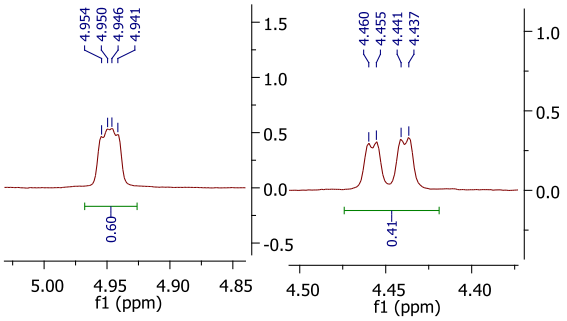
In summary, the lithiation-trapping of THF in different solvents was explored and the use of THF as both the substrate and the solvent provided the best results. In addition, there was no benefit of introducing TMEDA in the reaction mixture. Based on the results of the optimisation, we concluded that lithiation using *s*-BuLi/THF at –40 °C for 40 min were the best conditions as they provide a suitable balance between the rate of lithiation and the rate of decomposition of the lithiated intermediate *via* the retro [3+2] pathway. Thus, lithiation of THF was carried out under the newly developed conditions and trapping with a range of electrophiles to give the results shown in Scheme 3.32. Yields ranged from 20-32% of the products that were obtained.

Scheme 3.32



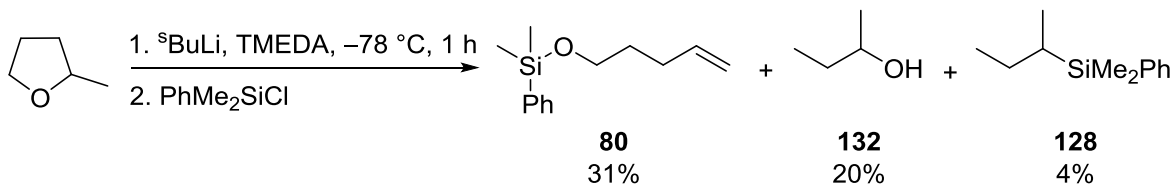
Both ^{1}H and ^{13}C NMR spectra of these three products confirmed that the lithiation-trapping had taken place. For the benzaldehyde trapping of the lithiated THF, it gave a 60:40 mixture (by ^{1}H NMR spectroscopy) of diastereomeric hydroxy THFs **118** in a total of 20% yield. As the diastereomeric hydroxy THFs **118** were inseparable, the ratio was calculated from the ^{1}H NMR spectrum of the mixture which (Figure 3.2). The two 1H double doublet signals at δ_H 4.91 and 4.42, which are assigned to the proton adjacent to the phenyl and OH group, indicated that the mixture contains a 60:40 ratio of diastereomeric hydroxy THFs **118**. Spectroscopic data were consistent with those reported in the literature.[88]

Figure 3.2



For comparison, lithiation-trapping of 2-MeTHF was explored. We started the investigation of 2-MeTHF lithiation at low temperature (–78 °C) in the knowledge that β-elimination of a proton in the methyl group would probably be a competing reaction. Lithiation of 2-MeTHF as substrate and solvent using *s*-BuLi/TMEDA complex at –78 °C was carried out for 1 h before trapping with $PhMe_2SiCl$ as the electrophile (Scheme 3.33). After purification, a 31% yield of β-elimination product, silyl ether alkene **80**, was obtained with 20% yield of 2-butanol **132** and a 4% yield of silane **128**.

Scheme 3.33



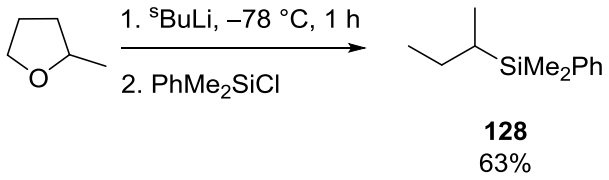
80 31% **132** 20% **128** 4%

There was no evidence of formation of the α-lithiaiton-trapping product. Clearly, β-elimination of the methyl group occurs readily at –78 °C (31% yield of **80**). The formation of 2-butanol **132** from *s*-BuLi reactions normally indicates that some oxygen was present

in the reaction set-up. The initial result suggested that 2-MeTHF is more reactive than THF at –78 °C. However, instead of the α-deprotonation of 2-MeTHF, *s*-BuLi preferred to deprotonate the β-proton in the methyl group which led to product **80**.

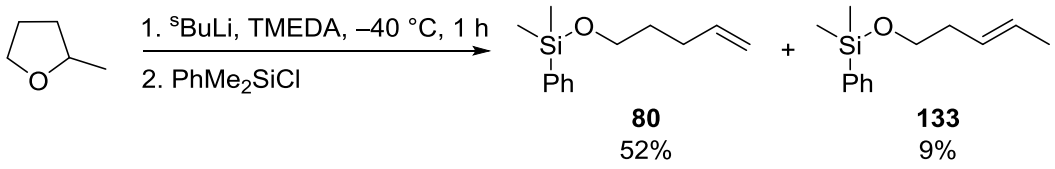
Next, the diamine-free version of this lithiation was explored at –78 °C (Scheme 3.34). The result was disappointing as neither α-substituted 2-MeTHF **82** nor the β-elimination product **80** was obtained. Only a 63% yield of direct-trapping product, silane **128** was isolated. This result indicated that the *s*-BuLi/2-MeTHF complex is not reactive to deprotonate at –78 °C, at either the α- or β-position.

Scheme 3.34



Since the *s*-BuLi/2-MeTHF complex is not reactive for deprotonation at low temperature, we decided to explore the lithiation at higher temperatures. Lithiation of 2-MeTHF using *s*-BuLi/TMEDA complex at –40 °C was carried out (Scheme 3.35). After trapping with $PhMe_2SiCl$, no α-substituted 2-MeTHF **82** was found but an inseparable 85:15 mixture (by ^{1}H NMR spectroscopy) of silyl ether alkenes **80** and **133** was isolated. This corresponds to a 52% yield of alkene **80** and a 9% yield of alkene **133**.

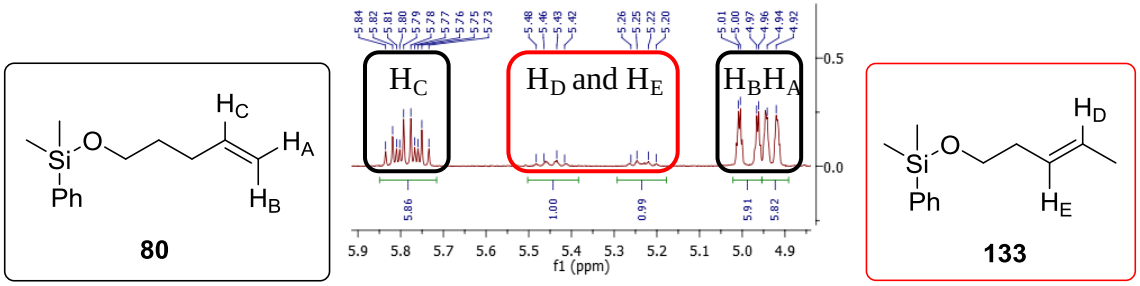
Scheme 3.35



In the ^{1}H NMR spectrum of the silyl ether alkene mixture, there were five 1H signals at δ_H 5.79 (ddt), 5.50-5.39 (m), 5.29-5.18 (m), 4.99 (ddt) and 4.93 (ddt) which were assigned to alkene protons (Figure 3.3). When comparing the ^{1}H NMR spectrum of this mixture with the independent synthesis of the silyl ether alkene **80** (see Scheme 2.9), it indicated that the signals at δ_H 5.50-5.39 (m) and 5.29-5.18 (m) belong to alkene **133** and the chemical shifts differ to the terminal alkene **80** (including a terminal alkene (δ_H 4.99 and 4.93) and a ddt

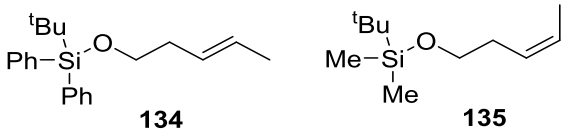
(δ_H 5.79). Based on the ^{1}H NMR spectrum, it suggested that the newly formed alkene **133** has a similar structure to terminal alkene **80** but with a different alkene chain.

Figure 3.3



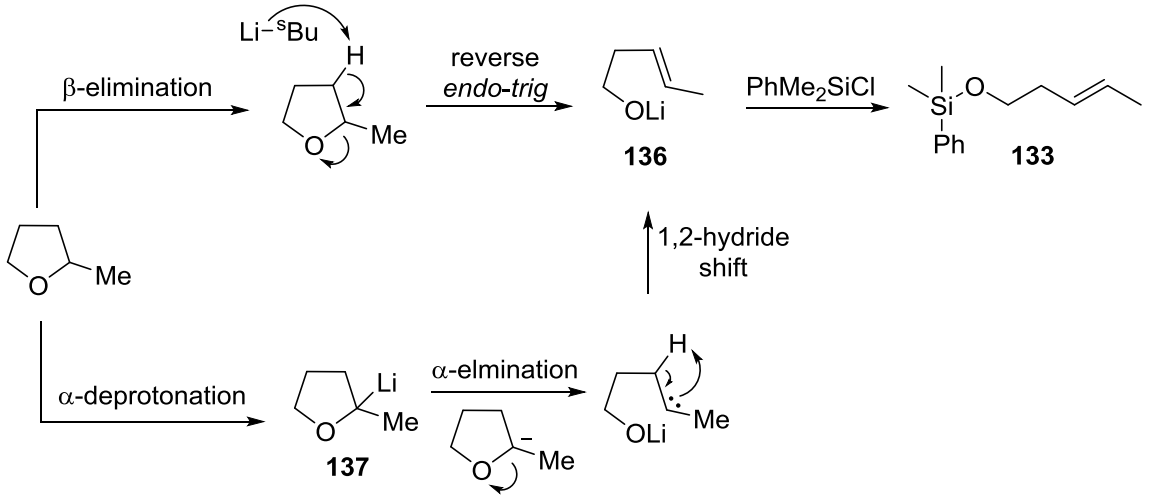
Although an independent synthesis of internal alkene **133** was not carried out, we compared the ^{1}H NMR spectroscopic data to known internal alkenes **134** and **135** with a different silyl protecting group (Figure 3.4). The chemical shifts of the alkene protons for (*E*)-alkene **134** are δ_H 5.53-5.37[91] and for (*Z*)-alkene **135** are δ_H 6.06-4.83.[92] Based on the ^{1}H NMR spectroscopic data, we tentatively assigned the internal alkene product as **133** (with an *E*-alkene stereochemistry).

Figure 3.4



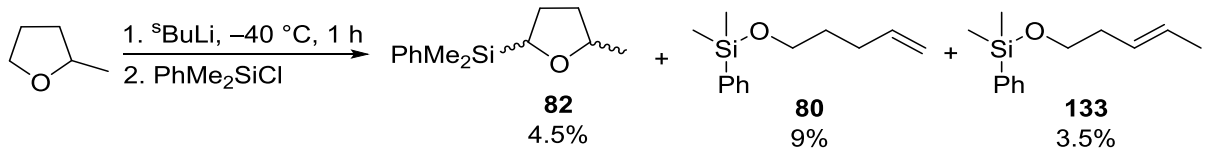
The synthesis route of (*E*)-alkene **133** from 2-MeTHF has not been reported before. We suggest two possible pathways for formation of the internal alkene (Scheme 3.36). *s*-BuLi could remove a β-proton in a β-elimination pathway to give lithiated alkoxide **136**. However, it should be noted that the geometry is unfavourable for E2-elimination in these five-membered ring compounds and the reverse 5-*endo-trig* is a Baldwin-disfavoured reaction (see Scheme 1.18).[93] The other possible pathway involves the α-lithiation of 2-MeTHF to give **137** followed by a 1,2-hydride shift to give **136**. However, this pathway is unlikely to happen due to the steric hindrance of the α-proton by the methyl group.

Scheme 3.36



Based on the TMEDA-mediated reactions at –78 °C and –40 °C, we suspected that the *s*-BuLi/TMEDA complex favoured the β-elimination pathway over the α-deprotonation. In order to investigate whether the presence of TMEDA is important for the lithiation-trapping of 2-MeTHF, lithiation of 2-MeTHF was carried out in the absence of TMEDA at –40 °C (Scheme 3.37). In this reaction, two inseparable mixture, a 20:10:70 mixture (by ^{1}H NMR spectroscopy) of terminal alkene **80**, internal alkene **133** and silyl 2-MeTHF **82** and a 75:25 mixture (by ^{1}H NMR spectroscopy) of terminal alkene **80** and internal alkene **133**, were isolated. In total, this corresponds to a 4.5% yield of the desired silyl 2-MeTHF **82**, a 9% yield of terminal alkene **80** and a 3.5% yield of internal alkene **133**.

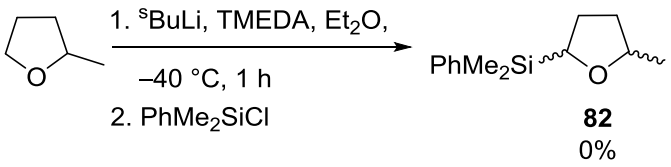
Scheme 3.37



The formation of silyl 2-MeTHF **82** under the diamine-free lithiation conditions was encouraging. Based on our results, we presume that the TMEDA is a more activating ligand for β-elimination than 2-MeTHF.

We then investigated whether the lithiation could be carried out in Et_2O under similar reaction conditions (Scheme 3.38). However, the ^{1}H NMR spectrum of the crude product showed no identifiable products.

Scheme 3.38

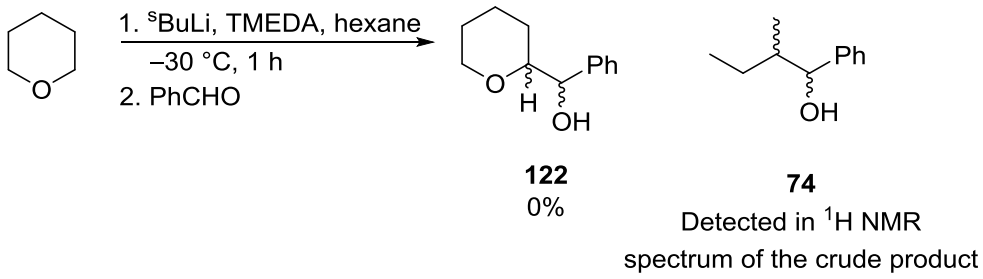


In summary, reaction conditions for the lithiation-trapping of 2-MeTHF were explored. Based on the results, the lithiation works best when using diamine-free conditions in 2-MeTHF as substrate and solvent at –40 °C for 1 h. However, less than 5% yield of the α-substituted 2-MeTHF **82** was obtained. TMEDA is considered to be an important factor for the 2-MeTHF lithiation as the β-elimination pathway (either at the methyl group or at the C-3 position) is more favourable when *s*-BuLi/TMEDA was used.

3.3 Lithiation-trapping of THP

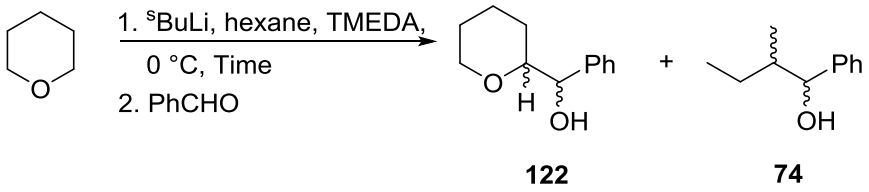
In this section, lithiation of the 6-membered ring oxygen heterocycle, THP, was studied. As discussed before, Schlosser reported that THP reacted approximately 25 times slower than THF, so we expected lithiation to be slower and it is likely that higher temperatures would be needed.[81] Unlike THF, the advantage of THP is that metallated THP could not undergo a retro [3+2] pathway for decomposition. Thus, the lithiation of THP might work satisfactorily at high temperatures. The inert solvent, hexanes was chosen for the lithiation of THP as it could be used at higher temperatures. Therefore, we started the investigation using 1 equivalent of THP as substrate lithiated using the *s*-BuLi/TMEDA in hexane at –30 °C (Scheme 3.39). The solution was stirred at –30 °C for 1 h before trapping with benzaldehyde as the electrophile. However, no α-substituted THP **122** was found in the ^{1}H NMR spectrum of the crude product. Instead, only the direct trapping product, alcohol **74** was observed.

Scheme 3.39



As we suspected that the *s*-BuLi/TMEDA complex was not reactive enough to lithiate THP at –30 °C, a higher temperature (0 °C) with longer lithiation times (1 or 2 h) were explored and the results are summarised in Table 3.3. In general, lithiation for both 1 and 2 h gave similar yields of a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **122** (29% and 26% respectively). As the diastereomeric alcohols **122** were inseparable, the ratio was calculated from the ^{1}H NMR spectrum of the mixture. The two 1H doublet signals at δ_H 4.83 and 4.43 which were assigned to the proton adjacent to the phenyl and OH group, indicated that the mixture contains a 50:50 ratio of diastereomers. Spectroscopic data were consistent with those reported in the literature.[127]

Table 3.3

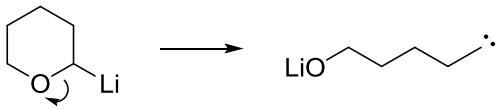


122 **74**

Entry	Time (h)	122 Yield (%)	74 Yield (%)
1	1	29	38
2	2	26	18

Based on the yield of the alcohol **74**, it appeared that more lithiation occurred for the 2 h lithiation. However, less diastereomeric alcohols **122** were formed. Presumably, the lithiated THP was chemically unstable and decomposed during the longer lithiation time. One of the possible decomposition pathways is the ring-opening of the lithiated THP which can generate carbene **138** (Scheme 3.40). Currently, however, we have no evidence to identify the decomposition pathway of the lithiated THP.

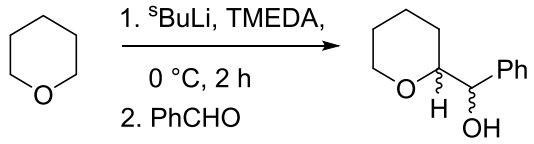
Scheme 3.40



138

Although lithiation for 1 h gave a slightly higher yield of diastereomeric alcohol **122**, we wanted to see if a better yield could be achieved by using THP as substrate and solvent for a 2 h lithiation using *s*-BuLi/TMEDA (Scheme 3.41). Surprisingly, the ^{1}H NMR spectrum of the crude product showed no identified products. We presume that all of the *s*-BuLi reacted with THP to generate lithiated THP which is chemically unstable during 2 h and this led to decomposition (*via* the pathway we suggest in Scheme 3.40) to unidentified compounds.

Scheme 3.41



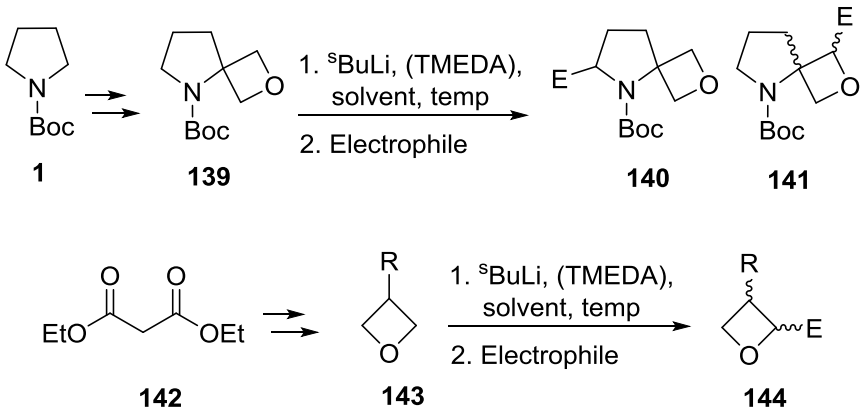
122
0%

In summary, lithiation of THP can be achieved using s-BuLi/TMEDA complex in hexane at 0 °C for 1 h. However, as the lithiated THP is chemically unstable at 0 °C for a certain amount of time, more investigation is needed to identify the optimised lithiation conditions.

3.4 Synthesis and Lithiation-trapping of Substituted Oxetanes

In this part of the project, we decided to explore the synthesis and α-functionalisation of the 4-membered cyclic ether, oxetane. Our proposed plans are summarised in Scheme 3.42. In one project, we planned to synthesise bicyclic *N*-Boc pyrrolidine oxetane **139** (starting from *N*-Boc pyrrolidine **1**) and study its lithiation-trapping. There are two possible deprotonation sites for *s*-BuLi to lithiate the α-substituted *N*-Boc pyrrolidine oxetane **139** (either α-position to the pyrrolidine ring or the oxetane ring). We hoped to identify conditions that would lead to α-nitrogen (to give **140**) and α-oxygen (to give **141**) lithiation. In the second project, more simple oxetane **143** (with suitable R groups to ensure that the oxetanes were not too volatile to work with) would be synthesised from diethyl malonate **142**. Then, their α-lithiation-trapping would be studied to give **144**, including diastereoselectivity aspects.

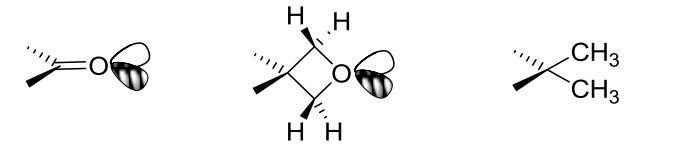
Scheme 3.42



3.4.1 Introduction to Oxetanes and Oxetane Synthesis

There is an increase of interest in compounds containing the oxetane in medicinal chemistry in the last two decades. The initial attention began as some pharmaceutical studies suggested that the 3-substituted oxetane is a good alternative group for carbonyl groups.[94,95,96] By comparing the electrophilic reactivity of the carbonyl group and 3-substituted oxetanes, compounds containing carbonyl groups might cause undesirable covalent binding whereas the more sterically hindered oxetanes could reduce any unwanted binding. Moreover, 3-substituted oxetanes and aliphatic carbonyl groups have a similarly high hydrogen bonding activity. Thus, compounds with oxetanes as surrogates for carbonyls are becoming more common as versatile building blocks in drug-like structures. In addition, oxetanes can also be considered a polar alternative to *gem*-dimethyl groups, which are commonly found in medicinal chemistry to introduce steric bulk. By comparing the carbonyl, oxetanyl and *gem*-dimethyl group (Figure 3.5), the oxetanyl group has the largest volume of occupancy and deeper oxygen placement suggesting a better shielding to prevent unnecessary covalent binding.

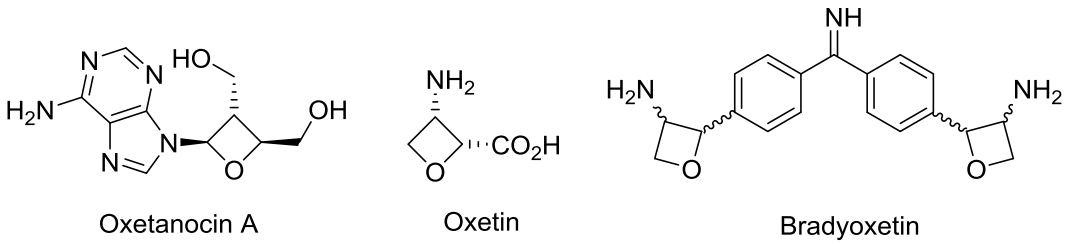
Figure 3.5



Carbonyl group Oxetanyl group *gem*-dimethyl group

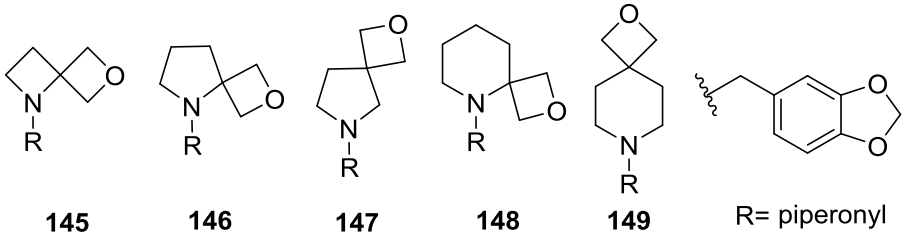
The pharmaceutical interest of oxetane was also extended to 2-substituted oxetanes as it is present in many natural products with a range of biological activities (Figure 3.6). For example, oxetanocin A was first isolated from the soil bacterium *Bacillus megaterium* NK84-0218 which inhibits the replication of HIV.[97] Oxetin was isolated from the fermentation broth of *Streptomyces sp.* OM-2317 and initial studies suggested that it presents herbicidal as well as antibacterial effects.[98] Bradyoxetin was found to be an extracellular secreted factor that is involved in symbiotic gene regulation in soybean.[99] The synthetic routes to these oxetane molecules involve different synthetic strategies but generally the formation of 2-substituted oxetanes involves intramolecular Williamson ether synthesis.

Figure 3.6



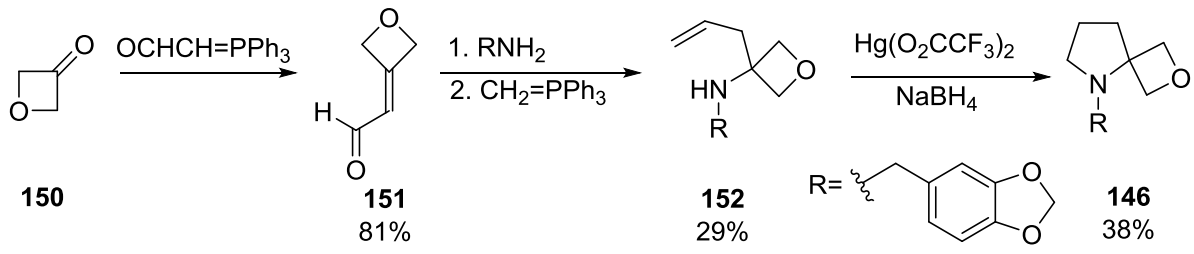
In 2008, Roger-Evans *et al.* studied a selection of spirocyclic oxetane amines which provide interesting 3-D-shapes building blocks for drug discovery (Figure 3.7).[95] By studying the physicochemical and biochemical properties of the spirocyclic oxetane amines **145-149** and compared them with the corresponding cyclic ketoamines and *gem*-dimethyl-substituted amines, they suggested that oxetane could be considered as a surrogate in the spirocyclic amines by introducing steric bulk to the molecules without increasing lipophilicity, while at the same time increasing aqueous solubility and keeping the metabolic stability of the compound.

Figure 3.7



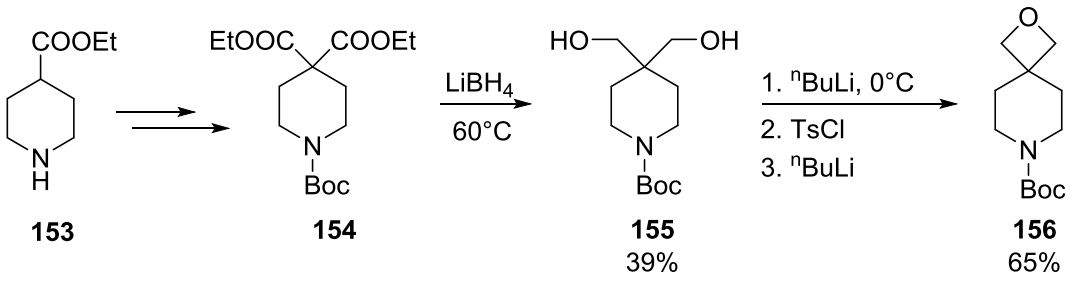
There are not many published synthetic routes to spirocyclic oxetane amines. In 2008, Carreira and co-workers reported a method to synthesise spirocyclic oxetane amine **146** (Scheme 3.43). Aldehyde **151** was prepared by reaction of commercially available oxetan-3-one **150** with the formylmethylene Wittig reagent. After the conjugate addition of an amine, a Wittig reaction gave **152**. Finally, cyclisation *via* electrophilic addition gave the desired oxetane **146**. In this approach, the oxetane ring was present at the start. Although oxetan-3-one **150** is commercially available, its expensive price is one of the limitations for this synthetic route.

Scheme 3.43



Xu *et al.* illustrated a different strategy to construct the oxetane ring from the readily available starting material ethyl isonipecotate **153** (Scheme 3.44).[100] Boc protection and addition of an ester at C-4 gave diester **154**. Reduction of diester **154** was carried out using $LiBH_4$ to give diol **155** in 39% yield. Diol **155** was cyclised to oxetane **156** *via* mono-tosylate. Tosylation of one alcohol of **155** was achieved using 1 equivalent of *n*-BuLi and TsCl. Addition of another 1.0 equivalent of *n*-BuLi deprotonated the alcohol (at 60 °C) which then cyclised to give oxetane **156** in 65% yield (Scheme 3.44).

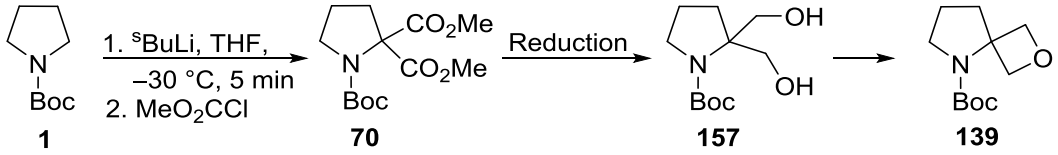
Scheme 3.44



3.4.2 Attempted Synthesis of *N*-Boc 2-oxa-5-azaspiro-[3,4] octane

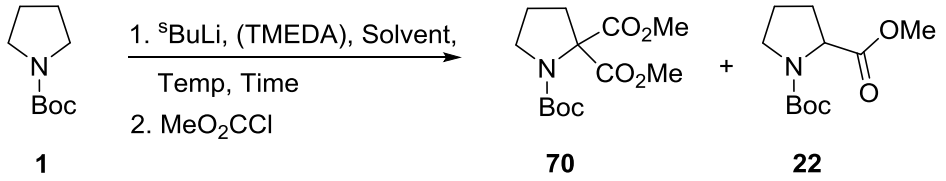
Since the synthesis of α-substituted *N*-Boc pyrrolidine oxetane **139** has not been reported before, we wondered whether we could synthesise it *via* a lithiation route. Our proposed plan is shown in Scheme 3.45. In 2010, our group reported the conversion of *N*-Boc pyrrolidine **1** into α,α-disubstituted methyl ester pyrrolidine **70** using 2.6 equivalent of *s*-BuLi and 3.0 equivalent of MeO_2CCl.[15] Thus, we planned to use this procedure to prepare **70**. Next, based on the procedures in Scheme 3.44, we would synthesise the oxetane ring *via* reduction of diester **70** to diol **157** followed by cyclisation.

Scheme 3.45



To start with, we investigated a range of conditions for the double lithiation-trapping of *N*-Boc pyrrolidine **1**. The results are shown in Table 3.4. In general, double lithiation-trapping using *s*-BuLi/THF complex at –78 °C gave the best yield (60%) of di-ester **70** with 10% of single substituted product **22** (entry 1). Subsequently, higher temperature lithiation in THF at –30 °C was attempted but the yield was lower (50% yield) (entry 2). We presumed that the excess of *s*-BuLi affected the yield and generated more side-products in the reaction. Thus, lithiation at –30 °C for 5 min with a reduced amount (2.0 eq.) of *s*-BuLi was tried but the yield of di-ester **70** improved only slightly with more mono-ester **22** isolated (18% yield) (entry 3). Lithiation at –20 °C gave a lower yield of di-ester **70** (45% yield) and this possibly suggested that the lithiated intermediate was chemically unstable and decomposed (entry 4).

Table 3.4



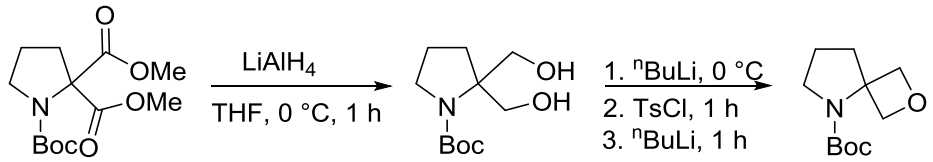
Entry	Solvent	*s*-BuLi (eq.)	Temp (°C)	Time	70 Yield (%)	22 Yield (%)
1	THF	2.6	–78	1 h	60	10
2	THF	2.6	–30	5 min	50	7
3	THF	2.0	–30	5 min	53	18
4	THF	2.2	–20	5 min	45	14
5	2-MeTHF	2.6	–78	1 h	53	24
6	2-MeTHF	2.2	–20	5 min	38	26
7	Et_2O with TMEDA	2.6	–30	5 min	21	0
8	2-MeTHF with TMEDA	2.6	–78	1 h	24	30

In comparison to diamine-free lithiation in THF, lithiation using the *s*-BuLi/2-MeTHF complex generally gave a lower yield of di-ester **70** (38-53% yield) (entries 5-6). More mono-ester **22** were found in the reactions (24-26% yield) suggesting the *s*-BuLi/2-MeTHF complex is less efficient in carrying out the enolate formation. TMEDA-mediated lithiation in Et_2O and 2-MeTHF generally gave poor yields (21-24%) of di-ester **70** (entries 7 and 8).

In summary, double lithiation-trapping *N*-Boc pyrrolidine **1** using the *s*-BuLi/THF complex at –78 °C gave the best yield (60%) of di-ester **70**. There was no difference in the yields of di-ester **70** but more mono-ester **22** generated when the equivalents of *s*-BuLi were reduced. This suggested that 2.0 equivalent was not enough to carry out full double lithiation.

Next, di-ester **70** was reduced using $LiAlH_4$ to give a 51% yield of diol **157** (Scheme 3.46). We then tried the cyclisation to give oxetane **139** *via* the tosylation of diol **157**. Treatment of diol **157** with 1 equivalent of *n*-BuLi and TsCl at 0 °C for 1 h should have given the mono-tosylate. Addition of another 1.0 equivalent of *n*-BuLi and reaction for 1 h at 0 °C did not give oxetane **139**. A longer reaction time for the cyclisation step was attempted but no oxetane **139** was found.

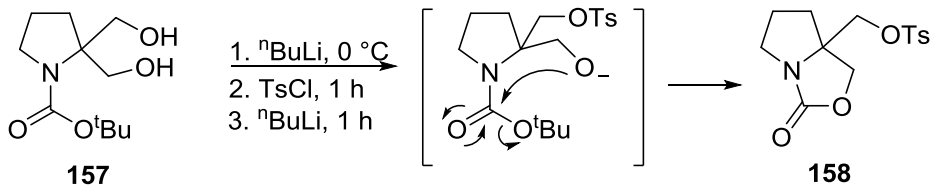
Scheme 3.46



70 **157** 51% **139** 0%

One of the possibilities to explain the unsuccessful cyclisation is that after the tosylation of one alcohol, the other alcohol was deprotonated by another equivalent of *n*-BuLi. Instead of attacking the carbon next to the tosylated oxygen to form the oxetane ring, it could cyclise onto the carbonyl in the Boc group to give **158** (Scheme 3.47). However, we could find no evidence for **158** in the ^{1}H NMR spectrum of the crude product.

Scheme 3.47



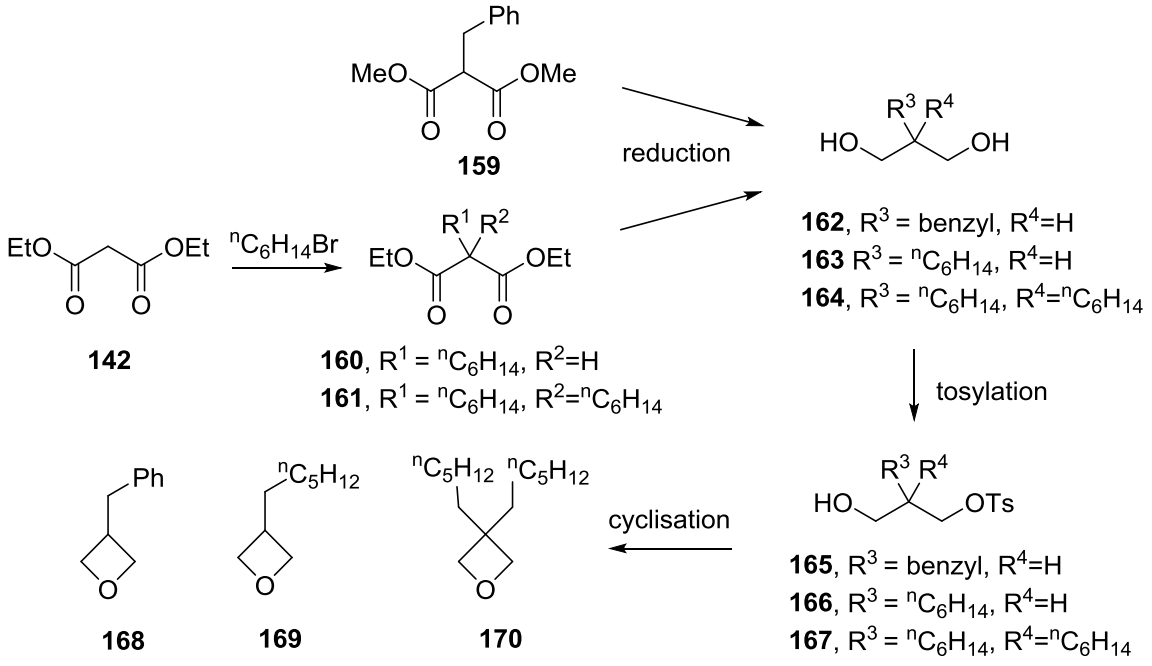
157 **158**

In summary, the synthesis of *N*-Boc pyrrolidine oxetane **139** has been explored. The best reaction conditions for the double lithiation of *N*-Boc pyrrolidine **1** are 2.6 equivalent of *s*-BuLi at –78 °C for 1 h in THF. However, the cyclisation of diol **157** was unsuccessful. It is presumed that the second deprotonated alcohol cyclised onto the carbonyl in the Boc group instead of the attacking the carbon next to the tosylated oxygen. Further investigation is needed for the characterisation the tosylated pyrrolidine separately before the final cyclisation step.

3.4.3 Synthesis and Lithiation-trapping of 3-substitued Oxetanes

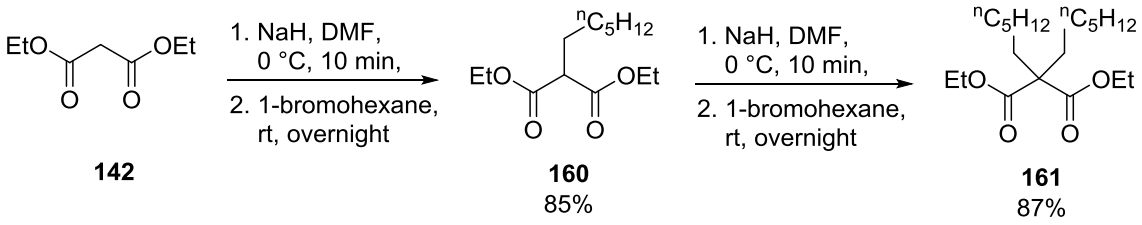
In this part of the project, synthesis and lithiation of 3-substitued oxetanes was carried out. Our plan to synthesise 3-substitued oxetanes **168**, **169** and **170** is shown in Scheme 3.48. The general route involves simple steps [101, 102] from the inexpensive starting material, diethyl malonate **142** or dimethyl benzyl malonate **159**, *via* alkylation of the malonate, reduction of the ester, mono-tosylation and cyclisation to give 3-substitued oxetanes **168**, **169** and **170**.

Scheme 3.48



We started with the alkylation of diethyl malonate **142** using NaH in DMF at 0 °C (Scheme 3.49). The mixture was then stirred with 1-bromohexane overnight at rt to give 2-hexylmalonate **160** in 85% yield following a literature procedure.[103] A second alkylation of 2-hexylmalonate **160** can be carried out under the same reaction conditions and this gave gave 2,2-dihexylmalonate **161** in 87% yield (Scheme 3.49).

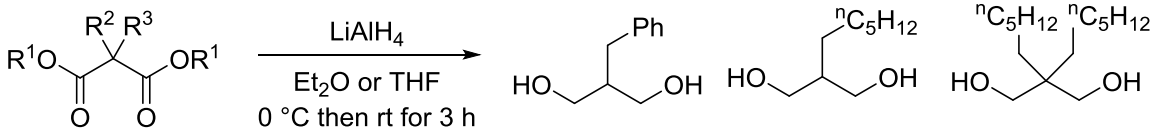
Scheme 3.49



142 | **160** 85% | **161** 87%

Reduction of 3-substituted malonates **159**, **160** and **161** was carried out using 4 equivalents of $LiAlH_4$ in Et_2O or THF at 0 °C (Scheme 3.50). The reaction mixtures were then warmed to rt for 3 h to give diols **162**-**164** in very good yields (85-93%). The full conversion of the reactions was confirmed by the ^{1}H NMR spectrum. For example, the ^{1}H NMR spectrum of diol **162** showed that there were two new ddd signals (4H integration) at δ_H 3.81 and 3.68 which suggested that the carbonyl group had been reduced to a CH_2 group. The ^{13}C NMR spectrum also indicated that the carbon signal for the carbonyl group (δ_C 174.5 in **160**) disappeared and there was a new signal at δ_C 65.7 due to the new OCH_2 group. The spectroscopic data of diols **162**, **163** and **164** were all consistent with those reported in the literature.[104,105,106]

Scheme 3.50

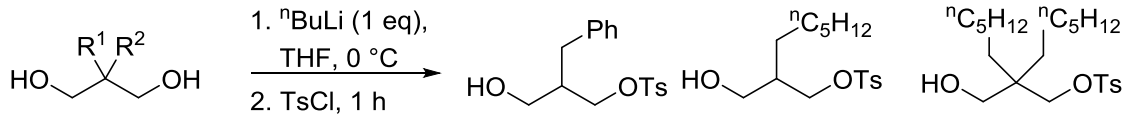


159, R^1=Me, R^2=benzyl, R^3=H
160, R^1=Et, R^2=$^{n}C_6H_{14}$, R^3=H
161, R^1=Et, R^2=$^{n}C_6H_{14}$, R^3=$^{n}C_6H_{14}$

162 93% (Et_2O) | **163** 85% (THF) | **164** 90% (THF)

Subsequently, diols **162**, **163** and **164** were deprotonated by 1 equivalent of *n*-BuLi at 0 °C. Then, *p*-TsCl was added to give good yields (83-90%) of tosylates **165**, **166** and **167** (Scheme 3.51). The ^{1}H and ^{13}C NMR spectra of tosylates **165**, **166** and **167** confirmed that only one alcohol had been tosylated.

Scheme 3.51



162, R^1 = benzyl, R^2=H
163, R^1 = $^nC_6H_{14}$, R^2=H
164, R^1 = C_6H_{14}, R^2=$^nC_6H_{14}$

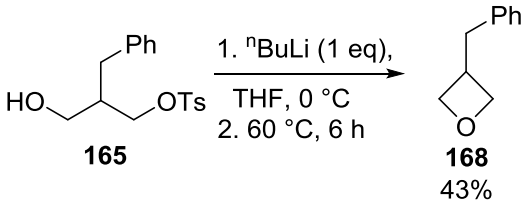
165 83%

166 88%

167 90%

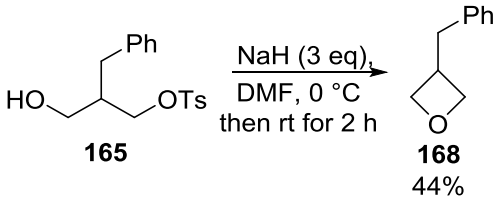
A literature procedure for the cyclisation of tosylate **165** was then followed.[100] Tosylate **165** was cyclised by using 1 equivalent of *n*-BuLi in THF at 0 °C. The reaction solution was heated at 60 °C for 6 h to give 3-benzyl oxetane **168** in a moderate 43% yield (Scheme 3.52). The ^{1}H NMR spectrum of 3-benzyl oxetane **168** confirmed that the product contains 4 protons adjacent to oxygen, each integrating for 2H, with signals at δ_H 4.79 (dd) and 4.48 (dd).

Scheme 3.52



We then tried an alternative cyclisation pathway to see if the yield could be improved. Tosylate **165** was deprotonated by using 3 equivalents of NaH in DMF at 0 °C. Then, the solution was allowed to warm to rt for 2 h to give the desired product in 44% yield (Scheme 3.53). Although both of the cyclisation procedures gave a very similar yield, we decided to cyclise tosylates **166** and **167** using NaH as it did not require heating.

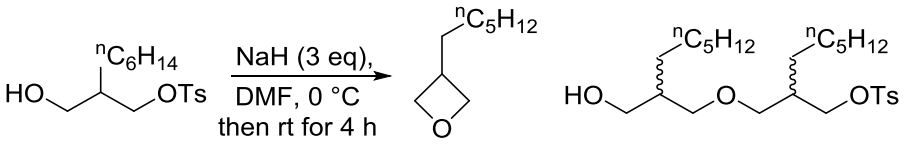
Scheme 3.53



Cyclisation of tosylate **166** using the NaH reaction conditions gave a good yield of 3-hexyloxetane **169** (71%). However, frustratingly, when the reaction was repeated under the

same reaction conditions, only a 15% yield of oxetane **169** was isolated and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric tosylates **171** (9% yield) was also observed. The formation of tosylates **171** was due to the lithium alkoxide reacting with another tosylate **166**. The presence of this compound explained the low yield of the desired product, oxetane **169**, as two equivalents of tosylate **166** are consumed for the formation of it. This result may also suggest that the intermolecular reaction of tosylate **165** could have happened here to account for the low yield (44%) of oxetane **168**. However, we did not find any evidence for the intermolecular reaction of tosylate **165**.

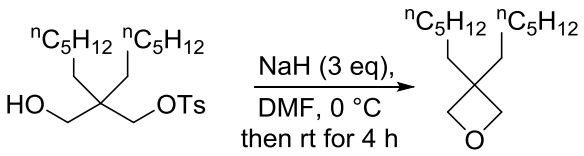
Scheme 3.54



166 | **169** 71% 15% (repeat) | **171** 0% 9% (repeat)

Next, the cyclisation of tosylate **167** using the NaH reaction conditions was carried out but it was unsuccessful (Scheme 3.55). One of the possibilities to explain this result is that an intermolecular reaction occurred (as with **166**). However, the ^{1}H NMR spectrum of the crude product showed no identifiable products.

Scheme 3.55

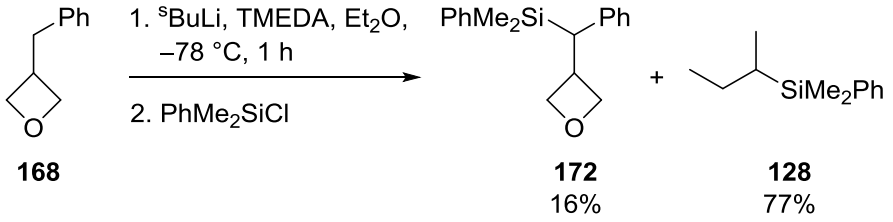


167 | **170** 0%

After the successful synthesis of oxetanes **168** and **169**, the lithiation-trapping of both these 3-substituted oxetanes was explored at low temperature. 3-Benzyl oxetane **168** was lithiated using *s*-BuLi/TMEDA in Et_2O at –78 °C before trapping with $PhMe_2SiCl$ (Scheme 3.56). This gave a 77% yield of silane **128** and an inseparable 66:34 mixture (by ^{1}H NMR spectroscopy) of silylated oxetane **172** and $PhMe_2SiCl$. This corresponds to a 16% yield of silylated oxetane **172**. In this reaction, deprotonation did not take place at the α-oxygen position but at the benzylic position. This suggested that the benzylic proton is

more acidic and could be a competitive site for deprotonation. In addition, a significant amount of silane **128** was recovered indicating that the lithiation was slow at –78 °C.

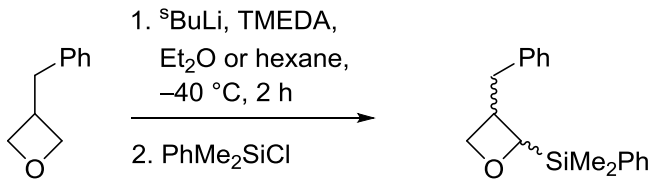
Scheme 3.56



168 **172** 16% **128** 77%

Since the *s*-BuLi/TMEDA complex did not lend to α-deprotonation at low temperature (–78 °C), we decided to explore the lithiation at higher temperatures. The potential drawback for high temperature lithiation of 3-benzyl oxetane **168** was that the deprotonation of the benzylic proton would be competing with the desired α-deprotonation. Lithiation of 3-benzyl oxetane **168** using *s*-BuLi/TMEDA complex was attempted at –40 °C for 2 h (Scheme 3.57). However, the ^{1}H NMR spectrum of the crude product showed no identifiable products. We suspected that some of the *s*-BuLi might have reacted with Et_2O at –40 °C, so we decided to investigate the lithiation conditions using hexane as solvent at similar reaction conditions. Disappointingly, no identifiable product was found. Since there was no starting material **168** or direct trapping product, silane **128** recovered, we suspected that the *s*-BuLi reacted with the oxetane **168** and, the lithiated oxetane is chemically unstable at –40 °C and decomposed.

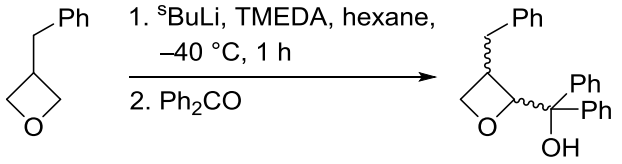
Scheme 3.57



168 **173** 0%

Hence, lithiation in hexane was carried out at –40 °C for a shorter lithiation time. After lithiating in hexane at –40 °C for 1 h and trapping with a different electrophile, benzophenone, no desired product was formed (Scheme 3.58).

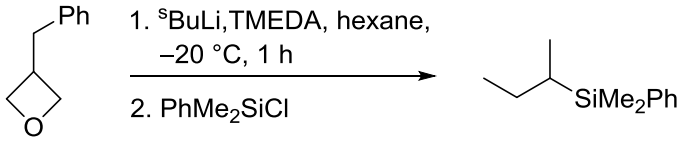
Scheme 3.58



168 **174** 0%

Since the lithiation gave no product at –40 °C, we decided to lithiate 3-benzyl oxetane **168** at –20 °C. However, lithiation using *s*-BuLi/TMEDA at –20 °C gave the direct trapping product, silane **128** (25% yield), and an unidentified mixture (Scheme 3.59). No starting material **168** or the α-substituted product **173** was found.

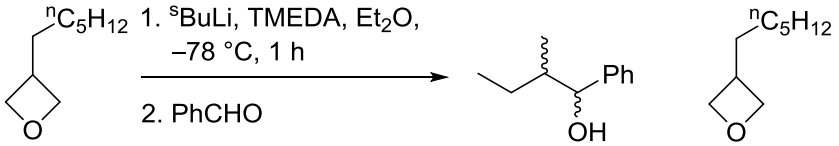
Scheme 3.59



168 **128** 25%

Next, lithiation-trapping of 3-hexyl oxetane **169** was explored. Unlike the competitive benzylic proton deprotonation of 3-benzyl oxetane **168**, deprotonation of 3-hexyl oxetane **169** should only occur at the α-oxygen position. Hence, lithiation of 3-hexyl oxetane **169** using *s*-BuLi/TMEDA in Et_2O was carried out at –78 °C followed by trapping with benzaldehyde (Scheme 3.60). In this reaction, a 64% yield of a 50:50 mixture (by ^1H NMR spectroscopy) of diastereomeric alcohols **74** was obtained, together with a 57% yield of recovered starting material. The recovery of the 3-hexyl oxetane **169** and the large amount of the direct trapping product **74** formed suggested that the lithiation of 3-hexyl oxetane **169** was slow at –78 °C.

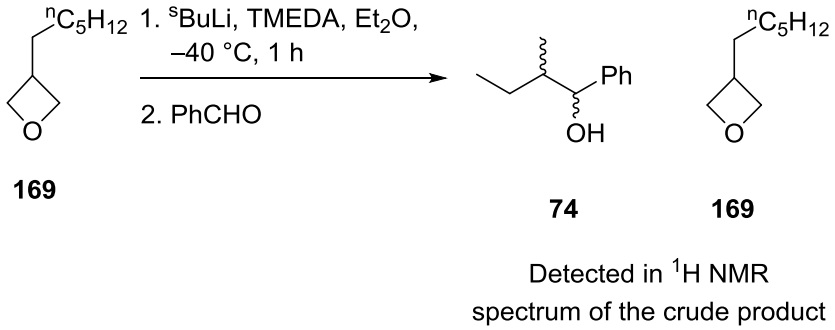
Scheme 3.60



169 **74** 64% **169** 57%

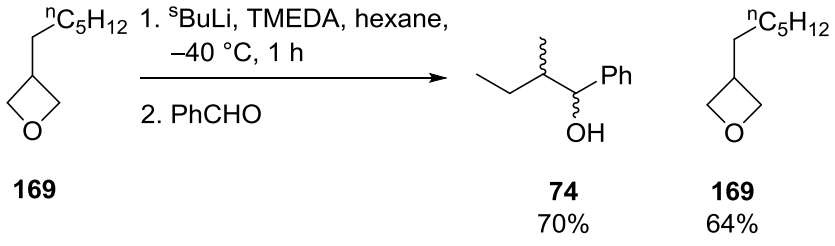
Subsequently, lithiation of 3-hexyl oxetane **169** was explored at higher temperatures. 3-hexyl oxetane **169** was lithiated using *s*-BuLi/TMEDA in Et_2O at –40 °C (Scheme 3.61). After trapping with benzaldehyde, the crude product contained a 56:44 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** and starting material **169**. As the ^{1}H NMR spectroscopy of the crude product showed no α-substituted product, we decided to investigate the lithiation conditions using hexane as solvent under similar reaction conditions.

Scheme 3.61



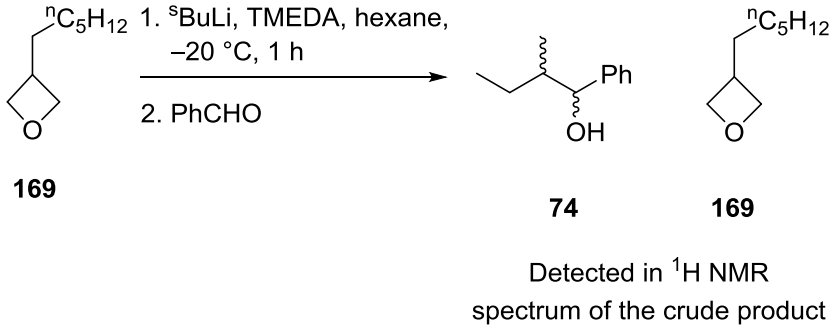
TMEDA-mediated lithiation in hexane was carried out under similar reaction conditions at –40 °C which is shown in Scheme 3.62. Disappointingly, a similar result was obtained. The reaction gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (70% yield) and starting material **169** (64% yield).

Scheme 3.62



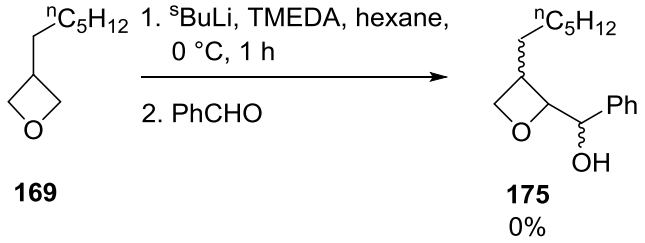
The recovery of a large amount of the starting material **169** for the lithiation at –40 °C indicated that the 3-hexyl oxetane **169** is not a reactive substrate. Hence, we decided to lithiate 3-hexyl oxetane **169** under similar reaction conditions at –20 °C (Scheme 3.63). However, the ^{1}H NMR spectrum of the crude product showed no desired product, Instead, a 55:45 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** and starting material **169** was formed.

Scheme 3.63



Finally, the lithiation of 3-hexyl oxetane **169** was attempted at 0 °C (Scheme 3.64). However, ^{1}H NMR spectroscopy of the crude product showed no desired product and purification was not attempted.

Scheme 3.64

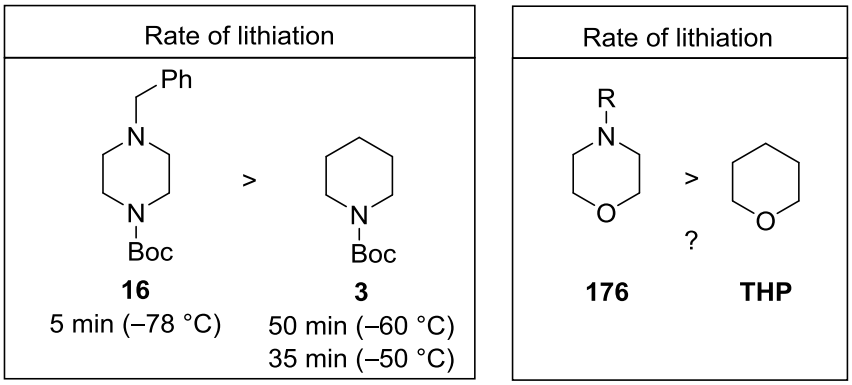


In summary, the synthesis and α-functionalisation of 3-substituted oxetanes **168**, **169** and **170** was explored. The synthetic route to 3-substituted oxetanes **168**, **169** and **170** *via* alkylation of the malonate, reduction of the ester and tosylation generally gave very good yields. Cyclisation of 3-benzyl tosylate **165** using 3 equivalents of NaH in DMF at 0 °C gave a moderate yield of 3-benzyl oxetane **168** (44%). When cyclisation of 3-hexyl tosylate **166** using similar reaction conditions was carried out, an intermolecular reaction of the alkoxide with another tosylate **166** occurred. The lithiation-trapping of 3-benzyl oxetane **168** and 3-hexyl oxetane **169** was attempted at –78 °C, –40 °C, –20 °C and 0 °C in different solvents. In the lithiation of **168** at –78 °C, deprotonation did not take place at the α-oxygen position but at the benzylic position to form the silylated oxetane **172**. This suggested that the benzylic proton is more acidic and it could be a competitive site for deprotonation. Disappointingly, all attempts at the α-lithiation-trapping of 3-substituted oxetanes were unsuccessful.

3.5 Lithiation-trapping of *N*-Substituted Morpholines

In this part of the project, an exploration of α-functionalisation of *N*-substituted morpholines using lithiation-trapping methodology will be presented. Based on the previous studies with *N*-Boc heterocycles within our group, the lithiation of *N*-Boc-*N*'-benzyl piperazine **16** takes a relatively shorter time than the lithiation of *N*-Boc piperidine **3** (Figure 3.8). Since the lithiation of THP is very slow, this led us to consider whether a similar trend will be observed on the reactivity of oxygen heterocycles, and that the *N*-substituted morpholines **176** will be more reactive towards lithiation than THP. In addition, decomposition of the lithiated morpholine *via* the retro [3+2] pathway would not be an issue.

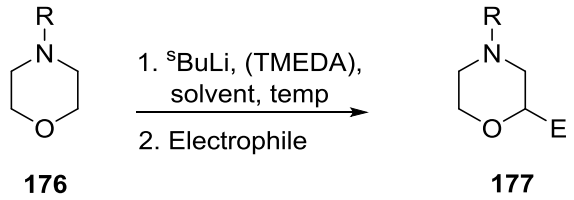
Figure 3.8



Lithiation using ^{s}BuLi/TMEDA complex

Hence, lithiation-trapping of *N*-substituted morpholines **176** with different R groups will be studied (including diastereoselectivity by introducing a chiral R group), along with a full exploration of the reaction conditions and limitations of the methodology (Scheme 3.65).

Scheme 3.65

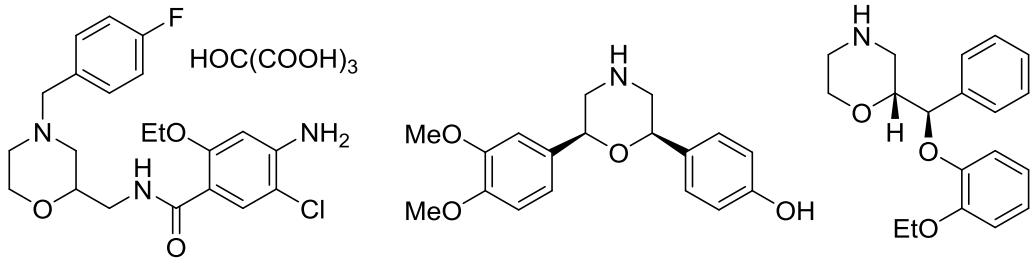


176 **177**

3.5.1 Introduction to Morpholines and 2-substituted Morpholine Synthesis

Morpholines are six-membered heterocycles that contain both amine and ether functional groups. Substituted morpholine derivatives are commonly found as sub-units in various natural products and biologically active compounds (Figure 3.9). For example, an α-substituted morpholine, mosapride citrate, is a gastroprokinetic agent that acts as a selective 5HT4 agonist to treat severe reflux oesophagitis or gastroesophageal reflux disease (GORD), to relieve symptoms like heartburn and dyspepsia.[107] A 2,6-disubstituted morpholine derivative, Chelonin C, is a natural product that is isolated from the marine sponge *Chelonaplysilla sp.* It exhibited antimicrobial activity against *Bacillus subtilis* and also an anti-inflammatory effect.[108,109] Noradrenaline reuptake inhibitor, Reboxetine, is used in the treatment of depressive disorder.[6] It is marketed as a racemic mixture of the (*R,R*) and (*S,S*) enantiomers but recent studies suggested that (S,S)-Reboxetine is more potent than its enantiomer with a better affinity and selectivity for the noradrenaline transporter (NAT).[110]

Figure 3.9

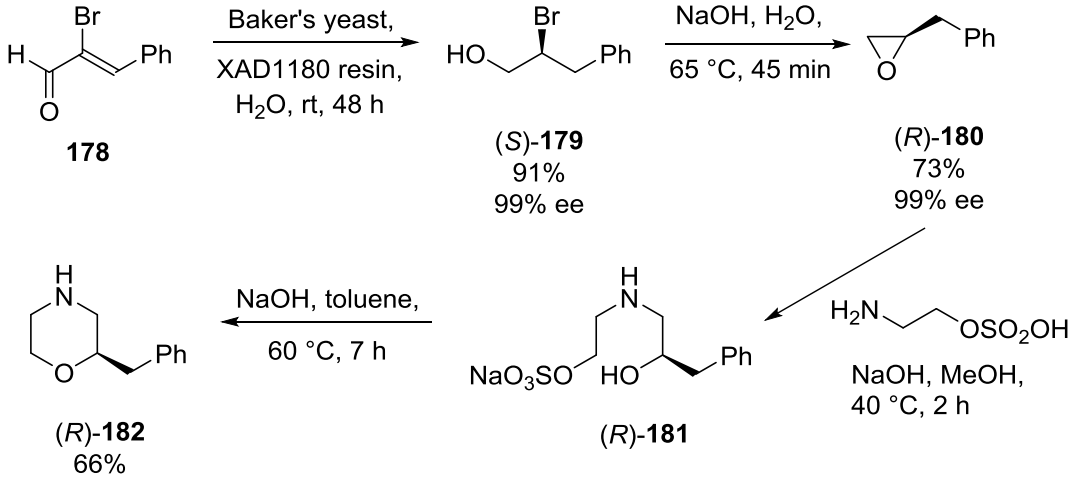


Although 2-substituted morpholines are often used as building blocks for a range of biologically active compounds, currently there is a very limited methodology for the direct introduction of functionality at the C-2 position α to oxygen.[111] Given that there is an increase of interest in compounds containing 2-substituted morpholines, there are a growing number of publications on developing different synthetic strategies. Generally, the synthesis of morpholines with a 2-substituent requires multiple steps to construct the morpholine ring, and substituents are often introduced with enantioselectivity at an early stage.

In 1998, Servi reported a chemo-enzymatic synthetic route to construct the *N*-H morpholine ring with a substituent adjacent to the oxygen (Scheme 3.66). [112]

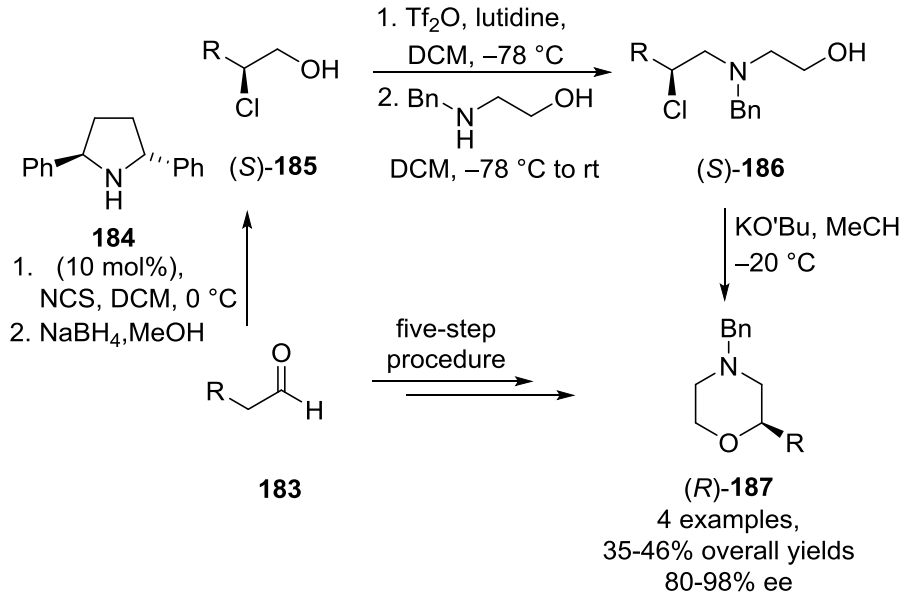
Enantioselective reduction of aldehyde **178** using an excess of Baker's yeast and XAD1180 resin in water gave bromo alcohol (*S*)-**179** in good yields and good % ee. Bromo alcohol (*S*)-**179** was then cyclised using NaOH to give benzyl epoxide **180** with (*R*) configuration. Benzyl epoxide (*R*)-**180** was reacted with ethanolamine-O-sulfate and NaOH to give (*R*)-**181** and subsequent cyclisation using NaOH gave 2-benzyl morpholine (*R*)-**182**.

Scheme 3.66



Lindsley illustrated a different strategy for the enantioselective synthesis of 2-substituted morpholines (*R*)-**187** *via* α-chlorination of aldehydes using organocatalysis (Scheme 3.67).[113] 2-Chloro alcohol (*S*)-**185** was prepared by α-chlorination of aldehydes using Jørgensen catalyst **184.**

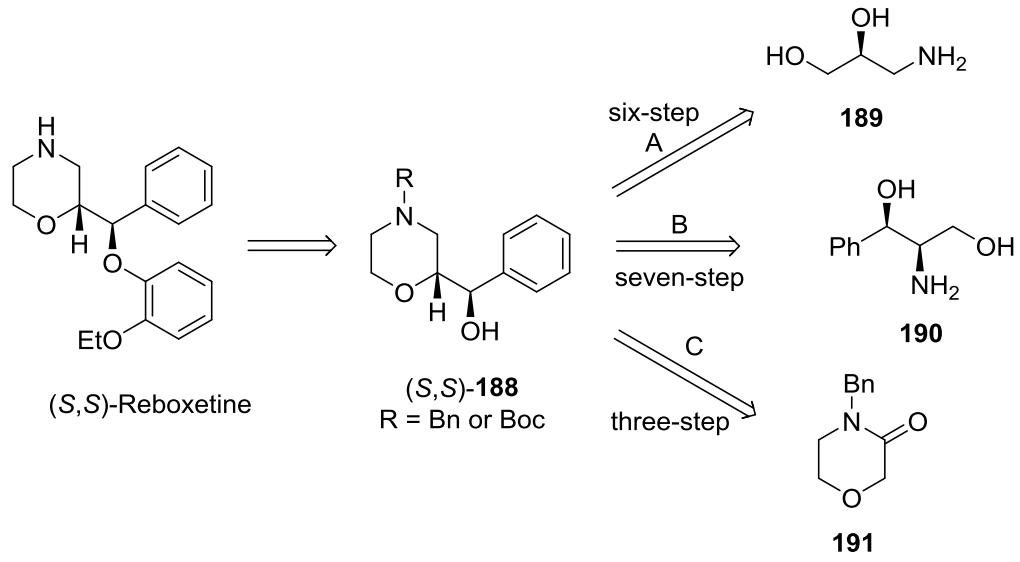
Scheme 3.67



After the reduction of the aldehyde using $NaBH_4$, activation of 2-chloro alcohol **185** with trific anhydride and nucleophilic substitution with *N*-benzylethanolamine gave (*S*)-**186** in good yields. Finally, base-induced cyclisation of (*S*)-**186** gave the desired 2-substituted *N*-benzyl morpholine (*R*)-**187** in 35-46% overall yields with 80-98% ee. Four different substituents were demonstrated in a five-step procedure.

As mentioned before, Reboxetine is an effective compound used in the treatment of depressive disorder and it has been widely studied for its pharmacological properties. Given the higher degree of interest in one of the enantiomers, (*S*,*S*)-Reboxetine, there is much demand in developing enantiomerically enriched synthesis routes. Generally, the synthesis of (*S*,*S*)-Reboxetine proceeds *via* the intermediate hydroxyl morpholine (*S*,*S*)-**188** with different *N*-protecting groups. As a result, numerous research groups have developed different strategies for the asymmetric synthesis of hydroxyl morpholine (*S*,*S*)-**188**. The challenges for the preparation of enantiomerically pure 2-substituted morpholine (*S*,*S*)-**188** are the long synthetic sequences and the choice of starting materials. There are other synthetic strategies for the formation of 2-substituted morpholine (*S*,*S*)-**188** but only three examples are listed here for brevity (Scheme 3.68).

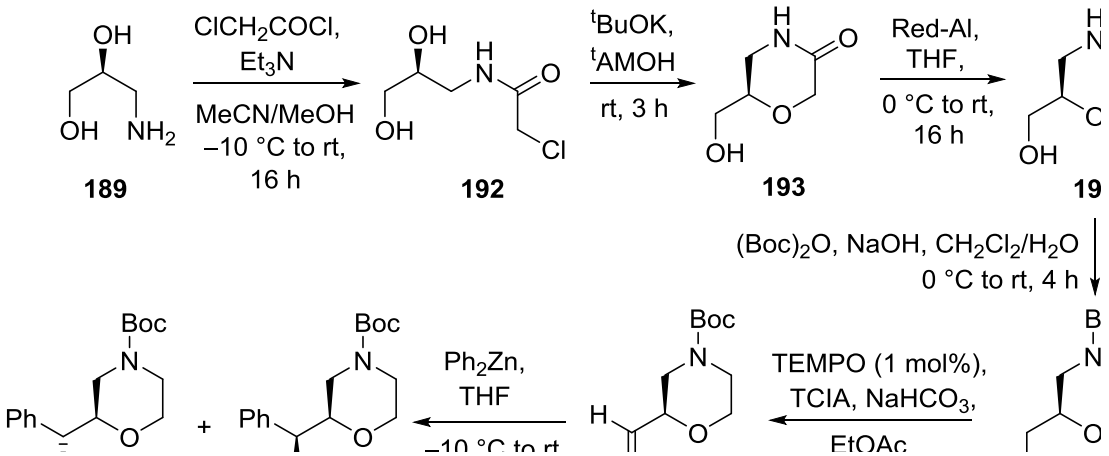
Scheme 3.68



In 2005, Tamagnan reported an asymmetric synthesis of (*S*,*S*)-Reboxetine *via* a new route to (*S*)-2-(hydroxymethyl)morpholine.[114] Their approach was to build the chiral morpholine moiety **188** before introducing the phenyl group and arloxy groups (Scheme 3.69). The synthesis started from commercially available 3-amino-1,2-propanediol (*S*)-**189**. Reaction

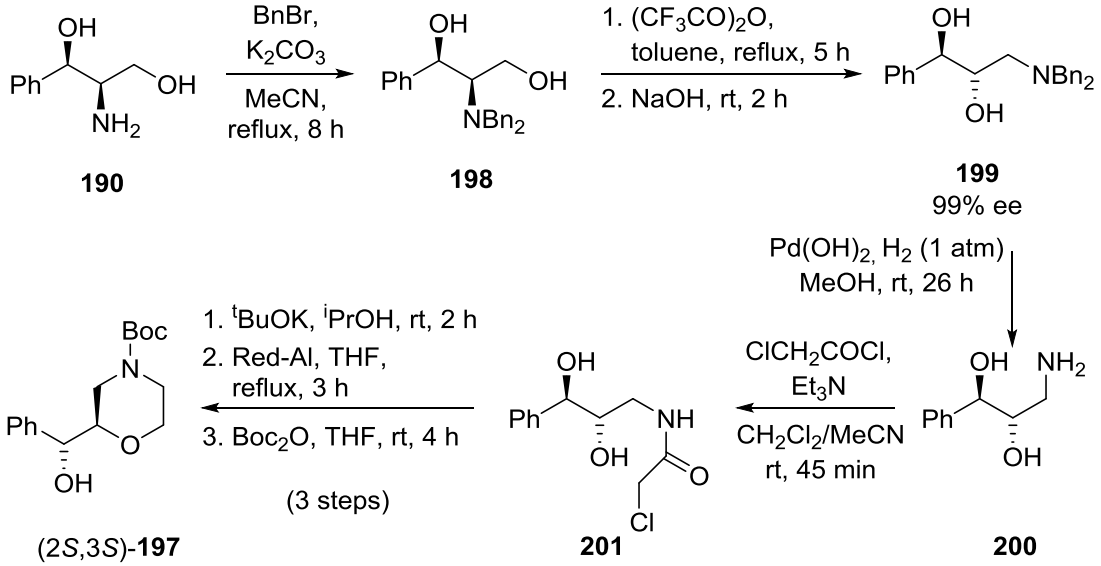
with chloroacetyl chloride gave amide **192** which was cyclised using *t*-BuOK to give morpholinone **193**. The morpholinone **13** was then reduced using Red-Al to **194** and Boc-protected to give **195**. Oxidation of **195** was initially attempted under Swern conditions but significant epimerization was observed. Consequently, oxidation using TEMPO under catalytic conditions gave aldehyde **196** in high enantiomeric purity. The phenyl group was introduced by adding aldehyde **196** to Ph_2Zn which was prepared *in situ* from PhMgBr and anhydrous $ZnBr_2$. The resulting diastereomers (2*S*,3*S*)-**197** and (2*S*,3*R*)-**197** were separated by flash chromatography and isolated in 60% and 19% respectively.

Scheme 3.69



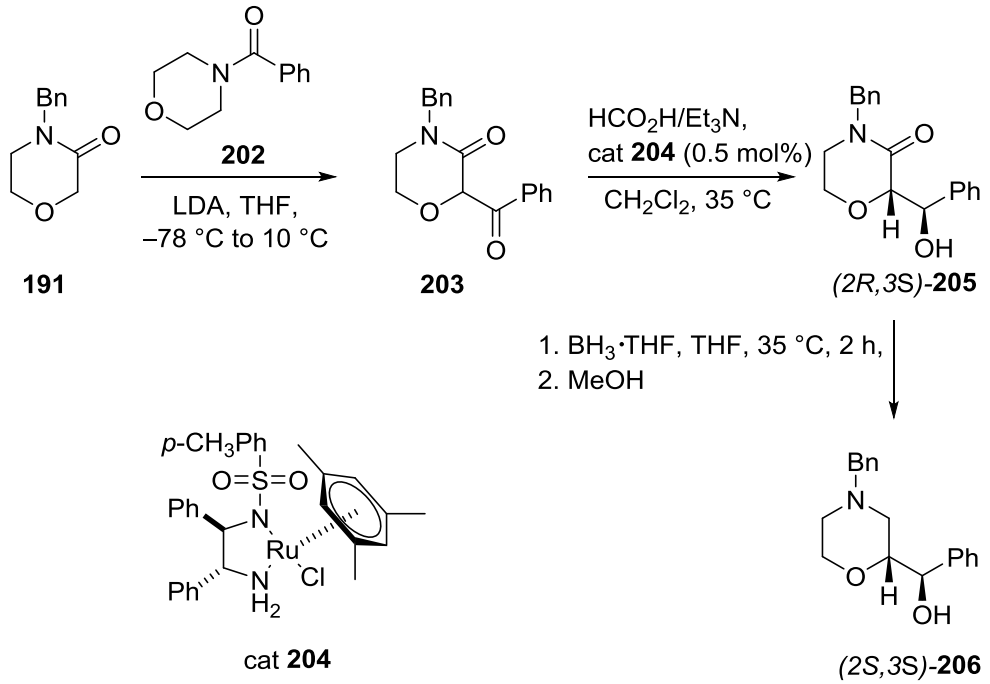
In 2008, Cossy reported an alternative route for the synthesis of intermediate morpholine (*S*,*S*)-**197** *via* a catalytic stereospecific rearrangement of β-amino alcohols.[115] The synthesis started with the *N*,*N*-dibenzylation of the commercially available **190** to give the corresponding tertiary amine **198** (Scheme 3.70). Reaction of amine **198** with $(CF_3CO)_2O$ gave the rearranged amine **199**. Subsequently, the benzyl group was removed to give **200** and substituted with chloroacetyl chloride to obtain **201**. Cyclisation using *t*-BuOK followed by another two-step sequence of oxidation and Boc protection gave (2*S*,3*S*)-**197**.

Scheme 3.70



Recently, Lee provided a short synthetic sequence that enables simultaneous stereochemical control of two contiguous stereogenic centres in a single step. The approach involves asymmetric transfer hydrogenation (ATH) of 2-substituted morpholinone **203** using a chiral transition metal catalyst (Scheme 3.71).

Scheme 3.71

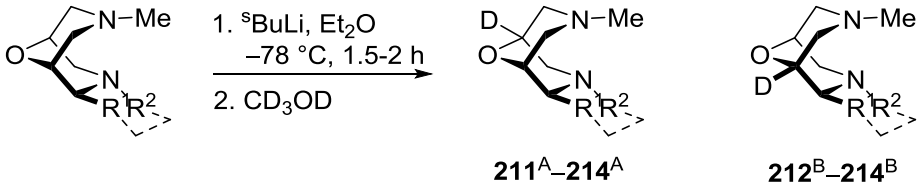


The racemic 2-substituted morpholinone **203** was prepared by Claisen condensation of morpholinone **191** and morpholine **202** using LDA. When the Ru-cataylst **204** was employed for the asymmetric transfer hydrogenation, an enantioselective reduction of the ketone took place to give (2*R*,3*S*)-**205**. The excellent stereoselectivity was due to the C-2 proton in **203** being configurationally labile, which results in a rapid racemisation of the substrate under the ATH reaction conditions. The reaction thus proceeds *via* a dynamic kinetic resolution. Finally, morpholinone **205** was reduced using BH_3•THF to give (2*S*,3*S*)-**197**.

Although these three examples provided (2*S*,3*S*)-**188** in high enantiomeric purity, most of these methods required the utilisation of expensive chiral catalysts or long (6-7 steps) reaction sequences.

The most related precedent for our proposed lithiation-trapping approach to 2-substituted morpholines was reported by Breuning. In 2009, Breuning reported an effective protocol for the direct lithiation of 9-oxabispidines **207-210** using *s*-BuLi which enabled stable α-lithio ethers to be formed and trapped with electrophiles (Table 3.5). Deprotonation of **207-210** using *s*-BuLi at –78 °C in Et_2O followed by quenching with CD_3OD gave the monodeuterated oxabispidines **211-214** in good yields (75-89%) and with high deuterium incorporation (73-100%) (entries 1-3).

Table 3.5



211^{A}–**214**^{A} **212**^{B}–**214**^{B}

Entry	Starting material	R^1	R^2	Product	Isolated yield (%)	D incorporation (%)	A/B[a]
1	**207**	H	Me	**211**^{A}	89	100	**211**^{A} = **211**^{B}
2	**208**	Et	Me	**212**^{A}	86	85	100:0
3	**209**	Ph	Me	**213**^{A}	75	73	100:0
4	**210**	-$(CH_2)_4$-		**214**	85	100	55:45

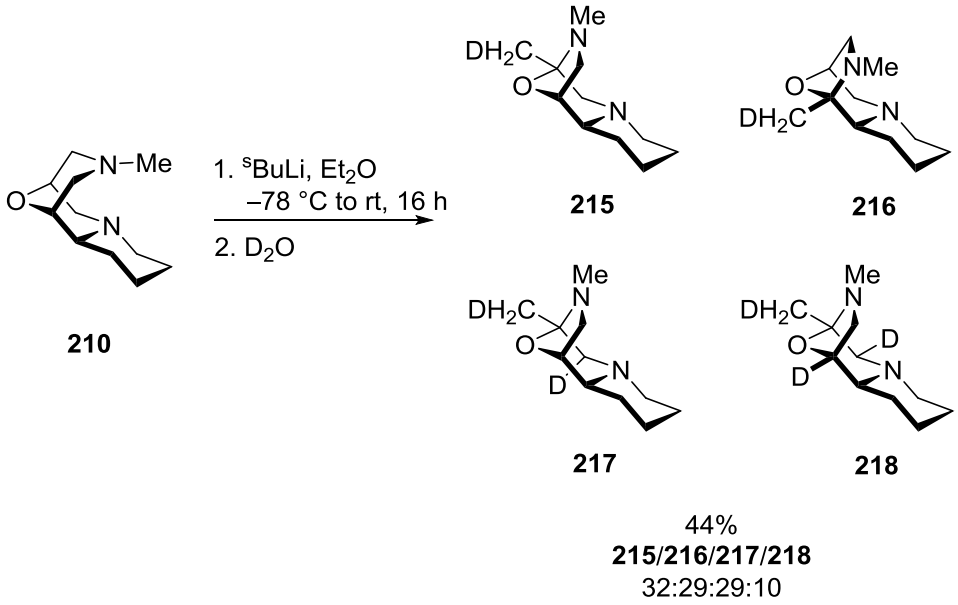
[a] Ratio determined from the ^{1}H NMR spectrum.

The formation of regioisomers **212**[A] and **213**[A] from the unsymmetric bicyclic systems **208** and **209** indicated a strong steric hindrance of the bridgehead proton at C-1 by the substituents (Et and Ph groups) (entries 2 and 3). However, there was no significant differentiation in the deprotonation of tricyclic diamine **210** (entry 4). Oxabispidines **207-210** benefit from double activation (two β-nitrogen atoms) which explains the successful α-lithiation at –78 °C.

Breuning also investigated the use of a weaker organolithium under the same reaction conditions. However, no reaction was observed at –78 °C with *n*-BuLi. The presence of a ligand in the reaction was also studied although the result indicated that an extra ligand (*e.g.* (–)-sparteine or TMEDA) is not required to activate the deprotonation.

When the tricyclic oxabispidines **210** was lithiated and slowly warmed to room temperature in the absence of an electrophile, a rearrangement reaction occurred (Scheme 3.72). By quenching the crude mixture with D_2O, they were able to obtain a 44% yield of a 32:29:29:10 mixture (by NMR spectroscopy) of compounds **215-217**.

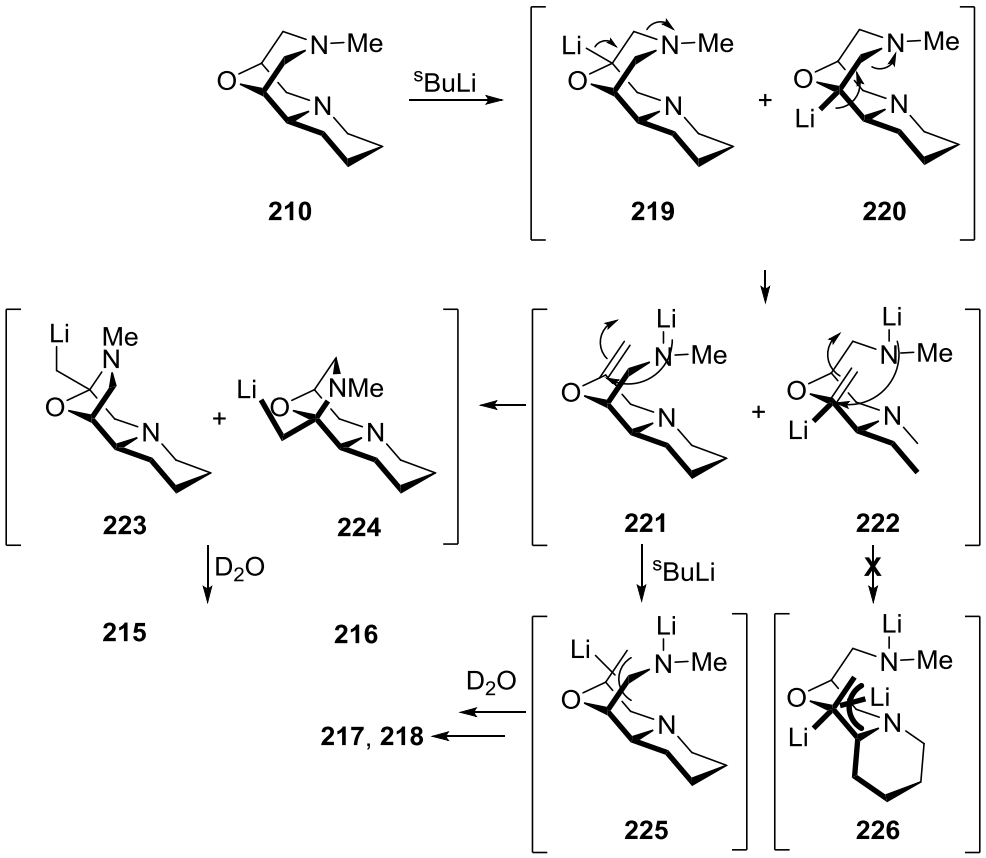
Scheme 3.72



A mechanism for the deprotonation-rearrangement of **210** was proposed. The initial unselective deprotonation of **210** would give the lithiated intermediate **219** and **220** at –78 °C (Scheme 3.73). As the temperature increased, the lithiated intermediates would become chemically unstable and β-elimination would occur. For the formation of **223** and **224**, intramolecular cyclisation of the amide group in **221** and **222** towards the enol ether could

take place to form **223** and **224**, which would then be deuterated to give the observed products **215** and **216**. In contrast, the formation of **217** and **218** is probably due to the fact that the intermediate **221** was lithiated again to give the stabilised allylic anion **225**. However, the intermediate **222** appeared to be resistant for further lithiation. Hence, intermediate **226** is unlikely to happen.

Scheme 3.73

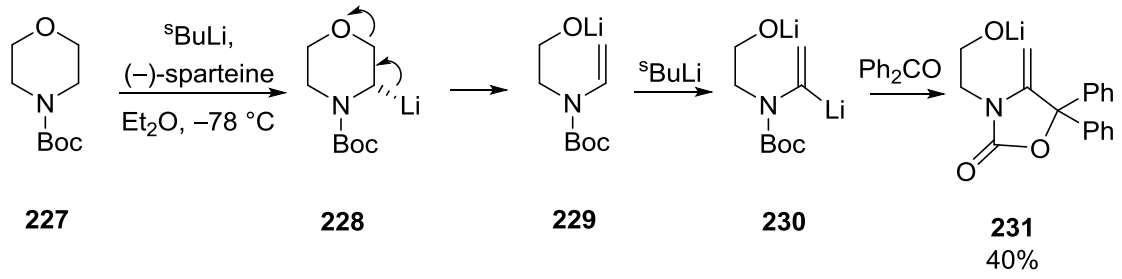


In summary, there is limited methodology to directly introduce functionalities into morpholines at the C-2 position. Functionalisation of morpholine with a 2-substituent often requires multiple synthetic steps and substituents are often introduced with enantioselectivity at the early stage, mostly before the cyclisation step. However, it requires using reactive materials, expensive catalysts and long synthetic steps to construct the enantiopure morpholine. The only lithiation-trapping route to 2-substituted morpholines is a very specific substrates, oxabispidines, as reported by Breuning.

3.5.2 Lithiation-trapping of *N*-substituted Morpholines

Since the direct functionalisation of monocyclic *N*-substituted morpholines has not been reported before, we wondered whether we could apply our newly developed α-oxygen lithiation methodology to morpholine derivatives. Based on the previous studies within our group, *N*-Boc morpholine **227** was found to undergo lithiation extremely rapidly at the α-nitrogen position even at low temperature. The lithiation reached completion within one minute when using the *s*-BuLi/(–)-sparteine complex at –78 °C (as shown by ReactIR spectroscopy).[11,12] When the lithiation was carried out using 2.6 equivalents of *s*-BuLi/(–)-sparteine, rapid deprotonation resulted in the formation of lithiated intermediate **228** which was found to be unstable (Scheme 3.74). Under the reaction conditions, the lithiated intermediate **228** undergoes ring-opening to give alkoxide **229**. After a subsequent vinylic lithiation which gave **230**, the intermediate was trapped with benzophenone and subsequent intramolecular cyclisation gave oxazolidinone **231** in 40% yield.

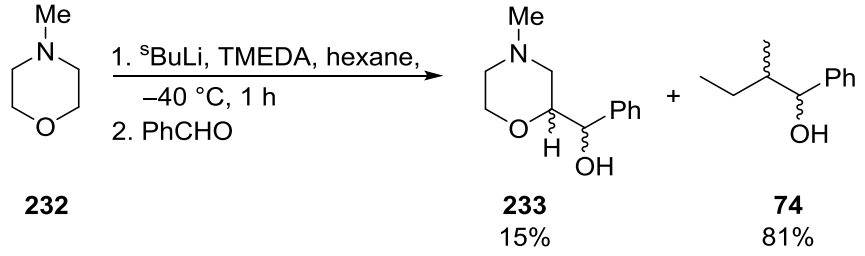
Scheme 3.74



As *N*-Boc morpholine **227** would lithiate at the α-nitrogen position, we considered whether morpholine lithiation could be achieved at the α-oxygen position with a different *N*-protecting group. Hence, lithiation-trapping of morpholine with different *N*-protecting groups is studied in this section.

We started the investigation by using commercially available *N*-methyl morpholine **232**. 1 equivalent of *N*-methyl morpholine **232** was lithiated using *s*-BuLi/TMEDA in hexane at –40 °C (Scheme 3.75). The reaction mixture was stirred for 1 h before trapping with benzaldehyde as the electrophile. After purification by column chromatography, an inseparable 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** was isolated in 15% yield. We also isloated an inseparable 50:50 mixture (by ^{1}H NMR spectroscopy) of the direct trapping product, diastereomeric alcohols **74**, in 81% yield.

Scheme 3.75

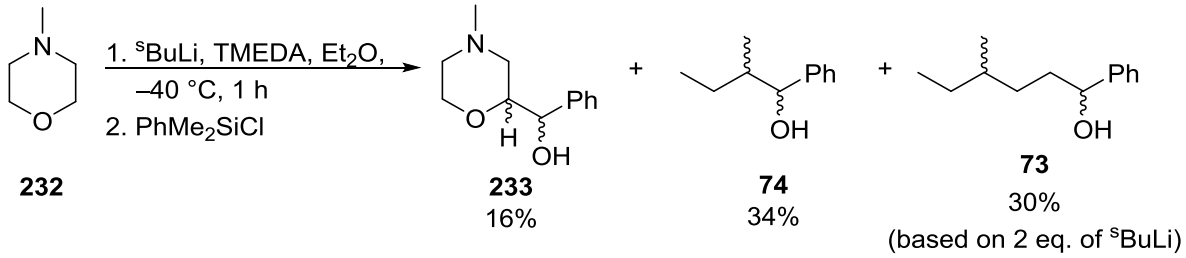


232 **233** 15% **74** 81%

To confirm that the isolated product was the desired 2-substituted morpholine **233**, the structure was carefully analysed by ^{1}H NMR spectroscopy. There were three signals at δ_H 4.03-3.92 (m, 1H), 3.79-3.67 (m, 1.5H) and 3.62 (ddd, 0.5H) which were assigned to protons adjacent to the oxygen, together with signals between δ_H 2.66-1.85 (4H) which were assigned to protons adjacent to the nitrogen. This confirmed that the lithiation-trapping took place at the C-2 α-oxygen position. As the diastereomeric alcohols **233** were inseparable, the ratio was calculated from the two 1H broad singlets at δ_H 4.89 and 4.52 which were assigned to the proton adjacent to the phenyl group and OH group.

Then, lithiation of *N*-methyl morpholine **232** was carried out using *s*-BuLi/TMEDA in Et_2O at –40 °C (Scheme 3.76). A similar yield of a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** was isolated (16%). The reaction also gave a 34% yield of diastereomeric alcohols **74** and the carbolithiation product **73** in 30% yield (based on 2 equivalents of *s*-BuLi). Since the carbolithiation product can only a generated from the solvent, Et_2O is not a suitable solvent for this chemistry.

Scheme 3.76

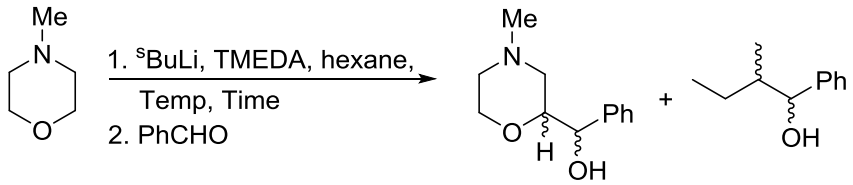


232 **233** 16% **74** 34% **73** 30% (based on 2 eq. of sBuLi)

The result of the lithiation at –40 °C for 1 h was an encouraging 15% yield of diastereomeric alcohols **233** with complete α-oxygen regioselectivity. However, the high yield of alcohols **74** suggested that the *s*-BuLi was not reacting completely with the morpholine at –40 °C for 1 h. It led us to further explore the lithiation conditions. Hence,

lithiation of *N*-methyl morpholine **232** was carried out using *s*-BuLi/TMEDA at various temperatures and lithiation times (Table 3.6). When morpholine **232** was lithiated at –40 °C for a longer time (3 h), the yield of the desired product increased to 42% with a decrease in the yield of alcohols **74** (entry 2). In general, as the lithiation temperature increased, higher yields of diastereomeric alcohols **233** were isolated. At 0 °C, lithiation for 1 h gave an excellent 89% yield of diastereomeric alcohols **233** with only a 2% yield of alcohols **74** (entry 6). Since we used an excess of *s*-BuLi (1.3 eq.) for the lithiation, we believe that the lithiation was fully completed in 1 h at 0 °C. When the lithiation was carried out at 20 °C for shorter lithiation times, the yields of the desired product **233** were lower (entries 7-8) but with no trace of alcohols **74** found. This suggested to us that the lithiated morpholine was chemically unstable at 20 °C and decomposed to some extent.

Table 3.6

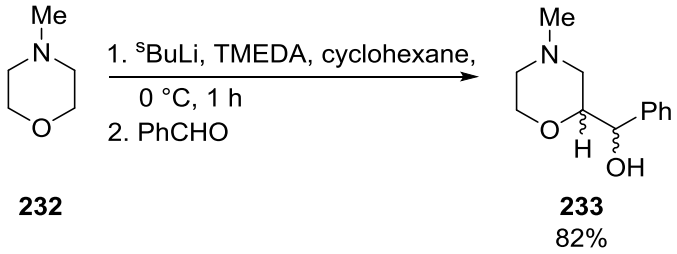


232 **233** **74**

Entry	Temp (°C)	Time	233 Yield (%)	74 Yield (%)
1	–40	1h	15	81
2	–40	3h	42	52
3	–30	1h	40	52
4	–30	2 h	49	37
5	–20	1h	63	43
6	0	1h	89	2
7	20	10 min	66	0
8	20	30 min	48	0

Up to this point, the conditions using *s*-BuLi/TMEDA in hexane at 0 °C for 1 h gave the best yield of the 2-substituted morpholine **232**. When the lithiation takes place in cyclohexane under similar reaction conditions, a similar high yield of diastereomeric alcohols **233** were obtained (82%) (Scheme 3.77).

Scheme 3.77



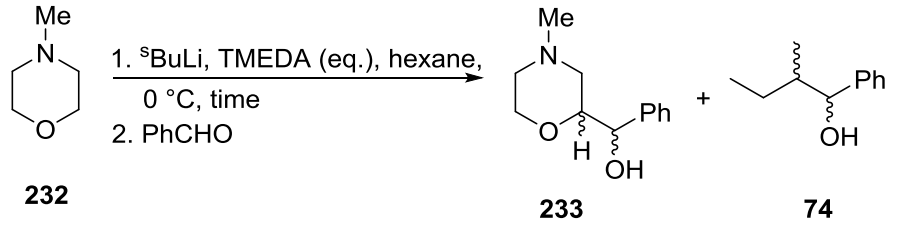
232 **233** 82%

As discussed in section 3.5.1, lithiation of bicyclic morpholines **207**-**209** does not require an extra diamine to activate the lithiation. Hence, we wanted to investigate whether TMEDA is needed for our new morpholine lithiation. Lithiation-trapping of *N*-methyl morpholine **232** was performed using *s*-BuLi with various equivalents of TMEDA at 0 °C for various lithiation times. The results are summarised in Table 3.7.

Lithiation using the standard 1.3 equivalents of TMEDA gave the highest yield of diastereomeric alcohols **233** (89%) (entry 1). As the equivalents of TMEDA were reduced from 1.3 to 0.1 for reactions under the same conditions, the yields of the desired products decreased (68-82%) with more alcohols **74** being generated (5-16%) (entries 2-4). This trend suggested that the lithiation of *N*-methyl morpholine **232** was not completed within 1 h at 0 °C when catalytic TMEDA was used.

Subsequently, we decided to carry out the catalytic lithiation for longer lithiation times. Despite this, lithiation using 0.05 equivalents of TMEDA for 2 h gave a lower 68% yield of diastereomeric alcohols **233** and a 16% yield of alcohols **74** (entry 5). An even worse yield of diastereomeric alcohols **233** was obtained (27%) when the lithiation was carried out with 0.01 equivalents and a 4 h lithiation time (entry 6). When diamine-free lithiation was carried out in hexane for 1 h, there was no desired product **233** formed but a 74% yield of alcohols **74** was isolated (entry 6). A longer reaction time (2 h) for the diamine-free conditions in hexane was unsuccessful as well (entry 8). Based on the results of the catalytic lithiation, TMEDA is required to activate the *s*-BuLi for lithiation of *N*-methyl morpholine **232**. As the equivalents of TMEDA were decreased in the lithiation, a longer reaction time was necessary to allow the deprotonation to proceed towards completion. However, the fact that a lithiation that is catalytic in TMEDA could be achieved is a significant discovery.

Table 3.7

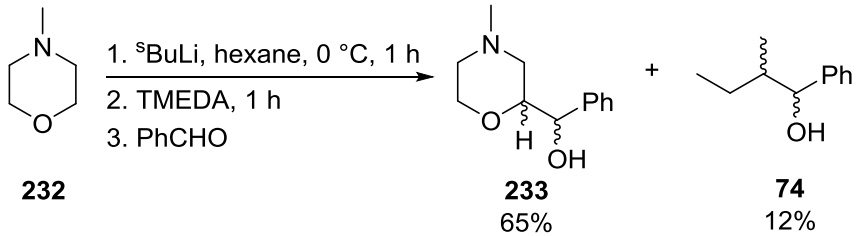


232 **233** **74**

Entry	TMEDA (eq.)	Time (h)	233 Yield (%)	74 Yield (%)
1	1.3	1	89	2
2	0.5	1	82	9
3	0.2	1	79	15
4	0.1	1	72	15
5	0.05	2	68	16
6	0.01	4	27	48
7	0	1	0	74
8	0	2	0	89

To confirm that the TMEDA is essential to activate the *s*-BuLi for lithiation of *N*-methyl morpholine **232**, we set up a control reaction. Firstly, *N*-methyl morpholine **232** was lithiated in the absence of TMEDA at 0 °C for 1 h (Scheme 3.78). The resulting reaction mixture was then mixed with 1.3 equivalents of TMEDA for another hour and trapped with benzaldehyde. This gave a 65% yield of diastereomeric alcohols **233** and a 12% yield of alcohols **74**.

Scheme 3.78

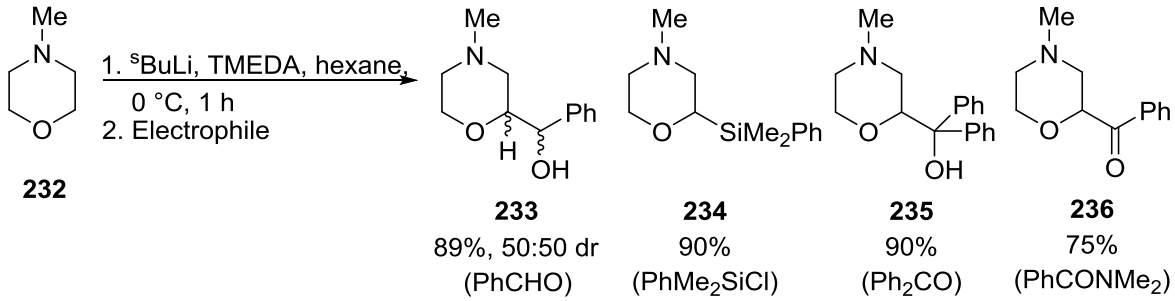


232 **233** 65% **74** 12%

In summary, reaction conditions for the lithiation-trapping of *N*-methyl morpholine **232** were explored. Based on the optimisation, lithiation using *s*-BuLi and 1.3 equivalents of TMEDA in hexane at 0 °C for 1 h gave the highest yield (89%) of the desired 2-substituted

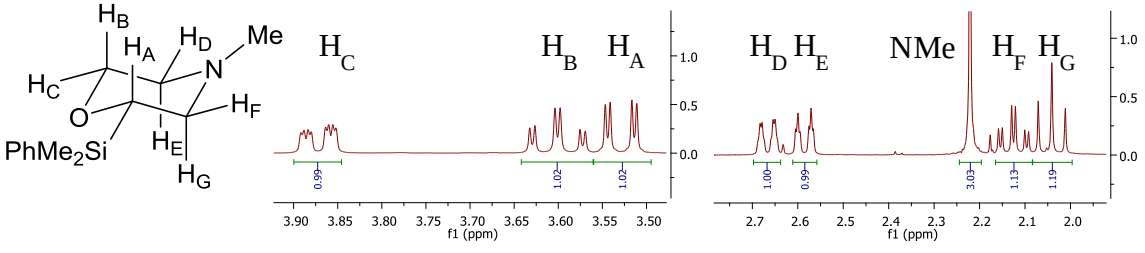
morpholine **233**. Thus, lithiation of *N*-methyl morpholine **232** was carried out under the newly-developed conditions and trapping with a range of electrophiles gave the results shown in Scheme 3.79. Generally, excellent yields, ranging from 75-90% of the products, were obtained.

Scheme 3.79



Both the ^{1}H and ^{13}C NMR spectra of these products confirmed that the lithiation-trapping had taken place at the α-oxygen position. For the $PhMe_2SiCl$ trapping of the lithiated morpholine, a 90% yield of silyl morpholine **234** was obtained and we were able to assign all of the protons in the ^{1}H NMR spectrum (Figure 3.10). In the ^{1}H NMR spectrum of silyl morpholine **234**, there are three 1H signals at δ_H 3.87 (ddd, H_C), 3.60 (ddd, H_B) and 3.52 (dd, H_A) which were assigned to protons next to the oxygen. Based on the *J* values of the signals of H_A (*J* = 12.0 and 2.5 Hz), we confirmed that the substituent sits in the expected equatorial position. There are four signals with different coupling for protons next to the nitrogen of the ring. The signal at δ_H 2.66 (dddd) was assigned to H_D as it has a small W-coupling (*J* = 2.0 Hz) with H_D.

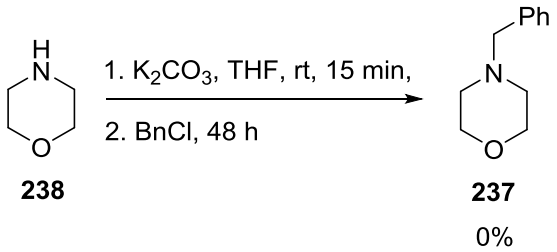
Figure 3.10



For comparison, lithiation-trapping of morpholines with different *N*-protecting groups was explored next. We chose to investigate the *N*-benzyl group due to its ready deprotection *via* hydrogenolysis. Thus, *N*-benzyl morpholine **237** needed to be prepared.

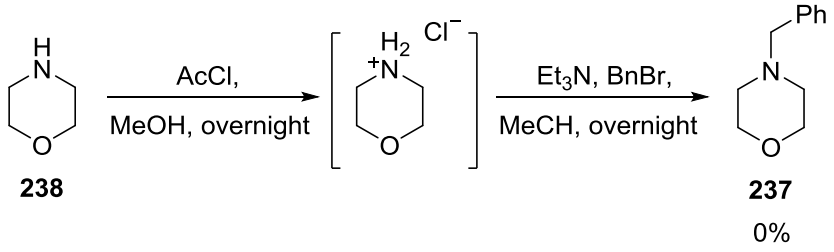
The first attempt for benzyl protection of morpholine was using a procedure reported by Khan.[116] Morpholine was reacted with K_2CO_3 in THF and BnCl to give *N*-benzyl morpholine **237** (Scheme 3.80). However, the ^{1}H NMR spectrum of the crude product showed that no *N*-benzyl morpholine **237** had been formed.

Scheme 3.80



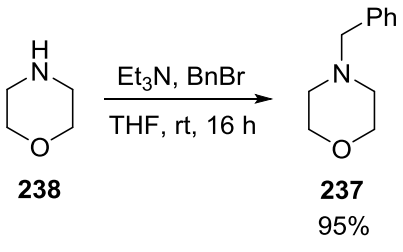
Subsequently, an alternative synthesis of *N*-benzyl morpholine **238** was carried out by using AcCl in MeOH to form the morpholine hydrochloride salt as an intermediate. Afterwards, it was reacted with BnBr and Et_3N, but, no *N*-benzyl morpholine **238** formed (Scheme 3.81).

Scheme 3.81



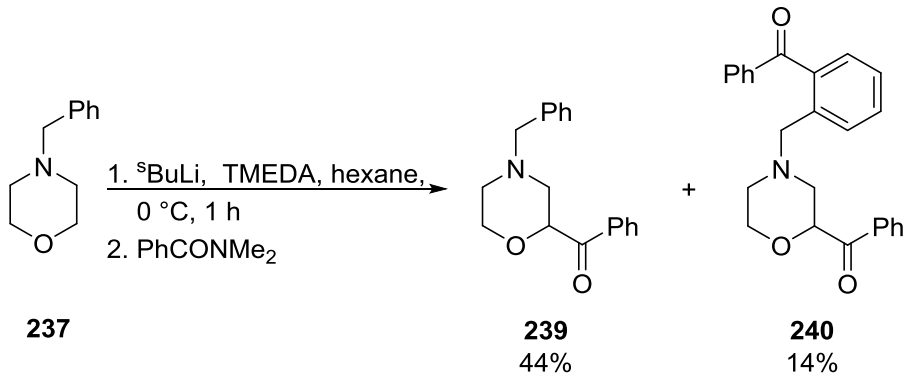
We then followed a literature procedure from Zhang.[117] BnBr was added to a stirred solution of morpholine and Et_3N in THF at room temperature. The resulting mixture was allowed to stir for 16 h to give a good yield of *N*-benzyl morpholine **237** (95%) (Scheme 3.82).

Scheme 3.82



After the successful benzyl protection of morpholine **238**, lithiation-trapping of *N*-benzyl morpholine **237** was carried out using the optimised reaction conditions for *N*-methyl morpholine **232**. Thus, *N*-benzyl morpholine **237** was lithiated using *s*-BuLi with 1.3 equivalents of TMEDA in hexane at 0 °C for 1 h (Scheme 3.83). The lithiated morpholine was then trapped with $PhCONMe_2$ as electrophile to give a 44% yield of ketone morpholine **239**. The structure of the mono-substituted morpholine **239** was confirmed by comparison with the data in the literature.[118] Surprisingly, an unexpected product **240** was also isolated and characterised.

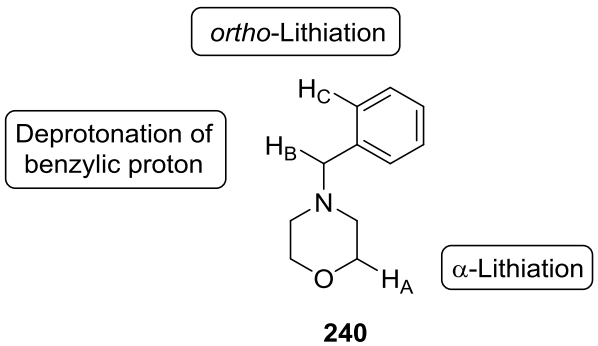
Scheme 3.83



237 **239** 44% **240** 14%

The ^1H NMR spectrum of the unexpected compound showed the presence of fourteen aromatic protons between δ_H 7.89-7.23 which suggested there were two benzoyl substituents attached in the compound. There are three possible sites where *N*-benzyl morpholine **237** could in principle be deprotonated, as shown in Figure 3.11. They are the desired α-lithiation process (H_A), benzylic deprotonation (H_B) and *ortho*-lithiation (H_C). To determine which two of these positions had reacted, careful analysis of the ^1H and ^{13}C NMR spectra was carried out.

Figure 3.11

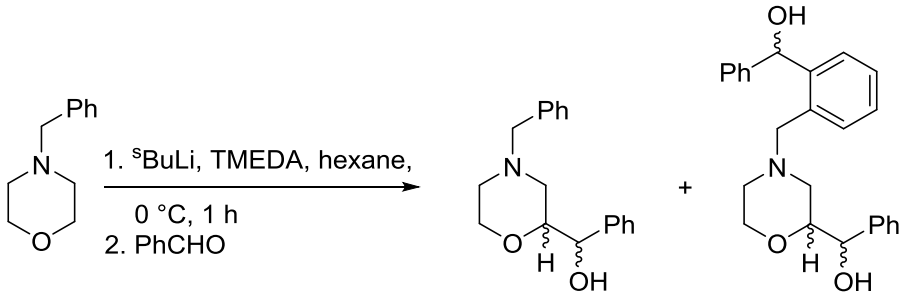


240

Firstly, we wanted to confirmed that α-lithiation had also happened in the unexpected product **240**. Based on the three 1H signals (δ_H 4.31 (dd), 3.75 (ddd) and 3.26 (ddd)) which were assigned to protons adjacent to oxygen, we assumed that α-deprotonation had taken place as expected. Since we had observed the deprotonation of the benzylic proton in 3-benzyl oxetane **168** (see section 3.4.3), we wondered if this could also have happened in this case. However, there were two benzylic proton signals at δ_H 3.52 and 3.48 which indicated that the deprotonation of the benzylic proton did not occur. Deprotonation of H_C *via ortho*-lithiation is well known and the total number of aromatic protons matched with the ^{1}H NMR spectrum, suggesting that *ortho*-lithiation had indeed occurred. The ^{13}C NMR spectrum confirmed that there were three *ipso*-Ar signals at δ_C 139.2 , 137.8 and 137.4, along with two signals at δ_C 77.2 (OCH) and 66.3 (OCH_2). Therefore, we assigned the structure of the di-substituted morpholine as **240**. In this reaction, a 14% yield of di-substituted morpholine **240** was obtained and it shows that the *N*-benzyl group is not a useful protecting group for α-lithiation-trapping. It is interesting that we only observed two products (**239** and **240**) from the reaction. We believe that di-substituted morpholine **240** is most likely formed *via* a dianion in which α-lithiation and *ortho*-lithiation have occurred.

For comparison, lithiation of *N*-benzyl morpholine **237** was carried out under the same reaction conditions and subsequently trapped with benzaldehyde (Scheme 3.84). In this reaction, a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric mono-substituted morpholines **206** in 56% yield was obtained, along with and a 48:32:12:8 mixture (by ^{1}H NMR spectroscopy) of diastereomeric di-substituted morpholines **241** in 17% yield.

Scheme 3.84

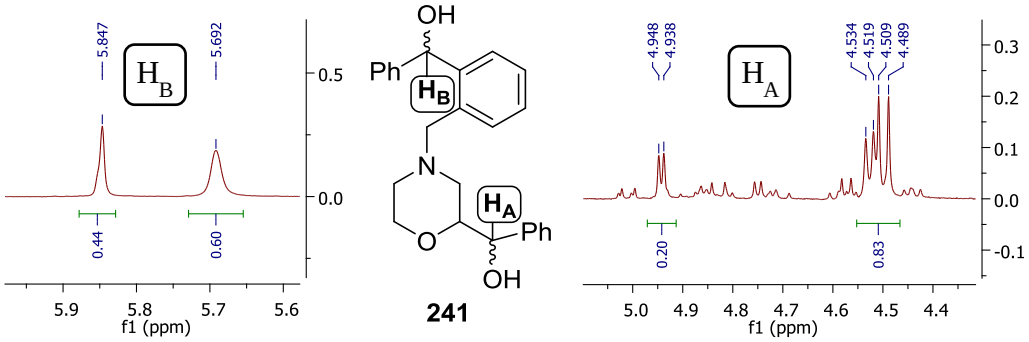


237 **206** 56% **241** 17%

As the diastereomeric di-substituted morpholines **241** were inseparable, the ratio of the four diastereomers was calculated from the ^{1}H NMR spectrum of the mixture (selected signals shown in Figure 3.12). There are two 1H broad singlet signals at δ_H 5.84 and 5.69

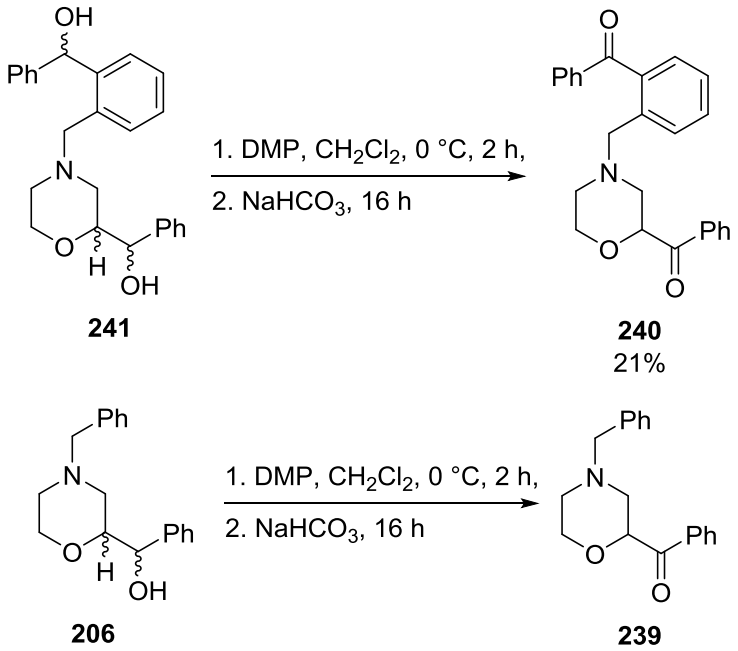
which were assigned to H_B at the *ortho*-lithiation position. The dd 1H signal at δ_H 4.94 and the multiplet 1H signal between δ_H 4.55-4.47 were assigned to H_A. Integration of all of these signals indicated that the mixture contains a 48:32:12:8 ratio of diastereomers.

Figure 3.12



The characterisation of diastereomeric di-substituted morpholines **241** was confirmed by performing an oxidation using DMP to oxidize the alcohols to ketones (Scheme 3.85). The idea was to reduce the number of chiral centres to one which would simplify the ^{1}H NMR spectrum. Furthermore, the spectroscopic data of the oxidized product were consistent with those from the PhCONMe$_2$-trapping. DMP oxidation of the mono-substituted morpholine **206** was also carried out (Scheme 3.85).

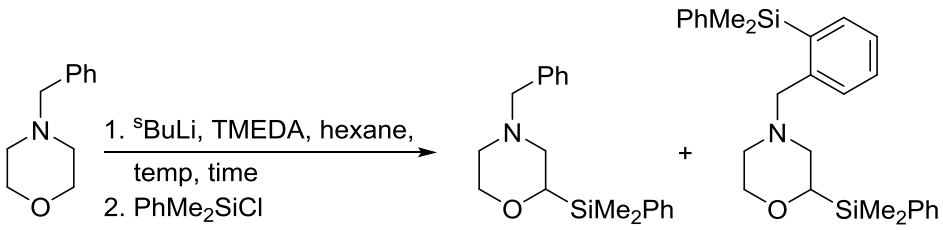
Scheme 3.85



Since the formation of di-substituted morpholine **241** would have consumed 2 equivalents of *s*-BuLi, we wondered if lithiating *N*-benzyl morpholine **237** at a lower temperature, the

rate of *ortho*-lithiation would be reduced. This could lead to an increase in yield of the desired mono-substituted product. Hence, lithiation of *N*-benzyl morpholine **237** at different temperatures (0 °C and –30 °C) was carried out, trapping with $PhMe_2SiCl$ (Table 3.8). Firstly, lithiation at 0 °C for 1 h gave a 42% yield of mono-silyl morpholine **242** and a 15% yield of di-silyl morpholine **243** (entry 1). When the lithiation was performed at –30 °C for 1 h, it gave a slightly lower yield of mono-silyl morpholine **242** (37%) and a very similar yield of di-silyl product **243** (16%) (entry 2). When the lithiation at –30 °C was carried out for a longer reaction time (3 h), only mono-silyl morpholine **242** was obtained in a very similar yield (40%) (entry 3).

Table 3.8

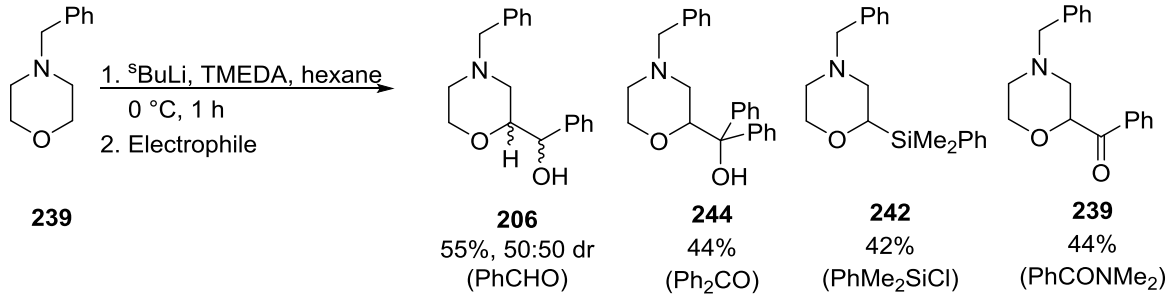


237 **242** **243**

Entry	Temp (°C)	Time (h)	242 Yield (%)	243 Yield (%)
1	0	1 h	42	15
2	–30	1 h	37	16
3	–30	3 h	40	0

In summary, lithiation-trapping of *N*-benzyl morpholine **237** was explored. Generally, the yields of 2-substituted morpholines were lower than the related products with the *N*-methyl protecting group. This was due to α- and *ortho*-lithiations occurring to generate a dilithiated intermediate, which consumed 2 equivalents of *s*-BuLi. Scheme 3.86 shows a summary of the lithiation of *N*-benzyl morpholine **237** at 0 °C for 1 h and trapping with a range of electrophiles. Yields ranged from 42-55% of the products that were obtained.

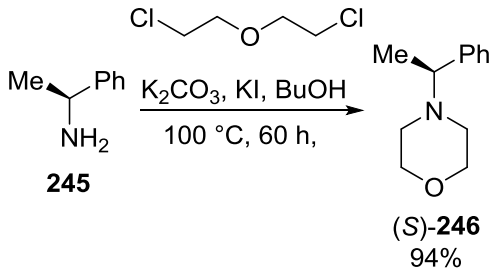
Scheme 3.86



Since *ortho*-lithiation appeared to be the major reason for the low yields in the lithiation-trapping of *N*-benzyl morpholine **239**, we decided to introduce a more sterically hindered *N*-alkyl group, the (*S*)-α-methylbenzyl group, in the hope that it would reduce the side-reaction. In addition, the (*S*)-α-methylbenzyl group could act as a chiral auxiliary. It might have slight preference for removal of a specific proton and give high diastereoselectivities. The use if this chiral auxiliary on a *N*-Boc piperazine **16** had previously been shown to be successful in our group (see Scheme 1.12) Hence, the lithiation-trapping of morpholine (*S*)-**246** with an (*S*)-α-methylbenzyl group was explored.

First, (*S*)-4-(1-phenylethyl) morpholine **246** needed to be synthesised from a chiral amine with dichlorodiethyl ether to construct the morpholine ring. The synthesis was carried out by followed a literature procedure that was carried out on a similar compound.[119] Thus, (*S*)-(−)-α-methylbenzylamine **245** was treated with K_2CO_3 and KI in *n*-BuOH at 0 °C. The resulting solution was stirred at 0 °C for 15 min before 2,2'-dichlorodiethyl ether was added. The reaction mixture was then heated at 100 °C for 16 h to give (*S*)-4-(1-phenylethyl) morpholine **246** in 94% yield (Scheme 3.87).

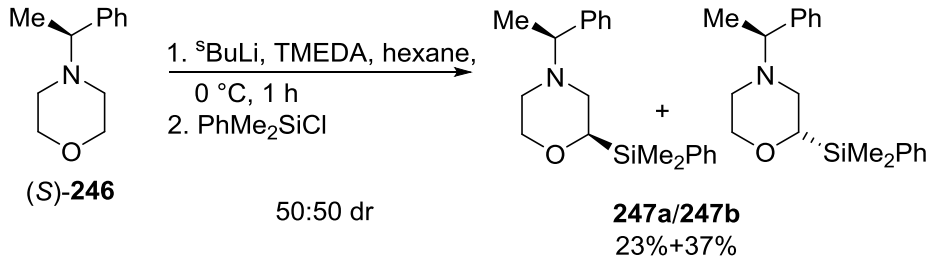
Scheme 3.87



After the successful synthesis of (*S*)-4-(1-phenylethyl) morpholine **246**, it was then subjected to lithiation using *s*-BuLi/TMEDA in hexane at 0 °C (Scheme 3.88). The

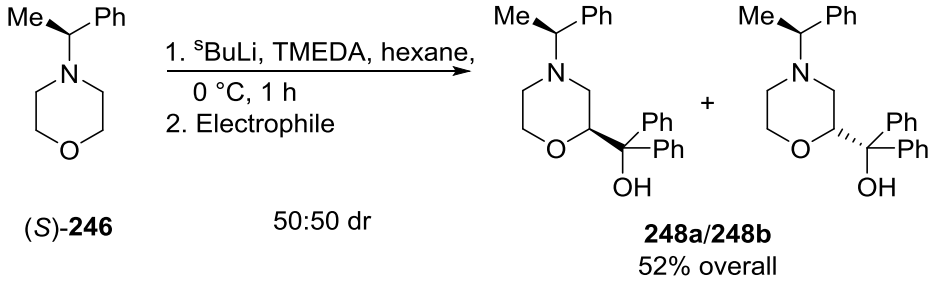
reaction mixture was stirred for 1 h and trapped with $PhMe_2SiCl$ to give a 50:50 mixture (by ^1H NMR spectroscopy) of diastereomeric silyl morpholine **247a** and **247b** in the crude product. After chromatography, silyl morpholines **247a** (23%) and **247b** (37%) were isolated separately. The total yield of silyl morpholines **247a** and **247b** was 60%. We have been unable to assign the stereochemistry in **247a** and **247b**.

Scheme 3.88



When (*S*)-4-(1-phenylethyl) morpholine **246** was lithiated under the same reaction conditions and trapped with benzophenone, it gave a 50:50 mixture of diastereomeric alcohols **248a** and **248b** by ^{1}H NMR spectroscopy of the crude product. Alcohols **248a** and **248b** were partially separable and isolated in a total of 52%.

Scheme 3.89

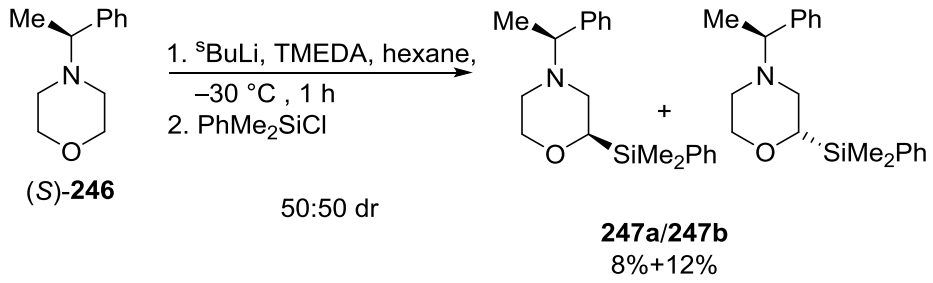


The overall yield of silyl morpholines **247a** and **247b** (60%) is higher than the yield of *N*-benzyl silyl morpholine **242** (42%) (Scheme 3.86). Similarly, the overall yield of alcohols **248a** and **248b** (52%) is higher than the corresponding *N*-benzyl reaction (44%) (Scheme 3.86). Thus, greater steric hindrance in the *N*-alkyl group did appear to have reduced the amount of *ortho*-lithiation. Due to the (*S*)-α-methylbenzyl group, it was possible to separate the diastereomeric silyl morpholines **247a** and **247b** and alcohols **238a**/**248b**, and this provides access to enantiopure α-substituted products. However, with a diastereoselectivity of 50:50, the process showed no selectivity. The poor diastereoselectivity was disappointing but understandable given the large distance between the chiral auxiliary and the site of deprotonation.

We then decided to carry out the lithiation at a lower temperature to see if the diastereoselectivity could be improved. However, lithiation at −30 °C for 1 h also gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of silyl morpholines **247a** and **247b** (Scheme 3.90). After purification, an 8% yield of silyl morpholine **247a** and a 12% yield of silyl

morpholine **247b** were obtained. The total yield of silyl morpholines **247a** and **247b** was 20%. Clearly, 1 h was not long enough for *s*-BuLi to deprotonate (*S*)-4-(1-phenylethyl) morpholine **246** at this lower temperature

Scheme 3.90

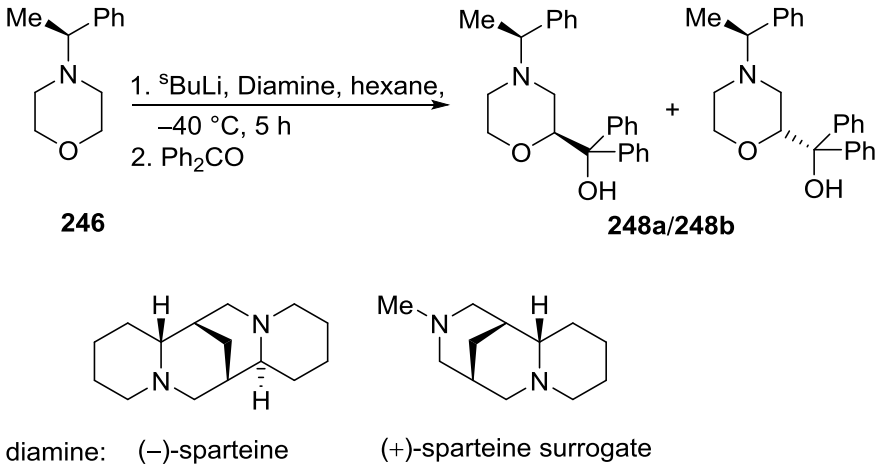


Since the diastereoselectivity of the formation of silyl morpholines **247a** and **247b** did not improve at lower temperature, we decided to investigate the asymmetric lithiation of (*S*)-4-(1-phenylethyl) morpholine **246** using chiral diamines. Based on the results with a *N*-Boc piperazine, the chiral auxiliary gave a slightly favoured preference for the removal of the pro-(*R*) proton. Thus, introducing a chiral diamine that also favoured the removal of the pro-(*R*) proton should give a 'matched' case and potentially improve the diastereoselectivity. In order to improve the diastereoselectivity and to reduce problems due to the potential configurational instability of the lithiated intermediate, a lower temperature (−40 °C) and a longer lithiation time (5 h) was employed. To simplify the results, only the combined total yield of **248a** and **248b** after trapping with benzophenone and purification by chromatography is shown (Table 3.9).

Firstly, lithiation using *s*-BuLi/TMEDA was carried out and trapped with benzophenone. The crude product, which contained a 60:40 mixture of **248a** and **248b** (by ^{1}H NMR spectroscopy), was purified and gave **248** in 41% **248a** and **248b** total yield and recovered starting material **246** in 46% yield (entry 1). The large amount of starting material recovered indicated that the lithiation did not complete within 5 h. Subsequently, lithiation using *s*-BuLi/(+)-sparteine surrogate was carried out. Disappointingly, the crude product contained a 51:49 mixture of **248a** and **248b** (by ^{1}H NMR spectroscopy) was formed (entry 2). A better total yield of **248a** and **248b** was obtained (63%) presumably due to the higher reactivity of the *s*-BuLi/(+)-sparteine surrogate complex. There was also an 11% yield of recovered starting material **246**. The result suggested that (+)-sparteine surrogate and the (*S*)-α-methylbenzyl group were a mismatched combination. Lithiation using *s*-BuLi/(−)-

sparteine was also carried out under the same conditions to give the crude product, which contained a 54:46 mixture of **248a** and **248b** (by ^{1}H NMR spectroscopy) (entry 3). This disappointing result showed that the *s*-BuLi/(−)-sparteine complex did not provide a better diastereomeric ratio. A lower total yield of **248a** and **248b** was obtained (31%) with a 62% yield of recovered starting material **246**, indicating the expected slower rate of lithiation of the *s*-BuLi/(−)-sparteine complex.

Table 3.9

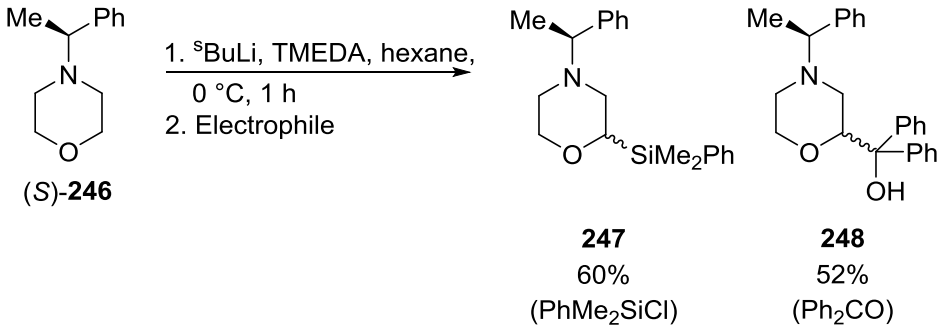


Entry	Diamine	dr[a]	248 Yield (%)	246 Yield (%)
1	TMEDA	60:40	41	46
2	(+)-Sparteine surrogate	51:49	63	11
3	(–)-Sparteine	54:46	31	62

[a] dr determined by ^{1}H NMR spectroscopy of the crude product.

In summary, lithiation-trapping of (*S*)-4-(1-phenylethyl) morpholine **246** using chiral diamines was explored. Generally, the yields of 2-substituted morpholines were better than the related products with the *N*-benzyl protecting group as *ortho*-lithiation did not occur. However, diastereomeric ratios were disappointing when the asymmetric lithiations were carried out. Scheme 3.91 shows a summary of lithiation of (*S*)-4-(1-phenylethyl) morpholine **246** at 0 °C for 1 h and trapping with selected electrophiles. Yields ranged from 52-60% of the diastereomeric products that were obtained.

Scheme 3.91



(*S*)-**246**

247
60%
($PhMe_2SiCl$)

248
52%
(Ph_2CO)

3.6 Conclusions and Future Work

A detailed exploration of lithiation-trapping of THF under different conditions was carried out. Based on the results of the optimisation, we concluded that the use of THF as both the substrate and the solvent provided the best results. The optimised reaction conditions were *s*-BuLi/THF at –40 °C for 40 min, as they provide a suitable balance between the rate of lithiation and the rate of decomposition of the lithiated intermediate *via* the retro [3+2] pathway. Moreover, there was no benefit of introducing TMEDA in the reaction mixture.

The exploration of lithiation-trapping of 2-MeTHF revealed that the rate of decomposition *via* the β-elimination pathway is much faster than the α-lithiation, and TMEDA is considered to be an important factor for 2-MeTHF lithiation as the β-elimination pathway (either at the methyl group or at the C-3 position) is more favourable when *s*-BuLi/TMEDA was used. The best reaction conditions for 2-MeTHF lithiation were using diamine-free conditions in 2-MeTHF as substrate and solvent at –40 °C for 1 h.

Lithiation of THP can be achieved using s-BuLi/TMEDA complex in hexane at 0 °C for 1 h. However, as the lithiated THP is chemically unstable at 0 °C for a certain amount of time, more investigation is needed to identify the optimised lithiation conditions.

The synthesis and α-functionalisation of 3-substituted oxetanes **168**, **169** and **170** was explored. The lithiation-trapping of 3-benzyl oxetane **168** and 3-hexyl oxetane **169** was attempted at –78 °C, –40 °C, –20 °C and 0 °C in different solvents. In the lithiation of **168** at –78 °C, deprotonation did not take place at the α-oxygen position but at the benzylic position to form the silylated oxetane **172**. This suggested that the benzylic proton is more acidic and it could be a competitive site for deprotonation. Disappointingly, all attempts at the α-lithiation-trapping of 3-substituted oxetanes were unsuccessful.

The discovery of the "high" temperature lithiation-trapping of *N*-substituted morpholines was exciting. Exploration of the reaction conditions and *N*-substituent revealed that the best substrate was *N*-methyl morpholine and the optimised lithiation conditions were *s*-BuLi/TMEDA in hexane at 0 °C for 1 h. Asymmetric lithiation of (*S*)-4-(1-phenylethyl) morpholine **246** using chiral diamines was explored. However, diastereomeric ratios were disappointing. Further study of the asymmetric lithiation of *N*-substituted morpholine at lower temperature is needed. In addition, exploration of synthetic applications for this newly developed methodology is recommended.

Below is a table that summarises the work undertaken in this Chapter.

Substrate	**Newly Developed Reaction Conditions**
THF	–40 °C for 40 min in THF as substrate and solvent
2-MeTHF	–40 °C for 1 h in 2-MeTHF as substrate and solvent
THP	0 °C for 1 h in hexane with TMEDA (Optimal conditions to be confirmed)
N-methyl morpholine **232**	0 °C for 1 h in hexane with TMEDA

Chapter 4: Experimental

4.1 General Methods

All non-aqueous reactions were carried out under oxygen free Ar using flame-dried glassware. Et_2O and THF were freshly distilled from sodium and benzophenone respectively. 2-MeTHF, TMEDA, Me_3SiCl, methyl chloroformate, toluene, hexane, (+)-sparteine surrogate and (–)-sparteine were purified by short-path distillation over CaH_2 before use. Me_2SO_4, benzaldehyde and $PhMe_2SiCl$ were purified by Kügelrohr distillation. DMF was used directly from the Pure Solv. MD-7 purification system. Dried CO_2 was freshly prepared by passing through CaOH and then bubbling into the reaction solution using a canula. Petrol refers to the fraction of petroleum ether boiling in the range of 40-60 °C and was purchased in Winchester quantities. Water is distilled water.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CHCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.27) and $CDCl_3$ (δ_H 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Boiling points for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Infared spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer with UATR attachment. Electospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer.

4.2 General Procedures

General procedure A: TMEDA-mediated lithiation-trapping of nitrogen heterocycles

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of nitrogen heterocycles (*N*-Boc pyrrolidine **1**, *N*-Boc *N*'-benzyl piperazine **16**, *N*-Boc piperidine **2** or *N*-Boc azepane **3**) (1.0 eq.) and TMEDA (1.3 eq.) in solvent (Et_2O, THF, 2-MeTHF, TBME or CPME) (7 mL) at the specified temperature (–78 °C – 20 °C) under Ar. The resulting solution was stirred at the specified temperature for the specific time (5 sec – 2 h). Then, the electrophile (DMF, PhCHO, Me_2SO_4, Me_3SiCl, MeOCOCl, $PhMe_2SiCl$ or Ph_2CO) (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure B: Diamine-free lithiation-trapping of nitrogen heterocycles

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of nitrogen heterocycles (*N*-Boc pyrrolidine **1** or *N*-Boc *N*'-benzyl piperazine **16**) (1.0 eq.) and TMEDA (1.3 eq.) in solvent (THF or 2-MeTHF) (7 mL) at the specified temperature (–30 °C – 20 °C) under Ar. The resulting solution was stirred at the specified temperature for the specific time (5 sec – 5 min). Then, the electrophile (DMF, PhCHO, Me_2SO_4, Me_3SiCl, MeOCOCl, $PhMe_2SiCl$ or Ph_2CO) (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure C: TMEDA-mediated lithiation-Me_3SiCl trapping of *N*-Boc pyrrolidine 1 with variation of temperature after lithiation

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in Et_2O or 2-MeTHF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. The reaction flask was transferred to a 0 °C bath and stirred for 5 or 30 min. Then, Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added. The resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure D: Diamine-free lithiation-Me_3SiCl trapping of *N*-Boc pyrrolidine 1 with variation of temperature after lithiation

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in THF or 2-MeTHF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. The reaction flask was transferred to a 0 °C bath and stirred to 0 °C for 5 or 30 min. Then, Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added. The resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure E: Diamine-mediated lithiation-trapping of oxygen heterocycles

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of oxygen heterocycles (THF, 2-MeTHF, THP, 3-benzyl oxetane **168**, 3-hexyl oxetane **169**, 4-methyl morpholine **232**, 4-benzyl morpholine **237**, or (*S*)-4-(1-Phenylethyl) morpholine **246**) (1.0 eq.) and TMEDA (1.3 eq.) in solvent (Et_2O, THF, 2-MeTHF, hexane or toluene) (7 mL) at the specified temperature (–78 °C – 20 °C) under Ar. The resulting solution was

stirred at the specified temperature for the specific time (5 sec – 4 h). Then, the electrophile (PhCHO, $PhMe_2SiCl$ or Ph_2CO) (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure F: TMEDA-mediated lithiation-trapping of THF and 2-MeTHF

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of TMEDA (151 mg, 195 µL, 1.3 mmol) in THF or 2-MeTHF (7 mL) at –78 °C or –40 °C under Ar. The resulting solution was stirred at the specified temperature for the specified time (10 min, 20 min or 1 h). Then, $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure G: Diamine-free lithiation-trapping of THF and 2-MeTHF

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise into THF or 2-MeTHF (7 mL) at –78 °C or –40 °C under Ar. The resulting solution was stirred at the specified temperature for the specified time (20 min, 40 min or 1 h). Then, $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure H: Diamine-free double lithiation-methyl chloroformate trapping of *N*-Boc pyrrolidine 1

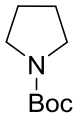
s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in THF (7 mL) at –78 °C, –30 °C or –20 °C under Ar. The resulting solution was stirred at –78 °C for 1 h, –30 °C for 5 min or –20 °C for 2 min. Then, methyl chloroformate (283 mg, 231 μL, 3.0 mmol) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure I: Catalytic TMEDA-mediated lithiation-trapping of *N*-methyl morpholine 232

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-methyl morpholine **232** (101 mg, 110 μL, 1.0 mmol, 1.0 eq.) and TMEDA (0.5 eq., 0.2 eq., 0.1 eq., 0.05 eq., 0.01 eq. or 0 eq.) in hexane (7 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h, 2 h or 4 h. Then, benzaldehyde (228 mg, 203 μL, 2.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

4.3 Experimental for Chapter 2

N-Boc pyrrolidine 1

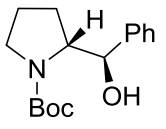


1

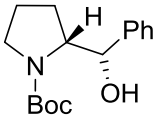
Pyrrolidine (4.29 g, 4.99 mL, 60.45 mmol) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (12.0 g, 56.05 mmol) in CH_2Cl_2 (120 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 3 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave *N*-Boc pyrrolidine **1** (10.5 g, 61%) as a colourless oil, bp 90-96 °C/2.0 mmHg (lit.,[120] bp 70-75 °C/0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32-3.29 (m, 4H, NCH_2), 1.86-1.80 (m, 4H, NCH_2CH_2), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.8 (C=O), 79.0 (CMe_3), 45.9 (NCH_2), 28.6 (CMe_3), 25.5 (NCH_2CH_2). Spectroscopic data consistent with those reported in the literature.[120]

Lab Book Reference: WSK/1/055

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester *syn*-25 and *anti*-25



syn-**25**



anti-**25**

Table 2.1, entry 1

Using general procedure B, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in THF (10 mL) at –30 °C for 5 min and benzaldehyde (318 mg, 305 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave starting material **1** (22 mg, 13%), pyrrolidine *syn*-**25** (253 mg, 46%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H, Ph), 5.93 (br s, 1 H,

OH), 4.53 (br d, *J* = 7.5 Hz 1H, OCH), 4.09 (td, *J* = 7.5, 5.0 Hz, 1H, NCH), 3.50-3.42 (m, 1H, NCH), 3.39-3.28 (m, 1H, NCH), 1.78-1.65 (m, 2H, CH), 1.65-1.56 (m, 2H, CH), 1.52 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.5 (C=O), 141.3 (*ipso*-Ph), 128.8 (Ph), 128.6 (Ph), 127.2 (Ph), 81.1 (OCH), 79.5 (CMe_3), 65.5 (NCH), 47.9 (NCH_2), 28.8 (CH_2), 28.7 (CMe_3), 24.0 (CH_2), a of 40:60 mixture (by ^1H NMR spectroscopy) of pyrrolidine *syn*-**25** and *anti*-**25** (11 mg, 2%) as a colourless oil and pyrrolidine *anti*-**25** (140 mg, 25%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.3; ^1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.41-7.22 (m, 5H, Ph), 5.49 (br s, 0.75H, OH), 5.17 (br s, 0.25H, OH), 4.86 (br s, 0.75H, OCH), 4.32 (br s, 0.75H, NCH), 3.97 (br s, 0.25H, OCH), 3.57 (br s, 0.25H, NCH), 3.30 (br s, 1H, NCH), 2.81 (br s, 0.75H, NCH), 2.30 (br s, 0.25H, NCH), 2.04-1.87 (m, 1H, CH), 1.86-1.66 (m, 1H, CH), 1.57 (br s, 3.5 H, CMe_3), 1.52 (br s, 5.5 H, CMe_3), 1.20-1.09 (m, 1H, CH), 0.93-0.79 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.8 (C=O), 157.4 (C=O), 141.9 (*ipso*-Ph), 141.3 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 128.1 (Ph), 127.4 (Ph), 127.1 (Ph), 126.1 (Ph), 80.5 (CMe_3), 80.4 (CMe_3), 76.3 (COH), 63.3 (NCH), 47.9 (NCH_2), 47.7 (NCH_2), 28.6 (CMe_3), 27.5 (CH_2), 26.1 (CH_2), 23.6 (CH_2), 22.6 (CH_2). Spectroscopic data consistent with those reported in the literature.[121] The total yield of *syn*-**25** and *anti*-**25** is 73%.

Lab Book Reference: WSK/1/036

(Table 2.1, entry 2)

Using general procedure B, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –30 °C for 5 min and benzaldehyde (318 mg, 305 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave starting material **1** (34 mg, 10%), pyrrolidine *syn*-**25** (200 mg, 36%) as a colourless oil and pyrrolidine *anti*-**25** (134 mg, 11%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 47%.

Lab Book Reference: WSK/1/040

(Table 2.1, entry 3)

Using general procedure B, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –30 °C for 5 min and benzaldehyde (318 mg, 305 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave starting material **1** (4 mg, 1%), pyrrolidine *syn*-**25** (218 mg, 39%) as a colourless oil, a mixture of pyrrolidines *syn*-**25** and *anti*-**25** (5 mg, 1%) as a colourless oil and pyrrolidine *anti*-**25** (155 mg, 28%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 68%.

Lab Book Reference: WSK/1/042

(Table 2.1, entry 4)

Using general procedure B, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol), and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at –20 °C for 5 min and benzaldehyde (318 mg, 305 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave starting material **1** (54 mg, 16%), pyrrolidine *syn*-**25** (106 mg, 17%) as a colourless oil and pyrrolidine *anti*-**25** (334 mg, 4%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 21%.

Lab Book Reference: WSK/1/035

(Table 2.1, entry 5)

Using general procedure A, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at –20 °C for 5 min and benzaldehyde (318 mg, 305 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave starting material **1** (85 mg, 25%), pyrrolidine *syn*-**25** (160 mg, 29%) as a colourless oil and pyrrolidine *anti*-**25** (87 mg, 16%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 45%.

Lab Book Reference: WSK/1/033

(Scheme 2.1)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at 0 °C for 5 sec and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**25** (92 mg, 33%), a 65:35 mixture (by ^{1}H NMR spectroscopy) of pyrrolidine *anti*-**25**and *syn*-**25** (7 mg, 1%) as a colourless oil and pyrrolidine *anti*-**25** (46 mg, 17%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 52%.

Lab Reference: WSK/3/074

(Scheme 2.1)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at 0 °C for 5 sec and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**25** (50 mg, 18%) and a 60:40 mixture (by ^{1}H NMR spectroscopy) of pyrrolidine *anti*-**25** and *syn*-**25** (110 mg, 40%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 58%.

Lab Reference: WSK/3/070

(Scheme 2.2)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at –20 °C for 2 min and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**25** (119 mg, 43%), a 65:35 mixture (by ^{1}H NMR spectroscopy) of pyrrolidine *anti*-**25**and *syn*-**25** (4 mg, 1%) as a colourless oil and pyrrolidine *anti*-**25** (70 mg, 25%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 69%.

Lab Reference: WSK/3/073

(Scheme 2.2)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 μL, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in 2-MeTHF (7 mL) at –20 °C for 2 min and benzaldehyde (228 mg, 203 μL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**25** (117 mg, 42%) and pyrrolidine *anti*-**25** (81 mg, 29%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 71%.

Lab Reference: WSK/3/069

(Table 2.10, entry 1)

Using general procedure B, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol), and *N*-Boc pyrrolidine **1** (342 mg, 350 μL, 2.0 mmol) in THF (10 mL) at 0 °C for 5 sec and benzaldehyde (318 mg, 305 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**25** (92.5 mg, 34%) as a colourless oil, a mixture of pyrrolidines *syn*-**25** and *anti*-**25** (11 mg, 4%) as a colourless oil and pyrrolidine *anti*-**25** (59 mg, 21%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 59%.

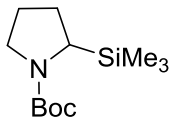
Lab Book Reference: WSK/1/058

(Table 2.10, entry 2)

Using general procedure A, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol), and *N*-Boc pyrrolidine **1** (342 mg, 350 μL, 2.0 mmol) in THF (10 mL) at 0 °C for 30 sec and benzaldehyde (318 mg, 305 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**25** (105 mg, 38%) as a colourless oil and pyrrolidine *anti*-**25** (62 mg, 22%) as a colourless oil. The total yield of *syn*-**25** and *anti*-**25** is 60%.

Lab Book Reference: WSK/1/059

2-Trimethylsilyl pyrrolidine-1-carboxylic acid *tert*-butyl ester 4



4

(Table 2.3, entry 2)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 μL, 2.0 mmol) in THF (10 mL) at –20 °C for 2 min and Me_3SiCl (326 mg, 381 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (315 mg, 65%) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56-3.41 (m, 1H, NCH), 3.29-3.23 (m, 1H, NCH), 3.19-3.12 (m, 1H, NCH), 2.06-1.95 (m, 1H, CH), 1.82-1.72 (m, 3H, CH), 1.45 (s, 9H, CMe_3), 0.04 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.6 (C=O), 79.2 (CMe_3), 78.3 (CMe_3), 47.6 (NCH), 47.0 (NCH_2), 46.6 (NCH_2), 28.5 (CMe_3), 27.9 (CH_2), 26.0 (CH_2) 24.9 (CH_2), –2.2 ($SiMe_3$). Spectroscopic data consistent with those reported in the literature.[25]

Lab Book Reference: WSK/1/057

(Table 2.2, entry 1)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 μL, 2.0 mmol) in THF (10 mL) at –30 °C for 5 min and Me_3SiCl (326 mg, 381 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (321 mg, 66%) as a colourless oil.

Lab Book Reference: WSK/1/051

(Table 2.2, entry 2)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –30 °C for 5 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (338 mg, 69%) as a colourless oil.

Lab Book Reference: WSK/1/060

(Table 2.2, entry 3)

Using general procedure A, *s*-BuLi (1 2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –30 °C for 5 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (370 mg, 76%) as a colourless oil.

Lab Book Reference: WSK/1/067

(Table 2.2, entry 4)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at –30 °C for 5 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (356 mg, 73%) as a colourless oil.

Lab Book Reference: WSK/1/063

(Table 2.3, entry 1)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in THF (10 mL) at –20 °C for 5 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column

chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (315 mg, 64%) as a colourless oil.

Lab Book Reference: WSK/1/056

(Table 2.3, entry 3)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –20 °C for 5 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (278 mg, 57%) as a colourless oil.

Lab Book Reference: WSK/1/058

(Table 2.3, entry 4)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –20 °C for 2 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (254 mg, 52%) as a colourless oil.

Lab Book Reference: WSK/1/092

(Table 2.3, entry 5)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –20 °C for 5 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (338 mg, 69%) as a colourless oil.

Lab Book Reference: WSK/1/068

(Table 2.3, entry 6)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –20 °C for 2 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (331 mg, 68%) as a colourless oil.

Lab Book Reference: WSK/1/069

(Table 2.3, entry 7)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at –20 °C for 5 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (348 mg, 71%) as a colourless oil.

Lab Book Reference: WSK/1/064

(Table 2.3, entry 8)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at –20 °C for 2 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (339 mg, 70%) as a colourless oil.

Lab Book Reference: WSK/1/065

(Table 2.4, entry 1)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 μL, 2.0 mmol) in THF (10 mL) at –10 °C for 5 min and Me_3SiCl (326 mg, 381 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (245 mg, 50%) as a colourless oil.

Lab Book Reference: WSK/1/062

(Table 2.4, entry 2)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 μL, 2.0 mmol) in THF (10 mL) at –10 °C for 1 min and Me_3SiCl (326 mg, 381 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (284 mg, 58%) as a colourless oil.

Lab Book Reference: WSK/1/074

(Table 2.4, entry 3)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in THF (7 mL) at –10 °C for 30 sec and Me_3SiCl (218 mg, 256 μL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (114 mg, 47%) as a colourless oil.

Lab Book Reference: WSK/2/014

(Table 2.4, entry 4)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 μL, 2.0 mmol) in 2-MeTHF (10 mL) at –10 °C for 2

min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (136 mg, 28%) as a colourless oil.

Lab Book Reference: WSK/1/076

(Table 2.4, entry 5)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –10 °C for 1 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (170 mg, 35%) as a colourless oil.

Lab Book Reference: WSK/1/075

(Table 2.4, entry 6)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at –10 °C for 30 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (223 mg, 46%) as a colourless oil.

Lab Book Reference: WSK/1/079

(Table 2.4, entry 7)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at –10 °C for 30 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (181 mg, 74%) as a colourless oil.

Lab Book Reference: WSK/2/015

(Table 2.4, entry 8)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at –10 °C for 1 min and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (326 mg, 67%) as a colourless oil.

Lab Book Reference: WSK/1/089

(Table 2.4, entry 9)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at –10 °C for 30 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (336 mg, 69%) as a colourless oil.

Lab Book Reference: WSK/1/088

(Table 2.5, entry 1)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in THF (10 mL) at 0 °C for 50 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (189 mg, 39%) as a colourless oil.

Lab Book Reference: WSK/1/081

(Table 2.5, entry 2)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in THF (10 mL) at 0 °C for 30 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (229 mg, 47%) as a colourless oil.

Lab Book Reference: WSK/1/080

(Table 2.5, entry 3)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in THF (10 mL) at 0 °C for 5 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (286 mg, 59%) as a colourless oil.

Lab Book Reference: WSK/1/096

(Table 2.5, entry 4)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at 0 °C for 10 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (150 mg, 31%) as a colourless oil.

Lab Book Reference: WSK/1/085

(Table 2.5, entry 5)

Using general procedure B, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at 0 °C for 5 sec

and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (167 mg, 50%) as a colourless oil.

Lab Book Reference: WSK/1/084

(Table 2.5, entry 6)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in 2-MeTHF (10 mL) at 0 °C for 5 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (306 mg, 63%) as a colourless oil.

Lab Book Reference: WSK/1/095

(Table 2.5, entry 7)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at 0 °C for 10 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (268 mg, 55%) as a colourless oil.

Lab Book Reference: WSK/1/087

(Table 2.5, entry 8)

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol), TMEDA (302 mg, 390 µL, 2.6 mmol, 2.6 eq.) and *N*-Boc pyrrolidine **1** (342 mg, 350 µL, 2.0 mmol) in Et_2O (10 mL) at 0 °C for 5 sec and Me_3SiCl (326 mg, 381 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (258 mg, 53%) as a colourless oil.

Lab Book Reference: WSK/1/086

(Table 2.6, entry 1)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in THF (7 mL) at rt for 2 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (53 mg, 22%) as a colourless oil.

Lab Book Reference: WSK/2/010

(Table 2.6, entry 2)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at 20 °C for 2 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (80 mg, 33%) as a colourless oil.

Lab Book Reference: WSK/2/011

(Table 2.6, entry 3)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at 20 °C for 2 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (40 mg, 16%) as a colourless oil.

Lab Book Reference: WSK/2/012

(Table 2.6, entry 4)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in Et_2O (7 mL) at 20 °C for 2 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (72 mg, 30%) as a colourless oil.

Lab Book Reference: WSK/2/013

(Table 2.7, entry 2)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in THF (7 mL) at 0 °C for 5 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (161 mg, 66%) as a colourless oil.

Lab Book Reference: WSK/2/067

(Table 2.7, entry 5)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in Et_2O (7 mL) at 0 °C for 5 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (48 mg, 20%) as a colourless oil.

Lab Book Reference: WSK/2/046

(Table 2.7, entry 7)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in TBME (7 mL) at 0 °C for 5 sec and

Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (34 mg, 14%) as a colourless oil.

Lab Book Reference: WSK/2/025

(Table 2.7, entry 8)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in TBME (7 mL) at 0 °C for 5 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (164 mg, 67%) as a colourless oil.

Lab Book Reference: WSK/2/026

(Table 2.7, entry 9)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in CPME (7 mL) at 0 °C for 5 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (34 mg, 14%) as a colourless oil.

Lab Book Reference: WSK/2/027

(Table 2.7, entry 10)

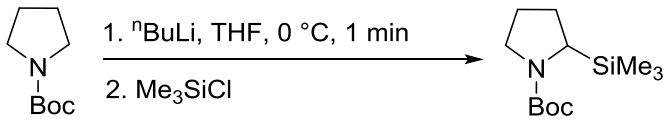
Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in CPME (7 mL) at 0 °C for 5 sec and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (72 mg, 29%) as a colourless oil.

Lab Book Reference: WSK/2/028

(Table 2.7, entry 11)

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.) and TMEDA (7 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 sec. Then, Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added. The resulting solution was stirred for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^1H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: WSK/2/070



1 **4**

(Table 2.8, entry 1)

n-BuLi (1.0 mL of a 2.5 M solution in hexanes, 2.5 mmol, 2.5 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.) in THF (7mL) at 0 °C under Ar. The resulting solution was stirred for 1 min. Then, Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added. The resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^1H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: WSK/2/029

(Table 2.8, entry 2)

n-BuLi (11.0 mL of a 2.5 M solution in hexanes, 2.5 mmol, 2.5 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.) and TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) in 2-MeTHF (7 mL) at 0 °C under Ar. The resulting solution was stirred for 5 min. Then, Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added. The resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^1H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: WSK/2/061

(Table 2.8, entry 3)

n-BuLi (11.0 mL of a 2.5 M solution in hexanes, 2.5 mmol, 2.5 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.) and TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) in 2-MeTHF (7 mL) at 0 °C under Ar. The resulting solution was stirred for 1 min. Then, Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added. The resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^1H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: WSK/2/062

(Table 2.11, entry 2)

Using general procedure D, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in THF (7 mL) at –30 °C for 5 min

before warming to 0 °C for 5 min. Me_3SiCl (218 mg, 256 μL, 2.0 mmol) was added to give the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (125 mg, 51%) as a colourless oil.

Lab Book Reference: WSK/2/063

(Table 2.11, entry 3)

Using general procedure D, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in THF (7 mL) at –30 °C for 5 min before warming to 0 °C for 30 min. Me_3SiCl (218 mg, 256 μL, 2.0 mmol) was added to give the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (9 mg, 4%) as a colourless oil.

Lab Book Reference: WSK/2/064

(Table 2.11, entry 5)

Using general procedure D, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in 2-MeTHF (7 mL) at –30 °C for 5 min before warming to 0 °C for 5 min. Me_3SiCl (218 mg, 256 μL, 2.0 mmol) was added to give the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (44 mg, 18%) as a colourless oil and starting material **1** (10 mg, 6%) as a colourless oil.

Lab Book Reference: WSK/2/071

(Table 2.11, entry 6)

Using general procedure D, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in 2-MeTHF (7 mL) at –30 °C for 5 min before warming to 0 °C for 30 min. Me_3SiCl (218 mg, 256 μL, 2.0 mmol) was added to give the crude product. Purification by flash column chromatography on silica with 8:2

petrol-Et_2O as eluent gave silylated pyrrolidine **4** (6 mg, 2%) as a colourless oil and starting material **1** (42 mg, 24%) as a colourless oil.

Lab Book Reference: WSK/2/066

(Table 2.11, entry 8)

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in Et_2O (7 mL) at –30 °C for 5 min before warming to 0 °C for 5 min. Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added to give the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (128 mg, 52%) as a colourless oil.

Lab Book Reference: WSK/2/068

(Table 2.11, entry 9)

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in Et_2O (7 mL) at –30 °C for 5 min before warming to 0 °C for 30 min. Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added to give the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave starting material **1** (35 mg, 20%) as a colourless oil.

Lab Book Reference: WSK/2/069

(Table 2.11, entry 11)

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at –30 °C for 5 min before warming to 0 °C for 5 min. Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added to give the crude product. Purification by

flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (60 mg, 25%) as a colourless oil.

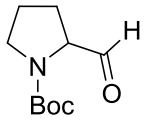
Lab Book Reference: WSK/3/054

(Table 2.11, entry 12)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at –30 °C for 5 min before warming to 0 °C for 30 min. Me_3SiCl (218 mg, 256 µL, 2.0 mmol) was added to give the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave silylated pyrrolidine **4** (5 mg, 2%) as a colourless oil.

Lab Book Reference: WSK/2/053

***N*-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxaldehyde 8**



8

(Scheme 2.2)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at –20 °C for 2 min and DMF (146 mg, 155 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-Et_2O as eluent gave aldehyde **8** (105 mg, 52%) as a colourless oil, R_F (1:1 hexane-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 9.56 (d, J = 2.0 Hz, 0.4H, CHO), 9.46 (d, J = 3.0 Hz, 0.6H, CHO), 4.24-4.17 (m, 0.4H, NCH), 4.05 (ddd, J = 8.5, 6.0, 3.0 Hz, 0.6H, NCH), 3.61-3.38 (m, 2H, NCH), 2.20-1.74 (m, 4H, CH), 1.48 (s, 4H, CMe_3), 1.43 (s, 5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 200.7 (C=O, CHO), 200.5 (C=O, CHO), 154.0 (C=O, Boc), 80.6 (CMe_3), 80.2 (CMe_3), 65.0 (NCH), 64.8 (NCH), 46.8 (NCH_2), 46.7 (NCH_2), 28.4

(C*Me*$_3$), 28.2 (C*Me*$_3$), 28.0 (CH_2), 26.7 (CH_2) 24.6 (CH_2), 23.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[15]

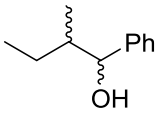
Lab Book Reference: WSK/3/075

(Scheme 2.2)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at –20 °C for 2 min and DMF (146 mg, 155 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-Et_2O as eluent gave aldehyde **8** (132 mg, 66%) as a colourless oil.

Lab Book Reference: WSK/3/061

2-Methyl-1-phenylbutan-1-ol 74



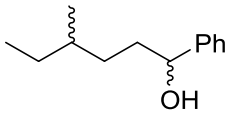
74

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of benzaldehyde (1.0 mmol, 138 mg, 132 µL, 1.3 mmol, 1.0 eq.) in THF (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave a 50:50 mixture of diastereomeric alcohols **74** (161 mg, 38%, 75% based on *s*-BuLi consumed) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H, Ph), 4.53 (d, J = 7.0 Hz, 0.5H, OCH), 4.44 (d, J = 7.0 Hz, 0.5H, OCH), 1.84 (br s, 1H, OH), 1.80-1.65 (m, 1.5H), 1.46-1.33 (m, 0.5H), 1.22-1.03 (m, 1H), 0.96-0.91 (m, 3H), 0.91-0.86 (m, 1.5H), 0.74 (d, J = 7.0 Hz, 1.5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.8 (*ipso*-Ph) , 143.5 (*ipso*-Ph), 128.1 (Ph), 127.4 (Ph), 127.2

(Ph), 126.6 (Ph), 126.3 (Ph), 78.7 (OCH), 78.0 (OCH), 41.9 (CH), 41.6 (CH), 25.8 (CH_2), 24.8 (CH_2), 15.0 (Me), 13.9 (Me), 11.6 (Me), 11.2 (Me). Spectroscopic data consistent with those reported in the literature.[122]

Lab Book Reference: WSK/2/039

4-Methyl-1phenylhexan-1-ol 73



73

Table 2.9 entry 3

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to THF (7 mL) at 0 °C under Ar for 30 min. Then, benzaldehyde (1.0 mmol, 138 mg, 132 μL, 1.3 mmol, 1.0 eq.) was added and the resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave a 50:50 mixture of diastereomeric alcohols **73** (97 mg, 39%, 77% based on 2 equivalents of *s*-BuLi being consumed) as a yellow oil, R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H, Ph), 7.31-7.27 (m, 1H, Ph), 4.64 (dd, J = 7.0, 3.0 Hz, 0.5H, OCH), 4.63 (dd, J = 7.0, 3.0 Hz, 0.5H, OCH), 1.89-1.64 (m, 2H), 1.64-1.54 (br s, 1H, OH), 1.52-1.40 (m, 1H), 1.37-1.24 (m, 3H), 1.15-0.98 (m, 1H), 0.88-0.78 (m, 6H, CH_2*Me*, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.9 (*ipso*-Ph) , 144.8 (*ipso*-Ph), 128.2 (Ph), 127.34 (Ph), 127.31 (Ph), 125.87 (Ph), 125.82 (Ph), 74.9 (OCH), 74.8 (OCH), 36.5 (CH_2), 36.4 (CH_2), 34.2 (CH), 34.2 (CH), 32.5 (CH_2), 32.4 (CH_2), 29.26 (CH_2), 29.23 (CH_2), 19.06 (Me), 19.01 (Me), 11.28 (Me), 11.25 (Me). Spectroscopic data consistent with those reported in the literature.[122]

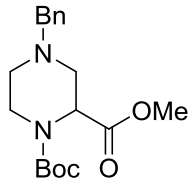
Lab Book Reference: WSK/2/017

(Table 2.9 entry 2)

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to THF (7 mL) at 0 °C under Ar for 5 min. Then, benzaldehyde (1.0 mmol, 138 mg, 132 µL, 1.3 mmol, 1.0 eq.) was added and the resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave a 50:50 mixture of diastereomeric alcohols **73** (118 mg, 48%, 95% based on 2 equivalents of *s*-BuLi being consumed) as a yellow oil.

Lab Book Reference: WSK/2/040

1-*tert*-Butyl 2-methyl 4-benzylpiperazine-1,2-dicarboxylate 24



24

Table 2.13, entry 1

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276 mg, 1.0 mmol), in THF (7 mL) at –30 °C for 5 min and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (231 mg, 69%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.34-7.21 (m, 5H, Ph), 4.71 (s, 0.5H, NCH), 4.54 (s, 0.5H, NCH), 3.86 (br d, J = 14.0 Hz, 0.5H, NCH), 3.80-3.67 (m, 0.5H, NCH), 3.73 (s, 1.5H, OMe), 3.71 (s, 1.5H, OMe), 3.59 (d, J = 13.0 Hz, 0.5H, CH_AH$_B$Ph), 3.56 (d, J = 13.0 Hz, 0.5H, CH_AH$_B$Ph), 3.45 (d, J = 14.0 Hz, 0.5H, CH$_A$$H_B$Ph), 3.41 (d, J = 14.0 Hz, 0.5H, CH$_A$$H_B$Ph), 3.35-3.23 (m, 2H, NCH_2), 3.18 (td, , J = 13.0, 3.0 Hz, 0.5H, NCH), 2.80 (d, J = 11.5 Hz, 0.5H, NCH), 2.75 (d, J = 11.5 Hz, 0.5H, NCH), 2.19 (td, J = 12.0, 3.0 Hz, 0.5H, NCH), 2.11 (d, J = 11.0 Hz, 0.5H, NCH), 2.08 (d, J = 11.0 Hz, 0.5H,

NCH), 1.47 (s, 4.8H, CMe_3), 1.42 (s, 4.2H, CMe_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ172.1 (CO_2Me), 171.3 (CO_2Me), 157.1 (NC=O), 156.0 (NC=O), 136.0 (*ipso*-Ph), 128.9 (Ph), 128.3 (Ph), 127.3 (Ph), 80.4 (CMe_3), 62.4 (NCH_2), 53.61 (NCH), 53.60 (NCH), 52.5 (NCH_2), 52.4 (NCH_2), 52.16 (NCH_2), 52.13 (OMe), 42.1 (NCH_2), 41.1 (NCH_2), 28.46 (CMe_3), 28.40 (CMe_3). Spectroscopic data consistent with those reported in the literature.[123]

Lab Book Reference WSK/2/004

(Table 2.12, entry 1)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in THF (7 mL) at –78 °C for 1 h and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (188 mg, 56%) as a colourless oil.

Lab Book Reference WSK/2/003

(Table 2.12, entry 2)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in 2-MeTHF (7 mL) at –78 °C for 1 h and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (230 mg, 69%) as a colourless oil.

Lab Book Reference WSK/2/009

(Table 2.13, entry 2)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in THF (7 mL) at –30 °C for 1 min and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product.

Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (193 mg, 58%) as a colourless oil.

Lab Book Reference WSK/2/006

(Table 2.13, entry 3)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in 2-MeTHF (7 mL) at –30 °C for 5 min and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (155 mg, 46%) as a colourless oil.

Lab Book Reference WSK/2/008

(Table 2.13, entry 4)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), TMEDA (90 mg, 117 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in Et_2O (7 mL) at –30 °C for 5 min and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (85 mg, 31%) as a colourless oil and starting material **16** (85 mg, 31%).

Lab Book Reference WSK/1/100

(Table 2.13, entry 5)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), TMEDA (90 mg, 117 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in Et_2O (7 mL) at –30 °C for 1 min and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (81 mg, 24%) as a colourless oil and starting material **16** (103 mg, 37%).

Lab Book Reference WSK/2/001

(Table 2.14, entry 1)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in THF (7 mL) at –20 °C for 5 min and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (177 mg, 53%) as a colourless oil.

Lab Book Reference WSK/2/005

(Table 2.14, entry 2)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in THF (7 mL) at –20 °C for 1 min and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (176 mg, 53%) as a colourless oil.

Lab Book Reference WSK/2/007

(Table 2.14, entry 3)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), TMEDA (90 mg, 117 µL, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in Et_2O (7 mL) at –30 °C for 1 min and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (61 mg, 18%) as a colourless oil and starting material **16** (84 mg, 30%).

Lab Book Reference WSK/1/101

(Table 2.15, entry 1)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in THF (7 mL) at 0 °C for 30 sec and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (167 mg, 50%) as a colourless oil.

Lab Book Reference WSK/2/019

(Table 2.15, entry 2)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in THF (7 mL) at 0 °C for 10 sec and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (112 mg, 33%) as a colourless oil.

Lab Book Reference WSK/2/018

(Table 2.15, entry 3)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in 2-MeTHF (7 mL) at 0 °C for 30 sec and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (92 mg, 28%) as a colourless oil.

Lab Book Reference WSK/2/021

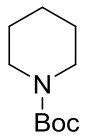
(Table 2.15, entry 4)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-benzyl piperazine **16** (276mg, 1.0 mmol) in THF (7 mL) at 0 °C for 10 sec and methyl chloroformate (189 mg, 156µL, 2.0 mmol) gave the crude product.

Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave piperazine **24** (105 mg, 31%) as a colourless oil.

Lab Book Reference WSK/2/020

_N_-Boc piperidine 2

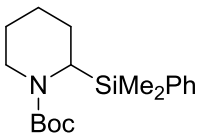


2

Piperidine (11.7 g, 11.7 mL, 137.5 mmol) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (20.0 g, 91.64 mmol) in THF (100 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 3 h. Then, 10% $NaHCO_{3(aq)}$ (100 mL) was added and the two layers were separated. The aqueous was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed wih saturated brine (300 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave *N*-Boc piperidine **2** (16.9 g, 66%) as a colourless oil, bp 95-100 °C/0.3 mmHg (lit.,[120] bp 60-70 °C/0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40-3.30 (m, 4H, NCH_2), 1.61-1.53 (m, 2H, CH_2), 1.53-1.46 (m, 4H, CH_2), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9 (C=O), 79.1 (*C*Me_3), 44.6 (br, NCH_2), 28.4 (C*Me*$_3$), 25.7 (CH_2), 24.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[120]

Lab Book Reference: WSK/2/083

2-(Dimethyl(phenyl)silyl)piperidine-1carboxylic acid *tert*-butyl ester 79



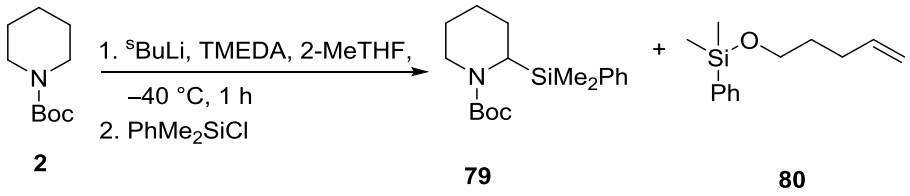
79

(Scheme 2.7)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc piperidine **2** (185 mg, 192 µL, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-Et_2O as eluent gave silyl piperidine **79** (119 mg, 37%) as a colourless oil, R_F (95:5 hexane-Et_2O) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.61-7.50 (m, 2H, Ph), 7.41-7.30 (m, 3H, Ph), 4.32-4.07 (m, 0.5H, NCH), 4.07-3.87 (m, 0.5H, NCH), 3.87-3.59 (m, 1H, NCH), 3.04-2.81 (m, 0.5H, NCH), 2.71-2.47 (m, 0.5H, NCH), 1.75-1.61 (m, 2H, CH), 1.61-1.46 (m, 2H, CH), 1.42 (s, 9H, CMe_3), 1.38-1.22 (m, 2H, CH), 0.43 (s, 3H, $SiMe_3$), 0.35 (s, 3H, $SiMe_3$) and starting material **2** (15 mg, 8%).

Lab Book Reference: WSK/3/085

2-(Dimethyl(phenyl)silyl)piperidine-1carboxylic acid *tert*-butyl ester 79, dimethyl(pet-4-enyloxy)(phenyl)silane 80



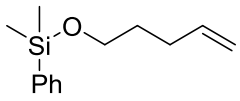
2 **79** **80**

(Scheme 2.8)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc piperidine **2** (185 mg, 192 µL, 1.0 mmol, 1.0 eq.) in 2-MeTHF (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-Et_2O as eluent gave 8:2 mixture (by ^{1}H NMR spectroscopy) of $PhMe_2SiCl$ and silylether **80** (219 mg, 183 mg of $PhMe_2SiCl$ and 36 mg, 12% yield of **80**) as a colourless oil, silyl piperidine **79** (74 mg, 23%) as a colourless oil and starting material **2** (23 mg, 11%).

Lab Book Reference: WSK/3/087

Dimethyl(pet-4-enyloxy)(phenyl)silane 80



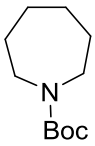
80

(Scheme 2.9)

$PhMe_2SiCl$ (171 mg, 182 µL, 1.1 mmol) was added dropwise to a solution of 4-penten-1-ol (86 mg, 103 µL, 1.0 mmol) and imidazole (136 mg, 2.0 mmol) in stirred DMF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The mixture was then diluted with Et_2O (10 mL) and washed with saturated NH_4Cl (10 mL) and the $brine_{(aq)}$ (2 × 10 mL). The organic layer was then dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave silylether **80** (153 mg, 69%) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.2; IR (ATR) 2952 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.55 (m, 2H, Ph), 7.42-7.34 (m, 3H, Ph), 5.79 (ddt, J = 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 4.99 (ddt, J = 17.0, 2.0, 1.0 Hz, 1H, CH=CH_2), 4.93 (ddt, J = 10.0, 2.0, 1.0 Hz, 1H, CH=CH_2), 3.60 (t, J = 8.0 Hz, OCH_2), 2.08 (dtdd, J = 7.0, 7.0, 1.0, 1.0 Hz, 2.0.H, CH_2CH=CH_2), 1.63 (tt, J = 8.0, 7.0 Hz, CH_2), 0.38 (s, 6H, $SiMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.4 (*ipso*-Ph), 138.0 (CH=*C*H_2), 133.5 (Ph), 129.5 (Ph), 127.8 (Ph), 114.6 (*C*H=CH_2), 62.5 (OCH_2), 31.7 (CH_2), 30.0 (CH_2), –1.8 ($SiMe_2$). Attempted characterisation by ESI mass spectrometry was not successful.

Lab Book Reference: WSK/3/094

***N*-Boc azepane 3**



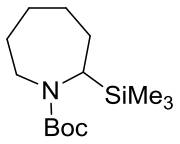
3

Hexamethylene imine (5.5 g, 6.19 mL, 55 mmol) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (9.8 g, 45 mmol) in THF (15 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 1 h. Then, 10% $NaHCO_{3(aq)}$

(20mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with saturated brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave *N*-Boc azepane **3** (7.4 g, 68%) as a colourless oil, bp 120-125 °C/1.0 mmHg (lit.,[120] bp 60-70 °C/0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 3.38 (t, J = 6.0 Hz, 2H, NCH_2), 3.31 (t, J = 6.0 Hz, 2H, NCH_2),1.72-1.59 (m, 4H, CH_2), 1.56-1.49 (m, 4H, CH_2), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.7 (C=O), 78.9 (*C*Me_3), 46.9 (NCH_2), 46.5 (NCH_2), 28.5 (C*Me*$_3$), 28.4 (CH_2), 27.4 (CH_2), 26.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[120]

Lab Book Reference: WSK/3/041

2-Trimethylsilyl azepane-1carboxylic acid *tert*-buyl ester 6



6

Scheme 2.11

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc azepane **3** (199 mg, 227 µL, 1.0 mmol) in Et_2O (7 mL) at –40 °C for 1 h and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et_2O as eluent gave silylated azepane **6** (148 mg, 55%) as a colourless oil, R_F (8:2 hexane-Et_2O) 0.4; (ATR) 2925, 1682, 830, 783, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 3.88-3.81 (m, 0.45H, NCH), 3.68-3.60 (m, 0.55H, NCH), 3.33 (dd, J = 13.0, 6.5 Hz, 0.55H, NCH), 3.43 (dd, J = 13.0, 6.5 Hz, 0.45H, NCH), 2.69 (ddd, J = 13.0, 11.0, 2.0 Hz, 0.55H, NCH), 2.55 (ddd, J = 13.0, 11.0, 2.0 Hz, 0.45H, NCH), 2.00-1.72 (m, 3H, CH), 1.72-1.61 (m, 1H, CH), 1.57-1.49 (m, 1H, CH), 1.46 (s, 4.05H, CMe_3), 1.44 (s, 4.95H, CMe_3), 1.40-1.07 (m, 3H, CH), 0.013 (s, 4.05H, $SiMe_3$), 0.010 (s, 4.95H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.7 (C=O), 155.6 (C=O), 78.9 (*C*Me_3), 78.4 (*C*Me_3), 47.4 (NCH), 46.9 (NCH), 44.9 (NCH_2), 44.1 (NCH_2), 29.8 (CH_2), 29.7 (CH_2),

29.6 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$), 27.5 (CH_2), 27.3 (CH_2), –2.56 ($SiMe_3$), –2.66 ($SiMe_3$) and recovered *N*-Boc azepane **3** (25 mg, 12 %) as a colourless oil. Attempted characterisation by ESI mass spectrometry was not successful.

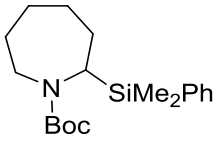
Lab Book Reference: WSK/3/055

Scheme 2.11

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc azepane **3** (199 mg, 227 µL, 1.0 mmol) in Et_2O (7 mL) at –40 °C for 2 h and Me_3SiCl (218 mg, 256 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et_2O as eluent gave silylated azepane **6** (145 mg, 53%) as a colourless oil and recovered *N*-Boc azepane **3** (12 mg, 6%) as a colourless oil.

Lab Book Reference: WSK/3/050

2-(Dimethyl(phenyl)silyl)azepane-1carboxylic acid *tert*-butyl ester 81



81

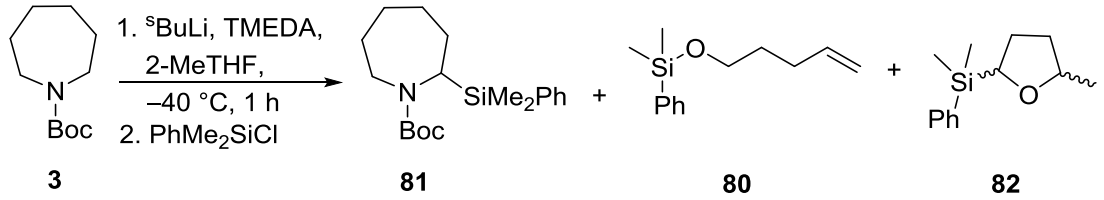
Scheme 2.11

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc azepane **3** (199 mg, 227 µL, 1.0 mmol) in Et_2O (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et_2O as eluent gave silylated azepane **81** (216 mg, 65%) as a colourless oil, R_F (8:2 hexane-Et_2O) 0.4; IR (ATR) 3069, 2965, 2928, 2856, 1681 (C=O), 1251, 1150, 1117, 829, 783, 699 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.57-7.46 (m, 2H, Ph), 7.42-7.29 (m, 3H, Ph), 3.80-3.74 (m, 0.45H, NCH), 3.70 (dd, *J* = 13.5, 6.0 Hz, 0.55H,

NCH), 3.63 (dd, *J* = 13.5, 6.0 Hz, 0.45H, NCH), 3.58-3.48 (m, 0.55H, NCH), 2.51 (ddd, *J* = 14.0, 11.0, 2.0 Hz, 0.55H, NCH), 2.36 (ddd, *J* = 14.0, 11.0, 2.0 Hz, 0.45H, NCH), 1.95-1.63 (m, 3H, CH), 1.44 (s, 4.05H, CMe_3), 1.42 (s, 4.95H, CMe_3), 1.31-1.00 (m, 3H, CH), 0.98-0.77 (m, 2H, CH), 0.33 (s, 6H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 162.9 (C=O), 134.1 (*ipso*-Ph), 134.0 (*ipso*-Ph), 133.0 (Ph), 129.2 (Ph), 128.9 (Ph), 127.8 (Ph), 127.7 (Ph), 127.6 (Ph), 79.0 (CMe_3), 78.5 (CMe_3), 58.0 (NCH), 57.8 (NCH), 47.3 (NCH_2), 46.8 (NCH_2), 29.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.52 (CMe_3), 28.50 (CMe_3), 27.4 (CH_2), 27.2 (CH_2), –4.0 (SiMe), –4.66 (SiMe), –4.67 (SiMe). Attempted characterisation by ESI mass spectrometry was not successful.

Lab Book Reference: WSK/3/077

2-(Dimethyl(phenyl)silyl)azepane-1carboxylic acid *tert*-butyl ester 81, dimethyl(pet-4-enyloxy)(phenyl)silane 80, 2-methyl-5-(dimethylphenylsilyl)tetrahydrofuran 82



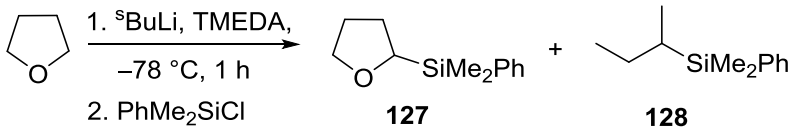
Scheme 2.12

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), TMEDA (151 mg, 195 µL, 1.3 mmol) and *N*-Boc azepane **3** (199 mg, 227 µL, 1.0 mmol) in 2-MeTHF (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et_2O as eluent gave silylether **80** (107 mg, 37%) as a colourless oil, silyl 2-MeTHF **82** (as a 70:30 mixture of diastereomers) (13 mg, 1%) as a colourless oil, silylated azepane **81** (67 mg, 20%) as a colourless oil, and recovered *N*-Boc azepane **3** (109 mg, 55%) as a colourless oil.

Lab Book Reference: WSK/3/086

4.4 Experimental for Chapter 3

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128

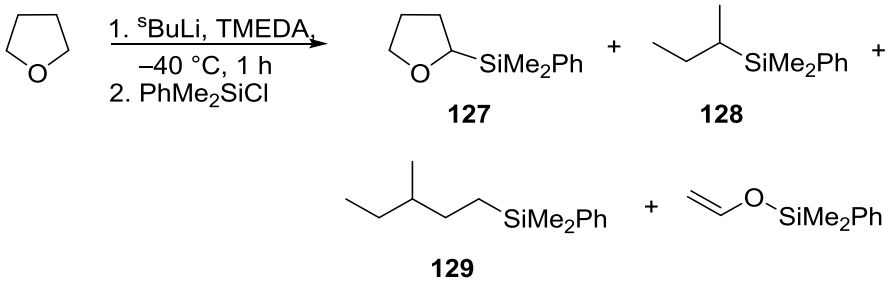


(Scheme 3.26)

Using general procedure F, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and TMEDA (151 mg, 195 μL, 1.3 mmol) in THF (7 mL) at –78 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 μL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave **128** (158 mg, 63%) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.47 (m, 2H, Ph), 7.39-7.31 (m, 3H, Ph), 1.62-1.49 (m, 1H, CH), 1.19-1.05 (m, 1H, CH), 0.94 (d, *J* = 7.0 Hz, 3H, CH*Me*), 0.90 (t, *J* = 7.5 Hz, 3H, CH_2*Me*), 0.83-0.71 (m, 1H, CH), 0.25 (s, 3H, SiMe), 0.24 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.9 (*ipso*-Ph), 133.9 (Ph), 128.7 (Ph), 127.6 (Ph), 24.6 (CH_2), 21.2 (CH_2*Me*), 13.54 (CH*Me*), 13.45 (CH*Me*), –4.7 (SiMe), –4.8 (SiMe) and silyl THF **127** (4 mg, 1%) as a colourless oil.

Lab Book Reference: WSK/3/100

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128, 3-methylpentanyldimethylphenylsilane 129, vinyloxydimethylphenylsilane

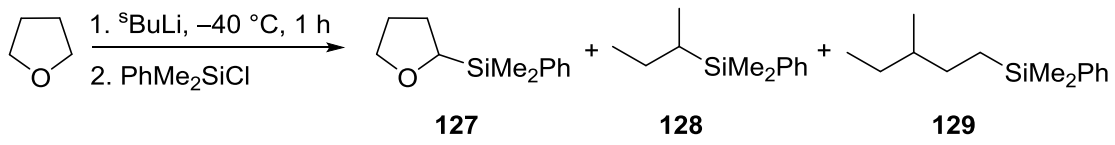


(Scheme 3.27)

Using general procedure F, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and TMEDA (151 mg, 195 μL, 1.3 mmol) in THF (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 μL, 2.0 mmol) gave the crude product, which contained a 45:15:20:20 mixture (by ^{1}H NMR spectroscopy) of **127**, **128**, **129** and the silyl enol ether. Diagnostic signals for the silyl snol ether: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, J = 13.5, 6.0 Hz, 1H, C*H*=CH_2), 4.47 (d, J = 13.5 Hz, 1H, =CH_2), 4.14 (d, J = 6.0 Hz, 1H, =CH_2). Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of **129** and **128** (47 mg, 34 mg (6% yield) of **129** and 13 mg (5% yield) of **128**) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.6; diagnostic signals for **129**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.20 (m, 2H, CH_2), 0.83 (d, J = 5.5 Hz, 3H, CH*Me*), 0.82 (t, J = 7.0 Hz, 3H, CH_2*Me*) and silyl THF **127** (77 mg, 29%) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.54 (m, 2H, Ph), 7.39-7.32 (m, 3H, Ph), 3.78 (ddd, J = 7.0, 7.0, 7.0 Hz, 1H, OCH), 3.68 (ddd, J = 7.0, 7.0, 7.0 Hz, 1H, OCH), 3.47 (dd, J = 11.0, 7.0 Hz, 1H, OCH), 2.03-1.92 (m, 1H, CH), 1.88-1.77 (m, 2H, CH), 1.70-1.59 (m, 1H, CH), 0.34 (s, 3H, SiMe), 0.32 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.2 (*ipso*-Ph), 134.0 (Ph), 129.1 (Ph), 127.8 (Ph), 71.6 (OCH), 69.4 (OCH_2), 28.1 (CH_2), 27.0 (CH_2), –5.3 (SiMe), –5.4 (SiMe). Attempted characterisation by ESI and ATCI mass spectrometry was not successful.

Lab Book Reference: WSK/3/092

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128, 3-methylpentanyldimethylphenylsilane 129



127 **128** **129**

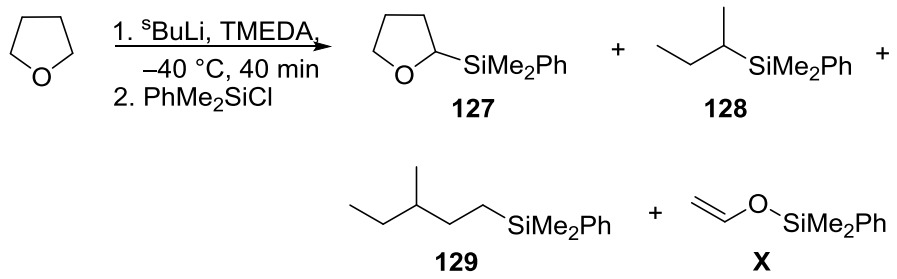
(Table 3.2, entry 2)

Using general procedure G, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) in THF (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 μL, 2.0 mmol) gave the crude product, which contained a 50:30:20 mixture (by ^{1}H NMR spectroscopy) of **127**, **128** and **129**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave a 55:45 mixture (by ^{1}H NMR spectroscopy) of **129** and **128** (59 mg, 30 mg

(5% yield) of **129** and 28 mg (11% yield) of **128**) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.2 and silyl THF **127** (79 mg, 29%) as a colourless oil.

Lab Book Reference: WSK/3/093

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128, 3-methylpentanyldimethylphenylsilane 129, vinyloxydimethylphenylsilane

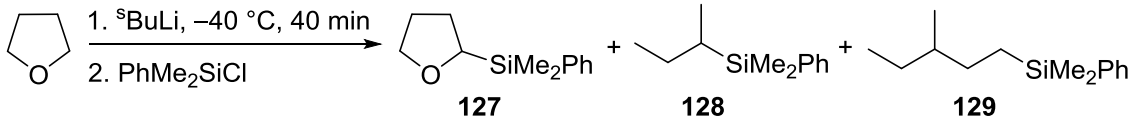


(Table 3.2, entry 3)

Using general procedure F, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and TMEDA (151 mg, 195 μL, 1.3 mmol) in THF (7 mL) at –40 °C for 40 min and $PhMe_2SiCl$ (314 mg, 336 μL, 2.0 mmol) gave the crude product, which contained a 45:40:10:5 mixture (by ^1H NMR spectroscopy) of **127**, **128**, **129** and the silyl enol ether. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave **128** (44 mg, 18%) as a colourless oil and silyl THF **127** (84 mg, 31%) as a colourless oil.

Lab Book Reference: WSK/4/009

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128, 3-methylpentanyldimethylphenylsilane 129



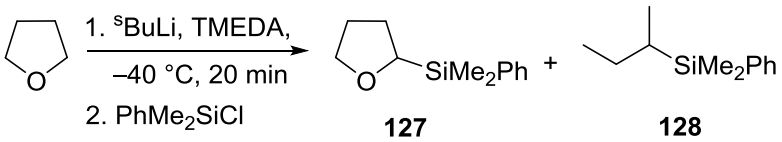
(Table 3.2, entry 4)

Using general procedure G, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) in THF (7 mL) at –40 °C for 40 min and $PhMe_2SiCl$ (314 mg, 336 μL, 2.0 mmol) gave the

crude product, which contained a 50:40:10 mixture (by ^{1}H NMR spectroscopy) of **128**, **127** and **129**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of **128** and **129** (92 mg, 67 mg (27% yield) of **128** and 26 mg (5%) of **129**) as a colourless oil and silyl THF **127** (81 mg, 30%) as a colourless oil.

Lab Book Reference: WSK/4/011

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128

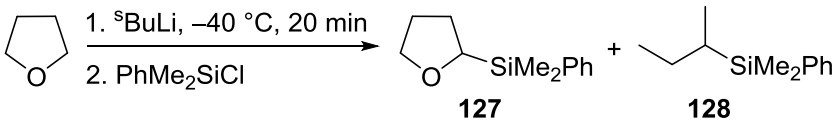


(Table 3.2, entry 5)

Using general procedure F, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and TMEDA (151 mg, 195 μL, 1.3 mmol) in THF (7 mL) at –40 °C for 20 min and $PhMe_2SiCl$ (314 mg, 336 μL, 2.0 mmol) gave the crude product, which contained a 70:30 mixture (by ^{1}H NMR spectroscopy) of **128** and **127**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave **128** (76 mg, 30%) as a colourless oil, a 55:45 mixture (by ^{1}H NMR spectroscopy) of **128** and $PhMe_2SiCl$ (57 mg, 29 mg (11% yield) of **128** and 29 mg of $PhSiMe_2Cl$) as a colourless oil and silyl THF **127** (68 mg, 14%) as a colourless oil.

Lab Book Reference: WSK/4/003

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128

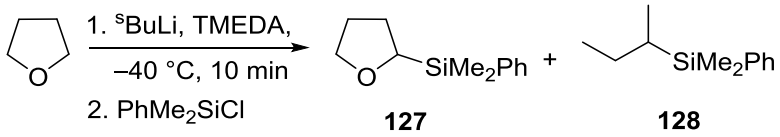


(Table 3.2, entry 6)

Using general procedure G, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) in THF (7 mL) at –40 °C for 20 min and $PhMe_2SiCl$ (314 mg, 336 μL, 2.0 mmol) gave the crude product, which contained a 70:30 mixture (by ^1H NMR spectroscopy) of **128** and **127**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave **128** (128 mg, 51%) as a colourless oil and and silyl THF **127** (26 mg, 21%) as a colourless oil.

Lab Book Reference: WSK/4/002

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128

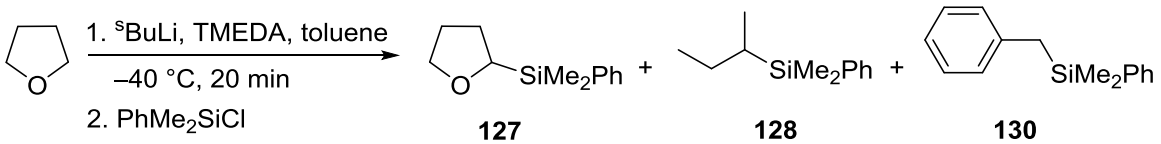


(Table 3.2, entry 7)

Using general procedure F, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and TMEDA (151 mg, 195 μL, 1.3 mmol) in THF (7 mL) at –40 °C for 10 min and $PhMe_2SiCl$ (314 mg, 336 μL, 2.0 mmol) gave the crude product, which contained a 95:5 mixture (by ^1H NMR spectroscopy) of **128** and **127**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave silyl THF **127** (30 mg, 11%) as a colourless oil.

Lab Book Reference: WSK/3/099

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128, benzylphenyldimethylsilane 130

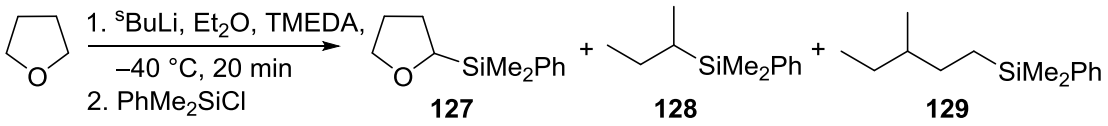


(Scheme 3.28)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), THF (72 mg, 81 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in toluene (7 mL) at –40 °C for 20 min and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product, which contained a 80:15:5 mixture (by ^{1}H NMR spectroscopy) of **130**, **128** and **127**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave **128** (19 mg, 8%) as a colourless oil, **130** (224 mg, 76%), R_F (98:2 hexane-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.44 (m, 2H, Ph), 7.38-7.33 (m, 3H, Ph), 7.21-7.15 (m, 2H, Ph), 7.10-7.03 (m, 1H, Ph), 6.96-6.91 (m, 2H, Ph), 2.31 (s, 2H, C*H*Ph), 0.25 (s, 6H, SiMe) and silyl THF **127** (9 mg, 5%) as a colourless oil. Spectroscopic data of **130** consistent with those reported in the literature.[124]

Lab Book Reference: WSK/4/006

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128, 3-methylpentanyldimethylphenylsilane 129

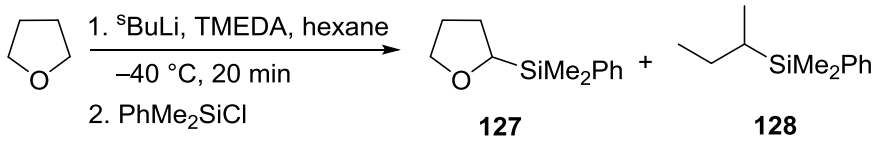


(Scheme 3.29)

Using general procedure **E**, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), THF (72 mg, 81 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in Et_2O (7 mL) at –40 °C for 20 min and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product, which contained a 90:10 mixture (by ^{1}H NMR spectroscopy) of **128** and **127**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave a 85:15 mixture (by ^{1}H NMR spectroscopy) of **128** and **129** (136 mg, 113 mg (45% yield) of **128** and 23 mg of **129**) as a colourless oil and silyl THF **127** (2 mg, 0.7%) as a colourless oil.

Lab Book Reference: WSK/4/010

2-(Dimethylphenylsilyl)tetrahydrofuran 127, 1-methylpropyldimethylphenylsilane 128,

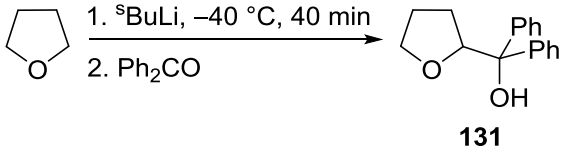


(Scheme 3.31)

Using general procedure **E**, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), THF (72 mg, 81 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –40 °C for 20 min and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product, which contained a 90:10 mixture (by ^1H NMR spectroscopy) of **128** and **127**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave **128** (93 mg, 37%) as a colourless oil and silyl THF **127** (21 mg, 10%) as a colourless oil.

Lab Book Reference: WSK/4/007

2-(diphenylhydroxymethyl)-tetrahydrofuran 131



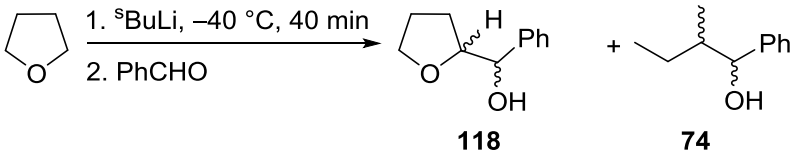
(Scheme 3.32)

Using general procedure G, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) in THF (7 mL) at –40 °C for 40 min and a solution of benzophenone (364 mg, 2.0 mmol) in THF (1 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave hydroxyl THF **131** (107 mg, 32%) as a white solid, mp 50-52 °C, R_F (9:1 petrol-EtOAc) 0.3; IR (ATR) 3483 (OH), 3024, 2869, 1447, 1062, 749, 697, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.55 (m, 2H, Ph), 7.43-7.37 (m, 2H, Ph), 7.34-7.27 (m, 4H, Ph), 7.25-7.15 (m, 2H, Ph), 4.89 (dd, J = 8.0, 6.5 Hz, 1H, OCH), 3.99-3.89 (m, 2H, OCH), 2.99 (s, 1H, OH), 1.95-1.78 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.5 (*ipso*-Ph), 144.4 (*ipso*-Ph), 128.1 (Ph), 128.0 (Ph), 127.0 (Ph),

126.8 (Ph), 126.6 (Ph), 125.5 (Ph), 82.9 (OCH), 78.3 (OCPh), 69.8 (OCH_2), 26.8 (CH_2), 26.2 (CH_2); MS (ESI) *m/z* 277 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}O_2$ ($M + Na)^+$ 277.1199, found 277.1194 (+1.5 ppm error).

Lab Book Reference: WSK/4/013

2-(α-Hydroxybenzyl) tetrahydrofuran 118, 2-methyl-1-phenylbutan-1-ol 74



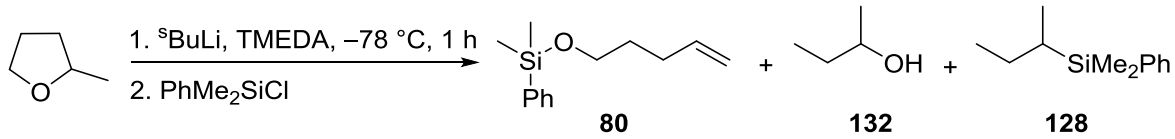
118 **74**

(Scheme 3.32)

Using general procedure G, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) in THF (7 mL) at –40 °C for 40 min and benzaldehyde (228 mg, 203 μL, 2.0 mmol) gave the crude product, which contained a 50:50 mixture (by ^{1}H NMR spectroscopy) of **74** and **118** (both as a 50: 50 mixture of diastereomers). Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (68 mg, 32%) as a colourless oil and a 60:40 mixture (by ^{1}H NMR spectroscopy) of diastereomeric hydroxy THFs **118** (71 mg, 20%) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.21 (m, 5H, Ph), 4.91 (d, *J* = 3.5 Hz, 0.6H, OC*H*Ph), 4.42 (d, *J* = 7.0 Hz, 0.4H, OC*H*Ph), 4.06 (ddd, *J* = 7.0, 7.0, 4.0 Hz, 0.6H, OCH), 4.00 (ddd, *J* = 7.0, 7.0 Hz, 0.4H, OCH), 3.94-3.74 (m, 3H, OCH), 3.07 (br s, 0.4H, OH), 2.63 (br s, 0.6H, OH), 1.96-1.48 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.5 (*ipso*-Ph), 140.4 (*ipso*-Ph), 128.3 (Ph), 128.2 (Ph), 127.9 (Ph), 127.4 (Ph), 126.9 (Ph), 126.0 (Ph), 83.4 (O*C*HPh), 83.1 (O*C*HPh), 76.9 (OCH), 73.9 (OCH), 69.0 (OCH_2), 68.4 (OCH_2), 27.9 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 24.7 (CH_2). Spectroscopic data consistent with those reported in the literature.[88,125]

Lab Book Reference: WSK/4/012

Dimethyl(pet-4-enyloxy)(phenyl)silane 80, 2-butanol 132, 1-methylpropyldimethyl phenylsilane 128

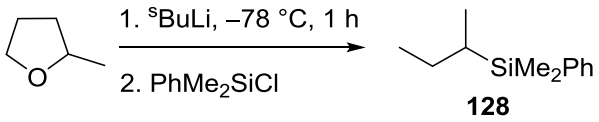


(Scheme 3.33)

Using general procedure **F**, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in 2-MeTHF (7 mL) at –78 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product, which contained a 35:25:40 mixture (by ^{1}H NMR spectroscopy) of alkene **80**, 2-butanol **132** and silane **128**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave silane **128** (9 mg, 4%) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.4 and a 60:40 mixture (by ^{1}H NMR spectroscopy) of alkene **80** and 2-butanol **132** (83 mg, 68 mg (31% yield) of **80** and 15 mg (20% yield) of **132**) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.2. Diagnostic signals for 2-butanol **132**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77-3.68 (m, 1H, OCH), 1.51-1.36 (m, 2H, CH), 1.10 (d, J = 6.0 Hz, 3H, CH*Me*), 0.84 (t, J = 7.5 Hz, CH_2*Me*). Spectroscopic data for 2-butanol **132** consistent with those reported in the literature.[126]

Lab Book Reference: WSK/3/091

1-methylpropyldimethyl phenylsilane 128

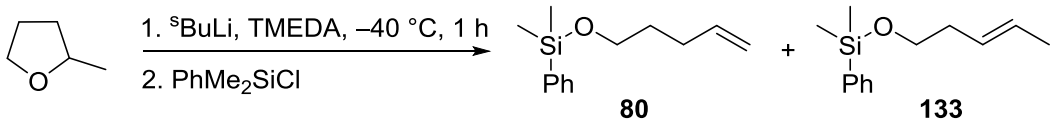


(Scheme 3.34)

Using general procedure **G**, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) in 2-MeTHF (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of **128** and $PhMe_2SiCl$ (333 mg, 156 mg (63%) of **128** and 117 mg of $PhMe_2SiCl$) as a colourless oil.

Lab Book Reference: WSK/3/098

Dimethyl(pet-4-enyloxy)(phenyl)silane 80, dimethyl(pet-3-enyloxy)(phenyl)silane 133

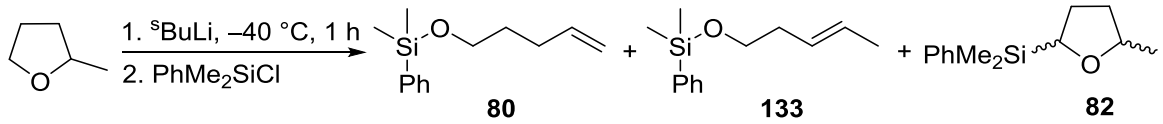


(Scheme 3.35)

Using general procedure F, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in 2-MeTHF (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product, which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of alkenes **80** and **133**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave an 85:15 mixture (by ^{1}H NMR spectroscopy) of alkenes **80** and **133** (175 mg, 61%, i.e. 52% yield of **80** and 9% yield of **133**) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.1; diagnostic signals for **133**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50-5.39 (m, 1H, =CH), 5.29-5.18 (m, 1H, =CH), 3.50 (t, J = 7.0 Hz, 2H, OCH_2), 2.18 (dt, J = 7.0, 7.0 Hz, 2H, $CH_2CH{=}CH_2$).

Lab Book Reference: WSK/3/089

Dimethyl(pet-4-enyloxy)(phenyl)silane 80, dimethyl(pet-3-enyloxy)(phenyl)silane 133, 2-methyl-5-(Dimethylphenylsilyl)tetrahydrofuran 82



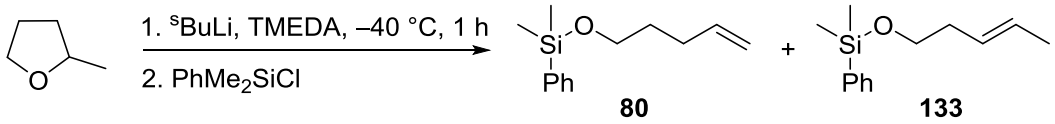
(Scheme 3.37)

Using general procedure G, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) in 2-MeTHF (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product, which contained a 55:15:30 mixture (by ^{1}H NMR spectroscopy) of **80**, **133** and **82** (as a 70:30 mixture of diastereomers). Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave a 75:25 mixture (by ^{1}H

NMR spectroscopy) of **80** and **133** (32 mg, 11%, i.e. 8% yield of **80** and 3% yield of **133**) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.2; a 20:10:70 mixture (by ^{1}H NMR spectroscopy) of **80**, **133** and **82** (13 mg, 5%, i.e. 1% yield of **80**, 0.5% yield of **133** and 3.5% yield of **82**) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.2 and **82** (as a 70:30 mixture of diastereomers) (3 mg, 1%) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.1; IR (ATR) 2966, 1710, 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.54 (m, 2H, Ph), 7.40-7.31 (m, 3H, Ph), 4.03-3.89 (m, 1H, OC*H*Me), 3.74 (dd, J = 11.0, 6.5 Hz, 0.7H, OCH), 3.57 (dd, J = 11.0, 6.5 Hz, 0.3H, OCH), 2.05-1.85 (m, 2H, CH), 1.79-1.64 (m, 1H, CH), 1.46-1.27 (m, 1H, CH), 1.20 (d, J = 6.0 Hz, 2.1H, CH*Me*), 1.15 (d, J = 6.0 Hz, 0.9H, CH*Me*), 0.33 (s, 4.2H, SiMe), 0.32 (s, 1.8H, SiMe). Attempted characterisation by ESI and ATCI mass spectrometry was not successful.

Lab Book Reference: WSK/3/090

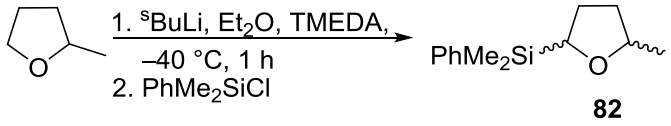
Dimethyl(pet-4-enyloxy)(phenyl)silane 80, dimethyl(pet-3-enyloxy)(phenyl)silane 133



s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of TMEDA (151 mg, 195 µL, 1.3 mmol) in 2-MeTHF (7 mL) at –40 °C under Ar. The resulting solution was stirred at –40 °C for 1 h. Then, $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) was added. The resulting solution was stirred at –40 °C for 10 min and then allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of alkenes **80** and **133**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave an 85:15 mixture (by ^{1}H NMR spectroscopy) of alkenes **80** and **133** (175 mg, 61%, i.e. 52% yield of **80** and 9% yield of **133**) as a colourless oil, R_F (98:2 hexane-EtOAc) 0.1; diagnostic signals for **133**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50-5.39 (m, 1H, =CH), 5.29-5.18 (m, 1H, =CH), 3.50 (t, J = 7.0 Hz, 2H, OCH_2), 2.18 (dt, J = 7.0, 7.0 Hz, 2H, C*H*$_2$CH=CH$_2$).

Lab Book Reference: WSK/3/089

2-methyl-5-(Dimethylphenylsilyl)tetrahydrofuran 82

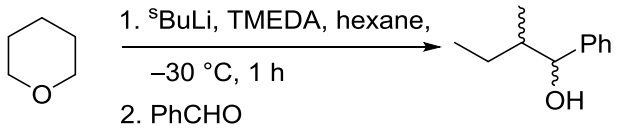


82

(Scheme 3.38)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 2-MeTHF (72 mg, 81 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in Et_2O (7 mL) at –40 °C for 1 h and $PhMe_2SiCl$ (314 mg, 336 µL, 2.0 mmol) gave the crude product. The ^1H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: WSK/3/095



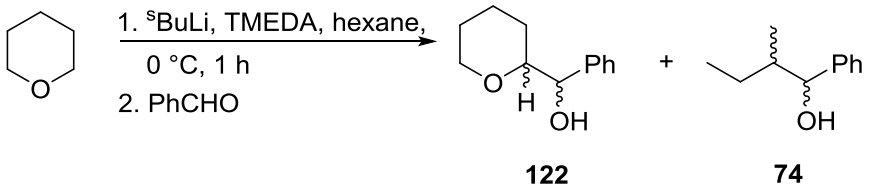
74

(Scheme 3.39)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), THP (86 mg, 98 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –30 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. The ^1H NMR spectrum of the crude product showed that only **74** was formed. Therefore, purification was not attempted.

Lab Book Reference: WSK/4/026

2-(α-Hydroxybenzyl) tetrahydropyran 122, 2-methyl-1-phenylbutan-1-ol 74



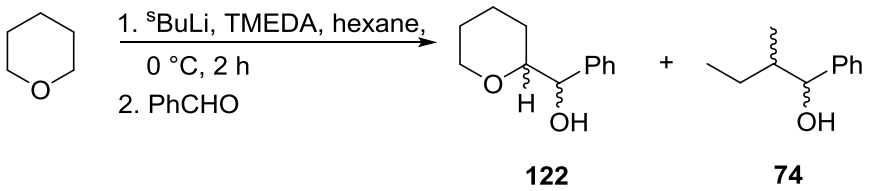
122 **74**

(Table 3.3, entry1)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), THP (86 mg, 98 μL, 1.0 mmol) and TMEDA (151 mg, 195 μL, 1.3 mmol) in hexane (7 mL) at 0 °C for 1 h and benzaldehyde (228 mg, 203 μL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (81 mg, 38%) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **122** (57 mg, 29%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H, Ph), 4.83 (d, J = 3.5 Hz, 0.5H, OC*H*Ph), 4.70 (s, 1H, OH), 4.43 (d, J = 8.0 Hz, 0.5H, OC*H*Ph), 4.12-4.01 (m, 1H, OCH), 3.54-3.44 (m, 1.5H, OCH), 3.35-3.28 (m,0.5H, OCH), 1.62-1.20 (m, 6H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.2 (*ipso*-Ph), 140.0 (*ipso*-Ph), 128.3 (Ph), 128.1 (Ph), 128.0 (Ph), 127.3 (Ph), 127.3 (Ph), 126.4 (Ph), 82.0 (O*C*HPh), 81.0 (O*C*HPh), 77.8 (OCH), 75.7 (OCH), 68.9 (OCH_2), 68.5 (OCH_2), 27.4 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 24.0 (CH_2), 22.9 (CH_2), 22.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[127]

Lab Book Reference: WSK/4/028

2-(α-Hydroxybenzyl) tetrahydropyran 122, 2-methyl-1-phenylbutan-1-ol 74

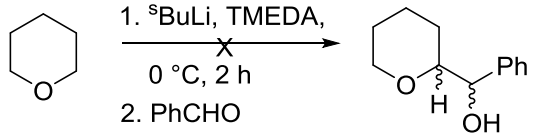


122 **74**

(Table 3.3, entry2)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), THP (86 mg, 98 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at 0 °C for 2 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (37 mg, 18%) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **122** (50 mg, 26%) as a colourless oil.

Lab Book Reference: WSK/5/005



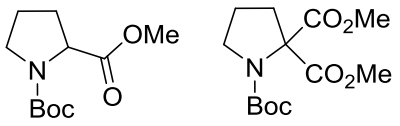
122

(Scheme 3.41)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in THP (7 mL) at 0 °C for 2 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) 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: WSK/5/006

Methyl *N*-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylate 22 and pyrrolidine-1,2,2-tricarboxylic acid 1-*tert*-butyl ester 2,2-dimethyl ester 70



22 **70**

(Table 3.4, entry 1)

Using general procedure H, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in THF (7 mL) at –78 °C for 1 h and methyl chloroformate (283 mg, 231 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave methyl ester **22** (24 mg, 10%) as a colourless oil, R_F (8:2 hexane-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 4.32 (dd, J = 8.5, 5.0 Hz, 0.4H, NCH), 4.22 (dd, J = 8.5, 4.5 Hz, 0.6H, NCH), 3.73 (s, 1.2H, OMe), 3.72 (s, 1.8H, OMe), 3.60-3.33 (m, 2H, NCH), 2.31-2.09 (m, 1H, CH), 2.07-1.77 (m, 3H, CH), 1.46 (s, 3.6H, CMe_3), 1.41 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 173.7 (C=O, CO_2Me), 153.7 (C=O, Boc), 79.8 (CMe_3), 59.0 (NCH), 58.6 (NCH), 52.0 (OMe), 51.9 (OMe), 46.5 (NCH_2), 46.2 (NCH_2), 30.8 (CH_2), 29.8 (CH_2), 28.3 (CMe_3), 28.2 (CMe_3), 24.3 (CH_2), 23.6 (CH_2) and dimethyl ester pyrrolidine **55** (174 mg, 60%) as a colourless oil, R_F (8:2 hexane-EtOAc) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 3.79 (s, 2.1H, OMe), 3.78 (s, 3.9H, OMe), 3.59 (t, J = 7.0 Hz, 1.35H, NCH), 3.52 (t, J = 7.0 Hz, 0.65H, NCH), 2.49 (t, J = 7.0 Hz, 1.3H, CH_2), 2.46 (t, J = 7.0 Hz, CH_2), 1.92-1.80 (m, 2H, CH_2), 1.46 (s, 3.15H, CMe_3), 1.39 (s, 5.85H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 169.8 (C=O, CO_2Me), 169.7 (C=O, CO_2Me), 153.8 (C=O, Boc), 153.2 (C=O, Boc), 80.5 (CMe_3), 80.2 (CMe_3), 71.9 (NCCH$_2$), 71.8 (NCCH$_2$), 52.9 (OMe), 52.7 (OMe), 47.3 (NCH_2), 47.2 (NCH_2), 38.2 (CH_2), 36.7 (CH_2), 28.2 (CMe_3), 28.0 (CMe_3), 23.6 (CH_2), 22.8 (CH_2). Spectroscopic data for **22**[128] and **70**[15] consistent with those reported in the literature.

Lab Book Reference: WSK/3/028

(Table 2.4, entry 2)

Using general procedure H, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in THF (7 mL) at –30 °C for 5 min and methyl chloroformate (283 mg, 231 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave methyl ester **22** (16 mg, 7%) as a colourless oil and dimethyl ester pyrrolidine **70** (143 mg, 50%) as a colourless oil.

Lab Book Reference: WSK/3/031

(Table 2.4, entry 3)

s-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. Then, methyl chloroformate (283 mg, 231 μL, 3.0 mmol) was added. The resulting solution was stirred at –30 °C for 10 min and allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave methyl ester **22** (41 mg, 18%) as a colourless oil and dimethyl ester pyrrolidine **5** (151 mg, 53%) as a colourless oil.

Lab Book Reference: WSK/3/040

(Table 2.4, entry 4)

Using general procedure H, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in THF (7 mL) at –20 °C for 5 min and methyl chloroformate (283 mg, 231 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave methyl ester **22** (32 mg, 14%) as a colourless oil and dimethyl ester pyrrolidine **70** (129 mg, 45%) as a colourless oil.

Lab Book Reference: WSK/3/033

(Table 2.4, entry 5)

Using general procedure H, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 μL, 1.0 mmol) in 2-MeTHF (7 mL) at –78 °C for 1 h and methyl chloroformate (283 mg, 231 μL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave methyl ester **22** (54 mg, 24%) as a colourless oil and dimethyl ester pyrrolidine **70** (152 mg, 53%) as a colourless oil.

Lab Book Reference: WSK/3/027

(Table 2.4, entry 6)

Using general procedure H, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) in 2-MeTHF (7 mL) at –20 °C for 5 min and methyl chloroformate (283 mg, 231 µL, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave methyl ester **22** (59 mg, 26%) as a colourless oil and dimethyl ester pyrrolidine **70** (109 mg, 38%) as a colourless oil.

Lab Book Reference: WSK/3/034

(Table 2.4, entry 7)

s-BuLi (1.6 mL of a 1.3 M solution in hexanes, 2.08 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) and TMEDA (302 mg, 390 µL, 2.6 mmol) in Et_2O (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. Then, methyl chloroformate (283 mg, 231 µL, 3.0 mmol) was added. The resulting solution was stirred at –30 °C for 10 min and allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave dimethyl ester pyrrolidine **70** (60 mg, 21%) as a colourless oil.

Lab Book Reference: WSK/3/032

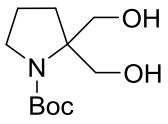
(Table 2.4, entry 8)

s-BuLi (1.6 mL of a 1.3 M solution in hexanes, 2.08 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175 µL, 1.0 mmol) and TMEDA (302 mg, 390 µL, 2.6 mmol) in 2-MeTHF (7 mL) at –30 °C under Ar. The resulting solution was

stirred at –78 °C for 1 h. Then, methyl chloroformate (283 mg, 231 μL, 3.0 mmol) was added. The resulting solution was stirred at –30 °C for 10 min and allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave methyl ester **22** (68 mg, 30%) as a colourless oil and dimethyl ester pyrrolidine **70** (70 mg, 24%) as a colourless oil.

Lab Book Reference: WSK/3/025

***tert*-Butyl 2,2-bis(hydroxymethyl)pyrrolidine-1-carboxylate 157**



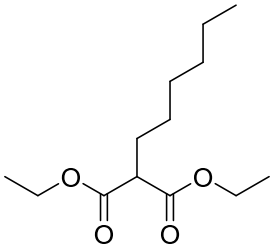
157

(Scheme 3.46)

A solution of dimethyl ester pyrrolidine **70** (915 mg, 3.2 mmol) in THF (2 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (241 mg, 6.4 mmol) in THF (20 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 1 h. Then, H_2O (2 mL), 20% $NaOH_{(aq)}$ (4 mL) and H_2O (10 mL) were added dropwise. The two layers were separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 EtOAc-hexane as eluent gave diol **157** (376 mg, 51%) as a white solid, R_F (9:1 EtOAc-hexane) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (d, J = 11.5 Hz, 2H, CHOH), 3.58 (d, J = 11.5 Hz, 2H, CHOH), 3.37 (t, J = 7.0 Hz, 2H, NCH_2), 2.64-2.32 (br s, 2H, OH), 1.84-1.72 (m, 4H, CH_2), 1.45 (s, 9H, $SiMe_3$).

Lab Book Reference: WSK/3/043

Diethyl 2-hexylmalonate 160



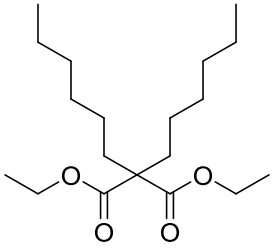
160

(Scheme 3.49)

A solution of diethyl malonate **142** (5.22 g, 5.0 mL, 32.6 mmol) in DMF (5 mL) was added dropwise to a stirred solution of NaH (1.44 g of a 60% dispersion in mineral oil, 35.9 mmol) in DMF (100 mL) at 0 °C under Ar. The resulting mixture was then stirred with 1-bromohexane at rt for 16 h. Ice-H_2O (40 mL) and EtOAc (120 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (5 × 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave hexylmalonate **160** (6.76 g, 85%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.3; IR (ATR) 2928, 2858, 1731 (C=O), 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, J = 7.0 Hz, 4H, OCH_2), 3.30 (t, J = 7.5 Hz, 1H, CH), 1.94-1.81 (m, 2H), 1.34-1.23 (m, 8H), 1.24 (t, J = 7.0 Hz, 6H, OCH_2*Me*), 0.87 (t, J = 7.0 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.6 (C=O), 61.2 (OCH_2), 52.1 (CH), 31.5 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 22.5 (CH_2), 14.1 (Me), 14.0 (Me). Spectroscopic data consistent with those reported in the literature.[129]

Lab Book Reference: WSK/4/090

Diethyl 2,2-dihexylmalonate 161



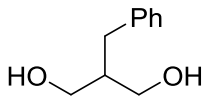
161

(Scheme 3.49)

A solution of diethyl 2-hexylmalonate **160** (2.70 g, 11.0 mmol) in DMF (10 mL) was added dropwise to a stirred solution of NaH (485 mg of a 60% dispersion in mineral oil, 12.1 mmol, 1.1 eq.) in DMF (80 mL) at 0 °C under Ar. The resulting mixture was then stirred with 1-bromohexane at rt for overnight. Ice-H_2O (20 mL) and EtOAc (50 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (5 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-Et_2O as eluent gave dihexylmalonate **161** (3.16 g, 87%) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.4; IR (ATR) 2956, 2925, 2858, 1730 (C=O), 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, J = 7.0 Hz, 4H, OCH_2), 1.90-1.81 (m, 4H, CH), 1.35-1.20 (m, 18H, CH), 1.19-1.08 (m, 4H, CH), 0.93-0.83 (m, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.1 (C=O), 61.0 (OCH_2), 57.5 ($C(CH_2)$), 32.0 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 23.8 (CH_2), 22.5 (CH_2), 14.1 (Me), 14.0 (Me); MS (ESI) *m/z* 351 [$(M + Na)^+$, 100], 329 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{19}H_{36}O_4$ $(M + Na)^+$ 351.2506, found 351.2501 (+1.2 ppm error), $(M + H)^+$ 329.2686, found 329.2680 (+1.4 ppm error).

Lab Book Reference: WSK/5/013

2-Benzylpropane-1,3-diol 162



162

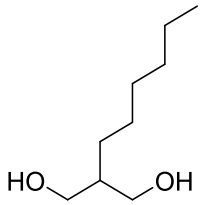
(Scheme 3.50)

A solution of diethylbenzylmalonate (1.00 g, 941 µL, 4.0 mmol) in Et_2O (3 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (660 mg, 16 mmol) in Et_2O (15 mL) at 0 °C under Ar. The resulting suspension was stirred at rt for 3 h. Then, ice-H_2O (10 mL), was added dropwise. The two layers were separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 hexane-acetone as eluent gave diol **162** (619 mg,

93%) as a white solid, mp 55-57 °C (lit.,[130] 51-53 °C); R_F (6:4 hexane-acetone) 0.2; IR (ATR) 3270 (OH), 2932, 1452, 1444, 1036, 1025, 744, 698, 547, 495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H, Ph), 7.24-7.15 (m, 3H, Ph), 3.81 (ddd, J = 10.5, 3.5, 3.5 Hz, 2H, OCH), 3.68 (ddd, J = 10.5, 7.0, 3.0 Hz, 2H, OCH), 2.63 (d, J = 7.5 Hz, 2H, CH_2Ph), 2.19 (br s, 2H, OH), 2.13-2.02 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.8 (*ipso*-Ph), 128.9 (Ph), 128.4 (Ph), 126.1 (Ph), 65.7 (OCH_2), 43.8 (CH), 34.2 (CH_2Ph); MS (ESI) *m/z* 189 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}O_2$ $(M + Na)^+$ 189.0886, found 189.0891 (+2.7 ppm error). Spectroscopic data consistent with those reported in the literature.[130,131]

Lab Book Reference: WSK/4/070

2-Hexylpropane-1,3-diol 163



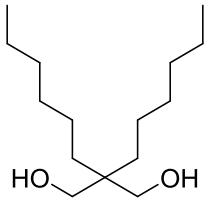
163

(Scheme 3.50)

A solution of hexylmalonate **160** (1.05 g, 4.3 mmol) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (711 mg, 17.2 mmol) in THF (15 mL) at 0 °C under Ar. The resulting suspension was stirred at rt for 3 h. Then, ice-H_2O (5 mL) was added dropwise and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane-acetone as eluent gave diol **163** (581 mg, 85%) as a colourless oil, R_F (7:3 hexane-acetone) 0.2; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (dd, J = 10.5, 4.0 Hz, 2H, OCH), 3.66 (dd, J = 10.5, 7.5 Hz, 2H, OCH), 2.06 (br s, 2H, OH), 1.84-1.70 (m, 1H, CH), 1.38-1.17 (m, 10H), 0.88 (t, J = 6.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 66.8 (OCH_2), 41.9 (CH), 31.7 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 27.2 (CH_2), 22.6 (CH_2), 14.1 (Me). Spectroscopic data consistent with those reported in the literature.[132]

Lab Book Reference: WSK/4/091

2,2-Dihexylpropane-1,3-diol 164



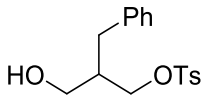
164

(Scheme 3.50)

A solution of dihexylmalonate **161** (1.65 g, 5.0 mmol) in THF (6 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (828 mg, 20.0 mmol) in THF (18 mL) at 0 °C under Ar. The resulting suspension was stirred at rt for 3 h. Then, ice-H_2O (6 mL) was added dropwise and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 85:15 hexane-acetone as eluent gave diol **164** (1.09 g, 90%) as a colourless oil, R_F (85:15 hexane-acetone) 0.2; IR (ATR) 3340 (OH), 2926, 2857, 1466, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.57 (d, J = 5.0 Hz, 4H, OCH_2), 2.14 (t, J = 5.0 Hz, 2H, OH), 1.37-1.13 (m, 20H, CH_2), 0.88 (t, J = 7.0 Hz, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 69.6 ($C(CH_2)_4$), 41.0 (CH_2), 31.8 (CH_2), 30.8 (CH_2), 30.2 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.1 (Me); MS (ESI) *m/z* 267 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{32}O_2$ $(M + Na)^+$ 267.2295, found 267.2289 (+2.1 ppm error). Spectroscopic data consistent with those reported in the literature.[133]

Lab Book Reference: WSK/5/017

2-Benzyl-3-hydroxypropyl 4-methylbenzenesulfonate 165



165

n-BuLi (2.77 mL of a 2.0 M solution in hexanes, 5.5 mmol) was added dropwise to a stirred solution of diol **162** (920 mg, 5.5 mmol) in THF (35 mL) at 0 °C under Ar. The

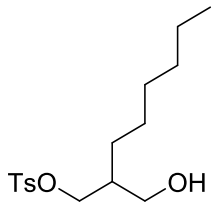
resulting solution was stirred at 0 °C for 10 min. Then, a solution of *p*-TsCl (1.05 g, 5.5 mmol) in THF (5 mL) was added. The resulting solution was stirred at 0 °C for 1 h and then allowed to warm to rt over 1 h. H_2O (20 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 Et_2O-hexane as eluent gave tosylate **165** (1.46 g, 83%) as a colourless oil, R_F (6:4 Et_2O-hexane) 0.2; IR (ATR) 3558 (OH), 2925, 1353, 1172, 944, 812, 665, 553 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H, Ar), 7.34 (d, *J* = 8.0 Hz, 2H, Ar), 7.25-7.15 (m, 3H, Ar), 7.08 (d, *J* = 8.0 Hz, 2H, Ar), 4.10 (dd, *J* = 10.0, 4.5 Hz, 1H, TsOCH), 3.99 (dd, *J* = 10.0, 5.5 Hz, 1H, TsOCH), 3.65 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H, HOC*H*), 3.57 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H, HOC*H*), 2.64 (dd, *J* = 11.5, 5.0 Hz, 1H, C*H*Ph), 2.59 (dd, *J* = 11.5, 5.0 Hz, 1H, C*H*Ph), 2.45 (s, 3H, Me), 2.20-2.03 (m, 1H, CH), 1.61 (t, *J* = 5.5 Hz, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.9 (*ipso*-Ar), 138.6 (*ipso*-Ar), 132.7 (*ipso*-Ar), 129.9 (Ar), 128.9 (Ar), 128.5 (Ar), 127.9 (Ar), 126.3 (Ar), 69.5 (TsO*C*H_2), 61.3 (OCH_2), 42.5 (CH), 33.5 (*C*H_2Ph), 21.6 (Me); MS (ESI) *m/z* 343 [$(M + Na)^+$, 100], 321 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}O_4S$ $(M + H)^+$ 321.1155, found 321.1138 (+4.0 ppm error), $(M + Na)^+$ 343.0975, found 343.0972 (+0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[131]

Lab Book Reference: WSK/4/071

n-BuLi (1.18 mL of a 2.2 M solution in hexanes, 2.6 mmol) was added dropwise to a stirred solution of tosylate **165** (842 mg, 2.6 mmol) in THF (20 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 60 °C for 6 h and then allowed to cool to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 Et_2O-hexane as eluent gave oxetane **168** (105 mg, 43%) as a colourless oil.

Lab Book Reference: WSK/4/063

2-(Hydroxymethyl)octyl 4-methylbenzenesulfonate 166



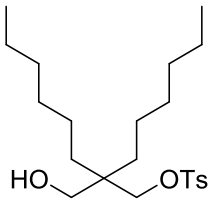
166

(Scheme 3.51)

n-BuLi (4.0 mL of a 2.5 M solution in hexanes, 10.0 mmol) was added dropwise to a stirred solution of diol **163** (1.60 g, 10.0 mmol) in THF (60 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 10 min. Then, a solution of *p*-TsCl (1.90 g, 10.0 mmol) in THF (5 mL) was added. The resulting solution was stirred at 0 °C for 1 h and then allowed to warm to rt over 1 h. H_2O (40 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave tosylate **166** (2.75 g, 88%) as a pale yellow oil, R_F (8:2 hexane-EtOAc) 0.1; IR (ATR) 3431 (OH), 2927, 1355, 1173, 942, 812, 666, 553 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H, *o*-$SO_2C_6H_4Me$), 7.35 (d, J = 8.0 Hz, 2H, *m*-$SO_2C_6H_4Me$), 4.11 (dd, J = 10.0, 4.5 Hz, 1H, TsOCH), 4.03 (dd, J = 10.0, 6.0 Hz, 1H, TsOCH), 3.63 (dd, J = 11.0, 4.5 Hz, 1H, HOC*H*), 3.55 (dd, J = 11.0, 6.5 Hz, 1H, HOC*H*), 2.45 (s, 3H, Me), 1.85-1.74 (m, 1H, CH), 1.34-1.14 (m, 10H), 0.86 (t, J = 6.5 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.8 (*ipso*-Ar), 132.9 (*ipso*-Ar), 129.9 (Ar), 127.9 (Ar), 70.3 ($TsOCH_2$), 61.9 ($HOCH_2$), 40.5 (CH), 31.6 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 21.6 ($SO_2C_6H_4$*Me*), 14.1 (Me); MS (ESI) *m/z* 337 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{26}O_4S$ $(M + Na)^+$ 337.1444, found 337.1445 (+0.2 ppm error).

Lab Book Reference: WSK/4/098

2-(Hydroxymethyl)octyl 4-methylbenzenesulfonate 167



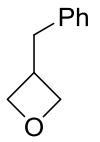
167

(Scheme 3.51)

n-BuLi (3.5 mL of a 2.5 M solution in hexanes, 8.9 mmol, 1.0 eq.) was added dropwise to a stirred solution of diol **164** (2.18 g, 8.9 mmol) in THF (60 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 10 min. Then, a solution of *p*-TsCl (1.70 g, 8.9 mmol) in THF (5 mL) was added. The resulting solution was stirred at 0 °C for 1 h and then allowed to warm to rt over 1 h. H_2O (40 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave tosylate **167** (3.19 g, 90%) as a pale yellow oil, R_F (8:2 hexane-EtOAc) 0.3; IR (ATR) 3564 (OH), 2929, 2858, 1739, 1359, 1175, 956, 666, 554 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H, *o*-$SO_2C_6H_4Me$), 7.35 (d, J = 8.0 Hz, 2H, *m*-$SO_2C_6H_4Me$), 3.68 (s, 2H, $TsOCH_2$), 3.40 (d, J = 7.0 Hz, 1H, $HOCH_2$), 2.45 (s, 3H, Me), 1.57 (br s, 1H, $HOCH_2$), 3.88-3.80 (m, 20H, CH_2), 0.87 (t, J = 6.5 Hz, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.8 (*ipso*-Ar), 132.9 (*ipso*-Ar), 129.9 (Ar), 127.9 (Ar), 72.3 ($TsOCH_2$), 64.3 (OCH_2), 41.4 (CCH_2), 31.7 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 22.6 (CH_2), 22.3 (CH_2), , 21.0 ($SO_2C_6H_4Me$), 14.2 (Me); MS (ESI) *m/z* 421 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{22}H_{38}O_4S$ $(M + Na)^+$ 421.2383, found 421.2375 (+2.7 ppm error).

Lab Book Reference: WSK/5/021

3-Benzyl oxetane 168

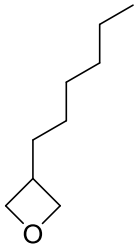


168

A solution of tosylate **165** (1.75 g, 5.5 mmol) in DMF (5 mL) was added dropwise to a stirred solution of NaH (657 mg of a 60% dispersion in mineral oil, 16.5 mmol) in DMF (20 mL) at 0 °C under Ar. The resulting mixture was then stirred at rt for 4 h. Ice-H_2O (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 Et_2O-hexane as eluent gave oxetane **168** (354 mg, 44%) as a colourless oil, R_F (6:4 Et_2O-hexane) 0.3; IR (ATR) 2957, 2955, 2865, 975, 850, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 7.5, 7.0 Hz, 2H, Ph), 7.21 (t, J = 7.5 Hz, 1H, Ph), 7.12 (d, J = 7.0 Hz, 2H, Ph), 4.79 (dd, J = 7.5, 6.5 Hz, 2H, OCH), 4.48 (dd, J = 6.5, 6.5 Hz, 2H, OCH), 3.39-3.24 (m, 1H, CH), 3.02 (d, J = 8.0 Hz, 2H, CH_2Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.4 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 126.3 (Ph), 77.2 (OCH_2), 39.6 (CH_2), 36.1 (CH); MS (ESI) *m/z* 171 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{12}O$ (M + Na)$^+$ 171.0780, found 171.0776 (+2.7 ppm error). Spectroscopic data consistent with those reported in the literature.[134]

Lab Book Reference: WSK/4/074

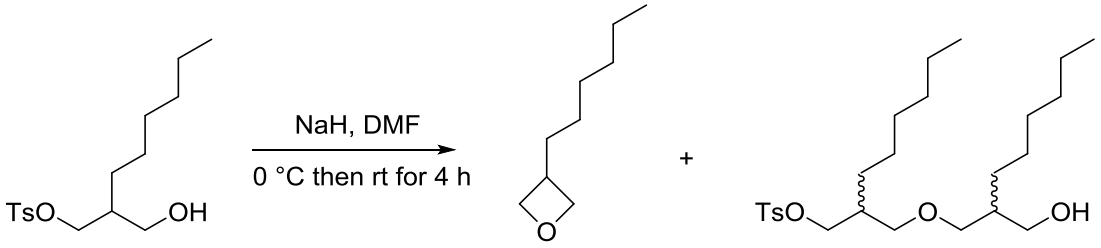
3-Hexyloxetane 169



169

A solution of tosylate **166** (637 mg, 2.0 mmol) in DMF (8 mL) was added dropwise to a stirred solution of NaH (243 mg of a 60% dispersion in mineral oil, 6.1 mmol) in DMF (40 mL) at 0 °C under Ar. The resulting mixture was then stirred at rt for 4 h. Ice-H_2O (20 mL) and EtOAc (60 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (5 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave oxetane **169** (204 mg, 71%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.4; IR (ATR) 2955, 2922, 2856, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77 (dd, J = 8.0, 6.0 Hz, 2H, OCH), 4.36 (dd, J = 6.0, 6.0 Hz, 2H, OCH), 3.02-2.88 (m, 1H, CH), 1.66 (dt, J = 7.5, 7.5 Hz, 2H, CH_2), 1.35-1.13 (m, 8H, CH_2), 0.87 (t, J = 6.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 77.9 (OCH_2), 35.3 (CH), 33.8 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.1 (Me). Attempted characterisation by ESI mass spectrometry was not successful.

Lab Book Reference: WSK/5/004



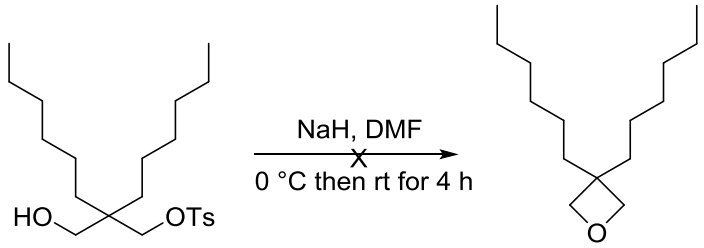
166 **168** **171**

A solution of tosylate **166** (637 mg, 2.0 mmol) in DMF (3 mL) was added dropwise to a stirred solution of NaH (243 mg of a 60% dispersion in mineral oil, 6.1 mmol) in DMF (10 mL) at 0 °C under Ar. The resulting mixture was then stirred at rt for 4 h. Ice-H_2O (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave oxetane **169** (42 mg, 15%) as a colourless oil and a 50:50 mixture (by ^1H NMR spectroscopy) of diastereomeric hydroxy tosylates **171** (84 mg, 9%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.4; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.5 Hz, 2H, *o*-

$SO_2C_6H_4Me$), 7.34 (d, J = 8.5 Hz, 2H, *m*-$SO_2C_6H_4Me$), 4.03 (dd, J = 9.5, 4.5 Hz, 0.5H, TsOCH), 4.02 (dd, J = 9.5, 4.5 Hz, 0.5H, TsOCH), 3.98 (dd, J = 9.5, 6.0 Hz, 1H, TsOCH), 3.64 (dd, J = 11.0, 3.5 Hz, 0.5H, OCH), 3.63 (dd, J = 11.0, 3.5 Hz, 0.5H, OCH), 3.53 (dd, J = 11.0, 7.0 Hz, 1H, OCH), 3.48 (dd, J = 9.0, 4.0 Hz, 0.5H, OCH), 3.46 (dd, J = 9.0, 4.0 Hz, 0.5H, OCH), 3.41-3.28 (m, 3H, OCH), 2.45 (s, 3H, Me), 1.91-1.80 (m, 2H, CH), 1.74 (br s, 1H, OH), 1.30-1.17 (m, 20H, CH_2), 0.88 (t, J = 6.5 Hz, 3H, Me), 0.86 (t, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of diastereomers) δ 144.7 (*ipso*-Ar), 132.9 (*ipso*-Ar), 129.8 (Ar), 127.9 (Ar), 74.9 (OCH_2), 74.8 (OCH_2), 70.4 (OCH_2), 70.3 (OCH_2), 65.94 (OCH_2), 65.91 (OCH_2), 40.5 (CH), 38.6 (CH), 31.8 (CH_2), 31.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 27.6 (CH_2), 27.2 (CH_2), 26.63 (CH_2), 22.62 (CH_2), 22.56 (CH_2), 21.6 (Me), 14.08 (Me), 14.04 (Me); MS (ESI) *m/z* 479 [$(M + Na)^+$, 100], 457 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{25}H_{44}O_5S$ $(M + Na)^+$ 479.2802, found 479.2784 (+3.2 ppm error), $(M + H)^+$ 457.2982, found 457.2968 (+4.3 ppm error).

Lab Book Reference: WSK/4/099

Attempted formation of 33-dihexyloxetane 170

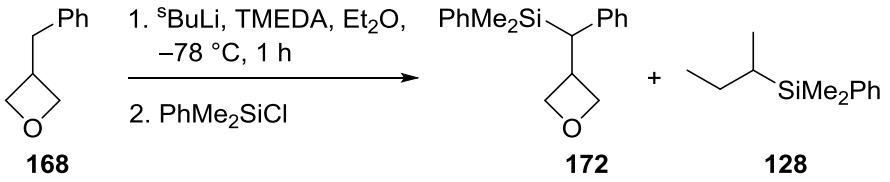


167 **170**

A solution of tosylate **167** (3.74 g, 8.9 mmol) in DMF (20 mL) was added dropwise to a stirred solution of NaH (1.07 g of a 60% dispersion in mineral oil, 26.7 mmol) in DMF (150 mL) at 0 °C under Ar. The resulting mixture was then stirred at rt for 4 h. Ice-H_2O (60 mL) and EtOAc (150 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give 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: WSK/5/023

2-(Dimethylphenylsilyl)benzyl-3-oxetane 172, 1-methylpropyldimethylphenylsilane 128

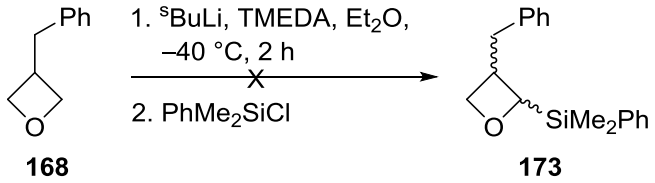


(Scheme 3.56)

Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), 3-benzyl oxetane **168** (165 mg, 1.1 mmol) and TMEDA (167 mg, 217 µL, 1.4 mmol) in Et_2O (7 mL) at –78 °C for 1 h and $PhMe_2SiCl$ (379 mg, 372 µL, 2.2 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave silane **128** (215 mg, 77%) and a 66:34 mixture (by ^1H NMR spectroscopy) of silylated oxetane **172** and $PhMe_2SiCl$ (91 mg, 49 mg (16%) of silylated oxetane **172** and 42 mg, (11%) of $PhMe_2SiCl$) as a colourless oil, R_F (98:2 CH_2Cl_2-Et_2O) 0.5. Diagnostic signals for silylated oxetane **172**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.57 (dd, J = 8.0, 6.0 Hz, 1H, OCH), 4.44 (dd, J = 8.0, 6.0 Hz, 1H, OCH), 4.18 (dd, J = 6.0, 6.0 Hz, 1H, OCH), 4.13 (dd, J = 6.0, 6.0 Hz, 1H, OCH), 3.69-3.56 (m, 1H, CH), 2.74 (d, J = 12.5 Hz, 1H, CHPh), 0.19 (s, 6H, SiMe).

Lab Book Reference: WSK/4/084

Attempted lithiation-trapping of 3-benzyl oxetane 168



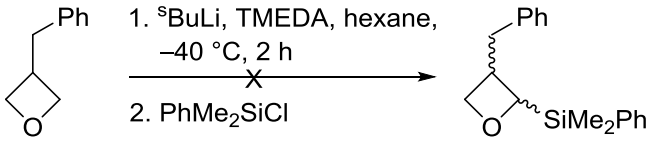
(Scheme 3.57)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 3-benzyl oxetane **168** (148 mg, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in Et_2O (7 mL) at –40 °C for 2 h and $PhMe_2SiCl$ (369 mg, 331 µL, 2.0 mmol) gave the crude

product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave an unidentifiable mixture (93 mg), R_F (98:2 CH_2Cl_2-Et_2O) 0.3. No starting material **168** or desired product **173** was found and therefore purification was not attempted.

Lab Book Reference: WSK/4/079

Attempted lithiation-trapping of 3-benzyl oxetane 168



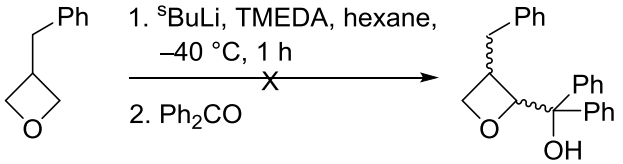
168 **173**

(Scheme 3.58)

Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), 3-benzyl oxetane **168** (161 mg, 1.1 mmol) and TMEDA (163 mg, 211 µL, 1.4 mmol) in hexane (7 mL) at –40 °C for 2 h and $PhMe_2SiCl$ (369 mg, 331 µL, 2.0 mmol) gave the crude product. The ^1H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: WSK/4/075

Attempted lithiation-trapping of 3-benzyl oxetane 168



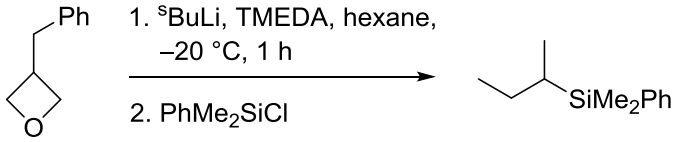
168 **174**

(Scheme 3.59)

Using general procedure E, *s*-BuLi (815 µL of a 1.3 M solution in hexanes, 1.0 mmol), 3-benzyl oxetane **168** (121 mg, 0.8 mmol) and TMEDA (123 mg, 159 µL, 1.0 mmol) in

hexane (7 mL) at –40 °C for 1 h and a solution of benzophenone (297 mg, 1.6 mmol) in hexane (1 mL) 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: WSK/4/068



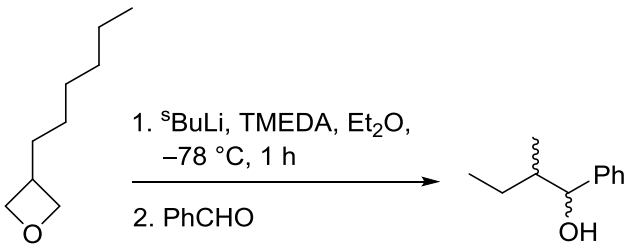
168 **128**

(Scheme 3.60)

Using general procedure E, *s*-BuLi (1.3 mL of a 1.3 M solution in hexanes, 1.6 mmol), 3-benzyl oxetane **168** (186 mg, 1.3 mmol) and TMEDA (189 mg, 244 µL, 1.6 mmol) in hexane (7 mL) at –20 °C for 1 h and $PhMe_2SiCl$ (427 mg, 413 µL, 2.5 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave silane **128** (77 mg, 25%) and an unidentifiable mixture (47 mg). No starting material **168** or desired product **173** was found.

Lab Book Reference: WSK/4/075

Attempted lithiation-trapping of 3-Hexyloxetane 175



169 **74**

(Scheme 3.61)

Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), 3-hexyl oxetane **169** (153 mg, 1.1 mmol) and TMEDA (162 mg, 209 µL, 1.4 mmol) in Et_2O

(7 mL) at –78 °C for 1 h and benzaldehyde (227 mg, 218 μL, 2.1 mmol) gave the crude product which contained a 53:47 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** and starting material **169**. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-Et_2O as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (147 mg, 64%) as a colourless oil and an starting material **169** (88 mg, 57%) as a colourless oil.

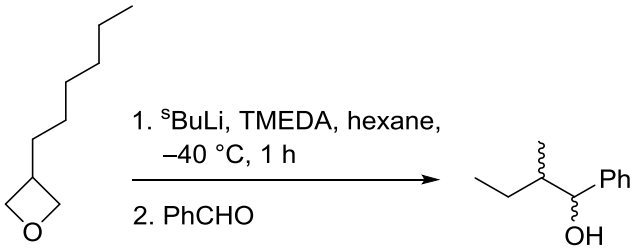
Lab Book Reference: WSK/5/008

169 **74**

(Scheme 3.62)

Using general procedure E, *s*-BuLi (1.3 mL of a 1.3 M solution in hexanes, 1.7 mmol), 3-hexyl oxetane **169** (182 mg, 1.3 mmol) and TMEDA (193 mg, 249 μL, 1.7 mmol) in Et_2O (7 mL) at –40 °C for 1 h and benzaldehyde (271 mg, 260 μL, 2.5 mmol) gave the crude product which contained a 56:44 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** and starting material **169**. The ^{1}H NMR spectroscopy of the crude product showed no desired product and therefore purification was not attempted.

Lab Book Reference: WSK/5/016

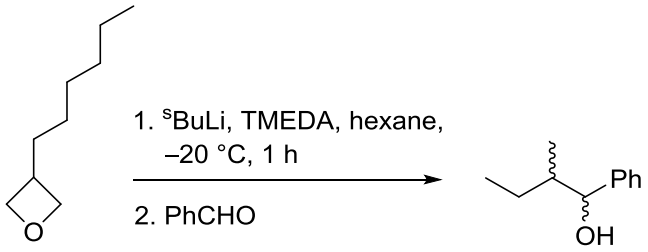


169 **74**

(Scheme 3.63)

Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), 3-hexyl oxetane **169** (155 mg, 1.1 mmol) and TMEDA (165 mg, 212 μL, 1.4 mmol) in hexane (7 mL) at –40 °C for 1 h and benzaldehyde (231 mg, 221 μL, 2.2 mmol) gave the crude product which contained a 58:42 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** and starting material **169**. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-Et_2O as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (163 mg, 70%) as a colourless oil and an starting material **169** (99 mg, 64%) as a colourless oil.

Lab Book Reference: WSK/5/018



169 **74**

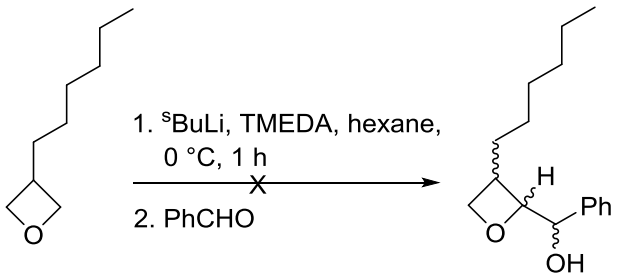
(Scheme 3.64)

Using general procedure E, *s*-BuLi (0.8 mL of a 1.3 M solution in hexanes, 1.0 mmol), 3-hexyl oxetane **169** (108 mg, 0.8 mmol) and TMEDA (114 mg, 148 μL, 1.0 mmol) in hexane (5 mL) at –20 °C for 1 h and benzaldehyde (161 mg, 154 μL, 1.5 mmol) gave the crude product which contained a 55:45 mixture (by ^{1}H NMR spectroscopy) of

diastereomeric alcohols **74** and starting material **169**. The ^{1}H NMR spectroscopy of the crude product showed no desired product and therefore purification was not attempted.

Lab Book Reference: WSK/5/024

Attempted lithiation-trapping of 3-benzyl oxetane 169



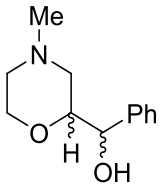
169 **175**

(Scheme 3.65)

Using general procedure E, *s*-BuLi (0.8 mL of a 1.3 M solution in hexanes, 1.1 mmol), 3-hexyl oxetane **169** (118 mg, 0.8 mmol) and TMEDA (125 mg, 161 µL, 1.1 mmol) in hexane (5 mL) at 0 °C for 1 h and benzaldehyde (176 mg, 168 µL, 1.6 mmol) gave the crude product. The ^{1}H NMR spectroscopy of the crude product showed no desired product and therefore purification was not attempted.

Lab Book Reference: WSK/5/025

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233



233

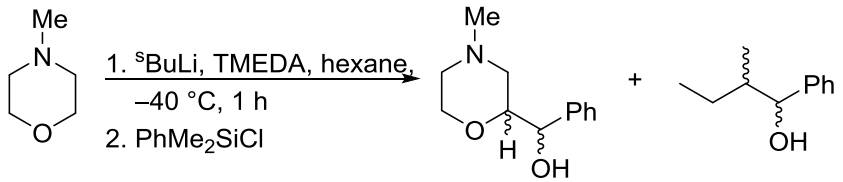
(Table 3.6, entry 6)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3

mmol) in hexane (7 mL) at 0 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (185 mg, 89%) as a white solid, mp 72-75 °C, R_F (acetone) 0.2; IR (ATR) 3124 (OH), 2939, 2854, 2808, 1449, 1118, 1104, 1029, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H, Ph), 4.89 (d, J = 4.0 Hz, 0.5H, OC*H*Ph), 4.52 (d, J = 8.0 Hz, 0.5H, OC*H*Ph), 4.03-3.92 (m, 1H, OCH), 3.79-3.67 (m, 1.5H, OCH), 3.62 (ddd, J = 11.0, 8.0, 2.5 Hz, 0.5H, OCH), 3.13 (br s, 0.5H, OH), 2.77 (br s, 0.5H, OH), 2.66-2.58 (m, 1H, NCH), 2.48 (br d, J = 11.0 Hz, 0.5H, NCH), 2.33 (br d, J = 11.0 Hz, 0.5H, NCH), 2.23 (s, 1.5H, NMe), 2.20 (s, 1.5H, NMe), 2.18-2.11 (m, 1H, NCH), 2.07 (dd, J = 11.0, 11.0 Hz, 0.5H, NCH), 1.85 (dd, J = 11.0, 11.0 Hz, 0.5H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.0 (*ipso*-Ph), 139.6 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 128.2 (Ph), 127.6 (Ph), 127.1 (Ph), 126.2 (Ph), 79.6 (O*C*HPh), 78.7 (O*C*HPh), 75.7 (OCH), 74.7 (OCH), 66.7 (OCH_2), 66.7 (OCH_2), 56.4 (NCH_2), 54.8 (NCH_2), 54.6 (NCH_2), 54.1 (NCH_2), 46.3 (NMe), 46.2 (NMe); MS (ESI) *m/z* 208 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO_2$ $(M + H)^+$ 208.1332, found 208.1329 (+1.4 ppm error).

Lab Reference: WSK/4/023

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



232 **233** **74**

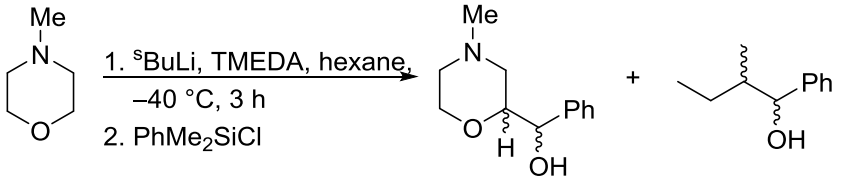
(Table 3.6, entry 1)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –40 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 68:32 mixture (by ^{1}H NMR spectroscopy) of **74** (as a 50:50

diastereomeric mixture) and benzaldehyde (186 mg, 109 mg (51%) of **74** and 77 mg (36%) of benzaldehyde) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (31 mg, 15%) as a white solid.

Lab Reference: WSK/4/017

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



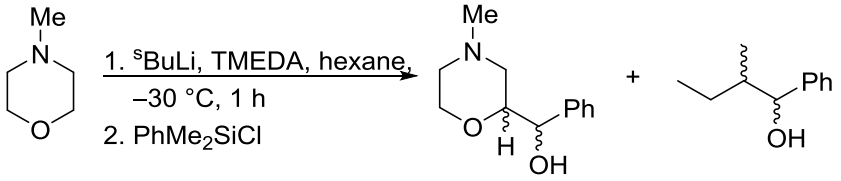
232 **233** **74**

(Table 3.6, entry 2)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –40 °C for 3 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (112 mg, 52%) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (88 mg, 42%) as a white solid.

Lab Reference: WSK/4/019

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



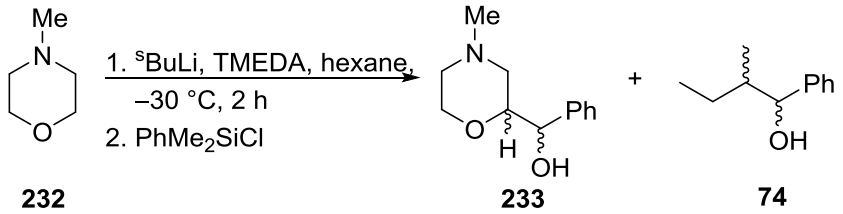
232 **233** **74**

(Table 3.6, entry 3)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –30 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (110 mg, 52%) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (83 mg, 40%) as a white solid.

Lab Reference: WSK/4/018

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



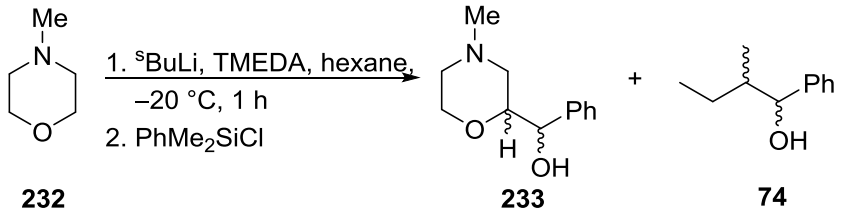
232 **233** **74**

(Table 3.6, entry 4)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –30 °C for 2 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 72:28 mixture (by ^{1}H NMR spectroscopy) of **74** (as a 50:50 mixture of diastereomeric alcohols) and benzaldehyde (125 mg, 78 mg (37%) of **74** and 47 mg (22%) of benzaldehyde) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (103 mg, 49%) as a white solid.

Lab Reference: WSK/4/021

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



232 **233** **74**

(Table 3.6, entry 5)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –20 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 59:41 mixture (by ^{1}H NMR spectroscopy) of **74** (as a 50:50 mixture of diastereomeric alcohols) and benzaldehyde (107 mg, 52 mg (24%) of **74** and 56 mg (26%) of benzaldehyde) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (130 mg, 63%) as a white solid.

Lab Reference: WSK/4/022

(Table 3.6, entry 7)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at 20 °C for 30 min and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (99 mg, 48%) as a white solid.

Lab Reference: WSK/4/032

(Table 3.6, entry 8)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at 20 °C for 10 min and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **74** (137 mg, 66%) as a white solid.

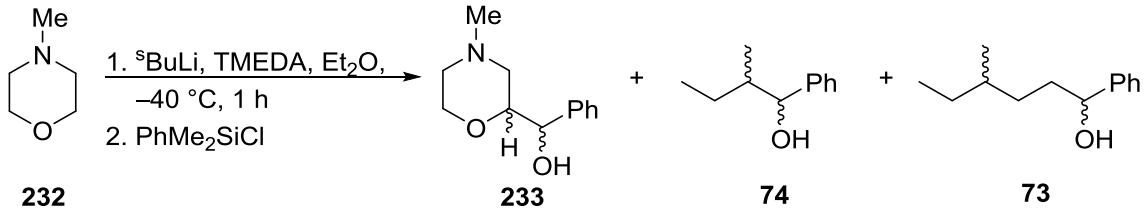
Lab Reference: WSK/4/032

(Scheme 3.77)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in cyclohexane (7 mL) at 0 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (169 mg, 82%) as a white solid.

Lab Reference: WSK/4/036

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74, 4-Methyl-1phenylhexan-1-ol 73



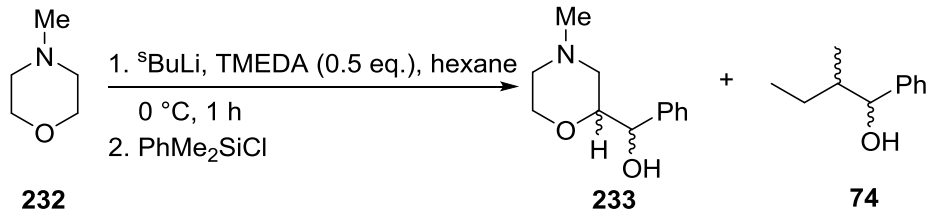
232 **233** **74** **73**

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in Et_2O (7 mL) at –40 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with

acetone as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of **74** and **73** (76 mg, 47 mg (34%) of **74** and 29 mg (15%, 30% based on 2 equivalents of *s*-BuLi being consumed) of **73**) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (33 mg, 16%) as a white solid.

Lab Reference: WSK/4/014

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



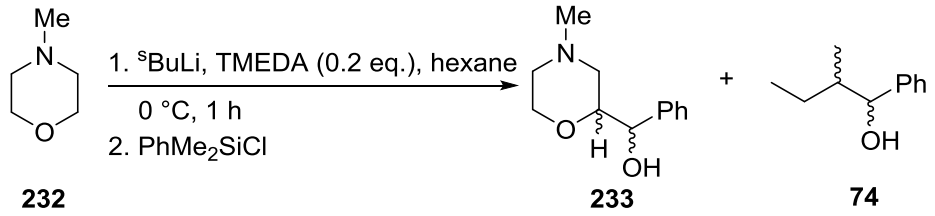
232 **233** **74**

(Table 3.7, entry 2)

Using general procedure I, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (58 mg, 75 µL, 0.5 mmol, 0.5 eq.) in hexane (7 mL) at 0 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 27:73 mixture (by ^{1}H NMR spectroscopy) of **74** (as a 50:50 mixture of diastereomeric alcohols) and benzaldehyde (56 mg, 11 mg (5%) of **74** and 45 mg (21%) of benzaldehyde) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (169 mg, 82%) as a white solid.

Lab Reference: WSK/4/035

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



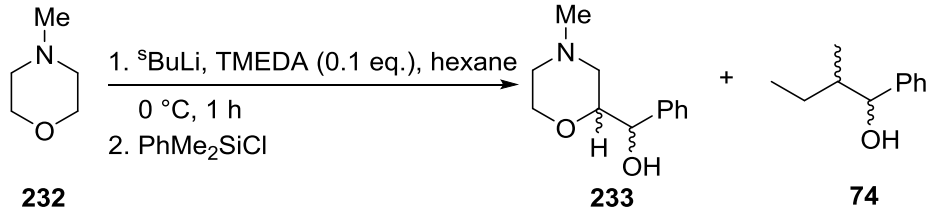
232 **233** **74**

(Table 3.7, entry 3)

Using general procedure I, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (23 mg, 30 µL, 0.2 mmol, 0.2 eq.) in hexane (7 mL) at 0 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 35:65 mixture (by ^{1}H NMR spectroscopy) of **74** (as a 50:50 mixture of diastereomeric alcohols) and benzaldehyde (67 mg, 17 mg (8%) of **X** and 50 mg (24%) of benzaldehyde) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (164 mg, 79%) as a white solid.

Lab Reference: WSK/4/037

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



232 **233** **74**

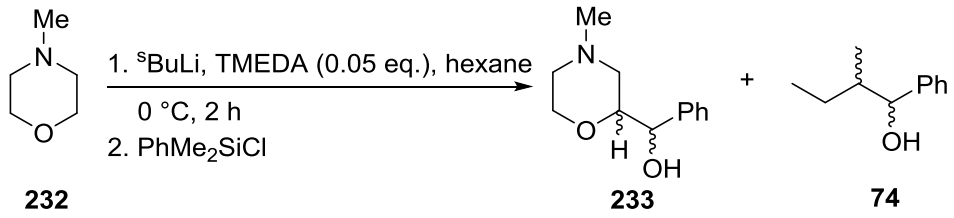
(Table 3.7, entry 4)

Using general procedure I, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (12 mg, 15 µL, 0.1 mmol, 0.1 eq.) in hexane (7 mL) at 0 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with

acetone as eluent gave a 33:67 mixture (by ^{1}H NMR spectroscopy) of **74** (as a 50:50 mixture of diastereomeric alcohols) and benzaldehyde (80 mg, 20 mg (9%) of **74** and 60 mg (28%) of benzaldehyde) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (150 mg, 72%) as a white solid.

Lab Reference: WSK/4/045

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



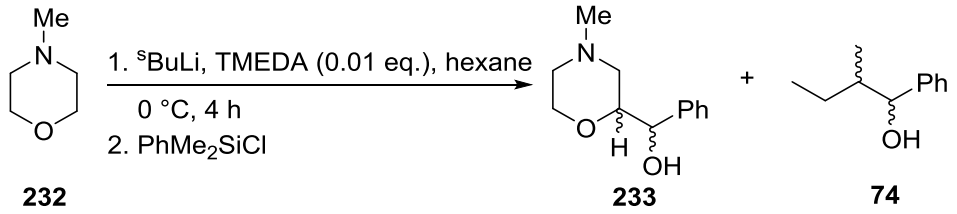
232 **233** **74**

(Table 3.7, entry 5)

Using general procedure I, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (150 µL of a 3.34×10^{-4} M solution in hexane, 0.05 mmol, 0.05 eq.) in hexane (7 mL) at 0 °C for 2 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 33:67 mixture (by ^{1}H NMR spectroscopy) of **74** (as a 50:50 mixture of diastereomeric alcohols) and benzaldehyde (84 mg, 20 mg (9%) of **74** and 60 mg (28%) of benzaldehyde) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (142 mg, 68%) as a white solid.

Lab Reference: WSK/4/050

4-Methyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 233, 2-methyl-1-phenylbutan-1-ol 74



232 **233** **74**

(Table 3.7, entry 6)

Using general procedure I, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (90 µL of a 1.11×10^{-4} M solution in hexane, 0.01 mmol, 0.01 eq.) in hexane (7 mL) at 0 °C for 4 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by 1H NMR spectroscopy) of diastereomeric alcohols **74** (102 mg, 48%) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (55 mg, 27%) as a white solid.

Lab Reference: WSK/4/060

(Table 3.7, entry 7)

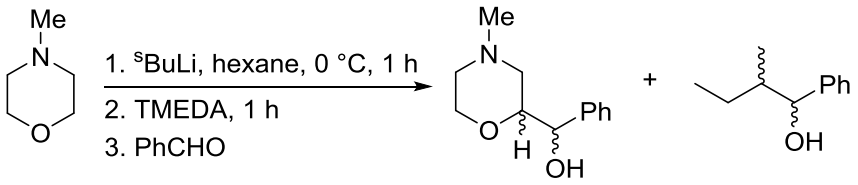
Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) in hexane (7 mL) at 0 °C for 1 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by 1H NMR spectroscopy) of diastereomeric alcohols **74** (159 mg, 74%) as a colourless oil. No desired product **233** was found.

Lab Reference: WSK/4/024

(Table 3.7, entry 8)

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) in hexane (7 mL) at 0 °C for 2 h and benzaldehyde (228 mg, 203 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by 1H NMR spectroscopy) of diastereomeric alcohols **74** (191 mg, 89%) as a colourless oil. No desired product **233** was found.

Lab Reference: WSK/4/086

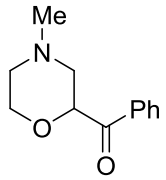


232 **233** **74**

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol, 1.0 eq.) in hexane (7 mL) at 0 °C under Ar. After stirring at 0 °C for 1 h, TMEDA (151 mg, 195 µL, 1.3 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 1 h. Then, benzaldehyde (228 mg, 203 µL, 2.0 mmol) was added and the resulting solution was stirred at 0 °C for 10 min. The solution was allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with acetone as eluent gave a 50:50 mixture (by 1H NMR spectroscopy) of diastereomeric alcohols **74** (26 mg, 12%) as a colourless oil and a 50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols **233** (135 mg, 65%) as a white solid.

Lab Reference: WSK/4/085

(4-Methylmorpholin-2-yl)(phenyl)methanone 236

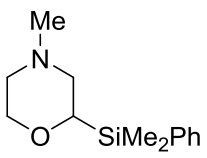


236

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at 0 °C for 1 h and a suspension of *N*,*N*-dimethylbenzamide (298 mg, 2.0 mmol) in Et_2O (2 mL) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave benzoyl morpholine **236** (153 mg, 75%) as a yellow oil, R_F (acetone) 0.3; IR (ATR) 2938, 2848, 2794, 1689 (C=O), 1448, 1118, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.5 Hz, 2H, Ph), 7.57 (dd, J = 7.5, 7.5 Hz, 1H, Ph), 7.46 (dd, J = 7.5, 7.5 Hz, 2H, Ph), 4.92 (dd, J = 7.5, 3.0 Hz, 1H, OCH), 4.06 (ddd, J = 11.0, 3.0, 2.0 Hz, 1H, OCH), 3.83 (ddd, J = 11.0, 11.0, 3.0 Hz, 1H, OCH), 3.04-2.98 (m, 1H, NCH), 2.72-2.65 (m, 1H, NCH), 2.33 (s, 3H, NMe), 2.29-2.18 (m, 2H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.7 (C=O), 134.9 (*ipso*-Ph), 133.5 (Ph), 128.9 (Ph), 128.6 (Ph), 77.9 (OCH), 66.9 (OCH_2), 56.7 (NCH_2), 54.5 (NCH_2), 46.3 (NMe); MS (ESI) *m/z* 206 [$(M + H)^+$, 100], 228 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_2$ $(M + H)^+$ 206.1176, found 206.1184 (–3.6 ppm error), $(M + Na)^+$ 228.0995, found 228.0994 (+0.1 ppm error).

Lab Book Reference: WSK/5/026

2-(Dimethyl(phenyl)silyl)-4-methylmorpholine 234



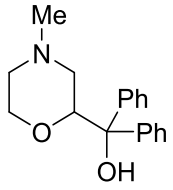
234

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3

mmol) in hexane (7 mL) at 0 °C for 1 h and $PhMe_2SiCl$ (341 mg, 333 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave silylated morpholine **234** (212 mg, 90%) as a yellow oil, R_F (acetone) 0.2; IR (ATR) 2956, 2935, 2786, 1247, 1095, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.51 (m, 2H, Ph), 7.41-7.32 (m, 3H, Ph), 3.87 (ddd, *J* = 11.0, 3.0, 1.5 Hz, 1H, OCH), 3.60 (ddd, *J* = 11.0, 11.0, 2.5 Hz, 1H, OCH), 3.52 (dd, *J* = 12.0, 2.5 Hz, 1H, OCH), 2.66 (dddd, *J* = 11.0, 2.0, 2.0, 2.0 Hz, 1H, NCH), 2.58 (ddd, *J* = 12.0, 2.0, 2.0 Hz, 1H, NCH), 2.22 (s, 3H, NMe), 2.12 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H, NCH), 2.04 (dd, *J* = 12.0, 12.0 Hz, 1H, NCH), 0.33 (s, 3H, SiMe), 0.32 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.4 (*ipso*-Ph), 134.1 (Ph), 129.3 (Ph), 127.8 (Ph), 71.1 (OCH), 68.8 (OCH_2), 56.6 (NCH_2), 55.7 (NCH_2), 46.4 (NMe), –5.2 (SiMe), –5.6 (SiMe); MS (ESI) *m/z* 236 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{21}NOSi$ $(M + H)^+$ 236.1465, found 236.1466 (+0.1 ppm error).

Lab Book Reference: WSK/4/029

4-Methyl-2-(1-hydroxy-1,1-diphenylmethyl)-morpholine 235



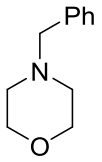
235

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-methyl morpholine **232** (101 mg, 110 µL, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at 0 °C for 1 h and a solution of benzophenone (364 mg, 2.0 mmol) in hexane (1 mL) gave the crude product. Purification by flash column chromatography on silica with acetone as eluent gave hydroxyl morpholine **235** (256 mg, 90%) as a white solid, mp 185-188 °C, R_F (acetone) 0.3; IR (ATR) 2957, 2846, 2808, 1448, 1116, 745, 699, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.47 (m, 2H, Ph), 7.43-7.37 (m, 2H, Ph), 7.35-7.27 (m, 4H, Ph), 7.24-7.15 (m, 2H, Ph), 4.52 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 3.96 (ddd, *J* = 11.0, 3.5, 1.5 Hz, 1H, OCH), 3.84 (ddd, *J* = 11.0, 11.0, 2.5 Hz, 1H, OCH), 3.33 (s, 1H, OH), 2.64 (br d, *J* = 11.0 Hz, 1H, NCH), 2.30-2.23 (m, 1H, NCH), 2.20 (s, 3H, NMe), 2.19-2.10 (m, 2H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.1 (*ipso*-Ph), 143.2 (*ipso*-Ph), 128.2 (Ph), 128.1 (Ph), 126.9 (Ph), 126.8 (Ph), 126.4 (Ph), 125.5 (Ph),

78.4 (O*C*Ph), 77.9 (OCH), 66.8 (OCH_2), 54.6 (NCH_2), 46.5 (NMe); MS (ESI) *m/z* 284 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO_2$ $(M + H)^+$ 284.1645, found 284.1647 (–0.8 ppm error).

Lab Reference: WSK/4/030

4-Benzyl morpholine 237



237

BnBr (2.94 g, 2.0 mL, 17.2 mmol, 1.5 eq.) was added to a stirred solution of morpholine (999 mg, 1.0 mL, 11.4 mmol, 1.0 eq.) and Et_3N (3.4 g, 4.7 mL, 34.4 mmol, 3.0 eq.) in THF (90 mL) at rt. The resulting solution was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave 4-benzyl morpholine **237** (1.94 g, 95%) as a colourless oil, R_F (1:1 hexane-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H, Ph), 3.71 (t, J = 4.5 Hz, 4H, OCH_2), 3.50 (s, 2H, CH_2Ph), 2.45 (t, J = 4.5 Hz, 4H, NCH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.7 (*ipso*-Ph), 129.2 (Ph), 128.2 (Ph), 127.1 (Ph), 67.0 (OCH_2), 63.5 (N*C*H_2Ph), 53.6 (NCH_2). Spectroscopic data consistent with those reported in the literature.[135]

Lab Reference: WSK/4/067

BnCl (570 mg, 518 µL, 4.5 mmol, 1.5 eq.) was added to a stirred solution of morpholine (261 mg, 262 µL, 3.0 mmol, 1.0 eq.) and Et_3N (310 mg, 418 µL, 9.0 mmol, 3.0 eq.) in THF (15 mL) at rt. The resulting solution was stirred at rt for ove16 h. Saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column

chromatography on silica with 1:1 hexane-EtOAc as eluent gave 4-benzyl morpholine **237** (258 mg, 49%) as a colourless oil.

Lab Reference: WSK/4/040

Morpholine (435 mg, 436 µL, 5.0 mmol, 1.0 eq.) was added to a stirred suspension of K_2CO_3 (1.38 g, 10.0 mmol, 2.0 eq.) in THF (50 mL) at rt. The resulting solution was stirred at rt for 15 min. Then, BnCl (633 mg, 575 µL, 5.0 mmol, 1.0 eq.) was added and the reaction mixture was stirred at rt for 48 h. Saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed no desired product **237** and therefore purification was not attempted.[136]

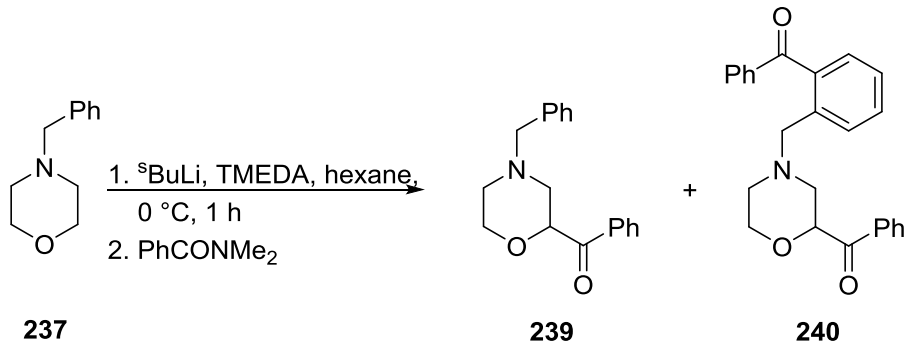
Lab Reference: WSK/4/034

Morpholine (261 mg, 261 µL, 3.0 mmol, 1.0 eq.) was added to a stirred solution of acetyl chloride (707 mg, 640 µL, 9.0 mmol, 3.0 eq.) in MeOH (20 mL) at rt. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure. MeOH (20 mL), Et_3N (910 mg, 418 µL, 9.0 mmol, 3.0 eq.) and BnCl (456 mg, 414 µL, 3.6 mmol, 1.2 eq.) were added and the reaction mixture was stirred at rt for 48 h. Saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed no desired product **237** and therefore purification was not attempted.

Lab Reference: WSK/4/039

(4-Benzylmorpholin-2-yl)(phenyl)methanone 239,

2-((4-benzylmorpholin-2-yl)(phenyl)methanone)-4-ylmethyl-benzophenone 240



237 **239** **240**

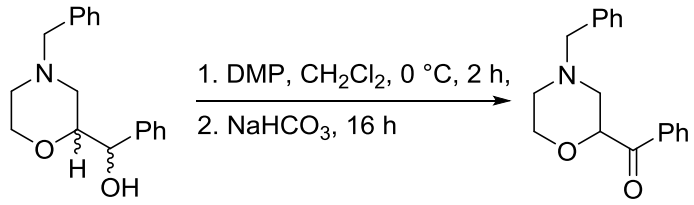
Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), 4-benzyl morpholine **237** (188 mg, 1.1 mmol) and TMEDA (160 mg, 207 µL, 1.4 mmol) in hexane (7 mL) at 0 °C for 1 h and a suspension of *N*,*N*-dimethylbenzamide (320 mg, 2.0 mmol) in hexane (1 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave di-substituted benzoyl morpholine **240** (56 mg, 14%) as a yellow oil, R_F (98:2 CH_2Cl_2-acetone) 0.5; IR (ATR) 2816, 1690 (C=O), 1660 (C=O), 1596, 1447, 1312, 1273, 1204, 1119, 763,694, 638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.82 (m, 4H, Ar), 7.60-7.52 (m, 2H, Ar), 7.51-7.34 (m, 7H, Ar), 7.30-7.23 (m, 1H, Ar), 4.31 (dd, *J* = 10.5, 3.0 Hz, 1H, OCH), 3.75 (ddd, *J* = 11.0, 3.0, 1.0 Hz, 1H, OCH), 3.52 (d, *J* = 14.0 Hz, 1H, NC*H*Ar), 3.48 (d, *J* = 14.0 Hz, 1H, NC*H*Ar), 3.26 (ddd, *J* = 11.0, 11.0, 3.0 Hz, 1H, OCH), 2.68 (ddd, *J* = 11.5, 3.0, 1.0 Hz, 1H, NCH), 2.32-2.24 (m, 1H, NCH), 2.16 (ddd, *J* = 11.5, 11.0, 3.0 Hz, 1H, NCH), 2.09 (dd, *J* = 11.5, 10.5 Hz, 1H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.5 (C=O), 196.3 (C=O), 139.2 (*ipso*-Ar), 137.8 (*ipso*-Ar), 137.4 (*ipso*-Ar), 134.6 (C=O*Ph*), 133.4 (Ar), 132.6 (Ar), 129.6 (Ar), 129.2 (Ar), 129.1 (Ar), 128.9 (Ar), 128.5 (Ar), 128.2 (Ar), 127.4 (Ar), 77.2 (OCH), 66.3 (OCH_2), 60.5 (NCH_2Ar), 54.1 (NCH_2), 5.6 (NCH_2) (one Ar signal not resolved); MS (ESI) *m/z* 408 [$(M + Na)^+$, 20], 386 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{25}H_{23}NO_3$ $(M + Na)^+$ 408.1570, found 408.1573 (–0.5 ppm error), $(M + H)^+$ 386.1751, found 386.1757 (–0.5 ppm error); and mono-substituted benzoyl morpholine **239** (133 mg, 44%) as a yellow oil, R_F (98:2 CH_2Cl_2-acetone) 0.4; IR (ATR) 2812, 1689, 1448, 1118, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00-7.94 (m, 2H, Ph), 7.60-7.53 (m, 1H, Ph), 7.48-7.38 (m, 3H, Ph), 7.36-7.28 (m, 4H, Ph), 4.93 (dd, *J* = 10.0, 2.5 Hz, 1H, OCH), 4.04 (ddd, *J* = 11.5, 3.5, 2.5 Hz, 1H, OCH), 3.83 (ddd, *J* = 11.0, 11.0, 3.0 Hz, 1H, OCH), 3.60 (d, *J* = 13.0 Hz, 1H, NC*H*Ph), 3.51 (d, *J* = 13.0 Hz, 1H, NC*H*Ph), 3.07 (br ddd, *J* = 11.5,

2.0, 2.0 Hz, 1H, NCH), 2.75-2.67 (m, 1H, NCH), 2.37-2.23 (m, 2H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.8 (C=O), 135.0 (*ipso*-Ph), 133.4 (*ipso*-Ph), 129.1 (Ph), 128.9 (Ph), 128.5 (Ph), 128.3 (Ph), 127.3 (Ph), 127.0 (Ph), 78.03 (OCH), 67.1 (OCH_2), 63.2 (NCH_2Ph), 55.1 (NCH_2), 52.5 (NCH_2); MS (ESI) *m/z* 282 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_2$ $(M + H)^+$ 282.1489, found 282.1482 (+2.7 ppm error).[137]

Lab Book Reference: WSK/5/032

Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), 4-benzyl morpholine **237** (188 mg, 1.1 mmol) and TMEDA (160 mg, 207 µL, 1.4 mmol) in hexane (7 mL) at –20 °C for 1 h and a suspension of *N*,*N*-dimethylbenzamide (320 mg, 2.0 mmol) in hexane (1mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave di-substituted benzoyl morpholine **240** (20 mg, 9%) as a yellow oil and mono-substituted benzoyl morpholine **239** (120 mg, 39%) as a yellow oil.

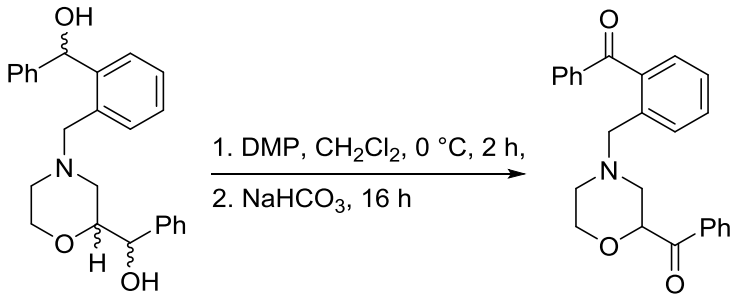
Lab Book Reference: WSK/5/031



206 **239**

A solution of a 50:50 mixture of diastereomeric alcohols **206** (50 mg, 0.17 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) was added dropwise to a stirred suspension of DMP (82 mg, 0.19 mmol, 1.1 eq.) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 2 h. Saturated $NaHCO_{3\,(aq)}$ (5 mL) was added and the solution was stirred at rt for 16h. The solids were removed by filtration and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed that benzoyl morpholine **239** was formed but no further purification was attempted.

Lab Book Reference: WSK/5/036

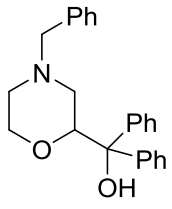


241 **240**

A solution of a diastereomeric mixture of alcohols **241** (50 mg, 0.13 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) was added dropwise to a stirred suspension of DMP (60 mg, 0.14 mmol, 1.1 eq.) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred for at rt 2 h. Saturated $NaHCO_{3\,(aq)}$ (5 mL) was added and the solution was stirred at rt for 16h. The solids were removed by filtration and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave di-substituted benzoyl morpholine **240** (10 mg, 21%) as a yellow oil.

Lab Book Reference: WSK/5/037

(4-Benzylmorpholin-2-yl)diphenylmethanol 244



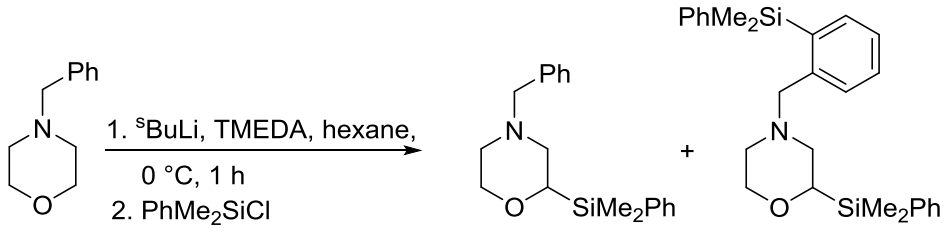
244

Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), 4-benzyl morpholine **237** (195 mg, 1.1 mmol) and TMEDA (166 mg, 214 µL, 1.4 mmol) in hexane (7 mL) at 0 °C for 1 h and a solution of benzophenone (400 mg, 2.2 mmol) in hexane (1 mL) gave the crude product. Purification by flash column chromatography on

silica with 1000:9:1 CH_2Cl_2-MeOH-NH_4OH as eluent gave hydroxy morpholine **244** (175 mg, 44%) as a white solid, mp 95-98 °C; R_F (1000:9:1 CH_2Cl_2-MeOH-NH_4OH) 0.5; IR (ATR) 1961, 1448, 1114, 744, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H, Ph), 7.41-7.36 (m, 2H, Ph), 7.35-7.13 (m, 11H, Ph), 4.54 (dd, J = 9.0, 3.0 Hz, 1H, OCH), 3.92 (ddd, J = 11.0, 2.5, 1.5 Hz, 1H, OCH), 3.77 (ddd, J = 11.0, 11.0, 3.0 Hz, 1H, OCH), 3.59-3.51 (d, J = 13.0 Hz, 1H, NC*H*Ph), 3.55 (br s, 1H, OH), 3.24 (d, J = 13.0 Hz, 1H, NC*H*Ph), 2.62-2.54 (m, 1H, NCH), 2.40-2.26 (m, 2H, NCH), 2.10 (ddd, J = 11.0, 11.0, 3.0 Hz, 1H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.0 (*ipso*-Ph), 143.2 (*ipso*-Ph), 137.4 (*ipso*-Ph), 129.2 (Ph), 128.2 (Ph), 128.1 (Ph), 127.9 (Ph), 127.1 (Ph), 126.8 (Ph), 126.7 (Ph), 126.5 (Ph), 125.5 (Ph), 78.7 (COH), 77.7 (OCH), 66.7 (OCH_2), 63.4 (N*C*H_2Ph), 53.5 (NCH_2), 52.0 (NCH_2); MS (ESI) *m/z* 360 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{24}H_{25}NO_2$ $(M + H)^+$ 360.1958, found 360.1956 (+0.6 ppm error).

Lab Book Reference: WSK/5/033

2-(Dimethyl(phenyl)silyl)-4-benzylmorpholine 242, 4-(*o*-Dimethyl(phenyl)silyl benzyl)-2-(Dimethyl(phenyl)silyl)-4-benzylmorpholine 243

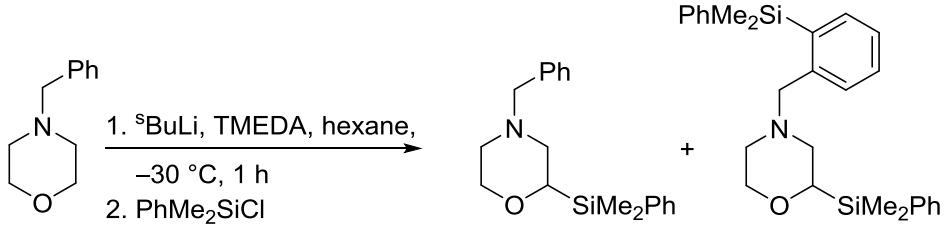


237 **242** **243**

Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), 4-benzyl morpholine **237** (199 mg, 1.1 mmol) and TMEDA (169 mg, 219 µL, 1.4 mmol) in hexane (7 mL) at 0 °C for 1 h and $PhMe_2SiCl$ (384 mg, 384 µL, 2.2 mmol) to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et_2O with 2% Et_3N as eluent gave di-silylated morpholine **243** (77 mg, 15%) as a colourless oil, R_F (8:2 hexane-Et_2O) 0.5; IR (ATR) 2953, 2802, 1427, 1247, 1086, 812, 729, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.45 (m, 1H, Ar), 7.44-7.37 (m, 2H, Ar), 7.36-7.30 (m, 2H, Ar), 7.29-7.07 (m, 9H, Ar), 3.60-3.53 (m, 1H, OCH), 3.31-3.18 (m, 3H), 3.04 (d, J = 13.0 Hz, NC*H*Ar), 2.29-2.23 (m, 1H, NCH), 2.24-2.18 (m, 1H, NCH), 1.82-

1.67 (m, 2H, NCH), 0.47 (s, 3H, SiMe), 0.45 (s, 3H, SiMe), 0.16 (s, 3H, SiMe), 0.13 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.3 (*ipso*-Ar), 139.5 (*ipso*-Ar), 137,0 (*ipso*-Ar), 136.7 (*ipso*-Ar), 135.9 (Ar), 134.1 (Ar), 133.8 (Ar), 129.6 (Ar), 129.2 (Ar), 128.7 (Ar), 127.7 (Ar), 127.7 (Ar), 126.3 (Ar), 70.7 (OCH), 68.6 (OCH_2), 63.6 (NCH_2), 54.9 (NCH_2), 53.3 (NCH_2), –0.5 (SiMe), –0.8 (SiMe), –5.2 (SiMe), –5.3 (SiMe) (one Ar signal not resolved); MS (ESI) *m/z* 446 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}NOSi_2$ $(M + H)^+$ 446.2330, found 446.2342 (–0.1 ppm error); and mono-silylated morpholine **242** (149 mg, 42%) as a colourless oil, R_F (8:2 hexane-Et_2O) 0.2; IR (ATR) 2954, 2801, 1427, 1247, 1086, 731, 697, 466 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.45 (m, 2H, Ph), 7.38-7.16 (m, 8H, Ph), 3.80 (ddd, *J* = 11.0, 3.0, 1.5 Hz, 1H, OCH), 3.59-3.49 (m, 2H), 3.53 (d, *J* = 13.0 Hz, 1H, NC*H*Ph), 3.28 (d, *J* = 13.0 Hz, 1H, NC*H*Ph), 2.65 (ddd, *J* = 11.0, 2.0, 1.5 Hz, 1H, NCH), 2.61 (dddd, *J* = 11.0, 3.0, 2.0, 2.0 Hz, 1H, NCH), 2.16 (dd, *J* = 12.0, 12.0 Hz, 1H, OCH), 2.08 (ddd, *J* = 12.0, 12.0, 2.0 Hz, 1H, NCH), 0.29 (s, 3H, SiMe), 0.28 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.8 (*ipso*-Ph), 136.5 (*ipso*-Ph), 134.1 (Ph), 129.2 (Ph), 129.2 (Ph), 128.2 (Ph), 127.8 (Ph), 127.0 (Ph), 71.0 (OCH), 68.9 (OCH_2), 63.5 (NCH_2Ph), 55.4 (NCH_2), 53.5 (NCH_2), –5.2 (SiMe), –5.4 (SiMe); MS (ESI) *m/z* 312 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{19}H_{25}NOSi$ $(M + H)^+$ 312.1778, found 312.1780 (–0.8 ppm error).

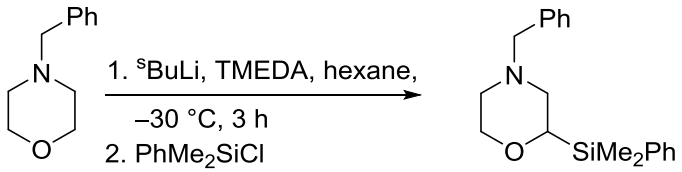
Lab Book Reference: WSK/5/034



237 **242** **243**

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-benzyl morpholine **237** (185 mg, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –30 °C for 1 h and $PhMe_2SiCl$ (222 mg, 215 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et_2O with 2% Et_3N as eluent gave di-substituted silylated morpholine **243** (26 mg, 6%) as a colourless oil, and mono-silylated morpholine **242** (121 mg, 37%) as a colourless oil.

Lab Book Reference: WSK/5/044



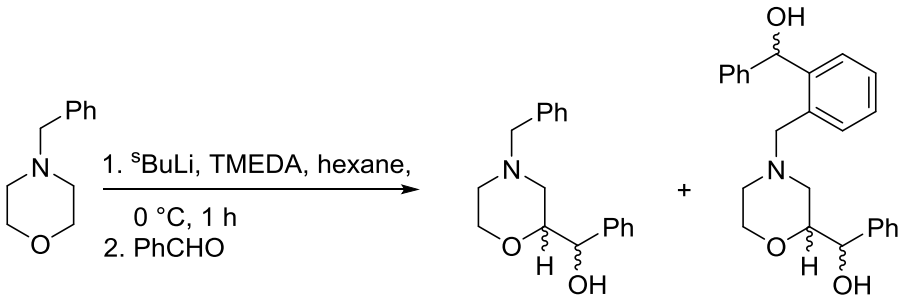
237 **242**

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), 4-benzyl morpholine **237** (185 mg, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –30 °C for 3 h and $PhMe_2SiCl$ (222 mg, 215 µL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et_2O with 2% Et_3N as eluent gave a 60:40 mixture (by ^1H NMR spectroscopy) of mono-silylated morpholine **242** and $PhMe_2SiCl$ (241 mg, 134 mg (40%) of **242** and 107 mg (29%) of $PhMe_2SiCl$) as a colourless oil and recovered starting material **237** (52 mg, 27%).

Lab Book Reference: WSK/5/053

4-benzyl-2-(1-hydroxy-1-phenylmethyl)-morpholine 206,

4-(*o*-Dimethyl(phenyl)silyl benzyl)-2-(1-hydroxy-1-phenylmethyl)-morpholine 241



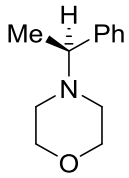
237 **206** **241**

Using general procedure E, *s*-BuLi (1.4 mL of a 1.3 M solution in hexanes, 1.8 mmol), 4-benzyl morpholine **237** (249 mg, 1.4 mmol) and TMEDA (212 mg, 274 µL, 1.4 mmol) in hexane (7 mL) at 0 °C for 1 h and benzaldehyde (298 mg, 285 µL, 2.8 mmol) gave the crude product. Purification by flash column chromatography on silica with 75:25 hexane-EtOAc as eluent gave recovered starting material **237** (30 mg, 12%) as a colourless oil, a

50:50 mixture (by ^{1}H NMR spectroscopy) of diastereomeric mono-substituted morpholines **206** (223 mg, 56%) as a yellow oil, R_F (75:25 hexane-EtOAc) 0.2; IR (ATR) 2814, 1452, 1113, 1024, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.18 (m, 10H, Ph), 4.88 (d, J = 4.5H, 0.5H, OC*H*Ph), 4.57 (d, J = 7.5 Hz, 0.5H, OC*H*Ph), 3.99-3.90 (m, 0.6H), 3.82-3.76 (m, 0.4H), 3.73-3.62 (m, 2H), 3.56 (d, J = 7.0 Hz, 0.5H, NC*H*Ph), 3.53 (d, J = 7.0 Hz, 0.5H, NC*H*Ph), 3.33 (d, J = 10.0 Hz, 0.5H, NC*H*Ph), 3.28 (d, J = 10.5 Hz, 0.5H, NC*H*Ph), 2.68-2.52 (m, 2H), 2.47 (br s, 0.5H, OH), 2.44 (br s, 0.5H, OH), 2.27-2.02 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.9 (*ipso*-Ph), 137.4 (*ipso*-Ph), 137.4 (*ipso*-Ph), 129.2 (Ph), 129.1 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 127.2 (Ph), 126.9 (Ph), 126.3 (Ph), 79.4, 78.5, 75.4, 75.3, 66.7, 66.5, 63.4, 63.2, 55.1, 52.8, 52.5, 52.2 (four Ph signals not resolved); MS (ESI) *m/z* 284 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO_2$ (M + H)$^+$ 284.1645, found 284.1656 (–3.6 ppm error) and a 48:32:12:8 mixture (by ^{1}H NMR spectroscopy) of diastereomeric di-substituted morpholines **241** (95 mg, 17%) as a yellow oil, R_F (75:25 hexane-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-6.91 (m, 14H, Ar), 5.84 (br s, 0.4H, OCH), 5.69 (br s, 0.6H, OCH), 4.94 (dd, J = 4.0 Hz, 0.2H, OCH), 4.55-4.47 (m, 0.8H), 4.00-3.80 (m, 1.5H), 3.77-3.58 (m, 2.5H), 3.53-3.48 (m, 0.5H), 3.28-3.22 (m, 0.5H), 3.03-2.95 (m, 0.5H), 2.93-2.79 (m, 1H), 2.65-2.46 (m, 2.5H), 2.16-2.00 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.6 (*ipso*-Ar), 144.5 (*ipso*-Ar), 143.8 (*ipso*-Ar), 142.9 (*ipso*-Ar), 139.7 (*ipso*-Ar), 139.3 (*ipso*-Ar), 134.5 (*ipso*-Ar), 134.5 (*ipso*-Ar), 132.4 (Ar), 132.1 (Ar), 131.1 (Ar), 129.8 (Ar), 128.7 (Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 127.8 (Ar), 127.7 (Ar), 127.4 (Ar), 127.1 (Ar), 126.9 (Ar), 126.7 (Ar), 126.4 (Ar), 126.2 (Ar), 126.0 (Ar), 125.3 (Ar), 125.2 (Ar), 79.8, 79.1, 78.8, 76.9, 75.4, 75.0, 74.8, 74.1, 66.6, 66.4, 66.2, 61.9, 61.7, 61.6, 54.4, 54.2, 51.9, 51.8, 51.2, 51.1, 30.9 (Ar not resolved); MS (ESI) *m/z* 390 [(M + H)$^+$, 100].[138,139]

Lab Book Reference: WSK/5/035

(*S*)-4-(1-Phenylethyl) morpholine 246



246

K_2CO_3 (2.68 g, 19.4 mmol, 5.0 eq.) and KI (1.42 g, 8.5 mmol, 2.2 eq.) were added to a stirred solution of (*S*)-(-)-α-methylbenzylamine (0.47 g, 0.5 mL, 3.8 mmol) in *n*-BuOH (15 mL) at 0 °C. The resulting solution was stirred at 0 °C for 15 min. Then, 2,2'-dichlorodiethyl ether (1.10 g, 0.91 mL, 7.7 mmol, 2.0 eq.) was added, and the reaction mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was allowed to cool to rt and the solids were removed by filtration. CH_2Cl_2 (50 mL) was added to the filtrate and washed with H_2O (2 × 10 mL) and saturated brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave morpholine **246** (321 mg, 43%) as a pale yellow oil, $[\alpha]_D$ –25.4 (*c* 0.5 in $CHCl_3$); R_F (1:1 hexane-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 4H, Ph), 7.28-7.21 (m, 1H, Ph), 3.73-3.64 (m, 4H, OCH), 3.29 (q, *J* = 7.0 Hz, 1H, NC*H*Me), 2.55-2.43 (m, 2H, NCH), 2.42-2.31 (m, 2H, NCH), 1.34 (d, *J* = 7.0 Hz, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.9 (*ipso*-Ph), 128.2 (Ph), 127.6 (Ph), 127.0 (Ph), 67.2 (OCH_2), 65.4 N*C*HPh), 51.3 (NCH_2), 19.8 (NCH*Me*). Spectroscopic data consistent with those reported in the literature.[140]

Lab Book Reference: WSK/5/038

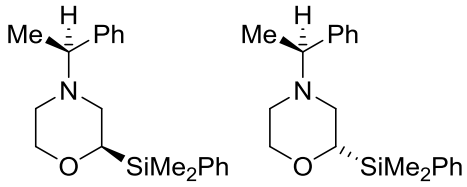
K_2CO_3 (10.81 g, 78.2 mmol, 5.0 eq.) and KI (5.77 g, 34.7 mmol, 2.2 eq.) were added to a stirred solution of (*S*)-(-)-α-methylbenzylamine (1.88 g, 2.0 mL, 15.5 mmol) in *n*-BuOH (60 mL) at 0 °C. The resulting solution was stirred at 0 °C for 15 min. Then, 2,2'-dichlorodiethyl ether (4.43 g, 3.6 mL, 31.0 mmol, 2.0 eq.) was added, and the reaction mixture was stirred and heated at 100 °C for 60 h. The reaction mixture was allowed to cool to rt and the solids were removed by filtration. CH_2Cl_2 (50 mL) was added to the filtrate and washed with H_2O (2 × 10 mL) and saturated brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave morpholine **246** (2.80 g, 94%) as a pale yellow oil.

Lab Book Reference: WSK/5/041

A reaction mixture of (*S*)-(-)-α-methylbenzylamine (0.47 g, 0.5 mL, 3.88 mmol, 1.0 eq.), 2,2'-dichlorodiethyl ether (721 mg, 591 μL, 5.04 mmol, 1.3 eq.), K_2CO_3 (2.15 g, 15.5 mmol, 4.0 eq.) and KI (129 mg, 0.78 mmol, 0.2 eq.) in EtOH (40 mL) was heated at reflux for 4 days. Then, the reaction mixture was allowed to cool to rt. The solution was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (2 × 10 mL) and saturated brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave morpholine **246** (200 mg, 29%) as a pale yellow oil.[141]

Lab Book Reference: WSK/5/039

2-(*R*/*S*)-2-(Dimethyl(phenyl)silyl)-4-((*S*)-1-phenylethyl)morpholine 247a and 247b

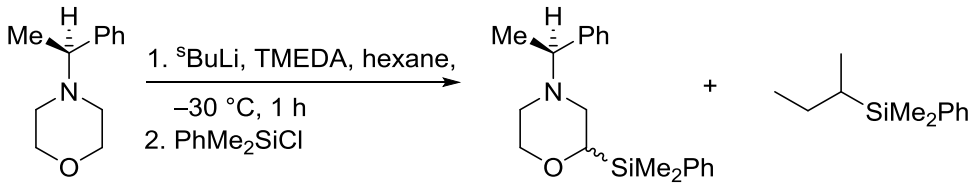


Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), (*S*)-4-(1-phenylethyl) morpholine **246** (211 mg, 1.1 mmol) and TMEDA (117 mg, 215 μL, 1.4 mmol) in hexane (7 mL) at 0 °C for 1 h and $PhSiMe_2Cl$ (377 mg, 365 μL, 2.2 mmol) gave the crude product, which contained a 50:50 mixture of **247a** and **247b** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave silylated morpholine **247a** (83 mg, 23%) as a colourless oil, $[\alpha]_D$ –5.0 (*c* 0.5 in $CHCl_3$); R_F (8:2 hexane-EtOAc) 0.3; IR (ATR) 2954, 2801, 1247, 1106, 1089, 814, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.54 (m, 2H, Ph), 7.41-7.33 (m, 3H, Ph), 7.33-7.19 (m, 5H, Ph), 3.74 (ddd, *J* = 11.0, 3.0, 1.5 Hz, 1H, OCH), 3.60 (dd, *J* = 11.5, 2.0 Hz, 1H, OCH), 3.50 (ddd, *J* = 11.0, 11.0, 2.0 Hz, 1H, OCH), 3.19 (q, *J* = 7.0 Hz, 1H, NC*H*Me), 2.91 (ddd, *J* = 11.5, 2.0, 1.5 Hz, 1H, NCH), 2.48 (dd, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.12 (dd, *J* = 11.5, 11.5 Hz, 1H, NCH), 1.98 (ddd, *J* = 11.5, 11.0, 3.0 Hz, 1H, NCH), 1.28 (d, *J* = 7.0 Hz, 3H, NCH*Me*), 0.34 (s, 3H, SiMe), 0.33 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.1 (*ipso*-Ph), 136.6 (*ipso*-Ph), 134.1 (Ph), 129.2 (Ph), 128.3 (Ph), 127.8 (Ph), 127.6 (Ph), 126.9 (Ph), 71.0 (OCH), 69.1 (OCH_2), 65.8 (NCH), 52.3 (NCH_2), 52.2 (NCH_2), 20.3 (NCH*Me*), –5.1 (SiMe), –5.3 (SiMe); MS (ESI) *m/z* 326 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{20}H_{27}NOSi$ $(M + H)^+$ 326.1943, found 326.1935 (–3.3 ppm

error), silylated morpholine **247b** (133 mg, 37%) as a colourless oil, $[\alpha]_D$ –39.0 (*c* 0.5 in $CHCl_3$); R_F (8:2 hexane-EtOAc) 0.2; IR (ATR) 2955, 2802, 1247, 1098, 814, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.42 (m, 2H, Ph), 7.37-7.15 (m, 8H, Ph), 3.89 (ddd, *J* = 11.0, 3.0, 1.5 Hz, 1H, OCH), 3.63 (ddd, *J* = 11.0, 11.0, 2.0 Hz, 1H, OCH), 3.46 (dd, *J* = 12.0, 2.0 Hz, 1H, OCH), 3.28 (q, *J* = 7.0 Hz, 1H, NC*H*Me), 2.85 (dd, *J* = 12.0, 2.0 Hz, 1H, NCH), 2.48 (ddd, *J* = 11.5, 2.0, 1.5 Hz, 1H, NCH), 2.20 (ddd, *J* = 11.5, 11.0, 3.0 Hz, 1H, NCH), 2.03 (dd, *J* = 12.0, 12.0 Hz, 1H, NCH), 1.31 (d, *J* = 7.0 Hz, 3H, NCH*Me*), 0.24 (s, 3H, SiMe), 0.20 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.7 (*ipso*-Ph), 136.6 (*ipso*-Ph), 133.9 (Ph), 129.1 (Ph), 128.1 (Ph), 127.7 (Ph), 127.6 (Ph), 126.8 (Ph), 71.2 (OCH), 69.0 (OCH_2), 65.1 (NCH), 52.8 (NCH_2), 50.7 (NCH_2), 19.1 (NCH*Me*), –5.3 (SiMe); MS (ESI) *m/z* 326 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{20}H_{27}NOSi$ $(M + H)^+$ 326.1943, found 326.1935 (–3.2 ppm error) and recovered starting material **X** (29 mg, 14%). The total yield of silyl morpholines **247a** and **247b** was 60%.

Lab Reference: WSK/5/046

2-(*R*/*S*)-2-(Dimethyl(phenyl)silyl)-4-((*S*)-1-phenylethyl)morpholine 247, 1-methylpropyl dimethylphenylsilane 128

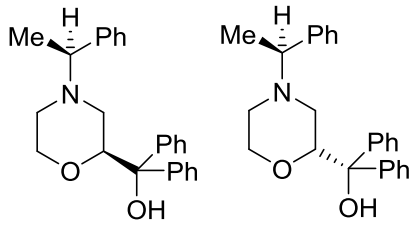


246 **247** **128**

Using general procedure E, *s*-BuLi (675 µL of a 1.3 M solution in hexanes, 0.8 mmol), (*S*)-4-(1-phenylethyl) morpholine **246** (99 mg, 0.7 mmol) and TMEDA (100 mg, 129 µL, 0.9 mmol) in hexane (7 mL) at –30 °C for 1 h and $PhSiMe_2Cl$ (227 mg, 222 µL, 1.3 mmol) gave the crude product, which contained a 50:50 mixture of **247a** and **247b** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave silane **128** (122 mg, 74%) as a colourless oil, R_F (8:2 hexane-EtOAc) 0.7, silylated morpholine **247a** (25 mg, 8%) as a colourless oil and silylated morpholine **247b** (18 mg, 12%) as a colourless oil. The total yield of silylated morpholines **247a** and **247b** was 20%.

Lab Reference: WSK/5/043

2-(*R*/*S*)-2-(Diphenyl)-4-((*S*)-1-phenylethyl)morpholin-2-yl)methanol 248a and 248b



Using general procedure E, *s*-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol), (*S*)-4-(1-phenylethyl) morpholine **246** (207 mg, 1.1 mmol) and TMEDA (163 mg, 211 µL, 1.4 mmol) in hexane (7 mL) at 0 °C for 1 h and a solution of benzophenone (395 mg, 2.2 mmol) in hexane (1 mL) gave the crude product, which contained a 50:50 mixture of **248a** and **248b** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxyl morpholine **248a** (62 mg, 15%) as a white solid, $[\alpha]_D$ –77.0 (*c* 0.5 in $CHCl_3$); mp 90-93 °C; R_F (98:2 CH_2Cl_2-acetone) 0.4; IR (ATR) 3026, 2971, 1491, 1448, 1116, 748, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.59 (m, 1H, Ph), 7.56-7.51 (m, 2H, Ph), 7.42-7.37 (m, 2H, Ph), 7.36-7.27 (m, 5H, Ph), 7.25-7.14 (m, 5H, Ph), 4.52 (dd, *J* = 9.5, 3.0 Hz, 1H, OCH), 3.88 (ddd, *J* = 11.0, 3.0, 3.0 Hz, 1H, OCH), 3.72 (ddd, *J* = 11.0, 11.0, 3.0 Hz, 1H, OCH), 3.61 (br s, 1H, OH), 3.21 (q, *J* = 6.5 Hz, NC*H*Me), 2.55-2.45 (m, 2H, NCH), 2.20 (dd, *J* = 11.0, 9.5 Hz, 1H, NCH), 2.05 (dd, *J* = 11.0, 3.0 Hz, 1H, NCH), 1.17 (d, *J* = 6.5 Hz, 3H, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.0 (*ipso*-Ph), 143.4 (*ipso*-Ph), 143.2 (*ipso*-Ph), 128.3 (Ph), 128.0 (Ph), 127.6 (Ph), 127.0 (Ph), 126.8 (Ph), 126.7 (Ph), 126.5 (Ph), 126.0 (Ph), 125.5 (Ph), 79.0 (O*C*Ph), 77.8 (OCH), 66.7 (OCH_2), 65.4 (N*C*Me), 50.5 (NCH_2), 50.5 (NCH_2), 19.7 (NC*Me*) (one Ph signal not resolved); MS (ESI) *m/z* 374 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{25}H_{27}NO_2$ (M + H)$^+$ 374.2115, found 374.2119 (–0.2 ppm error), a 60:40 mixture of **248b** and **248a** (89 mg, 22%, i.e. 13% of **248b** and 9% of **248a**) as a white solid, hydroxyl morpholine **248b** (61 mg, 15%) as a white solid, mp 90-93 °C; R_F (98:2 CH_2Cl_2-acetone) 0.3; IR (ATR) 3536 (OH), 3027, 2974, 2807, 1492, 1446, 1111, 747, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.46 (m, 2H, Ph), 7.35-7.05 (m, 13H, Ph), 4.43 (dd, *J* = 8.5, 3.0 Hz, 1H, OCH), 3.99 (ddd, *J* = 11.0, 3.0, 3.0 Hz, 1H, OCH), 3.84 (br s, 1H, OH), 3.78 (ddd, *J* = 11.0, 10.5, 3.0 Hz, 1H, OCH), 3.37 (q, *J* = 7.0 Hz, 1H, C*H*Me), 2.67 (br d, *J* = 11.5 Hz,

1H, NCH), 1.33-1.23 (m, 3H, NCH), 1.28 (d, *J* = 7.0 Hz, 3H, NC*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.9 (*ipso*-Ph), 143.6 (*ipso*-Ph), 142.6 (*ipso*-Ph), 128.1 (Ph), 127.98 (Ph), 127.90 (Ph), 127.5 (Ph), 126.9 (Ph), 126.7 (Ph), 126.5 (Ph), 126.4 (Ph), 125.3 (Ph), 79.1 (O*C*Ph), 77.9 (OCH), 66.6 (OCH_2), 64.3 (N*C*Me), 50.4 (NCH_2), 49.3 (NCH_2), 17.5 (NC*Me*); MS (ESI) *m/z* 374 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{25}H_{27}NO_2$ $(M + H)^+$ 374.2115, found 374.2111 (+1.2 ppm error) and recovered starting material **246** (36 mg, 18%) as a pale yellow oil. The total yield of hydroxyl morpholines **248a** and **248b** was 52%.

Lab Reference: WSK/5/047

Using general procedure E, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), (*S*)-4-(1-phenylethyl) morpholine **246** (196 mg, 1.0 mmol) and TMEDA (151 mg, 195 µL, 1.3 mmol) in hexane (7 mL) at –40 °C for 5 h and a solution of benzophenone (372 mg, 2.0 mmol) in hexane (1 mL) gave the crude product, which contained a 50:50 mixture of **248a** and **248b** (by ^{1}H NMR spectroscopy), a 25:20:55 mixture of **248a**, **248b** and starting material **246** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxyl morpholine **248a** (62 mg, 16%) as a white solid, a mixture of **248a** and **248b** (76 mg, 20%) as a white solid, hydroxyl morpholine **248b** (18 mg, 5%) as a white solid and recovered starting material **246** (90 mg, 46%) as a pale yellow oil. The total yield of hydroxyl morpholine **248a** and **248b** was 41%.

Lab Reference: WSK/5/048

s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol) was added dropwise to a stirred solution of (*S*)-4-(1-phenylethyl) morpholine **246** (215 mg, 1.1 mmol) and (+)-sparteine surrogate (283 mg, 1.4 mmol) in hexane (7 mL) at –40 °C under Ar. The resulting solution was stirred at –40 °C for 5 h. Then, a solution of benzophenone (408 mg, 2.2 mmol) in hexane (1 mL) was added and the resulting solution was stirred at the at –40 °C for 10 min. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –40 °C and the resulting solution was allowed to warm to rt over 1 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which contained a 50:50 mixture of **248a**

and **248b** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave a 50:50 mixture of **248a** and **248b** (262 mg, 63%) as a white solid and recovered starting material **246** (23 mg, 11%) as a pale yellow oil.

Lab Reference: WSK/5/048

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of (*S*)-4-(1-phenylethyl) morpholine **246** (196 mg, 1.0 mmol) and (–)-sparteine (305 mg, 306 μL, 1.3 mmol) in hexane (7 mL) at –40 °C under Ar. The resulting solution was stirred at –40 °C for 5 h. Then, a solution of benzophenone (373 mg, 2.0 mmol) in hexane (1 mL) was added and the resulting solution was stirred at the at –40 °C for 10 min. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –40 °C and the resulting solution was allowed to warm to rt over 1 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which contained a 65:20:15 mixture of starting material **246**, **248a** and **248b** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave a 55:45 mixture of **248a** and **248b** (119 mg, 31%) as a white solid and recovered starting material **246** (120 mg, 62%) as a pale yellow oil.

Lab Reference: WSK/5/048

Abbreviations

aq.	Aqueous
Ar	Aryl
Atm	Atmospheres
BDO	1,4-Butanediol
Bn	benzyl
Boc	*t*-Butoxycarbonyl
Bu	Butyl
bp	Boiling point
br	Broad
δ	Chemical shift
d	Doublet
DCE	1,2-Dichloroethene
dd	Doublet doublet
ddd	Doublet doublet doublet
dddd	Doublet doublet doublet doublet
DMAN	1,8-Bis(dimethylamino)-naphthalene
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DPBP	Bidentate phosphine
dr	Diastereomeric ratio Enantiomeric
er	Enantiomeric ratio
E^+	Electrophile
ESI	Electrospray ionisation
eq.	Equivalent(s)
Et	Ethyl
Et_2O	Diethyl ether

g	Gram(s)
GBL	γ-Butyrolactone
GVL	Valerolacetone
h	Hour(s)
HMF	Hydroxymethylfurfural
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
Hz	Hertz
*i*Pr	Isopropyl
IR	Infra-red
J	Coupling constant in Hz
LDA	Lithium diisopropylamide
µL	Microlitres
m	Multiplet
M	Molar
M^+	Molecular ion
Me	Methyl
mg	Milligrams
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mp	Melting point
MS	Mass spectrometry
MTBE	Methyl *tert*-butyl ether
m/*z*	Mass to charge ratio
NMR	Nuclear Magnetic Resonance
Petrol	Petroleum ether (fraction which boiling at 40-60 °C)

Ph	Phenyl
ppm	Parts per million
q	Quartet
R_F	Retention factor
rt	Room temperature
s	Singlet
(+)-sp.surr.	(+)-Sparteine surrogate
t	Triplet
Tf	Trifluoromethylsulfonyl trifluoroacetic
TBME	*tert*-Butyl methyl ether
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine

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