The Asymmetric Synthesis and Reactions of α-Functionalised Organometallic Reagents

Peter J. Rayner

PhD

University of York

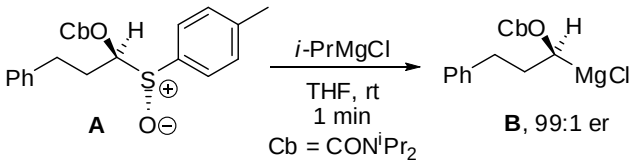
Chemistry

July 2013

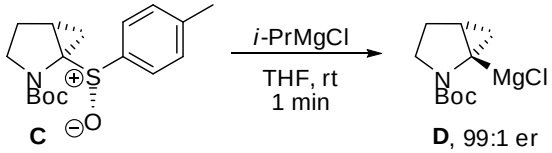
Abstract

This thesis describes the development of new methods for the asymmetric synthesis of *α*-alkoxy and *α*-amino organometallic reagents. Two approaches were taken: (i) sulfoxide → magnesium exchange; (ii) asymmetric lithiation-trapping using chiral bases. A review of this area is provided in Chapter One.

Chapter Two details the synthesis of *α*-alkoxy sulfoxides **A** in 99:1 er by asymmetric lithiation using *s*-BuLi and chiral diamines and trapping with Andersen's sulfinate. In addition, an investigation into the lack of stereospecificity at sulfur during the trapping process is presented. Finally, a sulfoxide → magnesium exchange was used to convert the *α*-alkoxy sulfoxides into *α*-alkoxy Grignard reagents **B** and subsequent trapping allows access to a range of products as single enantiomers. The remarkable configurational stability of *α*-alkoxy Grignard reagents when compared to their organolithium counterparts is of particular note.



Attempts to use a similar method to synthesise *α*-amino sulfoxides in 99:1 er is described in Chapter Three. Furthermore, insights are given into the surprising instability of unsubstituted *α*-amino sulfoxides. Novel *α*-amino sulfoxides **C** were designed to prohibit sulfoxide elimination. From the isolatable *α*-amino sulfoxides, the synthesis and reactions of *α*-amino Grignard reagents **D** in 99:1 er *via* sulfoxide → magnesium exchange is reported.



In Chapter Four, an investigation into the mechanism of the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **E** using *s*-BuLi and chiral diamines is presented. The configurational stability of the organolithium intermediate **F** was determined at −78 °C and the scope of electrophilic trapping was investigated.

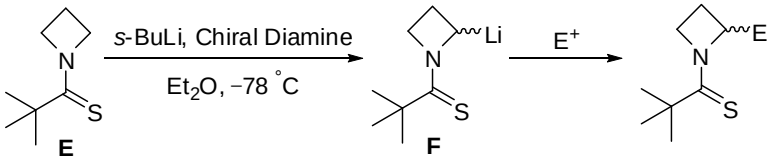


Table of Contents

List of Tables

Acknowledgements

The research presented in this thesis would not have been possible without the ideas, encouragement and scrupulousness of Professor Peter O'Brien. It has been a privilege to work under his tutelage over the past four years. In addition, I would like to thank Professor Richard Taylor for his assistance and guidance as my independent panel member.

I would also like to thank the members of the POB group that I have worked alongside during my time in York. In no particular order: Xiao, Donald, Giacomo, Graeme, Dave, Giorgio, Nah, Mary, Alice and Sarah. Thanks also to the additional D215 residents, Pete and Joe, for the good times and endless supply of glassware. Furthermore, my thanks go to the Organics football team which has provided a particular highlight of the week.

I would like to make particular mention of Chris Windle who has shared this whole experience with me. Through the ups and downs of PhD life, his friendship has helped me to reach the other side!

This research has benefitted considerably by support from the technical staff within the Department of Chemistry. Therefore, my sincere thanks go to Steve and Mike from stores, Heather and Amanda for the excellent NMR service, Trevor and Karl for mass spectrometry assistance and Graeme for copious amounts of dry solvents. I would also like to thank Dr Richard Horan, from GlaxoSmithKline, as my industrial supervisor. He has provided suggestions, support and an enjoyable CASE placement in Stevenage.

I would also like to thank my family, especially Mum and Dad, who have shown me unending love and support throughout my studies.

Finally, a special thanks to my wife, Sarah, who has always been there for me. More than anyone else, she has had to put up with the brunt of all the failed reactions yet has remained loving and full of encouragement throughout.

Author's Declaration

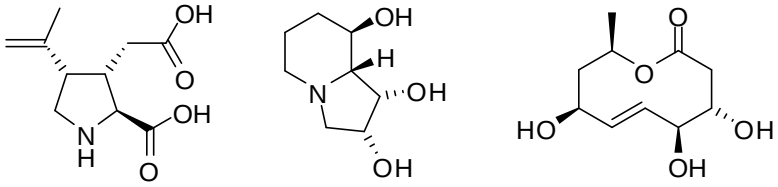
The research presented in this thesis is, to the best of my knowledge, original except where due reference has been made to other authors and/or co-workers.

Peter J. Rayner

Chapter One: Introduction

Nature shows an astonishing ability to distinguish between the enantiomers of chiral molecules. Indeed, the mirror image arrangements of a molecule can elicit contrasting responses in a whole host of biological receptors.[1] Therefore, the continued development of novel synthetic approaches towards diverse three-dimensional molecules remains of utmost importance to modern society.

Organometallic chemistry offers an attractive technique for the introduction of new stereogenic centres within complex molecules and has thus become a key part of the modern synthetic chemist's armoury. New methods for the synthesis of *α*-functionalised organolithium[2,3] and organomagnesium reagents are of particular interest.[4,5] In addition to their use in the synthesis of pharmaceutical products,[6-8] *α*-functionalised organometallics have been used in the stereo-inducing step in a number of natural product total syntheses, with some recent examples including (−)-kainic acid,[9] (−)-swainsonine[10] and (−)-decarestrictine D[11] (Figure 1.1).

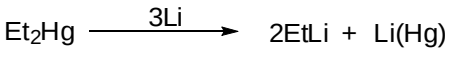


(–)-Kainic Acid (–)-Swainsonine (–)-Decarestrictine D

Figure 1.1

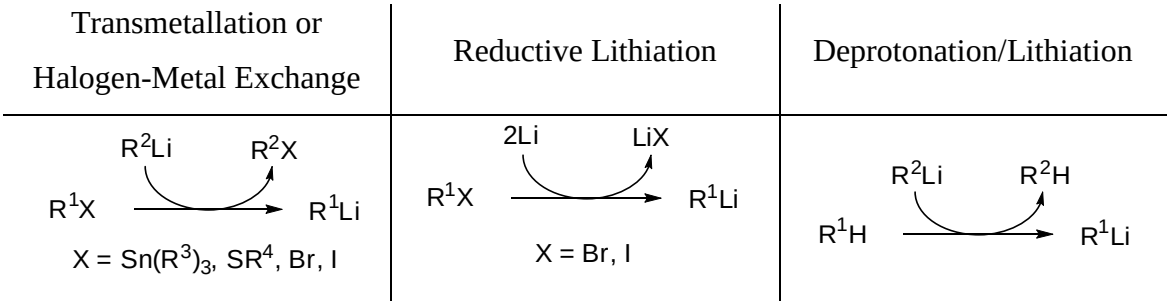
1.1 Asymmetric Synthesis of *α*-Functionalised Organolithium Reagents

Organolithium reagents were discovered by Wilhelm Schlenk in 1917.[12] The first synthetic route was an exchange reaction from the mercury derivative forming mercury amalgam (Scheme 1.1). Schlenk gave vivid descriptions of the organolithium reagents that were formed, with methyllithium being said to form a "*brilliant red flame with a shower of golden sparks*" when exposed to air.[13]



Scheme 1.1

Fortunately, the synthesis of organolithium reagents has been significantly improved over the past century. A contemporary organic chemist would typically synthesise an organolithium reagent *via* one of three general methods; transmetallation or halogen-metal exchange, reductive lithiation of alkyl halides with lithium metal, or deprotonation/lithiation (Scheme 1.2).



Scheme 1.2

For the synthesis of organolithium reagents in an asymmetric fashion, deprotonation using strong organolithium bases in the presence of chiral ligands is the premier approach. Significantly, asymmetric deprotonation avoids some mechanistic limitations of the alternative methods such as difficulties in synthesising secondary organolithium reagents[14] or planar radical intermediates.[15] Tin → lithium exchange offers the only real alternative for the synthesis of chiral organolithium reagents. This methodology was exemplified by Still and co-workers in 1980.[16]

By far the most important ligand used in asymmetric lithiation is (−)-sparteine, a naturally occurring chiral diamine (Figure 1.2). It was first used in as a bidentate ligand in organometallic chemistry in 1968[17] and since then, it has consistently outperformed other diamine ligands in terms of yield and enantioselectivity.[18] (−)-Sparteine is extracted from Scotch Broom and is commercially available but more recently, supplies have been variable. Its enantiomer, (+)-sparteine, is not commerically available. In 2002, our group reported the first readily accessible (+)-sparteine surrogate **1** which provides enantiocomplementary reactions to (−)-sparteine.[19] A review of the chemistry of the (+)-sparteine surrogate **1** was published in 2008.[20]

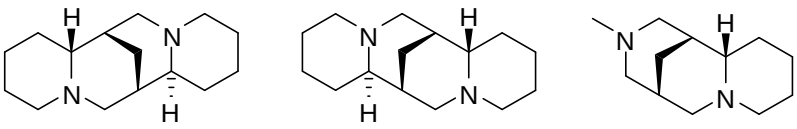


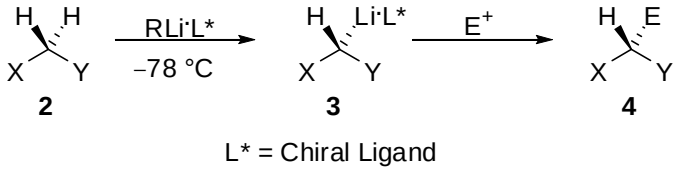
Figure 1.2

There are three possible mechanistic pathways that can lead to enantioenriched products by a lithiation-substitution process. The mechanisms are dictated by the configurational stability of the organolithium reagent and the relative rates of trapping with electrophiles. If the organolithium reagent is configurationally stable, then the reaction will proceed *via* an *enantioselective deprotonation* pathway. In contrast, if the organolithium reagent is configurationally unstable, then the reaction can proceed either by a *dynamic thermodynamic resolution* or a *dynamic kinetic resolution*.

1.1.1 Enantioselective Deprotonation as a Route to Organolithium Reagents

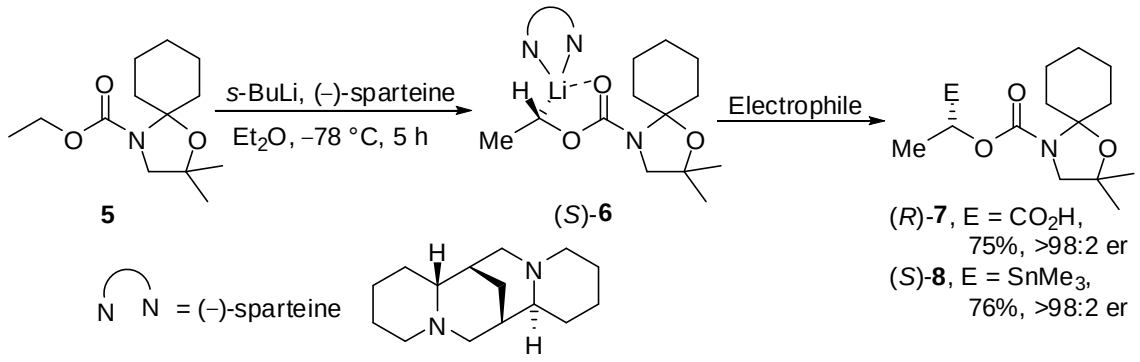
Clayden describes enantioselective deprotonation as '*conceptually the simplest sort of asymmetric organolithium reaction*'.[18] A general enantioselective deprotonation is depicted in Scheme 1.3. The complex of an organolithium reagent (RLi) and a chiral ligand (L^*) performs an enantioselective deprotonation of substrate **2** to form chiral organolithium reagent **3**. This is the stereo-inducing step and it is essential for the intermediate organolithium **3** to be configurationally stable under the reaction

conditions (typically −78 °C). Organolithium reagent **3** is then trapped by electrophiles to give enantioenriched products of type **4**.



Scheme 1.3

The first enantioselective deprotonation was reported in 1990 by Hoppe *et al.*[21] *O*-Alkyl carbamate **5** was treated with *s*-BuLi/(−)-sparteine in Et_2O at −78 °C for 5 hours to give lithiated intermediate (*S*)-**6** which was then trapped with carbon dioxide or trimethylsilyl chloride in good yields and enantiomeric ratio (Scheme 1.4). At the time, Hoppe postulated that activation of carbamate **5** occurred due to chelation and dipole stabilisation, a phenomenon which was later christened the 'Complex Induced Proximity Effect' (CIPE).[22]

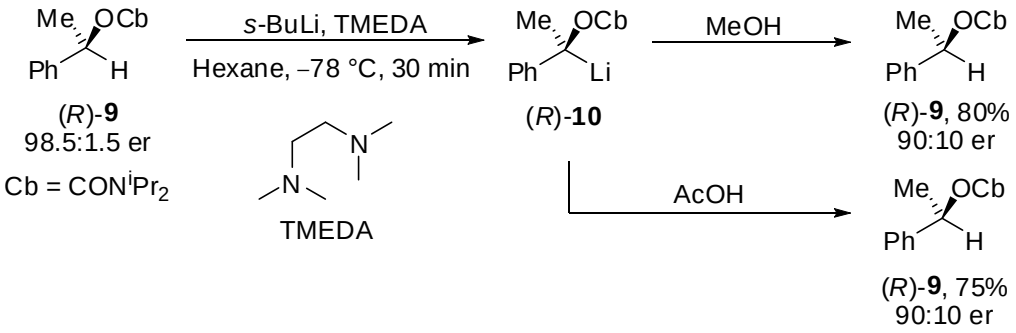


Scheme 1.4

The absolute configuration of (*R*)-**7** was determined by comparison to a known lactic acid derivative. Crucially, organolithium reagent (*S*)-**6** was configurationally stable under the reaction conditions[16] and trapping proceeded with retention of configuration at carbon.

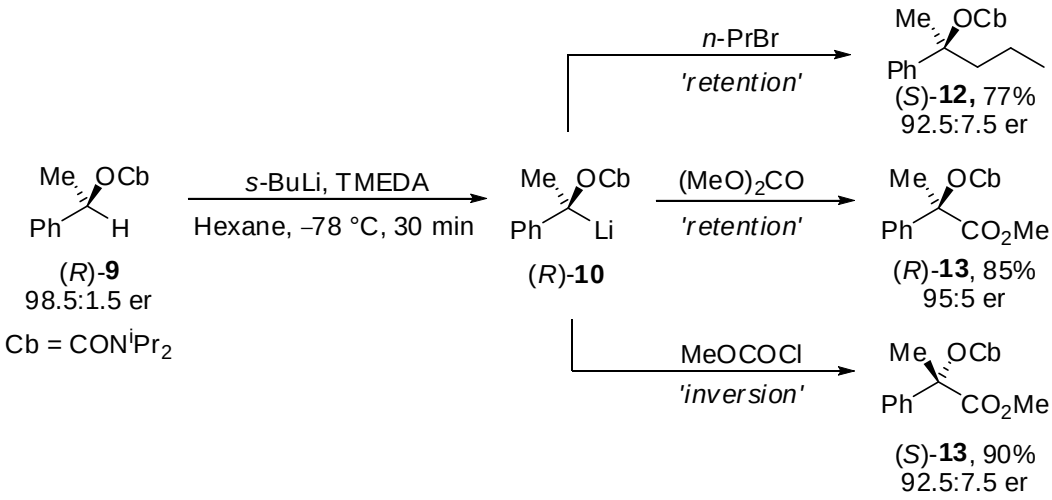
In contrast, Hoppe and co-workers reported that the lithiation-trapping of benzylic carbamate (*R*)-**9** proceeded with either retention or inversion of configuration, depending on the electrophile employed.[23] In this work, (*R*)-**9** (98.5:1.5 er) was treated with *s*-BuLi/TMEDA to give organolithium (*R*)-**10**. The lithiated intermediate was then

either reprotonated or trapped with electrophiles (Schemes 1.5 and 1.6). Reprotonation by methanol or acetic acid proceeded with retention of configuration to give (*R*)-**9** in 90:10 er. Interestingly, reprotonation by acetic acid was originally reported to proceed with inversion of configuration however, this has since been corrected.[24,25]



Scheme 1.5

Furthermore, alkylation of (*R*)-**10** with *n*-propyl bromide or dimethyl carbonate gave (*S*)-**12** (77%, 92.5:7.5 er) or (*R*)-**13** (85%, 95:5 er) respectively with retention of configuration. However, the trapping reaction with methyl chloroformate proceeded with inversion of configuration to give methyl ester (*S*)-**13** in 90% yield and 92.5:7.5 er.

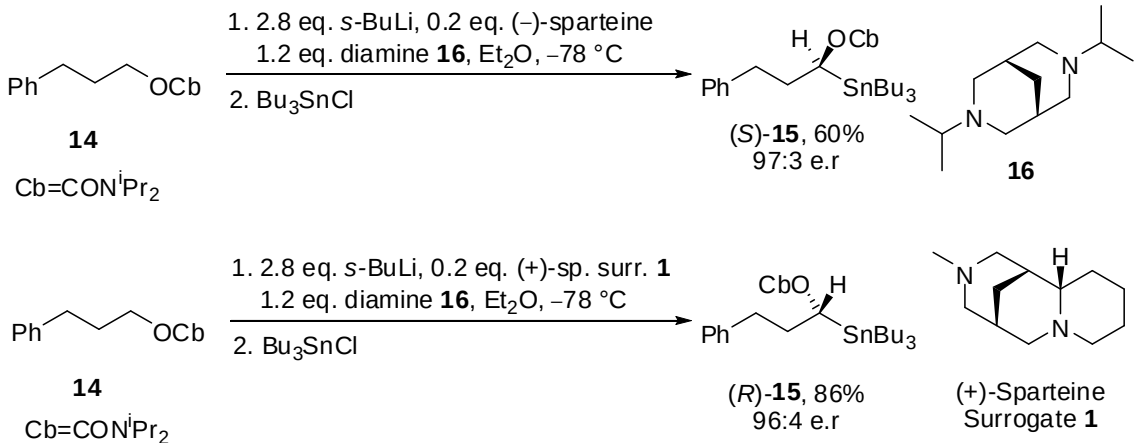


Scheme 1.6

For the case of α-oxybenzyl organolithium reagents, Hoppe suggested that the propensity for the trapping to occur with either retention or inversion of configuration is due to the close-lying activation energies for front-side and back-side attack. This was supported by theoretical calculations by Schleyer *et al*.[26] Therefore, the steric demand of

the electrophile and the interaction of the leaving group with the lithium ultimately determine the reaction pathway.

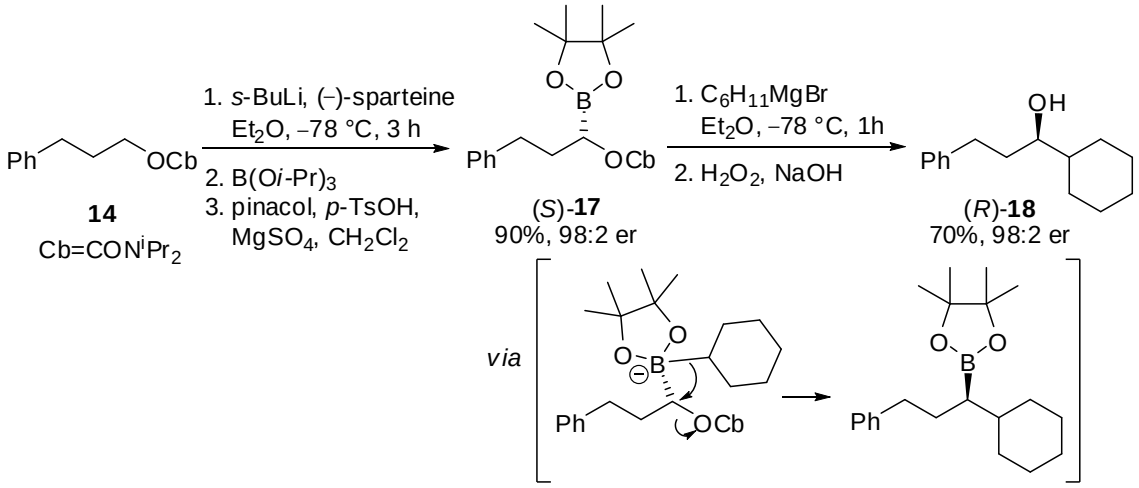
Our group has contributed to the *O*-alkyl carbamate deprotonation methodology by the introduction of a catalytic asymmetric variant.[27] It was reported that treatment of *O*-alkyl carbamate **14** with 2.8 equivalents of *s*-BuLi in the presence of just 0.2 equivalents of (−)-sparteine and 1.2 equivalents of achiral diamine **16** and trapping with tributyltin chloride gave stannane (*S*)-**15** in 60% yield and 97:3 er (Scheme 1.7). The opposite enantiomeric series was also accessible through the use of the (+)-sparteine surrogate **1**, giving stannane (*R*)-**15** in 86% yield and 96:4 er. The role of achiral diamine **16** is to displace the chiral ligand from the lithiated intermediate. Thus, the *s*-BuLi/chiral ligand complex is then available to deprotonate more *O*-alkyl carbamate **14**. Diamine **16** was a suitable ligand as its complex with *s*-BuLi has been shown to be a slow lithiator when compared to the *s*-BuLi complexes of (−)-sparteine and (+)-sparteine surrogate **1**.[28]



Scheme 1.7

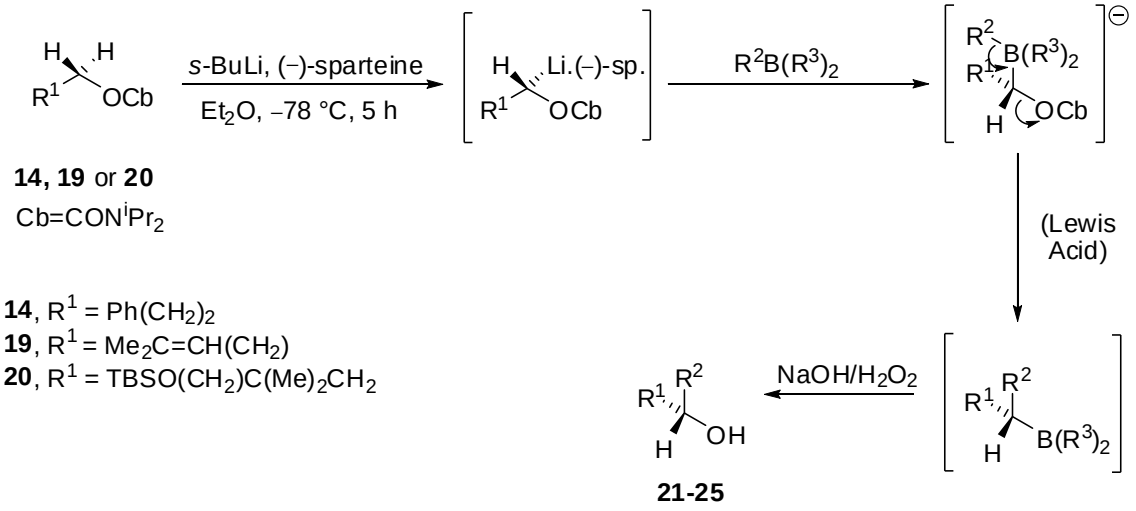
The lithiation-trapping of *O*-alkyl carbamates is a useful method for synthesising α-substituted protected alcohols in good yield and high enantiomeric ratio. Furthermore, due to the introduction of the (+)-sparteine surrogate **1**, both enantiomers of the products are accessible.[19] In order to access the synthetically desirable secondary alcohols, removal of the carbamate group would be necessary. This typically proceeds under harsh reductive conditions ($LiAlH_4$, THF, reflux).[29]

Hoppe developed an alternative approach to secondary alcohols that avoided the need to use harsh reductive conditions (Scheme 1.8).[30] Indeed, lithiation of *O*-alkyl carbamate **14** and trapping with boronates followed by treatment with Grignard reagents effected 1,2-metallate rearrangement with expulsion of the carbamate moiety. Finally, oxidation gave chiral alcohols in good yield and high enantiomeric ratio. An example (**14** → (*S*)-**17** → (*R*)-**18**) is shown in Scheme 1.8. However, until 2007, there was only one example of trapping of a lithiated carbamate with a borate ester to give *in situ* access to a chiral alcohol in 98:2 er.[31]



Scheme 1.8

In 2007, Aggarwal and co-workers reported a general procedure for the trapping of Hoppe-type lithiated *O*-alkyl carbamates with boranes and borates and subsequent conversion into chiral alcohols.[32] First, carbamates **14**, **19** and **20** were treated with *s*-BuLi/(−)-sparteine in Et_2O at −78 °C to give the lithiated intermediates. Subsequent addition of boranes or boronic esters to the lithiated carbamates gave ate-complexes which furnished secondary alcohols **21-25** *via* a 1,2-metallate rearrangement and subsequent oxidation (Scheme 1.9). Selected results are summarised in Table 1.1. Aggarwal *et al.* were able to conclude that the reaction of the lithiated carbamates with both boranes and boronic esters and subsequent 1,2 metallate rearrangement proceeded with retention of configuration. This supports what was previously reported in the literature.[27,30,33] The configurations of alcohols **21-25** were determined by comparison to known compounds. Furthermore, the sense of induction in the lithiation of *O*-alkyl carbamates using *s*-BuLi/(−)-sparteine is well established from Hoppe's work.[21]



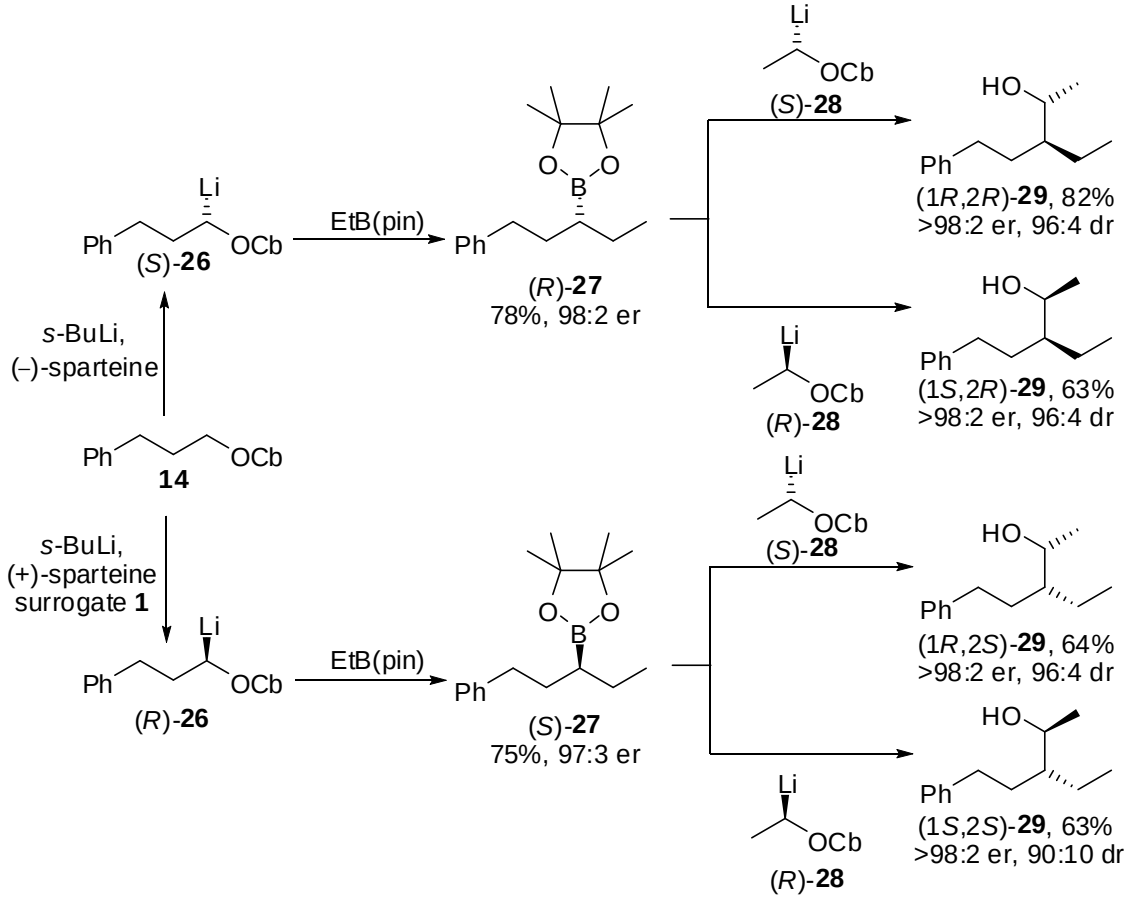
Scheme 1.9

Table 1.1: Lithiation-Boronate rearrangement of *O*-Alkyl Carbamates

Entry	SM	R^2	$(R^3)_2$	Lewis Acid	Product	Yield / %	er
1	**14**	Et	Et	-	**21**	91	98:2
2	**14**	Ph	9-BBN	-	**22**	85	88:12
3	**14**	Ph	9-BBN	$MgBr_2$	**22**	94	97:3
4	**19**	Et	Et	-	**23**	90	97:3
5	**19**	Et	pinacol	$MgBr_2$	**23**	75	97:3
6	**20**	Et	Et	-	**24**	67	95:5
7	**20**	Ph	pinacol	$MgBr_2$	**25**	64	98:2

The methodology was shown to tolerate a number of boranes and boronates. Use of triethyl borane gave good to excellent yields and excellent enantiomeric ratios in all cases (entries 1, 4 and 6). Interestingly, in the case of *B*-Ph-9-BBN, higher er was obtained in the presence of $MgBr_2$ (entry 3 vs. entry 2), but this was not found to be necessary in the case of aliphatic groups where high enantioselectivity was observed without addition of a Lewis acid (entry 1). It was postulated that the addition of $MgBr_2$ sequesters either (−)-sparteine or the carbamate leaving group, thus preventing it from binding to the borane which would cause homolysis of the benzylic carbon-boron bond. This would result in a lower enantiomeric ratio of the final alcohol. In addition, this was the first example of a clean migration of the boron substituent when the leaving group is not a halide. Finally, pinacol boronates were shown to give good yields (64-75%) and excellent enantioselectivity (97:3-98:2 er) (entries 5 and 7).

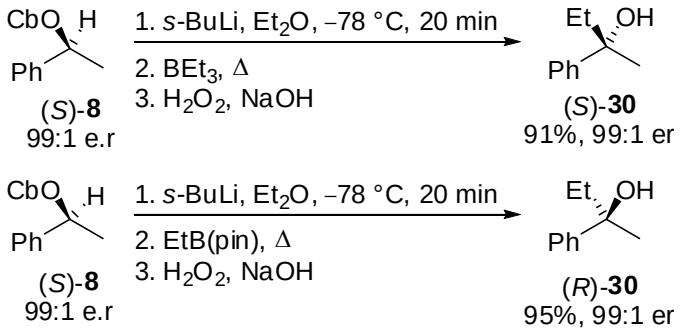
Extension of the methodology to include an iterative process with boronic esters allowed access to scaffolds bearing multiple adjacent stereocentres (Scheme 1.10). Lithiation of *O*-alkyl carbamate **14** with *s*-BuLi/(−)-sparteine gave lithiated intermediate (*S*)-**26**, trapping with ethyl pinacol boronate ester and subsequent 1,2-metallate rearrangement gave boronic ester (*R*)-**27**. A second homologation with lithiated carbamate (*S*)-**28** gave alcohol (1*R*,2*R*)-**29** in 82% yield, >98:2 er and 96:4 dr. Alcohol (1*S*,2*R*)-**29** was synthesised from boronic ester (*R*)-**27** and lithiated intermediate (*R*)-**28** in good yield (63%) and excellent stereoselectivity (>98:2 er and 96:4 dr). The enantiocomplementary alcohols (1*R*,2*S*)-**29** and (1*S*,2*S*)-**29** were accessed in good yields and stereoselectivity *via* lithiation of carbamate **14** with *s*-BuLi/(+)-sparteine surrogate **1** and electrophilic trapping with ethyl pinacol boronic acid to give boronate (*S*)-**27** and subsequent homologation with either (*S*)-**28** or (*R*)-**28**.



Scheme 1.10

In 2008, Aggarwal and co-workers used the 1,2-metallate rearrangement of boronate complexes to convert chiral secondary alcohols into tertiary alcohols.[34] To prove the

concept, carbamate (*S*)-**8** (99:1 er) was deprotonated with *s*-BuLi in Et_2O. Subsequent addition of the borane or boronic ester followed by oxidation gave the tertiary alcohols (*S*)-**30** or (*R*)-**30** in excellent yield and enantioselectivity. Two examples are shown in Scheme 1.11.

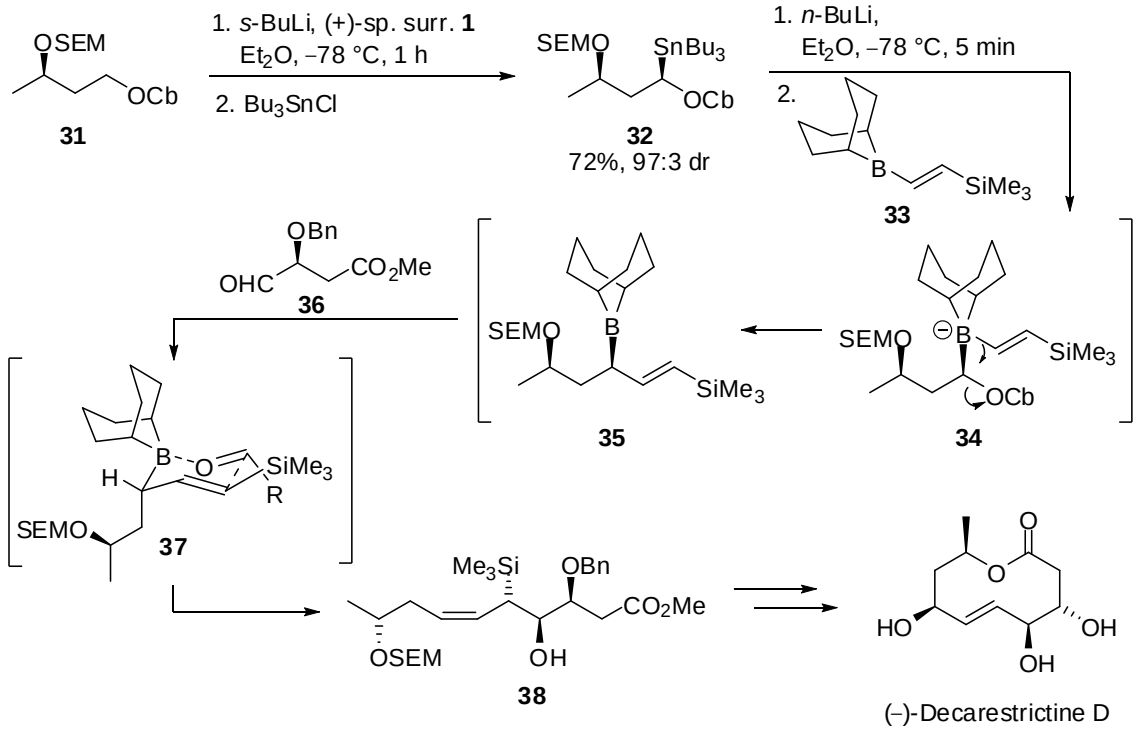


Scheme 1.11

Interestingly, when using boranes the reactions occurred with inversion of configuration, but the use of boronic esters caused the reaction to proceed with retention of configuration. Consequently, either enantiomeric series of alcohols can be accessed starting from (*S*)-**8**. Aggarwal suggested that for the case of boronic esters, coordination between the oxygen of the ester and the lithium of the metalated carbamate causes delivery on the same face as the metal. As boranes are unable to form the same complex, reaction occurred on the opposite face to the metal where there is significant electron density due to a partial-flattening of the carbanion because of its benzylic nature. This is in contrast to lithiated alkyl carbamates where both boranes and boronic esters react with retention of configuration due to a sp^3-hybridised carbanion which has very little electron density opposite the metal.

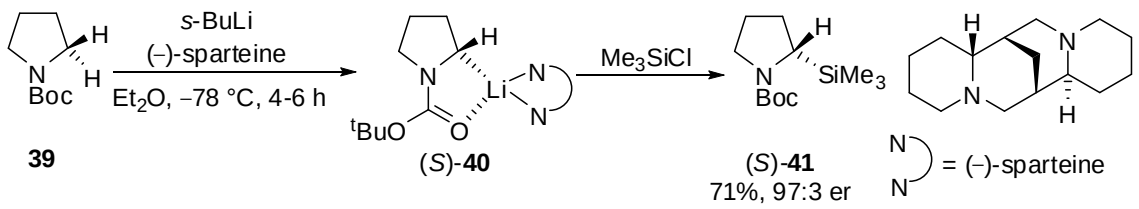
In summary, the lithiation of *O*-alkyl carbamates, trapping with boranes or boronic esters and subsequent 1,2-metallate rearrangement, affords chiral secondary and tertiary alcohols in good yield and excellent enantiomeric ratio. The expediency of the methodology is highlighted in a number of total syntheses.[11,35,36] For example, the stereo-determining step in the synthesis of (−)-decarestrictine D is shown in Scheme 1.12. Lithiation of *O*-alkyl carbamate **31** using *s*-BuLi/(+)-sparteine surrogate **1** and trapping with tributyltin chloride gave stannane **32** in 72% yield and 97:3 dr. Tin → lithium exchange of stannane **32** and trapping with silyl vinyl borane **33** gave adduct **34** which underwent 1,2-metallate rearrangement to give **35**. Subsequent addition of

aldehyde **36** gave *cis*-alkene **38**. This reaction proceeds *via* the six-membered transition state **37** in which the alkyl group has to occupy the axial position due to steric interaction with the boron ligand, thereby giving the *Z*-double bond. Intermediate **38** was then converted into (−)-decarestrictine D in six steps.[11,37]



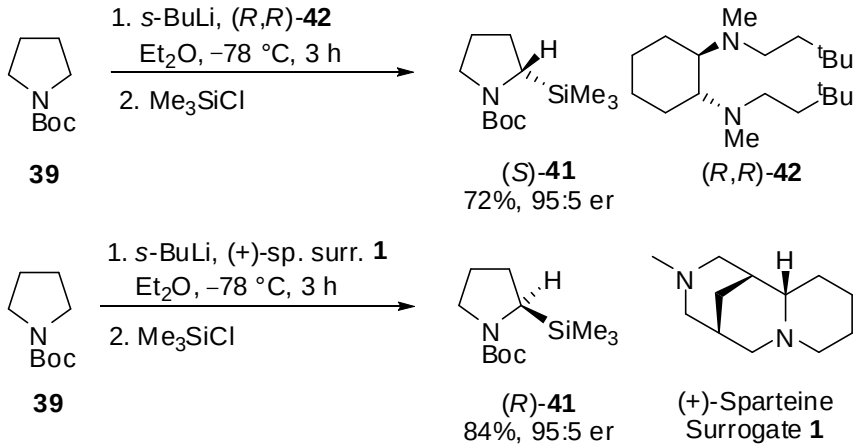
Scheme 1.12

Enantioselective deprotonation has also been exemplified on a wide array of nitrogen heterocycles. In 1991, Beak and Kerrick reported the asymmetric lithiation-trapping of *N*-Boc pyrrolidine **39** and it has since become the most extensively studied nitrogen heterocycle.[38] Lithiation of *N*-Boc pyrrolidine **39** using *s*-BuLi/(−)-sparteine gave chiral organolithium reagent (*S*)-**40**. Subsequent trapping with electrophiles generated *α*-substituted pyrrolidines in good yield (55-76%) and high enantioselectivity (≥94:6 er). For example, silylated pyrrolidine (*S*)-**41** was formed in 71% yield and 97:3 er (Scheme 1.13).



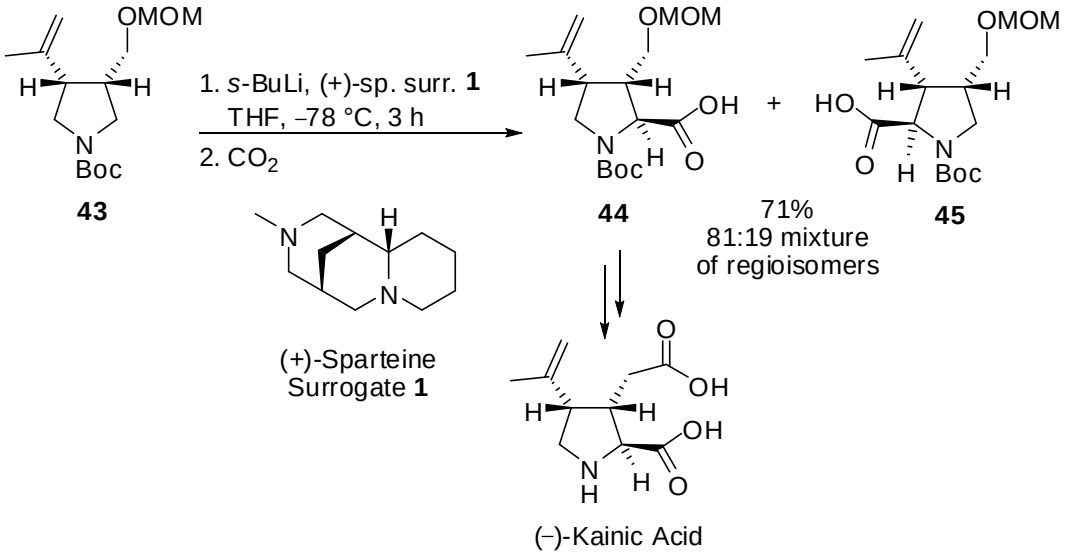
Scheme 1.13

Alternative diamine ligands have also been used to mediate the deprotonation of *N*-Boc pyrrolidine **39**. For example, lithiation using *s*-BuLi/diamine (*R*,*R*)-**42** and trapping with trimethylsilyl chloride gave (*S*)-**41** in 72% yield and 95:5 er (Scheme 1.14).[29] In addition, the opposite enantiomeric series is also readily available through the use of *s*-BuLi/(+)-sparteine surrogate **1**.[19] Indeed, lithiation of *N*-Boc pyrrolidine **39** using (+)-sparteine surrogate **1** as the ligand gave (*R*)-**41** in 84% yield and 95:5 er.



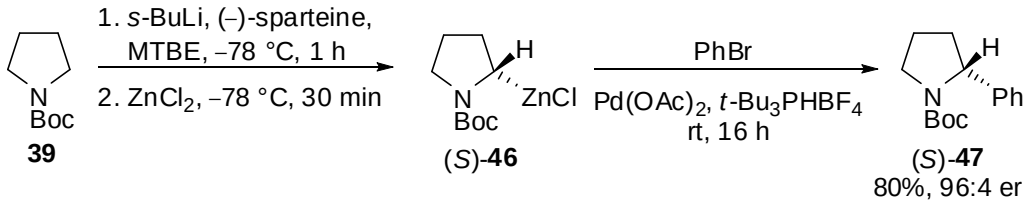
Scheme 1.14

Lithiation of an *N*-Boc pyrrolidine using *s*-BuLi/(+)-sparteine surrogate **1** was also used as a key step in the total synthesis of (−)-kainic acid (Scheme 1.15).[9] Treatment of subsituted pyrrolidine **43** with *s*-BuLi/(+)-sparteine surrogate **1** and subsequent trapping with carbon dioxide gave an 81:19 mixture of regioisomeric acids **44** and **45** in 71% total yield. Elaboration of acid **44** gave (−)-kainic acid in eight steps.



Scheme 1.15

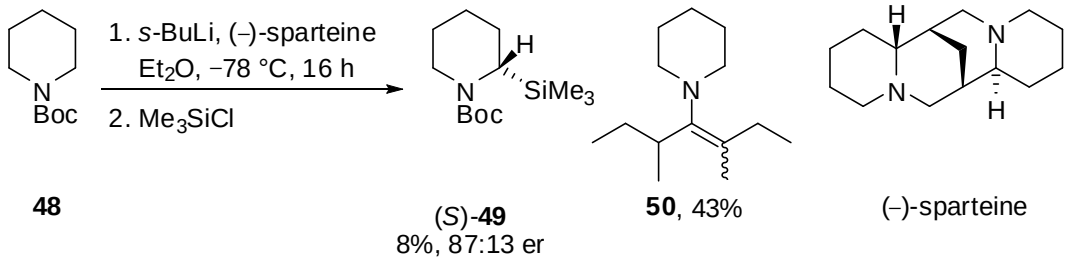
In 2006, Campos and co-workers reported the synthesis of chiral *α*-arylated *N*-Boc pyrrolidines (Scheme 1.16).[39] First, enantioselective deprotonation of *N*-Boc pyrrolidine **39** using *s*-BuLi and (−)-sparteine and subsequent transmetallation with zinc chloride gave organozinc reagent (*S*)-**46**. Then, palladium-catalysed Negishi coupling of organozinc reagent (*S*)-**46** with bromobenzene gave phenyl pyrrolidine (*S*)-**47** in 80% yield and 96:4 er.



Scheme 1.16

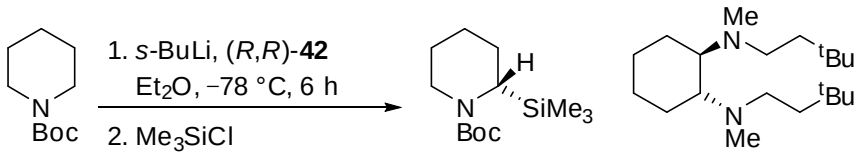
The wide scope of the transmetallation-Negishi methodology has been demonstrated by O'Brien, Campos *et al.* and the mechanism was probed by *in-situ* ReactIR® spectroscopic monitoring.[40] In addition, this type of enantioselective arylation has been scaled up to produce ~0.6 kg of a glucose kinase inhibitor.[6]

The enantioselective deprotonation of *N*-Boc piperidine **48** has also been explored. In 2002, Beak and co-workers reported that lithiation mediated by *s*-BuLi/(−)-sparteine and trapping with trimethylsilyl chloride gave *α*-substituted piperidine (*S*)-**49** in 87:13 er but only 8% yield (Scheme 1.17).[41] In addition, enamine **50** was formed as the major product (43% yield). It was suggested that, due to the very slow rate of deprotonation, enamine **50** is formed as the product of addition of *s*-BuLi to the carbonyl of the Boc group.



Scheme 1.17

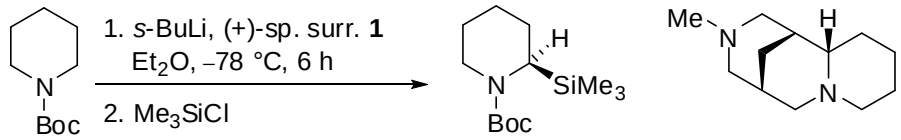
In an attempt to solve this problem, a collaboration between the O'Brien and Coldham groups led to the screening of fourteen chiral ligands for the asymmetric deprotonation of *N*-Boc piperidine **48**.[42] It was shown that increasing the steric bulk of the ligand dramatically reduced the yield of the lithiation-trapping. However, less sterically hindered ligands led to reduced enantioselectivity. The highest enantioselectivity was achieved by using *s*-BuLi/(*R*,*R*)-**42** to lithiated *N*-Boc piperidine **48** and trapping with trimethylsilyl chloride (Scheme 1.18). From this reaction, silylated piperidine (*S*)-**49** was isolated in 90:10 er but only 13% yield.



48 (*S*)-**49** 13%, 90:10 er (*R*,*R*)-**42**

Scheme 1.18

More recently, the first example of a high yielding asymmetric deprotonation of *N*-Boc piperidine **48** was reported by our group.[43] This lithiation was effected by *s*-BuLi/(+)-sparteine surrogate **1**. Trapping with trimethylsilyl chloride gave *α*-substituted piperidine (*R*)-**49** in 73% yield and 86:14 er (Scheme 1.19).



48 (*R*)-**49**, 73% 86:14 er (+)-sparteine surrogate **1**

Scheme 1.19

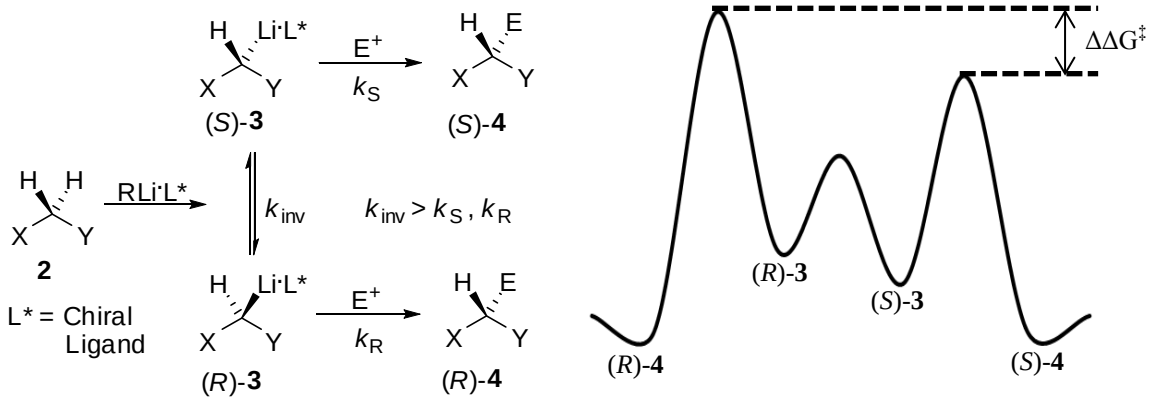
This methodology was then applied to a wide range of electrophiles. However, lower enantioselectivity was noted in trappings with phenyldimethylsilyl chloride, methyl iodide and dimethyl sulfate. It was speculated that, due to the steric bulk of the lithium-diamine complex, trapping with these electrophiles only occurred at temperatures where the organolithium was configurationally unstable.[44]

Enantioselective deprotonation offers an expedient method for the synthesis of α-functionalised organolithium reagents. Of particular note is the extensive studies of the

lithiation-trapping of *O*-alkyl carbamates and *N*-Boc heterocycles but enantioselective deprotonation has also been conducted on phosphine boranes,[45] phosphine sulfides[46] and ferrocenes.[47]

1.1.2 Dynamic Kinetic Resolution of Organolithium Reagents

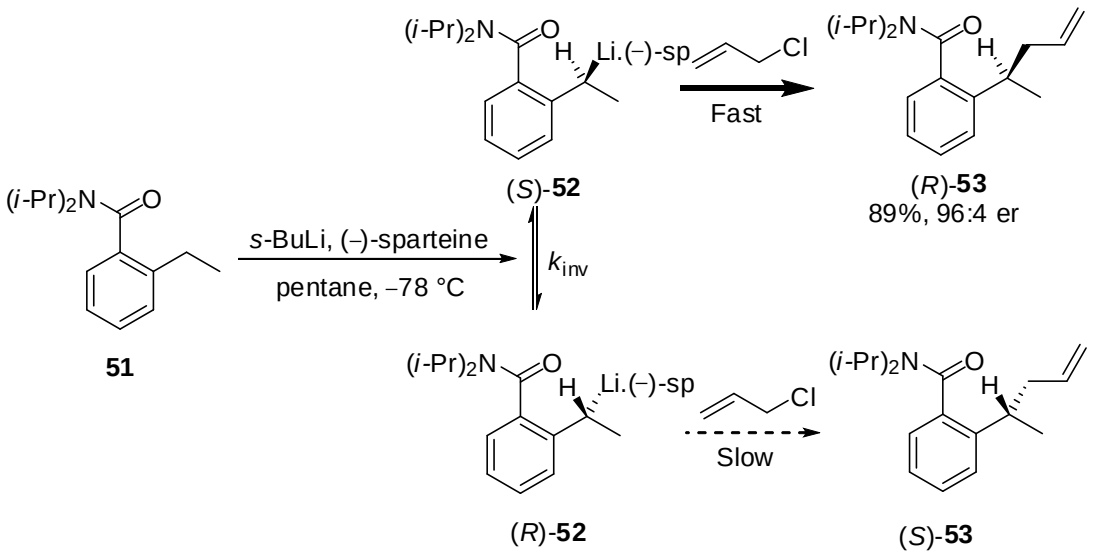
An alternative method for synthesising chiral organolithium reagents is by a dynamic kinetic resolution process. If the intermediate *α*-functionalised organolithium reagent is configurationally unstable in the presence of a chiral ligand on the timescale of reaction with the electrophile then the enantiomeric ratio of the products will reflect the rate of reaction not the ratio of the diastereomeric organolithium complexes. This process is known as a dynamic kinetic resolution and a general reaction pathway is depicted in Scheme 1.20.[18] The reaction begins by deprotonation of substrate **2** by the complex of an organolithium reagent (RLi) and a chiral ligand (L^*) which leads to the formation of diastereomeric organolithium reagents (*S*)-**3** and (*R*)-**3**. These organolithium reagents are able to interconvert under the reaction conditions at rate k_{inv}. On addition of an electrophile (E^+), each organolithium reagent will react with a different rate (k_S or k_R) to give products (*S*)-**4** and (*R*)-**4**. In a dynamic kinetic resolution process, the degree enantioselectivity is controlled by the difference in energy between the energies of the transition states of the electrophilic trap, $\Delta\Delta G^{\ddagger}$.



Scheme 1.20

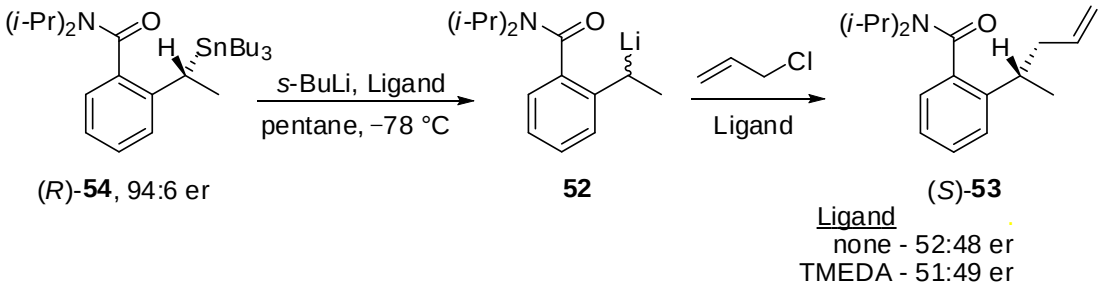
In 1994, Beak and co-workers reported the dynamic kinetic resolution of benzylic organolithium **52** (Scheme 1.21).[48] Lithiation of amide **51** by *s*-BuLi/(–)-sparteine gave

diastereomeric organolithium reagents (*S*)-**52** and (*R*)-**52** which were shown to be configurationally unstable at −78 °C. Upon addition of allyl chloride, trapping occurred to give (*R*)-**53** in 89% yield and 96:4 er.



Scheme 1.21

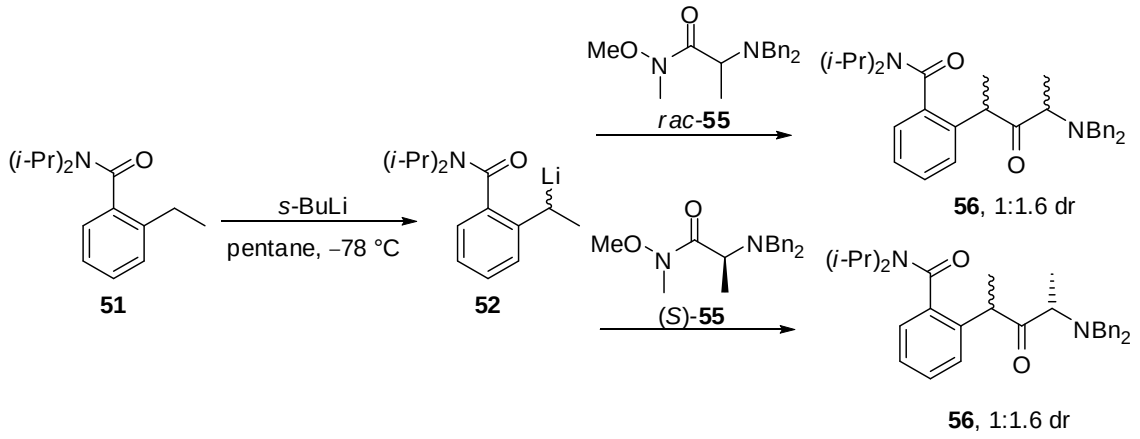
Organolithium reagent **52** was shown to be configurationally unstable by a tin → lithium exchange reaction from enantioenriched stannane (*R*)-**54** (Scheme 1.22). Treatment of stannane (*R*)-**54** (94:6 er) with *s*-BuLi in pentane at −78 °C gave organolithium **52** and trapping with allyl chloride generated (*S*)-**53** in only 52:48 er. Similarly, in the presence of TMEDA, (*S*)-**53** was isolated in 51:49 er. This reaction proved that the organolithium reagent was configurationally unstable and the enantioselectivity could not be attributed to an enantioselective deprotonation event.



Scheme 1.22

In addition, the configurational stability was also evaluated using the Hoffmann test.[49-51] The Hoffmann test determines the configurational stability of organolithium reagents on

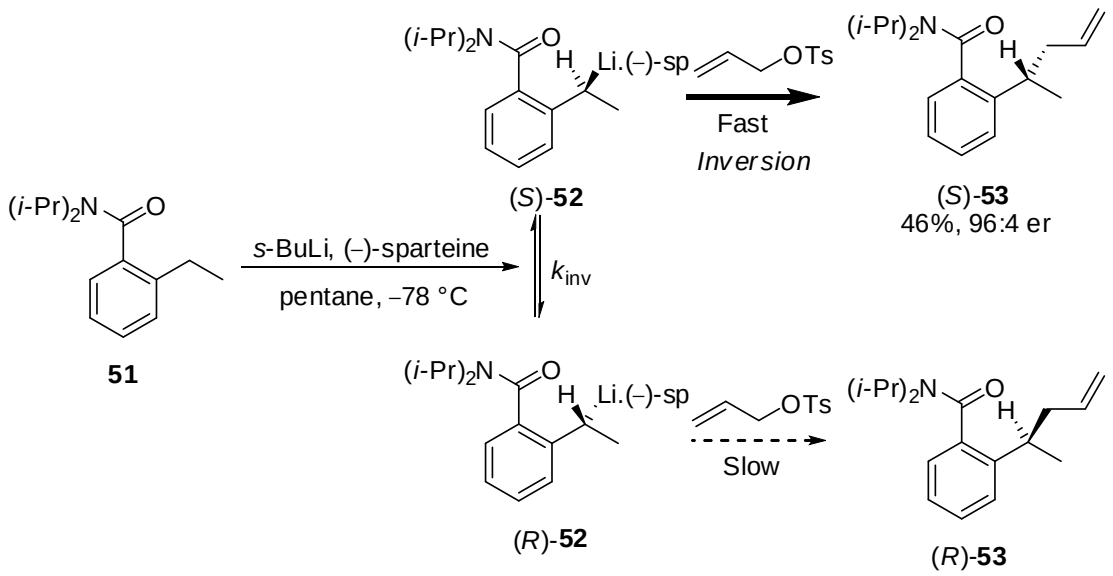
the timescale of reaction with electrophiles. Racemic lithiation of amide **51** (*s*-BuLi, pentane, −78 °C) gave racemic organolithium reagent **52**. Trapping with racemic amide *rac*-**55** gave ketone **56** as a 1:1.6 mixture of diastereoisomers. In addition, trapping with enantioenriched amide (*S*)-**55** also gave ketone **56** in 1:1.6 dr (Scheme 1.23).



Scheme 1.23

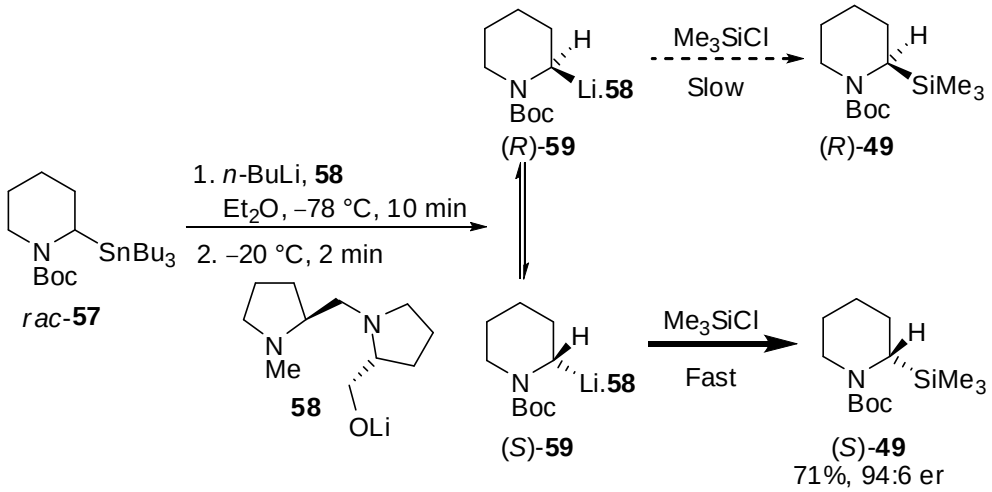
Due to the diastereoselectivity of the reactions with racemic and enantioenriched amide **56** being the same, it was concluded that organolithium reagent **52** was configurationally unstable on the timescale of reactions with the amide electrophile. Thus, a dynamic kinetic resolution process was occurring. If the diastereoselectivity had been different then the organolithium reagent would have been configurationally stable on the timescale of reaction with the amide and a dynamic thermodynamic resolution process would have been occurring (see Chapter 1.1.3).

Interestingly, the leaving group in the electrophile was revealed to have a dramatic effect on the enantioselectivity of the lithiation-trapping of **51**. Indeed, trapping with allyl tosylate gave (*S*)-**53** in 94:6 er (Scheme 1.24). This is the opposite enantiomer to that formed when allyl chloride was used. Beak suggests that this is due to electrophilic trapping of (*S*)-**52** occurring with inversion due to the change of the leaving group.



Scheme 1.24

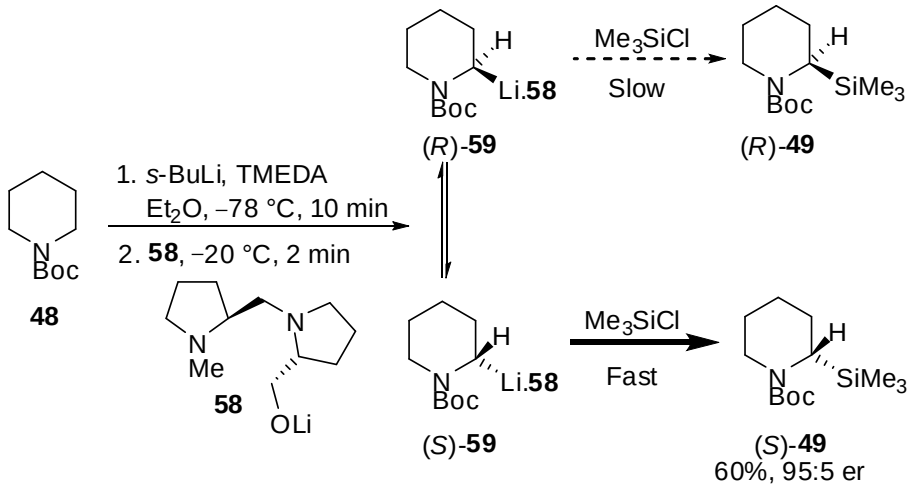
A dynamic kinetic resolution of *N*-Boc 2-lithiopiperidine **59** has also been reported by Coldham *et al*.[52] This is significant due to low yields for the enantioselective deprotonation of *N*-Boc piperidine **48** using *s*-BuLi/(−)-sparteine and other chiral diamines (see Scheme 1.17). The resolution protocol began with a tin → lithium exchange on stannane *rac*-**57** in the presence of chiral ligand **58** at −78 °C. Warming the reaction mixture to −20 °C and slow addition of trimethylsilyl chloride over 50 minutes gave (*S*)-**49** in 71% yield and 94:6 er (Scheme 1.25).



Scheme 1.25

A dynamic kinetic resolution process can also be carried out directly from *N*-Boc piperidine **48** (Scheme 1.26). Racemic lithiation of *N*-Boc piperidine **48** (*s*-BuLi, TMEDA, Et_2O, −78 °C, 3 hours) followed by addition of chiral ligand **58** at −20 °C and

slow addition of trimethylsilyl chloride over 50 minutes gave silylated piperidine (*S*)-**49** in 60% yield and 95:5 er.



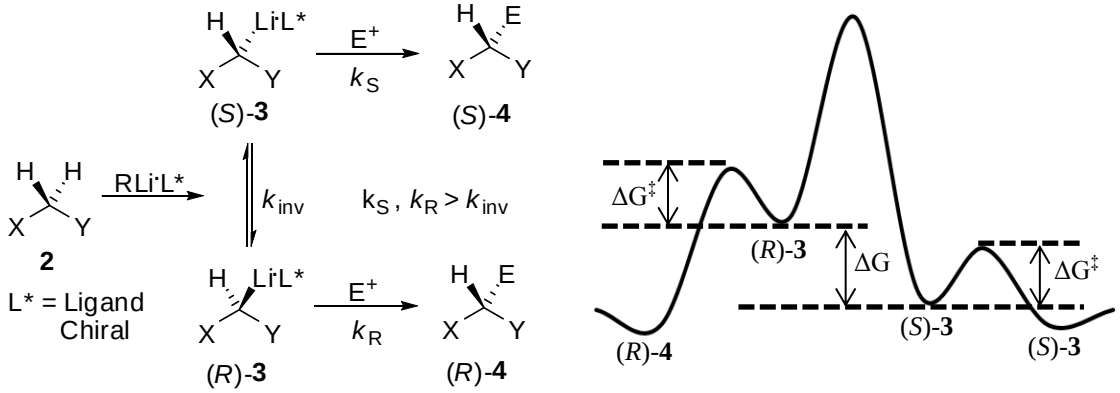
Scheme 1.26

Extensive work by Coldham *et al.* established that this was a dynamic kinetic resolution process. Unfortunately, high enantiomeric ratios were only achievable with slow reacting electrophiles. For example, use of tributyltin chloride, DMF or dimethyl sulfate gave products with little or no enantioselectivity. It was suggested that more reactive electrophiles are less able to discriminate between the diastereomeric organolithium reagents.

1.1.3 Dynamic Thermodynamic Resolution of Organolithium Reagents

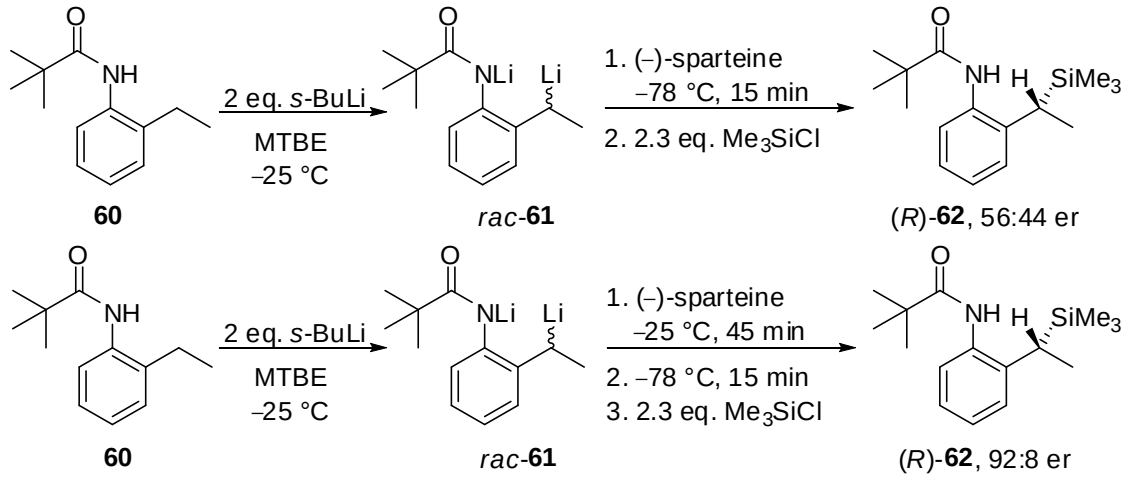
Another approach to synthesising organolithium reagents in high enantiomeric ratio is dynamic thermodynamic resolution. If the intermediate organolithium reagent is configurationally unstable in the presence of a chiral ligand but interconversion of the diastereomeric complexes does not occur on the timescale of reaction with the electrophile then the enantiomeric ratio of the products will reflect the ratio of the diastereomeric organolithium reagents. This process is known as a dynamic thermodynamic resolution and the organolithium reagents are said to have microscopic configurational stability (Scheme 1.27).[18] The process begins with the complex of an organolithium reagent (RLi) and a chiral ligand (L^*) deprotonating substrate **2** to give diastereomeric organolithium reagents (*S*)-**3** and (*R*)-**3**. These organolithium reagents

are able to interconvert under the reaction conditions at rate k_{inv} to give a thermodynamic ratio of diastereoisomers. When an electrophile (E^+) is added, each organolithium reagent will react with a different rate (k_S or k_R) to give products (*S*)-**4** and (*R*)-**4**. However, because k_S and k_R are greater than the rate of interconversion of the diastereomeric organolithium reagents (k_{inv}) the thermodynamic ratio will be trapped. The enantioselectivity of a dynamic thermodynamic resolution is determined by the difference in energy between the two diastereomeric lithiated intermediates (ΔG) and in the presence of an excess of electrophile the enantiomeric ratio of (*S*)-**4** and (*R*)-**4** will directly reflect the diastereomeric ratio of the organolithium intermediates.



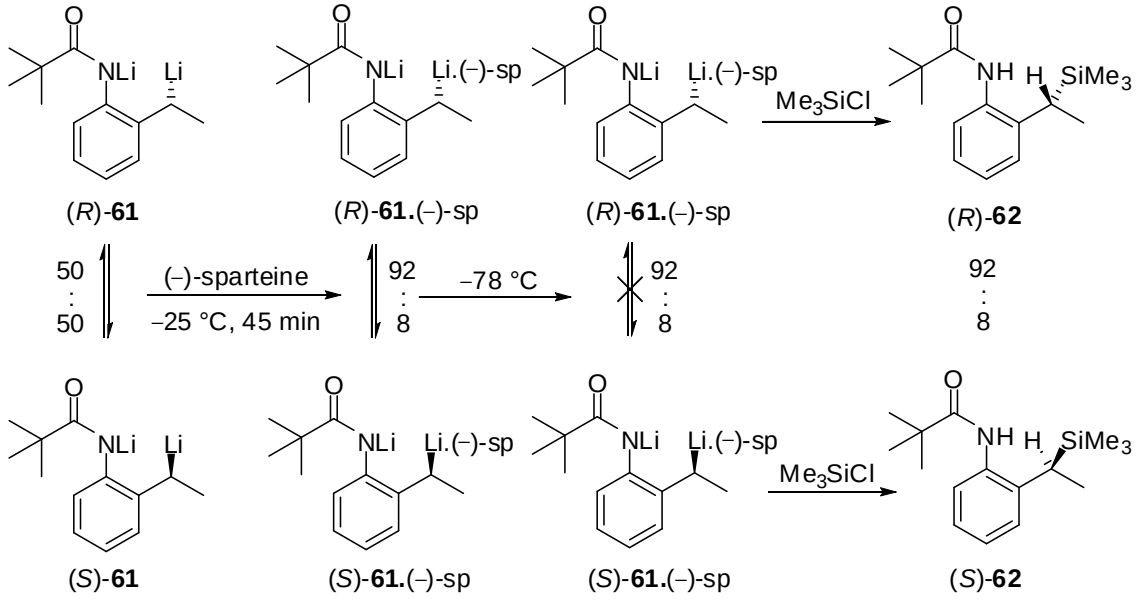
Scheme 1.27

An example of this process is shown in Scheme 1.28.[53] Lithiation of *N*-pivaloyl-*o*-ethylaniline **60** by *s*-BuLi in MTBE at −25 °C gave racemic organolithium reagent *rac*-**61**. Cooling the reaction to −78 °C followed by the addition of (−)-sparteine and trapping with trimethylsilyl chloride gave silylated product (*R*)-**62** in only 56:44 er. However, if (−)-sparteine was added at −25 °C, incubated at that temperature for 45 minutes and then cooled to −78 °C before trapping with trimethylsilyl chloride, then silylated product (*R*)-**62** was isolated in a dramatically improved 92:8 er.



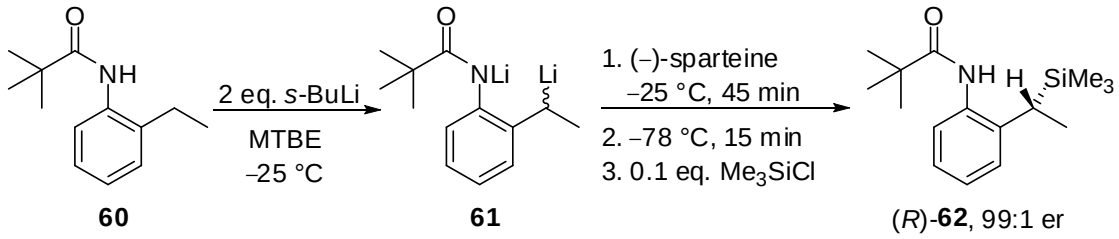
Scheme 1.28

The necessity for a warm-cool cycle to achieve high enantioselectivity indicates that the diastereomeric lithiated intermediates are interconverting at −25 °C but are not at −78 °C. This is shown schematically in Scheme 1.29. Initially, enantiomeric organolithium reagents (*R*)-**61** and (*S*)-**61** were present in a 50:50 ratio. Then, (−)-sparteine was added at −25 °C and diastereomeric organolithium reagents (*R*)-**61**.(−)-sp and (*S*)-**61**.(−)-sp are formed. The organolithium reagents then equilibrate to a 92:8 diastereomeric ratio. This ratio then remained on cooling to −78 °C, a temperature at which the organolithium reagents are configurationally stable. Addition of an excess of trimethylsilyl chloride traps the 92:8 mixture of diastereomeric organolithium reagents and this is reflected in the enantiomeric ratio of the product.



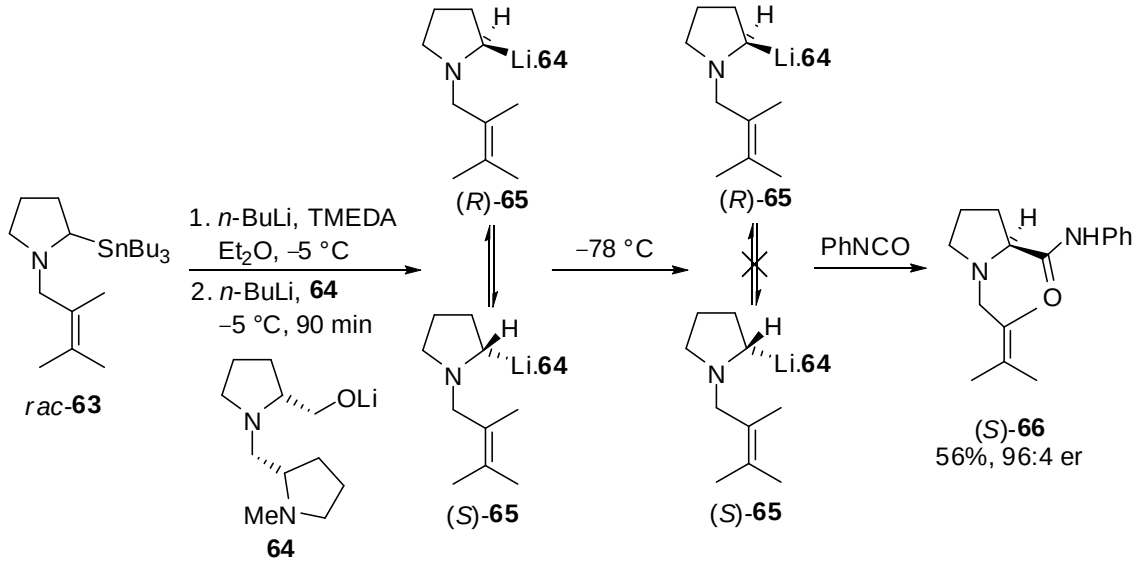
Scheme 1.29

Finally, Beak and co-workers also showed that it was possible to improve the enantiomeric ratio of the product be using a deficiency of the electrophile. Thus, addition of just 0.1 eq. of trimethylsilyl chloride gave silylated product (*R*)-**62** in 99:1 er but the yield is limited to 10% based on **60** (Scheme 1.30). Such a high enantioselectivity is a result of a kinetic resolution with organolithium (*R*)-**61**.(−)-sp reacting faster with the electrophile than organolithium (*S*)-**61**.(−)-sp, leading to a high enantioselectivity of the product (*R*)-**62**.



Scheme 1.30

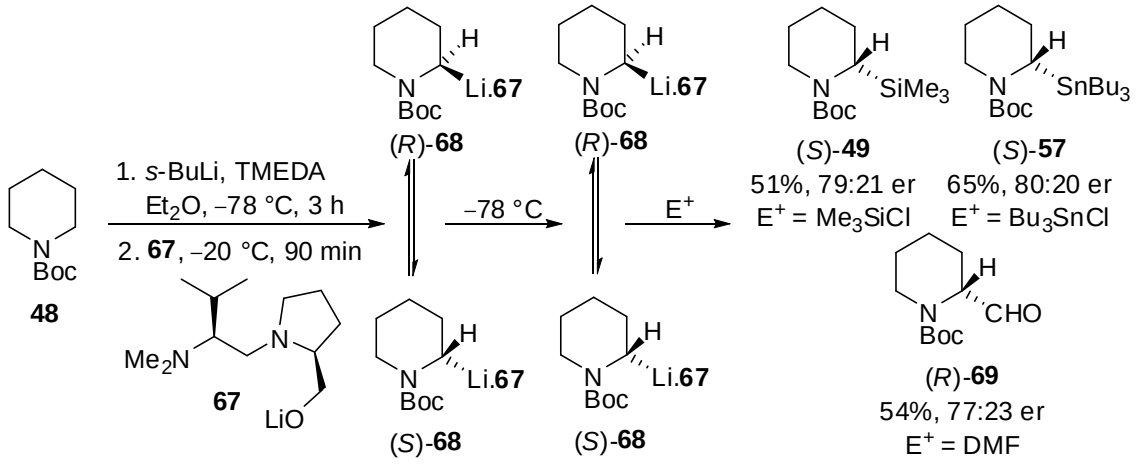
The dynamic thermodynamic resolution of *N*-alkyl and *N*-allyl-2-lithiopyrrolidines was reported by Coldham *et al*. in 2006.[52,54] Stannane *rac*-**63** was treated with *n*-BuLi/TMEDA in Et_2O followed by *n*-BuLi/**64** at −5 °C (Scheme 1.31). After stirring at −5 °C for 90 minutes, the reaction was cooled to −78 °C and phenylisocyanate was added. After chromatography, amide (*S*)-**66** was isolated in 56% yield and 96:4 er. Organolithium reagents (*R*)-**65** and (*S*)-**65** were shown to be configurationally labile at −5 °C but configurationally stable at −78 °C.



Scheme 1.31

The resolution of lithiated pyrrolidine **65** was later expanded by Gawley and co-workers to include a catalytic dynamic resolution process in the presence of just 0.15 equivalents of chiral ligand **64**.[55]

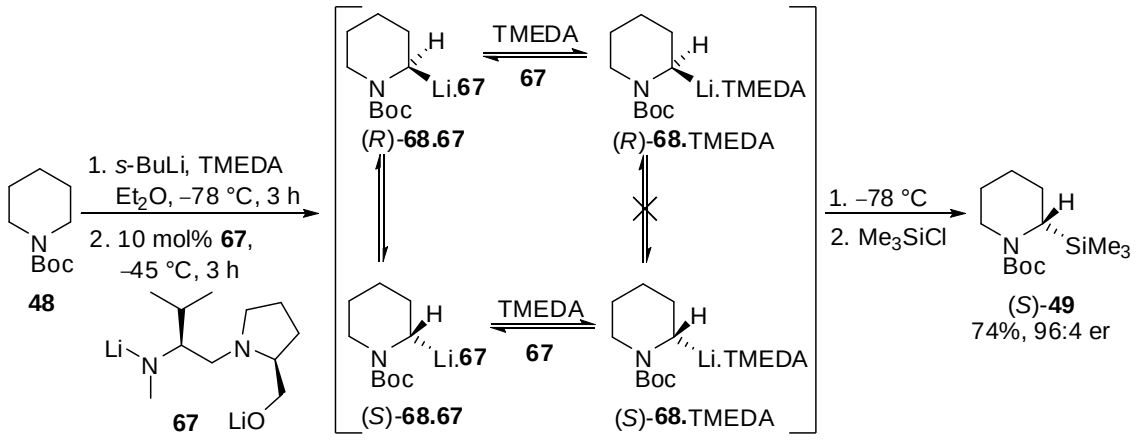
In 2008, Coldham reported the dynamic thermodynamic resolution of *N*-Boc 2-lithiopiperidine **68**.[56] Racemic lithiation of *N*-Boc piperidine **48** using *s*-BuLi/TMEDA in Et_2O at −78 °C was followed by addition of chiral ligand **67** at −20 °C (Scheme 1.32). The reaction was then incubated at −20 °C for 90 minutes to allow the equilibration of the diastereomeric lithiated intermediates (*S*)-**68** and (*R*)-**68**. Cooling to −78 °C prevented further interconversion and trapping with trimethylsilyl chloride, tributyltin chloride or DMF gave silylated piperidine (*S*)-**49** (79:21 er), stannane (*S*)-**57** (80:20 er) or aldehyde (*R*)-**70** (77:23 er) respectively. In contrast to a dynamic kinetic resolution, a wide range of electrophiles gave similar enantiomeric ratio in the dynamic thermodynamic resolution process.



Scheme 1.32

In more recent work, Gawley has reported a catalytic variant of the dynamic thermodynamic resolution of *N*-Boc 2-lithiopiperidine **68**.[57,58] Lithiation of *N*-Boc piperidine **48** (*s*-BuLi/TMEDA, −78 °C, 3 hours) followed by addition of 10 mol% of chiral ligand **67** at −45 °C presumably gave 10 mol% diastereomeric lithiated intermediates (*S*)-**68.67** and (*R*)-**68.67** which were able to interconvert (Scheme 1.33). In order to achieve high enantioselectivity, TMEDA must be able to displace chiral ligand **67** from the lithiated intermediates without perturbing the thermodynamic ratio and therefore (*R*)-**68**.TMEDA and (*S*)-**68**.TMEDA must be configurationally stable at

−45 °C. Chiral ligand **67** will then displace TMEDA from the lithiated intermediate allowing further equilibration of the organolithium reagents. Finally, cooling the reaction to −78 °C and addition of trimethylsilyl chloride gave silylated piperidine (*S*)-**49** in 74% yield and 96:4 er. This reaction has been further expanded to include examples of transmetallation-Negishi coupling.[59]

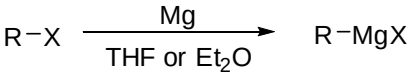


Scheme 1.33

To conclude, dynamic thermodynamic resolution can be used to synthesise chiral organolithium reagents which are than reacted with electrophiles to give substituted products. The enantiomeric ratio of the products is dependent upon the thermodynamic ratio of diastereomeric organolithium reagents. Unlike a dynamic kinetic resolution process, the enantioselectivity does not vary significantly between electrophiles allowing for a wide scope of products to be formed.

1.2 Asymmetric Synthesis of *α*-Functionalised Organomagnesium Reagents

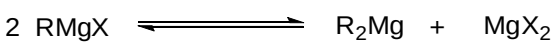
Since their preparation by Victor Grignard in 1900,[60,61] organomagnesium reagents have become ubiquitous within organic chemistry. The classic preparation of Grignard reagents – as they would later become known – is the oxidative insertion of magnesium into carbon-halogen bonds (Scheme 1.34). It is generally accepted that this reaction proceeds *via* a radical pathway.[62,63]



Scheme 1.34

The induction period for the insertion is typically dependent on the amount of moisture present and the nature of the surface of the magnesium turnings. Therefore, a number of chemical activation procedures have been developed, such as the addition of iodine,[64] 1,2-dibromoethane[65] and diisobutylaluminum hydride.[66] In addition, physical activation procedures have also been utilised (*e.g*. dry stirring magnesium turnings under an inert atmosphere[67] and removal of metal oxides from the surface of magnesium turnings[68]).

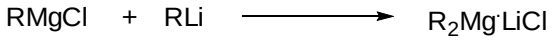
In 1929, Schlenk described the chemical equilibrium taking place within ethereal solutions of Grignard reagents (Scheme 1.35).[69] The equilibrium exists between 2 eq. of the alkyl or aryl magnesium halide and 1 eq. the dialkyl or diaryl magnesium species and the magnesium halide salt. The position of the equilibrium can be dependent upon temperature, solvents and additives such as [15]-crown-5 or 1,4-dioxane.[70,71]



Scheme 1.35

Knochel and co-workers have also reported the syntheses of the more reactive dialkyl or diaryl magnesium species without the need for manipulation of the Schlenk equilibrium

(Scheme 1.36).[71] Addition of an alkyllithium reagent to an alkyl magnesium halide gives the dialkylmagnesium lithium halide complex by a transmetallation process.

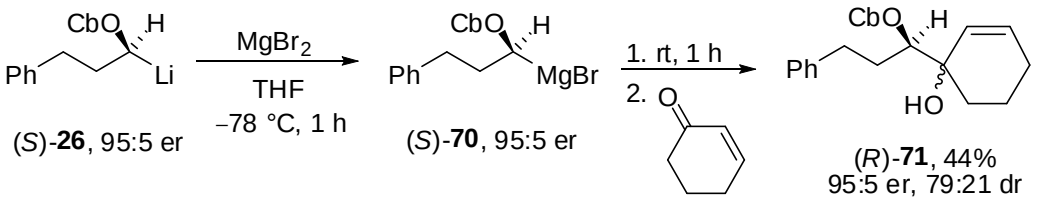


Scheme 1.36

Despite the common use of Grignard reagents in organic synthesis, there are very few methods for synthesising enantioenriched *α*-functionalised Grignard reagents reported in the literature. Two such methods are transmetallation of chiral organolithium reagents and sulfoxide → magnesium exchange of enantioenriched sulfoxides.

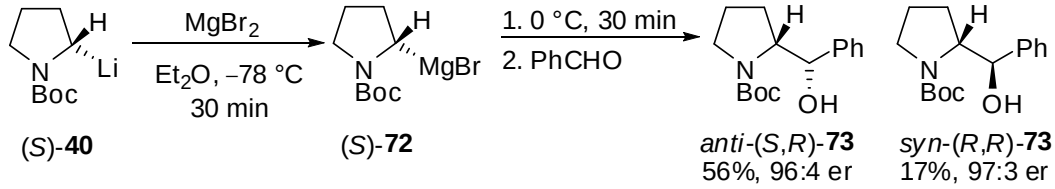
1.2.1 Asymmetric Synthesis of Grignard Reagents by Lithium → Magnesium Transmetallation

Chiral Grignard reagents can be synthesised by transmetallation of enantioenriched organolithium reagents. In 2001, Nakai and co-workers described the transmetallation of lithiated *O*-alkyl carbamates using $MgBr_2$ (freshly prepared from 1,2-dibromoethane and magnesium metal) to give enantioenriched Grignard reagents.[72] Treatment of organolithium (*S*)-**26** (formed by tin → lithium exchange) with $MgBr_2$ gave Grignard reagent (*S*)-**70** (Scheme 1.37). Subsequently, the reaction was warmed to room temperature for 1 hour and then cyclohexenone was added. From the reaction, alcohols (*R*)-**71** were isolated in 44% yield as a 79:21 mixture of diastereoisomers. Hydrogenation of (*R*)-**71** established the absolute configuration and enantiomeric ratio (95:5 er) by comparison with a known compound. The transmetallation and trapping was shown to proceed with retention of configuration from organolithium (*S*)-**26**. When compared to organolithium (*S*)-**26**, Grignard reagent (*S*)-**70** shows remarkable configurational and chemical stability up to room temperature. In contrast, (*S*)-**26** undergoes 1,2-carbamoyl migration at −20 °C.[73]



Scheme 1.37

A similar approach was used in our group to synthesise chiral *α*-amino Grignard reagents.[74] Transmetallation of organolithium reagent (*S*)-**40** (formed by enantioselective deprotonation of *N*-Boc pyrrolidine **39** using *s*-BuLi/(−)-sparteine) with $MgBr_2$ gave Grignard reagent (*S*)-**72** (Scheme 1.38). The reaction was then warmed to 0 °C for 30 minutes and addition of benzaldehyde gave a 70:30 mixture of diastereomeric alcohols *anti*-(*S*,*R*)-**73** and *syn*-(*R*,*R*)-**73** in 96:4 and 97:3 er respectively. Interestingly, when the organolithium reagent was trapped with benzaldehyde, *syn*-(*R*,*R*)-**73** was formed as the major diastereoisomer (75:25 dr).



(*S*)-**40** (*S*)-**72** *anti*-(*S*,*R*)-**73** 56%, 96:4 er *syn*-(*R*,*R*)-**73** 17%, 97:3 er

Scheme 1.38

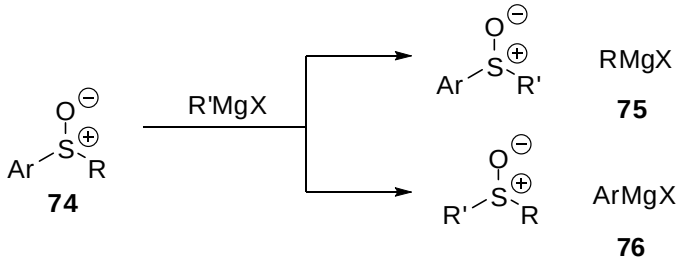
The configurational stability of Grignard reagent (*S*)-**72** was remarkable when compared to organolithium reagent (*S*)-**40**. The Grignard reagent was shown to be configurationally stable at 0 °C for at least 30 minutes, whereas the organolithium reagent is known to be configurationally labile at temperatures above −40 °C.[75,76]

The limitation of synthesising Grignard reagents by transmetallation of organolithium reagents is that the enantiomeric ratio of the products is dependent upon the enantioselectivity of the formation of the organolithium. Therefore, it may not be possible to access an array of *α*-alkoxy and *α*-amino Grignard reagents in ≥99:1 er using this method. Of significant note, however, *α*-alkoxy and *α*-amino Grignard reagents show increased configurational stability when compared to their organolithium counterparts.

1.2.2 Asymmetric Synthesis of Grignard Reagents by Sulfoxide → Magnesium Exchange

Since its discovery in 1962,[77] the sulfoxide → magnesium exchange reaction has been widely applied to the synthesis of enantiomerically pure sulfoxides. However, its use to form Grignard reagents has been given significantly less attention.[4] To this end, the

groups of Satoh, Knochel and Hoffmann have been the pioneers of sulfoxide → metal exchange reactions over the past two decades. Initially, much effort was given to the investigation of sulfoxide → lithium exchange as a method to synthesise chiral *N*-aryl aziridines, epoxides, allylic alcohols and *α*-amino carbonyls.[78,79] However, in 1988, Satoh reported the use of sulfoxide → magnesium exchange chemistry to synthesise *N*-aryl aziridines.[78,80] A general reaction between an alkyl aryl sulfoxide **74** and a Grignard reagent to give either an alkyl Grignard reagent **75** or an aryl Grignard reagent **76** is shown in Scheme 1.39. The structure of sulfoxide **74** and relative stabilities of the Grignard reagents **75** and **76** determine which of these routes is preferred.[81]

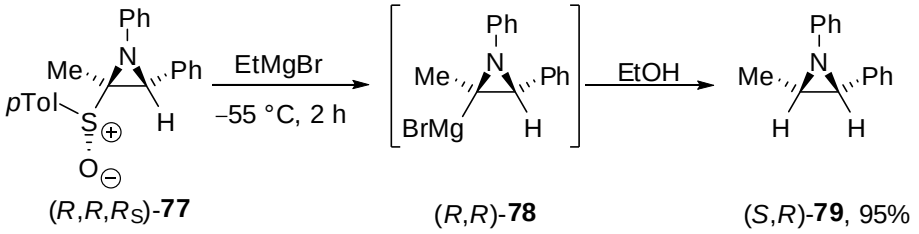


Scheme 1.39

Sulfoxide → magnesium exchange has been proved to be an expedient method for synthesising sp^2 hybridised Grignard reagents.[82] Selected examples of efficient sulfoxide → magnesium exchange include 1-halovinyl sulfoxides,[81,83] pyridyl and quinolyl sulfoxides,[84] *meta*- and *para*-difunctionalisation of arenes[85,86] and 2,3-funtionalisation of furans, benzofurans and thiophenes.[87]

Sulfoxide → magnesium exchange reactions that yield chiral Grignard reagents are of most relevance to the work described in this thesis. Indeed, there are limited alternatives to synthesise sp^3 hybridised Grignard reagents. One example of note is alkoxide directed iodine → magnesium exchange.[88]

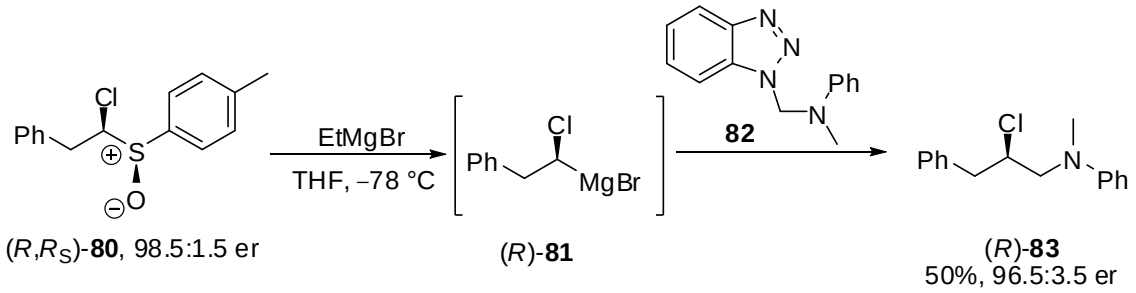
In 1989, Satoh and co-workers reported the synthesis of chiral *N*-aryl aziridines *via* sulfoxide → magnesium exchange (Scheme 1.40).[80] Treatment of sulfoxide (*R*,*R*,R_S)-**77** with EtMgBr gave chiral Grignard reagent (*S*,*R*)-**78** which was trapped with EtOH to give aziridine (*S*,*R*)-**79** in 95% yield. The reaction proceeds by attack of EtMgBr on the sulfoxide with displacement of the most stable anion, metalated aziridine (*S*,*R*)-**78** in this case. The authors report no observable loss of enantiomeric ratio under the reaction conditions, as determined by optical rotation.



(R,R,R_S)-**77** (R,R)-**78** (S,R)-**79**, 95%

Scheme 1.40

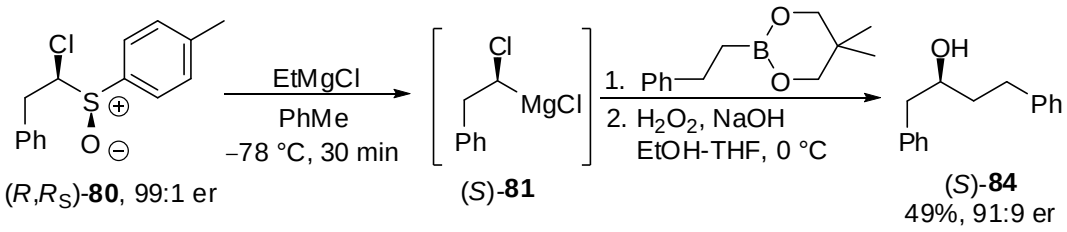
The synthesis of chiral Grignard reagents was further developed by Hoffmann and co-workers during the 1990s.[89,90] In 1999, Hoffmann and Neil reported the synthesis of α-chloro alkyl organomagnesium reagents in >95:5 er *via* sulfoxide → magnesium exchange (Scheme 1.41).[90] α-Chloro sulfoxide (R,R_S)-**80** (98.5:1.5 er) was treated with EtMgBr at −78 °C to give α-chloro Grignard reagent (R)-**81**. Grignard reagent (R)-**81** was then trapped with α-aminomethyl benzotriazole **82** to give chloro amine (R)-**83** in 50% yield and 96.5:3.5 er. The full versatility of this methodology was exemplified in 2000.[91]



(R,R_S)-**80**, 98.5:1.5 er (R)-**81** (R)-**83** 50%, 96.5:3.5 er

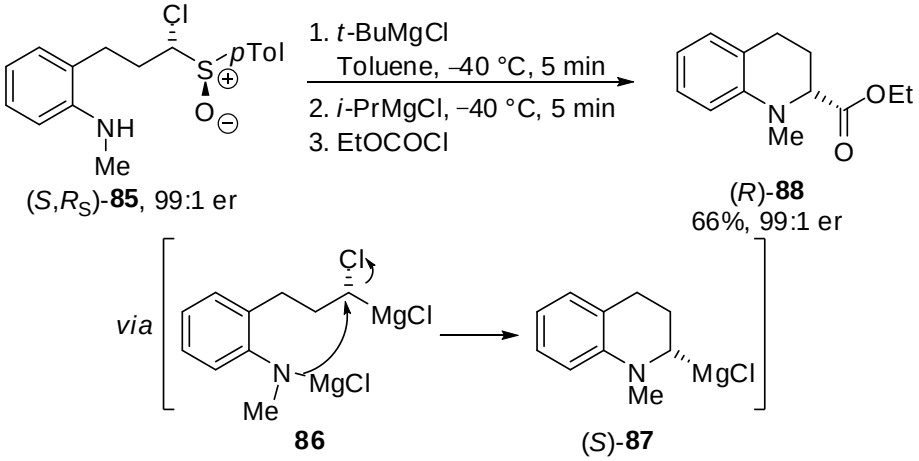
Scheme 1.41

In addition, Blakemore and co-workers have utilised the sulfoxide → magnesium exchange reaction to conduct a stereospecific reagent-controlled homologation starting from α-chloro sulfoxides (Scheme 1.42).[92] Trapping of Grignard reagent (S)-**81** (generated by sulfoxide → magnesium exchange from (R,R_S)-**80**) with Ph$(CH_2)_2$B-dioxaborinane followed by metallate rearrangement and oxidation (H_2O_2, NaOH) gave alcohol (S)-**84** in 49% yield and 91:9 er. The authors noted that the disappointing stereochemical control in the reaction could be improved by using organolithium reagents.



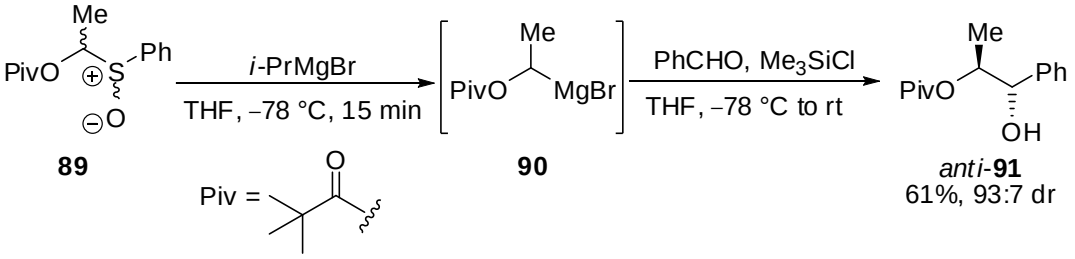
Scheme 1.42

In more recent work from the Satoh group, chiral *α*-chloro sulfoxides have also been used to synthesise cyclic *α*-amino acid derivatives *via* sulfoxide → magnesium exchange.[93] *t*-BuMgCl was added to sulfoxide (*S*,*R*$_S$)-**85** in order to deprotonate the aniline moiety and then addition of *i*-PrMgCl facilitated a sulfoxide → magnesium exchange to give adduct **86** (Scheme 1.43). Subsequent cyclisation to give Grignard reagent (*S*)-**87** and trapping with ethyl chloroformate gave (*R*)-**88** in 66% yield and 99:1 er.



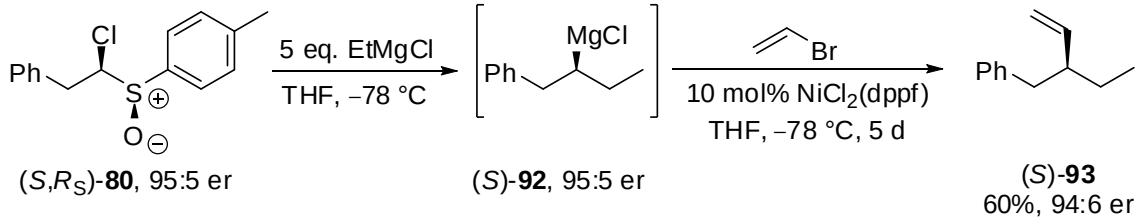
Scheme 1.43

In 1999, Knochel *et al*. reported the synthesis and trapping of *α*-alkoxy Grignard reagent **90** from sulfoxide **89** (Scheme 1.44).[94] Sulfoxide → magnesium exchange mediated by *i*-PrMgBr (THF, −78 °C, 15 minutes) gave Grignard reagent **90** and trapping with benzaldehyde gave alcohol *anti*-**91** in 61% yield and 93:7 dr.



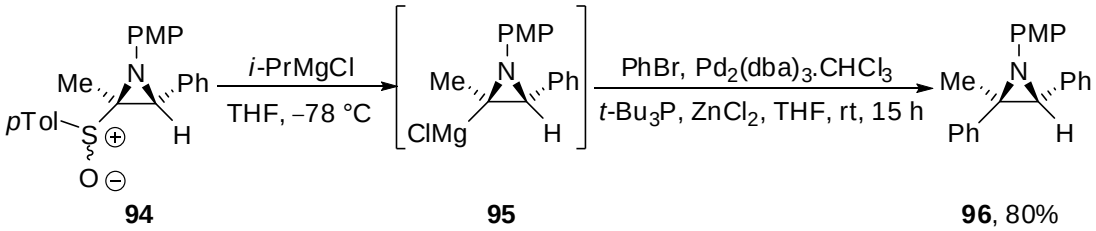
Scheme 1.44

Palladium-catalysed cross coupling of Grignard reagents formed by sulfoxide → magnesium exchange has also been reported. In 2003, Hoffmann and Hölzer reported the Kumada-Corriu[95,96] coupling of Grignard reagents derived from a sulfoxide → magnesium exchange (Scheme 1.45).[97] *α*-Chloro sulfoxide (*S*,R_S)-**80** was treated with 5 eq. of EtMgCl at −78 °C to give Grignard reagent (*S*)-**92** (which had previously been shown to be configurationally stable at −78 °C). Subsequent Kumada-type coupling with vinyl bromide gave the coupled product (*S*)-**93** in an optimised 60% yield and 94:6 er. This represents essentially full retention of configuration from Grignard reagent (*S*)-**92**.



Scheme 1.45

The major limitation of the Kumada-Corriu coupling as reported by Hoffmann is the need for extremely long reaction times (5 days) at −78 °C. One way to circumvent this problem is to conduct a transmetallation-Negishi coupling of the Grignard reagent. Indeed, Bull *et al*. reported the palladium-catalysed cross-coupling of aziridinylmetal species generated from sulfoxide → magnesium exchange in 2013 (Scheme 1.46).[98] Treatment of sulfoxide **94** (synthesised in three steps from ethyl *p*-tolyl sulfoxide[99]) with *i*-PrMgCl in THF at −78 °C gave Grignard reagent **95**. Subsequent *in situ* transmetallation of **95** with zinc chloride and Negishi coupling gave phenyl aziridine **96** in 80% yield.



94 **95** **96**, 80%

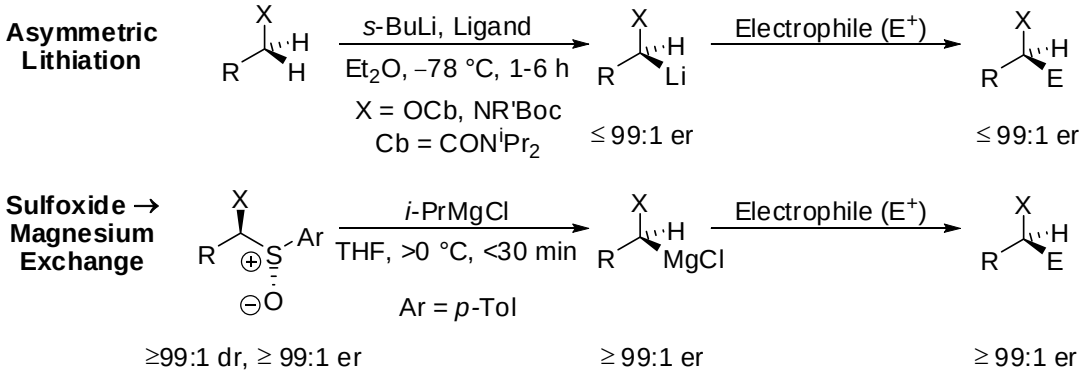
Scheme 1.46

To conclude, sulfoxide → magnesium exchange provides an expedient method for synthesising chiral Grignard reagents. However, only two examples of sulfoxide → magnesium exchange giving α-amino Grignard reagents in high enantiomeric ratio have been reported. Much attention has been focused on the synthesis of α-chloro Grignard reagents and their application in synthesis. Currently, there have been no examples reported of sulfoxide → magnesium exchange reactions being conducted at temperatures higher than −40 °C.

1.3 Project Outline

The aim of the research described in this thesis is to develop novel methods for synthesising chiral *α*-alkoxy and *α*-amino organometallic reagents. Two approaches will be taken; (i) synthesis of *α*-alkoxy and *α*-amino Grignard reagents by sulfoxide → magnesium exchange (Chapters Two and Three) and (ii) asymmetric lithiation of *N*-thiopivaloyl azetidine and pyrrolidine (Chapter Four).

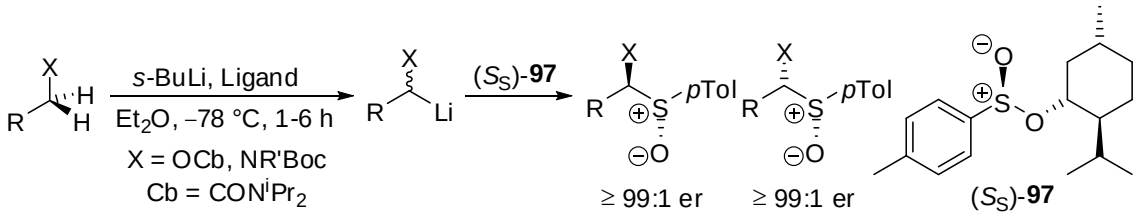
Asymmetric lithiation of *O*-alkyl carbamates and *N*-Boc heterocycles using *s*-BuLi/chiral ligands is typically performed at low temperatures (−78 °C) for long reaction times (1-6 hours). In addition, products are typically formed in ≤99:1 er. To address these limitations, we propose that enantiopure sulfoxides can be used as precursors for chiral Grignard reagents (Scheme 1.47). The Grignard reagents will be formed *via* sulfoxide → magnesium exchange, which will ideally take place at temperatures of 0 °C or above making it amenable to industrial-scale synthesis. Furthermore, we will particularly focus on substrates where asymmetric deprotonation chemistry cannot access organolithium reagents in ≥99:1 er. The results of this project are presented in Chapter Two (*α*-alkoxy Grignard reagents) and Chapter Three (*α*-amino Grignard reagents).



Scheme 1.47

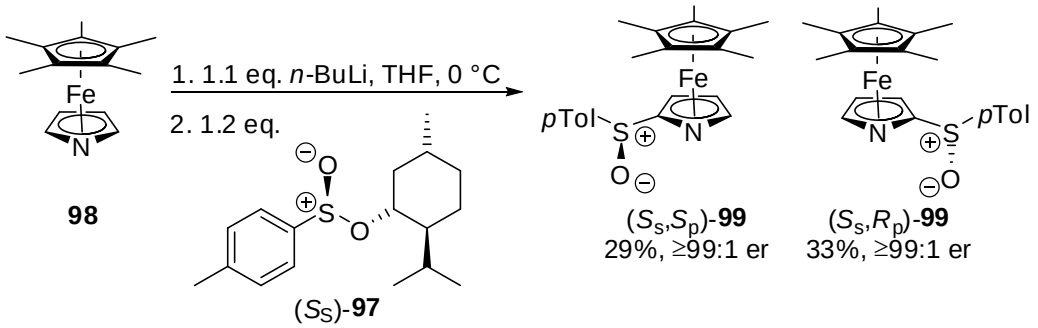
We believe that this methodology will provide significant benefits over asymmetric lithiation chemistry not least because the availability of (−)-sparteine has been variable during the course of the research described in this thesis. This is of much concern as (−)-sparteine generally gives the highest enantioselectivity over a wide range of reaction

types. The plan was that the enantiopure sulfoxides would be synthesised by lithiation of the corresponding *O*-alkyl carbamates or *N*-Boc heterocycles and trapping with Andersen's sulfinate (S_S)-**97** (Scheme 1.48). Subsequent sulfoxide → magnesium exchange would give access to the corresponding Grignard reagents. This would mean that one lithiation-trapping reaction would give access to an array of products in ≥99:1 er.



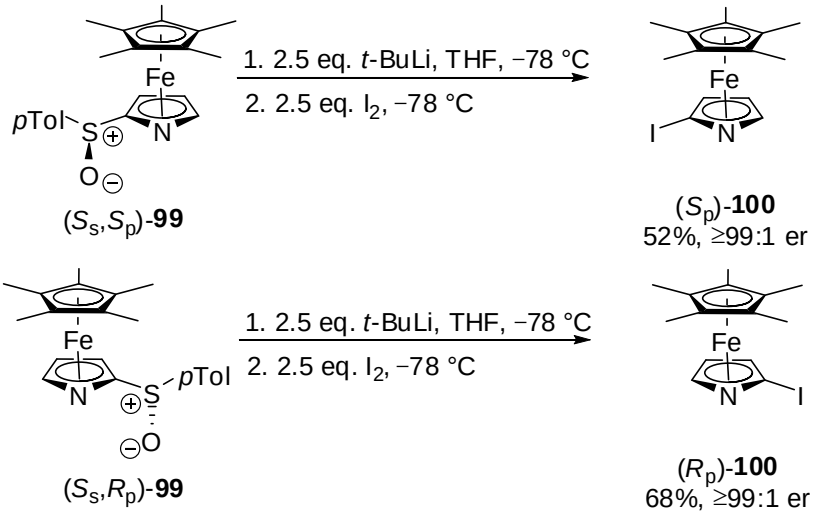
Scheme 1.48

One example of the use of sulfoxides as chiral auxiliaries in this way is shown in Scheme 1.49. In 2001, Johannsen and co-workers reported the use of a sulfoxide → lithium exchange as a route to optically pure azaferrocenyls.[100] *Ortho*-lithiation of azaferrocene **98** by *n*-BuLi followed by addition of Andersen's sulfinate (S_S)-**97** gave diastereomeric sulfoxides (S_S,S_P)-**99** and (S_S,R_P)-**99** in 29% yield and 33% yield respectively, both in ≥99:1 er. These are essentially enantiomeric ferrocenyl anion equivalents.



Scheme 1.49

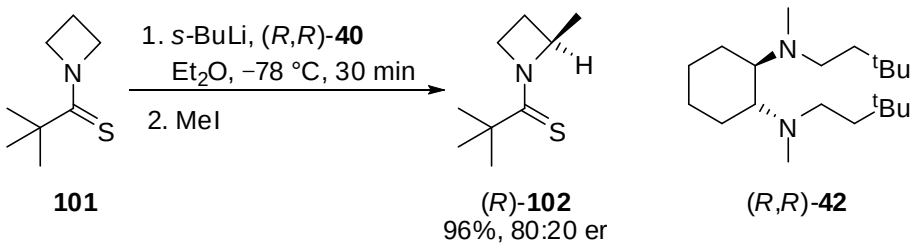
The authors then treated sulfoxide (S_S,S_P)-**99** with *t*-BuLi in THF at −78 °C to achieve a sulfoxide → lithium exchange. Subsequent trapping of the lithiated intermediate with iodine gave iodide (S_P)-**100** in 52% yield and ≥99:1 er (Scheme 1.50). In addition, enantiomeric iodide (R_P)-**100** was synthesised in similar fashion from sulfoxide (S_S,R_P)-**99** in 68% yield and ≥99:1 er.



Scheme 1.50

We propose that the use of sulfoxide → magnesium exchange would provide significant benefits. Not only does the use of Grignard reagents deliver a safety benefit (particularly if this chemistry is to become available to the industrial chemist), but chiral *α*-substituted Grignard reagents have been shown to have a higher degree of configurational stability than their organolithium counterparts.[72,74] This should allow our proposed methodology to be conducted at ambient temperatures.

In Chapter Four, an investigation into the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** is presented. Despite their importance as bioactive compounds, novel methods for synthesising substituted chiral azetidines have received limited attention from the academic community.[101] One approach is the lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi and chiral diamines although only one example has been reported in the literature (Scheme 1.51).[102] Lithiation of **101** using *s*-BuLi/(*R*,*R*)-**42** and trapping with methyl iodide gave methylated azetidine (*R*)-**102** in 96% yield and 80:20 er



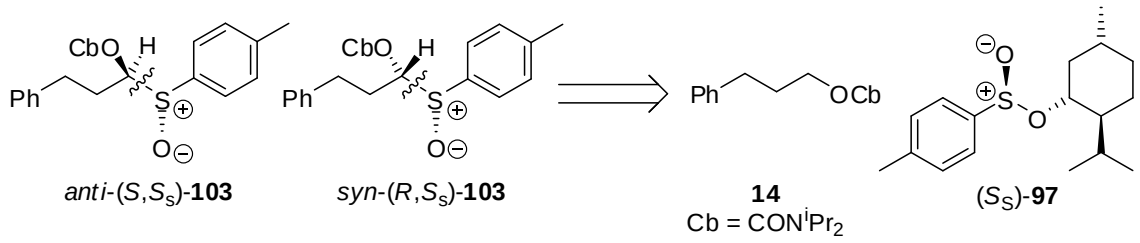
Scheme 1.51

To our surprise, lithiation of *N*-thiopivaloyl azetidine **101** proceeded with the opposite sense of induction to that observed for the asymmetric lithiation of *N*-Boc pyrrolidine **39**[38] and *N*-Boc piperidine **48**[41]. The authors offered no explanation for the differing enantio-induction between these examples but suggested that a directed enantioselective deprotonation may take place.

Our aim was to identify the mechanism by which asymmetric lithiation-substitution occurs. Therefore, a detailed mechanistic study of this reaction was undertaken and is described in Chapter Four.

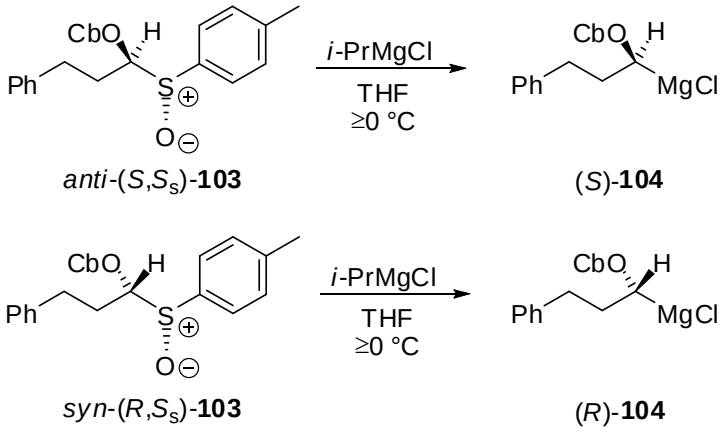
Chapter Two: Synthesis and Reactions of *α*-Alkoxy Grignard Reagents

Our goal was to synthesise enantiopure *α*-alkoxy Grignard reagents and exemplify their reaction profile. The plan was twofold. First, the intention was to synthesise diastereomeric sulfoxides *anti*-(*S*,*S*$_S$)-**103** and *syn*-(*R*,*S*$_S$)-**103** in ≥99:1 er (Scheme 2.1). It was envisaged that an expedient route would be *via* lithiation-trapping of *O*-alkyl carbamate **14**, with the *α*-alkoxy stereocentre being controlled by a chiral base and the sulfoxide stereocentre arising from Andersen's sulfinate (*S*$_S$)-**97**.



Scheme 2.1

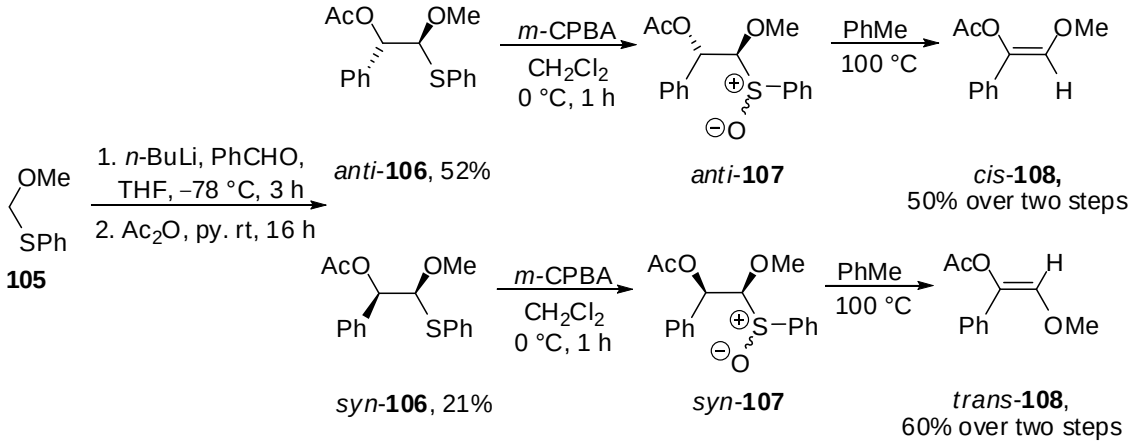
Second, a sulfoxide → magnesium exchange procedure would then be developed to allow access to either enantiomer of Grignard reagent **104** in ≥99:1 er, hopefully under ambient conditions (Scheme 2.2). Subsequent electrophilic trapping would generate *α*-substituted products in ≥99:1 er. Our efforts towards these aims are described in this chapter.



Scheme 2.2

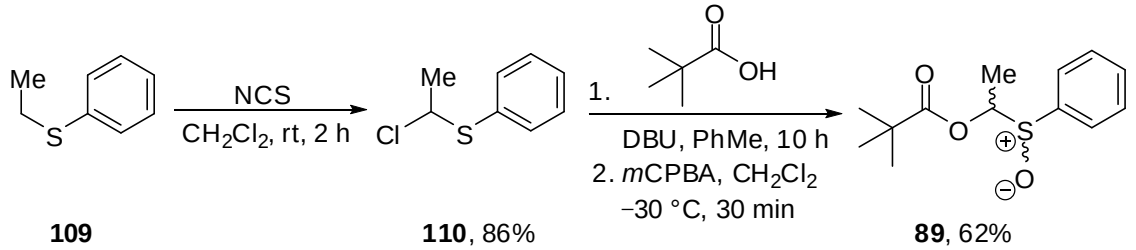
2.1 Previous Syntheses of *α*-Alkoxy Sulfoxides

Three different approaches for the synthesis of *α*-alkoxy sulfoxides have been reported in the literature. Each method requires a late-stage sulfide oxidation to yield the target molecule. First, Nozaki and co-workers reported the synthesis of sulfoxides *anti*-**107** and *syn*-**107** en route to isomeric alkenes *cis*-**108** and *trans*-**108** (Scheme 2.3).[103] This strategy began with the lithiation-trapping of sulfide **105** and subsequent acetylation to give sulfides *anti*-**106** and *syn*-**106**. Subsequent *m*-CPBA oxidation of *anti*-**106** furnished sulfoxide *anti*-**107** which was isolated before elimination at high temperature to give alkene *cis*-**108** in 50% yield over two steps. A similar procedure was used to convert sulfide *syn*-**106** into alkene *trans*-**108**.



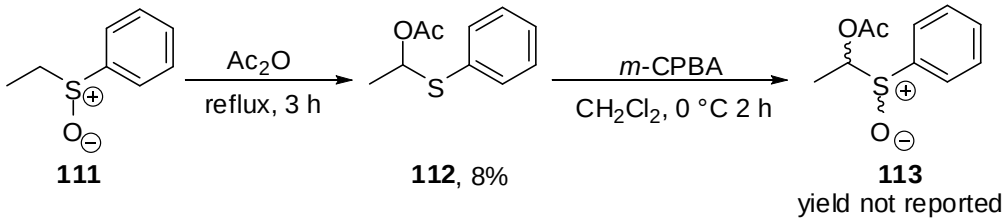
Scheme 2.3

In 1999, Knochel *et al*. reported the synthesis of *α*-alkoxy sulfoxide **89**.[94] The strategy began with chlorination of ethyl sulfide **109** using *N*-chlorosuccinimide. This gave chlorosulfide **110** in 86% yield. Nucleophilic addition of pivalic acid to chlorosulfide **110** followed by oxidation using *m*CPBA gave sulfoxide **89** in 62% yield over two steps (Scheme 2.4).



Scheme 2.4

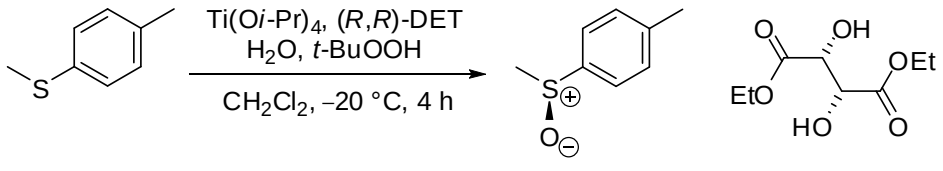
Finally, Yoshimura *et al.* have reported the synthesis of *α*-alkoxy sulfoxides *via* a Pummerer rearrangement and subsequent oxidation (Scheme 2.5).[104] Refluxing ethyl phenyl sulfoxide **111** in acetic anhydride gave sulfide **112** in poor yield (8%). *m*CPBA oxidation of sulfide **112** gave sulfoxide **113** although the yield for this step was not reported.



111 **112**, 8% **113** yield not reported

Scheme 2.5

None of the reported approaches to *α*-alkoxy sulfoxides control the sulfoxide configuration. Indeed, the use of oxidation chemistry to access sulfoxides provides a limitation when extending the methodology to encompass the synthesis of enantiomerically pure sulfoxides. Typically, asymmetric oxidation of sulfides gives products with varying enantioselectivity. The most useful protocol was published by Kagan *et al.* in 1984 and involved use of a modified Sharpless reagent which proceeds in 85:15-95:5 er (Scheme 2.6).[105] For example, when methyl *p*-tolylsulfide **114** was treated with Ti(O*i*-Pr)$_4$, (*R*,*R*)-diethyl tartrate, water and *t*-BuOOH, sulfoxide (*R*)-**115** was formed in 90% yield and 95:5 er. In limited examples, recrystallisation can afford sulfoxides in 99:1 er.[106]

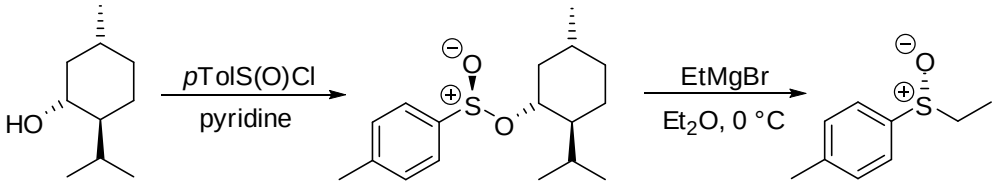


114 (*R*)-**115** 90%, 95:5 er (*R*,*R*)-DET

Scheme 2.6

Other reported methods for asymmetric sulfide oxidation include the use of chiral peracids and oxaziridines (<60:40 er),[107] electrochemical oxidation (78:22 er)[108] and oxidation using micro-organisms (<99:1 er).[109] However, none of these methods provides an improvement on the Kagan protocol.

An alternative approach to synthesise enantiopure sulfoxides is the use of sulfinyl transfer reagents. In 1962, Andersen reported the first synthesis of an enantiomerically pure sulfoxide from an enantiomerically pure sulfinate by addition of a Grignard reagent (Scheme 2.7).[110] Sulfinate (S_S)-**97** was first synthesised by Phillips *et al*. in 1926 from (−)-menthol and *p*-toluenesulfinyl chloride in 44% yield after two recrystallisations.[111] Andersen treated sulfinate (S_S)-**97** with EtMgBr to give ethyl *p*-tolylsulfoxide (*R*)-**116** in 64% yield.

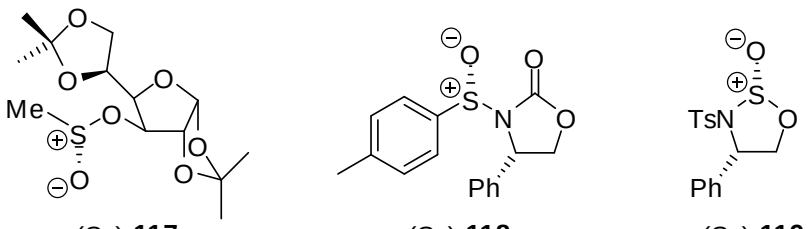


(S_S)-**97**, 44% (*R*)-**116**, 64%

Scheme 2.7

Later, Andersen used this method to synthesise a number of enantiomerically pure sulfoxides.[77,112] Detailed mechanistic studies have also shown that the nucleophilic addition to sulfinates and sulfoxides occurs with inversion of configuration at sulfur.[113,114]

Whilst Andersen's sulfinate (S_S)-**97** remains the archetypal precursor for the synthesis of chiral sulfoxides, other sulfinyl transfer reagents have been reported in the literature (Figure 2.1). In 1992, Alcudia and co-workers reported the synthesis of the sulfinate ester of diacetone-*D*-glucose (S_S)-**117**.[115] Addition of Grignard reagents to sulfinate (S_S)-**117** furnished an array of sulfoxides as single enantiomers.



(S_S)-**117** (S_S)-**118** (S_S)-**119**

Figure 2.1

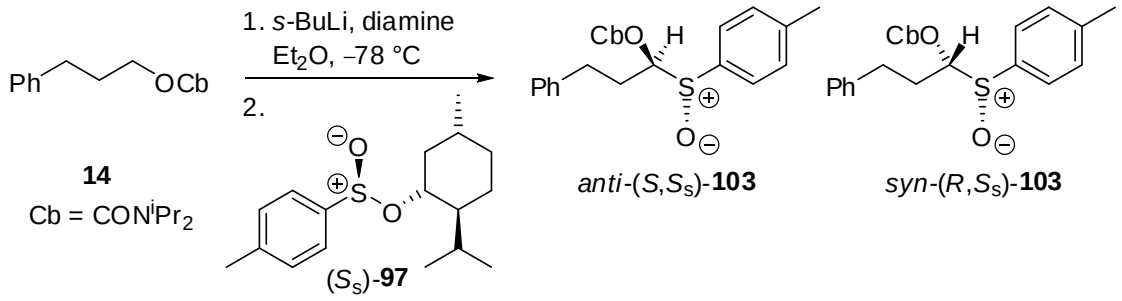
In the same year, Evans *et al*. reported the synthesis and reactions of *N*-sulfinyl oxazolidinone (S_S)-**118** to form chiral sulfoxides.[116] More recently, Stockman and co-

workers described the synthesis of oxathiazolidine oxide (S_S)-**119** from *L*-phenylalanine and thionyl chloride.[117,118] Oxathiazolidine oxide (S_S)-**119** has been used to form single enantiomers of sulfoxides, sulfonamides and sulfinimines.

To conclude, none of the reported methods offer a convenient approach to the synthesis of *α*-alkoxy sulfoxides as single enantiomers. However, modifications could be made to include an asymmetric sulfide oxidation of which the Kagan protocol would offer the best method. An alternative route to chiral sulfoxides would be the addition of organometallic reagents to sulfinyl transfer reagents although, prior to the work described in this thesis, this chemistry has not yet been applied to *α*-alkoxy sulfoxides.

2.2 Synthesis of *α*-Alkoxy Sulfoxides

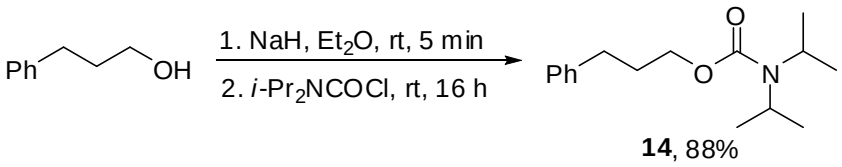
We envisaged that sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103** would be synthesised by lithiation chemistry from *O*-alkyl carbamate **14** and Andersen's sulfinate (S_S)-**97** as outlined in Scheme 2.8. Lithiation of *O*-alkyl carbamate **14** mediated by *s*-BuLi and a diamine and then trapping with inversion of configuration at sulfur with Andersen's sulfinate (S_S)-**97** would allow rapid access to the desired sulfoxides without the need to use asymmetric oxidation chemistry. It was hoped that use of a chiral diamine would allow access to the major diastereoisomer in high yield.



Scheme 2.8

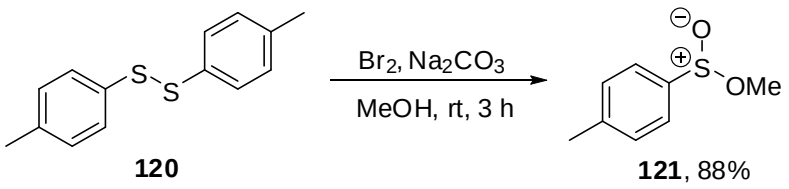
2.2.1 *s*-BuLi/TMEDA-Mediated Lithiation of *O*-Alkyl Carbamates and Trapping with Andersen's Sulfinate

First, the racemic synthesis of sulfoxides *anti-rac*-**103** and *syn-rac*-**103** was required in order to provide standards for CSP-HPLC analysis. Therefore, *O*-alkyl carbamate **14** was synthesised using a method previously reported by our group.[29] 3-Phenyl propanol was deprotonated using sodium hydride and diisopropylcarbamoyl chloride was added to give the desired carbamate **14** in 88% yield (Scheme 2.9).



Scheme 2.9

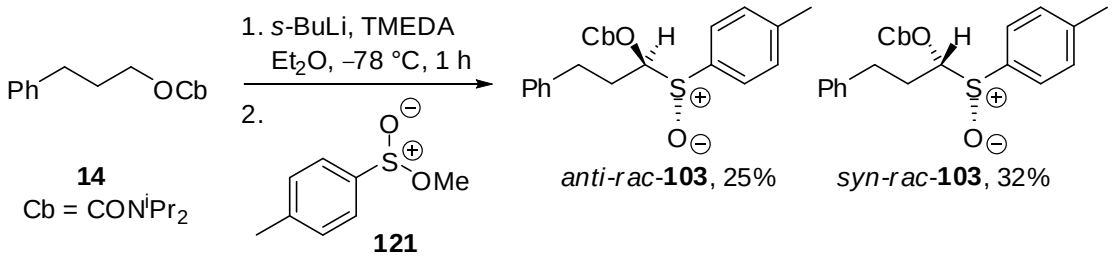
In addition, methyl *p*-tolyl sulfinate **121** was synthesised in 88% yield by oxidation of *p*-tolyl disulfide **120** with bromine in methanol (Scheme 2.10).[119] This would be used as the electrophile in the lithiation-trapping of *O*-alkyl carbamate **14** before investigating the trapping with Andersen's sulfinate (S_S)-**97**.



120 **121**, 88%

Scheme 2.10

Lithiation of *O*-alkyl carbamate **14** with 1.2 eq. of *s*-BuLi/TMEDA at −78 °C and trapping with methyl *p*-tolyl sulfinate **121** gave sulfoxides *anti*-*rac*-**103** and *syn*-*rac*-**103** in 25% and 32% yield respectively (Scheme 2.11). Importantly, the two diastereoisomers were readily separable by column chromatography and had distinctive ^{1}H and ^{13}C NMR spectra. The OCH signals for sulfoxide *anti*-*rac*-**103** were δ_H 5.45 (doublet of doublets, J = 10.0, 3.0 Hz) and δ_C 91.7 and for sulfoxide *syn*-*rac*-**103** were δ_H 5.72 (doublet of doublets, J = 9.5, 4.0 Hz) and δ_C 86.8. Each diastereoisomer was shown to be separable into a 50:50 mixture of enantiomers by CSP-HPLC. Assignment of the relative stereochemistry is provided later (see Scheme 2.24).



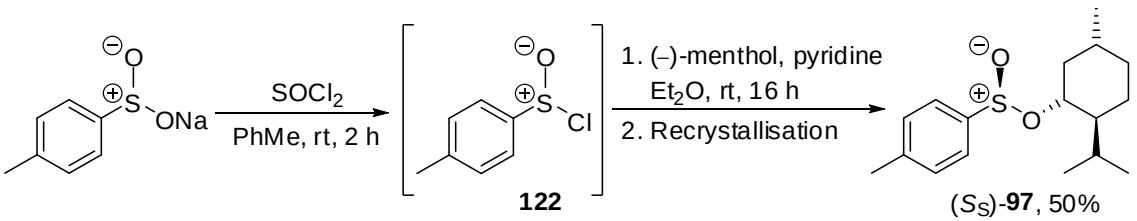
14
Cb = $CONiPr_2$

121

anti-*rac*-**103**, 25% *syn*-*rac*-**103**, 32%

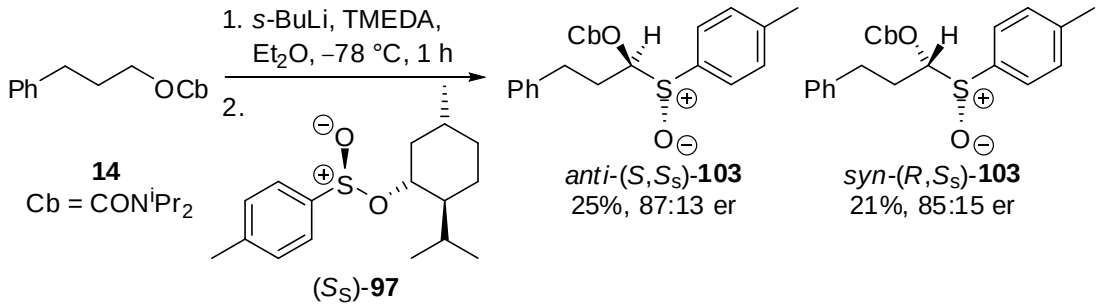
Scheme 2.11

Next, the use of Andersen's sulfinate (S_S)-**97** as the electrophile was explored. Andersen's sulfinate (S_S)-**97** was synthesised using a modified Solladié procedure.[120] First, sodium *p*-toluene sulfinate was treated with thionyl chloride to give sulfinyl chloride **122** (Scheme 2.12). Then, after removal of excess thionyl chloride by distillation, (−)-menthol was added to give a single diastereoisomer of Andersen's sulfinate (S_S)-**97** in 50% yield after recrystallisation.



Scheme 2.12

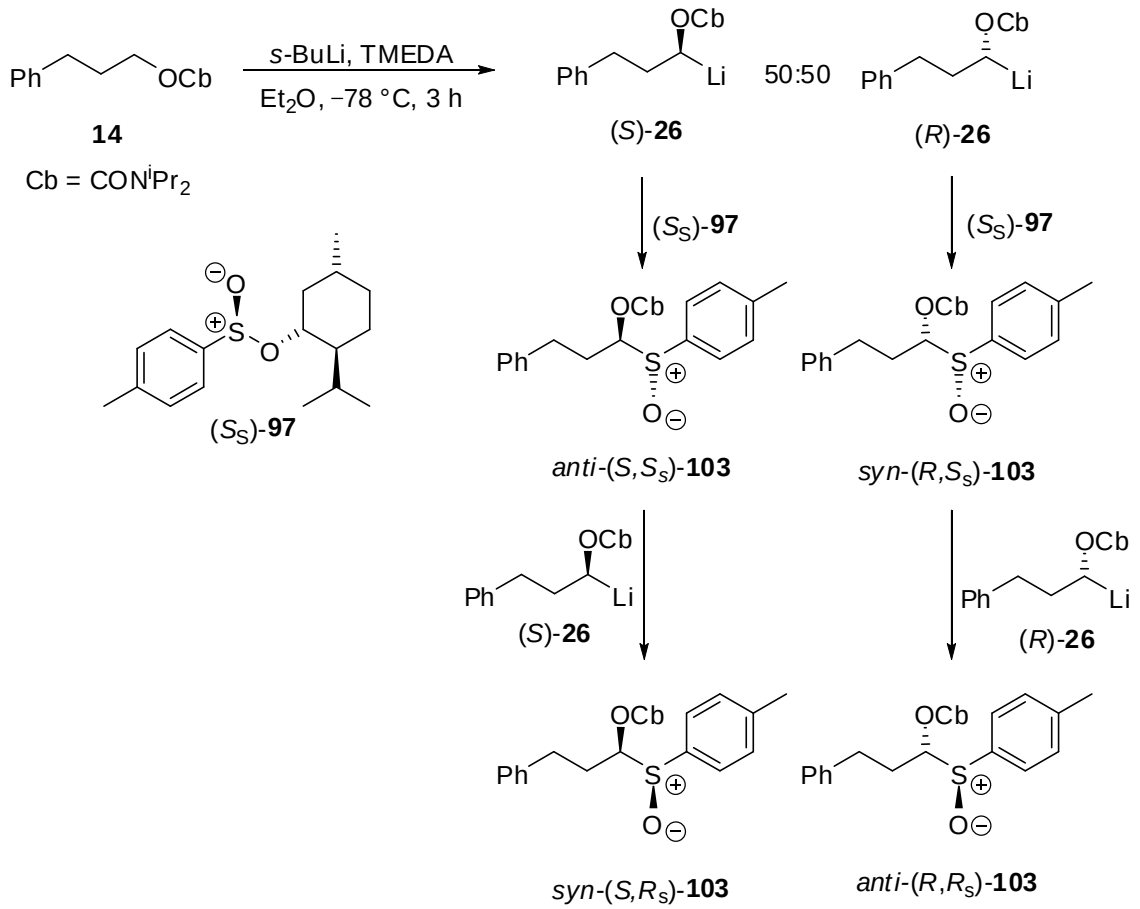
Due to extensive literature precedence,[110,112,113,121,122] it was anticipated that addition of the lithiated intermediate to Andersen's sulfinate (S_S)-**97** would proceed with complete inversion of configuration at sulfur, leading to the isolation of two enantiopure diastereomeric sulfoxides. However, this was not the case. Lithiation of *O*-alkyl carbamate **14** with *s*-BuLi/TMEDA and trapping with Andersen's sulfinate (S_S)-**97** gave diastereomeric sulfoxides *anti*-(S,S_s)-**103** (25%) and *syn*-(R,S_s)-**103** (21%) in 87:13 er and 85:15 er respectively (Scheme 2.13). The enantiomeric ratios were determined by CSP-HPLC and were much lower than expected.



Scheme 2.13

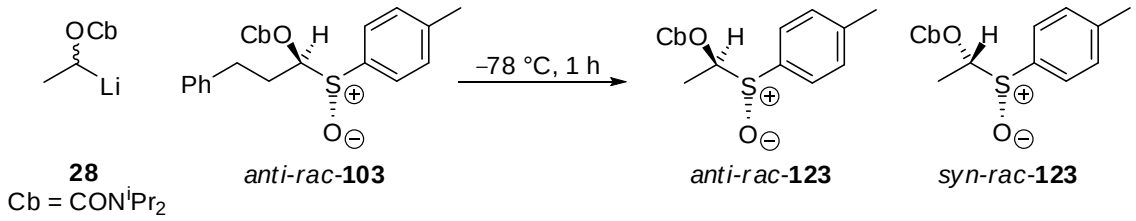
It was postulated that the lack of stereospecificity in the trapping reaction could be due to the electrophilicity of the sulfoxide products that are formed. This could cause a sulfoxide → lithium exchange to occur during the trapping procedure. Our proposed mechanistic scenario is shown in Scheme 2.14. The reaction begins with a racemic lithiation of carbamate **14** to give a 50:50 ratio of enantiomeric lithiated adducts (*S*)-**26** and (*R*)-**26**. Subsequent trapping with Andersen's sulfinate (S_S)-**97** would then give sulfoxides *anti*-(S,S_S)-**103** and *syn*-(R,S_S)-**103**. The trapping process is presumed to occur with inversion of configuration at sulfur in line with the literature precedent.[113] However, due to the stability of (*S*)-**26** and (*R*)-**26**, it is possible for a nucleophilic addition to the sulfoxide products to occur. This would expel organolithium reagents

(*S*)-**26** or (*R*)-**26** as a leaving group. In a similar fashion, the addition to the sulfoxide is presumed to occur with inversion of configuration at sulfur resulting in sulfoxides *syn*-(*S*,R_S)-**103** and *anti*-(*R*,R_S)-**103** being formed. These sulfoxides are the enantiomers of those formed in the initial trapping reaction. This mechanism would explain the reduction in enantiomeric ratio observed in the major products *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103**.



Scheme 2.14

To probe this mechanism, a crossover experiment was designed. This experiment would introduce an alternative lithiated *O*-alkyl carbamate into the presence of the sulfoxide products formed by lithiation-trapping of *O*-alkyl carbamate **14**. Our choice was to add lithiated *O*-ethyl carbamate **28** to sulfoxide *anti-rac*-**103** at −78 °C (Scheme 2.15). If ethyl sulfoxides *anti-rac*-**123** and *syn-rac*-**123** were isolated from this reaction then it would prove that a sulfoxide → lithium exchange reaction occurs between lithiated *O*-alkyl carbamates and the sulfoxide formed during the lithiation-trapping reaction.



28
Cb = CON^iPr_2

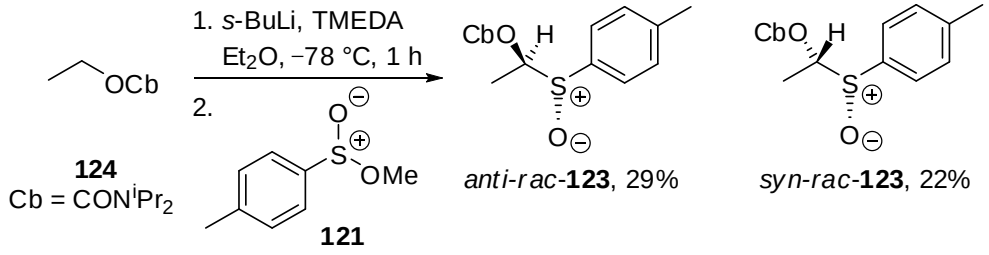
anti-rac-**103**

anti-rac-**123**

syn-rac-**123**

Scheme 2.15

Before carrying out the crossover experiment, ethyl sulfoxides *anti-rac*-**123** and *syn-rac*-**123** were independently synthesised by lithiation of *O*-ethyl carbamate **124** (synthesised from ethyl chloroformate and diisopropyl amine as reported in the literature)[123] using *s*-BuLi/TMEDA at −78 °C for 1 hour and trapping with methyl *p*-toluene sulfinate **121** (Scheme 2.16). Sulfoxides *anti-rac*-**123** and *syn-rac*-**123** were isolated in 29% and 22% yield respectively. The OCH signals provided key diagnostic information for sulfoxide *anti-rac*-**123** (δ_H 5.52, quartet, J = 6.5 Hz and δ_C 89.3) and for sulfoxide *syn-rac*-**123** (δ_H 5.80, quartet, J = 6.5 Hz and δ_C 84.0). Assignment of the relative stereochemistry is provided later (see Scheme 2.25).



124
Cb = CON^iPr_2

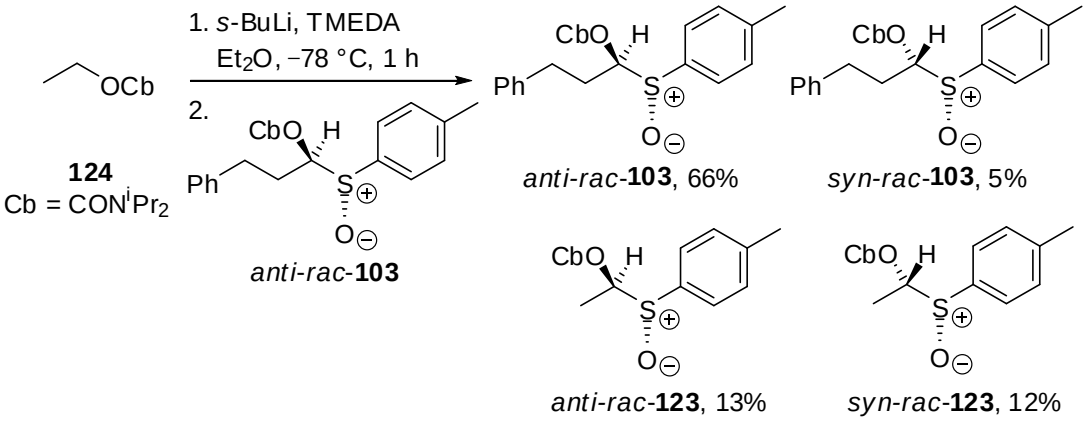
121

anti-rac-**123**, 29%

syn-rac-**123**, 22%

Scheme 2.16

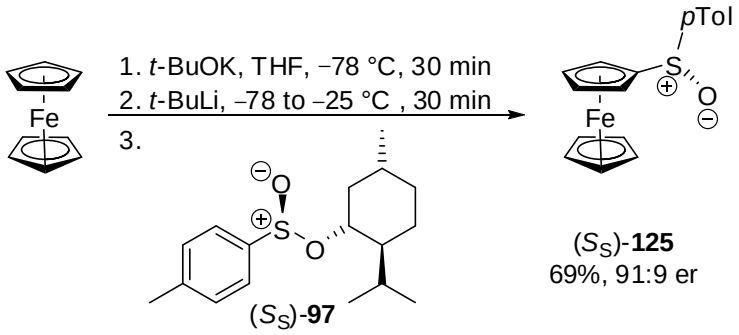
For the crossover experiment, *O*-ethyl carbamate **124** was lithiated by *s*-BuLi/TMEDA and then sulfoxide *anti-rac*-**103** was added. After stirring the reaction for 1 hour at −78 °C, the reaction was quenched with methanol. Purification by flash column chromatography gave a mixture of four inseparable sulfoxides. Analysis of the ^{1}H NMR spectrum of the sulfoxide mixture allowed the determination of yield based on sulfoxide *anti-rac*-**103**. Recovered *anti-rac*-**103** was isolated in 66% yield and its epimer, sulfoxide *syn-rac*-**103**, was formed in 5% yield. It is postulated that *syn-rac*-**103** could be formed by either a double substitution event or *α*-deprotonation of *anti-rac*-**103**. Crucially, ethyl carbamate sulfoxides *anti-rac*-**123** and *syn-rac*-**123** were formed in 13% and 12% yield respectively (Scheme 2.17).



Scheme 2.17

This experiment shows that during the lithiation-trapping reaction, it is possible for excess lithiated intermediate to attack the forming sulfoxides. This would cause a second inversion of configuration at sulfur to take place. Hence, sulfoxides *anti*-(S,S_S)-**103** and *syn*-(R,S_S)-**103** could be formed in reduced enantiomeric ratio.

Closer inspection of the literature revealed a number of isolated examples of low stereochemical fidelity during the reaction of organolithium reagents with enantiopure sulfinates.[124-126] One example is shown in Scheme 2.18. Kagan and co-workers reported that the lithiation of ferrocene and trapping with Andersen's sulfinate (S_S)-**97** gave sulfoxide (S_S)-**125** in 69% yield but only 91:9 er.



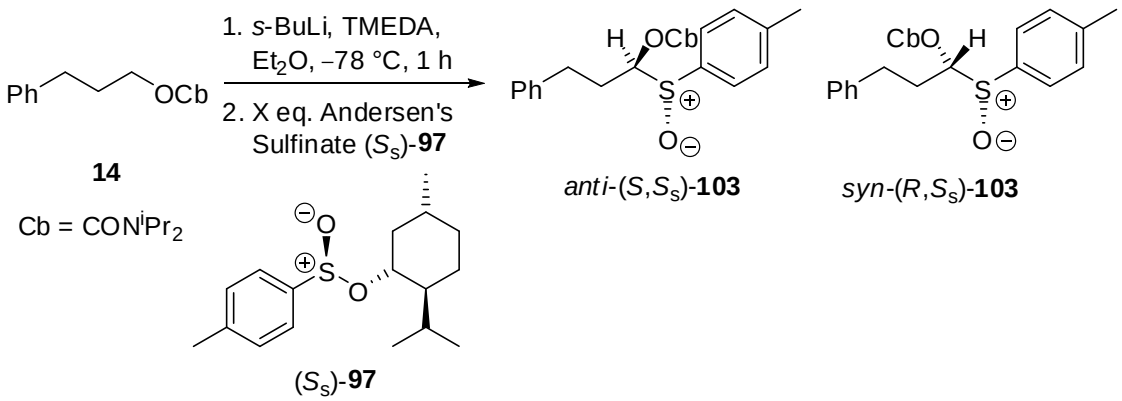
Scheme 2.18

We suggest that the loss of enantiomeric ratio of sulfoxide (S_S)-**125** could be explained using the mechanism outlined in Scheme 2.14. In this case, lithiated ferrocene would attack sulfoxide (S_S)-**125** as it forms, with inversion of configuration at sulfur giving

some of the enantiomeric sulfoxide (R_S)-**125**. The key to the lack of stereospecificity is having a moderately stabilised organolithium that can act as a leaving group.

With the mechanism for loss of enantiomeric ratio identified, a series of experiments were carried out in order to improve the enantioselectivity of the lithiation-trapping. The results are shown in Scheme 2.19 and Table 2.1 and the initial result from Scheme 2.13 is shown in entry 1. First, we hypothesised that the process of warming the reaction from −78 °C to room temperature over 16 hours was the cause of the lower enantiomeric ratio. Since we had already shown that sulfoxide → lithium exchange took place within 1 hour at −78 °C, we chose to quench the reaction 5 minutes after Andersen's sulfinate (S_S)-**97** was added. This allowed us to isolate sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103** in a significantly improved 88:12 er and 91:9 er respectively (entry 2).

The mechanism we proposed for the loss of enantiomeric ratio requires a second addition of nucleophile to the sulfoxide products in order to invert the configuration at sulfur. Therefore, when there is an excess of lithiated intermediates (*R*)-**26** and (*S*)-**26**, this inversion event is favoured. We postulated that by using a reverse addition protocol, whereby the lithiated intermediates are added to Andersen's sulfinate (S_S)-**97** *via* cannula transfer, there would never be an excess of nucleophile present within the reaction mixture. Using the reverse addition protocol did not significantly enhance the enantioselectivity as sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103** were isolated in 87:13 er and 90:10 er respectively (entry 3).



Scheme 2.19

Table 2.1: Optimisation of the Racemic Lithiation of *O*-Alkyl Carbamate **14** and Trapping with Andersen's sulfinate (S_S)-**97**

Entry	X	Reverse Addition	Trap Length / min	*anti*-(*S*,S_S)-103		*syn*-(*R*,S_S)-103	
				Yield / %	er[a]	Yield / %	er[a]
1	1.3	No	16 h [b]	25	83:17	21	85:15
2	1.3	No	5	23	88:12	32	91:9
3	1.3	Yes	5	25	87:13	29	90:10
4	2.0	Yes	5	21	92:8	24	95:5
5	3.0	Yes	5	26	90:10	31	93:7
6[c]	1.3	No	30	8	92:8	8	87:13

[a]er determined by CSP-HPLC, [b] Warmed from −78 °C to room temperature, [c] Transmetallation with $MgBr_2$ before addition of Andersen's sulfinate (S_S)-**97**

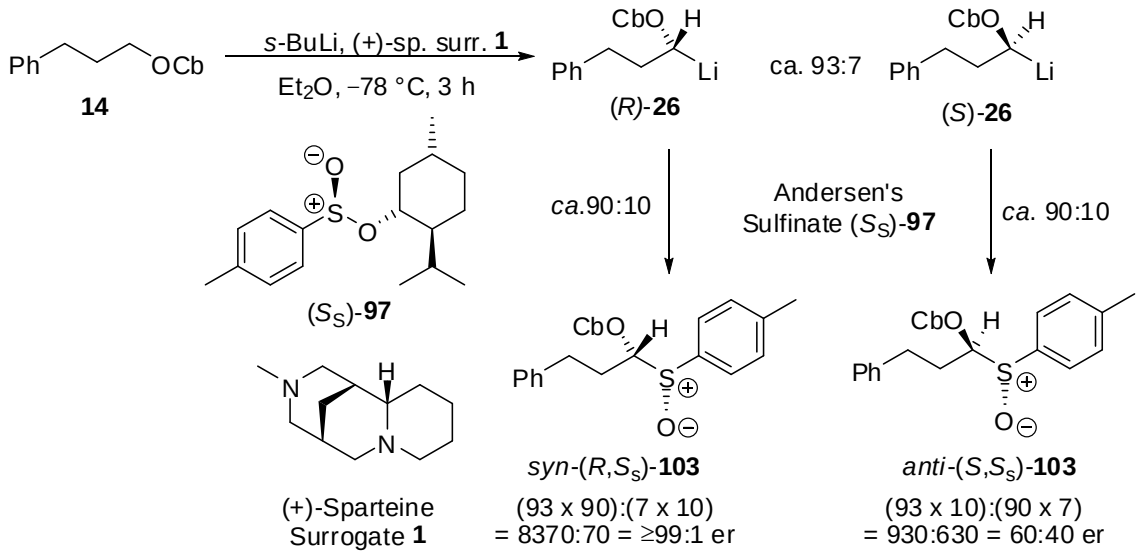
The enantioselectivity was further improved by using 2.0 eq. of Andersen's sulfinate (S_S)-**97** (entry 4) whereas use of 3.0 eq. of Andersen's sulfinate (S_S)-**97** did not lead to further improvement (entry 5). Finally, we attempted to transmetalate the lithiated intermediates by treatment with $MgBr_2$ (entry 6).[74] It was hypothesised that the nucleophilicity of the organometallic reagent could be influenced leading to a reduced propensity for addition to the sulfoxide product. Unfortunately, this led to a poor overall yield (16%) but there was a modest improvement in the enantioselectivity in both diastereomeric sulfoxides *anti*-(*S*,S_S)-**103** (92:8 er) and *syn*-(*R*,S_S)-**103** (87:13 er) compared to an analogous organolithium reaction (entry 1).

To conclude, our optimised conditions for the trapping of lithiated O-alkyl carbamates was using 2.0 eq. Andersen's sulfinate (S_S)-**97** and a reverse addition protocol (addition of lithiated carbamate to Andersen's sulfinate (S_S)-**97**). This gave sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103** in 92:8 er and 95:5 er respectively. However, we were unable to generate products in ≥99:1 er using the racemic lithiation method.

2.2.2 *s*-BuLi/Chiral Ligand-mediated Lithiation of *O*-Alkyl Carbamates and Trapping with Andersen's Sulfinate

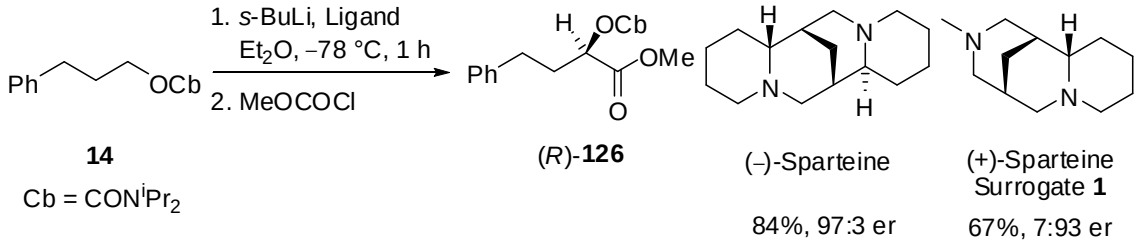
To overcome our inability to isolate the *α*-alkoxy sulfoxides in ≥99:1 er, our thoughts then turned to a chiral amplification strategy. It was postulated that an asymmetric lithiation of *O*-alkyl carbamate **14** mediated by *s*-BuLi/chiral diamine and subsequent trapping with Andersen's sulfinate (S_S)-**97** would lead to an increase in enantioselectivity in the major sulfoxide diastereoisomer (and a simultaneous loss of enantiomeric ratio in the minor diastereoisomer) due to two chiral partners reacting with one another. Furthermore, we would expect the enantiomeric ratio for the major diastereoisomer to be ($v \times y$):($w \times z$), where v:w is the enantiomeric ratio of the first enantioselective reaction and y:z is the enantiomeric ratio of the second.[32]

As an example, *s*-BuLi/(+)-sparteine surrogate **1** is reported in the literature to give 93:7 er[127] in the asymmetric lithiation of *O*-alkyl carbamate **14** and we have shown that, using the reverse addition protocol, Andersen's sulfinate (S_S)-**97** traps with *ca.* 90:10 er. Therefore, the enantiomeric ratio of the major diastereoisomer, sulfoxide *syn*-(R,S_S)-**103**, should be (93×90):(7×10) = (8370):(70) = >99:1 er (Scheme 2.20). The increase in the enantiomeric ratio observed in the major diastereoisomer will be at the expense of the enantiomeric ratio of the minor diastereoisomer which will be reduced.



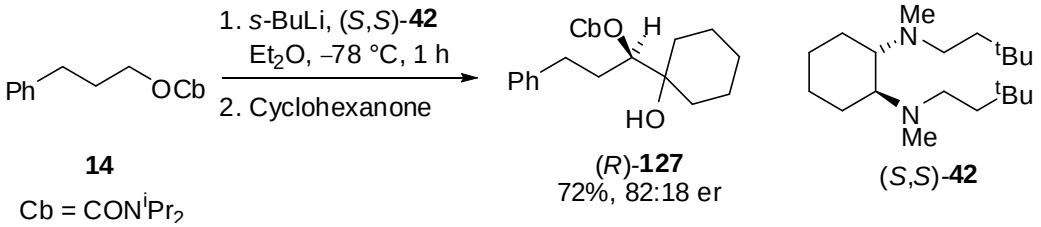
Scheme 2.20

With this in mind, it is essential to first know the enantioselectivity obtained with different ligands in the lithiation-trapping of *O*-alkyl carbamate **14**. The investigation would involve the use of (−)-sparteine, (+)-sparteine surrogate **1** and diamine (*S*,*S*)-**42**. Previously, our group has reported that lithiation of *O*-alkyl carbamate **14** with *s*-BuLi/(−)-sparteine and trapping with methyl chloroformate gave ester (*R*)-**126** in 84% yield and 97:3 er. In addition, lithiation with *s*-BuLi/(+)-sparteine surrogate **1** gave ester (*S*)-**126** in 67% yield and 93:7 er (Scheme 2.21). It is also worth noting that lithiation of *O*-alkyl carbamate **14** with *s*-BuLi/(−)-sparteine has been reported to give trapped products in 99:1 er in some cases.[128]



Scheme 2.21

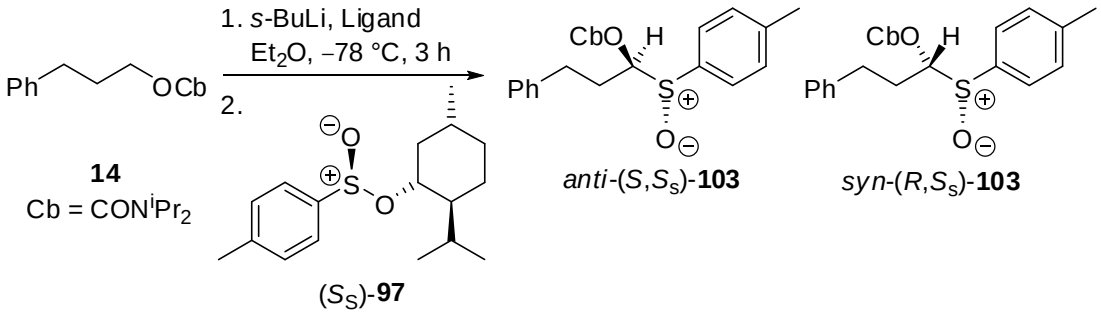
Alexakis introduced diamine **42** as a ligand to direct organolithium addition to imines.[129] It is readily available as either enantiomer and has been used in our group as a (+)-sparteine surrogate.[29] It is of particular interest due to the current global shortage of (−)-sparteine and only one enantiomer of (+)-sparteine surrogate **1** being readily available. In our hands, lithiation of *O*-alkyl carbamate **14** mediated by *s*-BuLi/(*S*,*S*)-**42** and trapping with cyclohexanone gave alcohol (*R*)-**127** in 72% yield and 82:18 er (Scheme 2.22).



Scheme 2.22

With knowledge of the inherent enantioselectivity of the different chiral diamines, we were now in a position to undertake the asymmetric lithiation of *O*-alkyl carbamate **14** and trapping with Andersen's sulfinate (S_S)-**97**. To our delight, lithiation mediated by *s*-

BuLi/(−)-sparteine gave *anti*-(*S*,S_S)-**103** in 53% yield and 99:1 er (Scheme 2.23, Table 2.2, entry 1). Diastereomeric sulfoxide *syn*-(*R*,S_S)-**103** was isolated in only 0.2% yield (enantiomeric ratio not determined). The opposite diastereoisomer was also synthesised as the major product by changing the ligand to the (+)-sparteine surrogate **1**. Lithiation of *O*-alkyl carbamate **14** with *s*-BuLi/(+)-sparteine surrogate **1** and trapping with Andersen's sulfinate (S_S)-**97** gave sulfoxide *anti*-(*S*,S_S)-**103** in 7% yield and 87:13 er and sulfoxide *syn*-(*R*,S_S)-**103** in 54% yield and 99:1 er (entry 2). Thus, either diastereoisomer of *α*-alkoxy sulfoxides was accessible in 99:1 er.



Scheme 2.23

Table 2.2: Asymmetric Lithiation of *O*-Alkyl Carbamate **14** and trapping with Andersen's Sulfinate (S_S)-**97**

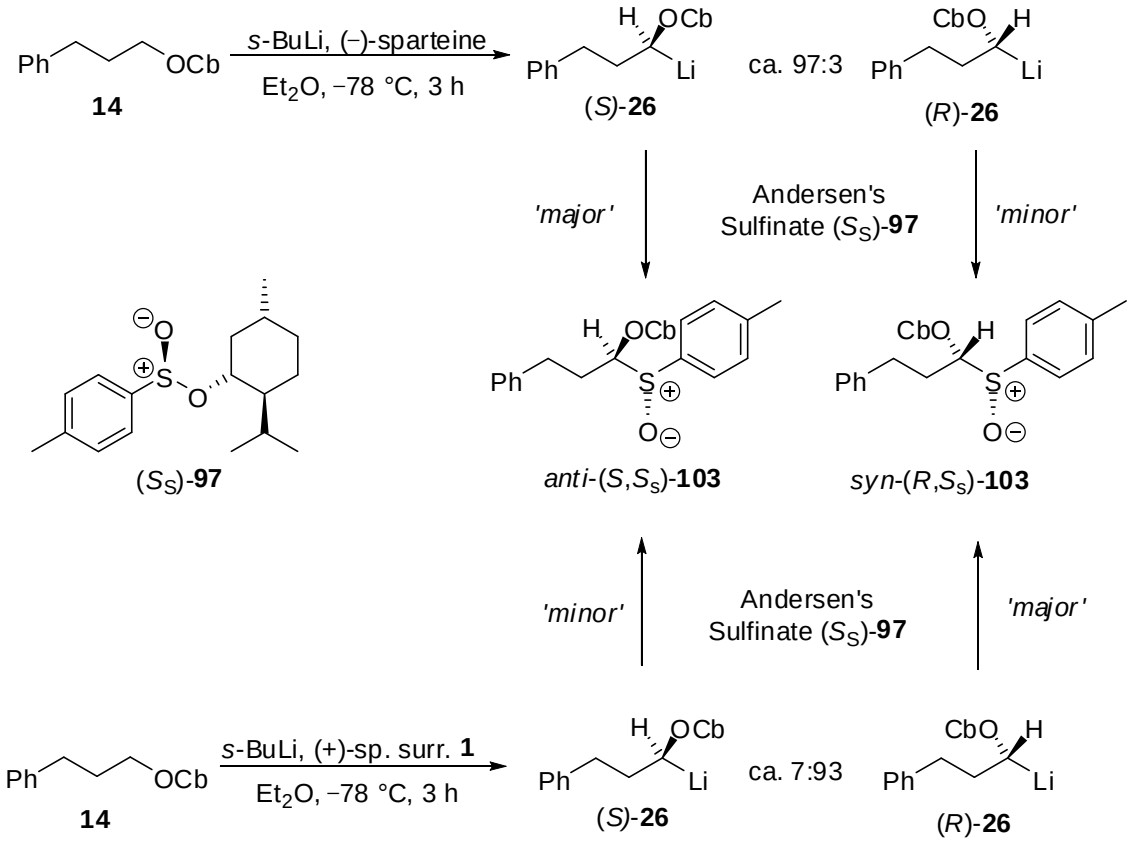
Entry	**Ligand**	***anti*-(*S*,S_S)-103**		***syn*-(*R*,S_S)-103**	
		Yield / %	**er**[a]	**Yield / %**	**er**[a]
1	(−)-sparteine	53	99:1	0.2	nd
2	(+)-sparteine surrogate **1**	7	87:13	45	99:1
3	(*S*,*S*)-**42**	17	95:5	54	99:1
4	(*R*,*R*)-**42**	56	99:1	14	93:7

[a]er determined by CSP-HPLC, nd = not determined

Furthermore, the lithiation using diamine (*S*,*S*)-**42** as the ligand gave sulfoxide *anti*-(*S*,S_S)-**42** in 17% yield and 95:5 er and sulfoxide *syn*-(*R*,S_S)-**103** in good yield (54%) and excellent enantiomeric ratio (99:1 er) (entry 3). Finally, lithiation mediated by *s*-BuLi/diamine (*R*,*R*)-**42** gave sulfoxide *anti*-(*S*,S_S)-**103** in 56% yield and 99:1 er and sulfoxide *syn*-(*R*,S_S)-**103** in 14% yield and 93:7 er (entry 4). Crucially, we can

synthesise either diastereoisomer in 99:1 er without the need to use (−)-sparteine or (+)-sparteine surrogate **1**.

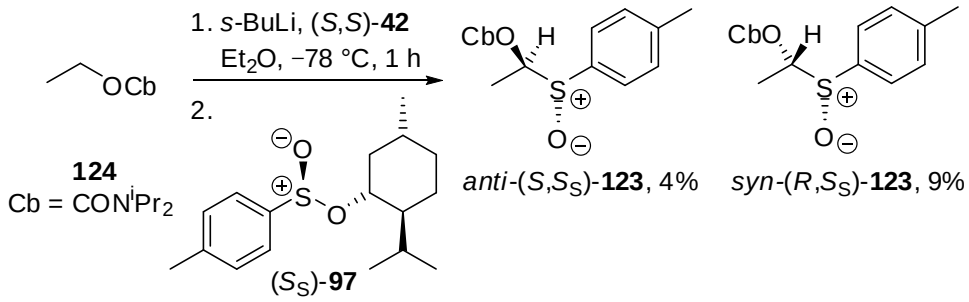
The successful asymmetric lithiation protocols also allowed us to assign the stereochemistry of the diastereomeric sulfoxides (Scheme 2.24). It is well established that the lithiation of *O*-alkyl carbamate **14** with *s*-BuLi/(−)-sparteine gives lithiated intermediate (*S*)-**26** in high enantiomeric ratio (*ca*. 97:3 er).[21] Trapping of (*S*)-**26** with Andersen's sulfinate (S_S)-**97** occurs with inversion of configuration at sulfur.[113] Therefore, it was expected that sulfoxide *anti*-(*S*,S_S)-**103** would be the major diastereomer in this case. On the other hand, lithiation of *O*-alkyl carbamate **14** mediated by *s*-BuLi/(+)-sparteine surrogate **1** is known to give (*R*)-**26** in 93:7 er.[127] Subsequent trapping of the lithiated intermediate with Andersen's sulfinate (S_S)-**97** would lead to the formation of *syn*-(*R*,S_S)-**103** as the major diastereoisomer.



Scheme 2.24

In a similar fashion, the relative stereochemistry of the *O*-ethyl sulfoxides was assigned. Lithiation of *O*-ethyl carbamate **124** mediated by *s*-BuLi/(*S*,*S*)-**42** and trapping with

Andersen's sulfinate (S_S)-**97** gave sulfoxides *anti*-(*S*,S_S)-**123** and *syn*-(*R*,S_S)-**123** in 4% and 9% yield respectively (Scheme 2.25). We were unable to determine the enantiomeric ratios by CSP-HPLC. Importantly, the relative stereochemistry can be assigned from the known[29,32] induction of diamine (*S*,*S*)-**42** and trapping of Andersen's sulfinate with inversion of configuration at sulfur to give *syn*-(*R*,S_S)-**123** as the major diastereomeric sulfoxide.



Scheme 2.25

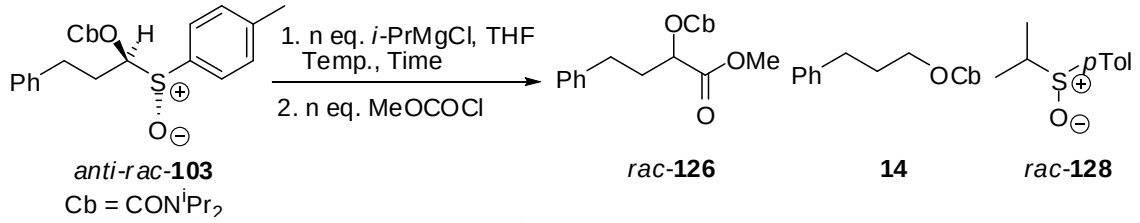
To conclude, by combining highly enantioselective lithiation reactions and trapping with Andersen's sulfinate (S_S)-**97**, it is possible to synthesis either diastereoisomer of sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103** in 45-54% yield and 99:1 er.

2.3 Sulfoxide → Magnesium Exchange of *α*-Alkoxy Sulfoxides

With a robust method for the synthesis of sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103** in hand, we set about using them to create *α*-alkoxy Grignard reagents in 99:1 er. The method of choice was sulfoxide → magnesium exchange, due to significant precedent for high stereochemical fidelity during the reaction (see Scheme 1.41).[90,91] In addition, we were expecting that the *α*-alkoxy Grignard reagents would have a higher degree of configurational stability when compared to their organolithium counterparts.[72] However, there is no precedent for carrying out sulfoxide magnesium → exchange reactions at higher temperatures, such as 0 °C or above. This was one of our key aims.

2.3.1 Optimising the Sulfoxide → Magnesium Exchange Reaction

It was hypothesised that the sulfoxide → magnesium exchange reaction would occur very quickly at temperatures ≥0 °C. Therefore, racemic sulfoxide *anti-rac*-**103** was treated with 1.1 eq. of *i*-PrMgCl in THF at 0 °C, and methyl chloroformate was added after just 10 seconds (Scheme 2.26, Table 2.3). This led to ester *rac*-**126** being isolated in 49% yield (entry 1). In addition, sulfoxide *rac*-**128** (formed as a by-product of the sulfoxide → magnesium exchange product whereby *i*-PrMgCl attacks at the sulfur atom) was isolated in 54% yield and starting sulfoxide *anti-rac*-**103** was recovered in 20% yield. With a significant amount of starting material being recovered, the number of equivalents of Grignard reagent and the reaction time were increased. Treatment of sulfoxide *anti-rac*-**103** with 1.3 eq. *i*-PrMgCl for 1 minute at 0 °C and trapping with methyl chloroformate gave ester *rac*-**126** in an improved 58% yield and a reduction in recovered sulfoxide *anti-rac*-**103** (3%) (entry 2). However, sulfoxide *rac*-**128** was isolated in 74% yield, indicating that the exchange reaction had occurred to a much larger degree than previously. Furthermore, carbamate **14** was isolated in 3% yield. Carbamate **14** was presumably formed by the Grignard reagent from the initial exchange reaction being quenched with a proton which could come from the *α*-proton in sulfoxide *rac*-**128** which is formed as the by-product from the sulfoxide → magnesium exchange reaction.



anti-rac-**103**
Cb = CON^iPr_2

rac-**126** **14** *rac*-**128**

Scheme 2.26

Table 2.3: Optimisation of the Sulfoxide → Magnesium Exchange of *anti-rac*-**103**

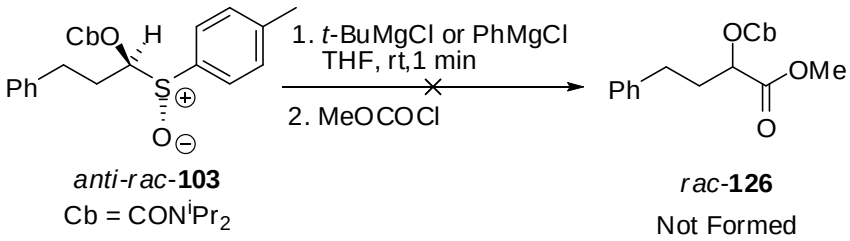
Entry	n	Temp. / °C	Time / min	Yield *rac*-126 / %	Yield 14 / %	Yield *rac*-128 / %	Recovered *anti*-103 / %
1	1.1	0	10 s	49	-	54	20
2	1.3	0	1	58	3	74	3
3	1.3	rt	20 s	56	1	71	5
4	1.3	rt	1	65	6	73	8
5	1.3	rt	5	48	14	81	4
6	1.5	rt	1	67	9	84	0
7	1.5	rt	5	42	17	82	0
8	2.5	rt	1	75	5	84	0

The yield of ester *rac*-**126** was further improved to 65% by carrying out the reaction at room temperature for 1 minute using 1.3 eq. of *i*-PrMgCl but the yield of carbamate **14** was also increased (6%) (entry 4). Repeating the reaction under the same conditions but reducing the time to 20 seconds led to ester *rac*-**126** being isolated in a reduced 56% yield (entry 3). Extension of the reaction time to 5 minutes gave ester *rac*-**126** in a poor 48% yield but sulfoxide *rac*-**128** was isolated in an improved 81% yield (entry 5). This suggests that the initial exchange reaction is high yielding but the intermediate Grignard reagent has more time to be protonated. An increased yield of carbamate **14** also supports this notion. Under each of these reaction conditions there was still a small amount of starting sulfoxide *anti-rac*-**103** recovered (4-8%).

Therefore, we decided to increase the number of equivalents of *i*-PrMgCl. Addition of 1.5 eq. of *i*-PrMgCl to sulfoxide *anti-rac*-**103** at room temperature for 1 minute gave ester *rac*-**126** in 67% yield and sulfoxide *rac*-**128** in 84% (entry 6). In addition, carbamate **14** was isolated in 9% yield indicating a small amount of protonation occurred under the reaction conditions. Extending the reaction to 5 minutes saw a

reduction in yield of ester *rac*-**126** (42%) but an increase in yield of carbamate **14** (17%) (entry 7). Finally, it was hypothesised that having a large excess of *i*-PrMgCl present within the reaction would lead to a reduction in the protonation of the Grignard intermediate. Indeed, using 2.5 eq. *i*-PrMgCl reduced the yield of carbamate **14** to 5% whilst increasing the yield of ester *rac*-**126** (75%) (entry 8). We postulate that the excess *i*-PrMgCl may deprotonate sulfoxide *rac*-**128** whilst it is being formed. However, deuteriation experiments proved inconclusive.

In an attempt to form a sulfoxide by-product without an α-proton, exchange reactions were carried using *t*-BuMgCl and PhMgCl (Scheme 2.27). Unfortunately, neither of these Grignard reagents facilitated sulfoxide → magnesium exchange. Instead starting sulfoxide *anti-rac*-**103** was recovered unchanged in each case.



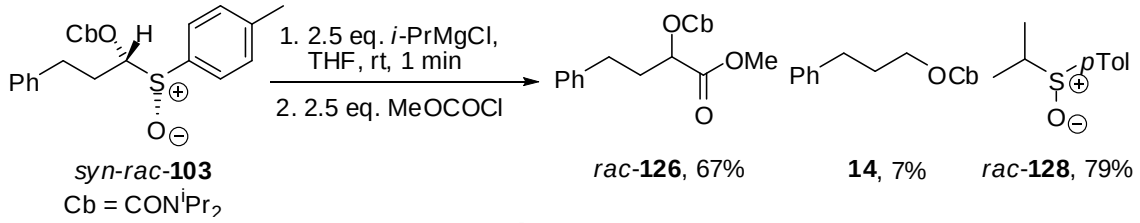
anti-rac-**103**
Cb = CON^iPr_2

rac-**126**
Not Formed

Scheme 2.27

The optimised conditions for the synthesis of *α*-alkoxy Grignard reagents by sulfoxide → magnesium exchange were found to be 2.5 eq. of *i*-PrMgCl at room temperature for 1 min (Table 2.3, entry 8). However, the 75% yield of ester *rac*-**126** is slightly disappointing given the high 84% yield of sulfoxide *rac*-**128** that was also isolated.

Finally, diastereomeric sulfoxide *syn-rac*-**103** was shown to give comparable reactivity under the optimised conditions (Scheme 2.28). Indeed, ester *rac*-**126** was isolated in 67% yield and sulfoxide *rac*-**128** in 79% yield. Furthermore, we isolated carbamate **14** in 7% yield indicating that protonation of the intermediate Grignard reagent occurred to a similar extent as previously observed.



syn-rac-**103**
Cb = CON^iPr_2

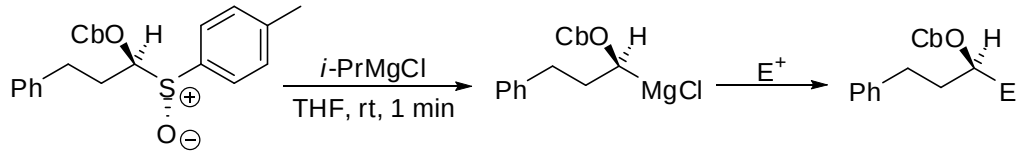
rac-**126**, 67% **14**, 7% *rac*-**128**, 79%

Scheme 2.28

2.3.2 Synthesis and Reactions of Enantiopure *α*-Alkoxy Grignard Reagents

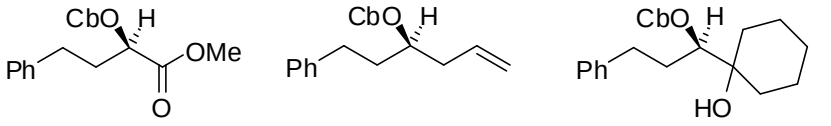
Next, we wanted to undertake a sulfoxide → magnesium exchange on sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103** of 99:1 er. In addition to synthesising a wide range of products in 99:1 er, this would also allow us to investigate the configurational stability of *α*-alkoxy Grignard reagents at room temperature.

Sulfoxide *anti*-(*S*,S_S)-**103** was treated with 2.5 eq. *i*-PrMgCl at room temperature for 1 minute and then methyl chloroformate was added (Scheme 2.29). To our delight, ester (*R*)-**126** was isolated in 73% yield and 99:1 er. Comparison to the literature data for ester (*R*)-**126**[127] allows us to conclude that sulfoxide → magnesium exchange and trapping proceeds with retention of configuration at carbon. Grignard reagent (*S*)-**104** was also trapped with allyl bromide (with 10 mol% $CuBr.SMe_2$ as a catalyst) and cyclohexanone which gave alkene (*R*)-**129** and alcohol (*R*)-**127** in good yields and excellent enantioselectivity. All three racemic compounds were prepared in a similar way from *anti-rac*-**103** and separated by CSP-HPLC.



anti-(*S*,S_S)-**103**, 99:1 er

(*S*)-**104**



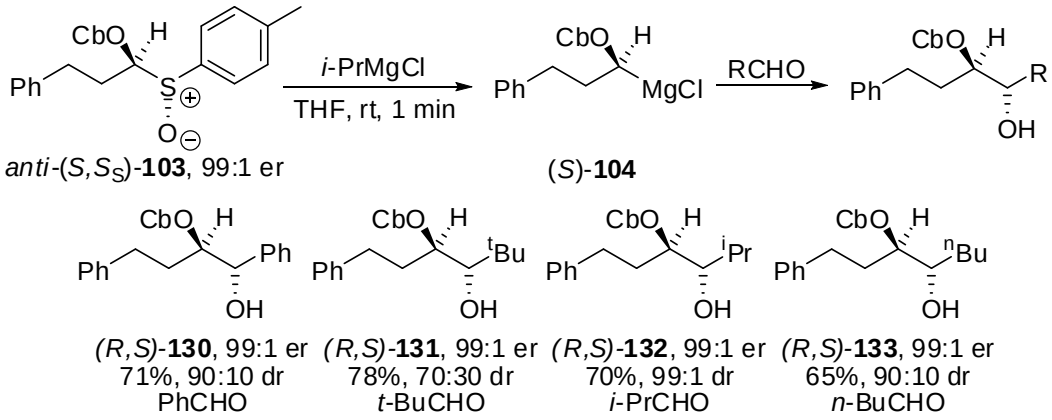
(R)-**126**
73%, 99:1 er
E^+= MeOCOCl

(R)-**129**
70%, 99:1 er
E^+= allyl-Br
(10 mol% $CuBr.SMe_2$)

(R)-**127**
71%, 99:1 er
E^+= cyclohexanone

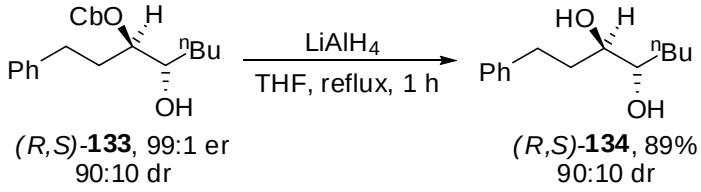
Scheme 2.29

Reaction of Grignard reagent (*S*)-**104** with aldehydes was also explored (Scheme 2.30). Grignard reagent (*S*)-**104** was synthesised from sulfoxide (S,S_S)-**103** and subsequent addition of aldehydes gave mono-protected diols (*R,S*)-**130**-**133** with *anti*-diastereoselectivity (70:30 to ≥99:1 dr, inseparable mixtures) in 65-78% yields with each diastereoisomer being formed in 99:1 er.



Scheme 2.30

Reduction of (*R,S*)-**133** using $LiAlH_4$ gave known[130] diol (*R,S*)-**134** in 89% yield (Scheme 2.31). Comparison of the ^1H NMR and ^{13}C NMR spectra allowed assignment of the relative stereochemical configuration. Alcohols (*R,S*)-**130**-**133** were assigned by analogy.

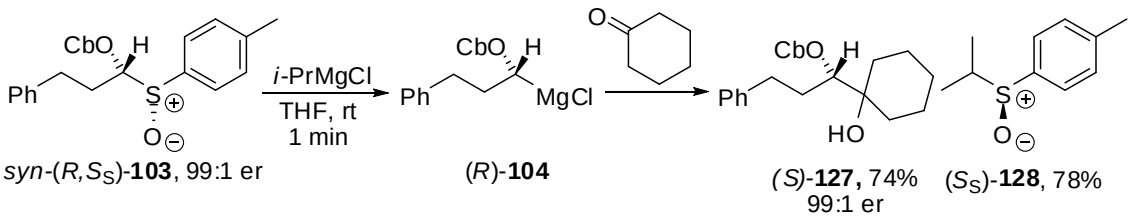


Scheme 2.31

Sulfoxide → magnesium exchange and trapping with aldehydes offers an attractive connective strategy for the synthesis of *anti*-1,2-diols which are typically synthesised in two steps by Wittig reaction and asymmetric dihydroxylation. A related approach was recently reported by Shen and co-workers starting from $TsCH_2OCb$ and aldehydes.[131]

The opposite enantiomer of all the products would be equally accessible from sulfoxide (R,S_S)-**103**. To demonstrate this, treatment of sulfoxide *syn*-(R,S_S)-**103** with *i*-PrMgCl

gave Grignard reagent (*R*)-**104** and trapping with cyclohexanone gave alcohol (*S*)-**127** in 74% yield and 99:1 er (Scheme 2.32).

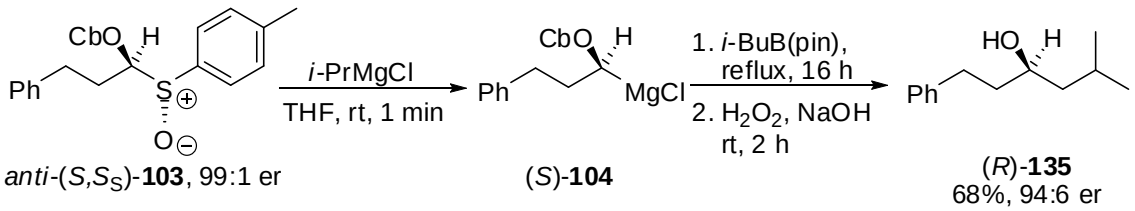


syn-(*R*,S_S)-**103**, 99:1 er (*R*)-**104** (*S*)-**127**, 74% 99:1 er (S_S)-**128**, 78%

Scheme 2.32

Moreover, sulfoxide (S_S)-**128** was isolated in 78% yield from this reaction. Comparison of the optical rotation with that reported in the literature confirms the absolute configuration of sulfoxide (S_S)-**128**; our synthesised (S_S)-**128** had $[\alpha]_D$ −194.2 (*c* 1.0 in EtOH) and the literature value was $[\alpha]_D$ −187 (*c* 2.4 in EtOH).[115] Sulfoxide (S_S)-**128** is the expected product of double inversion from Andersen's sulfinate (S_S)-**97** and allows confirmation of the assignment of the configuration in sulfoxides *anti-(S,*S_S*)*-**103** and *syn-(R,*S_S*)*-**103**

The major limitation with the use of *O*-alkyl carbamate **14** is that a carbamate deprotection is required to furnish the synthetically desirable secondary alcohols. However, boronate rearrangements, as reported initially by Hoppe[30,33] and later developed by Aggarwal,[32] allow direct access to the alcohol (see Schemes 1.8 and 1.9). Hence, we were interested in exploring this chemistry *via* our methodology. Therefore, *i*-PrMgCl was added to sulfoxide *anti-(S,*S_S*)*-**103** followed by trapping with *i*-BuB-pinacolate. After refluxing for 16 hours, subsequent oxidation (H_2O_2, NaOH) gave alcohol (*R*)-**135** in 68% yield but only 94:6 er (Scheme 2.33).

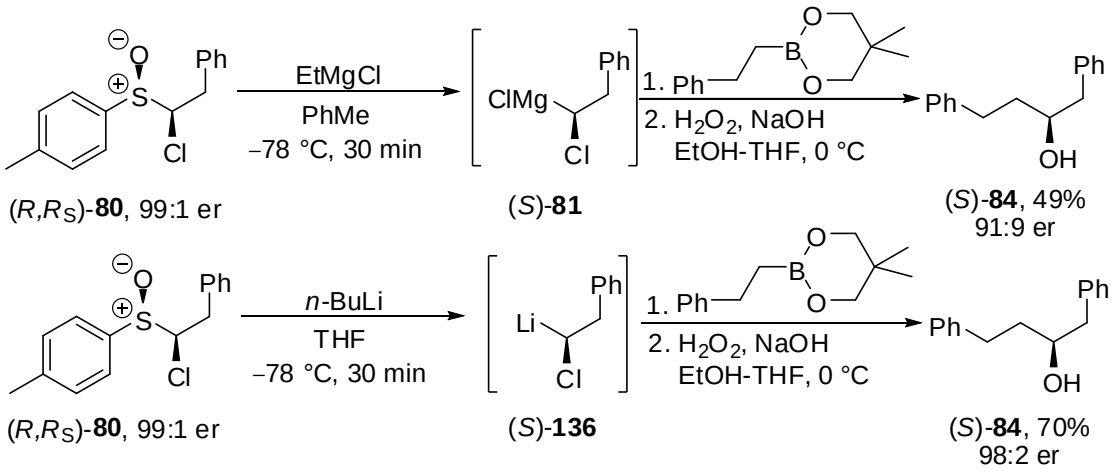


anti-(*S*,S_S)-**103**, 99:1 er (*S*)-**104** (*R*)-**135** 68%, 94:6 er

Scheme 2.33

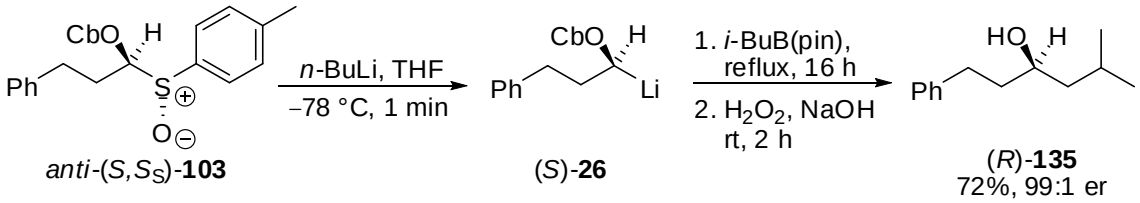
The loss of enantiomeric ratio in the metallate rearrangement with magnesium has been previously observed by Blakemore and co-workers (and later commented on by

Aggarwal).[32,92,121] Indeed, reaction of Grignard reagent (*S*)-**81**, generated by sulfoxide → magnesium exchange from (*R*,R_S)-**80**, with $Ph(CH_2)_2$B-dioxaborinane and subsequent oxidation (H_2O_2, NaOH) gave alcohol (*S*)-**84** in 49% yield but only 91:9 er (Scheme 2.34). Alternatively, use of organolithium (*S*)-**136** (formed by sulfoxide → lithium exchange) allowed access to alcohol (*S*)-**84** in a much improved 98:2 er. No further explanation for this increase in stereochemical fidelity was offered.



Scheme 2.34

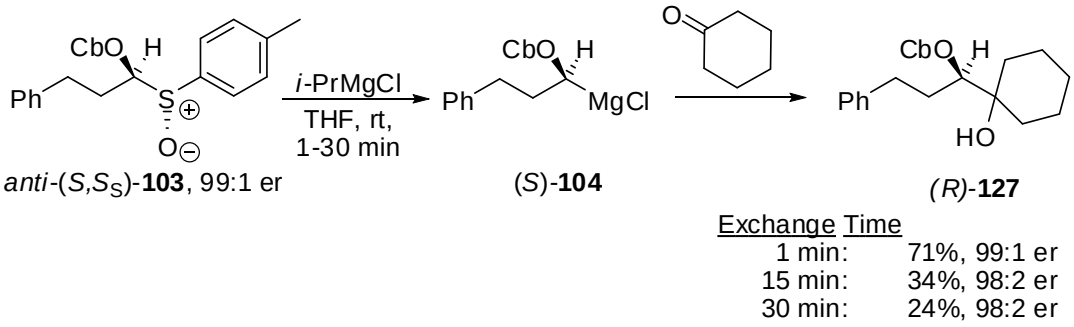
We too turned to organolithium reagents to solve the loss of configuration within the 1,2-metallate rearrangement. To our delight, sulfoxide → lithium exchange of *anti*-(*S*,S_S)-**103** using *n*-BuLi (THF, −78 °C, 1 min) and reaction with *i*-BuB-pinacolate followed by oxidation with H_2O_2 and NaOH gave alcohol (*R*)-**135** in 72% yield and 99:1 er (Scheme 2.35).



Scheme 2.35

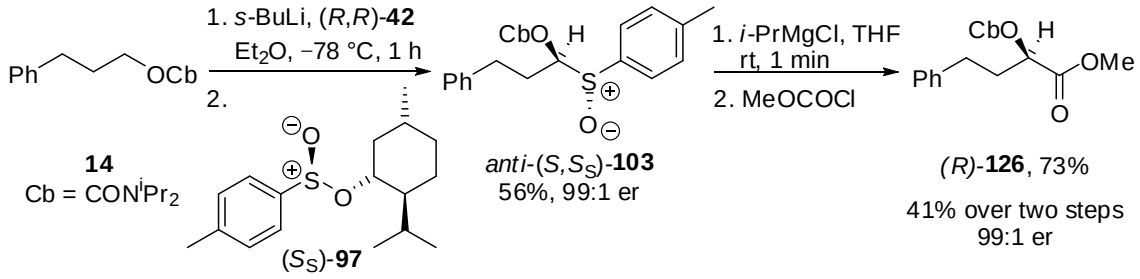
Finally, we investigated the configurational stability of Grignard reagent (*S*)-**104** at room temperature over longer times than 1 minute. Extended sulfoxide → magnesium exchange reaction times of 15 and 30 minutes and trapping with cyclohexanone gave alcohol (*R*)-**127** in 98:2 er in both cases (Scheme 2.36). It is believed that reduced yields (34% and 24% yield respectively) with extended sulfoxide → magnesium

exchange times are due to protonation of Grignard reagent (*S*)-**104** by the sulfoxide by-product as previously discussed. Furthermore, no evidence of 1,2-carbamoyl migration was observed (this process is reported to take place in corresponding organolithium reagents at −20 °C)[73]. From this marginal loss of enantiomeric ratio in the products (within the error limits of HPLC detection), it is concluded that Grignard reagent (*S*)-**104** is configurationally table at room temperature for 30 minutes. This is consistent with observations made by Nakai and co-workers.[72]



Scheme 2.36

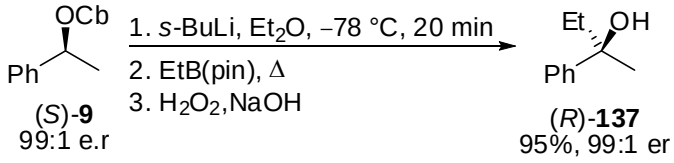
To conclude, we can access *α*-substituted *O*-alkyl carbamates *via* our lithiation-trapping and subsequent sulfoxide → magnesium exchange methodology. For example, ester (*R*)-**126** was isolated in 41% yield and 99:1 er over two steps from *O*-alkyl carbamate **14** (Scheme 2.37). Importantly, this reaction sequence does not require the use of (−)-sparteine and the divergent electrophilic trapping step can be carried out at room temperature over short reaction times. Significantly, *α*-alkoxy Grignard reagents have been shown to be configurationally stable at room temperature for up to 30 minutes.



Scheme 2.37

2.4 Synthesis of Tertiary Alcohols from Sulfoxides *via* Sulfoxide → Magnesium Exchange

In 2008, Aggarwal *et al.* reported the enantioselective synthesis of tertiary alcohols (*e.g.* (*R*)-**137**) from secondary benzylic *O*-alkyl carbamates (*e.g.* (*S*)-**9**) using lithiation-boronate rearrangement methodology (Scheme 2.38).[34] This chemistry was reviewed in detail in Chapter 1.1.1. The requirement of the phenyl substituent to lower the *p*Ka of the *α*-proton for the deprotonation reaction is a still a major limitation as the phenyl substituent then remains in the product.

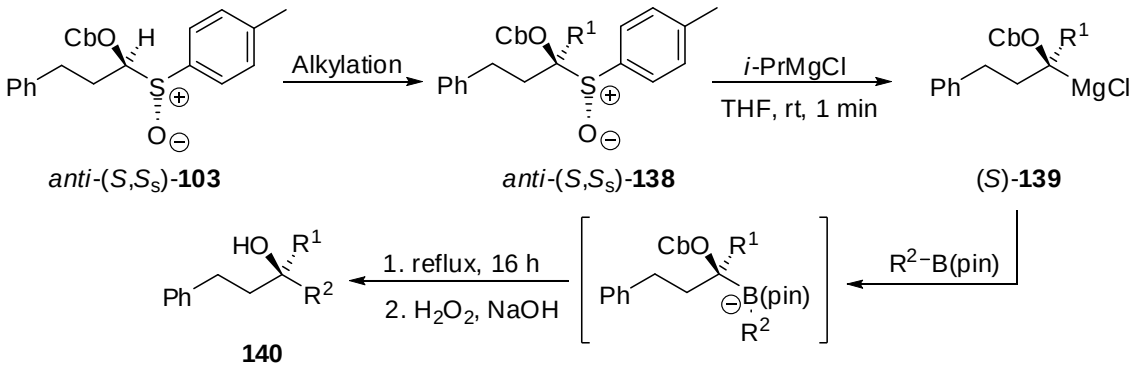


(*S*)-**9**
99:1 e.r

(*R*)-**137**
95%, 99:1 er

Scheme 2.38

It was proposed that sulfoxide → magnesium exchange methodology could offer an improvement in the synthesis of tertiary alcohols by allowing access to products lacking an aryl substituent (Scheme 2.39). Our plan would be two-fold. First, the synthesis of quaternary *α*-alkoxy sulfoxides *anti*-(*S*,*S*$_S$)-**138** by alkylation of *anti*-(*S*,*S*$_S$)-**103** would be explored. Second, sulfoxide → magnesium exchange to give (*S*)-**139** and subsequent boronate rearrangement would allow access to a wide range of chiral tertiary alcohols **140**.



anti-(*S*,*S*$_S$)-**103**

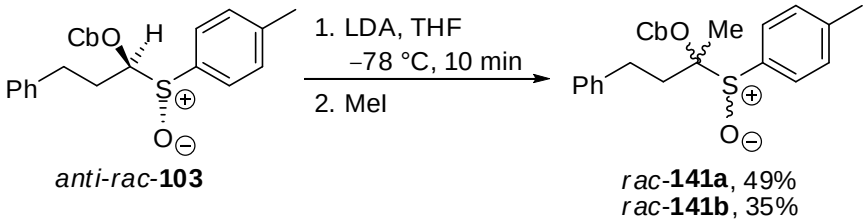
anti-(*S*,*S*$_S$)-**138**

(*S*)-**139**

140

Scheme 2.39

We began by investigating the alkylation of sulfoxide *anti-rac*-**103** using lithium amide bases.[120,132] *α*-Deprotonation of *anti-rac*-**103** using LDA in THF at −78 °C for 10 minutes and trapping with methyl iodide gave diastereomeric sulfoxides *rac*-**141a** and *rac*-**141b** in 49% and 35% yield respectively (Scheme 2.40). It was not possible to calculate the diastereomeric ratio from the ^{1}H NMR spectrum of the crude product. The relative stereochemistry has not been determined. Isolation of diastereomeric sulfoxides indicates that either the reaction proceeds *via* a planar carbanion or that the lithiated intermediate is configurationally unstable. A similar phenomenon was observed by Hoppe in the lithiation-trapping of benzylic *O*-alkyl carbamates (see Schemes 1.5 and 1.6).[23]

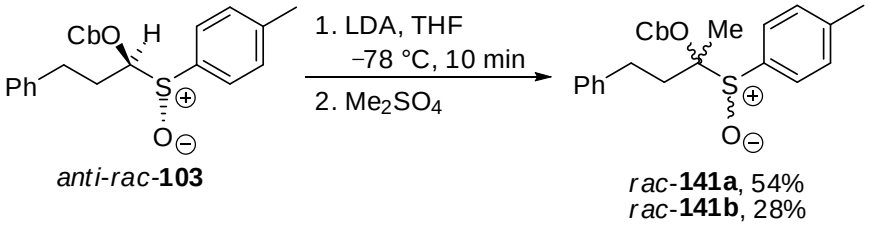


anti-rac-**103**

rac-**141a**, 49%
rac-**141b**, 35%

Scheme 2.40

We attempted to improve the diastereoselectivity of the alkylation by using dimethyl sulfate as the methylating agent (Scheme 2.41). From this reaction sulfoxide *rac*-**141a** was isolated in 54% yield and *rac*-**141b** was isolated in 28% yield.

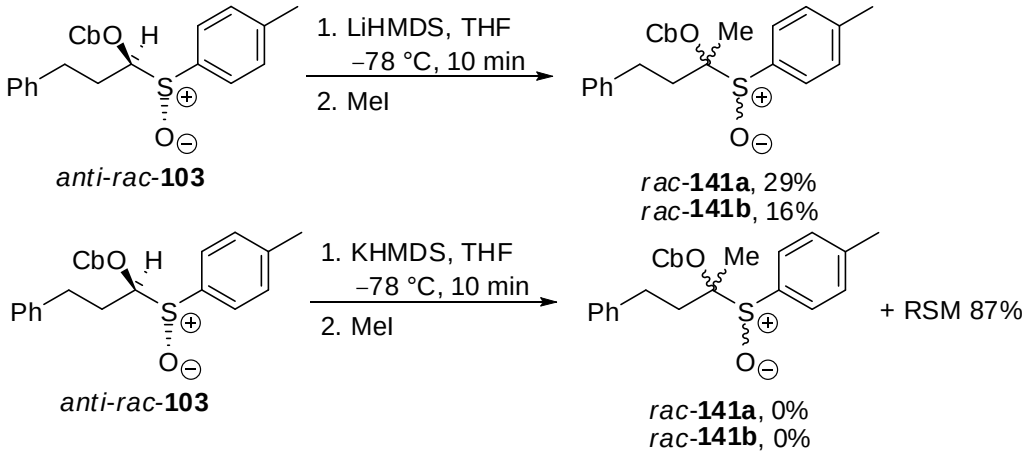


anti-rac-**103**

rac-**141a**, 54%
rac-**141b**, 28%

Scheme 2.41

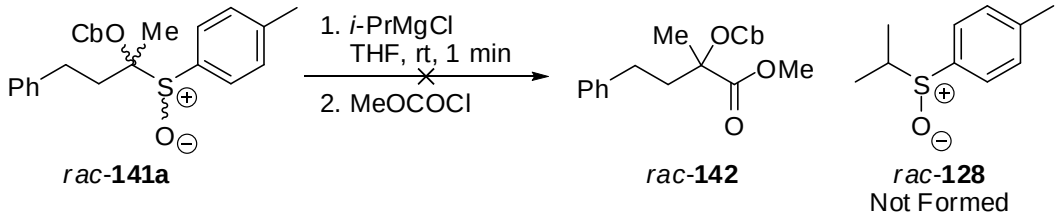
In addition, we investigated using alternative amide bases (Scheme 2.42). First, deprotonation by LiHMDS and trapping with methyl iodide gave sulfoxides *rac*-**141a** and *rac*-**141b** in disappointing yields (29% and 16% yield respectively). Use of KHMDS and trapping with methyl iodide gave none of the desired products and starting material was recovered in 87% yield.



Scheme 2.42

In conclusion, we have been able to synthesise diastereomeric sulfoxides *rac*-**141a** and *rac*-**141b** in modest yields. We have been unable to significantly improve the diastereoselectivity within the alkylation procedure.

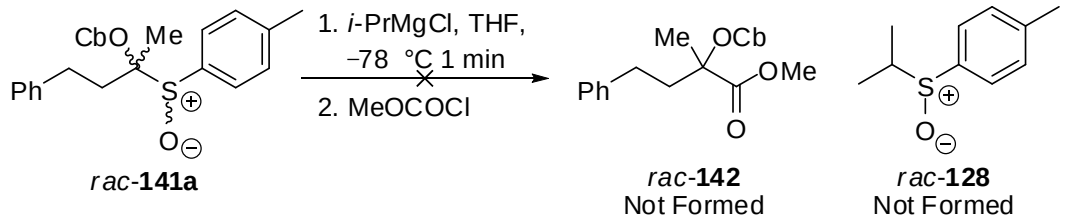
With sulfoxides *rac*-**141a** and *rac*-**141b** in hand, sulfoxide → magnesium exchange chemistry was attempted in order to synthesise tertiary alcohols. Therefore, sulfoxide *rac*-**141a** was treated with *i*-PrMgCl in THF at room temperature for 1 minute and trapped with methyl chloroformate (Scheme 2.43). Unfortunately, ester *rac*-**142** was not formed and the ^{1}H NMR spectrum of the crude product showed a complex mixture of products. Purification by flash column chromatography gave no identifiable products. No starting material was remaining at the end of the reaction and sulfoxide *rac*-**128**, the by-product of sulfoxide → magnesium exchange, was not formed.



Scheme 2.43

We postulated that the Grignard intermediate may be chemically unstable at high temperature. A similar phenomenon has been observed in the lithiation of *O*-alkyl carbamates due to 1,2-carbamoyl migration.[73] Therefore, we reduced the temperature of the sulfoxide → magnesium exchange reaction to −78 °C (Scheme 2.44).

Unfortunately, the reaction again gave a complex mixture of unidentified products by ^{1}H NMR spectroscopy of the crude mixture.



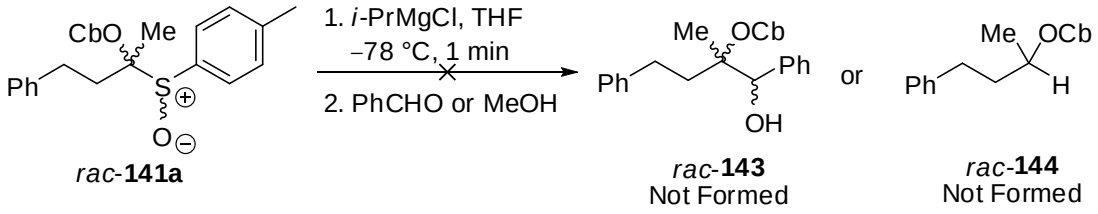
rac-**141a**

rac-**142**
Not Formed

rac-**128**
Not Formed

Scheme 2.44

We postulated that the inability to form the desired product could be due to the choice of electrophile. Therefore, we attempted to trap with benzaldehyde or quench the exchange reaction with methanol (Scheme 2.45). In each case the desired products, alcohols *rac*-**143** or carbamate *rac*-**144** respectively, were not isolated.



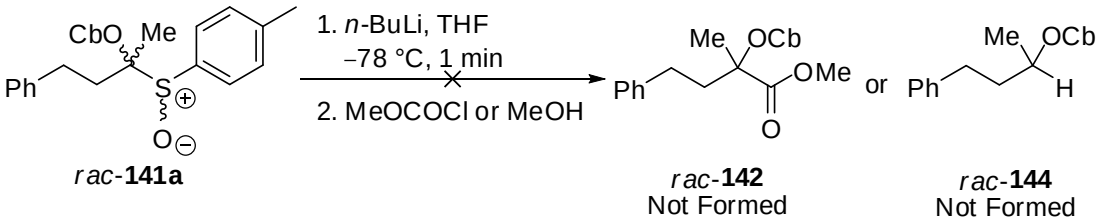
rac-**141a**

rac-**143**
Not Formed

rac-**144**
Not Formed

Scheme 2.45

Finally, we turned to sulfoxide → lithium exchange to see if the problems were due to the organometallic reagent. *n*-BuLi was added to sulfoxide *rac*-**141a** at −78 °C in THF and trapping with methyl chloroformate gave a complex mixture of products (Scheme 2.46). In addition, quenching the sulfoxide → lithium exchange with MeOH also gave an unidentified mixture of products.



rac-**141a**

rac-**142**
Not Formed

rac-**144**
Not Formed

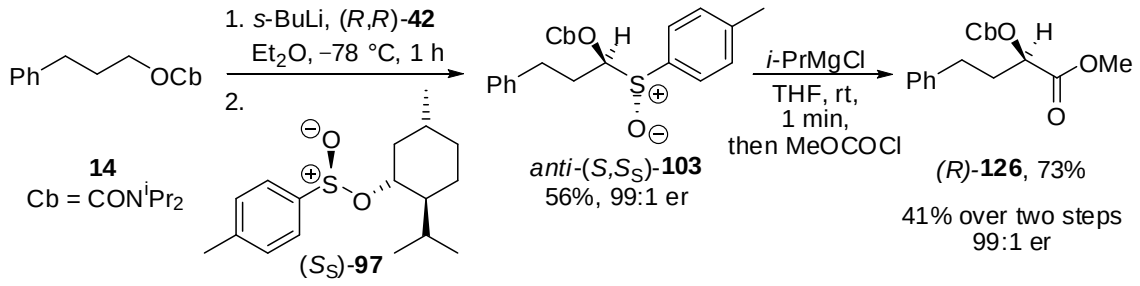
Scheme 2.46

To conclude, we have been unable to find conditions to carry out a sulfoxide → magnesium exchange of sulfoxide *rac*-**141a**. Unfortunately, all attempts have led to a complex mixture of products being formed. In addition, using *n*-BuLi to carry out a sulfoxide → lithium exchange was unsuccessful. Therefore, boronate rearrangements have not been attempted.

2.5 Conclusions and Future Work

A procedure for the synthesis of *α*-alkoxy Grignard reagents in 99:1 er has been successfully developed. The method begins with asymmetric lithiation of *O*-alkyl carbamate **14** and trapping with Andersen's sulfinate (S_S)-**97** to give diastereomeric sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103**. Interestingly, a loss of enantiomeric ratio is observed on trapping and we have shown that this is due to sulfoxide → lithium taking place under the lithiation-trapping conditions. Thus, a reverse addition protocol (addition of the intermediate organolithium to Andersen's sulfinate (S_S)-**97**) was utilised to improve the enantiomeric ratio of the products. Furthermore, use of chiral diamine ligands allows for the isolation of either sulfoxide *anti*-(*S*,S_S)-**103** or sulfoxide *syn*-(*R*,S_S)-**103** in 99:1 er *via* chiral amplification. Significantly, the procedure does not require the use of (−)-sparteine.

Then, a sulfoxide → magnesium exchange protocol was employed to generate *α*-alkoxy Grignard reagents. The optimised conditions were 2.5 eq. of *i*-PrMgCl in THF at room temperature for 1 minute. Trapping with electrophiles gave an array of *α*-substituted products in 99:1 er. For example, ester (*R*)-**126** was formed in 41% yield and 99:1 er over two steps from *O*-alkyl carbamate **14** (Scheme 2.47). Furthermore, our work is the first example of a sulfoxide → magnesium exchange process occurring at room temperature. Of particular note, *α*-alkoxy Grignard reagents have been shown to be configurationally stable for up to 30 minutes at room temperature.

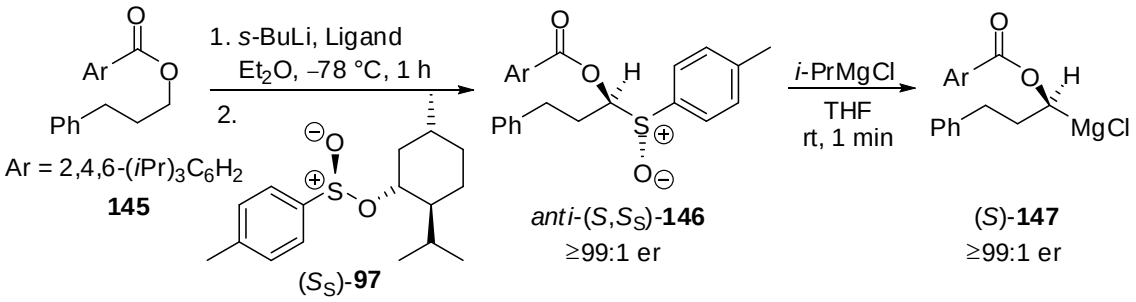


Scheme 2.47

The synthesis of tertiary alcohols *via* sulfoxide → magnesium exchange was attempted. Sulfoxide *anti*-*rac*-**103** was alkylated using LDA and methyl iodide to give a mixture of diastereomeric sulfoxides *rac*-**141a** and *rac*-**141b**. Unfortunately all attempts to

conduct a sulfoxide → magnesium exchange on these substrates were unsuccessful. In addition, sulfoxide → lithium exchange using *n*-BuLi in THF at −78 °C gave a complex mixture of unidentified products.

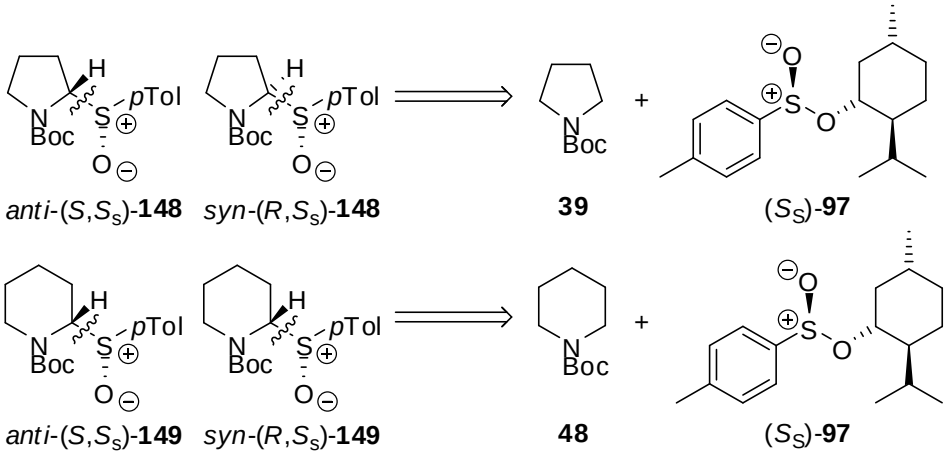
Future work would see the expansion of our methodology to include other *O*-alkyl carbamates and esters. This would allow an array of *α*-alkoxy Grignard reagents to be synthesised in ≥99:1 er. One system of interest is ester **145** which was reported by Aggarwal in 2012.[133] Ester **145** has been shown to be superior in the lithiation-boronate rearrangement methodology to carbamates. However, lithiation of ester **145** using *s*-BuLi/(−)-sparteine only give products in ≤96:4 er. Therefore, using our method to generate *α*-alkoxy Grignard reagent (*S*)-**147** in 99:1 er from sulfoxide *anti*-(*S*,S_S)-**146** would provide significant benefits (Scheme 2.48).



Scheme 2.48

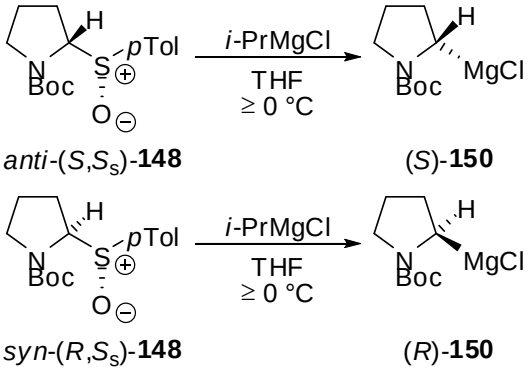
Chapter Three: Synthesis and Reactions of *α*-Amino Grignard Reagents

Described in this chapter are our efforts towards the synthesis of chiral *α*-amino Grignard reagents. Of particular interest was the formation of pyrrolidinyl sulfoxides *anti*-(*S*,S_S)-**148** and *syn*-(*R*,S_S)-**148** and piperidinyl sulfoxides *anti*-(*S*,S_S)-**149** and *syn*-(*R*,S_S)-**149** in ≥99:1 er (Scheme 3.1). It was proposed that lithiation of *N*-Boc pyrrolidine **39** or *N*-Boc piperidine **48** and trapping with Andersen's sulfinate (S_S)-**97** would provide an expedient route to the desired sulfoxides.



Scheme 3.1

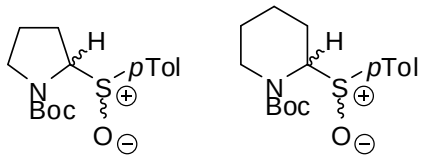
Subsequently, a sulfoxide → magnesium exchange protocol would be developed to synthesise Grignard reagents in high yield and enantioselectivity. For example, Grignard reagent (*S*)-**150** would be formed from *anti*-(*S*,S_S)-**148** and its enantiomer, (*R*)-**150**, would be synthesised from *syn*-(*R*,S_S)-**148** (Scheme 3.2).



Scheme 3.2

3.1 Previous Syntheses of α-Amino Sulfoxides, Sulfides and Sulfones

Surprisingly, the synthesis of simple cyclic *N*-Boc α-amino sulfoxides, such as **148** and **149** (Figure 3.1), has not been reported previously. Therefore, in this section a short review of the known methods of synthesising cyclic α-amino sulfides and sulfones is presented. In addition, the syntheses of two structurally related α-sulfinyl lactams are discussed.

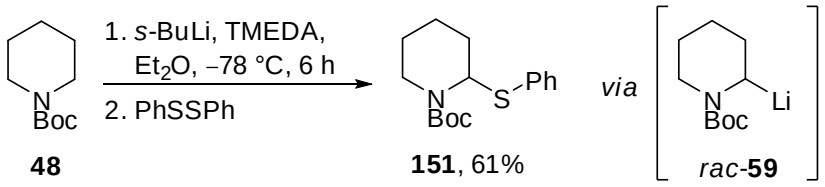


148 **149**

Figure 3.1

There are three general synthetic strategies towards cyclic α-amino sulfides: (i) deprotonation of *N*-Boc heterocycles and trapping with disulfides; (ii) addition of thiols to cyclic iminium ions; (iii) Pummerer rearrangement of amino sulfoxides.

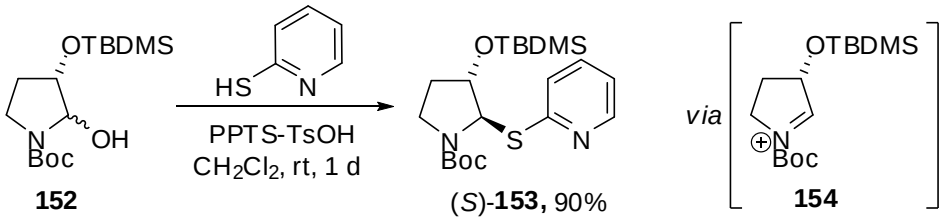
In 1989, Beak and Lee reported the lithiation of *N*-Boc piperidine **48** and trapping with diphenyl disulfide to give sulfide **151** in 61% yield (Scheme 3.3).[134] This reaction proceeds *via* organolithium reagent *rac*-**59**. Since then, this approach has been expanded to include a number of *N*-Boc heterocycles, including imidazolidines[135] and pyrimidines.[136]



48 **151**, 61% *rac*-**59**

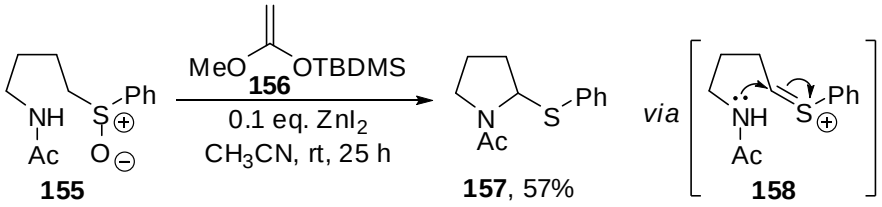
Scheme 3.3

Another popular method of synthesising α-amino sulfides is the addition of thiols to cyclic iminium ions. For example, Huang *et al.* reported the acid-catalysed elimination of hydroxy pyrrolidine **152** in the presence of 2-mercaptopyridine gave sulfide **153** in 90% yield (Scheme 3.4).[137] This reaction proceeds via iminium ion **154**. A similar approach has also been described by Chiba and co-workers to synthesise 2,5-subsituted pyrrolidines.[138]



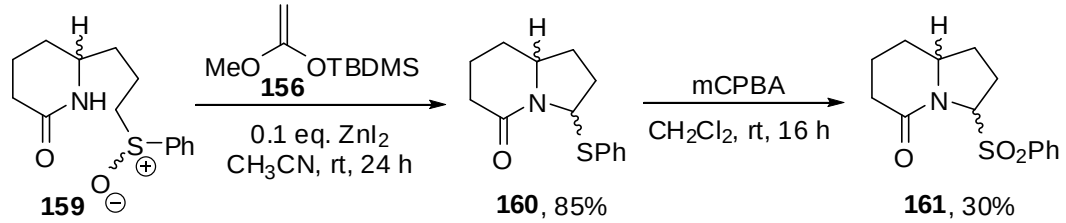
Scheme 3.4

Cyclic *α*-amino sulfides have also been synthesised *via* an intramolecular Pummerer rearrangement.[139] Sulfoxide **155** was treated with *O*-silylated ketene acetal **156** (which acts as an *O*-silylation reagent) in the presence of catalytic zinc iodide (Scheme 3.5). The reaction proceeded *via* adduct **158** and gave sulfide **157** in 57% yield.



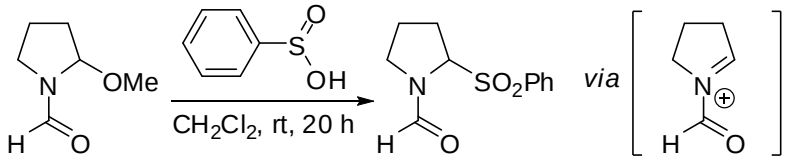
Scheme 3.5

The Pummerer rearrangement was also found to be an expedient method for synthesising indolizidine sulfides **160**.[140] Treatment of amino sulfoxides **159** with *O*-silylated ketene acetal **156** and catalytic zinc iodide gave indolizidine sulfides **160** in 85% yield (Scheme 3.6). In addition, subsequent oxidation of **160** by *m*-CPBA formed sulfones **161** in 30% yield. Presumably the oxidation proceeds *via* a sulfoxide intermediate.



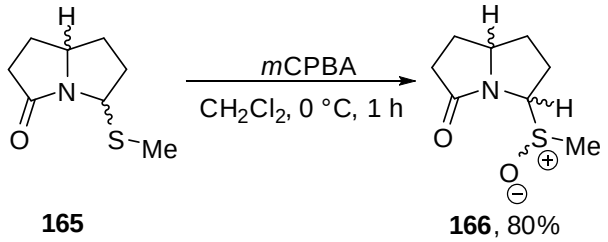
Scheme 3.6

Furthermore, 2-sulfonyl pyrrolidines have also been successfully synthesised. For example, Ley and co-workers reported the synthesis of a number of cyclic *α*-amino sulfones.[141] The typical synthetic procedure is shown in Scheme 3.7 whereby methoxy *N*-formyl pyrrolidine **162** was treated with benzenesulfinic acid. This reaction presumably proceeds *via* iminium adduct **164** to give sulfone **163** in 89% yield.



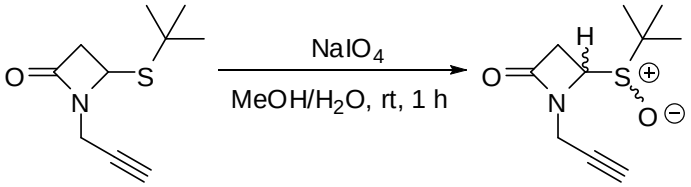
Scheme 3.7

Whilst there are no simple *α*-amino sulfoxides reported in the literature, two lactams have been reported bearing an *α*-amino sulfoxide moiety. Thomas *et al*. synthesised pyrrolizidinone sulfoxides **166** in 80% yield by oxidation of sulfides **165** using *m*CPBA (Scheme 3.8).[142]



Scheme 3.8

Finally, a number of syntheses of 2-sulfinyl azetidinones have been reported due to them being a common intermediate for the synthesis of penem-derived antibiotics.[143,144] Typically, their synthesis involves oxidation of the sulfide precursor as shown in Scheme 3.9.[145] Oxidation of sulfide **167** using sodium periodate in aqueous methanol gave a mixture of diastereomeric sulfoxides **168** in 93% yield.

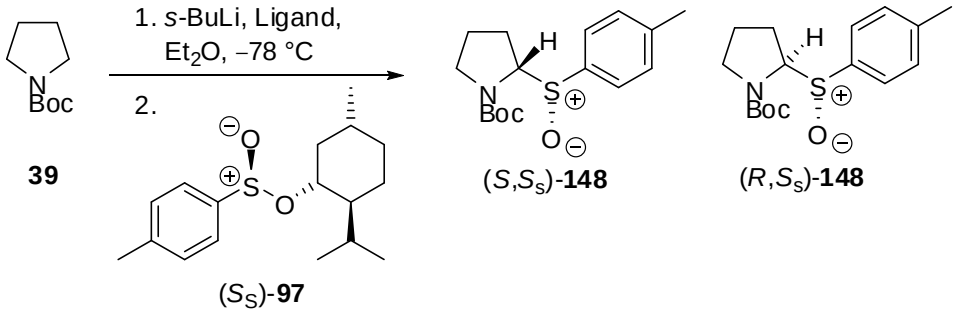


Scheme 3.9

To summarise, there are no examples of simple *α*-amino sulfoxides such as **148** and **149** reported in the literature. In contrast, a number of methods to synthesise *α*-amino sulfides and sulfones have been described.

3.2 Attempted synthesis of Pyrrolidinyl and Piperidinyl *α*-Amino Sulfoxides

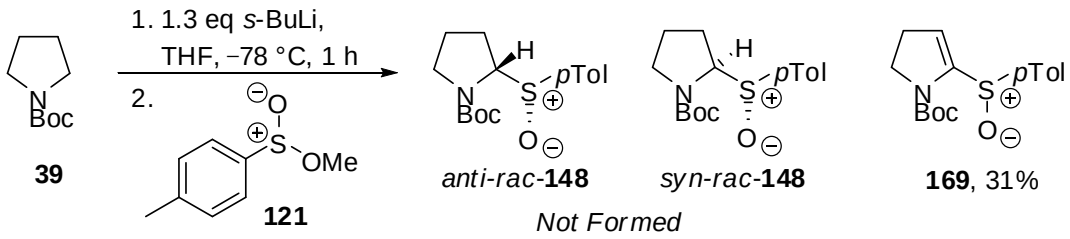
At the start of our project, there were no examples of compounds containing the *N*-Boc-*α*-sulfinyl motif reported in the literature. Despite this, we postulated that sulfoxides *anti*-(*S*,S_S)-**148** and *syn*-(*R*,S_S)-**148** could be synthesised by lithiation of *N*-Boc pyrrolidine **39** and trapping with Andersen's sulfinate (S_S)-**97** (Scheme 3.10). Furthermore, we expected that this methodology could be easily expanded to include other *N*-Boc heterocycles.



Scheme 3.10

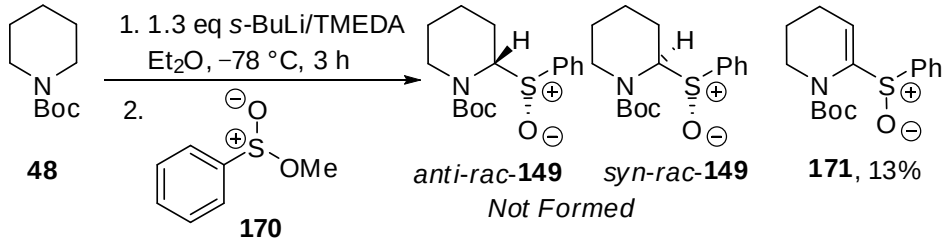
3.2.1 Attempted Synthesis of Pyrrolidinyl and Piperidinyl *α*-Amino Sulfoxides *via* Lithiation-Trapping

We began our investigation with the racemic lithiation of *N*-Boc pyrrolidine **39** and trapping with methyl *p*-toluenesulfinate **121**. *N*-Boc pyrrolidine **39** was lithiated using a diamine-free racemic lithiation protocol developed within our group (*s*-BuLi, THF, −78 °C, 1 hour).[146] However, trapping with sulfinate **121** did not give the expected diastereomeric sulfoxides *anti*-*rac*-**148** and *syn*-*rac*-**148** (Scheme 3.11). Instead, after column chromatography, we isolated dihydropyrrole **169** in 31% yield. Key spectroscopic data that allowed the structure of dihydropyrrole **169** to be identified include two alkene signals at δ_c 143.8 (quaternary C) and 124.2 (CH) in the ^{13}C NMR spectrum and an alkene CH signal (δ_H 5.99) in the ^{1}H NMR spectrum. Compound **169** also gave satisfactory HRMS data. In addition, *N*-Boc pyrrolidine **39** was recovered in 43% yield from this reaction.



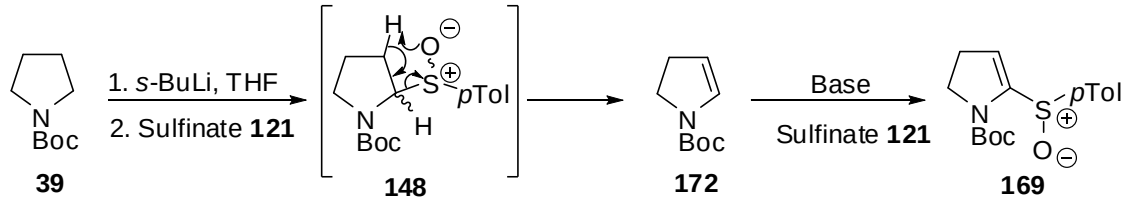
Scheme 3.11

The racemic lithiation of *N*-Boc piperidine **48** and trapping with methyl benzenesulfinate **170** was also attempted. In this case, the lithiation conditions were *s*-BuLi/TMEDA in Et_2O at −78 °C for 3 hours[147] since the diamine free protocol does not lithiate *N*-Boc piperidine **48**.[146] The expected sulfoxides *anti-rac*-**149** and *syn-rac*-**149** were not formed and tetrahydropyridine **171** was isolated in 13% yield (Scheme 3.12). This product was identified by two alkene signals (δ_c 143.5 and 113.7) in the ^{13}C NMR spectrum and an alkene CH signal (δ_H 6.37, triplet) in the ^{1}H NMR spectrum. *N*-Boc piperidine **48** was also recovered in 52% yield.



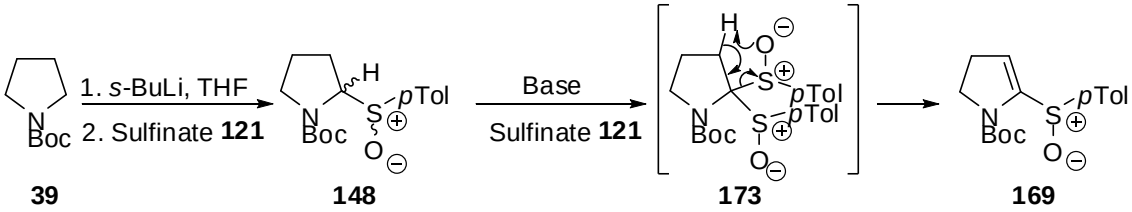
Scheme 3.12

In response to these disappointing results, we postulated two mechanisms for the formation of dihydropyrrole **169** and tetrahydropyridine **171**. These are summarised in Schemes 3.13, 3.14 and 3.15 for the pyrrolidine system. In the first mechanism, lithiation and electrophilic trapping would give sulfoxides **148**, which could then undergo elimination *via* a cycloreversion process to give dihydropyrrole **172** (Scheme 3.13). Vinylic lithiation of adduct **172** as reported by Beak in 1993[148] and subsequent trapping with sulfinate **121** would give dihydropyrrole **169**. Although cycloreversion of sulfoxides is a well-established procedure for the synthesis of carbon-carbon double bonds,[149-151] it is typical for elimination of aryl sulfinates to proceed at temperatures of 25-80 °C.[152] Therefore, it is possible that this mechanism may not be occurring under our low temperature conditions.



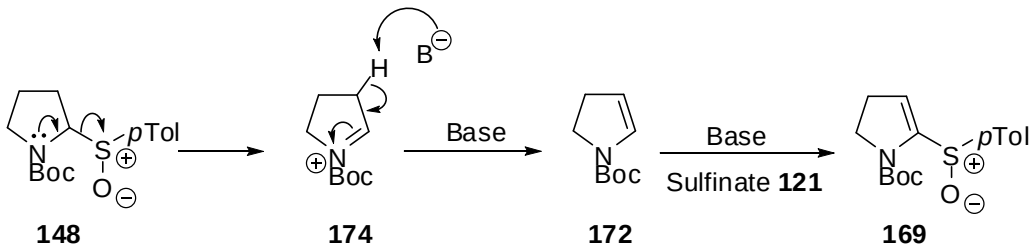
Scheme 3.13

Alternatively, due to the increased acidity of the *α*-proton in sulfoxide **148**, a second deprotonation and trapping could occur to give adduct **173**. This disubstitution could increase the propensity for a cycloreversion to occur to give dihydropyrrole **169** (Scheme 3.14). Doubly, *α*,*α*-substituted products of lithiation-trapping reactions analogous to **173** have been previously seen within the group when methyl chloroformate was used as the electrophile.[146]



Scheme 3.14

The second mechanism is dependent upon the *α*-elimination of the sulfoxide moiety by the nitrogen lone pair. In this process, sulfoxide **148** would be formed by lithiation-trapping and subsequent *α*-elimination would give iminium ion **174**. Deprotonation of the *β*-proton would lead to the formation of dihydropyrrole **172**. This could undergo vinylic lithiation[148] and trapping with sulfinate **121** would then give dihydropyrrole **169** as with the cycloreversion mechanism (Scheme 3.15). It is worth noting that *α*-amino sulfones are commonly used as iminium ion precursors although this is usually conducted in the presence of a Lewis acid.[141,153]



Scheme 3.15

It is possible that the conformation of sulfoxides **148** and **149** may cause *α*-elimination to be favoured (Figure 3.2). To avoid steric interaction between the sulfoxide and the planar NCO moieties (1,3-allylic type strain),[154] the sulfoxide occupies the axial position. This causes an alignment between the *N*-lone pair orbital and the anti-bonding $\sigma^*_{C\text{-}S}$ orbital and hence elimination is potentially favoured.

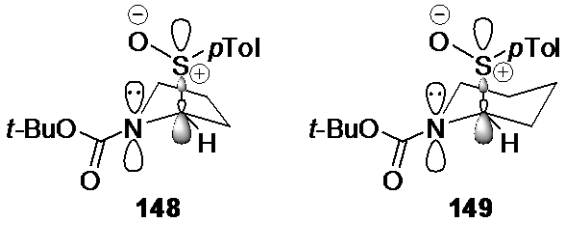
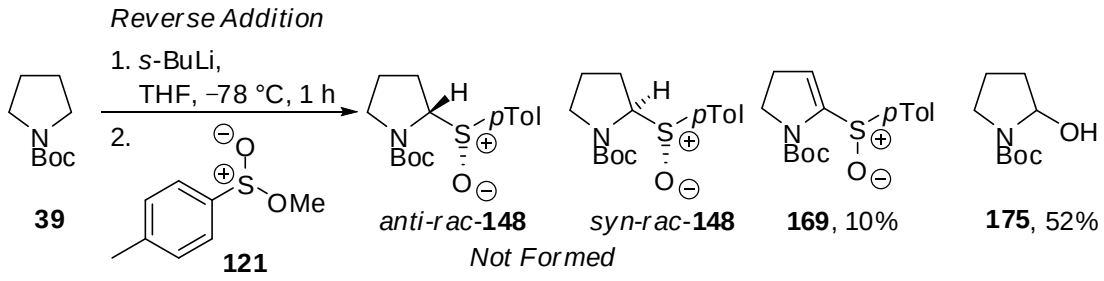


Figure 3.2

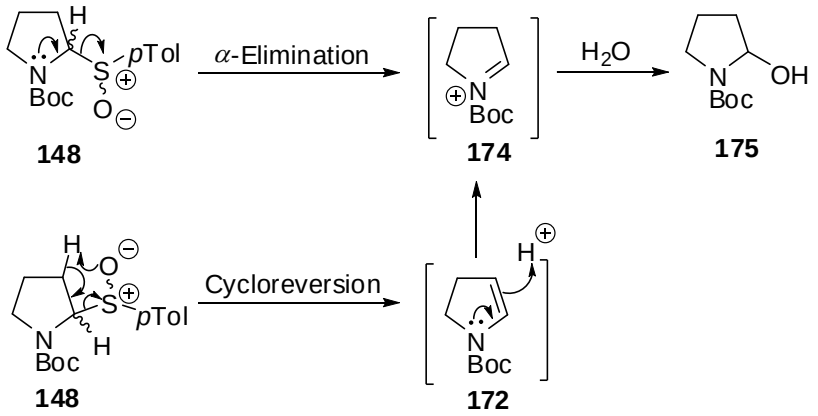
Both of the proposed mechanisms require an excess of base to be present within the reaction mixture. Therefore, a reverse addition protocol was explored in which lithiated *N*-Boc pyrrolidine was added to sulfinate **121**. This ensured that there was never an excess of base during the electrophilic trapping step. From this reaction, a reduction in the yield of dihydropyrrole **169** (10%) was observed. However, hydroxy pyrrolidine **175** was now isolated as the major product in 52% yield (Scheme 3.16). The desired sulfoxides *anti-rac*-**148** and *syn-rac*-**148** were not evident in the ^{1}H NMR spectrum of the crude product.



Scheme 3.16

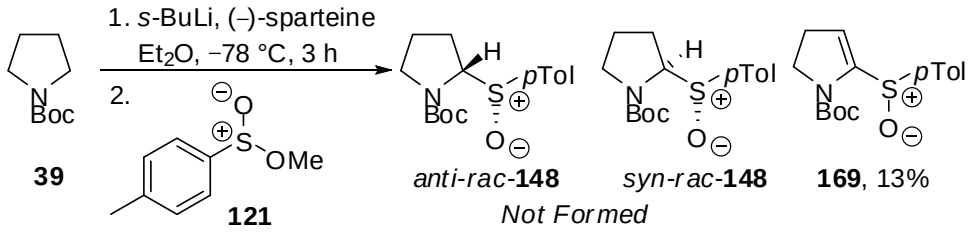
Hydroxy pyrrolidine **175** could be formed by either of the elimination processes previously discussed. These mechanisms assume the initial formation of sulfoxide **148** and are summarised in Scheme 3.17. In the case of *α*-elimination of the sulfoxide from **148** by the nitrogen lone pair, iminium ion **174** would be formed. Iminium ion **174** may then be quenched with water during the aqueous work-up to give hydroxy pyrrolidine

175. On the other hand, cycloreversion of the sulfoxide from **148** would give dihydropyrrole **172**. Protonation on work up could lead to the formation of iminium ion **174** which would be quenched to give hydroxy pyrrolidine **175** as previously discussed.



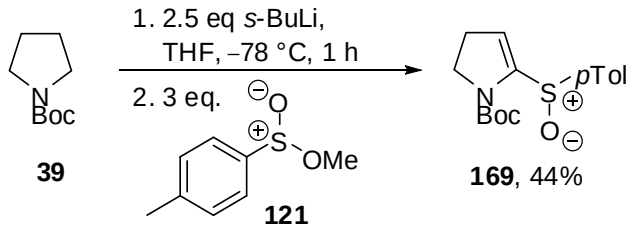
Scheme 3.17

Chiral diamines can modulate the reactivity of organolithium reagents. Therefore, we hoped that use of (−)-sparteine may hinder the formation of formation of dihydropyrrole **169**. Unfortunately, lithiation of *N*-Boc pyrrolidine **39** using *s*-BuLi/(−)-sparteine and trapping with sulfinate **121** gave dihydropyrrole in 13% yield. *N*-Boc pyrrolidine **39** was recovered in 65% yield (Scheme 3.18).



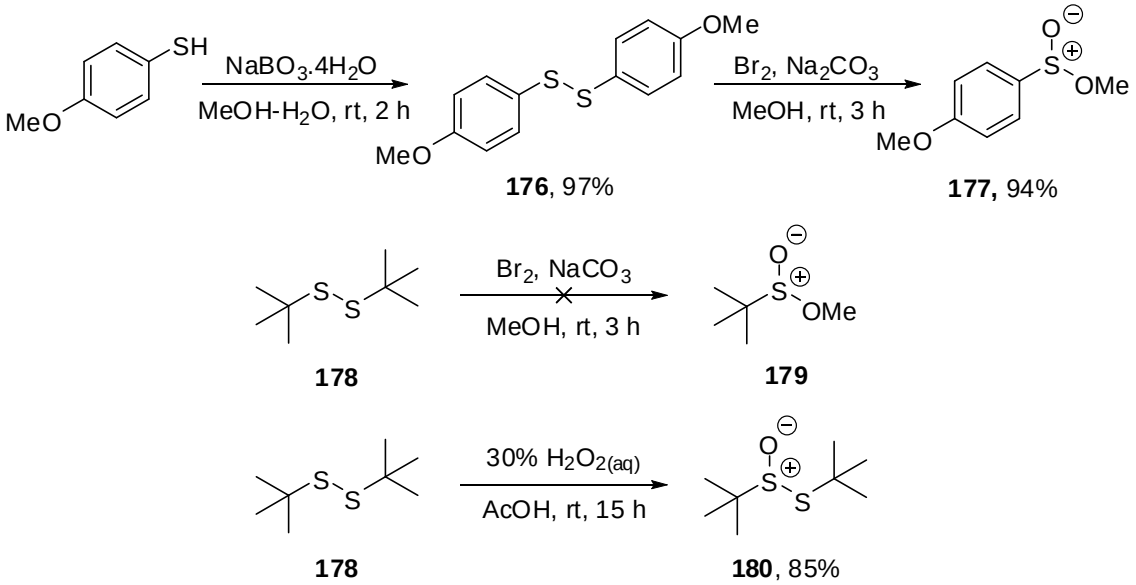
Scheme 3.18

As an aside, attempts were made to improve the yield of dihydropyrrole sulfoxide **169**. The formation of dihydropyrrole sulfoxide **169** requires at least two equivalents of base and sulfinate **121** and therefore, the amount of *s*-BuLi and methyl *p*-toluene sulfinate **121** was increased. Lithiation of *N*-Boc pyrrolidine **39** with 2.5 eq. of *s*-BuLi in THF and trapping with 3 eq. of **121** gave dihydropyrrole sulfoxide **169** in 44% yield (Scheme 3.19). This is compared to 31% yield when 1.3 eq. of *s*-BuLi and 2 eq. of **121** were used (see Scheme 3.11).



Scheme 3.19

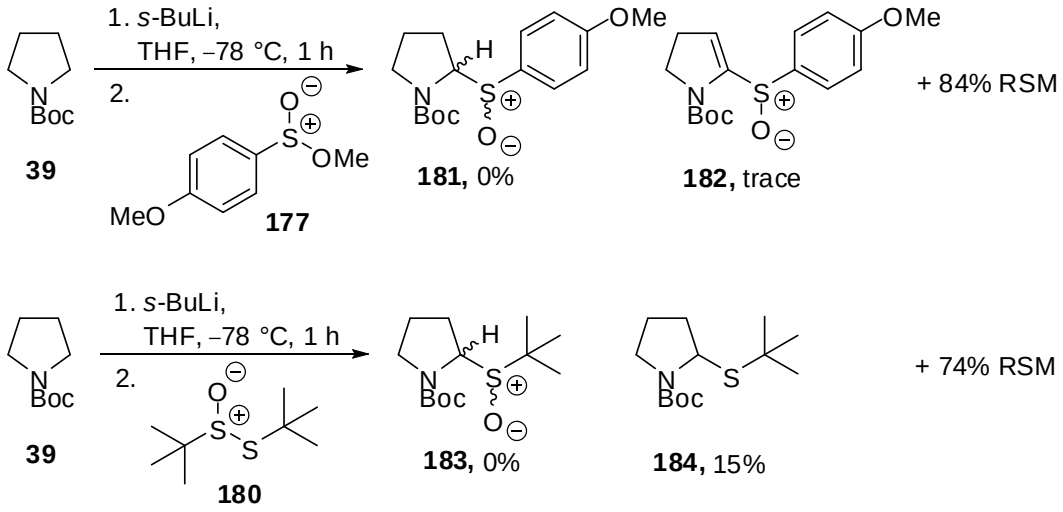
As a further attempt to synthesise *N*-Boc heterocyclic sulfoxides *via* direct lithiation and electrophilic trapping, more electron-rich aryl sulfinates and alkyl sulfinates were used with the aim of reducing the leaving group capability of the sulfoxide. In particular, alkyl sulfinates are known to require temperatures of up to 130 °C to facilitate sulfoxide elimination *via* a cycloreversion process.[152] First, methyl *p*-methoxybenzenesulfinate **177** was synthesised in two steps from *p*-methoxybenzenethiol in 91% overall yield (Scheme 3.20).[119,155] Next, we targeted methyl *t*-butylsulfinate **179**. Unfortunately, the synthesis of sulfinate **179** from *t*-butyldisulfide **178** using the Meyers procedure (Br_2, Na_2CO_3, MeOH)[119] was unsuccessful, with the reaction returning unreacted starting disulfide **178**. However, sulfinothioate **180** was successfully synthesised by oxidation of *t*-butyldisulfide **178** with 30% hydrogen peroxide *via* a known procedure.[156] We reasoned that sulfinothioate **180** could be used in an analogous way to sulfinate **179**.



Scheme 3.20

With sulfinate **177** and sulfinothioate **180** in hand, the lithiation and electrophilic trapping of *N*-Boc pyrrolidine **39** was attempted. Lithiation was carried out using *s*-

BuLi in THF and when using sulfinate **177** as the electrophile, sulfoxides **181** were not formed. However, there was limited evidence of a small amount of dihydropyrrole **182** in the ^{1}H NMR spectrum of the crude product (δ_H 5.96 ppm, double doublet, =CH). However, it was not possible to isolate dihydropyrrole **182** after flash column chromatography. In this case, starting *N*-Boc pyrrolidine **39** was recovered in 84% yield. The reaction using sulfinothioate **180** gave sulfide **184** in 15% yield (formed by preferential attack of the lithiated *N*-Boc pyrrolidine at the sulfanyl centre) and recovered starting *N*-Boc pyrrolidine **39** in 74% yield (Scheme 3.21). There was no evidence for the formation of the desired sulfoxides **183**.



Scheme 3.21

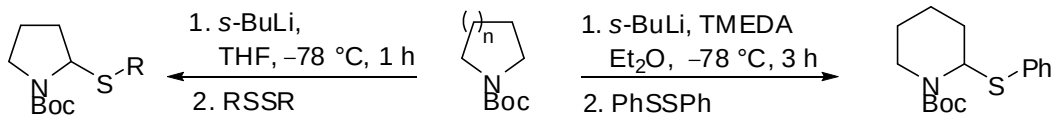
To conclude, we have been unable to synthesise pyrrolidinyl *α*-amino sulfoxides **148** *via* lithiation and trapping with sulfinate **121**. In all cases, dihydropyrrole **169** or hydroxy pyrrolidine **175** were formed in modest yields. Similarly, trapping with alternative sulfinates was unsuccessful. Furthermore, piperidinyl *α*-amino sulfoxides **149** were not formed by our lithiation-trapping procedure. Instead, tetrahydropyridine **171** was isolated as the major product.

3.2.2 Attempted synthesis of Pyrrolidinyl and Piperidinyl *α*-Amino Sulfoxides *via* Oxidation of Sulfides

Due to the lack of success with the sulfinate trapping, our attention then turned to the lithiation and electrophilic trapping with disulfides followed by a subsequent oxidation

to form the desired *N*-Boc-*α*-sulfinyl heterocycles. Investigation of this alternative route would also allow us to further investigate whether the desired *N*-Boc-*α*-sulfinyl heterocycles are inherently unstable or if the instability is due to the conditions used for the lithiation and electrophilic trapping.

First, *α*-amino sulfides were synthesised using a known procedure (see Scheme 3.3).[147] Indeed, lithiation-trapping of *N*-Boc piperidine **48** was carried out in the same fashion (*s*-BuLi, TMEDA, Et_2O, −78 °C, 3 hours) to give sulfide **151** in 63% yield (Scheme 3.22). With *N*-Boc pyrrolidine **39**, lithiation using *s*-BuLi in THF (−78 °C, 1 hour) worked well and the lithiated intermediate was trapped with a number of alky and aryl disulfides giving sulfides **184-187** in 14-59% yield.



185, R = Ph, 44 %
186, R = *p*Tol, 52 %
187, R = 4-$MeOC_6H_4$,14%
184, R = CMe_3, 59%

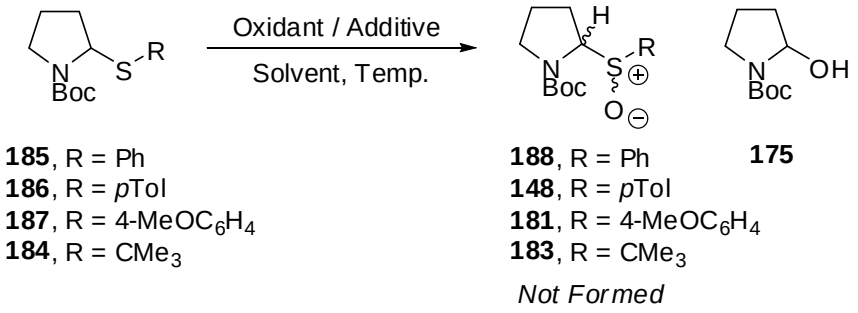
39 n = 1
48 n = 2

151, 63 %

Scheme 3.22

With sulfide **185** in hand, oxidation using *m*CPBA was attempted (Scheme 3.23, Table 3.1). Using conditions reported by Fodor and Feldman[157] (*m*CPBA, Na_2CO_3, CH_2Cl_2, room temperature), sulfoxides **188** were not formed (entry 1). However, hydroxy pyrrolidine **175** (which had previously been isolated when using the reverse addition protocol, see Scheme 3.16) was formed in 31% yield. Hydroxy pyrrolidine **175** could have been formed by sulfoxide *α*-elimination as previously postulated. Alternatively, over-oxidation to the sulfone may have occurred. This would act as a better leaving group for decomposition by *α*-elimination by the nitrogen lone pair to give hydroxy pyrrolidine **175** on work-up. In an attempt to ensure over-oxidation was prevented, a protocol developed by Ramesh *et al*.[158] (*m*CPBA, KF, CH_3CN/H_2O, rt) was employed. However, this reaction still gave hydroxy pyrrolidine **175** in 57% yield (entry 2). A lower temperature oxidation was also attempted following a known procedure[93] (*m*CPBA, CH_2Cl_2, −40 °C) and this time hydroxy pyrrolidine **175** was isolated in 86% yield (entry 3). In addition, this procedure was used for the oxidation of sulfides **186**,

187 and **184**, but sulfoxides **148, 181** and **183** were not formed and hydroxy pyrrolidine **175** was isolated in each case in 74-81% yield (entries 4-6).



185, R = Ph
186, R = *p*Tol
187, R = 4-MeOC$_6$H$_4$
184, R = CMe$_3$

188, R = Ph
148, R = *p*Tol
181, R = 4-MeOC$_6$H$_4$
183, R = CMe$_3$
Not Formed

175

Scheme 3.23

Table 3.1: Oxidation of *N*-Boc 2-Sulfanyl Pyrrolidines

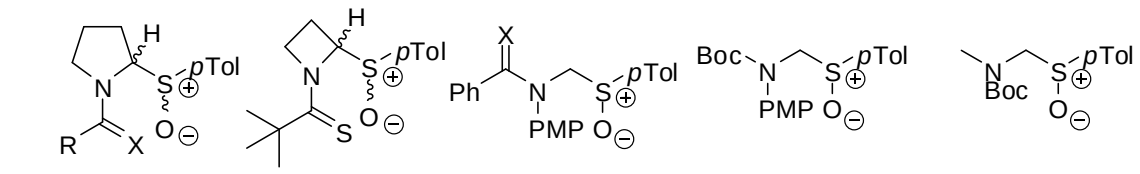
Entry	Sulfide	Oxidant	Additive	Solvent	Temp / °C	Yield of 175 / %
1	**185**	*m*CPBA	Na_2CO_3	CH_2Cl_2	rt	31
2	**185**	*m*CPBA	KF	MeCN/H_2O	rt	57
3	**185**	*m*CPBA	-	CH_2Cl_2	−40	86
4	**186**	*m*CPBA	-	CH_2Cl_2	−40	81
5	**187**	*m*CPBA	-	CH_2Cl_2	−40	74
6	**184**	*m*CPBA	-	CH_2Cl_2	−40	77
7	**186**	H_2O_2	-	HFIP	rt	43
8	**186**	Me_3SiCl/KO_2	-	CH_3CN	−15	52

As oxidation using *m*CPBA did not give the desired sulfoxide products, alternative oxidation methods were attempted with sulfide **186**. These included, a procedure published by Bonnet-Delpon *et al.* that uses hydrogen peroxide in hexafluoroisopropanol (HFIP),[159] and a protocol devised by Huang and co-workers mediated by trimethylsilyl chloride and potassium superoxide.[160] Both these methods also gave hydroxy pyrrolidine **175** in 43% and 52% yield respectively (entries 7 and 8).

To conclude, lithiation-trapping of *N*-Boc pyrrolidine **39** and *N*-Boc piperidine **48** with disulfides was successful giving a number of *α*-sulfanyl *N*-Boc heterocycles. Unfortunately, oxidation of these products proved to be unsuccessful, with the reaction instead giving good yields of hydroxy pyrrolidine **175**.

3.3 Attempted Synthesis of Cyclic and Acyclic *α*-Amino Sulfoxides

We wanted to further investigate whether the instability of *N*-Boc *α*-amino sulfoxides is due to a cycloreversion process or because of an *α*-elimination of the aryl sulfoxide by the nitrogen lone pair. Therefore, a series of substrates that would allow these two mechanisms to be probed were identified (Figure 3.3). Sulfoxides **189**-**191**, with *N*-amido and *N*-thioamido groups, were designed to have an increased electron withdrawing effect on the nitrogen atom. It was hoped that the nitrogen lone pair would be less available for *α*-elimination. In addition, azetidine sulfoxides **192** were designed to have a reduced propensity for elimination *via* either of the pathways. This is due to placing a double bond (an intermediate in both processes) in the four membered ring would cause additional strain in the system. Finally, sulfoxides **193**-**196** have no *β*-protons and, therefore, a cycloreversion of the sulfoxide moiety could not occur.



189, R = CPh_3, X = O
190, R = CMe_3, X = O
191, R = CMe_3, X = S

192

193, X = O
194, X = S

195

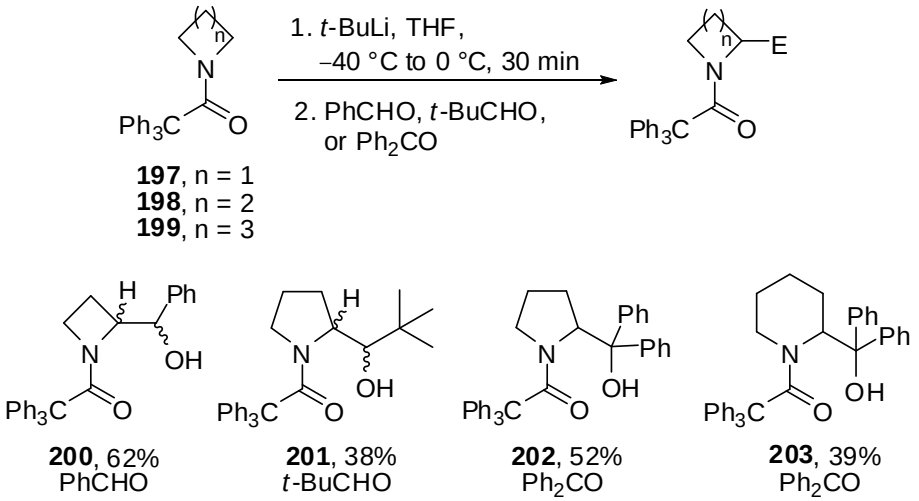
196

Figure 3.3

3.3.1 Attempted Synthesis of Cyclic *N*-Amido and *N*-Thioamide Sulfoxides

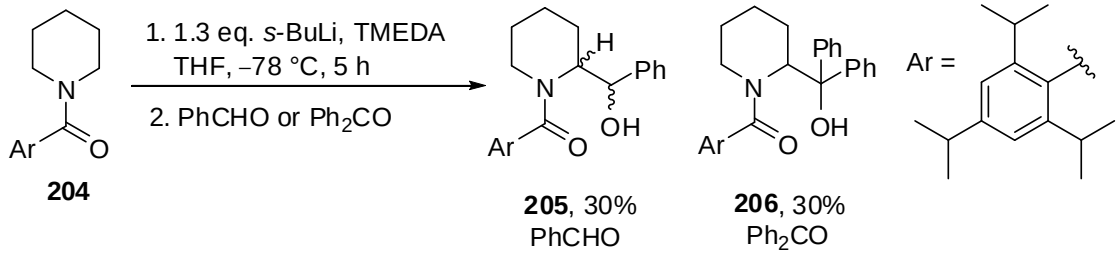
There are limited examples of lithiation-trapping of cyclic amides reported in the literature. In 1981, Seebach and co-workers reported the lithiation and electrophilic trapping at the *α*-position of the triphenylacetamides of azetidine **197**, pyrrolidine **198** and piperidine **199**.[161] The amides were treated with *t*-BuLi in THF at −40 °C for 10 minutes, before being allowed to warm to 0 °C for a further 20 minutes. The lithiated intermediates were then trapped with electrophiles to give *α*-substituted *N*-heterocycles **200**-**203** in 38-62% yield. Selected results are shown in Scheme 3.24. These lithiation-

trappings proceeded in modest yield but the main drawback of this procedure is the use of pyrophoric *t*-BuLi.



Scheme 3.24

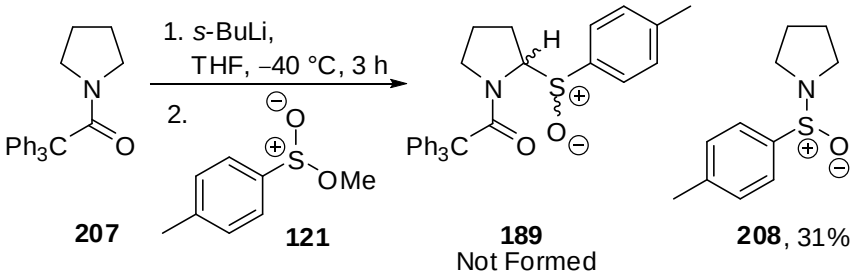
In 1984, Beak *et al.* described the *s*-BuLi/TMEDA-mediated lithiation of *N*-aryl piperidine **204** (Scheme 3.25).[162] Trapping with benzaldehyde or benzophenone gave alcohols **205** or **206** respectively, both in 30% yield. The 2,4,6-triisopropylbenzamide was chosen due to its sterically bulky nature, which hinders nucleophilic attack by *s*-BuLi at the carbonyl group.



Scheme 3.25

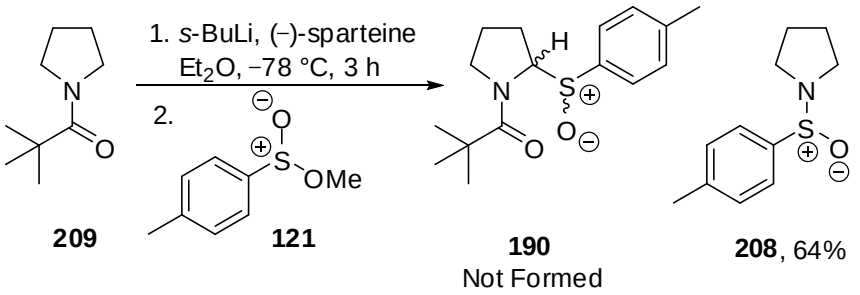
Our investigations focused on the lithiation-trappings of *N*-triphenylacetyl pyrrolidine **207** and *N*-pivaloyl pyrrolidine **209**. First, lithiation and electrophilic trapping of *N*-triphenylacetyl pyrrolidine **207** (prepared by acylation of pyrrolidine with pivaloyl chloride) was attempted using similar conditions to those reported by Seebach and co-workers (*s*-BuLi, THF, −40 °C, 3 hours).[161] Unfortunately, when trapping with sulfinate **121**, sulfoxide **189** was not formed and sulfinamide **208** was isolated in 31%

yield (Scheme 3.26). Presumably, sulfinamide **208** is formed by initial nucleophilic attack of *s*-BuLi at the amide carbonyl group, a phenomenon which has been previously observed by Beak *et al.* in the attempted lithiation of amides derived from piperidine.[162] The lithium amide this generates is then trapped by methyl *p*-toluenesulfinate **121** to give **208**.



Scheme 3.26

The lithiation of *N*-pivaloyl pyrrolidine **209** was attempted at lower temperature and using a chiral ligand (*s*-BuLi, (−)-sparteine, Et_2O, −78 °C, 3 hours) (Scheme 3.27). Disappointingly, electrophilic trapping with methyl *p*-toluenesulfinate **121** gave sulfinamide **208** in 64% yield.

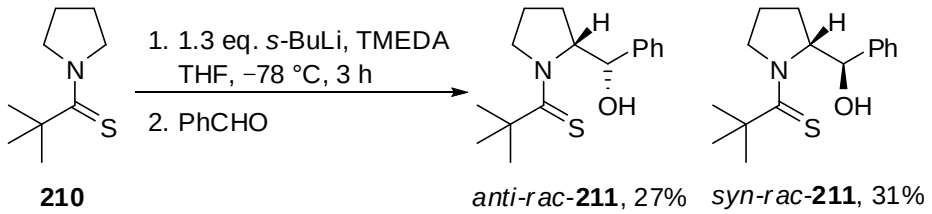


Scheme 3.27

The lithiation-trapping of amides was unsuccessful due to nucleophilic addition of the organometallic base to the amide carbonyl group. This problem has been seen previously in the lithiation of amides by Beak *et al.*,[162] therefore it may not be possible to access amido sulfoxides **189** and **190** *via* lithiation chemistry.

It was hoped that the reduced electrophilicity of the thioamide functionality would combat the problem of nucleophilic attack of *s*-BuLi at the carbonyl group of amides **207** and **209**. Therefore, *N*-pivaloyl pyrrolidine **209** was treated with phosphorus(V) sulfide in pyridine to give *N*-thiopivaloyl pyrrolidine **210** in quantitative yield. Initially,

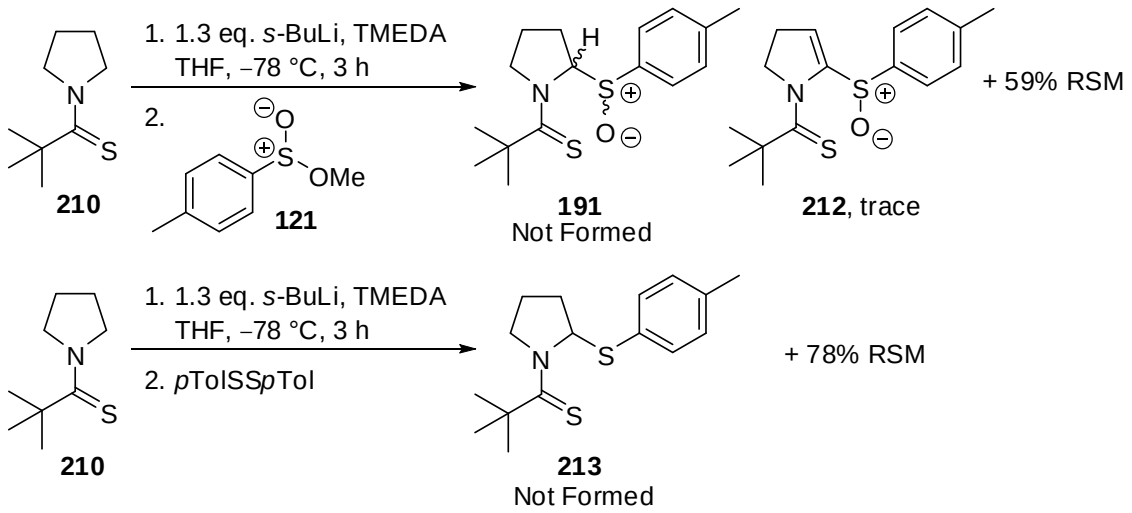
N-thiopivaloyl pyrrolidine **210** was lithiated using conditions reported by Hodgson and Kloesges for the lithiation of *N*-thiopivaloyl azetidine **101** (1.2 eq. *s*-BuLi, 2.4 eq. TMEDA, THF, −78 °C, 3 hours),[102] but after addition of different electrophiles (benzaldehyde, *p*-tolyldisulfide or methyl *p*-toluenesulfinate **121**) no trapped product was observed and starting *N*-thiopivaloyl pyrrolidine **210** was recovered in high yield. Therefore, the lithiation was repeated with 1.3 eq. of *s*-BuLi and TMEDA. This led to the first example of a successful lithiation-trapping of *N*-thiopivaloyl pyrrolidine **210**. Electrophilic trapping with benzaldehyde gave a 60:40 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols *syn-rac*-**211** *anti-rac*-**211** which were isolated in 31% and 27% yields respectively (Scheme 3.28). The assignment of the relative stereochemistry of *syn-rac*-**211** and *anti-rac*-**211** and is presented in Chapter Four (see Scheme 4.44).



210 *anti-rac*-**211**, 27% *syn-rac*-**211**, 31%

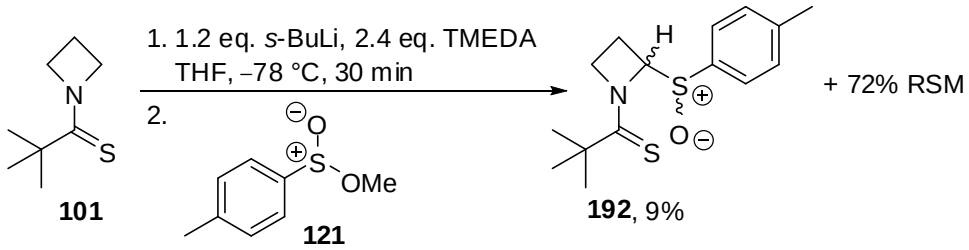
Scheme 3.28

Unfortunately, from the lithiation-trapping with methyl *p*-toluenesulfinate **121** under the same lithiation conditions (1.3 eq. *s*-BuLi/TMEDA, THF, −78 °C, 3 hours), the desired *N*-thiopivaloyl pyrrolidine sulfoxide **191** was not isolated. The ^{1}H NMR spectrum of the crude product showed trace amounts of dihydropyrrole **212** (δ_H 5.92, triplet, =C), which could not be isolated by flash column chromatography. Starting thioamide **210** was recovered in 59% yield. In a similar way, when trapping with *p*-tolyldisulfide, sulfide **213** was not formed and thioamide **210** was recovered in 78% yield (Scheme 3.29).



Scheme 3.29

Our attention turned to the synthesis of *N*-thiopivaloyl azetidine sulfoxides **192**. It was hoped that the four membered ring system would inhibit the sulfoxide elimination allowing stable compounds to be isolated. We began our investigation with the racemic lithiation of *N*-thiopivaloyl azetidine **101** (1.2 eq. *s*-BuLi, 2.4 eq. TMEDA, THF, −78 °C, 30 min)[102] and trapping with methyl *p*-tolyl sulfinate **121** (Scheme 3.30). From this reaction, a 91:9 mixture of diastereomeric sulfoxides **192** were evident in the ^{1}H NMR spectrum of the crude product. The NCH signal provided key diagnostic information (δ_H 5.55, double doublet for the major diastereoisomer and δ_H 5.72, double doublet for the minor diastereoisomer). However, after chromatography only the major diastereomeric sulfoxide **192** was isolated in 9% yield. Unfortunately, the relative stereochemistry was unable to be determined. In addition, *N*-thiopivaloyl azetidine **101** was recovered in 72% yield.

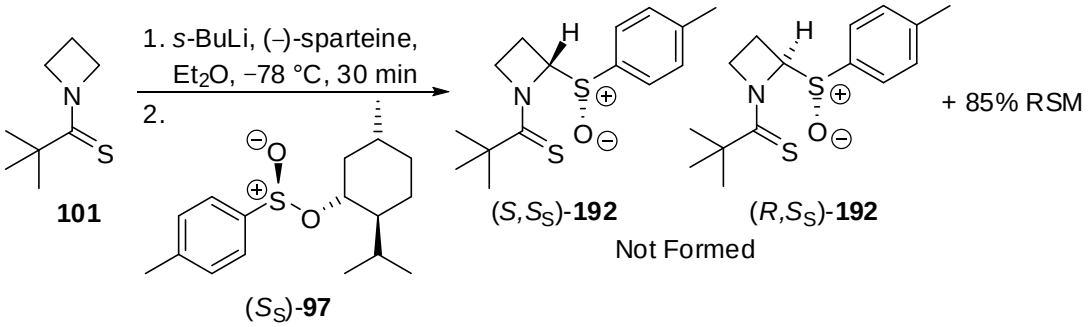


Scheme 3.30

N-Thiopivaloyl azetidine sulfoxide **192** is the first example of an isolable *α*-amino sulfoxide. We postulate that due to ring constraints both *α*-elimination and

cycloreversion are disfavoured. Furthermore, the thiopivalamide group provides an increased electron withdrawing effect when compared to the Boc protecting group. Thus, the nitrogen lone pair may be less available to eliminate the sulfoxide moiety.

It was hoped that the using a chiral ligand may improve the yield of the sulfoxide products. It would also allow the assignment of the configuration in a similar fashion to that of *O*-alkyl carbamate sulfoxides *anti*-(*S*,S_S)-**103** and *syn*-(*R*,S_S)-**103** (see Scheme 2.24). *N*-Thiopivaloyl azetidine **101** was lithiated using *s*-BuLi/(−)-sparteine in Et_2O at −78 °C and trapped with Andersen's sulfinate (S_S)-**97** (Scheme 3.31). Unfortunately, no product was evident in the ^{1}H NMR spectrum of the crude product and *N*-thiopivaloyl azetidine **101** was recovered in 85% yield.

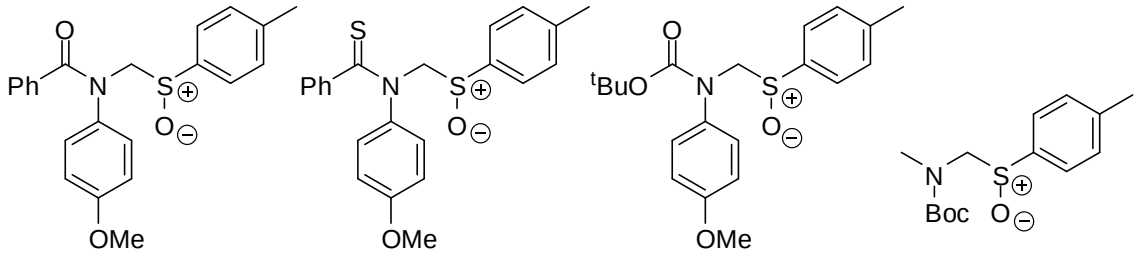


Scheme 3.31

To conclude, we were able to successfully synthesise *N*-thiopivaloyl azetidine sulfoxide **192** by lithiation-trapping. However, the yield of the reaction was disappointing and our attempts to increase the yield were fruitless. In contrast, pyrrolidinyl sulfoxides **191** were not formed from the lithiation of *N*-thiopivaloyl pyrrolidine **210** and trapping with methyl *p*-toluene sulfinate **121**.

3.3.2 Synthesis of Acyclic *α*-Amino Sulfoxides

The synthesis of sulfoxides without *β*-protons was targeted next and acyclic sulfoxides **193-196** were designed to probe this (Figure 3.4). This would allow us to explore whether elimination was occurring *via* a cycloreversion process as well as varying the electron withdrawing groups on the nitrogen atom.

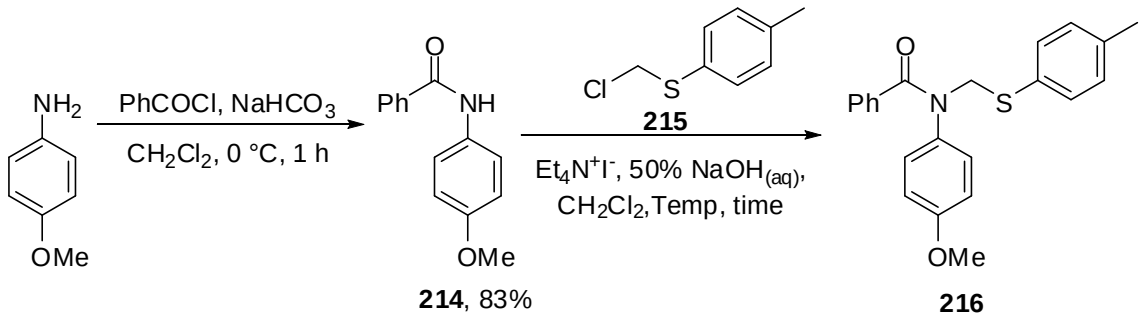


193 **194** **195** **196**

Figure 3.4

It was decided that the best route to sulfinyl benzamide **193** would be *via* alkylation of *N*-PMP benzamide **214** with a chlorosulfide and subsequent oxidation. This route avoids the use of lithiation chemistry which may result in nucleophilic attack of the organolithium base at the carbonyl of the amide group. In 1972, Colonna *et al*. reported that *α*-halogeno sulfoxides are unreactive towards nucleophilic substitution, whereas nucleophilic substitution of *α*-halogeno sulfides is facile.[163] Furthermore, Hiyama and co-workers reported that alkylation of a similar *N*-PMP amide with chloromethyl phenyl sulfide proceeds in 53% yield.[164]

To start with, benzamide **214** was synthesised by acylation of *p*-anisidine with benzoyl chloride in 83% yield (Scheme 3.32).[165] Then, alkylation of benzamide **214** with chlorosulfide **215** (formed by reaction of methyl *p*-tolylsulfide and *N*-chlorosuccinimide[166]) was attempted. First, following Hiyama's method (1.5 eq. chlorosulfide **215**, room temperature, 1 hour) gave sulfanyl benzamide **216** in 51% yield (Table 3.2, entry 1). The alkylation was repeated using 2.0 eq. of chlorosulfide **215** over 18 hours and sulfanyl benzamide **216** was isolated in 62% yield (entry 2). The yield was further improved by warming the reaction to 50 °C over the same time period. This gave sulfanyl benzamide **216** in 68% yield (entry 3). A final attempt to optimise this alkylation by increasing the amount of chlorosulfide **215** from 2.0 eq. to 2.5 eq. showed no improvement in the yield of sulfanyl benzamide **216** (entry 4).

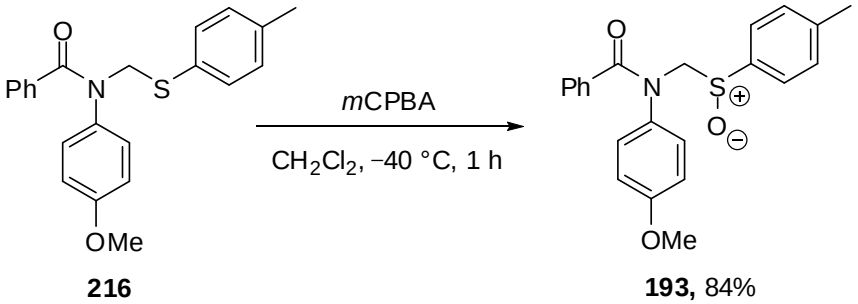


Scheme 3.32

Table 3.2: Optimisation of the alkylation of *N*-benzoyl anisidine **214**

Entry	Eq. Chlorosulfide 215	Temp. / °C	Time / h	Yield of 216 / %
1	1.5	rt	1	51
2	2.0	rt	18	62
3	2.0	50	18	68
4	2.5	50	18	68

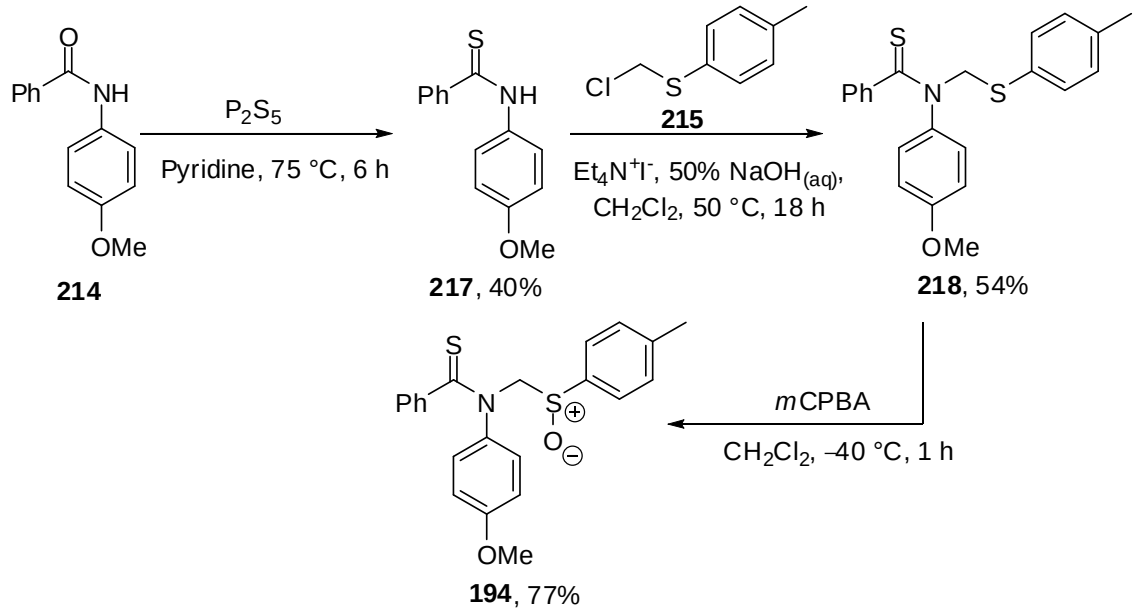
Sulfanyl benzamide **216** was then oxidised using *m*CPBA (CH_2Cl_2, −40 °C, 1 hour) to form sulfoxide **193** in 84% yield (Scheme 3.33). To our delight, *α*-amino sulfoxide **193** was stable and readily isolatable. Sulfoxide **193** has no *β*-protons and therefore cycloreversion is not possible. In addition, the increased electron-withdrawing amide group (when compared to Boc) on the nitrogen atom should reduce the propensity for *α*-elimination of the aryl sulfoxide by the nitrogen lone pair. Therefore, the successful isolation of *α*-amino sulfoxide **216** does not discriminate between the two proposed mechanisms for the breakdown *N*-Boc *α*-sulfinyl heterocycles.



Scheme 3.33

The thiobenzamide analogue, sulfoxide **194**, was also synthesised *via* a similar route (Scheme 3.34). This synthesis began with the conversion of benzamide **214** using

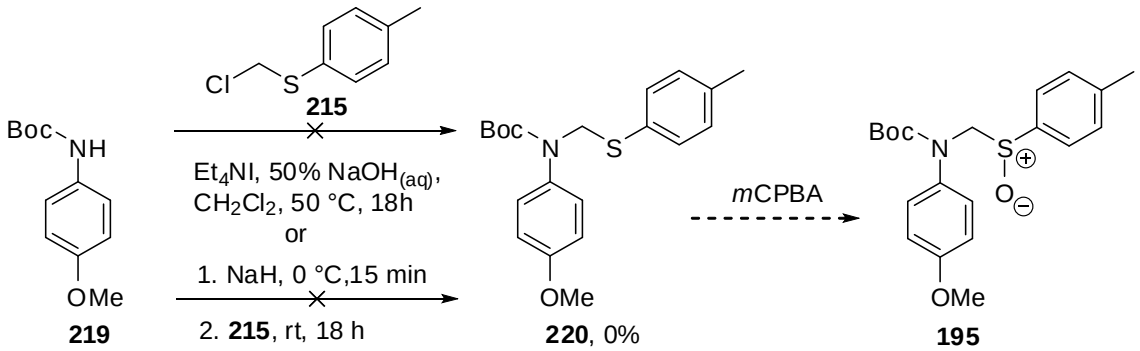
phosphorus(V) sulfide into thiobenzamide **217** which proceeded in a moderate 40% yield.



Scheme 3.34

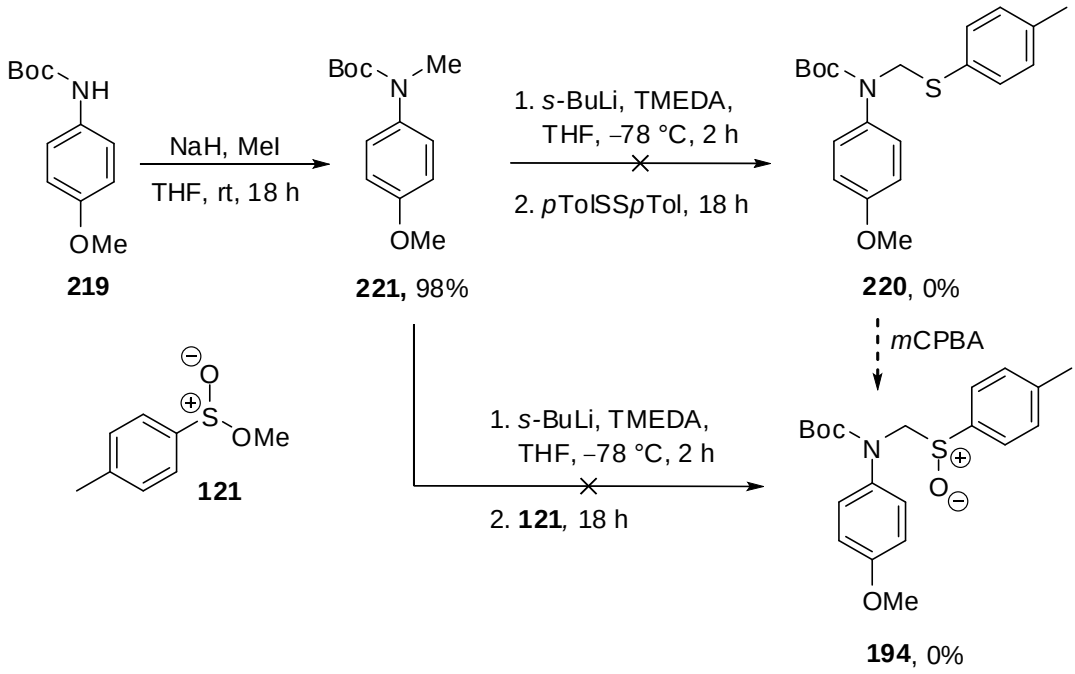
Thiobenzamide **217** was then alkylated under our previously optimised conditions (2.0 eq. chlorosulfide **215**, 50 °C, 18 hours) to give sulfanyl thiobenzamide **218** in 54% yield. Finally, sulfanyl thiobenzamide **218** was oxidised using *m*CPBA to give sulfoxide **194** in 77% yield. Sulfoxide **194** was our second example of an isolable acyclic *α*-amino sulfoxide.

Attempts were also made towards the synthesis of *N*-Boc sulfoxide **195** but the routes investigated were unsuccessful (Schemes 3.35 and 3.36). Initially, alkylation of *N*-Boc *p*-anisidine **219** with chlorosulfide **215** using the modified Hiyama method[164] (2.0 eq. chlorosulfide **215**, 50 °C, 18 hours) was investigated. Unfortunately, *N*-Boc sulfide **220** was not formed, and *N*-Boc *p*-anisidine **219** was recovered quantitatively (Scheme 3.35). Then, we attempted an alkylation which began with deprotonation of *N*-Boc *p*-anisidine **219** using sodium hydride and subsequent addition of chlorosulfide **215**. The reaction did not produce any of the desired *N*-Boc sulfide **220** and *N*-Boc *p*-anisidine **219** was recovered in 100% yield. As a result, the planned oxidation to sulfoxide **195** could not be investigated.



Scheme 3.35

Our attention then turned to the use of lithiation chemistry to access either *N*-Boc sulfide **220** or *N*-Boc sulfoxide **194**. *N*-Boc *N*-methyl *p*-anisidine **221** was synthesised from *N*-Boc *p*-anisidine **220** by alkylation with methyl iodide, but subsequent lithiation-trapping was unsuccessful (Scheme 3.36). When attempting to trap with *p*-tolyl disulfide, a product was isolated, but we were unable to determine its structure (we do not believe it to be the product of an *ortho*-lithiation). In addition, starting *N*-Boc *N*-methyl *p*-anisidine **221** was recovered in 52% yield. Finally, when using methyl *p*-toluenesulfinate **121** as the electrophile, sulfoxide **194** was not formed. In addition, *N*-Boc *N*-methyl *p*-anisidine **221** was recovered in 83% yield. The reason for the failure of these reactions is unclear.

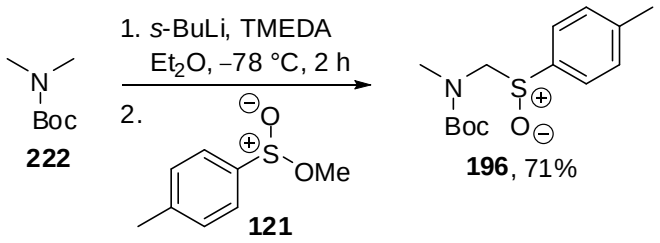


Scheme 3.36

Unfortunately, the synthesis of *N*-Boc sulfoxide **194** was unsuccessful *via* alkylation and when using lithiation chemistry. Currently, there is no evidence that this is because the desired sulfoxide is unstable. Instead, it is suggested that these are not viable routes to *N*-Boc sulfoxide **194**.

Finally, we targeted *N*-Boc dimethylamine sulfoxide **196** as lithiation chemistry would provide an expedient route to the desired compound. In 1989, Beak and Lee reported the lithiation-trapping of *N*-Boc dimethylamine **222** to give substituted products in good yield.[147] In addition, Dieter and co-workers have also used the lithiation of *N*-Boc dimethylamine **222** to exemplify coupling of *α*-lithio amines with aryl and vinyl iodides.[167,168]

The lithiation of *N*-Boc dimethylamine **222** was carried out using conditions published by Beak *et al*. (*s*-BuLi, TMEDA, Et_2O, −78 °C, 2 hours).[169] Trapping with methyl *p*-toluene sulfinate **121** gave *N*-Boc dimethylamine sulfoxide **196** in 71% yield (Scheme 3.37). It should be noted that it was necessary that 1% Et_3N to be added to the eluent for chromatography to avoid decomposition on silica, possibly *via* silica-promoted *α*-elimination of the sulfoxide group.



Scheme 3.37

Sulfoxide **196** is the first example of an isolable compound containing the *N*-Boc-*α*-sulfinyl motif. In contrast, our attempts to synthesise pyrrolidinyl sulfoxides **148** and piperidinyl sulfoxides **149** were unsuccessful (see Schemes 3.11 and 3.12). Instead, dihydropyrrole sulfoxide **169** and tetrahydropyridine sulfoxide **171** were isolated from these reactions. We propose that the stability of sulfoxide **196** could be due to the absence of *β*-protons in the molecule. Thus, cycloreversion of the sulfoxide moiety is possible. However, as sulfoxide **196** is unstable on silica (in the absence of Et_3N), we

cannot fully rule out *α*-elimination of the sulfoxide by the nitrogen lone pair as a cause of the general instability of cyclic *α*-amino sulfoxides.

So far we have managed to synthesise one cyclic and three acyclic *α*-amino sulfoxides either by lithiation-trapping or alkylation-oxidation (Figure 3.5). Disappointingly, cyclic *N*-Boc *α*-amino sulfoxides **148** and **149** were not formed using a variety of methods.

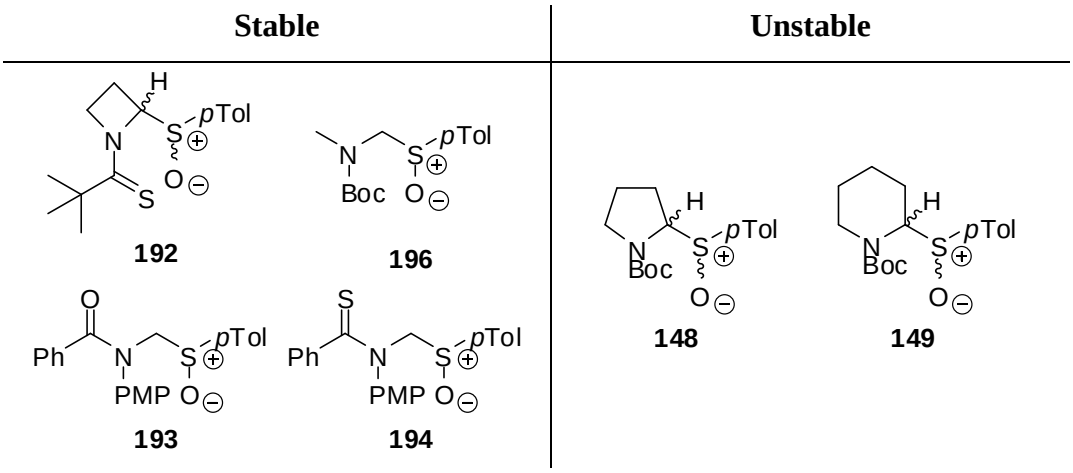
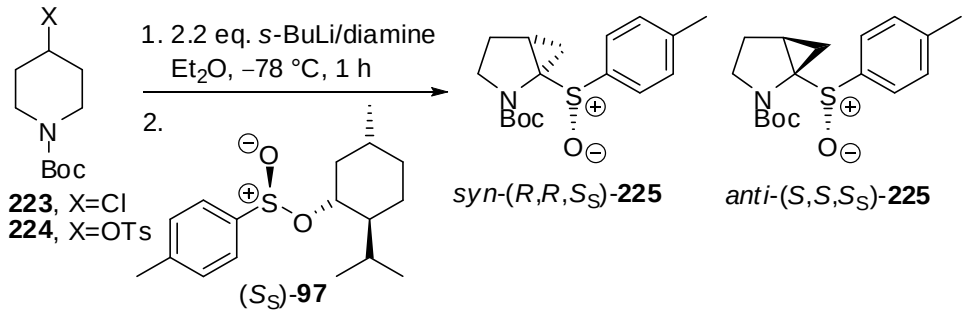


Figure 3.5

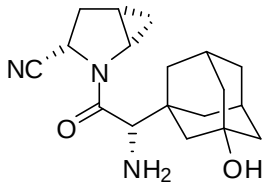
3.4 Synthesis of Azabicyclo[3.1.0]hexane Sulfoxides

Our attention turned to designing a cyclic *α*-amino sulfoxide in which both *α*-elimination and cycloreversion were disfavoured. An attractive option was the synthesis of azabicyclo[3.1.0]hexanes sulfoxides *syn*-(*R*,*R*,S_s)-**225** and *anti*-(*S*,*S*,R_s)-**225**. From these substrates, sulfoxide elimination is prohibited due to Bredt's rule.[170,171] In addition, we proposed that they could be expediently synthesised by lithiation of *N*-Boc 4-chloro or 4-tosyloxy piperidines **223** or **224** and trapping with Andersen's sulfinate (S_S)-**97** (Scheme 3.38). The lithiation-cyclisation of *N*-Boc 4-chloro and 4-tosyloxy piperidines **223** and **224** has been previously studied by Beak *et al*. and the highest enantioselectivity achieved in these lithiation processes were 78:22 er.[41,172] Therefore, we believed that our methodology could provide significant improvements in this arena.



Scheme 3.38

Substituted azabicyclo[3.1.0]hexanes have been shown to have a wide range of pharmacological activity. Indeed, they act as kinase and protease inhibitors[173,174] and also show good efficacy in the treatment of the hepatitis C virus.[175] Furthermore, one analogue, saxagliptin, has recently been approved in the treatment of type II diabetes (Figure 3.6).[176,177]

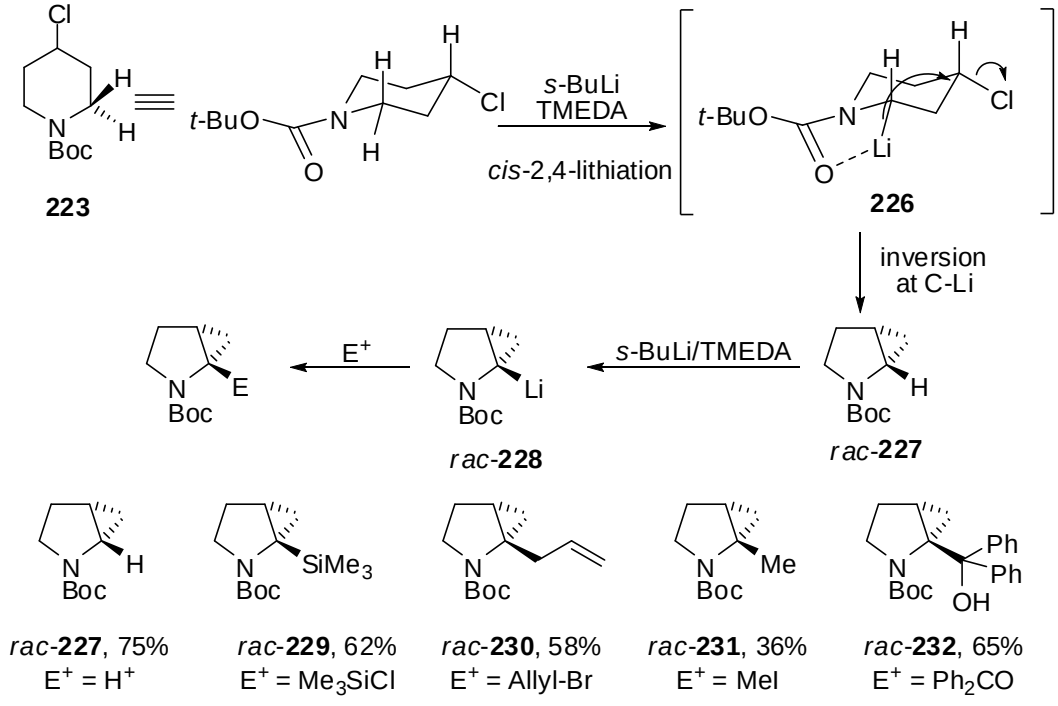


Saxagliptin

Figure 3.6

3.4.1 Lithiation-Trapping of *N*-Boc 4-Chloro and 4-Sulfonyl Piperidines

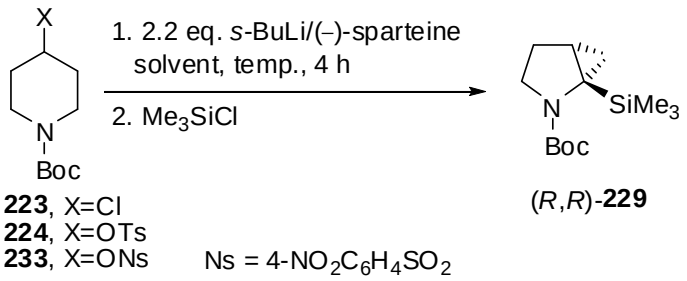
In 1994, Beak and co-workers reported the facile construction of azabicyclo[3.1.0] hexanes in racemic fashion by the lithiation-cyclisation of *N*-Boc 4-chloro piperidine **223**. Treatment of *N*-Boc 4-chloro piperidine **223** with 2.2 eq. of *s*-BuLi/TMEDA gave 2-substituted products **227, 229-232** in 36-75% yield (Scheme 3.39).[178] This reaction proceeds *via* α-lithiated piperidine **226** which immediately cyclises to give bicycle *rac*-**227**. In **223**, the chlorine atom will presumably be in the equatorial position and equatorial α-lithiation will occur to give 2,4-*cis*-diastereoselectivity.[179] In addition, the intramolecular cyclisation occurs with inversion of configuration at the α-carbon to give *rac*-**227**. Due to the increased acidity of the cyclopropanyl proton in *rac*-**227** when compared with starting piperidine **223**, this second deprotonation event is favoured leading to lithiated intermediate **228**. Finally, trapping with an array of electrophiles furnishes the desired 2-subsituted azabicyclo[3.1.0]hexanes **227, 229-232**.



Scheme 3.39

Two years later, Beak and Park investigated the asymmetric lithiation-trapping of 4-chloro piperidine **223**.[172] Lithiation of *N*-Boc 4-chloro piperidine **223** with 2.2 eq. *s*-BuLi/(−)-sparteine in Et_2O at −78 °C and trapping with trimethylsilyl chloride gave bicycle *rac*-**229** in 71% yield but 50:50 er (Scheme 3.40 and Table 3.3, entry 1). This is a surprising result given that lithiation of *N*-Boc piperidine with *s*-BuLi/(−)-sparteine

and trapping with electrophiles is known to give a 2-subsituted product in low yield but good enantioselectivity (87:13 er).[41] In an attempt to overcome this problem, Beak and Park studied whether the leaving group affected the enantioselectivity of the intramolecular cyclisation. Lithiation of tosylate **224** with 2.2 eq. *s*-BuLi/(−)-sparteine at −78 °C in Et_2O and trapping with trimethylsilyl chloride gave bicycle (*R*,*R*)-**229** in good yield (77%) and satisfactory enantioselectivity (78:22 er) (entry 2).



Scheme 3.40

Table 3.3: Asymmetric lithiation-cyclisation of 4-subsituted piperidines

Entry	SM	Solvent	Temp. / °C	Yield / %	er
1	**223**	Et_2O	−78	71	50:50
2	**224**	Et_2O	−78	77	78:22
3	**224**	Et_2O	−100	41	79:21
4	**224**	Et_2O-pentane	−78	51	74:26
5	**224**	*t*-BuOMe	−78	63	72:28
6	**224**	THF	−78	81	59:41
7	**233**	Et_2O	−78	43	71:29

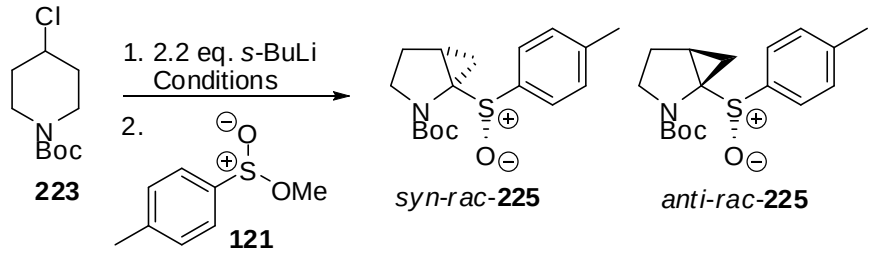
Further attempts to optimise this reaction were unsuccessful: neither lower temperature (entry 3) nor different solvents (entries 4-6) improved the enantioselectivity. When nosylate **233** was lithiated under the same conditions used for tosylate **224**, bicycle (*R*,*R*)-**229** was formed in 43% yield and 71:29 er (entry 7).

In 2002, Beak and co-workers reported the lithiation-cyclisation of tosylate **224** under the same conditions as was previously reported (2.2 eq. *s*-BuLi/(−)-sparteine, Et_2O, −78 °C, 4 hours). Although trapping with trimethylsilyl chloride gave bicycle (*R*,*R*)-**229** in comparable enantioselectivity (75:25 er), the yield reported was vastly reduced (26%).[41] No explanation for the difference between this result and that shown in Table 3.3, entry

2 (78% yield and 78:22 er) was provided. In this work, the absolute configuration of the major enantiomer, (*R*,*R*)-**229**, was established by X-ray crystallography of the *p*-bromobenzamide derivative.

3.4.2 *s*-BuLi/TMEDA-Mediated Lithiation of *N*-Boc 4-Chloro Piperidine and Trapping with Andersen's Sulfinate

We began our investigation with the racemic lithiation of *N*-Boc 4-chloro piperidine **223** using conditions reported by Beak *et al.* (2.2 eq. *s*-BuLi/TMEDA, Et_2O, −78 °C, 6 hours[178]) and electrophilic trapping with sulfinate **121**. This gave sulfoxides *syn-rac*-**225** and *anti-rac*-**225** in 35% and 36% yield respectively (Scheme 3.41, Table 3.4, entry 1). Our design had worked; we had successfully isolated a cyclic *N*-Boc *α*-amino sulfoxide. The assignment of the stereochemistry of the diastereomeric sulfoxides was made from the products of asymmetric lithiation which are presented later. Crucially, the diastereomeric sulfoxides were readily separated by flash column chromatography and had distinctive ^{1}H and ^{13}C NMR spectra. In addition, each diastereoisomer was separable into a 50:50 mix of enantiomers by CSP-HPLC.



Scheme 3.41

Table 3.4: Optimisation of the racemic lithiation of 4-chloro piperidine **223** and trapping with sulfinate **121**

Entry	Conditions	Yield of *syn-rac*-225 / %	Yield of *anti-rac*-225 / %
1	TMEDA, Et_2O, −78 °C, 6 h	35	36
2	TMEDA, Et_2O, −78 °C, 1 h	34	35
3	THF, −78 °C, 1 h	33	32
4	THF, −30 °C, 5 min	21	18

A reduction in lithiation time from 6 hours to 1 hour showed no reduction in yield, with *syn-rac*-**225** and *anti-rac*-**225** being isolated in 34% and 35% yield respectively (entry 2). This indicated that significant lithiation occurred within 1 hour. A diamine-free lithiation[146] (*s*-BuLi/THF, 1 hour) at −78 °C gave both diastereoisomers in good yields (entry 3). In contrast, repeating the lithiation at −30 °C for 5 minutes (conditions that had previously been optimised by our group for the lithiation of a number of *N*-Boc heterocycles)[146] gave sulfoxide *syn-rac*-**225** in 21% yield and sulfoxide *anti-rac*-**225** in 18% yield (entry 4).

The difference in reactivity between *N*-Boc piperidine **48** and *N*-Boc 4-chloro piperidine **223** towards *α*-lithiation is remarkable. ReactIR™ spectroscopic data recorded within our group suggests that full lithiation of *N*-Boc piperidine **48** with *s*-BuLi/TMEDA takes in excess of 90 minutes. [180] However, lithiation of *N*-Boc 4-chloro piperidine **223** under the same conditions required only 2 minutes for complete lithiation. In addition, the reactivity difference is also apparent in isolated yields. It has been reported that the *s*-BuLi/THF complex is unable to lithiate *N*-Boc piperidine[146] whereas our results show that the diamine-free lithiation of *N*-Boc 4-chloro piperidine **223** gives significant yields at −78 °C (65% yield, Table 3.4, entry 3).

We postulate that the reactivity difference between *N*-Boc piperidine **48** and *N*-Boc 4-chloro piperidine **223** arises due to an overlap between the back lobe of the C-H σ-bonding orbital and the C-Cl σ* antibonding orbital. This would cause a weakening of the C-H bond, effectively making the proton more acidic. Therefore, deprotonation is more facile in *N*-Boc 4-chloro piperidine **223** than in *N*-Boc piperidine **48**, where this interaction does not exist (Figure 3.7).

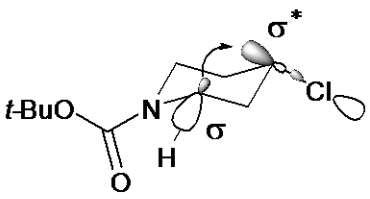
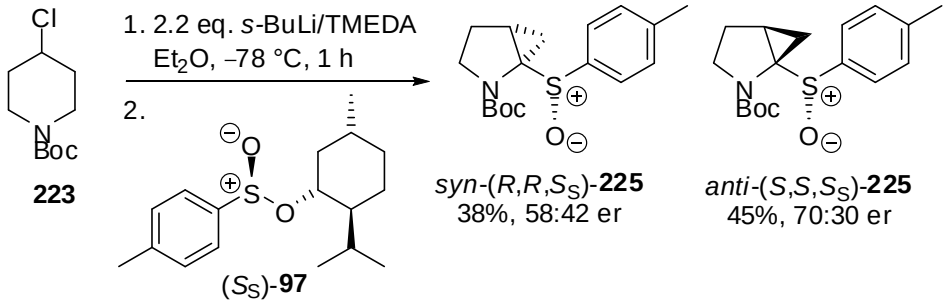


Figure 3.7

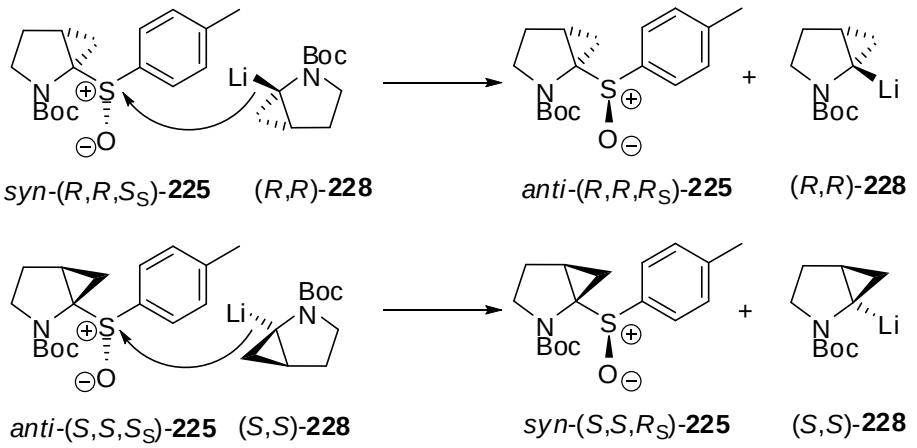
Our attention then turned to the enantioselective synthesis of sulfoxides *syn*-(*R*,*R*,S_S)-**225** and *anti*-(*S*,*S*,S_S)-**225**. First, the racemic lithiation (2.2 eq. *s*-BuLi/TMEDA, Et_2O, −78 °C, 1 hour) of *N*-Boc 4-chloro piperidine **223** and trapping with 2.2 eq. Andersen's

sulfinate (S_S)-**97** was investigated because we were concerned about a similar loss of enantiomeric ratio during the trapping procedure as was observed in the case of *O*-alkyl carbamate **14** (see Scheme 2.13). In fact, the reduction in enantiomeric ratio was even more dramatic. Sulfoxide *syn*-(*R*,*R*,S_S)-**225** was isolated in 38% yield but only 58:42 er and sulfoxide *anti*-(*S*,*S*,S_S)-**225** was isolated in 45% yield and 70:30 er (Scheme 3.42).



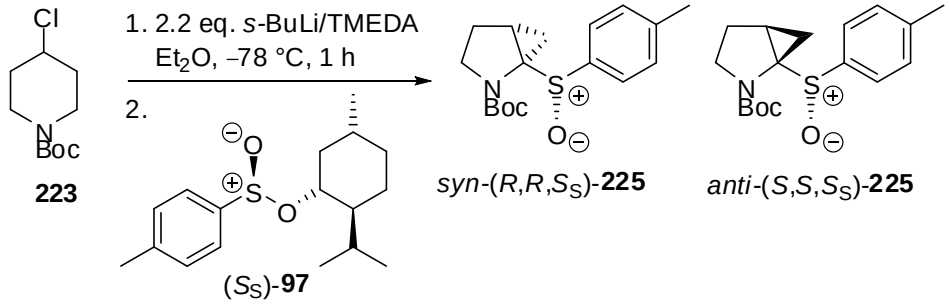
Scheme 3.42

We postulate that the loss of enantiomeric ratio in the sulfoxide products occurs *via* a similar process to that identified for *α*-alkoxy sulfoxides (see Scheme 2.14). Lithiation-cyclisation of *N*-Boc 4-chloro piperidine **223** using *s*-BuLi/TMEDA will generate a 50:50 mixture of organolithium reagents (*R*,*R*)-**228** and (*S*,*S*)-**228**. As an example, trapping of (*R*,*R*)-**228** with Andersen's sulfinate (S_S)-**97** would give sulfoxide *syn*-(*R*,*R*,S_S)-**225**. As the amount of *syn*-(*R*,*R*,S_S)-**225** increases, competitive sulfoxide → lithium exchange occurs mediated by (*R*,*R*)-**228** as shown in Scheme 3.43. This would give sulfoxide *anti*-(*R*,*R*,R_S)-**225**. An analogous process by sulfoxide *anti*-(*S*,*S*,S_S)-**225** and organolithium (*S*,*S*)-**228** would form sulfoxide *syn*-(*S*,*S*,R_S)-**225**. It is in this manner that the enantiomers of the expected major products, sulfoxides *syn*-(*R*,*R*,S_S)-**225** and *anti*-(*S*,*S*,S_S)-**225** are formed. Hence a loss of enantiomeric ratio in the products is observed. In addition, we suggest that organolithium reagents (*R*,*R*)-**228** and (*S*,*S*)-**228** are better leaving groups than lithiated *O*-alkyl carbamate, thus a greater loss of enantiomeric ratio is observed in this system.



Scheme 3.43

Fortunately, the enantioselectivity was improved by modifying the procedure in a similar fashion to that observed for the lithiation-trapping of *O*-alkyl carbamate **14** (Scheme 3.44, Table 3.5).



Scheme 3.44

Table 3.5: Optimisation of the racemic lithiation of *N*-Boc 4-choro piperidine **223** and trapping with Andersen's sulfinate (*S*S)-**97**.

Entry	Reverse Addition?	Length of Trap at −78 °C / min	*syn*-(*R*,*R*,*S*s)-225		*anti*-(*S*,*S*,*S*s)-225	
			Yield / %	er[a]	Yield / %	er[a]
1	No	16 h [b]	38	58:42	45	70:30
2	No	5	36	80:20	47	78:22
3	Yes	5	39	89:11	44	88:12
4[c]	Yes	5	41	90:10	43	91:9

[a]er determined by CSP-HPLC, [b]Warmed from −78 °C to rt, [c]3.0 eq. of Andersen's sulfinate (*S*S)-**97** used.

Indeed, we found that quenching the reaction after 5 minutes at −78 °C gave *syn*-(*R*,*R*,S_S)-**225** in 36% yield and 80:20 er and *anti*-(*S*,*S*,S_S)-**225** in 47% yield and 78:22 er (entry 2). This was a significant improvement compared to allowing the electrophilic trapping warm to room temperature overnight (entry 1). Next, a reverse addition protocol further improved the enantioselectivity to 89:11 er and 88:12 er for *syn*-(*R*,*R*,S_S)-**225** and *anti*-(*S*,*S*,S_S)-**225** respectively (entry 3). Increasing the amount of Andersen's sulfinate (S_S)-**97** to 3.0 eq. did not further improve the enantiomeric ratio of the products (entry 4).

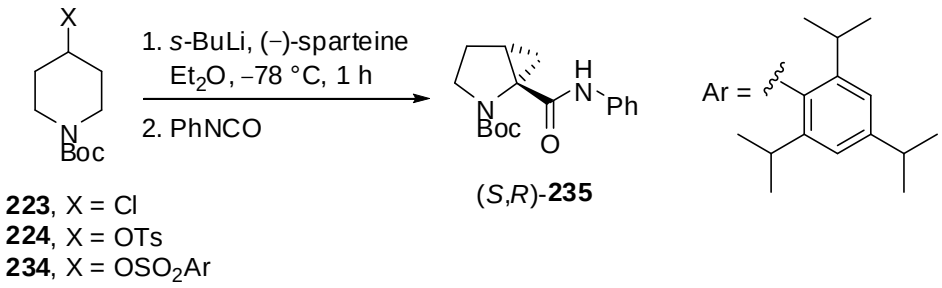
To conclude, we were able to improve the enantiomeric ratio in the lithiation of *N*-Boc 4-chloro piperidine **223** and trapping with Andersen's sulfinate (S_S)-**97** by using a reverse addition protocol. Unfortunately, a significant loss of enantiomeric ratio during the trapping process was still observed and therefore sulfoxides *syn*-(*R*,*R*,S_S)-**225** and *anti*-(*S*,*S*,S_S)-**225** were not isolated in ≥99:1 er.

3.4.3 *s*-BuLi/Chiral Diamine-Mediated Lithiation of *N*-Boc 4-Chloro Piperidine and Trapping with Andersen's Sulfinate

Previously, we successfully carried out a chiral amplification during the asymmetric lithiation of *O*-alkyl carbamate **14** and trapping with Andersen's sulfinate (S_S)-**97** (see Scheme 2.23). A similar strategy was envisaged for the synthesis of sulfoxides *syn*-(*R*,*R*,S_S)-**225** and *anti*-(*S*,*S*,S_S)-**225**. Therefore, our next step would be to introduce an asymmetric lithiation followed by trapping with Andersen's sulfinate (S_S)-**97** to give the *α*-amino sulfoxides in 99:1 er.

Since Beak and co-workers reported that the leaving group has a dramatic effect on the enantioselectivity of the lithiation-trapping procedure, we envisaged that using 4-sulfonyl derivatives would give products in good enantiomeric ratio. Consequently, we investigated the asymmetric lithiation of 4-substituted piperidines **223** (4-Cl), **224** (4-OTs) and **234** (4-OSO_2Ar, Ar = 2,4,6-triisopropylbenzene) with *s*-BuLi/(−)-sparteine (Et_2O, −78 °C, 1 hour) and subsequent electrophilic trapping with phenylisocyanate (Scheme 3.45, Table 3.6). Lithiation of *N*-Boc 4-chloro piperidine **223** with *s*-BuLi/(−)-sparteine and electrophilic trapping with phenylisocyanate gave amide (*S*,*R*)-**235** in 94% yield but low enantiomeric ratio (56:44 er) (entry 1). The low enantioselectivity was

unsurprising as Beak had previously shown that lithiation-trapping of *N*-Boc 4-chloro piperidine **223** gave racemic products.[172]



223, X = Cl
224, X = OTs
234, X = OSO_2Ar

(*S*,*R*)-**235**

Scheme 3.45

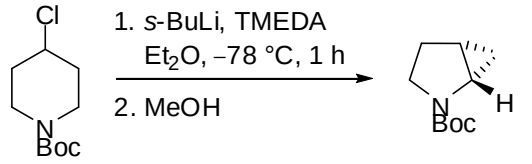
Table 3.6: Asymmetric lithiation of 4-subsituted piperidines **223**, **224** and **234** and trapping with phenyl isocyanate

Entry	Starting Material	Yield / %	er[a]
1	**223**	94	56:44
2	**224**	-[b]	-
3	**234**	84	58:42

[a]er determined by CSP-HPLC, [b]Starting tosylate **224** was recovered in 92% yield.

Then, we attempted the enantioselective lithiation-trapping of *N*-Boc 4-tosyloxy piperidine **224**. However, none of the expected amide (*S*,*R*)-**235** was isolated and starting tosylate **224** was recovered in 92% yield (entry 2). This result is consistent across a number of repeats, and we have been unable to successfully lithiate and trap *N*-Boc 4-tosyloxy piperidine **224**. Our result is clearly at odds with those reported by Beak (see Table 3.3, entry 2). It is possible that *N*-Boc 4-tosyloxy piperidine **224** undergoes *ortho*-lithiation but is not trapped by the electrophile and therefore reprotonated on work-up. As an alternative to *N*-Boc 4-tosyloxy piperidine **224**, *N*-Boc 4-sulfonyl piperidine **234** was lithiated with *s*-BuLi/(−)-sparteine. This substrate cannot undergo *ortho*-lithiation. Subsequent trapping with phenylisocyanate gave amide (*S*,*R*)-**235** in good yield (84%) but in only 58:42 er (entry 3). In contrast to Beak's observations, we did not see a significant improvement in enantioselectivity of the lithiation-trapping when changing the leaving group. Unfortunately, such low enantioselectivity for the lithiation-trapping would not provide significant benefits for our chiral amplification protocol.

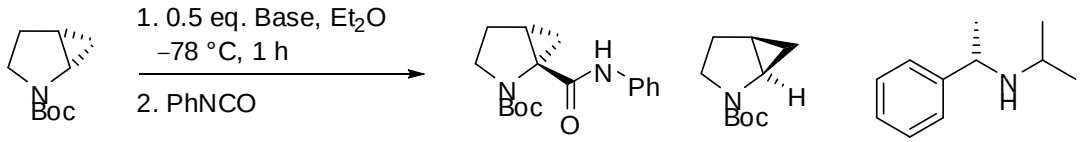
A higher enantioselectivity was required and so a new approach was considered. We postulated that a kinetic resolution of azabicycle **227** could be carried out to give amide (*S*,*R*)-**235** in high enantioselectivity. This would require one enantiomer of *rac*-**227** to be deprotonated faster than the other enantiomer when using 0.5 eq. of a chiral base. The required substrate was prepared by lithiation of *N*-Boc 4-chloro piperidine **223** with *s*-BuLi/TMEDA and quenching with methanol to furnish azabicycle *rac*-**227** in 87% yield (Scheme 3.46).



223 *rac*-**227,** 87%

Scheme 3.46

Kinetic resolution of azabicycle *rac*-**227** was then attempted by deprotonation with 0.5 eq. of a chiral base in Et_2O at −78 °C for 1 hour (Scheme 3.47, Table 3.7). Deprotonation with *s*-BuLi/(−)-sparteine and trapping with phenylisocyanate gave amide (*R*,*S*)-**235** in 36% yield and 56:44 er (entry 1). Azabicycle (*R*,*S*)-**227** was also isolated in 30% yield and was presumed to be in improved enantiomeric ratio but this has not been determined



rac-**227** (*S*,*R*)-**235** (*R*,*S*)-**227** (*S*)-**236**

Scheme 3.47

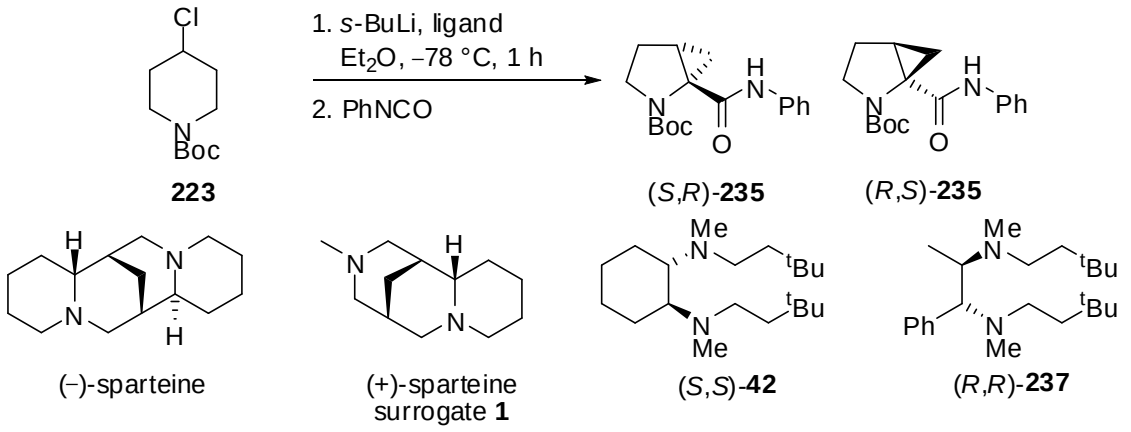
Table 3.7: Kinetic resolution of *rac*-**227**

Entry	**Base**	**(*S*,*R*)-235**		**(*R*,*S*)-227**	
		Yield / %	**er**[a]	**Yield / %**	**er**[a]
1	*s*-BuLi/(−)-sparteine	36	56:44	30	nd
2	*n*-BuLi/(−)-sparteine	44	56:44	52	nd
3	*n*-BuLi/(*S*)-**236**[b]	-	-	91	nd

[a]er determined by CSP-HPLC, nd – not determined, [b]reaction carried out in THF

We hypothesised that due to the acidity of the cyclopropyl proton in *rac*-**227**, *s*-BuLi/(−)-sparteine was such a strong base that both enantiomers of azabicycle *rac*-**227** react at a similar rate under the reaction conditions leading to a trapped product with low enantiomeric ratio. By using the less basic *n*-BuLi/(−)-sparteine we hoped that we would see an improvement in enantioselectivity during the kinetic resolution. Unfortunately, amide (*S*,*R*)-**235** was isolated in 44% yield and only 56:44 er from this reaction (entry 2). The pK_a of the base was further reduced by using *n*-BuLi/(*S*)-**227** in THF, which is reported to act as a chiral LDA equivalent.[181] However, treatment of azabicycle *rac*-**227** with *n*-BuLi/(*S*)-**236** did not lead to the formation of the desired amide (*S*,*R*)-**235** and the starting material was recovered in 91% yield (entry 3). The high recovery of *rac*-**227** suggests that the lithium amide base was not strong enough deprotonate the cyclopropyl proton.

Undeterred, we hoped that changing the ligand used in the asymmetric lithiation of *N*-Boc 4-chloro piperidine **223** would have a positive influence on the enantioselectivity of the reaction (Scheme 3.48, Table 3.8). Lithiation of *N*-Boc 4-chloro piperidine **223** by *s*-BuLi/(+)-sparteine surrogate **1** and trapping with phenylisocyanate gave amide (*R*,*S*)-**235** in good yield (79%) but low enantiomeric ratio (54:46 er) (entry 2). When the deprotonation was mediated by *s*-BuLi/(*S*,*S*)-**42**, amide (*R*,*S*)-**235** was isolated in 74% yield and an improved 67:33 er (entry 3). Finally, lithiation of *N*-Boc 4-chloro piperidine **223** using (*R*,*R*)-**237**[182] as a ligand and trapping with phenylisocyanate gave amide (*S*,*R*)-**235** in 81% yield and 62:38 er (entry 4).



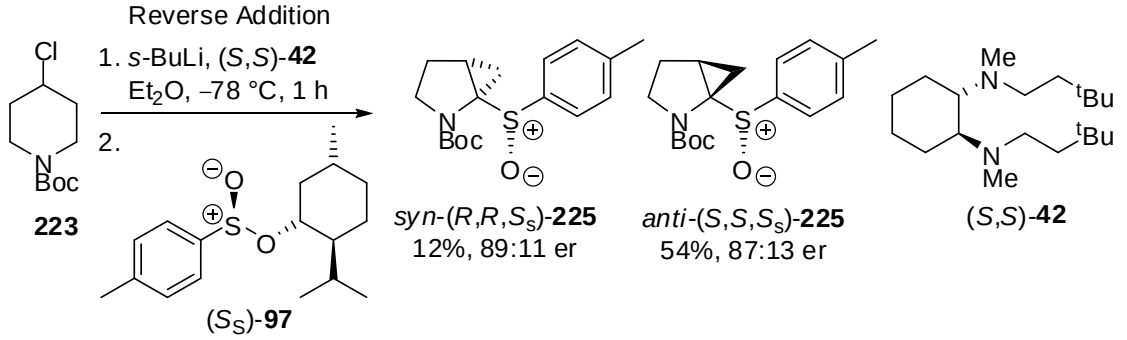
Scheme 3.48

Table 3.8: Asymmetric lithiation of *N*-Boc 4-chloro piperidine **223** using *s*-BuLi/chiral ligands and trapping with phenyl isocyanate

Entry	Ligand	Yield / %	er (*S*,*R*):(*R*,*S*)[a]
1	(−)-sparteine	94	56:44
2	(+)-sparteine surrogate **1**	79	46:54
3	(*S*,*S*)-**42**	74	33:67
4	(*R*,*R*)-**237**	81	62:38

[a]er determined by CSP-HPLC

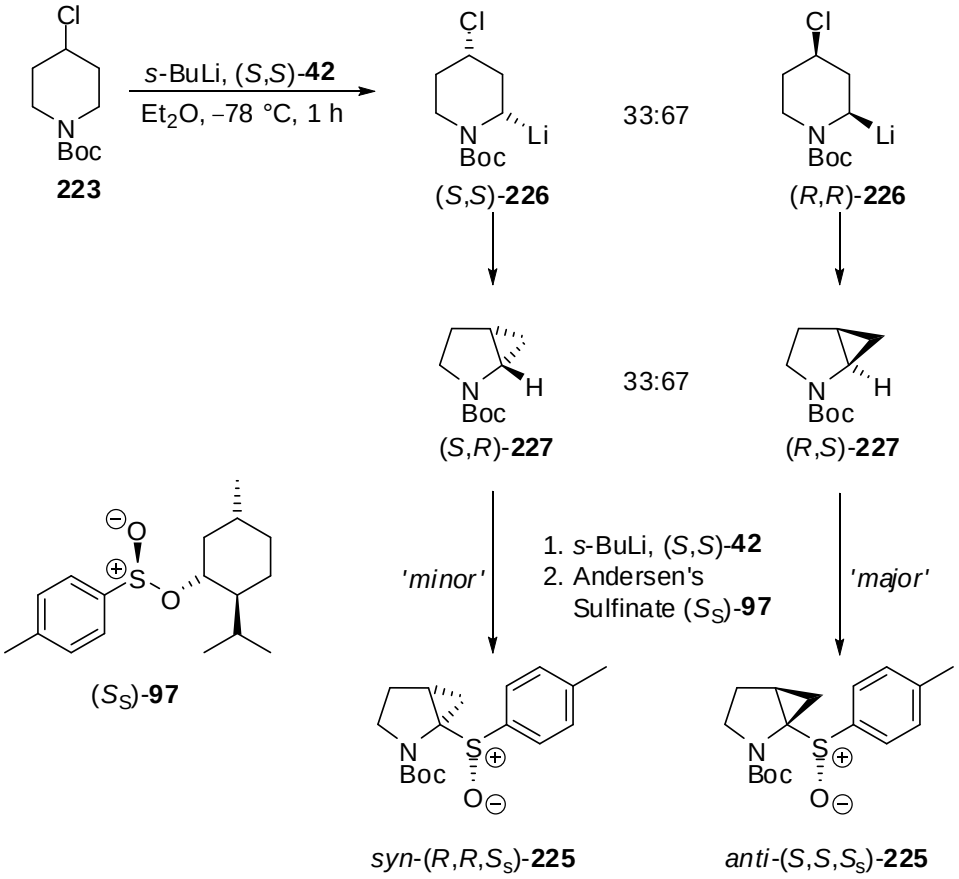
The lithiation of *N*-Boc 4-chloro piperidine **223** with *s*-BuLi/(*S*,*S*)-**42** gave the highest enantioselectivity that we have been able to achieve (67:33 er). However, we were uncertain if this would be significant enough in the chiral amplification protocol to give *α*-amino sulfoxides in ≥99:1 er. To investigate this, we repeated the lithiation under the same conditions and trapped with Andersen's sulfinate (S_S)-**97** using the reverse addition procedure (Scheme 3.49). From the reaction, sulfoxide *syn*-(*R*,*R*,S_s)-**225** was isolated in 12% yield and 89:11 er and sulfoxide *anti*-(*S*,*S*,R_s)-**225** was isolated in 54% yield and 87:13 er. Disappointingly, neither diastereoisomer was isolated in 99:1 er.



Scheme 3.49

The enantioselective lithiation and trapping with Andersen's sulfinate (S_S)-**97** allows assignment of the absolute configuration of the diastereomeric sulfoxides. Lithiation of *N*-Boc 4-chloro piperidine **223** with *s*-BuLi/(*S*,*S*)-**42** is believed to give organolithium reagents (*S*,*S*)-**226** and (*R*,*R*)-**226** in 67:33 er which immediately cyclises to give (*R*,*S*)-**227** and (*S*,*R*)-**227** in 67:33 er (Scheme 3.50). Lithiation of piperidines by *s*-BuLi/(*S*,*S*)-**42** has been shown to occur with opposite enantioselectivity to *s*-BuLi/(−)-sparteine.[42] Therefore we are able to compare our result with that reported in the literature for the

lithiation of *N*-Boc 4-tosyloxy piperidine **224** by *s*-BuLi/(−)-sparteine to confirm the stereochemistry of (*R*,*S*)-**227** and (*S*,*R*)-**227**.[41,172] Subsequent lithiation of (*R*,*S*)-**227** and trapping with inversion[113] of Andersen's sulfinate (S_S)-**97** would give sulfoxide *anti*-(*S*,*S*,S_s)-**225** as the major diastereoisomer.

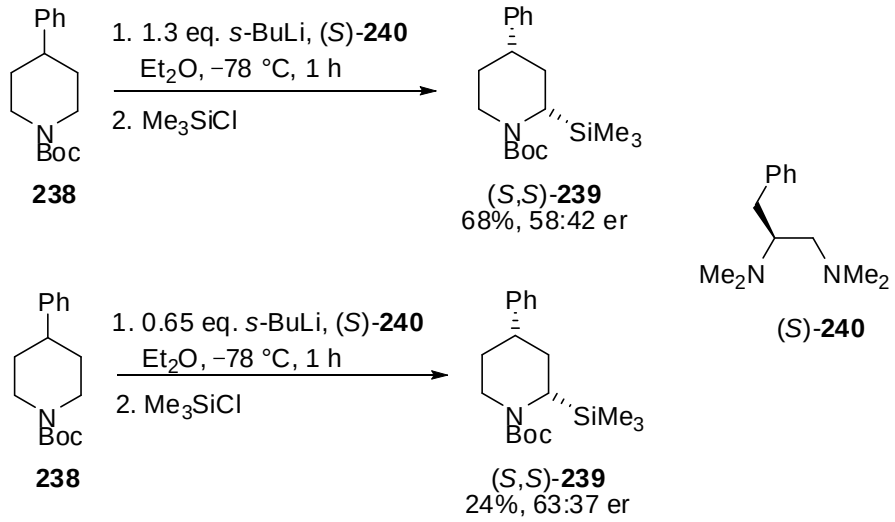


Scheme 3.50

We believed there were two possible reasons for our inability to synthesise the major diastereomeric sulfoxide *anti*-(*S*,*S*,S_s)-**225** in 99:1 er. First, we thought that the poor enantioselectivity of the initial lithiation reaction was causing a reduction in enantiomeric ratio of the trapped products. Second, there may be a match-mismatch effect caused by the chiral lithiated intermediate reacting with a chiral electrophile.

Our initial efforts focused upon improving the enantioselectivity of the lithiation-cyclisation of *N*-Boc 4-chloro piperidine **223**. In 2007, the groups of Coldham and O'Brien reported that the enantioselectivity of lithiation of *N*-Boc 4-phenyl piperidine **238** was improved when using 0.65 eq. of *s*-BuLi.[42] It was suggested that *N*-Boc 4-phenyl piperidine **238** exists as two rotameric species in solution at −78 °C and ring-

flipping is not thought to occur at this temperature due to the substituent at C4. Furthermore, it is well established in the literature that during the lithiation of *N*-Boc heterocycles only the equatorial proton is removed.[41,148] Therefore, when effecting a deprotonation using *s*-BuLi and chiral diamines we see a '*matched*' rotamer and a '*mismatched*' rotamer. An example of this is shown in Scheme 3.51. Deprotonation of *N*-Boc 4-phenyl piperidine **238** with 1.3 eq. of *s*-BuLi/diamine (*S*)-**240** gave silyl piperidine (*S*,*S*)-**239** in 68% yield and 58:42 er. An improvement in enantioselectivity was observed when using 0.65 eq. of *s*-BuLi/diamine (*S*)-**240** with silyl piperidine (*S*,*S*)-**239** being isolated in 24% yield and 63:37 er. Although the increase in enantiomeric ratio is not large, it provides evidence that there is no rotation of the *N*-Boc group at −78 °C.

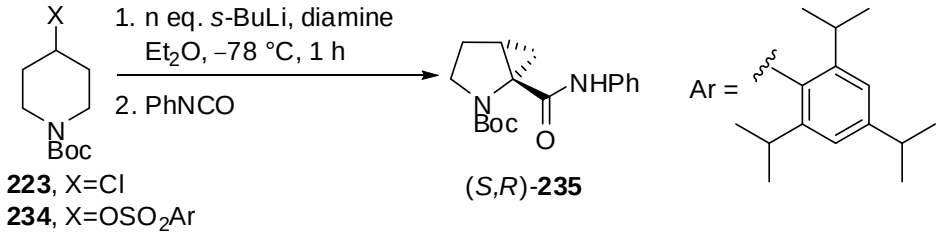


Scheme 3.51

We hoped that a similar type of kinetic resolution could be carried out for the deprotonation of *N*-Boc 4-chloro and 4-sulfonyl piperidines **223** and **234**. Therefore, piperidines **223** and **234** were treated with 1.1 eq. of *s*-BuLi/chiral diamine at −78 °C and trapped with phenylisocyanate (Scheme 3.52). One equivalent of *s*-BuLi will deprotonate the piperidine and the second will deprotonate the intermediate cyclopropyl proton. The results for lithiation with 2.2 eq. and 1.1 eq. *s*-BuLi/chiral diamine are summarised in Table 3.9.

Overall, no improvement in enantiomeric ratio was observed when reducing the amount of *s*-BuLi/chiral diamine to 1.1 eq. when compared with results obtained with 2.2 eq. of *s*-BuLi/chiral diamine. This is highlighted with the lithiation of *N*-Boc 4-chloro

piperidine **223** with *s*-BuLi/(−)-sparteine and trapping with phenylisocyanate which gave amide (*S*,*R*)-**235** in 45% yield and 56:44 er (entry 1). This is the same enantiomeric ratio as the product isolated previously (entry 2). A similar result was observed with *N*-Boc 4-sulfonyl piperidine **234** (entries 3 and 4).



223, X=Cl
234, X=OSO_2Ar

(*S*,*R*)-**235**

Scheme 3.52

Table 3.9: Kinetic resolution of 4-substituted piperidines **223** and **234**

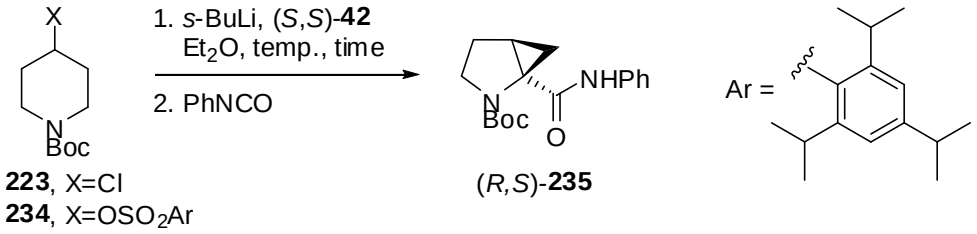
Entry	n	Starting Material	Diamine	Yield / %	er (*S*,*R*):(*R*,*S*)[a]
1	1.1	**223**	(−)-sparteine	45	56:44
2	2.2	**223**	(−)-sparteine	93	56:44
3	1.1	**234**	(−)-sparteine	42	58:42
4	2.2	**234**	(−)-sparteine	84	58:42
5	1.1	**223**	(*S*,*S*)-**42**	43	43:57
6	2.2	**223**	(*S*,*S*)-**42**	74	33:67

[a]er determined by CSP-HPLC

When effecting the kinetic resolution of *N*-Boc 4-chloro piperidine **223** using *s*-BuLi/(*S*,*S*)-**42**, amide (*R*,*S*)-**235** was isolated in 43% yield and 57:43 er (entry 5). The reduction in enantiomeric ratio when compared to the standard reaction (67:33 er, entry 6) is likely to be due to the capricious nature of the lithiation reaction.

Later, it was postulated that by increasing the temperature of the lithiation step the rotamers may be able to freely interconvert around the N-CO bond. This could allow the matched rotamer to be lithiated in both high yield and higher enantiomeric ratio than the 67:33 er which is exhibited at −78 °C. Therefore, 4-substituted piperidines **223** and **234** were deprotonated with *s*-BuLi/(*S*,*S*)-**42** at −40 and −30 °C (Scheme 3.53 and Table 3.10). First, *N*-Boc 4-chloro piperidine **223** was lithiated with *s*-BuLi/(*S*,*S*)-**42** at −30 °C for 5 minutes and trapping with phenylisocyanate to give amide (*R*,*S*)-**235** in 52:48

er (entry 2). Disappointingly, there was a reduction in enantiomeric ratio when compared to the product of the lithiation-trapping at −78 °C (67:33 er, entry 1).



223, X=Cl
234, X=OSO_2Ar

(*R,S*)-**235**

Scheme 3.53

Table 3.10: Investigating the temperature effect on the lithiation-cyclisation of 4-subsituted piperidine **223** and **234**

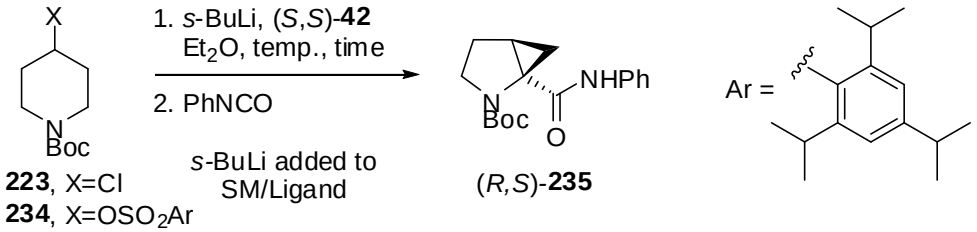
Entry	Starting Material	Temp. / °C	Time / min	Yield / %	er[a]
1	**223**	−78	60	74	67:33
2	**223**	−30	5	74	52:48
3	**223**	−40	60	69	67:33
4	**234**	−40	60	73	58:42

[a]er determined by CSP-HPLC

By lowering the temperature of lithiation to −40 °C, amide (*R,S*)-**235** was isolated in 69% yield and 67:33 er (entry 3). However, this is not an improvement upon the enantiomeric ratio observed at −78 °C. Finally, lithiation of *N*-Boc 4-sulfonyl piperidine **234** at −40 °C and trapping with phenylisocyanate gave amide (*R,S*)-**235** in 73% yield and 58:42 er (entry 4). From these results we could conclude that changing the temperature does not have a significant effect on the enantioselectivity of the reaction.

In an attempt to improve the control of the reaction conditions, we added *s*-BuLi to **223** and **234** *via* syringe pump over 30 minutes (Scheme 3.54, Table 3.11). Unfortunately, no improvement in enantiomeric ratio was seen. Lithiation of *N*-Boc 4 chloro piperidine **223** with *s*-BuLi/(*S,S*)-**42** at −78 °C gave amide (*R,S*)-**235** in 53% yield and 59:41 er (entry 1). However at −40 °C, amide (*R,S*)-**235** was isolated in 69% yield and 67:33 er (entry 2). Whilst the enantiomeric ratio was better at −40 °C, it is still

comparable to that which can be obtained through the standard lithiation-trapping procedure.



223, X=Cl
234, X=OSO_2Ar

(*R,S*)-**235**

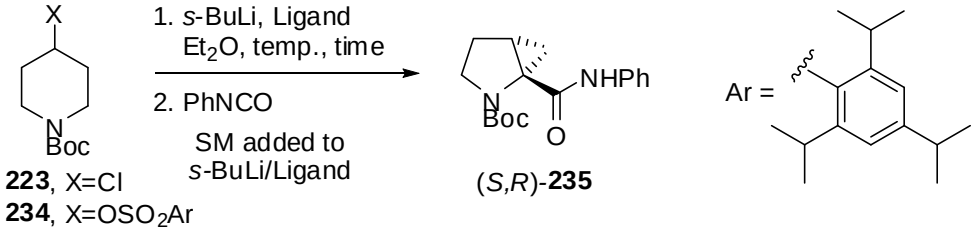
Scheme 3.54

Table 3.11: Lithiation of 4-substituted piperidines **223** and **234** with slow addition of *s*-BuLi and trapping with phenyl isocyanate

Entry	Starting Material	Temp. / °C	Yield / %	er[a]
1	**223**	−78	53	59:41
2	**223**	−40	69	67:33
3	**234**	−78	76	57:43
4	**234**	−40	98	58:42

[a]er determined by CSP-HPLC

In a similar fashion, we added a solution of 4-substitued piperidines **223** and **234** *via* syringe pump over 30 minutes to a stirred solution of *s*-BuLi/chiral diamines (Scheme 3.55 and Table 3.12). No improvement in enantiomeric ratio was observed at −78 °C or −40 °C. Indeed, when (*S,S*)-**42** was used as a ligand, amide (*R,S*)-**235** was isolated in 62:38 er at −78 °C (entry 1) and 60:40 er at −40 °C (entry 2). Furthermore, changing the ligand to (−)-sparteine led to amide (*S,R*)-**235** being isolated in 54:46 er at −78 °C (entry 3) and 58:42 er at −40 °C (entry 4).



223, X=Cl
234, X=OSO_2Ar

(*S,R*)-**235**

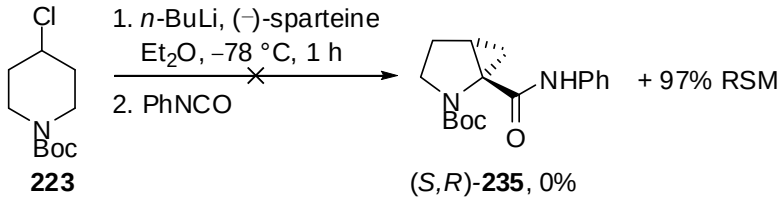
Scheme 3.55

Table 3.12: Lithiation-of 4-substituted piperidines **223** and **234** with slow addition of starting material and trapping with phenyl isocyanate

Entry	Starting Material	Ligand	Temp. / °C	Yield / %	er (*S*,*R*):(*R*,*S*)[a]
1	**223**	(*S*,*S*)-**42**	−78	70	38:62
2	**223**	(*S*,*S*)-**42**	−40	71	40:60
3	**223**	(−)-sparteine	−78	68	54:46
4	**223**	(−)-sparteine	−40	73	58:42
5	**234**	(−)-sparteine	−78	99	56:44

[a]er determined by CSP-HPLC

Due to the apparently facile lithiation of *N*-Boc 4-chloro piperidine **223** using *s*-BuLi/(−)-sparteine, we postulated that the deprotonation may be effected with *n*-BuLi. Thus, *N*-Boc 4-chloro piperidine **223** was treated with 2.2 eq. *n*-BuLi/(−)-sparteine followed by addition of phenylisocyanate (Scheme 3.56). Unfortunately, amide (*S*,*R*)-**235** was not evident in the ^{1}H NMR spectrum of the crude product and *N*-Boc 4-chloro piperidine **223** was recovered in 97% yield.

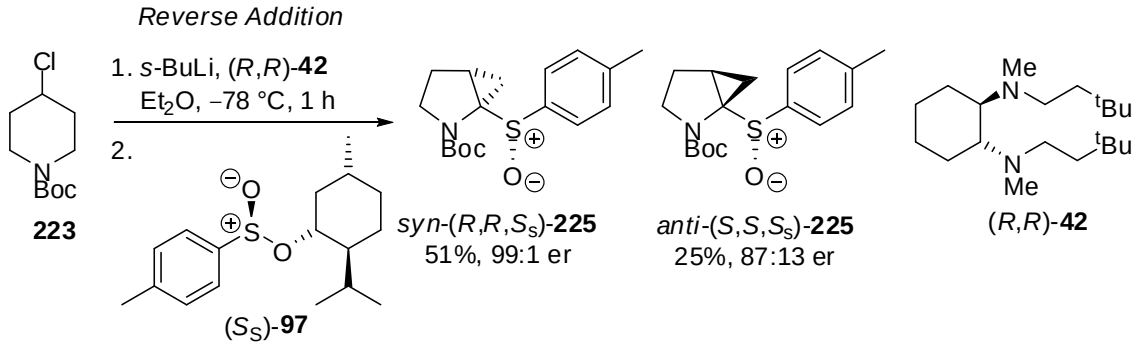


Scheme 3.56

To summarise, it was not possible to improve the enantioselectivity in the lithiation-trapping of *N*-Boc 4-chloro piperidine **223** and *N*-Boc 4-sulfonyl piperidine **234**. We have also been unable to reproduce Beak's result with *s*-BuLi/(−)-sparteine and *N*-Boc 4-tosyloxy piperidine **224**. The best enantiomeric ratio achieved so far has been for the lithiation of *N*-Boc 4-chloro piperidine **223** mediated by *s*-BuLi/(*S*,*S*)-**42** and trapping with phenyl isocyanate (67:33 er).

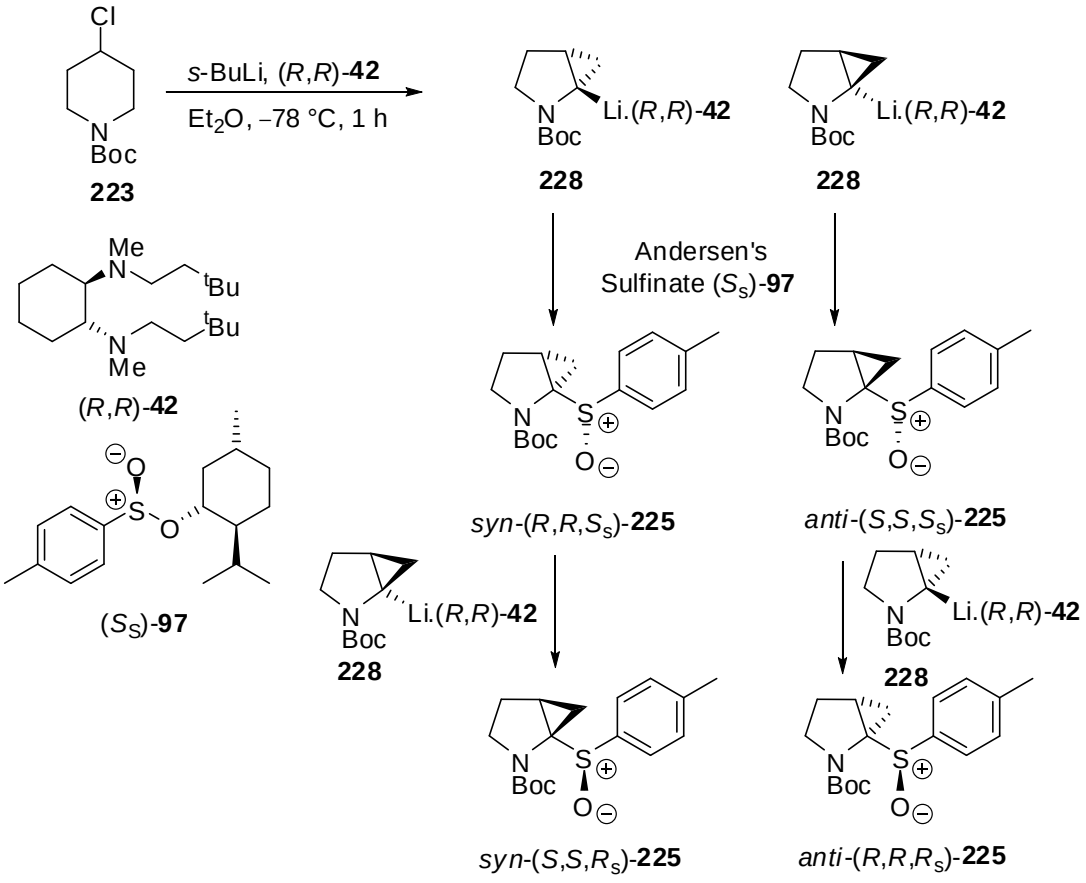
Next, we wanted to investigate any match/mismatch effect between the chiral lithiated intermediates and Andersen's sulfinate (S_S)-**97**. The lithiation of *N*-Boc 4-chloro

piperidine **223** using *s*-BuLi/(*S*,*S*)-**42** and trapping with Andersen's sulfinate (S_S)-**97** had previously given disappointing enantioselectivity: sulfoxides *syn*-(*R*,*R*,S_s)-**225** and *anti*-(*S*,*S*,R_s)-**225** were isolated in 89:11 er and 87:13 er respectively (see Scheme 3.49). Therefore, we wanted to carry out the "diastereomeric reaction" mediated by *s*-BuLi/(*R*,*R*)-**42** and trapping with the same enantiomer of Andersen's sulfinate (S_S)-**97**. To our delight, we were able to isolate sulfoxide *syn*-(*R*,*R*,S_s)-**225** in 51% yield and 99:1 er together with *anti*-(*S*,*S*,R_s)-**225** in 25% yield and 87:13 er (Scheme 3.57).



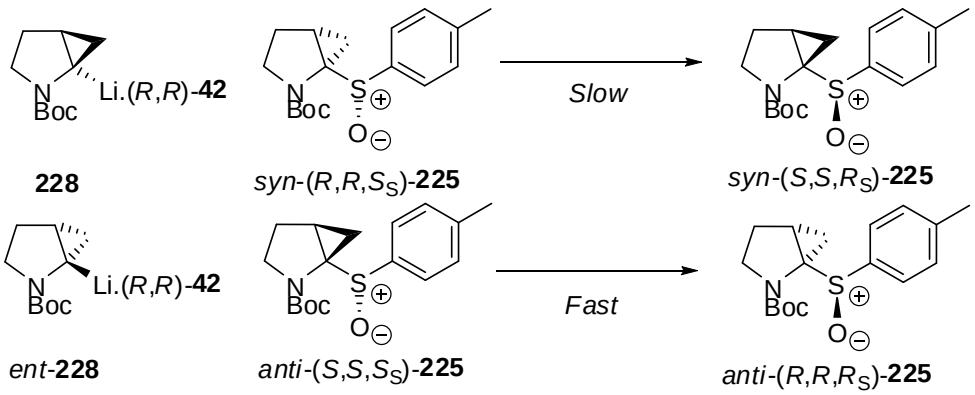
Scheme 3.57

To understand this match/mismatch effect, the mechanism which accounts for the reduction of enantiomeric ratio of the products needs to be considered. As we have previously shown for *O*-alkyl carbamate **14** (see Scheme 2.17), a reduction in enantiomeric ratio is caused by attack of the lithiated intermediate on the forming sulfoxide products causing a second inversion at sulfur to take place. Based on the inherent enantioselectivity of this reaction (67:33 er determined by lithiation-trapping with phenylisocyanate, see Scheme 3.48), lithiation-cyclisation of *N*-Boc 4-chloro piperidine **223** mediated by *s*-BuLi/(*R*,*R*)-**42** will give diastereomeric lithiated intermediates **228** in a 67:33 ratio (Scheme 3.58). The lithiated intermediates are then trapped by Andersen's sulfinate (S_S)-**97** with inversion at sulfur to give sulfoxides *syn*-(*R*,*R*,S_S)-**225** and *anti*-(*S*,*S*,R_S)-**225**. Due to the electrophilicity of these products, the lithiated intermediates **228** and **228** can attack the sulfoxide moiety, with inversion at sulfur, to give enantiomeric sulfoxides *syn*-(*S*,*S*,R_S)-**225** and *anti*-(*R*,*R*,S_S)-**225**.



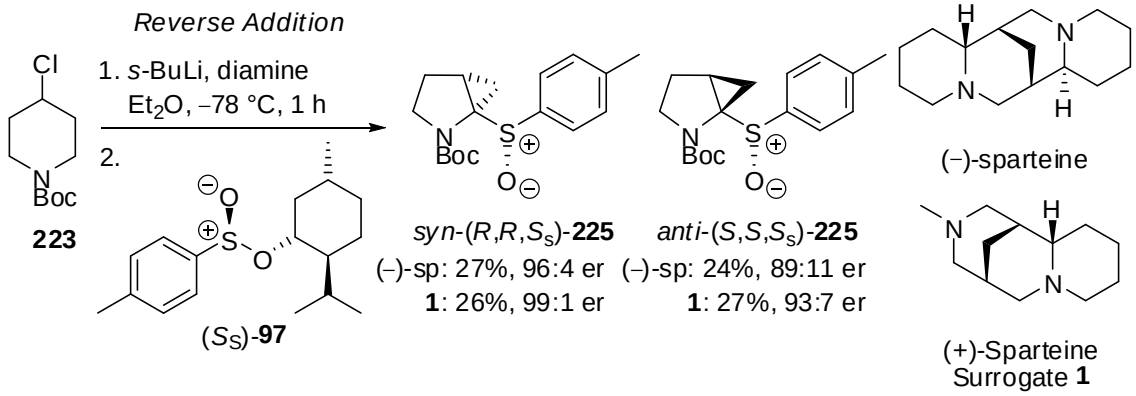
Scheme 3.58

When the enantiomeric ligand (*S*,*S*)-**42** is used for the lithiation-trapping process, a "diastereomeric reaction" occurs. For example, consider the minor lithiated species in the reaction with the major sulfoxide product formed in each case (Scheme 3.59). For the lithiation mediated by *s*-BuLi/(*R*,*R*)-**42**, lithiated intermediate **228** reacts with sulfoxide *syn*-(*R*,*R*,S_S)-**225** slowly to give sulfoxide *syn*-(*S*,*S*,R_S)-**225**. When the lithiation is mediated by (*S*,*S*)-**42** the minor lithiated intermediate is now *ent*-**228** which quickly reacts with sulfoxide *anti*-(*S*,*S*,S_S)-**225** to give *anti*-(*R*,*R*,R_S)-**225**. The key difference is that the major sulfoxides formed in each reaction have the same configuration at sulfur, but the lithiated intermediates are enantiomeric. This gives rise to diastereomeric transition states which result in differing rates of reaction. Experimental evidence would suggest that the reaction of *ent*-**228** with sulfoxide *anti*-(*S*,*S*,S_S)-**225** is a more facile process. Thus, a greater loss of stereospecificity in the trapping reaction is observed.



Scheme 3.59

Finally, the lithiation was conducted using (−)-sparteine and (+)-sparteine surrogate **1** and then trapped with Andersen's sulfinate (*S*S)-**97** (Scheme 3.60). From the reaction mediated by (−)-sparteine, sulfoxide *syn*-(*R*,*R*,*S*S)-**225** was isolated in 27% yield and 96:4 er and sulfoxide *anti*-(*S*,*S*,*S*S)-**225** was isolated in 24% yield and 89:11 er. Use of (+)-sparteine surrogate **1** gave sulfoxide *syn*-(*R*,*R*,*S*S)-**225** in 26% yield and 99:1 er and sulfoxide *anti*-(*S*,*S*,*S*S)-**225** in 27% yield and 93:7 er. To our surprise the predicted minor diastereoisomer from this reaction gave the higher enantiomeric ratio. However, we propose that this is because of a 'matched' effect similar to that observed with diamine (*R*,*R*)-**42**. The poor diastereoselectivity in both of these reactions is due to the poor enantioselectivity of the initial lithiation-cyclisation reaction (*ca.* 56:44 er, see Scheme 3.49).



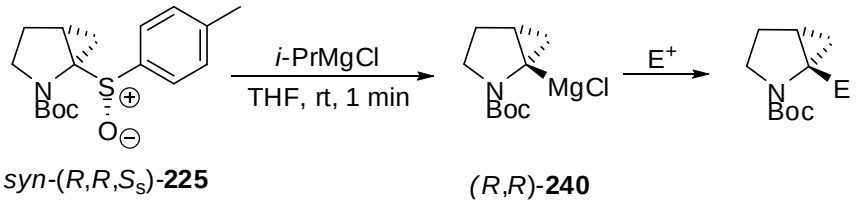
Scheme 3.60

To conclude, we have been able to synthesise *syn*-(*R*,*R*,*S*S)-**225** in 99:1 er by the lithiation-trapping of *N*-Boc 4-chloro piperidine **223** with Andersen's sulfinate (*S*S)-**225**. Despite the low enantioselectivity (67:33 er) of the initial lithiation-cyclisation, we were

able to utilise a matched effect between diamine (*R*,*R*)-**42** and Andersen's sulfinate to increase the stereochemical fidelity within the reaction. Unfortunately, diastereomeric sulfoxide *anti*-(*S*,*S*,S_S)-**225** could not be synthesised in 99:1 er. This was due to a mismatch effect between diamine (*S*,*S*)-**42** and Andersen's sulfinate (S_S)-**97** which caused an erosion in enantiomeric ratio at sulfur within the trapping reaction. Sulfoxide *syn*-(*S*,*S*,R_S)-**225** could be synthesised in 99:1 er by lithiation of *N*-Boc 4-chloro piperidine **223** mediated by *s*-BuLi/(*S*,*S*)-**42** and trapping with *ent*-Andersen's sulfinate (R_S)-**97**. Enantiomeric sulfoxides *syn*-(*R*,*R*,S_S)-**225** and *syn*-(*S*,*S*,R_S)-**225** would then allow access to *α*-amino Grignard reagents in both enantiomeric series *via* sulfoxide → magnesium exchange. Significantly, we do not need to use (−)-sparteine to generate *N*-Boc amino sulfoxide *syn*-(*R*,*R*,S_S)-**225** in 99:1 er.

3.5 Sulfoxide → Magnesium Exchange

Our next goal was to synthesise *α*-amino Grignard reagent (*R*,*R*)-**240** in 99:1 er from sulfoxide *syn*-(*R*,*R*,S_S)-**225**. It was hoped that sulfoxide → magnesium exchange would prove to be an efficient method of accessing a range of 2-subsitited products as single enantiomers (Scheme 3.61).

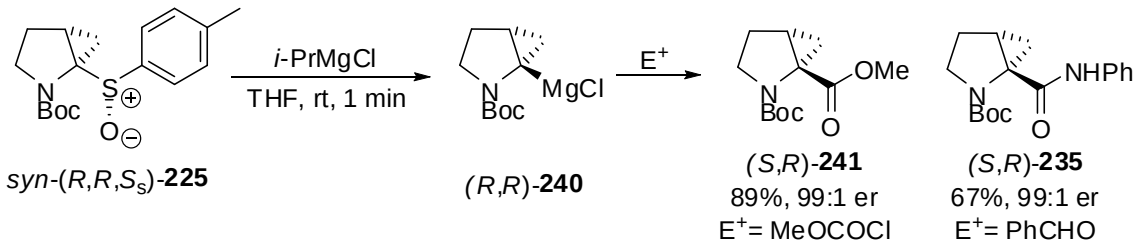


syn-(*R*,*R*,S_S)-**225** (*R*,*R*)-**240**

Scheme 3.61

3.5.1 Sulfoxide → Magnesium Exchange Reactions

We began our investigation by using sulfoxide → magnesium exchange conditions previously optimised for *α*-alkoxy sulfoxides *anti*-(*S*,S_s)-**103** and *syn*-(*R*,S_s)-**103** (*i*-PrMgCl, THF, rt, 1 min, see Scheme 2.26, Table 2.3). Thus, sulfoxide *syn*-(*R*,*R*,S_S)-**225** was treated with *i*-PrMgCl to form Grignard reagent (*R*,*R*)-**240** and then electrophiles were added (Scheme 3.62). Trapping with methyl chloroformate gave ester (*S*,*R*)-**241** in 89% yield and 99:1 er and trapping with phenylisocyanate gave amide (*S*,*R*)-**235** in 67% yield and 99:1 er. All racemic compounds were prepared from *syn-rac*-**225** and separated by CSP-HPLC



syn-(*R*,*R*,S_S)-**225**

(*R*,*R*)-**240**

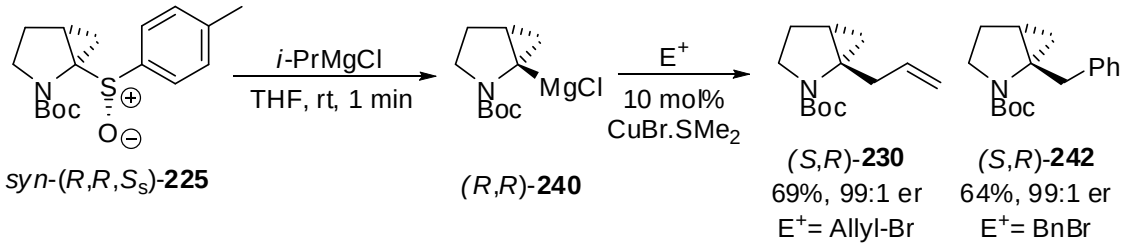
(*S*,*R*)-**241**
89%, 99:1 er
E^+= MeOCOCl

(*S*,*R*)-**235**
67%, 99:1 er
E^+= PhCHO

Scheme 3.62

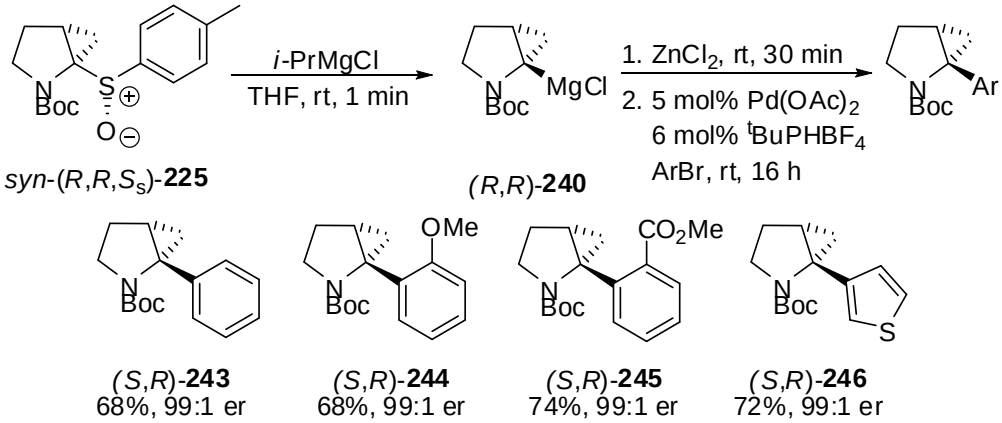
We also trapped Grignard reagent (*R*,*R*)-**240** with allyl bromide and benzyl bromide (Scheme 3.63). Use of catalytic CuBr.SMe_2 in both cases gave access to alkene (*S*,*R*)-

230 and (*R*,*R*)-**242** respectively, with both being isolated in good yields and 99:1 er. If CuBr.SMe_2 is absent from the trapping procedure then lower yields are observed.



Scheme 3.63

Grignard reagent (*R*,*R*)-**240**, formed by sulfoxide → magnesium exchange from *syn*-(*R*,*R*,S_S)-**225**, was also coupled to aryl bromides (Scheme 3.64). This process proceeds *via* transmetallation to zinc and palladium-mediated Negishi coupling in similar fashion to that developed for *α*-lithiated *N*-Boc pyrrolidine by Campos and co-workers.[39,40] In this way, a series of arylated heterocycles (*S*,*R*)-**243**-**246** were generated in good yields and 99:1 er. During the course of this thesis, Bull *et al*. reported a similar transmetallation-Negishi reaction of Grignard reagents formed by sulfoxide → magnesium exchange (see Scheme 1.46).[98]

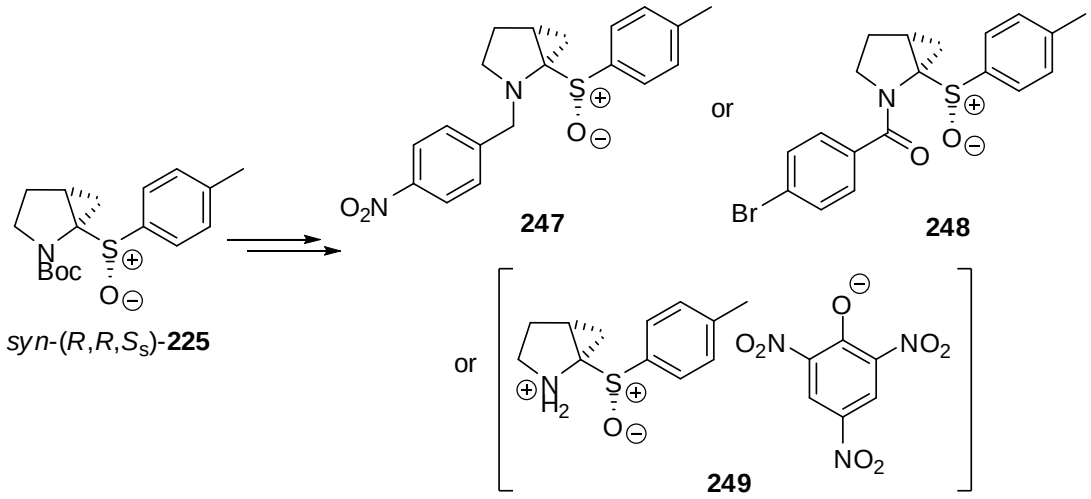


Scheme 3.64

3.5.2 Proof of Stereochemistry and Formal Synthesis of Saxagliptin

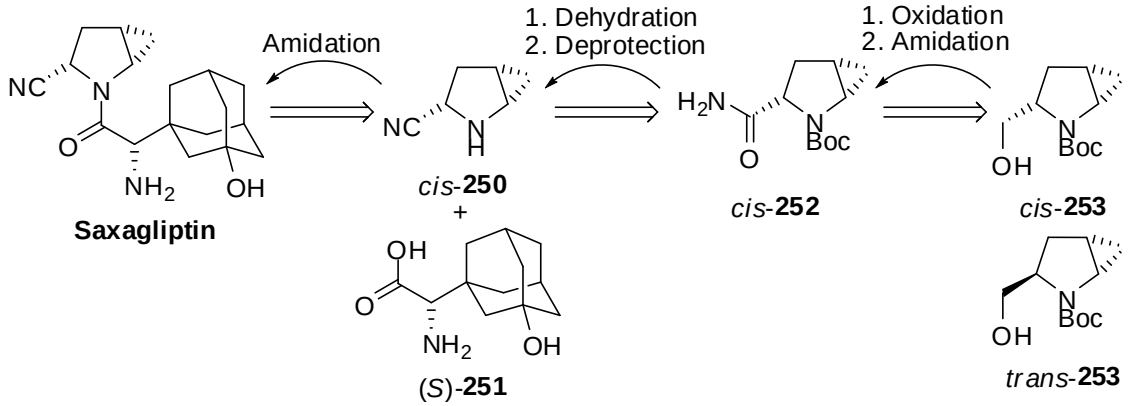
We wanted to prove the absolute stereochemistry of sulfoxide *syn*-(*R*,*R*,S_S)-**225**. A number of attempts to grow crystals of sulfoxides *syn*-(*R*,*R*,S_S)-**225** and *anti*-(*S*,S_S)-**225** for X-ray diffraction proved unsuccessful. In addition, endeavours were made to synthesise a number of derivatives of *syn*-(*R*,*R*,S_S)-**225** (Scheme 3.65). Unfortunately,

the syntheses of nitrobenzylamine **247** and *p*-bromobenzamide **248** were unsuccessful and all attempts to grow crystals of picrate salt **249** were fruitless.



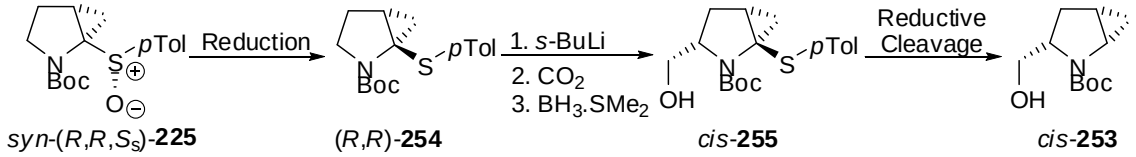
Scheme 3.65

Therefore, we planned to convert sulfoxide *syn*-(*R*,*R*,S_S)-**225** into known alcohol *cis*-**253**.[183] Alcohols *cis*-**253** and *trans*-**253** are reported in the literature although no characterisation data is available. However, Professor Hanessian kindly supplied full data for each compound for comparison.[184] In addition, synthesis of alcohol *cis*-**253** would also constitute a formal synthesis of the oral hypoglycaemic drug, saxagliptin.[176,177,185] Saxagliptin was first developed by Bristol-Myers-Squibb in 2004 and later brought to market in collaboration with AstraZeneca under the brand name Onglyza in 2009. The reported synthesis of saxagliptin concludes with a late-stage amide coupling of commerically available amino acid (*S*)-**251** to amine *cis*-**250**.[177] Amine *cis*-**250** was synthesised from *N*-Boc amide *cis*-**252** *via* amide dehydration and Boc deprotection.[176] Finally, amide *cis*-**252** can be synthesised in two steps from alcohol *cis*-**253** (Scheme 3.66).



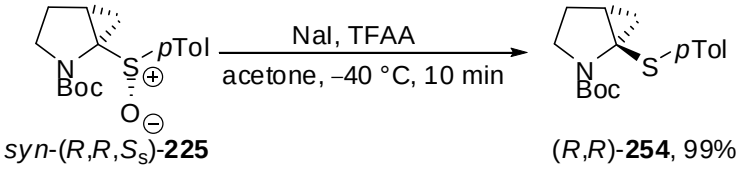
Scheme 3.66

Our planned synthesis of alcohol *cis*-**253** is shown in Scheme 3.67. It was envisaged that the synthesis would begin by reduction of sulfoxide *syn*-(*R*,*R*,S_S)-**225** to give sulfide (*R*,*R*)-**254**. The next step would be a diastereoselective lithiation-trapping with carbon dioxide. It was hoped that the sulfide moiety would provide suitable protection of the acidic cyclopropyl position. Moreover, if the substrate-controlled lithiation did not give a *cis*-selective lithiation, a chiral ligand could be used to direct the lithiation to the desired product.[29] Then, reduction of the carboxylic acid would give alcohol *cis*-**255** and reductive cleavage of the sulfide would complete the synthesis of alcohol *cis*-**253**.



Scheme 3.67

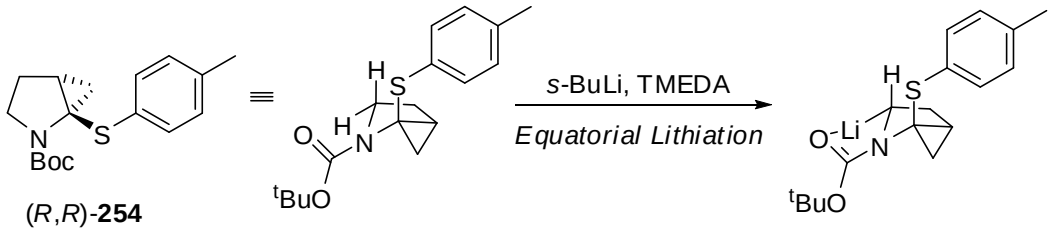
First, we attempted the reduction of sulfoxide *syn*-(*R*,*R*,S_S)-**225**. A number of conditions were explored but they returned quantitative amounts of unreacted starting material ($RhCl(PPh_3)_3$/catechol borane,[186] or sodium borohydride/iodine[187]) or a complex mixture of unidentified products ($BF_3.Et_2O$/sodium iodide[188] or triflic anhydride/potassium iodide[189]). To our delight, reduction of sulfoxide *syn*-(*R*,*R*,S_S)-**225** using trifluoroacetic anhydride/sodium iodide (acetone, −40 °C, 10 minutes[190,191]) gave sulfide (*R*,*R*)-**254** in 99% yield (Scheme 3.68).



Scheme 3.68

Next, we investigated the diastereoselective lithiation-trapping reaction. Beak and co-workers have reported that *α*-lithiation of 2-substituted piperidines occurred in the 6-position with almost exclusively *trans*-diastereoselectivity.[148,192] This is due to the 2-substituent preferably occupying an axial position in order to minimise steric interaction with the Boc group. Thus, subsequent equatorial lithiation[41,148] gives the *trans*-product. Whilst this effect is not as prevalent in 2-subituted pyrrolidines,[148] we postulated that a

similar situation could occur for the lithiation of (*R*,*R*)-**254** due to configurational constraints of the fused cyclopropyl ring (Scheme 3.69).



Scheme 3.69

In addition, sulfide (*R*,*R*)-**254** has the potential to exist in two rotameric forms (Figure 3.8). The Boc carbonyl group is known to direct the lithiation of *N*-Boc heterocycles[22] and therefore in unsymmetrical systems the rotameric forms would give different lithiation regioisomers. This phenomenon was observed in the lithiation of *N*-Boc 2-phenyl pyrrolidine.[193] In the case of sulfide (*R*,*R*)-**254**, rotamer **A** would be unreactive as there are no *α*-protons whereas rotamer **B** would direct lithiation to the required *α*-position. Therefore, a low yield in the lithiation-trapping of sulfide (*R*,*R*)-**254** could be indicative of slow interconversion of the rotameric species at −78 °C.

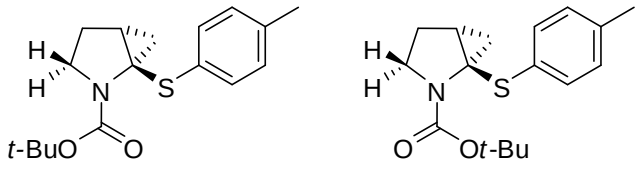
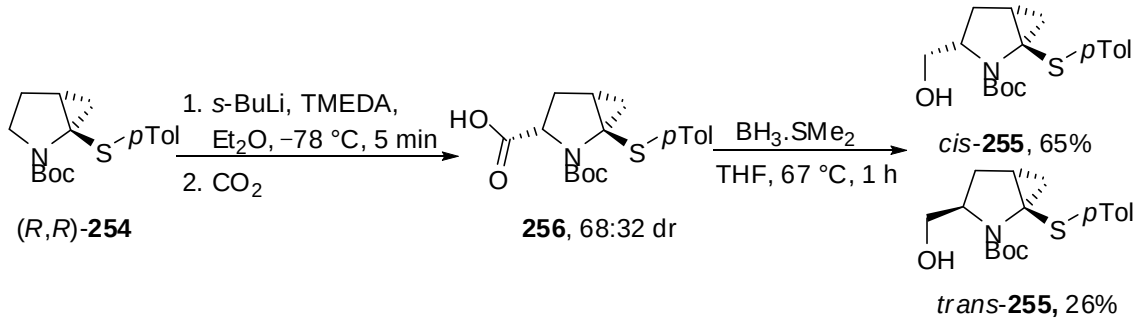


Figure 3.8

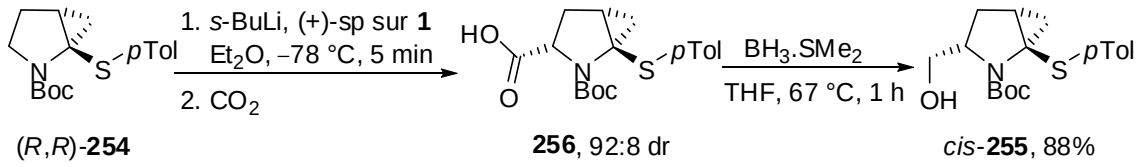
We began our investigation by undertaking the substrate-directed lithiation of sulfide (*R*,*R*)-**254** using *s*-BuLi/TMEDA in Et_2O at −78 °C for 10 minutes. Trapping with carbon dioxide and subsequent reduction of crude acid **256** with $BH_3.SMe_2$ gave alcohol *cis*-**255** in 65% yield and *trans*-**255** in 26% yield (Scheme 3.70). The ^{1}H NMR spectrum of the crude intermediate acid **256** showed a moderate diastereoselectivity of 68:32 dr. Unfortunately, the diastereomeric ratio of alcohols *cis*-**255** and *trans*-**255** could not be calculated from the ^{1}H NMR spectrum of the crude product due to overlapping signals. The high yield from this reaction sequence (91% total yield over

two steps) indicates that sulfide (*R*,*R*)-**254** either exists solely as reactive rotamer **B** or the rotamers are able to rapidly interconvert at −78 °C. The relative stereochemistry was established by conversion of *cis*-**255** into known[183,184] *cis*-**253** as outlined below (see Scheme 3.72).



Scheme 3.70

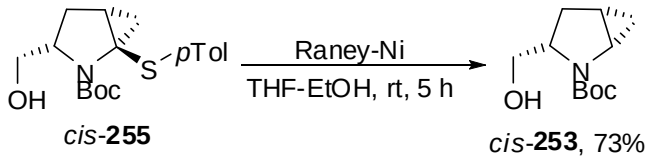
The diastereoselectivity was improved by carrying out a ligand-directed lithiation, an approach which has previously been used in our group for the synthesis of 2,5-substituted pyrrolidines.[29] Use of *s*-BuLi/(+)-sparteine surrogate **1** to mediate the lithiation of (*R*,*R*)-**254** and trapping with carbon dioxide gave acid **256** in 92:8 dr (Scheme 3.71). After borane reduction, *cis*-**255** was isolated as the only product in 84% yield over the two steps; diastereomeric alcohol *trans*-**255** was not isolated after flash column chromatography.



Scheme 3.71

Finally, reductive cleavage (Raney-nickel®, THF-EtOH, rt, 5 hours) of the sulfide moiety gave known[183,184] alcohol *cis*-**253** in 73% yield (Scheme 3.72). Comparison of key diagnostic signals in the ^{1}H NMR spectrum (δ_H 2.46, dddd, J = 13.5, 11.0, 6.5, 1.0 Hz, 1H, CH) and ^{13}C NMR spectrum (δ_C 54.5, CH_2OH and 38.8, NCH) to those provided by Professor Hanessian allowed assignment of the relative configuration of alcohol *cis*-**253**.[184] The spectroscopic data for *trans*-**253** was also provided which confirmed that the other diastereomer was not formed. In addition, the absolute

configuration was assigned by comparison of optical rotation: our sample had $[\alpha]_D$ +6.6 (*c* 0.5 in $CHCl_3$) whereas Hanessian's sample had $[\alpha]_D$ +12.0 (*c* 0.75 in $CHCl_3$).[184]



cis-**255** *cis*-**253**, 73%

Scheme 3.72

The synthesis of *cis*-**253** allows assignment of each of the compounds in each of the synthetic sequence. Importantly, this allows confirmation of the absolute stereochemistry of the core of sulfoxide *syn*-(*R*,*R*,S_S)-**225** and, coupled with our rationale for the sulfoxide configuration (see Scheme 3.50), we can be confident of the absolute stereochemical assignment. In addition, the stereochemistry of all products reported in this Chapter formed by sulfoxide → magnesium exchange from sulfoxide *syn*-(*R*,*R*,S_S)-**225** can be assigned.

3.6 Conclusions and Future Work

The synthesis of a number of *α*-amino sulfoxides has been attempted. Pyrrolidinyl sulfoxides *anti*-(*S*,*S*$_S$)-**148** and *syn*-(*R*,*S*$_S$)-**148** and piperidinyl sulfoxides *anti*-(*S*,*S*$_S$)-**149** and *syn*-(*R*,*S*$_S$)-**149** could not be formed by either lithiation-trapping or oxidation of *α*-amino sulfides (Figure 3.9). We believe that this is due to decomposition of the *α*-amino sulfoxides either by cycloreversion or by *α*-elimination by the nitrogen lone pair.

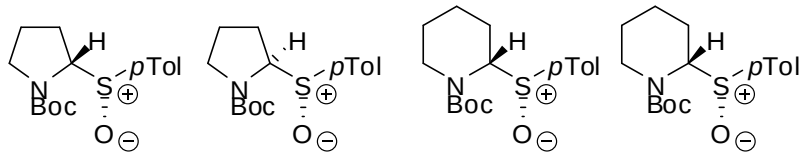
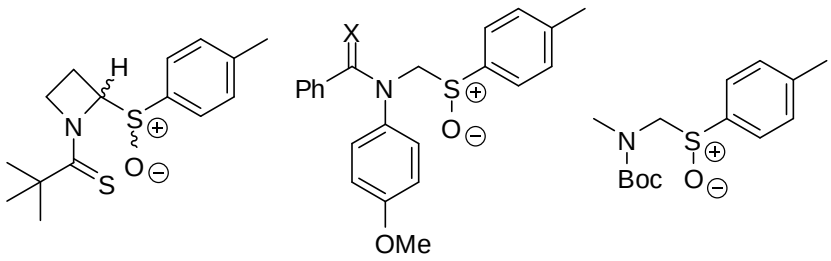


Figure 3.9

N-Thiopivaloyl azetidine sulfoxide **192** was synthesised but the yield of the reaction was disappointing. In addition, acyclic amido sulfoxide **193** and thioamide sulfoxide **194** were successfully isolated. Their synthesis involved a late-stage oxidation by *m*CPBA. In addition, acyclic *N*-Boc dimethylamine sulfoxide **196** was isolated from the lithiation-trapping of *N*-Boc dimethyl amine **222**. This was the first example of a stable compound containing the *N*-Boc *α*-sulfinyl motif (Figure 3.10).

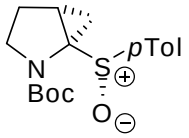


192 **193**, X = O **194**, X = S **196**

Figure 3.10

We then designed an *α*-substituted system in which sulfoxide elimination was prohibited. Indeed, bicyclic sulfoxide *syn*-(*R*,*R*,*S*$_S$)-**225** was synthesised in 99:1 er by lithiation of *N*-Boc 4-chloro piperidine **223** using *s*-BuLi/(*R*,*R*)-**42** and trapping with Andersen's sulfinate (*S*$_S$)-**97** (Figure 3.11). Unfortunately, lithiation of *N*-Boc 4-chloro piperidine **223** using *s*-BuLi/(*R*,*R*)-**42** and trapping with Andersen's sulfinate (*S*$_S$)-**97**

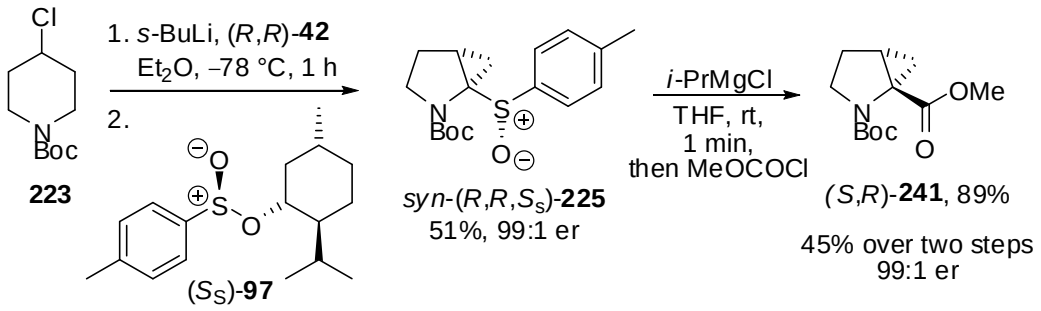
did not lead to the isolation of sulfoxide *anti*-(*S*,*S*,S_S)-**225** as the major diastereomer in 99:1 er.



syn-(*R*,*R*,S_S)-**225**

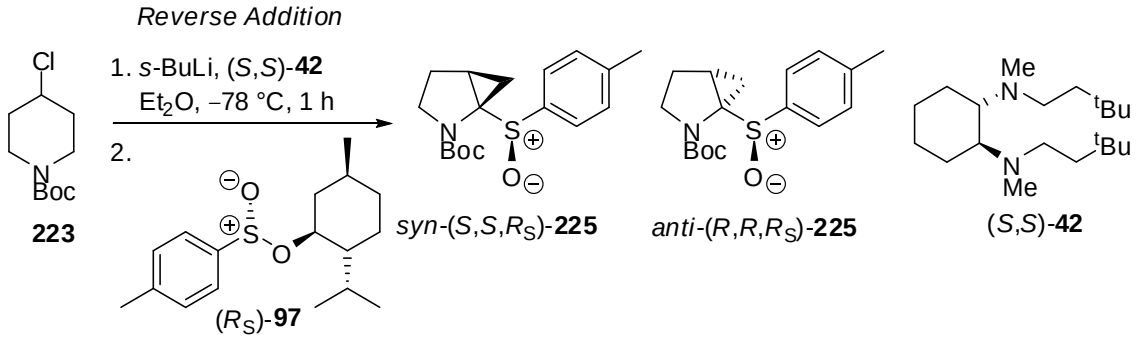
Figure 3.11

Subsequently, a sulfoxide → magnesium exchange protocol was successfully developed for bicyclic sulfoxide *syn*-(*R*,*R*,S_S)-**225** allowing *α*-amino Grignard reagent (*R*,*R*)-**240** to be formed in 99:1 er. These Grignard reagents were then trapped with an array of electrophiles to give products as single enantiomers. As an example, ester (*S*,*R*)-**241** was isolated in 45% yield and 99:1 er over two steps from *N*-Boc 4-chloro piperidine **223** (Scheme 3.73) In addition, a transmetallation-Negishi coupling protocol was developed allowing *α*-arylated products to be isolated in good yields and in 99:1 er. Sulfoxide *syn*-(*R*,*R*,S_S)-**225** was also transformed into alcohol *cis*-**253** which constituted a formal synthesis of saxagliptin.



Scheme 3.73

Future work should synthesise enantiomeric bicyclic sulfoxide *syn*-(*S*,*S*,R_S)-**225**. Lithiation of *N*-Boc 4-chloro piperidine **223** using *s*-BuLi/(*S*,*S*)-**42** and trapping with *ent*-Andersen's sulfinate (R_S)-**97** (Scheme 3.74) would give sulfoxide *syn*-(*S*,*S*,R_S)-**225** in 99:1 er. Sulfoxide → magnesium of sulfoxide *syn*-(*S*,*S*,R_S)-**225** would then give Grignard (*S*,*S*)-**240** in 99:1 er.

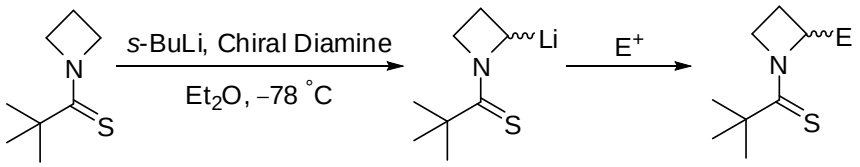


Scheme 3.74

Finally, we still harbour ambitions to synthesise a number of other cyclic α-amino sulfoxides. However, as the mechanism by which decomposition of α-amino sulfoxides occurs is still unknown, initial studies should focus on further elucidating this mechanism.

Chapter Four: Synthesis of *N*-Thiopivaloyl Azetidine Organolithium Reagents

An expedient method of synthesising *α*-substituted azetidines is by lithiation-trapping of *N*-thiopivaloyl azetidine **101** using chiral organolithium bases (Scheme 4.1). However, until now, only one example of the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** has been reported and the mechanism of enantiocontrol remained uncertain.[102]



101 **257**

Scheme 4.1

Our objective was to study the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** using *s*-BuLi and chiral diamines with a view to establishing the mechanism by which the enantioselectivity of the products is determined. To do this, the configurational stability of the lithiated intermediate **257** would need to be investigated and the electrophilic scope would need to be broadened. Furthermore, comparisons to *N*-thiopivaloyl pyrrolidine **210** will be made.

4.1 Lithiation-Trapping of *N*-Thiopivaloyl Azetidines

As well as their appearance in a number of pharmaceutical products,[194-196] α-substituted azetidines are found in a number of natural products. For example, an antithrombotic,[197] mugineic acid,[198] peneazetidine A,[199] and calydaphinone[200] all contain an α-substituted azetidine and are shown in Figure 4.1.

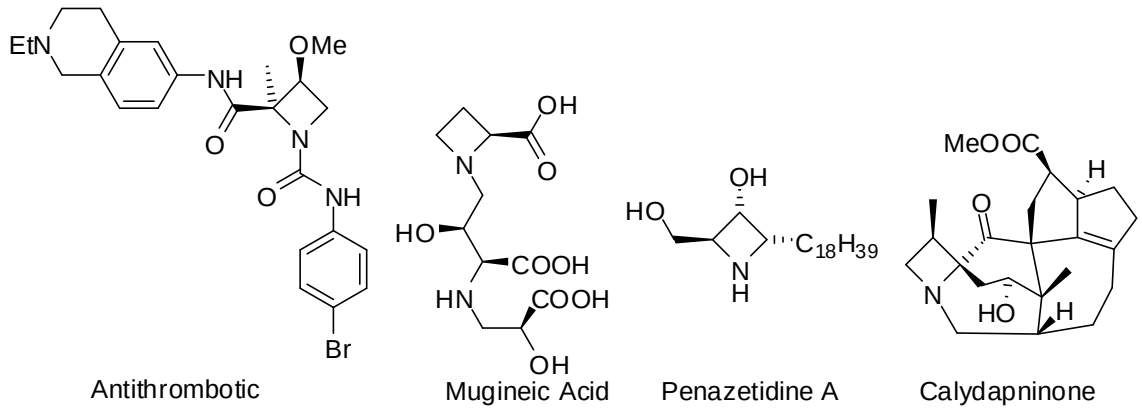
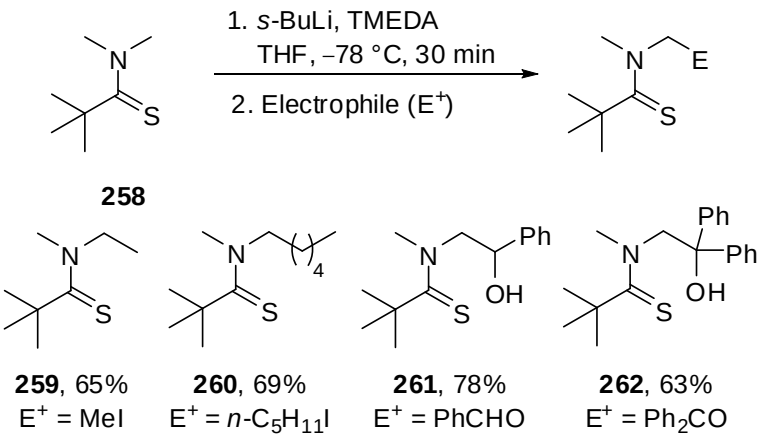


Figure 4.1

Azetidines have typically been synthesised by cyclisation of amine nucleophiles onto an appropriate electrophilic site and these methods have been reviewed in detail by Brandi *et al*.[101] More recently, lithiation-trapping of *N*-thiopivaloyl azetidines has provided an expedient route to α-substituted azetidines.

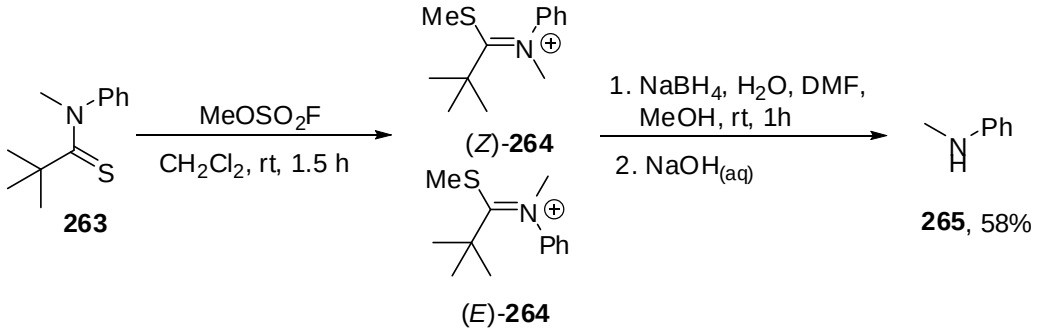
4.1.1 Racemic Lithiation-Trapping of *N*-Thiopivaloyl Azetidines

In 2010, Hodgson and Kloesges reported the first lithiation-trapping of *N*-thiopivaloyl azetidine **101**.[102] Interestingly, the rarely-studied *N*-thiopivalamide group was essential for high yielding α-lithiation-trapping. Prior to 2010, there is only one reported example of successfully using the thiopivaloyl group to direct lithiation α to nitrogen. Seebach and Lubosch carried out the *s*-BuLi/TMEDA-mediated lithiation of *N*,*N*-dimethyl thiopivalamide **258**. Subsequent trapping with a range of electrophiles gave α-substituted products in 17-82% yield. Selected examples are shown in Scheme 4.2.[201,202]



Scheme 4.2

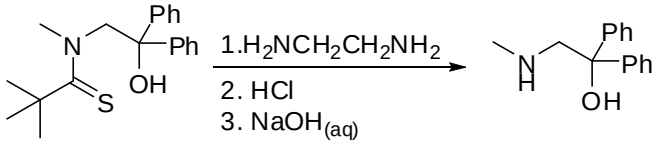
Seebach and co-workers subsequently reported that attempts to use the thiopivalamide directing group in the lithiation-trapping of 11 other acyclic and cyclic *N*-thopivalamides (including that derived from piperidine) were unsuccessful.[203] This lack of versatility may indicate why the thiopivaloyl group has not been more widely adopted. Furthermore, removal of the thiopivaloyl group can require relatively harsh conditions. In 1980, Seebach and Lubosch reported three methods for removing the thioamide functionality.[203] In the first method, addition of methyl fluorosulfonate to aniline derived *N*-thiopivalamide **263** gave a 3:2 mixture of (*E*)-**264** and (*Z*)-**264** in quantitative yield. The mixture was then treated with sodium borohydride and basic-work up gave amine **265** in 58% yield (Scheme 4.3). Unfortunately, using this method to deprotect products from the lithiation-trapping of *N*,*N*-dimethyl thiopivalamide **258** was unsuccessful. This may indicate that aniline moiety is essential for the deprotection to proceed smoothly.



Scheme 4.3

The second procedure offers a more versatile method for the removal of the thioamide group, as shown by the deprotection of benzophenone-trapped product **262** (Scheme

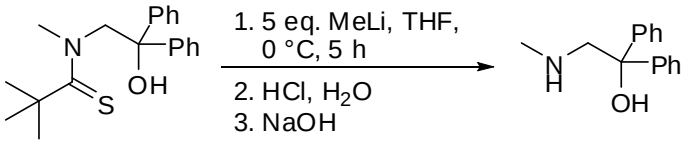
4.4). Ethylene diamine was added to hydroxy thioamide **262** and heated at reflux. After cooling to room temperature, hydrochloric acid was added and basic work-up gave hydroxy amine **266** in 75% yield.



262 **266**, 75%

Scheme 4.4

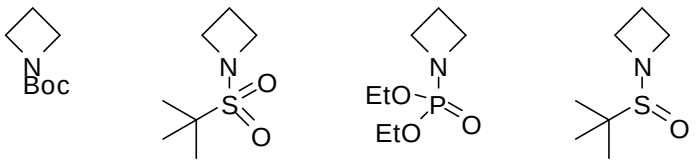
Finally, hydroxy thioamide **262** can also be deprotected using an excess of MeLi to afford hydroxy amine **266** in 80% yield (Scheme 4.5). These are also the conditions preferred by Hodgson and Kloesges.[102] Presumably, this deprotection proceeds *via* nucleophilic attack at the carbonyl of the thioamide group.



262 **266**, 80%

Scheme 4.5

Despite the limitations of using the *N*-thiopivalamide protecting group to direct *α*-lithiation-trapping, Hodgson and Kloesges found that it gave the best results on the azetidine system.[102] Initial attempts to use more common protecting groups gave disappointing results (Figure 4.2). For example, lithiation of *N*-Boc azetidine **267** with either lithium amides or *s*-BuLi (both with and without TMEDA) gave no reaction and *N*-*tert*-butylsulfonyl azetidine **268** and *N*-diethylphosphonyl azetidine **269** similarly resisted lithiation under a variety of conditions. Furthermore, *N*-sulfinylazetidine **270** decomposed under lithiation conditions.

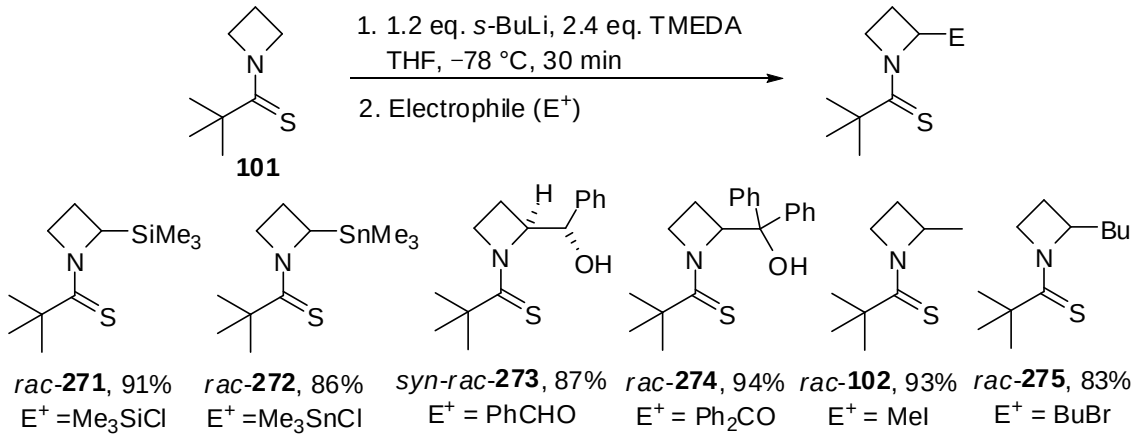


267 **268** **269** **270**

Figure 4.2

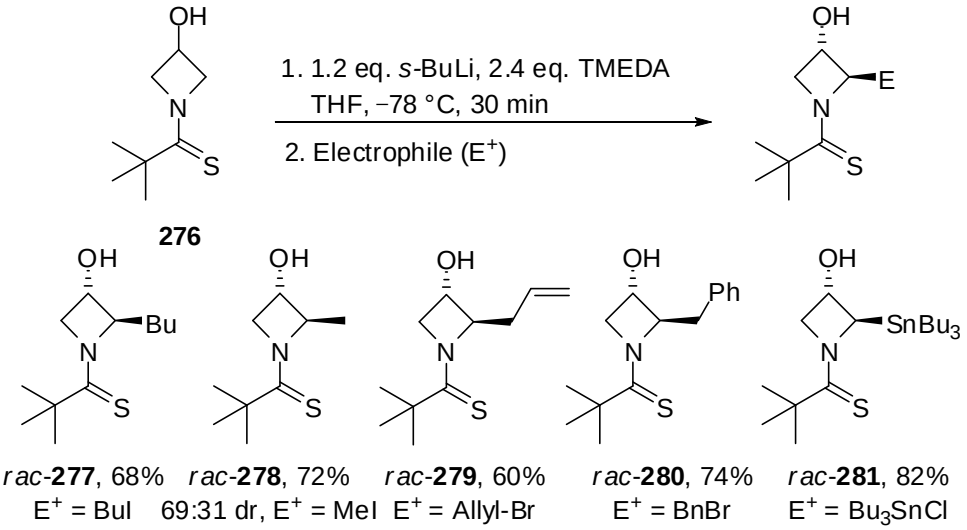
Conversely, lithiation of *N*-thiopivaloylazetidine **101** using *s*-BuLi/TMEDA in THF at −78 °C for 30 minutes and subsequent electrophilic trapping gave *α*-substituted

azetidines *rac*-**102**, **271**-**275** in 83-94% yield (Scheme 4.6). The reaction tolerated a wide range of electrophiles, including alkyl halides, aldehydes, ketones, trimethylsilyl chloride and trimethyltin chloride. Interestingly, the product of lithiation and trapping with benzaldehyde, alcohol *syn-rac*-**273**, was reported to be isolated as a single diastereoisomer.



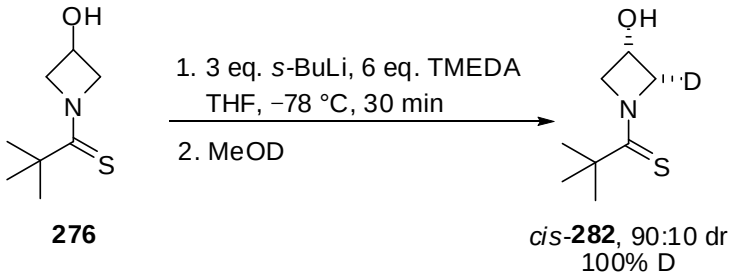
Scheme 4.6

More recently, Hodgson and co-workers have reported the lithiation-trapping of *N*-thiopivaloyl azetidin-3-ol **276**.[204] Lithiation of **276** mediated by 3 eq. *s*-BuLi/6 eq. TMEDA in THF at −78 °C for 30 minutes and trapping with electrophiles gave 2,3 substituted azetidines *rac*-**277**-**281** exclusively as the *trans*-diastereoisomer, with the exception of the methyl iodide trapped product *rac*-**278** which had a *trans*:*cis* ratio of 69:31. Selected results are shown in Scheme 4.7. This reaction proceeds by deprotonation of the hydroxyl moiety before α-lithiation-trapping.



Scheme 4.7

In contrast to lithiation-trapping with electrophiles, lithiation-deuteriation occurs predominantly *cis* to the hydroxyl group. Lithiation of *N*-thiopivaloyl azetidin-3-ol **276** using 3 eq. *s*-BuLi/6 eq. TMEDA and addition of MeOD gave *cis*-**282** as a 90:10 mixture of diastereoisomers (Scheme 4.8). Further mechanistic study showed that the stereochemical outcome of the lithiation-trapping or lithiation-deuteriation is independent of which *α*-proton is removed (*cis* or *trans* to the hydroxyl group). Electrophiles were shown to have a preference for *trans*-products and protonation occurs with *cis*-selectivity.



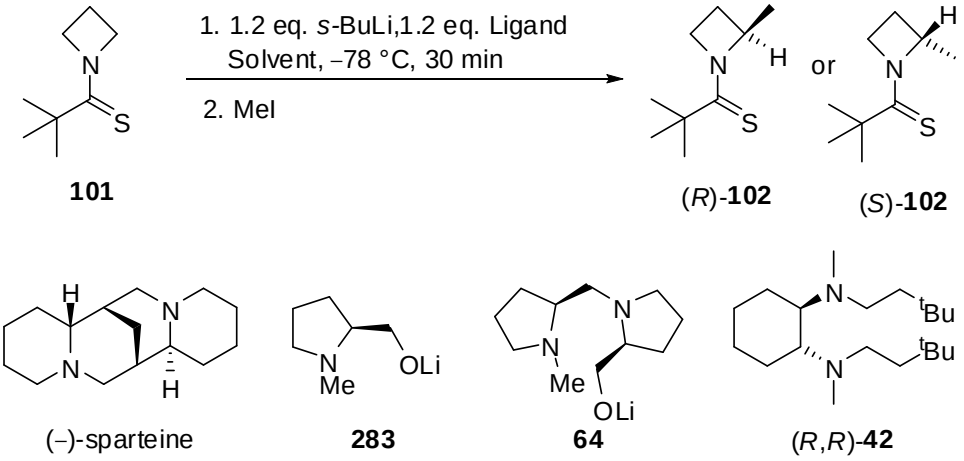
276

cis-**282**, 90:10 dr
100% D

Scheme 4.8

4.1.2 Asymmetric Lithiation-Trapping of *N*-Thiopivaloyl Azetidines

There is only one example of an asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** reported in the literature. Hodgson and Kloesges screened four ligands and different conditions in order to optimise the asymmetric lithiation and trapping with methyl iodide to give enantioenriched methylated azetidine (*R*)-**102** or (*S*)-**102**.[102] The stereochemical control for each ligand during the lithiation-trapping is summarised in Scheme 4.9 and Table 4.1. First, the use of (−)-sparteine in Et_2O gave (*R*)-**102** in 61:39 er (entry 1) and changing the solvent to hexane gave (*R*)-**102** in 72:28 er (entry 2). Use of alkoxy amine **283** as the ligand in hexane gave (*S*)-**102** in a disappointing 54:46 er (entry 3). The use of alkoxy diamine **64** gave (*S*)-**102** in 63:37 er (entry 4) and, finally, Alexakis diamine[129] (*R*,*R*)-**42** gave (*R*)-**102** in 80:20 er (entry 5).



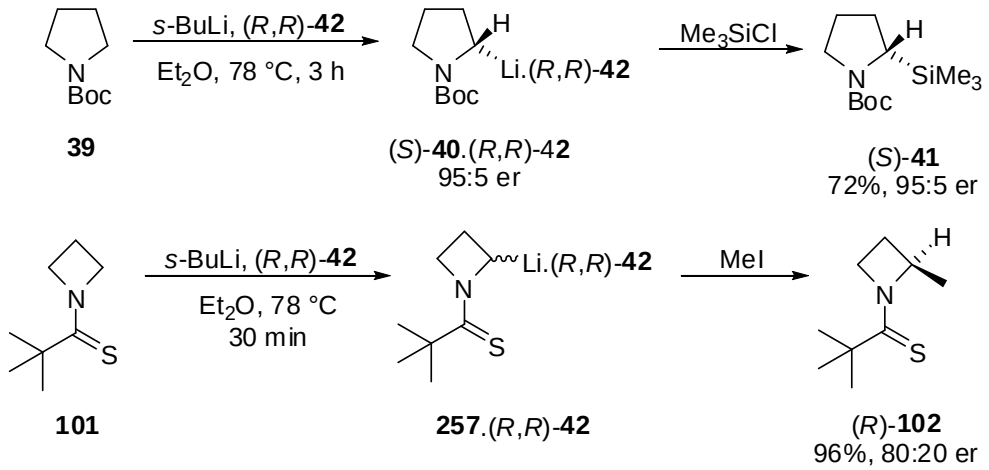
Scheme 4.9

Table 4.1: Asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101**

Entry	Ligand	Solvent	er (*R*:*S*)	Conversion (102:101)[a]
1	(−)-sparteine	Et_2O	61:39	99:1
2	(−)-sparteine	Hexane	72:28	99:1
3	**283**	Hexane	46:54	97:3
4	**64**	Et_2O	37:63	78:22
5	(*R*,*R*)-**42**	Et_2O	80:20	96[b]

[a]Conversion determined by GC, [b]Yield of isolated (*R*)-**102** after column chromatography

To our surprise, lithiation and trapping proceeded with the opposite sense of induction to that observed for the asymmetric lithiation-trapping of a number of *N*-Boc heterocycles.[38,41,136,205] Scheme 4.10 shows a comparison between the lithiation-trapping of *N*-Boc pyrrolidine **39** and *N*-thiopivaloyl azetidine **101** using *s*-BuLi and diamine (*R*,*R*)-**42**. Lithiation of *N*-Boc pyrrolidine **39** using *s*-BuLi/diamine (*R*,*R*)-**42** in Et_2O at −78 °C gave intermediate organolithium (*S*)-**40**.(*R*,*R*)-4**2**. Subsequent trapping with trimethylsilyl chloride gave (*S*)-**41** in 72% yield and 95:5 er.[29] Organolithium (*S*)-**40** has been previously shown to be configurationally stable at −78 °C and an enantioselective deprotonation was responsible for the enantioselectivity observed in the product (see Chapter 1.1.1).[38,206]



Scheme 4.10

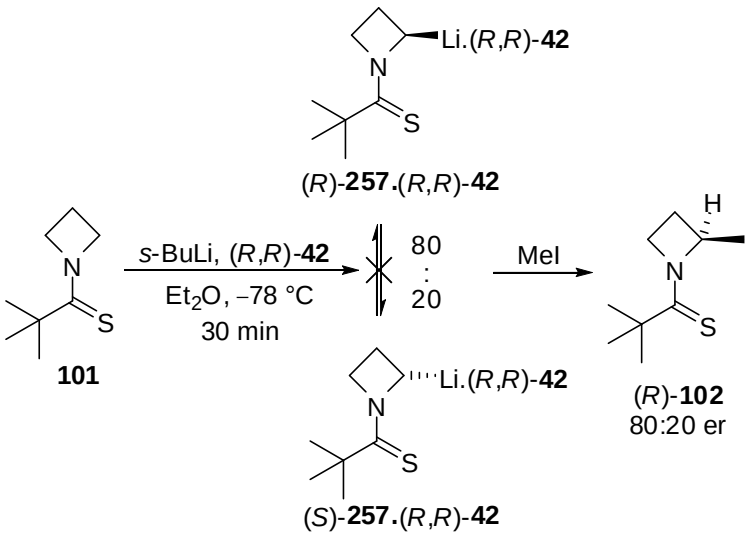
In contrast, lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(*R*,*R*)-**42** and trapping with methyl iodide gave (*R*)-**102** in 96% yield and 80:20 er. The configurational stability of organolithium **257**.(*R*,*R*)-**42** at −78 °C is unknown and, therefore, the mechanism by which enantiocontrol arises cannot be determined. Hodgson and Kloesges offered no explanation for the differing enantio-induction between the systems.

4.2 Asymmetric Lithiation-Trapping of *N*-Thiopivaloyl Azetidine 101

Our objective in this project was to determine the mechanism for the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101**. An introduction to each of the three mechanisms (enantioselective deprotonation, dynamic kinetic resolution and dynamic thermodynamic resolution) was presented in Chapter 1.1.

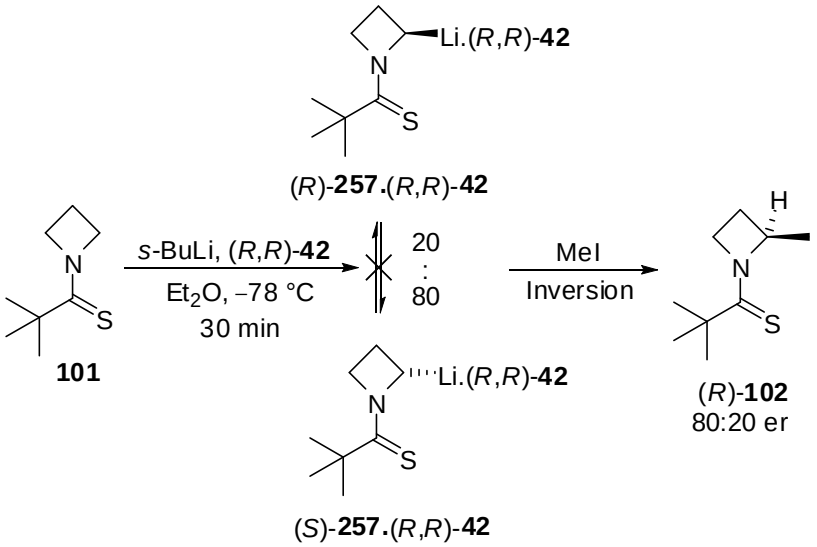
Due to the opposite sense of induction being observed in the lithiation-trapping of *N*-thiopivaloyl azetidine **101** when compared to *N*-Boc heterocycles with the same ligand, it seemed unlikely that an enantioselective deprotonation was occurring. However, we initially considered that there were five possible scenarios that could explain this difference in selectivity.

1. An enantioselective deprotonation occurs at −78 °C to give an 80:20 mixture of diastereomeric lithiated intermediates (*R*)-**257**.(*R*,*R*)-**42** and (*S*)-**257**.(*R*,*R*)-**42**. The lithiated intermediates are configurationally stable at −78 °C (Scheme 4.11). However, the sense of induction of the enantioselective deprotonation was opposite to that observed *N*-Boc pyrrolidine **39** due to conformational changes associated with a reduction in ring size. Alternatively, the sense of induction could be reversed due to the use of *N*-thiopivaloyl group rather than *N*-Boc for directing the lithiation.



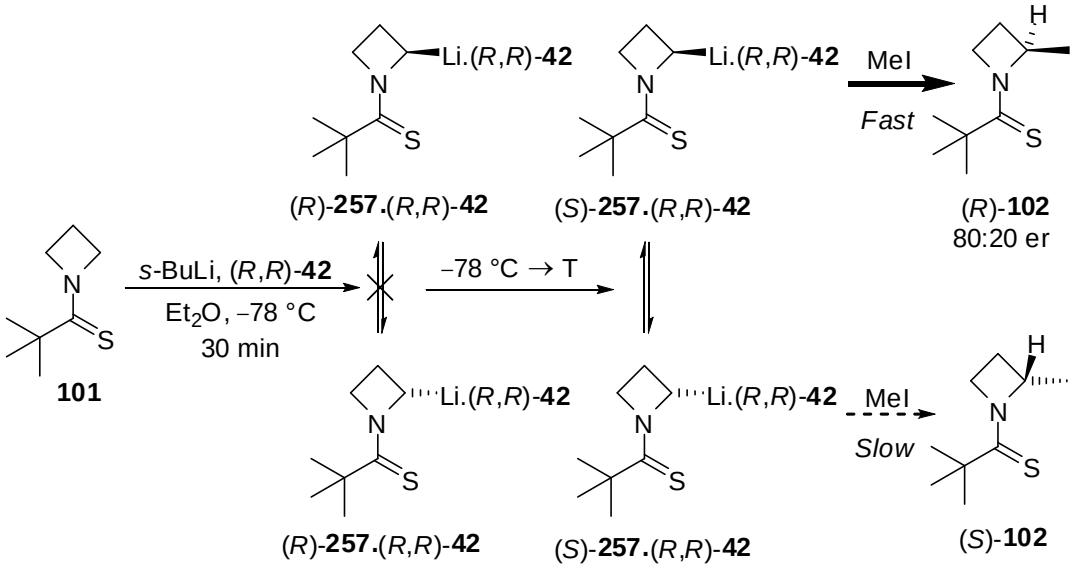
Scheme 4.11

2. An enantioselective deprotonation occurs at −78 °C and proceeds with the same sense of induction to that observed with *N*-Boc pyrrolidine **39**. This would form an 80:20 mixture of diastereomeric lithiated intermediates, (*S*)-**257**.(*R*,*R*)-**42** and (*R*)-**257**.(*R*,*R*)-**42**, which are configurationally stable at −78 °C. Trapping with methyl iodide then proceeds with inversion of configuration at −78 °C to give (*R*)-**102** in 80:20 er (Scheme 4.12). This process usually requires stabilised (*e.g.* benzylic or allylic) organolithium reagents.[23,207]



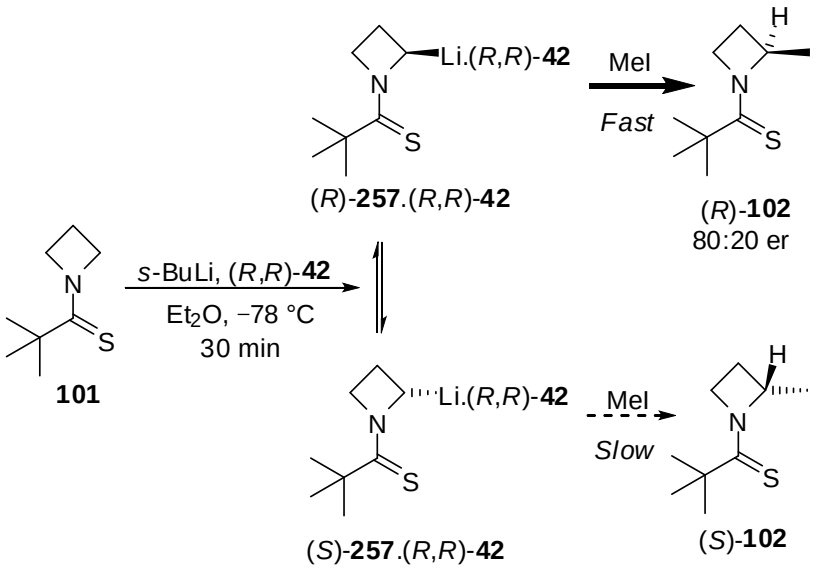
Scheme 4.12

3. An enantioselective deprotonation occurs at −78 °C to give an unknown mixture of diastereomeric lithiated intermediates, (*S*)-**257**.(*R*,*R*)-**42** and (*R*)-**257**.(*R*,*R*)-**42**, which are configurationally stable at −78 °C. Methyl iodide does not react with the organolithium reagents at −78 °C but instead the reaction is allowed to warm up to a temperature where the lithiated intermediates may interconvert. A dynamic kinetic resolution then takes place at this elevated temperature whereby, methyl iodide then reacts preferentially with (*R*)-**257**.(*R*,*R*)-**42** (Scheme 4.13). A similar phenomenon was responsible for the loss of enantiomeric ratio when lithiated *N*-Boc piperidine was trapped with methyl iodide.[43]



Scheme 4.13

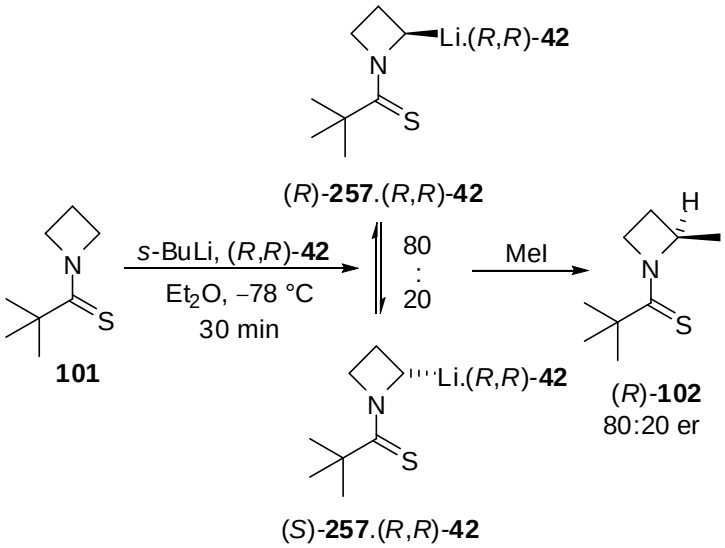
4. The lithiated intermediates are configurationally unstable at −78 °C and, as a result, the sense of induction does not arise from an enantioselective deprotonation. Instead, a dynamic kinetic resolution is taking place. Methyl iodide preferentially reacts with (*R*)-**257**.(*R*,*R*)-**42** to give (*R*)-**102** in 80:20 er (Scheme 4.14).



Scheme 4.14

5. The lithiated intermediates are configurationally unstable at −78 °C and a dynamic thermodynamic resolution process accounts for the enantiomeric ratio observed in the product of trapping with methyl iodide. At −78 °C, an 80:20 thermodynamic ratio of lithiated intermediates (*R*)-**257**.(*R*,*R*)-**42** and (*S*)-**257**.(*R*,*R*)-**42** will form.

On addition of methyl iodide, the organolithium reagents are trapped to give (*R*)-**102** in 80:20 er (Scheme 4.15).



Scheme 4.15

Our plan was to design a number of experiments that would reveal which of these scenarios gives rise to the enantioselectivity. Of utmost importance would be the determination of the configurational stability of lithiated *N*-thiopivaloyl azetidine at −78 °C. This would allow us conclude whether the enantioselectivity observed in the products was due to an enantioselective deprotonation or a dynamic resolution process. In addition, alternative electrophiles would be used to establish whether the enantioselectivity was electrophile dependent. Finally, comparisons would be made between the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** and *N*-thiopivaloyl pyrrolidine **210**. This comparison will expose differences between the four and five membered heterocycles. Moreover, *N*-thiopivaloyl pyrrolidine **210** could be directly compared *N*-Boc pyrrolidine **39** to observe differences between the *N*-thiopivalamide and *N*-Boc protecting groups.

4.2.1 Investigating the Configurational Stability of Lithiated *N*-Thiopivaloyl Azetidine

In order to determine the mechanism by which the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** occurs, it was essential to determine the configurational stability of the lithiated intermediates. If the organolithium reagent was configurationally stable at the temperature of the trapping, then we would be able to

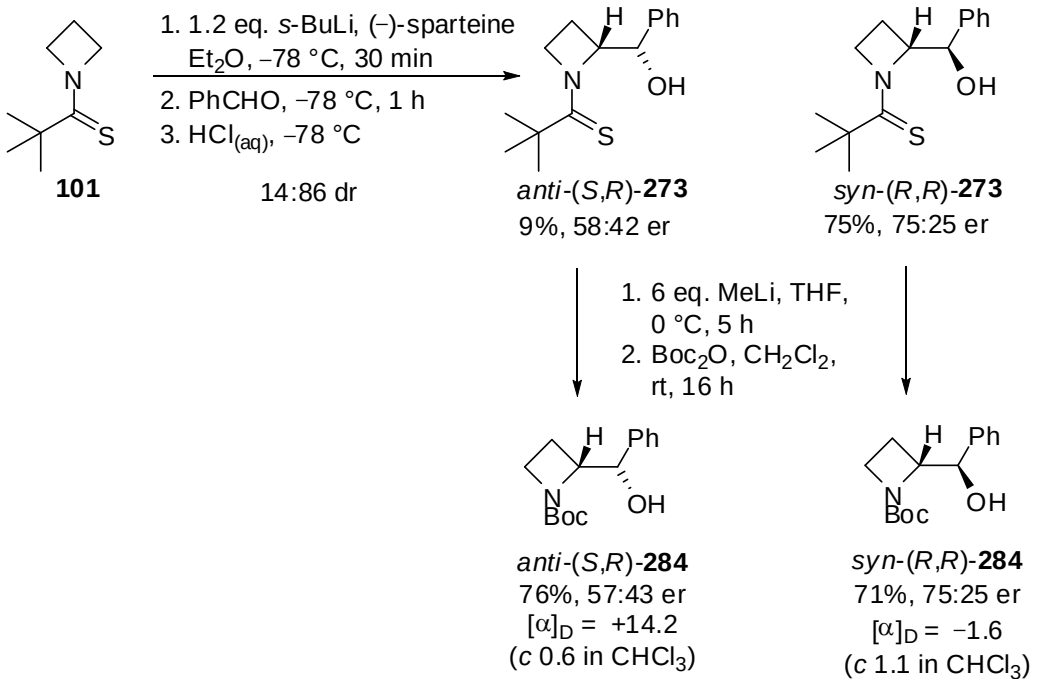
conclude that an enantioselective deprotonation was occurring. In contrast, if the organolithium reagent was configurationally unstable at the temperature of trapping then we could be certain that a dynamic resolution process (kinetic or thermodynamic) was taking place.[18]

The method of choice for exploring the configurational stability of the lithiated intermediate was tin → lithium exchange from an enantioenriched stannane and trapping with an electrophile. If the enantiomeric ratio of the products after tin → lithium exchange and trapping was lower than that of the starting stannane, then we can conclude that the organolithium intermediate was configurationally unstable (see Scheme 1.22 for an example).

Before conducting the tin → lithium exchange, an asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** needed to be carried out in order for us to have a reaction with which to compare our results. Our choice was using *s*-BuLi/(−)-sparteine and trapping with benzaldehyde. The absolute configuration of the products of trapping lithiated *N*-thiopivaloyl azetidine with benzaldehyde could be established by comparison with products synthesised from commerically available (*S*)-2-azetidine carboxylic acid. In addition, we were confident that trapping with benzaldehyde would occur at −78 °C.[180] In contrast, with methyl iodide, it has been shown that trapping of lithiated *N*-Boc piperidine **48** did not occur until temperatures at which the lithiated intermediate was configurationally unstable (−40 °C).[43] This led to products in reduced enantiomeric ratio.

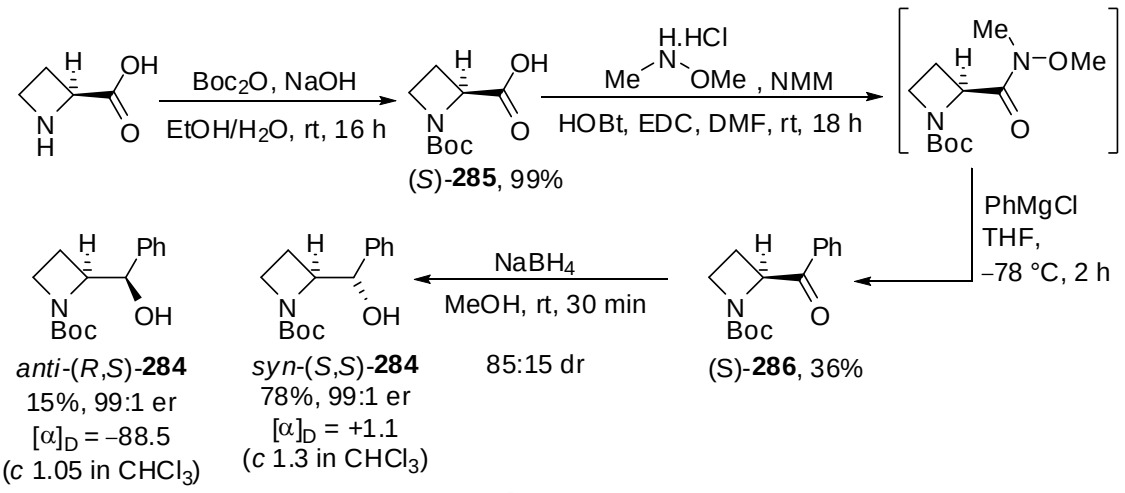
N-Thiopivaloylazetidine **101** was lithiated using conditions reported by Hodgson and Kloesges (1.2 eq. *s*-BuLi, (−)-sparteine, Et_2O, −78 °C, 30 min). Subsequent trapping with benzaldehyde at −78 °C for 1 hour and quenching the reaction with hydrochloric acid at −78 °C gave diastereomeric alcohols *anti*-(*S*,*R*)-**273** and *syn*-(*R*,*R*)-**273** in 9% yield and 58:42 er and 75% yield and 75:25 er respectively (Scheme 4.16). Interestingly, Hodgson and co-workers only isolated a single diastereoisomer from the racemic lithiation-trapping with benzaldehyde.[102] We were able to prove the absolute configuration of alcohols *anti*-(*S*,*R*)-**273** and *syn*-(*R*,*R*)-**273** by conversion into *N*-Boc amino alcohols *anti*-(*S*,*R*)-**284** and *syn*-(*R*,*R*)-**284** respectively. This was achieved by removal of the thiopivalamide group using excess MeLi and subsequent Boc protection.

In addition, the relative configuration of *anti*-(*S*,*R*)-**273** was confirmed by X-ray crystallography within our group.[208] The relative configuration of *syn*-(*R*,*R*)-**273** was confirmed by comparison of the ^{1}H and ^{13}C NMR spectra to those reported in the literature for *syn-rac*-**273**.[102]



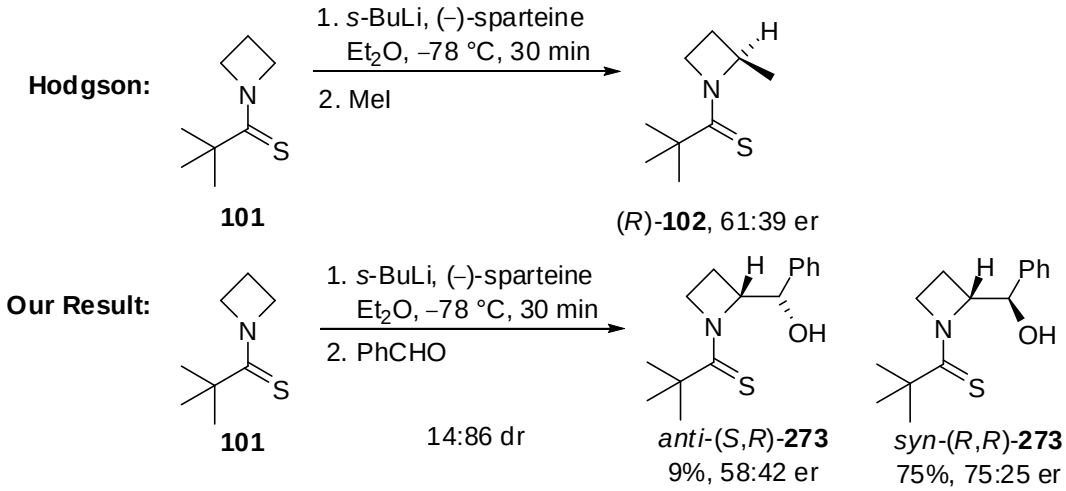
Scheme 4.16

Enantiomeric *N*-Boc amino alcohols *anti*-(*R*,*S*)-**284** and *syn*-(*S*,*S*)-**284** were synthesised from commerically available (*S*)-2-azetidine carboxylic acid in order to establish the absolute configuration (Scheme 4.17). Boc protection of (*S*)-2-azetidine carboxylic acid proceeded smoothly to give *N*-Boc amino acid (*S*)-**285** in 99% yield. Subsequent EDC/HOBt-mediated amide coupling with *N*,*O*-dimethylhydroxylamine.HCl furnished the Weinreb amide which was reacted directly with PhMgCl to give ketone (*S*)-**286** in a modest 36% yield over two steps. Reduction of ketone (*S*)-**286** with sodium borohydride gave diastereomeric alcohols *anti*-(*R*,*S*)-**284** (15%) and *syn*-(*S*,*S*)-**284** (78%) in 93% overall yield.



Scheme 4.17

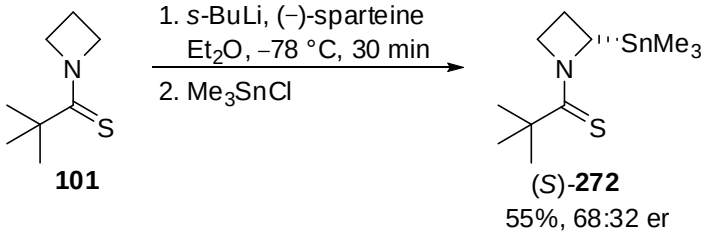
By comparison of optical rotation and CSP-HPLC data between alcohols *anti*-**284** and *syn*-**284** synthesised from lithiation-trapping and those obtained from (*S*)-2-azetidine carboxylic acid, we concluded that lithiation-trapping proceeded with the opposite sense of induction to that reported by Hodgson and Kloesges.[102] Indeed, lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(−)-sparteine and trapping with methyl iodide gave (*R*)-**102** in 61:39 er (Scheme 4.18). In contrast, when we trapped the reaction with benzaldehyde, diastereomeric alcohols *anti*-(*S*,*R*)-**273** and *syn*-(*R*,*R*)-**273** were isolated in 58:42 er and 75:25 er respectively. This difference clearly indicated that the enantioselectivity of the lithiation-trapping procedure is electrophile dependent.



Scheme 4.18

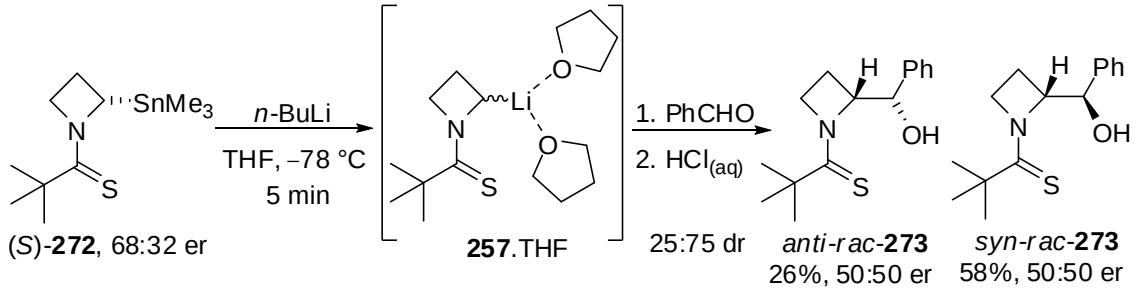
With a suitable comparison reaction in hand, attention turned to the configurational stability study using tin → lithium exchange. The required stannane was synthesised by

asymmetric lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(−)-sparteine and trapping with trimethyltin chloride. Stannane (*S*)-**272** was isolated in 55% yield and 68:32 er (Scheme 4.19). The stereochemical assignment was not proven but was assigned by analogy with the enantioinduction observed in the benzaldehyde trapping.



Scheme 4.19

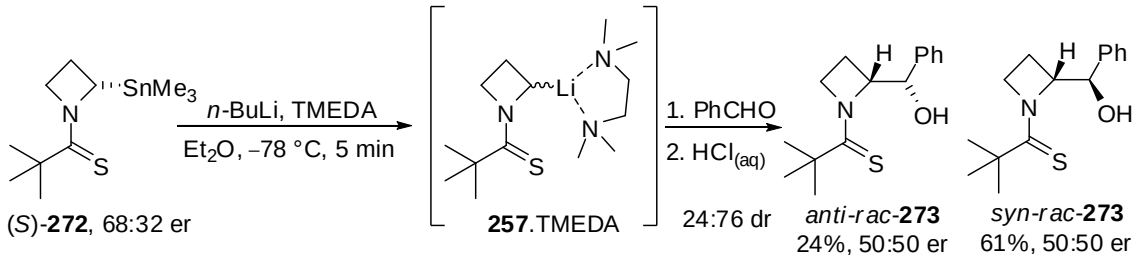
With stannane (*S*)-**272** in hand, the configurational stability of the intermediate organolithium reagent at −78 °C was investigated. Treatment of (*S*)-**272** with *n*-BuLi in THF at −78 °C for 5 minutes and trapping with benzaldehyde gave diastereomeric alcohols *anti-rac*-**273** and *syn-rac*-**273** in 26% yield and 58% yield respectively (Scheme 4.20). Both alcohols were isolated in 50:50 er. Thus, we conclude that under these reaction conditions (THF, −78 °C) lithiated intermediate **257**.THF was configurationally unstable over 5 minutes.



Scheme 4.20

The conditions used for the tin → lithium exchange reaction (THF, −78 °C) are significantly different to those used for the asymmetric lithiation of *N*-thiopivaloyl azetidine **101** (diamine, Et_2O, −78 °C). It is possible that the introduction of a diamine to the tin → lithium exchange protocol may result in a configurationally stabilised lithiated intermediate and thus, after trapping with benzaldehyde, enantioenriched products may be isolated. Therefore, tin → lithium exchange mediated by *n*-BuLi/TMEDA in Et_2O at −78 °C for 5 minutes and trapping with benzaldehyde was

undertaken. However, this also led to the isolation of diastereomeric alcohols *anti-rac*-**273** (24%) and *syn-rac*-**273** (61%) in 50:50 er (Scheme 4.21).

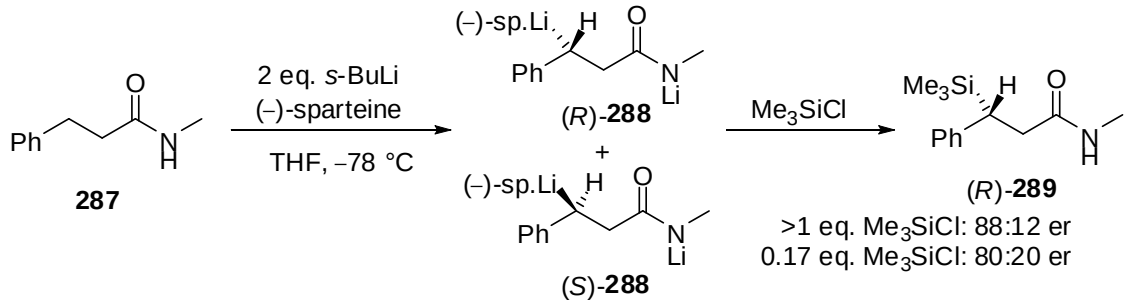


Scheme 4.21

From the tin → lithium exchange reactions, it was concluded that lithiated *N*-thiopivaloyl azetidine was configurationally unstable at −78 °C. This was unexpected because lithiated *N*-Boc pyrrolidine and piperidine are configurationally stable under these conditions.[52,56] Further discussion of this difference is presented in Chapter 4.3.

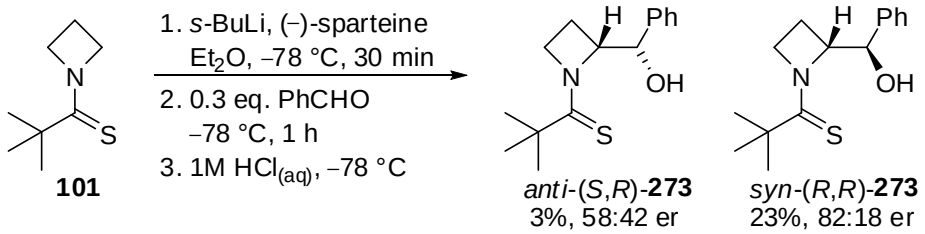
Use of a substoichiometric amount of electrophile can be used to detect whether a lithiated intermediate is configurationally stable on the timescale of reaction with the electrophile. This approach was christened "the poor man's Hoffmann test" by Beak *et al*. in 1996.[209] If a change in enantioselectivity is observed with a substoichiometric amount of electrophile when compared to an excess of electrophile, then it can be concluded that the organolithium is configurationally stable on the timescale of reaction with the electrophile. If the same enantiomeric ratio is observed in both reactions then no definitive conclusion can be drawn.[210]

An example of the "poor man's Hoffmann test" is shown in Scheme 4.22.[210] Benzylic organolithium reagents (*R*)-**288** and (*S*)-**288** were trapped with an excess of trimethylsilyl chloride to give silylated products (*R*)-**289** in 88:12 er. When the reaction was repeated with just 0.17 eq. of trimethylsilyl chloride, (*R*)-**289** was isolated in 80:20 er. This change in enantiomeric ratio led to the conclusion that the lithiation intermediate showed a degree of configurational stability on the timescale of reaction with the electrophile.



Scheme 4.22

Hence, we carried out the lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(−)-sparteine and trapped with 0.3 equivalents of benzaldehyde (Scheme 4.23). From this reaction, diastereomeric alcohols *anti*-(*S*,*R*)-**273** and *syn*-(*R*,*R*)-**273** were isolated in 3% yield and 58:42 er and 23% yield and 82:18 er respectively. Yields are with respect to *N*-thiopivaloyl azetidine **101**.



Scheme 4.23

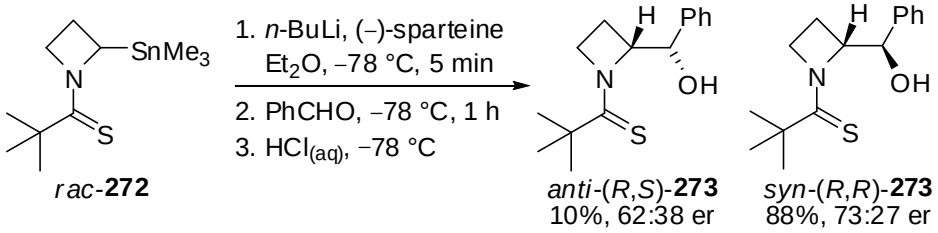
The enantiomeric ratio of the minor diastereomer, *anti*-(*S*,*R*)-**273**, isolated from the reaction with substoichiometric electrophile was the same as that isolated from the reaction with excess electrophile (see Scheme 4.16). Furthermore, only a small difference in enantiomeric ratio was observed in alcohol *syn*-(*R*,*R*)-**273** (82:18 er vs. 75:25 er). Therefore, we cannot draw any definitive conclusions on the configurational stability of the organolithium reagents with respect to rate of trapping with the electrophile.

It is thus concluded that the lithiated azetidine is configurationally unstable at −78 °C. Therefore, we were confident that the enantioselectivity of the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** was not determined by an enantioselective deprotonation mechanism. Instead, a dynamic resolution process is taking place but, at this point, we cannot be certain whether this process is kinetic or thermodynamic in nature.

4.2.2 Dynamic Resolution of Lithiated *N*-Thiopivaloyl Azetidine

The conclusion from the configurational stability study was that a dynamic resolution process was occurring. To prove this, it should be possible to resolve a racemic lithiated intermediate by the addition of a chiral diamine. The chiral diamine ligand would then cause either one diastereomeric lithiated intermediate to react faster on addition of an electrophile (*dynamic kinetic resolution*, see Chapter 1.1.2) or a thermodynamic ratio of diastereomeric lithiated intermediates would form which would then be trapped with an electrophile (*dynamic thermodynamic resolution*, see Chapter 1.1.3).

Therefore, *n*-BuLi/(−)-sparteine was added to stannane *rac*-**272** (Et_2O, −78 °C, 5 minutes) and trapped with benzaldehyde. This gave diastereomeric alcohols *anti*-(*R*,*S*)-**273** and *syn*-(*R*,*R*)-**273** in 62:38 er and 73:27 er respectively (Scheme 4.24). The enantiomeric ratios of the products are similar to those obtained by asymmetric lithiation of *N*-thiopivaloyl azetidine **101**: alcohol *anti*-(*R*,*S*)-**273** was isolated in 58:42 er and alcohol *syn*-(*R*,*R*)-**273** was isolated in 75:25 er (see Scheme 4.16). This result proves that a dynamic resolution process is indeed occurring.



rac-**272**

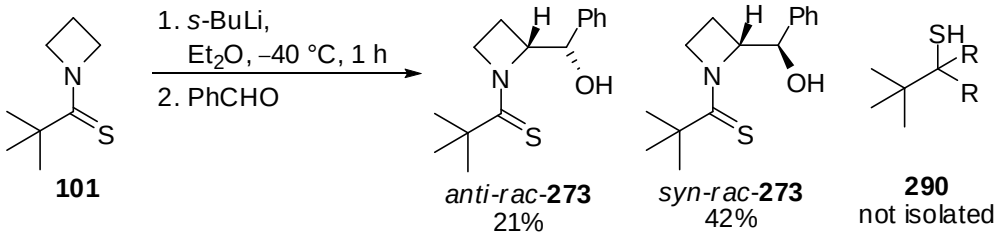
anti-(*R*,*S*)-**273**
10%, 62:38 er

syn-(*R*,*R*)-**273**
88%, 73:27 er

Scheme 4.24

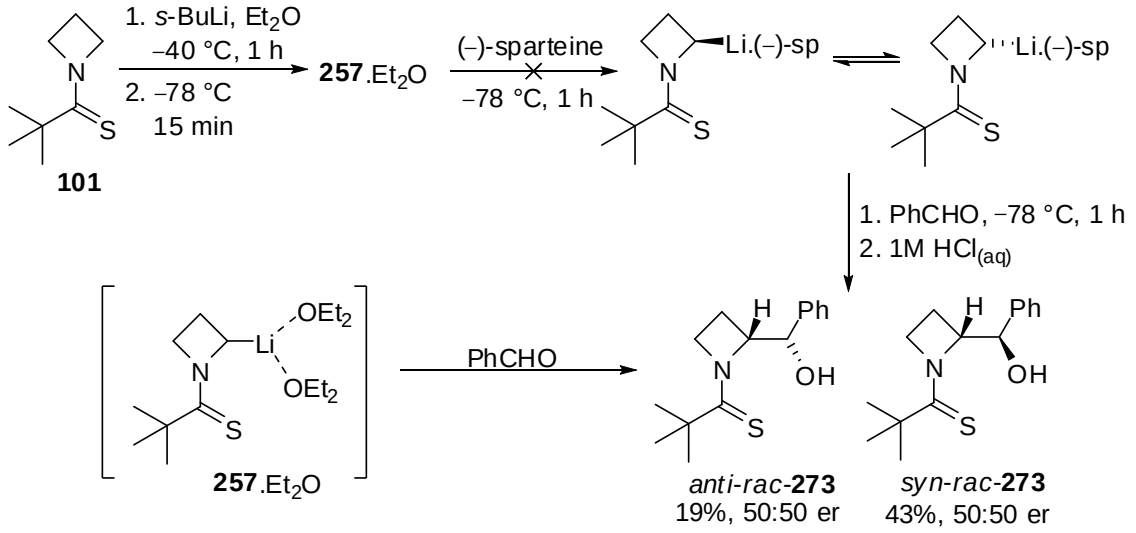
In order to better recreate the direct lithiation conditions, formation of a racemic lithiated intermediate starting from *N*-thiopivaloyl azetidine **101** was attempted. Since it is known that (−)-sparteine is unable to displace TMEDA and THF from the lithiated intermediate,[127] Hodgson and Kloesges' original conditions for the racemic lithiation of *N*-thiopivaloyl azetidine **101** (*s*-BuLi/TMEDA, THF, −78 °C 30 minutes) were not suitable. Hence, we attempted to find a protocol for the racemic lithiation of *N*-thiopivaloyl azetidine **101** in the absence of TMEDA and THF.

To our delight, lithiation of *N*-thiopivaloyl azetidine **101** mediated by *s*-BuLi in Et_2O at −40 °C for 1 hour and trapping with benzaldehyde gave diastereomeric alcohols *anti-rac*-**273** and *syn-rac*-**273** in 21% yield and 41% yield respectively (Scheme 4.25). It is possible that the reduction in yield may be due to the competitive addition of *s*-BuLi or the lithiated intermediate to the thiopivaloyl group. However, thiols of type **290** were not isolated from the reaction.



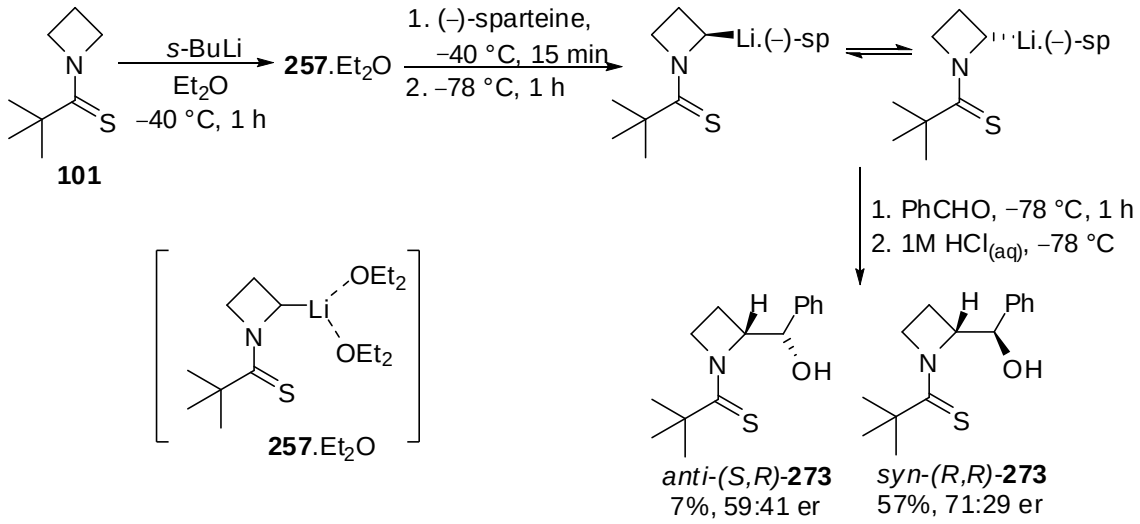
Scheme 4.25

With a procedure for the formation of the racemic lithiated intermediate in hand, a dynamic resolution process was attempted. *N*-Thiopivaloyl azetidine **101** was lithiated by *s*-BuLi in Et_2O at −40 °C to give the racemic lithiated intermediate. The reaction was then cooled to −78 °C and (−)-sparteine was added. However, after trapping with benzaldehyde, alcohols *anti-rac*-**273** (19%) and *syn-rac*-**273** (43%) were isolated in 50:50 er (Scheme 4.26).



Scheme 4.26

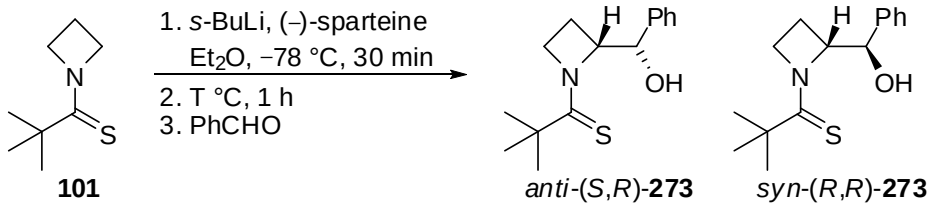
This result is at odds with the tin → lithium exchange approach presented in Scheme 4.24. Our hypothesis was that (−)-sparteine was not complexing to the lithium at −78 °C and hence racemic lithiated intermediate **257**.Et_2O was being trapped by benzaldehyde giving racemic products. It was postulated that we could perturb the binding kinetics by carrying out the complexation with (−)-sparteine at higher temperature. Therefore, the reaction was repeated but adding (−)-sparteine at −40 °C and incubating at this temperature for 15 minutes (Scheme 4.27). The reaction was then cooled to −78 °C for 1 hour before benzaldehyde was added. This gave alcohol *anti*-(*S*,*R*)-**273** in 7% yield and 59:41 er and alcohol *syn*-(*R*,*R*)-**273** in 58% yield and 72:28 er respectively. Crucially, isolation of products with similar levels of enantioenrichment to those from direct lithiation-trapping at −78 °C (see Scheme 4.16) allows us to conclude that a dynamic resolution process is occurring under the reaction conditions.



Scheme 4.27

Temperature can have a dramatic effect on the dynamic resolution processes.[53,54,56] In a dynamic kinetic resolution, a change in temperature can affect the rates at which each of the diastereomeric lithiated intermediates reacts with the electrophile. This change of rate is reflected in the enantiomeric ratio of the products. In addition, in a dynamic thermodynamic resolution, a change in temperature can affect the diastereomeric ratio of the lithiated intermediates. When an electrophile is added, this diastereomeric ratio determines the enantiomeric ratio of the products. Therefore, we wanted to investigate the effect of changing the temperature in the lithiation-trapping of *N*-thiopivaloyl azetidine **101**.

N-Thiopivaloyl azetidine **101** was lithiated using *s*-BuLi/(−)-sparteine (Et_2O, −78 °C, 30 minutes). The reaction was then warmed to a higher temperature and incubated at that temperature for 1 hour. Subsequent trapping with benzaldehyde gave diastereomeric alcohols *anti*-(*S*,*R*)-**273** and *syn*-(*R*,*R*)-**273** (Scheme 4.28, Table 4.2). For comparison, the lithiation-trapping of *N*-thiopivaloyl azetidine **101** at −78 °C is reported in entry 1. When the reaction was warmed to −50 °C, trapping with benzaldehyde led to the isolation of alcohol *anti*-(*S*,*R*)-**273** in 13% yield and 58:42 er and alcohol *syn*-(*R*,*R*)-**273** in 82% yield and a slightly reduced 68:32 er (entry 2) when compared to the enantiomeric ratio at −78 °C.



101 *anti*-(*S*,*R*)-**273** *syn*-(*R*,*R*)-**273**

Scheme 4.28

Table 4.2: Temperature effect on the enantioselectivity of the lithiation-trapping of *N*-thiopivaloyl azetidine **101**

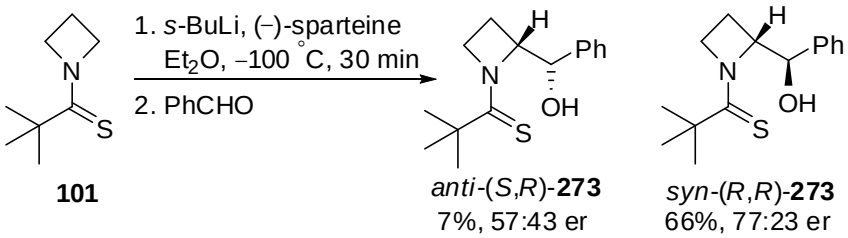
Entry	T (°C)	***anti*-(*S*,*R*)-273**		***syn*-(*R*,*R*)-273**	
		Yield (%)	**er (*S*,*R*):(*R*,*S*)**	**Yield (%)**	**er (*R*,*R*):(*S*,*S*)[a]**
1	−78[b]	9	58:42	75	75:25
2	−50	13	58:42	82	68:32
3	−40	14	56:44	84	62:38
4	−30	11	55:45	76	59:41
5	−30[c]	7	59:41	72	75:25

[a]er determined by CSP-HPLC, [b]Lithiation and trapping conducted at this temperature, [c]Reaction cooled to −78 °C for 30 min before addition of electrophile.

More significant reductions in enantioselectivity were observed in the major diastereoisomer when warming to −40 °C and −30 °C. Indeed, alcohol *anti*-(*S*,*R*)-**273** was isolated in 14% yield and 56:44 er and alcohol *syn*-(*R*,*R*)-**273** in 84% yield and 62:38 er at −40 °C (entry 3). Alcohol *anti*-(*S*,*R*)-**273** was isolated in 11% yield and 55:45 er and alcohol *syn*-(*R*,*R*)-**273** in 76% yield and only 59:41 er at −30 °C (entry 4). Finally, we carried out a lithiation-trapping with a warm cool cycle. *N*-Thiopivaloyl

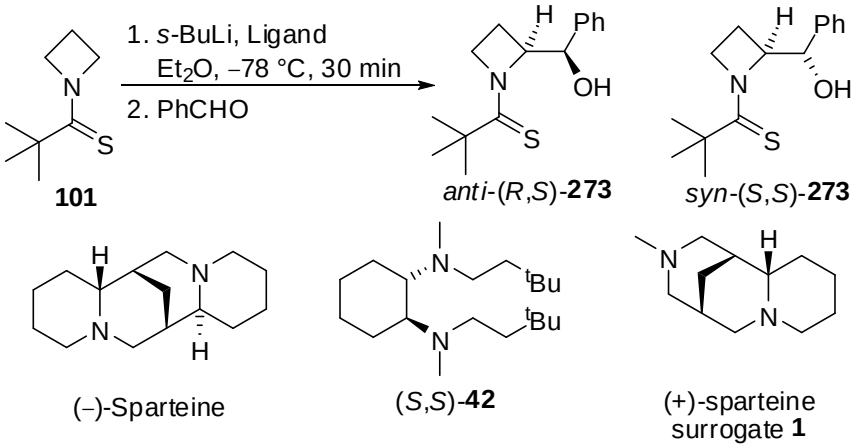
azetidine **101** was lithiated using *s*-BuLi/(−)-sparteine at −78 °C for 30 minutes. Then, the reaction was warmed to −30 °C and stirred at this temperature for 1 hour, before cooling to −78 °C and incubating for a further 30 minutes. Subsequent electrophilic trapping with benzaldehyde gave diastereomeric alcohols *anti*-(*S,R*)-**273** and *syn*-(*R,R*)-**273** in 7% and 59:41 er and 72% and 75:25 er respectively (entry 5). Significantly, the products isolated had equivalent enantioselectivity to those isolated from the direct lithiation-trapping at −78 °C. This further proves that the lithiated intermediate is configurationally unstable at −78 °C.

The lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(−)-sparteine in Et_2O at −100 °C was also attempted (Scheme 4.29). Trapping with benzaldehyde gave alcohol *anti*-(*S,R*)-**273** in 7% yield and 57:43 er and alcohol *syn*-(*R,R*)-**273** in 66% yield and 77:23 er. It is unknown if lithiated *N*-thiopivaloyl azetidine **101** is configurationally unstable at this temperature.



Scheme 4.29

Using different chiral ligands can have a dramatic effect on the enantioselectivity of the dynamic resolution process.[52,56] Therefore, the lithiation-trapping of *N*-thiopivaloyl azetidine **101** was carried out using other diamine ligands (Scheme 4.30, Table 4.3). For comparison, the result when (−)-sparteine was used as the ligand is presented in entry 1. Diamine **42** had previously given the highest enantiomeric ratio in the lithiation-trapping of *N*-thiopivaloyl azetidine **101** reported by Hodgson.[102] In our hands, lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(*S,S*)-**42** and trapping with benzaldehyde gave alcohol *anti*-(*R,S*)-**273** in 20% yield and 65:35 er and alcohol *syn*-(*S,S*)-**273** in 73% yield and 53:47 er (entry 2). Disappointingly, this was not an improvement on the use of (−)-sparteine as the ligand.



Scheme 4.30

Table 4.3: Asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/chiral ligands.

Entry	Ligand	*anti*-(*R*,*S*)-273		*syn*-(*S*,*S*)-273	
		Yield (%)	er (*R*,*S*):(*S*,*R*)[a]	Yield (%)	er (*S*,*S*):(*R*,*R*)[a]
1	(−)-sparteine	9	42:58	75	25:75
2	(*S*,*S*)-**42**	20	65:35	73	53:47
3	(+)-sp. surr. **1**	7	54:46	70	54:46

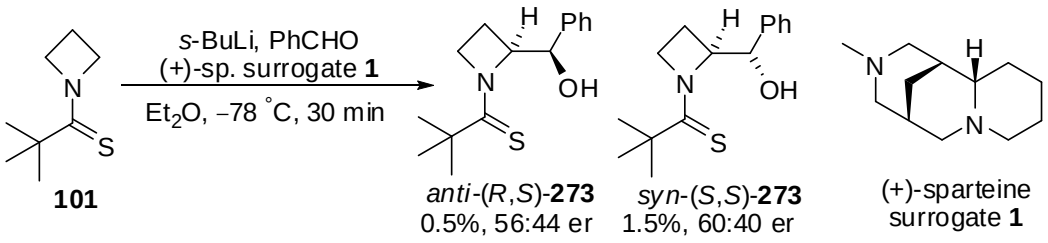
[a]er determined by CSP-HPLC

Lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(+)-sparteine surrogate **1** and trapping with benzaldehyde gave alcohol *anti*-(*R*,*S*)-**273** in 7% yield and alcohol *syn*-(*S*,*S*)-**273** in 70% yield, with both diastereoisomers giving a disappointing 54:46 er (entry 3). This was surprising given that (+)-sparteine surrogate **1** typically gives enantiomeric ratios of similar magnitude to (−)-sparteine.[19] In this case, the enantiomeric ratios are much lower when (+)-sparteine surrogate **1** is used as the ligand. This disparity has been previously observed in dynamic kinetic and dynamic thermodynamic resolutions and this lends further support to an enantioselective deprotonation not taking place under the asymmetric lithiation conditions.[20]

The *s*-BuLi/(+)-sparteine surrogate **1** complex has been shown to be more reactive towards lithiation than *s*-BuLi/(−)-sparteine.[43] Therefore, it was postulated that deprotonation of *N*-thiopivaloyl azetidine **101** may occur in the presence of benzaldehyde giving the intermediate organolithium reagent which would immediately react with benzaldehyde. This experiment would give an indication if an initial

enantioselective deprotonation occurred prior to equilibration of the diastereomeric lithiated intermediates.

Hence, *s*-BuLi/(+)-sparteine surrogate **1** was added to *N*-thiopivaloyl azetidine **101** and benzaldehyde (Scheme 4.31). After purification by flash column chromatography, alcohol *anti*-(*R*,*S*)-**273** was isolated in 0.5% yield and 56:44 er and alcohol *syn*-(*S*,*S*)-**273** was isolated in 1.5% yield and 60:40 er.



Scheme 4.31

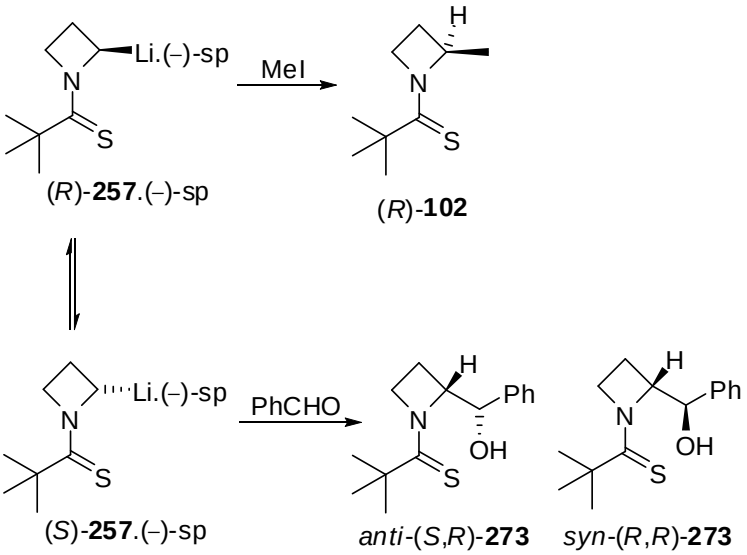
The enantiomeric ratio of *anti*-(*R*,*S*)-**273** is the same as that from the lithiation of *N*-thiopivaloyl azetidine **101** and subsequent trapping with benzaldehyde. In contrast, there is a slight improvement in the enantiomeric ratio of *syn*-(*S*,*S*)-**273**. It is possible that this indicates the initial deprotonation has a higher enantioselectivity than that observed in the trapped products.

In summary, we have shown that a dynamic resolution process is occurring at −78 °C during the lithiation-trapping of *N*-thiopivaloyl azetidine **101**. A racemic lithiated intermediate, formed either by tin → lithium exchange or racemic lithiation of *N*-thiopivaloyl azetidine **101**, was successfully resolved. Currently, we have not been able to prove whether a dynamic kinetic resolution or a dynamic thermodynamic resolution is taking place with benzaldehyde.

4.2.3 Lithiation of *N*-Thiopivaloyl Azetidine 101 and Trapping with Methyl Iodide

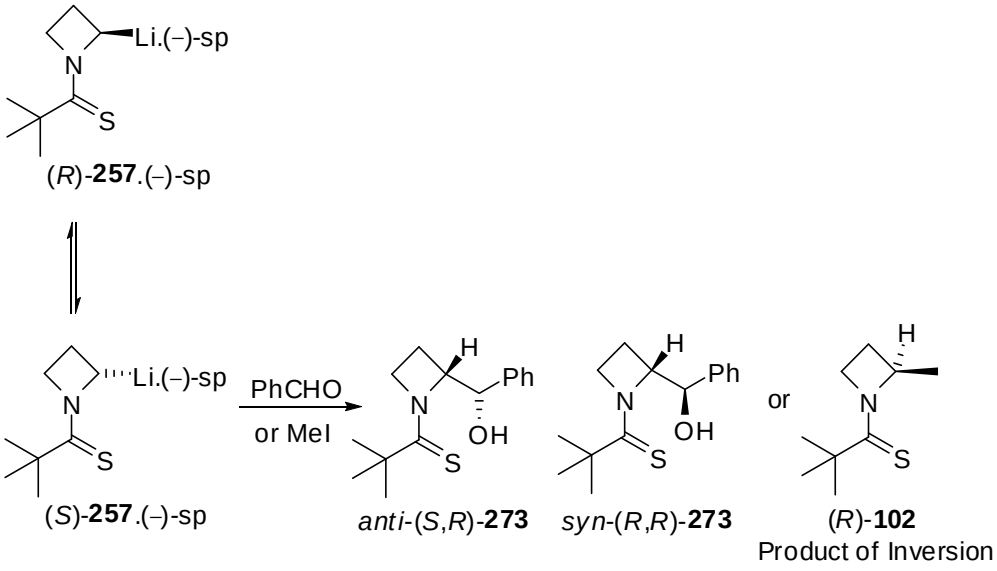
Our attention turned to using methyl iodide as the electrophile in the lithiation-trapping of *N*-thiopivaloyl azetidine **101**. Of particular interest was investigating the reason for the opposite sense of induction when using methyl iodide when compared to what we have shown for benzaldehyde (see Scheme 4.18).[102] We had three hypotheses that could explain this difference. These are summarised in Schemes 4.32, 4.33 and 4.34 for the lithiation using (−)-sparteine as the ligand. In the first mechanism, a dynamic

kinetic resolution was occurring when trapping with either methyl iodide or benzaldehyde. However, methyl iodide would react preferentially with organolithium (*R*)-**257**.(−)-sp, whereas benzaldehyde reacts faster with the organolithium reagent (*S*)-**257**.(−)-sp (Scheme 4.32). The difference in rates of trapping would arise from the different energies of the transition states.



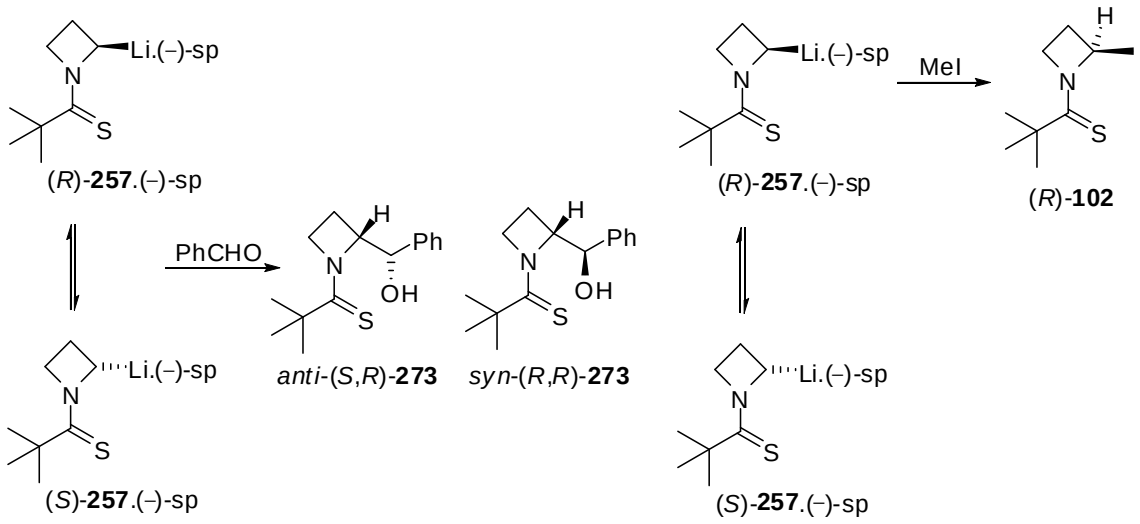
Scheme 4.32

Alternatively, both electrophiles react preferentially with organolithium (*S*)-**257**.(−)-sp but methyl iodide reacts with inversion of configuration at carbon to give (*R*)-**102** (Scheme 4.33). The reaction of organolithium reagents with methyl iodide proceeding with inversion of configuration has been previously observed although typically a stabilised (*e.g.* allylic or benzylic) organolithium reagent is necessary.[207]



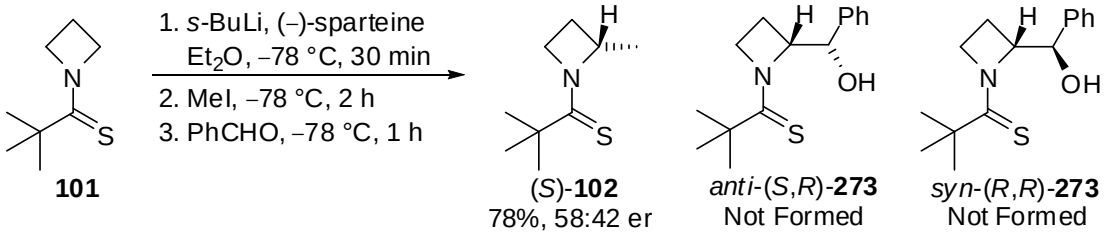
Scheme 4.33

In the third scenario, we propose that a dynamic thermodynamic resolution is occurring with the fast trapping benzaldehyde electrophile. Therefore, the outcome is dependent upon the diastereomeric ratio of the organolithium intermediates. Based on the enantiomeric ratios of *anti*-(*S*,*R*)-**273** and *syn*-(*R*,*R*)-**273** we suggest that the diastereomeric ratio of (*S*)-**257**.(−)-sp and (*R*)-**257**.(−)-sp would be *ca*. 70:30 dr at −78 °C. In contrast, when methyl iodide is used as the electrophile, a dynamic kinetic resolution process takes place. This could be due to the slower reacting nature of methyl iodide when compared to benzaldehyde (Scheme 4.34).



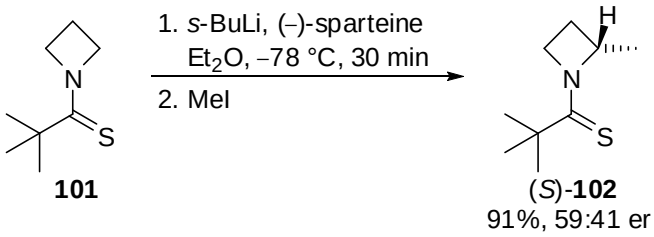
Scheme 4.34

Our plan was to design a number of experiments that would distinguish between these mechanisms. In the first place, we wanted to investigate whether the lithiated intermediate was trapped by methyl iodide at −78 °C. Therefore, the lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(−)-sparteine was carried out and methyl iodide was added at −78 °C (Scheme 4.35). The reaction was then incubated at −78 °C for 2 hours before benzaldehyde was then added. If methyl iodide reacts at −78 °C then we would expect the formation of (*S*)-**102** as the only product. However, if the lithiated intermediate is not trapped by methyl iodide at −78 °C then alcohols *anti*-(*S*,*R*)-**273** and *syn*-(*R*,*R*)-**273** would be isolated. This reaction gave methyl azetidine (*S*)-**102** in 78% yield and 58:42 er. The products of trapping with benzaldehyde, alcohols *anti*-(*S*,*R*)-**273** and *syn*-(*R*,*R*)-**273**, were not evident in the ^{1}H NMR spectrum of the crude product indicating that all the lithiated intermediate had reacted with the methyl iodide prior to the addition of benzaldehyde.



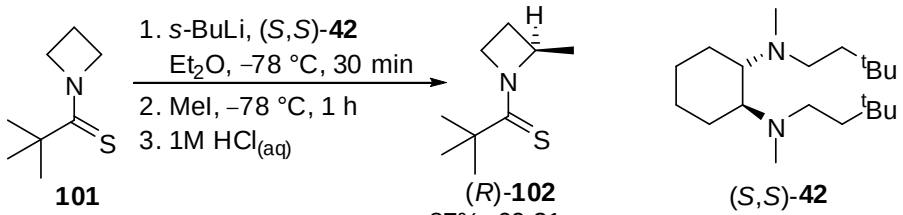
Scheme 4.35

Most significantly, what we believe to be the opposite enantiomer to that reported in the literature was isolated from this reaction (see stereochemical assignment in Scheme 4.37). Furthermore, repeating this reaction under the same conditions reported by Hodgson and Kloesges gave methyl azetidine (*S*)-**102** in 91% yield and 59:41 er (Scheme 4.36). This is the same major enantiomer as we observed when trapping with benzaldehyde. In contrast, Hodgson and Kloesges reported that this reaction gave methyl azetidine (*R*)-**102** in 61:39 er (see Scheme 4.9 and Table 1.1).[102]



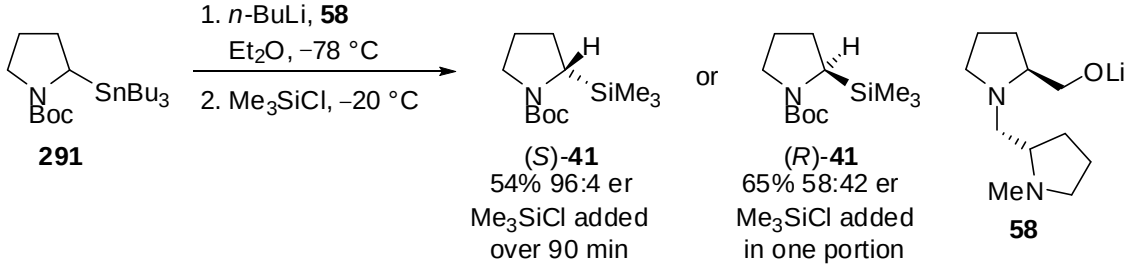
Scheme 4.36

The best enantiomeric ratio reported for trapping the lithiated intermediate with methyl iodide was achieved with diamine (*R,R*)-**42**. Indeed, methyl azetidine (*R*)-**102** was isolated in 96% yield and 80:20 er (see Scheme 4.9 and Table 1.1). We conducted the enantiomeric reaction, namely the lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/diamine (*S,S*)-**42** and trapping with methyl iodide. To our surprise, methyl azetidine (*R*)-**102** was isolated in 87% yield and 69:31 er (Scheme 4.37). This is the same enantiomer to that reported by Hodgson and therefore opposite to what we were expecting to isolate. Comparison of optical rotation for (*R*)-**102** to that reported in the literature allowed assignment of absolute configuration.



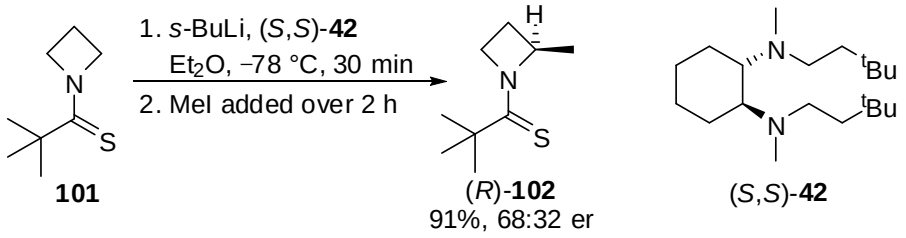
Scheme 4.37

Attempts were made to improve the enantioselectivity of the lithiation-trapping procedure by adding methyl iodide over 2 hours. A similar effect has been reported by Coldham *et al*. in the dynamic kinetic resolution of *N*-Boc-2-lithiopyrrolidine (Scheme 4.38).[54] Indeed, tin → lithium exchange of stannane *rac*-**291** using *n*-BuLi/**58** in Et_2O at −78 °C and then warming to −20 °C before slow addition of trimethylsilyl chloride over 90 minutes gave silylated pyrrolidine (*S*)-**41** in 96:4 er. Warming to −20 °C was necessary to ensure that enantiomerisation of the lithiated intermediate could occur. The 96:4 er achieved by this slow addition approach is in contrast to the isolation of (*R*)-**41** in 58:42 er when trimethylsilyl chloride was added in one portion.



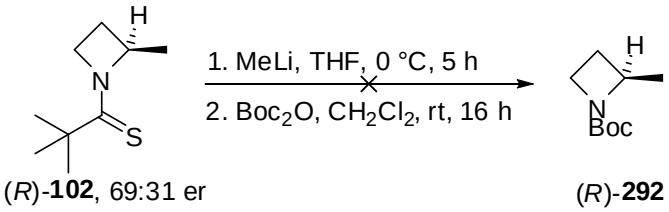
Scheme 4.38

N-Thiopivaloyl azetidine **101** was lithiated using *s*-BuLi/(*S*,*S*)-**42** and then methyl iodide was added over 2 hours at −78 °C (Scheme 4.39). This gave methyl azetidine (*R*)-**102** in 91% yield and 68:32 er. Unfortunately, no improvement in enantiomeric ratio was observed when compared to adding the electrophile in one portion (69:31 er, see Scheme 4.37).



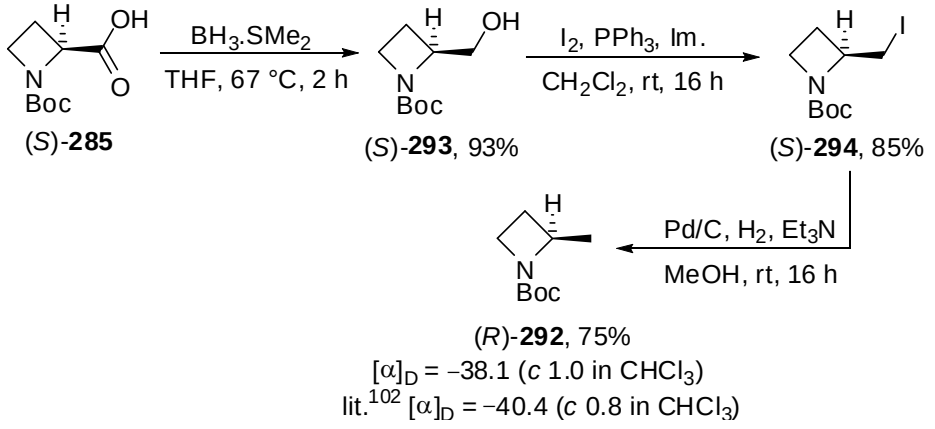
Scheme 4.39

Due to the rather small optical rotation value for our synthesised sample of (*R*)-**102**, we attempted to transform it into known *N*-Boc methyl azetidine (*R*)-**292** which has a higher optical rotation value ($[\alpha]_D$ −40.5 (*c* 0.80 in $CHCl_3$)).[102] This would confirm that our stereochemical assignment was correct. Unfortunately, removal of the thiopivaloyl group using MeLi and subsequent protection using Boc_2O was unsuccessful (Scheme 4.40).



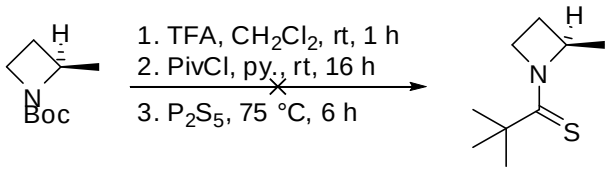
Scheme 4.40

We then set about the synthesis of (*R*)-**292** starting from *N*-Boc acid (*S*)-**285** (previously prepared from commerically available (*S*)-2-azetidine carboxylic acid, see Scheme 4.14). First, acid (*S*)-**285** was reduced to alcohol (*S*)-**293** in 93% yield using $BH_3.SMe_2$ (Scheme 4.41). Treatment of alcohol (*S*)-**293** under Appel iodination conditions (iodine, triphenylphosphine, imidazole) gave iodide (*S*)-**294** in 85% yield. Finally, hydrogenolysis of (*S*)-**294** gave *N*-Boc methyl azetidine (*R*)-**292** in 75% yield.



Scheme 4.41

The conversion of *N*-Boc methyl azetidine (*R*)-**292** into *N*-thiopivaloyl methyl azetidine (*R*)-**102** has been previously reported.[102] Therefore, we repeated this reaction under the same conditions (Scheme 4.42). Unfortunately, (*R*)-**102** was not evident in the ^{1}H NMR spectrum of the crude product. No improvements were obtained when repeating the reaction and any attempts to isolate the *N*-pivalamide intermediate were unsuccessful. In addition, alternative acylation conditions (Et_3N, DMAP, CH_2Cl_2) did not lead to any of the desired product being isolated.



(*R*)-**292** (*R*)-**102**

Scheme 4.42

Whilst the absolute configuration of methyl azetidine (*R*)-**102** has not been unequivocally established, we are confident that, despite the small magnitude of the optical rotation, the sense of induction for the lithiation of *N*-thiopivaloyl azetidine **101** and trapping with methyl iodide is the same as that observed when trapping with benzaldehyde. This conclusion is in contradiction to the sense of induction reported by Hodgson and Kloesges and therefore further proof will need to be garnered prior to publication.

So far, we have shown that lithiated *N*-thiopivaloyl azetidine **101** is configurationally unstable at −78 °C. Thus, an enantioselective deprotonation mechanism cannot be invoked to explain the enantioselectivity observed in the products from lithiation-trapping reactions. Instead, a dynamic resolution process must be occurring. We are currently unable to determine whether a dynamic kinetic or a dynamic thermodynamic resolution is occurring under the asymmetric lithiation conditions. Interestingly, the products isolated from the lithiation-trapping of *N*-thiopivaloyl azetidine **101** have the opposite configuration to that reported by Hodgson and Kloesges.[102]

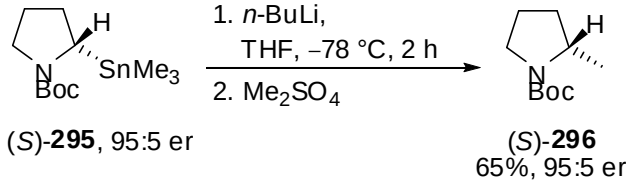
The configurational instability of lithiated *N*-thiopivaloyl azetidine at −78 °C is remarkable when compared to lithiated *N*-Boc pyrrolidine and piperidine, both of which are configurationally stable at −78 °C. We suggest that the configurational instability of lithiated *N*-thiopivaloyl azetidine is due to either the smaller ring size or the *N*-

thiopivaloyl protecting group. Therefore, our next goal was to investigate the asymmetric lithiation of *N*-thiopivaloyl pyrrolidine **210**.

4.3 Lithiation-Trapping of *N*-Thiopivaloyl Pyrrolidine 210

In light of lithiated *N*-thiopivaloyl azetidine **101** being configurationally unstable at −78 °C, we were interested in investigating the configurational stability of lithiated *N*-thiopivaloyl pyrrolidine **210**. This comparison would allow us to determine whether the configurational instability of the lithiated intermediate at −78 °C was due to the reduction in ring size or the thiopivaloyl protecting group.

It has previously been shown that lithiated *N*-Boc pyrrolidine **210** is configurationally stable at −78 °C.[54,76] For example, Beak and Gross reported that the tin → lithium exchange of stannane (*S*)-**295** (95:5 er) using *n*-BuLi in THF at −78 °C for 2 hours and trapping with dimethyl sulfate gave methylated pyrrolidine (*S*)-**296** in 65% yield and 95:5 er (Scheme 4.43).[206] The retention of the enantiomeric ratio proves that the organolithium intermediate is configurationally stable at −78 °C.



(*S*)-**295**, 95:5 er

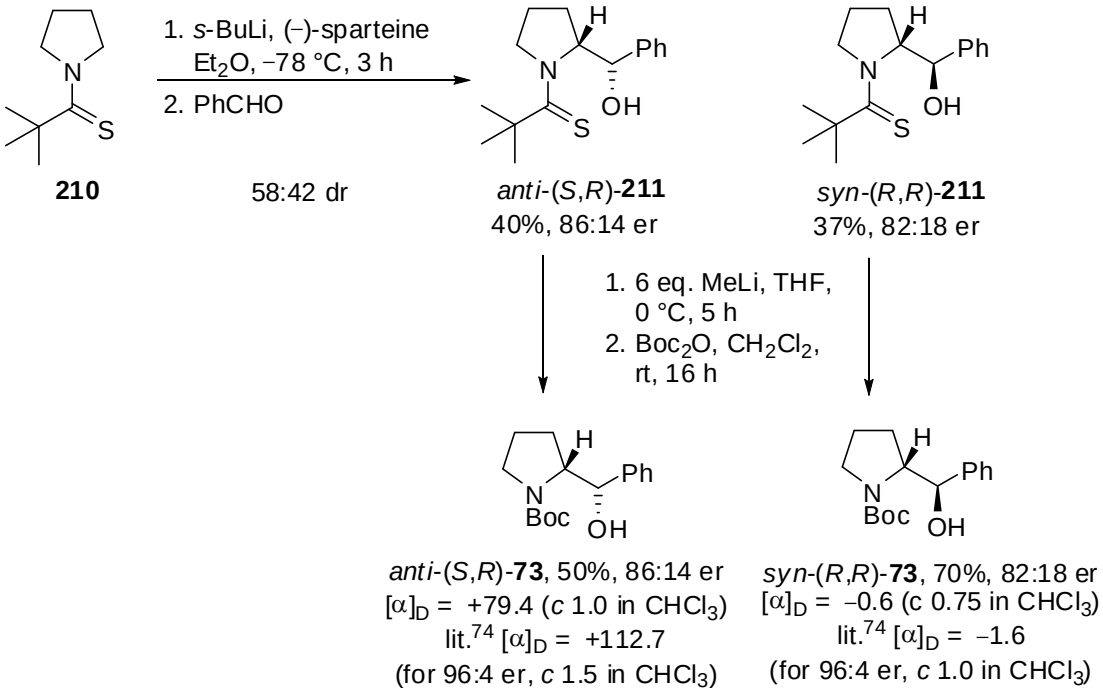
(*S*)-**296**
65%, 95:5 er

Scheme 4.43

4.3.1 Investigating the Configurational Stability of Lithiated *N*-Thiopivaloyl Pyrrolidine

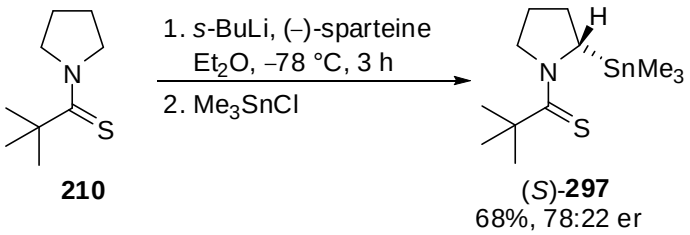
Our plan to determine the configurational stability of lithiated *N*-thiopivaloyl pyrrolidine **210** was to carry out a tin → lithium exchange from an enantioenriched stannane at −78 °C. First, it was necessary to carry out an asymmetric lithiation of *N*-thiopivaloyl pyrrolidine **210** and trapping with benzaldehyde. This would provide a reaction with which to compare our results from the tin → lithium exchange process.
Therefore, *N*-thiopivaloyl pyrrolidine **210** was lithiated using *s*-BuLi/(−)-sparteine in Et_2O for 3 hours at −78 °C. Trapping with benzaldehyde gave diastereomeric alcohols *anti*-(*S*,*R*)-**211** in 40% yield and 86:14 er and *syn*-(*R*,*R*)-**211** in 37% yield and 82:18 er (Scheme 4.44). Conversion into known[74] alcohols *anti*-(*S*,*R*)-**73**and *syn*-(*R*,*R*)-**73** by

deprotection of the thiopivaloyl group using MeLi and subsequent Boc protection allowed the assignment of the relative and absolute configuration. It can be concluded that lithiation-trapping of *N*-thiopivaloyl pyrrolidine **210** shows the same sense of induction as the asymmetric lithiation-trapping of *N*-Boc pyrrolidine **39**.[38]



Scheme 4.44

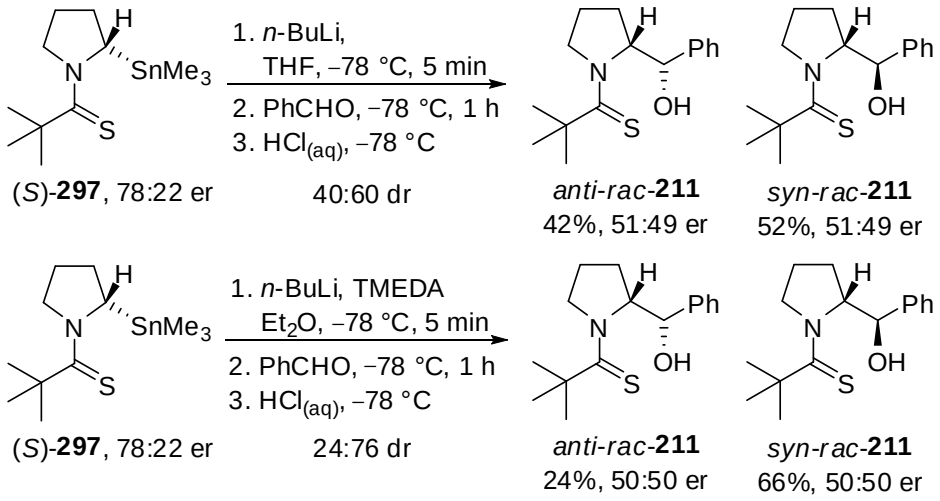
In addition, stannane (*S*)-**297** was synthesised by lithiation of *N*-thiopivaloyl pyrrolidine **210** and trapping with trimethyltin chloride in 68% yield and 78:22 er (Scheme 4.45). The absolute configuration of stannane (*S*)-**297** has not been proved but is assigned by analogy to the benzaldehyde-trapped products.



Scheme 4.45

With stannane (*S*)-**297** in hand, we attempted tin → lithium exchange at −78 °C to investigate the configurational stability of the lithiated intermediate. Treatment of

stannane (*S*)-**297** with *n*-BuLi in THF at −78 °C followed by trapping with benzaldehyde gave diastereomeric alcohols *anti-rac*-**211** and *syn-rac*-**211** in 42% yield and 51:49 er and 52% yield and 51:49 er respectively. Similarly, use of *n*-BuLi/TMEDA gave alcohols *anti-rac*-**211** (24%) and *syn-rac*-**211** (66%), each in 50:50 er (Scheme 4.46).



Scheme 4.46

Remarkably, from these tin → lithium exchange reactions, we conclude that the lithiated intermediate is configurationally unstable at −78 °C. This is in in contrast with *α*-lithiated *N*-Boc pyrrolidine which is configurationally stable at −78 °C.[54,76] By comparison of lithiated *N*-thiopivaloyl azetidine to *N*-thiopivaloyl pyrrolidine we can conclude that the labile nature of the lithiated intermediates is not due to a decrease in ring size. Instead, it is suggested that the *N*-thiopivaloyl protecting group is not as efficient at stabilising the lithiated intermediate when compared to *N*-Boc pyrrolidine **39**. We speculate that this variation may arise from the difference in bond lengths of the Boc carbonyl (C=O) and the C=S of the *N*-thiopivalamide. C=O bonds in carbamates are typically *ca.* 1.25 Å in length whereas C=S bonds in thioamides are *ca*. 1.67 Å long.[211] The longer C=S bond may cause an increase in length of the C-Li bond due to chelation to the lithium to the sulfur. Thus, a reduction in strength of the C-Li would be observed making the barrier to enantiomerisation lower (Figure 4.3).

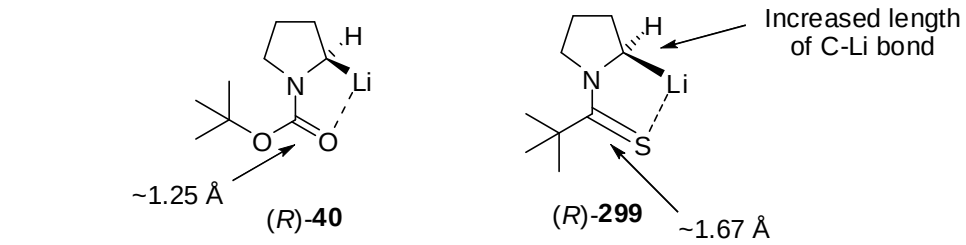
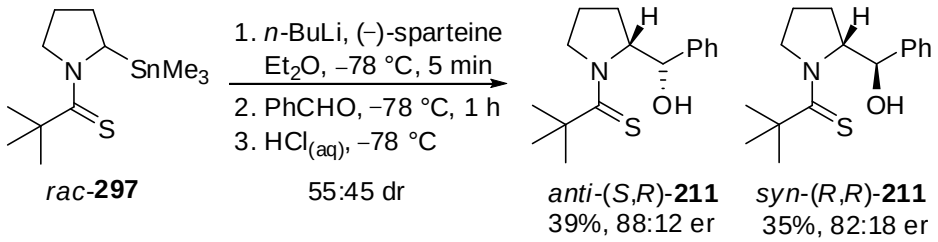


Figure 4.3

4.3.2 Dynamic Resolution of Lithiated *N*-Thiopivaloyl Pyrrolidine

Since lithiated *N*-thiopivaloyl pyrrolidine **210** was shown to be configurationally unstable at −78 °C, an enantioselective deprotonation mechanism can be ruled out. Therefore, the enantioselectivity observed in the lithiation-trapping of *N*-thiopivaloyl pyrrolidine **210** is due to a dynamic resolution process. This means that addition of a chiral diamine to the racemic organolithium reagent should allow isolation of enantioenriched products.

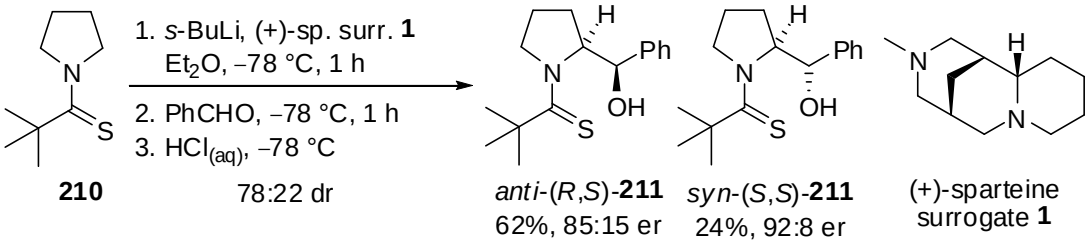
Treatment of stannane *rac*-**297** (formed in 76% yield by racemic lithiation-trapping) with *n*-BuLi/(−)-sparteine in Et_2O at −78 °C for 5 minutes and trapping with benzaldehyde gave alcohol *anti*-(*S*,*R*)-**211** in 39% yield and 88:12 er and *syn*-(*R*,*R*)-**211** 37% yield and 82:18 er (Scheme 4.47). Importantly, the enantiomeric ratio observed from the tin → lithium exchange are comparable to those achieved from the asymmetric lithiation of *N*-thiopivaloyl pyrrolidine **210** using *s*-BuLi/(−)-sparteine (see Scheme 4.44).



Scheme 4.47

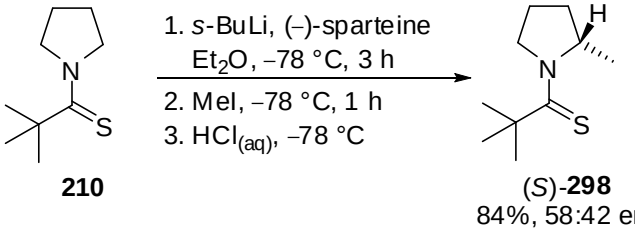
The lithiation of *N*-thiopivaloyl pyrrolidine **210** was also carried out using (+)-sparteine surrogate **1** as the ligand. It was hoped that this would allow access to the opposite enantiomeric series of trapped products in high enantiomer ratio. Indeed, treatment of *N*-thiopivaloyl pyrrolidine **210** with *s*-BuLi/(+)-sparteine surrogate **1** and trapping with

benzaldehyde gave alcohol *anti*-(*R*,*S*)-**211** in 62% yield and 85:15 er and alcohol *syn*-(*S*,*S*)-**211** in 24% yield and 92:8 er (Scheme 4.48). This is the highest gave the highest enantioselectivity we have achieved (92:8 er), albeit for the minor diastereoisomer.



Scheme 4.48

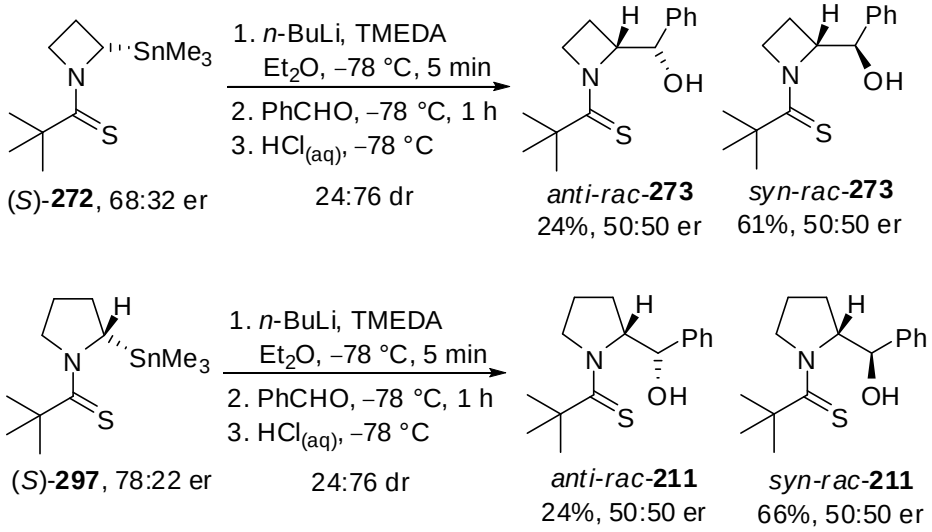
Finally, methyl iodide was used as the electrophile. Previously, in the lithiation-trapping of *N*-thiopivaloyl azetidine **101**, methyl iodide had given products with lower enantiomeric ratio when compared with benzaldehyde (see Scheme 4.36). Lithiation of *N*-thiopivaloyl pyrrolidine **210** using *s*-BuLi/(−)-sparteine and trapping with methyl iodide gave (*S*)-**298** in 84% yield and 58:42 er (Scheme 4.49). The enantiomeric ratio of (*S*)-**298** was significantly lower than the products of benzaldehyde-trapping. Thus, we suggest a dynamic kinetic resolution process is occurring, although further work will be required to unequivocally establish this. The absolute configuration of the major enantiomer was assigned by comparison to unpublished work within our group.[212]



Scheme 4.49

4.4 Conclusions and Future Work

Remarkably, lithiated *N*-thiopivaloyl azetidine and *N*-thiopivaloyl pyrrolidine have been shown to be configurationally unstable at −78 °C. This was established by tin → lithium exchange (*n*-BuLi, TMEDA, Et_2O, −78 °C, 5 min) from stannanes (*S*)-**272** (68:32 er) and (*S*)-**297** (78:22 er) and trapping with benzaldehyde. In both reactions, products were isolated in 50:50 er (Scheme 4.49). Therefore, we are able to conclude that a dynamic resolution process is taking place under the asymmetric lithiation conditions (*s*-BuLi, chiral diamine, Et_2O, −78 °C). Hence, the enantioselectivity observed in the products does not arise from an enantioselective deprotonation.

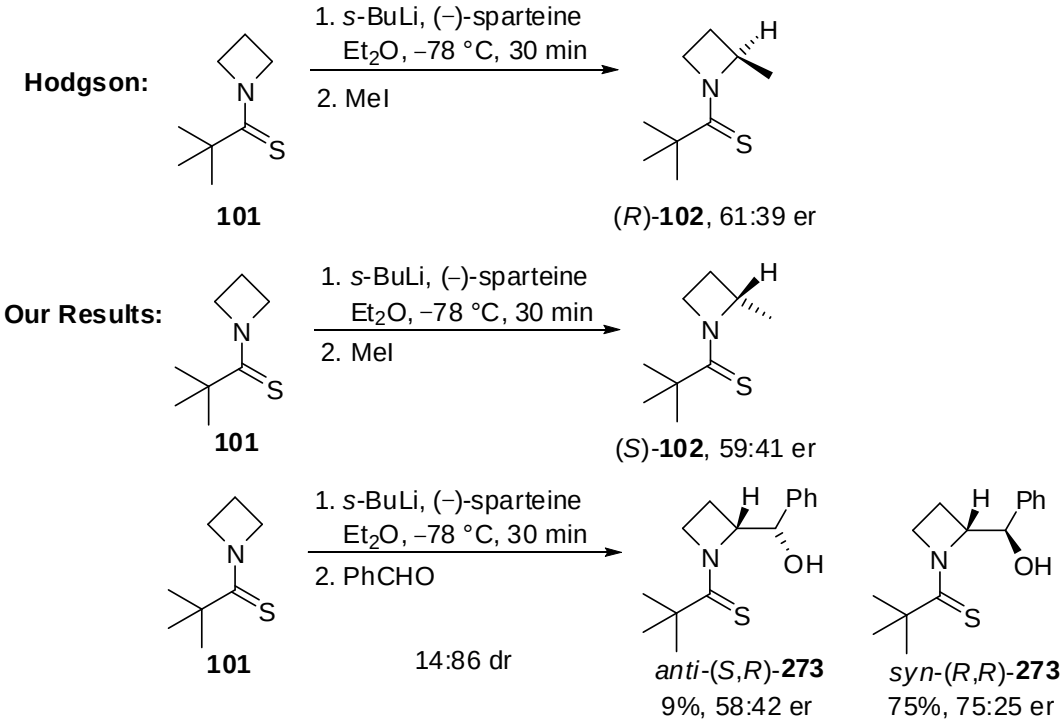


Scheme 4.49

The configurational instability of lithiated *N*-thiopivaloyl azetidine and *N*-thiopivaloyl pyrrolidine is in contrast with lithiated *N*-Boc pyrrolidine and piperidine which are known to be configurationally stable at −78 °C.[52,54,56] Therefore, we conclude that the configurational instability is due to the thiopivaloyl directing group. We speculate that this may be due to the increased C=S thioamide bond length when compared to the Boc carbonyl.

We also found that lithiation of *N*-thiopivaloyl azetidine **101** using *s*-BuLi/(−)-sparteine and trapping with benzaldehyde gave a diastereomeric mixture of alcohols *anti*-(*S,R*)-**273** and *syn*-(*R,R*)-**273**. The sense of enantiomeric induction was established by

comparison to a sample synthesised with known stereochemistry and was found to be opposite configuration to that reported in the literature for methyl iodide trapping.[102] Similarly, we believe that trapping with methyl iodide gave products with opposite configuration to that reported by Hodgson and Kloesges (Scheme 4.50). However, further work is necessary to unequivocally establish the configuration of the methyl trapped product.

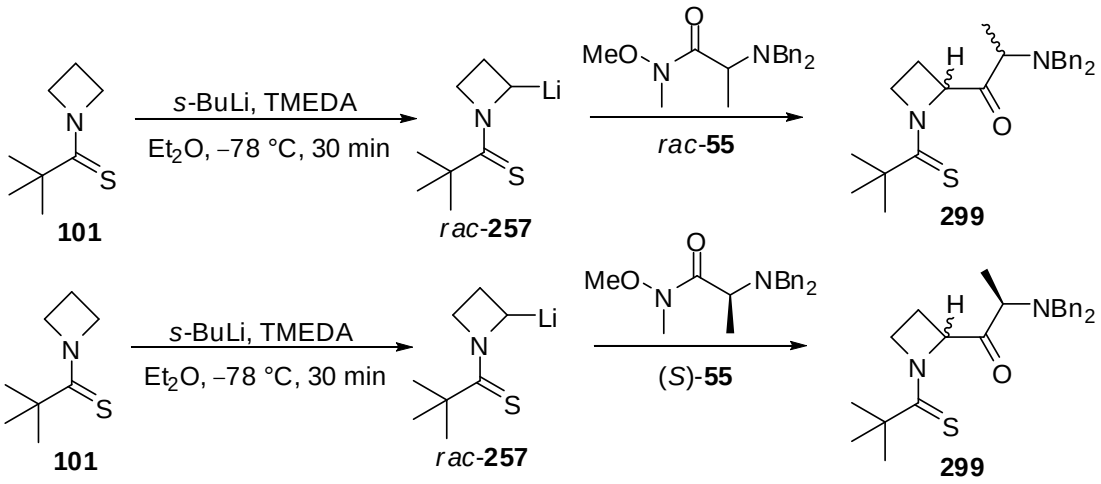


Scheme 4.50

Future work will look to further optimise the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **101**. In particular, the use of alternative chiral ligands will be explored especially those that have been shown to engender good enantiomeric induction in dynamic resolution processes of nitrogen heterocycles.[52,56] Investigations will also take place to study the effect of electrophiles on the enantioselectivity of the lithiation-trapping process.

Furthermore, the Hoffmann test could be used to determine whether the intermediate organolithium reagents are configurationally unstable on the timescale of trapping (see Scheme 1.23). Two reactions will be carried out. First, organolithium *rac*-**257** will be trapped with racemic amide *rac*-**55** to give ketone **299**. Second, organolithium *rac*-**257** will be trapped with enantiomerically pure amide (*S*)-**55** to give ketone **299** (Scheme

4.51). If the diastereomeric ratios of these two reactions are the same then we can conclude that a dynamic thermodynamic resolution process is occurring. If the diastereomeric ratios are different then it can be concluded that a dynamic kinetic resolution is taking place. Finally, the Hoffman test will also be used to distinguish between a dynamic thermodynamic and a dynamic kinetic resolution in the asymmetric lithiation of *N*-thiopivaloyl pyrrolidine **210**.



Scheme 4.51

Chapter Five: Experimental

5.1 General Methods

Water is distilled water. Brine refers to a saturated aqueous solution of NaCl. All non-aqueous reactions were carried out under oxygen-free Ar using flame-dried glassware. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[170] All diamines and electrophiles were distilled over CaH_2 before use. Et_2O and THF were freshly distilled from sodium and benzophenone ketyl. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using Merck F254 aluminium-backed silica plates. ^1H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument with an internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to $CHCl_3$ (δ_H 7.27) and or $CDCl_3$ (δ_C 77.0, central line of triplet). ^{13}C NMR spectra were recorded with broadband proton decoupling. ^{13}C NMR spectra were assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. IR spectra were recorded on an ATI Matteson Genesis FT-IR spectrometer. Melting points were measured on a Gallenkamp melting point apparatus. Electrospray high and low resolution mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Chiral stationary phase HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector.

The following diamine ligands were made according to the reported procedures: (+)-sparteine surrogate **1**[19] and diamines (*R*,*R*)-**42** and (*S*,*S*)-**42**.[29]

5.2 General Procedures

General Procedure A: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *O*-alkyl carbamate 14 or *O*-Alkyl carbamate 125

s-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.) was added dropwise to a stirred solution of carbamate **14** or **125** (1.00 mmol, 1.0 eq.) and diamine (1.20 mmol, 1.2 eq.) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, the electrophile (2.00 mmol, 2.0 eq.) was added dropwise and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure B: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *O*-alkyl carbamate 14 (Quench at −78 °C)

s-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.) was added dropwise to a stirred solution of carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and diamine (1.20 mmol, 1.2 eq.) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, the electrophile (2.00 mmol, 2.0 eq.) was added dropwise and the solution was stirred at −78 °C for 5 min. Then, MeOH (2 mL) was added and the resulting solution was allowed to warm to rt over 30 min. The solution was poured into 1 M $HCl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure C: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *O*-alkyl carbamate 14 with reverse addition to Andersen's sulfinate (S_s)-97

s-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.) was added dropwise to a stirred solution of carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and diamine (1.20 mmol, 1.2 eq.) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h and then added dropwise *via* cannula transfer to a stirred solution of Andersen's sulfinate (S_s)-**97** (589 mg, 2.00 mmol, 2.0 eq.) in THF (4 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then,

$MeOH_{(aq)}$ (2 mL) was added and the resulting solution was allowed to warm to rt over 30 min. The solution was poured into 1 M $HCl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure D: Sulfoxide → Magnesium Exchange Reactions

i-PrMgCl (0.13-0.25 mL of a 2.0 M solution in THF, 0.26-0.50 mmol, 1.3-2.5 eq.) was added dropwise to a stirred solution of the sulfoxide (0.20 mmol, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1-30 min. Then, the electrophile (0.26-0.50 mmol, 1.3-2.5 eq.) was added dropwise and the resulting solution was stirred at rt for 5 min. Saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure E: *s*-BuLi-mediated lithiation-electrophilic trapping of *N*-Boc pyrrolidine 39 in THF

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **39** (171 mg, 1.00 mmol, 1.0 eq.) in THF (7 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, the electrophile (2.00 mmol, 2.0 eq.) was added dropwise. The solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure F: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *N*-Boc pyrrolidine 39, *N*-Boc piperidine 48 or *N*-pivaloyl pyrrolidine 209

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **39**, *N*-Boc piperidine **48** or *N*-pivaloyl pyrrolidine **209** (1.00 mmol, 1.0 eq.) and diamine (1.30 mmol, 1.3 eq.) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1-3 h. Then, the electrophile (2.00 mmol, 2.0 eq.) was added dropwise and the solution was allowed to

warm to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure G: *m*CPBA oxidation of *α*-amino sulfides

*m*CPBA (208 mg of ~77% purity, 1.20 mmol, 1.1 eq.) was added to a stirred solution of the sulfide (1.10 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 1 h. Then, saturated $Na_2SO_{3(aq)}$ (7 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure H: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *N*-Boc 4-chloro piperidine 223

s-BuLi (1.69 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.) was added dropwise to a stirred solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.0 mmol, 1.0 eq.) and diamine (2.20 mmol, 2.2 eq.) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, the electrophile (2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure I: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *N*-Boc 4-chloro piperidine 223 (Quench at −78 °C)

s-BuLi (1.69 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.) was added dropwise to a stirred solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.0 mmol, 1.0 eq.) and diamine (2.20 mmol, 2.2 eq.) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, the electrophile (2.20 mmol, 2.2 eq.) was added dropwise and the solution was stirred at −78 °C for 5 min. Then, MeOH (2 mL) was added and the resulting solution was allowed to warm to rt over 30 min. The solution was poured into 1 M $HCl_{(aq)}$ (10 mL) and the two layers were separated. The

aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure J: *s*-BuLi/diamine-mediated lithiation of *N*-Boc 4-chloro piperidine 223 with reverse addition to Andersen's sulfinate (S_s)-97

s-BuLi (1.69 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.) was added dropwise to a stirred solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.0 mmol, 1.0 eq.) and diamine (2.20 mmol, 2.2 eq.) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h and then added dropwise *via* cannula transfer to a stirred solution of Andersen's sulfinate (S_s)-**97** (647 mg, 2.20 mmol, 2.2 eq.) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, MeOH (2 mL) was added and the resulting solution was allowed to warm to rt over 30 min. The solution was poured into 1 M $HCl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure K: Sulfoxide → Magnesium Exchange Reactions with Transmetallation-Negishi Coupling

i-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.5 mmol, 2.5 eq.) was added dropwise to a stirred solution of sulfoxide *syn*-(*R*,*R*,S_S)-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, $ZnCl_2$ (0.12 mmol of a 1.0 M solution in Et_2O, 0.6 eq.) was added dropwise. The solution was stirred at rt for 30 min. Then, $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and aryl bromide (0.24 mmol, 1.2 eq.) were added sequentially. The resulting brown solution was stirred at rt for 16 h. Then, $NH_4OH_{(aq)}$ (0.1 mL) was added and the resulting solution was stirred for 30 min. The solids were removed by filtration through Celite® and the filtrate was washed with water (5 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure L: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *N*-thiopivaloyl azetidine 101

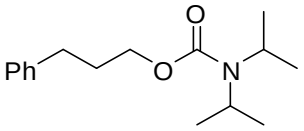
s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.50 mmol, 1.0 eq.) and diamine (0.60 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the electrophile (0.75 mmol, 1.5 eq.) was added dropwise and the solution was stirred at −78 °C for 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure M: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *N*-thiopivaloyl pyrrolidine 210

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl pyrrolidine **210** (86 mg, 0.50 mmol, 1.0 eq.) and diamine (0.65mmol, 1.3 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, the electrophile (0.75 mmol, 1.5 eq.) was added dropwise and the solution was stirred at −78 °C for 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

5.3 Experimental for Chapter Two

3-Phenylpropyl diisopropylcarbamate 14[29]

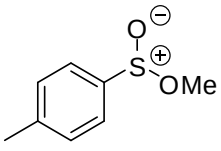


14

3-Phenyl-1-propanol (2.00 g, 14.68 mmol, 1.2 eq.) was added dropwise to a stirred suspension of NaH (0.70 g of 60% wt in mineral oil, 17.12 mmol, 1.4 eq., prewashed with 3 × 10 mL Et_2O) in Et_2O (5 mL) at rt under Ar. The resulting suspension was stirred at rt for 5 min. Then, a solution of *N*,*N*-diisopropylcarbamoyl chloride (2.02 g, 12.22 mmol, 1.0 eq.) in Et_2O (16 mL) was added dropwise. The resulting solution was stirred at rt for 18 h. Then, 2 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with 1 M $NaOH_{(aq)}$, dried (2:1 $MgSO_4$/$NaHCO_3$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 3:2 petrol-Et_2O as eluent gave carbamate **14** (2.82 g, 88%) as a colourless oil, R_F (3:2 petrol-Et_2O) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H, Ph), 7.22-7.20 (m, 3H, Ph), 4.21-3.61 (br m, 2H, NCH), 4.13 (t, J = 6.5 Hz, 2H, OCH_2), 2.73 (t, J = 7.5 Hz, 2H, CH_2Ph), 2.01-1.97 (m, 2H, CH_2), 1.23 (d, J = 7.0 Hz, 12H, NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.8 (C=O), 141.5 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph), 125.9 (Ph), 64.0 (OCH_2), 45.7 (NCH), 32.5 (CH_2), 30.9 (CH_2), 20.9 (Me). Spectroscopic data consistent with those reported in the literature.[213]

Lab Book Reference: PJR 1/52A

Methyl *p*-toluenesulfinate 121

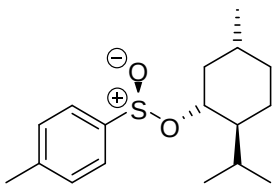


121

Bromine (4.36 g, 1.40 mL, 27.6 mmol, 3.0 eq.) was added to a stirred suspension of Na_2CO_3 (4.87 g, 46.0 mmol, 5.0 eq.) and *p*-tolyl disulfide (2.27 g, 9.2 mmol, 1.0 eq.) in MeOH (195 mL) at rt. The resulting yellow suspension was stirred at rt for 3 h during

which time the suspension became colourless. Then, the solvent was evaporated under reduced pressure. CH_2Cl_2 (100 mL) and water (100 mL) were added to the residue and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated $NH_4Cl_{(aq)}$ (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by Kügelrohr distillation gave sulfinate **121** (2.93 g, 93%) as a colourless oil, bp 91-94 °C/2.0 mmHg (lit.,[214] 129-130 °C/16.0 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.25 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 3.37 (s, 3H, OMe), 2.34 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.8 (*ipso*-Ar), 140.7 (*ipso*-Ar), 129.7 (Ar), 125.3 (Ar), 49.3 (OMe), 21.4 (Me). Spectroscopic data consistent with those reported in the literature.[215]

(*S*)-(−)-Menthyl *p*-toluenesulfinate (S_S)-97



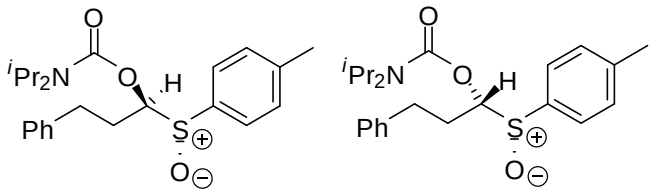
(S_S)-**97**

Thionyl chloride (46.0 mL, 828 mmol, 4.5 eq.) was added dropwise to a stirred suspension of sodium *p*-toluenesulfinate (32.8 g, 184 mmol, 1.0 eq., dried *via* azeotropic distillation from 3 x 75 mL toluene) in toluene (110 mL) at 0 °C over 30 min. The resulting solution was stirred at rt for 2 h. Then, the volatiles were evaporated under reduced pressure and the residue was dissolved in toluene (75 mL). The volatiles were evaporated under reduced pressure to give the crude sulfinyl chloride. The crude sulfinyl chloride was dissolved in Et_2O (90 mL) and added dropwise over 30 min to a stirred solution of (−)-menthol (35.9 g, 230 mmol, 1.25 eq.) in pyridine (33 mL) and Et_2O (150 mL) at 0 °C. A white precipitate immediately formed and the resulting suspension was stirred at rt for 16 h. Then, the suspension was poured into water (150 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with 1 M $HCl_{(aq)}$ (3 x 60 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The resulting solid was recrystallised from hot acetone (20 mL). A second recrystallisation of the solid from hot acetone (20 mL) gave Andersen's sulfinate (S_S)-**97** (8.65 g, 16%)

as colourless needles. Then, 3 drops of conc. $HCl_{(aq)}$ were added to the mother liquor to effect equilibrium of the sulfinate diastereomers. This resulted in crystallisation of Andersen's sulfinate (S_S)-**97**. A recrystallisation of the solid from hot acetone (20 mL) gave Andersen's sulfinate (S_S)-**97** (18.23 g, 34%) as colourless needles. Total yield from two crops = 26.88 g (50 %) as colourless needles, mp 107-108 °C (lit.,[92] mp 107-109 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.33 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 4.13 (td, J = 10.5, 4.5 Hz, 1H, CHOS(O)), 2.42 (s, 3H, C_6H_4Me), 2.31-2.26 (m, 1H), 2.14 (dtd, J = 14.0, 7.0, 3.0 Hz, 1H), 1.72-1.66 (m, 2H), 1.50 (m, 1H), 1.36 (ddt, J = 14.0, 10.5, 3.0 Hz, 1H), 1.28-1.24 (m, 1H), 1.10-0.79 (m, 2H), 0.97 (d, J = 8.0 Hz, 3H, Me), 0.87 (d, J = 8.0 Hz, 3H, Me), 0.72 (d, J = 8.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.1 (*ipso*-Ar), 142.4 (*ipso*-Ar), 129.6 (Ar), 125.0 (Ar), 80.1 (CHO), 47.8 (CH), 42.9 (CH_2), 34.0 (CH_2), 31.7 (CH), 25.2 (CH), 23.1 (CH_2), 22.1 (Me), 21.5 (Me), 20.8 (Me), 14.4 (Me); $[\alpha]_D$ −199.3 (*c* 1.05 in acetone) (lit.,[92] $[\alpha]_D$ −204 (*c* 2.24 in acetone)). Spectroscopic data consistent with those reported in the literature.[92]

(1*S*)-1-(*p*-Tolylsulfinyl)-3-phenylpropyl *N*,*N*-diisopropylcarbamate *anti*-(*S*,*S*$_s$)-103 and (1*R*)-1-(*p*-tolylsulfinyl)-3-phenylpropyl *N*,*N*-diisopropylcarbamate *syn*-(*R*,*S*$_s$)-103

(Table 2.1, Entry 1)



anti-(*S*,*S*$_S$)-**103** *syn*-(*R*,*S*$_S$)-**103**

Using general procedure A, *s*-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.), carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and TMEDA (139 mg, 1.20 mmol, 1.2 eq.) in Et_2O (5 mL) and a solution of Andersen's sulfinate (S_s)-**97** (382 mg, 1.3 mmol, 1.3 eq.) in THF (1 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S,S*$_s$*)*-**103** (100 mg, 25%, 83:17 er by CSP-HPLC) as a white solid, mp 58-60 °C; R_F (3:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2971, 1697 (C=O), 1436, 1370, 1286, 1091,

1035, 910, 812, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.28 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 7.21 (t, J = 7.0 Hz, 2H, *m*-Ph), 7.16 (d, J = 7.0 Hz, 1H, *p*-Ph), 7.02 (d, J = 7.0 Hz, 2H, *o*-Ph), 5.45 (dd, J = 10.0, 3.0 Hz, 1H, OCH), 3.94 (br s, 2H, NCH), 2.74 (ddd, J = 14.0, 10.0, 5.0 Hz, 1H, PhCH_AH_B), 2.56 (ddd, J = 14.0, 10.0, 7.0 Hz, 1H, PhCH_AH_B), 2.40 (s, 3H, Me) 2.36-2.25 (m, 1H, CH), 2.06-1.98 (m, 1H, CH), 1.26 (br s, 12H, NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.5 (C=O), 141.2 (*ipso*-Ar), 140.3 (*ipso*-Ar), 137.4 (*ipso*-Ar), 129.7 (Ar), 128.3 (Ar), 128.1 (Ar), 126.0 (Ar), 124.4 (Ar), 91.7 (OCH), 46.7 (br, NCH), 46.0 (br, NCH), 31.1 (CH_2), 26.0 (CH_2), 21.3 (Me), 20.2 (br, Me); MS (ESI) *m/z* 424 [$(M + Na)^+$, 100], 402 [$(M + H)^+$, 20]; HRMS *m/z* calcd for $C_{23}H_{31}NO_3S$ $(M + Na)^+$ 424.1917 (+1.3 ppm error), found 424.1911; CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R*,R_s)-**103** 12.8 min, *anti*-(*S*,S_s)-**103** 14.0 min and sulfoxide *syn-(R*,S_s*)*-**103** (84 mg, 21%, 85:15 er by CSP-HPLC) as a colourless oil, R_F (3:1 petrol-EtOAc) 0.20; IR (film) 2971, 2968, 1707 (C=O), 1434, 1370, 1291, 1136, 1091, 1038, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.28-7.24 (m, 4H, Ar), 7.21-7.14 (m, 3H, Ar), 5.72 (dd, J = 9.5, 4.0 Hz, 1H, OCH), 3.99 (br s, 1H, NCH), 3.57 (br s, 1H, NCH), 2.79-2.75 (m, 2H, PhCH_2), 2.41-2.33 (m, 1H, CH), 2.37 (s, 3H, Me), 2.17-2.08 (m, 1H, CH), 1.21-0.99 (m, 12H, CHMe_2), ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.3 (C=O), 141.5 (*ipso*-Ar), 140.3 (*ipso*-Ar), 136.0 (*ipso*-Ar), 129.5 (Ar), 128.5 (Ar), 128.4 (Ar), 126.3 (Ar), 125.3 (Ar), 86.8 (OCH), 46.3 (br, NCH) 45.9 (br, NCH), 31.7 (CH_2), 30.3 (CH_2), 21.3 (Me), 21.1 (Me), 20.8 (Me), 20.2 (Me), 20.1 (Me); MS (ESI) *m/z* 424 [$(M + Na)^+$, 90], 402 [$(M + H)^+$, 100]; HRMS *m/z* calcd for $C_{23}H_{31}NO_3S$ $(M + Na)^+$ 424.1917, found 424.1905 (+2.7 ppm error); CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S*,R_s)-**103** 21.3 min, *syn*-(*R*,S_s)-**103** 23.8 min.

(Table 2.1, Entry 2)

Using general procedure B, *s*-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.), carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and TMEDA (139 mg, 1.20 mmol, 1.2 eq.) in Et_2O (5 mL) and a solution of Andersen's sulfinate (S_s)-**97** (382 mg, 1.3 mmol, 1.3 eq.) in THF (4 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S*,S_s*)*-**103** (93 mg, 23%, 88:12 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R*,R_s)-**103** 12.9 min, *anti*-(*S*,S_s)-**103** 14.2 min and sulfoxide *syn-(R*,S_s*)*-**103** (130 mg, 32%, 91:9 er by CSP-HPLC)

as a colourless oil, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S*,R_s)-**103** 22.3 min, *syn*-(*R*,S_s)-**103** 24.5 min.

(Table 2.1, Entry 3)

Using general procedure C, *s*-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.), carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and TMEDA (139 mg, 1.20 mmol, 1.2 eq.) in Et_2O (5 mL) and a solution of Andersen's sulfinate (S_s)-**97** (382 mg, 1.3 mmol, 1.3 eq.) in THF (4 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S,*S_s*)*-**103** (100 mg, 25%, 87:13 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R*,R_s)-**103** 13.0 min, *anti*-(*S*,S_s)-**103** 14.3 min and sulfoxide *syn-(R,*S_s*)*-**103** (116 mg, 29%, 90:10 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S*,R_s)-**103** 22.3 min, *syn*-(*R*,S_s)-**103** 24.5 min.

(Table 2.1, Entry 4)

Using general procedure B, *s*-BuLi (0.92 mL of a 1.3M solution in hexanes, 1.20 mmol, 1.2 eq.), carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and TMEDA (139 mg, 1.20 mmol, 1.2 eq.) in Et_2O (5 mL) and a solution of Andersen's sulfinate (S_s)-**97** (587 mg, 2.0 mmol, 2.0 eq.) in THF (6 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S,*S_s*)*-**103** (84 mg, 21%, 92:8 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R*,R_s)-**103** 13.2 min, *anti*-(*S*,S_s)-**103** 14.6 min and sulfoxide *syn-(R,*S_s*)*-**103** (96 mg, 24%, 95:5 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S*,R_s)-**103** 21.9 min, *syn*-(*R*,S_s)-**103** 24.2 min and sulfoxide.
Lab Book Reference: PJR 3/224

(Table 2.1, Entry 5)

Using general procedure B, *s*-BuLi (0.92 mL of a 1.3M solution in hexanes, 1.20 mmol, 1.2 eq.), carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and TMEDA (139 mg, 1.20 mmol, 1.2 eq.) in Et_2O (5 mL) and a solution of Andersen's sulfinate (S_s)-**97** (882 mg, 3.0 mmol, 3.0 eq.) in THF (8 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide

anti-(S,S$_s$*)*-**103** (104 mg, 26%, 90:10 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R,R*$_s$)-**103** 13.1 min, *anti*-(*S,S*$_s$)-**103** 14.4 min and sulfoxide *syn-(R,S*$_s$*)*-**103** (125 mg, 31%, 93:7 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S,R*$_s$)-**103** 22.0 min, *syn*-(*R,S*$_s$)-**103** 24.4 min and sulfoxide.

Lab Book Reference: PJR 3/228

(Table 2.1, Entry 6)

s-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.) was added dropwise to a stirred solution of carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and TMEDA (139 mg, 1.20 mmol, 1.2 eq.) in Et_2O (5.0 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, a freshly prepared solution of $MgBr_2$ [prepared from 1,2-dibromoethane (0.12 mL, 1.3 mmol) and Mg turnings (50 mg, 1.95 mmol)] in THF was added. Resulting solution is stirred at −78 °C for 1 h and then a solution of Andersen's sulfinate (*S*$_s$)-**97** (382 mg, 2.0 mmol, 2.0 eq.) in THF (4.0 mL) at −78 °C. The resulting solution was stirred at −78 °C for 5 min. Then, MeOH (2.0 mL) was added and the resulting solution allowed to warm to rt. The solution was then poured into sat. $NH_4Cl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S,S*$_s$*)*-**103** (32 mg, 8%, 92:8 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R,R*$_s$)-**103** 12.9 min, *anti*-(*S,S*$_s$)-**103** 13.9 min and sulfoxide *syn-(R,S*$_s$*)*-**103** (30 mg, 8%, 87:13 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S,R*$_s$)-**103** 21.7 min, *syn*-(*R,S*$_s$)-**103** 23.4 min and sulfoxide.

Lab Book Reference: PJR 4/225

(Table 2.2, Entry 1)

Using general procedure A, *s*-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.80 mmol, 1.2 eq.), carbamate **14** (395 mg, 1.50 mmol, 1.0 eq.) and (−)-sparteine (422 mg, 1.80 mmol, 1.2 eq.) in Et_2O (6 mL) and a solution of Andersen's sulfinate (*S*$_s$)-**97** (882

mg, 3.0 mmol, 2.0 eq.) in THF (2 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S,S$_s$)*-**103** (319 mg, 53%, 99:1 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) anti-(*R*,*R*$_s$)-**103** 13.1 min, *anti*-(*S*,*S*$_s$)-**103** 14.2 min and sulfoxide *syn-(R,S$_s$)*-**103** (1.5 mg, 0.2%, er not determined) as a colourless oil.

(Table 2.2, Entry 2)

Using general procedure A, *s*-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.), carbamate **14** (263 mg, 1.00 mmol, 1.0 eq.) and the (+)-sparteine surrogate (233 mg, 1.20 mmol, 1.2 eq.) in Et_2O (5 mL) and a solution of Andersen's sulfinate (*S*$_s$)-**97** (382 mg, 1.3 mmol, 1.3 eq.) in THF (1 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S,S$_s$)*-**103** (32 mg, 7%, 87:13 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) anti-(*R*,*R*$_s$)-**103** 12.7 min, *anti*-(*S*,*S*$_s$)-**103** 13.5 min and sulfoxide *syn-(R,S$_s$)*-**103** (180 mg, 45%, 99:1 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*R*$_s$)-**103** 21.1 min, *syn*-(*R*,*S*$_s$)-**103** 23.6 min.

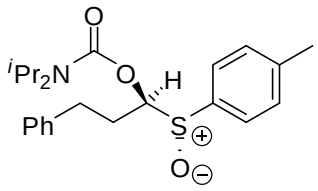
(Table 2.2, Entry 3)

Using general procedure C, *s*-BuLi (1.85 mL of a 1.3 M solution in hexanes, 2.4 mmol, 1.2 eq.), carbamate **14** (526 mg, 2.0 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (745 mg, 2.4 mmol, 1.2 eq.) in Et_2O (10 mL) and a solution of Andersen's sulfinate (*S*$_s$)-**97** (1176 mg, 4.0 mmol, 2.0 eq.) in THF (8 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S,S$_s$)*-**103** (133 mg, 17%, 95:5 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +27.6 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R*,*R*$_s$)-**103** 13.9 min, *anti*-(*S*,*S*$_s$)-**103** 15.1 min and sulfoxide *syn-(R,S$_s$)*-**103** (436 mg, 54%, 99:1 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +43.7 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*R*$_s$)-**103** 25.0 min, *syn*-(*R*,*S*$_s$)-**103** 26.6 min.

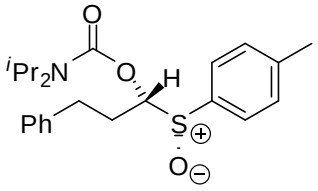
(Table 2.2, Entry 4)

Using general procedure C, *s*-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.2 mmol, 1.2 eq.), carbamate **14** (263 mg, 1.0 mmol, 1.0 eq.) and diamine (*R*,*R*)-**42** (371 mg, 1.2 mmol, 1.2 eq.) in Et_2O (5 mL) and a solution of Andersen's sulfinate (S_s)-**97** (589 mg, 2.0 mmol, 2.0 eq.) in THF (4 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-(S,S*$_s$*)*-**103** (225 mg, 56%, 99:1 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +26.9 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R*,*R*$_s$)-**103** 13.0 min, *anti*-(*S*,*S*$_s$)-**103** 14.0 min and sulfoxide *syn-(R,S*$_s$*)*-**103** (56 mg, 14%, 93:7 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +43.4 (*c* 0.55 in $CHCl_3$); CSP-HPLC: Chiracel OD (97.5:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*R*$_s$)-**103** 22.1 min, *syn*-(*R*,*S*$_s$)-**103** 24.7 min.

1-(*p*-Tolylsulfinyl)-3-phenylpropyl *N*,*N*-diisopropylcarbamate *anti-rac*-103 and *syn-rac*-103



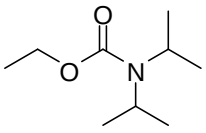
anti-rac-**103**



syn-rac-**103**

Using general procedure A, *s*-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.80 mmol, 1.2 eq.), carbamate **14** (395 mg, 1.50 mmol, 1.0 eq.) and TMEDA (208 mg, 1.80 mmol, 1.2 eq.) in Et_2O (6 mL) and methyl *p*-toluenesulfinate **121** (510 mg, 2.00 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-rac*-**103** (148 mg, 25%) as a viscous colourless oil and sulfoxide *syn-rac*-**103** (190 mg, 32%) as a colourless oil.

Ethyl diisopropylcarbamate 124[123]



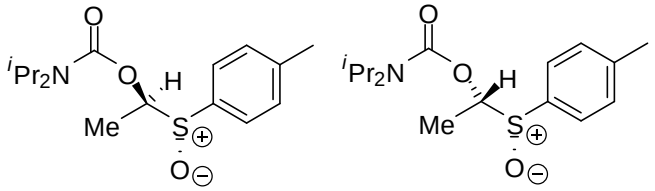
124

Diisopropylamine (8.39 mL, 60 mmol, 3.0 eq.) was added dropwise to a stirred solution of ethyl chloroformate (1.89 mL, 20 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) at 0 °C under

Ar. The resulting solution was stirred at 0 °C for 30 min. Then, 1 M $HCl_{(aq)}$ (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave carbamate **124** (3.39 g, 98%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (q, J = 7.0 Hz, 2H, OCH_2), 4.12-3.62 (m, 2H, NCH), 1.23 (t, J = 7.0 Hz, 3H, OCH_2*Me*), 1.17 (d, J = 6.5 Hz, 12H, NCH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.7 (C=O), 60.2 (OCH_2), 45.7 (br, NCH), 20.7 (Me), 14.5 (Me). Spectroscopic data consistent with those reported in the literature.[32]

Lab Book Reference: PJR 8/670

(1*S*)-(*p*-Tolylsulfinyl)-ethyl *N*,*N*-diisopropylcarbamate *anti*-(*S*,*S*$_s$)-123 and (1*R*)-(*p*-Tolylsulfinyl)-ethyl *N*,*N*-diisopropylcarbamate *syn*-(*R*,*S*$_s$)-123

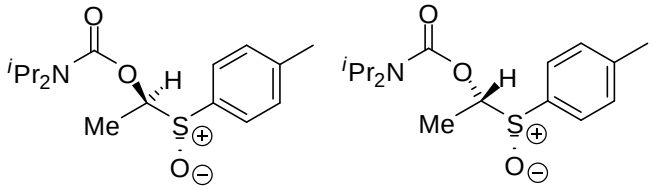


anti-(*S*,*S*$_S$)-**123** *syn*-(*R*,*S*$_S$)-**123**

Using general procedure A, *s*-BuLi (1.85 mL of a 1.3 M solution in hexanes, 2.40 mmol, 1.2 eq.), carbamate **124** (346 mg, 2.00 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (744 mg, 2.40 mmol, 1.2 eq.) in Et_2O (12 mL) and a solution of Andersen's sulfinate (*S*$_s$)-**97** (1.18 g, 4.0 mmol, 2.0 eq.) in THF (10 mL) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti*-(*S*,*S*$_s$)-**123** (24 mg, 4%, er not determined) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.4; IR (film) 2971, 2959, 1694 (C=O), 1531, 1475, 1312, 1296, 1050, 910, 854, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.32 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 5.52 (q, J = 6.5 Hz, 1H, OCH), 4.04 (br s, 1H, NCH), 3.86 (br s, 1H, NCH), 2.40 (s, 3H, Me) 1.36 (d, J = 6.5 Hz, 1H, Me), 1.29-1.21 (br m, 12H, NCH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.8 (C=O), 141.2 (*ipso*-Ar), 137.7 (*ipso*-Ar), 129.8 (Ar), 124.3 (Ar), 89.3 (OCH), 46.8 (br, NCH), 45.9 (br, NCH), 21.5 (br, Me), 21.4 (Me), 20.3 (br, Me), 9.4 (Me); MS (ESI) *m/z* 334 [(M + Na)$^+$, 100], 312 [(M + H)$^+$, 80]; HRMS *m/z* calcd for $C_{16}H_{25}NO_3S$ (M + Na)$^+$ 334.1447, found

334.1448 (−0.1 ppm error) and sulfoxide *syn-(R,S$_S$)*-**123** (55 mg, 9%, er not determined) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.30; IR (film) 2992, 2978, 2970, 1700 (C=O), 1530, 1472, 1450, 1390, 1291, 1122, 1078, 910, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.29 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 5.80 (q, J = 6.5 Hz, 1H, OCH), 3.90 (br s, 1H, NCH), 3.70 (br s, 1H, NCH), 2.39 (s, 3H, Me), 1.48 (d, J = 6.5 Hz, 1H, Me), 1.15-1.04 (m, 12H, CH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.5 (C=O), 141.7 (*ipso*-Ar), 136.0 (*ipso*-Ar), 129.4 (Ar), 125.4 (Ar), 84.0 (OCH), 47.6 (NCH) 46.1 (NCH), 21.5 (Me), 21.4 (Me), 20.8 (Me), 20.5 (Me), 20.1 (Me), 13.7 (Me); MS (ESI) *m/z* 334 [(M + Na)$^+$, 70], 312 [(M + H)$^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{25}NO_3S$ (M + Na)$^+$ 334.1447, found 334.1447 (+0.1 ppm error).

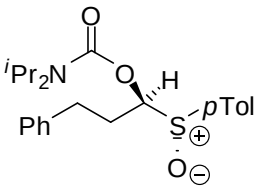
1-(*p*-Tolylsulfinyl)-ethyl *N,N*-diisopropylcarbamate *anti-rac*-123 and 1-(*p*-tolylsulfinyl)-ethyl *N,N*-diisopropylcarbamate *syn-rac*-123



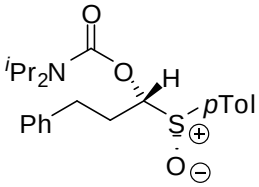
anti-rac-**123** *syn-rac*-**123**

Using general procedure A, *s*-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.), carbamate **124** (173 mg, 1.00 mmol, 1.0 eq.) and TMEDA (179 μL, 1.20 mmol, 1.2 eq.) in Et_2O (5 mL) and methyl *p*-tolyl sulfinate **121** (255 mg, 1.5 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-rac*-**123** (90 mg, 29%) as a colourless oil and sulfoxide *syn-rac*-**123** (69 mg, 22%) as a colourless oil.

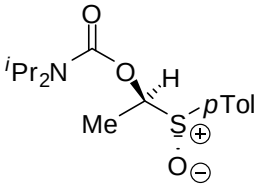
1-(*p*-Tolylsulfinyl)-3-phenylpropyl *N*,*N*-diisopropylcarbamate *anti-rac*-103, 1-(*p*-tolylsulfinyl)-3-phenylpropyl *N*,*N*-diisopropylcarbamate *syn-rac*-103, 1-(*p*-tolylsulfinyl)-ethyl *N*,*N*-diisopropylcarbamate *anti-rac*-123 and 1-(*p*-tolylsulfinyl)-ethyl *N*,*N*-diisopropylcarbamate *syn-rac* 123 (Scheme 2.17)



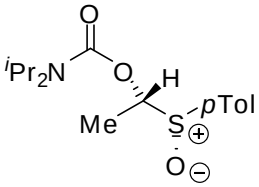
anti-rac-**103**



syn-rac-**103**



anti-rac-**123**



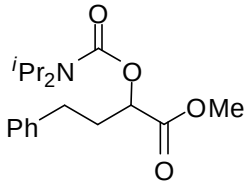
syn-rac-**123**

s-BuLi (0.38 mL of a 1.3 M solution in hexanes, 0.50 mmol, 1.0 eq.) was added to a stirred solution of carbamate **124** (87 mg, 0.50 mmol, 1.0 eq.) and TMEDA (75 μL, 0.50 mmol, 1.0 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, a solution of sulfoxide *anti-rac*-**103** (200 mg, 0.50 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise and the resulting solution was stirred at −78 °C for 1 h. MeOH (1 mL) was added and the solution was warmed to rt over 30 min. The solution was poured into saturated $NH_4Cl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1-3:1 petrol-EtOAc + 1% Et_3N as eluent gave recovered carbamate **124** (51 mg, 59%) as a colourless oil and a 70:5:13:12 mixture (by ^1H NMR spectroscopy) of sulfoxides *anti-rac*-**103**, *syn-rac*-**103**, *anti-rac*-**123**, *syn-rac*-**123** (180 mg, 66%, 5%, 13%, 12% respectively based on sulfoxide *anti-rac*-**103**) as a pale yellow oil.

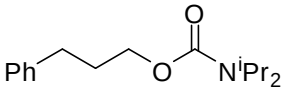
Optimisation of Sulfoxide → Mg Exchange Reaction (Table 2.3)

Methyl 2-[(*N*,*N*-diisopropylcarbamoyl)oxy]-4-phenylbutanoate *rac*-126, *O*-alkyl carbamate 14, and *i*-propyl *p*-tolyl sulfoxide *rac*-128

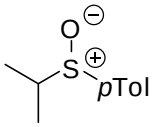
(Table 2.3, Entry 1)



rac-**126**



14



rac-**128**

Using general procedure D, *i*-PrMgCl (0.11 mL of a 2.0 M solution in THF, 0.22 mmol, 1.1 eq.) and sulfoxide *anti-rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at 0 °C for 10 s and methyl chloroformate (19 mg, 0.22 mmol, 1.1 eq.) at 0 °C for 5 min gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester *rac*-**126** (31 mg, 49%) as a colourless oil, recovered sulfoxide *anti-rac*-**103** (16 mg, 20%) and sulfoxide *rac*-**128** (20 mg, 54%) as a colourless oil.
Lab Book Reference: PJR 4/282

(Table 2.3, Entry 2)
Using general procedure D, *i*-PrMgCl (0.13 mL of a 2.0 M solution in THF, 0.26 mmol, 1.3 eq.) and sulfoxide *anti-rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at 0 °C for 1 min and methyl chloroformate (25 mg, 0.26 mmol, 1.3 eq.) at 0 °C for 5 min gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester *rac*-**126** (37 mg, 58%) as a colourless oil, *O*-alkyl carbamate **14** (2 mg, 3 %) as a colourless oil, recovered sulfoxide *anti-rac*-**103** (3 mg, 3%) and sulfoxide *rac*-**128** (27 mg, 74%).
Lab Book Reference: PJR 4/284

(Table 2.3, Entry 3)
Using general procedure D, *i*-PrMgCl (0.13 mL of a 2.0 M solution in THF, 0.26 mmol, 1.3 eq.) and sulfoxide *anti-rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 20 s and methyl chloroformate (25 mg, 0.26 mmol, 1.3 eq.) at rt for 5 min gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester *rac*-**126** (35 mg, 56%) as a colourless oil, *O*-alkyl carbamate **14** (1 mg, 1%) as a colourless oil, recovered sulfoxide *anti-rac*-**103** (4 mg, 5%) and sulfoxide *rac*-**128** (26 mg, 71%).
Lab Book Reference: PJR 4/288

(Table 2.3, Entry 4)
Using general procedure D, *i*-PrMgCl (0.13 mL of a 2.0 M solution in THF, 0.26 mmol, 1.3 eq.) and sulfoxide *anti-rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and methyl chloroformate (25 mg, 0.26 mmol, 1.3 eq.) at rt for 5 min gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-

EtOAc as eluent gave ester *rac*-**126** (37 mg, 65%) as a colourless oil, *O*-alkyl carbamate **14** (4 mg, 6%) as a colourless oil, recovered sulfoxide *anti*-*rac*-**103** (16 mg, 8%) and sulfoxide *rac*-**128** (27 mg, 73%).

(Table 2.3, Entry 5)

Using general procedure D, *i*-PrMgCl (0.13 mL of a 2.0 M solution in THF, 0.26 mmol, 1.3 eq.) and sulfoxide *anti*-*rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 5 min and methyl chloroformate (25 mg, 0.26 mmol, 1.3 eq.) at rt for 5 min gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester *rac*-**126** (27 mg, 48%) as a colourless oil, *O*-alkyl carbamate **14** (9 mg, 14%) as a colourless oil, recovered sulfoxide *anti*-*rac*-**103** (8 mg, 4%) and sulfoxide *rac*-**128** (30 mg, 81%).

(Table 2.3, Entry 6)

Using general procedure D, *i*-PrMgCl (0.15 mL of a 2.0 M solution in THF, 0.30 mmol, 1.5 eq.) and sulfoxide *anti*-*rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and methyl chloroformate (29 mg, 0.30 mmol, 1.5 eq.) at rt for 5 min gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester *rac*-**126** (38 mg, 67%) as a colourless oil, *O*-alkyl carbamate **14** (6 mg, 9%) as a colourless oil and sulfoxide *rac*-**128** (31 mg, 84%).

(Table 2.3, Entry 7)

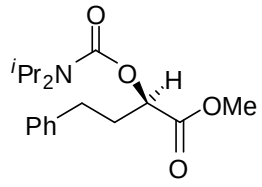
Using general procedure D, *i*-PrMgCl (0.15 mL of a 2.0 M solution in THF, 0.30 mmol, 1.5 eq.) and sulfoxide *anti*-*rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 5 min and methyl chloroformate (29 mg, 0.30 mmol, 1.5 eq.) at rt for 5 min gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester *rac*-**126** (24 mg, 42%) as a colourless oil, *O*-alkyl carbamate **14** (9 mg, 17%) as a colourless oil and sulfoxide *rac*-**128** (30 mg, 82%).

(Table 2.3, Entry 8)

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti*-*rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and methyl chloroformate (48 mg, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent

gave ester *rac*-**126** (48 mg, 75%) as a colourless oil, *O*-alkyl carbamate **14** (2.5 mg, 5%) as a colourless oil and sulfoxide *rac*-**128** (31 mg, 84%).

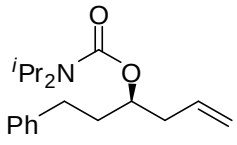
Methyl (2*R*)-[*N*,*N*-(diisopropylcarbamoyl)oxy]-4-phenylbutanoate (*R*)-126



(*R*)-**126**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti*-(*S*,S_s)-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) and methyl chloroformate (48 mg, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester (*R*)-**126** (46 mg, 73%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.5 Hz, 2H, *m*-Ph), 7.23-7.19 (m, 3H, Ph), 5.08 (t, J = 6.5 Hz, 1H, OCH), 4.11 (br s, 1H, NCH), 3.80 (br s, 1H, NCH), 3.73 (s, 3H, OMe), 2.79-2.75 (m, 2H, $PhCH_2$), 2.21-2.15 (m, 2H, CH), 1.35-1.20 (br m, 12H, NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (CO_2Me), 154.8 (*i*-Pr_2NC=O), 140.7 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 126.2 (Ph), 72.0 (OCH), 52.0 (OMe), 45.4 (br, NCH), 33.3 (CH_2), 31.8 (CH_2), 20.4 (br, Me); $[\alpha]_D$ −17.8 (*c* 0.55 in CH_2Cl_2) [lit.[127], $[\alpha]_D$ −17.3 (*c* 1.0 in CH_2Cl_2) for (*R*)-**126** of 97:3 er)]; CSP-HPLC: Chiracel OD (95:5 Hexane-*i*PrOH, 0.5 mL min^{-1}) (*S*)-**126** 10.7 min, (*R*)-**126** 11.9 min. Spectroscopic data consistent with those reported in the literature.[127]

1-Phenylhex-5-en-(3*R*)-yl *N*,*N*-diisopropylcarbamate (*R*)-129

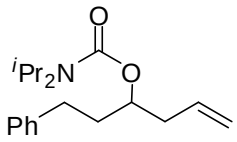


(R)-**129**

i-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) was added dropwise to a stirred solution of sulfoxide *anti*-(*S*,S_s)-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, a

solution of $CuBr.SMe_2$ (8.2 mg, 0.04 mmol, 0.2 eq.) in THF (1.0 mL) and allyl bromide (43 μL, 0.50 mmol, 2.5 eq.) were added sequentially. The solution was stirred at rt for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave carbamate (*R*)-**129** (43 mg, 70%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.3; IR (film) 3047, 2901, 2874, 1654 (C=O), 1597, 1487, 1301, 1298, 1275, 1117, 1054, 893 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H, Ph), 7.19-7.15 (m, 3H, Ph), 5.85-5.76 (m, 1H, CH_2=C*H*), 5.11-5.04 (m, 2H, CH_2=CH), 5.00-4.93 (m, 1H, OCH), 4.10 (br s, 1H, NCH), 3.74 (br s, 1H, NCH), 2.74-2.60 (m, 2H, CH), 1.96-1.83 (m, 2H, CH), 1.25-1.21 (br m, 12H, NCH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.4 (C=O), 142.0 (*ipso*-Ph), 134.1 (CH_2=*C*H), 128.4 (Ph), 128.3 (Ph) 125.8 (Ph), 117.5 (*C*H_2=CH), 73.2 (OCH), 46.2 (br, NCH), 39.0 (CH_2), 35.9 (CH_2), 31.9 (CH_2), 20.8 (br, NCH*Me*$_2$); MS (ESI) *m/z* 326 [$(M + Na)^+$, 100], 304 [$(M + H)^+$, 20]; HRMS *m/z* calcd for $C_{19}H_{29}NO_2$ $(M + Na)^+$ 326.2091, found 326.2082 (+2.5 ppm error). $[\alpha]_D$ +3.0 (*c* 0.45 in $CHCl_3$); CSP-HPLC: Chiracel OD-H (99:1 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*)-**129** 5.4 min, (*S*)-**129** 6.7 min.

1-Phenylhex-5-en-3-yl *N,N*-diisopropylcarbamate *rac*-129

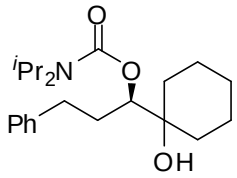


rac-**129**

i-PrMgCl (0.15 mL of a 2.0 M solution in THF, 0.30 mmol, 1.5 eq.) was added dropwise to a stirred solution of sulfoxide *anti-rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, a solution of $CuBr.SMe_2$ (8.2 mg, 0.04 mmol, 0.2 eq.) in THF (1.0 mL) and allyl bromide (26 μL, 0.30 mmol, 1.5 eq.) were added sequentially. The solution was stirred at rt for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave carbamate *rac*-**129** (31 mg, 51%) as a colourless oil.

(1*R*)-(1-Hydroxycyclohexyl)-3-phenylpropyl *N*,*N*-diisopropylcarbamate (*R*)-127



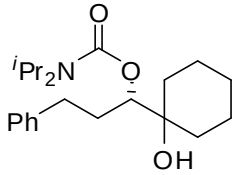
(*R*)-**127**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti-(S,S$_s$)*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and cyclohexanone (52 μL, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-Et_2O as eluent gave alcohol (*R*)-**127** (52 mg, 71%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (95:5 CH_2Cl_2-Et_2O) 0.2; IR (film) 3392 (OH), 2920, 2889, 1647 (C=O), 1417, 1347, 1278, 1138, 1117, 1034, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H, Ph), 7.20-7.17 (m, 3H, Ph), 4.88-4.81 (m, 1H, OCH), 4.09 (br s, 1H, NCH), 3.87 (br s, 1H, NCH), 2.75-2.58 (m, 2H, CH), 1.98-1.94 (m, 2H, CH), 1.84 (br s, 1H, OH), 1.63-1.25 (br m, 22H, CH + NCH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.9 (C=O), 142.1 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph) 125.8 (Ph), 80.1 (OCH), 73.2 (COH), 46.5 (br, NCH), 45.4 (br, NCH), 34.3 (CH_2), 33.2 (CH_2), 32.7 (CH_2), 31.2 (CH_2), 25.8 (CH_2), 21.8 (br, NCH*Me*$_2$), 21.5 (CH_2), 21.4 (CH_2), 20.5 (br, NCH*Me*$_2$); MS (ESI) *m/z* 384 [$(M + Na)^+$, 90], 219 (100), 90 (80); HRMS *m/z* calcd for $C_{22}H_{35}NO_3$ $(M + Na)^+$ 384.2509, found 384.2493 (+4.1 ppm error); $[\alpha]_D$ +29.1 (*c* 0.6 in $CHCl_3$); CSP-HPLC: Chiracel OD (98:2 Hexane-*i*PrOH, 0.5 $mLmin^{-1}$) (*R*)-**127** 14.5 min, (*S*)-**127** 21.2 min.

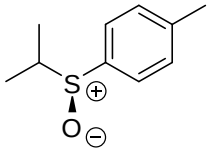
Using general procedure D, *i*-PrMgCl (0.13 mL of a 2.0 M solution in THF, 0.25 mmol, 2.5 eq.) and sulfoxide *anti-(S,S$_s$)*-**103** (40 mg, 0.10 mmol, 1.0 eq.) in THF (4 mL) at rt for 15 min and cyclohexanone (26 μL, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-Et_2O as eluent gave alcohol (*R*)-**127** (12 mg, 34%, 98:2 er by CSP-HPLC) as a colourless oil.

Using general procedure D, *i*-PrMgCl (0.13 mL of a 2.0 M solution in THF, 0.25 mmol, 2.5 eq.) and sulfoxide *anti-(S,S$_S$)*-**103** (40 mg, 0.10 mmol, 1.0 eq.) in THF (4 mL) at rt for 30 min and cyclohexanone (26 μL, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-Et_2O as eluent gave alcohol (*R*)-**127** (8.5 mg, 24%, 98:2 er by CSP-HPLC) as a colourless oil.

(1*S*)-(1-Hydroxycyclohexyl)-3-phenylpropyl *N,N*-diisopropylcarbamate (*S*)-127 and (*S*)-isopropyl *p*-tolyl sulfoxide (*S*)-128



(*S*)-**127**

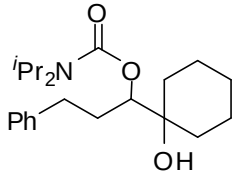


(*S*)-**128**

Using general procedure D, *i*-PrMgCl (0.43 mL of a 2.0 M solution in THF, 0.60 mmol, 2.5 eq.) and sulfoxide *syn-(R,S$_S$)*-**103** (96 mg, 0.24 mmol, 1.0 eq.) in THF (9 mL) at rt for 1 min and cyclohexanone (62 μL, 0.60 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-Et_2O as eluent gave alcohol (*S*)-**127** (65 mg, 74%, 99:1 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ −28.6 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiracel OD (98:2 Hexane-*i*PrOH, 0.5 mLmin^{-1}) (*R*)-**127** 13.4 min, (*S*)-**127** 21.4 min and sulfoxide (*S*)-**128** (31 mg, 78%) as a colourless oil, R_F (95:5 CH_2Cl_2-Et_2O) 0.05; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.31 (d, *J* = 8.0 Hz, 2H, *o*-C_6H_4Me), 2.82 (sept, *J* = 7.0 Hz, 1H, S(O)CH), 2.82 (s, 3H, Me), 1.19 (d, *J* = 7.0 Hz, 3H, CH*Me*), 1.15 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.5 (*ipso*-Ar), 138.5 (*ipso*-Ar), 129.6 (Ar), 125.1 (Ar), 54.6 (C*H*Me_2), 21.5 (Me), 15.8 (Me), 14.2 (Me); $[\alpha]_D$ −194.2 (*c* 1.0 in EtOH) [lit.[115], $[\alpha]_D$ −187 (*c* 2.4 in EtOH)]. Spectroscopic data consistent with those reported in the literature.[216]

The isolation of sulfoxide (*S*)-**128** allows assignment of the configuration in sulfoxides *anti-(S,S$_S$)*-**103** and *syn-(R,S$_S$)*-**103**. Sulfoxide (*S*)-**128** is the expected product of double inversion from Andersen's sulfinate (S_S)-**97**.

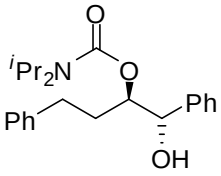
1-(1-Hydroxycyclohexyl)-3-phenylpropyl *N*,*N*-diisopropylcarbamate *rac*-127



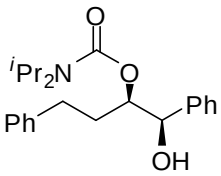
rac-**127**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti*-*rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and cyclohexanone (52 μL, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-Et_2O as eluent gave alcohol *rac*-**127** (45 mg, 62%) as a colourless oil.

1-Hydroxy-1,4-diphenylbutan-2-yl *N*,*N*-diisopropylcarbamate (*R*,*S*)-130 and (*R*,*R*)-130



(*R*,*S*)-**130**

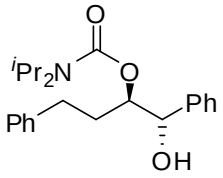


(*R*,*R*)-**130**

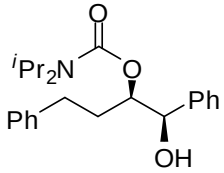
Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti*-(*S*,S_s)-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and benzaldehyde (51 μL, 0.50 mmol, 2.5 eq.) gave the crude product which contained a 90:10 mixture of (*R*,*S*)-**130** and (*R*,*R*)-**130** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 95:5-9:1 petrol-EtOAc as eluent gave a 96:4 mixture (by ^{1}H NMR spectroscopy) of alcohols (*R*,*S*)-**130** and (*R*,*R*)-**130** (42 mg, 58%, each diastereoisomer 99:1 er by CSP-HPLC) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; IR (film) 3378 (OH), 2923, 2881, 1653 (C=O), 1572, 1451, 1358, 1139, 1118, 943 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (m, 4H, Ph), 7.28-7.26 (m, 3H, Ph), 7.21-7.17 (m, 1H, Ph), 7.14-7.12 (m, 2H, Ph), 5.12-5.08 (m, 0.96H, OCH), 5.06-5.01 (m, 0.04H, OCH), 4.89 (d, J = 3.0 Hz, 1H, C*H*OH), 3.98-3.81 (m, 2H, NCH), 2.77-2.70 (m, 1H, PhCH_AH_B), 2.64-2.57 (m, 1H, PhCH_AH_B), 1.94-1.88 (m, 2H, CH), 1.27-1.08 (m, 12H, NCH*Me*$_2$), OH not resolved; ^{13}C NMR (100.6 MHz, $CDCl_3$) for (*R*,*S*)-**130** δ 156.1 (C=O), 141.4 (*ipso*-Ph), 140.1 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph)

128.0 (Ph), 127.5 (Ph), 127.0 (Ph), 126.8 (Ph), 78.6 (OCH), 76.3 (OCH), 46.3 (br, NCH), 32.4 (CH_2), 32.0 (CH_2), 20.4 (br, NCH*Me*$_2$); MS (ESI) *m/z* 392 [$(M + Na)^+$, 100], 370 [$(M + H)^+$, 35]; HRMS *m/z* calcd for $C_{19}H_{29}NO_2$ $(M + Na)^+$ 392.2202, found 392.2202 (+0.3 ppm error), CSP-HPLC: Chiracel OD (95:5 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*S*,*S*)-**130** 14.5 min, (*R*,*S*)-**130** 16.7 min, (*R*,*R*)-**130** 18.6 min, (*S*,*R*)-**130** 26.5 min.

1-Hydroxy-1,4-diphenylbutan-2-yl *N*,*N*-diisopropylcarbamate *anti-rac*-130 and *syn-rac*-130



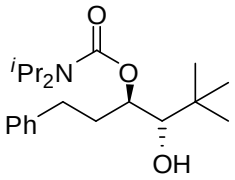
anti-rac-**130**



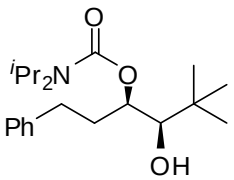
syn-rac-**130**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti*-(*S*,S_s)-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and benzaldehyde (51 μL, 0.50 mmol, 2.5 eq.) gave the crude product which contained a 90:10 mixture of (*R*,*S*)-**130** and (*R*,*R*)-**130** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 95:5-9:1 petrol-EtOAc as eluent gave a 92:8 mixture (by ^{1}H NMR spectroscopy) of alcohols (*R*,*S*)-**130** and (*R*,*R*)-**130** (36 mg, 49%) as a colourless oil.

4-Hydroxy-5,5-dimethyl-1-phenylhexan-3-yl *N*,*N*-bis(propan-2-yl)carbamate (*R*,*S*)-131 and (*R*,*R*)-131



(*R*,*S*)-**131**

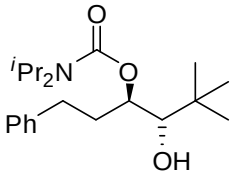


(*R*,*R*)-**131**

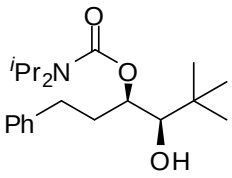
Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti-(S,S$_s$)*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and pivaldehyde (54 μL, 0.50 mmol, 2.5 eq.) gave the crude product which contained a 60:40 mixture of (*R*,*S*)-**131** and (*R*,*R*)-**131** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as

eluent gave a 70:30 mixture (by ^{1}H NMR spectroscopy) of alcohols (*R*,*S*)-**131** and (*R*,*R*)-**131** (54 mg, 78%, minor diastereoisomer 99:1 er by CSP-HPLC of the diol, major diastereoisomer er not determined) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.2; IR (film) 3383 (OH), 2914, 2889, 1648 (C=O), 1429, 1300, 1271, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H, Ph), 7.22-7.17 (m, 3H, Ph), 5.19 (br t, *J* = 8.0 Hz, 0.3H, OCH), 4.98 (dt, *J* = 10.0, 2.5 Hz, 0.7H, OCH), 4.04-3.90 (br m, 2H, NCH), 3.48 (d, *J* = 2.5 Hz, 0.7H, C*H*OH), 3.24 (d, *J* = 1.0 Hz, 0.3H, C*H*OH), 2.78 (ddd, *J* = 14.0, 10.5, 5.0 Hz, 0.7H, CH), 2.68-2.60 (m, 1.3H, CH), 2.32 (br s, 1H, OH), 2.20-2.10 (m, 1H, CH), 2.00-1.91 (m, 1H, CH), 1.28-1.26 (m, 12H, NCH*Me*$_2$), 0.96 (s, 6.3H, C*Me*$_3$), 0.95 (s, 2.7H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) for (*R*,*S*)-**131** and (*R*,*R*)-**131** δ 155.3 (C=O), 154.3 (C=O), 142.0 (*ipso*-Ph), 141.7 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph) 128.3 (Ph), 128.3 (Ph), 125.8 (Ph) 125.8 (Ph), 80.9 (OCH), 79.8 (OCH), 76.2 (OCH), 72.8 (OCH), 46.0 (br, NCH), 45.5 (br, NCH), 35.1 (*C*Me$_3$), 34.6 (*C*Me$_3$), 32.41 (CH_2), 32.40 (CH_2), 32.1 (CH_2), 26.6 (C*Me*$_3$), 26.4 (C*Me*$_3$) 21.6 (br, NCH*Me*$_2$), 20.5 (br, NCH*Me*$_2$); MS (ESI) *m/z* 372 [(M + Na)$^+$, 100], 350 [(M + H)$^+$, 50]; HRMS *m/z* calcd for $C_{20}H_{34}NO_3$ (M + Na)$^+$ 372.2509, found 372.2496 (+3.4 ppm error).

4-Hydroxy-5,5-dimethyl-1-phenylhexan-3-yl *N*,*N*-bis(propan-2-yl)carbamate *anti-rac*-131 and *syn-rac*-131



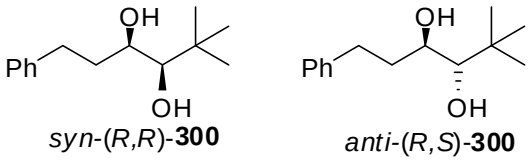
anti-rac-**131**



syn-rac-**131**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti-rac*-**6** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and pivaldehyde (54 μL, 0.50 mmol, 2.5 eq.) gave the crude product which contained a 60:40 mixture of *anti-rac*-**19** and *syn-rac*-**19** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave a 70:30 mixture (by ^{1}H NMR spectroscopy) of alcohols *anti-rac*-**19** and *syn-rac*-**19** (48 mg, 69%) as a colourless oil.

(3*R*,4*R*)-5,5-Dimethyl-1-phenylhexane-3,4-diol *syn*-(*R*,*R*)-300 and (3*R*,4*S*)-5,5-dimethyl-1-phenylhexane-3,4-diol *anti*-(*R*,*S*)-300

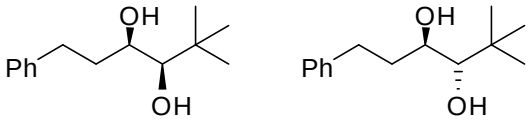


syn-(*R*,*R*)-**300** *anti*-(*R*,*S*)-**300**

A 70:30 mixture of alcohols *anti*-(*R*,*S*)-**131** and *syn*-(*R*,*R*)-**131** (13 mg, 0.037 mmol, 1.0 eq.) in THF (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (9 mg, 0.22 mmol, 6.0 eq.) in THF (2 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 70 °C for 1 h. Then, the solution was cooled to 0 °C and water (1 mL), 2 M $NaOH_{(aq)}$ (2 mL) and $MgSO_4$ were added sequentially. The solids were removed by filtration. The filtrate was washed with water (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 70:30 mixture of *anti*-(*R*,*S*)-**300** and *syn*-(*R*,*R*)-**300** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 4:1-3:1 petrol-EtOAc as eluent gave diol *syn*-(*R*,*R*)-**300** (1.5 mg, 18%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (3:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.23-7.18 (m, 3H, Ph), 3.82 (ddd, J = 8.0, 5.0, 1.0 Hz 1H, C*H*OH), 3.10 (d, J = 1.0 Hz, 1H, C*H*OH), 2.80 (ddd, J = 14.0 10.0, 6.0 Hz, 1H, PhCH_AH_B), 2.70 (ddd, J = 14.0, 9.5, 6.5 Hz, 1H, CH), 1.98 (br s, 2H, OH), 1.93 (dddd, J = 14.0, 9.5, 8.0, 6.0 Hz 1H, CH), 1.80 (dddd, J = 14.0, 10.0, 6.5, 5.0 Hz, 1H, CH), 0.94 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.8 (*ipso*-Ph), 128.41 (Ph), 128.37 (Ph) 125.9 (Ph), 79.9 (CHOH), 68.9 (CHOH), 38.5 (CH_2), 35.0 (*C*Me_3) 32.1 (CH_2), 26.2 (C*Me*$_3$); MS (ESI) *m/z* 245 [(M + Na)$^+$, 100]; HRMS *m/z* calcd for $C_{14}H_{22}O_2$ (M + Na)$^+$ 245.1512, found 245.1505 (+2.8 ppm error); CSP-HPLC: Chiracel AD-H (98:2 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*R*)-**300** 20.5 min, (*S*,*S*)-**300** 22.2 min and diol *anti*-(*R*,*S*)-**300 (**4.5 mg, 55%, er not determined) as a colourless oil, R_F (3:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.24-7.17 (m, 3H, Ph), 3.73 (ddd, J = 10.0, 4.0, 3.0 Hz 1H, C*H*OH), 3.39 (d, J = 4.0 Hz, C*H*OH), 2.92 (ddd, J = 14.0 10.0 (9.5), 5.0 Hz, 1H, PhCH_AH_B), 2.69 (ddd, J = 14.0, 9.5, 7.0 Hz, 1H, CH), 1.96 (dddd, J = 14.0, 9.5, 7.0, 3.0 Hz 1H, CH), 1.89-1.79 (m, 3H, CH + OH), 0.95 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.1 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph) 125.8 (Ph), 82.8 (CHOH), 72.0 (CHOH), 34.3 (*C*Me_3), 33.9

(CH_2), 32.2 (CH_2), 26.7 (C*Me*$_3$); MS (ESI) *m/z* 245 [$(M + Na)^+$, 100]; HRMS *m/z* calcd for $C_{14}H_{22}O_2$ $(M + Na)^+$ 245.1512, found 245.1514 (−0.6 ppm error).

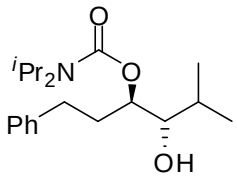
5,5-Dimethyl-1-phenylhexane-3,4-diol *syn-rac*-300 and *anti-rac*-300



syn-rac-**300** *anti-rac*-**300**

An 80:20 mixture of alcohols *anti-rac*-**131** and *syn-rac*-**131** (90 mg, 0.26 mmol, 1.0 eq.) in THF (4 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (60 mg, 1.56 mmol, 6.0 eq.) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 70 °C for 1 h. Then, the solution was cooled to 0 °C and water (2 mL), 2 M $NaOH_{(aq)}$ (4 mL) and $MgSO_4$ were added sequentially. The solids were removed by filtration. The filtrate was washed with water (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 80:20 mixture of *anti-rac*-**300** and *syn-rac*-**300** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 4:1-3:1 petrol-EtOAc as eluent gave diol *syn-rac*-**300 (**9 mg, 16%) as a colourless oil and diol *anti-rac*-**300** (28 mg, 49%) as a colourless oil

(3*R*,4*S*) 4-Hydroxy-5-methyl-1-phenylhexan-3-yl *N*,*N*-diisopropylcarbamate (*R*,*S*)-132

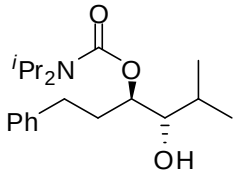


(*R*,*S*)-**132**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti-(S,S$_s$)*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and isobutyraldehyde (46 μL, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave alcohol (*R*,*S*)-**132** (46 mg, 70%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.3; IR (film) 3389 (OH), 2923, 2889, 1648 (C=O), 1418, 1348,

1280, 1139, 1118, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.27 (m, 2H, Ph), 7.20-7.18 (m, 3H, Ph), 4.98 (dt, *J* = 10.5, 3.5 Hz, 1H, OCH), 4.10-3.89 (br m, 2H, NCH), 3.48 (dd, *J* = 7.0, 3.5 Hz, 1H, C*H*OH), 2.78 (ddd, *J* = 14.0, 10.5, 5.0 Hz, 1H, PhCH_AH_B), 2.64 (ddd, *J* = 14.0, 10.5, 6.5 Hz, 1H, PhCH_AH_B), 2.17 (br s, 1H, OH), 2.06 (dtd, *J* = 14.5, 10.5, 5.0 Hz, 1H, CH), 1.91 (dddd, *J* = 14.5, 10.5, 6.5, 3.5 Hz, 1H, CH), 1.70 (oct, *J* = 7.0 Hz, 1H, C*H*Me_2), 1.26 (d, *J* = 7.0 Hz, 12H, NCH*Me*$_2$), 0.99 (d, *J* = 7.0 Hz, 3H, CH*Me*$_2$), 0.91 (d, *J* = 7.0 Hz, 3H, CH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3 (C=O), 141.9 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph) 125.9 (Ph), 78.3 (OCH), 76.1 (CHOH), 46.0 (br, NCH), 32.3 (CH_2), 31.0 (CH_2), 30.2 (*C*HMe_2), 21.5 (br, NCH*Me*$_2$), 20.5 (br, NCH*Me*$_2$), 19.3 (Me), 18.4 (Me); MS (ESI) *m/z* 358 [$(M + Na)^+$, 100], 336 [$(M + H)^+$, 80]; HRMS *m/z* calcd for $C_{20}H_{34}NO_3$ $(M + Na)^+$ 358.2353, found 358.2347 (+1.5 ppm error); $[\alpha]_D$ +21.22 (*c* 0.40 in $CHCl_3$); CSP-HPLC: Chiracel OD (95:5 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R,S*)-**132** 5.8 min, (*S,R*)-**132** 7.8 min.

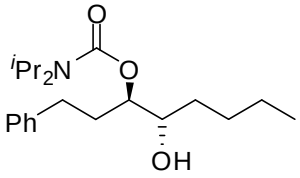
4-Hydroxy-5-methyl-1-phenylhexan-3-yl *N,N*-diisopropylcarbamate *anti-rac*-132



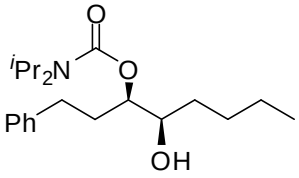
anti-rac-**132**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti-rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and isobutyraldehyde (46 μL, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave alcohol *anti-rac*-**132** (49 mg, 75%) a colourless oil.

4-Hydroxy-1-phenyloctan-3-yl *N,N*-diisopropylcarbamate (*R,S*)-133 and (*R,R*)-133



(*R,S*)-**133**

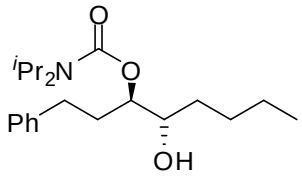


(*R,R*)-**133**

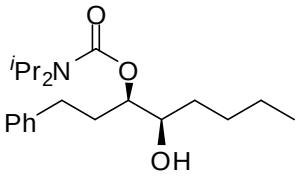
Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti-(S,S$_s$)*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt

for 1 min and valeraldehyde (53 μL, 0.50 mmol, 2.5 eq.) gave the crude product which contained a 90:10 mixture of (*R*,*S*)-**133** and (*R*,*R*)-**133** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave a 90:10 mixture (by ^{1}H NMR spectroscopy) of alcohols (*R*,*S*)-**133** and (*R*,*R*)-**133** (45 mg, 65%, each diastereoisomer 99:1 er by CSP:HPLC) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.3; IR (film) 3399 (OH), 2923, 2878, 1647 (C=O), 1428, 1291, 1239, 1117, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H, Ph), 7.20-7.16 (m, 3H, Ph), 4.87 (dt, J = 8.0, 3.5 Hz, 0.9H, OCH), 4.85-4.80 (m, 0.1H, OCH), 4.06 (br s, 1H, NCH), 3.84 (br s, 1H, NCH), 3.69 (dt, J = 9.0, 3.5 Hz, 0.9H, C*H*OH), 3.65-3.61 (m, 0.1H, C*H*OH), 2.79-2.59 (m, 2H, CH), 2.04-1.94 (m, 1H, CH), 1.90-1.81 (m, 1H, CH), 1.55-1.24 (m, 18H), 0.88 (t, J = 8.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) for (*R*,*S*)-**21** δ 156.2 (C=O), 141.6 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph) 126.0 (Ph), 78.6 (OCH), 73.9 (CHOH), 45.6 (br, NCH), 32.5 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 30.2 (*C*HMe_2), 31.9 (CH_2), 22.7 (CH_2), 20.4 (br, NCH*Me*$_2$), 14.0 (Me); MS (ESI) *m/z* 372 [(M + Na)$^+$, 100], 350 [(M + H)$^+$, 30]; HRMS *m/z* calcd for $C_{21}H_{35}NO_3$ (M + Na)$^+$ 372.2509, found 372.2493 (+4.3 ppm error); CSP-HPLC: Chiracel OD (99:1 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*R*)-**133** 16.8 min, (*R*,*S*)-**133** 19.3 min, (*S*,*S*)-**133** 19.3 min, (*S*,*R*)-**133** 28.3 min.

4-Hydroxy-1-phenyloctan-3-yl *N*,*N*-diisopropylcarbamate *anti-rac*-133 and *syn-rac*-133



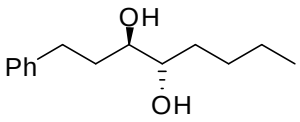
anti-rac-**133**



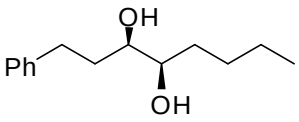
syn-rac-**133**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *anti-rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and valeraldehyde (53 μL, 0.50 mmol, 2.5 eq.) gave the crude product which contained a 90:10 mixture of (*R*,*S*)-**133** and (*R*,*R*)-**133** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave a 90:10 mixture (by ^{1}H NMR spectroscopy) of alcohols *anti-rac*-**133** and *syn-rac*-**133** (37 mg, 53%) as a colourless oil.

1-Phenyloctane-3,4-diol *anti-rac*-134 and *syn-rac*-134



anti-rac-**134**

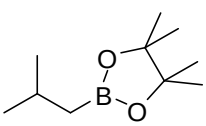


syn-rac-**134**

A 90:10 mixture of alcohols *anti-rac*-**134** and *syn-rac*-**134** (30 mg, 0.086 mmol, 1.0 eq.) in THF (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (20 mg, 0.52 mmol, 6.0 eq.) in THF (2 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 70 °C for 1 h. Then, the solution was cooled to 0 °C and water (1 mL), 2 M $NaOH_{(aq)}$ (2 mL) and $MgSO_4$ were added sequentially. The solids were removed by filtration. The filtrate was washed with water (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 90:10 mixture of *anti-rac*-**134** and *syn-rac*-**134** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc as eluent gave a 90:10 mixture (by ^{1}H NMR spectroscopy) of diols *anti-rac*-**134** and *syn-rac*-**134** (17 mg, 89%) as a colourless oil, R_F (3:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.24-7.18 (m, 3H, Ph), 3.65-3.60 (m, 1.8H, C*H*OH), 3.46-3.44 (m, 0.2H, C*H*OH), 2.93-2.83 (m, 1H, CH), 2.76-2.64 (m, 1H, CH), 2.04-1.94 (m, 1H, CH), 1.81-1.77 (m, 5H, CH + OH), 1.50-1.25 (m, 6H, CH), 0.91 (t, J = 8.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) for *anti-rac*-**134** δ 142.0 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph) 126.2 (Ph), 74.5 (CHOH), 74.0 (CHOH), 32.9 (CH_2), 32.4 (CH_2), 31.1 (CH_2), 28.2 (CH_2), 22.8 (CH_2), 14.1 (Me). Spectroscopic data for *syn-rac*-**134** consistent with those reported in the literature.[130]

This experiment enabled the relative stereochemistry of *anti-rac*-**133** to be unequivocally established.

Isobutyl boronic acid pinacol ester 301[217]

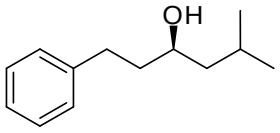


301

Isobutyl boronic acid (1.0 g, 9.90 mmol, 1.0 eq.) was added to a stirred suspension of pinacol (1.17 g, 9.90 mmol, 1.0 eq.) and $MgSO_4$ (1.78 g, 14.85 mmol, 1.0 eq.) in Et_2O (12 mL) at rt under Ar. The resulting suspension was stirred at rt for 18 h. The suspension was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in hexane (15 mL), washed with water (3 x 10 mL), dried ($MgSO_4$) and (100.6 MHz, $CDCl_3$) evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave isobutyl boronic acid pinacol ester **301** (1.40 g, 77%) as a colourless oil, bp 52-55 °C/8 mmHg (lit.,[217] 71 °C/14 mmHg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (nontet, J = 6.5 Hz, 1H, C*H*Me_2), 1.22 (s, 12H, Me), 0.90 (d, J = 6.5 Hz, 6H, CH*Me*$_2$), 0.71 (d, J = 6.5 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 82.8 (OC), 25.3 (Me), 24.8 (CH_2), 24.75 (Me), 15.8 (CH). Spectroscopic data consistent with those reported in the literature.[217]

Lab Book Reference PJR 6/486

(3*R*)-5-Methyl-1-phenylhexan-3-ol (*R*)-135



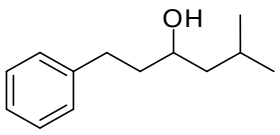
(R)-**135**

i-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) was added dropwise to a stirred solution of sulfoxide *anti*-(*S*,*S*$_s$)-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, a solution of isobutylboronic acid pinacol ester **301** (107 μL, 0.50 mmol, 2.5 eq.) in THF (1 mL) was added dropwise. The solution was stirred at rt for 30 min and then stirred and heated at 67 °C for 16 h. The reaction mixture was cooled to 0 °C and 3 M $NaOH_{(aq)}$ (0.5 mL) and 30 % $H_2O_{2(aq)}$ (0.25 mL) were added sequentially. The resulting solution was stirred at rt for 2 h and then 2 M $NaOH_{(aq)}$ (7 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5-9:1 petrol-EtOAc as eluent gave alcohol (*R*)-**135** (26 mg, 68%, 94:6 er by CSP-HPLC) as a white solid, mp 44-45 °C (lit.,[217] 45-47 °C); R_F (8:2 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.23-7.18 (m, 3H, Ph), 3.76-3.70 (m,

1H, C*H*OH), 2.81 (ddd, *J* = 13.5, 10.0, 6.0 Hz, 1H, PhCH_AH_B), 2.69 (ddd, *J* = 13.5, 10.0, 6.5 Hz, 1H, PhCH_AH_B), 1.82-1.68 (m, 3H, PhCH_2CH_2 + CH), 1.48-1.40 (m, 2H, CH + OH), 1.30-1.28 (m, 1H, CH), 0.93 (d, *J* = 8.0 Hz, 3H, CH*Me*$_2$), 0.91 (d, *J* = 8.0 Hz, 3H, CH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.2 (*ipso*-Ph), 128.4 (4, Ph), 125.8 (Ph) 69.5 (CHOH), 46.8 (CH_2), 39.8 (CH_2), 32.2 (CH_2), 24.8 (CH or Me), 23.6 (CH or Me), 22.2 (CH or Me); $[\alpha]_D$ +16.0 (*c* 0.55 in $CHCl_3$) [lit.[217] , $[\alpha]_D$ +16.00 (*c* 0.70 in $CHCl_3$) for (*R*)-**135** of 97:3 er)]; CSP-HPLC: Chiracel OD (98:2 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*S*)-**135** 13.4 min, (*R*)-**135** 22.2 min. Spectroscopic data consistent with those reported in the literature.[217]

n-BuLi (0.23 mL of a 2.2 M solution in hexanes, 0.50 mmol, 2.5 eq.) was added dropwise to a stirred solution of sulfoxide *anti*-(*S*,*S*$_s$)-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 min. Then, a solution of isobutylboronic pinacol ester **301** (107 μL, 0.50 mmol, 2.5 eq.) was added dropwise. The solution was stirred at −78 °C for 30 min and then stirred and heated at 67 °C for 16 h. The reaction mixture was cooled to 0 °C and 3 M $NaOH_{(aq)}$ (0.5 mL) and 30 % $H_2O_{2(aq)}$ (0.25 mL) were added sequentially. The resulting solution was stirred at rt for 2 h and then 2 M $NaOH_{(aq)}$ (7 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_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 alcohol (*R*)-**135** (28 mg, 72%, 99:1 er by CSP-HPLC) as a white solid, mp 47-48 °C (lit.,[217] 45-47 °C); $[\alpha]_D$ +15.6 (*c* 0.65 in $CHCl_3$) [lit.,[217] $[\alpha]_D$ +16.00 (*c* 0.70 in $CHCl_3$) for (*R*)-**135** of 97:3 er)]; CSP-HPLC: Chiracel OD-H (98:2 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*S*)-**135** 12.9 min, (*R*)-**135** 21.4 min. Spectroscopic data consistent with those reported in the literature.[217]

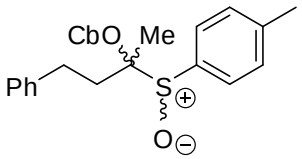
5-Methyl-1-phenylhexan-3-ol *rac*-135



rac-**135**

i-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) was added dropwise to a stirred solution of sulfoxide *anti-rac*-**103** (80 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, a solution of isobutylboronic acid pinacol ester **301** (107 μL, 0.50 mmol, 2.5 eq.) in THF (1 mL) was added dropwise. The solution was stirred at rt for 30 min and then stirred and heated at 67 °C for 16 h. The reaction mixture was cooled to 0 °C and 3 M $NaOH_{(aq)}$ (0.5 mL) and 30 % $H_2O_{2(aq)}$ (0.25 mL) were added sequentially. The resulting solution was stirred at rt for 2 h and then 2 M $NaOH_{(aq)}$ (7 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5-90:10 petrol-EtOAc as eluent gave alcohol *rac*-**135** (25 mg, 65%) as a white solid.

2-[(4-Methylbenzene)sulfinyl]-4-phenylbutan-2-yl *N*,*N*-diisopropylcarbamate 141a and 141b



141a/141b

n-BuLi (0.31 mL of a 2.5 M solution in hexane, 0.78 mmol, 1.2 eq.) was added dropwise to a stirred solution of diisopropylamine (110 μL, 0.78 mmol, 1.2 eq.) in THF (3 mL) at −78 °C under Ar. The resulting solution was warmed to 0 °C over 5 min and stirred at 0 °C for 15 min. Then, the solution was cooled to −78 °C, stirred at −78 °C for 10 min and a solution of sulfoxide *anti-rac*-**103** (260 mg, 0.65 mmol, 1.0 eq.) in THF (7 mL) was added dropwise over 10 min. The resulting solution was stirred at −78 °C for 10 min and MeI (62 μL, 0.98 mmol, 1.5 eq.) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2-95:5 CH_2Cl_2-Et_2O as eluent gave sulfoxide **141a** (132 mg, 49%) as a colourless oil, R_F (95:5 CH_2Cl_2-Et_2O) 0.3; IR (film) 2970, 2963, 1693 (C=O), 1541, 1465, 1321, 1296, 1052, 910, 850, 732 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.31-7.20 (m, 7H, Ar), 4.01-3.94 (m, 1H, NCH), 3.78-3.68 (m, 1H, NCH), 3.07 (ddd, J = 14.0, 10.0, 7.0 Hz, 1H, $PhCH_AH_B$), 2.79-2.67 (m, 2H, $PhCH_AH_B$ + CH), 2.52-2.41 (m, 1H, CH), 2.41 (s, 3H, C_6H_4Me), 1.46 (s, 3H, Me), 1.31 (d, J = 6.5 Hz, 3H, $NCHMe_2$), 1.28 (d, J = 6.5 Hz, 3H, $NCHMe_2$), 1.12 (d, J = 6.5 Hz, 3H, $NCHMe_2$), 0.93 (d, J = 6.5 Hz, 3H, $NCHMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.5 (C=O), 141.5 (*ipso*-Ar), 140.9 (*ipso*-Ar), 136.7 (*ipso*-Ar), 130.0 (Ar), 129.1 (Ar) 128.5 (Ar), 126.4 (Ar), 124.8 (Ar), 96.6 (OC), 46.4 (br, NCH), 36.0 (CH_2), 30.1 (CH_2), 21.4 (Me), 20.9 (br, Me), 20.4 (br, Me), 15.5 (Me); MS (ESI) *m/z* 438 [$(M + Na)^+$, 100], 416 [$(M + H)^+$, 70]; HRMS *m/z* calcd for $C_{24}H_{33}NO_3S$ $(M + Na)^+$ 438.2089, found 438.2089 (+0.0 ppm error) and sulfoxide **141b** (94 mg, 35%) as a colourless oil, R_F (95:5 CH_2Cl_2-Et_2O) 0.2; IR (film) 2965, 2959, 1690 (C=O), 1528, 1480, 1450, 1326, 1286, 1052, 912, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.29-7.24 (m, 4H, Ar), 7.20 (tt, J = 7.5, 2.0 Hz, 1H, *p*-Ph), 7.14-7.12 (m, 2H, Ar), 4.05-3.99 (m, 1H, NCH), 3.76-3.70 (m, 1H, NCH), 2.72-2.59 (m, 2H, CH), 2.39 (s, 3H, C_6H_4Me), 2.26-2.13 (m, 2H, CH), 1.81 (s, 3H, Me), 1.30 (d, J = 6.5 Hz, 3H, $NCHMe_2$), 1.28 (d, J = 6.5 Hz, 3H, $NCHMe_2$), 1.19 (d, J = 6.5 Hz, 3H, $NCHMe_2$), 1.08 (d, J = 6.5 Hz, 3H, $NCHMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.9 (C=O), 141.5 (*ipso*-Ar), 141.0 (*ipso*-Ar), 136.8 (*ipso*-Ar), 129.3 (Ar), 128.5 (Ar) 128.3 (Ar), 126.2 (Ar), 126.1 (Ar), 96.9 (OC), 46.5 (br, NCH), 46.2 (br, NCH), 32.9 (CH_2), 30.0 (CH_2), 21.4 (Me), 20.6 (br, Me), 20.4 (br, Me), 18.3 (Me); MS (ESI) *m/z* 438 [$(M + Na)^+$, 100], 416 [$(M + H)^+$, 70]; HRMS *m/z* calcd for $C_{24}H_{33}NO_3S$ $(M + Na)^+$ 438.2079, found 438.2083 (+0.5 ppm error).
Lab Book Reference PJR 8/667

n-BuLi (0.20 mL of a 2.5 M solution in hexane, 0.50 mmol, 1.2 eq.) was added dropwise to a stirred solution of diisopropylamine (70 μL, 0.50 mmol, 1.2 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was warmed to 0 °C over 5 min and stirred at 0 °C for 15 min. Then, the solution was cooled to −78 °C, stirred at −78 °C for 10 min and a solution of sulfoxide *anti-rac*-**103** (170 mg, 0.42 mmol, 1.0 eq.) in THF (4 mL) was added dropwise over 10 min. The resulting solution was stirred at −78 °C for 10 min and Me_2SO_4 (59 μL, 0.63 mmol, 1.5 eq.) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and

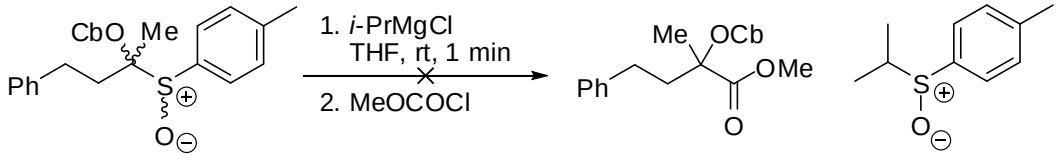
evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2-95:5 CH_2Cl_2-Et_2O as eluent gave sulfoxide **141a** (94 mg, 54%) as a colourless oil and sulfoxide **141b** (49 mg, 28%) as a colourless oil.

Lab Book Reference 5/374

A solution of sulfoxide *anti-rac*-**103** (170 mg, 0.42 mmol, 1.0 eq.) in THF (4 mL) was added dropwise over 10 min to a stirred solution of LHMDS (0.50 mL of a 1.0 M solution in THF, 0.50 mmol, 1.2 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 10 min. Then, MeI (40 μL, 0.63 mmol, 1.5 eq.) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2-95:5 CH_2Cl_2-Et_2O as eluent gave sulfoxide **141a** (51 mg, 29%) as a colourless oil and sulfoxide **141b** (28 mg, 16%) as a colourless oil.

Lab Book Reference 8/610

Attempted synthesis of methyl 2-(diisopropylcarbamoyloxy)-2-methyl-4-phenylbutanoate *rac*-142



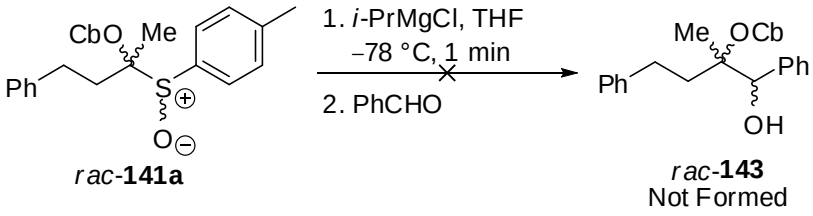
rac-**141a** *rac*-**142** *rac*-**128** Not Formed

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *rac*-**141a** (83 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min and methyl chloroformate (38 μL, 0.50 mmol, 2.5 eq.) gave the crude product. The ^{1}H NMR spectrum of the crude product showed a complex mixture of products. Sulfoxide *rac*-**141a** or sulfoxide *rac*-**128** were not evident. No further purification was attempted.

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *rac*-**141a** (83 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at −78 °C for 1 min and methyl chloroformate (38 μL, 0.50 mmol, 2.5 eq.) gave the crude product. The ^{1}H NMR spectrum of the crude product showed a complex mixture of products. Sulfoxide *rac*-**141a** or sulfoxide *rac*-**128** were not evident. No further purification was attempted.

n-BuLi (0.20 mL of a 2.5 M solution in hexanes, 0.50 mmol, 2.5 eq.) was added dropwise to a stirred solution of sulfoxide *rac*-**141a** (0.20 mmol, 1.0 eq.) in THF (8 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 min. Then, methyl chloroformate (38 μL, 0.50 mmol, 2.5 eq.) was added dropwise and the resulting solution was stirred at −78 °C for 1 h. Saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed a complex mixture of products and no further purification was attempted.

Attempted synthesis of 1-hydroxy-2-methyl-1,4-diphenylbutan-2-yl diisopropylcarbamates 143

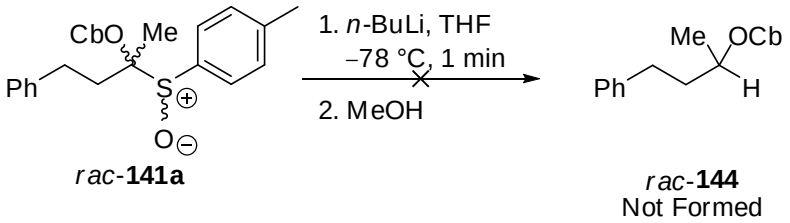


rac-**141a**

rac-**143**
Not Formed

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *rac*-**141a** (83 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at −78 °C for 1 min and benzaldehyde (50 μL, 0.50 mmol, 2.5 eq.) gave the crude product. The ^{1}H NMR spectrum of the crude product showed a complex mixture of products and no further purification was attempted.

Attempted synthesis of 4-phenylbutan-2-yl diisopropylcarbamate 144



rac-**141a**

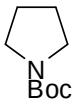
rac-**144**
Not Formed

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *rac*-**141a** (83 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at −78 °C for 1 min and MeOH (1 mL) gave the crude product. The ^{1}H NMR spectrum of the crude product showed a complex mixture of products and no further purification was attempted

n-BuLi (0.20 mL of a 2.5 M solution in hexanes, 0.50 mmol, 2.5 eq.) was added dropwise to a stirred solution of sulfoxide *rac*-**141a** (0.20 mmol, 1.0 eq.) in THF (8 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 min. Then, MeOH (1 mL) was added dropwise. Saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed a complex mixture of products and no further purification was attempted.

5.4 Experimental for Chapter Three

N-*tert*-Butoxycarbonyl pyrrolidine 39[167]

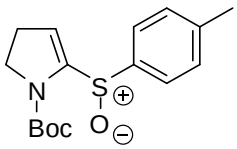


39

A solution of di-*tert*-butyl dicarbonate (2.84 g, 13.0 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL) was added to a stirred solution of pyrrolidine (1.17 mL, 14.0 mmol, 1.1 eq.) in CH_2Cl_2 (15 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave *N*-Boc pyrrolidine **39** (2.07 g, 93%) as a colourless oil, bp 86-92 °C/2.0 mmHg (lit.,[167] 77-75 °C/0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28-3.20 (m, 4H, NCH_2), 1.80-1.76 (m, 4H,CH_2), 1.40 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 154.7 (C=O), 78.8 (*C*Me_3), 45.9 (CH_2N), 45.6 (CH_2N), 28.5 (C*Me*$_3$), 25.7 (CH_2), 24.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[167]

Lab Book Reference: PJR 1/1

N-*tert*-Butoxycarbonyl-5-(*p*-tolylsulfinyl)-2,3-dihydropyrrole 169



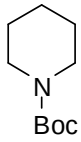
169

Using general procedure E, *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **39** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) and methyl *p*-toluenesulfinate **121** (510 mg, 3.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave dihydropyrrole **169** (145 mg, 31%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2980, 1678 (C=O), 1369, 1306, 1153, 1093, 901, 809, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (br d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.24 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 5.96 (t, J = 3.0 Hz 1H, =CH), 3.97 (br s, 1H, NCH_2), 3.85-3.76 (m, 1H, NCH_2), 2.84-2.74 (m, 1H, NCH_2CH_2), 2.64 (dddd, J = 17.0, 11.5, 6.0, 3.0 Hz, 1H,

NCH_2CH_2), 2.37 (s, 3H, Me), 1.37 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 174.3 (C=O), 150.2 (C=O), 142.1 (i*pso*-Ar), 140.9 (=C)140.8 (=C), 136.5 (Ar), 135.4 (Ar), 130.2 (Ar), 127.7 (Ar), 126.6 (*ipso*-Ar), 126.2 (*ipso*-Ar), 124.3 (=CH), 82.7 (CMe_3), 46.4 (NCH_2), 32.9 (CH_2), 28.1 (CMe_3), 28.0 (CMe_3), 21.5 (br, Me), 17.4 (CH_2); (MS (ESI) *m/z* 330 [$(M + Na)^+$, 100], 208 (40), 238 (100); HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3S$ $(M + Na)^+$ 330.1134, found, 330.1122 (3.7 ppm error).
Lab Book Reference: PJR 1/32

Using general procedure E, *s*-BuLi (1.92 mL of a 1.3 M solution in hexanes, 2.50 mmol, 2.5 eq.) and *N*-Boc pyrrolidine **39** (171 mg, 1.00 mmol, 1.0 eq.) in THF (6 mL) and methyl *p*-toluenesulfinate **121** (510 mg, 3.0 mmol, 3.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave dihydropyrrole **169** (136 mg, 44%) as a colourless oil.
Lab Book Reference: PJR 1/68

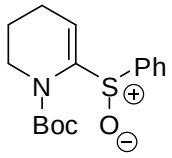
_N_-*tert*-Butyl piperidine-1-carboxylate 48[148]



48

Piperidine (7.33 g, 8.50 mL, 68.7 mmol, 1.0 eq.) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (12.51 g, 57.3 mmol, 0.8) in THF (62.5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt and stirred at rt for 1 h. 10% $NaHCO_{3(aq)}$ (70 mL) was added and the mixture was extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with brine (100 mL), dried (K_2CO_3) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave *N*-Boc piperidine **48** (9.68 g, 64%) as a colourless oil, bp 72-74 °C/1.3 mmHg (lit.,[148] 65 °C/1.0 mmHg); ^1H NMR (400 MHz, $CDCl_3$) δ 3.30-3.27 (m, 4H, NCH_2), 1.51-1.42 (m, 6H, CH_2), 1.38 (s, 9H, CMe_3). Spectroscopic data consistent with those reported in the literature.[148]
Lab Book Reference: PJR 1/21

***N*-*tert*-Butylcarbonyl-6-(phenylsulfinyl)-3,4-dihydro-2*H*-pyridine 171**

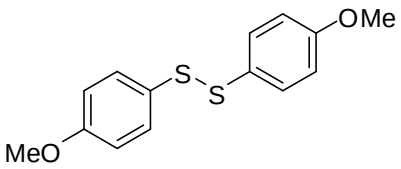


171

Using general procedure F, *s*-BuLi (2.50 mL of a 1.3 M solution in hexanes, 3.25 mmol, 1.3 eq.), TMEDA (378 mg, 0.49 mL, 3.25 mmol, 1.3 eq.) and *N*-Boc piperidine **48** (463 mg, 2.50 mmol, 1.0 eq.) in Et_2O (8 mL) at −78 °C for 3 h and methyl benzenesulfinate **170** (624 mg, 4.00 mmol, 1.6 eq.) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave tetrahydropyridine **171** (100 mg, 13%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.30; IR (Film) 2975, 1693 (C=O), 1511, 1454, 1391, 1366, 1246, 1166, 1033, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H, *o*-Ph), 7.41-4.40 (m, 3H, Ph), 6.37 (t, J = 3.5 Hz, 1H, =CH), 3.97 (br d, J = 11.5 Hz, 1H, NCH_AH_B), 2.71 (br s, 1H, NCH_AH_B), 2.39 (ddt, J = 18.5, 6.5, 3.5 Hz, 1H, $=CHCH_2$), 2.28 (dddd, J = 18.5, 10.0, 7.0, 3.5 Hz, 1H, $=CHCH_2$), 1.86-1.69 (m, 2H, CH_2), 1.37 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.3 (C=O), 144.7 (*ipso*-Ph), 143.5 (=C) 131.0 (Ph), 128.7 (Ph), 126.4 (Ph), 113.7 (br, =CH), 82.1 (CMe_3), 44.9 (NCH_2), 28.1 (CMe_3), 23.2 (CH_2), 22.0 (CH_2); MS (ESI) *m/z* 330 $[(M + Na)^+, 100]$, 308 $[(M + H)^+, 30]$, 252 (70); HRMS *m/z* calcd for $C_{16}H_{21}NO_3S$ $(M + Na)^+$ 330.1134, found 330.1127 (2.2 ppm error).

Lab Book Reference: PJR 1/22C

***p*-Methoxybenzene disulfide 176[218]**



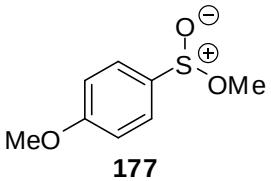
176

$NaBO_3.4H_2O$ (2.46 g, 16.0 mmol, 2.0 eq.) was added to a stirred solution of *p*-methoxybenzenethiol (1.12 g, 8.0 mmol, 1.0 eq.) in 7:3 MeOH/water (28 mL) at rt. The resulting solution was stirred at rt for 2 h. Then, water (20 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was then extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (30 mL), dried

(Na_2SO_4) and evaporated under reduced pressure to give crude disulfide **176** (1.08 g, 97%) as a colourless oil which was sufficiently pure (by ^{1}H NMR spectroscopy) for subsequent use, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 4H, *m*-C_6H_4OMe), 6.85 (d, J = 8.5 Hz, 4H, *o*-C_6H_4OMe), 3.81 (s, 3H, OMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.0 (*ipso*-C_6H_4OMe), 132.8 (Ar), 128.5 (*ipso*-C_6H_4S), 114.7 (Ar), 55.5 (OMe). Spectroscopic data consistent with those reported in the literature.[218]

Lab Book Reference: PJR 2/99

Methyl *p*-methoxybenzenesulfinate 177[119]

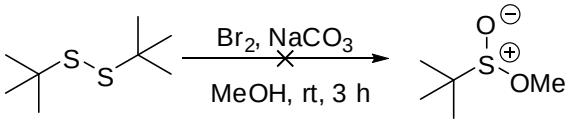


177

Bromine (0.46 mL, 9.0 mmol, 3.0 eq.) was added to a stirred suspension of Na_2CO_3 (1.58 g, 15.0 mmol, 5.0 eq.) and *p*-methoxybenzenedisulfide **176** (832 mg, 3.0 mmol, 1.0 eq.) in MeOH (75 mL) at rt. The resulting yellow suspension was stirred at rt for 3 h during which time the suspension became colourless. Then, the solvent was evaporated under reduced pressure. CH_2Cl_2 (50 mL) and water (50 mL) were added to the residue and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with saturated $NH_4Cl_{(aq)}$ (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by Kügelrohr distillation gave sulfinate **177** (1.05 g, 94%) as a colourless oil, bp 111-116 °C/0.8 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.5 Hz, 2H, *m*-C_6H_4OMe), 7.00 (d, J = 8.0 Hz, 2H, *o*-C_6H_4OMe), 3.84 (s, 3H, C_6H_4OMe), 3.42 (s, 3H, OMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.1 (*ipso*-C_6H_4OMe), 132.9 (Ar), 141.8 (*ipso*-C_6H_4S), 114.7 (Ar), 55.6 (OMe). Spectroscopic data consistent with those reported in the literature.[219]

Lab Book Reference: PJR 2/105

Attempted synthesis of methyl *tert*-butylsulfinate 179[119]

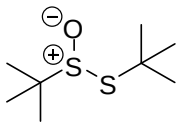


178 **179**

Bromine (1.71 mL, 33.6 mmol, 3.0 eq.) was added to a stirred suspension of Na_2CO_3 (5.93 g, 56.0 mmol, 5.0 eq.) and *t*-butyldisulfide **178** (2.00 g, 11.2 mmol, 1.0 eq.) in MeOH (200 mL) at rt. The resulting yellow suspension was stirred at rt for 3 h during which time the suspension became colourless. Then, the solvent was evaporated under reduced pressure. CH_2Cl_2 (100 mL) and water (100 mL) were added to the residue and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated $NH_4Cl_{(aq)}$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil. The ^{1}H NMR spectrum of the crude product showed only unreacted *t*-butyldisulfide **179** and no purification was attempted.

Lab Book Reference: PJR 2/91

(*tert*-Butyl) 2-methylpropane-2-sulfinothioate 180[156]

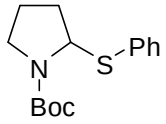


180

t-Butyl disulfide **178** (2.00 mL, 12.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of glacial AcOH (8.30 mL) and 30% $H_2O_{2(aq)}$ (1.26 mL, 41.0 mmol, 3.4 eq.) at 0 °C. The resulting solution was stirred at rt for 15 h. Then, the solution was cooled to 0 °C and water (10 mL) and CH_2Cl_2 (10 mL) were added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated $NaHSO_{3(aq)}$ (15 mL), $NaHCO_{3(aq)}$ (3 × 10 mL), and water (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a pale yellow oil. Purification by Kügelrohr distillation gave sulfinothioate **180** (1.99 g, 85%) as a colourless oil, bp 74-77 °C/2.0 mmHg (lit.,[220] 70-71 °C/1.7 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H, S(O)CMe_3), 1.36 (s, 9H, SCMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 59.4 (*C*Me_3), 48.4 (*C*Me_3), 32.5 (C*Me*$_3$), 25.1 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[156]

Lab Book Reference: PJR 2/93

***N*-*tert*-Butylcarbonyl-2-(phenylsulfanyl)pyrrolidine 185**

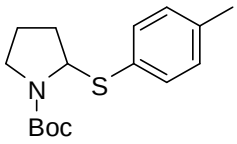


185

Using general procedure E, *s*-BuLi (2.62 mL of a 1.3 M solution in hexanes, 3.40 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **39** (445 mg, 2.60 mmol, 1.0 eq.) in THF (10 mL) and a solution of diphenyl disulfide (1.14 g, 5.2 mmol, 2.0 eq.) in THF (2 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave sulfide **185** (301 mg, 44%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.7; IR (film) 2976, 2931, 1695 (C=O), 1444, 1406, 1367, 1143, 1078, 1049, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.54-7.42 (m, 2H, Ph), 7.31-7.29 (m, 3H, Ph), 5.38 (br s, 0.4H, NCH), 5.29-5.27 (m, 0.6H, NCH), 3.51-3.34 (m, 1.2H, NCH), 3.33-2.22 (m, 0.8H, NCH), 2.20-1.98 (m, 2.4H, CH_2CH_2), 1.93-1.83 (m, 1.6H, CH_2CH_2), 1.44 (s, 3.6H, CMe_3), 1.35 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.3 (C=O), 134.4 (*ipso*-Ph), 133.8 (Ph), 128.7 (Ph), 127.7 (Ph), 79.8 (CMe_3), 66.8 (NCH), 45.3 (NCH_2), 33.7 (CH_2), 28.0 (CMe_3), 22.0 (CH_2); MS (ESI) *m/z* 302 [$(M + Na)^+$, 100], 208 (25), 114 (50); HRMS *m/z* calcd for $C_{15}H_{21}NO_2S$ $(M + Na)^+$ 302.1185, found, 302.1181 (+1.4 ppm error).

Lab Book Reference: PJR 1/4A

***N*-*tert*-Butylcarbonyl-2-(*p*-tolylsulfanyl)pyrrolidine 186**



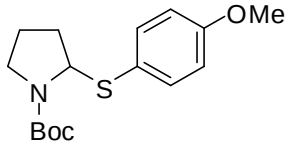
186

Using general procedure E, *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **39** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) and a solution of *p*-tolyl disulfide (739 mg, 3.0 mmol, 2.0 eq.) in THF (2 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave sulfide **186** (301 mg, 44%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.40; IR (film) 2974, 2933, 1710 (C=O), 1527, 1390, 1366, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.43 (d, J = 7.5 Hz, 0.8H, *o*-

C_6H_4Me), 7.38 (d, J = 7.5 Hz, 1.2H, *o*-C_6H_4Me), 7.12 (d, J = 7.5 Hz, 2H, *m*-C_6H_4Me), 5.32 (br s, 0.4H, NCH), 5.22 (br d, J = 5.5 Hz, 0.6H, NCH), 3.46-3.39 (m, 1.2H, NCH), 3.30-3.27 (m, 0.8H, NCH), 2.34 (s, 3H, Me), 2.21-2.03 (m, 2.4H, CH_2CH_2), 2.01-1.86 (m, 1.6H, CH_2CH_2), 1.45 (s, 3.6H, CMe_3), 1.36 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.7 (C=O), 138.3 (*ipso*-Ar), 135.1 (Ar), 130.3 (*ipso*-Ar), 129.8 (Ar), 80.1 (CMe_3), 67.1 (NCH), 45.6 (NCH_2), 33.8 (CH_2), 32.5 (CH_2), 28.5 (CMe_3), 21.3 (Me); MS (ESI) *m/z* 316 [$(M + Na)^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{23}NO_2S$ $(M + Na)^+$ 316.1342, found 316.1342 (0.0 ppm error).

Lab Book Reference: PJR 1/35B

***N*-*tert*-Butylcarbonyl-2-(*p*-methoxyphenylsulfanyl)pyrrolidine 187**

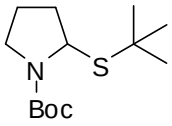


187

Using general procedure E, *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **39** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) and *p*-methoxyphenyldisulfide **176** (745 mg, 3.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave sulfide **187** (65 mg, 14%) as a colourless oil, R_F (98:2 CH_2Cl_2-Et_2O) 0.30; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.48 (d, J = 8.0 Hz, 0.8H, *o*-C_6H_4OMe), 7.42 (d, J = 8.0 Hz, 1.2H, *o*-C_6H_4OMe), 6.84 (d, J = 8.0 Hz, 2H, *m*-C_6H_4OMe), 5.25 (br s, 0.4H, NCH), 5.16 (br d, J = 6.0 Hz, 0.6H, NCH), 3.80 (s, 3H, C_6H_4O*Me*), 3.45-3.28 (m, 2H, NCH), 2.14-1.99 (m, 2.4H, CH), 1.89-1.81 (m, 1.6H, CH), 1.43 (s, 3.6H, CMe_3), 1.36 (s, 5.4H, CMe_3; MS (ESI) *m/z* 332 [$(M + Na)^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{23}NO_3S$ $(M + Na)^+$ 332.1291, found 332.1289 (+0.5 ppm error).

Lab Book Reference: PJR 2/103B

***N*-*tert*-Butylcarbonyl-2-(*tert*-butylsulfanyl)pyrrolidine 184**

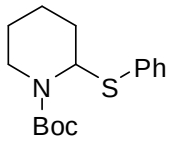


184

Using general procedure E, *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **39** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) and *p*-tolyldisulfide **178** (535 mg, 3.0 mmol, 2.0 eq) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave sulfide **184** (230 mg, 59%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.40; IR (film) 2979, 1689 (C=O), 1393, 1367, 1254, 1163, 1117, 1042, 921, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 5.22 (br s, 0.5H, NCH), 5.03 (br s, 0.5H, NCH), 3.39-3.34 (m, 1H, NCH), 3.30-3.22 (m, 1H, NCH), 2.20-2.03 (m, 2H, CH), 1.99-1.85 (m, 2H, CH), 1.44 (br s, 9H, CMe_3), 1.38 (br s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.4 (C=O), 82.7 (*C*Me_3), 79.4 (*C*Me_3), 60.7 (NCH), 45.3 (br, NCH_2), 43.5 (br, NCH_2), 36.6 (CH_2), 35.6 (CH_2), 31.5 (C*Me*$_3$), 28.5 (C*Me*$_3$); MS (ESI) *m/z* 282 [(M + Na)$^+$, 90], 210 (50), 114 (100); HRMS *m/z* calcd for $C_{13}H_{25}NO_2S$ (M + Na)$^+$ 282.1498, found 282.1477 (+7.7 ppm error).
Lab Book Reference: PJR 2/94A

Using general procedure E, *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **39** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) and *t*-butylsulfinothioate **180** (582 mg, 3.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 4:1 CH_2Cl_2-Et_2O as eluent gave sulfide **184** (60 mg, 15%) as a colourless oil.
Lab Book Reference: PJR 2/95A

***N*-*tert*-Butylcarbonyl-2-(phenylsulfanyl)piperidine 151**



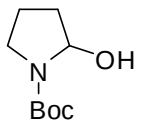
151

Using general procedure F, *s*-BuLi (2.50 mL of a 1.3 M solution in hexanes, 3.25 mmol, 1.3 eq.), TMEDA (378 mg, 0.49 mL, 3.25 mmol, 1.3 eq.) and *N*-Boc piperidine **48** (463 mg, 2.50 mmol, 1.0 eq.) in Et_2O (8 mL) at −78 °C for 3 h and a solution of diphenyl disulfide (1.36 g, 6.25 mmol, 2.5 eq.) in Et_2O (3 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave sulfide **151** (460 mg, 63%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.49 (br s, 2H, Ph), 7.29 (br s, 3H, Ph), 6.05 (br s, 0.35H, NCH), 5.79 (br s, 0.65H, NCH), 4.07 (br d, J = 11.5 Hz, 0.65H, NCH), 3.86 (br s, 0.35H, NCH), 3.29 (td, J = 13.0, 3.0 Hz, 1H, NCH), 1.98-1.49 (m, 6H, CH), 1.30 (s, 3.15H, CMe_3), 1.15 (s, 6.85H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 153.8 (C=O), 135.1 (*ipso*-Ar), 133.9 (br, Ar), 129.4 (Ar), 129.0 (Ar), 128.9 (br, Ar), 128.0 (br, Ar), 125.7 (Ar), 79.8 (CMe_3), 64.1 (br, NCH), 61.7 (br, NCH), 39.4 (br, NCH_2), 38.0 (br, NCH_2), 31.2 (br, CH_2), 30.2 (br, CH_2), 28.3 (CMe_3), 27.9 (br, CH_2), 25.4 (CH_2), 19.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[147]

Lab Book Reference: PJR 1/25C

***N*-*tert*-Butyl carbonyl-2-hydroxypyrrolidine 175**

(Table 3.1, entry 1)



175

*m*CPBA (77 mg of ~77% purity, 0.35 mmol, 1.0 eq) was added dropwise to a stirred solution of phenylsulfanyl pyrrolidine **185** (100 mg, 0.35 mmol, 1.0 eq.) and Na_2CO_3 (80 mg, 0.74 mmol, 2.1 eq.) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, saturated $Na_2SO_{3(aq)}$ (7 mL) and CH_2Cl_2 (7 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-aceteone as eluent gave recovered sulfanyl pyrrolidine **185** (26 mg, 26%) as a colourless oil and hydroxy pyrrolidine **175** (21 mg, 31%) as a colourless oil, R_F (9:1 CH_2Cl_2-acetone) 0.3; IR (Film) 3452 (OH), 2976, 1695

(C=O), 1478, 1392, 1254, 1163, 1112, 1041, 916 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 5.48 (br s, 0.6H, NCH), 5.39 (br m, 0.4H, NCH), 3.56-3.46 (m, 1H, NCH), 3.34-3.17 (m, 1H, NCH), 2.11-1.78 (m, 4H, CH), 1.50 (s, 3.6H, CMe_3), 1.47 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3 (C=O), 81.5 (NCHOH), 80.0 (CMe_3), 45.9 (NCH_2), 32.6 (CH_2), 28.4 (CMe_3), 22.7 (CH_2); MS (ESI) *m/z* 379 [(M Dimer + $Na)^+$, 100], 266 (50), 210 [(M + $Na)^+$, 20]; HRMS *m/z* calcd for $C_9H_{17}NO_3$ (M + $Na)^+$ 210.1101, found 210.101 (−0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[167]

Lab Book Reference: PJR 1/8

(Table 3.1, entry 2)

*m*CPBA (89 mg of ~77% purity, 0.41 mmol, 1.1 eq) was added to a stirred solution of KF (40 mg, 0.69 mmol, 1.8 eq.) in 4:1 MeCN-water (3 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. Then, phenylsulfanyl pyrrolidine **185** (107 mg, 0.38 mmol, 1.0 eq.) was added. The resulting solution was stirred at 0 °C for 30 min. Then, saturated $Na_2SO_{3(aq)}$ (7 mL) and Et_2O (7 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 7 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine **175** (40 mg, 57%) as a colourless oil.

Lab Book Reference: PJR 1/7

(Table 3.1, entry 3)

Using general procedure G, *m*CPBA (208 mg of ~77% purity, 1.20 mmol, 1.1 eq.) and phenylsulfanyl pyrrolidine **185** (309 mg, 1.10 mmol, 1.0 eq.) in CH_2Cl_2 (2.2 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine **175** (179 mg, 86%) as a colourless oil.

Lab Book Reference: PJR 1/19

(Table 3.1, entry 4)

Using general procedure G, *m*CPBA (118 mg of ~77% purity, 0.52 mmol, 1.1 eq.) and *p*-tolylsulfanyl pyrrolidine **186** (140 mg, 0.47 mmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1

CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine **175** (72 mg, 81%) as a colourless oil.

Lab Book Reference: PJR 1/36

(Table 3.1, entry 5)

Using general procedure G, *m*CPBA (47 mg of ~77% purity, 0.21 mmol, 1.1 eq.) and *p*-methoxyphenylsulfanyl pyrrolidine **187** (60 mg, 0.19 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc as eluent gave hydroxy pyrrolidine **175** (27 mg, 74%) as a colourless oil.

Lab Book Reference: PJR 2/106

(Table 3.1, entry 6)

Using general procedure G, *m*CPBA (112 mg of ~77% purity, 0.51 mmol, 1.1 eq.) and *t*-butylsulfanyl **184** (120 mg, 0.46 mmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave hydroxy pyrrolidine **175** (65 mg, 77%) as a colourless oil.

Lab Book Reference: PJR 2/96

(Table 3.1, entry 7)

H_2O_2 (0.07 mL of a 30% aqueous solution, 0.61 mmol, 1.8 eq.) was added dropwise to a stirred solution of sulfanyl pyrrolidine **186** (100 mg, 0.34 mmol, 1.0 eq.) in hexafluoroisopropanol (0.7 mL) at rt under Ar. The resulting solution was stirred at rt for 10 min. Then, saturated $Na_2SO_{3(aq)}$ (5 mL) and Et_2O (5 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-aceteone as eluent gave recovered sulfanyl pyrrolidine **186** (42 mg, 42%) and hydroxy pyrrolidine **175** (26 mg, 43%) as a colourless oil.

Lab Book Reference: PJR 1/42

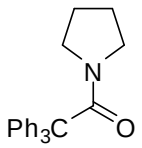
(Table 3.1, entry 8)

s-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **39** (257 mg, 1.50 mmol, 1.0 eq.) in

THF (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h and then added dropwise *via* cannula transfer to methyl *p*-toluenesulfinate **121** (765 mg, 4.50 mmol, 3.0 eq.) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 15 min. Then, saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-acetone as eluent gave dihydropyrrole **169** (45 mg, 10%) and hydroxy pyrrolidine **175** (142 mg, 52%) as a colourless oil.
Lab Book Reference: PJR 1/50

s-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 0.8 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **39** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h and then added dropwise *via* cannula transfer to methyl *p*-toluenesulfinate **121** (765 mg, 4.50 mmol, 3.0 eq.) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 15 min. Then, saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine **175** (135 mg, 48%) as a colourless oil.
Lab Book Reference: PJR 1/51

2,2,2-Triphenyl-1-pyrrolidin-1-ylethanone 207



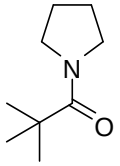
207

Thionyl chloride (3.0 mL, 15.4 mmol, 1.5 eq.) was added to a stirred solution of triphenylacetic acid (2.97 g, 10.3 mmol, 1.0 eq.) in THF (30 mL) at room temperature under Ar. The resulting solution was heated at 70 °C and for 3 h. Then, the solution was allowed to cool to rt. The solvent was evaporated under reduced pressure to give the crude acid chloride (3.51 g) as a brown solid (3.51 g). To a stirred solution of the

crude acid chloride in THF (20 mL) at 0 °C, pyridine (0.90 mL, 12.5 mmol, 1.2 eq.) and pyrrolidine (0.85 mL, 10.3 mmol, 1.0 eq.) were added. The resulting solution was heated at 70 °C for 16 h. The solution was allowed to cool to rt and then saturated $NH_4Cl_{(aq)}$ (30 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as yellow solid. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave amide **207** (3.01 g, 86%) as a white solid, mp 186-189 °C (lit.,[221] 188.5 °C); R_F (7:3 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.21 (m, 15H, Ph), 3.68 (t, J = 7.0, 2H, NCH_2), 2.46 (t, J = 7.0, 2H, NCH_2), 1.71 (quintet, J = 7.0, 2H, CH_2), 1.57 (quintet, J = 7.0, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7 (C=O), 142.9 (*ipso*-Ph), 130.5 (Ph), 127.7 (Ph), 126.6 (Ph), 54.8 (CPh$_3$), 48.3 (NCH_2), 26.6 (CH_2). Spectroscopic data consistent with those reported in the literature.[221]

Lab Book Reference: PJR 2/62A

2,2-Dimethyl-1-pyrrolidin-1-yl-propanone 209

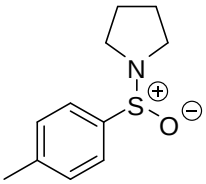


209

Trimethylacetyl chloride (3.87 g, 32.0 mmol, 1.0 eq.) was added to a stirred solution of pyridine (4.30 mL, 54.0 mmol, 1.7 eq.) and pyrrolidine (2.89 mL, 32.0 mmol, 1.0 eq.) in $CHCl_3$ (28 mL) at 0 °C. The resulting solution was heated at 65 °C and stirred for 16 h. The solution was allowed to cool to rt and then water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow solid. Recrystallisation from $CHCl_3$ gave amide **209** (5.09 g, 100%) as colourless needles, mp 53-56 °C (lit.,[222] 56-59 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (br s, 4H, NCH_2), 1.86 (br s, 4H, CH_2), 1.25 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.4 (C=O), 47.8 (NCH_2), 38.9 (CMe$_3$), 27.5 (CMe_3), 23.0 (CH_2). Spectroscopic data consistent with those reported in the literature.[223]

Lab Book Reference: PJR 1/55

1-(Toluene-4-sulfinyl)pyrrolidine 208



208

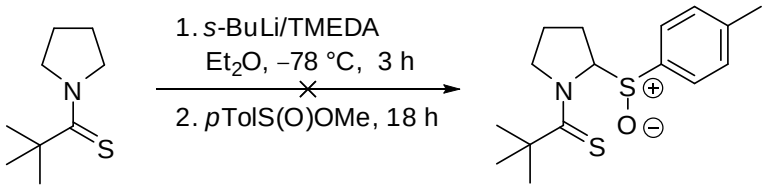
Using general procedure F, *s*-BuLi (1.30 mL of a 1.3 M solution in hexanes, 1.69 mmol, 1.3 eq.), (−)-sparteine (396 mg, 1.69 mmol, 1.3 eq.) and amide **207** (208 mg, 1.30 mmol, 1.0 eq.) in Et_2O (5 mL) at −78 °C for 3 h and methyl *p*-toluenesulfinate **121** (443 mg, 2.60 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave sulfinamide **208** (171 mg, 64%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.23 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 3.33-3.26 (m, 2H, NCH_2), 2.98-2.92 (m, 2H, NCH_2), 2.35 (s, 3H, Me), 1.82-1.76 (m, 4H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.4 (*ipso*-Ar), 140.7 (*ipso*-Ar), 129.4 (Ar), 125.7 (Ar), 45.9 (NCH_2), 25.9 (CH_2), 21.3 (Me). Spectroscopic data consistent with those reported in the literature.[224]

Lab Book Reference: PJR 1/57B

s-BuLi (1.58 mL of a 1.3 M solution in hexanes, 1.50 mmol, 1.0 eq.) was added dropwise to a stirred solution of triphenylacetamide **209** (512 mg, 1.50 mmol, 1.0 eq.) in THF (15 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 3 h. Then, methyl *p*-toluenesulfinate **121** (255 mg, 1.5 mmol, 1.0 eq.) was added dropwise. The resulting solution was stirred at −40 °C for 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 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave sulfinamide **208** (83 mg, 31%) as a colourless oil,

Lab Book Reference: PJR 2/69

Attempted synthesis of 1-[2-(*p*-tolylsulfinyl)pyrrolidin-1-yl]-2,2-dimethyl-propanthione 191

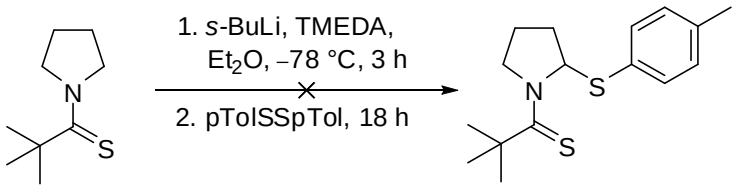


210 **191**

Using general procedure M, *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), TMEDA (227 mg, 1.95 mmol, 1.3 eq.) and thioamide **210** (257 mg, 1.50 mmol, 1.0 eq.) in Et_2O (6 mL) at −78 °C for 3 h and methyl *p*-toluenesulfinate **191** (510 mg, 3.0 mmol, 2.0 eq.) gave the crude product which contained none of the desired product by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave starting thioamide **210** (151 mg, 59%) as pale yellow needles.

Lab Book Reference: PJR 2/113

Attempted synthesis of 1-[2-(*p*-tolylsulfanyl)pyrrolidin-1-yl]-2,2-dimethyl-propanthione 213

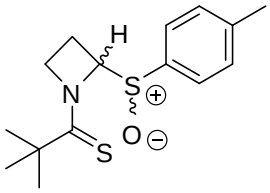


210 **213**

Using general procedure M, *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), TMEDA (227 mg, 1.95 mmol, 1.3 eq.) and thioamide **210** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) at −78 °C for 3 h and a solution of *p*-tolyldisulfide (739 mg, 3.0 mmol, 2.0 eq.) in THF (1 mL) gave the crude product which contained none of the desired product by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave starting thioamide **210** (201 mg, 78%) as pale yellow needles.

Lab Book Reference: PJR 2/114

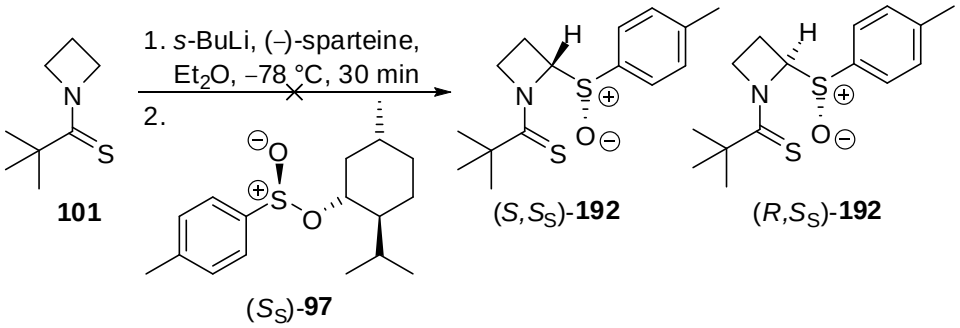
2,2-Dimethyl-1-(2-(*p*-tolylsulfinyl)azetidin-1-yl)propane-1-thione 192



192

s-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **101** (157 mg, 1.00 mmol, 1.0 eq.) and TMEDA (358 μL, 2.40 mmol, 2.4 eq.) in THF (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, methyl *p*-toluenesulfinate **121** (340 mg, 2.0 mmol, 2.0 eq.) and the solution was allowed to warm to rt over 2 h and stirred at rt for 16h. 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained a 91:9 mixture of diastereoisomers by ^{1}H NMR. Purification by flash column chromatography on silica with 8:2-1:1 petrol-EtOAc as eluent gave sulfoxide **192** (27 mg, 9%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.2; IR (film) 2987, 2954, 1502, 1480, 1424, 1395, 1240, 1140, 1025, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H, *m*-C_6H_4Me), 7.32 (d, J = 8.0 Hz, 1H, *o*-C_6H_4Me), 5.55 (dd, J = 9.0, 4.5 Hz, 1H, NCH), 4.50 (dt, J = 9.0, 7.0 Hz, 1H, NCH_ACH_B), 4.34 (dt, J = 9.0, 4.5 Hz, 1H, $NCH_AC\mathit{H}_B$), 2.83 (ddt, J = 12.0, 9.0, 4.5 Hz, 1H, $C\mathit{H}_ACH_B$), 2.41 (s, 3H, Me), 2.06 (dtd, J = 12.0, 9.0, 7.0 Hz, 1H, $C\mathit{H}_ACH_B$), 1.39 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.5 (C=S), 141.3 (*ipso*-Ar), 137.3 (*ipso*-Ar), 129.9 (Ar), 123.9 (Ar), 86.0 (NCH), 56.5 (NCH_2), 43.8 ($\mathit{C}Me_3$), 29.7 ($C\mathit{Me}_3$), 21.3 (Me) 17.3 (CH_2); MS (ESI) *m/z* 318 [(M + Na)$^+$, 100], 296 [(M + H)$^+$, 50]; HRMS *m/z* calcd for $C_{15}H_{21}NOS_2$ (M + Na)$^+$ 318.0962, found 318.0960 (−0.5 ppm error) and recovered *N*-thiopivaloyl azetidine **101** (113 mg, 72%). Diagnostic signal for other diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (dd, J = 9.0, 4.0 Hz, 1H, NCH).
Lab Book Reference: PJR 5/360

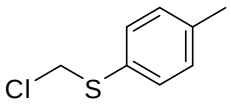
Attempted synthesis of 2,2-dimethyl-1-((*S*)-2-((*S*)-p-tolylsulfinyl)azetidin-1-yl)propane-1-thione (*S*,S_S)-192 and 2,2-dimethyl-1-((*R*)-2-((*S*)-p-tolylsulfinyl)azetidin-1-yl)propane-1-thione (*R*,S_S)-192



Using general procedure L, s-BuLi (0.92 mL of a 1.3M solution in hexanes, 1.20 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **101** (158 mg, 1.00 mmol, 1.0 eq.) and (−)-sparteine (0.28 mL, 1.20 mmol, 1.2 eq.) in Et_2O (7 mL) and a solution of Andersen's sulfinate (441 mg, 1.50 mmol, 1.5 eq.) gave the crude product. The ^{1}H NMR spectrum of the crude product showed no evidence of sulfoxides (*S*,S_S)-**192** and (*R*,S_S)-**192**. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O gave recovered *N*-thiopivaloyl azetidine **101** (134 mg, 85%)

Lab Book Reference 8/692

Chloromethyl *p*-tolylsulfide 215[166]



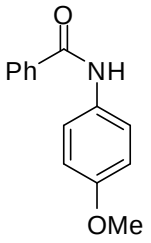
215

N-Chlorosuccinimide (3.67 g, 27.5 mmol, 1.1 eq., recrystallised from glacial AcOH) was added to a stirred solution of methyl *p*-tolylsulfide (3.45 g, 25.0 mmol, 1.0 eq.) in $CHCl_3$ (25 mL) at 0 °C. The resulting solution was allowed to warm to rt over 5 min and then stirred at rt for 18 h. Then, 4% $NaI_{(aq)}$ (50 mL) was added and the two layers were separated. The organic layer was washed with 10% $Na_2S_2O_{3(aq)}$ (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give a 90:10 mixture (by ^{1}H NMR spectroscopy) of chlorosulfide **215** and methyl *p*-tolylsulfide (4.12 g, 90% yield of chlorosulfide **215**) as a pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0

Hz, 2 H, *o*-C_6H_4Me), 7.18 (d, *J* = 8.0 Hz, 2 H, *m*-C_6H_4Me), 4.92 (s, 2H, CH_2), 2.36 (s, 3H, Me). Attempted purification by flash column chromatography on silica gel and by fractional distillation led to product decomposition.

Lab Book Reference: PJR 1/31

_N_-(4-Methoxyphenyl)benzamide 214[165]

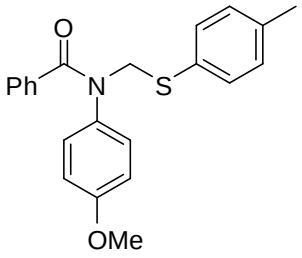


214

Benzoyl chloride (2.92 mL, 25.1 mmol, 1.1 eq.) was added dropwise to a stirred suspension of *p*-anisidine (2.80 g, 22.8 mmol, 1.0 eq.) and $NaHCO_3$ (5.76 g, 68.4 mmol, 3.0 eq.) in CH_2Cl_2 (120 mL) at 0 °C under Ar. The resulting suspension was stirred at 0 °C for 1 h. Then, water (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave benzamide **214** (4.28 g, 83%) as purple crystals, mp 146-149 °C, (lit.,[225] 153-156 °C); R_F (7:3 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 2H, *o*-Ph), 7.73 (br s, 1H, NH), 7.57-7.50 (m, 5H, Ar), 6.92 (d, *J* = 9.0 Hz, 2H, Ar), 3.83 (s, 3H, OMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.6 (C=O), 156.6 (*ipso*-C_6H_4OMe), 135.0 (*ipso*-Ar), 131.7 (Ar), 131.0 (*ipso*-Ar), 128.8 (Ar), 128.4 (Ar), 127.1 (Ar), 122.2 (Ar), 114.3 (Ar), 55.6 (OMe). Spectroscopic data consistent with those reported in the literature.[226]

Lab Book Reference: PJR 2/64A

***N*-(4-Methoxyphenyl)-*N*-*p*-tolylsulfanylmethyl benzamide 216[164]**

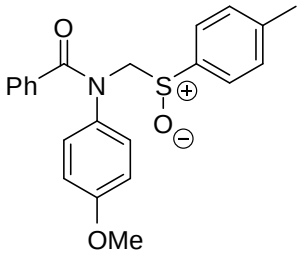


216

A 90:10 mixture (by ^{1}H NMR spectroscopy) of chlorosulfide **215** and methyl *p*-tolylsulfide (1.80 g, 9.38 mmol of chlorosulfide **215**, 2.5 eq.) was added to a stirred solution of tetraethylammonium iodide (430 mg, 1.88 mmol, 0.5 eq.) and benzamide **214** (850 mg, 3.75 mmol, 1.0 eq.) in CH_2Cl_2 (7.5 mL) at rt. The resulting solution was cooled to 0 °C and 50% $NaOH_{(aq)}$ (17.5 mL) was added. The resulting solution was heated at 50 °C for 18 h. Then, the solution was allowed to cool to rt and poured into saturated $NH_4Cl_{(aq)}$ (50 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 65:35 petrol-EtOAc as eluent gave benzamide **216** (922 mg, 67%) as a colourless oil, R_F (65:35 petrol-EtOAc) 0.4; IR (film) 2955, 1649 (C=O), 1510, 1493, 1446, 1372, 1250, 1144, 1039, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.21 (m, 5H, Ar), 7.16 (t, J = 7.5 Hz, 2H, Ar), 7.04 (d, J = 8.0 Hz, 2H, Ar), 6.93 (d, J = 8.0 Hz, 2H, Ar), 6.69 (d, J = 8.0 Hz, 2H, Ar), 5.30 (s, 2H, NCH_2), 3.73 (s, 3H, OMe), 3.00 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (C=O), 158.3 (*ipso*-C_6H_4OMe), 137.1 (*ipso*-Ar), 135.3 (*ipso*-Ar), 135.1 (*ipso*-Ar), 132.2 (Ar), 130.9 (*ipso*-Ar), 130.4 (Ar), 129.7 (Ar), 129.4 (Ar), 128.6 (Ar), 127.6 (Ar), 114.2 (Ar), 55.9 (NCH_2), 55.3 (OMe), 21.0 (Me); MS (ESI) *m/z* 386 [$(M + Na)^+$, 100], 364 [$(M + H)^+$, 20], 240 (50); HRMS *m/z* calcd for $C_{22}H_{21}NO_2S$ $(M + Na)^+$ 386.1185, found 386.1175 (+2.6 ppm error).

Lab Book Reference: PJR 2/70A

_N_-(4-Methoxyphenyl)-_N_-_p_-tolylsulfinylmethyl benzamide 193

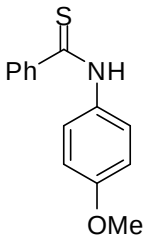


193

Using general procedure G, *m*-CPBA (68 mg of ~77% purity, 0.31 mmol, 1.1 eq.) and sulfanyl benzamide **216** (100 mg, 0.28 mmol, 1.0 eq.) in CH_2Cl_2 (1.8 mL) gave the crude product as a viscous foam. Purification by flash column chromatography on silica with 7:3 EtOAc-petrol as eluent gave sulfoxide **193** (88 mg, 84%) as an orange oil, R_F (7:3 EtOAc-petrol) 0.3; IR (film) 3056, 2932, 2837, 1650 (C=O), 1513, 1446, 1359, 1294, 1178, 1084, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.32 (d, J = 7.5, 2H Hz, *o*-Ph), 7.30 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 7.26 (br t, J = 7.5 Hz, 1H, *p*-Ph), 7.16 (t, J = 7.5 Hz, 2H, *m*-Ph), 7.10 (d, J = 8.5 Hz, 2H, Ar), 6.69 (d, J = 8.5 Hz, 2H, Ar), 5.20 (d, J = 12.5 Hz, 1H, NCH_2), 4.49 (d, J = 12.5 Hz, 1H, NCH_2), 3.70 (s, 3H, OMe), 2.38 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7 (C=O), 158.3 (*ipso*-C_6H_4OMe), 141.7 (*ipso*-Ar), 138.8 (*ipso*-Ar), 135.9 (*ipso*-Ar), 134.3 (*ipso*-Ar), 130.2 (Ar), 129.9 (Ar), 128.9 (Ar), 128.8 (Ar), 127.8 (Ar), 124.3 (Ar), 114.3 (Ar), 76.9 (NCH_2), 55.3 (OMe), 21.4 (Me); MS (ESI) *m/z* 402 [$(M + Na)^+$, 100], 240 [$(M - S(O)C_6H_4Me)^+$, 50]; HRMS *m/z* calcd for $C_{22}H_{21}NO_3S$ $(M + Na)^+$ 402.1134, found 402.1124 (+2.5 ppm error).

Lab Book Reference: PJR 2/74A

_N_-(4-Methoxyphenyl)thiobenzamide 217



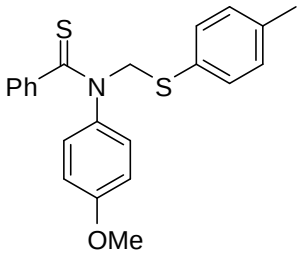
217

Phosphorous(V) sulfide (918 mg, 4.13 mmol, 1.25 eq.) was added to a stirred solution benzamide **214** (750 mg, 3.30 mmol, 1.0 eq.) in pyridine (15 mL) at rt under Ar. The

resulting solution was heated at 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M $HCl_{(aq)}$ (50 mL). 1 M HCl(aq) was added until pH 3 was obtained. The resulting solution was stirred for 2 h and then extracted with CH_2Cl_2 (3 × 50 ml). Combined organic extracts were washed with 1 M $HCl_{(aq)}$ (50 mL), water (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave thiobenzamide **217** (320 mg, 40%) as a pale yellow oil, R_F (4:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (br s, 1H, NH), 7.88 (dd, J = 7.0, 1.5 Hz, 2H, *o*-Ph), 7.67 (d, J = 8.5 Hz, 2H, Ar), 7.52 (dddd, J = 7.0, 7.0, 1.5, 1.5 Hz, 1H, *p*-Ph), 7.45 (dd, J = 7.0, 7.0 1.5 Hz, 2H, *m*-Ph), 6.98 (d, J = 8.5 Hz, 2H, Ar), 3.86 (s, 3H, OMe); MS (ESI) *m/z* 266 [$(M + Na)^+$, 20], 244 [$(M + H)^+$, 100], 159 (30), 141 (30), 125 (30); HRMS *m/z* calcd for $C_{14}H_{13}NOS$ $(M + H)^+$ 244.0791, found 244.0786 (+2.0 ppm error).

Lab Book Reference: PJR 2/119A

_N_-(4-Methoxyphenyl)-_N_-_p_-tolylsulfanylmethylthiobenzamide 218[164]



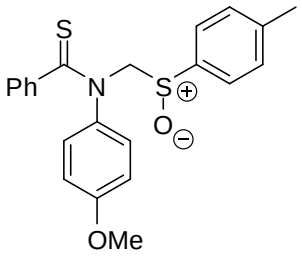
218

A 90:10 mixture (by ^{1}H NMR spectroscopy) of chlorosulfide **215** and methyl *p*-tolylsulfide (481 mg, 2.48 mmol of chlorosulfide **215**, 2.5 eq.) was added to a stirred solution of tetraethylammonium iodide (112 mg, 0.50 mmol, 0.5 eq.) and thiobenzamide **217** (240 mg, 0.99 mmol, 1.0 eq.) in CH_2Cl_2 (4.5 mL) at rt. The resulting solution was cooled to 0 °C and then 50% $NaOH_{(aq)}$ (2.5 mL) was added. The resulting solution was heated at 50 °C for 18 h. Then, the solution was allowed to cool to rt and poured into saturated $NH_4Cl_{(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_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 sulfanyl thiobenzamide **218** (204 mg, 54%) as a colourless oil, R_F (9:1 petrol-

EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H, Ar), 7.24-7.14 (m, 5H, Ar), 6.93 (br s, 2H, Ar), 6.70 (d, J = 8.5 Hz, 2H, Ar), 6.60 (d, J = 8.5 Hz, 2H, Ar), 4.64 (s, 2H, NCH_2), 3.74 (s, 3H, OMe), 2.35 (s, 3H, Me); MS (ESI) *m/z* 402 [(M + Na)$^+$, 100], 380 [(M + H)$^+$, 50]; HRMS *m/z* calcd for $C_{22}H_{21}NOS_2$ (M + Na)$^+$ 402.0962, found 402.0968 (+2.5 ppm error).

Lab Book Reference: PJR 2/130A

_N_-(4-Methoxyphenyl)-_N_-_p_-tolylsulfinylmethyl thiobenzamide 194

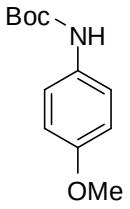


194

Using general procedure G, *m*-CPBA (141 mg of ~70% purity, 0.57 mmol, 1.1 eq.) and sulfanyl thiobenzamide **218** (200 mg, 0.52 mmol, 1.0 eq.) in CH_2Cl_2 (3.5 mL) gave the crude product as a viscous foam. Purification by flash column chromatography on silica with 7:3 EtOAc-petrol as eluent gave sulfoxide **194** (158 mg, 77%) as a viscous orange foam, R_F (7:3 EtOAc-petrol) 0.2; IR ($CHCl_3$) 2833, 1613 (C=S), 1502, 1443, 1242, 1178, 1047, 956, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.34-7.19 (m, 7H, Ar), 6.69 (d, J = 8.0 Hz, 2H, Ar), 6.51 (d, J = 8.5 Hz, 2H, Ar), 4.57 (d, J = 13.0 Hz, 1H, NCH_AH$_B$), 4.45 (d, J = 13.0 Hz, 1H, NCH$_A$$H_B$), 3.74 (s, 3H, OMe), 2.40 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 208.1 (C=S), 156.1 (*ipso*-C_6H_4OMe), 141.7 (*ipso*-Ar), 140.1 (*ipso*-Ar), 135.1 (br, *ipso*-Ar), 130.0 (*ipso*-Ar), 129.6 (Ar), 128.5 (Ar), 128.0 (Ar), 127.5 (Ar), 124.7 (Ar), 122.7 (Ar), 113.9 (Ar), 60.4 (NCH_2), 55.8 (OMe), 55.3 (OMe), 21.4 (Me), 14.6 (Me); MS (ESI) *m/z* 396 [(M + H)$^+$, 100]; HRMS *m/z* calcd for $C_{22}H_{21}NO_2S_2$ (M + H)$^+$ 396.1086, found 396.1092 (−0.4 ppm error).

Lab Book Reference: PJR 2/134A

***tert*-Butyl *N*-(4-methoxyphenyl)carbamate 219**[227]

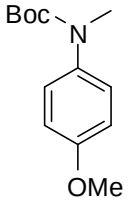


219

A solution of di-*tert*-butyl dicarbonate (4.80 g, 22.0 mmol, 1.0 eq.) in THF (15 mL) was added to a stirred solution of *p*-Anisidine (3.69, 30.0 mmol, 1.3 eq.) in THF (15 mL) at rt under Ar. The resulting solution was stirred at rt for 18 h. Then, CH_2Cl_2 (50 mL) and water (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as colourless oil. Purification by flash column chromatography on silica with 7:3 EtOAc-petrol as eluent gave *N*-Boc *p*-anisidine **219** (3.98 g, 81%) as a white solid, mp 84-87 °C, (lit.,[227] 92-94 °C); R_F (7:3 petrol-EtOAc) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (br d, J = 8.0 Hz, 2H, Ar), 6.84 (d, J = 8.0 Hz, 2H, Ar), 6.34 (br s, 1H, NH), 3.79 (s, 3H, OMe), 1.57 (s, 9H, CMe_3), Spectroscopic data consistent with those reported in the literature.[227]

Lab Book Reference: PJR 2/65A

***tert*-Butyl *N*-(4-methoxyphenyl) *N*-methylcarbamate 221**[228]



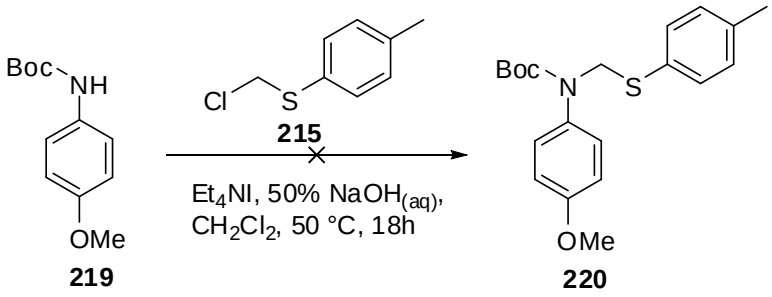
221

A solution of *N*-Boc *p*-anisidine **219** (256 mg, 1.15 mmol, 1.0 eq.) in THF (3 mL) was added to a stirred solution of NaH (51 mg of 60% wt in mineral oil, 1.27 mmol, 1.1 eq.) and methyl iodide (179 mg, 1.27 mmol, 1.1 eq.) in THF (2 mL) at rt under Ar. The resulting solution was stirred at rt for 18 h. Then, the reaction was cooled to 0 °C and water (7 mL) and Et_2O (7 mL) were added. The two layers were separated and the aqueous layer was extracted with E_2O (2 × 10 mL). The combined organic layers were

dried ($MgSO_4$) and evaporated under reduced pressure to give *N*-Boc *N*-methyl *p*-ansidine **221** (265 mg, 98%) as colourless oil which was sufficiently pure (by ^{1}H NMR spectroscopy) for subsequent use, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (br d, J = 8.0 Hz, 2H, Ar), 6.85 (d, J = 8.0 Hz, 2H, Ar), 3.80 (s, 3H, OMe), 3.22 (s, 3H, NMe), 1.44 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.9 (*ipso*-C_6H_4OMe), 155.2 (C=O), 135.2 (*ipso*-Ar), 122.6 (Ar), 117.5 (Ar), 79.8 (CMe_3), 57.6 (OMe), 28.7 (CMe_3), 28.3 (NMe). Spectroscopic data consistent with those reported in the literature.[229]

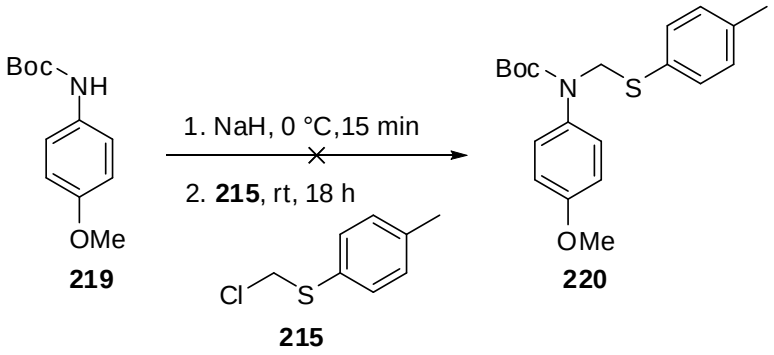
Lab Book Reference: PJR 2/82

Attempted synthesis of *tert*-Butyl *N*-(4-Methoxyphenyl)-*N*-*p*-tolylsulfanylmethyl carbamate 220 (*via* alkylation)



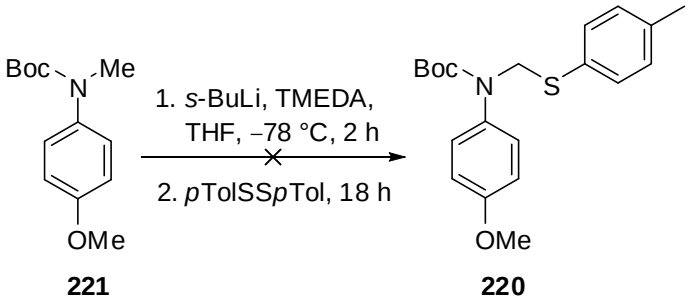
A 90:10 mixture (by ^{1}H NMR spectroscopy) of chlorosulfide **215** and methyl *p*-tolylsulfide (430 mg, 2.25 mmol of chlorosulfide **215**, 3.0 eq.) was added to a stirred solution of tetraethylammonium iodide (86 mg, 0.38 mmol, 0.5 eq.) and *N*-Boc *p*-anisidine **219** (167 mg, 0.75 mmol, 1.0 eq.) in CH_2Cl_2 (3.5 mL) at rt. The resulting solution was cooled to 0 °C and then 50% $NaOH_{(aq)}$ (1.5 mL) was added. The resulting solution was heated at 50 °C for 18 h. Then, the solution was allowed to cool to rt and poured into saturated $NH_4Cl_{(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave recovered *N*-Boc *p*-anisidine **219** (165 mg, 100%) as a white solid.

Lab Book Reference: PJR 2/75



A solution of *N*-Boc *p*-anisidine **219** (256 mg, 1.15 mmol, 1.0 eq.) in THF (3 mL) was added to a stirred solution of NaH (51 mg of 60% wt in mineral oil, 1.27 mmol, 1.1 eq.) in THF (2 mL) at rt under Ar. The resulting solution was stirred at rt for 15 min. Then, a 90:10 mixture (by ^{1}H NMR spectroscopy) of chlorosulfide **215** and methyl *p*-tolylsulfide (287 mg, 1.50 mmol of chlorosulfide **215**, 2.0 eq.) was added. The resulting solution was stirred for 18 h at rt. Then, water (7 mL) and Et_2O (7 mL) were added. The two layers were separated and the aqueous layer was extracted with E_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed no formation of sulfanyl anisidine **220**, therefore no further purification was attempted.
Lab Book Reference: PJR 2/79

Attempted synthesis of *tert*-Butyl *N*-(4-Methoxyphenyl)-*N*-*p*-tolylsulfanylmethyl carbamate 220 (*via* lithiation-trapping)

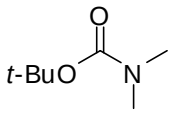


s-BuLi (1.97 mL of a 1.3 M solution in hexanes, 1.51 mmol, 1.2 eq.) was added dropwise to a stirred solution of the *N*-Boc *N*-methyl *p*-anisidine **221** (300 mg, 1.26 mmol, 1.0 eq.) and TMEDA (288 mg, 2.52 mmol, 2.0 eq.) in THF (5.0 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 2 h. Then, a solution of *p*-tolyldisulfide (610 mg, 2.52 mmol, 2.0 eq.) in THF (1.0 mL) was added dropwise. The

solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 petrol-Et_2O as eluent gave recovered *N*-Boc *N*-methyl *p*-anisidine **221** (155 mg, 52%) as a colourless oil.

Lab Book Reference: PJR 2/85

N-*tert*-Butoxycarbonyl-*N*,*N*-dimethylamine 222[167]

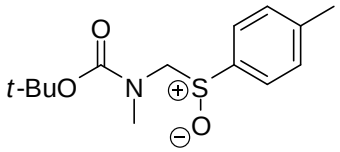


222

A solution of di-*tert*-butyl dicarbonate (5.24 g, 24.0 mmol, 1.2 eq.) in 1:1 THF-water (100 mL) was added to a stirred solution of dimethylamine (2.28 mL of a 40% wt solution in water, 20.0 mmol, 1.0 eq.) and $NaHCO_3$ (2.00 g, 24.0 mmol, 1.2 eq.) in 1:1 THF-water (100 mL) at rt under Ar. The resulting solution was stirred at rt for 18 h. Then, Et_2O (100 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as colourless oil. Purification by Kügelrohr distillation gave *N*-Boc dimethylamine **222** (2.09 g, 72%) as a colourless oil, bp 84-86 °C/2.0 mmHg (lit.,[167] 75-80 °C/16-17 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (s, 6H, NMe_2), 1.44 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.2 (C=O), 79.8 (*C*Me_3), 36.5 (NMe_2), 28.4 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[167]

Lab Book Reference: PJR 3/174

N-Methyl *N*-*p*-tolylsulfinylmethyl carbamic acid *tert*-butyl ester 196

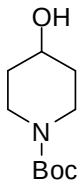


196

Using general procedure F, *s*-BuLi (1.00 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.), TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.) and *N*-Boc dimethylamine **222** (145 mg, 1.00 mmol, 1.0 eq.) in Et_2O (2 mL) at −78 °C for 2 h and methyl *p*-toluenesulfinate **121** (340 mg, 2.00 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2: CH_2Cl_2-acetone with 1% Et_3N as eluent gave sulfoxide **196** (202 mg, 71%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone with 1% Et_3N) 0.3; IR (Film) 2977, 2930, 1712 (C=O), 1493, 1454, 1370, 1288, 1163, 1045, 871 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.55 (d, J = 8.0 Hz, 1H, *m*-C_6H_4Me), 7.51 (d, J = 8.0 Hz, 1H, *m*-C_6H_4Me), 7.35 (d, J = 8.0 Hz, 1H, *o*-C_6H_4Me), 7.33 (d, J = 8.0 Hz, 1H, *o*-C_6H_4Me), 4.58 (d, J = 13.0 Hz, 0.5H, NCH_AH_B), 4.37 (d, J = 13.0 Hz, 0.5H, NCH_AH_B), 4.30 (d, J = 13.0 Hz, 0.5H, NCH_AH_B), 4.11 (d, J = 13.0 Hz, 0.5H, NCH_AH_B), 3.06 (s, 1.5H, NMe), 2.94 (s, 1.5H, NMe), 2.42 (s, 1.5H, C_6H_4Me), 2.41 (s, 1.5H, C_6H_4Me), 1.43 (s, 4.5H, CMe_3), 1.39 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 155.2 (C=O), 154.2 (C=O), 142.0 (*ipso*-$C_6H_4S(O)$), 141.7 (*ipso*-$C_6H_4S(O)$), 138.7 (*ipso*-C_6H_4Me), 138.4 (*ipso*-C_6H_4Me), 130.1 (Ar), 129.9 (Ar), 124.3 (Ar), 124.2 (Ar), 81.2 (CMe_3), 81.0 (CMe_3), 74.6 (NCH_2), 74.5 (NCH_2), 37.0 (NMe), 36.3 (NMe), 28.2 (CMe_3), 28.0 (CMe_3), 21.4 (br, C_6H_4Me); MS (ESI) *m/z* 306 [$(M + Na)^+$, 100]; HRMS *m/z* calcd for $C_{14}H_{21}NO_3S$ $(M + Na)^+$ 306.1134, found 306.1135 (−0.3 ppm error).

Lab Book Reference: PJR 3/178B

tert-Butyl 4-hydroxypiperidine-1-carboxylate 302

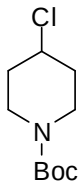


302

$NaBH_4$ (200 mg, 7.5 mmol, 1.5 eq.) was added to a stirred solution of *N*-Boc piperidin-4-one (1.00 g, 5.0 mmol, 1.0 eq.) in EtOH (5 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 4 h. Then, the mixture was cooled to 0 °C and saturated $NH_4Cl_{(aq)}$ (20 mL) was added dropwise. The solvent was evaporated under reduced pressure and EtOAc (15 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The

combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-acetone as eluent gave *N*-Boc 4-hydoxy piperidine **302** (984 mg, 98%) as a white solid, mp 66-68 °C (lit.,[230] 64.6-66.5 °C); R_F (9:1 CH_2Cl_2-Acetone) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82-3.72 (m, 3H, NCH_AH$_B$ + C*H*OH), 2.97 (ddd, J = 13.0, 10.0, 3.0 Hz, 2H, NCH$_A$$H_B$), 2.67 (br s, 1H, OH), 1.83-1.78 (m, 2H, NCH$_2$CH_AH$_B$), 1.46-1.37 (m, 2H, NCH$_2$CH$_A$$H_B$), 1.41 (s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.7 (C=O), 79.5 (*C*Me$_3$), 67.4 (CHOH), 41.3 (br, NCH$_2$), 34.0 (NCH$_2$*C*H$_2$), 28.3 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[230]

tert-Butyl 4-chloropiperidine-1-carboxylate 223

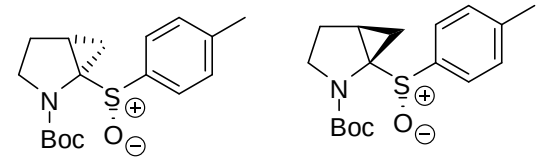


223

A solution of hexachloroethane (7.05 g, 29.8 mmol, 2.0 eq.) in CH_2Cl_2 (25 mL) was added to a stirred solution of *N*-Boc 4-hydroxy piperidine **302** (3.00 g, 14.9 mmol, 1.0 eq.) and PPh_3 (7.82 g, 29.8 mmol, 2.0 eq.) in CH_2Cl_2 (75 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave *N*-Boc 4-chloro piperidine **223** (2.13 g, 67%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; IR (film) 2974, 2932, 1696 (C=O), 1477, 1420, 1365, 1277, 1169, 1112, 1002 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (tt, J = 7.5, 3.5 Hz, 1H, CHCl), 3.69 (ddd, J = 13.0, 7.0, 3.5 Hz, 2H, NCH_AH$_B$), 3.29 (ddd, J = 13.0, 7.5 Hz, 2H, NCH$_A$$H_B$), 2.01 (ddt, J = 13.5, 7.0, 3.5 Hz, 2H, NCH$_2$CH_AH$_B$), 1.78 (dtd, J = 13.5, 7.5, 3.5 Hz, 2H, NCH$_2$CH$_A$$H_B$), 1.45 (s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 79.7 (*C*Me$_3$), 56.9 (CHCl), 41.2 (br, NCH$_2$), 34.8 (NCH$_2$*C*H$_2$), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 244 [(^{37}M + Na)$^+$, 10], 242 [(^{35}M + Na)$^+$, 30], 166 (30), 164 (100); HRMS *m/z* calcd for $C_{10}H_{18}{}^{35}ClNO_2$ (M + Na)$^+$ 242.0918, found 242.0911 (+3.1 ppm error).

***tert*-Butyl (1*R*,5*R*)-(*p*-tolylsulfinyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate *syn*-(*R*,*R*,*S*$_S$)-225 and *tert*-Butyl (1*S*,5*S*)-(*p*-tolylsulfinyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate *anti*-(*S*,*S*,*S*$_S$)-225**

(Table 3.5, Entry 1)



syn-(*R*,*R*,*S*$_S$)-**225** *anti*-(*S*,*S*,*S*$_S$)-**225**

Using general procedure H, *s*-BuLi (1.70 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and TMEDA (256 mg, 2.20 mmol, 2.2 eq.) in Et_2O (6 mL) at −78 °C for 1 h and a solution of Andersen's sulfinate (*S*$_S$)-**97** (647 mg, 2.20 mmol, 2.2 eq.) in THF (2 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-(*R*,*R*,*S*$_S$)-**225** (129 mg, 38%, 58:42 er by CSP-HPLC) as a white solid, mp 163-166 °C; R_F (3:2 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2975, 2931, 1703 (C=O), 1492, 1454, 1393, 1368, 1257, 1168, 1083, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H, *m*-C_6H_4Me), 7.28 (d, *J* = 8.0 Hz, 2H, *o*-C_6H_4Me), 3.47 (br s, 1H, NC*H*$_A$H$_B$), 2.84 (br s, 1H, NCH$_A$*H*$_B$), 2.41 (s, 3H, Me), 2.28 (br s, 1H, CH), 1.93-1.90 (m, 1H, CH), 1.77-1.74 (m, 2H, CH), 1.52 (br s, 9H, CMe_3), 1.16-1.13 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.0 (br, C=O), 141.9 (*ipso*-Ar), 141.6 (*ipso*-Ar), 141.1 (*ipso*-Ar), 139.5 (*ipso*-Ar), 129.7 (br, Ar), 125.5 (Ar), 124.8 (Ar), 81.2 (br, *C*Me$_3$), 61.2 (N*C*S(O)Ar), 61.1 (N*C*S(O)Ar), 52.3 (br, NCH_2), 28.5 (C*Me*$_3$), 26.1 (br, CH_2), 23.7 (CH_2), 22.3 (CH_2), 21.6 (Me), 11.9 (CH), 11.7 (CH); MS (ESI) *m/z* 344 [(M + Na)$^+$, 30], 322 [(M + H)$^+$, 100]; HRMS *m/z* calcd for $C_{17}H_{23}NO_3S$ (M + Na)$^+$ 344.1291, found 344.1286 (+1.5 ppm error); CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*-PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*S*,*R*$_S$)-**225** 10.1 min, *syn*-(*R*,*R*,*S*$_S$)-**225** 11.5 min and sulfoxide *anti*-(*S*,*S*,*S*$_S$)-**225** (152 mg, 45%, 70:30 er by CSP-HPLC) as a colourless oil, R_F (3:2 petrol-EtOAc) 0.2; IR (film) 2977, 2932, 1696 (C=O), 1477, 1384, 1335, 1257, 1168, 1083, 1048, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.26 (d, *J* = 8.0 Hz, 2H, *o*-C_6H_4Me), 3.79-3.72 (m, 1H, NC*H*$_A$H$_B$), 3.61 (br s, 1H, NCH$_A$*H*$_B$), 2.37 (s, 3H, Me), 2.27-2.18 (m, 1H, CH), 2.05 (dtd, *J* = 8.0, 7.0, 1.5 Hz, 1H, NCC*H*), 1.83-1.75 (m, 1H, CH), 1.49 (s, 9H, CMe_3), 1.09 (t, *J* = 7.0 Hz, 1H, H), 1.05-1.01 (br m, 1H, CH); ^{13}C NMR (100.6

MHz, $CDCl_3$) δ 155.5 (C=O), 141.4 (*ipso*-Ar), 138.0 (*ipso*-Ar), 129.5 (Ar), 124.8 (Ar), 80.9 (*C*Me_3), 69.9 (br, N*C*S(O)Ar), 52.5 (br, NCH_2), 29.9 (br, CH_2), 28.4 (C*Me*$_3$), 26.8 (CH_2), 24.3 (br, CH), 21.3 (Me); MS (ESI) *m/z* 344 [$(M + Na)^+$, 40], 322 [$(M + H)^+$, 100]; HRMS *m/z* calcd for $C_{17}H_{23}NO_3S$ $(M + Na)^+$ 344.1291, found 344.1286 (+1.3 ppm error); CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*S*,*S*,S_s)-**225** 9.0 min, *anti*-(*R*,*R*,R_s)-**225** 12.3 min.

(Table 3.5, Entry 2)

Using general procedure I, *s*-BuLi (1.70 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and TMEDA (256 mg, 2.20 mmol, 2.2 eq.) in Et_2O (6 mL) at −78 °C for 1 h and a solution of Andersen's sulfinate (S_s)-**97** (647 mg, 2.20 mmol, 2.2 eq.) in THF (2 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-(*R*,*R*,S_S)-**225** (122 mg, 36%, 80:20 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*-PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*S*,R_S)-**225** 10.7 min, *syn*-(*R*,*R*,S_S)-**7** 12.3 min and sulfoxide *anti*-(*S*,*S*,S_S)-**225** (157 mg, 47%, 78:22 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*S*,*S*,S_s)-**225** 9.4 min, *syn*-(*R*,*R*,R_s)-**225** 13.1 min.

(Table 3.5, Entry 3)

Using general procedure J, *s*-BuLi (1.70 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and TMEDA (256 mg, 2.20 mmol, 2.2 eq.) in Et_2O (6 mL) and a solution of Andersen's sulfinate (S_s)-**97** (647 mg, 2.20 mmol, 2.2 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-(*R*,*R*,S_S)-**225** (132 mg, 39%, 89:11 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*-PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*S*,R_S)-**225** 13.2 min, *syn*-(*R*,*R*,S_S)-**225** 15.2 min and sulfoxide *anti*-(*S*,*S*,S_S)-**225** (146 mg, 44%, 88:12 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*S*,*S*,S_s)-**225** 11.8 min, *syn*-(*R*,*R*,R_s)-**225** 16.1 min.

Using general procedure J, *s*-BuLi (1.70 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and (−)-sparteine (504 mg, 2.20 mmol, 2.2 eq.) in Et_2O (6 mL) and a solution of Andersen's sulfinate

(S_s)-**97** (647 mg, 2.20 mmol, 2.2 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-(*R*,*R*,S_S)-**7** (88 mg, 27%, 96:4 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*-PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*S*,R_S)-**7** 10.2 min, *syn*-(*R*,*R*,S_S)-**7** 11.6 min and sulfoxide *anti*-(*S*,*S*,S_S)-**7** (78 mg, 24%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*S*,*S*,S_s)-**225** 8.7 min, *syn*-(*R*,*R*,R_s)-**225** 11.9 min.

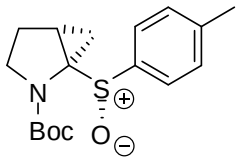
Using general procedure J, *s*-BuLi (0.85 mL of a 1.3 M solution in hexanes, 1.10 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (110 mg, 0.50 mmol, 1.0 eq.) and (+)-sparteine surrogate (213 mg, 1.10 mmol, 2.2 eq.) in Et_2O (4 mL) and a solution of Andersen's sulfinate (S_s)-**97** (324 mg, 1.10 mmol, 2.2 eq.) in THF (3 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-(*R*,*R*,S_S)-**225** (42 mg, 26%, 99:1 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*-PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*S*,R_S)-**225** 9.6 min, *syn*-(*R*,*R*,S_S)-**225** 10.9 min and sulfoxide *anti*-(*S*,*S*,S_S)-**225** (43 mg, 27%, 93:7 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*S*,*S*,S_s)-**225** 8.6 min, *syn*-(*R*,*R*,R_s)-**225** 11.6 min.

Using general procedure J, *s*-BuLi (1.70 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and diamine (*R*,*R*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (6 mL) and a solution of Andersen's sulfinate (S_s)-**97** (647 mg, 2.20 mmol, 2.2 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-(*R*,*R*,S_S)-**225** (163 mg, 51%, 99:1 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −43.7 (*c* 0.65 in $CHCl_3$); CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*-PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*S*,R_S)-**225** 9.9 min, *syn*-(*R*,*R*,S_S)-**225** 11.5 min and sulfoxide *anti*-(*S*,*S*,S_S)-**225** (80 mg, 25%, 87:13 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +64.6 (*c* 0.9 in $CHCl_3$); CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*S*,*S*,S_s)-**225** 8.7 min, *syn*-(*R*,*R*,R_s)-**225** 12.4 min.

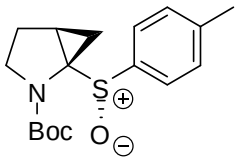
Using general procedure J, *s*-BuLi (1.70 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (6 mL) and a solution of Andersen's

sulfinate (S_s)-**97** (647 mg, 2.20 mmol, 2.2 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-(*R*,*R*,S_S)-**225** (38 mg, 12%, 89:11 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −43.2 (*c* 0.7 in $CHCl_3$); CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*-PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*S*,R_S)-**225** 12.2 min, *syn*-(*R*,*R*,S_S)-**225** 14.2 min and sulfoxide *anti*-(*S*,*S*,S_S)-**225** (174 mg, 54%, 87:13 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +86.1 (*c* 0.7 in $CHCl_3$); CSP-HPLC: Chiralcel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*S*,*S*,S_s)-**225** 8.1 min, *syn*-(*R*,*R*,R_s)-**225** 11.4 min.

tert-Butyl 1-(*p*-tolylsulfinyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate *syn-rac*-225 and *anti-rac*-225



syn-rac-**225**



anti-rac-**225**

(Table 3.4, entry 1)

Using General procedure H, *s*-BuLi (2.11 mL of a 1.3 M solution in hexanes, 2.75 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (275 mg, 1.25 mmol, 1.0 eq.) and TMEDA (319 mg, 2.75 mmol, 2.2 eq.) in Et_2O (8 mL) at −78 °C for 6 h and methyl *p*-toluenesulfinate **121** (468 mg, 2.75 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn-rac*-**225** (142 mg, 35%) as a white solid, mp 161-163 °C and sulfoxide *anti-rac*-**225** (144 mg, 36%) as a colourless oil.

(Table 3.4, entry 2)

Using General procedure H, *s*-BuLi (2.11 mL of a 1.3 M solution in hexanes, 2.75 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (275 mg, 1.25 mmol, 1.0 eq.) and TMEDA (319 mg, 2.75 mmol, 2.2 eq.) in Et_2O (8 mL) at −78 °C for 1 h and methyl *p*-toluenesulfinate **121** (468 mg, 2.75 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn-rac*-**225** (138 mg, 35%) as a white solid and sulfoxide *anti-rac*-**225** (141 mg, 35%) as a colourless oil.

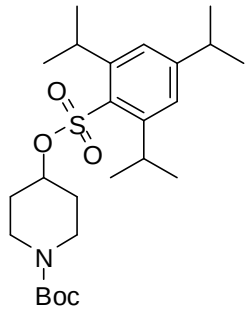
(Table 3.4, entry 3)

s-BuLi (2.11 mL of a 1.3 M solution in hexanes, 2.75 mmol, 2.2 eq.) was added to a stirred solution of *N*-Boc 4-chloro piperidine **223** (275 mg, 1.25 mmol, 1.0 eq.) in THF (8 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, methyl *p*-toluenesulfinate **121** (468 mg, 2.75 mmol, 2.2 eq.) was added and the resulting solution was allowed to warm to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-*rac*-**225** (132 mg, 33%) as a white solid and sulfoxide *anti*-*rac*-**225** (129 mg, 36%) as a colourless oil.

(Table 3.4, entry 4)

s-BuLi (2.11 mL of a 1.3 M solution in hexanes, 2.75 mmol, 2.2 eq.) was added to a stirred solution of *N*-Boc 4-chloro piperidine **223** (275 mg, 1.25 mmol, 1.0 eq.) in THF (8 mL) at −30 °C under Ar. The resulting solution was stirred at −30 °C for 5 min. Then, methyl *p*-toluenesulfinate **121** (468 mg, 2.75 mmol, 2.2 eq.) was added and the resulting solution was allowed to warm to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *syn*-*rac*-**225** (85 mg, 21%) as a white solid and sulfoxide *anti*-*rac*-**225** (72 mg, 18%) as a colourless oil.

***tert*-Butyl 4-[[(2,4,6-triisopropylbenzene)sulfonyl]oxy]piperidine-1-carboxylate 234**

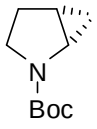


234

Triisopropylsulfonyl chloride (4.89 g, 16.15 mmol, 1.3 eq.) was added portionwise to a stirred solution of *N*-Boc 4-hydroxy piperidine **302** (2.50 g, 12.42 mmol, 1.0 eq.), Et_3N (1.90 mL, 13.66 mmol, 1.1 eq.) and DMAP (14 mg, 0.12 mmol, 0.01 eq.) in CH_2Cl_2 (30 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 3 h. Then, water (20 mL) was added and the two layers were separated. The organic layer was washed with 1 M $HCl_{(aq)}$ (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave *N*-Boc 4-sulfonyl piperidine **234** (984 mg, 98%) as a pale yellow solid, mp 71-73 °C; R_F (4:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 2H, Ar), 4.84 (tt, J = 7.5, 4.0 Hz, 1H, C*H*OSO_2Ar), 4.16 (sept, J = 7.0 Hz, 2H, C*H*Me_2), 3.67 (ddd, J = 13.0, 7.0, 4.0 Hz, 2H, NC*H*$_A$H$_B$), 3.26 (ddd, J = 13.0, 8.0, 4.0 Hz, 2H, NCH$_A$*H*$_B$), 2.92 (sept, J = 7.0 Hz, 1H, C*H*Me_2), 1.88 (ddt, J = 13.5, 7.0, 4.0, 2H, NCH_2C*H*$_A$H$_B$), 1.76 (dtd, J = 13.5, 7.0, 4.0, 2H, NCH_2CH$_A$*H*$_B$), 1.45 (s, 9H, CMe_3) 1.27 (d, J = 7.0 Hz, 12H, CH*Me*$_2$), 1.27 (d, J = 7.0 Hz, 6H, CH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.7 (C=O), 153.7 (*ipso*-Ar), 150.4 (*ipso*-Ar), 130.8 (*ipso*-Ar), 123.8 (Ar), 80.0 (*C*Me_3), 76.9 (*C*HOSO_2Ar), 34.3 (*C*HMe_2), 31.7 (br, NCH_2), 29.8 (br, NCH_2*C*H_2), 29.7 (*C*HMe_2) 28.5 (C*Me*$_3$), 24.8 (CH*Me*$_2$), 23.6 (CH*Me*$_2$).

Lab Book Reference: PJR 3/245

***tert*-Butyl 2-azabicyclo[3.1.0]hexane-2-dicarboxylate *rac*-227**

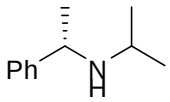


rac-**227**

Using general procedure H, *s*-BuLi (7.70 mL of a 1.3M solution in hexanes, 10.01 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (1.00 g, 4.55 mmol, 1.0 eq.) and TMEDA (1.16 g, 10.01 mmol, 2.2 eq.) in Et_2O (20.0 mL) at −78 °C for 1 h and MeOH (2.0 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave bicycle *rac*-**227** (723 mg, 87%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; IR (film) 2974, 2879, 1670 (C=O), 1411, 1365, 1344, 1254, 1171, 1111, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (br s, 1H, NCH_AH_B), 3.33-3.26 (br m, 1H, NCH), 2.82 (q, J = 9.0 Hz, 1H, NCH_AH_B), 1.97 (br s, 1H, $NCH_2CH_AH_B$), 1.82 (dtd, J = 12.5, 9.0, 3.0 Hz, 1H, $NCH_2CH_AH_B$), 1.45-1.34 (m, 1H, NCHC*H*), 1.37 (s, 9H, CMe_3), 0.57 (br s, 1H, NCHCH_AH_B), 0.42 (td, J = 5.0, 3.0 Hz, 1H, $NCHCH_AH_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C=O), 79.0 (*C*Me_3), 43.4 (br, NCH_2), 35.3 (NCH), 28.3 (C*Me*$_3$), 25.4 (CH_2), 14.8 (NCH*C*H), 10.7 (CH_2); MS (ESI) *m/z* 206 [$(M + Na)^+$, 80], 128 (100); HRMS *m/z* calcd for $C_{10}H_{17}NO_2$ $(M + Na)^+$ 206.1156, found 206.1151 (−2.0 ppm error).

Lab Book Reference: PJR 4/251 + PJR 4/256

[(1*S*)-1-phenylethyl]isopropylamine 236[231]



(*S*)-**236**

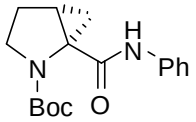
A stirred solution of (*S*)-*α*-methylbenzylamine (3.87 mL, 30.0 mmol, 1.0 eq.) in acetone (300 mL) was heated to 60 °C and stirred at 60°C for 16 h. Then, the solution was cooled to rt and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (100 mL) and $NaBH_4$ (1.70 g, 45.0 mmol, 1.5eq.) was added portionwise at 0°C under Ar. The resulting solution was stirred at rt for 2h. Then, the solution was cooled to 0 °C and sat. $NH_4Cl_{(aq)}$ (40 mL) was added dropwise. The solvent was evaporated under reduced pressure and the reaction mixture was taken up in EtOAc (25mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). Combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave amine (*S*)-**236** (4.86 g, 99%) as a colourless oil, bp 84-86 °C at 9 mm Hg (lit., 104 °C at 20 mm Hg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.20 (m, 5H, Ph), 3.88 (q, J = 6.5 Hz, 1H, NC*H*Ph), 2.61 (sept., J = 6.0 Hz, 1H, NC*H*Me_2), 1.34 (d, J =

6.5 Hz, 3H, NCH(Ph)*Me*), 1.02 (d, *J* = 6.0 Hz, 6H, NCH*Me*$_A$Me$_B$), 0.99 (d, *J* = 6.0 Hz, 6H, NCHMe$_A$*Me*$_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.9 (*ipso*-Ph), 128.4 (Ph), 126.7 (Ph), 126.4 (Ph), 55.0 (N*C*HPh), 45.6 (N*C*HMe$_2$), 24.8 (Me), 24.0 (Me), 22.1 (Me). Spectroscopic data consistent with those reported in the literature.[231]

Lab Book Reference: PJR 5/352

tert-Butyl-(1*S*,5*R*)-(phenylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (*S*,*R*)-235

(Table 3.6, Entry 1)



(S,R)-**235**

Using general procedure H, *s*-BuLi (1.69 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and (−)-sparteine (516 mg, 2.20 mmol, 2.2 eq.) in Et_2O (8 mL) and phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**235** (283 mg, 94%, 56:44 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.2 min, (*S*,*R*)-**235** 13.6 min. Full characterisation data is presented later.

(Table 3.6, Entry 3)

Using general procedure H, *s*-BuLi (1.95 mL of a 1.3M solution in hexanes, 2.53 mmol, 2.2 eq.), *N*-Boc 4-sulfonyl piperidine **234** (540 mg, 1.15 mmol, 1.0 eq.) and (−)-sparteine (593 mg, 2.53 mmol, 2.2 eq.) in Et_2O (6.5 mL) at −78 °C for 1 h and phenylisocyanate (301 mg, 2.53 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**234** (291 mg, 84%, 58:42 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**234** 7.2 min, (*S*,*R*)-**234** 14.1 min.

Lab Book Reference: PJR 4/246

Kinetic Resolution of *rac*-227

(Table 3.7, Entry 1)

s-BuLi (0.70 mL of a 1.3M solution in hexanes, 0.91 mmol, 0.5 eq.) was added dropwise to a stirred solution of azabicyco[3.1.0] hexane *rac*-**227** (333 mg, 1.82 mmol, 1.0 eq.) and (−)-sparteine (213 mg, 0.91 mmol, 0.5 eq.) in Et_2O (5.5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, phenylisocyanate (130 mg, 1.09 mmol, 0.6 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave recovered azabicyco[3.1.0] hexane (*R*,*S*)-**227** (99 mg, 30%, er not determined) and amide (*S*,*R*)-**235** (198 mg, 36%, 56:44 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.1 min, (*S*,*R*)-**235** 13.7 min.

Lab Book Reference: PJR 4/252

(Table 3.7, Entry 2)

n-BuLi (0.23 mL of a 2.5M solution in hexanes, 0.58 mmol, 0.5 eq.) was added dropwise to a stirred solution of azabicyco[3.1.0] hexane *rac*-**227** (210 mg, 1.15 mmol, 1.0 eq.) and (−)-sparteine (136 mg, 0.58 mmol, 0.5 eq.) in Et_2O (5.0 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, phenylisocyanate (69 mg, 0.58 mmol, 0.5 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave recovered azabicyco[3.1.0] hexane (*R*,*S*)-**227** (110 mg, 52%, er not determined) and amide (*S*,*R*)-**235** (146 mg, 42%, 56:44 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.4 min, (*S*,*R*)-**235** 14.8 min..

Lab Book Reference: PJR 4/257

(Table 3.8, Entry 4)

Using general procedure H, *s*-BuLi (1.27 mL of a 1.3M solution in hexanes, 1.65 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (164 mg, 0.75 mmol, 1.0 eq.) and diamine (*R*,*R*)-**237** (572 mg, 1.65 mmol, 2.2 eq.) in Et_2O (5 mL) at −78 °C for 1 h and phenylisocyanate (196 mg, 1.65 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**235** (182 mg, 81%, 62:38 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.4 min, (*S*,*R*)-**235** 14.8 min.

Lab Book Reference: PJR 4/263

(Table 3.9, Entry 1)

Using general procedure H, *s*-BuLi (0.84 mL of a 1.3M solution in hexanes, 1.20 mmol, 1.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and (−)-sparteine (281 mg, 1.20 mmol, 1.2 eq.) in Et_2O (8 mL) at −78 °C for 1 h and phenylisocyanate (143 mg, 1.20 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**235** (138 mg, 45%, 56:44 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.2 min, (*S*,*R*)-**235** 13.3 min..

Lab Book Reference: PJR 4/241

(Table 3.9, Entry 3)

Using general procedure H, *s*-BuLi (0.98 mL of a 1.3M solution in hexanes, 1.26 mmol, 1.1 eq.), *N*-Boc 4-sulfonyl piperidine **234** (540 mg, 1.15 mmol, 1.0 eq.) and (−)-sparteine (296 mg, 1.26 mmol, 1.1 eq.) in Et_2O (6.5 mL) at −78 °C for 1 h and phenylisocyanate (151 mg, 1.26 mmol, 1.1 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**235** (145 mg, 42%, 58:42 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.4 min, (*S*,*R*)-**235** 14.5 min.

Lab Book Reference: PJR 4/248

(Table 3.12, Entry 3)

A solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) in Et_2O (3.0 mL) was added dropwise over 30 min to a stirred solution of *s*-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol, 2.2 eq.) and (−)-sparteine (515 mg, 2.20 mmol, 2.2 eq.) in Et_2O (3.5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**235** (205 mg, 68%, 54:46 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.0 min, (*S*,*R*)-**235** 13.4 min.

Lab Book Reference: PJR 5/348

(Table 3.12, Entry 4)

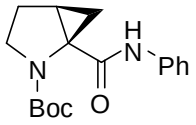
A solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) in Et_2O (3.0 mL) was added dropwise to a stirred solution of *s*-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol, 2.2 eq.) and (−)-sparteine (515 mg, 2.20 mmol, 2.2 eq.) in Et_2O (3.5 mL) at −78 °C under Ar. The resulting solution was stirred at −40 °C for 1 h. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**235** (205 mg, 73%, 58:42 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.2 min, (*S*,*R*)-**235** 14.1 min.

Lab Book Reference: PJR 5/350

(Table 3.12, Entry 5)

A solution of *N*-Boc 4-sulfonyl piperidine **234** (350 mg, 0.75 mmol, 1.0 eq.) in Et_2O (3.0 mL) was added dropwise over 30 min *via* syringe pump to a stirred solution of *s*-BuLi (1.28 mL of a 1.3M solution in hexanes, 1.65 mmol, 2.2 eq.) and (−)-sparteine (386 mg, 1.65 mmol, 2.2 eq.) in Et_2O (3.5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, phenylisocyanate (196 mg, 1.65 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**235** (227 mg, 99%, 56:44 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.0 min, (*S*,*R*)-**235** 13.5 min.

tert-Butyl (1*R*,5*S*)-(phenylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (*R*,*S*)-235



(R,S)-**235**

(Table 3.8, entry 2)

Using general procedure H, *s*-BuLi (1.51 mL of a 1.3 M solution in hexanes, 1.96 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (194 mg, 0.89 mmol, 1.0 eq.) and (+)-sparteine surrogate **1** (381 mg, 1.96 mmol, 2.2 eq.) in Et_2O (5.5 mL) and phenylisocyanate (233 mg, 1.96 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (212 mg, 79%, 54:46 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.4 min, (*S*,*R*)-**235** 14.8 min.

(Table 3.8, entry 3)

Using general procedure H, *s*-BuLi (1.35 mL of a 1.3 M solution in hexanes, 1.76 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (175 mg, 0.80 mmol, 1.0 eq.) and

diamine (*S*,*S*)-**42** (547 mg, 1.76 mmol, 2.2 eq.) in Et_2O (5.0 mL) and phenylisocyanate (124 mg, 1.04 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (178 mg, 74%, 67:33 er by CSP-HPLC) as a pale yellow solid,); $[\alpha]_D$ +45.5 (*c* 1.1 in $CHCl_3$); CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.3 min, (*S*,*R*)-**235** 14.3 min .

(Table 3.9, Entry 5)

Using general procedure H, *s*-BuLi (0.68 mL of a 1.3M solution in hexanes, 0.88 mmol, 1.1 eq.), *N*-Boc 4-chloro piperidine **223** (175 mg, 0.80 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (274 mg, 0.88 mmol, 1.1 eq.) in Et_2O (5.0 mL) at −78 °C for 1 h and phenylisocyanate (124 mg, 1.04 mmol, 1.3 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (178 mg, 43%, 57:43 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.3 min, (*S*,*R*)-**235** 14.3 min.

Lab Book Reference: PJR 4/281

(Table 3.10, Entry 2)

A solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) in Et_2O (3.0 mL) was added dropwise to a stirred solution of *s*-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol, 2.2 eq.) and diamine (*S*,*S*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (3.5 mL) at −78 °C under Ar. The resulting solution was stirred at −30 °C for 5 min. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (223 mg, 74%, 52:48 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.1 min, (*S*,*R*)-**235** 14.0 min.

Lab Book Reference: PJR 5/337

(Table 3.10, Entry 3)

Using general procedure H, *s*-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.40 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (683 mg, 2.40 mmol, 2.2 eq.) in Et_2O (8.0 mL) at −40 °C for 1 h and phenylisocyanate (262 mg, 2.40 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (208 mg, 69%, 67:33 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.4 min, (*S*,*R*)-**235** 13.3 min.

Lab Book Reference: PJR 4/275

(Table 3.10, Entry 4)

Using general procedure H, *s*-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.40 mmol, 2.2 eq.), *N*-Boc 4-sulfonyl piperidine **234** (466 mg, 1.00 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (683 mg, 2.40 mmol, 2.2 eq.) in Et_2O (8.0 mL) at −40 °C for 1 h and phenylisocyanate (262 mg, 2.40 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (220 mg, 73%, 58:42 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.4 min, (*S*,*R*)-**235** 14.5 min.

Lab Book Reference: PJR 4/275

(Table 3.11, Entry 1)

s-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol, 2.2 eq.) was added dropwise over 30 min *via* syringe pump to a stirred solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (5.0 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (160 mg, 53%, 59:41 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC:

Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.2 min, (*S*,*R*)-**235** 13.9 min.

Lab Book Reference: PJR 5/346

(Table 3.11, Entry 2)

s-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol, 2.2 eq.) was added dropwise over 30 min *via* syringe pump to a stirred solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (5.0 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 1 h. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (208mg, 69%, 67:33 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.0 min, (*S*,*R*)-**235** 13.5 min.

Lab Book Reference: PJR 5/351

(Table 3.11, Entry 3)

s-BuLi (1.28 mL of a 1.3M solution in hexanes, 1.65 mmol, 2.2 eq.) was added dropwise over 30 min *via* syringe pump to a stirred solution of *N*-Boc 4-sulfonyl piperidine **234** (350 mg, 0.75 mmol, 1.0 eq.) and (*S*,*S*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (5.0 mL) at −40 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (160 mg, 76%, 57:43 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.3 min, (*S*,*R*)-**235** 12.7 min.

Lab Book Reference: PJR 5/348

(Table 3.11, Entry 4)

s-BuLi (1.28 mL of a 1.3M solution in hexanes, 1.65 mmol, 2.2 eq.) was added dropwise over 30 min *via* syringe pump to a stirred solution of *N*-Boc 4-sulfonyl piperidine **234** (350 mg, 0.75 mmol, 1.0 eq.) and (*S*,*S*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (5.0 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 1 h. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (221mg, 98%, 58:42 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.1 min, (*S*,*R*)-**235** 13.7 min.

Lab Book Reference: PJR 5/357

(Table 3.12, Entry 1)

A solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) in Et_2O (3.0 mL) was added dropwise over 30 min *via* syringe pump to a stirred solution of *s*-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol, 2.2 eq.) and diamine (*S*,*S*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (3.5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (210 mg, 70%, 62:38 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*S*)-**235** 7.1 min, (*S*,*R*)-**235** 13.8 min.

Lab Book Reference: PJR 5/345

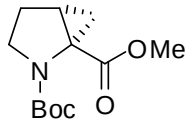
(Table 3.12, Entry 2)

A solution of *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) in Et_2O (3.0 mL) was added dropwise over 30 min *via* syringe pump to a stirred solution of *s*-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol, 2.2 eq.) and diamine (*S*,*S*)-**42** (683 mg, 2.20 mmol, 2.2 eq.) in Et_2O (3.5 mL) at −78 °C under Ar. The resulting solution was stirred at −40 °C for 1 h. Then, phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) was added dropwise. The solution was allowed to warm slowly to rt over 2 h and stirred at rt for 16 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). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**235** (210 mg, 71%, 60:40 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.1 min, (*S*,*R*)-**235** 13.6 min.

Lab Book Reference: PJR 5/341

Sulfoxide → Magnesium Exchange Reactions

2-*tert*-Butyl (1*S*,5*R*)-1-methyl-2-azabicyclo[3.1.0]hexane-1,2-dicarboxylate (1*S*,5*R*)-241

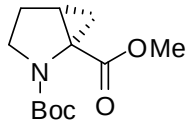


(*S*,*R*)-**241**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *syn*-(*R*,*R*,*S*$_S$)-**225** (65 mg, 0.20 mmol, 1.0 eq., 99:1 er) in THF (8 mL) at rt for 1 min and methyl chloroformate (39 μL, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester (*S*,*R*)-**241** (43 mg, 89%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.3; IR ($CDCl_3$) 2979, 1732 (C=O, CO_2Me), 1682 (C=O, Boc), 1529, 1444, 1368, 1164, 908, 881, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (ddd, J = 11.0, 9.5, 6.0 Hz, 1H, NCH_AH$_B$), 3.73 (s, 3H, OMe), 3.50 (br s, 1H, NCH$_A$$H_B$), 2.25 (ddt, J = 13.0, 9.5, 6.0 Hz, 1H, CH), 2.08-2.02 (m, 1H, CH), 1.96 (dd, J = 9.0, 5.5, Hz, 1H, CH), 1.98-1.87 (m, 1H, CH), 1.43 (s, 9H, CMe_3), 1.02 (t, J = 5.5

Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5 (CO_2Me) 155.5 (NCO_2CMe_3), 80.0 (CMe_3), 52.1 (OMe), 50.2 (NCH_2), 47.5 (NC), 31.0 (br, CH_2), 28.4 (CH), 28.3 (CMe_3), 26.4 (br, CH_2); MS (ESI) *m/z* 264 [$(M + Na)^+$, 100], 186 (20), 142 (30); HRMS *m/z* calcd for $C_{12}H_{19}NO_4$ $(M + Na)^+$ 264.1203, found 264.1206 (+1.3 ppm error); $[\alpha]_D$ −121.05 (*c* 0.20 in $CHCl_3$); CSP-HPLC: Chiracel OD (99:1 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*S*,*R*)-**241** 13.0 min, (*R*,S)-**241** 15.4 min.

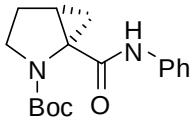
2-*tert*-Butyl 1-methyl-2-azabicyclo[3.1.0]hexane-1,2-dicarboxylate *rac*-241



rac-**241**

Using general procedure D, *i*-PrMgCl (0.15 mL of a 2.0 M solution in THF, 0.30 mmol, 1.5 eq.) and sulfoxide *syn-rac*-**225** (65 mg, 0.20 mmol, 1.0 eq.,) in THF (8 mL) at rt for 1 min and methyl chloroformate (23 μL, 0.30 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave ester *rac*-**241** (24 mg, 50%) as a colourless oil.

***tert*-Butyl (1*S*,5*R*)-(phenylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (*S*,*R*)-235**

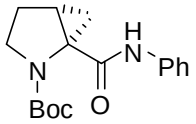


(S,R)-**235**

Using general procedure D, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *syn*-(*R*,*R*,S_s)-**225** (65 mg, 0.20 mmol, 1.0 eq., 99:1 er) in THF (8 mL) at rt for 1 min and phenylisocyanate (60 mg, 0.50 mmol, 2.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**235** (31 mg, 67%, 99:1 er by CSP-HPLC) as a pale yellow solid, mp 102-103 °C; R_F (98:2 CH_2Cl_2-Et_2O) 0.2; IR ($CDCl_3$) 3408 (NH), 2979, 1689 (C=O), 1682 (C=O), 1529, 1444, 1368, 1164, 908, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (br s, 1H, NH), 7.49 (d, *J* = 8.0 Hz, 2H, *o*-Ph), 7.30 (t, *J* = 8.0 Hz, 2H, *m*-Ph), 7.07 (d, *J* = 8.0 Hz, 1H, *p*-Ph), 3.75 (ddd, *J* = 11.5, 9.0, 6.5 Hz, 1H, NCH_AH_B), 3.66

(ddd, J = 11.5, 8.5, 5.5 Hz, 1H, NCH_AH_B), 2.24 (ddt, J = 13.0, 9.0, 6.5 Hz, 1H, CH), 2.17-2.12 (m, 1H,CH), 2.07 (dd, J = 9.0, 5.0 Hz, 1H, CH), 1.94 (dddd, J = 13.0, 8.5, 6.5, 1.5 Hz, 1H, CH), 1.42 (s, 9H, CMe_3), 1.02 (t, J = 5.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.6 (PhN*C*O) 156.9 (N*C*$O_2$$CMe_3$), 137.8 (*ipso*-Ph), 128.9 (Ph), 123.9 (Ph), 119.3 (Ph), 81.2 (*C*Me_3), 51.3 (NCH_2), 50.6 (NC), 31.1 (CH), 28.1 (C*Me*$_3$), 26.4 (CH_2), 24.8 (CH_2); MS (ESI) *m/z* 325 [$(M + Na)^+$, 30], 303 [$(M + H)^+$, 100]; HRMS *m/z* calcd for $C_{17}H_{22}N_2O_3$ $(M + Na)^+$ 325.1523, found 325.1523 (−0.2 ppm error);); $[\alpha]_D$ −58.6 (*c* 0.7 in $CHCl_3$); CSP-HPLC: Chiracel OD (90:10 Hexane-*i*PrOH, 1.0 mLmin^{-1}) (*R*,*S*)-**235** 7.4 min, (*S*,*R*)-**235** 14.5 min..

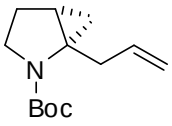
tert-Butyl 1-(phenylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate _rac_-235



rac-**235**

Using general procedure D, *s*-BuLi (1.69 mL of a 1.3 M solution in hexanes, 2.20 mmol, 2.2 eq.), *N*-Boc 4-chloro piperidine **223** (219 mg, 1.00 mmol, 1.0 eq.) and TMEDA (255 mg, 2.20 mmol, 2.2 eq.) in Et_2O (8 mL) and phenylisocyanate (262 mg, 2.20 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide *rac*-**235** (290 mg, 96%) as a pale yellow solid.

tert-Butyl (1_S_,5_R_)-1-(prop-2-en-1-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (_S_,_R_)-230

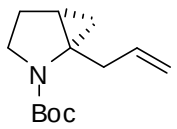


(*S*,*R*)-**230**

i-PrMgCl (0.25 mL, 0.50 mmol, 2.5 eq.) was added dropwise to a stirred solution of sulfoxide *syn*-(*R*,*R*,S_S)-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, a solution of CuBr.SMe_2 (8 mg, 20 mol%, 0.2 eq.) in THF (1 mL) was added dropwise. The solution was stirred at rt for 10 min. Then, allyl bromide (63 mg, 0.50 mmol, 2.5 eq.) was added

dropwise and the resulting solution was stirred at rt for 2 h. Saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two were layers separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave allylated pyrrolidine (*S*,*R*)-**230** (31 mg, 69%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.3; IR ($CDCl_3$) 2941, 1685 (C=O), 1519, 1434, 1378, 1164, 1062, 910, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (dtd, J = 14.0, 7.0, 6.5 Hz, 1H, C*H*=CH_2), 5.10-5.01 (m, 2H, =CH_2), 3.62 (ddd, J = 11.0, 9.5, 6.0 Hz, 1H, NCH_AH_B), 3.38 (br s, 1H, NCH_AH_B), 3.21 (br s, 1H, CH), 2.13-2.00 (m, 2H, CH), 1.82-1.75 (m, 1H, CH), 1.47 (s, 9H, CMe_3), 1.40-1.34 (m, 1H, CH), 0.91 (dd, J = 8.5, 5.5 Hz, 1H, CH), 0.67 (t, J = 5.5 Hz, 1H, CH) ; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.0 (C=O), 135.2 (*C*H=CH_2), 116.7 (CH=*C*H_2), 79.3 (br, *C*Me_3), 50.0 (br, NCH_2), 46.7 (NC), 37.5 (br, *C*H_2CH=), 28.5 (C*Me*$_3$), 25.9 (CH_2), 23.3 (CH), 21.8 (CH_2); MS (ESI) *m/z* 246 [$(M + Na)^+$, 70], 168 (100); HRMS *m/z* calcd for $C_{13}H_{21}NO_2$ $(M + Na)^+$ 246.1466, found 246.1465 (−0.5 ppm error); $[\alpha]_D$ +2.4 (*c* 0.45 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (99.5:0.5 Hexane-*i*PrOH, 0.3 $mLmin^{-1}$) (*R*,*S*)-**230** 11.0 min, (*S*,*R*)-**230** 11.8 min.

***tert*-Butyl 1-(prop-2-en-1-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate *rac*-230**

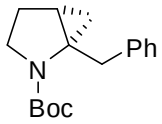


rac-**230**

i-PrMgCl (0.15 mL, 0.30 mmol, 1.5 eq.) was added dropwise to a stirred solution of sulfoxide *syn-rac*-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) at rt for 1 min at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, a solution of $CuBr.SMe_2$ (8 mg, 20 mol%, 0.2 eq.) in THF (1 mL) was added dropwise. The solution was stirred at rt for 10 min. Then, allyl bromide (38 mg, 0.30 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at rt for 2 h. Saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column

chromatography on silica with 95:5 petrol-EtOAc as eluent gave allylated pyrrolidine *rac*-**230** (26 mg, 58%) as a colourless oil.

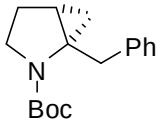
***tert*-Butyl (1*R*,5*R*)-1-benzyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (*R*,*R*)-242**



(R,R)-**242**

i-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) was added to a stirred solution of sulfoxide *syn*-(*R*,*R*,S_S)-**225** (65 mg, 0.20 mmol, 1.0 eq., 99:1 er) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, a solution of CuBr.SMe_2 (8 mg, 0.04 mmol, 0.2 eq.) in THF (0.5 mL) and benzyl bromide (89 mg, 0.50 mmol, 2.5 eq.) was added sequentially and the solution was stirred at rt for 2 h. Saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave benzylated pyrrolidine (*R*,*R*)-**242** (35 mg, 64%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.2; IR ($CDCl_3$) 2985, 2810, 1679 (C=O), 1559, 1487, 1378, 1201, 1164, 908, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H, Ph), 7.22-7.19 (m, 3H, Ph), 3.76 (br s, 1H, NCH_AH_B), 3.42-3.16 (br m, 2H,CH), 2.57 (d, J = 14.0 Hz, 1H, CH), 1.99 (tdd, J = 14.0, 7.0, 2.8 Hz, 1H, CH), 1.77-1.70 (m, 1H, CH), 1.50-1.44 (m, 1H, CH), 1.50 (s, 9H, CMe_3), 0.98 (dd, J = 9.0, 5.0 Hz, 1H, CH) 0.73 (t, J = 5.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.9 (C=O), 139.4 (*ipso*-Ph), 129.4 (Ph), 128.2 (Ph), 126.2 (Ph), 79.4 (*C*Me_3), 48.4 (br, NCH_2), 43.5 (br, NC), 41.0 (br Ph*C*H_2), 32.6 (br, CH), 28.6 (C*Me*$_3$), 26.1 (CH_2), 23.7 (CH_2); MS (ESI) *m/z* 296 [(M + Na)$^+$, 70], 218 (100); HRMS *m/z* calcd for $C_{17}H_{24}NO_2$ (M + Na)$^+$ 296.1621, found 296.1611 (+3.2 ppm error); $[\alpha]_D$ −13.6 (*c* 0.2 in $CHCl_3$); CSP-HPLC: Chiracel OD (99:1 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*R*,*R*)-**242** 5.6 min, (*S*,*S*)-**242** 6.6 min.

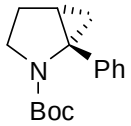
tert-Butyl 1-benzyl-2-azabicyclo[3.1.0]hexane-2-carboxylate _rac_-242



rac-**242**

i-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) was added to a stirred solution of sulfoxide *syn-rac*-**225** (65 mg, 0.20 mmol, 1.0 eq., 99:1 er) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, a solution of $CuBr.SMe_2$ (8 mg, 0.04 mmol, 0.2 eq.) in THF (0.5 mL) and benzyl bromide (89 mg, 0.50 mmol, 2.5 eq.) was added sequentially and the solution was stirred at rt for 2 h. Saturated $NH_4Cl_{(aq)}$ (7 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave benzylated pyrrolidine *rac*-**242** (32 mg, 59%) as a colourless oil.

2-_tert_-Butyl (1_S_,5_R_)-1-phenyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (1_S_,5_R_)-243

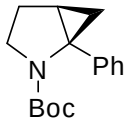


(1*S*,5*R*)-**243**

Using general procedure K, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *syn*-(*R*,*R*,S_S)-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) and $ZnCl_2$ (0.12 mL of a 1.0 M solution in Et_2O, 0.12 mmol, 0.6 eq.), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and bromobenzene (39 mg, 0.24 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-petrol as eluent gave arylated pyrrolidine (1*S*,5*R*)-**243** (35 mg, 68%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (98:2 CH_2Cl_2-petrol) 0.3; IR ($CDCl_3$) 2874, 2791, 1681 (C=O) 1540, 1521, 1444, 1368, 908, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 4H, Ph), 7.21-7.16 (m, 1H, Ph), 3.90 (ddd, J = 11.5, 9.5, 6.0 Hz, 1H, NCH_AH_B), 3.61 (ddd, J = 11.5, 9.0, 6.0 Hz, 1H, NCH_AH_B), 2.32 (ddt, J = 12.5, 9.5, 6.0 Hz, 1H, CH), 1.97 (dddd, J = 12.5, 9.0, 6.0, 1.0

Hz, 1H, CH), 1.81 (dd, *J* = 9.0, 5.5 Hz, 1H, CH), 1.62-1.56 (m, 1H, CH), 1.22 (br s, 9H, CMe_3), 1.02 (t, *J* = 5.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.7 (C=O), 133.6 (*ipso*-Ph), 132.7 (Ph), 127.9 (Ph), 125.9 (Ph), 79.4 (CMe_3), 50.1 (NCH_2), 49.7 (NC), 30.3 (NC*C*H), 28.2 (C*Me*$_3$), 26.7 (CH_2), 22.3 (CH_2); MS (ESI) *m/z* 282 [(M + Na)$^+$, 100], 204 (30); HRMS *m/z* calcd for $C_{16}H_{21}NO_2$ (M + Na)$^+$ 282.1465, found 282.1470 (−2.1 ppm error); $[\alpha]_D$ +8.2 (*c* 0.65 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (99:1 Hexane-*i*PrOH, 0.5 mLmin^{-1}) (1*S*,5*R*)-**36** 8.5 min, (1*S*,5*R*)-**36** 10.0 min.

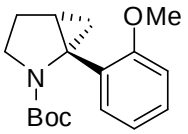
tert-Butyl 1-phenyl-2-azabicyclo[3.1.0]hexane-2-carboxylate _rac_-243



rac-**243**

Using general procedure K, *i*-PrMgCl (0.15 mL of a 2.0 M solution in THF, 0.30 mmol, 1.5 eq.) and sulfoxide *syn-rac*-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) and $ZnCl_2$ (0.12 mL of a 1.0 M solution in Et_2O, 0.12 mmol, 0.6 eq.), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and bromobenzene (22 mg, 0.14 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-petrol as eluent gave arylated pyrrolidine *rac*-**243** (20 mg, 55%) as a colourless oil.

tert-Butyl 1-[2-methoxyphenyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate (1*S*,5*R*)-244

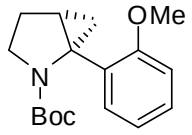


(1*S*,5*R*)-**244**

Using general procedure K, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *syn*-(*R*,*R*,S_S)-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) and $ZnCl_2$ (0.12 mL of a 1.0 M solution in Et_2O, 0.12 mmol, 0.6 eq.), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and methyl 2-bromoanisole (45 mg, 0.24 mmol, 1.20 eq.) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-Et_2O as eluent gave arylated

pyrrolidine (1*S*,5*R*)-**244** (39 mg, 68%) as a colourless oil, R_F (7:3 petrol-Et_2O) 0.2; IR ($CDCl_3$) 2875, 2782, 1685 (C=O), 1421, 1444, 1368, 913, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (br d, J = 7.5 Hz, 1H, Ar), 7.22 (td, J = 7.5, 2.0 Hz, 1H, Ar), 6.88 (br t, J = 7.5 Hz, 1H, Ar), 6.83 (br d, J = 7.5 Hz, 1H, Ar), 3.97 (td, J = 12.0, 4.5 Hz, 1H, NCH_AH_B), 3.84 (s, 3H, OMe), 3.60-3.53 (br m, 1H, NCH_AH_B), 2.37 (dddd, J = 12.5, 7.5, 4.5, 1.5 Hz, 1H, CH), 1.97-1.90 (m, 1H, CH), 1.60-1.53 (m, 2H, CH), 1.22 (br s, 9H, CMe_3), 0.90 (t, J = 4.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.8 (C=O), 155.5 (*ipso*-C_6H_4OMe), 131.6 (Ar), 128.7 (Ar), 128.2 (*ipso*-Ar), 119.6 (Ar), 110.1 (Ar), 79.0 (CMe_3), 55.5 (OMe), 50.5 (NCH_2), 46.8 (NC), 28.3 (CMe_3), 27.3 (br, CH), 26.9 (CH_2), 22.8 (CH_2); MS (ESI) *m/z* 312 [$(M + Na)^+$, 100], 234 (70), 190 (30); HRMS *m/z* calcd for $C_{17}H_{23}NO_3$ $(M + Na)^+$ 321.1572, found 312.1570 (−0.5 ppm error); $[\alpha]_D$ −6.9 (*c* 0.65 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (99:1 Hexane-*i*PrOH, 0.5 $mLmin^{-1}$) (1*S*,5*R*)-**244** 7.5 min, (1*R*,5*S*)-**244** 8.3 min.

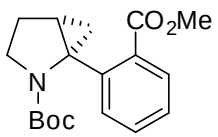
***tert*-Butyl 1-[2-methoxyphenyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate *rac*-244**



rac-**244**

Using general procedure K, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *syn-rac*-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) and $ZnCl_2$ (0.12 mL of a 1.0 M solution in Et_2O, 0.12 mmol, 0.6 eq.), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and methyl 2-bromoanisole (26 mg, 0.14 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-Et_2O as eluent gave arylated pyrrolidine *rac*-**244** (19 mg, 48%) as a colourless oil.

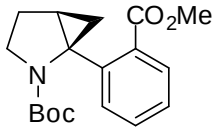
***tert*-Butyl 1-[2-(methoxycabronyl)phenyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate (1*S*,5*R*)-245**



(1*S*,5*R*)-**245**

Using general procedure K, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.), sulfoxide *syn*-(*R*,*R*,S_S)-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL), $ZnCl_2$ (0.12 mL of a 1.0 M solution in Et_2O, 0.12 mmol, 0.6 eq.), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and methyl 2-bromobenzoate (51 mg, 0.24 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-Et_2O as eluent gave arylated pyrrolidine (1*S*,5*R*)-**245** (47 mg, 74%) as a colourless oil, R_F (7:3 petrol-Et_2O) 0.1; IR ($CDCl_3$) 2874, 1726 (C=O, CO_2Me), 1679 (C=O, Boc), 1532, 1454, 1268, 908, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.0, 1.5 Hz, 1H, *o*-$C_6H_4CO_2Me$), 7.38 (br t, J = 8.0 Hz 1H, *p*-$C_6H_4CO_2Me$), 7.32-7.25 (m, 2H, Ar), 3.87 (s, 3H, OMe), 3.76 (dt, J = 11.0, 4.0 Hz, 1H, NCH_AH_B), 3.37-3.30 (br m, 1H, NCH_AH_B), 2.58-2.49 (m, 1H, CH), 2.00 (dtd, J = 12.0, 9.0, 4.0 Hz, 1H, CH), 1.79-1.74 (m, 1H, CH), 1.81 (dd, J = 9.0, 5.5 Hz, 1H, CH), 1.07 (br s, 9H, CMe_3), 0.90 (t, J = 5.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.3 (*C*O_2Me), 155.9 (N*C*O_2CMe_3), 134.4 (*ipso*-Ar), 132.1 (Ar), 130.5 (br, Ar), 128.9 (Ar), 128.8 (Ar), 126.5 (Ar), 79.4 (*C*Me_3), 52.0 (OMe), 48.7 (NC), 48.6 (NCH_2), 30.0 (CH), 27.9 (C*Me*$_3$), 25.6 (CH_2), 18.5 (CH_2); MS (ESI) *m/z* 340 [(M + Na)$^+$, 100], 318[(M + H)$^+$, 40], 262 (40), 218 (40); HRMS *m/z* calcd for $C_{18}H_{23}NO_4$ (M + Na)$^+$ 340.1518, found 340.1519 (+0.4 ppm error); $[\alpha]_D$ −46.4 (*c* 1.00 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (99:1 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (1*S*,5*R*)-**245** 9.7 min, (1*R*,5*S*)-**245** 15.8 min.

***tert*-Butyl 1-[2-(methoxycabronyl)phenyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate *rac*-245**

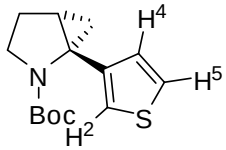


rac-**245**

Using general procedure K, *i*-PrMgCl (0.15 mL of a 2.0 M solution in THF, 0.30 mmol, 1.5 eq.) and sulfoxide *syn-rac*-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) and $ZnCl_2$ (0.12 mL of a 1.0 M solution in Et_2O, 0.12 mmol, 0.6 eq.), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and methyl 2-bromobenzoate (30 mg, 0.14 mmol, 0.7 eq.) gave the crude product. Purification by

flash column chromatography on silica with 7:3 petrol-Et_2O as eluent gave arylated pyrrolidine *rac*-**245** (32 mg, 72%) as a colourless oil.

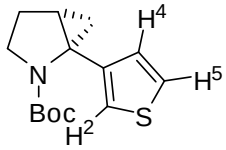
2-*tert*-Butyl (1*S*,5*R*)-1-(thiophen-3-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1*S*,5*R*)-246



(1*S*,5*R*)-**246**

Using general procedure K, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *syn*-(*R*,*R*,S_S)-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) and $ZnCl_2$ (0.12 mL of a 1.0 M solution in Et_2O, 0.12 mmol, 0.6 eq.), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and 3-bromothiophene (23 μL, 0.24 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1-98:2 CH_2Cl_2-Et_2O as eluent gave arylated pyrrolidine (1*S*,5*R*)-**246** (38 mg, 72%) as a colourless oil, R_F (98:2 CH_2Cl_2-Et_2O) 0.5; IR ($CDCl_3$) 2910, 2874, 1675 (C=O), 1555, 1532, 1268, 908, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 5.0, 3.0 Hz, 1H, H^5), 6.98 (dd, J = 5.0, 1.5 Hz 1H, H^4), 6.94 (dd, J = 3.0, 1.5 Hz, 1H, H^2), 3.86 (ddd, J = 11.5, 9.5, 6.0 Hz, 1H, NCH_AH_B), 3.55 (ddd, J = 11.5, 9.0, 6.0 Hz, 1H, NCH_AH_B), 2.34-2.25 (m, 1H, CH), 1.93 (dddd, J = 13.0, 9.0, 6.0, 1.5 Hz, 1H, CH), 1.68-1.60 (m, 2H, CH), 1.28 (br s, 9H, CMe_3), 1.04 (t, J = 5.0 Hz, 1H, $NCCH_AH_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.2 (C=O), 132.6 (*ipso*-Ar), 126.4 (Ar), 125.0 (br, Ar), 118.7 (Ar), 79.4 (CMe_3), 49.9 (NC), 46.6 (NCH_2), 30.8 (br, CH), 28.2 (CMe_3), 26.5 (CH_2), 23.5 (CH_2); MS (ESI) *m/z* 288 [$(M + Na)^+$, 100], 210 (40); HRMS *m/z* calcd for $C_{14}H_{19}NO_2S$ $(M + Na)^+$ 288.1029, found 288.1027 (+0.6 ppm error); $[\alpha]_D$ −42.0 (*c* 0.5 in $CHCl_3$); CSP-HPLC: Chiracel OD-H (99:1 Hexane-*i*PrOH, 1.0 $mLmin^{-1}$) (*S*,*R*)-**246** 7.7 min, (*R*,S)-**246** 8.6 min.

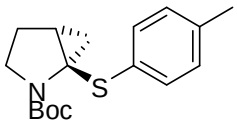
***2-tert*-Butyl 1-(thiophen-3-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate *rac*-246**



rac-**246**

Using general procedure K, *i*-PrMgCl (0.25 mL of a 2.0 M solution in THF, 0.50 mmol, 2.5 eq.) and sulfoxide *syn-rac*-**225** (65 mg, 0.20 mmol, 1.0 eq.) in THF (8 mL) and $ZnCl_2$ (0.12 mL of a 1.0 M solution in Et_2O, 0.12 mmol, 0.6 eq.), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 0.05 eq.), *t*-$Bu_3PH.BF_4$ (3.5 mg, 0.012 mmol, 0.06 eq.) and 3-bromothiophene (23 μL, 0.24 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1-98:2 CH_2Cl_2-Et_2O as eluent gave arylated pyrrolidine *rac*-**246** (33 mg, 62%) as a colourless oil.

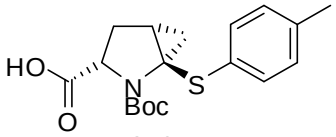
***tert*-Butyl 3-(hydroxymethyl)-1-[(4-methylphenyl)sulfanyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate (1*R*,5*R*)-254**[190,191]



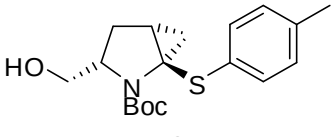
(*R*,*R*)-**254**

Trifluoroacetic anhydride (318 μL, 2.25 mmol, 3.0 eq.) was added dropwise to a stirred suspension of sulfoxide *syn*-(*R*,*R*,S_S)-**225** (240 mg, 0.75 mmol, 1.0 eq.) and NaI (225 mg, 1.50 mmol, 2.0 eq.) in acetone (9 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 10 min. Then, saturated $Na_2SO_{3(aq)}$ (5 mL) and saturated $NaHCO_{3(aq)}$ (5 mL) were added sequentially and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave sulfide **254** (228 mg, 99%) as a pale yellow oil, R_F (8:2 petrol-EtOAc) 0.4; IR (film) 2948, 2912, 2877, 1656 (C=O), 1557, 1552, 1348, 1278, 912, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 7.11 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 3.52-3.48 (m, 2H, NCH_2), 2.34 (s, 3H, Me), 2.11-2.00 (m, 1H, CH), 1.82-1.72 (m, 2H, CH), 1.63 (dd, J = 9.0, 5.0 Hz, 1H, CH), 1.52 (s, 9H, CMe_3), 1.13 (t, J = 5.0 Hz, 1H, CH_AH_B); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.5 (C=O), 137.3 (*ipso*-C_6H_4S), 132.1 (*ipso*-C_6H_4Me), 132.0 (Ar), 129.5 (Ar), 80.0 (CMe_3), 53.7 (NC), 51.2 (NCH_2), 29.1 (CH_2), 28.6 (CMe_3), 28.4 (CH), 26.8 (CH_2), 21.2 (Me); MS (ESI) *m/z* 328 [$(M + Na)^+$, 100], 306 [$(M + H)^+$, 25]; HRMS *m/z* calcd for $C_{17}H_{23}NO_2S$ $(M + Na)^+$ 328.1347, found 328.1347 (0.0 ppm error); $[\alpha]_D$ –45.8 (*c* 0.6 in $CHCl_3$).

***tert*-Butyl 3-(hydroxymethyl)-1-[(4-methylphenyl)sulfanyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate *cis*-(1*R*,3*S*,5*R*)-255**



256

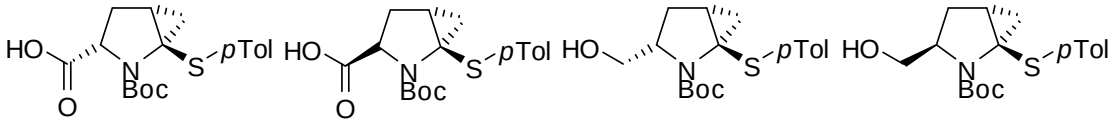


cis-**255**

s-BuLi (0.75 mL of a 1.3 M solution in hexanes, 0.98 mmol, 1.3 eq.) was added dropwise to a stirred solution of sulfide **254** (228 mg, 0.75 mmol, 1.0 eq.) and (+)-sparteine surrogate (191 mg, 0.98 mmol, 1.3 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, CO_2 was bubbled through the solution for 10 min and the resulting solution allowed to warm to rt. Water (5 mL) and 1 M $NaOH_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was acidified (pH 1) with 2 M $HCl_{(aq)}$ and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained a 92:8 mixture (by ^{1}H NMR spectroscopy) of diastereoisomeric acids **256** which required no further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H, OH), 7.28 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 7.12 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 4.55 (br s, 0.92H, NCH), 4.21 (dd, J = 10.0, 5.0 Hz, 0.08H, NCH), 2.68 (br s, 0.08H, 1H, CH), 2.54-2.50 (br m, 0.92H, 1H, CH), 2.34 (s, 2.76H, Me), 2.33 (s, 0.24, Me), 2.07 (dd, J = 13.0, 4.5 Hz, 0.08H, CH_AH_B), 1.99 (dd, J = 13.0, 7.0 Hz, 0.92H, CH_AH_B), 1.78-1.76 (m, 1H, CH), 1.70-1.65 (m, 1H, CH), 1.52-1.43 (m, 1H, CH), 1.47 (br s, 9H, CMe_3). Borane dimethyl sulfide complex (77 μL, 0.82 mmol, 1.3 eq.) was added dropwise to a stirred solution of the crude acids **256** (218 mg, 0.63 mmol, 1.0 eq.) in THF (5 mL) at 0 °C under Ar. After gas evolution ceased, the resulting solution was stirred and heated at 66 °C for 1 h. Then, the solution was cooled to rt and MeOH (5 mL) was added dropwise. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *cis*-(1*R*,3*S*,5*R*)-**255** (211 mg, 84% over two steps) as a colourless oil, R_F (8:2 petrol-EtOAc) 0.3; IR (film) 3315 (OH), 2892, 2877, 1688 (C=O), 1565, 1488, 1258, 912, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 7.14 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 5.32 (br s, 1H, OH), 4.03-3.97 (m, 1H, NCH), 3.52-3.42 (m, 2H, CH_2OH), 2.35 (s, 3H, Me), 2.18-2.11 (m, 1H, CH), 1.64-1.60 (m, 2H, CH), 1.57 (s, 9H, CMe_3), 1.33-1.25 (m, 1H, CH),

1.16-1.14 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 138.1 (*ipso*-C_6H_4S), 133.1 (Ar), 131.2 (*ipso*-C_6H_4Me), 129.8 (Ar), 81.1 (CMe_3), 70.4 (NCH), 65.0 (CH_2OH), 57.0 (NC), 34.2 (CH_2), 31.9 (CH_2), 28.4 (CMe_3), 25.7 (CH), 21.1 (Me); MS (ESI) *m/z* 358 [$(M + Na)^+$, 90], 336 [$(M + H)^+$, 40], 280 (100); HRMS *m/z* calcd for $C_{18}H_{25}NO_3S$ $(M + Na)^+$ 358.1447, found 358.1443 (+1.1 ppm error); $[\alpha]_D$ –139.8 (*c* 0.7 in $CHCl_3$).

tert-Butyl 3-(hydroxymethyl)-1-[(4-methylphenyl)sulfanyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate _cis-rac_-255 and _tert_-Butyl 3-(hydroxymethyl)-1-[(4-methylphenyl)sulfanyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate _trans-rac_-255

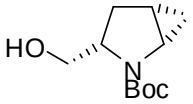


cis-**256** *trans*-**256** *cis-rac*-**255** *trans-rac*-**255**

s-BuLi (3.61 mL of a 1.3 M solution in hexanes, 4.69 mmol, 1.3 eq.) was added dropwise to a stirred solution of sulfide *rac*-**254** (1.10 g, 3.61 mmol, 1.0 eq.) and TMEDA (701 μL, 4.69 mmol, 1.3 eq.) in Et_2O (15 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, CO_2 was bubbled through the solution for 10 min and the resulting solution allowed to warm to rt. Water (5 mL) and 1 M $NaOH_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was acidified (pH 1) with 2 M $HCl_{(aq)}$ and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained a 68:32 mixture (by ^{1}H NMR spectroscopy) of diastereoisomeric acids **256** which required no further purification. Borane dimethyl sulfide complex (0.36 mL, 3.72 mmol, 1.3 eq.) was added dropwise to a stirred solution of the crude acids **256** (1.00 g, 2.86 mmol, 1.0 eq.) in THF (20 mL) at 0 °C under Ar. After gas evolution ceased, the resulting solution was stirred and heated at 66 °C for 1 h. Then, the solution was cooled to rt and MeOH (5 mL) was added dropwise. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *cis-rac*-**255** (615 mg, 51% over two steps) as a colourless oil and *trans-rac*-**255** (258 mg, 21% over two steps) as a colourless oil, R_F (8:2 petrol-EtOAc) 0.2; IR (film)

3312 (OH), 2901, 2896, 2867, 1698 (C=O), 1495, 1487, 1305, 1132, 915, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 7.17 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 3.88-3.82 (m, 1H, NCH), 3.30 (br s, 1H, OH), 3.25-3.23 (m, 1H, CH_AH_BOH), 2.97 (t, J = 8.5 Hz, 1H, CH_AH_BOH) 2.36 (s, 3H, Me), 2.03-1.98 (m, 1H, CH), 1.76-1.64 (m, 3H, CH), 1.57 (s, 9H, CMe_3), 1.04 (t, J = 5.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.0 (C=O), 138.8 (*ipso*-C_6H_4S), 134.5 (Ar), 130.5 (*ipso*-C_6H_4Me), 129.8 (Ar), 81.3 (CMe_3), 66.5 (CH_2OH), 64.7 (NCH), 55.5 (NC), 29.8 (CH_2), 29.7 (CH_2), 28.4 (CMe_3), 27.4 (CH), 21.2 (Me); MS (ESI) *m/z* 358 [$(M + Na)^+$, 100], 336 [$(M + H)^+$, 30], 280 (100); HRMS *m/z* calcd for $C_{18}H_{25}NO_3S$ $(M + Na)^+$ 358.1447, found 358.1449 (−0.5 ppm error).

tert-Butyl 3-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate _cis_-(1_S_,3_S_,5_R_)-253

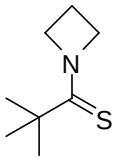


cis-**253**

Raney®-Nickel 2400 (1.5 mL of a 50% suspension in water) was added dropwise to a stirred solution of alcohol *cis*-(1*R*,3*S*,5*R*)-**255** (211 mg, 0.63 mmol, 1.0 eq.) in 1:2 THF-EtOH (6 mL) at rt under Ar. The resulting solution was stirred at rt for 5 h. Then, CH_2Cl_2 (10 mL) and $MgSO_4$ were added and the solids were removed by filtration through Celite®. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-acetone as eluent gave alcohol *cis*-(1*S*,3*S*,5*R*)-**253** (98 mg, 73%) as a colourless oil, R_F (8:2 petrol-acetone) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32-4.28 (br m, 1H, CH), 3.51-3.43 (m, 4H, CH + OH), 2.46 (dddd, J = 13.5, 11.0, 6.5, 1.0 Hz, 1H, CH), 1.58-1.52 (m, 1H, CH), 1.50 (s, 9H, CMe_3), 1.50-1.47 (m, 1H, CH_AH_B), 0.80 (dtd, J = 9.0, 6.0, 1.0 Hz, 1H, CH), 0.43-0.40 (br m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 156.6 (br, C=O), 80.6 (CMe_3), 80.3 (CMe_3), 67.6 (br, N*C*HCH_2OH), 54.5 (CH_2OH), 38.8 (NCH), 37.4 (CH_2), 32.0 (CH), 30.6 (CH_2), 28.4 (CMe_3), 28.4 (CMe_3), 16.9 (CH_2), 14.7 (CH_2); MS (ESI) *m/z* 236 [$(M + Na)^+$, 100], 213 [$(M + H)^+$, 40]; HRMS *m/z* calcd for $C_{11}H_{19}NO_3$ $(M + Na)^+$ 236.1263, found 236.1263 (0.0 ppm error); $[\alpha]_D$ +6.6 (*c* 0.5 in $CHCl_3$) [lit.[184], $[\alpha]_D$ +12.0 (*c* 0.75 in $CHCl_3$)]. Spectroscopic data consistent with those reported in the literature.[184]

5.5 Experimental for Chapter Four

2,2-Dimethyl-1-azetidinyl-1-ylpropan-1-thione 101[102]

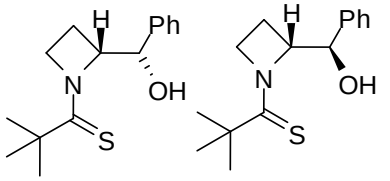


101

Trimethylacetyl chloride (7.21 mL, 58.6 mmol, 1.1 eq.) was added to a stirred solution of azetidine hydrochloride (5.00 g , 53.3 mmol, 1.0 eq.) and Et_3N (37.1 mL, 266 mmol, 5.0 eq.) in CH_2Cl_2 (75 mL) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1 M HCl(aq) (15 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduce pressure to give the crude *N*-pivaloyl azetidine. The residue was dissolved in pyridine (150 mL) and phosphorous(V) sulfide (14.80 g, 66.6 mmol, 1.25 eq.) was added. The resulting solution was heated to 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M $HCl_{(aq)}$ (150 mL). 1 M $HCl_{(aq)}$ was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with 1 M $HCl_{(aq)}$ (50 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave thioamide **101** (6.40 g, 78%) as a yellow oil, R_F (8:2 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (br t, J = 7.5 Hz, 2H, NCH_2), 4.29 (br t, J = 7.5 Hz, 2H, NCH_2), 2.33-2.25 (m, 2H, CH_2), 1.36 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.1 (C=S), 56.6 (NCH_2), 56.0 (NCH_2) 43.1 (CMe_3), 29.8 (CMe_3), 14.6 (CH_2). Spectroscopic data consistent with those reported in the literature.[102]

Lab Book Reference: PJR 2/110A

1-[(2*R*)-2-[(*S*)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *anti*-(*S*,*R*)-273 and 1-[(2*R*)-2-[(*R*)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *syn*-(*R*,*R*)-273



anti-(*S*,*R*)-**273** *syn*-(*R*,*R*)-**273**

Using general procedure L, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained an 86:14 mixture of alcohols *syn*-(*R*,*R*)-**273** and *anti*-(*S*,*R*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S*,*R*)-**273** (12 mg, 9%, 58:42 er by CSP-HPLC) as a white solid, mp 151-153 °C; R_F (4:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3203 (OH), 2921, 1441, 1414, 1341, 1242, 1126, 996, 980, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 2H, *o*-Ph), 7.36 (t, J = 8.0 Hz, 2H, *m*-Ph), 7.31 (d, J = 8.0 Hz, 1H, Ph), 5.46 (br d, J = 5.0 Hz 1H, CHO), 5.28-5.24 (m, 1H, NCH), 4.56 (d, J = 5.0 Hz, 1H, OH), 4.21 (td, J = 10.0, 5.0 Hz, 1H, NCH_AH$_B$), 3.92-3.85 (m, 1H NCH$_A$$H_B$), 2.35-2.26 (m, 1H, C$H_AH_B$), 2.16-2.08 (m, 1H, CH$_A$$H_B$), 1.30 (s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.1 (C=S), 139.6 (*ipso*-Ph), 128.2 (Ph), 127.7 (Ph), 126.7 (Ph), 73.7 (OCH or NCH), 73.5 (OCH or NCH), 56.1 (NCH_2), 43.4 (*C*Me$_3$) 29.5 (C*Me*$_3$), 17.2 (CH_2); MS (ESI) *m/z* 286 [(M + Na)$^+$, 100], 264 [(M + H)$^+$, 30], 208 (100); HRMS *m/z* calcd for $C_{15}H_{21}NO_3$ (M + Na)$^+$ 286.1414, found 286.1414 (0.0 ppm error); $[\alpha]_D$ +40.9 (*c* 0.65 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.4 min, (*R*,*S*)-**273** 10.0 min and alcohol *syn*-(*R*,*R*)-**273** (99 mg, 75%, 75:25 er by CSP-HPLC) as a white solid, mp 109-111 °C (lit.,[102] 116-117 °C); R_F (4:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H, Ph), 7.39-7.29 (m, 3H, Ph), 5.32 (d, J = 7.5 Hz, 1H, CHOH), 5.22 (dddd, J = 9.0, 7.5, 5.0, 1.5 Hz, 1H, NCH), 5.17 (br s, 1H, OH), 4.31 (td, J = 10.0, 5.0 Hz, 1H, NCH_AH$_B$), 4.20-4.13 (m, 1H, NCH$_A$$H_B$), 2.20 (dddd, J = 12.0, 10.0, 9.0, 7.5 Hz, 1H, CH_AH$_B$), 1.86 (ddt, J = 12.0, 9.5, 5.0 Hz, 1H, CH$_A$$H_B$), 1.35 (s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.3 (C=S), 139.9 (*ipso*-Ph), 128.3 (Ph), 128.1 (Ph), 127.3 (Ph), 76.3 (OCH or NCH), 73.8

(OCH or NCH), 56.0 (NCH_2), 43.6 (CMe_3), 29.6 (CMe_3), 18.3 (CH_2); $[\alpha]_D$ +74.8 (*c* 0.75 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 17.8 min, (*S*,*S*)-**273** 20.4 min. Spectroscopic data for *syn*-*rac*-**273** is consistent with those reported in the literature.[102]

Lab Book Reference 8/624

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.50 mmol, 1.0 eq.) in Et_2O (5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, (−)-sparteine (0.14 mL, 0.60 mmol, 1.2 eq.) was added and the resulting solution was stirred for 15 min. The solution was then cooled to −78 °C and stirred at −78 °C for 30 min. Benzaldehyde (38 μL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 81:19 mixture of alcohols *syn*-(*R*,*R*)-**273** and *anti*-(*S*,*R*)-**273** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S*,*R*)-**273** (9 mg, 7%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.5 min, (*R*,*S*)-**273** 10.1 min and alcohol *syn*-(*R*,*R*)-**273** (76 mg, 57%, 71:29 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.2 min, (*S*,*S*)-**273** 20.2 min.

Lab Book Reference 8/665

(Table 4.2, Entry 2)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −50 °C and stirred for 1 h. Benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −50 °C for 10 min. Then, 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 80:20 mixture of

alcohols *syn*-(*R*,*R*)-**273** and *anti*-(*S*,*R*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S*,*R*)-**273** (17 mg, 13%, 58:42 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.5 min, (*R*,*S*)-**273** 10.2 min and alcohol *syn*-(*R*,*R*)-**273** (108 mg, 82%, 68:32 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.4 min, (*S*,*S*)-**273** 20.9 min.

Lab Book Reference 8/657

(Table 4.2, Entry 3)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −40 °C and stirred for 1 h. Benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −40 °C for 10 min. Then, 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 80:20 mixture of alcohols *syn*-(*R*,*R*)-**273** and *anti*-(*S*,*R*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S*,*R*)-**273** (19 mg, 14%, 56:44 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.5 min, (*R*,*S*)-**273** 10.1 min and alcohol *syn*-(*R*,*R*)-**273** (111 mg, 84%, 62:38 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.2 min, (*S*,*S*)-**273** 20.8 min.

Lab Book Reference 8/656

(Table 4.2, Entry 4)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −30 °C and stirred for 1 h. Benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added

dropwise and the resulting solution was stirred at −30 °C for 10 min. Then, 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of alcohols *syn*-(*R*,*R*)-**273** and *anti*-(*S*,*R*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S*,*R*)-**273** (15 mg, 11%, 55:45 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.5 min, (*R*,*S*)-**273** 10.2 min and alcohol *syn*-(*R*,*R*)-**273** (100 mg, 76%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.5 min, (*S*,*S*)-**273** 20.5 min.

Lab Book Reference 8/658

(Table 4.2, Entry 5)

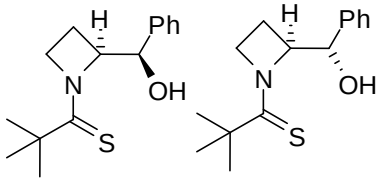
s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −30 °C and stirred for 1 h. The solution was then cooled to −78 °C and stirred at −78 °C for 30 min. Benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −30 °C for 10 min. Then, 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 86:14 mixture of alcohols *syn*-(*R*,*R*)-**273** and *anti*-(*S*,*R*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S*,*R*)-**273** (9 mg, 7%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.4 min, (*R*,*S*)-**273** 10.1 min and alcohol *syn*-(*R*,*R*)-**273** (95 mg, 72%, 75:25 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.3 min, (*S*,*S*)-**273** 20.5 min.

Lab Book Reference 8/664

A solution of stannane (*S*)-**272** (50 mg, 0.16 mmol, 1.0 eq.) in Et_2O (3 mL) was added dropwise to a stirred solution of *n*-BuLi (0.07 mL of a 2.5 M solution in hexanes, 0.18 mmol, 1.1 eq.) and (−)-sparteine (42 μL, 0.18 mmol, 1.1 eq.) in Et_2O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (19 μL, 0.19 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 87:13 mixture of alcohols *syn*-(*R*,*R*)-**273** and *anti*-(*S*,*R*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S*,*R*)-**273** (4 mg, 10%, 62:38 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.6 min, (*R*,*S*)-**273** 10.3 min and alcohol *syn*-(*R*,*R*)-**273** (37 mg, 88%, 73:27 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.7 min, (*S*,*S*)-**273** 20.8 min.
Lab Book Reference 8/685

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −100 °C under Ar. The resulting solution was stirred at −100 °C for 30 min. Then, benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −100 °C for 1 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 87:13 mixture of alcohols *syn*-(*R*,*R*)-**273** and *anti*-(*S*,*R*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S*,*R*)-**273** (9 mg, 7%, 57:43 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.4 min, (*R*,*S*)-**273** 10.0 min and alcohol *syn*-(*R*,*R*)-**273** (87 mg, 66%, 77:23 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.4 min, (*S*,*S*)-**273** 20.8 min.
Lab Book Reference 8/625

1-[(2*S*)-2-[(*R*)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *anti*-(*R*,*S*)-273 and 1-[(2*S*)-2-[(*S*)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *syn*-(*S*,*S*)-273



anti-(*R*,*S*)-**273** *syn*-(*S*,*S*)-**273**

Using general procedure L, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate **1** (116 mg, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained an 86:14 mixture of alcohols *syn*-(*S*,*S*)-**273** and *anti*-(*R*,*S*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*R*,*S*)-**273** (9 mg, 7%, 54:46 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.5 min, (*R*,*S*)-**273** 10.2 min and alcohol *syn*-(*R*,*R*)-**273** (91 mg, 70%, 54:46 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.2 min, (*S*,*S*)-**273** 20.4 min.

Lab Book Reference 8/660

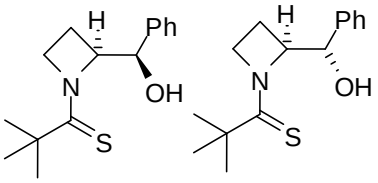
Using general procedure L, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.), diamine (*S*,*S*)-**42** (186 mg, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained a 77:23 mixture of alcohols *syn*-(*S*,*S*)-**273** and *anti*-(*R*,*S*)-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*R*,*S*)-**273** (26 mg, 20%, 65:35 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.5 min, (*R*,*S*)-**273** 10.2 min and alcohol *syn*-(*R*,*R*)-**273** (96 mg, 73%, 53:47 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.7 min, (*S*,*S*)-**273** 20.9 min.

Lab Book Reference 8/681

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate **1** (116 mg, 0.6 mmol, 1.2 eq.) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 76:24 mixture of alcohols *syn*-(*S*,*S*)-**273** and *anti*-(*R*,*S*)-**273** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*R*,*S*)-**273** (0.5 mg, 0.5%, 56:44 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.5 min, (*R*,*S*)-**273** 10.2 min and alcohol *syn*-(*R*,*R*)-**273** (2 mg, 1.5%, 60:40 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.3 min, (*S*,*S*)-**273** 20.3 min and recovered **273** (58 mg, 73%) as a pale yellow oil.

Lab Book Reference 8/661

1-[2-[Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *anti-rac*-273 and 1-[(2-[hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *syn-rac*-273



anti-rac-**273** *syn-rac*-**273**

s-BuLi (0.23 mL of a 1.3 M solution in hexanes, 0.3 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **101** (40 mg, 0.25 mmol, 1.0 eq.) in Et_2O (5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, benzaldehyde (38 μL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −40 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 62:38 mixture of alcohols *syn-rac*-**273** and

anti-rac-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc gave alcohol *anti-rac*-**273** (14 mg, 21%) as a white solid and alcohol *syn-rac*-**273** (27 mg, 42%) as a white solid.
Lab Book Reference 8/640

s-BuLi (0.23 mL of a 1.3M solution in hexanes, 0.3 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **101** (40 mg, 0.25 mmol, 1.0 eq.) in Et_2O (5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min and then cooled to −78 °C and stirred at −78 °C for 10 min. Then, (−)-sparteine (68 μL, 0.30 mmol, 1.2 eq.) was added at the resulting solution was stirred for 30 min. Benzaldehyde (38 μL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred for 10 min at −78 °C and 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of alcohols *syn-rac*-**273** and *anti-rac*-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti-rac*-**273** (12 mg, 19%) as a white solid and alcohol *syn-rac*-**273** (28 mg, 43%) as a white solid.
Lab Book Reference 8/643

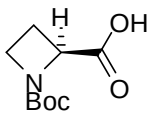
n-BuLi (0.06 mL of a 2.5 M solution in hexanes, 0.14 mmol, 1.1 eq.) was added dropwise to a stirred solution of stannane (*S*)-**272** (43 mg, 0.13 mmol, 1.0 eq., 68:32 er) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (16 μL, 0.16 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of alcohols *syn-rac*-**273** and *anti-rac*-**273** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti-rac*-**273** (9 mg, 26%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.3 min, (*R*,*S*)-**273** 9.8 min and alcohol *syn-rac*-**273** (20 mg, 58%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC:

Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.0 min, (*S*,*S*)-**273** 20.3 min.

Lab Book Reference 8/628

n-BuLi (0.06 mL of a 2.5 M solution in hexanes, 0.14 mmol, 1.1 eq.) was added dropwise to a stirred solution of stannane (*S*)-**272** (43 mg, 0.13 mmol, 1.0 eq., 68:32 er) and TMEDA (21 μL, 0.14 mmol, 1.1 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (16 μL, 0.16 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 76:24 mixture of alcohols *syn*-*rac*-**273** and *anti*-*rac*-**273** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-*rac*-**273** (8 mg, 24%, 50:50 er by CSP-HPLC) as a white solid CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**273** 7.4 min, (*R*,*S*)-**273** 10.1 min and alcohol *syn*-*rac*-**273** (21 mg, 61%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**273** 18.5 min, (*S*,*S*)-**273** 20.4 min.

(*S*)-1-(*tert*-Butoxycarbonyl)azetidine-2-carboxylic acid (*S*)-285[232]



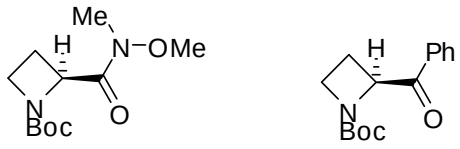
(*S*)-**285**

NaOH (420 mg, 10.5 mmol, 1.05 eq.) was added to a stirred solution of (*S*)-2-azetidine carboxylic acid (1.00 g, 10.0 mmol, 1.0 eq.) and di-*tert*-butyl dicarbonate (2.83 g, 12.5 mmol, 1.25 eq.) in 2:1 EtOH-water (30 mL) at rt. The resulting solution was stirred at rt for 16 h. Then, the volatiles were evaporated under reduced pressure and the remaining suspension was acidified with 1 M $HCl_{(aq)}$ (20 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give acid (*S*)-**285** (1.96 g, 99%) as a white solid, mp 97-99 °C (lit.,[233] 97-98 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (br s, 1H, OH), 4.77

(br s, 1H, NCH), 3.96-3.85 (m, 2H, NCH_2), 2.46 (br s, 2H, CH_2), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.5 (C=O, COOH), 156.6 (C=O, Boc), 82.7 (*C*Me_3), 60.7 (br, NCH), 47.1 (NCH_2), 28.2 (C*Me*$_3$), 19.7 (CH_2); $[\alpha]_D$ −168.1 (*c* 0.7 in $CHCl_3$) (lit.,[102] $[\alpha]_D$ −116.1 (*c* 0.75 in $CHCl_3$)). Spectroscopic data consistent with those reported in the literature.[232]

Lab Book Reference 7/512

tert-Butyl 2*S*-benzoylazetidine-1-carboxylate (*S*)-286[234]



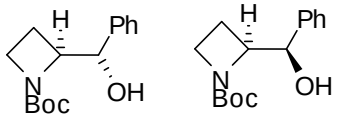
(*S*)-**286**

N-Me morpholine (0.62 mL, 5.6 mmol, 1.2 eq.), HOBt (870 mg, 5.6 mmol, 1.2 eq.) and EDC (0.98 mL, 5.6 mmol, 1.2 eq.) were added sequentially to a stirred solution of acid (*S*)-**285** (1.00 g, 4.6 mmol, 1.0 eq.) and *N*,*O*-dimethylhydroxylamine.HCl (550 mg, 5.6 mmol, 1.2 eq.) in DMF (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Then, EtOAc (30 mL) was added and the solution was washed with 1 M $HCl_{(aq)}$ (10 mL), 2 M $NaOH_{(aq)}$ (2 x 10 mL) and brine (3 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude Weinreb amide (565 mg, 50%) as a pale yellow solid, ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd, *J* = 8.5, 5.5 Hz, 1H, NCH), 4.04 (ddd, *J* = 9.0, 8.0, 6.0 Hz, 1H, NCH_AH_B), 3.87 (ddd, *J* = 9.0, 8.0, 6.0 Hz, 1H, NCH_AH_B), 3.71 (s, 3H, OMe), 3.22 (s, 3H, NMe), 2.51-2.42 (m, 1H, CH_AH_B), 2.12 (ddt, *J* = 11.0, 9.0, 5.5 Hz, 1H, CH_AH_B), 1.43 (s, 9H, CMe_3). PhMgCl (1.72 mL of a 2.0 M solution in THF, 3.44 mmol, 1.5 eq.) was added dropwise to a stirred solution of the crude Weinreb amide (565 mg, 2.3 mmol, 1.0 eq.) in THF (10 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (15 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1-3:1 petrol-EtOAc as eluent gave ketone (*S*)-**286** (430 mg, 36% over two steps) as a white solid, mp 77-79 °C; R_F (3:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2981, 1720 (C=O, PhCO), 1675 (C=O, Boc), 1426, 1375, 1210, 1010, 920, 815, 730 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H, *o*-Ph), 7.52 (d, J = 7.5 Hz, 1H, *p*-Ph), 7.41 (t, J = 7.5 Hz, 2H, *m*-Ph), 5.50 (dd, J = 9.5, 5.5 Hz, 1H, NCH), 3.99-3.87 (m, 2H, NCH_2), 2.61 (dddd, J = 11.0, 9.5, 9.0, 6.0 Hz, 1H, CH_AH_B), 2.06 (ddt, J = 11.0, 9.0, 5.5 Hz, 1H, CH_AH_B), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 195.7 (C=O, PhCO), 155.8 (C=O, Boc), 134.4 (*ipso*-Ph), 133.6 (Ph), 128.9 (Ph), 128.2 (Ph), 79.8 (CMe_3), 63.6 (br, NCH), 46.9 (br, NCH_2), 28.32 (CMe_3), 21.3 (CH_2); MS (ESI) *m/z* 284 [$(M + Na)^+$, 100]; HRMS *m/z* calcd for $C_{15}H_{19}NO_3$ $(M + Na)^+$ 284.1257, found 284.1249 (+3.0 ppm error); $[\alpha]_D$ −140.9 (*c* 0.65 in $CHCl_3$).

Lab Book Reference 7/524

tert-Butyl (2*S*)-2-[(*S*)-hydroxy(phenyl)methyl]azetidine-1-carboxylate _syn_-(*S*,*S*)-284 and _tert_-butyl (2S)-2-[(*R*)-hydroxy(phenyl)methyl]azetidine-1-carboxylate _anti_-(*R*,*S*)-284



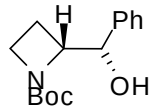
syn-(*S*,*S*)-**284** *anti*-(*R*,*S*)-**284**

$NaBH_4$ (73 mg, 1.93 mmol, 1.2 eq.) was added to a stirred solution of ketone (*S*)-**286** (420 mg, 1.61 mmol, 1.0 eq.) in MeOH (5 mL) at 0 °C. The resulting solution was stirred at rt for 30 min. Then, the solution was cooled to 0 °C and saturated $NH_4Cl_{(aq)}$ (5 mL) was added dropwise. The resulting solution was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 85:15 mixture of alcohols *syn*-(*S*,*S*)-**284** and *anti*-(*R*,*S*)-**284** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *syn*-(*S*,*S*)-**284** (330 mg, 78%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3348 (OH), 2976, 2952, 1687 (C=O), 1445, 1424, 1375, 1246, 1045, 1025, 915, 800, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.36 (m, 2H, *o*-Ph), 7.34-7.25 (m, 3H, Ph), 5.75 (br s, 1H, OH), 4.75 (d, J = 8.0 Hz, 1H, OCH), 4.34 (q, J = 8.0 Hz, 1H, NCH), 3.83-3.72 (m, 2H, NCH_2), 1.93-1.80 (m, 2H, CH_2), 1.48 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.1 (C=O), 139.2 (*ipso*-Ph), 128.3 (Ph), 127.9 (Ph), 127.0 (Ph), 80.1 (OCH), 79.1 (CMe_3), 67.8 (NCH), 46.1 (NCH_2), 28.3 (CMe_3), 18.7 (CH_2); MS (ESI) *m/z* 286 [$(M + Na)^+$, 100], 264 [$(M + H)^+$, 50], 208 (100), 190 (90);

HRMS *m/z* calcd for $C_{15}H_{21}NO_3$ $(M + Na)^+$ 286.1414, found 286.1408 (+2.1 ppm error); $[\alpha]_D$ +1.0 (*c* 1.3 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**284** 11.1 min, (*S*,*S*)-**284** 24.0 min and alcohol *anti*-(*R*,*S*)-**284** (65 mg, 15%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.2; IR (film) 3421 (OH), 2970, 1692 (C=O), 1446, 1420, 1378, 1186, 1050, 1040, 910, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.36 (m, 2H, *o*-Ph), 7.34-7.25 (m, 3H, Ph), 5.75 (br s, 1H, OH), 4.94 (d, *J* = 2.5 Hz, 1H, OCH), 4.57 (td, *J* = 7.5, 2.5 Hz, 1H, NCH), 3.73 (dt, *J* = 8.5, 1.5 Hz, 1H, NCH_AH_B), 3.48-3.43 (m, 1H, NCH_AH_B), 2.16-2.04 (m, 1H, CH_AH_B), 1.93 (dddd, *J* = 11.5, 8.5, 7.5 5.0 Hz, 1H, CH_AH_B), 1.48 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.4 (C=O), 139.6 (*ipso*-Ph), 128.3 (Ph), 127.6 (Ph), 126.7 (Ph), 80.4 (CMe_3), 75.3 (OCH), 66.8 (NCH), 46.7 (NCH_2), 28.5 (CMe_3), 16.2 (CH_2); MS (ESI) *m/z* 286 [$(M + Na)^+$, 100]; HRMS *m/z* calcd for $C_{15}H_{21}NO_3$ $(M + Na)^+$ 286.1414, found 286.1398 (+5.3 ppm error); $[\alpha]_D$ −88.5 (*c* 1.05 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**284** 11.3 min, (*S*,*S*)-**284** 25.7 min.

Lab Book Reference 7/527

tert-Butyl (2*R*)-2-[(*S*)-hydroxy(phenyl)methyl]azetidine-1-carboxylate _anti_-(*S*,*R*)-284



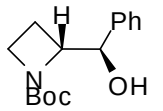
anti-(*S*,*R*)-**284**

MeLi (0.38 mL of a 1.6 M solution in Et_2O, 0.60 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol *anti*-(*S*,*R*)-**273** (26 mg, 0.25 mmol, 1.0 eq., 58:42 er) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise. The resulting solution was extracted with Et_2O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M $NaOH_{(aq)}$ and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH_2Cl_2 (5 mL) and di-*tert*-butyl dicarbonate (60 mg, 0.28 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The

aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-(*S,R*)-**284** (20 mg, 76%, 57:43 er by CSP HPLC) as a colourless oil, $[\alpha]_D$ +14.2 (*c* 0.60 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 0.5 mL min^{-1}) (*S,R*)-**284** 14.9 min, (*R,S*)-**284** 15.8 min.

Lab Book Reference 8/684

tert-Butyl (2*R*)-2-[(*R*)-hydroxy(phenyl)methyl]azetidine-1-carboxylate _syn_-(*R,R*)-284

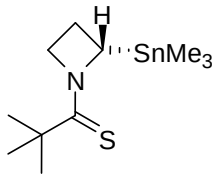


syn-(*R*,*R*)-**284**

MeLi (0.94 mL of a 1.6 M solution in Et_2O, 1.50 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol *syn*-(*R,R*)-**273** (65 mg, 0.25 mmol, 1.0 eq., 75:25 er.) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise. The resulting solution was extracted with Et_2O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M $NaOH_{(aq)}$ and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH_2Cl_2 (5 mL) and di-*tert*-butyl dicarbonate (60 mg, 0.28 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *syn*-(*R,R*)-**284** (47 mg, 71%, 75:25 er by CSP HPLC) as a colourless oil, $[\alpha]_D$ −1.56 (*c* 1.1 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R,R*)-**284** 11.1 min, (*S,S*)-**284** 25.5 min.

Lab Book Reference 7/526

(*S*)-2,2-dimethyl-1-(2-(trimethylstannyl)azetidin1-yl)propane-1-thione (*S*)-272

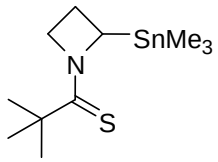


(*S*)-**272**

Using general procedure L, *s*-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.8 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **101** (236 mg, 1.5 mmol, 1.0 eq.) and (−)-sparteine (0.41 mL, 1.8 mmol, 1.2 eq.) in Et_2O (8 mL) and Me_3SnCl (2.25 mL of a 1.0 M in hexane, 2.25 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5-9:1 petrol-Et_2O as eluent gave stannane (*S*)-**272** (263 mg, 55%, 68:32 er by CSP-HPLC) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65-4.47 (m, 3H, NCH), 2.57-2.48 (m, 1H, CH), 2.26-2.18 (m, 1H, CH), 1.33 (s, 9H, CMe_3), 0.15 (s, 9H, $SnMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.4 (C=S), 61.6 (NCH), 56.8 (NCH_2), 42.4 (*C*Me_3), 29.9 (C*Me*$_3$), 18.3 (CH_2), −7.7 (Sn*Me*$_3$); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**272** 5.4 min, (*R*)-**272** 8.1 min. Spectroscopic data consistent with those reported in the literature.[102] The absolute configuration of the major enantiomer is assumed by analogy with the benzaldehyde trapping.

Lab Book Reference 8/620 637 629

2,2-Dimethyl-1-(2-(trimethylstannyl)azetidin1-yl)propane-1-thione *rac*-272

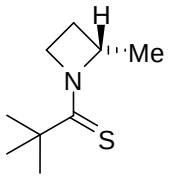


rac-**272**

Using general procedure L, *s*-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.8 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **101** (236 mg, 1.5 mmol, 1.0 eq.) and TMEDA (0.27 mL, 1.8 mmol, 1.2 eq.) in Et_2O (8 mL) and Me_3SnCl (2.25 mL of a 1.0 M in hexane, 2.25 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5-9:1 petrol-Et_2O as eluent gave stannane *rac*-**272** (284 mg, 60%) as a colourless oil.

Lab Book Reference 8/680

(*S*)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (*S*)-102



(*S*)-**102**

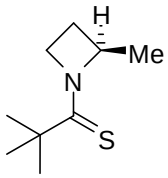
Using general procedure L, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **101** (79 mg, 0.50 mmol, 1.0 eq.) and (−)-sparteine (0.14 mL, 0.60 mmol, 1.2 eq.) in Et_2O (5 mL) and methyl iodide (47 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave methylated azetidine (*S*)-**102** (79 mg, 91%, 59:41 er by CSP-HPLC) as a colourless oil, R_F (8:2 petrol-Et2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91-4.82 (m, 1H, NCH), 4.57 (dddd, J = 10.5, 9.0, 7.0, 1.5 Hz, 1H, NCH_AH$_B$), 4.43 (dddd, J = 10.5, 10.0, 5.0, Hz, 1H, NCH$_A$$H_B$), 2.54 (dddd, J = 11.0, 10.0, 9.0, 7.0 Hz, 1H, CH_AH$_B$), 1.85 (ddt, J = 11.0, 9.5, 5.0 Hz, 1H, NCH$_A$$H_B$), 1.62 (d, J = 6.0 Hz, 3H, Me), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 209.6 (C=S), 65.7 (NCH), 64.8 (NCH), 55.6 (NCH_2), 53.7 (NCH_2), 43.2 (*C*Me_3), 30.85 (C*Me*$_3$), 29.6 (C*Me*$_3$), 23.1 (CH_2), 18.5 (Me); $[\alpha]_D$ +0.2 (*c* 1.0 in $CHCl_3$) (lit.,[102] $[\alpha]_D$ −21.3 (*c* 1.15 in $CHCl_3$ for (*R*)-**102** of 99:1 er)); CSP-HPLC: Chiracel OD-H (99.9:0.1 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*)-**102** 11.1 min, (*S*)-**102** 11.9 min. Spectroscopic data consistent with those reported in the literature.[102]

Lab Book Reference 8/649

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Methyl iodide (47 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −78 °C for 2 h. Then, benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added. The resulting solution was stirred at −78 °C for 1 h and 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as

eluent gave methylated azetidine (*S*)-**102** (67 mg, 78%, 58:42 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel OD-H (99.9:0.1 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*)-**102** 11.0 min, (*S*)-**102** 12.0 min.
Lab Book Reference 8/659

***(R)*-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (*R*)-102**



(*R*)-**102**

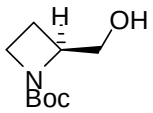
Using general procedure L, *s*-BuLi (0.46 mL of a 1.3M solution in hexanes, 0.60 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **101** (79 mg, 0.50 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (186 mg, 0.60 mmol, 1.2 eq.) in Et_2O (5 mL) and methyl iodide (47 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O gave methylated azetidine (*R*)-**102** (76 mg, 88%, 69:31 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ −2.0 (*c* 0.95 in $CHCl_3$) (lit.,[102] $[\alpha]_D$ −21.3 (*c* 1.15 in $CHCl_3$ for (*R*)-**102** of 99:1 er)); CSP-HPLC: Chiracel OD-H (99.9:0.1 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*)-**102** 14.0 min, (*S*)-**102** 15.4 min.
Lab Book Reference 8/668

s-BuLi (0.46 mL of a 1.3M solution in hexanes, 0.60 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **101** (79 mg, 0.50 mmol, 1.0 eq.) and diamine (*S*,*S*)-**42** (186 mg, 0.60 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, a solution of methyl iodide (31 μL, 0.50 mmol, 1.0 eq.) in Et_2O (5 mL) was added dropwise *via* syringe pump over 2 h. The resulting solution was stirred for 10 min at −78 °C and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave methylated azetidine (*R*)-**102** (78 mg, 91%, 68:32 er by CSP-HPLC) as a colourless oil, CSP-

HPLC: Chiracel OD-H (99.9:0.1 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*)-**102** 13.9 min, (*S*)-**102** 15.4 min.

Lab Book Reference 8/669

(*S*)-*tert*-Butyl 2-(hydroxymethyl)azetidine-1-carboxylate (*S*)-293

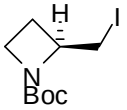


(*S*)-**293**

Borane dimethyl sulfide complex (0.51 mL, 5.42 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc acid (*S*)-**285** (840 mg, 4.17 mmol, 1.0 eq.) in THF (10 mL) at 0 °C under Ar. After gas evolution ceased, the resulting solution was stirred and heated at 66 °C for 1 h. Then, the solution was cooled to rt and MeOH (5 mL) was added dropwise. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4-1:1 petrol-EtOAc as eluent gave alcohol (*S*)-**293** (725 mg, 93%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (br s, 1H, NCH), 4.25 (br s, 1H, OH), 3.88-3.82 (m, 1H, NCH_AH$_B$), 3.79-3.68 (m, 3H, NCH$_A$$H_B$ + OCH_2), 2.16 (tdd, J = 11.5, 9.0, 5.0 Hz, 1H, CH_AH$_B$), 1.91 (br s, 1H, CH$_A$$H_B$), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.5 (C=O), 80.3 (*C*Me_3), 67.0 (OCH_2), 63.7 (NCH), 46.7 (NCH_2), 28.3 (C*Me*$_3$), 17.9 (CH_2); $[\alpha]_D$ −19.8 (*c* 0.45 in $CHCl_3$) (lit.,[102] $[\alpha]_D$ −21.5 (*c* 0.83 in $CHCl_3$)). Spectroscopic data consistent with those reported in the literature.[102]

Lab Book Reference 8/686

(*S*)-*tert*-Butyl 2-(iodomethyl)azetidine-1-carboxylate (*S*)-294[235]



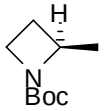
(*S*)-**294**

Iodine (1.28 g, 5.06 mmol, 1.5 eq.) was added in three portions to a stirred solution of imidazole (459 mg, 6.74 mmol, 2.0 eq.) and triphenylphosphine (1.33 g, 5.06 mmol, 1.5 eq.) in CH_2Cl_2 (15 mL) at 0 °C over 30 min. The resulting solution was allowed to warm to rt and then stirred at rt for 10 min. Then, a solution of alcohol (*S*)-**293** (630

mg, 4.17 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was added dropwise and the resulting solution was stirred at rt for 16 h. The solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (25 mL) and the solids were removed by filtration. The organic layer was washed with sat. $Na_2S_2O_{3(aq)}$ (15 mL), 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 iodide (*S*)-**294** (851 mg, 85%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2975, 2968, 1695 (C=O), 1510, 1446, 1420, 1278, 1190, 1035, 915, 815, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21-4.15 (m, 1H, NCH), 3.81-3.69 (m, 2H, NCH), 3.51 (br d, J = 9.0 Hz, 1H, CH_AH$_B$I), 3.37 (t, 9.0 Hz, CH$_A$$H_B$I), 2.29 (dddd, J = 11.5, 9.0, 8.0, 5.5 Hz, 1H, CH_AH$_B$), 1.89 (dddd, J = 11.5, 9.0, 6.5, 6.0 Hz, 1H, CH$_A$$H_B$), 1.43 (s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 79.7 (*C*Me$_3$), 61.1 (NCH), 44.9 (NCH$_2$), 28.3 (C*Me*$_3$), 23.4 (CH$_2$), 11.6 (CH$_2$I); MS (ESI) *m/z* 320 [(M + Na)$^+$, 60], 241 (100); HRMS *m/z* calcd for $C_9H_{16}INO_2$ (M + Na)$^+$ 320.0118, found 320.0108 (+3.0 ppm error); $[\alpha]_D$ −88.7 (*c* 0.95 in $CHCl_3$).

Lab Book Reference 8/687

(*R*)-*tert*-Butyl-2-methylazetidine-1-carboxylate (*R*)-292[236]



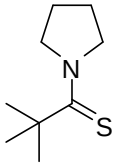
(*R*)-**292**

5% Pd/C (65 mg, 10 wt% of (*S*)-**294**) was added to a stirred solution of iodide (*S*)-**294** (650 mg, 2.18 mmol, 1.0 eq.) and Et_3N (0.30 mL, 2.18 mmol, 1.0 eq.) in MeOH (10 mL) at rt. Then, the reaction flask evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H_2 was attached and the reaction mixture was stirred vigorously at rt under H_2 for 16 h. The solids were removed by filtration through Celite® and washed with CH_2Cl_2 (15 mL). Then, the filtrate was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (15 mL) and washed with 1 M $HCl_{(aq)}$ (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave methyl azetidine (*R*)-**292** (280 mg, 75%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$)

δ 4.26 (pent, J = 6.5 Hz 1H, NCH), 3.81-3.77 (m, 2H, NCH_2), 2.30-2.21 (m, 1H, CH_AH_B), 1.74 (dtd, J = 11.0, 8.0, 6.0 Hz, 1H, CH_AH_B), 1.42 (s, 9H, CMe_3), 1.35 (d, J = 6.5 Hz, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.4 (C=O), 78.9 (CMe_3), 57.9 (br, NCH), 45.7 (br, NCH_2), 28.4 (CMe_3), 23.6 (CH_2), 21.5 (Me); $[\alpha]_D$ −38.1 (*c* 1.0 in $CHCl_3$) (lit.,[102] $[\alpha]_D$ −40.5 (*c* 0.80 in $CHCl_3$)). Spectroscopic data consistent with those reported in the literature.[102]

Lab Book Reference: PJR 8/688A

2,2-Dimethyl-1-pyrrolidin-1-ylpropan-1-thione 210[102]

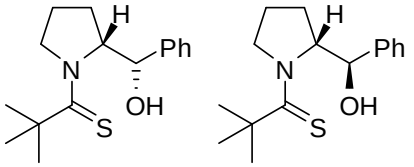


210

Phosphorous(V) sulfide (17.78 g, 80.0 mmol, 1.25 eq.) was added to a stirred solution amide **209** (10.0 g, 64 mmol, 1.0 eq.) in pyridine (100 mL) at rt under Ar. The resulting solution was heated at 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M $HCl_{(aq)}$ (150 mL). 1 M $HCl_{(aq)}$ was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with 1 M $HCl_{(aq)}$ (100 mL), water (100 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave thioamide **210** (5.09 g, 100%) as pale yellow needles, mp 32-35 °C (lit.,[237] 33-35 °C); R_F (7:3 petrol-EtOAc) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (t, J = 7.0 Hz, 2H, NCH_2), 3.74 (t, J = 7.0 Hz, 2H, NCH_2), 1.95 (quintet, J = 7.0 Hz, 2H, CH_2), 1.81 (quintet, J = 7.0 Hz, 2H, CH_2), 1.29 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 208.4 (C=S), 57.5 (NCH_2), 52.7 (NCH_2) 43.4 (CMe_3), 30.1 (CMe_3), 27.2 (CH_2), 22.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[237]

Lab Book Reference: PJR 2/110A

1-((*R*)-2-((*S*)-Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione *anti*-(*S*,*R*)-211 and 1-((*R*)-2-((*R*)-hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione *syn*-(*R*,*R*)-211



anti-(*S*,*R*)-**211** *syn*-(*R*,*R*)-**211**

Using general procedure M, *s*-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (145 μL, 0.65 mmol, 1.3 eq.) and *N*-thiopivaloyl pyrrolidine **210** (86 mg, 0.50 mmol, 1.0 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained a 58:42 mixture of diastereomeric alcohols *anti*-(*S*,*R*)-**211** and *syn*-(*R*,*R*)-**211** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave alcohol *anti*-(*S*,*R*)-**211** (55 mg, 40%, 86:14 er by CSP-HPLC) as a white solid, mp 169-174 °C; R_F (7:3 petrol-Et_2O) 0.2; IR ($CHCl_3$) 3386 (OH), 2972, 2876, 1604, 1478, 1411, 1383, 1365, 1160, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.0 Hz, 2H, *o*-Ph), 7.34 (t, J = 7.0 Hz, 2H, *m*-Ph), 7.26 (t, J = 7.0 Hz, 1H, *p*-Ph), 5.90 (br s, 1H, OCH), 5.36-5.32 (m, 1H, NCH), 4.27-4.22 (m, 1H, NCH_AH$_B$), 3.52 (td, , J = 11.0, 6.0 Hz, 1H, NCH$_A$$H_B$), 2.28 (br s, 1H, OH), 2.12-1.97 (m, 2H, CH), 1.75-1.64 (m, 2H, CH), 1.44 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.1 (C=S), 141.9 (*ipso*-Ph), 128.1 (Ph), 127.2 (Ph), 125.5 (Ph), 71.4 (OCH or NCH), 70.4 (OCH or NCH), 54.7 (NCH_2), 44.2 (CMe_3), 30.7 (CMe_3), 25.0 (CH_2), 22.4 (CH_2); MS (ESI) *m/z* 300 [(M + Na)$^+$, 20], 278 [(M + H)$^+$, 100], 260 (30), 125 (40); HRMS *m/z* calcd for $C_{16}H_{23}NOS$ (M + H)$^+$ 278.1573, found 278.1579 (−2.0 ppm error); $[\alpha]_D$ −7.0 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**211** 11.3 min, (*R*,*S*)-**211** 14.7 min and alcohol *syn*-(*R*,*R*)-**211** (50 mg, 37%, 82:18 er by CSP-HPLC) as a colourless oil, R_F (7:3 petrol-Et_2O) 0.1; IR (film) 3387 (OH), 2973, 2876, 1605, 1452, 1411, 1383, 1365, 1162, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H, Ph), 5.68 (td, J = 8.0, 3.5 Hz, 1H, NCH), 5.29-5.26 (m, 1H, OCH), 4.11 (dt, J = 11.5, 5.5 Hz, 1H, NCH_AH$_B$), 3.97 (br d, J = 5.0 Hz, 1H, OH), 3.25-3.18 (m, 1H, NCH$_A$$H_B$), 1.90-1.73 (m, 4H, CH), 1.45 (s, 9H, CMe_3); ^{13}C NMR rotamers (100.6 MHz, $CDCl_3$) δ 212.6 (C=S), 141.8 (*ipso*-Ph), 128.3 (Ph), 128.5 (Ph), 128.3 (Ph), 127.8 (Ph),

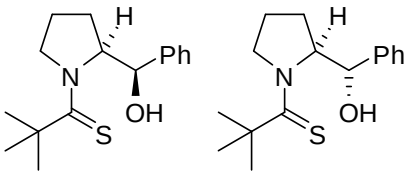
127.6 (Ph), 127.1 (Ph), 127.0 (Ph), 74.4 (br, OCH), 69.8 (NCH), 65.3 (NCH_2), 52.7 (NCH_2), 44.3 (*C*Me_3), 30.7 (C*Me*$_3$), 24.3 (CH_2), 24.1 (CH_2); MS (ESI) *m/z* 300 [(M + Na)$^+$, 20], 278 [(M + H)$^+$, 100], 260 (20), 125 (20); HRMS *m/z* calcd for $C_{16}H_{23}NOS$ (M + H)$^+$ 278.1573, found 278.1570 (1.1 ppm error); $[\alpha]_D$ +94.2 (*c* 0.8 in $CHCl_3$); CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**211** 10.6 min, (*S*,*S*)-**211** 22.4 min.

Lab Book Reference PJR 8/636 6/501

A solution of stannane *rac*-**297** (100 mg, 0.30 mmol, 1.0 eq.) in Et_2O (3 mL) was added to a stirred solution of *n*-BuLi (0.13 mL of a 2.5 M solution in hexane, 0.33 mmol, 1.1 eq.) and (−)-sparteine (77 μL, 0.33 mmol, 1.1 eq.) in Et_2O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (46 μL, 0.45 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 1 h and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 55:45 mixture of diastereomeric alcohols *anti*-(*S*,*R*)-**211** and *syn*-(*R*,*R*)-**211** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave alcohol *anti*-(*S*,*R*)-**211** (32 mg, 39%, 88:12 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**211** 11.7 min, (*R*,*S*)-**211** 15.2 min and alcohol *syn*-(*R*,*R*)-**211** (29 mg, 35%, 82:18 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**211** 9.8 min, (*S*,*S*)-**211** 18.8 min.

Lab Book Reference PJR 8/700

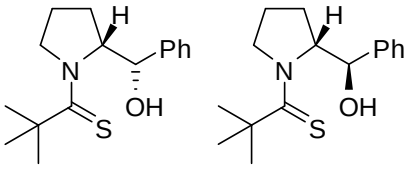
1-((*S*)-2-((*R*)-Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione *anti*-(*R*,*S*)-211 and 1-((*S*)-2-((*S*)-hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione *syn*-(*S*,*S*)-211



anti-(*R*,*S*)-**211** *syn*-(*S*,*S*)-**211**

Using general procedure M, *s*-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate **1** (120 mg, 0.65 mmol, 1.3 eq.) and *N*-thiopivaloyl pyrrolidine **210** (86 mg, 0.50 mmol, 1.0 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained a 78:22 mixture of diastereomeric alcohols *anti*-(*R*,*S*)-**211** and *syn*-(*S*,*S*)-**211** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave alcohol *anti*-(*R*,*S*)-**211** (86 mg, 62%, 85:15 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**211** 11.2 min, (*R*,*S*)-**211** 14.6 min and alcohol *syn*-(*S*,*S*)-**211** (33 mg, 24%, 92:8 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**211** 10.8 min, (*S*,*S*)-**211** 19.8 min.
Lab Book Reference 8/662

1-(2-(Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione *anti-rac*-211 and 1-(2-(hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione *syn-rac*-211



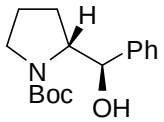
anti-rac-**211** *syn-rac*-**211**

n-BuLi (26 μL of a 2.5M solution in hexanes, 0.066 mmol, 1.1 eq.) was added to a stirred solution of stannane (*S*)-**297** (20 mg, 0.06 mmol, 1.0 eq., 78:22 er) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (7 μL, 0.07 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 60:40 mixture of alcohols *syn-rac*-**211** and *anti-rac*-**211** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti-rac*-**211** (7 mg, 42%, 51:49 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**211** 11.2 min, (*R*,*S*)-**211** 14.6 min and alcohol *syn-rac*-**211**

(9 mg, 52%, 51:49 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**211** 10.6 min, (*S*,*S*)-**211** 23.1 min.
Lab Book Reference 8/634

n-BuLi (26 μL of a 2.5M solution in hexanes, 0.066 mmol, 1.1 eq.) was added to a stirred solution of stannane (*S*)-**297** (20 mg, 0.06 mmol, 1.0 eq., 78:22 er) and TMEDA (10 μL, 0.066 mmol, 1.1 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (7 μL, 0.07 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 76:24 mixture of alcohols *syn*-*rac*-**211** and *anti*-*rac*-**211** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *anti*-*rac*-**211** (8 mg, 24%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**211** 11.3 min, (*R*,*S*)-**211** 14.7 min and alcohol *syn*-*rac*-**211** (21 mg, 61%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**211** 10.6 min, (*S*,*S*)-**211** 23.0 min.
Lab Book Reference 8/635

***tert*-Butyl (2*R*)-2-[(*R*)-hydroxy(phenyl)methyl]pyrrolidine-1-carboxylate *syn*-(*R*,*R*)-73**

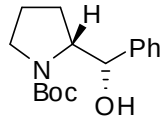


syn-(*R*,*R*)-**73**

MeLi (0.58 mL of a 1.6 M solution in Et_2O, 0.93 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol *syn*-(*R*,*R*)-**211** (43 mg, 0.16 mmol, 1.0 eq., 82:18 er) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0°C for 5 h. Then, 1 M HCl(aq) (5 mL) was added dropwise. The resulting solution was extracted with Et_2O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M $NaOH_{(aq)}$ and extracted with Et_2O (3 x 10 mL). The combined organic layers were

dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH_2Cl_2 (5 mL) and di-*tert*-butyl dicarbonate (37 mg, 0.17 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol *syn*-(*R,R*)-**73** (30 mg, 70%, 82:18 er by CSP HPLC) as a colourless oil, $[\alpha]_D$ −0.6 (*c* 0.75 in $CHCl_3$) (lit.,[74] $[\alpha]_D$ −1.6 (*c* 1.0 in $CHCl_3$ for (*R,R*)-**73** of 97:3 er)); CSP-HPLC: Chiracel OD (98:2 Hexane-*i*PrOH, 0.5 mL min^{-1}) (*R,R*)-**73** 28.6 min, (*S,S*)-**73** 35.7 min. Spectroscopic data consistent with those reported in the literature.[74]
Lab Book Reference 8/648

tert-Butyl (2*R*)-2-[(*S*)-hydroxy(phenyl)methyl]pyrrolidine-1-carboxylate _anti_-(*S,R*)-73



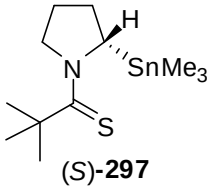
syn-(*S,R*)-**73**

MeLi (0.45 mL of a 1.6 M solution in Et_2O, 0.72 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol *anti*-(*S,R*)-**211** (33 mg of 86:14 er, 0.12 mmol, 1.0 eq.) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0°C for 5 h. Then, 1 M HCl(aq) (5 mL) was added dropwise. The resulting solution was extracted with Et_2O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M $NaOH_{(aq)}$ and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH_2Cl_2 (5 mL) and di-*tert*-butyl dicarbonate (28 mg, 0.13 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol *anti*-(*S,R*)-**73** (17 mg, 50%, 86:14 er by CSP HPLC) as a colourless oil, $[\alpha]_D$

+79.4 (*c* 1.0 in $CHCl_3$) (lit.,[74] $[\alpha]_D$ +112.7 (*c* 1.5 in $CHCl_3$ for (*S*,*R*)-**73** of 96:4 er)); CSP-HPLC: Chiracel OD (99:1 Hexane-*i*PrOH, 0.5 mL min^{-1}) (*S*,*R*)-**73** 25.7 min, (*R*,*S*)-**73** 28.3 min. Spectroscopic data consistent with those reported in the literature.[74]

Lab Book Reference 8/647

(*S*)-2,2-Dimethyl-1-(2-(trimethylstannyl)pyrrolidin-1-yl)propane-1-thione (*S*)-297

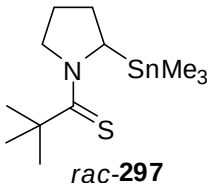


(*S*)-**297**

Using general procedure M, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.), *N*-thiopivaloyl pyrrolidine **210** (171 mg, 1.00 mmol, 1.0 eq.) and (−)-sparteine (296 μL, 1.30 mmol, 1.3 eq.) in Et_2O (7 mL) and trimethyltin chloride (1.50 mL of a 1.0 M solution in hexanes, 1.5 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave stannane (*S*)-**297** (228 mg, 68%, 78:22 er by CSP-HPLC) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.3; IR (film) 2978, 1500, 1482, 1448, 1390, 1370, 1246, 1074, 1036, 912, 809, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37-4.28 (m, 1H, NCH), 3.91-3.78 (m, 2H, NCH_2), 2.20-2.09 (m, 2H, CH_2), 2.07-2.01 (m, 1H, CH), 1.98-1.88 (m, 1H, CH), 1.40 (s, 9H, CMe_3), 0.07 (s, 9H, $SnMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.0 (C=S), 63.7 (NCH), 53.1 (NCH_2), 43.1 (CMe_3), 30.7 (CMe_3), 28.2 (CH_2), 27.6 (CH_2), −6.7 ($SnMe_3$); MS (ESI) *m/z* 336 [(M(^{120}Sn) + H)$^+$, 100], 334 [(M(^{118}Sn) + H)$^+$, 70], 332 [(M(^{116}Sn) + H)$^+$, 30]; HRMS *m/z* calcd for $C_{12}H_{25}NS^{120}Sn$ (M + Na)$^+$ 336.0803 (−1.0 ppm error), found 336.0806; $[\alpha]_D$ +290.89 (*c* 0.70 in $CHCl_3$); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**297** 4.9 min, (*R*)-**297** 6.4 min. The absolute configuration of the major enantiomer is assumed by analogy to benzaldehyde-trappings.

Lab Book Reference: PJR 8/630A

(*S*)-2,2-Dimethyl-1-(2-(trimethylstannyl)pyrrolidin-1-yl)propane-1-thione *rac*-297

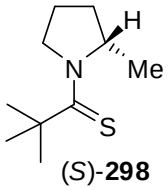


rac-**297**

Using general procedure M, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.), *N*-thiopivaloyl pyrrolidine **210** (171 mg, 1.00 mmol, 1.0 eq.) and TMEDA (194 μL, 1.30 mmol, 1.3 eq.) in Et_2O (7 mL) and trimethyltin chloride (1.50 mL of a 1.0 M solution in hexanes, 1.5 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave stannane *rac*-**297** (254 mg, 76%) as a colourless oil.

Lab Book Reference 8/699

(*S*)-2,2-dimethyl-1-(2-methylpyrrolidin-1-yl)propane-1-thione *(S)*-298



(*S*)-**298**

Using general procedure M, *s*-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-thiopivaloyl pyrrolidine **210** (86 mg, 0.50 mmol, 1.0 eq.) and (−)-sparteine (0.15 mL, 0.65 mmol, 1.3 eq.) in Et_2O (5 mL) and methyl iodide (47 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave methylated pyrrolidine (*S*)-**298** (78 mg, 84%, 58:42 er by CSP-HPLC) as a colourless oil. R_F (8:2 petrol-Et_2O) 0.3; IR (film) 2975, 2876, 1530, 1458, 1410, 1325, 1116, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 85:15 mixture of rotamers δ 5.15-5.07 (m, 0.85H, NCH), 4.84-4.78 (m, 0.15H, NCH), 4.21 (dt, J = 14.5, 8.5 Hz, 0.15H, NCH_AH_B), 4.00 (ddd, J = 13.5, 12.0, 7.0 Hz, 0.85H, NCH_AH_B), 3.83-3.76 (m, 0.15H, NCH$_A$$H_B$), 3.67 (dt, J = 13.5, 6.5 Hz, 0.85H, NCH$_A$$H_B$), 2.13-1.86 (m, 3H, CH), 1.66-1.59 (m, 1H, CH), 1.43 (s, 1.35H, CMe_3), 1.39 (s, 7.65H, CMe_3), 1.33 (d, J = 6.5 Hz, 2.55H, Me), 1.24 (d, J = 6.0 Hz, 0.45H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.8 (C=S), 61.8 (NCH), 52.0 (NCH_2), 44.0 (CMe_3), 30.6 (CMe_3), 30.4 (CH_2), 24.9 (CH_2), 17.7 (Me); MS (ESI) *m/z* 208 [$(M + Na)^+$, 100],

186 [$(M + H)^+$, 20]; HRMS *m/z* calcd for $C_{10}H_{19}NS$ $(M + Na)^+$ 208.1136, found 208.1131 (−0.5 ppm error); $[\alpha]_D$ −10.1 (*c* 0.95 in $CHCl_3$); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**298** 8.0 min, (*R*)-**298** 9.0 min. The absolute configuration of the major enantiomer was assigned by comparison to unpublished results within our group (conversion of (*S*)-**298** into known compound).[212]

Lab Book Reference 8/650

Chapter Six: Abbreviations

Ac	Acetyl
aq.	Aqueous
Bn	Benzyl
Boc	*t*-butoxycarbonyl
bp	Boiling Point
br	Broad
Bu	Butyl
Cb	*N*,*N*-Diisoproylcarbamoyl
CIPE	Complex induced proximity effect
cm^{-1}	Wavenumber
CSP-HPLC	Chiral Stationary Phase High Performance Liquid Chromatography
δ	Chemical shift
d	Doublet
DET	Diethyl tartrate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
dr	Diastereomeric ratio
E^+	Electrophile
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray ionisation
eq.	Equivalent(s)
er	Enantiomeric ratio
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HFIP	Hexafluoroisopropanol

HOBt	Hydroxybenzotriazole
HRMS	High resolution mass spectrometry
Hz	Hertz
i-Pr	Isopropyl
IR	Infra-red
J	Coupling constant in Hz
KHMDS	Potassium hexamethyldisilazide
LHMDS	Lithium hexamethyldisilazide
M	Molar
M^+	Molecular ion
m	Multiplet
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrams
min	Minutes
mL	Millilitre
mmol	Millimole
mol	Mole
MOM	Methoxymethyl ether
mp.	Melting Point
MS	Mass Spectrometry
MTBE	Methyl *tert*-butyl ether
m/z	Mass to charge ratio
NCS	*N*-Chlorosuccinimide
NMR	Nuclear Magnetic Resonance
Ns	4-Nitrobenzenesulfonyl
Petrol	Petroleum ether (Fraction which boils at 40-60 °C)
Ph	Phenyl

PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
q	Quartet
R	Alkyl group
RSM	Recovered starting material
R_F	Retention factor
rt	Room temperature
s	Singlet
SEM	[2-(Trimethysilyl)ethoxy]methyl
sp.	Sparteine
(+)-sp. surr.	(+)-Sparteine surrogate
s-Bu	*s*-Butyl
t	Triplet
TBDMS	*tert*-Butyldimethylsilyl
t-Bu	*t*-Butyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Think layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet

Chapter Seven: Bibliography

(1) Crossley, R. *Tetrahedron* **1992**, *48*, 8155.

(2) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2283.

(3) O'Brien, P.; Bilke, J. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 2734.

(4) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225.

(5) Satoh, T. *Chem. Soc. Rev.* **2007**, *36*, 1561.

(6) Klapars, A.; Campos, K. R.; Waldman, J. H.; Zewge, D.; Dormer, P. G.; Chen, C.-y. *J. Org. Chem.* **2008**, *73*, 4986.

(7) Cossy, J.; Belotti, D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1989.

(8) Le Bourdonnec, B.; Goodman, A. J.; Graczyk, T. M.; Belanger, S.; Seida, P. R.; DeHaven, R. N.; Dolle, R. E. *J. Med. Chem.* **2006**, *49*, 7290.

(9) Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2005**, *7*, 4337.

(10) Oxenford, S. J.; Moore, S. P.; Carbone, G.; Barker, G.; O'Brien, P.; Shipton, M. R.; Gilday, J.; Campos, K. R. *Tetrahedron: Asymmetry* **2010**, *21*, 1563.

(11) Binanzer, M.; Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 4264.

(12) Schlenk, W.; Holtz, J. *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 262.

(13) Tidwell, T. T. *Angew. Chem. Int. Ed.* **2001**, *40*, 331.

(14) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

(15) Andrieux, C. P.; Gallardo, I.; Savaent, J. M.; Su, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 638.

(16) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.

(17) Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, *9*, 4097.

(18) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Tetrahedron Organic Chemistry Series, Vol. 23, PERGAMON, **2002**; 226.

(19) O'Brien, P.; Dearden, M. J.; Firkin, C. R.; Hermet, J. P. R. *J. Am. Chem. Soc.* **2002**, *124*, 11870.

(20) O'Brien, P. *Chem. Comm.* **2008**, 655.

(21) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed.* **1990**, *29*, 1422.

(22) Beak, P.; Gallagher, D. J. *J. Org. Chem.* **1995**, *60*, 7092.

(23) Hoppe, D.; Carstens, A.; Krámer, T. *Angew. Chem. Int. Ed.* **1990**, *29*, 1424.

(24) Hammerschmidt, F.; Hanninger, A. *Chemische Berichte* **1995**, *128*, 1069.

(25) Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149.

(26) Jemmis, E. D.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1979**, *101*, 527.

(27) McGrath, M. J.; O'Brien, P. *Synthesis* **2006**, *2006*, 2233.

(28) O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. R.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480.

(29) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.

(30) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, *2004*, 2275.

(31) Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193.

(32) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491.

(33) Beckmann, E.; Hoppe, D. *Synthesis* **2005**, 217.

(34) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778.

(35) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760.

(36) Robinson, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 6673.

(37) Radha Krishna, P.; Narasimha Reddy, P. V. *Tetrahedron Lett.* **2006**, *47*, 7473.

(38) Beak, P.; Kerrick, S. T. *J. Am. Chem. Soc.* **1991**, *113*, 9708.

(39) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538.

(40) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936.

(41) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.

(42) Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2113.

(43) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260.

(44) Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 716.

(45) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.

(46) Gammon, J. J.; Gessner, V. H.; Barker, G. R.; Granander, J.; Whitwood, A. C.; Strohmann, C.; O'Brien, P.; Kelly, B. *J. Am. Chem. Soc.* **2010**, *132*, 13922.

(47) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.

(48) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755.

(49) Hirsch, R.; Hoffmann, R. W. *Chemische Berichte* **1992**, *125*, 975.

(50) Hoffmann, R. W.; Rühl, T.; Harbach, J. *Liebigs Ann. Chem.* **1992**, *1992*, 725.

(51) Klute, W.; Dress, R.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1993**, *0*, 1409.

(52) Coldham, I.; Patel, J. J.; Raimbault, S.; Whittaker, D. T. E. *Chem. Comm.* **2007**, 4534.

(53) Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718.

(54) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J. J.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2006**, *128*, 10943.

(55) Beng, T. K.; Yousaf, T. I.; Coldham, I.; Gawley, R. E. *J. Am. Chem. Soc.* **2009**, *131*, 6908.

(56) Coldham, I.; Raimbault, S.; Chovatia, P. T.; Patel, J. J.; Leonori, D.; Sheikh, N. S.; Whittaker, D. T. E. *Chem. Comm.* **2008**, *0*, 4174.

(57) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216.

(58) Beng, T. K.; Tyree, W. S.; Parker, T.; Su, C.; Williard, P. G.; Gawley, R. E. *J. Am. Chem. Soc.* **2012**, *134*, 16845.

(59) Beng, T. K.; Gawley, R. E. *Org. Lett.* **2011**, *13*, 394.

(60) Grignard, V. *C.R. Acad. Sci.* **1900**, *130*, 1322.

(61) Grignard, V. *Ann. Chim.* **1901**, *24*, 433.

(62) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286.

(63) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95.

(64) Lai, Y.-H. *Synthesis* **1981**, 585.

(65) Pearson, D. E.; Cowan, D.; Beckler, J. D. *J. Org. Chem.* **1959**, *24*, 504.

(66) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 906.

(67) Mendel, A. *J. Organomet. Chem.* **1966**, *6*, 97.

(68) Fürstner, A. *Angew. Chem. Int. Ed.* **1993**, *32*, 164.

(69) Schlenk, W. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 920.

(70) Andersen, R. A.; Wilkinson, G.; Lappert, M. F.; Pearce, R. In *Inorganic Syntheses*; John Wiley & Sons, Inc.: 2007, p 262.

(71) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

(72) Tomooka, K.; Shimizu, H.; Nakai, T. *J. Organomet. Chem.* **2001**, *624*, 364.

(73) Tomooka, K.; Shimizu, H.; Inoue, T.; Shibata, H.; Nakai, T. *Chem. Lett.* **1999**, *28*, 759.

(74) Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935.

(75) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515.

(76) Ashweek, N. J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R. E.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, *127*, 449.

(77) Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93.

(78) Satoh, T.; Oohara, T.; Yamakawa, K. *Tetrahedron Lett.* **1988**, *29*, 4093.

(79) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130.

(80) Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3973.

(81) Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557.

(82) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

(83) Satoh, T.; Takano, K.; Someya, H.; Matsuda, K. *Tetrahedron Lett.* **1995**, *36*, 7097.

(84) Furukawa, N.; Shibutani, T.; Matsumura, K.; Fujihara, H.; Oae, S. *Tetrahedron Lett.* **1986**, *27*, 3899.

(85) Rauhut, C. B.; Melzig, L.; Knochel, P. *Org. Lett.* **2008**, *10*, 3891.

(86) Melzig, L.; Rauhut, C. B.; Knochel, P. *Synthesis* **2009**, 1041.

(87) Melzig, L.; Rauhut, C. B.; Knochel, P. *Chem. Comm.* **2009**, *0*, 3536.

(88) Fleming, F. F.; Gudipati, S.; Vu, V. A.; Mycka, R. J.; Knochel, P. *Org. Lett.* **2007**, *9*, 4507.

(89) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049.

(90) Hoffmann, R. W.; Nell, P. G. *Angew. Chem. Int. Ed.* **1999**, *38*, 338.

(91) Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem.-Eur. J.* **2000**, *6*, 3359.

(92) Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006**, *8*, 773.

(93) Satoh, T.; Mitsunaga, S.; Ohbayashi, T.; Sugiyama, S.; Saitou, T.; Tadokoro, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1697.

(94) Avolio, S.; Malan, C.; Marek, I.; Knochel, P. *Synlett* **1999**, 1820.

(95) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

(96) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144a.

(97) Holzer, B.; Hoffmann, R. W. *Chem. Comm.* **2003**, 732.

(98) Hughes, M.; Boultwood, T.; Zeppetelli, G.; Bull, J. A. *J. Org. Chem.* **2013**, *78*, 844.

(99) Satoh, T.; Ozawa, M.; Takano, K.; Chyouma, T.; Okawa, A. *Tetrahedron* **2000**, *56*, 4415.

(100) Hansen, J. G.; SÃ¸tofte, I.; Johannsen, M. *Org. Lett.* **2001**, *3*, 499.

(101) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.

(102) Hodgson, D., M.; Kloesges, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 2900.

(103) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116.

(104) Yoshimura, T.; Sakae, H.; Yoshizawa, M.; Hasegawa, K.; Tsukurimichi, E. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 1162.

(105) Kagan, H. B.; Pitchen, P.; Dunach, E.; Deshmukh, M. N. *J. Am. Chem. Soc.* **1984**, *106*, 8188.

(106) Pitchen, P.; France, C. J.; McFarlane, I. M.; Newton, C. G.; Thompson, D. M. *Tetrahedron Lett.* **1994**, *35*, 485.

(107) Davis, F. A.; Jenkins, R. H.; Awad, S. B.; Stringer, O. D.; Watson, W. H.; Galloy, J. *J. Am. Chem. Soc.* **1982**, *104*, 5412.

(108) Komori, T.; Nonaka, T. *J. Am. Chem. Soc.* **1983**, *105*, 5690.

(109) Auret, B. J.; Boyd, D. R.; Henbest, H. B.; Ross, S. *J. Chem. Soc. C* **1968**, 2371.

(110) Andersen, K. K. *Tetrahedron Lett.* **1962**, 93.

(111) Harrison, P. W. B.; Kenyon, J.; Phillips, H. *J. Chem. Soc.* **1926**, 2079.

(112) Andersen, K. K. *J. Org. Chem.* **1964**, *29*, 1953.

(113) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637.

(114) Johnson, C. R.; McCants, D. *J. Am. Chem. Soc.* **1965**, *87*, 5404.

(115) Fernandez, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789.

(116) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977.

(117) Roe, C.; Hobbs, H.; Stockman, R. A. *Chem.-Eur. J.* **2011**, *17*, 2704.

(118) Roe, C.; Hobbs, H.; Stockman, R. A. *J. Org. Chem.* **2011**, *76*, 9452.

(119) Resek, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 7051.

(120) Solladié, G. *Synthesis* **1981**, 185.

(121) Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068.

(122) Phillips, H. *Journal of the Chemical Society, Transactions* **1925**, *127*, 2552.

(123) Wright, A. D.; Bowen, R. D.; Jennings, K. R. *J. Chem. Soc., Perkin Trans. 2* **1989**, *0*, 1521.

(124) Hua, D. H.; Lagneau, N. M.; Chen, Y.; Robben, P. M.; Clapham, G.; Robinson, P. D. *J. Org. Chem.* **1996**, *61*, 4508.

(125) El Ouazzani, H.; Khiar, N.; Fernández, I.; Alcudia, F. *J. Org. Chem.* **1997**, *62*, 287.

(126) Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511.

(127) Carbone, G.; O'Brien, P.; Hilmersson, G. r. *J. Am. Chem. Soc.* **2010**, *132*, 15445.

(128) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 6317.

(129) Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 8893.

(130) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165.

(131) Ma, L.; Zhao, D.; Chen, L.; Wang, X.; Chen, Y.-L.; Shen, J. *Tetrahedron* **2012**, *68*, 8704.

(132) Davis, R.; Kern, J. R.; Kurz, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873.

(133) Larouche-Gauthier, R.; Fletcher, C. J.; Couto, I.; Aggarwal, V. K. *Chem. Comm.* **2012**, *47*, 12592.

(134) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197.

(135) Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.* **1991**, *1991*, 1323.

(136) Ashweek, N. J.; Coldham, I.; Haxell, T. F. N.; Howard, S. *Org. Biomol. Chem.* **2003**, *1*, 1532.

(137) Zheng, X.; Feng, C.-G.; Ye, J.-L.; Huang, P.-Q. *Org. Lett.* **2005**, *7*, 553.

(138) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735.

(139) Kita, Y.; Tamura, O.; Miki, T.; Tamura, Y. *Tetrahedron Lett.* **1987**, *28*, 6479.

(140) Kuhakarn, C.; Seehasombat, P.; Jaipetch, T.; Pohmakotr, M.; Reutrakul, V. *Tetrahedron* **2008**, *64*, 1663.

(141) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311.

(142) Thomas, E. W.; Rynbrandt, R. H.; Zimmermann, D. C.; Bell, L. T.; Muchmore, C. R.; Yankee, E. W. *J. Org. Chem.* **1989**, *54*, 4535.

(143) Herak, J. J.; Vinković, M.; Mandić, Z.; Lukić, I.; Tomić, M.; Kovačević, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1605.

(144) Cooke, M. D.; Ross, B. C. In *United States Patent , US 4684640* 1987.

(145) Arrowsmith, J. E.; Greengrass, C. W. *Tetrahedron Lett.* **1982**, *23*, 357.

(146) Barker, G.; O'Brien, P.; Campos, K. R. *Org. Lett.* **2010**, 4176.

(147) Beak, P.; Lee, W. K. *Tetrahedron Lett.* **1989**, *30*, 1197.

(148) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

(149) Emerson, D. W.; Craig, A. P.; Potts, I. W. *J. Org. Chem.* **1967**, *32*, 102.

(150) Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051.

(151) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.

(152) Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453.

(153) Fujitani, M.; Tsuchiya, M.; Okano, K.; Takasu, K.; Ihara, M.; Tokuyama, H. *Synlett* **2010**, 822.

(154) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(155) McKillop, A.; Koyunçu, D.; Krief, A.; Dumont, W.; Renier, P.; Trabelsi, M. *Tetrahedron Lett.* **1990**, *31*, 5007.

(156) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317.

(157) Feldman, K. S.; Fodor, M. D. *J. Org. Chem.* **2009**, *74*, 3449.

(158) Mohanakrishnan, A. K.; Ramesh, N. *Tetrahedron Lett.* **2005**, *46*, 4231.

(159) Ravikumar, K. S.; Zhang, Y. M.; Begue, J. P.; Bonnet-Delpon, D. *Eur. J. Org. Chem.*, **1998**, 2937.

(160) Chen, Y.-J.; Huang, Y.-P. *Tetrahedron Lett.* **2000**, *41*, 5233.

(161) Wykypiel, W.; Lohmann, J. J.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1337.

(162) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010.

(163) Cinquini, M.; Colonna, S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1883.

(164) Kawabata, T.; Minami, T.; Hiyama, T. *J. Org. Chem.* **1992**, *57*, 1864.

(165) Dong, Q.-L.; Liu, G.-S.; Zhou, H.-B.; Chen, L.; Yao, Z.-J. *Tetrahedron Lett.* **2008**, *49*, 1636.

(166) Theobald, P. G.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 741.

(167) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726.

(168) Dieter, R. K.; Li, S.; Chen, N. *J. Org. Chem.* **2004**, *69*, 2867.

(169) Beak, P.; Kerrick, S. T.; Wu, S. D.; Chu, J. X. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

(170) Bredt, J. *Justus Liebigs Annalen der Chemie* **1924**, *437*, 1.

(171) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683.

(172) Park, Y. S.; Beak, P. *Tetrahedron* **1996**, *52*, 12333.

(173) Caravatti, G.; Fairhurst, R. A.; Furet, P.; Guagnano, V.; Imbach, P. In *US. Appl. to Novartis AG, US 20090163469* 2009.

(174) De Nanteuil, G.; Gloanec, P.; Verberen, T.; Rupin, A. In *United States Patent to Agir de Compagnie, US6288077* 2001.

(175) Ruebsam, F.; Sun, Z.; Ayida, B.; Zhou, Y.; Xiang, A. X. In *Int. Appl. to Anadys Pharmaceuticals, WO 2008073987A1* 2008.

(176) Augeri, D. J.; Robl, J. A.; Betebenner, D. A.; Magnin, D. R.; Khanna, A.; Robertson, J. G.; Wang, A.; Simpkins, L. M.; Taunk, P.; Huang, Q.; Han, S.-P.; Abboa-Offei, B.; Cap, M.; Xin, L.; Tao, L.; Tozzo, E.; Welzel, G. E.; Egan, D. M.; Marcinkeviciene, J.; Chang, S. Y.; Biller, S. A.; Kirby, M. S.; Parker, R. A.; Hamann, L. G. *J. Med. Chem.* **2005**, *48*, 5025.

(177) Savage, S. A.; Jones, G. S.; Kolotuchin, S.; Ramrattan, S. A.; Vu, T.; Waltermire, R. E. *Org. Process Res. Dev.* **2009**, *13*, 1169.

(178) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276.

(179) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578.

(180) Firth, J. D.; O'Brien, P. *unpublished results* **2013**.

(181) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755.

(182) Perron, Q.; Alexakis, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2503.

(183) Hanessian, S.; Reinhold, U.; Gentile, G. *Angew. Chem. Int. Ed.* **1997**, *36*, 1881.

(184) Hanessian, S. *personal communication* **2012**.

(185) Magnin, D. R.; Robl, J. A.; Sulsky, R. B.; Augeri, D. J.; Huang, Y.; Simpkins, L. M.; Taunk, P. C.; Betebenner, D. A.; Robertson, J. G.; Abboa-Offei, B. E.; Wang, A.; Cap, M.; Xin, L.; Tao, L.; Sitkoff, D. F.; Malley, M. F.; Gougoutas, J. Z.; Khanna, A.; Huang, Q.; Han, S.-P.; Parker, R. A.; Hamann, L. G. *J. Med. Chem.* **2004**, *47*, 2587.

(186) Harrison, D. J.; Tam, N. C.; Vogels, C. M.; Langler, R. F.; Baker, R. T.; Decken, A.; Westcott, S. A. *Tetrahedron Lett.* **2004**, *45*, 8493.

(187) Karimi, B.; Zareyee, D. *Synthesis* **2003**, 335.

(188) Vankar, Y. D.; Trinadha Rao, C. *Tetrahedron Lett.* **1985**, *26*, 2717.

(189) Bahrami, K.; Khodaei, M. M.; Karimi, A. *Synthesis* **2008**, 2543.

(190) Kudzin, Z. H.; Kudzin, M. H.; Drabowicz, J.; Kotyński, A. *ARKIVOC* **2007**, *vi*, 112.

(191) Ambrosi, P.; Arnone, A.; Bravo, P.; Bruché, L.; De Cristofaro, A.; Francardi, V.; Frigerio, M.; Gatti, E.; Germinara, G. S.; Panzeri, W.; Pennacchio, F.; Pesenti, C.; Rotundo, G.; Roversi, P. F.; Salvadori, C.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 8336.

(192) Beak, P.; Wilkinson, T. J.; Stehle, N. W. *Org. Lett.* **2000**, *2*, 155.

(193) Sheikh, N. S.; Leonori, D.; Barker, G.; Firth, J. D.; Campos, K. R.; Meijer, A. J. H. M.; O'Brien, P.; Coldham, I. *J. Am. Chem. Soc.* **2012**, *134*, 5300.

(194) Slade, J.; Bajwa, J.; Liu, H.; Parker, D.; Vivelo, J.; Chen, G.-P.; Calienni, J.; Villhauer, E.; Prasad, K.; Repič, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2007**, *11*, 825.

(195) Evans, G. B.; Furneaux, R. H.; Greatrex, B.; Murkin, A. S.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2008**, *51*, 948.

(196) Hart, T.; Macias, A. T.; Benwell, K.; Brooks, T.; D'Alessandro, J.; Dokurno, P.; Francis, G.; Gibbons, B.; Haymes, T.; Kennett, G.; Lightowler, S.; Mansell, H.; Matassova, N.; Misra, A.; Padfield, A.; Parsons, R.; Pratt, R.; Robertson, A.; Walls, S.; Wong, M.; Roughley, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4241.

(197) Matsuo, K.-., Nishiyashiro-cho, Himeji-shi, Hyogo, 670-0876, JP), Tsukuya, Kentaro (6-31-17-2208, Shioya-cho Tarumi-ku, Kobe-shi, Hyogo, 655-0872, JP); Kaneka Corporation (2-4, Nakanoshima 3-chome, Kita-ku, Osaka-shi, Osaka, 530-0005, JP): 2004.

(198) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *33*, 7917.

(199) Alvi, K. A.; Jaspars, M.; Crews, P.; Strulovici, B.; Oto, E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2447.

(200) Di, Y.-T.; He, H.-P.; Wang, Y.-S.; Li, L.-B.; Lu, Y.; Gong, J.-B.; Fang, X.; Kong, N.-C.; Li, S.-L.; Zhu, H.-J.; Hao, X.-J. *Org. Lett.* **2007**, *9*, 1355.

(201) Seebach, D.; Lubosch, W. *Angew. Chem.* **1976**, *88*, 339.

(202) Seebach, D.; Lubosch, W. *Angew. Chem. Int. Ed.* **1976**, *15*, 313.

(203) Lubosch, W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102.

(204) Hodgson, D. M.; Pearson, C. I.; Thompson, A. L. *J. Org. Chem.* **2013**, *78*, 1098.

(205) Coldham, I.; Copley, R. C. B.; Haxell, T. F. N.; Howard, S. *Org. Lett.* **2001**, *3*, 3799.

(206) Gross, K. M. B.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.

(207) Loewe, M. F.; Boes, M.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3295.

(208) Smith, J.; O'Brien, P. *unpublished results* **2013**.

(209) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(210) Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391.

(211) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, *0*, S1.

(212) Ward, J.-P.; O'Brien, P. *unpublished results* **2013**.

(213) Karin, B.; Roland, F.; Oliver, M.; Dieter, H. *Eur. J. Org. Chem.*, **1998**, *1998*, 2397.

(214) Hajipour, A. R.; Falahati, A. R.; Ruoho, A. E. *Tetrahedron Lett.* **2006**, *47*, 2717.

(215) Burchat, A. F.; Chong, J. M.; Nielson, N. *Organomet. Chem.* **1997**, 281.

(216) Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2006**, *8*, 5951.

(217) Webster, M. P.; Partridge, B. M.; Aggarwal, V. *Organic Syntheses* **2011**, *88*.

(218) Banfield, S. C.; Omori, A. T.; Leisch, H.; Hudlicky, T. *J. Org. Chem.* **2007**, *72*, 4989.

(219) Hans, D.; Vien Van, T.; My-Ngoc, U.-T. *Magn. Res. Chem.* **1991**, *29*, 897.

(220) Mikolajczyk, M.; Drabowicz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2510.

(221) Seebach, D.; Wykypiel, W.; Lohmann, J.-J. *Helv. Chim. Acta* **1981**, *64*, 1337.

(222) Wilson, W. *Can. J. Chem.* **1970**, *48*, 983.

(223) Rao, Y.; Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12924.

(224) Harmata, M.; Zheng, P.; Huang, C.; Gomes, M. G.; Ying, W.; Ranyanil, K.-O.; Balan, G.; Calkins, N. L. *J. Org. Chem.* **2006**, *72*, 683.

(225) Nishiwaki, T.; Azechi, K.; Fujiyama, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1867.

(226) Faler, C. A.; Joullié, M. M. *Tetrahedron Lett.* **2006**, *47*, 7229.

(227) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507.

(228) Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537.

(229) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574.

(230) Chang, D.; Feiten, H.-J. r.; Engesser, K.-H.; van Beilen, J. B.; Witholt, B.; Li, Z. *Org. Lett.* **2002**, *4*, 1859.

(231) Leleu, S. p.; PapamicaÃ«l, C.; Marsais, F.; Dupas, G.; Levacher, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3919.

(232) Chu, W.; Zhang, J.; Zeng, C.; Rothfuss, J.; Tu, Z.; Chu, Y.; Reichert, D. E.; Welch, M. J.; Mach, R. H. *J. Med. Chem.* **2005**, *48*, 7637.

(233) Hagiwara, D.; Miyake, H.; Igari, N.; Karino, M.; Maeda, Y.; Fujii, T.; Matsuo, M. *J. Med. Chem.* **1994**, *37*, 2090.

(234) Balboni, G.; Marastoni, M.; Merighi, S.; Andrea Borea, P.; Tomatis, R. *European Journal of Medicinal Chemistry* **2000**, *35*, 979.

(235) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621.

(236) Ku, Y.-Y.; Pu, Y.-M.; Grieme, T.; Sharma, P.; Bhatia, A. V.; Cowart, M. *Tetrahedron* **2006**, *62*, 4584.

(237) Smith, D. C.; Lee, S. W.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 348.