Synthesis of Phosphine-Alkene Ligands and 3-Hydroxy Piperidines Using Organolithium Chemistry

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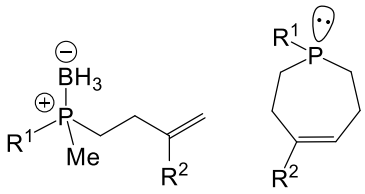
Abstract

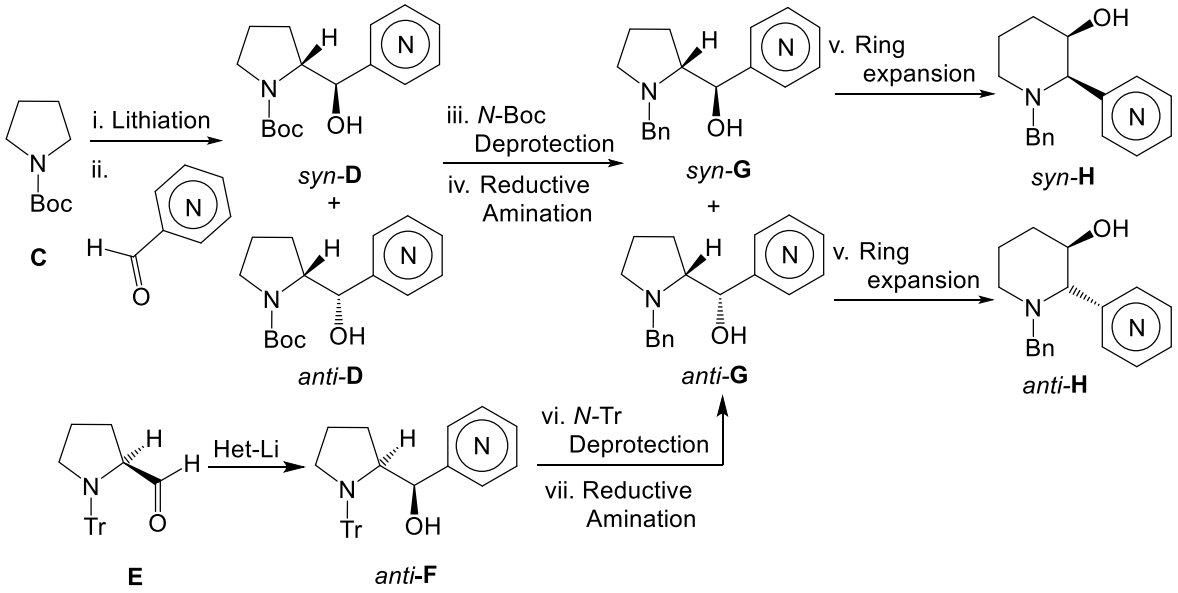
This thesis describes synthetic routes to *P*-stereogenic phosphine-alkene ligands and 3-hydroxy piperidines containing heteroaromatics *via* lithiation-trapping of phosphine boranes or *N*-Boc pyrrolidine. Both topics are introduced in chapter 1.

Chapter 2 presents a route to a new type of *P*-stereogenic phosphine-alkene ligand **B** prepared by racemic lithiation of *t*-butyldimethylphosphine borane or dimethylphenylphosphine borane using *s*-BuLi. Different allylic halides were used to trap the lithiated intermediate to give chiral alkene-phosphine boranes **A**.



R^1 = Ph, *t*-Bu
R^2 = H, Me, Br

In chapter 3, 3-hydroxy piperidines were synthesised from the ring expansion of hydroxy pyrrolidines. Two novel, short and simple synthetic routes were developed (as shown below). Lithiation-trapping reaction of *N*-Boc pyrrolidine **C** using pyridine carboxaldehydes gave *N*-Boc pyrrolidine alcohols *syn*-**D** and *anti*-**D**. On the other hand, an alternative approach to obtain 3-hydroxy piperidines *anti*-**H** starting from *N*-trityl prolinal **E** derived from (*S*)-proline was investigated. Addition of lithiated heteroaromatics, generated from a Br/Li exchange reaction, to *N*-trityl prolinal **E** diastereoselectively gave *N*-trityl alcohols *anti*-**F**. The Boc or trityl deprotection and reductive amination then gave *N*-benzyl pyrrolidines *syn*-**G** and *anti*-**G**. Finally, the ring expansion *via* an aziridinium ion of alcohols *syn*-**G** and *anti*-**G** gave 3-hydroxy piperidines *syn*-**H** and *anti*-**H**. The stereochemistry of 3-hydroxy piperidines *syn*-**H** and *anti*-**H** was proven using *J*-values in the ^{1}H NMR spectra.



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Finally, I would like to thank my beloved mum and dad, who are always with me through the highs and lows, give me unconditional love and have encouraged me throughout my stay in the U.K.

Author's Declaration

This research project in this thesis is my own and was carried out at the University of York between April 2011 and March 2016. This work is, to the best of my knowledge, original except where due reference has been made to other authors and/or co-workers.

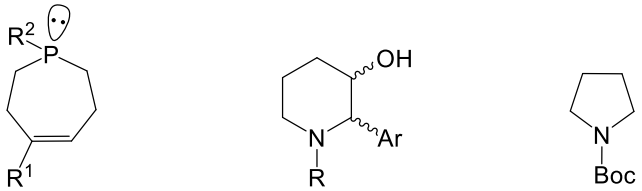
Part of this work has been reproduced in a published paper:

Lüthy, M.; Wheldon, M. C.; Haji-Cheteh, C.; Atobe, M.; Bond, P. S.; O'Brien, P.; Hubbard, R. E.; Fairlamb, I. J. S.; Lead-oriented synthesis: Investigation of organolithium-mediated routes to 3-D scaffolds and 3-D shape analysis of a virtual lead-like library, *Bioorg. Med. Chem.* **2015**, *23*, 2680-2694.

Chapter 1 Introduction

This thesis contains research into the synthesis of two different types of heterocyclic structures. The first topic involved the design and synthesis of a new class of *P*-stereogenic phosphine-alkene ligands shown by phosphines **1** (Figure 1.1). The second topic concerned the development of new methodology for the synthesis of 2-aryl-3-hydroxy piperidines **2** (Figure 1.1). Although both target molecules **1** and **2** have very different structures, one of the key synthetic steps to each of them involved the use of strong organolithium bases such as *n*-BuLi and *s*-BuLi to carry out a lithiation or deprotonation step. In the phosphine project (Chapter 2), lithiation of phosphine boranes was used. In contrast, in the piperidines project (Chapter 3), *N*-Boc pyrrolidine **3** was lithiated, trapped and eventually ring-expanded.

Figure 1.1



1 **2** **3**

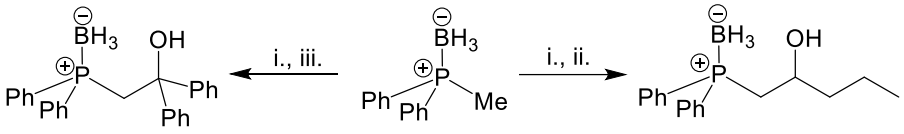
1.1 Introduction to Organolithium Reagents

Over the past decades, organolithium reagents have continued to play an important role in modern organic synthesis. Due to their powerful basicity, most deprotonation chemistry makes use of organolithium reagents.[1] A number of total syntheses of natural products and drug compounds make use of the wide range of organolitium reagents such as MeLi, *n*-BuLi, *s*-BuLi, *t*-BuLi and PhLi as strong bases. In the work described in this thesis, the commercially available reagents *n*-BuLi and *s*-BuLi were used to deprotonate the starting phosphine borane or *N*-Boc pyrrolidine to form the respective lithiated intermediates. Compared to *s*-BuLi, *n*-BuLi is less basic and less reactive. It is well known that alkyllithium reagents are likely to aggregate with the solvent. Therefore, selection of the solvent for a reaction can make a great impact on the reactivity of organolithium reagents. According to decomposition rates of organolithiums in solution, a 90% solution of *n*-BuLi in hexane and a 10-12% solution of *s*-BuLi in *i*-pentane at 35 ˚C, 0.11% of *n*-BuLi and 0.32% of *s*-BuLi can be lost in a day.[2] Hence, most reactions are carried out at low temperatures (*e.g.* −78 ˚C) in order to avoid the decomposition of the organolithium reagents.

1.2 Overview of Lithiation-Trapping of Phosphine Boranes

In 1985, Imamoto and co-workers examined the reactivity of phosphine boranes by investigation of the deprotonation of various phosphine boranes using *s*-BuLi in THF at –78 ˚C[3] according to a procedure which was initially carried out and studied in Schmidbaur's group.[4] For instance, diphenylphosphine borane **4** was deprotonated and trapped with butanal to give phosphine borane **5** in 92% yield (Scheme 1.1). Similarly, trapping of the lithiated intrermediate with benzophenone gave phosphine borane **6** in 94% yield (Scheme 1.1).

Scheme 1.1

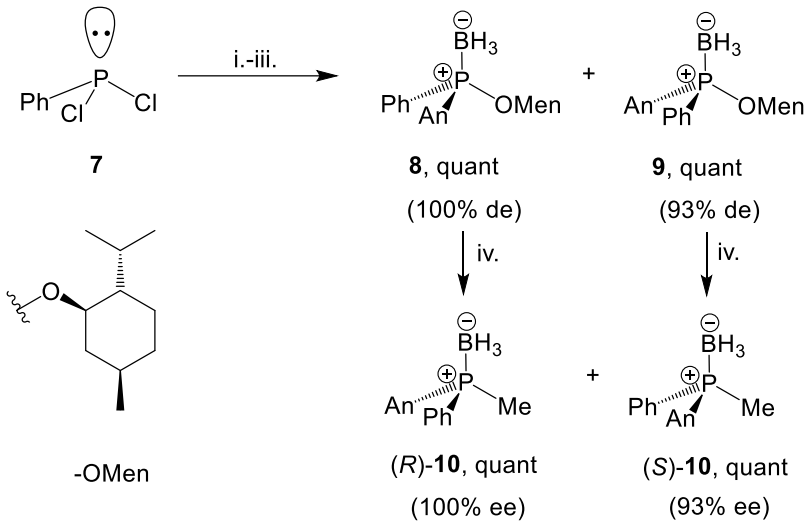


6, 94% **4** **5**, 92%

Reagents and conditions: i. *s*-BuLi, –78 ˚C, THF; ii. *n*-C_3H_7CHO; iii. benzophenone.

Since then, the lithiation-trapping of phosphine boranes has been widely studied mostly for the synthesis of phosphine ligands. To obtain enantiomerically enriched phosphine boranes, lithiation of optically pure starting materials was the first approach investigated to produce various *P*-stereogenic phosphine ligand precursors. As an example, Imamoto and co-workers explored the preparation of phosphine boranes starting from the lithiation of optically active phosphine boranes (Scheme 1.2).[5] In the research, dichlorophenylphosphine **7** was treated with *o*-anisylmagnesium bromide and then (–)-menthol in the presence of pyridine. Finally, the free phosphine was protected with BH_3•THF to obtain optically active diastereomers which were separated by flash chromatography on silica gel to give each diastereomer **8** and **9**. Finally, nucleophilic substitution of the menthoxy group using MeLi in each of **8** and **9** gave the desired optically active phosphine boranes (*R*)-**10** and (*S*)-**10** respectively in quantitative yield.

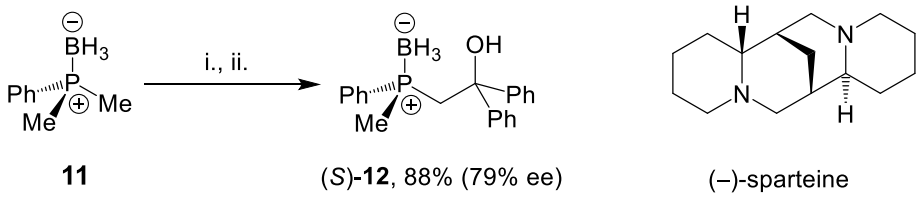
Scheme 1.2



Reagents and conditions: i. *o*-Anisylmagnesium bromide; ii. (–)-menthol, pyridine; iii. BH_3•THF; iv. MeLi, benzene. An = *o*-$MeOC_6H_4$

Subsequently, lithiation of phosphine boranes using *n*-BuLi or *s*-BuLi in the presence of chiral diamine ligands was an alternative route that was investigated for the synthesis of *P*-stereogenic phosphine boranes. Thus, Evans and co-workers explored the enantioselective deprotonation of dimethylphosphine boranes using *s*-BuLi in the presence of (–)-sparteine.[6] For example, asymmetric deprotonation of phenyl dimethylphosphine borane **11** was carried out using *s*-BuLi and (–)-sparteine in Et_2O at –78 ˚C. The lithiated intermediate was then trapped with benzophenone in THF to give phosphine borane adduct (*S*)-**12** in 88% yield and 79% ee (Scheme 1.3).

Scheme 1.3

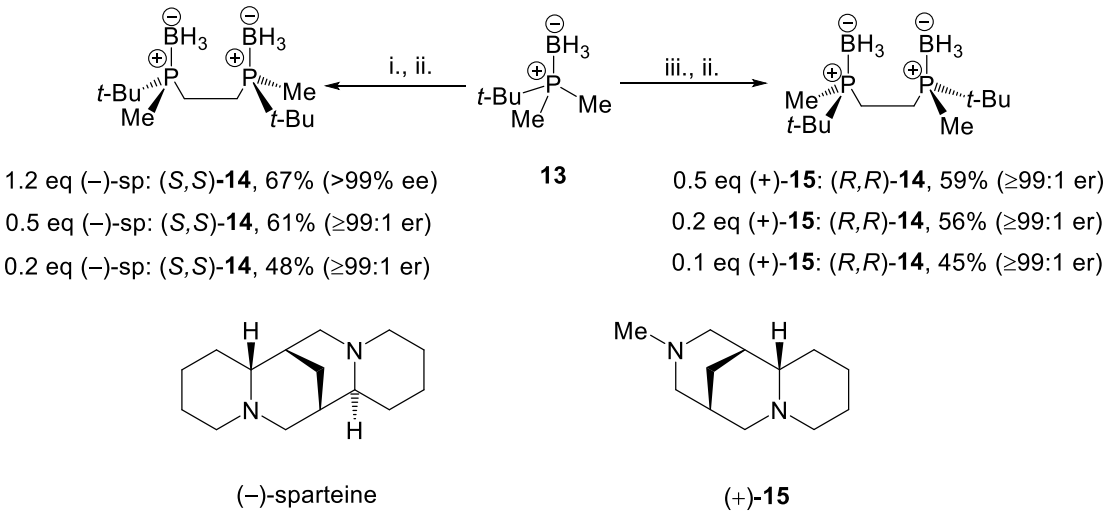


Reagents and conditions: i. *s*-BuLi, (–)-sparteine, –78 ˚C, Et_2O, ii. benzophenone, –20 ˚C, THF.

Next, Imamoto exploited Evans' procedure in the synthesis of *P*-stereogenic bisphosphine ligands.[7,8] To begin with, *t*-butyldimethyl phosphine borane **13** was asymmetrically deprotonated using *s*-BuLi in the presence of (–)-sparteine. Then, dimerisation of the lithiated intermediate using copper(II) chloride gave the desired bisphosphine borane

(*S*,*S*)-**14** in 67% yield and >99% ee (Scheme 1.4).[9] Similarly, O'Brien and co-workers reported the catalytic asymmetric synthesis of (*S*,*S*)-**14** *via* the same approach using 0.2 and 0.5 equivalents of (–)-sparteine.[10] On the other hand, the opposite enantiomer (*R*,*R*)-**14** was successfully prepared using the (+)-sparteine surrogate, (+)-**15** which was developed in the O'Brien group.[11–13] Phosphine borane **13** was catalytically and asymmetrically lithiated using *s*-BuLi and 0.1-0.5 equivalents of (+)-**15** to give enantiomerically enriched (*R*,*R*)-**14** in moderate yields (45-59%).

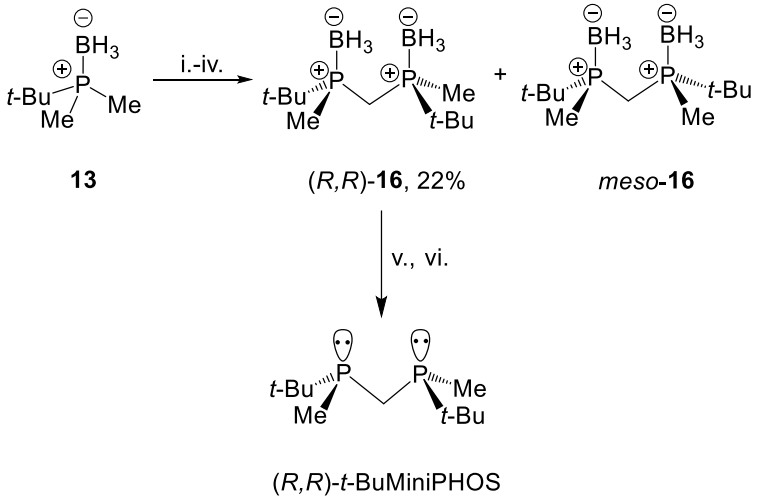
Scheme 1.4



Reagents and conditions: i. *s*-BuLi, (–)-sparteine, –78 ˚C, Et_2O; ii. $CuCl_2$, –78 ˚C to rt; iii. *s*-BuLi, (+)-**15**, –78 ˚C, Et_2O.

In 1999, Imamoto applied Evans' procedure to prepare methylene-bridged *P*-stereogenic diphosphines, known as MiniPHOS ligands.[14,15] These ligands are characterised by having a small methyl group and a sterically bulky alkyl group attached to the phosphorus atom. A synthesis of (*R*,*R*)-*t*-BuMiniPHOS is shown in Scheme 1.5. The synthetic route started with phosphine borane **13** which was prepared from a substitution of PCl_3 with *t*-butyl magnesium bromide and then methyl magnesium bromide. Next, *s*-BuLi and (–)-sparteine were used to deprotonate phosphine borane **13**. This was followed by reaction with *t*-$BuPCl_2$, methyl magnesium bromide and BH_3-THF to obtain optically active (*R*,*R*)-**16** in a 22% yield after recrystallisation, and some of *meso*-**16** (Scheme 1.5). After borane removal by treatment with trifluoromethanesulfonic acid and aqueous KOH, (*R*,*R*)-*t*-BuMiniPHOS was obtained (Scheme 1.5).

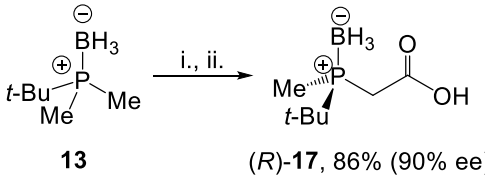
Scheme 1.5



Reagents and conditions: i. *s*-BuLi, (–)-sparteine, −78 ˚C, 3 h, Et_2O; ii. *t*-$BuPCl_2$, −78 ˚C to rt, Et_2O; iii. MeMgBr, 0 ˚C; iv. BH_3-THF, 0 ˚C; v. TfOH, 0 ˚C, 30 min; vi. KOH_{aq}, 50 ˚C, 2 h.

Based on Evans' work, Kann and co-workers investigated mixed *P*-stereogenic phosphine-heteroatom ligands which were prepared by asymmetric deprotonation in the presence of the (+)-sparteine surrogate, (+)-**15**.[16] To start the synthesis, phosphine borane **13** was deprotonated in an asymmetric fashion using *s*-BuLi and (+)-**15** and the lithiated intermediate was then reacted with CO_2 to generate *α*-carboxyphosphine borane (*R*)-**17** in 86% yield and 90% ee (Scheme 1.6).

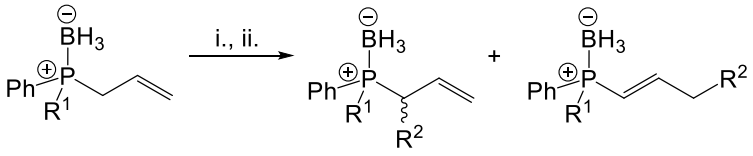
Scheme 1.6



Reagents and conditions: i. *s*-BuLi, (+)-**15**-, −78 ˚C, 1 h, Et_2O; ii. CO_2, −78 ˚C to rt, 1 h.

In 2011, Pietrusiewicz and co-workers investigated the lithiation-trapping of allylic phosphine boranes.[17] In this research, various sp^3-electrophiles were used. The results showed that small electrophiles preferentially trapped the lithiated intermediate at the α-carbon (Scheme 1.7, Table 1.1, entries 1-6). On the other hand, bulky electrophiles mainly reacted at the γ-position (entries 7-10). This work showed that phosphine alkene boranes can be synthesised by lithiation using *n*-BuLi in preference to using *s*-BuLi. However, in the case where the R^1 was *t*-butyl group, the authors did not comment on the diastereoselectivity.

Scheme 1.7



18, R^1 = *t*-Bu
19, R^1 = Ph

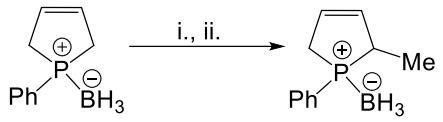
Reagents and conditions: i. *n*-BuLi (1.2 eq.), –78 ˚C, 30 min, THF; ii. alkyl halide (2.0 eq.), –78 ˚C to rt, 2.5 h,

Table 1.1

Entry	**SM**	**R^2X**	**α-Alkylation, Yield (%)**	**γ-Alkylation, Yield (%)**
1	**18**	MeI	68	15
2	**19**	MeI	88	-
3	**18**	BnCl	29	21
4	**19**	BnCl	76	13
5	**18**	AllylCl	13	62
6	**19**	AllylCl	42	42
7	**18**	*c*-HexBr	-	47
8	**19**	*c*-HexBr	22	47
9	**18**	Me_3SiCl	-	91
10	**18**	$BrCH_2CO_2Et$	-	20

Furthermore, lithiation of cyclic phosphine alkene borane **20** was investigated in the same group. Thus, phosphine borane **20** was deprotonated using *n*-BuLi and the lithiated intermediate was then trapped with methyl iodide. As a result, only α-alkylation product **21** was formed in 48% yield (Scheme 1.8), although no information of the diastereoselectivity was provided.

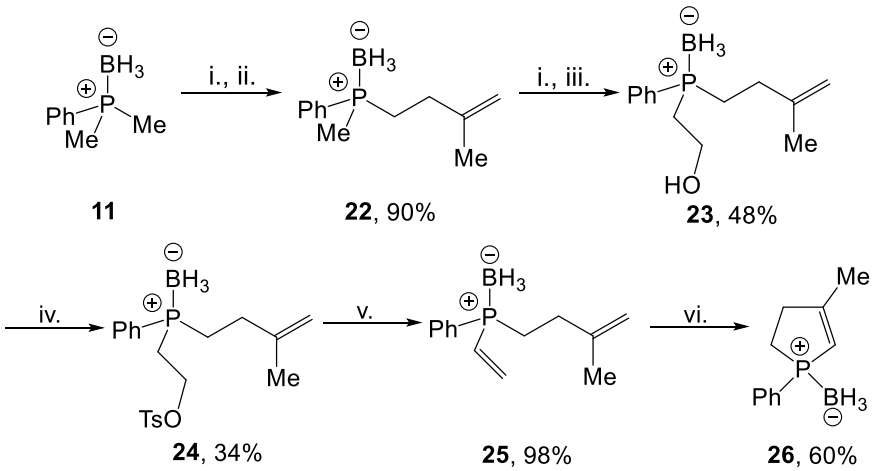
Scheme 1.8



Reagents and conditions: i. *n*-BuLi (1.2 eq.), −78 ˚C, 30 min, THF; ii. MeI (2.0 eq.), −78 ˚C to rt, 2.5 h,

Recently, O'Brien and co-workers presented a synthetic route to phosphine alkene boranes starting from phenyl dimethyl phosphine **11**.[18] The synthesis began with the lithiation of phosphine borane **11** using *s*-BuLi and trapping with methallyl bromide to give homoallylic phosphine borane **22** in 90% yield (Scheme 1.9). Then, the phosphine borane **22** was regioselectively lithiated at the methyl group (as it is less sterically hindered) to give the lithiated intermediate which was subsequently trapped with paraformaldehyde to give alcohol **23** in 48% yield. Next, the hydroxy group was eliminated *via* tosylation to provide dialkene phosphine borane **25** in 98% yield. Finally, ring-closing metathesis using Hoveyda-Grubbs II catalyst gave phosphine alkene **26** in 60% yield.

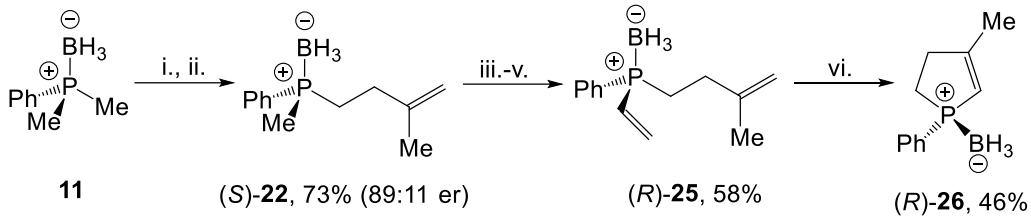
Scheme 1.9



Reagents and conditions: i. *s*-BuLi, −78 ˚C, 1 h, THF; ii. methallyl bromide; iii. paraformaldehyde, THF; iv. *p*-toluenesulfonyl chloride, pyridine, CH_2Cl_2, rt, 16 h; v. KO*t*-Bu, Et_2O, rt, 2 h; vi. Hoveyda-Grubbs II catalyst, CH_2Cl_2.

Regarding an asymmetric approach, O'Brien used the enantioselective lithiation of phenyl phosphine borane **11** using *s*-BuLi and (–)-sparteine under Evans'conditions and trapped with methallyl bromide to give allylic phosphine (*S*)-**22** in 73% yield and 89:11 er (Scheme 1.10). Then, the same sequence as the previous preparation (Scheme 1.10) was carried out to give the desired phosphine alkene borane (*R*)-**26** in 46% yield.

Scheme 1.10



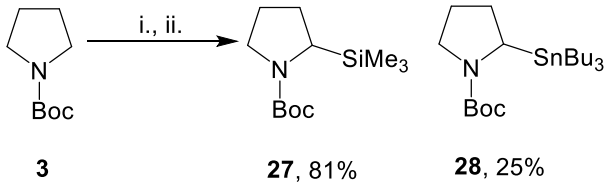
Reagents and conditions: i. *s*-BuLi, (–)-sparteine, −78 ˚C, 3 h, Et_2O; ii. methallyl bromide; iii. paraformaldehyde, THF; iv. *p*-TsCl, pyridine, CH_2Cl_2; v. KO*t*-Bu, Et_2O; vi. 10 mol% Hoveyda-Grubbs II catalyst, CH_2Cl_2.

In summary, lithiation-trapping, including asymmetric deprotonation, is a useful strategy for the synthesis of a wide range of substituted phosphine boranes.

1.3 Overview of Lithiation-Trapping of *N*-Boc Pyrrolidine

In 1989, Beak and Lee reported the first examples of the racemic lithiation-trapping of *N*-Boc pyrrolidine **3**.[19] In this work, lithiation was carried out using *s*-BuLi in the presence of a diamine ligand, TMEDA, at −78 ˚C in Et_2O. After trapping with electrophiles such as Me_3SiCl and Bu_3SnCl, the desired racemic products **27** and **28** were isolated in 81% and 25% yield respectively (Scheme 1.11).

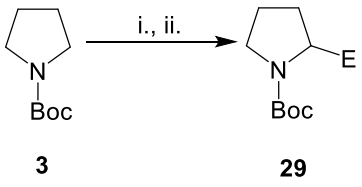
Scheme 1.11



Reagents and conditions: i. *s*-BuLi, TMEDA, Et_2O, −78 ˚C, 3.5 h; ii. Me_3SiCl or Bu_3SnCl, −78 ˚C to rt.

Since then, these reaction conditions have been widely used to give α-substituted products from *N*-Boc pyrrolidine **3**.[19–22] In the O'Brien group, racemic lithiation of *N*-Boc pyrrolidine **3** without the use of the diamine was investigated.[23] Interestingly, the lithiation could be carried out at a higher temperature than most lithiation reactions in this area, −30 ˚C, for only 5 minutes as long *s*-BuLi was used in THF solvent (Scheme 1.12). Electrophilic trapping of the lithiated intermediate gave the desired products **29** in good yields (49-77%) (Scheme 1.12, Table 1.2, entries 1-7). Clearly, THF is able to activate the *s*-BuLi for lithiation in a similar way to the diamine TMEDA.

Scheme 1.12



Reagents and conditions: i. *s*-BuLi, THF, −30 ˚C, 5 min; ii. electrophiles.

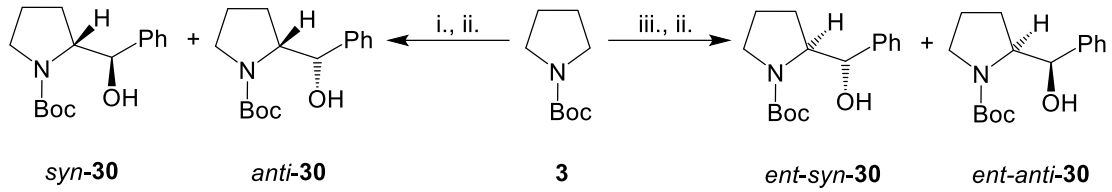
Table 1.2

Entry	Electrophile	Yield (%)
1	Me_2SO_4	70
2	allylBr[a]	65
3	CO_2	49
4	MeCOCl	51
5	Me_3SiCl	71
6	DMF	67
7	$PhCONMe_2$	77

a Trapping with allylbromide *via* Li/Cu exchange

To study the asymmetric deprotonation of *N*-Boc pyrrolidine **3**, chiral diamine ligands were used in an attempt to give enantioenriched products as first reported by Beak in 1991.[24] For example, O'Brien and co-workers investigated the asymmetric deprotonation of *N*-Boc pyrrolidine **3** in the presence of chiral diamine ligands such as (–)-sparteine and the (+)-sparteine surrogate, (+)-**15** (Scheme 1.13).[25] This investigation showed that the asymmetric lithiation using chiral diamine ligands in different solvents gave different enantioselectivity. Thus, lithiation of *N*-Boc pyrrolidine **3** using *s*-BuLi and (–)-sparteine in THF or 2-Me-THF gave the desired products *syn*-**30** and *anti*-**30** with no significant enantioselectivity (Scheme 1.13, Table 1.3, entries 2 and 4), while using the same ligand in Et_2O or TBME gave enantioenriched products *syn*-**30** and *anti*-**30** (entries 1 and 3). These results can be explained by the fact that THF must complex to the *s*-BuLi in preference to the (–)-sparteine ligand. To obtain the enantiomeric products, *ent*-*syn*-**30** and *ent*-*anti*-**30**, (+)-sparteine surrogate, (+)-**15**, was used. Unlike (–)-sparteine, asymmetric lithiation using (+)-**15** and trapping with benzaldehyde gave the desired products *ent*-*syn*-**30** and *ent*-*anti*-**30** with excellent enantioselectivity (93:7-95:5 er) in all solvents. Thus, it was concluded that the (+)-sparteine surrogate, (+)-**15**, did not coordinate to the *s*-BuLi even in THF.

Scheme 1.13



syn-**30** *anti*-**30** **3** *ent-syn*-**30** *ent-anti*-**30**

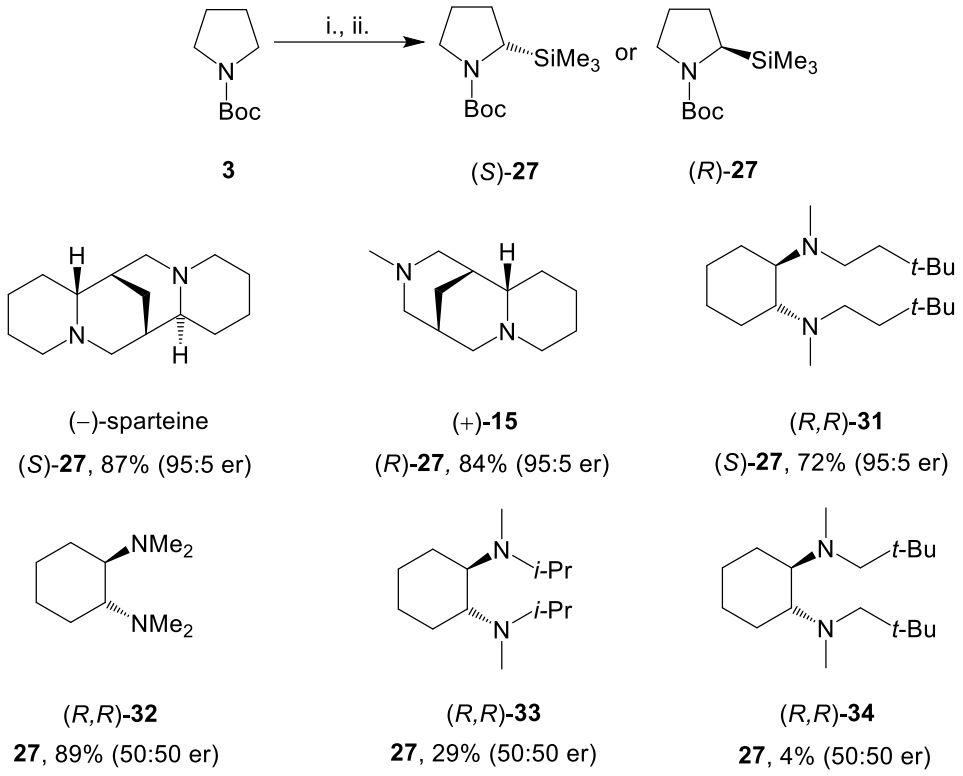
Reagents and conditions: i. *s*-BuLi, (–)-sparteine, –78 ˚C, 30 min, solvent; ii. PhCHO; iii. *s*-BuLi, (+)-**15**, –78 ˚C, 30 min, solvent.

Table 1.3

Entry	**Solvent**	*syn*-**30**, **Yield (%), er**	*anti*-**30**, **Yield (%), er**	*ent-syn*-**30**, **Yield (%), er**	*ent-anti*-**30**, **Yield (%), er**
1	Et_2O	63, 97:3	23, 97:3	58, 95:5	23, 94:6
2	THF	50, 51:49	14, 51:49	45, 95:5	20, 95:5
3	TBME	51, 97:3	24, 98:2	56, 94:6	31, 93:7
4	2-Me-THF	50, 59:41	29, 55:45	53, 93:7	22, 93:7

In addition, asymmetric lithiation of *N*-Boc pyrrolidine **3** was carried out in the presence of various chiral diamine ligands to investigate the enantioselectivity.[26,27] Thus, *N*-Boc pyrrolidine **3** was enantioselectively deprotonated using *s*-BuLi with chiral ligands and trapping with Me_3SiCl (Scheme 1.14). As a result, (–)-sparteine and the (+)-sparteine surrogate, (+)-**15**, effectively gave enantioenriched *N*-Boc pyrrolidine (*S*)-**27** and (*R*)-**27** (95:5 er) in 87% and 84% yield respectively. With Alexakis ligands,[28–32] (*R*,*R*)-**31** gave enantioenriched (*S*)-**27** in excellent yield (72 %) and 95:5 er but (*R*,*R*)-**32**, (*R*,*R*)-**33** and (*R*,*R*)-**34** gave no enantioselectivity (Scheme 1.14).

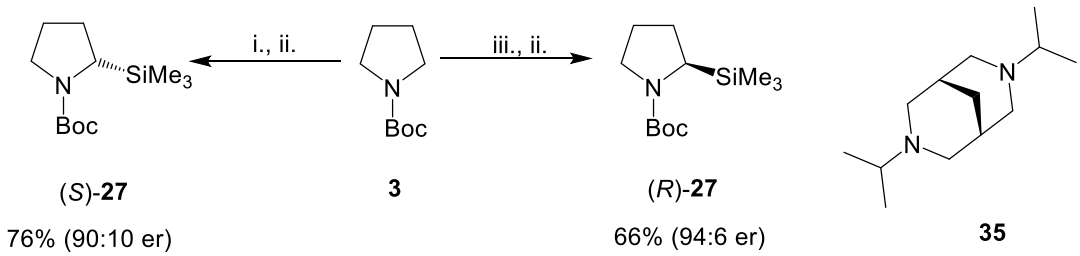
Scheme 1.14



Reagents and conditions: i. *s*-BuLi, chiral diamine ligand, −78 ˚C, 3 h, Et_2O; ii. Me_3SiCl, −78 ˚C to rt, 16 h.

Finally, the O'Brien group has studied the catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **3**.[33] Thus, with *s*-BuLi and 0.2 equivalents of (−)-sparteine together with a stoichiometric amount of achiral diamine **35**, the enantioenriched product (*S*)-**27** was obtained in excellent yield (76%) and 90:10 er (Scheme 1.15). In addition, use of 0.2 equivalents of (+)-sparteine surrogate, (+)-**15**, gave (*R*)-**27** in 66% yield and 94:6 er.

Scheme 1.15



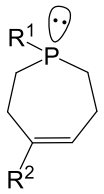
Reagents and conditions: i. *s*-BuLi, (−)-sparteine (0.2 eq.), **35** (1.2 eq.), −78 ˚C, Et_2O; ii. Me_3SiCl; iii. *s*-BuLi, (+)-**15** (0.2 eq.), −78 ˚C, Et_2O.

In summary, the lithiation-trapping of *N*-Boc pyrrolidine **3** is widely used, including the use in the large-scale synthesis of the drug Telaprevir, hepatitis C virus (HCV) protease inhibitior.[34] In particular, the asymmetric version is also commonly used, for example in Merck's synthesis of a glucokinase activator.[35]

Chapter 2 Investigation of the Synthesis of *P*-Stereogenic Phosphine-Alkene Ligands

In this chapter, we describe some of our preliminary studies into the synthesis of novel *P*-stereogenic phosphine-alkene ligands **1** (Figure 2.1). Our plan was to build a 7-membered ring by ring-closing metathesis of a suitable diene precursor. First, the synthesis of dienes *via* two sequential lithiation-trapping reactions of a dimetylphosphine borane is decribed. The synthetic route needed to be flexible enough to allow different groups on the phosphorus and the alkene to be prepared. Second, the asymmetric synthesis of phosphine-alkene ligands are also studied through this synthetic method. The literature background on chiral phosphine-alkenes and their synthesis are summarised in Sections 2.1 and 2.2. Then, after the project outline in Section 2.3, the investigation of our proposed route is discussed in Sections 2.4-2.9.

Figure 2.1

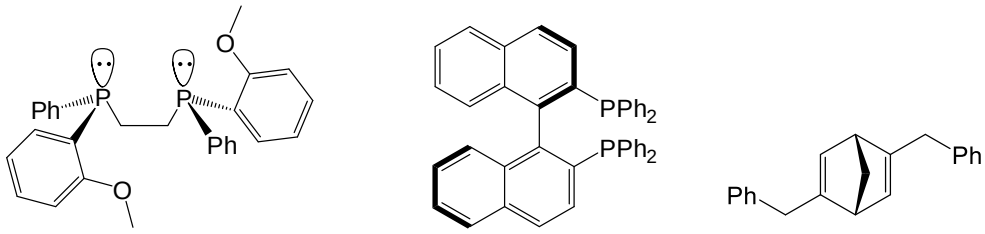


1

2.1 Introduction to Chiral Phosphine-Alkene Ligands

Over the past few decades, numerous chiral phosphine ligands have been designed and synthesised. For example, a successful synthesis of the bisphosphine DIPAMP was described by Knowles[36,37] in 1977 and exploration of BINAP was first reported by Noyori[38] in 1980 (Figure 2.2). These phosphine ligands motivated researchers to design and develop various chiral phosphine ligands which could have improved reactivity in catalytic reactions. To synthesise the active ligands with high enantiomeric ratio, different synthetic routes have been used and investigated. Meanwhile, alkenes are interesting compounds that can also be used as ligands. Alkene ligands can use π-electrons to coordinate weakly to transition metals such as Pd, Rh and Ir. For instance, chiral diene ligand **36** (Figure 2.2), reported by Hayashi in 2003, was coordinated with Rh and used as a catalyst in the 1,4-conjugate addition reaction of phenylboronic acid to cyclohexenone.[39]

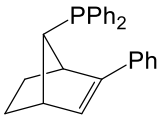
Figure 2.2



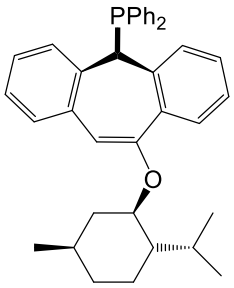
(*R*,*R*)-DiPAMP (*R*)-BINAP **36**

Although chiral diene ligands are effective chelating compounds in transition-metal catalysed asymmetric processes, there are some weak points in the use of these dienes. For example, the coordination ability of diene ligands to transition metals is normally weaker than that of phosphorus-based ligands.[40] To maintain the advantages of chiral dienes but solving their weak coordination problem, Hayashi designed the first chiral phosphine-alkene ligands in 2005 which have the high coordination ability of phosphorus and an alkene in a good chiral environment.[41] Since then, many other chiral phosphine-alkene ligands have been prepared. The known chiral phosphine-alkene ligands are shown in Figure 2.3.

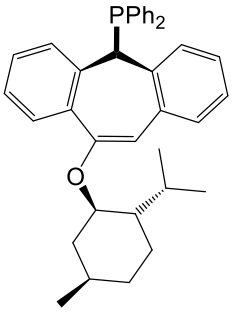
Figure 2.3



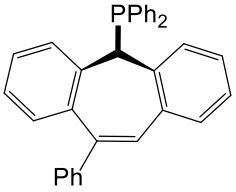
(+)-**37**



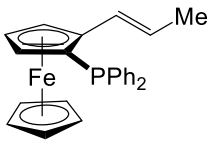
(*R*,*R*)-**38**



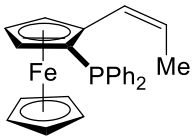
(*S*,*R*)-**38**



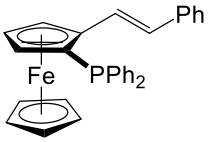
(*S*)-**39**



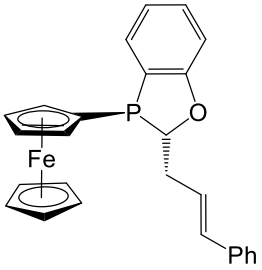
(*E*)-**40**



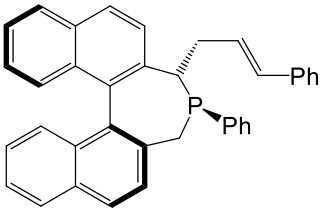
(*Z*)-**40**



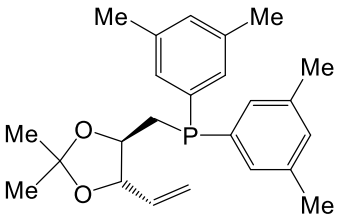
(*E*)-**41**



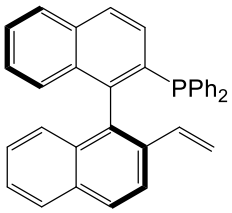
42



(*S*,S_a,S_p)-**43**



44



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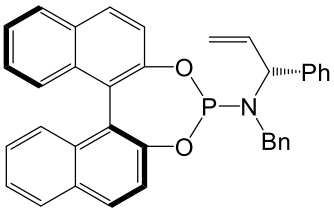
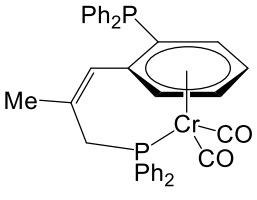
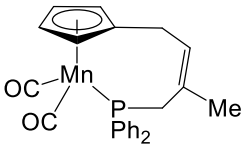


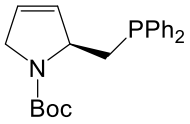
46



(*R*)-**47**



48

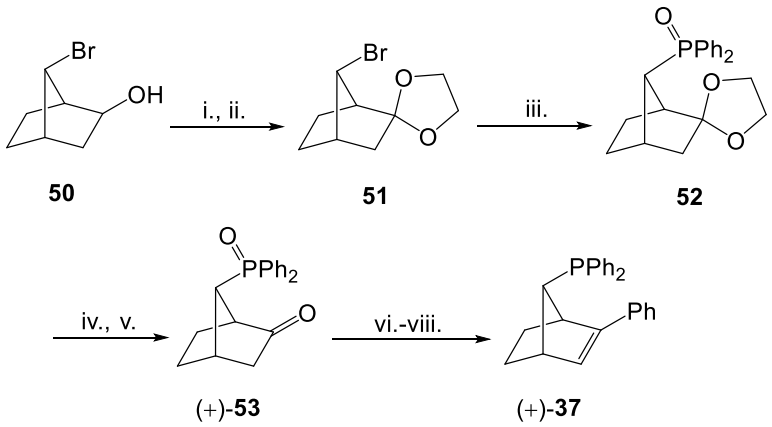


(*S*)-**49**

2.2 Synthesis of Chiral Phosphine-Alkene Ligands

The synthesis of Hayashi's ligand (+)-**37** is shown in Scheme 2.1. To start with, a known bromobicyclic compound **50** was converted into a bromoketone *via* Swern oxidation. This was followed by ketalisation with ethylene glycol to give ketal **51**. Ketal **51** then underwent Br/Li exchange using *t*-BuLi. The organolithium was trapped with Ph_2PCl and oxidised to give phosphine oxide **52**. Chiral stationary phase HPLC was used to resolve phosphine oxide **52** to afford each enantiomer. The resolved ketal was cleaved to give enantiopure ketone (+)-**53** which was then converted into an enol triflate. The enol triflate was reacted in a Grignard cross-coupling and reduction with silane then gave phosphine-alkene ligand (+)-**37** in 36% overall yield over the eight steps (Scheme 2.1).[41] Although this reaction was a good starting point for chiral phosphine-alkene ligand synthesis, the synthetic route was long and gave a moderate overall yield.

Scheme 2.1

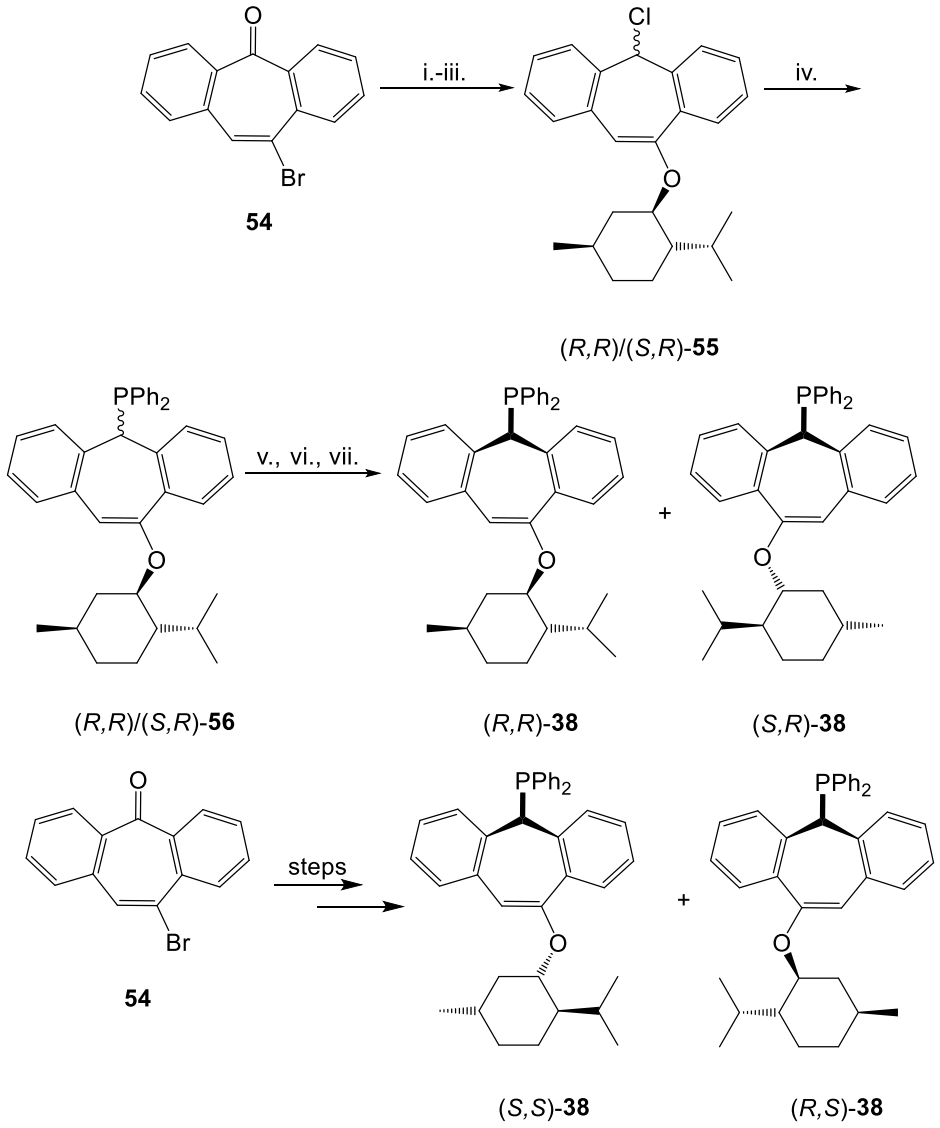


Reagents and conditions: i. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ii. cat. *p*-TsOH, ethylene glycol, benzene; iii. a) *t*-BuLi, THF, then Ph_2PCl; b) $H_2O_{2(aq)}$, acetone; iv. Chiral HPLC (OD-H column); v. $HCl_{(aq)}$ (1 N), THF; vi. LDA, THF, then $PyNTf_2$; vii. cat. $[PdCl_2(dppf)]$, PhMgBr, Et_2O; viii. $HSiCl_3$, Et_3N, benzene.

Around the same time as Hayashi's work, Grützmacher prepared a new type of chiral phosphine-alkene ligand, 5-phosphanyl-5*H*-dibenzo[*a*,*d*]cycloheptene (tropp), with a rigid and concave shape.[42–44] The chiral tropp ligand contained an unsymmetrically substituted alkene unit which was prepared from 10-bromodibenzo[*a*,*d*]cycloheptan-5-one **54**. Potassium (*R*)-mentholate was added to transform the bromotricycle into 10-[(1*R*)-menthoxy]dibenzo [*a*,*d*]cyclohepten-5-one. The ketone was converted into a mixture of (5*R*/5*S*)-diastereomers of cyclohepten-5-ol by the reaction with $NaBH_4$. The cycloheptenol

was then transformed into the chloro compounds (*R*,*R*)-**55** and (*S*,*R*)-**55** without further purification. To avoid the formation of a phosphine oxide, the diastereomers were protected as boranes. These diastereomeric borane adducts were then separated by column chromatography. The phosphine boranes were deprotected with morpholine and recrystallized from acetonitrile to give colourless crystals of enantiomerically pure phosphine-alkenes (*R*,*R*)-**38** and (*S*,*R*)-**38** (Scheme 2.2). The same sequence of transformations with potassium (*S*)-mentholate also provided the phosphine-alkenes (*S*,*S*)-**38** and (*R*,*S*)-**38**. However, this synthetic route has many steps and free phosphines **38** and **38** had to be carefully purified by chromatography under an argon atmosphere.

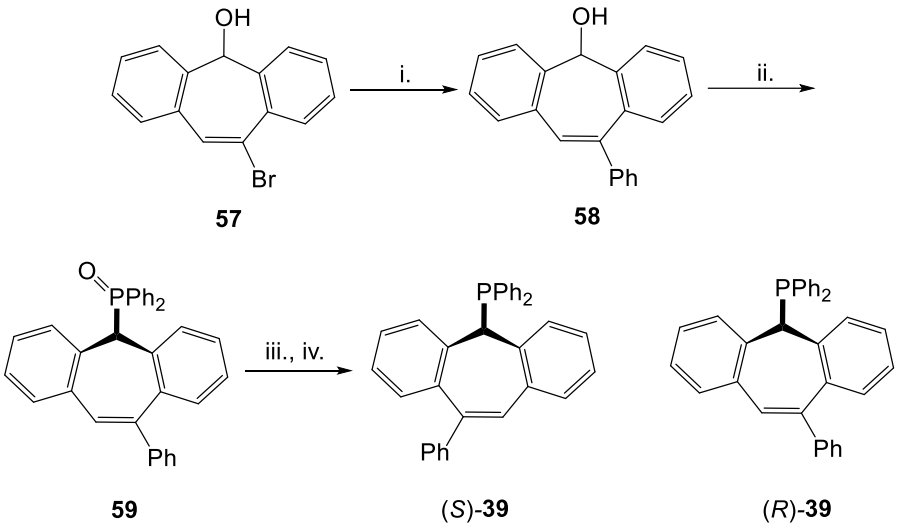
Scheme 2.2



Reagents and conditions: i. potassium (*R*)-mentholate, dioxane, reflux, 3 h; ii. $NaBH_4$, NaOH, MeOH; iii. $SOCl_2$, toluene; iv. Ph_2PH; v. $BH_3 \bullet Me_2S$, toluene; vi. chromatography, SiO_2; vii. morpholine.

Two years later, Grützmacher developed the chiral tropp ligand into a new ligand: ^{Ph}troppo^{Ph}. To begin with, 10-bromo-5*H*-dibenzo[*a*,*d*]cycloheptan-5-ol **57** was coupled with phenylboronic acid in the presence of 2.5 mol% $Pd(PPh_3)_4$ to give 10-phenyl-5*H*-dibenzo[*a*,*d*]cycloheptan-5-ol **58**. The cycloheptanol was then reacted with Ph_2PCl under acidic conditions to afford the oxophosphorane ^{Ph}troppo^{Ph} **59**. The racemic mixture was easily separated by chiral stationary phase HPLC and subsequently reacted with $HSiCl_3$ to give the phosphanes (*S*)-^{Ph}tropp^{Ph} ((*S*)-**39**) and (*R*)-^{Ph}tropp^{Ph} ((*R*)-**39**) in 85% overall yield (Scheme 2.3).[45]

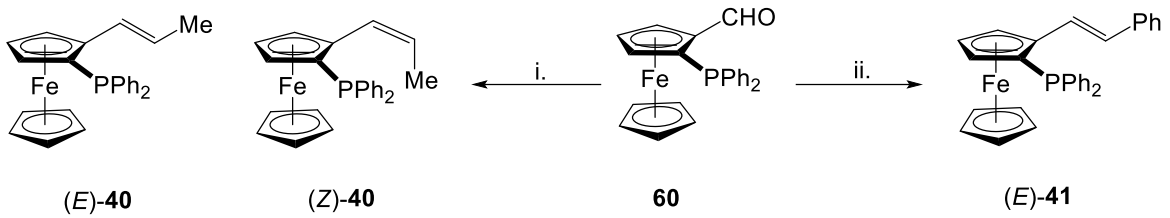
Scheme 2.3



Reagents and conditions: i. $PhB(OH)_2$, 2.5 mol% $[Pd(PPh_3)_4]$, $Na_2CO_{3(aq)}$, DME, EtOH; ii. Ph_2PCl, TFA, THF; iii. Chiral HPLC (OD-H) column; iv. $HSiCl_3$, 90 ˚C, toluene.

Štěpnička and Císařová synthesized and studied the coordination behaviour of a series of planar-chiral ferrocene phosphine-alkenes in 2006.[46] These ferrocene ligands contain π-donating alkenyl groups. The ferrocene-based phosphines can be obtained as *E* or *Z* configurational isomers depending on the alkenylation route. The coordination behaviour of the ferrocene-alkenylphosphines is that the flexibility of donor groups attached to the rigid ferrrocene moiety facilitates the coordination in the structure. The vinyl phosphine ligands were prepared from (S_p)-2-(diphenylphosphino)-1-ferrocenecarboxaldehyde **60** which was then reacted in a Wittig vinylation with different phenyl phosphines to give the vinylferrocenes (*E*)-**40**, (*E*)-**41** and (*Z*)-**40** (Scheme 2.4).

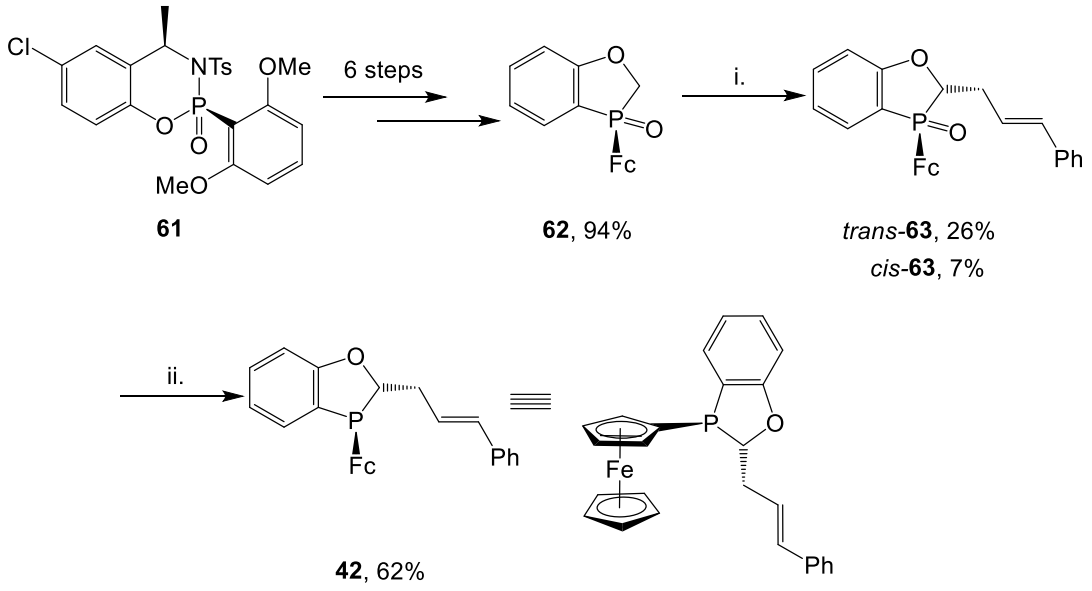
Scheme 2.4



Reagents and conditions: i. *n*-BuLi, $[PPh_3Et]Br$, 0 ˚C, 30 min then 60 ˚C, 16 h, THF; ii. *n*-BuLi, $PhCH_2P(O)(OEt)_2$, −78 ˚C, 30 min then rt, 90 min and 60 ˚C, 16 h, THF

Recently, Sieber and co-workers developed a new family of *P*-chiral *P*,π-hybrid ligands named JoshPhos ligands.[47] The synthesis of one of the JoshPhos ligands began with the six-step preparation of a benzo-oxaphosphole **62** from phosphine oxide **61**. Then, **62** was deprotonated using LDA and trapped with cinnamyl chloride to give allylic phosphine *trans*-**63** in 26% yield and *cis*-**63** in 7% yield (Scheme 2.5). Eventually, a chemoselective titanium-mediated reduction of *trans*-**63** was carried out to provide the desired product **42** in 62% yield.

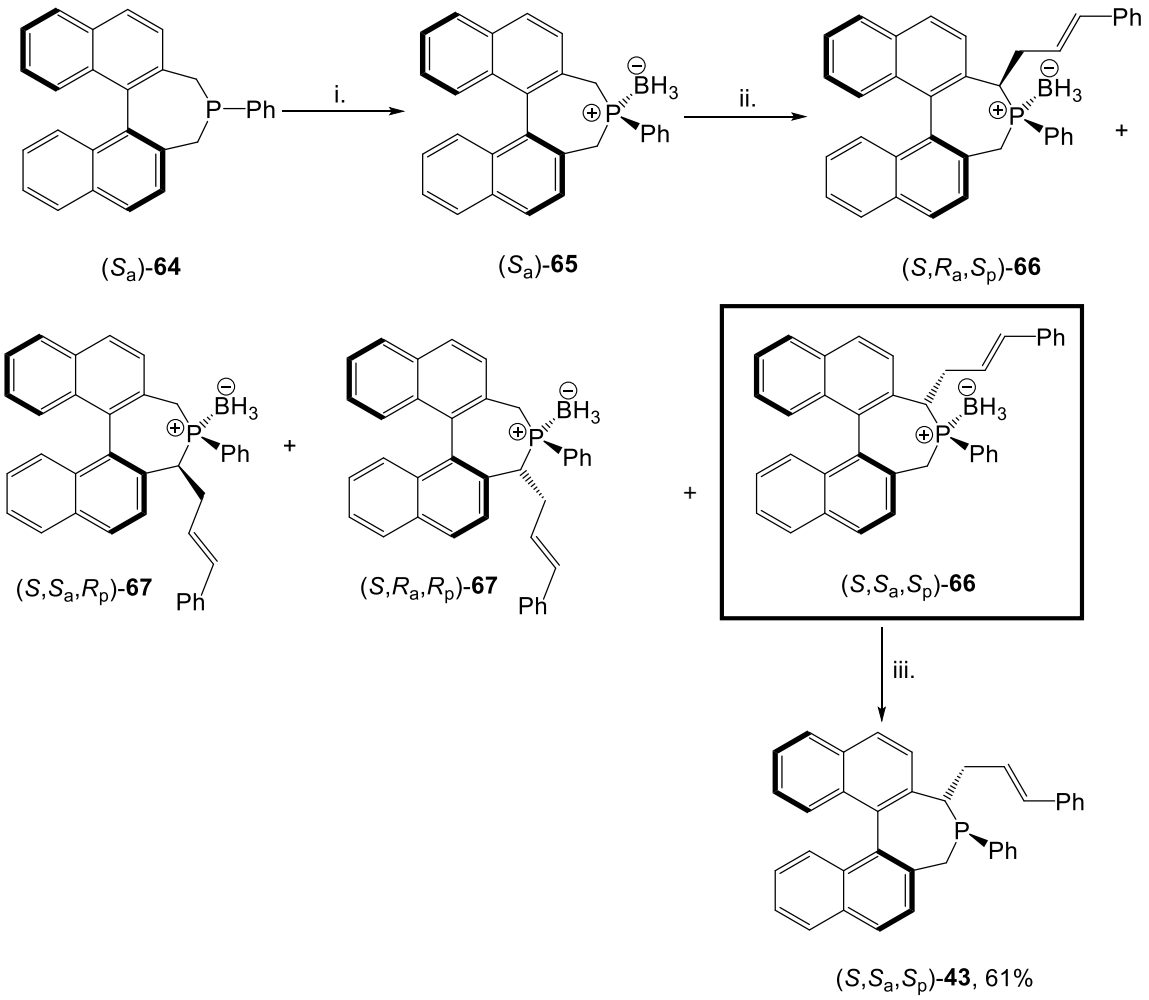
Scheme 2.5



Reagents and conditions: i. LDA, cinnamyl chloride; ii. PMHS, $Ti(O\text{-}i\text{-}Pr)_4$, MeTHF, ($F_c$ = ferrocenyl).

In related work, Widhalm prepared a new chiral phosphine with a (pseudo)-C_2 symmetric ligand from an enantiopure 2,2´-dimethyl-1,1´-binaphthyl precursor (S_a)-**64**.[48–50] Deprotonation of borane-dinaphthophosphepine (S_a)-**65** with *n*-BuLi[51] and reaction with cinnamyl bromide gave different diastereomers of phosphine boranes **66**-**67**. However, only one diastereomeric phosphine borane (S,S_a,S_p)-**66** was isolated as a white solid after purification by treatment with acetone, sonication and filtration. Then, the borane group was removed using Et_2NH to give (S,S_a,S_p)-**43** in 61% yield (Scheme 2.6).[52–55]

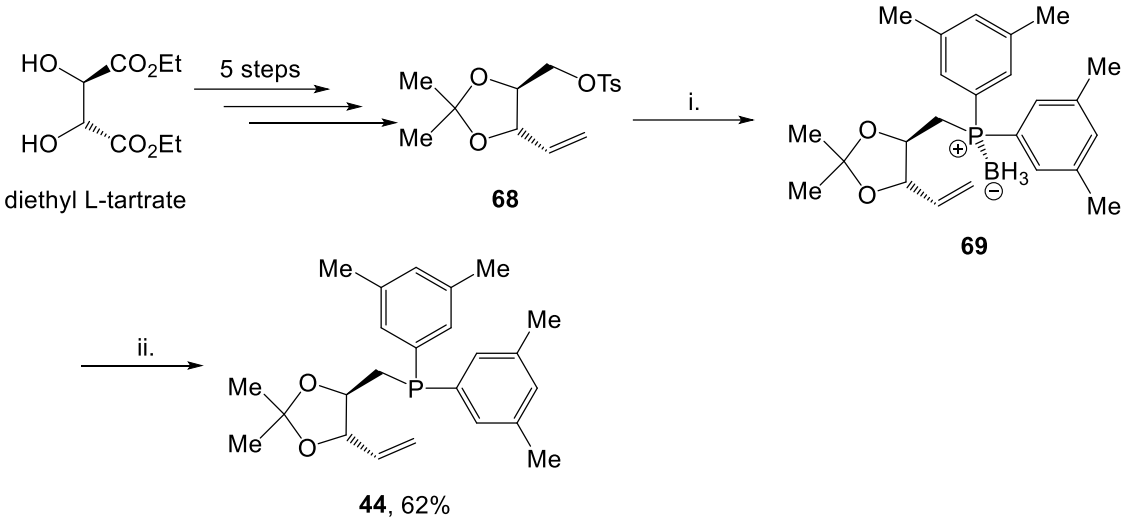
Scheme 2.6



Reagents and conditions: i. BH_3•THF, 0 ˚C to rt; ii. *n*-BuLi, –70 ˚C to –40 ˚C then cinnamyl bromide; iii. Et_2NH, 50 ˚C, THF.

Recently, Du has developed a series of chiral terminal-alkene-phosphine hybrid ligands. Thus, according to the reported synthetic route,[56–59] alkene tosylate **68** was obtained from diethyl L-tartrate as a starting material. To obtain phosphine-alkene ligand **44**, the bis(3,5-dimethylphenyl)-phosphine borane complex was lithiated with *n*-BuLi and then reacted with tosylate **68** to give phosphine borane **69** after purification by chromatography (Scheme 2.7). Then, morpholine was utilized to remove the borane group to give phosphine-alkene ligand **44** in 62% yield after purification by chromatography over an argon atmosphere.[60]

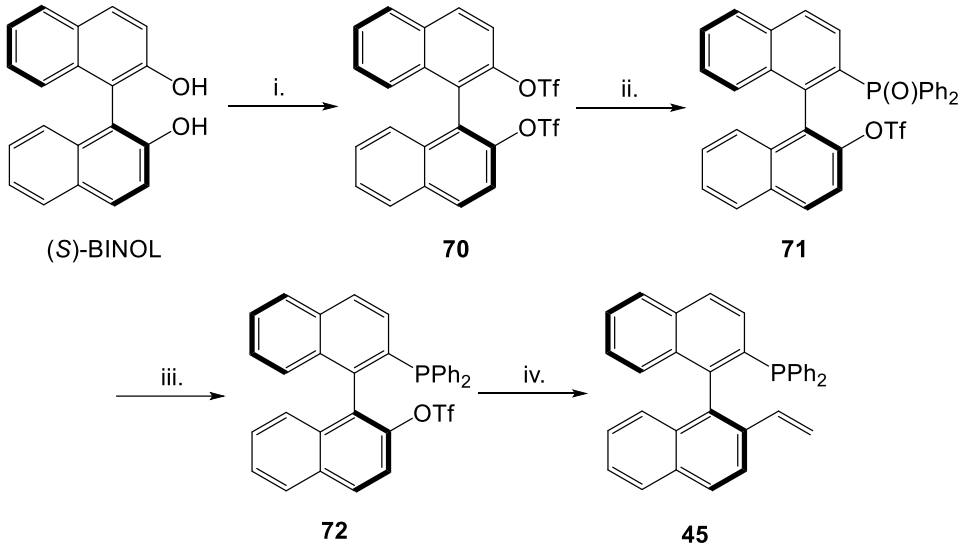
Scheme 2.7



Reagents and conditions: i. $(3,5\text{-}Me_2C_6H_3)_2\text{-}PBH_3$, *n*-BuLi, −70 ˚C 5 min then rt 30 min, and 50 ˚C, 16 h, THF; ii. morpholine, 80 ˚C, 2 h

Moreover, Du also developed different chiral phosphine-alkene ligands starting from (*S*)-BINOL. The starting material was reacted with Et_3N and Tf_2O to afford triflate **70**.[61] Without further purification, triflate **70** was then coupled with diphenylphosphine oxide in the presence of $Pd(OAc)_2$, dppb and *i*-Pr_2NEt to give phosphine oxide **71**.[62] The phosphine oxide was reduced using $HSiCl_3$ and Et_3N to give free phosphine **72**. Then, a coupling reaction of free phosphine **72** with potassium vinyltrifluoroborate using $Pd(PPh_3)_4$ as a catalyst gave chiral phosphine-alkene ligand **45** (Scheme 2.8).[63]

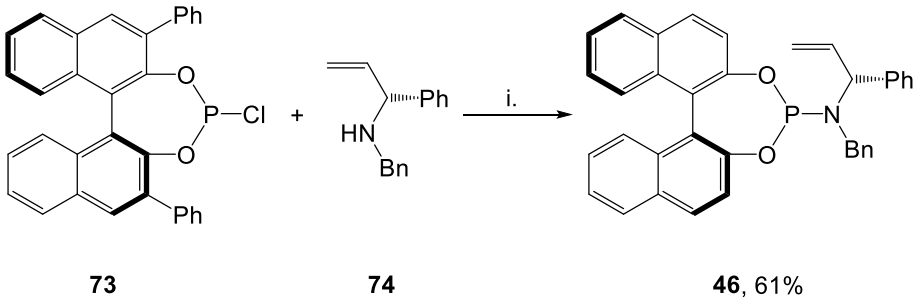
Scheme 2.8



Reagents and conditions: i. Tf_2O, Et_3N, CH_2Cl_2, –78 ˚C then 0 ˚C, 2 h; ii. Ph_2POH, $Pd(OAc)_2$, dppb, *i*-Pr_2NEt, DMSO, 100 ˚C, 12 h; iii. $HSiCl_3$, Et_3N, toluene, 0 ˚C then 100 ˚C, 12 h; iv. CH_2=$CHBF_3K$, $Pd(PPh_3)_4$, Et_3N, dioxane, 104 ˚C, 3 h

Similarly, an alternative motif for the investigation of chiral phosphine-alkene ligands was to incorporate a different type of terminal alkene since terminal alkenes in chiral phosphine-alkene ligands were effective binding elements for Rh-catalysed asymmetric reactions.[60] Therefore, Du and co-workers combined a terminal alkene with phosphochloridite of Ph_2-BINOL according to a reported procedure.[64] To begin with, allylic amine **74** was deprotonated using *n*-BuLi and the lithiated intermediate was then reacted directly with chlorophosphine **73** to provide chiral phosphine-alkene ligand **46** in 61% yield (Scheme 2.9).

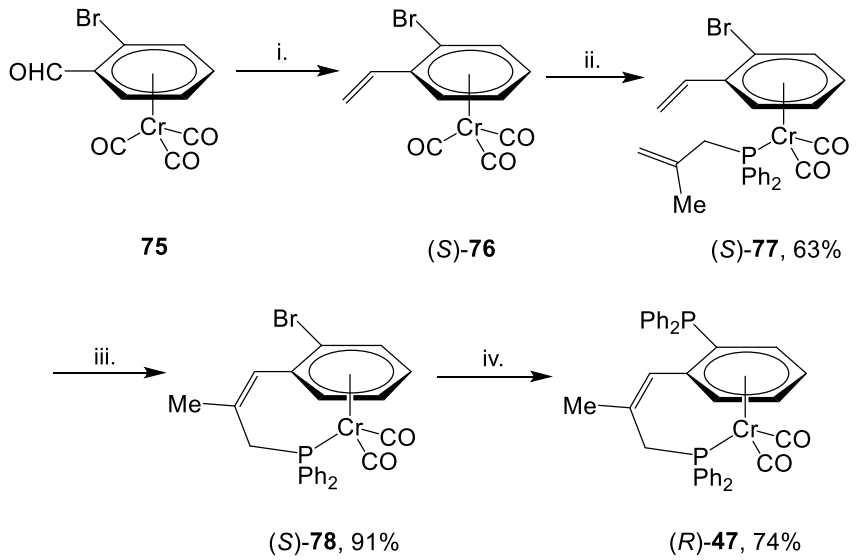
Scheme 2.9



Reagents and conditions: i. *n*-BuLi, THF, –78 ˚C, 0.5 h then 40 ˚C.

In addition, ring-closing metathesis was an alternative method for the synthesis of phosphine-alkene ligands. For example, Ogasawara and co-workers developed planar-chiral (phosphine-alkene) Cr-complexed ligands.[65] The synthesis started with a Wittig reaction of bromobenzaldehyde chromium complex **75** to give *o*-bromostyrene complex (*S*)-**76** in quantitative yield and >99.9% ee (Scheme 2.10). Then, one of the CO ligands was replaced by an allyl phosphine to give chromium complex (*S*)-**77** in 63% yield (>99.9% ee). Next, ring-closing metathesis of (*S*)-**77** using the 2nd generation Grubbs catalyst was carried out and provided bromoarene phosphine-alkene complex (*S*)-**78** in 91% yield. Finally, Br/Li exchange of (*S*)-**78** using *t*-BuLi and subsequent reaction with chlorodiphenylphosphine gave the desired phosphine-alkene ligand (*R*)-**47** in 74% yield (Scheme 2.10).

Scheme 2.10

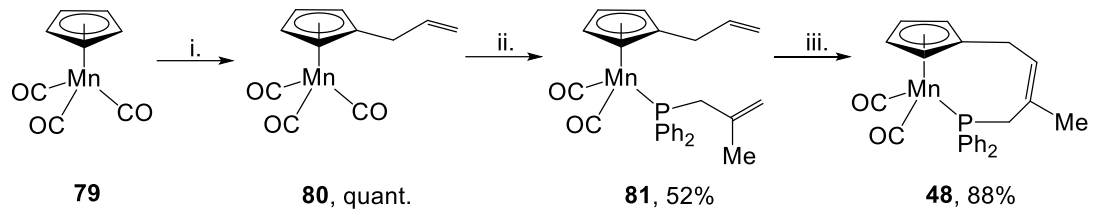


75 (*S*)-**76** (*S*)-**77**, 63% (*S*)-**78**, 91% (*R*)-**47**, 74%

Reagents and conditions: i. $Ph_3P{=}CH_2$, benzene, hv, 7 h; ii. 2-methylallylphosphine, benzene, hv, 7 h; iii. Grubbs II catalyst, CH_2Cl_2, 50 ˚C, 18 h; iv. *t*-BuLi, Ph_2PCl, THF, rt, 2 h.

Recently, the same group developed (phosphine-alkene)manganese(I) complexes *via* the same ring-closing metathesis synthetic strategy.[66] Lithiation of cymantrene **79** and trapping with allyl bromide gave manganese tricarbonyl complex **80** in excellent yield (Scheme 2.11). Then, a photo-induced CO/phosphine exchange reaction was carried out in benzene to give diallylic phosphine complex **81** in 52% yield. Finally, ring-closing metathesis of **81** using the 2nd generation Grubbs catalyst gave phosphine-alkene complex **48** in 88% yield.

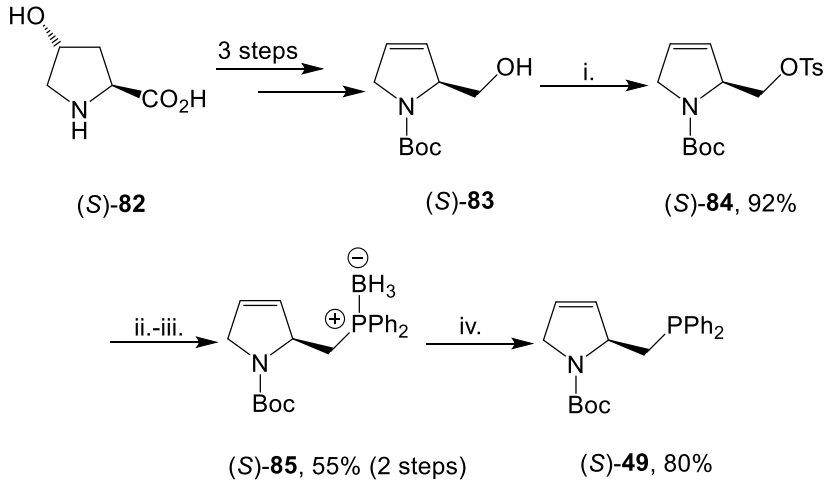
Scheme 2.11



Reagents and conditions: i. *t*-BuLi, allyl bromide, −78 ˚C, THF; ii. (2-methyl)allyldiphenylphosphine, benzene, hν, 15 h; iii. 2.5 mol% Grubbs II catalyst, CH_2Cl_2, 12 h.

To obtain enantioenriched phosphine-alkene ligands, the synthesis of the ligands from a chiral pool starting material is an alternative approach to various chiral phosphine-alkene ligands with high enantiomeric ratio. Therefore, Hayashi and co-workers recently presented a new chiral phosphine-alkene ligand (*S*)-**49** from hydroxyproline (*S*)-**82**.[67] The key intermediate, prolinol alkene (*S*)-**83**, was prepared from hydroxyproline (*S*)-**82** in 3 steps. Next, tosylation gave tosylate (*S*)-**84** in 92% (Scheme 2.12). Then, substitution of tosylate group using potassium diphenylphosphine gave phosphine-borane complex (*S*)-**85** was in 55% yield over two steps. Finally, the borane group was removed using DABCO to give chiral phosphine-alkene ligand (*S*)-**49** in 80% yield.

Scheme 2.12



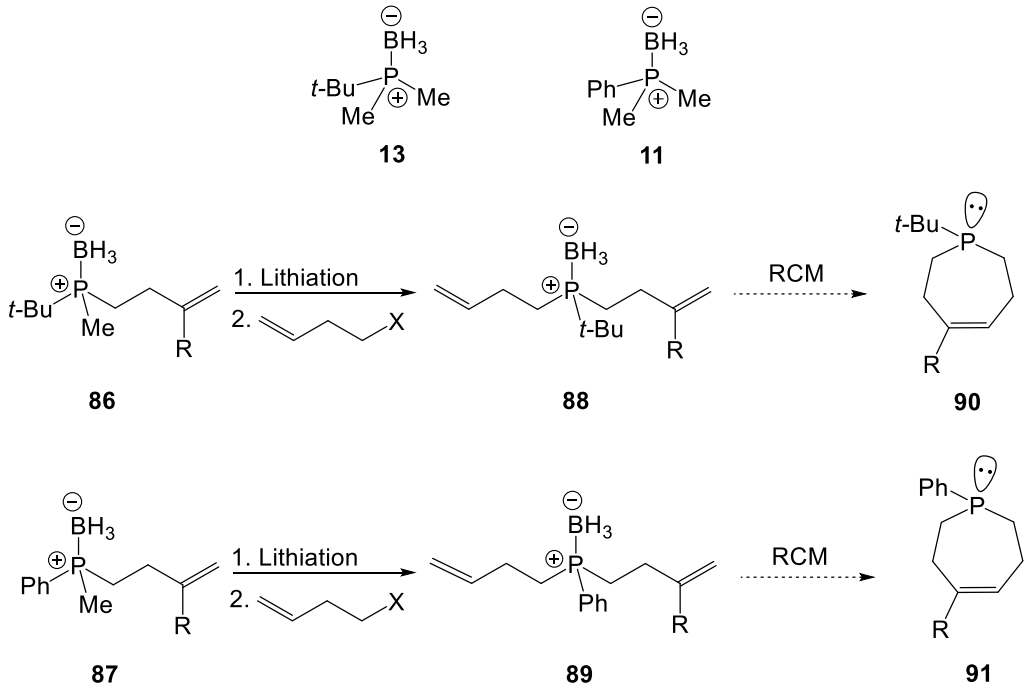
Reagents and conditions: i. *p*-TsCl, Et_3N, CH_2Cl_2, 7 h; ii. $KPPh_2$, THF, 0 ˚C, 0.5 h; BH_3•Me_2S, THF, rt, 2 h; iv. DABCO, THF, rt, 5 h.

In summary, although several types of chiral phosphine-alkene ligands have been synthesised and published, most of them have long synthetic routes and sometimes the phosphines needed to be purified under an argon atmosphere. Moreover, some ligands have to be resolved by preparative chiral HPLC which is an expensive method. However, only one *P*-stereogenic phosphine-alkene ligand (*S*,S_a,S_p)-**43** has been reported and the overall yield was not high (39%). Therefore, it appears that *P*-stereogenic phosphine-alkene ligands are a good motif to be studied and investigated.

2.3 Project Outline

The aim of this project was to synthesise new types of *P*-stereogenic phosphine-alkene ligands such as **90** and **91** (Scheme 2.13). To begin with, our plan was to prepare homoallylic phosphine boranes **86** and **87** from dimethylphosphineboranes **13** and **11** using an approach previously developed in our group.[18] Phosphine-alkenes **86** and **87** would then be lithiated using *s*-BuLi and trapped with alkyl halides to give unsymmetrical dihomoallylic phosphine boranes **88** and **89**. Next, to afford seven-membered ring phosphine-alkene ligands **90** and **91**, ring closing metathesis of phosphine boranes **88** and **89** would be applied and the borane group would eventually be removed using DABCO. It was imagined that vinyl bromides **90** and **91** (R = Br) would be cross-coupled to give a range of aryl-alkene groups.

Scheme 2.13



Since the ligands contain one phosphorus lone pair which can give strong coordinating ability and one C=C bond which has a weaker coordinating ability, the chiral ligands could be complexed to transition metals such as palladium and rhodium. In the future, it was expected that the *P*-metal complexes could be used as catalysts in organic reactions such as the 1,4-conjugate addition of arylboronic acids to enones.

2.4 Synthesis of Dimethylphosphine Boranes

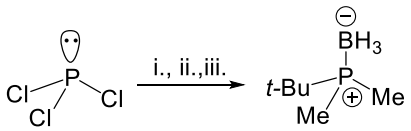
In terms of substrates, dimethylphosphine boranes **13** and **11** were used as starting materials (Figure 2.4). *t*-Butyldimethylphosphine borane **13** and dimethylphenylphosphine borane **11** were prepared from PCl_3 or $PhPCl_2$ respectively.

Figure 2.4

13 **11**

The synthesis of *t*-butyldimethylphosphine borane **13** was carried out on a multi-gram scale according to Imamoto's procedure.[9] Thus, a solution of PCl_3 **92** was reacted with 1.0 equivalent of *t*-butyl magnesium chloride to replace one of the chlorine atoms to form *t*-$BuPCl_2$ *in situ*. Then, 2.2 equivalents of methyl magnesium bromide was added to substitute the remaining two chlorine atoms and provide the free phosphine. To avoid oxidation of *t*-$BuPMe_2$ to the phosphine oxide, 1.5 equivalents of BH_3•Me_2S was added to give phosphine borane **13** in 54% yield after recrystallization from hot hexane (Scheme 2.14).

Scheme 2.14

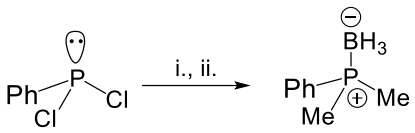


92 **13**, 54%

Reagents and conditions: i. *t*-BuMgCl (1.0 eq.), −78 ˚C for 1 h then rt for 3 h, THF; ii. MeMgBr (2.2 eq.), 0 ˚C to rt, 2h, THF; iii. BH_3•Me_2S (1.3 eq.) 0 ˚C, rt, 3 h.

In a similar way, phosphine borane **11** was synthesised from $PhPCl_2$ **93**. Thus, a solution of $PhPCl_2$ was reacted with 2.2 equivalents of methyl magnesium bromide to substitute the two chlorine atoms. Then, 1.5 equivalents of BH_3•Me_2S was added *in situ* to give phosphine borane **11** in 70% yield after chromatography (Scheme 2.15).

Scheme 2.15



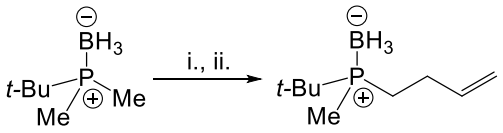
93 **11**, 70%

Reagents and conditions: i. MeMgBr (2.2 eq.), 0 °C to rt, 16 h, THF; ii. BH_3•Me_2S (1.5 eq.) 0 ˚C to rt, 2 h.

2.5 Racemic Lithiation of *t*-Butyl Dimethylphosphine Borane and Trapping with Allylic Halides under Different Conditions

To begin with, *t*-butyl-substituted phosphine borane **13** was deprotonated using 1.2 equivalents of *s*-BuLi in THF at −78 ˚C for 1 hour. Then, the lithiated intermediate was trapped with 1.2 equivalents of allyl bromide to give allyl phosphine borane **94** in 56% yield after purification by chromatography (Scheme 2.16).

Scheme 2.16



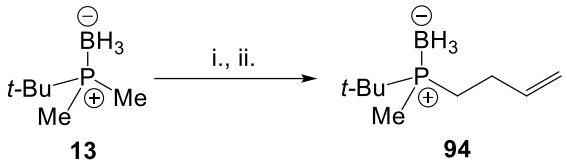
13 **94**, 56%

Reagents and conditions: i. *s*-BuLi (1.2 eq.), −78 ˚C, 1 h, THF; ii. allyl bromide (1.2 eq.), −78 ˚C, 16 h, THF.

The ^{1}H NMR spectrum of phosphine borane **94** contained a 1H multiplet at δ_H 5.82-5.74 ppm, assigned to the alkene CH-proton which couples to the *trans*-, *cis*- and two vicinal protons. There was also a 1H double quartet (J = 17.5, 1.5 Hz) at δ_H 5.0 ppm due to one of the protons on the C=CH_2 which couples to the *trans*-, *geminal*- and allylic protons. The ^{31}P NMR spectrum of phosphine borane **94** contained a quartet (J = 63.0 Hz) at δ_P 26.6 ppm confirming that the BH_3 group was still attached. The NMR spectroscopic data was consistent with that previously reported in the group.[18]

The racemic lithiation of phosphine borane **13** was repeated at higher temperatures in an attempt to improve the yield. The results of this study are shown in Scheme 2.17, Table 2.1.

Scheme 2.17



13 **94**

Reagents and conditions: i. *s*-BuLi (1.2 eq.), temp, 1 h, THF; ii. allyl bromide (1.2 eq.), temp, 16 h, THF.

Table 2.1

Entry	Temp (˚C)	Yield (%) [a]
1	–78	56, 40 [b]
2	–40	56, 51 [b]
3	0	68, 59, 44, 33 [b]

[a] Yield after purification by chromatography.

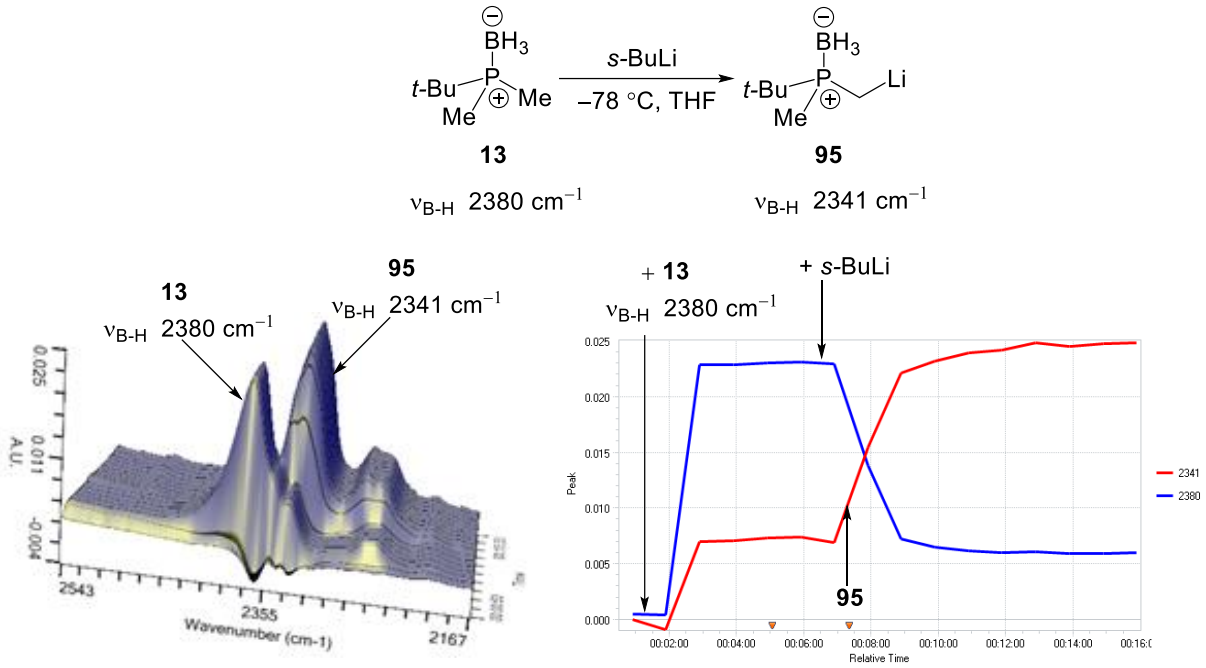
[b] Yields from different runs of the same experiment.

Phosphine borane **13** was lithiated using 1.2 equivalents of *s*-BuLi in THF at –40 ˚C for 1 hour. Trapping with 1.2 equivalents of allyl bromide for 16 hours gave allyl phosphine borane **94** in 56% yield (Entry 2). Lithiation at even higher temperature was also studied. The phosphine borane **13** was also deprotonated using *s*-BuLi at 0 ˚C. The reaction was repeated four times to give phosphine borane **94** in variable yields (33-68%). However, the highest yield obtained was 68% on a multi-gram scale (Entry 3).

To study the racemic lithiation of phosphine borane **13** in more detail, *in situ* infra-red spectroscopy was used to directly observe the lithiation. Such a technique has been very successfully studied in our group for the lithiation of *N*-Boc heterocycles.[25,68–71] In our study, the following standard conditions were used. The reactions were prepared by adding 12 mL of THF in a 100 mL two-necked round-bottomed flask and the ReactIR probe was put into the solvent to collect background IR spectra. The flask was set with a continuous N_2 flow over the reaction process. Then, a solution of 1.0 mmol of phosphine borane **13** in 5 mL of THF was added. This concentration of phosphine borane **13** in the reaction flask, 0.06 M in THF, was used as a standard concentration for ReactIR monitoring.

When a solution of phosphine borane **13** in THF was added and stirred at −78 ˚C, there was a peak at 2380 cm^{-1}. This was assigned to be a B-H stretch in of phosphine borane **13**. After the peak intensity did not change for 7 minutes, 1.2 equivalents of *s*-BuLi were added. As a result, the $\nu_{B\text{-}H}$ at 2380 cm^{-1} of phosphine borane **13** dramatically decreased whereas there was a sharp increase in a new absorbance at 2341 cm^{-1}. The lower wavenumber signal can be explained by the $\nu_{B\text{-}H}$ of lithiated intermediate **95** that was formed. From this ReactIR monitoring, it was found that the lithiation of phosphine borane **13** required only 2 minutes to reach completion (Scheme 2.18). This is the first time that the lithiation of a phosphine borane has been studied by ReactIR spectroscopy.

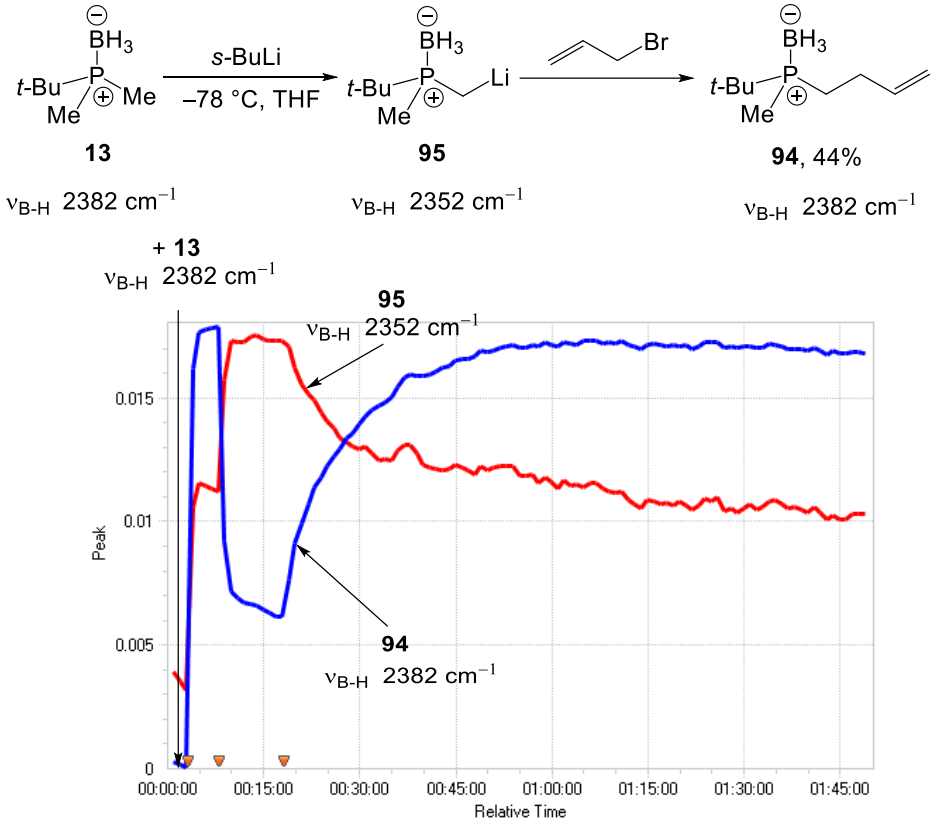
Scheme 2.18



Furthermore, ReactIR spectroscopy was also used to investigate the reactivity of the electrophile trapping step of the lithiated phosphine intermediate **95**. To start with, the experiment was set up with the standard concentration of phosphine borane **13** (0.06 M in THF) at −78 ˚C. Since lithiation of phosphine borane **13** using 1.2 equivalents of *s*-BuLi was believed not to be fully complete (Scheme 2.18), 1.5 equivalents of *s*-BuLi was added (Scheme 2.19). The ReactIR spectra indicated that the lithiation occurred in 2 minutes. Then, 2.0 equivalents of allyl bromide were added to the reaction mixture. The ReactIR monitoring showed that the absorbance at 2382 cm^{-1} gradually increased. Hence, we assumed that the lithiated phosphine borane **95** was trapped with allyl bromide and formed the allyl phosphine

borane **94** which showed the same wavenumber ($\nu_{B\text{-}H}$ 2382 cm^{-1}) as starting phosphine borane **13**. At the same time, the lithiated intermediate **95** ($\nu_{B\text{-}H}$ 2352 cm^{-1}) slowly decreased. After 45 minutes, both absorbances at 2382 and 2352 cm^{-1} had levelled off and we concluded that the electrophilic trapping of the lithiated phosphine borane **95** was finished. The reaction mixture was worked up and the crude product was purified by chromatography to give allyl phosphine borane **94** in 44% yield (Scheme 2.19).

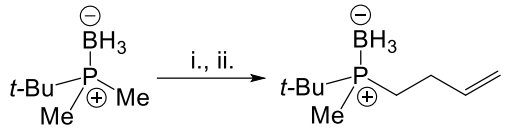
Scheme 2.19



Next, the lithiation of phosphine borane **13** using 1.5 equivalents of *s*-BuLi was repeated in the laboratory. The concentration of the substrate was different: 1.52 mmol of phosphine borane **13** in 7 mL THF (0.22 M in THF). This is the standard concentration used in all of the laboratory experiments. Then, 1.5 equivalents of *s*-BuLi were added at –78 ˚C. Although ReactIR had shown that deprotonation of phosphine borane **13** occurred in only 2 minutes, the reaction mixture was stirred at –78 ˚C for 1 hour to compare with the other laboratory reactions (Table 2.1). The lithiated intermediate was then trapped with 2.0 equivalents of allyl bromide and the resulting mixture was stirred at rt for 16 hours in a similar way to the other reactions. After work-up, the crude product was purified by chromatography and phosphine borane **94** was obtained in 57% yield (Scheme 2.20). The higher yield of the

reaction in the laboratory set-up is probably due to the fact that the reaction was better sealed and free from H_2O or O_2 compared to the one in the ReactIR set-up.

Scheme 2.20

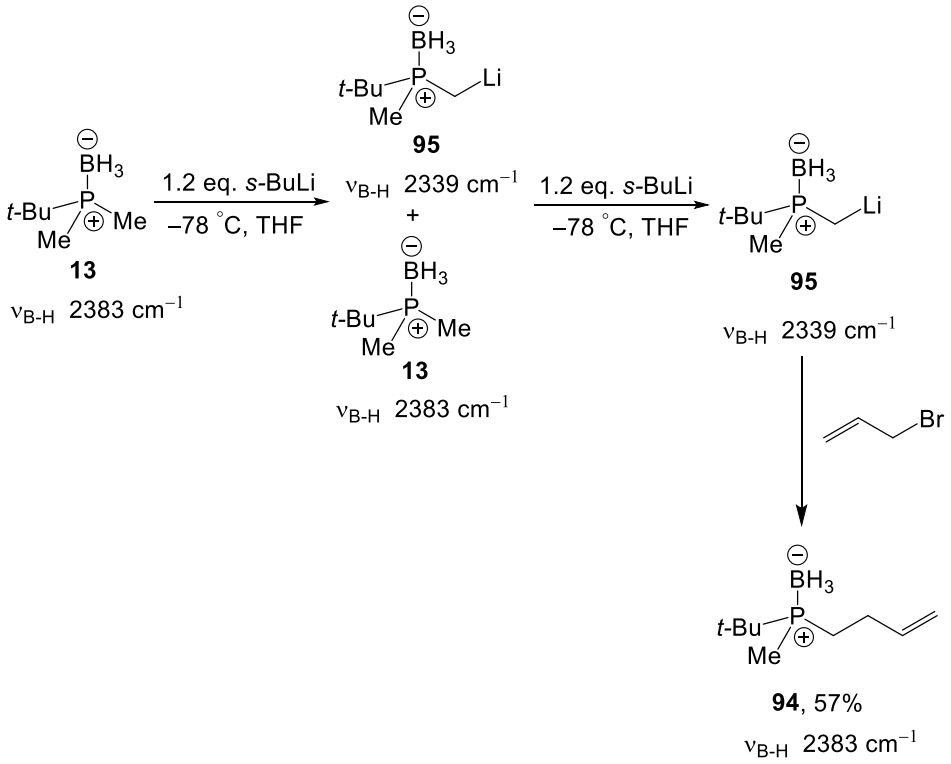


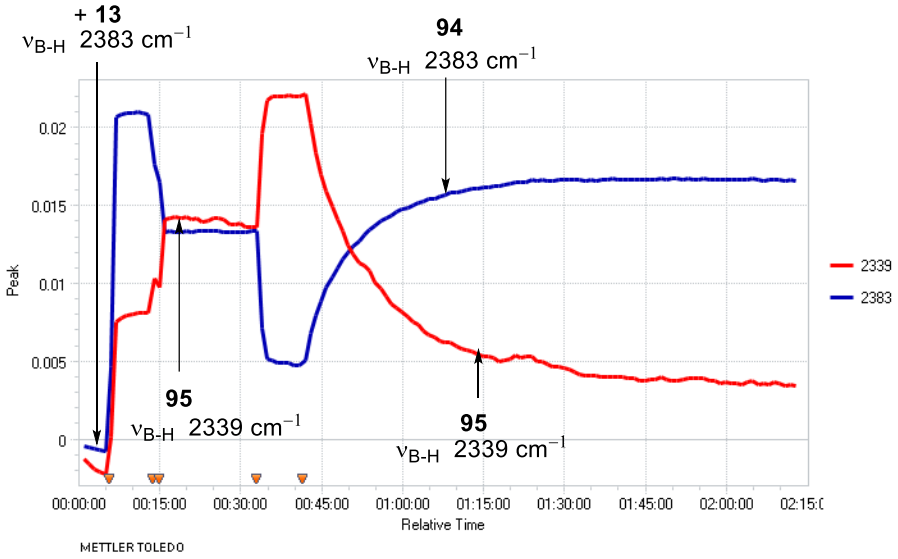
13 **94**, 57%

Reagents and conditions: i. *s*-BuLi (1.5 eq.), −78 ˚C, 1 h, THF; ii. allyl bromide (2.0 eq.), −78 ˚C, 16 h, THF.

Since the use of 1.5 equivalents of *s*-BuLi with phosphine borane **13** in THF did not give high yields, we decided to monitor the reaction at −78 ˚C by ReactIR using two sequential additions of *s*-BuLi. After addition of 1.2 equivalents of *s*-BuLi to phosphine borane **13**, a second amount of 1.2 equivalents of *s*-BuLi would be added and we would investigated if any more lithiation occurred using ReactIR before trapping with the electrophile. Thus, the ReactIR experiment was prepared using our usual concentration of phosphine borane **13** (0.06 M in THF). The first 1.2 equivalents of *s*-BuLi was added (Scheme 2.21). Formation of lithiated intermediate **95** ($\nu_{B\text{-}H}$ 2339 cm^{-1}) was observed and there was a decrease in the substrate peak ($\nu_{B\text{-}H}$ 2383 cm^{-1}). The resulting mixture was stirred for 15 minutes and another 1.2 equivalents of *s*-BuLi was added. ReactIR monitoring showed that the phosphine borane **13** ($\nu_{B\text{-}H}$ 2383 cm^{-1}) was deprotonated further and more lithiated intermediate **95** ($\nu_{B\text{-}H}$ 2339 cm^{-1}) was formed. After stirring for 5 minutes, 1.2 equivalents of allyl bromide was added and there was a gradual appearance of the allyl phosphine borane **94** ($\nu_{B\text{-}H}$ 2383 cm^{-1}) in 45 minutes before the absorbance started levelling off. The desired product **94** was obtained in 57% yield which was slightly higher than the yield obtained using only 1.5 equivalents of *s*-BuLi in the ReactIR experiment.

Scheme 2.21

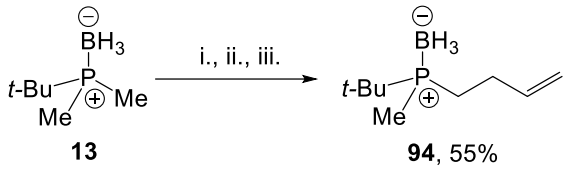




In a similar way, the reaction was repeated in the laboratory using a 0.22 M solution of phosphine borane **13** in THF at −78 ˚C. 1.2 Equivalents of *s*-BuLi were added and the resulting mixture was stirred for 10 minutes to make sure that the substrate was deprotonated. Then, another 1.2 equivalents of *s*-BuLi were added and the reaction mixture was stirred for 10 minutes. The lithiated intermediate was then trapped with 2.4 equivalents of allyl bromide for 16 hours. Allyl phosphine borane **94** was obtained in 55% yield (Scheme 2.22),

essentially the same as the yield (57%) from the ReactIR experiment. Thus, the concentration of phosphine borane **13** in THF did not affect the reaction outcome.

Scheme 2.22



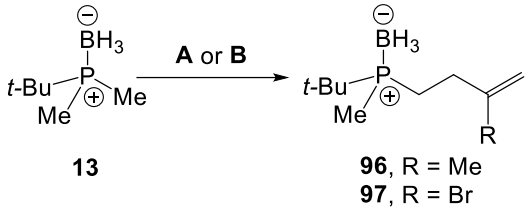
13 **94**, 55%

Reagents and conditions: i. *s*-BuLi (1.2 eq.), −78 ˚C, 10 min, THF; ii. *s*-BuLi (1.2 eq.), −78 ˚C, 10 min, THF; iii. allyl bromide (2.4 eq.), −78 ˚C, 16 h, THF.

The next stage of the project was to synthesise other racemic allyl phosphine boranes. For this, different allyl halides such as 3-chloro-2-methylpropene and 2,3-dibromoprop-1-ene were used as electrophiles. For example, to synthesise phosphine borane **96**, phosphine borane **13** was deprotonated using 1.2 equivalents of *s*-BuLi in THF at 0 ˚C for 1 hour and the lithiated intermediate was then trapped with 1.2 equivalents of 3-chloro-2-methylpropene. This gave phosphine borane **96** in 36% yield after chromatography (Scheme 2.23, Table 2.2, entry 1). In an attempt to improve the yield, transmetallation was carried out after the lithiated intermediate was formed. Thus, a solution of a 1:2 ratio of CuCl and LiCl in THF was added to the lithiated species at 0 ˚C and stirred for 1 hour. Trapping with 1.2 equivalents of 3-chloro-2-methylpropene gave phosphine borane **96** in 43% yield (Table 2.2, entry 2). The yield was only slightly increased when using the transmetallation process. There are two points to note with the transmetallation process. First, the LiCl should be thoroughly dried before use and second, the LiCl/CuCl mixture should be stirred in the dark to avoid oxidation to Cu(II).

In the ^{1}H NMR spectrum of allyl phosphine borane **96**, there was a 1H broad singlet at δ_H 4.73 ppm and a 1H broad singlet at δ_H 4.70 ppm. Both signals were assigned to the CH_2 alkene protons. A 3H singlet was observed at δ_H 1.72 ppm due to the methyl group on the alkene. The ^{31}P NMR spectrum of allyl phosphine borane **96** contained a quartet (J = 58.0 Hz) at δ_P 26.7 ppm due to coupling to the boron in the borane group. These data were consistent with those in the literature.[18]

Scheme 2.23



13 **96**, R = Me; **97**, R = Br

Reagents and conditions: **A**. i. *s*-BuLi (1.2 eq.), 0 ˚C, 1 h, THF; ii. 3-chloro-2-methylpropene or 2,3-dibromoprop-1-ene (1.2 eq.), 0 ˚C, 16 h, THF. or **B**. i. *s*-BuLi (1.2 eq.), 0 ˚C, 1 h, THF; ii. LiCl (1.2 eq.) and CuCl (0.6 eq.), 0 ˚C, 1 h, THF, iii. 3-chloro-2-methylpropene or 2,3-dibromoprop-1-ene (1.2 eq.), 0 ˚C, 16 h, THF.

Table 2.2

Entry	R	LiCl:CuCl	Product	Yield (%) [a]
1	Me	-	**96**	36
2	Me	2:1	**96**	43
3	Br	-	**97**	0
4	Br	2:1	**97**	56

[a] Yield after purification by chromatography.

Initial attempts to prepare allyl phosphine borane **97** using direct lithiation and trapping were not successful. No product was obtained (Scheme 2.23, Table 2.2, entry 3). As a result, transmetallation of the lithiated intermediate with a 1:2 ratio of CuCl and LiCl was carried out and followed by reaction with 2,3-dibromoprop-1-ene. In this case, allyl phosphine borane **97** was obtained in 56% yield after purification by chromatography (Table 2.2, entry 4). This shows that the transmetallation is important for the synthesis of allyl phosphine borane **97** using 2,3-dibromoprop-1-ene as an electrophile.

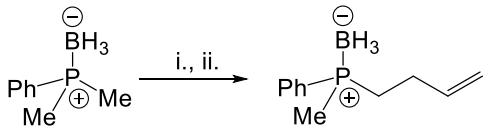
The ^{1}H NMR spectrum of allyl phosphine borane **97** contained a 1H double triplet (J = 2.0, 1.0 Hz) at δ_H 5.67 ppm and a broad doublet (J = 2.0 Hz) which were both assigned to the two alkene protons. In the ^{13}C NMR spectrum, there was a singlet at δ_C 117.5 ppm corresponding to the CH_2 alkene carbon.

In summary, the ReactIR spectroscopic monitoring showed that the phosphine borane **13** was deprotonated in only 2 minutes at −78 ˚C and the electrophilic trapping finished in less than an hour. Moreover, transmetallation was a useful method for improving the yield of allyl phosphine boranes **96** and **97**.

2.6 Racemic Lithiation of Phenyl Dimethylphosphine Borane and Trapping with Allylic Halides under Different Conditions

Next, the same type of optimisation of the lithiation conditions was carried out with phenyl dimethylphosphine borane **11**. Thus, phosphine borane **11** was deprotonated using 1.2 equivalents of *s*-BuLi in THF at −78 ˚C for 1 hour. The lithiated intermediated was then trapped with 1.2 equivalents of allyl bromide to give phosphine borane **98** in 61% yield after purification by chromatography (Scheme 2.24).

Scheme 2.24



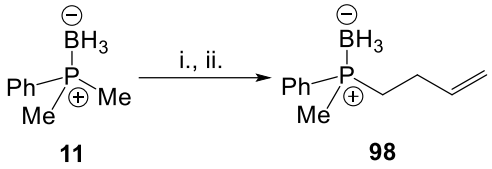
11 **98**, 61%

Reagents and conditions: i. *s*-BuLi (1.2eq.), −78 ˚C, 1 h, THF; ii. allyl bromide (1.2eq.), −78 ˚C, 16 h, THF.

The ^{1}H NMR spectrum of phosphine borane **11** contained a 2H double double doublet (J = 8.0, 2.0, 0.5 Hz) at δ_H 7.70 ppm and a 3H multiplet at δ_H 7.49-7.38 ppm. Both signals were assigned to the five phenyl protons. A 1H double doublet triplet (J = 17.0, 10.5, 6.5 Hz) at δ_H 5.72 ppm, a broad doublet (J = 17.0 Hz) at δ_H 4.96 ppm and a broad doublet (J = 10.5 Hz) at δ_H 4.91 ppm were assigned to the three alkene protons. The NMR spectroscopic data was consistent with that previously reported in the group.[18]

In a similar way to the *t*-butyl phosphine borane **13**, the racemic lithiation of phosphine borane **11** was also studied at high temperature (0 ˚C) in an attempt to improve the yield. The results are shown in Scheme 2.25, Table 2.3.

Scheme 2.25



11 **98**

Reagents and conditions: i. *s*-BuLi (1.2 eq.), temp, 1 h, THF; ii. allyl bromide (1.2 eq.), temp, 16 h, THF.

Table 2.3

Entry	Temp (˚C)	Yield (%) [a]
1	–78	61
2	0	60, 68, 75 [b]

[a] Yield after purification by chromatography.

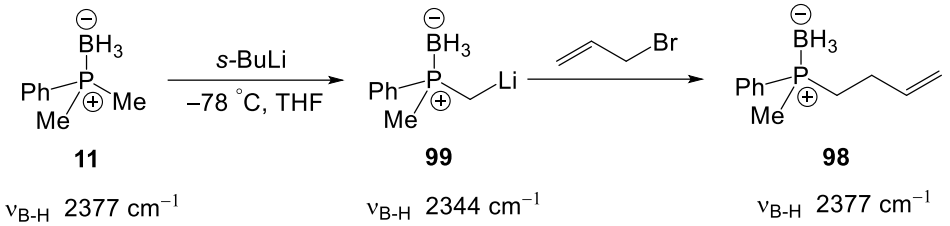
[b] Yields from different runs of the same experiment.

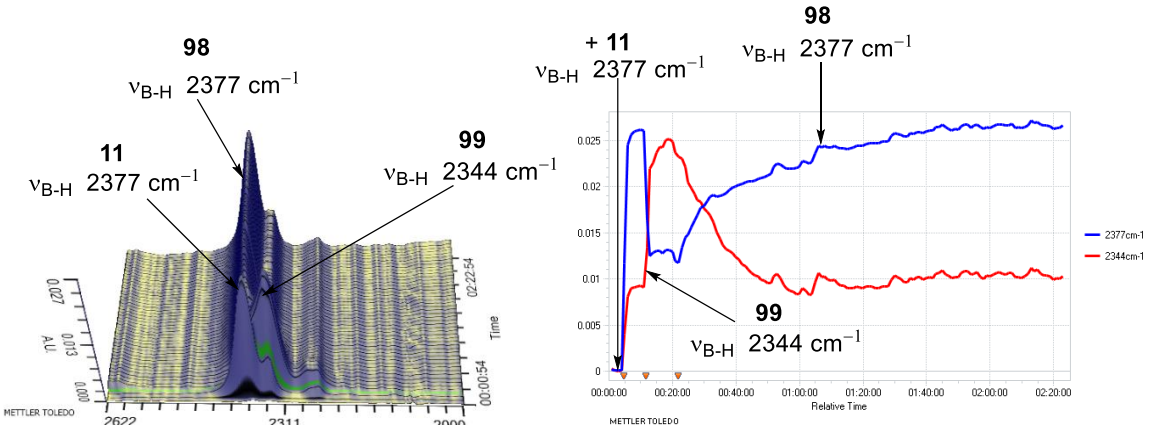
To investigate a simple procedure at high temperature, phosphine borane **11** was lithiated using 1.2 equivalents of *s*-BuLi at 0 ˚C for 1 hour. The lithiated intermediate was then trapped with 1.2 equivalents of allyl bromide to give phosphine borane **98**. The reaction was repeated three times to give phosphine borane **98** in variable yields (60-75%). However, the highest yield obtained was 75% (Entry 2). This racemic lithiation-trapping of phenyl phosphine borane **11** is successful at both low and high temperatures.

Furthermore, to study the reactivity of phenyl phosphine borane **11** under the racemic lithiation conditions, ReactIR spectroscopy was used to monitor the lithiation occurring. To compare the difference between the reactivity of *t*-butyl phosphine borane **13** and phenyl phosphine borane **11**, the reaction was also carried out at –78 ˚C. In terms of the ReactIR experiment, the phenyl phosphine borane **11** was prepared with the standard concentration, 0.06 M in THF. During the monitoring, an absorbance at 2377 cm^{-1} was observed (Scheme 2.26). This peak was assigned to the B-H stretch in phosphine borane **11**. After *s*-BuLi was added, the lithiated intermediate was immediately formed because the $\nu_{B\text{-}H}$ at 2344 cm^{-1} increased at the same time that the phosphine borane **11** ($\nu_{B\text{-}H}$ 2377 cm^{-1}) was deprotonated. Then, the lithiated intermediate **99** was trapped with allyl bromide. The electrophilic trapping resulted in a gradual formation of allyl phosphine borane **98**. The ReactIR monitoring indicated that the phenyl phosphine borane **11** can be deprotonated using *s*-BuLi

in only 3 minutes and the electrophilic trapping occurred in 90 minutes which was longer than that of *t*-butyl phosphine borane **13**.

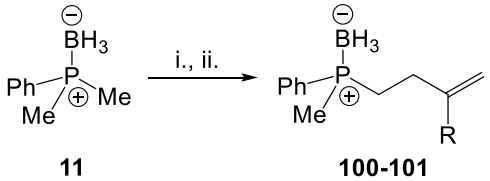
Scheme 2.26





In a similar way, to synthesise other racemic allyl phosphine boranes, different allyl halides such as 3-chloro-2-methylpropene and 2,3-dibromoprop-1-ene were also used as electrophiles. Although we knew from the ReactIR monitoring that the lithiation of phenyl phosphine borane **11** at –78 ˚C occurred in only 3 minutes, the previous study showed that the lithiation at 0 ˚C for 1 hour was also possible. Therefore, we decided to synthesise the other racemic allyl phosphine boranes through lithiation using *s*-BuLi at 0 ˚C for 1 hour to allow complete deprotonation (Scheme 2.27). However, the concentration of the phosphine borane **11** for the reaction in the laboratory was 0.19 M in THF which was more concentrated than the one for the ReactIR experiment (0.06 M in THF).

Scheme 2.27

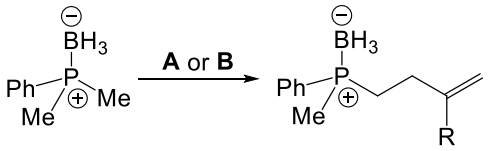


Reagents and conditions: i. *s*-BuLi (1.2 eq.), 0 ˚C, 1 h, THF; ii. allyl halides (1.2 eq.), 0 ˚C, 16 h, THF.

To start with, the phenyl phosphine borane **11**, 0.19 M in THF, was deprotonated using 1.2 equivalents of *s*-BuLi at 0 ˚C for 1 hour. The lithiated intermediate was trapped with 3-chloro-2-methylpropene. The resulting mixture was then worked-up to give the crude product, which gave allyl phosphine borane **100** in 56% yield after chromatography (Scheme 2.28, Table 2.4, entry 1). By comparison with *t*-butyl phosphine borane **13**, transmetallation was used to improve the yield by reacting with the lithiated intermediate and then trapping with 3-chloro-2-methylpropene. As we expected, the allyl phosphine borane **100** was obtained in a slightly increased 64% yield (Entry 2).

The ^{1}H NMR spectrum of phosphine borane **100** contained a 1H broad singlet at δ_H 4.72 ppm as well as a 1H broad doublet (J = 0.5 Hz) at δ_H 4.68 ppm which were due to the alkene protons. A 3H singlet was observed at δ_H 1.69 ppm corresponding to the methyl group on the alkene. The NMR spectroscopic data was consistent with that previously reported in the group.[18]

Scheme 2.28



11 **100**, R = Me; **101**, R = Br

Reagents and conditions: **A**. i. *s*-BuLi (1.2 eq.), 0 ˚C, 1 h, THF; ii. 3-chloro-2-methylpropene or 2,3-dibromoprop-1-ene (1.2 eq.), 0 ˚C, 16 h, THF. or **B**. i. *s*-BuLi (1.2 eq.), 0 ˚C, 1 h, THF; ii :LiCl (1.2 eq.) and CuCl (0.6 eq.), 0 ˚C, 1 h, THF, iii. 3-chloro-2-methylpropene or 2,3-dibromoprop-1-ene (1.2 eq.), 0 ˚C, 16 h, THF.

Table 2.4

Entry	R	LiCl:CuCl	Product	Yield (%) [a]
1	Me	-	**100**	56
2	Me	2:1	**100**	64
3	Br	-	**101**	0
4	Br	2:1	**101**	39

[a] Yield after purification by chromatography

Not surprisingly, when 2,3-dibromoprop-1-ene was used to trap the lithiated intermediate of phenyl phosphine borane **11** without transmetallation, the allyl phosphine borane **101** was not obtained (Scheme 2.28, Table 2.4, entry 3). On the other hand, when transmetallation with a ratio 1:2 CuCl and LiCl was carried out to generate the Cu(I)-lithiated intermediate and trapping with 2,3-dibromoprop-1-ene, better results were obtained. Allyl phosphine borane **101** was isolated in 41% yield after purification by chromatography (Entry 4).

In the ^{1}H NMR spectrum of bromophosphine borane **101**, there was a 1H doublet (J = 1.0 Hz) at δ_H 5.60 ppm due to an alkene proton CBr=CH_AH$_B$ and a 1H doublet (J = 1.0 Hz) at δ_H 5.37 ppm assigned to the other alkene proton CBr=CH$_A$$H_B$.

In summary, the ReactIR spectroscopy monitoring showed that the lithiation of phosphine borane **11** occurred in less than 5 minutes at −78 ˚C. However, at 0 ˚C the racemic lithiation and trapping with 3-chloro-2-methylpropene was still possible and transmetallation was important for the synthesis of allyl phosphine borane **101** when 2,3-dibromoprop-1-ene was used as an electrophile.

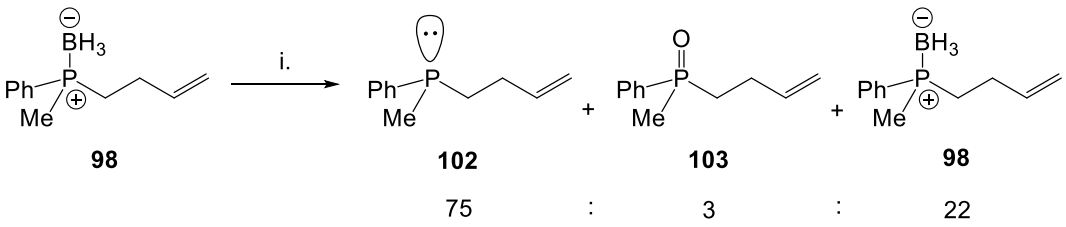
2.7 Investigation of Borane Deprotection

The next stage involved an investigation of the borane deprotection step as it was important to show that the borane group could be successfully removed. Based on the work of Imamoto,[72] we planned to treat the phosphine borane with DABCO in refluxing THF to remove the borane group. In our work, we chose allyl phenyl phosphine borane **98** as a starting point. This is because we believed that the benzene ring would stabilize the lone pair of electrons on the phosphorus atom to avoid oxidation of the resulting phosphine.

To carry out the borane deprotection, a mixture of phenyl allyl phosphine borane **98** and 1.1 equivalents of DABCO were refluxed in degassed THF for 16 hours (Scheme 2.29). After the reaction was cooled to rt, the solvent was removed under reduced pressure. Then, degassed hexane was added to the crude product and the resulting mixture was stirred for 10 minutes under argon. As a result, there was a white precipitate of DABCO•BH_3 in the solution. We used a cannula which was sealed with filter paper to separate the solid from the solution. The solvent was then removed from the filtrate to give the crude product. In the ^{31}P NMR spectrum of the crude product, there was a singlet at δ_P −34.9 ppm due to the free

phosphine **102**. There was also a singlet at δ_P 37.5 ppm corresponding to phosphine oxide **103** and a quartet (J = 60.5 Hz) at δ_P 9.8 ppm which was assigned to starting phosphine borane **98**. The ^{31}P NMR spectrum indicated a 75:3:22 ratio of free phosphine **102**, phosphine oxide **103** and phosphine borane **98** (Scheme 2.29).

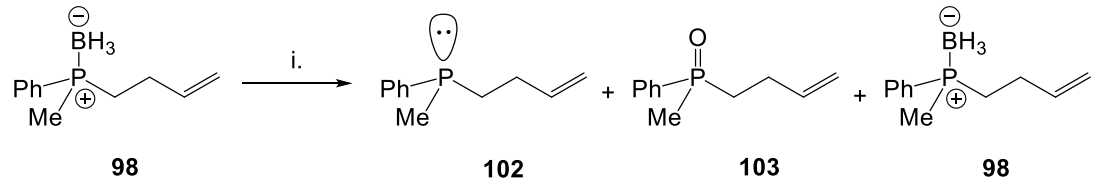
Scheme 2.29



Reagents and conditions: i. DABCO, reflux, 16 h, degassed THF.

In order to obtain a higher yield of the free phosphine borane **102**, different amounts of DABCO were investigated. In addition, toluene was also investigated as the solvent. According to the ^{31}P NMR spectrum of the crude product, starting phosphine **98** was still in the crude product even though 1.1 equivalents of DABCO were used (Scheme 2.30, Table 2.5, entry 1). Hence, the amount of DABCO was increased to 1.5 equivalents (Table 2.5, entry 2). Nevertheless, there was evidence that more phosphine oxide **103** had formed (7%) as well as some phosphine borane **98** (13%). Hence, degassed toluene was explored as another option. Thus, a solution of allyl phosphine borane **98** in toluene was refluxed using 1.5 equivalents of DABCO (Table 2.5, entry 3). Unfortunately, this gave less free phosphine **102** (68%) and more phosphine oxide **103** (18%) than in THF.

Scheme 2.30



Reagents and conditions: i. DABCO, reflux, 16 h, degassed THF or toluene.

Table 2.5

Entry	Solvent	DABCO (eq.)	phosphine : P=O :P-BH_3 [a]
1	THF	1.1	75:3:22
2	THF	1.5	80:7:13
3	Toluene	1.5	68:18:14

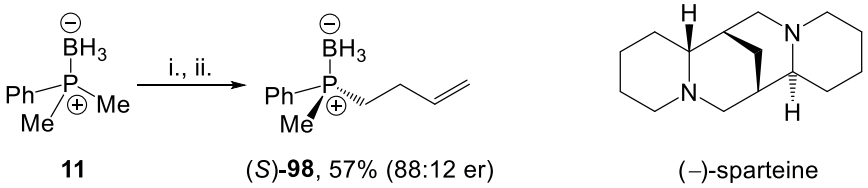
[a] Ratio determined from the ^{31}P NMR spectrum of the crude product.

Based on our results, 1.5 equivalents of DABCO in refluxing THF could remove most of borane group and gave the best conversion to free phosphine **102** even though oxidation to the phosphine oxide was not completely avoided.

2.8 Asymmetric Lithiation of Phenyl Dimethylphosphine Borane and Trapping with Allyl Bromide

Asymmetric deprotonation of dimethylphosphine borane **11** and trapping with electrophiles was first presented by Evans in 1995.[6] This approach has recently been applied in the O'Brien group to prepare allylated phosphine borane (*S*)-**98**.[73] In that work, asymmetric lithiation of phosphine borane **11** was carried out using 1.1 equivalents of *s*-BuLi in the presence of (–)-sparteine (1.2 eq.) in Et_2O at −78 ˚C for 2 hours. The lithiated intermediate was then trapped with 1.2 equivalents of allyl bromide. The resulting mixture was allowed to warm to rt over 1 hour. The crude product was purified by flash chromatography to afford enantioenriched *P*-stereogenic phosphine-alkene (*S*)-**98** (57%, 88:12 er) (Scheme 2.31).

Scheme 2.31

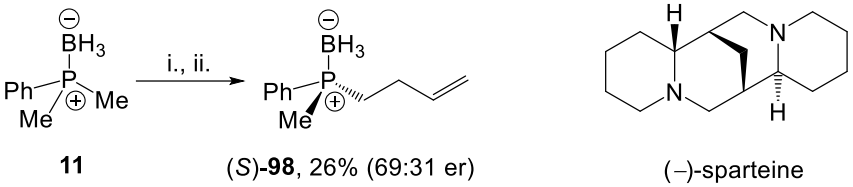


11 (*S*)-**98**, 57% (88:12 er) (–)-sparteine

Reagents and conditions: i. (–)-sparteine (1.2 eq.), *s*-BuLi (1.1 eq.), −78 ˚C, 2 h, Et_2O; ii. allyl bromide (1.2 eq.), −78 ˚C to rt, 1 h.

Thus, we planned to use a similar approach to prepare the chiral alkene-phosphine boranes. To start with, the asymmetric synthesis of (*S*)-**98** was attempted. Thus, a 0.22 M solution of phenyl phosphine borane **11** in Et_2O was asymmetrically deprotonated with *s*-BuLi in the presence of (−)-sparteine (1.5 eq.) at −78 ˚C for 10 minutes. The lithiated intermediate was then trapped with allyl bromide at −78 ˚C and the reaction was stirred to rt for 16 hours. The resulting mixture was quenched and worked-up to give *P*-stereogenic phosphine borane (*S*)-**98** in 26% yield and 69:31 er after purification by chromatography (Scheme 2.31). The lower yield of phosphine borane (*S*)-**98** could be a result of an incomplete asymmetric lithiation but it is not clear why the enantioselectivity is lower.

Scheme 2.31

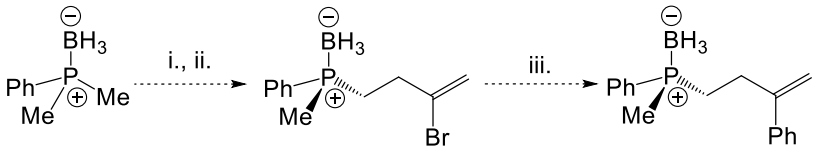


11 (*S*)-**98**, 26% (69:31 er) (−)-sparteine

Reagents and conditions: i. (−)-sparteine (1.5 eq.), *s*-BuLi (1.5 eq.), −78 ˚C, 10 min, Et_2O; ii. allyl bromide (2.0 eq.), −78 ˚C to rt, 16 h.

Even if we could synthesise *P*-stereogenic allyl phosphine borane (*S*)-**98** with 88:12 er, we could not easily improve the enantiomer ratio to 99:1 er because phosphine borane (*S*)-**98** is an oil and so recrystallisation is not available. Therefore, an asymmetric lithiation of phenyl phosphine borane **11** using *s*-BuLi-(−)-sparteine and trapping with 2,3-dibromoprop-1-ene which would give the bromo phosphine borane (*S*)-**101** was considered. Thus, the cross coupling of the bromo phosphine borane (*S*)-**101** with phenyl boronic acid in the presence of Pd as a catalyst was expected to give chiral phosphine borane (*S*)-**104** which we hoped would be a solid (Scheme 2.33). Hence, the enantiomeric ratio could be improved by recrystallisation. However, this idea has not been investigated further due to time constraints.

Scheme 2.33



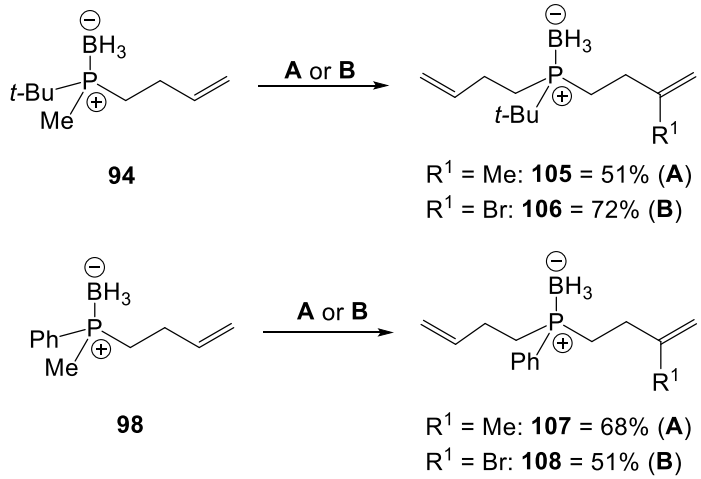
11 (*S*)-**101** (*S*)-**104**

Reagents and conditions: i. (−)-sparteine (1.5 eq.), *s*-BuLi (1.5 eq.), −78 ˚C, 2 h, Et_2O; ii. 2,3-dibromoprop-1-ene (2.0 eq.), −78 ˚C to rt, 1 h; iii. $PhB(OH)_2$, Pd catalyst.

2.9 Synthesis of Dihomoallylic Phosphine Boranes

The next part of our project was to synthesise the racemic dihomoallylic phosphine boranes. The synthetic route began with the lithiation of phosphine boranes **94** or **98** which was followed by trapping with different allyl halides as electrophiles. The results are shown in Scheme 2.34. In an attempt to synthesise an unsymmetrical dihomoallylic phosphine borane **105** by lithiation without transmetallation, the lithiated intermediate was then trapped with 3-chloro-2-methylpropene. Purification by chromatography afforded the desired product **105** in 51% yield. The ^{1}H NMR spectrum of dihomoallylic phosphine borane **105** contained a 1H singlet at δ_H 4.75 ppm and a 1H singlet at δ_H 4.71 ppm assigned to the two alkene protons CMe=C*H*$_2$. In addition, there was a 3H singlet at δ_H 1.74 ppm due to the methyl group on the alkene C*Me*=CH$_2$. The ^{31}P NMR spectrum of methyl phosphine borane **105** contained a quartet (J = 78.0 Hz) at δ_P 31.5 ppm confirming the presence of the borane group.

Scheme 2.34



Reagents and conditions: **A**. i. *s*-BuLi (1.2 eq.), 0 ˚C, 1 h, THF; ii. 3-chloro-2-methylpropene, 0 ˚C, 16 h, THF. or **B**. i. *s*-BuLi (1.2 eq.), 0 ˚C, 1 h, THF; ii LiCl (1.2 eq.) and CuCl (0.6 eq.), 0 ˚C, 1 h, THF, iii. 2,3-dibromoprop-1-ene, 0 ˚C, 16 h, THF.

In order to introduce a vinyl bromide into one of the side chains, allyl *t*-butylphosphine borane **94** was lithiated using *s*-BuLi in THF, then the lithiated intermediate was transmetallated using a mixture of 2:1 LiCl:CuCl in THF before trapping with 2,3-dibromoprop-1-ene. As a result, dihomoallylic phosphine borane **106** was provided in 72% yield after chromatography. In the ^{1}H NMR spectrum of phosphine borane **106**, there was a 1H singlet at δ_H 5.65 ppm which was assigned to one of the protons on the alkene

CBr=CH_AH$_B$ and a 1H doublet (J = 1.5 Hz) at δ_H 5.40 ppm due to the other proton on the same alkene CBr=CH$_A$$H_B$. The ^{31}P NMR spectrum of phosphine borane **106** contained a quartet (J = 70.5 Hz) at δ_P 31.8 ppm for the phosphine borane group.

In addition, an unsymmetrical phenyl phosphine borane **107** was also prepared using 3-chloro-2-methylpropene. The desired product **107** was provided in 68% yield. In the ^{1}H NMR spectrum of phenyl phosphine borane **107**, there was a 1H singlet at δ_H 4.72 ppm and the other 1H singlet at δ_H 4.68 ppm, both assigned to the two alkene protons of CMe=CH_2. A 3H singlet of the methyl group attached to the alkene was observed at δ_H 1.68 ppm. The ^{31}P NMR spectrum contained a quartet (J = 74.5 Hz) at δ_P 16.4 ppm.

Finally, bromoallylic phenyl phosphine borane **108**, was also prepared by deprotonation of phenyl phosphine borane **98** using *s*-BuLi and transmetallation using 2:1 ratio of LiCl:CuCl in THF. The intermediate was then trapped with 2,3-dibromopro-1-ene to give unsymmetrical dihomoallylic phenyl phosphine borane **108** in 51% yield after chromatography (Scheme 2.34). The ^{1}H NMR spectrum of phenyl phosphine borane **108** contained a 1H double triplet (J = 2.0, 1.0 Hz) at δ_H 5.60 ppm according to one of the alkene protons on CBr=CH_AH$_B$ and also a 1H doublet (J = 2.0 Hz) at δ_H 5.37 ppm due to the geminal alkene proton, CBr=CH$_A$$H_B$.

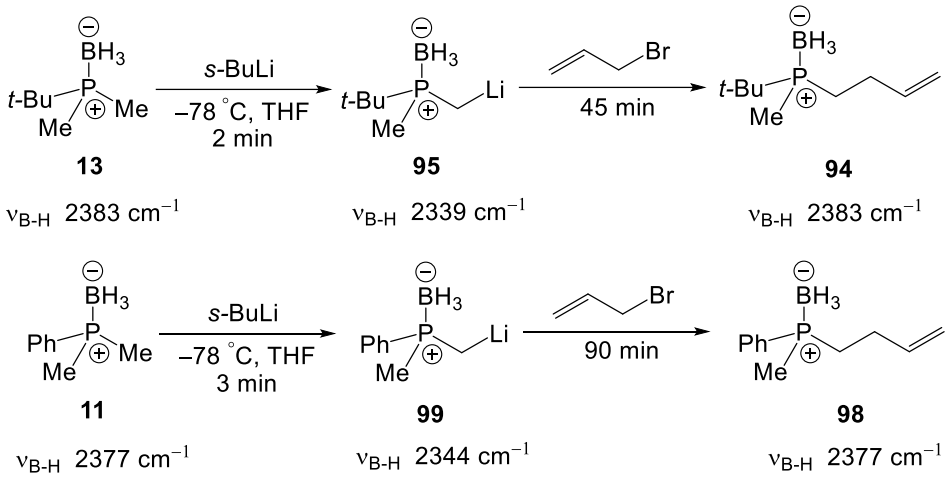
2.10 Conclusions and Future Work

Racemic deprotonation of phosphine boranes **13** and **11** was carried out and the lithiated intermediate was trapped with different allyl halides to give a range of homoallylic phosphine boranes **94**, **96-98** and **100-101**. Of note, we showed that transmetallation using LiCl/CuCl gave higher yields when trapping with 2,3-dibromopro-1-ene as an electrophile.

To study the lithiation and electrophilic trapping of phosphine boranes **13** and **11** at low temperature (−78 ˚C), ReactIR spectroscopy was used to monitor the process. Monitoring by ReactIR revealed different rates of electrophile trapping for lithiated intermediates derived from *t*-butylphosphine borane **13** and phenylphosphine borane **11**. It was found that both phosphine boranes **13** and **11** could be deprotonated using *s*-BuLi at −78 ˚C in THF in <5 minutes. In addition, the wavenumbers of the lithiated intermediates were lower than those

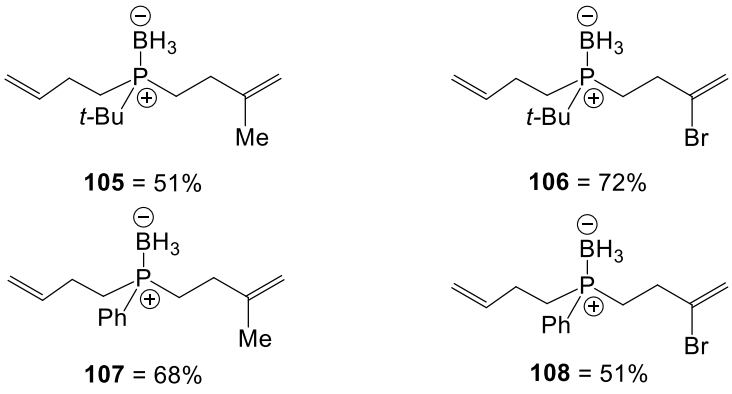
of the phosphine borane substrates, and a similar trend was seen with $\nu_{C=O}$ in *N*-Boc heterocycles when they are lithiated.[69,71] However, the electrophile trapping rates of the phosphine boranes **13** and **11** were different. Thus, ReactIR spectroscopy monitoring showed that the allyl *t*-butylphosphine borane **94** took 45 minutes to completely form whereas the allyl phenylphosphine borane **98** took 90 minutes (Scheme 2.35).

Scheme 2.35



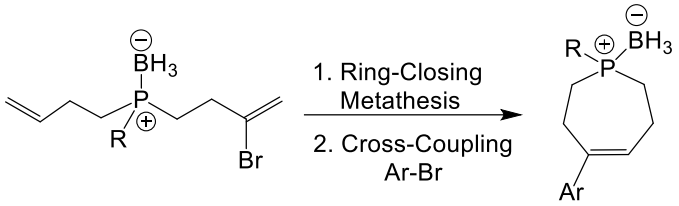
For the synthesis of dihomoallylic phosphine borane **105-108**, when *t*-butylallylic phosphine borane **94** or phenylallylic phosphine borane **98** were deprotonated by *s*-BuLi, the lithiated intermediates were then trapped with methallyl chloride without transmetallation. In contrast, when 2,3-dibromoprop-1-ene was used as an electrophile, the lithiated intermediates had to be transmetallated using 2:1 ratio of LiCl:CuCl before electrophilic trapping. The lithiation reactions gave different unsymmetrical dihomoallylic phosphine boranes **105-108** (Figure 2.5) in variable yields (51-72%). This is the first time that such unsymmetrical dihomoallylic phosphine boranes have been prepared.

Figure 2.5



Future work should focus on the asymmetric synthesis of alkene-phosphine boranes, the ring-closing metathesis to generate cyclic phosphine boranes and the borane deprotection step. In addition, using vinyl bromides **106** and **108**, ring-closing metathesis and subsequent cross-coupling would give aryl-alkenes **109** (Scheme 2.36). Then, with chiral phosphine-alkenes prepared, they could be investigated in catalytic asymmetric reactions such as the 1,4-addition of boronic acids to enones. Due to the disappointing results for the asymmetric reaction and the issues with borane deprotection, work on this project was stopped in order to explore a different project, as described in the next chapter.

Scheme 2.36



106 R = *t*-Bu
108 R = Ph

109

Chapter 3 Investigation of New Routes to 2-Heteroaryl 3-Hydroxy Piperidines

This chapter describes our efforts at developing new approaches for the synthesis of 2-heteroaryl 3-hydroxy piperidines *anti*-**2** and *syn*-**2** (Figure 3.1). The route that we planned to develop involved the ring expansion of hydroxyl pyrrolidines to 3-hydroxy piperidines (*via* aziridinium ions). The route needed to address two main aspects. First, it should be possible to readily introduce a range of heteroaromatic groups at the 2-position. Second, diastereoselective access to *anti*-**2** and *syn*-**2** would be preferable. Relevant literature background on 3-hydroxy piperidines and previous synthetic routes are described in Sections 3.1 and 3.2. Then, the investigations of our new routes are presented in Sections 3.3-3.6.

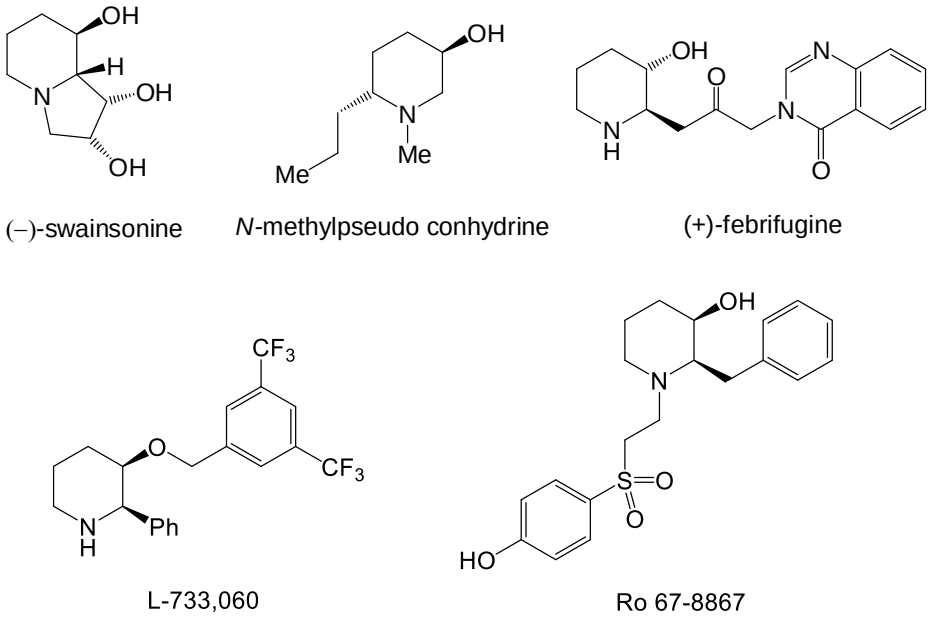
Figure 3.1

syn-**2** *anti*-**2**

3.1 Brief Introduction of New Routes to 3-Hydroxy Piperidines

The 3-hydroxy piperidine structure is common in natural products and is a heterocyclic skeleton that has been found to show biological activity. For example, (–)-swainsonine is a powerful inhibitor of lysosomal α-mannosidase,[74] *N*-methyl pseudo conhydrine is a toxic natural product from hemlock *Conium maculatum* L.[75] and (+)-febrifugine is an antimalarial isolated from a Chinese medical plant *Dichroa febrifuga*[76] (Figure 3.2). Within the pharmaceutical industry, many 3-hydroxy piperidine derivatives have been researched and developed as potential drugs. Examples include L-733,060 which shows biological activity as an NK_1 receptor[77] antagonist and has anti-cancer properties[78] and Ro 67-8867, an *N*-methyl-D-aspartate (NMDA) receptor antagonist.[79]

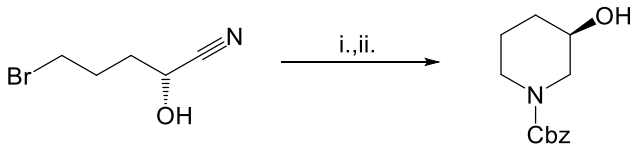
Figure 3.2



3.2 Overview of Synthetic Routes to 3-Hydroxy Piperidines

A wide range of methods have been developed for the synthesis of 3-hydroxy piperidines and this section provides an overview of the most common strategies. In 1999, Gotor and co-workers synthesised 3-hydroxy piperidine **111** in high % ee.[80] To begin with, optically active bromocyanohydrin **110** was prepared by an enzymatic procedure.[81] The nitrile was reduced using BH_3•THF to an amine which cyclised and was then protected with benzylchloroformate to give benzyloxycarbonyl-hydroxy piperidine **111** in 40% yield and 96% ee (Scheme 3.1).

Scheme 3.1

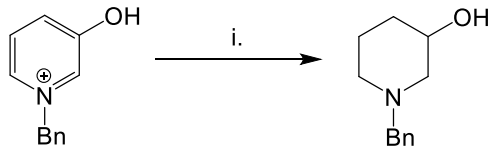


110 **111**, 40% (96% ee)

Reagents and conditions: i. BH_3•THF, rt, 6 h; ii. CbzCl, Na_2CO_3, 6 h, H_2O.

Recently, Xiao and co-workers studied a rhodium-catalyzed transfer hydrogenation of pyridines to piperidines.[82] For the synthesis of 3-hydroxy piperidine **113**, *N*-benzyl pyridine **112** was chemoselectively reduced using the rhodium complex dimer, $[Cp^*RhCl_2]_2$. Hydrogenation using 0.05 mol% of the rhodium catalyst gave 3-hydroxy piperidine **113** in excellent yield (99%) whereas the yield dramatically dropped to 63% with 0.005 mol% catalyst loading (Scheme 3.2).

Scheme 3.2



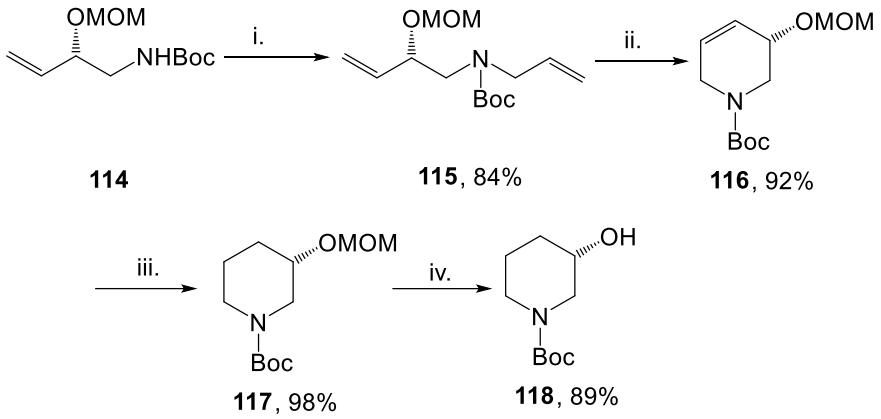
112 **113**, 99% (63%)[a]

Reagents and conditions: i. $[Cp^*RhCl_2]_2$ (0.05 mol%), HCO_2H-Et_3N, azeotrope, KI, 40 °C, 24 h.

a Yield obtained with 0.005 mol% catalyst

Rao and co-workers reported a ring closing metathesis route to 3-hydroxy piperidines.[83] For example, treatment of amine **114** with allyl bromide in the presence of NaH gave the key precursor **115** in 84% yield. Next, ring closing metathesis of **115** with Grubbs I catalyst gave piperidine **116** in 92% yield. Subsequent hydrogenation of piperidine **116** gave *N*-Boc piperidine **117** in 98% yield. Treatment with HCl in MeOH resulted in removal of the MOM and Boc groups. The free amine of 3-hydroxy piperidine was then Boc protected to furnish *N*-Boc piperidine **118** in 89% yield (Scheme 3.3).

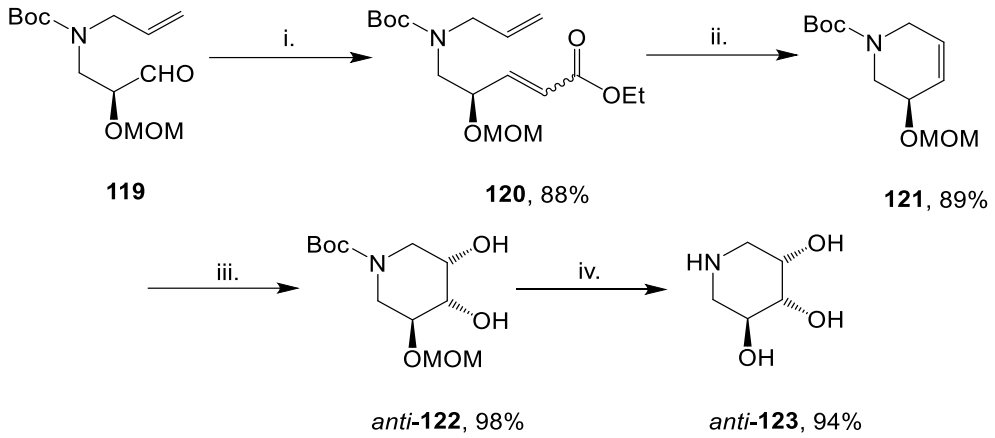
Scheme 3.3



Reagents and conditions: i. NaH, allyl bromide, cat TBAI, THF, rt, 4 h; ii. Grubbs I catalyst, rt, 24 h, 92%; iii. H_2/PtO_2, EtOAc, rt, 1 h; iv. (a) 6 N HCl, MeOH, rt, 7 h; (b) Et_3N, Boc_2O, rt, 30 min.

Similarly, the ring closing metathesis strategy was also used to give polyhydroxypiperidines. Thus, Han synthesised a mannose analogue **123** starting from aldehyde **119** prepared in 6 steps from protected allyl alcohol.[84] Then, Horner-Wadsworth-Emmons reaction of aldehyde **119** gave the ring closing metathesis precursor **120** in 88% yield (Scheme 3.4). Next, treatment of **120** with Grubbs II catalyst gave six-membered ring **121** in 89% yield. Dihydroxylation of cyclic alkene **121** gave dihydroxy piperidine *anti*-**122** in excellent yield (98% yield) which was finally deprotected to form the mannose analogue a*nti*-**123** in 94% yield.

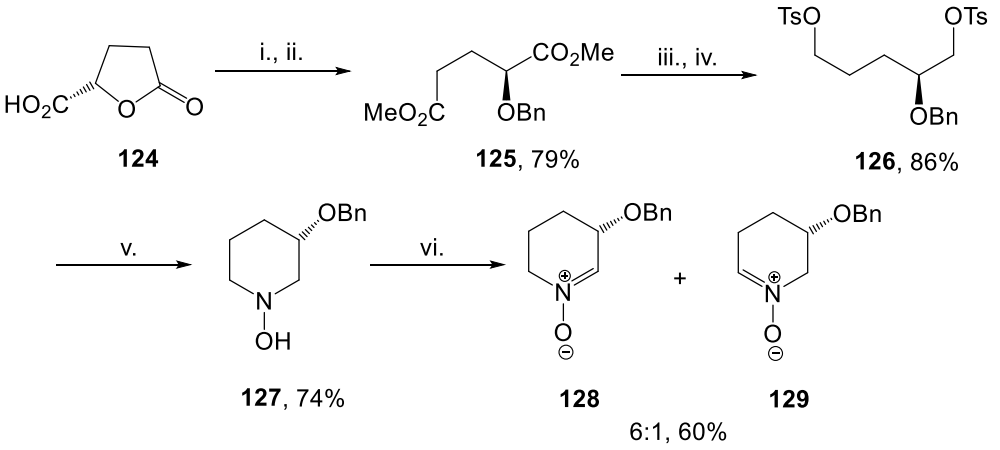
Scheme 3.4



Reagents and conditions: i. triethyl phosphonoacetate, LiBr, DBU, THF; ii. Grubbs II catalyst, CH_2Cl_2; iii. OsO_4, NMO, MeCN-H_2O 1:1; iv. 6 N HCl, 80 ˚C.

The potent anti-malarial alkaloid, (+)-febrifugine, was synthesised by Caprio and Amir in 2005.[85] In this work, nitrone **129** was used as a key intermediate. The synthesis started with an acid-catalysed ring opening of lactone **124** which was derived from L-glutamic acid. Next, the resulting hydroxydiester was benzyl-protected to give benzyl ether **125** in 79% yield. Reduction of diester **125** followed by ditosylation provided 1,5-ditosylate **126** in 86% yield. Cyclisation of ditosylate **126** was carried out by refluxing with hydroxylamine hydrochloride in Et_3N to obtain *N*-hydroxy-3-benzyloxypiperidine **127** in 74% yield. Finally, oxidation of piperidine **127** using MnO_2 gave a 6:1 mixture of separable regioisomeric nitrones **128** and **129** in 60% overall yield (Scheme 3.5).[86]

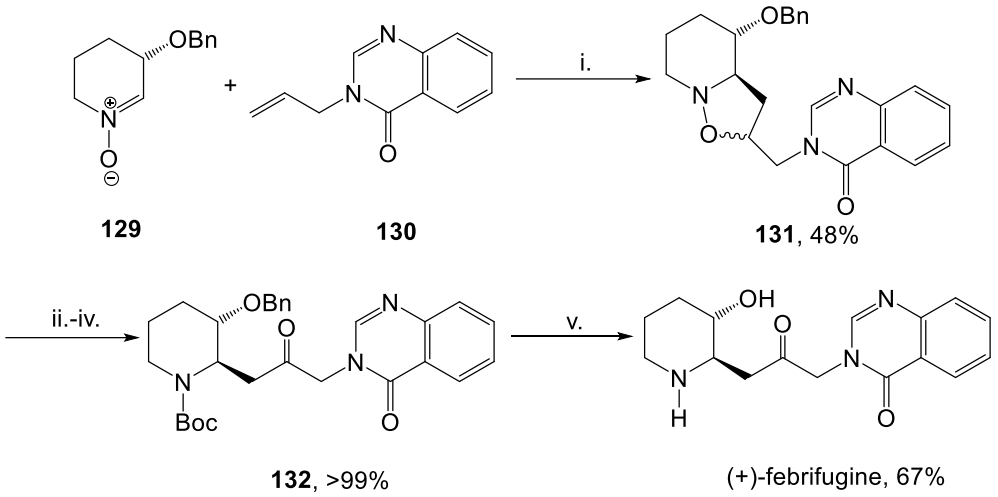
Scheme 3.5



Reagents and conditions: i. $HCl_{(concd)}$, MeOH, reflux, 12 h; ii. BnBr, Ag_2O, EtOAc, rt, 48 h; iii. $LiAlH_4$, Et_2O, 24 h; iv. *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, rt, 12 h; v. $NH_2OH.HCl$, Et_3N, reflux, 4 h; vi. MnO_2, CH_2Cl_2, 0 ˚C, 12 h.

The 1,3-dipolar cycloaddition of nitrone **129** and dipolarophile **130** gave isoxazolidine **131** in 48% yield. Then, reductive cleavage of cycloadduct **131** was achieved by refluxing in the presence of zinc and acetic acid. The resulting free amine was Boc-protected and oxidised using Dess-Martin periodinane to provide ketone **132**. Eventually, the Boc and benzyl groups were removed to give (+)-febrifugine in 67% yield (Scheme 3.6).

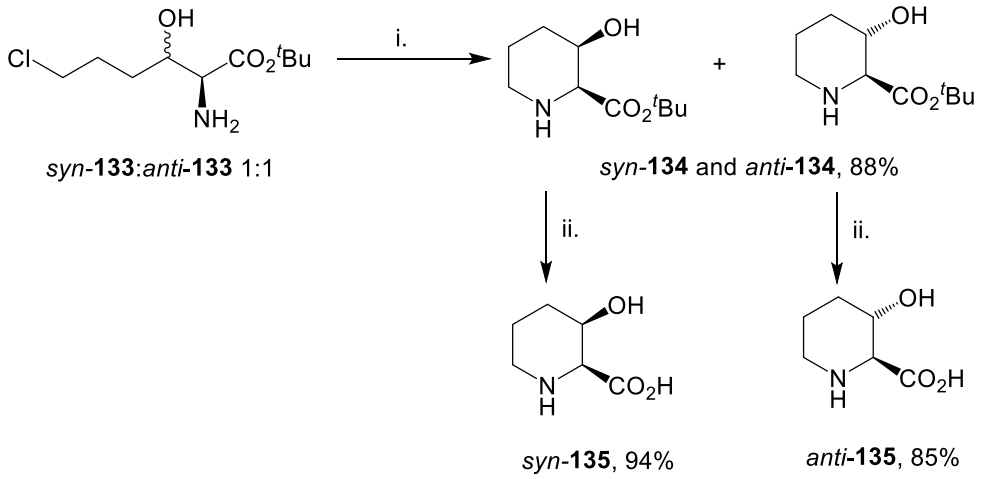
Scheme 3.6



Reagents and conditions: i. PhMe, reflux, 24 h; ii. Zn, HOAc, reflux; iii. Boc_2O, Et_3N, CH_2Cl_2; iv. Dess-Martin periodinane, pyridine, CH_2Cl_2; v. 6 M $HCl_{(aq)}$, reflux.

In 1999, Corey and co-workers presented a synthetic approach to 3-hydroxy piperidines.[87] The synthesis started with an aldol reaction using a silyl enol ether derivative synthesized from L-glutamic acid which gave a 1:1 mixture of hydroxy esters *syn*- and *anti*-**133**. Then, cyclization of esters *syn*- and *anti*-**133** gave 3-hydroxy piperidines *syn*-and *anti*-**134** which were seperable (total yield 88%). After treatment of esters *syn*-and *anti*-**134** with TFA, 3-hydroxy pipecolic acids *syn*-and *anti*-**135** were obtained in 94% and 85% yield respectively (Scheme 3.7). These two compounds are well-known intermediates for the synthesis of swainsonine.

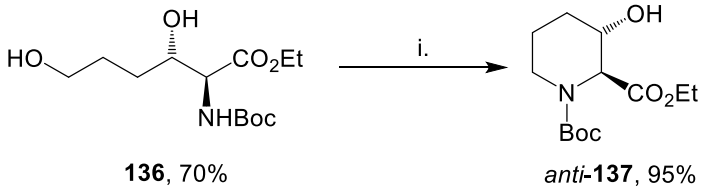
Scheme 3.7



Reagents and conditions: i. $NaHCO_3$, MeCN, 100 °C, 30 min; ii. TFA, CH_2Cl_2.

In a related method, Kumar and Bodas reported a synthetic approach starting from 1,4-butanediol.[88] Amino alcohol **136** was prepared in six steps and the stereochemistry was set up by a Sharpless asymmetric dihydroxylation reaction. Starting from amino alcohol **136**, addition of methanesulfonyl chloride in the presence of Et_3N formed a mesylate on the least sterically hindered alcohol and subsequent cyclization gave 3-hydroxy piperidine *anti*-**137** in 95% yield (Scheme 3.8).[89]

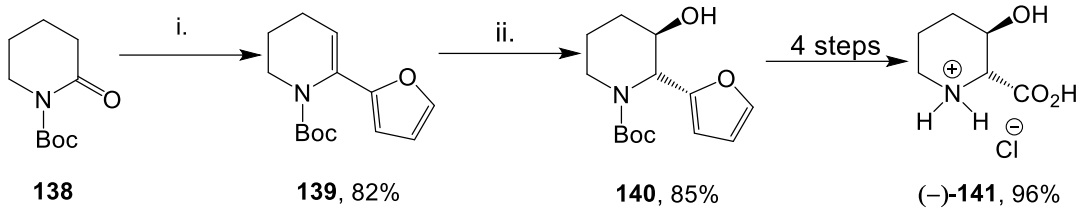
Scheme 3.8



Reagents and conditions: i. MsCl, Et_3N, CH_2Cl_2, −78 °C.

Recently, Occhiato and co-workers reported a short, chemo-enzymatic synthesis of *syn*- and *anti*-3-hydroxy pipecolic acid.[90] The key step was the Suzuki-Miyaura reaction of an enol phosphate derived from lactam **138** with furanylboronic acid to give a furanyl carboxylate **139** in 82% yield (Scheme 3.9). Then, hydroboration was carried out to give 3-hydroxy piperidine **140** in 85% yield. The *anti*-stereochemistry in **140** comes from the *syn* stereospecificity of the hydroboration reaction. To obtain an enantioenriched compound, a lipase-catalyzed kinetic resolution of racemic **140** was employed to give piperidine (−)-**140** in 60% yield and 99% ee. Finally, four more steps[91] were carried out to give the hydrochloride salt of 3-hydroxy pipecolic acid (−)-**141** in 96% yield.

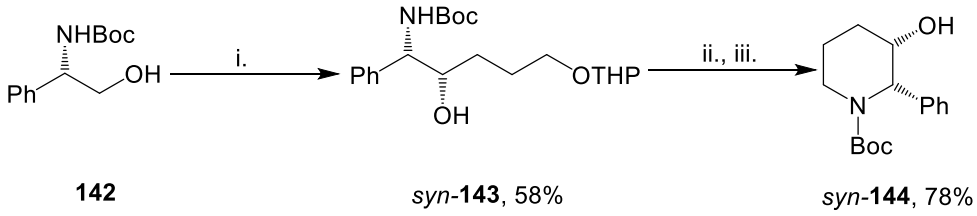
Scheme 3.9



Reagents and conditions: i. a) $(PhO)_2POCl$, KHMDS, THF, −78 ˚C; b) furanylboronic acid, $(Ph_3P)_2PdCl_2$, Na_2CO_3 (2 M, THF), 40 ˚C; ii. BH_3•THF, THF, 0 ˚C then Me_3NO, THF, 65 ˚C.

In 2004, a 3-hydroxy piperidine derivative **144** containing an aromatic ring at the 2-position was prepared from L-phenylglycine.[92] Swern oxidation of alcohol **142** generated an aldehyde *in situ*. Next, addition of 3-(tetrahydropyran-2-yloxy)propylmagnesium bromide to the aldehyde gave amino alcohol *syn*-**143** in 58% yield as a single diastereomer (Scheme 3.10).[93] The THP group in *syn*-**143** was removed using *p*-toluenesulfonic acid to give a diol which was then mesylated and cyclized using NaH to finally afford 3-hydroxy phenyl piperidine *syn*-**144** in 78% yield.[94]

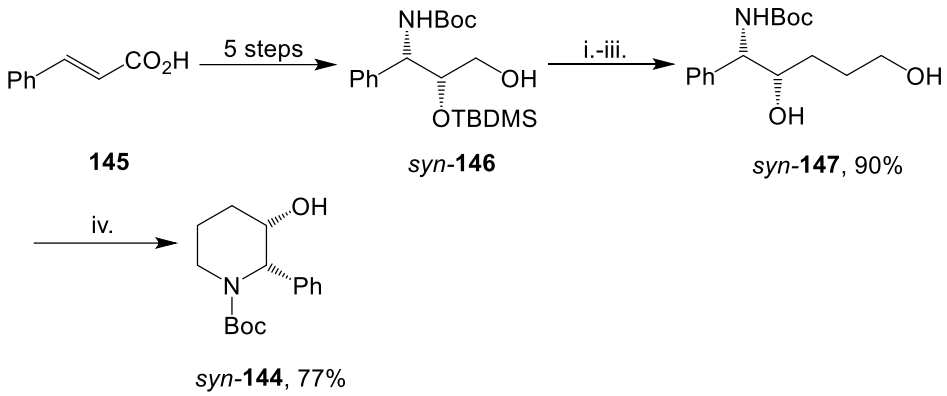
Scheme 3.10



Reagents and conditions: i. DMSO, $(COCl)_2$, CH_2Cl_2, *i*-Pr_2NEt then $BrMg(CH_2)_3OTHP$, THF, rt, 2 h; ii. *p*-TsOH, MeOH, rt, 2 h; iii. a) MsCl, Et_3N, CH_2Cl_2, 0 ˚C to rt, 3 h; b) NaH, THF, rt.

A different synthetic approach was used to access the same type of cyclization precursor, diol *syn*-**147**.[95] Starting from cinnamic acid **145**, Sharpless asymmetric aminohydroxylation was used to control the stereochemistry.[96] Then, treatment of alcohol *syn*-**146** with PCC was followed by a Wittig reaction to give an alkene. Hydrogenation, TBDMS removal and ester reduction gave diol *syn*-**147** in 90% yield. Finally, cyclisation to 3-hydroxy piperidine *syn*-**144** was achieved in 77% yield using methanesulfonyl chloride (Scheme 3.11).

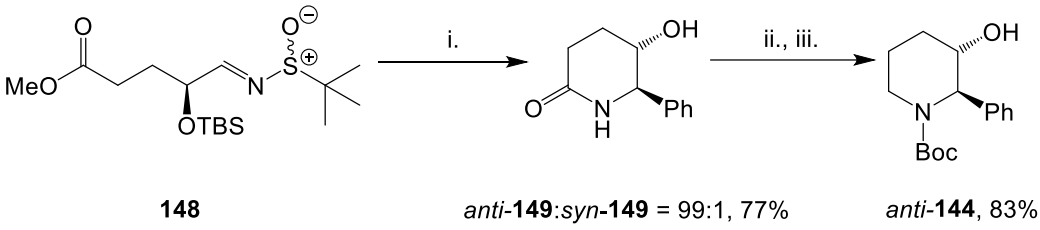
Scheme 3.11



Reagents and conditions: i. a) PCC, NaOAc, Celite, 25 ˚C, 5 h; b) $Ph_3P{=}CHCO_2Et$, THF, 25 ˚C, 24 h; ii. 10% Pd/C, MeOH, 25 ˚C, 6 h; iii. DIBAL-H, CH_2Cl_2, 0-25 ˚C, 3 h; iv. MsCl, Et_3N, CH_2Cl_2, –78 ˚C, 1 h.

Recently, Wei and co-workers reported a diastereoselective synthetic approach to 3-hydroxy piperidines using *N-tert* butylsulfinyl aldimine **148** as a key intermediate.[97] Pioneered by Ellman and Davis,[98–100] *N-tert* butanesulfinyl imines are important intermediates in modern asymmetric synthesis. In this approach, aldimine **148** was prepared from L-glutamic acid and addition of PhMgBr gave a 99:1 mixture of 3-hydroxy piperidinones *anti*- and *syn*-**149** in 77% yield (Scheme 3.12). Then, lactam **149** was reduced using $LiAlH_4$ and Boc protection gave *N*-Boc 3-hydroxy piperidine *anti*-**144** in 83% yield.

Scheme 3.12

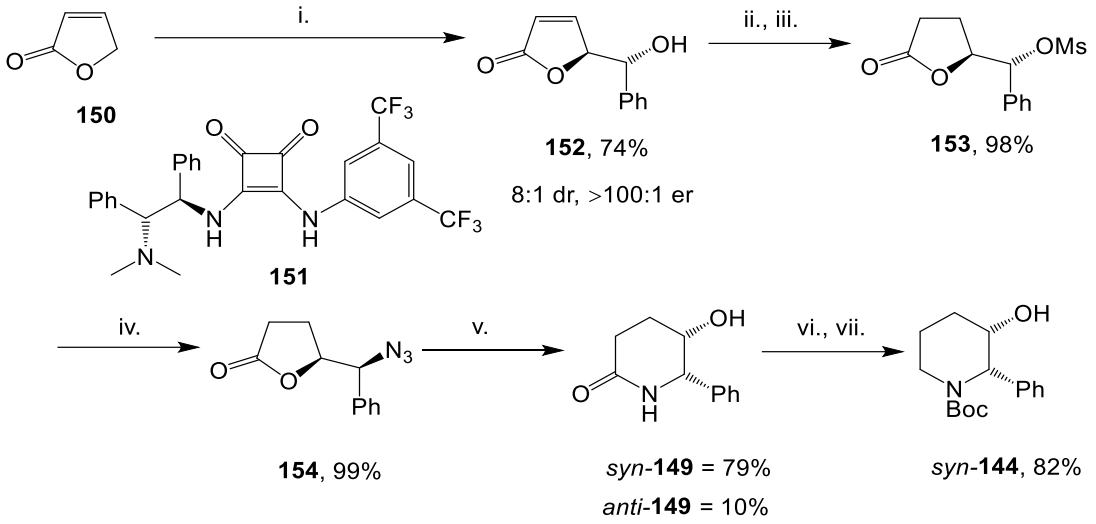


Reagents and conditions: i. PhMgBr, THF, –78 ˚C, 3 h; ii. $LiAlH_4$, 60 ˚C, 6 h; iii. Boc_2O, CH_2Cl_2, 12 h.

An alternative route to phenyl 3-hydroxypiperidine *anti*-**144** was described by Pansare and Paul.[101] Their approach used γ-butenolide **152** as a key intermediate. The synthesis started from the aldol-like reaction of γ-crotonolactone **150** and benzaldehyde using aminosquaramide **151** as an organocatalyst to give an 8:1 mixture of diastereomeric γ-butenolides *anti*-and *syn*-**152** in 74% yield and >100:1 er (Scheme 3.13). Then, hydrogenation and subsequent mesylation gave mesylate **153** in 98% yield. Next, reaction with sodium azide gave an inversion of configuration to form azido butyrolactone **154** in 99% yield. Hydrogenation and then rearrangement gave piperidinones *syn*- and *anti*-**149** in

79% and 10% yield respectively. Finally, reduction of lactam *syn*-**149** using BH_3•THF and a Boc protection gave 3-hydroxy piperidine *syn*-**144** in 82% yield over two steps.

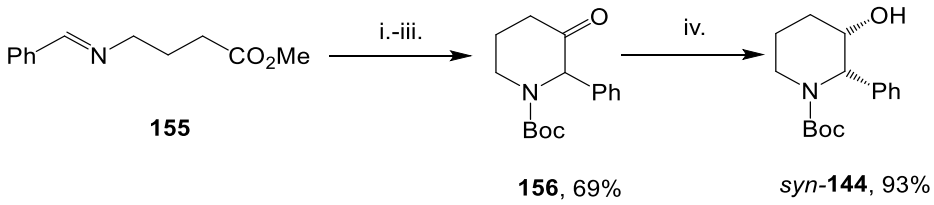
Scheme 3.13



Reagents and conditions: i. PhCHO, **151**, CH_2Cl_2, rt; ii. H_2, Pd/C, rt, 4 h; iii. MsCl, Et_3N, CH_2Cl_2, 0 ˚C, 1 h; iv. NaN_3, DMF, 80 ˚C, 4 h; v. H_2, Pd/C, K_2CO_3, MeOH; vi. BH_3•THF, reflux, 5 h then 3 M $HCl_{(aq)}$, rt, 30 min; vii. Boc_2O, Et_3N, DMAP, CH_2Cl_2.

In addition, Kise and co-workers presented an electroreductive intramolecular coupling of a β-amino ester for the synthesis of 3-hydroxy piperidine *syn*-**144**.[102] In this route, *N*-benzylidene methyl ester **155** prepared from γ-aminobutyric acid and benzaldehyde was a key intermediate in the electroreduction using trimethylsilyl chloride and a Pb cathode. *N*-Silylation and 2-electron reduction of the iminium ion gave a benzyl carbanion which cyclised onto the ester to give a silyl-protected ketal (Scheme 3.14). Then, Boc protection and hydrolysis provided ketone **156** in 69% yield. Finally, ketone reduction using $NaBH_4$ gave 3-hydroxy piperidine *syn*-**144** in 93% yield.

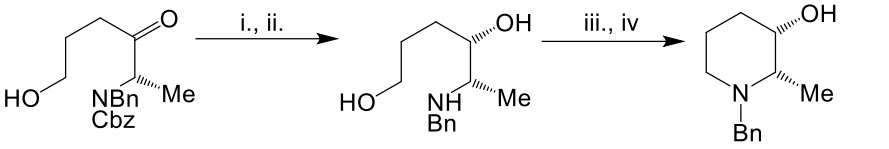
Scheme 3.14



Reagents and conditions: i. +e, Pb cathode, Me_3SiCl/Et_3N; ii. Boc_2O, Et_3N; iii. 1 M HCl; iv. $NaBH_4$, MeOH, 5 ˚C.

Recently, Huy and Koskinen developed a stereodivergent synthetic route using ketone **157** as a key intermediate.[103] The synthesis started from L-alanine. Ketone reduction using L-selectride selectively gave a single diastereomeric alcohol (due to the Felkin-Ahn control) and Cbz removal using H_2 in the presence of Pd/C provided diol **158** in 85% yield (Scheme 3.15). Finally, alcohol **158** was reacted with ethyl phosphite in the presence of iodine and saponification during the work-up gave 2-methyl 3-hydroxy piperidine *syn*-**159** in 82% yield and ≥99% ee.

Scheme 3.15

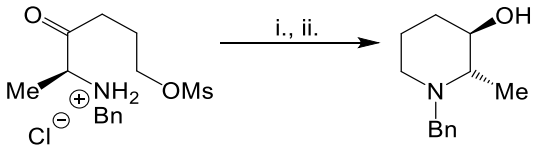


157 **158**, 85% *syn*-**159**, 82% (≥19:1 dr, ≥99% ee)

Reagents and conditions: i. L-selectride, THF; ii. H_2, Pd/C, MeOH (one pot); iii. I_2, $P(OEt)_3$, Et_3N/ CH_2Cl_2, –78 to rt °C; iv. work-up with OH^-

In addition, a route to the other diastereomer was investigated. Thus, hydrochloride salt **160** was prepared from *N*-benzyl-*N*-Cbz protected L-alanine. Then, treatment with DBU gave the free amine *in situ* and reduction using L-selectride and cyclization afforded 3-hydroxy piperidine *anti*-**159** in 71% yield and 99% ee (Scheme 3.16). In this case, a Cram chelation model was proposed to explain the opposite diastereoselectivity in the reduction step.

Scheme 3.16



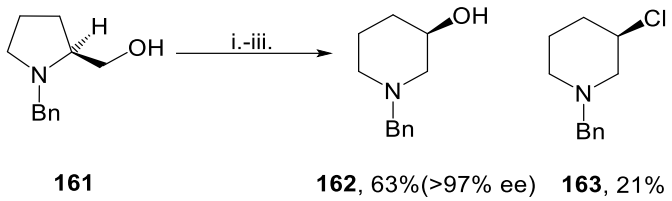
160, 87% *anti*-**159**, 71% (99% ee)

Reagents and conditions: i. DBU then L-selectride, –78 °C; ii. HCl then Et_3N.

In 1995, Cossy and co-workers introduced a simple route for obtaining a 3-hydroxy piperidine in high % ee from an *N*-alkylpyrrolidine. To start with, *N*-benzylpyrrolidine **161** prepared from (*S*)-proline was reacted with trifluoroacetic anhydride and Et_3N in THF. After refluxing in THF, hydrolysis with NaOH led to the formation of 3-hydroxy *N*-benzylpiperidine **162** in 63% yield (Scheme 3.17).[104] In this case, the solvent was found

to be an important issue that affected the yield and the formation of a by-product. Thus, when the ring expansion of the *N*-benzylpyrrolidine **161** was carried out in dichloromethane, the reaction was very slow and chlorinated analogue **163** was formed in 21% yield together with 3-hydroxypiperidine **162**.

Scheme 3.17

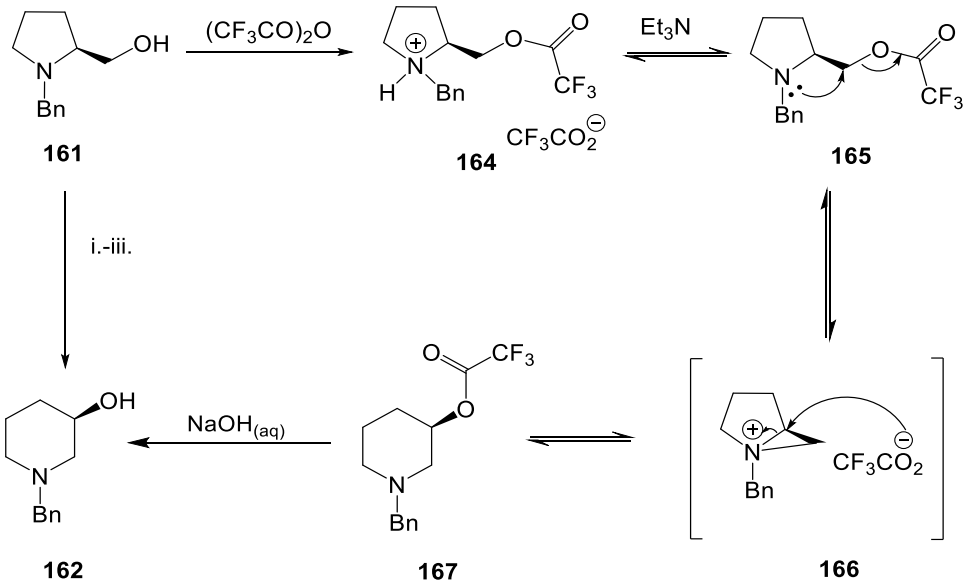


161 **162**, 63%(>97% ee) **163**, 21%

Reagents and conditions: i. TFAA, reflux, THF; ii. Et_3N; iii. 10% $NaOH_{(aq)}$.

Cossy proposed a mechanism for this formation of 3-hydroxy piperidines from pyrrolidines. The ring expansion mechanism started with esterification using trifluoroacetic anhydride to generate a quaternary ammonium salt **164** (Scheme 3.18). Then, treatment with Et_3N allowed an equilibrium between amino ester **165** and aziridinium ion **166** to be set up, *via* an intramolecular nucleophilic substitution. Finally, NaOH was added to provide 3-hydroxy piperidine **162**. Presumably, the piperidine trifluoroacetate **167** is the thermodynamically preferred product.

Scheme 3.18

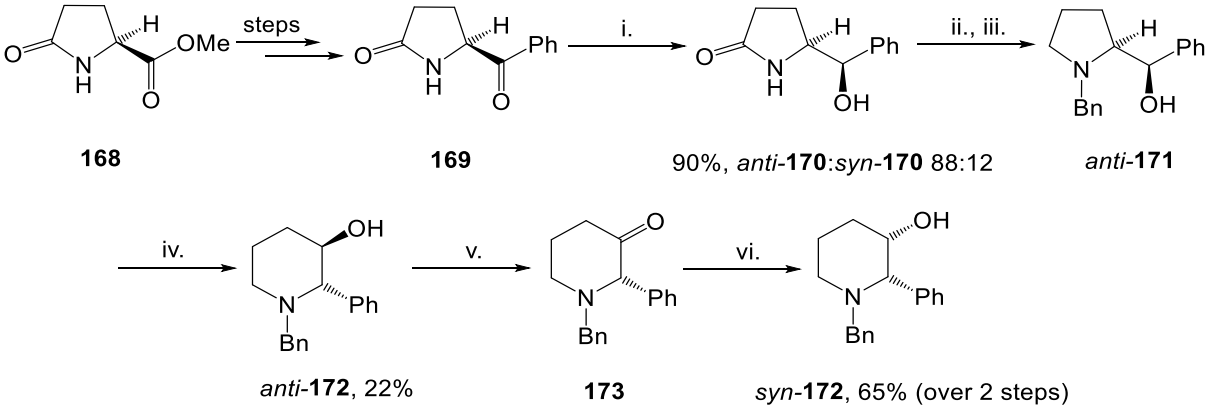


161 **164** **165** **162** **167** **166**

Reagents and conditions: i. TFAA, reflux, THF; ii. Et_3N; iii. 10% $NaOH_{(aq)}$.

A few years later, Langlois and co-workers developed a synthesis of 2-phenyl 3-hydroxypiperidine *anti*-**172** starting from (*S*)-methylpyroglutamate.[105] The key intermediate of this approach was phenyl ketone **169** which was prepared from methyl ester **168** *via* a Weinreb amide.[106] Then, ketone reduction using $NaBH_4$ in a 99:1 mixture of THF and MeOH gave an 88:12 mixture of diastereomeric alcohols *anti*-and *syn*-**170**, in 90% yield. Lactam reduction using $LiAlH_4$ and benzyl protection afforded seperable *N*-benzyl alcohols *anti*-and *syn*-**171**. Finally, ring expansion of *N*-benzyl pyrrolidine *anti*-**171** under Cossy's conditions was carried out to give 2-phenyl 3-hydroxy piperidine *anti*-**172** in 22% yield (Scheme 3.19). In later work, Langlois and Calvez reported the synthesis of *N*-benzyl 3-hydroxypiperidine *syn*-**172** through Swern oxidation and subsequent stereoselective reduction.[107] The ketone **173** was selectively reduced using L-selectride to give *N*-benzyl 3-hydroxypiperidine *syn*-**172** as a single diastereomer in 65% yield over two steps (Scheme 3.19).

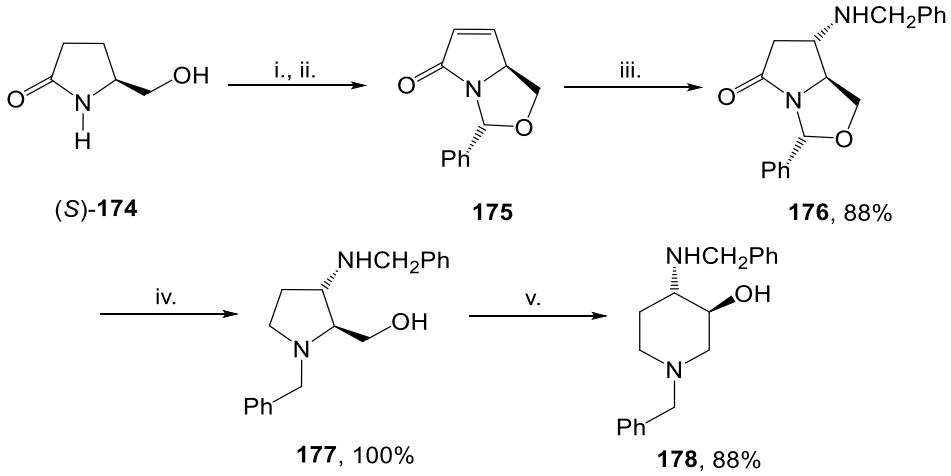
Scheme 3.19



Reagents and conditions: i. $NaBH_4$, THF-MeOH; ii. $LiAlH_4$; iii. BnBr, K_2CO_3, MeOH; iv. TFAA, Et_3N, NaOH; v. DMSO, $(COCl)_2$, *i*-Pr_2NEt, –20°C; vi. L-selectride, –78°C, 3 h.

In addition, a single diastereomer of piperidine **178** was prepared by the same group.[108] The synthesis started from (*S*)-pyroglutaminol **174** which was converted into unsaturated γ-lactam **175**. Then, conjugate addition of benzylamine provided γ-lactam **176** diastereoselectively in 88% yield. Next, the lactam **176** was reduced by $LiAlH_4$ with concurrent opening of the oxazolidine ring in quantitative yield.[109] Then, functionalised 3-aminoprolinol **177** was treated with trifluoroacetic anhydride and Et_3N. The ring-expansion reaction was followed by hydrolysis of the trifluoroacetoxy group by NaOH which finally led to piperidine **178** (Scheme 3.20).

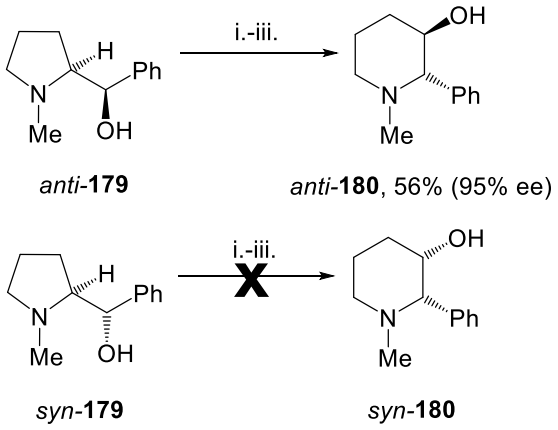
Scheme 3.20



Reagents and conditions: i. PhCHO, *p*-TsOH, reflux, 9 h, toluene; ii. $PhSO_2Me$, KH, rt, 2 h, THF; iii. $BnNH_2$, H_2O, rt; iv. $LiAlH_4$, reflux, 18 h, THF; v. (a) TFAA, −78°C, 3 h, THF; (b). Et_3N, −78°C, 15 min then reflux, 40 h; (c). 2.5 M $NaOH_{(aq)}$, rt, 2 h.

In 1999, Cossy and co-workers found that the ring expansion of various *N*-alkylated prolinols with *N*-alkyl groups such as benzyl, methyl and dimethylpropyl occurred readily to give 3-hydroxy *N*-alkylated piperidines. However, the secondary amine of prolinol or *N*-(*p*-nitrophenyl) prolinol did not undergo ring expansion.[110] In addition, ring enlargement under standard conditions of both *N*-methyl phenyl prolinols *anti*-and *syn*-**179** was investigated. Only amino alcohol *anti*-**179** underwent ring expansion and resulted in the formation of *N*-methyl 3-hydroxypiperidine *anti*-**180** in 56% yield and 95% ee (Scheme 3.21). In contrast, diastereomeric *N*-methyl 3-hydroxypiperidine *syn*-**180** was not formed from *syn*-**179** under the same conditions.

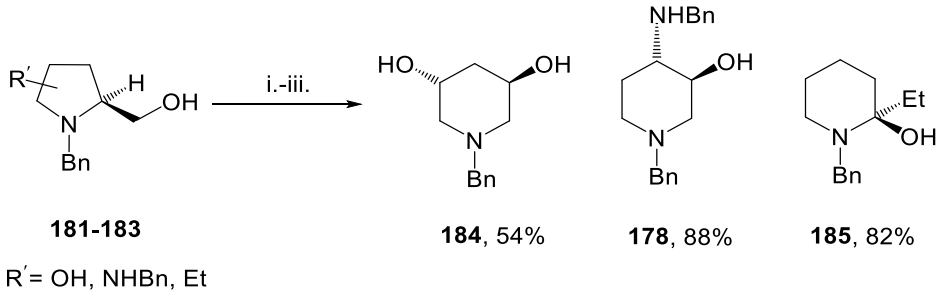
Scheme 3.21



Reagents and conditions: i. TFAA, reflux, THF; ii. Et_3N; iii. 10% $NaOH_{(aq)}$.

Interestingly, disubstituted 3-hydroxy piperidines could be successfully synthesised by this ring expansion reaction. For example, *N*-benzyl prolinols **181-183** were transformed into 3-hydroxypiperidines **178**, **184** and **185** in good yield and high enantiomeric excess (Scheme 3.22).

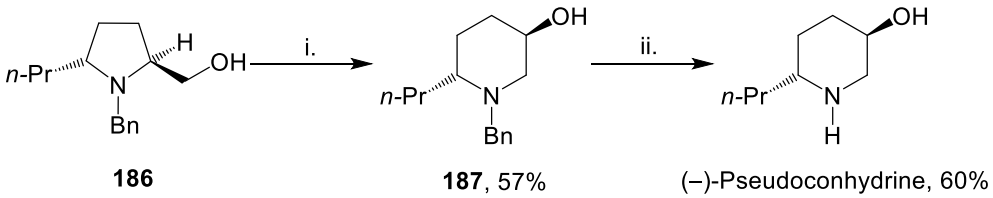
Scheme 3.22



Reagents and conditions: i. TFAA, reflux, THF; ii. Et_3N; iii. 10% $NaOH_{(aq)}$.

The utility of the ring expansion reaction for the synthesis of biologically active compounds was shown. (–)-Pseudoconhydrine, an alkaloid from hemlock (*Conium maculatum* L.),[111,112] was synthesised *via* a short and simple route by Cossy and co-workers.[113] To begin with, 5-propylpyrrolidine alcohol **186** was prepared over five steps from (*S*)-proline. Then, alcohol **186** was treated with trifluoroacetic anhydride, Et_3N and NaOH to form 3-hydroxy piperidine **187** in 57% yield (Scheme 3.23). Finally, debenzylation by hydrogenolysis in the presence of $Pd(OH)_2$ successfully gave the desired (–)-pseudoconhydrine in 60% yield.

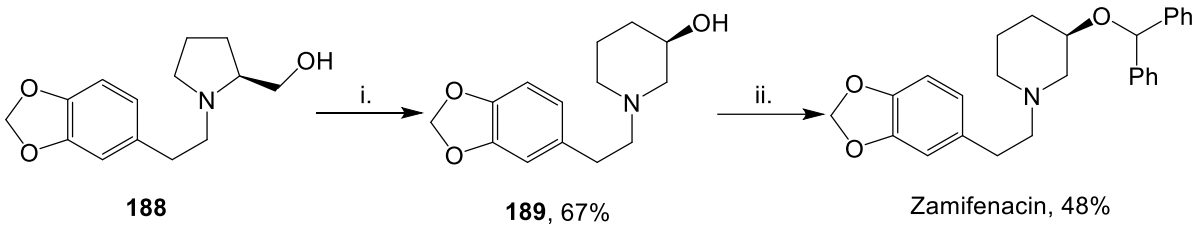
Scheme 3.23



Reagents and conditions: i. TFAA, Et_3N then NaOH; ii. H_2, $Pd(OH)_2$, MeOH.

In a similar way, Cossy's ring enlargement conditions were also used to synthesise Zamifenacin, a muscarinic M_3 receptor antagonist.[114] To start the synthesis, (*S*)-proline was converted into alcohol **188**. Then, ring expansion gave 3-hydroxy piperidine **189** in 67% yield and O-alkylation gave Zamifenacin in 48% yield (Scheme 3.24).

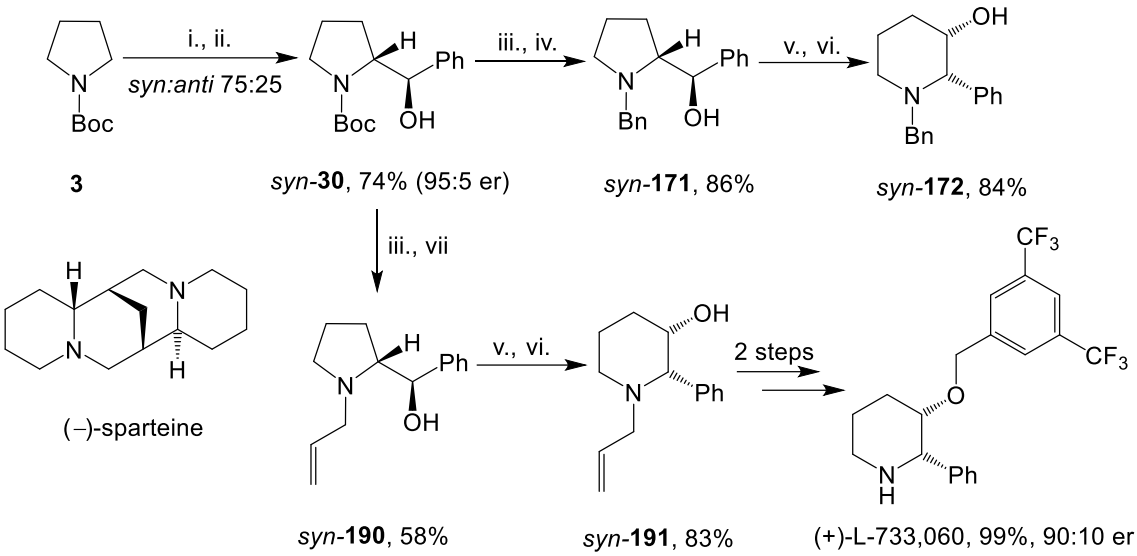
Scheme 3.24



Reagents and conditions: i. TFAA, Et_3N then NaOH; ii. Ph_2CHCl, 100 °C.

To prepare the amino alcohols *anti*-and *syn*-**30**, an alternative route to Cossy's was investigated in the O'Brien group.[115] The route used asymmetric lithiation of *N*-Boc pyrrolidine **3** using the chiral diamine ligand (–)-sparteine as the key step.[116] To start with, *N*-Boc pyrrolidine **3** was deprotonated using *s*-BuLi and (–)-sparteine in Et_2O and trapped with benzaldehyde to give a 75:25 mixture of hydroxy pyrrolidines *syn*-and *anti*-**30**. After chromatography, hydroxy pyrrolidine *syn*-**30** was obtained in 74% yield and 95:5 er (Scheme 3.25). Next, the Boc group of hydroxy pyrrolidine *syn*-**30** was removed and *N*-benzylated to give *N*-benzyl pyrrolidine *syn*-**171** in 86% yield over two steps. Finally, the formation of 2-phenyl 3-hydroxy piperidine *syn*-**172** was carried out in 84% yield using Cossy's standard conditions. It is worth noting that *N*-benzyl 3-hydroxy pyrrolidine *syn*-**171** underwent the ring enlargement whereas the *N*-methyl anolouge *syn*-**179** did not give the six-membered ring *syn*-**180** under the same conditions (see Scheme 3.21). In this research, the ring expansion reaction was applied to synthesise a well-known NK_1 receptor antagonist, (+)-L-733,060. Thus, *N*-Boc pyrrolidine *syn*-**30** was converted into *N*-allyl pyrrolidine *syn*-**190** in 58% yield *via* Boc deprotection and *N*-allylation. Standard ring expansion of *syn*-**190** was carried out to give *N*-allyl 3-hydroxy piperidine *syn*-**191** in 83% yield. Only two steps were then needed to give the desired product, (+)-L-733,060, in excellent yield (99%) and 90: 10 er.

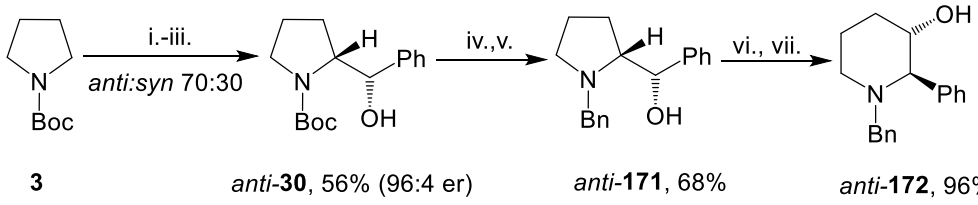
Scheme 3.25



Reagents and conditions: i. *s*-BuLi, (–)-sparteine, Et_2O, –78˚C, 3 h; ii. PhCHO; iii. TFA, CH_2Cl_2, rt, 20 h; iv. K_2CO_3, BnBr, MeCN, rt, 6 h; v. TFAA, Et_3N, THF, reflux, 48 h; vi. $NaOH_{(aq)}$; vii. K_2CO_3, allyl bromide, MeCN, rt, 6 h.

A route to the *anti*-diastereomer was also developed.[115] *N*-Boc pyrrolidine **3** was lithiated using *s*-BuLi/(–)-sparteine and the lithiated intermediate was transmetallated using $MgBr_2$. Trapping with benzaldehyde gave a 70:30 mixture of alcohols *anti*-and *syn*-**30**. As a result, *N*-Boc alcohol *anti*-**30** was obtained in 56% yield and 96:4 er after chromatography. Then, *N*-Boc pyrrolidine *anti*-**30** was converted into *N*-benzyl pyrrolidine *anti*-**171** *via* the same route and alcohol *anti*-**172** was obtained in 96% overall yield (Scheme 3.26).

Scheme 3.26

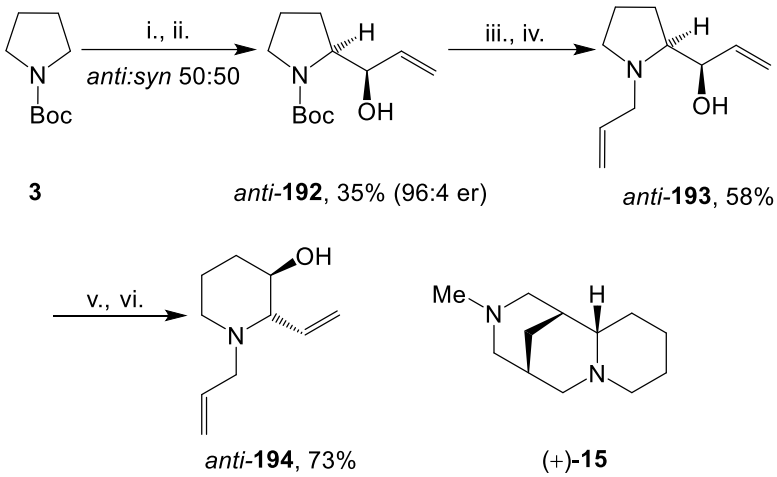


Reagents and conditions: i. *s*-BuLi, (–)-sparteine, Et_2O, –78˚C, 3 h; ii. $MgBr_2$, –78˚C to rt; iii PhCHO; iv. TFA, CH_2Cl_2, rt, 20 h; v. BnBr, K_2CO_3, MeCN, rt, 6 h; vi. TFAA, Et_3N, THF, reflux, 48 h; vii. $NaOH_{(aq)}$.

In addition, asymmetric lithiation of *N*-Boc pyrrolidine **3** using *s*-BuLi and the (+)-sparteine surrogate, (+)-**15** was studied in the O'Brien group to prepare 3-hydroxy piperidine *anti*-**193**, a key intermediate in a synthesis of (–)-swainsonine.[117] To begin with, *N*-Boc pyrrolidine **3** was deprotonated by *s*-BuLi and (+)-**15**. Trapping with acrolein gave ~50:50

mixture of diastereomeric alcohols *anti*-and *syn*-**192**. After chromatography, alcohol *syn*-**192** was obtained in 35% yield and 96:4 er (Scheme 3.27). Then, the Boc group was removed and *N*-allylation was carried out to give *anti*-**193** in 58% yield. The ring enlargement under Cossy's conditions was then carried out and 3-hydroxy piperidine *anti*-**194** was formed in 73% yield. The preparation of *anti*-**194** completed a formal synthesis of (−)-swainsonine.

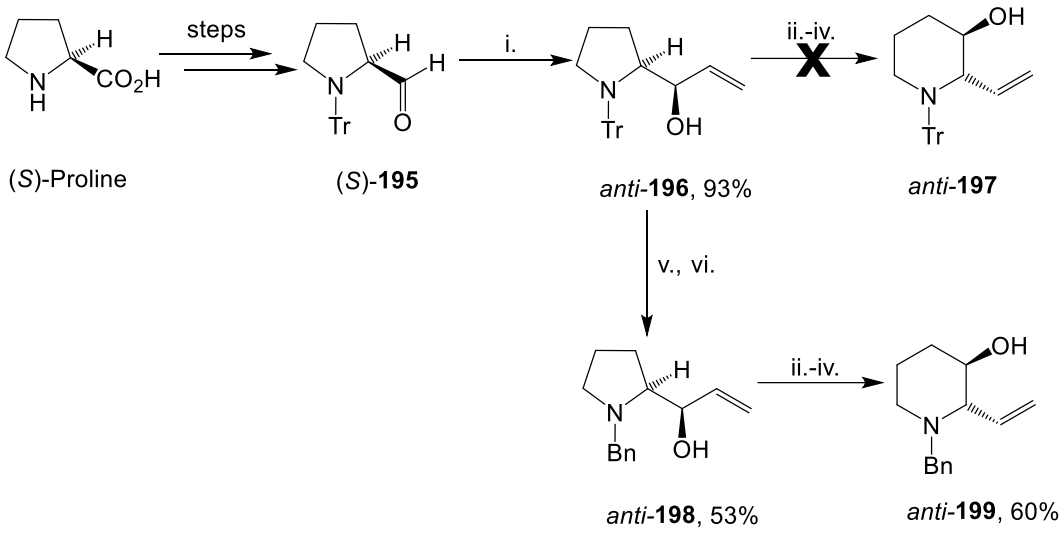
Scheme 3.27



Reagents and conditions: i. *s*-BuLi, (+)-**15**, Et_2O, −78°C, 3 h; ii. acrolein; iii. TFA, CH_2Cl_2, rt, 20 h; iv. allyl bromide, K_2CO_3, MeOH, rt, 12 h; v. TFAA, Et_3N, THF, reflux, 48 h; vi. $NaOH_{(aq)}$, rt, 2 h.

Cossy reported an alternative approach for the synthesis of (−)-swainsonine starting from (*S*)-proline.[118] An air-stable *N*-trityl prolinal (*S*)-**195** was prepared *via* a methyl ester derivative. Then, addition of vinyl magnesium chloride to the aldehyde (*S*)-**195** gave allylic alcohol *anti*-**196** in 93% yield. Cossy's standard ring expansion conditions were then attempted in order to obtain *N*-trityl 3-hydroxy piperidine *anti*-**197**. Unfortunately, the desired product, *anti*-**197** was not obtained and starting material *anti*-**196** was recovered. Hence, trityl removal and *N*-benzylation of alcohol *anti*-**196** gave *N*-benzyl prolinol *anti*-**198** in 53% yield (Scheme 3.28). Finally, the standard ring expansion of alcohol *anti*-**198** provided the desired 3-hydroxy piperidine *anti*-**199**, a key intermediate for the synthesis of (−)-swainsonine.

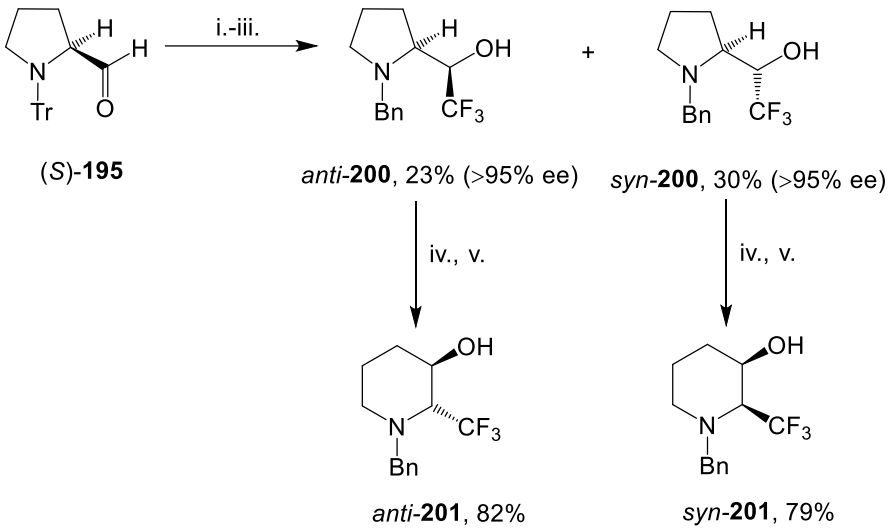
Scheme 3.28



Reagents and conditions: i. CH_2=CHMgCl, Et_2O, −78°C, 3 h; ii. TFAA, THF, 0°C, 15 min; iii. Et_3N, THF, reflux, 24 h; iv. 2.5 M $NaOH_{(aq)}$, rt, 2 h; v. HCl, Et_2O; vi. BnBr, $NaHCO_3$, MeOH.

Recently, Cossy and co-workers introduced a new ring expansion conditions under kinetic control.[119] As shown in Scheme 3.29, the previously used trifluoroacetic acid conditions are believed to proceed under thermodynamic conditions.[120–123] In this work, trifluoromethyl prolinols derived from *N*-trityl prolinal (*S*)-**195** were used. The enantioenriched prolinal (*S*)-**195** was treated with TMS-CF_3 in the presence of CsF in THF to give the trifluoromethyl alcohols. Then, the trityl group was removed and *N*-benzylation gave trifluoromethyl alcohol *anti*-**200** in 23% yield and >95% ee and *syn*-**200** in 30% yield and >95% ee (Scheme 3.29). Finally, the ring expansion of both *N*-benzyl alcohol *anti*-and *syn*-**200** were investigated using the new conditions. To begin with, alcohol *anti*-**200** was treated with triflic anhydride in the presence of *N,N,N',N'*-tetramethylnaphthalene-1,8-diamine in CH_2Cl_2 to generate the aziridinium intermediate which was reacted with H_2O to finally form the trifluoromethyl 3-hydroxy piperidine *anti*-**201** in 82% yield. The same conditions were applied to the alcohol *syn*-**200** and the desired piperidine *syn*-**201** was obtained in 79% yield (Scheme 3.29).

Scheme 3.29



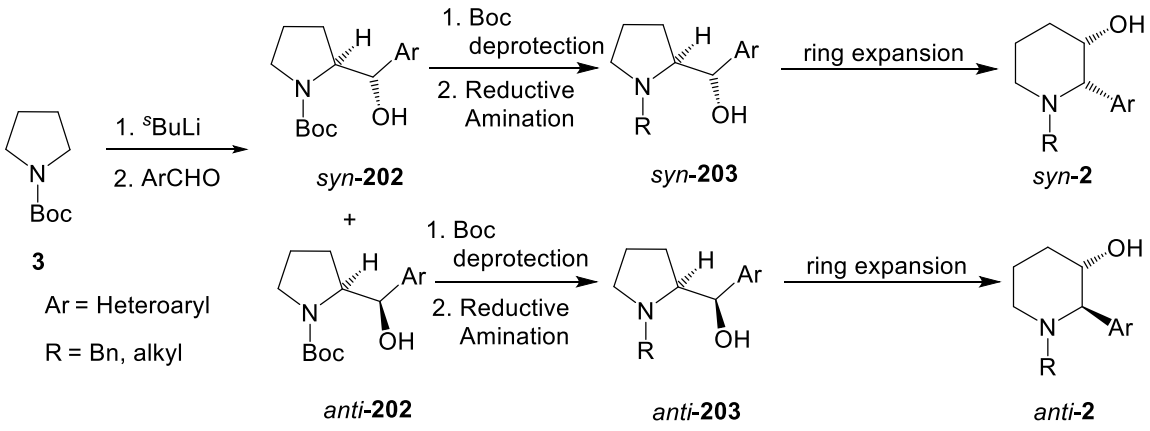
Reagents and conditions: i. CsF, $TMSCF_3$, THF, rt, 24 h; ii. 3 M $HCl_{(aq)}$, MeOH, rt, 1.5 h; iii. BnBr, Et_3N, CH_2Cl_2, reflux, 3.5 h; iv. *N,N,N',N'*-tetramethylnaphthalene-1,8-diamine, Tf_2O, CH_2Cl_2, –15 °C, 1-1.5h; v. H_2O, CH_2Cl_2, rt, 4 h for *syn*-**201** or 18 h for *anti*-**201**.

In summary, 3-hydroxy piperidines can be prepared through many different synthetic routes. A number of approaches provided efficient results in terms of high diastereoselectivity. However, most asymmetric routes are limited by a large number of steps to give satisfactory products. In addition, low overall yield was one of the limitations that encouraged us to investigate an alternative approach to synthesise 3-hydroxy piperidines. As a result, ring expansion of 3-hydroxy pyrrolidines to 3-hydroxy piperidines was our choice for further investigation. In addition, this approach could be applied to an asymmetric synthesis to produce the target molecules with high diastereoselectivity. Since many steps synthesis was a limitation, ring expansion was an excellent approach, which contained less steps. Therefore, the ring expansion was the most promising alternative route for the 3-hydroxy piperidines synthesis.

3.3 Project Outline

In our project, we planned to synthesise 3-hydroxy piperidines *via* a simple and short route. To start with, *N*-Boc pyrrolidine **3** would be lithiated using *s*-BuLi in THF and trapped with aldehydes as electrophiles to give β-hydroxy *N*-Boc pyrrolidines *syn*- and *anti*-**202**. Then, the Boc group would be converted into *N*-alkyl or *N*-benzyl alcohols *syn*- and *anti*-**203** *via* reductive amination. Eventually, those β-hydroxy *N*-alkyl or *N*-benzyl pyrrolidines *syn*- and *anti*-**203** would be reacted with trifluoroacetic anhydride, Et_3N and then NaOH to give 3-hydroxy piperidines *syn*- and *anti*-**2** (Scheme 3.30). The main aim was to introduce heteroaromatic groups (e.g. 2-, 3- and 4-pyridines) at the R^1 position in order to produce a medicinally interesting small library of 3-hydroxypiperidines.

Scheme 3.30



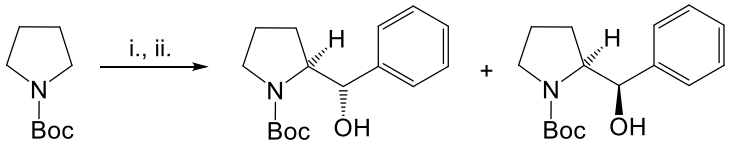
3.4 Investigation of Synthetic Routes from *N*-Boc Pyrrolidine

3.4.1 Lithiation-Trapping of *N*-Boc Pyrrolidine

In order to prepare hydroxy *N*-Boc pyrrolidines which contained an aromatic ring, benzaldehyde was initially used to give simple phenyl hydroxy *N*-Boc pyrrolidines *syn*- and *anti*-**30**. Diamine-free lithiation conditions, which were previously studied in the O'Brien group, showed that lithiation by *s*-BuLi at –30 °C for 5 minutes and trapping with benzaldehyde gave a good yield of trapped products (84% yield).[124] Hence, we used these conditions to carry out all of the lithiation steps in this work.

To start with, *N*-Boc pyrrolidine **3** was deprotonated by *s*-BuLi at –30 °C in THF. The lithiated intermediate was then trapped with benzaldehyde to give diastereomeric hydroxy pyrrolidines *syn*- and *anti*-**30** in 56% and 12% yield respectively, after separation by flash chromatography (Scheme 3.31). To assign the stereochemistry of the hydroxy pyrrolidines, our obtained products were compared to the known compound, hydroxy pyrrolidine *anti*-**30**, which was previously prepared in our group and the relative stereochemistry had been confirmed by X-ray crystallographic data.[115]

Scheme 3.31



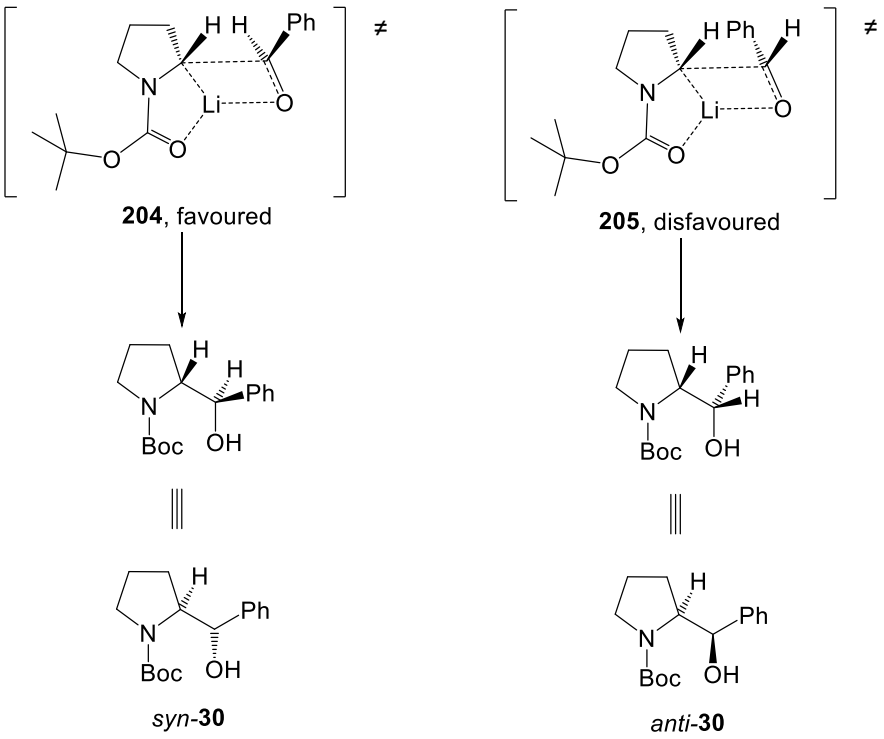
3 *syn*-**30**, 56% *anti*-**30**, 12%

Reagents and conditions: i. *s*-BuLi (1.3 eq.), –30 °C, 5 min, THF; ii. PhCHO, –30 °C, 10 min then rt, 2 h.

An explanation for the diastereoselectivity of the aldehyde trapping has not been proposed either in our group or in the literature. The formation of hydroxy pyrrolidine *syn*-**30** as the major product can be explained by the transition state models shown in Figure 3.3. After the lithiated intermediate was formed, the carbonyl oxygen of the aldehyde can coordinate to the lithium. There are two possible transition states for the addition of the nucleophile to the aldehyde, **204** and **205**. The first possibility is when the phenyl ring aligns in a *syn*-position to the methine proton of *N*-Boc pyrrolidine **3**. This transition state **204** is favourable as there is less steric hindrance between the phenyl of benzaldehyde and the pyrrolidine ring. This alignment leads to hydroxy pyrrolidine *syn*-**30** as the major product. On the other hand, when

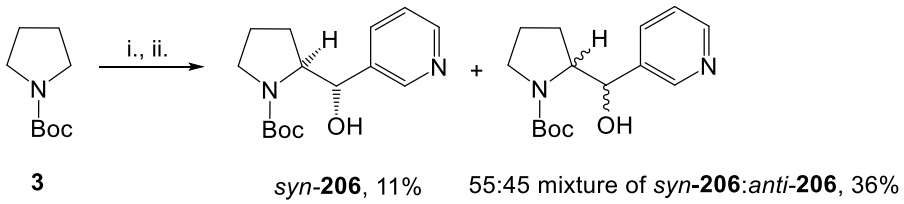
the phenyl ring is in an *anti*-position to the methine proton of *N*-Boc pyrrolidine **3**, there is a steric interaction between the pyrrolidine ring and the phenyl ring. Transition state **205** is less favourable and gives hydroxy pyrrolidine *anti*-**30** as the minor product.

Figure 3.3



Next, the aim was to show that this lithiation-trapping approach worked with heteroaromatic aldehydes containing 2-, 3- and 4-pyridyl groups. To begin with, *N*-Boc pyrrolidine **3** was lithiated using *s*-BuLi in THF at –30 °C to generate the organolithium which was then trapped with 3-pyridine carboxaldehyde. The crude product contained a mixture of hydroxy *N*-Boc pyrrolidines *syn*- and *anti*-**206** (by ^{1}H NMR spectroscopy). Purification by flash chromatography gave 3-pyridyl hydroxy *N*-Boc pyrrolidine *syn*-**206** in 11% yield and a 55:45 mixture of *syn*- and *anti*-**206** in 36% yield (Scheme 3.32). Unfortunately, we were not able to isolate *anti*-**206** as a single diastereomer.

Scheme 3.32

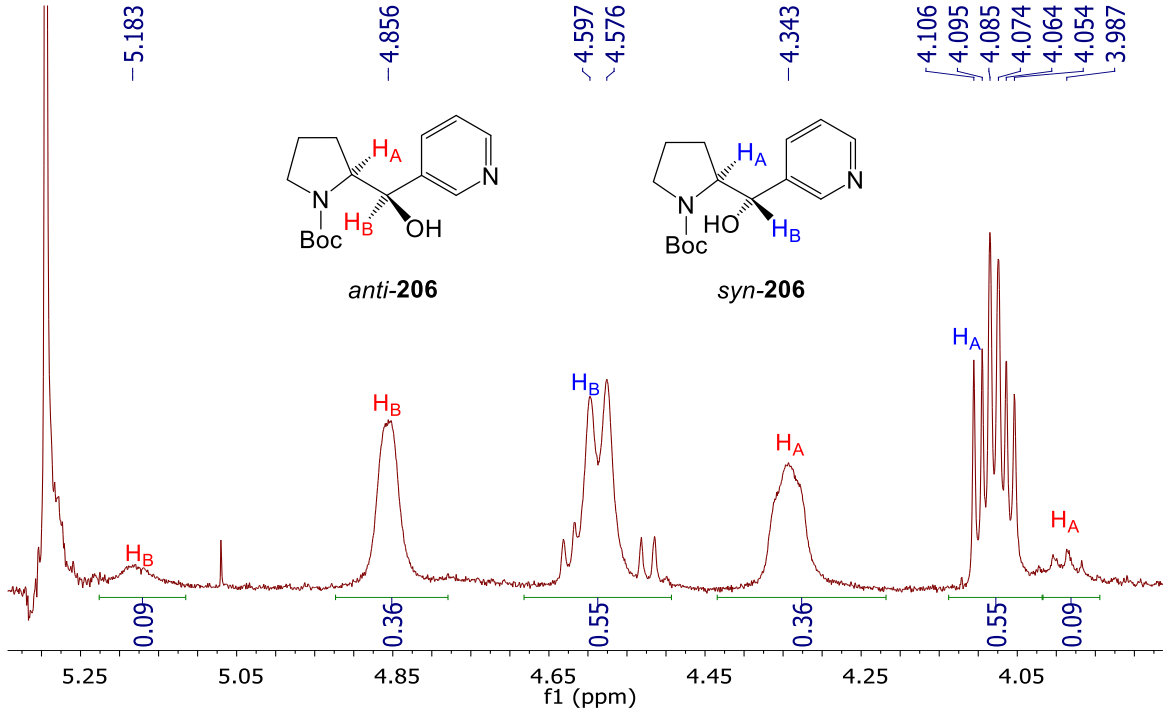


3 *syn*-**206**, 11% 55:45 mixture of *syn*-**206**:*anti*-**206**, 36%

Reagents and conditions: i. *s*-BuLi (1.3 eq.), –30 °C, 5 min, THF; ii. 3-pyridine carboxaldehyde, –30 °C, 10 min then rt, 2 h.

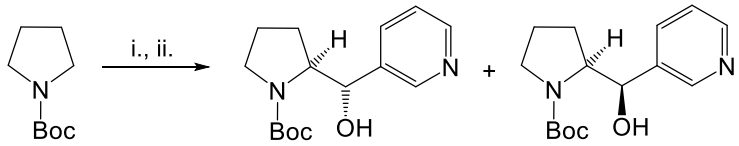
The ^{1}H NMR spectrum of the mixture of hydroxy *N*-Boc pyrrolidines *syn*- and *anti*-**206** was complicated and initially difficult to interpret due to the presence of *N*-Boc rotamers for *anti*-**206**. As described later (see Section 3.4.5), pure samples of *syn*- and *anti*-**206** were obtained from a different route. In addition, the stereochemistry of *syn*- and *anti*-**206** was assigned by an analysis that is also presented in Section 3.4.5. The ^{1}H NMR spectra of pure *syn*- and *anti*-**206** allowed us to determine the 55:45 ratio. The δ_H 5.34-3.86 ppm region of the ^{1}H NMR spectrum of the 55:45 mixture of *syn*- and *anti*-**206** is shown in Figure 3.4. In the spectrum, there was a 1H doublet (J = 8.0 Hz) at δ_H 4.58 ppm and a 1H double double doublet (J = 8.0, 8.0, 4.0 Hz) at δ_H 4.08 ppm which were assigned to the methine protons next to OH and *N*-Boc respectively. These two signals were for *syn*-**206**. Signals for the 80:20 mixture of rotamers for *anti*-**206** are also shown in the ^{1}H NMR spectrum of the mixture of *N*-Boc pyrrolidines *syn*- and *anti*-**206**. Thus, there was a 0.2H broad singlet at δ_H 5.18 ppm and a 0.8H broad singlet at δ_H 4.86 ppm which were assigned to the methine proton on the hydroxyl carbon in *anti*-**206**. There was also a 0.8H broad singlet at δ_H 4.34 and a 0.2H broad singlet 3.99 ppm due to the methine proton next to the *N*-Boc group in *anti*-**206**. Integration of the signals at δ_H 5.18 (0.09H) and 4.86 (0.36H) for *anti*-**206** and δ_H 4.58 (0.55H) for *syn*-**206** showed the ratio to be 55:45. It is interesting to note that the pyridine compound *anti*-**206** showed the same rotameric features as in the ^{1}H NMR spectrum of the phenyl compound *anti*-**206**.

Figure 3.4



Trapping with 3-pyridine carboxaldehyde was repeated on both small and large scales and gave variable yields (Table 3.1). The initial reaction (2.0 mmol scale) from Scheme 3.33 is shown in entry 1 and gave a total yield of *syn*- and *anti*-**206** of 47%. Presumably, the low yield was due to protonation of the pyridine nitrogen after quenching the reaction with $NH_4Cl_{(aq)}$ and removal of some of the pyridinium salt into the aqueous layer during the work-up. To support this theory, 4.0 mmol and 11.6 mmol scale reactions were quenched with water and gave improved yields of 72% and 64% (entries 2 and 3). However, the yield (43%) dramatically dropped when a 17.5 mmol scale reaction was carried out even though water was used in the work-up (entry 4).

Scheme 3.33 Lithiation-trapping in different scales and work-up.



3 *syn*-**206** *anti*-**206**

Reagents and conditions: i. *s*-BuLi (1.3 eq.), –30 °C, 5 min, THF; ii. 3-pyridine carboxaldehyde, –30 °C, 10 min then rt, 2 h.

Table 3.1

Entry	Scale/mmol	Work-up	Yield (%)[a]	*syn*:*anti*[b]
1	2.0	$NH_4Cl_{(aq)}$	47	-[c]
2	4.0	H_2O	72	60:40
3	11.6	H_2O	64	60:40
4	17.5	H_2O	43	70:30

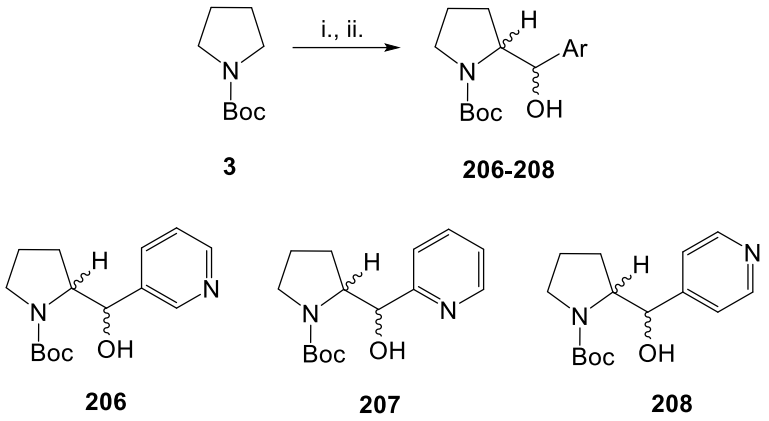
a Yield of a mixture of diastereomers after flash chromatography.

b The ratio was determined by ^{1}H NMR spectroscopy.

c 11% yield of *syn*-**206** and 36% yield of a 55:45 mixture of *syn*-**206** and *anti*-**206**

We also investigated using 2- and 4-pyridine carboxaldehyde as the electrophile (Scheme 3.34, Table 3.2). 2-Pyridine carboxaldehyde was distilled over CaH_2 by Kügelrohr distillation before use. After the lithiation and trapping, an inseperable 60:40 mixture of *anti*- and *syn*-**207** (by ^{1}H NMR spectroscopy) was obtained in 69% yield after purification by flash chromatography (Table 3.2, entry 2). In this case, the major product was shown to have *anti* stereochemistry (see Section 3.4.5) which is different to both the 3- and 4-pyridine carboxaldehyde results. We suggest that the lone pair of electrons on the adjacent nitrogen in 2-pyridine carboxaldehyde may chelate to the lithium and provide a competing reaction pathway. This could lead to a different diastereoselectivity compared to the other aldehydes.

Scheme 3.34 Lithiation-trapping with different electrophiles



Reagents and conditions: i. *s*-BuLi (1.3 eq.), –30 °C, 5 min, THF; ii. 2- or 3- or 4-pyridine carboxaldehyde (2.0 eq.), –30 °C, 10 min then rt, 2 h.

Table 3.2

Entry	Ar	SM, Scale/mmol	Yield (%)[a]	*syn*:*anti*[b]
1	3-pyridyl	17.5	43	70:30
2	2-pyridyl	2.0	69	40:60
3	4-pyridyl	17.5	45	60:40

a Yield of a mixture of diastereomers after flash chromatography.

b The ratio was determined by ^{1}H NMR spectroscopy.

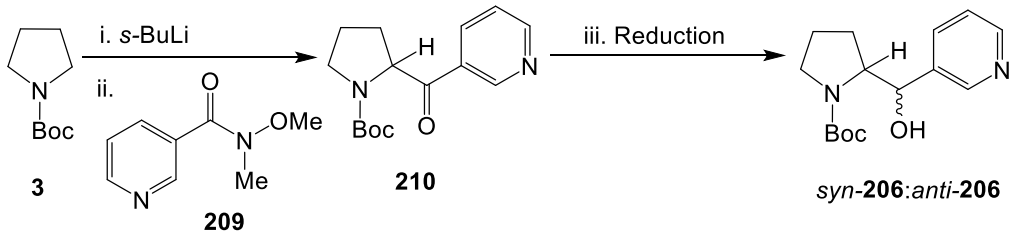
Unfortunately, 4-pyridine carboxaldehyde decomposed during attempted purification by distillation. Therefore, 4-pyridine carboxaldehyde was dried with CaH_2 at room temperature under vacuum and the electrophile was then assumed to be dry enough for the lithiation reaction. A 60:40 mixture of *syn*- and *anti*-**208** (by ^{1}H NMR spectroscopy) was obtained in 45% yield (entry 3). For the diastereoselectivity, we assume that the major product is of *syn* stereochemistry. However, proof of the stereochemistry for *syn*- and *anti*-**208** could not be obtained because both of the *N*-benzyl piperidines containing a 4-pyridyl ring, *syn*- and *anti*-**228**, could not be successfully obtained *via* ring expansion (see Section 3.4.5).

In summary, although we were able to synthesise various hydroxy *N*-Boc pyrrolidines containing pyridinyl groups from the lithiation-trapping reactions, most of the diastereomeric hydroxy pyrrolidines were inseparable after flash chromatography. Moreover, the obtained hydroxy pyrrolidines were not formed with high diastereoselectivity. However, the mixture of *syn*- and *anti*-diastereomers were still useful as the reactions to form them were an efficient synthetic route to generate multi-gram quantities in one step.

3.4.2 Reduction of *N*-Boc Pyrrolidinones

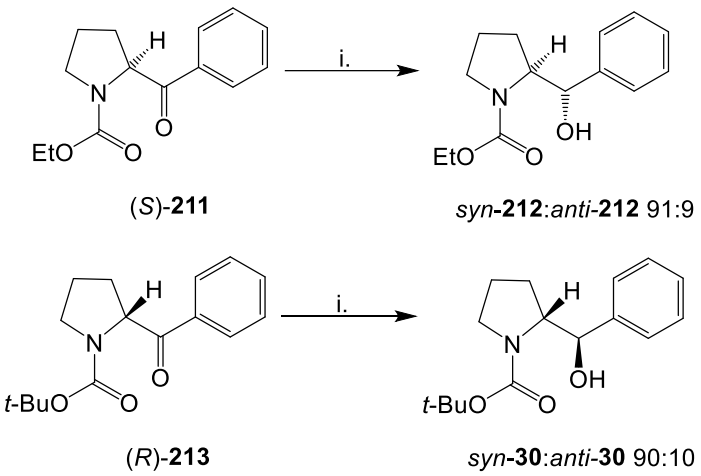
According to the results obtained *via* lithiation-trapping of *N*-Boc pyrrolidine **3** using *s*-BuLi and pyridine carboxaldehydes, the diastereoselectivity of all of the desired products **206-208** was not significantly high. Hence, to improve the diastereoselectivity, an alternative route was investigated. We planned to carry out the reduction of *N*-Boc pyrrolidinone **210** using different reducing agents such as DIBAL-H, $NaBH_4$ and L-selectride. Our plan started with the lithiation of *N*-Boc pyrrolidine **3** and trapping with a Weinreb amide[125] (**209**) to obtain ketone **210**. Then, different reducing agents would be used to reduce the ketone **210** in an attempt to give higher diastereoselectivity (Scheme 3.35).

Scheme 3.35



Reductions of amino ketones similar to **211** and **213** have been described in the literature. For example, the reduction of *N*-carbamate protected ketone (*S*)-**211** with different reducing agents was reported by Soai.[126,127] In his work, the reduction of phenyl *N*-ethoxycarbonyl pyrrolidinone (*S*)-**211** using L-selectride provided a 91:9 mixture of diastereomeric alcohols *syn*- and *anti*-**212** (Scheme 3.36). In the same way, K-selectride gave 100% *syn*-selectivity and hydroxy pyrrolidine *syn*-**212** was isolated in 97% yield.[126] In 2008, O'Brien reported the same approach to provide a diastereoselective synthesis of phenyl *N*-Boc pyrrolidine *syn*-**30** Thus, reduction of *N*-Boc pyrrolidinone (*R*)-**213** using L-selectride gave a 90:10 mixture of hydroxy *N*-Boc pyrrolidines *syn*- and *anti*-**30** (Scheme 3.36).[128]

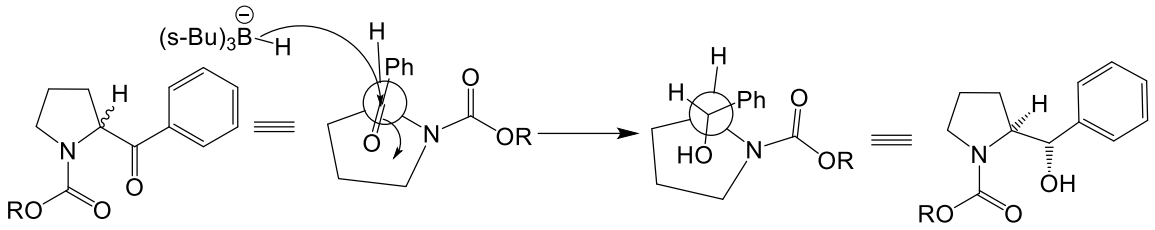
Scheme 3.36



Reagents and conditions: i. L-selectride, –78 ˚C, 1 h, THF.

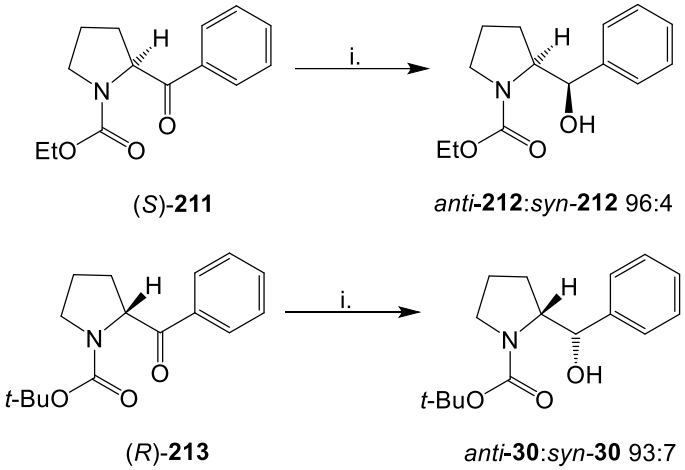
The selective formation of the *syn* diastereomers after ketone reduction using L-selectride can be explained in the following way. We suggest that there is no chelation to the carbonyl group. Due to a Felkin-Ahn model,[129] the hydride ion attacks the carbonyl group with the most hindered *N*-ethoxy carbonyl group perpendicular to the ketone and the aryl group pointing away from the pyrrolidine ring. As a result, *syn*-**212** or *syn*-**30** was selectively formed (Figure 3.5).

Figure 3.5



On the other hand, Soai reported that reduction of *N*-carbamate ketone (*S*)-**211** using DIBAL-H gave *anti* diastereoselectivity and a 96:4 mixture of *N*-carbamate alcohols *anti*- and *syn*-**212** was formed (Scheme 3.37). In the same way, *N*-Boc ketone (*R*)-**213** synthesised in our group was reduced by DIBAL-H and gave a 93:7 diastereomeric mixture of *N*-Boc alcohols *anti*- and *syn*-**30**.[128]

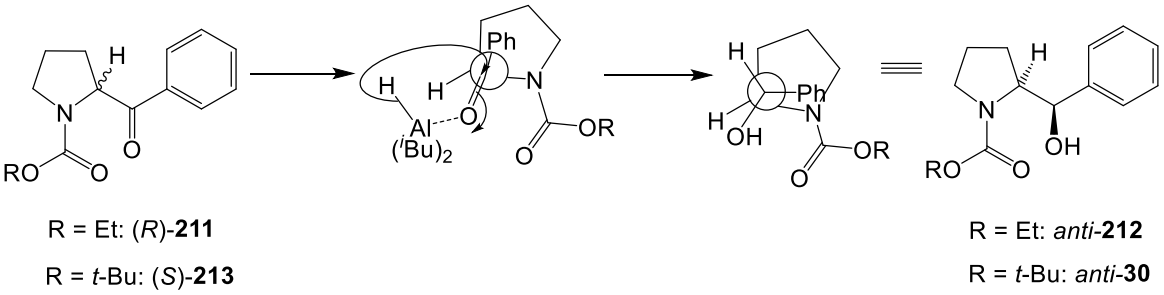
Scheme 3.37



Reagents and conditions: i. DIBAL-H, –78 ˚C, 1 h, THF.

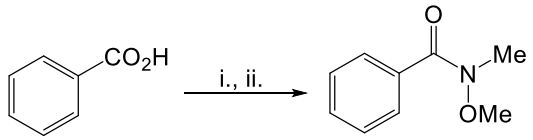
The opposite diastereoselectivity of the ketone reduction using DIBAL-H can be explained by a chelation effect (Figure 3.6). The DIBAL-H will coordinate to the carbonyl group of the ketone (*S*)-**211** or (*R*)-**213**. This makes the carbonyl group sterically larger than the phenyl group. Thus, placing the bulky *N*-alkoxy carbonyl group perpendicular to the carbonyl group and the aluminate away from the pyrrolidine ring will be more favoured. This leads to hydride attack from the opposite side where there is less hindrance. As a result, *anti*-**212** or *anti*-**30** was formed as the major diastereomer.

Figure 3.6



To start with, we verified the reduction route using the known *N*-Boc phenyl ketone **213**. In our work, the phenyl *N*-Boc pyrrolidinone **213** was prepared by a different route compared to Soai's. Recently, in our group, a modern amide coupling reagent, T3P was used in the synthesis of Weinreb amides.[130,131] Therefore, Weinreb amide **215** was prepared from benzoic acid **214**, *N*,*O*-dimethylhydroxylamine hydrochloride, *i*-Pr_2NEt and T3P in CH_2Cl_2. This gave *N*-methoxy-*N*-methylbenzamide **215** in 98% yield (Scheme 3.38).

Scheme 3.38

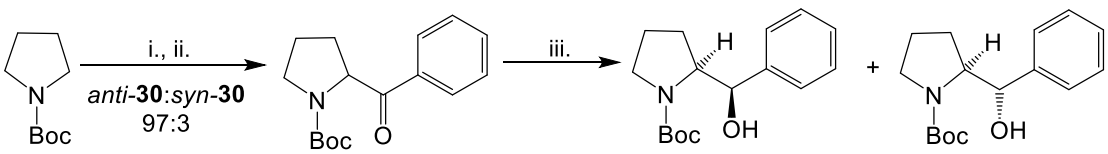


214 **215**, 98%

Reagents and conditions: i. *N*,*O*-dimethylhydroxylamine hydrochloride, *i*-Pr_2NEt, T3P (50% w/v solution in THF), rt, 16 h, CH_2Cl_2.

Next, phenyl *N*-Boc pyrrolidinone **213** was prepared *via* lithiation-trapping using *s*-BuLi and Weinreb amide **215**. After purification by flash chromatography, phenyl *N*-Boc pyrrolidinone **213** was obtained in 56% yield (Scheme 3.39). Then, reduction of *N*-Boc pyrrolidinone **213** was carried out using DIBAL-H at 0 °C for 1 hour (in contrast to –78 °C which was used previously[128]). This gave the crude product which contained a 97:3 mixture of phenyl hydroxy *N*-Boc pyrrolidines *anti*- and *syn*-**30** (by ^{1}H NMR spectroscopy). After purification by flash chromatography, hydroxy *N*-Boc pyrrolidine *anti*-**30** (93%) and *syn*-**30** (3%) were isolated (Table 3.3, entry 1). This result is interesting as the reduction using DIBAL-H can be carried out at 0 °C without a reduction of diastereoselectivity or yield. The use of L-selectride gave *syn* diastereoselectivity as the crude product contained a 92:8 mixture of alcohols *syn*- and *anti*-**30** (by ^{1}H NMR spectroscopy). Then, the major *N*-Boc amino alcohol *syn*-**30** was isolated in 82% yield and diastereomer *anti*-**30** was obtained in 12% yield (entry 2). Finally, reduction of ketone **213** using $NaBH_4$ showed less *syn* diastereoselectivity then the use of L-selectride. Thus, a 71:29 mixture of hydroxy *N*-Boc pyrrolidines *syn*- and *anti*-**30** (by ^{1}H NMR spectroscopy) was purified by chromatography and the alcohols *syn*- and *anti*-**30** were isolated in 68% and 27% respectively (entry 3).

Scheme 3.39



3 **213**, 56% *anti*-**30** *syn*-**30**

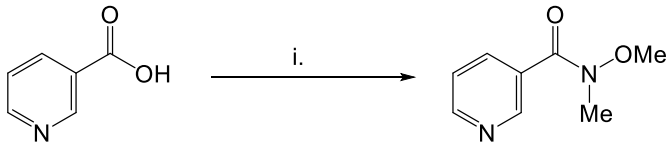
Reagents and conditions: i. *s*-BuLi (1.3 eq.), –30 °C, 5 min, THF; ii. *N*-methoxy-*N*-methylbenzamide **215** (2.0 eq.), –30 °C, 10 min then rt, 2 h.; iii. reducing agents.

Table 3.3

Entry	Reducing agent	Temp (˚C)	Time (h)	*syn*-30, Yield (%)	*anti*-30, Yield (%)
1	DIBAL-H	0	1	3	93
2	L-selectride	–78	1	82	12
3	$NaBH_4$	0 to rt	16	68	27

In addition, the same approach was applied to prepare an *N*-Boc pyrrolidinone containing a heteroaryl group. To start with, Weinreb amide **209** containing a 3-pyridyl group was prepared from an amide coupling of nicotinic acid **216**, *N*,*O*-dimethylhydroxylamine hydrochloride, Et_3N and DCC in dichloromethane according to a literature method.[132] This gave *N*-methoxy-*N*-methylnicotinamide **209** in 83% yield after purification by chromatography (Scheme 3.40).

Scheme 3.40

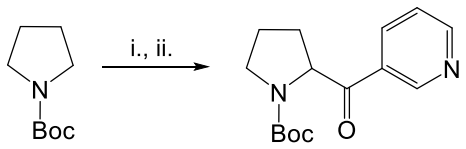


216 **209**, 83%

Reagents and conditions: i. *N*,*O*-dimethylhydroxylamine hydrochloride, Et_3N, DCC, rt, 16 h, CH_2Cl_2.

With 3-pyridine Weinreb amide **209** in hand, it was used as an electrophile in a lithiation-trapping reaction. *N*-Boc pyrrolidine **3** was deprotonated by *s*-BuLi at –30 ˚C in THF. The lithiated intermediate was then trapped with Weinreb amide **209** to give *N*-Boc pyrrolidinone **210** in 38% yield after purification by column chromatography (Scheme 3.41).

Scheme 3.41

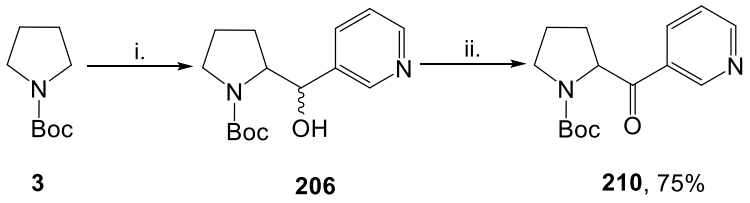


3 **210**, 38%

Reagents and conditions: i. *s*-BuLi (1.3 eq.), –30 ˚C, 5 min, THF; ii. *N*-methoxy-*N*-methylnicotinamide **209** (2.0 eq.), –30 ˚C, 10 min then rt, 2 h.

An alternative route to prepare ketone **210** was investigated. Thus, a crude mixture of alcohols *syn*- and *anti*-**206** was prepared by lithiathion-trapping of *N*-Boc pyrrolidine **3** (Scheme 3.42). Then, oxidation of the alcohols *syn*- and *anti*-**206** using Dess-Martine periodinane gave the desired ketone **210** in 75% yield over the two steps. This is a much more efficient synthetic route.

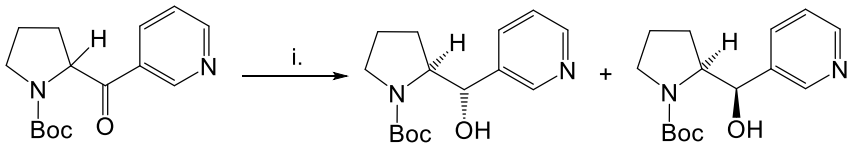
Scheme 3.42



Reagents and conditions: i. *s*-BuLi, 3-pyridine carboxaldehyde, –78 °C, THF; ii. Dess-Martin periodinane, CH_2Cl_2, 0 °C then rt, 16 h.

3-Pyridyl ketone **210** was first reduced by $NaBH_4$ to provide a mixture of alcohols *syn*- and *anti*-**206** in 94% yield (Scheme 3.43, Table 3.4, entry 1). The diastereomeric ratio of *syn*- and *anti*-**206** was only 70:30 (by ^{1}H NMR spectroscopy) after purification by chromatography. On the other hand, reduction of ketone **210** using the more sterically hindered L-selectride at –78 °C for 3 hours selectively gave alcohol *syn*-**206** as the major product. A 97:3 mixture of pyrrolidines *syn*- and *anti*-**206** was obtained in 31% yield (entry 2). As expected, using DIBAL-H to reduce pyrrolidinone **210** gave opposite diastereoselectivity. Reaction at 0 °C for 1 hour gave an 88:12 mixture of hydroxyl pyrrolidines *anti*- and *syn*-**206** in 97% yield (entry 3).

Scheme 3.43



Reagents and conditions: i. reducing agents (2.0 eq.), temp, time, THF.

Table 3.4

Entry	Reducing agent	Temp (˚C)	Time (h)	Yield (%) [a], *syn*-**206**:*anti*-**206** [b]
1	$NaBH_4$	0 to rt	2	94, 70:30
2	L-selectride	–78	3	31, 97:3
3	DIBAL-H	0	1	88, 12:88

a Yield of a mixture of diastereomers after flash chromatography.

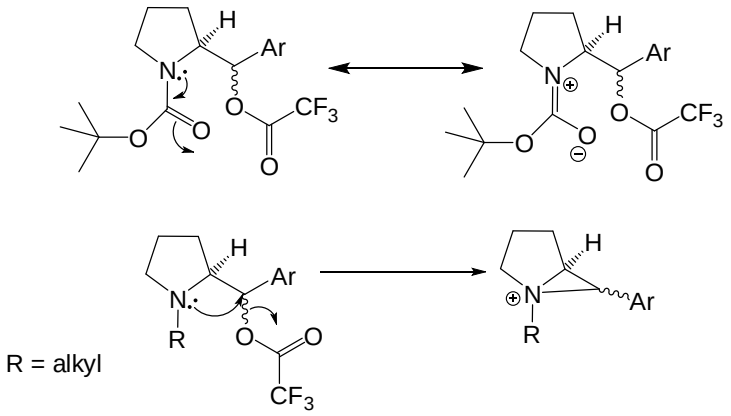
b The ratio was determined by ^{1}H NMR spectroscopy.

In conclusion, *N*-Boc pyrrolidinone **210** was prepared *via* reaction with Weinreb amide **209**. The overall yield of the reaction sequence was limited by the formation of the ketone **210** in only 38% yield. In addition, reduction of *N*-Boc pyrrolidinone **210** using different reducing agents improved the diastereoselectivity of the hydroxy pyrrolidines *syn*- and *anti*-**206**. However, there was a problem in some cases. For example, reduction of ketone **210** by L-selectride gave a high *syn*-selectivity (97:3 mixture of *syn*- and *anti*-**206**) but the isolated yield was poor (31%) whereas using DIBAL-H provided an excellent yield (97%) and a reasonable 88:12 diastereomeric ratio of the *anti*- and *syn*-**206**. Overall, as the ketone synthesis was low yielding, we preferred to use the mixture of diastereomers *syn*- and *anti*-**206** prepared from the direct lithiation route in our subsequent studies.

3.4.3 Ring Expansion of *N*-Methyl Hydroxy Pyrrolidines to Piperidines

The next stage involved studying the ring expansion step from the five-membered to the six-membered ring. We planned to use Cossy's ring expansion conditions using trifluoroacetic anhydride.[104,113] The *N*-Boc protecting group was not suitable. This is because the lone pair of electrons on the nitrogen atom are delocalized to the carbonyl group rather than attacking the carbon atom which is attached to the trifluoroacetate group. In order to obtain a piperidine *via* ring expansion, the Boc group should be converted into an alkyl group. When a nitrogen has an electron donating alkyl group attached, it will be more nucleophilic than an electron poor Boc group. Without an alkyl group on the nitrogen atom, aziridinium ion formation cannot occur (Scheme 3.44).

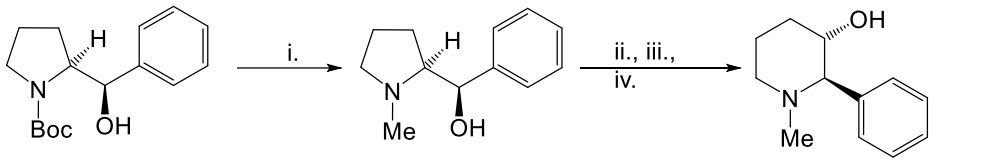
Scheme 3.44



Hence, the *N*-Boc group needed to be converted into an *N*-alkyl group. For the synthesis of *N*-alkyl pyrrolidines, we considered three potential approaches. First, the Boc group could be removed and the free amine could be alkylated using alkyl halides. Second, the Boc group could be removed and the free amine could be utilised in a reductive amination reaction. Last, use of reducing agents would directly convert the Boc group into a methyl group. In previous work in our group,[128] Boc deprotection and alkylation were used to produce the *N*-alkyl group (see Scheme 3.26). However, since the synthesis was carried out in a two-step procedure, we considered a shorter and potentially simpler route to generate the *N*-alkyl group. As a result, the direct reduction of the Boc group to give the methyl group was chosen to be investigated first.

To investigate the preparation of *N*-methyl pyrrolidines, we started with the model phenyl pyrrolidine *anti*-**30**. Thus, Boc reduction of pyrrolidine *anti*-**30** using $LiAlH_4$ in THF at reflux gave *N*-methyl pyrrolidine *anti*-**179** and the crude product was used in the ring enlargement step without further purification due to the polarity of tertiary amine *anti*-**179**. Cossy's conditions for ring enlargement were used.[110] This involved reaction of *anti*-**179** with Et_3N and trifluoroacetic anhydride (reflux for 48 hours) and then ester hydrolysis with NaOH. In this way, 3-hydroxy *N*-methyl piperidine *anti*-**180** was obtained in 28% yield over two steps (Scheme 3.45).

Scheme 3.45

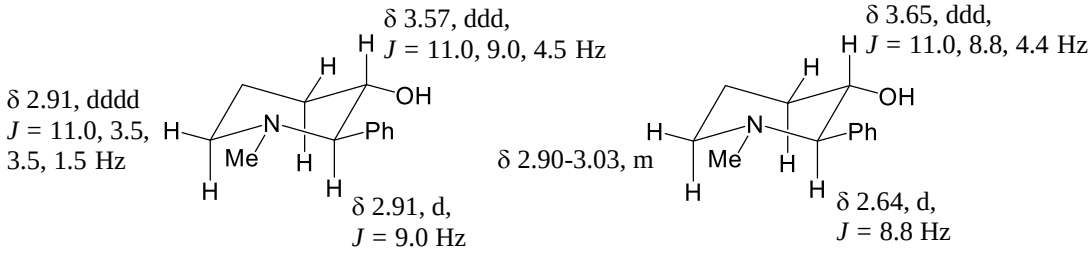


anti-**30** *anti*-**179** *anti*-**180**, 28% over 2 steps

Reagents and conditions: i. $LiAlH_4$, 0 °C then reflux, 16 h, THF; ii. TFAA, –78 °C, 1 h, THF; iii. Et_3N, –78 °C, 1 h, then reflux, 48 h, THF; iv. 20% $NaOH_{(aq)}$, rt, 2 h.

To prove that we had successfully formed the six-membered ring of piperidine *anti*-**180**, we compared its ^1H NMR spectrum to the one that was reported by Cossy.[16] Our ^1H NMR spectroscopic data was found to match with Cossy's data (Figure 3.7). Thus, there was a 1H double double doublet (J = 11.0, 9.0, 4.5 Hz) at δ_H 3.57 ppm which was assigned to the axial proton on the hydroxyl-carbon. There was also a 1H double double double doublet (J = 11.0, 3.5, 3.5, 1.5 Hz) at δ_H 2.91 ppm due to the equatorial proton adjacent to the nitrogen. There was a doublet (J = 9.0 Hz) at δ_H 2.58 ppm which was assigned to the axial proton between the nitrogen atom and the hydroxyl-carbon (Figure 3.7). The large ^3J *trans*-diaxial coupling between the protons α to the phenyl and hydroxy group of 9.0 Hz proves that the six-membered ring product is *anti*. These data show that the ring expansion reaction of *N*-Me pyrrolidine *anti*-**179** to *N*-Me piperidine *anti*-**180** had occurred successfully.

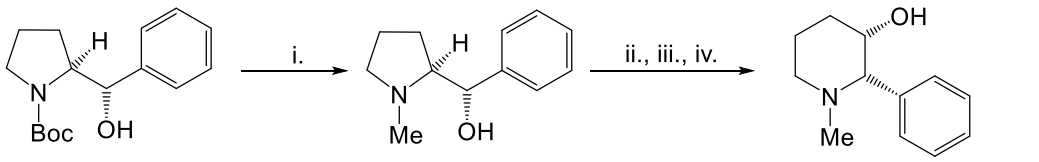
Figure 3.7



anti-**180** Cossy's data[110]

In addition, the same ring expansion conditions were used to prepare phenyl *N*-methyl piperidine *syn*-**180**. Phenyl 3-hydroxy piperidine *syn*-**180** was obtained in 6% yield over two steps after purification by chromatography (Scheme 3.46). Although the isolated yield was very low, it is noteworthy because Cossy had previously reported that *syn*-**179** could not be converted into ring-expanded *syn*-**180** (see Scheme 3.21).[133] Since we found that *syn*-**180** was not soluble in CH_2Cl_2 or $CDCl_3$, we wondered whether the low solubility could account for Cossy's observation.[134]

Scheme 3.46

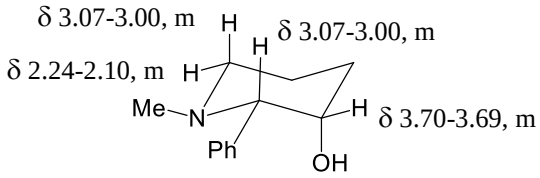


syn-**30** *syn*-**179** *syn*-**180**, 6% over 2 steps

Reagents and conditions: i. $LiAlH_4$, 0 °C then reflux, 16 h, THF; ii. TFAA, –78°C, 1 h, THF; iii. Et_3N, –78°C, 1 h, then reflux, 48 h, THF; iv. 20% $NaOH_{(aq)}$, rt, 2 h.

Hence, to prove that *N*-Me pyrrolidine *syn*-**179** was successfully converted into 3-hydroxy piperidine *syn*-**180**, the ^1H NMR spectrum of the product *syn*-**180** was recorded in CD_3OD. There was a multiplet at δ_H 3.70-3.69 ppm which was assigned to the equatorial proton with the hydroxyl group at the axial position. There were also a 2H multiplet at δ_H 3.07-3.00 ppm due to one of the methylene protons next to the nitrogen atom and an axial proton between the hydroxyl carbon and the nitrogen (Figure 3.8). The absence of a large ^3J value between the protons α to the phenyl and hydroxy group indicates that this compound has *syn* stereochemistry.

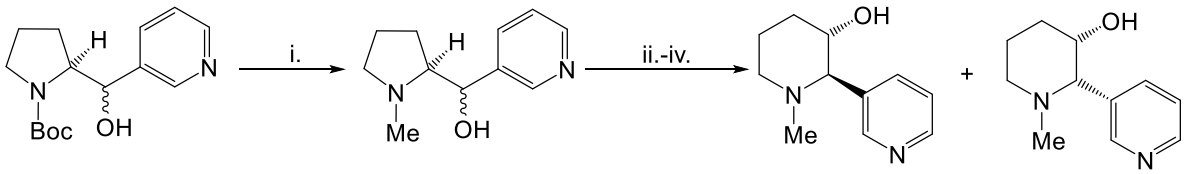
Figure 3.8



syn-**180**

Next, to investigate the ring expansion of *N*-alkyl pyrrolidines containing heteroaromatic groups, 3-pyridine hydroxy pyrrolidines *syn*- and *anti*-**206** were utilised in a similar synthetic route. Thus, a 60:40 mixture of *N*-Boc hydroxy 3-pyridyl pyrrolidines *syn*- and *anti*-**206** was reduced using $LiAlH_4$ to give a mixture of *N*-methyl hydroxy 3-pyridyl pyrrolidines *syn*- and *anti*-**217**. Without further purification, ring expansion was carried out. However, the ring expansion was not very successful as, after chromatography, a 60:40 mixture of the 3-hydroxy piperidines *syn*- and *anti*-**218** was isolated in only 10% yield over the 2 steps (Scheme 3.47).

Scheme 3.47



60:40 mixture of *syn*-**206**:*anti*-**206**

mixture of s*yn*-**217**:a*nti*-**217**

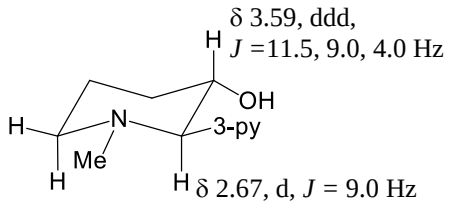
60:40 mixture of *anti*-**206**:*syn*-**206** 10% over 2 steps

Reagents and conditions: i. $LiAlH_4$, 0 ˚C then reflux, 16 h, THF; ii. TFAA, −78˚C, 1 h, THF; iii. Et_3N, −78˚C, 1 h, then reflux, 48 h, THF; iv. 20% $NaOH_{(aq)}$, rt, 2 h.

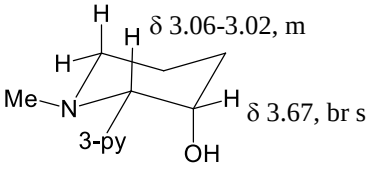
The ^1H NMR spectrum of the 60:40 mixture of hydroxy piperidines *anti*- and *syn*-**218** contained a 1H double double doublet (J = 11.5, 9.0, 4.0 Hz) at δ_H 3.59 ppm which was assigned to the methine proton on the hydroxyl carbon of the major product. Moreover, there was a 1H doublet (J = 9.0 Hz) at δ_H 2.67 ppm due to the proton between the nitrogen atom and the hydroxyl carbon of *anti*-**218**. In this case, the coupling constants indicate that the major product was *anti*-**218** (Figure 3.9). There was also a broad singlet at δ_H 3.67 ppm which was assigned to the methine proton on the hydroxyl carbon of the minor product. The absence of a large ^3J value indicated that the minor product was *syn*-**218**. There was also a multiplet at δ_H 3.06-3.02 ppm which was assigned to the methine proton geminal to the

3-pyridyl group of *syn*-**218**. Although the starting material was enriched in *syn*-**206**, *anti*-**218** was obtained as the major six-membered ring product after the ring expansion.

Figure 3.9



anti-**218**



syn-**218**

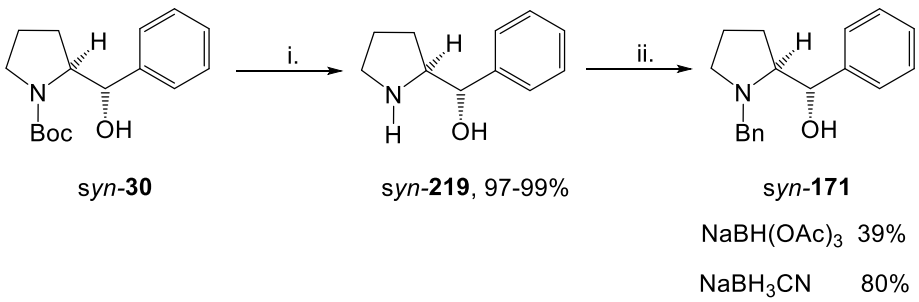
To summarise, 3-hydroxy phenyl piperidine *syn*-**180** was obtained in 6% overall yield. Although the yield was not very good, the formation of *syn*-**180** had not previously been observed *via* the same route in the literature.[133] In addition, 3-hydroxy *N*-methyl piperidines containing a 3-pyridyl group were successfully synthesised even though the desired products, *syn*- and *anti*-**218**, were inseparable after chromatography and obtained in low yield (10% over 2 steps). However, these were the first 3-hydroxy *N*-methyl piperidines containing a heteroaromatic ring to be synthesised according to ring expansion. We believe that the reduction of the *N*-Boc group to an *N*-methyl substituent was the main problem that led to these unsatisfactory results. Therefore, we planned to explore other synthetic approaches.

3.4.4 Ring Expansion of *N*-Benzyl Hydroxy Pyrrolidines to Piperidines

Since the Boc reduction route was not very successful, another synthetic approach needed to be investigated. We decided to investigate Boc deprotection with TFA and then reductive amination using benzaldehyde as a route to *N*-benzyl amino alcohols. Some suitable conditions for the reductive amination were identified from the literature.[135] This involved reaction of the amine with benzaldehyde and sodium triacetoxyborohydride or sodium cyanoborohydride in 1,2-dichloroethane.[136] Moreover, Abdel-Magid and co-workers reported that the presence of acetic acid allowed the reaction to proceed faster.[137]

Therefore, to investigate the reductive amination route, phenyl *N*-Boc pyrrolidine *syn*-**30** was used as the starting point to identify a suitable reducing agent and conditions. To start with, the Boc group was removed by treatment with TFA in CH_2Cl_2 to give the free amine *syn*-**219** after an aqueous work-up. Due to high polarity, the free amine was then used in the reductive amination without further purification. The reductive amination was carried out in 1,2-dichloroethane. Reductive amination using 2.0 equivalents of sodium triacetoxyborohydride in the presence of 4.0 equivalents of acetic acid gave *N*-benzyl pyrrolidine *syn*-**171** in 39% yield whereas use of 2.0 equivalents of sodium cyanoborohydride and 2.0 equivalents of acetic acid gave *N*-benzyl pyrrolidine *syn*-**171** in 80% yield (Scheme 3.48). These different yields suggested carrying out the reductive amination reaction under acid conditions using sodium cyanoborohydride was more preferable. However, the reaction using sodium triacetoxyborohydride could alternatively be investigated in the case of disappointing results from the use of sodium cyanoborohydride.

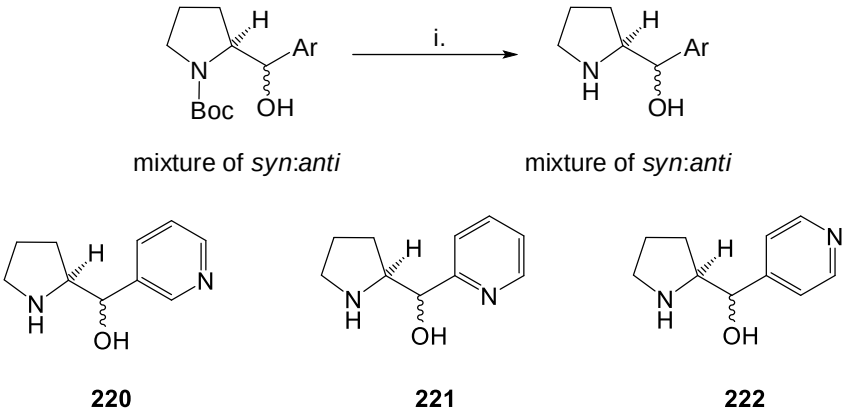
Scheme 3.48



Reagents and conditions: i. TFA, rt, CH_2Cl_2; ii. $NaBH(OAc)_3$ (2.0 eq.), AcOH (4.0 eq.) or $NaBH_3CN$ (2.0 eq.) , AcOH (2.0 eq.), rt, 16 h, DCE.

To prepare *N*-benzyl pyrrolidines **223**-**225** from amino alcohols **206**-**208** containing pyridyl groups, the Boc group was removed using TFA in CH_2Cl_2 to give the secondary amines. Due to high polarity of the compounds, all the mixtures of *syn*- and *anti*-free amines **220**-**222** were used in the next step without further purification. In addition, the yields after Boc deprotection were relatively high (78-85%) and the purity was good (by ^{1}H NMR spectroscopy) (Scheme 3.49, Table 3.5, entries 1-3).

Scheme 3.49



Reagents and conditions: i. TFA, CH_2Cl_2, 0 °C then rt, 2 h.

Table 3.5

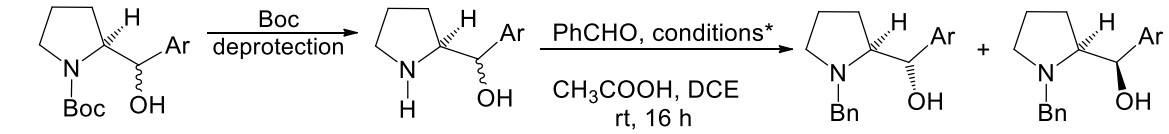
Entry	SM (Ar)	SM (*syn*:*anti*)[a]	% Yield[b], *syn*:*anti*[a]
1	3-pyridyl	70:30	85%, 70:30
2	2-pyridyl	40:60	80%, 40:60
3	4-pyridyl	60:40	78%, 65:35

a The ratio was determined by ^{1}H NMR spectroscopy.

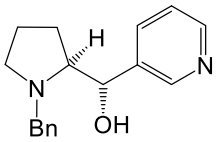
b Yield of a mixture of diastereomers after chromatography.

Next, to synthesise different *N*-benzyl pyrrolidines containing heteroaromatics, a reductive amination under acid conditions was used (Scheme 3.50). To begin with, a 70:30 mixture of crude free amine of 3-pyridyl pyrrolidines *syn*- and *anti*-**220** was used in the presence of a stoichiometric amount of acetic acid (4.0 equivalents) and sodium triacetoxyborohydride. As a result, *N*-benzyl 3-pyridyl pyrrolidines *syn*- and *anti*-**223** were obtained in 18% and 25% yield respectively after flash chromatography (Table 3.6, entry 1). Use of 0.2 equivalents of acetic acid and sodium triacetoxyborohydride gave increased yields of *N*-benzyl 3-pyridyl pyrrolidines *syn*- and *anti*-**223** (30% each) (entry 2). However, when 0.2 equivalents of acetic acid was used with sodium cyanoborohydride, the obtained yield of *N*-benzyl 3-pyridyl pyrrolidine *syn*-**223** slightly dropped to 13% but the yield of pyrrolidine *anti*-**223** slightly increased to 14% (entry 3). Interestingly, increasing the amount of acetic acid to 2.0 equivalents improved the yield of *syn*-**223** to 29% (entry 4) whereas 3.0 equivalents of acid dramatically decreased the yield of both *syn*- and *anti*-**223** to 11% and 12% respectively (entry 5). In the case of the 2-pyridyl group, a reductive amination of pyrrolidines *syn*- and *anti*-**207** using sodium triacetoxyborohydride and 0.2 equivalents of acetic acid gave *N*-benzyl 2-pyridyl pyrrolidines *syn*- and *anti*-**224** in 11% and 28% yield respectively (entry 6). In contrast, use of sodium cyanoborohydride and a stoichiometric amount of acetic acid (2.0 and 3.0 equivalents) decreased the overall yields of pyrrolidines *syn*- and *anti*-**224** (entries 7 and 8). Considering the 4-pyridyl group, reductive amination of pyrrolidines *syn*- and *anti*-**208** in the presence 0.2 equivalents of acetic acid and sodium triacetoxyborohydride gave moderate yields of *N*-benzyl 4-pyridyl pyrrolidines *syn*- and *anti*-**225**, both in 27% yields (entry 9). Similarly, the isolated yields in both *syn*- and *anti*-**225** dropped when using sodium cyanoborohydride and a stoichiometric amount of acetic acid (2.0 and 3.0 equivalents) (entries 10 and 11). In summary, the use of sodium triacetoxyborohydride and 0.2 equivalents of acetic acid gave the best yields of hydroxy pyrrolidines (39-60% total yields) (entries 2, 6 and 9).

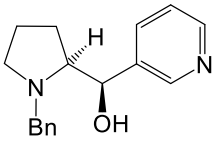
Scheme 3.50



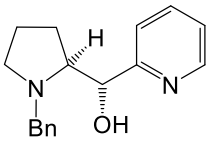
Reagents and conditions: i. reducing agents (2.0-4.0 eq.), AcOH (0.2-4.0 eq.), THF.



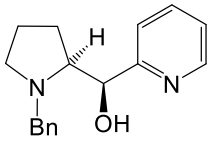
syn-**223**



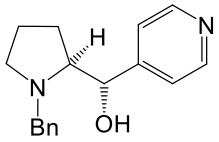
anti-**223**



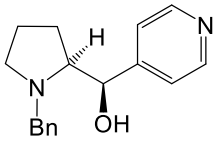
syn-**224**



anti-**224**



syn-**225**



anti-**225**

Table 3.6

Entry	SM (Ar)	conditions	AcOH (eq)	Product, *syn* (% yield)[g]	Product, *anti* (% yield)[g]
1[a]	3-pyridyl	$NaBH(OAc)_3$	4.0	18	25
2[a]	3-pyridyl	$NaBH(OAc)_3$	0.2	30	30
3[b]	3-pyridyl	$NaCNBH_3$	0.2	13	14
4[a]	3-pyridyl	$NaCNBH_3$	2.0	29	12
5[a]	3-pyridyl	$NaCNBH_3$	3.0	11	12
6[c]	2-pyridyl	$NaBH(OAc)_3$	0.2	11	28
7[d]	2-pyridyl	$NaCNBH_3$	2.0	3	22
8[c]	2-pyridyl	$NaCNBH_3$	3.0	6	23
9[e]	4-pyridyl	$NaBH(OAc)_3$	0.2	27	27
10[f]	4-pyridyl	$NaCNBH_3$	2.0	12	21
11[f]	4-pyridyl	$NaCNBH_3$	3.0	4	9

a Ratio of *syn*:*anti*-free amine **220** is 70:30, b Ratio of *syn*:*anti*-free amine **220** is 65:35.

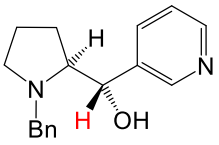
c Ratio of *anti*:*syn*-free amine **221** is 60:40, d Ratio of *anti*:*syn*-free amine **221** is 65:35

e Ratio of *syn*:*anti*-free amine **222** is 60:40, f Ratio of *syn*:*anti*-free amine **222** is 65:35

g Yield after flash chromatography over 2 steps.

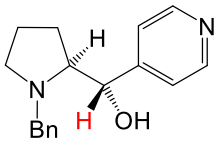
The *N*-benzyl pyrrolidinols **223** and **225** have similar trends in the ^{3}J value of the benzylic proton in the *syn*- and *anti*-diastereomers. According to the ^{1}H NMR spectra of the *N*-benzyl pyrrolidines *syn*-**223** and *syn*-**225**, each compound contained a doublet with a small ^{3}J value (3.5 and 3.0 Hz) at δ_H 4.86 and 4.73 ppm respectively due to the methine proton on the hydroxyl carbon (Figure 3.10). On the other hand, the *N*-benzyl pyrrolidines *anti*-**223** and *anti*-**225** contained a doublet with a slightly larger ^{3}J value (5.5 and 4.5 Hz) at δ_H 4.41 and 4.44 ppm respectively for the same proton. This trend was not, however, followed with the 2-pyridyl *N*-benzyl pyrrolidines *syn*- and *anti*-**224** which contained a doublet with the same ^{3}J value (3.5 Hz each) at δ_H 4.97 and 4.64 respectively.

Figure 3.10



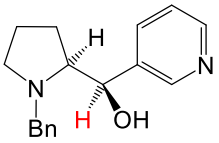
δ 4.86, d, *J* = 3.5 Hz

syn-**223**



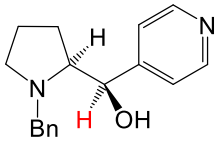
δ 4.73, d, *J* = 3.0 Hz

syn-**225**



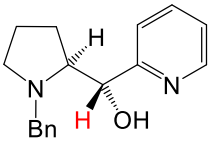
δ 4.41, d, *J* = 5.5 Hz

anti-**223**



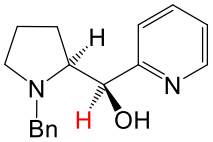
δ 4.44, d, *J* = 4.5 Hz

anti-**225**



δ 4.97, d, *J* = 3.5 Hz

syn-**224**

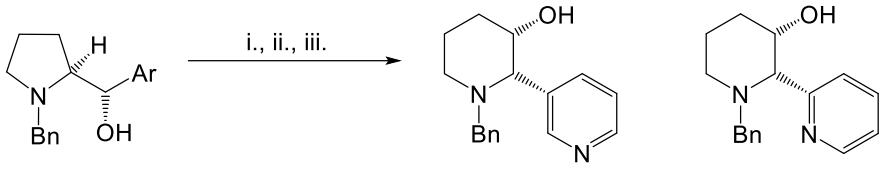


δ 4.64, d, *J* = 3.5 Hz

anti-**224**

With pyridyl *N*-benzyl pyrrolidines *syn*- and *anti*-**223-225** in hand, each pure diastereomer was used in the ring expansion step to give 3-hydroxy piperidines *syn*- and *anti*-**226-228**. For instance, ring enlargement of 3-pyridyl *N*-benzyl pyrrolidine *syn*-**223** was carried out under Cossy's conditions using trifluoroacetic acid anhydride and Et_3N. Finally, ester hydrolysis by NaOH provided 3-hydroxy piperidine *syn*-**226** in 76% yield after chromatography (Scheme 3.51). Similarly, the same conditions were used with 2-pyridyl *N*-benzyl pyrrolidine *syn*-**224** which resulted in the formation of 2-pyridyl *N*-benzyl piperidine *syn*-**227** in 46% yield.

Scheme 3.51

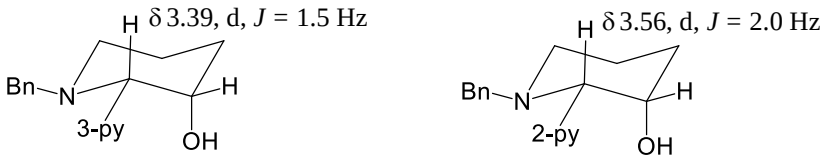


syn *syn*-**226**, 76% *syn*-**227**, 46%

Reagents and conditions: i. TFAA, −78 °C, 1 h; ii. Et_3N, −78 °C, 1 h then reflux, 48 h; iii. 20% $NaOH_{(aq)}$, rt, 2 h.

The successful formation of 3-hydroxy piperidines *syn*-**226** and *syn*-**227** was proved and the stereochemistry was identified in the same way as for the *N*-methyl compounds. In the case of piperidines *syn*-**226** and *syn*-**227**, the ^{1}H NMR spectra of these compounds contained 1H doublets (J = 1.5 and 2.0 Hz) at δ_H 3.39 and 3.56 ppm respectively due to the methine proton on the benzylic position (Figure 3.11). Both piperidines *syn*-**226** and *syn*-**227** have a small ^3J value (J = 1.5-2.0 Hz) which proves that those piperidines have *syn* stereochemistry.

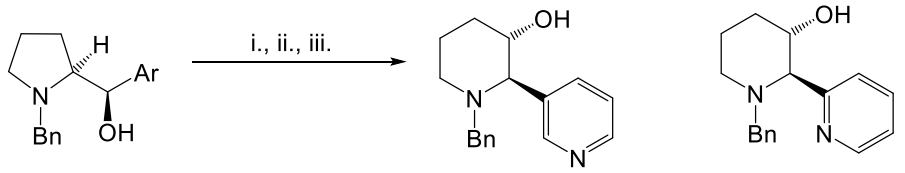
Figure 3.11



syn-**226** *syn*-**227**

In the same way, Cossy's standard conditions were applied to the formation of 3-hydroxy piperidines *anti*-**226** and *anti*-**227**. Thus, both five-membered rings of *anti*-**223** and *anti*-**224** were expanded to the six-membered rings *anti*-**226** and *anti*-**227** and excellent yields were obtained (79% and 69% respectively) after chromatography (Scheme 3.52).

Scheme 3.52

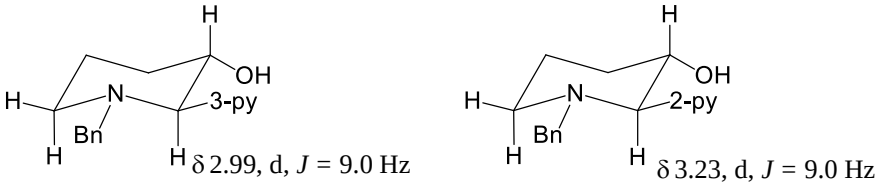


anti *anti*-**226**, 79% *anti*-**227**, 69%

Reagents and conditions: i. TFAA, –78 °C, 1 h; ii. Et_3N, –78 °C, 1 h then reflux, 48 h; iii. 20% $NaOH_{(aq)}$, rt, 2 h.

To prove that we had successfully synthesised the 3-hydroxy piperidines *anti*-**226** and *anti*-**227**, the ^3J coupling constants were also used to identify the stereochemistry of both piperidines *anti*-**226** and *anti*-**227**. In the ^{1}H NMR spectra of *anti*-**226** and *anti*-**227**, the methine proton at the benzylic positon contained a doublet (J = 9.0 Hz) at δ_H 2.99 and 3.23 ppm respectively (Figure 3.12). The appearance of a large ^3J value (J = 9.0 Hz) proved that these two piperidines have *anti* stereochemistry.

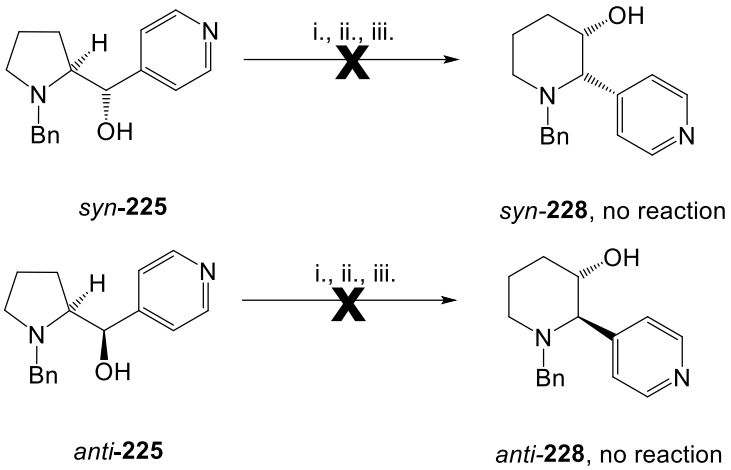
Figure 3.12



anti-**226** *anti*-**227**

Unfortunately, in the attempted synthesis of 3-hydroxy piperidines containing a 4-pyridyl substituent, *syn*- and *anti*-**228**, under the standard conditions as shown in Scheme 3.52, there was no evidence for the formation of the desired products (by ^{1}H NMR spectroscopy). It is not clear why these ring expansion reactions were not successful.

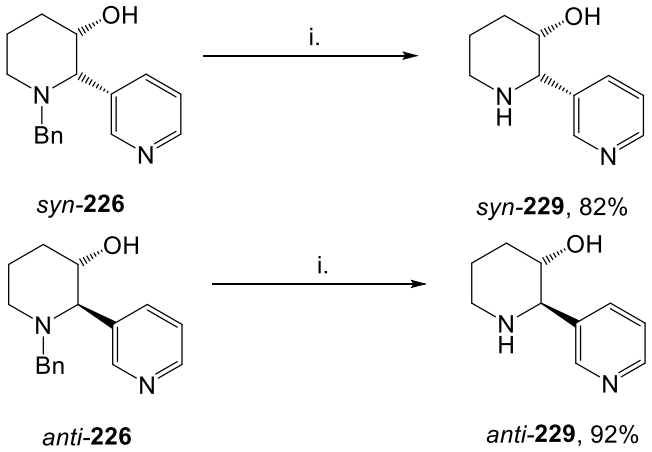
Scheme 3.52



Reagents and conditions: i. TFAA, –78 ˚C, 1 h; ii. Et_3N, –78 ˚C, 1 h then reflux, 48 h; iii. 20% $NaOH_{(aq)}$, rt, 2 h.

Finally, to show that the novel 3-hydroxy piperidines could be used as building blocks for the potential synthesis of a library of drug-like molecules, the benzyl group needed to be removed so that *N*- or *O*-functionalisation could in principle be carried out. *N*-Benzyl deprotection of 3-hydroxy piperidines with 3-pyridyl group, *syn*- and *anti*-**226**, was carried out under using $Pd(OH)_2$/C and ammonium formate which gave the amino alcohols *syn*- and *anti*-**229** in 82% and 92% yield respectively (Scheme 3.53).

Scheme 3.53



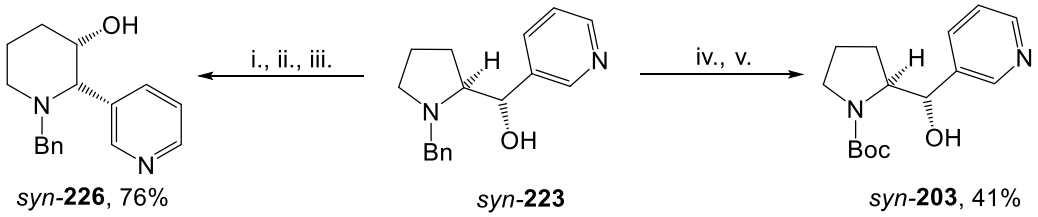
Reagents and conditions: i. $Pd(OH)_2$/C (20 wt %), HCO_2NH_4, reflux, 16 h, EtOH.

In conclusion, 3-hydroxy piperidines containing 2- and 3-pyridyl groups were successfuly synthesised *via* ring expansion according to Cossy's conditions in good yields. Unfortunately, both 4-pyridyl substituted hydroxy piperidines *syn*- and *anti*-**228** were not obtained from a similar synthetic sequence.

3.4.5 Proof of Stereochemistry of Hydroxy Pyrrolidines

The stereochemistry of *N*-Boc pyrrolidines *syn*- and *anti*-**206**-**208** and *N*-benzyl pyrrolidines *syn*- and *anti*-**223**-**225** was proven in the following way. The stereochemistry of *N*-benzyl piperidine *syn*-**226** was assigned since there was not a large *trans*-diaxial ^{3}J value in the ^{1}H NMR spectrum (see Figure 3.11). Since the ring expansion goes *via* a stereospecific mechanism,[104,133] the starting material for the synthesis of *N*-benzyl piperidine *syn*-**226** must also have *syn*-stereochemistry i.e. the stereochemistry of *syn*-**223** is established. Finally, in order to determine the stereochemistry of *syn*-**206**, it was synthesised from known *syn*-**223** *via* hydrogenolysis and Boc protection reactions which do not change the stereochemistry (Scheme 3.54).

Scheme 3.54

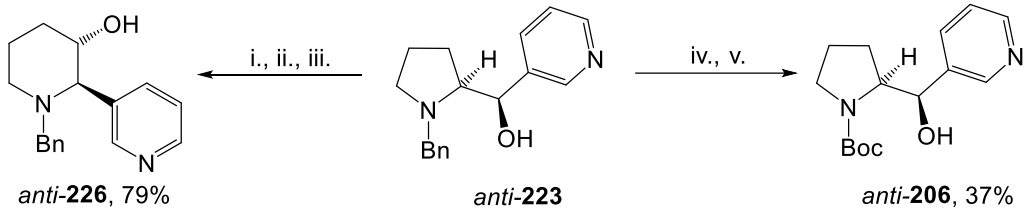


syn-**226**, 76% *syn*-**223** *syn*-**203**, 41%

Reagents and conditions: i. TFAA, –78 °C, 1 h; ii. Et_3N, –78 °C, 1 h then reflux, 48 h; iii. 20% $NaOH_{(aq)}$, rt, 2 h; iv. $Pd(OH)_2/C$, NH_4Cl, reflux, 2-5 h, EtOH; v. Boc_2O, 50 °C, 16 h.

In addition, the stereochemistry of *N*-Boc pyrrolidine *anti*-**206** was also proven in a similar way. The ^{1}H NMR spectrum of *anti*-**226** had a large *trans*-diaxial ^{3}J value (see Figure 3.12), which established the stereochemistry of *anti*-**226** and *anti*-**227**. Also, conversion of *anti*-**223** into *anti*-**206** proved the stereochemistry of *anti*-**206** (Scheme 3.55).

Scheme 3.55

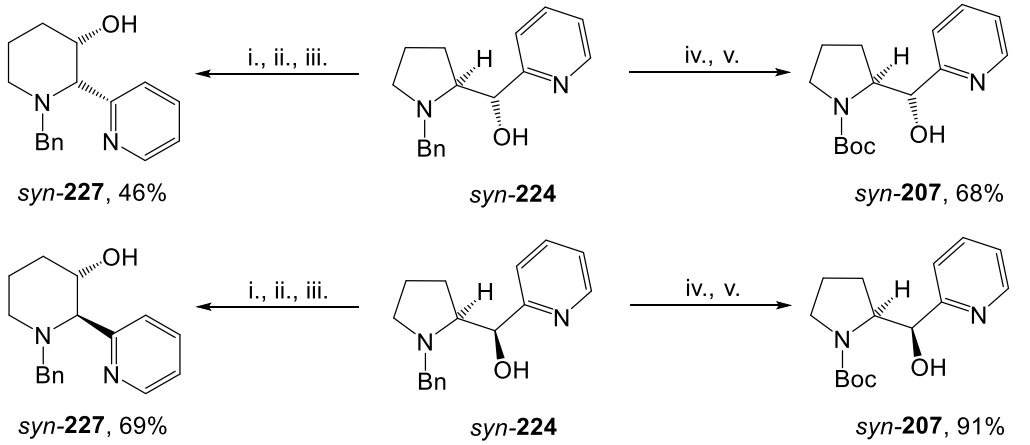


anti-**226**, 79% *anti*-**223** *anti*-**206**, 37%

Reagents and conditions: i. TFAA, –78 °C, 1 h; ii. Et_3N, –78 °C, 1 h then reflux, 48 h; iii. 20% $NaOH_{(aq)}$, rt, 2 h; iv. $Pd(OH)_2/C$, NH_4Cl, reflux, 2-5 h, EtOH; v. Boc_2O, 50 °C, 16 h.

In the case of the 2-pyridyl series, the same sequences were used to prove the stereochemistry (Scheme 3.56).

Scheme 3.56



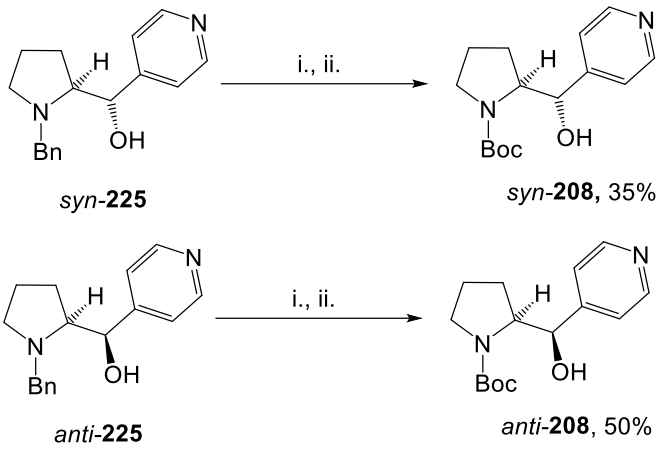
syn-**227**, 46% *syn*-**224** *syn*-**207**, 68%

syn-**227**, 69% *syn*-**224** *syn*-**207**, 91%

Reagents and conditions: i. TFAA, –78 °C, 1 h; ii. Et_3N, –78 °C, 1 h then reflux, 48 h; iii. 20% $NaOH_{(aq)}$, rt, 2 h; iv. $Pd(OH)_2/C$, HCO_2NH_4, reflux, EtOH, 2-5 h; v. Boc_2O, 50 °C, 16 h.

Since the ring expansion of 4-pyridyl *N*-benzyl pyrrolidines *syn*- and *anti*-**225** were not successful, the stereochemistry of 4-pyridyl *N*-Boc pyrrolidines *syn*- and *anti*-**208** could not be assigned for certain. However, two assumptions were used to identify the stereochemistry as far as possible. First, addition of lithiated *N*-Boc pyrrolidine **3** to aldehydes is generally *syn*-selective (see Scheme 1.13).[115] With 4-pyridine carboxaldehyde, a 60:40 diastereomeric mixture of products was obtained and we assume that the major product is *syn*-**208**. Second, with *N*-benzyl hydroxy pyrrolidines **223** and **224**, the *syn* diastereomer has a lower R_F value than the *anti* for each compound and we assume that the same trend is observed with the 4-pyridyl series. To support these assumptions, *syn*-**225** was converted into *syn*-**208** and *anti*-**225** was converted into *anti*-**208** (Scheme 3.57).

Scheme 3.57



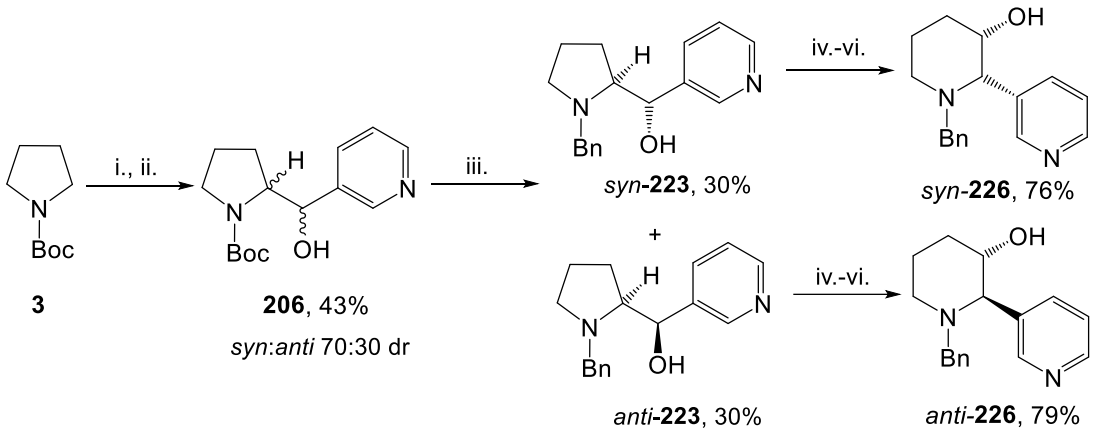
Reagents and conditions: i. $Pd(OH)_2/C$, HCO_2NH_4, reflux, EtOH, 2-5 h; ii. Boc_2O, 50 °C, 16 h.

In conclusion, the stereochemistry of hydroxy pyrrolidines **206**-**208** could be proved by both analysis of ^1H NMR spectroscopy data of the six-membered ring and converting the protecting groups from the benzyl to the Boc group. However, in the case of 4-pyridyl hydroxy pyrrolidines **208**, the stereochemistry was assumed from the trend of selectively obtaining the *syn*-product after lithiation and trapping and the R_F value of the *N*-benzyl pyrrolidines **225**, in which *syn* is normally lower than *anti*.

3.4.6 Overview and Limitations of Initial Route

A summary of our initial synthetic route from *N*-Boc pyrrolidine **3** to *N*-benzyl piperidines *syn*-**226** and *anti*-**226** is shown in Scheme 3.58. The heteroaromatic group was introduced in the lithiation and aldehyde trapping step which is the first step of overall route. *N*-Boc hydroxy pyrrolidines **206-208** were obtained as mixtures of *syn* and *anti* diastereomers with low diastereoselectivity (40:60-70:30 *syn*:*anti*). Reductive amination was then applied to introduce an *N*-benzyl group. Fortunately, *N*-benzyl pyrrolidines *syn*-and *anti*-**223-225** were seperable. Then, these single pure *syn*-and *anti*-forms were used in the ring expansion to give 3-hydroxy piperidines containing heteroaromatic groups.

Scheme 3.58



Reagents and conditions: i. *s*-BuLi (1.3 eq.), –30 °C, 5 min, THF; ii. 2- or 3- or 4-pyridine carboxaldehyde (2.0 eq.), –30 °C, 10 min then rt, 2 h; iii. $NaBH(OAc)_3$ (2.0eq.), AcOH (0.2 eq.), THF; iv. TFAA, –78 °C, 1 h; v. Et_3N, –78 °C, 1 h then reflux, 48 h; vi. 20% $NaOH_{(aq)}$, rt, 2 h.

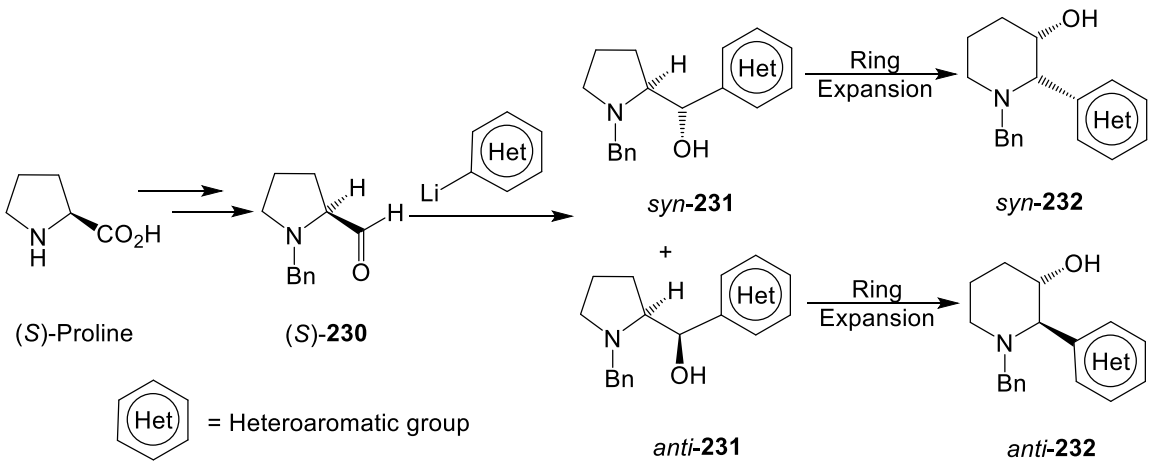
There are two main limitations of this initial route. First, the heteroaromatic group is introduced in the first step which means that synthesising a library of compounds with different heteroaromatic groups is time consuming. Second, the low diastereoselectivity is a disadvantage. Hence, other routes were investigated in an attempt to address these limitations.

3.5 Investigation of Synthetic Routes from (*S*)-Proline

3.5.1 Synthesis and Reactions of *N*-Benzyl Pyrrolidinal and *N*-Benzyl Pyrrolidinones

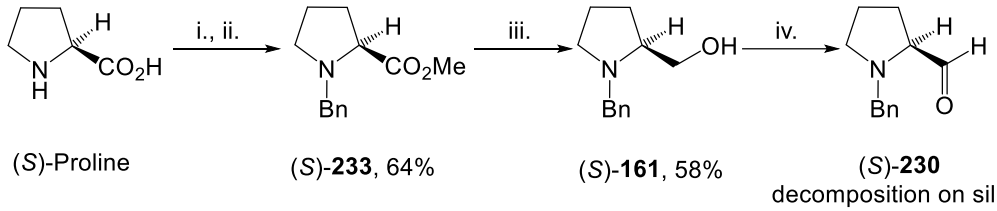
The initial route was not ideal mainly because the heteroaromatic groups were introduced at the start of the synthetic route. Thus, each new analogue must be synthesised from the initial step. Therefore, a better approach would be to introduce the heteroaromatics later in the synthesis and our proposed route is shown in Scheme 3.59. The method was modified from Juaristi's procedure[138] which started from (*S*)-proline and proceeded *via* formation of *N*-benzyl prolinal (*S*)-**230**. The next step would be addition of a lithiated heteroaromatic compound to give separable amino alcohols *syn*- and *anti*-**231**. Finally, Cossy's ring expansion conditions would be carried out in the usual way to provide the desired 3-hydroxy *N*-benzyl piperidines *syn*- and *anti*-**232**.

Scheme 3.59



To begin our work, esterification and *N*-benzylation of (*S*)-proline was carried out using a literature procedure to give the *N*-benzyl proline methyl ester (*S*)-**233** in 64% yield (Scheme 3.60).[139,140] Then, *N*-benzyl ester (*S*)-**233** was reduced by $LiAlH_4$ to give *N*-benzyl prolinol (*S*)-**161** in 58% yield which was then oxidized *via* Swern oxidation.[141] Unfortunately, *N*-benzyl prolinal (*S*)-**230** was not obtained because of decomposition after an attempt to purify it by flash chromatography. Therefore, we decided to use crude *N*-benzyl prolinal (*S*)-**230** for the next step as its ^{1}H NMR spectrum was consistent with that in the literature.[142]

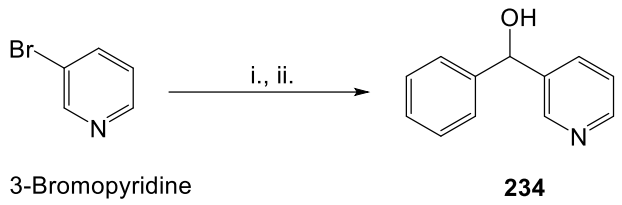
Scheme 3.60



Reagents and conditions: i. MeCOCl, rt, 15 h, MeOH; ii. BnBr, Et_3N, rt, 12 h, MeCN; iii. $LiAlH_4$, rt, 16 h, THF; iv. a) $(COCl)_2$, DMSO, −78 °C, 10 min, CH_2Cl_2; b) (*S*)-**161**, −78 °C, 20 min, Et_3N, −78 °C then 0 °C, 2 h, CH_2Cl_2.

The next planned step was the addition of 3-pyridyllithium to aldehyde (*S*)-**230**. However, before the nucleophilic addition reaction was investigated, we carried out a study to verify that the Br/Li or Br/Mg exchange procedures could be carried out successfully.[143–145] In addition, a LiCl-mediated Br/Mg exchange reaction reported by Knochel and Krasovsky was included in this study.[146,147] To begin with, benzaldehyde was used as a model aldehyde. Thus, 3-bromopyridine was lithiated using *n*-BuLi at −78 °C for 30 min.[144] The 3-pyridyllithium was then trapped by benzaldehyde to give phenyl 3-pyridyl alcohol **234** in 59% yield (Scheme 3.61, Table 3.7, entry 1). Next, a Br/Mg exchange reaction using *i*-PrMgCl[145] was carried out at rt for 1 hour and the amino alcohol **234** was obtained in 65% yield (entry 2). Finally, using *i*-PrMgCl•LiCl[146] at 0 °C for 1 hour gave alcohol **234** in 61% yield (entry 3). Since all three conditions gave similar yields, the Br/Li exchange reaction using *n*-BuLi at −78 °C for 30 min was selected for application with aldehyde (*S*)-**230**.

Scheme 3.61



3-Bromopyridine **234**

Reagents and conditions: i. Reagents, Br/Li or Br/Mg exchange time, temp, THF; ii. Benzaldehyde, temp, time.

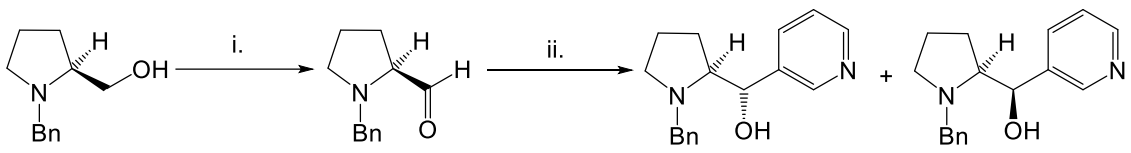
Table 3.7

Entry	Reagent	Br/Li or Br/Mg exchange time (min), temp (˚C)	Temp (˚C)	Time (h)	Yield (%)[a]
1	*n*-BuLi	30, –78	–78 then rt	2	59
2	*i*-PrMgCl	60, rt	rt	2	65
3	*i*-PrMgCl•LiCl	60, 0	0	1	61

a Yield after flash chromatography.

Next, with *N*-benzyl prolinol (*S*)-**161** in hand, the Swern oxidation of alcohol (*S*)-**161** was carried out to give crude *N*-benzyl prolinal (*S*)-**230** which was instantly used in the next step. Crude aldehyde (*S*)-**230** was reacted with 3-pyridyllithium generated by the Br/Li exchange reaction of 3-bromopyridine using *n*-BuLi at –78 ˚C in THF. This gave diastereomeric *N*-benzyl alcohols *syn*- and *anti*-**223** in 15% and 20% yield respectively after chromatography (Scheme 3.62).

Scheme 3.62

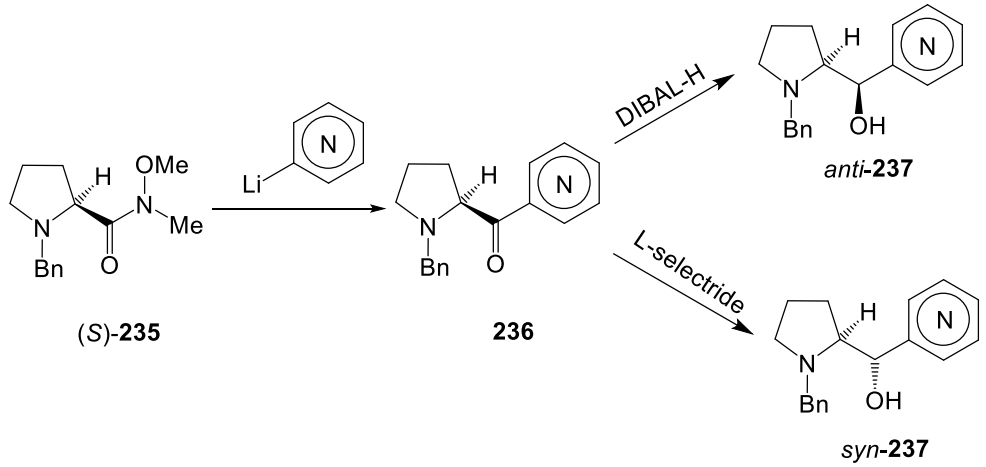


(*S*)-**161** (*S*)-**230** *syn*-**223**, 15% *anti*-**223**, 20%

Reagents and conditions: i. a) $(COCl)_2$, DMSO, –78 ˚C, 10 min, CH_2Cl_2; b) (*S*)-**161**, –78 ˚C, 20 min, Et_3N, –78 ˚C then 0 ˚C, 2 h, CH_2Cl_2; ii. a) 3-bromopyridine, *n*-BuLi, –78 ˚C, 30 min, THF; b) crude (*S*)-**230**, –78 ˚C, 10 min, then rt, 16 h, THF.

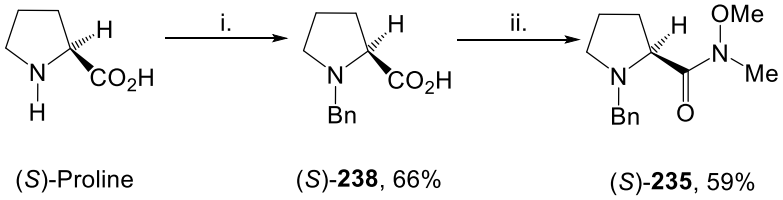
Due to the instability of *N*-benzyl aldehyde (*S*)-**230** and the low yield of alcohols *syn*- and *anti*-**233** obtained, another approach was considered. We planned to synthesise *N*-benzyl ketones containing heteroaromatic groups which would then be reduced using DIBAL-H and L-selectride to diastereoselectively provide the *N*-benzyl alcohols *syn*- and *anti*-**237** (Scheme 3.63). In this synthetic approach, the *N*-benzyl ketones **236** would be prepared *via* the lithiation-trapping of *N*-benzyl Weinreb amide (*S*)-**235** which would be a key intermediate (Scheme 3.63).

Scheme 3.63



To prepare *N*-benzyl proline Weinreb amide (*S*)-**235**, (*S*)-proline was treated with benzyl chloride and KOH in *i*-PrOH to give *N*-benzyl proline (*S*)-**238** in 66% yield after purification by recrystallization from acetone (Scheme 3.64).[148] Then, the reaction of *N*-benzyl proline (*S*)-**238** with *N,O*-dimethylhydroxylamine hydrochloride, *i*-Pr_2NEt and T3P gave the desired Weinreb amide (*S*)-**235** in 59% yield after column chromatography (Scheme 3.64).

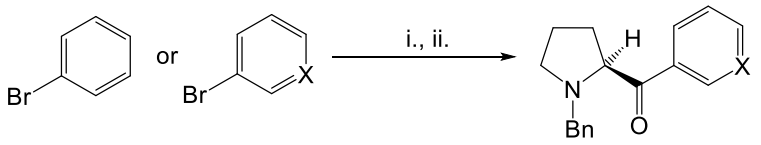
Scheme 3.64



Reagents and conditions: i. BnCl, KOH, 40 °C, 6 h, *i*-PrOH; ii. *N,O*-dimethylhydroxylamine hydrochloride, *i*-Pr_2NEt, T3P (50% w/v solution in THF), rt, 2 h, CH_2Cl_2.

With Weinreb amide (*S*)-**235** in hand, Br/Li exchange using bromobenzene and 3-bromopyridine was used to investigate the synthesis of amino ketones **239** and **240** (Scheme 3.65). Br/Li exchange of bromobenzene or 3-bromopyridine using *n*-BuLi at −78 °C for 30 min and trapping with Weinreb amide (*S*)-**235** gave the *N*-benzyl ketones (*S*)-**239** and (*S*)-**240** in 15% and 22% yield respectively after column chromatography (Scheme 3.65). Unfortunately, the obtained *N*-benzyl ketones (*S*)-**239** and (*S*)-**240** were found to completely decompose after standing at rt for 24-48 hours (by ^{1}H NMR spectroscopy).

Scheme 3.65

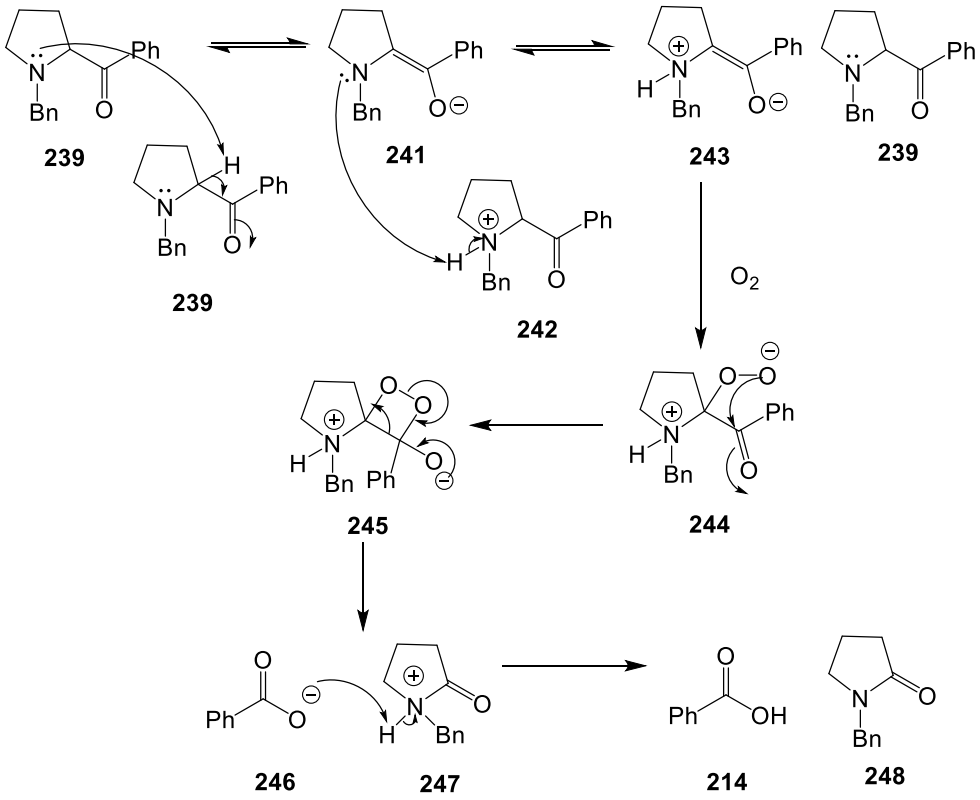


X = CH; (*S*)-**239**, 15%[a]
X = N; (*S*)-**240**, 22%[b]

Reagents and conditions: i. *n*-BuLi (2.0 eq.), −78 °C, 30 min, THF; ii. *N*-Benzyl Weinreb amide (*S*)-**235**, −78 °C, 2 h then rt, 16 h, THF. a. On standing at rt, this compound decomposed within 24 h (by ^{1}H NMR spectroscopy), b. On standing at rt, this compound decomposed within 48 h (by ^{1}H NMR spectroscopy)

An explanation for the instability of *N*-benzyl amino ketones (*S*)-**239** and (*S*)-**240** was needed. Fortunately, a literature search revealed that West and co-workers had proposed a mechanism for the instability of phenyl *N*-benzyl ketone **239** in 2009.[149] Thus, one amino ketone could act as a base to deprotonate an α-proton of another amino ketone to generate an enolate **241** and a pyrrolidinium ion **242**. Then, proton transfer could occur to give zwitterion **243** and starting ketone **239**. Finally, oxidation of the zwitterion **243** (*via* the enolate reacting with oxygen) could lead to *N*-benzyl pyrrolidinone **248** and benzoic acid which was proved by mass spectrometry (Scheme 3.66).

Scheme 3.66

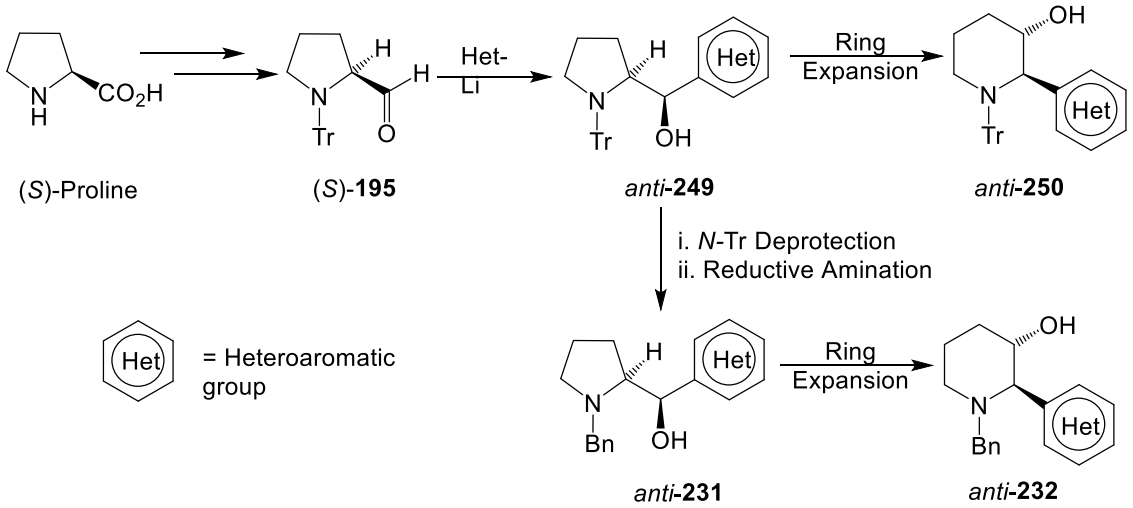


In conclusion, both *N*-benzyl pyrrolidine aldehyde **230** and *N*-benzyl ketones (*S*)-**239** and (*S*)-**240** were not stable at ambient conditions, probably due to decomposition *via* the mechanism proposed by West. Therefore, routes *via* these intermediates were not going to be suitable for our studies and our attention turned elsewhere.

3.5.2 Synthesis of 3-Hydroxy Piperidines from *N*-Trityl Pyrrolidinal

Due to the instability of *N*-benzyl pyrrolidine aldehyde **230** and *N*-benzyl pyrrolidinones (*S*)-**239** and (*S*)-**240**, other *N*-protected pyrrolidine aldehydes or ketones derived form (*S*)-proline were considered. Interestingly, Chemla and co-workers reported that *N*-trityl aldehyde (*S*)-**195** was chemically stable and did not racemize at room temperature. In addition, the synthesis of *N*-trityl pyrrolidine aldehyde (*S*)-**195** starting from (*S*)-proline proceeded in good yield (80%) and high enantiomeric excess (>95% ee) over four steps.[150] Hence, our plan was to prepare multi-gram quantities of *N*-trityl prolinal (*S*)-**195** as a key building block so that several heteroaryl groups could be introduced at a late stage to give various novel *N*-trityl amino alcohols which could be ring-expanded (Scheme 3.67). If the *N*-trityl hydroxy pyrrolidines did not ring-expand then the trityl group could be removed and reductive amination could be applied to give *N*-benzyl pyrrolidinols, whose ring expansion has already been established.

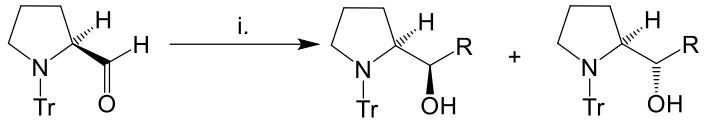
Scheme 3.67



In Chemla's work, *N*-trityl aldehyde (*S*)-**195** was treated with various organometallic nucleophiles such as *n*-BuLi, *n*-BuMgBr, TMS-C≡C-Li and PhMgBr to give *N*-trityl alcohols (Scheme 3.68, Table 3.7). For example, the nucleophilic addition of *n*-BuLi to *N*-trityl prolinal (*S*)-**195** in Et_2O gave a 93:7 diastereomeric mixture of alcohols *anti*- and *syn*-**251** in 67% yield (Table 3.7, entry 1) whereas the same reaction in THF gave lower diastereoselectivity (86:14 dr) (entry 2). In addition, reaction of *N*-trityl prolinal (*S*)-**195** with *n*-BuMgBr gave a single diastereomer (>98:2 dr) of alcohol *anti*-**251** in excellent yield (entry

3). Similarly, use of TMS-C≡C-Li and PhMgBr in Et_2O gave the single diastereomers (>98:2 dr) of *N*-trityl alcohols *anti*-**252** and *anti*-**253** (entries 4 and 5).

Scheme 3.68



(*S*)-**195** *anti*-**251-253** *syn*-**251-253**

Reagents and conditions: i. Reagents, –80 °C, Et_2O or THF.

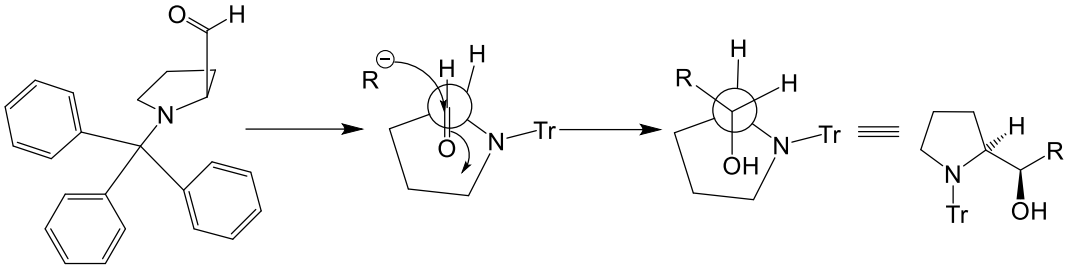
Table 3.8

Entry	**Reagent**	**Solvent**	**Yield (%)**[a]	**dr**[b], *anti*:*syn*
1	*n*-BuLi	Et_2O	65	93:7
2	*n*-BuLi	THF	n.d.[c]	86:14
3	*n*-BuMgBr	Et_2O	78	>98:2
4	TMS-C≡C-Li	Et_2O	88	>98:2
5	PhMgBr	Et_2O	90	>98:2

a Isolated yield of the major product after flash chromatography.
b Diastereomeric ratio measured by ^{1}H NMR spectroscopy of the crude material.
c Not determined.

The stereoselective formation of *N*-trityl alcohol *anti*-**251-253** can be explained by the Felkin-Ahn model shown in Figure 3.12.[151] Thus, the presence of a sterically hindered trityl group which points away from the five-membered ring led to nucleophile attack on the carbonyl group from the opposite side to avoid the steric effect. Therefore, the *anti*-form was observed as the major diastereomer.

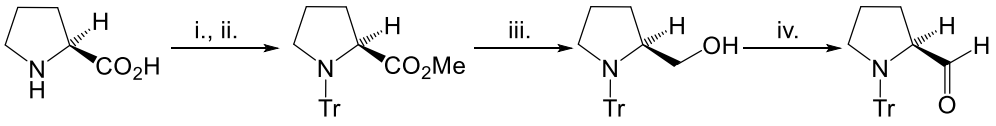
Figure 3.12



(*S*)-**192** *anti*-**251-253**

To begin with, the synthesis of the *N*-trityl prolinal (*S*)-**195** was carried out according to Chemla's procedure. Thus, an esterification (using thionyl chloride in MeOH) and trityl protection of (*S*)-proline gave methyl ester (*S*)-**254** in 62% yield after recrystallisation from Et_2O (Scheme 3.69). Then, ester (*S*)-**254** was reduced using $LiAlH_4$ to give *N*-trityl alcohol (*S*)-**255** in 70% yield which was then Swern oxidised to obtain the air-stable *N*-trityl prolinal (*S*)-**195** in 47% yield after chromatography. Multi-gram amounts of aldehyde (*S*)-**195** were prepared and could be stored without decomposition or epimerisation.

Scheme 3.69

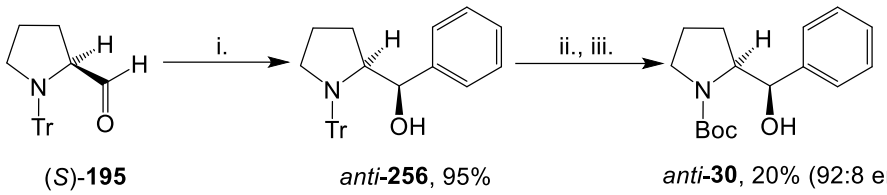


(*S*)-Proline (*S*)-**254**, 62% (*S*)-**255**, 70% (*S*)-**195**, 47%

Reagents and conditions: i. $SOCl_2$, –10 °C then rt, 18 h, MeOH; ii. TrCl, Et_3N, rt, 18 h, $CHCl_3$; iii. $LiAlH_4$, rt, 2 h, THF; iv. a) $(COCl)_2$, DMSO, –78 °C, 10 min, CH_2Cl_2; b) (*S*)-**255**, –78 °C, 1.5 h, Et_3N, –78 °C, 1.5 h, CH_2Cl_2.

In order to determine the enantiomeric ratio of *N*-trityl prolinal (*S*)-**195**, we decided to convert it into *N*-Boc amino alcohol *anti*-**30** (Scheme 3.70) as the chiral stationary phase HPLC separation of the enantiomers of *anti*-**30** has previously been carried out in our group.[115] Thus, addition of PhMgBr to the *N*-trityl aldehyde (*S*)-**195** gave *N*-trityl alcohol *anti*-**256** in 95% yield. Then, *N*-trityl removal using 5 M $HCl_{(aq)}$ and Boc protection proceeded to give enantiomerically enriched *N*-Boc amino alcohol *anti*-**30** in 20% yield and 92:8 er (Scheme 3.70). This showed that there was some erosion of enatiomeric ratio the starting of (*S*)-proline. Based on this result, we assumed that all products derived from *N*-trityl aldehyde (*S*)-**195** must also be of 92:8 er.

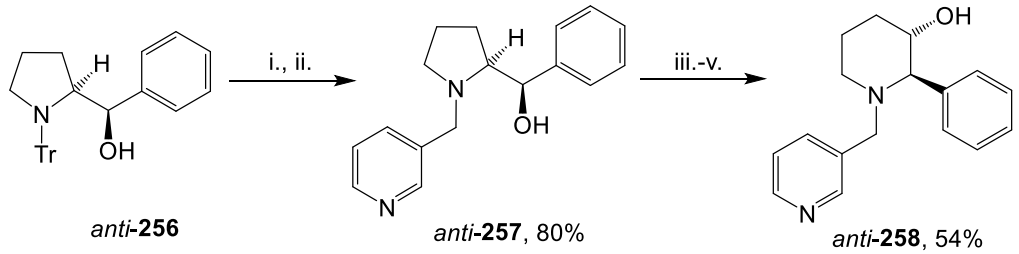
Scheme 3.70



Reagents and conditions: i. PhMgBr, Et_2O, −78 °C then rt, 16 h; ii. 5 M $HCl_{(aq)}$, CH_2Cl_2, rt, 3 h; iii. Boc_2O, CH_2Cl_2, 0 °C then rt, 16 h.

At this point, we decided to use *N*-trityl alcohol *anti*-**256** as a starting material for the synthesis of a ring-expanded 3-hydroxy piperidine with a heteroaromatic group on the tertiary amine. The *N*-trityl group was removed using 5 M $HCl_{(aq)}$ to give the free amine and reductive amination using 3-pyridine carboxaldehyde gave *N*-methyl pyridyl alcohol *anti*-**257** in 80% yield over the two steps (Scheme 3.71). Then, standard ring expansion conditions gave the desired 3-hydroxypiperidine *anti*-**258** in moderate yield (54%). This was the first time that a 3-hydroxypiperidine with an *N*-heteroaryl group was successfully prepared by ring expansion.

Scheme 3.71

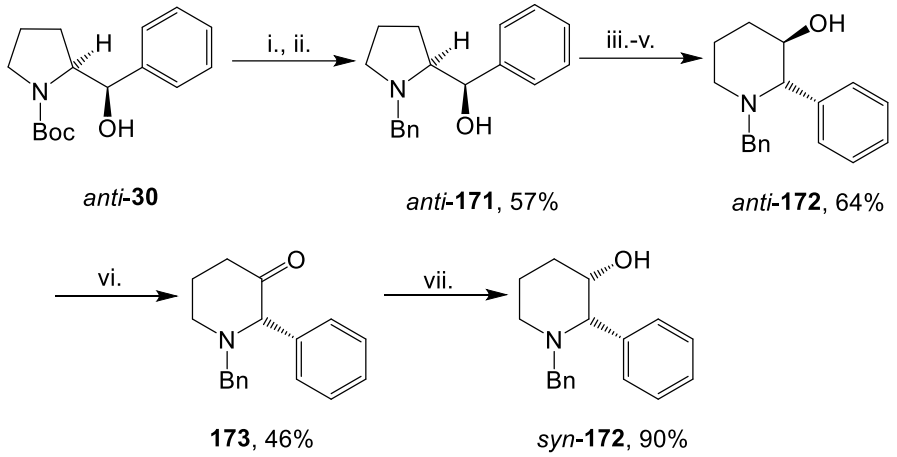


Reagents and conditions: i. 5 M $HCl_{(aq)}$, CH_2Cl_2, rt, 3 h; ii. Heteroaryl carboxaldehyde, $NaBH(OAc)_3$, AcOH, DCE; iii. TFAA, −78 °C, 1 h; iv. Et_3N, −78 °C, 1 h then reflux, 48 h; v. 20% $NaOH_{(aq)}$, rt, 2 h.

With optically active *N*-Boc amino alcohol *anti*-**30** in hand, conversion into *N*-benzyl amino alcohol *anti*-**171** *via* Boc deprotection and reductive amination was carried out and the desired product *anti*-**171** was obtained in 57% yield (Scheme 3.72) Next, ring expansion using Cossy's standard conditions gave *N*-benzyl 3-hydroxypiperidine *anti*-**172** in moderate yield (64%). In contrast to the work reported by Langlois and Calvez (see Scheme 3.19), alcohol *anti*-**172** was oxidised using Dess-Martin periodinane to give ketone **173** in 46% yield. Finally, reduction of **173** gave *N*-benzyl 3-hydroxypiperidine *syn*-**172** in excellent yield (90%). This synthetic route was very interesting as it could shorten the reaction steps

and was less time consuming. Therefore, in order to synthesise the diastereomers *N*-benzyl 3-hydroxypiperidine *syn*- and *anti*-**172**, there was no need to start the synthesis from the *N*-Boc hydroxy pyrrolidines *syn*- and *anti*-**30**.

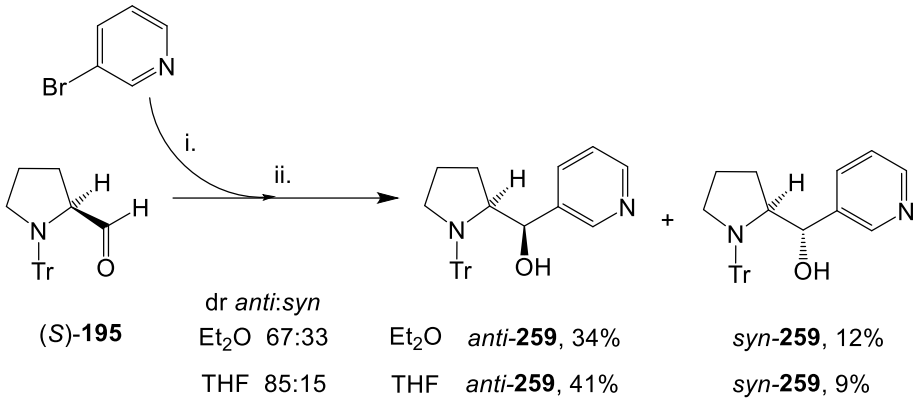
Scheme 3.72



Reagents and conditions: i. 5 M $HCl_{(aq)}$, CH_2Cl_2, rt, 3 h; ii. PhCHO, $NaBH(OAc)_3$, AcOH, DCE; iii. TFAA, –78 °C, 1 h; iv. Et_3N, –78 °C, 1 h then reflux, 48 h; v. 20% $NaOH_{(aq)}$, rt, 2 h; vi. Dess-Martin periodinane, CH_2Cl_2, 0 °C then rt, 30 min; vii. L-selectride, MeOH, –78 °C, 1 h.

Next, to synthesise *N*-trityl alcohols containing different heteroaryl groups from *N*-trityl prolinal (*S*)-**195**, the 3-pyridyl group was selected first. To start the synthesis, 3-pyridyllithium was generated *via* a Br/Li exchange by treatment of 3-bromopyridine with *n*-BuLi. In this step, different solvents such as Et_2O and THF were utilised and different outcomes resulted. Thus, when 3-bromopyridine was treated with *n*-BuLi in Et_2O to give the lithiated intermediate, trapping with *N*-trityl prolinal (*S*)-**195** gave a 67:33 mixture of alcohols *anti*- and *syn*-**259** (by ^{1}H NMR spectroscopy). After chromatography, the desired alcohols *anti*- and *syn*-**259** were isolated in 34% and 12% yield respectively (Scheme 3.73). However, Br/Li exchange in THF and reaction with *N*-trityl prolinal (*S*)-**195** selectively gave an 85:15 mixture of alcohols *anti*- and *syn*-**259** (by ^{1}H NMR spectroscopy). In this case, the desired alcohols *anti*- and *syn*-**259** were isolated in 41% and 9% yield respectively. As the overall yield of each reaction was similar, the lithiation in THF was selected and utilised for the Br/Li exchange step.

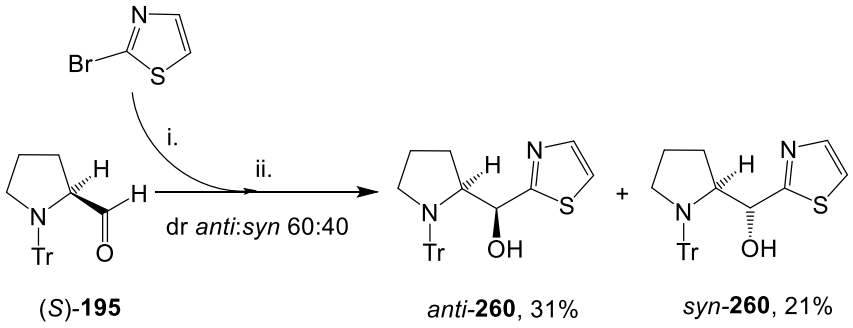
Scheme 3.73



Reagents and conditions: i. 3-Bromopyridine, *n*-BuLi, –78 °C, 30 min, THF or Et_2O; ii. *N*-trityl prolinal (*S*)-**195**, –78 °C then rt, 16-18 h, Et_2O.

Since the synthesis of 3-pyridine *N*-trityl prolinols *anti*- and *syn*-**259** from *N*-trityl prolinal (*S*)-**195** was successful, we decided to investigate other heteroaryl groups. To begin with, the Br/Li exchange of 2-bromothiazole was carried out using *n*-BuLi in THF to generate the 2-lithiothiazole (Scheme 3.74). Our Br/Li exchange procedure was based on one described in the literature.[143] After trapping with *N*-trityl prolinal (*S*)-**195**, a 60:40 mixture of the thiazole *N*-trityl alcohols *anti*- and *syn*-**260** was obtained (by ^{1}H NMR spectroscopy) and the isolated yields were 31% and 21% respectively.

Scheme 3.74

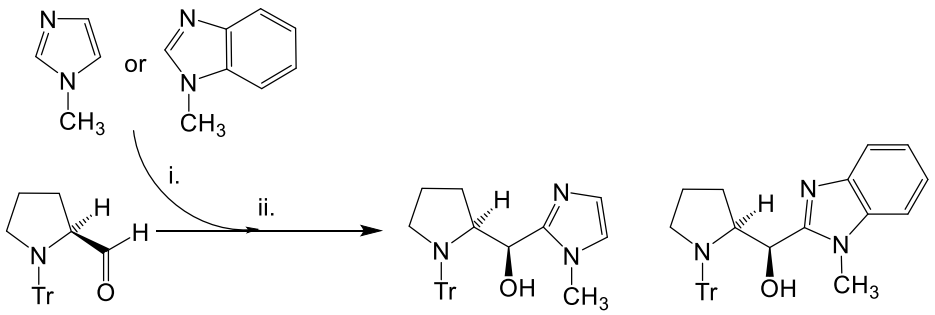


Reagents and conditions: i. *n*-BuLi, –78 °C, 30 min, THF; ii. *N*-trityl prolinal (*S*)-**195**, –78 °C then rt, 16-18 h, Et_2O.

As shown by these results, the diastereoselectiviy of the *N*-trityl alcohols containing 3-pyridyl and thiazolyl substituents, **259** and **260**, were lower than those reported by Chemla using *n*-BuLi or PhMgBr (see Table 3.7). We wondered whether the LiBr salt which is formed in the Br/Li exchange step could be responsible for the lower diastereoselectivity of *N*-trityl alcohols **259** and **260**.

Next, we explored the addition of lithiated 1-methyl imidazole and 1-methyl benzimidazole to *N*-trityl aldehyde (*S*)-**195**. In these cases, Br/Li exchange was not needed since Klumpp and Boblak reported that 1-methyl imidazole and benzimidazole can be directly deprotonated inbetween the two nitrogen atoms to give the lithiated intermediates.[152] Based on this literature procedure, the deprotonation of 1-methyl imidazole and 1-methyl benzimidazole using *n*-BuLi in THF was carried out at –78 °C for 30 minutes to generate the lithiated intermediates which were then trapped with *N*-trityl prolinal (*S*)-**195**. As a result, a single diastereomer of 1-methyl imidazole *N*-trityl alcohol *anti*-**261** and 1-methyl benzimidazole *N*-trityl alcohol *anti*-**262** were obtained in 76% and 56% yield respectively (Scheme 3.75). These highly diastereoselective additions are consistent with Chemla's result and support our theory that LiBr has a role in lowering the diastereomeric ratio in the 3-pyridyl and thiazolyl reactions.

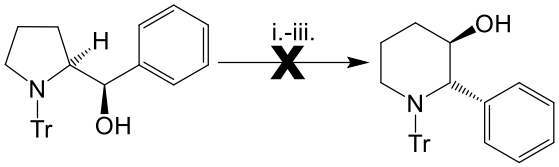
Scheme 3.75



Reagents and conditions: i. *n*-BuLi, –78 °C, 30 min, Et_2O; ii. *N*-trityl prolinal (*S*)-**195**, –78 °C then rt, 16-18 h, Et_2O.

At this point, it was decided to see whether the *N*-trityl group could be used in a ring expansion. Previously, Cossy had attempted a similar reaction and it was not successful (see Scheme 3.28).[118] *N*-Trityl alcohol *anti*-**256** was chosen and the ring expansion was attempted using Cossy's standard conditions. Similar to the Cossy's report, none of the 3-hydroxy *N*-trityl piperidine *anti*-**263** was observed in the crude product (by ^{1}H NMR spectroscopy) (Scheme 3.76). The failure to obtain the aimed product was probably due to steric hindrance form the trityl group.

Scheme 3.76

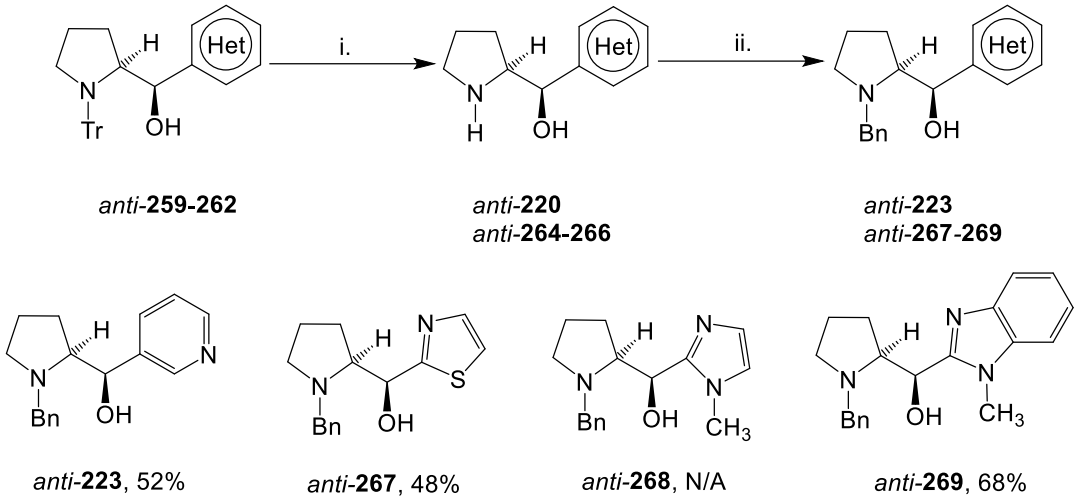


anti-**256** *anti*-**263**

Reagents and conditions: i. TFAA, –78 °C, 1 h; ii. Et_3N, –78 °C, 1 h then reflux, 48 h; iii. 20% $NaOH_{(aq)}$, rt, 2 h.

Therefore, it was necessary to convert the *N*-trityl group into the *N*-benzyl group *via* deprotection of the trityl group and reductive amination. In this study, after the trityl group was removed using 5 M $HCl_{(aq)}$ to give the free amine, reductive amination using benzaldehyde, sodium triacetoxyborohydride and acetic acid was carried out to give *N*-benzyl protected amino alcohols (Scheme 3.77). Only *anti* diastereomeric forms of each of the *N*-trityl alcohols **259**-**262** were selected to be converted into *N*-benzyl amino alcohols *anti*-**223** and *antii*-**267**-**269**. Unfortunately, with the 1-methylimidazole group, there was none of the desired 1-methylimidazole *N*-benzyl alcohol *anti*-**268** obtained (by ^{1}H NMR spectroscopy) even when the reaction was repeated. However, *N*-benzyl alcohols *anti*-**223**, *anti*-**267** and *anti*-**269** were obtained in 52%, 48% and 68% yield respectively.

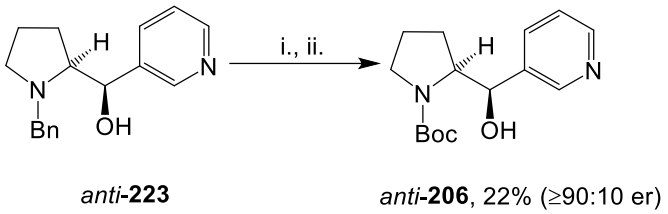
Scheme 3.77



Reagents and conditions: i. 5 M $HCl_{(aq)}$, rt, 4 h, CH_2Cl_2; ii. Benzaldehyde, $NaBH(OAc)_3$, AcOH (0.2 eq.), DCE.

With enantiomerically enriched *N*-benzyl 3-pyridyl alcohol *anti*-**223** successfully prepared, the *N*-benzyl group was converted into a *N*-Boc group using 5 M $HCl_{(aq)}$ to generate the free amine and addition of Boc_2O. This gave the *N*-Boc 3-pyridyl alcohol *anti*-**206** in 22% yield (Scheme 3.78). The enantiomeric ratio of *anti*-**206**, determined by chiral stationary phase HPLC was ≥90:10. A more accurate ratio could not be obtained due to poor resolution of the two peaks.

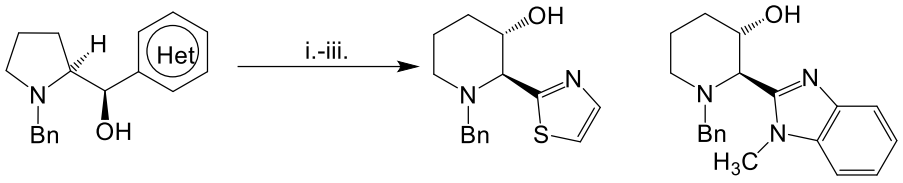
Scheme 3.78



Reagents and conditions: i. 5 M $HCl_{(aq)}$, rt, 4 h, CH_2Cl_2; ii. Boc_2O, 0 ˚C then rt, 16 h.

With the novel *N*-benzyl amino alcohols *anti*-**267** and *anti*-**269** in hand, standard ring expansion conditions were applied to give novel 3-hydroxy *N*-benzyl piperidines *anti*-**270** and *anti*-**271** (Scheme 3.79). Thus, the amino alcohols were treated with trifluoroacetic anhydride, Et_3N and then $NaOH_{(aq)}$ to give the aimed 3-hydroxy *N*-benzyl piperidines *anti*-**270** and *anti*-**271** in good yields over two steps, 55% and 63% respectively.

Scheme 3.79



anti-**267**
anti-**269**

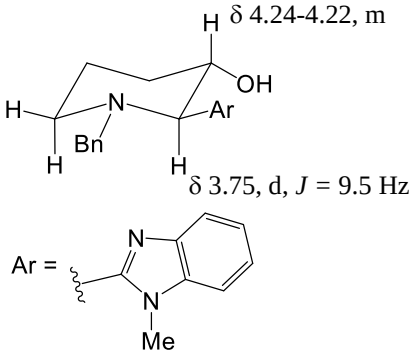
anti-**270**, 55%

anti-**271**, 63%

Reagents and conditions: i. TFAA, −78°C, 1 h, THF; ii. Et_3N, −78°C, 1 h, then reflux, 48 h, THF; iii. 20% $NaOH_{(aq)}$, rt, 2 h.

The ^{1}H NMR spectrum of 1-methyl benzimidazole 3-hydroxy piperidine *anti*-**271** was used to prove its stereochemistry. There was a 1H doublet (J = 9.5 Hz) at δ_H 3.75 ppm which was assigned to the axial proton next to the nitrogen. The large ^3J *trans*-diaxial coupling between the CHN and CHO protons of 9.5 Hz proves that the six-membered ring product has *anti* stereochemistry (Figure 3.13). In contrast, the ^{1}H NMR spectrum of the thioazolyl 3-hydroxy piperidine *anti*-**270** contained a 2H multiplet at δ_H 3.71-3.63 ppm which was assigned to the CHN and CHO protons. Therefore, the stereochemistry of *anti*-**270** was not definitely confirmed, but it is assumed by analogy with other examples (Figure 3.13).

Figure 3.13



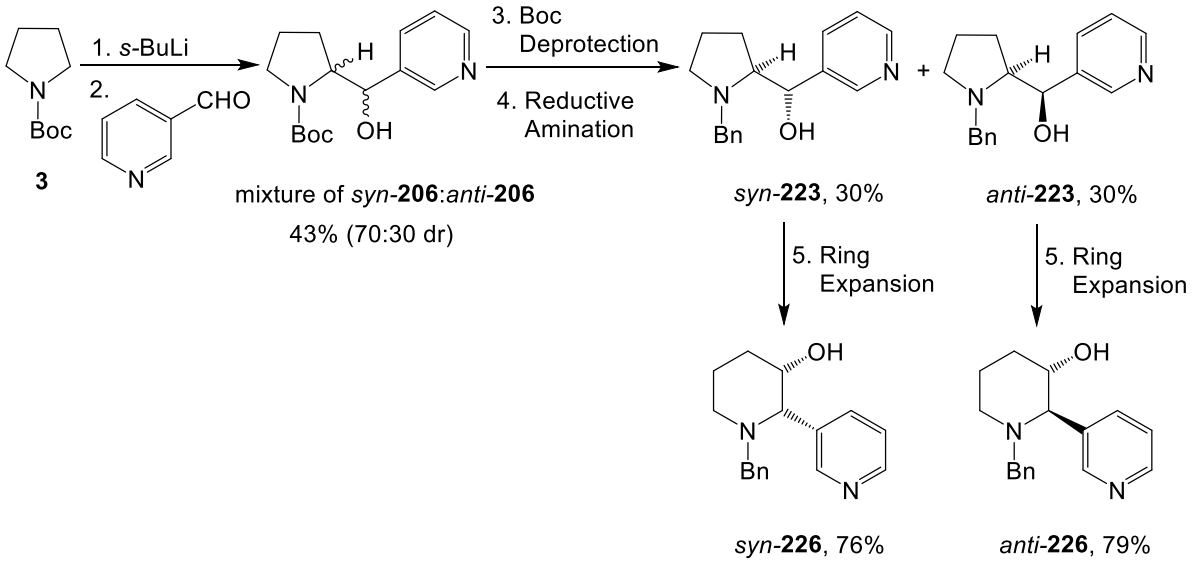
anti-**271**

To our delight, the obtained 3-hydroxy *N*-benzyl piperidines *anti*-**270** and *anti*-**271** are the first examples of such products successfully synthesised in our group. The route is short and simple to carry out and the overall yields were satisfactory. Our synthetic approach started from the direct addition of lihiated heterocycles to *N*-trityl prolinal (*S*)-**195** to give the *N*-trityl alcohols containing different heteroaryls **259**-**262**. Then, trityl deprotection and reductive amination using benzaldehyde converted the *N*-trityl alcohols into *N*-benzyl alcohols **223**, **267**-**269** and, finally, the ring expansion reaction was used to obtain 3-hydroxy piperidines *anti*-**270** and *anti*-**271**. This is an interesting approach and suitable for the preparation of a wide variety of 3-hydroxy piperidines for use in medicinal chemistry projects.

3.6 Conclusions and Future Work

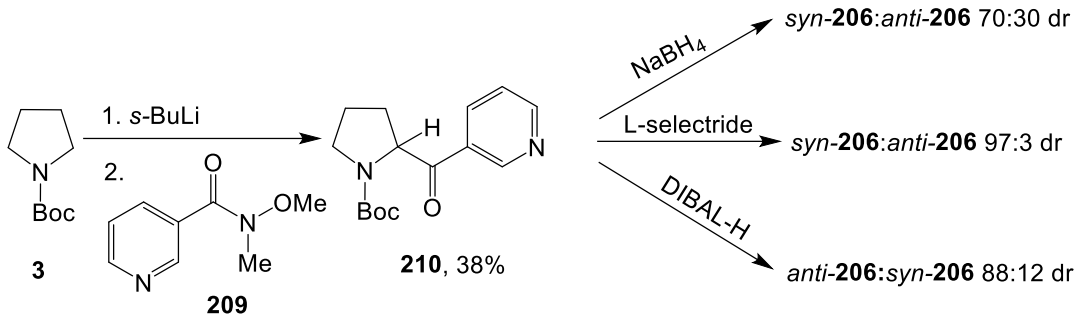
Our initial route from *N*-Boc pyrrolidine **3** to *N*-benzyl piperidine *syn*- and *anti*-**223** started with lithiation-trapping and the heteroaryl group was introduced in this step (Scheme 3.80). After chromatography, the inseparable mixture of diastereomers *syn*- and *anti*-**206** were obtained with low diastereoselectivity (70:30 dr). Then, the Boc group was removed and reductive amination was applied to give a separable mixture of *N*-benzyl alcohols *syn*- and *anti*-**223**. Finally, each of diastereomers *syn*- and *anti*-**223** were ring-expanded and 3-pyridyl *N*-benzyl piperidines *syn*- and *anti*-**226** were successfully synthesised in excellent yield. The overall route required 5 steps.

Scheme 3.80



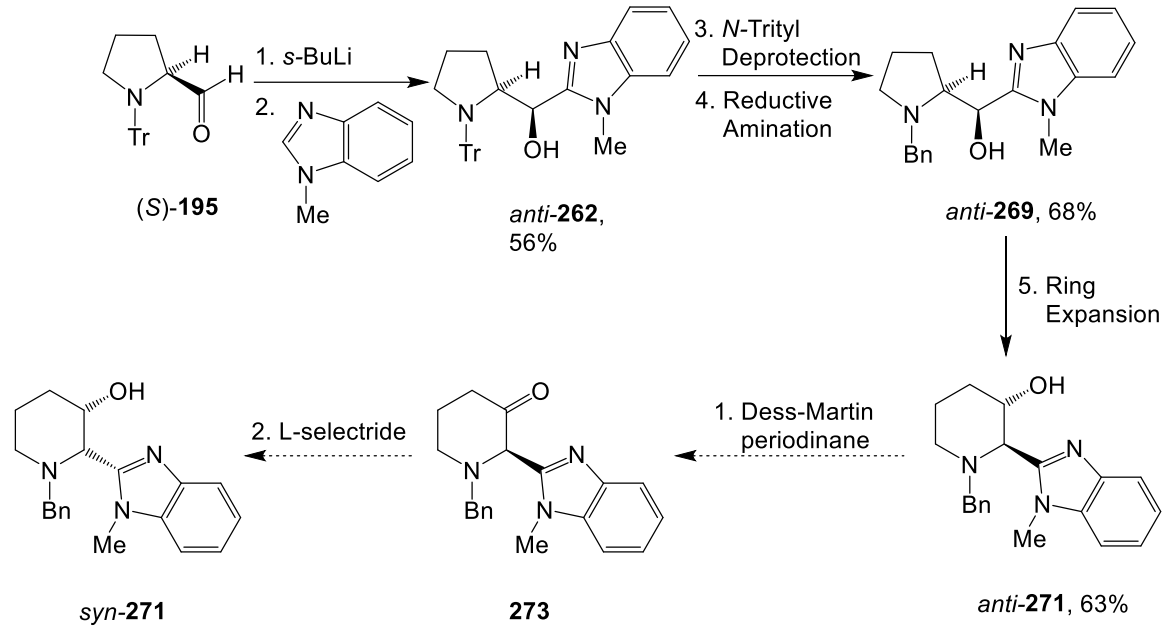
Due to the low diastereoselectivity obtained from the direct lithiation-trapping of *N*-Boc pyrrolidine **3**, reduction of *N*-Boc pyrrolidinone **210** was chosen as an alternative approach (Scheme 3.81). Thus, ketone **210**, prepared from lithiation of *N*-Boc pyrrolidine **3** and trapping with 3-pyridine Weinreb amide **209**, was reduced using $NaBH_4$, L-selectride and DIBAL-H. As a result, the diastereoselectivity of the *N*-Boc hydroxy pyrroldines *syn*- and *anti*-**206** was improved as use of $NaBH_4$ and L-selectride gave *syn* diastereoselectivity, while use of DIBAL-H gave *anti* diastereoselectivity.

Scheme 3.81



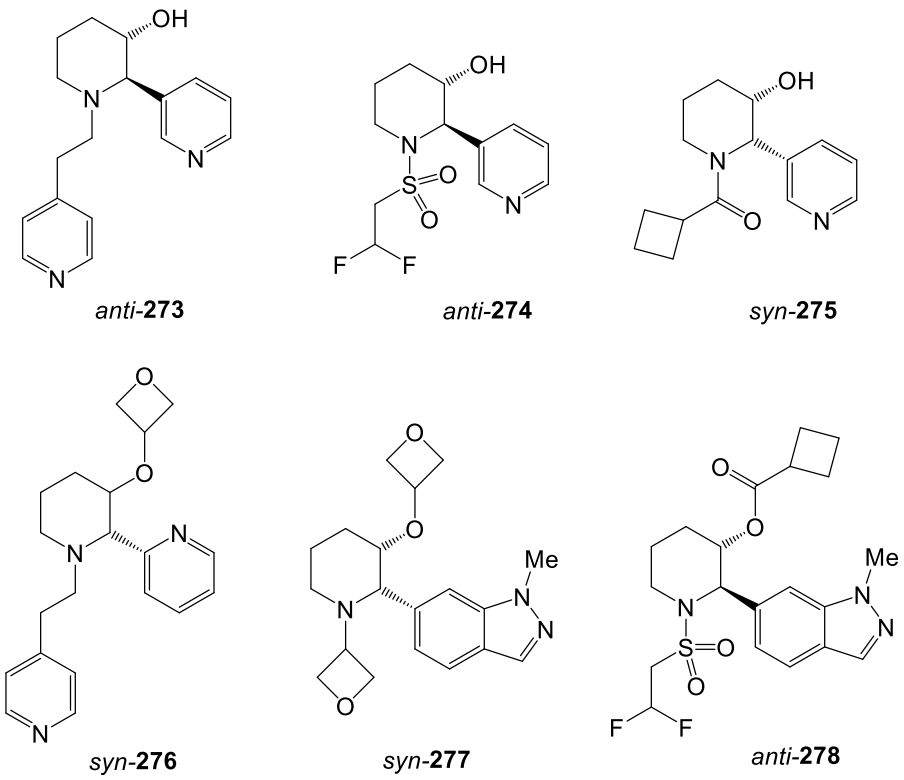
Since the limitations of our initial route were low yields, low diastereoselectivity and introduction of the heteroaryl group in the first step, a synthetic approach from (*S*)-proline was chosen as the heteroaromatics could be introduced later in the synthesis. As an example, addition of lihiated benzimidazole to *N*-trityl prolinal (*S*)-**195** gave the *N*-trityl alcohol *anti*-**262** as a single diastereomer (Scheme 3.82). Then, removal of the *N*-trityl group and reductive amination gave the desired *N*-benzyl alcohol *anti*-**269** which, finally, was ring-expanded to give the novel 1-methyl benzimidazole *N*-benzyl 3-hydroxy piperidine *anti*-**271**. To obtain diastereomer *syn*-**271**, the 3-hydroxy piperidine *anti*-**271** could, in future work, be oxidised to ketone **272** and subsequently reduced to give *syn*-**271**.

Scheme 3.82



Future work should also focus on the synthesis of different *N*-alkyl or *N*-aryl 3-hydroxy piperidines containing a wider range of heteroaromatics to give a large library of drug-like molecules (Figure 3.14). In addition, the synthesis of 3-hydroxy piperidines containing heteroaryl groups using Cossy's new conditions ring expasion[119] could be investigated.

Figure 3.14



Chapter 4 Experimental

4.1 General Methods

H_2O is distilled water. Brine refers to a saturated aqueous solution of NaCl. Et_2O, THF, hexane and toluene were freshly distilled from benzophenone ketyl or dispensed from a Pure Solv MD-7 solvent purification system under a N_2 atmosphere. (−)-Sparteine was distilled over CaH_2 by Kügelrohr distillation before use. Petrol refers to the fraction of petroleum ether boiling in the range of 40-60 ˚C. *s*-BuLi was titrated against *N*-benzylbenzamide before use.[153] All reactions were carried out under O_2-free Ar using oven-dried and/or flame-dried glassware. Flash column chromatography was carried out using Fluka Silica gel 60 (0.035-0.070 mm particle size). Thin layer chromatography was carried out using Merck F_{254} aluminium-backed silica plates.

^1H (400 MHz), ^{13}C (100.6 MHz) and ^{31}P (161 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument with internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to $CHCl_3$ (δ_H: 7.27), $CDCl_3$ (δ_C: 77.0, centre line of triplet). ^{13}C and ^{31}P 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. MS and HRMS were obtained using ESI or EI methods and recorded using a Bruker Daltronics microOTOF spectrometer. Chiral stationary phase (CSP) HPLC was performed on an Agilent 1200 series instrument. *In situ* ReactIR infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC10 spectrometer with a silicon-tipped (SiComp) probe.

4.2 General Procedures

General Procedure A: Lithiation-trapping of phosphine boranes

s-BuLi (1.3 M solution in cyclohexane, 1.2 eq.) was added dropwise to a stirred solution of the phosphine borane (1.52 mmol, 1.0 eq.) in THF (5 mL) at 0 ˚C under Ar. The resulting solution was stirred at 0 ˚C for 1 h. Then, a solution of the allylic halide (1.2 eq.) in THF (3 mL) was added dropwise *via* a syringe and the solution was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise over 10 min and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure B: Lithiation-trapping of phosphine boranes *via* transmetallation with LiCl/CuCl

s-BuLi (1.3 M solution in cyclohexane, 1.2 eq.) was added dropwise to a stirred solution of the phosphine borane (1.52 mmol, 1.0 eq.) in THF (5 mL) at 0 ˚C under Ar. The resulting solution was stirred at 0 ˚C for 1 h. Then, a mixture of LiCl (1.2 eq.) and CuCl (0.6 eq.) was added in one portion and the mixture was stirred at 0 °C for 1 h. Then, a solution of the allylic halide (1.2 eq.) in THF (3 mL) was added dropwise *via* a syringe and the mixture was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise over 10 min and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure C: Lithiation-trapping of *N*-Boc pyrrolidine 3

s-BuLi (1.3 M solution in cyclohexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **3** (17.5 mmol) in THF (150 mL) at –30 ˚C under Ar. The resulting yellow solution was stirred at –30 ˚C for 5 min. Then, the aldehyde (2.0-2.6 eq.) was added dropwise and the resulting solution was stirred at –30 ˚C for 10 min and allowed to warm to rt over 2 h. Saturated $NH_4Cl_{(aq)}$ (150 mL) or water (150 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product

General procedure D: *N*-Boc deprotection

TFA (4.0 eq.) was added to a stirred solution of a mixture of *syn*- and *anti*-*N*-Boc hydroxy pyrrolidines (1.80 mmol) in CH_2Cl_2 (8 mL) at 0 ˚C under Ar. The resulting solution was allowed to warm to rt and then stirred at rt for 3 h. 20% $NaOH_{(aq)}$ (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude hydroxy pyrrolidines.

General procedure E: Reductive amination

Aldehyde (1.1 eq.) was added to a stirred solution of crude hydroxy pyrrolidines (0.47 mmol), sodium triacetoxyborohydride or sodium cyanoborohydride (2.0 eq.) and AcOH (0.2, 2.0, 3.0 or 4.0 eq.) in 1,2-dichloroethane (15 mL) at rt. The resulting solution was stirred at rt for 16 h. CH_2Cl_2 (15 mL) and saturated $NaHCO_{3(aq)}$ (15 mL) were added to the resulting mixture and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure F: Ring expansion from pyrrolidines to piperidines

Trifluoroacetic anhydride (3.0 eq.) was added to a stirred solution of *N*-benzyl hydroxy pyrrolidine (0.46 mmol) in THF (10 mL) at −78 ˚C under Ar. The resulting solution was stirred at −78 ˚C for 1 h and then Et_3N (3.0 eq.) was added dropwise. The resulting solution was stirred at −78 ˚C for 1 h. Then, the resulting mixture was allowed to warm to rt and stirred and heated at reflux for 48 h. The reaction was allowed to cool to rt and 20% $NaOH_{(aq)}$ (10 mL) was added dropwise. Then, the resulting mixture was stirred at rt for 2 h. CH_2Cl_2 (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure G: Debenzylation and *N*-Boc protection

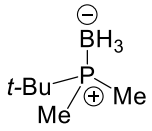
Palladium hydroxide on carbon (20 wt. %, 0.35 eq.) and ammonium formate (5.0-15.0 eq.) were added to a stirred solution of *N*-benzyl hydroxy pyrrolidine (0.23 mmol) in EtOH (10 mL) under Ar. The resulting mixture was stirred and heated at reflux for 2-5 h. Then, the reaction mixture was allowed to cool to 50 ˚C and Boc_2O (1.1 eq.) was added. The reaction mixture was stirred and heated at 50 ˚C for 16 h. EtOH (10 mL) was added and the solids were removed by filtration through a plug of Celite® and washed with EtOH (15 mL). The filtrate was evaporated under reduced pressure to give the crude product.

General procedure H: *N*-Trityl deprotection

5 M $HCl_{(aq)}$ (2 mL) was added to a stirred solution of *syn*- or *anti*-*N*-trityl hydroxy pyrrolidine (0.47 mmol) in CH_2Cl_2 (2 mL) at rt. The resulting solution was stirred at rt for 3-5 h. Then, 20% $NaOH_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude hydroxy pyrrolidines.

4.3 Experimental for Chapter 2

tert-Butyldimethylphosphine borane 13

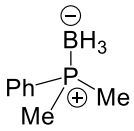


13

t-BuMgCl (32.0 mL of a 2.0 M solution in Et_2O, 64.1 mmol) was added dropwise over 30 min to a stirred solution of PCl_3 (8.0 g, 58.2 mmol) in THF (85 mL) at −78 ˚C under Ar. The resulting heterogeneous mixture was stirred at −78 ˚C for 1 h and allowed to warm to rt and stirred at rt for 2 h. The reaction mixture was cooled to 0 ˚C and MeMgBr (43.0 mL of a 3.0 M solution in Et_2O, 128.1 mmol) was added dropwise over 20 min. The resulting mixture was allowed to warm to rt over 2 h. Then, the resulting heterogeneous mixture was cooled to 0 °C and BH_3•Me_2S (35.2 mL of a 2.0 M solution in Et_2O, 69.9 mmol) was added dropwise and the mixture was allowed to warm to rt and stirred at rt for 16 h. Then, the mixture was poured onto ice/water (130 mL) and conc. $HCl_{(aq)}$ (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (50 mL), water (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane (40 mL) gave phosphine borane **13** (4.18 g, 54%) as a white solid, mp 162-164 ˚C (lit.,[40] 164-165 ˚C); R_F (4:1 hexane-EtOAc) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (d, *J* = 10.0 Hz, 6H, PMe), 1.16 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 0.45 (qd, *J* = 98.0, 18.5 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 26.6 (d, *J* = 34.5, P*C*Me_3), 24.7 (d, *J* = 2.5 Hz, PC*Me*$_3$), 7.23 (d, *J* = 35.5 Hz, PMe); ^{31}P{^{1}H} NMR (161 MHz, $CDCl_3$) δ: 20.9 (q, *J* = 60.5 Hz, PBH_3). Spectroscopic data consistent with those reported in the literature.[9]

Lab book reference: chc/1/2

Dimethylphenylphosphine borane 46

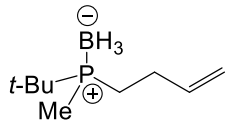


11

MeMgBr (38.0 mL of a 3.0 M solution in Et_2O, 113.4 mmol) was added dropwise over 30 min to a stirred solution of $PhPCl_2$ (9.2 g, 51.6 mmol) in THF (100 mL) at 0 ˚C under Ar. The resulting mixture was allowed to warm to rt over 2 h. Then, the resulting heterogeneous mixture was allowed to warm to rt and stirred at rt for 16 h. BH_3•Me_2S (31.0 mL of a 2.0 M solution in Et_2O, 62.0 mmol) was added dropwise at 0 ˚C and the mixture was allowed to warm to rt and stirred at rt for 2 h. Then, the mixture was poured onto ice/water (130 mL) and conc. $HCl_{(aq)}$ (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (50 mL), water (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 9:1 hexane-EtOAc as eluent gave phosphine borane **11** (5.53 g, 70%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77-7.70 (m, 2H, PPh), 7.55-7.45 (m, 3H, Ph), 1.58 (d, *J* = 10.5 Hz, 6H, PMe), 0.78 (qd, *J* = 96.0, 15.0 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 131.1 (d, *J* = 2.5 Hz, Ph), 130.9 (d, *J* = 55.5, *ipso*-Ph), 130.8 (d, *J* = 9.5 Hz, Ph), 128.7 (d, *J* = 10.0 Hz, Ph), 12.9 (d, *J* = 39.0 Hz, PMe); ^{31}P{^{1}H} NMR (161 MHz, $CDCl_3$) δ: 3.43 (q, *J* = 63.0 Hz, PBH_3). Spectroscopic data consistent with those reported in the literature.[6]

Lab book reference: chc/1/6

But-3-enyl *tert*-butylmethylphosphine borane 94



94

Table 2.1, entry 1

s-BuLi (1.50 mL of a 1.3 M solution in cyclohexane, 1.83 mmol) was added dropwise to a stirred solution of the phosphine borane **13** (200 mg, 1.52 mmol) in THF (5 mL) at −78 ˚C under Ar. The resulting mixture was stirred at −78 ˚C for 1 h. Then, a solution of the allyl bromide (226 mg, 1.83 mmol) in THF (2 mL) was added dropwise and the solution was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise at rt over 10 min and the resulting mixture was stirred at rt for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave allyl phosphine borane **94** (147 mg, 56%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.5; IR (NaCl) 3032, 2930, 2863, 2826, 2334, 2334, 2222, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.82-5.74 (m, 1H, C*H*=CH_2), 5.01 (br d, *J* = 17.0 Hz, 1H, *trans*-HC=CH_AH_B), 4.92 (br d, *J* = 10.0 Hz, 1H, *cis*- HC=CH_AH_B), 2.38-2.26 (m, 1H, CH), 2.15-2.04 (m, 1H, CH), 1.64-1.53 (m, 2H, CH), 1.12 (d, *J* =10.0 Hz,3H, PMe), 1.08 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 0.43 (br q, *J* = 87.5 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 137.6 (d, *J* = 13.0 Hz, H*C*=CH_2), 114.9 (HC=*C*H_2), 27.1 (d, *J* = 35.5 Hz, P*C*Me_3), 27.0 (*C*H_2-CH=CH_2), 24.7 (PC*Me*$_3$), 20.1 (d, *J* = 30.5 Hz, PCH_2), 4.9 (d, *J* = 34.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 26.6 (q, *J* = 63.0 Hz, PBH_3); MS (ESI) *m/z* 195 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_9H_{22}BP$ $(M + Na)^+$ 195.1446, found 195.1445. The NMR spectroscopic data was consistent with that previously reported in the group.[18]

Lab book reference: chc/1/60

Table 2.1, entry 2

s-BuLi (1.50 mL of a 1.3 M solution in cyclohexane, 1.83 mmol) was added dropwise to a stirred solution of the phosphine borane **13** (200 mg, 1.52 mmol) in THF (5 mL) at –40 ˚C under Ar. The resulting mixture was stirred at –40 ˚C for 1 h. Then, a solution of the allyl bromide (226 mg, 1.83 mmol) in THF (2 mL) was added dropwise and the solution was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise over 10 min and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave allyl phosphine borane **94** (145 mg, 56%) as a colourless oil.

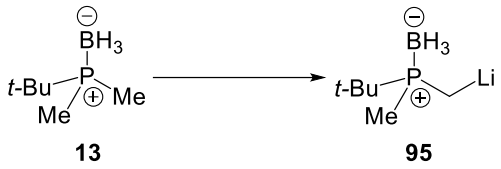
Lab book reference: chc/1/63

Table 2.1, entry 3

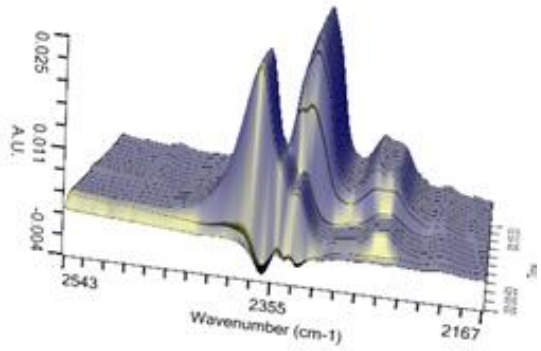
Using general procedure A, *s*-BuLi (1.50 mL of a 1.3 M solution in cyclohexane, 27.5 mmol) and phosphine borane **13** (3.0 g, 22.8 mmol) in THF (70 mL) and allyl bromide (3.39 g, 27.5 mmol) in THF (45 mL) gave the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave allyl phosphine borane **94** (2.67 g, 68%) as a colourless oil.

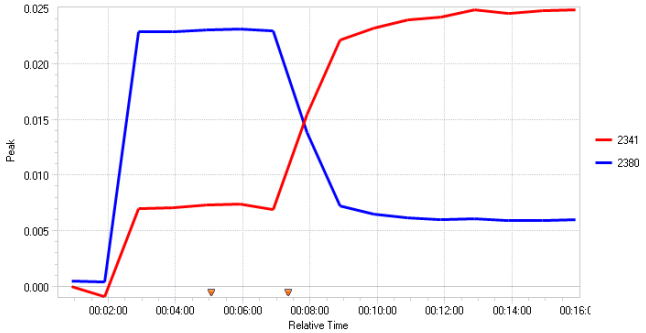
Lab book reference: chc/1/26

ReactIR monitoring of the lithiation of phosphine borane 13 (THF, –78 ˚C)



13 **95**



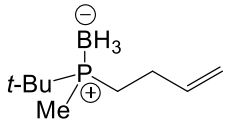


THF (12 mL) was added to a two-necked round bottom flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 ˚C, a solution of phosphine borane **13** (132 mg, 1.0 mmol) in THF (5 mL) was added. The solution was stirred for 2 min (to verify the stability of read out on ReactIR). Then, *s*-BuLi (0.92 mL of 1.3 M solution in cyclohexane, 1.2 mmol, 1.2 eq.) was added dropwise. The solution was stirred at –78 ˚C for 10 min.

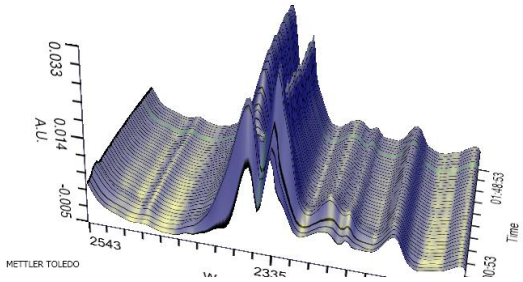
For *t*-butyldimethylphosphine borane **13**, a peak at 2380 cm^{-1} was observed and assigned to $\nu_{B\text{-}H}$. After addition of *s*-BuLi, a new peak at 2341 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ in the lithiated intermediate **95**. After a lithiation time for 2 min, complete lithiation of *t*-butyldimethylphosphine borane **13** to give the lithiated intermediate **95** was observed.

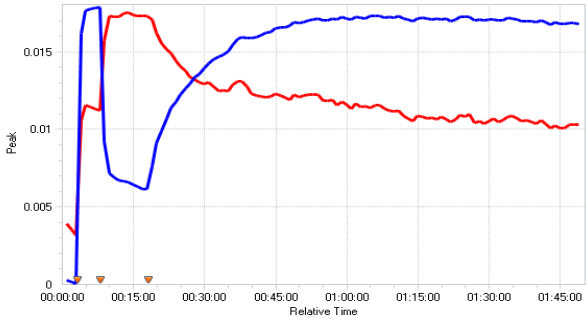
Lab book reference: chc/1/65

But-3-enyl *tert*-butylmethylphosphine borane 94



94

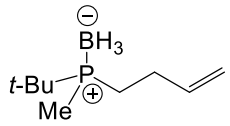




THF (12 mL) was added to a two-necked round bottom flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 ˚C, a solution of phosphine borane **13** (132 mg, 1.0 mmol) in THF (5 mL) was added. The solution was stirred for 2 min (to verify the stability of read out on ReactIR). A peak at 2382 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ of phosphine borane **13**. Then, *s*-BuLi (1.15 mL of 1.3 M solution in cyclohexane, 1.5 mmol, 1.5 eq.) was added dropwise. A new peak at 2352 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ in the lithiated intermediate. The solution was stirred at –78 ˚C for 2 min. Then, allyl bromide (242 mg, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 2352 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ in the allyl phosphine borane **94**. The solution was stirred at –78 ˚C for 1 h. Complete trapping of lithiated intermediate to give allyl phosphine borane **94** was observed after 1 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise over 10 min and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave allyl phosphine borane **94** (76 mg, 44%) as a colourless oil.

Lab book reference: chc/2/3

But-3-enyl *tert*-butylmethylphosphine borane 94

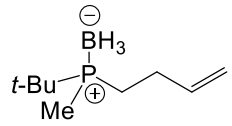


94

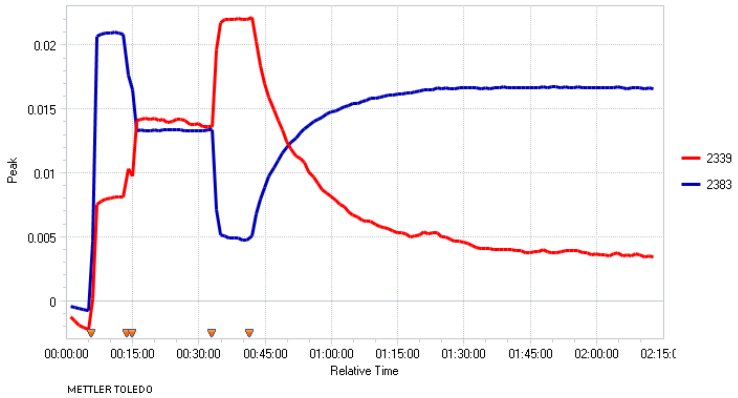
s-BuLi (1.80 mL of a 1.3 M solution in cyclohexane, 2.28 mmol) was added dropwise to a stirred solution of the phosphine borane **13** (200 mg, 1.52 mmol) in THF (5 mL) at −78 ˚C under Ar. The resulting mixture was stirred at −78 ˚C for 1 h. Then, a solution of the allyl bromide (368 mg, 3.04 mmol) in THF (2 mL) was added dropwise and the solution was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise over 10 min and the resulting mixture was stirred at rt for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave allyl phosphine borane **94** (150 mg, 57%) as a colourless oil.

Lab book reference: chc/1/81

But-3-enyl *tert*-butylmethylphosphine borane 94



94

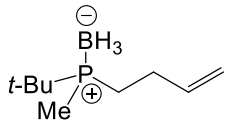


THF (12 mL) was added to a two-necked round bottom flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 ˚C, a solution of phosphine borane **13** (132 mg, 1.0 mmol) in THF (5 mL) was added. The solution was stirred for 2 min (to verify the stability of read out on ReactIR). A peak at 2383 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ of phosphine borane **13**. Then, *s*-BuLi (1.15 mL of 1.3 M solution in cyclohexane, 1.2 mmol, 1.2 eq.) was added dropwise. A new peak at 2339 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ in the lithiated intermediate. The lithiation time was 3 min. The solution was stirred at –78 ˚C for 20 min. It was believed that phosphine borane **13** was not completely lithiated since there was not a reduction of $\nu_{B\text{-}H}$ to zero absorbance. Therefore, more *s*-BuLi (1.15 mL of 1.3 M solution in cyclohexane, 1.2 mmol, 1.2 eq.) was added dropwise. ReactIR spectroscopy monitoring showed that $\nu_{B\text{-}H}$ of phosphine borane **13** (2383 cm^{-1}) decreased more whereas the peak of the lithiated intermediate also increased more. The solution stirred at –78 ˚C for 5 min. Then, allyl bromide (145 mg, 1.2 mmol, 1.2 eq.) was added dropwise. A new peak at 2383 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ in the allyl phosphine borane **94**. The reaction mixture was stirred for 90 min. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise over 10 min and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica

with 9:1 petrol-EtOAc as eluent gave allyl phosphine borane **94** (98 mg, 57%) as a colourless oil.

Lab book reference: chc/1/73

But-3-enyl *tert*-butylmethylphosphine borane 94

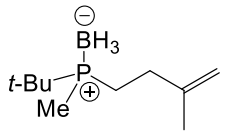


94

s-BuLi (1.80 mL of a 1.3 M solution in cyclohexane, 2.28 mmol) was added dropwise to a stirred solution of the phosphine borane **13** (200 mg, 1.52 mmol) in THF (5 mL) at −78 ˚C under Ar. Then, a solution of the allyl bromide (736 mg, 6.08 mmol) in THF (5 mL) was added dropwise and the solution The resulting mixture was stirred at −78 ˚C for 10 min. Then, *s*-BuLi (1.80 mL of a 1.3 M solution in cyclohexane, 2.28 mmol) was added dropwise to a stirred solution and the reaction solution was stirred at −78 ˚C for 10 min. The reaction solution was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise over 10 min and the resulting mixture was stirred at rt for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave allyl phosphine borane **94** (145 mg, 57%) as a colourless oil.

Lab book reference: chc/1/80

tert-Butylmethyl(3-methylbut-3-enyl)phosphine borane 96



96

Table 2.2, entry 1

Using general procedure A, *s*-BuLi (1.50 mL of a 1.3 M solution in cyclohexane, 1.83 mmol) and phosphine borane **13** (200 mg, 1.52 mmol) in THF (5 mL) and 3-chloro-2-methylpropene (166 mg, 1.83 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 9:1 hexane-EtOAc as eluent gave phosphine borane **96** (102 mg, 36%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.4; IR (NaCl) 3034, 2928, 2337, 2210, 1452, 1198, 895, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.73 (br s, 1H, MeC=CH_AH$_B$), 4.70 (br s, 1H, MeC=CH$_A$$H_B$), 2.36-2.24 (m, 1H, CH), 2.13-2.00 (m, 1H, CH), 1.76-1.57 (m, 2H, 2 × CH), 1.72 (s, 3H, *Me*C=CH$_2$), 1.16 (d, *J* = 12.0 Hz, 6H, PMe), 1.11 (d, *J* = 14.5 Hz, 9H, PCMe$_3$), 0.36 (qd, *J* = 92.0, 13.0 Hz, 3H, PBH$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 144.8 (d, *J* = 12.5 Hz, *C*=CH$_2$), 110.1 (C=*C*H$_2$), 30.8 (*C*H$_2$C(Me)=CH$_2$), 27.1 (d, *J* = 34.0 Hz, P*C*Me$_3$), 24.9 (PC*Me$_3$*). 22.2 (*Me*C=C), 19.2 (d, *J* = 31.0 Hz, PCH$_2$), 4.9 (d, *J* = 34.5 Hz, PMe); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 26.7 (q, *J* = 58.0 Hz, PBH$_3$); MS (ESI) *m/z* 209 [(M + Na) $^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{24}BP$ $(M + Na)^+$ 209.1603, found 209.1601.

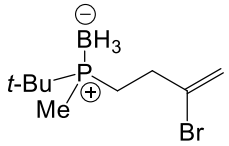
Lab book reference: chc/1/23

Table 2.2, entry 2

Using general procedure B, *s*-BuLi (1.50 mL of a 1.3 M solution in cyclohexane, 1.83 mmol) and phosphine borane **13** (200 mg, 1.52 mmol) in THF (5 mL), a mixture of LiCl (78 mg, 1.83 mmol) and CuCl (75 mg, 0.76 mmol) and 3-chloro-2-methylpropene (166 mg, 1.83 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave phosphine borane **96** (121 mg, 43%) as a colourless oil.

Lab book reference: chc/1/30

tert-Butylmethyl(3-bromobut-3-enyl) phosphine borane 97



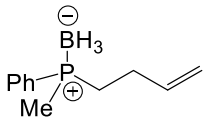
97

Table 2.2, entry 4

Using general procedure B, *s*-BuLi (1.50 mL of a 1.3 M solution in cyclohexane, 1.83 mmol) and phosphine borane **13** (200 mg, 1.52 mmol) in THF (5 mL), a mixture of LiCl (78 mg, 1.83 mmol) and CuCl (75 mg, 0.76 mmol) and 2,3-dibromoprop-1-ene (166 mg, 1.83 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave phosphine borane **97** (213 mg, 56%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.5; IR (NaCl) 2973, 2917, 2338, 2309, 1603, 1196, 1052, 894, 748, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.67 (dt, *J* = 2.0, 1.0 Hz, 1H, BrC=CH_AH_B), 5.41 (d, *J* = 2.0 Hz, 1H, BrC=CH_AH_B), 2.76-2.66 (m, 1H, CH), 2.58-2.47 (m, 1H, CH), 1.85-1.74 (m, 2H, CH), 1.19 (d, *J* = 10.0 Hz, 3H, PMe), 1.14 (d, *J* = 13.5 Hz, 9H, $PCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 133.4 (d, *J* = 14.5 Hz, CH_2C(Br)=CH_2), 117.5 (CH_2C(Br)=CH_2), 53.4 (CH_2C(Br)=CH_2), 27.2 (d, *J* = 35.5 Hz, PCMe_3), 24.8 (d, *J* = 2.5 Hz, PCMe_3), 20.1, (d, *J* = 32.5 Hz, PCH_2), 5.2 (d, *J* = 35.5 Hz, P*Me*); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 26.9 (q, *J* = 57.0 Hz, PBH_3); MS (ESI) *m/z* 249 [($^{79}M - H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_9H_{21}B^{79}BrP$ $(M - H)^+$ 249.0575, found 249.0578.

Lab book reference: chc/1/24

But-3-enylmethylphenylphosphine borane 98



98

Table 2.3, entry 1

s-BuLi (18.5 mL of a 1.3 M solution in cyclohexane, 23.76 mmol) was added dropwise to a stirred solution of the phosphine borane **11** (3.0 g, 19.8 mmol) in THF (75 mL) at −78 ˚C under Ar. The resulting mixture was stirred at −78 ˚C for 1 h. Then, a solution of the allyl bromide (2.70 g, 23.76 mmol) in THF (45 mL) was added dropwise *via* a syringe and the solution was allowed to warm to rt over 16 h to give the crude product. Purification by flash chromatography on silica with 9:1 hexane-EtOAc as eluent gave phosphine borane **98** (2.28 g, 61%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.5; IR (NaCl) 3098, 3031, 3012, 2935, 2871, 2545, 2321, 2220, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70 (ddd, *J* = 8.0, 2.0, 0.5, 2H, Ph,), 7.49-7.38 (m, 3H, Ph), 5.72 (ddt, *J* = 17.0. 10.0, 6.5 Hz, 1H, C*H*=CH_2), 4.96 (br d, *J* = 17.0 Hz, 1H, *trans*-CH=CH_AH_B), 4.91 (br d, *J* = 10.0 Hz, 1H, *cis*-CH=CH_AH_B), 2.27-2.16 (m, 1H, CH), 2.13-2.02 (m, 1H, CH), 1.97-1.86 (m, 2H, 2 × CH), 1.51 (d, *J* = 10.0 Hz, 3H, PMe), 0.81 (br q, *J* = 86.0 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 136.9 (d, *J* = 14.0 Hz, H*C*=CH_2), 131.1 (d, *J* = 9.5 Hz, Ph), 130.9 (d, *J* = 2.5 Hz, Ph), 129. 1 (d, *J* = 54.0 Hz, *ipso*-Ph), 128.4 (d, *J* = 9.5 Hz, Ph), 114.9 (HC=*C*H_2), 26.6 (H_2C-CH=CH_2), 26.1 (d, *J* = 36.0 Hz, PCH_2), 10.4 (d, *J* = 38.5 Hz, PMe); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 9.9 (q, *J* = 55.5 Hz, PBH_3); MS (ESI) *m/z* 191 [$(M - H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{18}BP$ [$(M - H)^+$ 191.1157, found 191.1152. The NMR spectroscopic data was consistent with that previously reported in the group.[18]

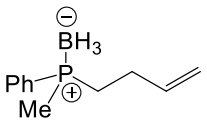
Lab book reference: chc/1/36

Table 2.3, entry 2

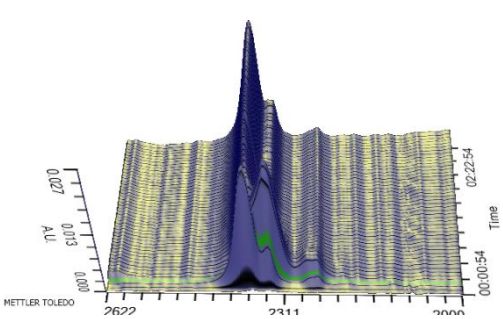
Using general procedure A, *s*-BuLi (5.1 mL of a 1.3 M solution in cyclohexane, 7.25 mmol) and phosphine borane **11** (1.0 g, 6.60 mmol) in THF (25 mL) and allyl bromide (0.90 g, 7.25 mmol) in THF (15 mL) gave the crude product. Purification by flash chromatography on silica with 9:1 hexane-EtOAc as eluent gave phosphine borane **98** (945 mg, 75%) as a colourless oil.

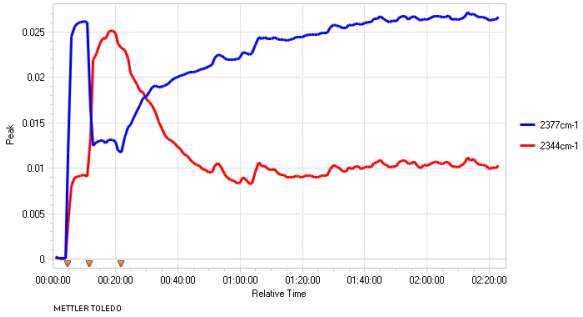
Lab book reference: chc/1/13

But-3-enylmethylphenylphosphine borane 98



98



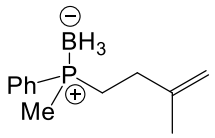


THF (12 mL) was added to a two-necked round bottom flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 ˚C, a solution of phosphine borane **11** (152 mg, 1.0 mmol) in THF (5 mL) was added. The solution was stirred for 2 min (to verify the stability of read out on ReactIR). A peak at 2377 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ of phosphine borane **11**. Then, *s*-BuLi (0.93 mL of 1.3 M solution in cyclohexane, 1.2 mmol, 1.2 eq.) was added dropwise. A new peak at 2344 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ in the lithiated intermediate. The lithiation time was 3 min. The solution was stirred at –78 ˚C for 10 min. Phosphine borane **11** was not completely lithiated since there was not a reduction of $\nu_{B\text{-}H}$ to zero absorbance. Then, allyl bromide (154 mg, 1.2 mmol, 1.2 eq.) was added dropwise. A new peak at 2377 cm^{-1} was observed which was assigned to $\nu_{B\text{-}H}$ in the allyl phosphine borane **98**. The reaction mixture was stirred for 2 h. Complete trapping of lithiated intermediate to give allyl phosphine borane **98** was observed after 90 min. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise over 10 min and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash

chromatography on silica with 9:1 hexane-EtOAc as eluent gave phenyl phosphine **98** (128 mg, 67%) as a colourless oil.

Lab book reference: chc/1/74

Methyl (3-methylbut-3-enyl)phenylphosphine borane 100



100

Table 2.4, entry 1

Using general procedure A, *s*-BuLi (1.20 mL of a 1.3 M solution in cyclohexane, 1.45 mmol) and phosphine borane **11** (200 mg, 1.32 mmol) in THF (5 mL) and 3-chloro-2-methylpropene (132 mg, 1.45 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 9:1 hexane-EtOAc as eluent gave phosphine borane **100** (112 mg, 56%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.4; IR (NaCl) 2963, 2340, 2309, 2212, 1629, 1415, 1198, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.75-7.71 (m, 2H, Ph), 7.48-7.45 (m, 3H, Ph), 4.71 (br s, 1H, MeC=C$H_A$$H_B$), 4.67 (br s, 1H, MeC=C$H_A$$H_B$), 2.20-2.02 (m, 1H, CH), 2.01-1.94 (m, 3H, CH), 1.67 (s, 3H, *Me*C=CH_2), 1.56 (d, *J* = 12.0 Hz, 3H, PMe), 0.71 (br q, *J* = 84.0 Hz, 3H, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 144.3 (d, *J* = 14.0 Hz, Me*C*=CH_2), 131.2 (d, *J* = 8.5 Hz, Ph), 131.1 (d, *J* = 2.5 Hz, Ph), 129.2 (d, *J* = 54.0 Hz, *ipso*-Ph), 128.7 (d, *J* = 10.0 Hz, Ph), 110.1 (C=*C*H_2), 30.5 (*C*H_2C(Me)=CH_2), 25.4 (d, *J* = 37.0 Hz, PCH_2), 22.1 (CH_2C(*Me*)=CH_2), 10.5 (d, *J* = 39.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 9.9 (q, *J* = 54.5 Hz, PBH_3); MS (ESI) *m/z* 229 [(M + Na) $^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{20}BP$ $(M + Na)^+$ 229.1290, found 229.1285. The NMR spectroscopic data was consistent with that previously reported in the group.[18]

Lab book reference: chc/1/20

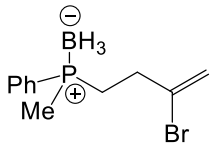
Table 2.4, entry 2

Using general procedure B, *s*-BuLi (2.10 mL of a 1.3 M solution in cyclohexane, 2.68 mmol) and phosphine borane **11** (340 mg, 2.24 mmol) in THF (7 mL), a mixture of LiCl (114 mg, 2.68 mmol) and CuCl (133 mg, 1.34 mmol) and 3-chloro-2-methylpropene (243 mg, 2.68

mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 9:1 hexane-EtOAc as eluent gave phosphine borane **100** (294 mg, 64%) as a colourless oil.

Lab book reference: chc/1/31

3-Bromobut-3-enylmethylphenylphosphine borane 101



101

Table 2.4, entry 4

Using general procedure B, *s*-BuLi (1.60 mL of a 1.3 M solution in cyclohexane, 2.02 mmol) and phosphine borane **11** (255 mg, 1.68 mmol) in THF (5 mL), a mixture of LiCl (85 mg, 2.02 mmol) and CuCl (83 mg, 1.01 mmol) and 2,3-dibromoprop-1-ene (310 mg, 2.02 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 5:4.7:0.3 hexane-petrol-EtOAc as eluent gave phosphine borane **101** (180 mg, 41%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.5; IR (NaCl) 3201, 3011, 2872, 2548, 2326, 2217, 1605, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.82-7.64 (m, 2H, Ph), 7.58-7.41 (m, 3H, Ph), 5.60 (d, *J* = 1.0 Hz, 1H, BrC=CH_AH$_B$), 5.37 (d, *J* = 1.0 Hz, 1H, BrC=CH$_A$$H_B$), 2.74-2.55 (m, 1H, CH), 2.50-2.34 (m, 1H, CH), 2.22-2.00 (m, 2H, 2 × CH), 1.59 (d, *J* = 10.5 Hz, 3H, PMe), 0.76 (br q, *J* = 96.0 Hz, 3H, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 132.7 (d, *J* = 16.0 Hz, CH_2*C*(Br)=CH_2), 131.4 (d, *J* = 3.0 Hz, Ph), 131.2 (d, *J* = 9.0 Hz, Ph), 128.8 (d, *J* = 10.0 Hz, Ph), 128.6 (d, *J* = 55.5 Hz, *ipso*-Ph), 117.5 (CH_2C(Br)=*C*H_2), 35.0 (*C*H_2C(Br)=CH_2), 26.2 (d, *J* = 36.5 Hz, PCH_2), 10.9 (d, *J* = 38.5 Hz, PMe); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 9.9 (q, *J* = 45.5 Hz, PBH_3); MS (ESI) *m/z* 293 [(^{79}M + Na) $^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{17}B^{79}BrP$ $(M + Na)^+$ 293.0239, found 293.0240.

Lab book reference: chc/1/25

Deboronation of Phenylphosphine borane 98 using DABCO

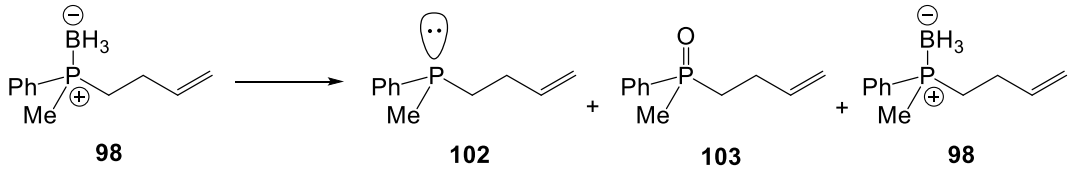


Table 2.5, entry 1

A solution of the phenylphosphine borane **98** (112 mg, 0.58 mmol, 1.0 eq.) and DABCO (79 mg, 0.70 mmol, 1.1 eq.) in degassed THF (5 mL) was stirred and refluxed for 16 hr under Ar. Then, the reaction mixture was allowed to cool to rt and the solvent was removed under reduced pressure. Degassed hexane (5 mL) was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product (126 mg) which contained a 75:3:22 ratio of free phosphine **102**; $^{31}P\{^{1}H\}$ NMR (161 MHz, $CDCl_3$) δ: –34.9 ppm, phosphine oxide **103**; $^{31}P\{^{1}H\}$ NMR (161 MHz, $CDCl_3$) δ: 9.8 (q, *J* = 60.5 Hz, P=O) and phosphine borane **98**; $^{31}P\{^{1}H\}$ NMR (161 MHz, $CDCl_3$) δ: 9.9 (q, *J* = 55.5 Hz, PBH_3).

Lab book reference: chc/1/98

Table 2.5, entry 2

A solution of the phenylphosphine borane **98** (112 mg, 0.58 mmol, 1.0 eq.) and DABCO (98 mg, 0.87 mmol, 1.5 eq.) in degassed THF (5 mL) was stirred and refluxed for 16 hr under Ar. Then, the reaction mixture was allowed to cool to rt and the solvent was removed under reduced pressure. Degassed hexane (5 mL) was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product (115 mg) which contained a 80:7:13 ratio of free phosphine **102**, phosphine oxide **103** and phosphine borane **98**.

Lab book reference: chc/1/99

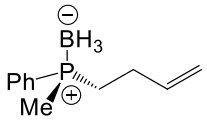
Table 2.5, entry 3

A solution of the phenylphosphine borane **98** (118 mg, 0.61 mmol, 1.0 eq.) and DABCO (103 mg, 1.5 eq.) in degassed toluene (5 mL) was stirred and refluxed for 16 hr under Ar. Then, the reaction mixture was allowed to cool to rt and the solvent was removed under reduced pressure. Degassed hexane (5 mL) was added and the solids were removed by

filtration. The filtrate was evaporated under reduced pressure to give the crude product (116 mg) which contained a 68:18:14 ratio of free phosphine **102**, phosphine oxide **103** and phosphine borane **98**.

Lab book reference: chc/2/1

But-3-enylmethylphenylphosphine borane (*S*)-98



(*S*)-**98**

s-BuLi (1.3 M solution in cyclohexane, 1.1 eq.) was added dropwise to a stirred solution of (−)-sparteine (1.2 eq.) in Et_2O (2 mL) at −78 ˚C under Ar. After stirring for 15 min, a solution of phosphine borane **11** (151 mg, 1.0 mmol) in Et_2O (10 mL) was added dropwise over 10 min. The resulting mixture was stirred at −78 ˚C for 2 hr. Then, a solution allyl bromide (145 mg, 1.2 mmol) in THF (2 mL) was added dropwise and the mixture was allowed to warm to rt for 1 h. Then, 1 M $HCl_{(aq)}$ (6 mL) was added and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 85:15 hexane-EtOAc as eluent gave phosphine borane (*S*)-**98** (110 mg, 57%, 88:22 er) as a colourless oil,

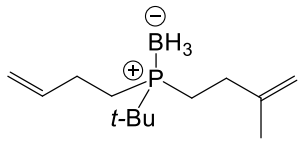
Lab book reference: chc/1/97

s-BuLi (1.3 M solution in cyclohexane, 1.5 eq.) was added dropwise to a stirred solution of (−)-sparteine (1.5 eq.) in Et_2O (2 mL) at −78 ˚C under Ar. After stirring for 15 min, a solution of phosphine borane **11** (152 mg, 1.0 mmol) in Et_2O (10 mL) was added dropwise over 10 min. The resulting mixture was stirred at −78 ˚C for 10 min. Then, a solution allyl bromide (242 mg, 2.0 mmol) in THF (2 mL) was added dropwise and the mixture was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (6 mL) was added and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were

washed with 1 M $HCl_{(aq)}$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 85:15 hexane-EtOAc as eluent gave phosphine borane (*S*)-**98** (50 mg, 26%, 69:31 er) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.6. CSP-HPLC: Chiracel AD-H, 99.5:0.5 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 12.9 min (*S*)-**98**, 16.7 min (*R*)-**98**.

Lab book reference: chc/1/91

(But-3-enyl(*tert*-butyl)(3-methylbut-3-enyl)phosphine borane 105

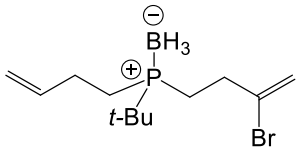


105

Using general procedure A, *s*-BuLi (1.10 mL of a 1.3 M solution in cyclohexane, 1.39 mmol) and phosphine borane **94** (200 mg, 1.16 mmol) in THF (5 mL) and 3-chloro-2-methylpropene (126 mg, 1.39 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc as eluent gave dihomoallylic phosphine borane **105** (134 mg, 51%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.5; IR (NaCl) 2973, 2916, 2340, 2309, 1197, 909, 748, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.83 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.06 (dd, *J* = 17.5, 1.5 Hz, 1H, *trans*-CH=CH_AH_B), 5.00 (d, *J* = 10.5 Hz, 1H, *cis*-CH=CH_AH_B), 4.75 (s, CMe=CH_AH_B), 4.71 (s, CMe=CH_AH_B), 2.37-2.13 (m, 4H, CH), 1.74 (s, 3H, C*Me*=CH_2), 1.73-1.58 (m, 4H, CH), 1.17 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 0.38 (br q, *J* = 100.0 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 145.2 (d, *J* = 13.0 Hz, *C*Me=CH_2), 137.9 (d, *J* = 13.0 Hz, *C*H=CH_2), 115.0 (C=*C*H_2), 110.1 (C=*C*H_2), 31.4 (*C*H_2-C=CH_2), 28.2 (d, *J* = 32.5 Hz, P*C*Me_3), 27.8 (*C*H_2-C=CH_2), 25.5 (d, *J* = 1.5 Hz, PC*Me*$_3$), 22.3 (C*Me*=CH_2), 19.8 (d, *J* = 32.5 Hz, PCH_2), 18.9 (d, *J* = 30.5 Hz, PCH_2); ^{31}P{^{1}H} NMR (161 MHz, $CDCl_3$) δ: 31.5 (q, *J* = 78.0 Hz, PBH_3); MS (ESI) *m/z* 249 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{28}BP$ (M + Na)$^+$ 249.1916, found 249.1912.

Lab book reference: chc/1/28

(3-Bromobut-3-enyl)(but-3-enyl)(*tert*-butyl)phosphine borane 106

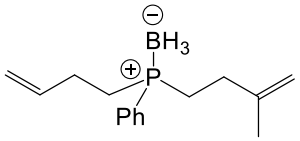


106

Using general procedure B, *s*-BuLi (1.10 mL of a 1.3 M solution in cyclohexane, 1.39 mmol) and phosphine borane **94** (200 mg, 1.16 mmol) in THF (5 mL), a mixture of LiCl (59 mg, 1.39 mmol) and CuCl (69 mg, 0.70 mmol) and 2,3-dibromoprop-1-ene (278 mg, 1.39 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc as eluent gave dihomoallylic phosphine borane **106** (244 mg, 72%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.4; IR (NaCl) 2916, 2827, 2339, 2309, 2210, 1002, 895, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.65 (s, 1H, CBr=C$H_A$$H_B$), 5.40 (d, *J* = 1.5 Hz, 1H, CBr=C$H_A$$H_B$), 5.05 (dd, *J* = 17.0, 1.0 Hz, 1H, *trans*-HC=C$H_A$$H_B$), 4.99 (d, *J* = 10.0 Hz, 1H, *cis*-HC=C$H_A$$H_B$), 2.76-2.52 (m, 2H, CH), 2.42-2.28 (m, 1H, CH), 2.28-2.14 (m, 1H, CH), 1.92-1.75 (m, 2H, CH), 1.74-1.54 (m, 2H, CH), 1.15 (d, *J* = 13.0 Hz, 9H, $PCMe_3$), 0.34 (br q, *J* = 102.5 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 137.5 (d, *J* = 14.0 Hz, *C*H=CH_2), 133.4 (d, *J* = 15.5 Hz, *C*Br=CH_2), 117.2 (C=*C*H_2), 115.1 (C=*C*H_2), 35.8 (*C*H_2-C=CH_2), 28.2 (d, *J* = 34.0 Hz, P*C*Me_3), 27.5 (*C*H_2-C=CH_2), 25.3 (d, *J* =1.5 Hz, PC*Me*$_3$), 19.8 (d, *J* = 29.5 Hz, P*C*H_2), 19.4 (d, *J* = 30.0 Hz, P*C*H_2); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 31.8 (q, *J* = 70.5 Hz, PBH_3); MS (ESI) *m/z* 289 [($^{79}M - H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{24}B^{79}BrP$ $(M - H)^+$ 289.0889, found 289.0890.

Lab book reference: chc/1/32

But-3-enyl(3-methylbut-3-enyl)(phenyl)phosphine borane 107

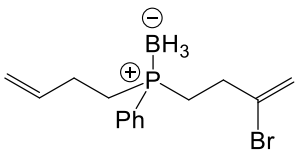


107

Using general procedure A, *s*-BuLi (1.00 mL of a 1.3 M solution in cyclohexane, 1.25 mmol) and phosphine borane **98** (200 mg, 1.04 mmol) in THF (5 mL) and 3-chloro-2-methylpropene (114 mg, 1.25 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc as eluent gave dihomoallylic phosphine borane **107** (175 mg, 68%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.45; IR (NaCl) 3303, 2930, 2342, 2309, 2211, 1616, 1415, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.76-7.71 (m, 2H, Ph), 7.53-7.45 (m, 3H, Ph), 5.78 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1H, C*H*=CH_2), 5.01 (dq, *J* = 17.0, 1.5 Hz, *trans*-HC=C*H*$_A$H$_B$), 4.96 (dq, *J* = 10.0, 1.0 Hz, *cis*-HC=CH$_A$*H*$_B$), 4.72 (s, 1H, CMe=C*H*$_A$H$_B$), 4.68 (s, 1H, CMe=CH$_A$*H*$_B$), 2.38-2.21 (m, 2H, CH), 2.15-1.92 (m, 6H, CH), 1.68 (s, C*Me*=CH_2), 0.75 (br q, *J* = 80.5 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 144.5 (d, *J* = 14.0 Hz, *C*Me=CH_2), 137.2 (d, *J* = 14.0 Hz, Ph), 131.8 (d, *J* = 8.5 Hz, Ph), 131.3 (d, *J* = 2.5 Hz, *C*H=CH_2), 128.7 (d, *J* = 10.0 Hz, Ph), 127.7 (d, *J* = 60.0 Hz, *ipso*-Ph), 115.1 (C=*C*H_2), 110.1 (C=*C*H_2), 30.3 (*C*H_2-C=CH_2), 26.8 (*C*H_2-C=CH_2), 24.8 (d, *J* = 35.5 Hz, PCH_2), 23.8 (d, *J* = 36.0 Hz, PCH_2), 22.2 (C*Me*=CH_2); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 16.4 (q, *J* = 74.5 Hz, PBH_3); MS (ESI) *m/z* 246 [(M + Na) $^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{24}BP$ $(M + Na)^+$ 269.1604, found 269.1597.

Lab book reference: chc/1/29

(3-Bromobut-3-enyl)(but-3-enyl)(phenyl)phosphine borane 108



108

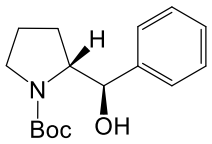
Using general procedure B, *s*-BuLi (1.00 mL of a 1.3 M solution in cyclohexane, 1.25 mmol) and phosphine borane **98** (200 mg, 1.04 mmol) in THF (5 mL), a mixture of LiCl (53 mg, 1.25 mmol) and CuCl (74 mg, 0.75 mmol) and 2,3-dibromoprop-1-ene (250 mg, 1.25 mmol) in THF (3 mL) gave the crude product. Purification by flash chromatography on silica with

95:5 petrol-EtOAc as eluent gave phosphine borane **108** (164 mg, 51%) as a white solid, mp 76-78 °C; R_F (95:5 petrol-EtOAc) 0.25; IR (NaCl) 3033, 2877, 2810, 2342, 2308, 2212, 1604, 1415, 981 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.78-7.67 (m, 2H, Ph), 7.57-7.42 (m, 3H, Ph), 5.84-5.70 (m, 1H, C*H*=CH_2), 5.60 (dt, *J* = 2.0, 1.0 Hz, 1H, CBr=CH_AH_B), 5.37 (d, *J* = 2.0 Hz, 1H, CBr=CH_AH_B), 5.02 (ddt, *J* = 17.0, 2.0, 2.0 Hz, 1H, *trans*-HC=CH_AH_B), 4.97 (dd, *J* = 10.0, 2.0 Hz, 1H, *cis*-HC=CH_AH_B), 2.75-2.62 (m, 1H, CH), 2.60-1.89 (m, 7H, CH), 0.73 (br q, *J* = 84.0 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 137.1 (d, *J* = 14.0 Hz, Ph), 132.9 (d, *J* = 16.0 Hz, *C*Br=CH_2), 131.9 (d, *J* = 9.5 Hz, Ph), 131,6 (d, *J* = 2.5 *C*H=CH_2), 128.9 (d, *J* = 9.5 Hz, Ph), 127.1 (d, *J* = 51.5 Hz, *ipso*-Ph), 117.5 (C=*C*H_2), 115.3 (C=*C*H_2), 34.9 (*C*H_2-C=CH_2), 26.7 (*C*H_2-C=CH_2), 25.0 (d, *J* = 35.5 Hz, PCH_2), 24.6 (d, *J* = 36.0 Hz, PCH_2); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 9.8 (q, *J* = 58.5 Hz, PBH_3); MS (ESI) *m/z* 333 [(^{79}M + Na) $^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{21}B^{79}BrP$ $(M + Na)^+$ 333.0552, found 333.0545.

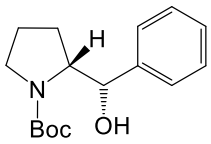
Lab book reference: chc/1/33

4.4 Experimental for Chapter 3

tert-Butyl 2-hydroxy(phenyl)methylpyrrolidine-1-carboxylate *syn*-30 and *anti*-30



syn-**30**



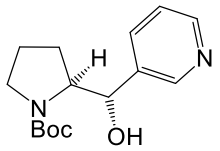
anti-**30**

Using general procedure C, *N*-Boc pyrrolidine **3** (2.0 g, 11.7 mmol), *s*-BuLi (12.0 mL of a 1.3 M solution in cyclohexanes, 15.2 mmol) and benzaldehyde (2.48 g, 2.40 mL, 23.4 mmol) in THF (60 mL) quenching with $NH_4Cl_{(aq)}$ gave the crude product as a yellow oil. Purification by flash chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave a hydroxypyrrolidine *syn*-**30** (1.83 g, 56%) as a yellow oil, R_F (98:2 CH_2Cl_2-acetone) 0.3; IR (ATR) 3396 (OH), 2975, 2931, 2880, 1691 (C=O), 1663 (C=O), 1391, 1365, 1161, 1115, 914, 753, 701 cm^{-1}; ^1H NMR (400, $CDCl_3$) δ 7.34-7.27 (m, 5H, Ph), 5.87 (br s, 1H, OH), 4.51 (br d, *J* = 8.5 Hz, 1H, OCH), 4.08 (ddd, *J* = 8.5, 8.5, 5.0 Hz, 1H, NCH), 3.49-3.43 (m, 1H, NCH_AH_B), 3.36 (br s, 1H, NCH_AH_B), 1.77-1.58 (m, 4H, CH), 1.51 (s, 9H, CMe_3); ^{13}C

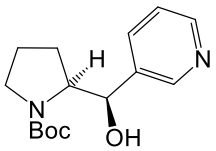
NMR (100.6 MHz, $CDCl_3$) 158.2 (C=O), 142.6 (*ipso*-Ph), 128.3 (Ph), 127.8 (Ph), 127.3 (Ph), 80.7 (*C*Me_3), 79.2 (OCH), 64.2 (NCH), 47.7 (NCH_2), 28.7 (CH_2), 28.5 (C*Me*$_3$), 23.8 (CH_2); MS (ESI) *m/z* 300 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_3$ $(M + Na)^+$ 300.1570, found 300.1566 (+1.2 ppm error) and hydroxypyrrolidine *anti*-**30** (404 mg, 12%) as a yellow oil, R_F (98:2 CH_2Cl_2-acetone) 0.2; IR (ATR) 3372 (OH), 2968, 2882, 1665 (C=O), 1408, 1124, 926, 741, 701 cm^{-1}; ^{1}H NMR (400, $CDCl_3$) δ 7.34-7.24 (m, 5H, Ph), 5.51 (br s, 1H, OH), 4.88 (br s, 1H, OCH), 4.30 (br s, 1H, NCH), 3.31 (br s, 1H, NCH), 2.83 (br s, 1H, NCH), 1.99-1.59 (m, 3H, CH), 1.52 (s, 9H, CMe_3), 1.17 (br s, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) 157.2 (C=O), 154.8 (C=O), 141.7 (*ipso*-Ph), 141.3 (*ipso*-Ph), 128.3 (Ph), 128.0 (Ph), 127.2 (Ph), 127.0 (Ph), 126.1 (Ph), 125.8 (Ph), 80.3 (*C*Me_3), 80.0 (*C*Me_3), 74.1 (OCH), 74.0 (OCH), 63.5 (NCH), 63.3 (NCH), 47.8 (NCH_2), 47.5 (NCH_2), 28.6 (C*Me*$_3$), 27.3 (CH_2), 23.6 (CH_2); MS (ESI) *m/z* 300 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_3$ $(M + Na)^+$ 300.1570, found 300.1561 (+3.0 ppm error). The ^{1}H NMR spectroscopic data are consistent with those reported in the literature.[26]

Lab book: chc/2/72CA and chc/2/72CB

tert-Butyl-2-(hydroxy(pyridine-3-yl)methyl)pyrrolidine-1-carboxylate _syn_-206 and _anti_-206



syn-**206**



anti-**206**

Using general procedure C, *N*-Boc pyrrolidine **3** (342 mg, 2.0 mmol), *s*-BuLi (2.0 mL of a 1.3 M solution in cyclohexanes, 2.6 mmol) and 3-pyridine-carboxaldehyde (428 mg, 0.37 mL, 4.0 mmol) in THF (20 mL) quenching with saturated $NH_4Cl_{(aq)}$ gave the crude product as a yellow oil. Purification by flash chromatography on silica with 98:2 CH_2Cl_2-MeOH as eluent gave hydroxypyrrolidine *syn*-**206** (62 mg, 11%) as a colourless oil and a 55:45 mixture (by ^{1}H NMR spectroscopy) of hydroxypyrrolidines *syn*-**206** and *anti*-**206** (203 mg, 36%) as a yellow oil. Full characterisation of *syn*-**206** and *anti*-**206** is described later.

Lab book: chc/2/13B and chc/2/13C

Table 3.1, entry 2

Using general procedure C, *N*-Boc pyrrolidine **3** (684 mg, 4.0 mmol), *s*-BuLi (4.0 mL of a 1.3 M solution in cyclohexanes, 5.2 mmol) and 3-pyridine-carboxaldehyde (856 mg, 0.75 mL, 8.0 mmol) in THF (50 mL) quenching with saturated water gave the crude product as a yellow oil. Purification by flash chromatography on silica with 98:2 CH_2Cl_2-MeOH as eluent gave a 60:40 mixture (by ^{1}H NMR spectroscopy) of hydroxypyrrolidines *syn*-**206** and *anti*-**206** (801 mg, 72%) as a colourless oil. Full characterisation of *syn*-**206** and *anti*-**206** is described later.

Lab book: chc/2/18C

Table 3.1, entry 3

Using general procedure C, *N*-Boc pyrrolidine **3** (2.0 g, 11.6 mmol), *s*-BuLi (11.8 mL of a 1.3 M solution in cyclohexanes, 15.2 mmol) and 3-pyridine-carboxaldehyde (2.50 g, 2.19 mL, 45.6 mmol) in THF (65 mL) quenching with water gave the crude product as a yellow oil. Purification by flash chromatography on silica with 97:3 CH_2Cl_2-MeCN as eluent gave a 60:40 mixture (by ^{1}H NMR spectroscopy) of hydroxypyrrolidines *syn*-**206** and *anti*-**206** (2.06 g, 64%) as a yellow oil. Full characterisation of *syn*-**206** and *anti*-**206** is described later.

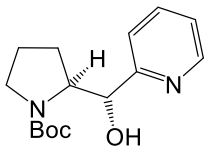
Lab book: chc/3/25B

Table 3.1, entry 4

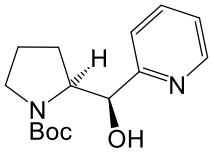
Using general procedure C, *N*-Boc pyrrolidine **3** (3.0 g, 17.5 mmol), *s*-BuLi (18.0 mL of a 1.3 M solution in cyclohexanes, 22.8 mmol) and 3-pyridine-carboxaldehyde (4.87 g, 4.30 mL, 45.6 mmol) in THF (150 mL) quenching with water gave the crude product as a yellow oil. Purification by flash chromatography on silica with 97:3 CH_2Cl_2-MeCN as eluent gave a 70:30 mixture (by ^{1}H NMR spectroscopy) of hydroxypyrrolidines *syn*-**206** and *anti*-**206** (2.07 g, 43%) as a yellow oil. Full characterisation of *syn*-**206** and *anti*-**206** is described later.

Lab book: chc/2/90C

***tert*-Butyl-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate *syn*-207 and *anti*-207**



syn-**207**



anti-**207**

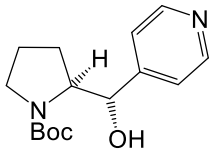
Using general procedure C, *N*-Boc pyrrolidine **3** (342 mg, 2.0 mmol), *s*-BuLi (2.0 mL of a 1.3 M solution in cyclohexanes, 2.6 mmol) and 2-pyridine-carboxaldehyde (429 mg, 4.0 mmol) in THF (14 mL), quenching with water gave the crude product as a yellow oil. Purification by flash chromatography on silica with 98:2 CH_2Cl_2:MeOH as eluent gave a 60:40 mixture of hydroxypyrrolidines *anti*-**207** and *syn*-**207** (384 mg, 69%) as a yellow oil. Full characterisation of *syn*-**207** and *anti*-**207** is described later.

Lab book: chc/2/11I

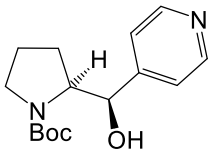
Using general procedure C, *N*-Boc pyrrolidine **3** (2.0 g, 11.68 mmol), *s*-BuLi (11.8 mL of a 1.3 M solution in cyclohexanes, 15.2 mmol) and 2-pyridine-carboxaldehyde (3.26 g, 30.4 mmol) in THF (65 mL), quenching with water gave the crude product as a yellow oil. Purification by flash chromatography on silica with 98:2 CH_2Cl_2:MeOH as eluent gave a 60:40 mixture of hydroxypyrrolidines *anti*-**207** and *syn*-**207** (1.62 g, 50%) as a yellow oil. Full characterisation of *syn*-**207** and *anti*-**207** is described later.

Lab book: chc/3/1B

***tert*-Butyl-2-(hydroxy(pyridin-4-yl)methyl)pyrrolidine-1-carboxylate *syn*-208 and *anti*-208**



syn-**208**



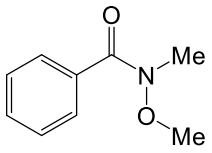
anti-**208**

Using general procedure C, *N*-Boc pyrrolidine **3** (1.37 g, 1.40 mL, 17.50 mmol), *s*-BuLi (8.0 mL of a 1.3 M solution in cyclohexanes, 10.40 mmol) and 4-pyridine-carboxaldehyde (1.71

g, 15.0 mL, 16.00 mmol) in THF (30 mL), quenching with water gave the crude product as a yellow oil. Purification by flash chromatography on silica with 7:3 to 6:5 petrol-EtOAc as eluent gave a 60:40 mixture (by ^{1}H NMR spectroscopy) of hydroxypyrrolidines *syn*-**208** and *anti*-**208** (1.02 g, 45%) as a yellow oil. Full characterisation of *syn*-**208** and *anti*-**208** is described later.

Lab book: chc/3/2B

_N_-Methoxy-_N_-methylbenzamide 215

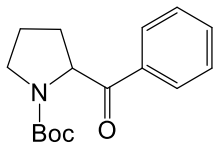


215

N,*O*-dimethylhydroxylamine hydrochloride salt (2.64 g, 27.03 mmol) was added to a stirred solution of benzoic acid **214** (3.0 g, 24.57 mmol), DIPEA (12.90 mL, 7.80 mmol) in CH_2Cl_2 (60 mL) at rt under Ar. The resulting solution was stirred at rt for 10 min. Then, T3P (23.47 g of a 50% w/v solution in THF, 36.86 mmol) was added dropwise and the resulting solution was stirred at rt for 2 h. 1 M $HCl_{(aq)}$ (60 mL) was added to the resulting solution and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). 20% $NaOH_{(aq)}$ was added to the combined organics and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 2:3 hexane-EtOAc as eluent gave *N*-benzyl Weinreb amide **215** (3.99 g, 98%) as a colourless oil, R_F (2:3 hexane-EtOAc) 0.4; IR (ATR) 2962, 1654 (C=O), 1420, 1257, 1109, 1028, 907, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H, Ph), 7.41-7.31 (m, 3H, Ph), 3.48 (s, 3H, OMe), 3.28 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.8 (C=O), 134.1 (*ipso*-Ph), 130.5 (Ph), 128.0 (Ph), 127.9 (Ph), 60.9 (OMe), 33.7 (NMe). Spectroscopic data are consistent with those reported in the literature.[154]

Lab book: chc/3/74A

tert-Butyl 2-benzoylpyrrolidine-1-carboxylate 213



213

s-BuLi (11.7 mL of a 1.3 M solution in cyclohexanes, 15.2 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **3** (2.0 g, 11.7 mmol) in THF (80 mL) at −30 ˚C under Ar. The resulting yellow solution was stirred at −30 ˚C for 5 min. Then, a solution of phenyl Weinreb amide **215** (1.94 g, 11.7 mmol) in THF (45 mL) was added dropwise and the resulting solution was stirred at −30 ˚C for 10 min and allowed to warm to rt over 2 h. Water (150 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 4:1 hexane-EtOAc as eluent gave ketopyrrolidinone **213** (1.79 g, 56%) as a yellow oil, R_F (4:1 hexane-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.99 (dd, *J* = 7.5, 1.5 Hz, 0.8H, Ph), 7.95 (dd, *J* = 7.5, 1.5 Hz, 1.2H, Ph), 7.61-7.53 (m, 1H, Ph), 7.50-7.43 (m, 2H, Ph), 5.33 (dd, *J* = 9.0, 3.5 Hz, 0.4H, NCH), 5.19 (dd, *J* = 9.0, 3.5 Hz, 0.6H, NCH), 3.72-3.44 (m, 2H, NCH), 2.38-2.24 (m, 1H, CH), 1.99-1.88 (m, 3H, CH), 1.46 (s, 3.6H, C*Me*$_3$), 1.26 (s, 5.4H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (rotamers) 198.9 (PhC=O), 198.4 (PhC=O), 145.5 (NC=O), 153.8 (NC=O), 135.2 (*ipso*-Ph), 135.1 (*ipso*-Ph), 133.3 (Ph), 133.2 (Ph), 128.7 (Ph), 128.2 (Ph), 128.6 (Ph), 128.5 (Ph), 79.7 (*C*Me$_3$), 79.6 (*C*Me$_3$), 61.3 (NCH), 61.1 (NCH), 46.8 (NCH_2), 46.6 (NCH_2), 30.9 (CH_2), 29.8 (CH_2), 28.5 (C*Me*$_3$), 28.2 (C*Me*$_3$), 24.2 and 23.6 (CH_2); MS (ESI) *m/z* 276 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3$ $(M + H)^+$ 276.1615, found 276.1622 (+4.1 ppm error). Spectroscopic data are consistent with those reported in the literature.[115]

Lab book: chc/3/76B

***tert*-Butyl-2-hydroxy(phenyl)methylpyrrolidine-1-carboxylate *syn*-30 and *anti*-30**

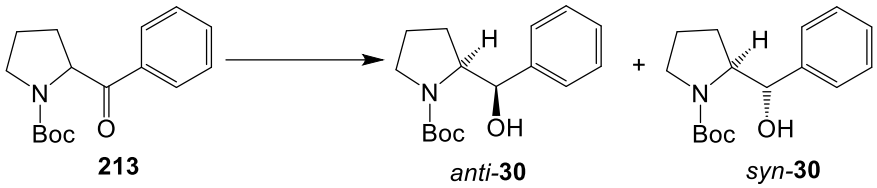


Table 3.3, entry 1

DIBAL-H (0.74 mL of a 1.0 M solution in hexanes, 0.74 mmol) was added to a stirred solution of ketone **213** (102 mg, 0.37 mmol) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, MeOH (5 mL) was added dropwise (caution: vigorous effervescence). 20% Rochelle's $salt_{(aq)}$ (15 mL) and Et_2O (15 mL) were added and the resulting mixture was allowed to warm to rt and stirred vigorously for 2 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organics were washed with water (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 99**:**1 mixture of *anti*-**30** and *syn*-**30** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine *syn*-**30** (3 mg, 3%) as a yellow oil and hydroxy pyrrolidine *anti*-**30** (95 mg, 93%) as a yellow oil.

Lab book: chc/3/88A and chc/3/88C

Table 3.3, entry 2

L-selectride (1.08 mL of a 1.0 M solution in THF, 1.08 mmol) was added to a stirred solution of ketone **213** (100 mg, 0.36 mmol) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, MeOH (5 mL) was added dropwise (caution: vigorous effervescence). Water (15 mL) and Et_2O (15 mL) were added and the resulting mixture was allowed to warm to room temperature and stirred vigorously for 2 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organics were washed with water (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 92:8 mixture of *syn*-**30** and *anti*-**30** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine *syn*-**30** (82 mg, 82%) as a yellow oil and hydroxy pyrrolidine *anti*-**30** (12 mg, 12%) as a yellow oil.

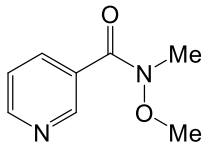
Lab book: chc/3/80A and chc/3/80C

Table 3.3, entry 3

$NaBH_4$ (42 mg, 1.09 mmol) was added in one portion to a stirred solution of ketone **213** (100 mg, 0.36 mmol) in MeOH (3 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt over 16 h. Then, water (10 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 71:29 mixture of *syn*-**30** and *anti*-**30** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent hydroxy pyrrolidine *syn*-**30** (68 mg, 68%) as a yellow oil and hydroxy pyrrolidine *anti*-**30** (27 mg, 27%) as a yellow oil.

Lab book: chc/3/77A and chc/3/77B

_N_-Methoxy-_N_-methylnicotinamide 209



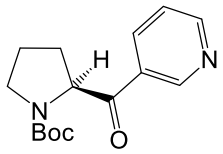
209

Nicotinic acid **216** (6.15 g, 50.0 mmol) was added to a stirred suspension of *N,O*-dimethylhydroxylamide hydrochloride salt (5.40 g, 55.0 mmol), triethylamine (7.75 mL, 55.0 mmol) and *N,N'*-dicyclohexylcarbodiimide (11.35 g, 55.0 mmol) in CH_2Cl_2 (50 mL) at 0°C under Ar. The resulting suspension was allowed to warm to rt and stirred for 16 h. Hexane (50 mL) was added and solids were removed by filtration and washed with hexane (50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:2 then 95:5 to 70:10 CH_2Cl_2-acetone as eluent gave Weinreb amide **209** (6.94 g, 83%) as a colourless oil, R_F (95:5 CH_2Cl_2-acetone) 0.25, IR (ATR) 3454, 2972, 2936, 1636, 1588, 1412, 1380, 1221, 977, 725, 561 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 1.5 Hz, 1H, Ar), 8.65 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar), 8.00 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar), 7.33 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar), 3.52 (s, 3H, OCH_3), 3.36 (NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.5 (C=O), 151.4 (Ar), 149.4 (Ar), 136.2 (Ar), 129.9

(*ipso*-Ar), 123.1 (Ar), 61.3 (OCH_3), 33.2 (NCH_3); MS (ESI) *m/z* 167 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_8H_{10}N_2O_2$ $(M + H)^+$ 167.0815, found 167.0817 (–0.9 ppm error). Spectroscopic data are consistent with those reported in the literature.[28]

Lab book: chc/2/55G

tert-Butyl-2-nicotinoylpyrrolidine-1-carboxylate 210

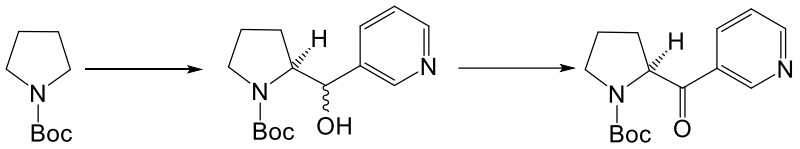


210

Using general procedure C, *N*-Boc pyrrolidine **3** (2.0 g, 11.7 mmol), *s*-BuLi (12.0 mL of a 1.3 M solution in cyclohexanes, 15.2 mmol) and *N*-methoxy-*N*-methylnicotinamide **209** (3.38 g, 20.3 mmol) in THF (35 mL), quenching with water gave the crude product as a yellow oil. Purification by flash chromatography on silica with 95:5 CH_2Cl_2-acetone and then 90:10 CH_2Cl_2-acetone as eluent gave ketopyrrolidinone **210** (1.23 g, 38%) as a yellow oil, R_F (9:1 CH_2Cl_2-acetone) 0.4; IR (ATR) 2980, 2938, 2871, 1686 (C=O), 1393, 1232, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 9.19 (d, *J* = 2.0 Hz, 0.45H, Ar), 9.17 (d, *J* = 2.0 Hz, 0.55H, Ar), 8.80 (dd, *J* = 5.0, 2.0 Hz, 0.55H, Ar), 8.77 (dd, *J* = 5.0, 2.0 Hz, 0.45H, Ar), 8.28 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 0.45H, Ar), 8.24 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 0.55H, Ar), 7.45 (dd, *J* = 8.0, 5.0 Hz, 0.45H, Ar), 7.42 (dd, *J* = 8.0, 5.0 Hz, 0.55H, Ar), 5.29 (dd, *J* = 8.0, 4.0 Hz, 0.45H, NCH), 5.20 (dd, *J* = 8.0, 4.0 Hz, 0.55H, NCH), 3.69-3.51 (m, 2H, CH), 2.38-2.34 (m, 1H, CH), 1.99-1.90 (m, 3H, CH), 1.47 (s, 4.05H, CMe_3), 1.27 (s, 4.95H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 198.1 (Ar-C=O), 197.8 (Ar-C=O), 154.5 (C=O, Boc), 153.8 (Ar), 153.7 (C=O, Boc), 153.6 (Ar), 149.7 (Ar), 149.5 (Ar), 136.1 (Ar), 135.7 (Ar), 130.8 (*ipso*-Ar), 130.7 (*ipso*-Ar), 123.9 (Ar), 123.8 (Ar), 80.2 (CMe_3), 80.1 (CMe_3), 61.6 (NCH), 61.4 (NCH), 46.9 (NCH_2), 46.7 (NCH_2), 30.8 (CH_2), 29.7 (CH_2), 28.5 (CMe_3), 28.3 (CMe_3), 24.4 (CH_2), 23.7 (CH_2); MS (ESI) *m/z* 299 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}N_2O_3$ $(M + Na)^+$ 299.1366, found 299.1369 (–1.0 ppm error). The ^1H NMR spectroscopic data are consistent with those reported in the literature.[34]

Lab book: chc/2/63B

tert-Butyl-2-nicotinoylpyrrolidine-1-carboxylate 210



Using general procedure C, *N*-Boc pyrrolidine **3** (200 mg, 1.17 mmol), *s*-BuLi (1.20 mL of a 1.3 M solution in cyclohexanes, 1.52 mmol) and 3-pyridine-carboxaldehyde (250 mg, 0.22 mL, 2.34 mmol) in THF (8 mL), quenching with water (10 mL), gave the crude hydroxy pyrrolidines as a yellow oil. Dess-Martin periodinane (595 mg, 1.40 mmol) was added to a stirred solution of the hydroxy pyrrolidines *syn*-**206** and *anti*-**206** in CH_2Cl_2 (5 mL) at 0 ˚C. The resulting suspension was allowed to warm to rt and stirred for 16 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the resulting suspension was stirred for 1 h. CH_2Cl_2 (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics 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-MeOH as eluent gave *N*-Boc pyrrolidinone **210** (244 mg, 75%) as a yellow oil.

Lab book: chc/3/98B

tert-Butyl-2-(hydroxy(pyridine-3-yl)methyl)pyrrolidine-1-carboxylate _syn_-206 and _anti_-206

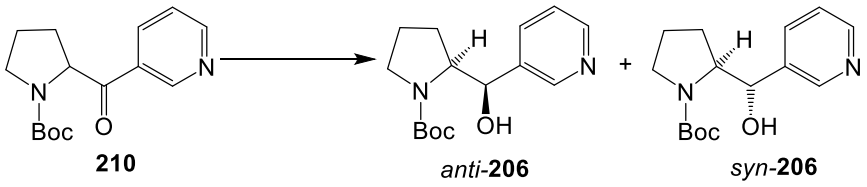


Table 3.4, entry 1

$NaBH_4$ (41 mg, 1.08 mmol) was added in one portion to a stirred solution of ketone **210** (100 mg, 0.36 mmol) in MeOH (3 mL) at 0 ˚C under Ar. The resulting mixture was allowed to warm to rt over 2 h. Then, water (10 mL) and CH_2Cl_2 (10 mL) were added and the two layers

were separated. The aqueous layer was extracted with CH_2Cl_2 (3 ×15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-MeCN as eluent gave a 70:30 mixture (by ^{1}H NMR spectroscopy) of hydroxy pyrrolidines *syn*-**206** and *anti*-**206** (94 mg, 94%) as a colourless oil.

Lab book: chc/3/83A

Table 3.4, entry 2

L-selectride (0.74 mL of a 1.0 M solution in THF, 0.74 mmol) was added to a stirred solution of ketone **210** (136 mg, 0.49 mmol) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, water (10 mL) and Et_2O (10 mL) were added and the resulting mixture was allowed to warm to rt and stirred for 1 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-MeCN as eluent gave a 95:5 mixture (by ^{1}H NMR spectroscopy) of hydroxy pyrrolidines *syn*-**206** and *anti*-**206** (43 mg, 31%) as a colourless oil.

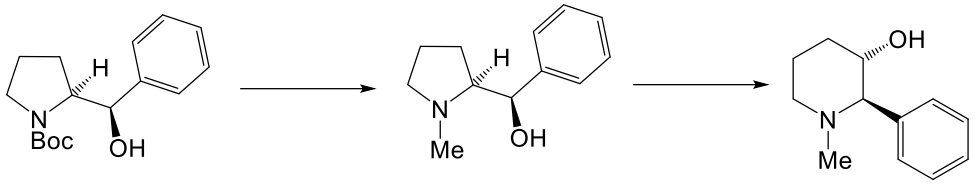
Lab book: chc/3/90E

Table 3.4, entry 3

DIBAL-H (0.80 mL of a 1.0 M solution in hexanes, 0.80 mmol) was added to a stirred solution of ketone **210** (110 mg, 0.40 mmol) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at at 0 °C for 1 h. Then, MeOH (5 mL) was added dropwise (caution: vigorous effervescence). 20% Rochelle's $salt_{(aq)}$ (15 mL) and Et_2O (15 mL) were added and the resulting mixture was allowed to warm to rt and stirred vigorously for 2 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 ×15 mL). The combined organics were washed with water (10 mL), 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-MeCN as eluent gave an 88:12 mixture (by ^{1}H NMR spectroscopy) of hydroxy pyrrolidines *anti*-**206** and *syn*-**206** (97 mg, 88%) as a colourless oil.

Lab book: chc/3/89A

1-Methylpyrrolidin-2-yl(phenyl)methanol *anti*-180



anti-**30** *anti*-**179** *anti*-**180**

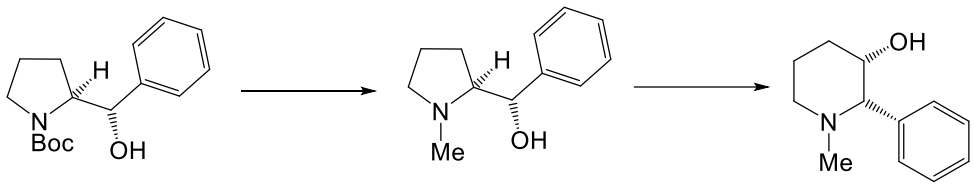
A solution of *N*-Boc pyrrolidine *anti*-**30** (420 mg, 1.52 mmol) in THF (4 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (180 mg, 4.59 mmol) in THF (11 mL) at 0 ˚C under Ar. The resulting mixture was stirred and heated at reflux for 16 h. Then, the reaction mixture was allowed to cool to 0 ˚C and 20% $NaOH_{(aq)}$ (0.1 mL) was added. The resulting mixture was stirred vigorously at rt for 30 min. $MgSO_4$ (5.0 g) was added and the solids were removed by filtration through a plug of Celite® and washed with Et_2O (30 mL). The filtrate was evaporated under reduced pressure to give the crude product (209 mg, 72%) as a yellow oil. The crude product was used in the next step without further purification.

Trifluoroacetic anhydride (0.50 mL, 3.27 mmol) was added to a stirred solution of crude *N*-methyl pyrrolidines (209 mg, 1.09 mmol) in THF (15 mL) at −78 ˚C. The resulting solution was stirred at −78 ˚C for 1 h and then Et_3N (0.50 mL, 3.27 mmol) was added dropwise. The resulting solution was stirred at −78 ˚C for 1 h. Then, the resulting mixture was allowed to warm to rt and stirred and heated at reflux for 48 h. The reaction was cooled to rt and 20% $NaOH_{(aq)}$ (15 mL) was added dropwise. Then, the resulting mixture was stirred at rt for 2 h. Et_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark brown oil. Purification by flash column chromatography on silica with 99:1 EtOAc:MeOH as eluent gave 3-hydroxy piperidine *anti*-**180** (81 mg, 28%) as a yellow oil, R_F (99:1 EtOAc-acetone) 0.20; IR (ATR) 3152 (OH), 2946, 2862, 2807, 1449, 1259, 1108, 1063, 956, 750, 696, 539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H, Ar), 3.57 (ddd, J = 11.0, 9.0, 4.5 Hz, 1H, OCH), 2.91 (dddd, J = 11.0, 3.5, 3.5, 1.5 Hz, 1H, NCH), 2.58 (d, J = 9.0 Hz, 1H, NCH), 2.13-2.05 (m, 2H, NCH and CH), 1.94 (s, 3H, Me), 1.78-1.71 (m, 2H, CH), 1.41-1.31 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.4 (*ipso*-Ar), 129.1 (Ar), 128.8 (Ar), 128.0 (Ar), 77.7 (OCH), 73.0 (NCH), 56.7 (NCH_2), 44.1 (NMe), 32.3 (CH_2), 23.5 (CH_2); MS (ESI) *m/z* 192 [$(M + H)^+$,

100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO$ $(M + H)^+$ 192.1383, found 192.1385 (–1.1 ppm error). The ^1H NMR spectroscopic data are consistent with those reported in the literature.[16]

Lab book: chc/2/75B

1-Methylpyrrolidin-2-yl(phenyl)methanol *syn*-180



syn-**30** *syn*-**179** *syn*-**180**

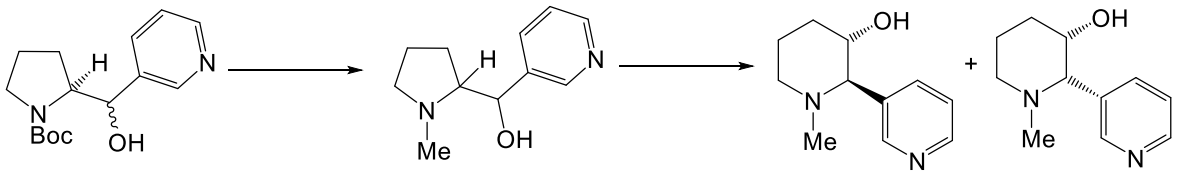
A solution of *N*-Boc pyrrolidine *syn*-**30** (458 mg, 1.65 mmol) in THF (4 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (195 mg, 4.96 mmol) in THF (11 mL) at 0 ˚C under Ar. The resulting mixture was stirred and heated at reflux for 16 h. Then, the reaction mixture was allowed to cool to 0 ˚C and 20% $NaOH_{(aq)}$ (0.1 mL) was added. The resulting mixture was stirred vigorously at rt for 30 min. $MgSO_4$ (5.0 g) was added and the solids were removed by filtration through a plug of Celite® and washed with Et_2O (30 mL). The filtrate was evaporated under reduced pressure to give the crude product (315 mg, 99%) as a yellow oil. The crude product was used in the next step without further purification.

Trifluoroacetic anhydride (0.80 mL, 4.96 mmol) was added to a stirred solution of crude *N*-methyl pyrrolidines (315 mg, 1.65 mmol) in THF (15 mL) at –78 ˚C. The resulting solution was stirred at –78 ˚C for 1 h and then Et_3N (0.80 mL, 4.96 mmol) was added dropwise. The resulting solution was stirred at –78 ˚C for 1 h. Then, the resulting mixture was allowed to warm to rt and stirred and heated at reflux for 48 h. The reaction was allowed to cool to rt and 20% $NaOH_{(aq)}$ (15 mL) was added dropwise. Then, the resulting mixture was stirred at rt for 2 h. Et_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark brown oil. Purification by flash column chromatography on silica with 2:1 EtOAc-acetone and 9:1 EtOAc:MeOH as eluent gave 3-hydroxy piperidine *syn*-**180** (19 mg, 6%) as a yellow oil, R_F (4:1 EtOAc-acetone) 0.15; IR (ATR) 3346 (OH), 1446, 1286, 1192, 1134, 847, 800, 722, 518 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.40 (br d, *J* = 7.5 Hz, 2H, Ar), 7.31 (ddd, *J* = 7.5, 7.5, 1.5 Hz,

2H, Ar), 7.25-7.21 (m, 1H, Ar), 3.70-3.69 (m, 1H, OCH), 3.07-3.00 (m, 2H, NCH), 2.24-2.10 (m, 2H, NCH and CH), 1.99 (s, 3H, NMe), 1.95-1.88 (m, 1H, CH), 1.67 (dddd, *J* = 13.0, 13.0, 4.5, 3.0 Hz, 1H, CH), 1.59-1.52 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CD_3OD) δ 142.1 (*ipso*-Ar), 130.0 (Ar), 129.1 (Ar), 128.2 (Ar), 75.7 (OCH), 70.1 (NCH), 58.4 (NCH_2), 44.9 (NMe), 32.8 (CH_2), 21.0 (CH_2); MS (ESI) *m/z* 192 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO$ $(M + H)^+$ 192.1383, found 192.1393 (–5.3 ppm error).

Lab book: chc/2/77BA

syn- and _anti_-(1-Methylpyrrolidin-2-yl)(pyridin-3-yl)methanol and 1-methyl-2-(pyridin-3-yl)piperidin-3-ol _syn_-218 and _anti_-218



syn-**206** + *anti*-**206** *syn*-**217** + *anti*-**217** *anti*-**218** *syn*-**218**

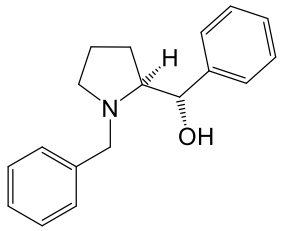
A solution of a 60:40 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**206** and *anti*-**206** (736 mg, 2.65 mmol) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (313 mg, 7.95 mmol) in THF (10 mL) at 0 ˚C under Ar. The resulting mixture was stirred and heated at reflux for 16 h. Then, the reaction mixture was allowed to cool to 0 ˚C and 20% $NaOH_{(aq)}$ (0.1 mL) was added. The resulting mixture was stirred vigorously at rt for 30 min. $MgSO_4$ (5 g) was added and the solids were removed by filtration through a plug of Celite® and washed with Et_2O (30 mL). The filtrate was evaporated under reduced pressure to give the crude product (222 mg, 43%) as a yellow oil. The crude product was used in the next step without further purification.

Trifluoroacetic anhydride (0.50 mL, 3.54 mmol) was added to a stirred solution of crude *N*-methyl pyrrolidines (222 mg, 1.18 mmol) in THF (8 mL) at −78 ˚C. The resulting solution was stirred at −78 ˚C for 1 h and then Et_3N (0.50 mL, 3.54 mmol) was added dropwise. The resulting solution was stirred at −78 ˚C for 1 h. The resulting mixture was allowed to warm to rt and stirred and heated at reflux for 48 h. The reaction was cooled to rt and 20% $NaOH_{(aq)}$ (10 mL) was added dropwise. Then, the resulting mixture was stirred at rt for 2 h. Et_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with

Et_2O (3 × 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark brown oil. Purification by flash column chromatography on silica with 95:5-9:1 CH_2Cl_2-MeOH as eluent gave a 60:40 mixture of 3-hydroxy piperidine *anti*-**218** and *syn*-**218** (50 mg, 10%) as a yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.1; IR (ATR) 3375 (OH), 2935, 2854, 2786, 1575, 1423, 1127, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H, $Ar_{anti+syn}$), 8.39 (d, J = 5.0 Hz, 0.4H, Ar_{syn}), 8.31 (d, J = 5.0 Hz, 0.6H, Ar_{anti}), 7.75 (d, J = 7.5 Hz, 0.4H, Ar_{syn}), 7.70 (d, J = 7.5 Hz, 0.6H, Ar_{anti}), 7.25-7.20 (m, 1H, $Ar_{anti+syn}$), 3.67 (br s, 0.4H, OCH_{syn}), 3.59 (ddd, J = 11.5, 9.0, 4.0 Hz, 0.6H, OCH_{anti}), 3.06-3.02 (m, 0.8H, 2×NCH_{syn}), 2.94 (ddd, J = 9.0, 4.0, 4.0 Hz, 0.6H, NCH_{anti}), 2.67 (d, J = 9.0 Hz, 0.6H, NCH_{anti}), 2.23-2.04 (m, 1.6H, 2×CH_{syn} and CH_{anti}), 2.02 (s, 1.2H, NMe_{syn}), 1.94 (s, 1.8H, NMe_{anti}), 1.79-1.72 (m, 1H, $CH_{anti+syn}$), 1.65-1.60 (m, 0.8H, 2×CH_{syn}), 1.44-1.34 (m, 0.6H, CH_{anti}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.4 (Ar), 149.7 (Ar), 148.8 (Ar), 148.7 (Ar), 136.8 (*ipso*-Ar), 136.7 (Ar), 136.4 (*ipso*-Ar), 136.1 (Ar), 123.8 (Ar), 123.4 (Ar), 75.1 (OCH), 72.8 (OCH), 71.8 (NCH), 69.3 (NCH), 57.2 (NCH_2), 56.5 (NCH_2), 44.4 (NMe), 44.1 (NMe), 33.0 (CH_2), 31.4 (CH_2), 23.4 (CH_2), 19.7 (CH_2); MS (ESI) *m/z* 193 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{16}N_2O$ $(M + H)^+$ 193.1335, found 193.1334 (+0.8 ppm error).

Lab book: chc/2/29C

***syn*-Benzylpyrrolidin-2-yl)(phenyl)methanol *syn*-171**



syn-**171**

Using general procedure D, *N*-Boc hydroxy pyrrolidines *syn*-**30** (680 mg, 2.46 mmol) and TFA (1.40 mL, 9.83 mmol) in CH_2Cl_2 (4 mL) gave the crude hydroxy pyrrolidines (425 mg, 97%) as a yellow oil. The crude product was used in the next step without further purification.

Using general procedure E, crude hydroxy pyrrolidines *syn*-**219** (425 mg, 2.39 mmol), benzaldehyde (0.45 mL, 2.64 mmol), sodium triacetoxyborohydride (1.20 g, 4.78 mmol) and

AcOH (0.60 mL, 9.56 mmol) in 1,2-dichloroethane (15 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *syn*-**171** (287 mg, 39%) as a yellow oil.

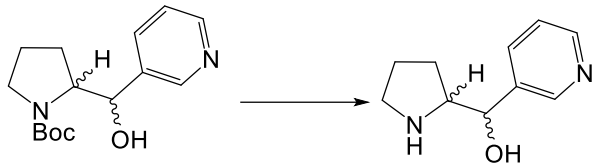
Lab book: chc/2/88B

Using general procedure D, *N*-Boc hydroxy pyrrolidines *syn*-**30** (340 mg, 1.23 mmol) and TFA (0.70 mL, 4.92 mmol) in CH_2Cl_2 (2 mL) gave the crude hydroxy pyrrolidines (217 mg, 99%) as a yellow oil. The crude product was used in the next step without further purification.

Using general procedure E, crude hydroxy pyrrolidines *syn*-**219** (217 mg, 2.13 mmol), benzaldehyde (0.25 mL, 1.35 mmol), sodium cyanoborohydride (163 mg, 2.46 mmol) and AcOH (0.15 mL, 2.46 mmol) in 1,2-dichloroethane (10 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *syn*-**171** (264 mg, 80%) as a yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.23 (m, 10H, Ph), 4.51 (d, *J* = 5.5 Hz, 1H, CHO), 3.83 (d, *J* = 13.0 Hz, 1H, NC$H_A$$H_B$Ph), 3.47 (d, *J* = 13.0 Hz, 1H, NCH$_A$$H_B$Ph), 3.17 (m, 1H, CHN), 3.08-3.03 (m, 1H, NCH), 2.51(ddd, *J* = 8.0, 8.0, 7.0 Hz, 1H, NCH), 1.95-1.89 (m, 1H, CH), 1.86-1.75 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.3 (*ipso*-Ph), 138.1 (*ipso*-Ph), 129.2 (Ph), 128.6 (Ph), 128.5 (Ph), 127.6 (Ph), 127.5 (Ph), 126.4 (Ph), 75.1 (CHO), 70.7 (CHN), 61.2 (PhCH_2N), 54.2 (CH_2N), 29.2 (CH_2), 24.2 (CH_2). Spectroscopic data consistent with that reported in the literature.[15]

Lab book: chc/2/96B

syn-and _anti_-Pyridin-3-yl(pyrrolidin-2-yl)methanol _syn_-220 and _anti_-220



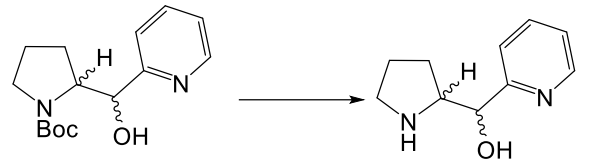
syn-**206** + *anti*-**206** *syn*-**220** + *anti*-**220**

Table 3.5, entry 1

Using general procedure D, a 70:30 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**206** and *anti*-**206** (500 mg, 1.80 mmol) and TFA (1.10 mL, 7.20 mmol) in CH_2Cl_2 (8 mL) gave the crude hydroxy pyrrolidines (271 mg, 85%) as a yellow oil, which contained a 70:30 mixture of *syn*-**220** and *anti*-**220** (by ^{1}H NMR spectroscopy), IR (ATR) 3177 (OH), 2961, 2872, 1423, 1200, 1025, 800, 714, 627 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.0 Hz, 0.3H, Ar_{anti}), 8.34 (d, *J* = 2.0 Hz, 0.7H, Ar_{syn}), 8.26 (dd, *J* = 5.0, 1.5 Hz, 0.7H, Ar_{syn}), 8.24 (d, *J* = 5.0, 1.5 Hz, 0.3H, Ar_{anti}), 7.57-7.53 (m, 1H, $Ar_{syn+anti}$), 7.10-7.06 (m, 1H, $Ar_{syn+anti}$), 4.61 (d, *J* = 4.5 Hz, 0.3H, OCH_{anti}), 4.47 (br s, 2H, OH and NH), 4.20 (d, *J* = 7.5 Hz, 0.7H, OCH_{syn}), 3.14-3.07 (m, 1H, $NCH_{syn+anti}$), 2.83-2.72 (m, 1.7H, NCH_{syn} and NCH_{anti}), 2.68-2.62 (m, 0.3H, NCH_{anti}), 1.67-1.22 (m, 3.7H, $CH_{syn+anti}$), 0.73-0.57 (m, 0.3H, CH_{syn}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.4 (Ar_{syn}), 148.0 (Ar_{syn}), 147.9 (Ar_{anti}), 147.5 (Ar_{anti}), 138.6 (*ipso*-$Ar_{syn+anti}$), 134.3 (Ar_{syn}), 133.8 (Ar_{anti}), 123.2 (Ar_{syn}), 123.1 (Ar_{anti}), 73.6 (OCH_{syn}), 71.3 (OCH_{anti}), 64.5 (NCH_{syn}), 64.0 (NCH_{anti}), 46.5 (NCH_{2anti}), 45.8 (NCH_{2syn}), 27.8 (CH_{2syn}), 25.3 (CH_{2syn}), 25.2 (CH_{2anti}), 25.1 (CH_{2anti}); MS (ESI) *m/z* 178 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_2O$ $(M + H)^+$ 179.1179, found 179.1181 (–1.4 ppm error).

Lab book: chc/2/91crude

syn- and _anti_-Pyridin-2-yl(pyrrolidin-2-yl)methanol _syn_-221 and _anti_-221



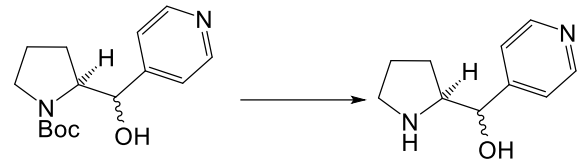
syn-**207** + *anti*-**207** *syn*-**221** + *anti*-**221**

Table 3.5, entry 2

Using general procedure D, an 60:40 mixture of *N*-Boc hydroxy pyrrolidines *anti*-**207** and *syn*-**207** (811 mg, 2.92 mmol) and TFA (1.90 mL, 11.68 mmol) in CH_2Cl_2 (15 mL) gave the crude hydroxy pyrrolidines (418, 80%) as a yellow oil, which contained a 60:40 mixture of *anti*-**221** and *syn*-**221** (by ^{1}H NMR spectroscopy). IR (ATR) 3371 (OH), 3063, 2977, 2883, 1391, 1365, 1163, 1113, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (br d, *J* = 5.0 Hz, 0.6H, Ar), 8.36 (br d, *J* = 5.0 Hz, 0.4H, Ar), 7.59-7.53 (m, 1H, Ar), 7.37 (d, *J* = 8.0 Hz, 0.6H, Ar), 7.32 (d, *J* = 8.0 Hz, 0.4H, Ar), 7.07-7.04 (m, 1H, Ar), 5.26 (br s, 2H, OH and NH), 4.83 (d, *J* = 4.0 Hz, 0.6H, OCH_{anti}), 4.48 (d, *J* = 6.0 Hz, 0.4H, OCH_{syn}), 3.59 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 0.6H, NCH_{anti}), 3.42 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 0.4H, NCH_{syn}), 2.99-2.78 (m, 2H, $CH_{anti+syn}$) 1.72-1.49 (m, 3H, $CH_{anti+syn}$), 1.37-1.28 (m, 1H, $CH_{anti+syn}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.7 (*ipso*-Ar), 160.8 (*ipso*-Ar), 148.5 (Ar), 148.2 (Ar), 136.6 (Ar), 122.4 (Ar), 122.2 (Ar), 121.2 (Ar), 120.8 (Ar), 74.8 (OCH), 72.6 (OCH), 63.5 (NCH), 63.4 (NCH), 46.6 (NCH_2), 46.0 (NCH_2), 27.9 (CH_2), 25.4 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 24.6 (CH_2); MS (ESI) *m/z* 179 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_2O$ $(M + H)^+$ 179.1179, found 179.1184 (–3.0 ppm error).

Lab book: chc/3/12crude

syn- and _anti_-pyridin-4-yl(pyrrolidin-2-yl)methanol _syn_-222 and _anti_-222



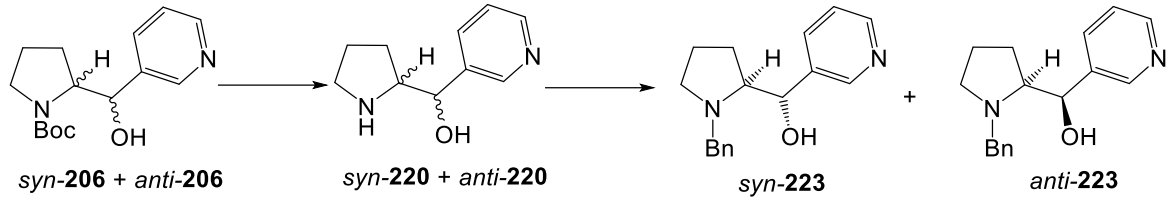
syn-**208** + *anti*-**208** *syn*-**222** + *anti*-**222**

Table 3.5, entry 3

Using general procedure D, a 60:40 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**208** and *anti*-**208** (454 mg, 1.64 mmol) and TFA (1.10 mL, 6.56 mmol) in CH_2Cl_2 (8 mL) gave the crude hydroxy pyrrolidines (227, 78%) as a yellow oil, which contained a 65:35 mixture of *syn*-**222** and *anti*-**222** (by ^{1}H NMR spectroscopy). The crude product was used in the next step without further purification. IR (ATR) 3218 (OH), 2964, 2872, 1412, 1199, 1117, 1063, 992, 814, 621 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-30 (m, 2H, $Ar_{syn+anti}$), 7.26-7.15 (m, 2H, Ar), 4.71 (d, J = 3.5 Hz, 0.35H, OCH_{anti}), 4.41 (br s, 2H, OH and NH), 4.26 (d, J = 5.5 Hz, 0.65H, OCH_{syn}), 3.28-3.25 (m, 0.35H, NCH_{anti}), 3.16 (ddd, J = 7.0, 7.0, 7.0 Hz, 0.65H, NCH_{syn}), 2.90-2.87 (m, 0.70H, $NCH_{syn+anti}$), 2.85-2.70 (m, 1.30H, $NCH_{syn+anti}$), 1.71-1.42, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.6 (*ipso*-Ar_{syn}), 152.2 (*ipso*-Ar_{anti}), 149.4 (Ar_{syn}), 149.3 (Ar_{anti}), 121.6 (Ar_{syn}), 121.1 (Ar_{anti}), 74.1 (OCH_{syn}), 71.8 (OCH_{anti}), 64.3 (NCH_{syn}), 63.6 (NCH_{anti}), 46.7 (NCH_{2anti}), 46.1 (NCH_{2syn}), 28.3 (CH_{2syn}), 25.7 (CH_{2syn}), 25.5 (CH_{2anti}), 24.7 (CH_{2anti}); MS (ESI) *m/z* 179 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_2O$ $(M + H)^+$ 179.1179, found 179.1187 (–4.8 ppm error)

Lab book: chc/3/13crude

syn- and _anti_-1-Benzylpyrrolidin-2-yl)(pyridin-3-yl)methanol _syn_-223 _anti_-223



syn-**206** + *anti*-**206** *syn*-**220** + *anti*-**220** *syn*-**223** *anti*-**223**

Table 3.6, entry 1

Using general procedure D, a 70:30 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**206** and *anti*-**206** (500 mg, 1.80 mmol) and TFA (1.10 mL, 7.20 mmol) in CH_2Cl_2 (8 mL) gave the crude hydroxy pyrrolidines (271 mg, 85%) as a yellow oil, which contained a 70:30 mixture of *syn*-**220** and *anti*-**220** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 70:30 mixture of crude hydroxy pyrrolidines *syn*-**220** and *anti*-**220** (271 mg, 1.52 mmol), benzaldehyde (0.35 mL, 1.68 mmol), sodium triacetoxyborohydride (771 mg, 3.06 mmol) and AcOH (0.50 mL, 6.12 mmol) in 1,2-dichloroethane (15 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**223** (123 mg, 25%), as a yellow oil, R_F (96:4 CH_2Cl_2-MeOH) 0.2; IR (ATR) 3226 (OH), 2963, 2797, 1453, 1164, 1111, 1091, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (br s, 1H, Ar), 8.42 (d, *J* = 3.0 Hz, 1H, Ar), 7.72 (br d, *J* = 8.0 Hz, 1H, Ar), 7.34-7.33 (m, 4H, Ar), 7.29-7.23 (m, 2H, Ar), 4.86 (d, *J* = 3.5 Hz, 1H, OCH), 4.12 (d, *J* = 13.0 Hz, 1H, PhCH_AH$_B$N), 3.49 (d, *J* = 13.0 Hz, 1H, PhCH_AH$_B$N), 3.04 (ddd, *J* = 9.0, 5.0, 5.0 Hz, 1H, NCH), 2.88 (ddd, *J* = 9.0, 6.0, 3.5 Hz, 1H, NCH), 2.35 (ddd, *J* = 9.0, 9.0, 9.0 Hz, NCH), 1.69-1.59 (m, 3H, CH), 1.38-1.31 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.4 (Ar), 147.6 (Ar), 138.5 (*ipso*-Ar), 137.0 (*ipso*-Ar), 133.5 (Ar), 129.0 (Ar), 128.7 (Ar), 127.5 (Ar), 123.4 (Ar), 69.0 (OCH or NCH), 68.6 (OCH or NCH), 58.4 ($PhCH_2N$), 54.9 (NCH_2), 24.2 (CH_2), 23.3 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1648, found 269.1645 (+1.1 ppm error) and *N*-benzyl pyrrolidine *syn*-**223** (86 mg, 18%), as a yellow oil, R_F (96:4 CH_2Cl_2-MeOH) 0.1, IR (ATR) 3205 (OH), 2962, 2795, 1452, 1191, 1117, 1061, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 1.5 Hz, 1H, Ar), 8.45 (dd, *J* = 4.5, 1.5 Hz, 1H, Ar), 7.69 (ddd, *J* = 7.5, 1.5, 1.5 Hz, 1H, Ar), 7.34-7.21 (m, 6H, Ar), 4.41 (d, *J* = 5.5 Hz, 1H, OCH), 3.70 (d, *J* = 13.5 Hz, 1H, PhCH_AH$_B$N), 3.44 (d, *J* = 13.5 Hz, PhCH$_A$$H_B$N), 3.06 (ddd, *J* = 9.0, 5.5, 3.5 Hz, 1H, NCH), 3.00-2.94 (m, 1H, NCH), 2.46-2.40 (m, 1H, NCH), 1.97-1.86 (m, 1H, CH), 1.79-1.65 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.8 (Ar), 148.3 (Ar), 138.7 (*ipso*-Ar), 138.1

(*ipso*-Ar), 134.2 (Ar), 129.0 (Ar), 128.6 (Ar), 127.6 (Ar), 123.5 (Ar), 73.1 (OCH or NCH), 70.3 (NCH or OCH), 61.3 ($PhCH_2N$), 54.2 (NCH_2), 28.9 (CH_2), 24.2 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1648, found 269.1659 (–3.8 ppm error).

Lab book: chc/2/92A and chc/2/92B

Table 3.6, entry 2

Using general procedure D, a 70:30 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**206** and *anti*-**75** (196 mg, 0.71 mmol) and TFA (0.48 mL, 2.82 mmol) in CH_2Cl_2 (3 mL) gave the crude hydroxy pyrrolidines (108 mg, 86%) as a yellow oil, which contained a 70:30 mixture of *syn*-**220** and *anti*-**220** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 70:30 mixture of crude hydroxy pyrrolidines *syn*-**220** and *anti*-**220** (108 mg, 0.61 mmol), benzaldehyde (0.13 mL, 0.67 mmol), sodium triacetoxyborohydride (272 mg, 1.22 mmol) and AcOH (0.01 mL, 0.12 mmol) in 1,2-dichloroethane (4 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**223** (57 mg, 30%) as a yellow oil and *N*-benzyl pyrrolidine *syn*-**223** (58 mg, 30%).

Lab book: chc/3/22A and chc/3/22B

Table 3.6, entry 1

Using general procedure D, a 65:35 mixture of *N*-Boc hydroxy pyrrolidines *anti*-**206** and *syn*-**206** (295 mg, 1.06 mmol) and TFA (0.72 mL, 4.24 mmol) in CH_2Cl_2 (5 mL) gave the crude hydroxy pyrrolidines (152 mg, 80%) as a yellow oil, which contained a 65:35 mixture of *anti*-**220** and *syn*-**220** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 65:35 mixture of crude hydroxy pyrrolidines *anti*-**220** and *syn*-**220** (152 mg, 0.85 mmol), benzaldehyde (0.18 mL, 0.94 mmol), sodium cyanoborohydride (113 mg, 1.71 mmol) and AcOH (0.02 mL, 0.17 mmol) in 1,2-dichloroethane (7 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**223** (39 mg, 14%) as a yellow oil and *N*-benzyl pyrrolidine *syn*-**223** (37 mg, 13%) as a yellow oil.

Lab book: chc/3/20C and chc/3/20D

Table 3.6, entry 4

Using general procedure D, a 70:30 mixture of *N*-Boc hydroxy pyrrolidines *anti*-**206** and *syn*-**206** (516 mg, 1.80 mmol) and TFA (1.10 mL, 7.20 mmol) in CH_2Cl_2 (8 mL) gave the crude hydroxy pyrrolidines (320 mg, 99%) as a yellow oil, which contained a 70:30 mixture of *anti*-**220** and *syn*-**220** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 70:30 mixture of crude hydroxy pyrrolidines *syn*-**220** and *anti*-**220** (320 mg, 1.80 mmol), benzaldehyde (0.36 mL, 1.98 mmol), sodium cyanoborohydride (238 mg, 3.60 mmol) and AcOH (0.22 mL, 3.60 mmol) in 1,2-dichloroethane (15 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**223** (61 mg, 12%) as a yellow oil and *N*-benzyl pyrrolidine *syn*-**223** (142 mg, 29%).

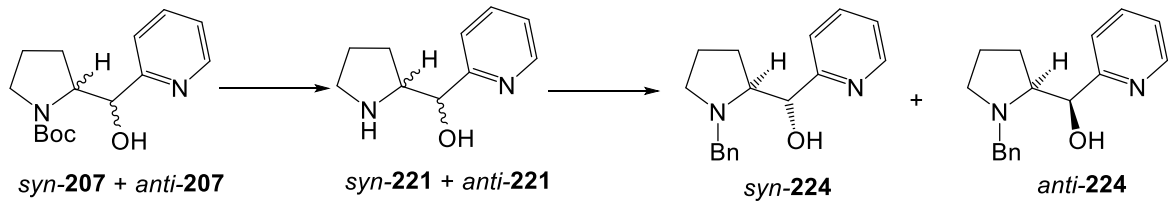
Lab book: chc/2/99B and chc/2/99D

Table 3.6, entry 5

Using general procedure D, a 70:30 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**206** and *anti*-**206** (419 mg, 1.51 mmol) and TFA (1.0 mL, 6.04 mmol) in CH_2Cl_2 (10 mL) gave the crude hydroxy pyrrolidines (236 mg, 88%) as a yellow oil, which contained a 70:30 mixture of *syn*-**220** and *anti*-**220** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 70:30 mixture of crude hydroxy pyrrolidines *syn*-**220** and *anti*-**220** (236 mg, 1.33 mmol), benzaldehyde (0.27 mL, 1.46 mmol), sodium cyanoborohydride (176 mg, 2.66 mmol) and AcOH (0.25 mL, 3.99 mmol) in 1,2-dichloroethane (12 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**223** (50 mg, 12%) as a yellow oil and *N*-benzyl pyrrolidine *syn*-**223** (46 mg, 11%).

Lab book: chc/3/11A and chc/3/11C

syn-and _anti_-1-Benzylpyrrolidin-2-yl(pyridin-2-yl)methanol _syn_-224 and _anti_-224



syn-**207** + *anti*-**207** *syn*-**221** + *anti*-**221** *syn*-**224** *anti*-**224**

Table 3.6, entry 6

Using general procedure D, an 65:35 mixture of *N*-Boc hydroxy pyrrolidines *anti*-**207** and *syn*-**207** (894 mg, 3.21 mmol) and TFA (2.05 mL, 12.85 mmol) in CH_2Cl_2 (15 mL) gave the crude hydroxy pyrrolidines (419, 73%) as a yellow oil, which contained a 65:35 mixture of *anti*-**221** and *syn*-**221** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 65:35 mixture of the crude hydroxy pyrrolidines *anti*-**221** and *syn*-**221** (419 mg, 2.35 mmol), benzaldehyde (0.50 mL, 2.59 mmol), sodium triacetoxyborohydride (1.05 g, 4.70 mmol) and AcOH (0.04 mL, 0.47 mmol) in 1,2-dichloroethane (14 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**224** (178 mg, 28%) as a yellow oil and *N*-benzyl pyrrolidine *syn*-**224** (91 mg, 11%) as a yellow oil.

Lab book: chc/3/48A and chc/3/48D

Table 3.6, entry 7

Using general procedure D, an 60:40 mixture of *N*-Boc hydroxy pyrrolidines *anti*-**207** and *syn*-**207** (778 mg, 2.80 mmol) and TFA (1.80 mL, 11.19 mmol) in CH_2Cl_2 (15 mL) gave the crude hydroxy pyrrolidines (463, 93%) as a yellow oil, which contained a 60:40 mixture of *anti*-**221** and *syn*-**221** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 60:40 mixture of the crude hydroxy pyrrolidines *anti*-**221** and *syn*-**221** (463 mg, 2.60 mmol), benzaldehyde (0.55 mL, 2.86 mmol), sodium cyanoborohydride (345 mg, 5.20 mmol) and AcOH (0.35 mL, 5.20 mmol) in 1,2-dichloroethane (20 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**224** (168 mg, 22%) as a yellow oil, R_F (96:4 CH_2Cl_2-MeOH) 0.2; IR (ATR) 3362 (OH), 2977, 2883, 2797, 1436, 1116, 1028, 750, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br d, J = 5.0 Hz, 1H, Ar), 7.69 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H, Ar), 7.56 (d, J = 8.0 Hz, 1H, Ar), 7.39-7.32 (m, 4H, Ar), 7.29-7.25 (m, 1H, Ar), 7.16 (ddd, J = 8.0, 5.0, 1.0 Hz, 1H, Ar), 4.97 (d, J = 3.5 Hz, 1H, OCH), 4.75 (br s, 1H, OH),

4.26 (d, *J* = 13.0 Hz, 1H, NC*H*$_A$H$_B$Ph), 3.52 (d, *J* = 13.0 Hz, 1H, NCH$_A$*H*$_B$Ph), 3.31 (ddd, *J* = 9.5, 6.0, 3.5 Hz, 1H, NCH), 3.06 (ddd, *J* = 9.5, 5.0, 5.0 Hz, 1H, NCH), 2.39 (ddd, *J* = 9.0, 9.0, 9.0 Hz, 1H, NCH), 1.68-1.57 (m, 3H, CH), 1.44-1.37 (m, 1H, CH)); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.1 (*ipso*-Ar), 148.7 (Ar), 138.2 (*ipso*-Ar), 136.8 (Ar), 129.0 (Ar), 128.6 (Ar), 127.5 (Ar), 122.2 (Ar), 120.8 (Ar), 71.1 (OCH), 68.4 (NCH), 58.4 (Ph*C*H$_2$N), 54.5 (N*C*H$_2$), 24.3 (CH$_2$), 23.2 (CH$_2$); (MS (ESI) *m/z* 269 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ (M + H)$^+$ 269.1648, found 269.1658 (–3.5 ppm error) and *N*-benzyl pyrrolidine *syn*-**224** (25 mg, 3%) as a yellow oil, R_F (96:4 CH_2Cl_2-MeOH) 0.1, IR (ATR) 3396 (OH), 2960, 2797, 1435, 1209, 1102, 1070, 749, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 4.0, 1.5, 1.5 Hz, 1H, Ar), 7.69-7.63 (m, 2H, Ar), 7.31-7.20 (m, 5H, Ar), 7.15 (ddd, *J* = 7.0, 5.0, 1.5 Hz, 1H, Ar) , 4.64 (d, *J* = 3.5 Hz, 1H, OCH), 4.13 (br s, 1H, OH), 3.49 (d, *J* = 13.0 Hz, 1H, NC*H*$_A$H$_B$Ph), 3.43 (ddd, *J* = 9.5, 4.5, 3.5 Hz, NCH), 3.27 (d, *J* = 13.0 Hz, 1H, NCH$_A$*H*$_B$Ph), 2.96 (ddd, *J* = 9.5, 7.0, 3.5 Hz, 1H, NCH), 2.37 (ddd, *J* = 9.5, 9.5, 6.5 Hz, 1H, NCH), 2.14-2.04 (m, 1H, CH), 1.92-1.85 (m, 1H, CH), 1.75-1.59 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.2 (*ipso*-Ar), 148.8 (Ar), 138.6 (*ipso*-Ar), 136.8 (Ar), 128.9 (Ar), 128.5 (Ar), 127.4 (Ar), 122.4 (Ar), 121.2 (Ar), 74.4 (OCH), 68.5 (NCH), 60.4 (Ph*C*H$_2$N), 54.6 (NCH$_2$), 29.4 (CH$_2$), 24.3 (CH$_2$); MS (ESI) *m/z* 291 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2NaO$ (M + Na)$^+$ 291.1468, found 291.1462 (+2.2 ppm error).

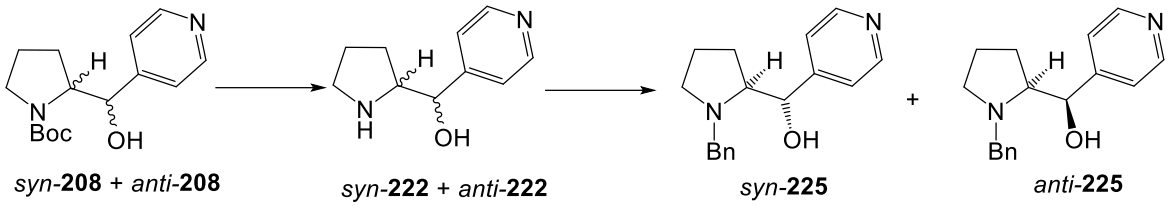
Lab book: chc/3/6A and chc/3/6J

Table 3.6, entry 8

Using general procedure D, an 60:40 mixture of *N*-Boc hydroxy pyrrolidines *anti*-**207** and *syn*-**207** (811 mg, 2.92 mmol) and TFA (1.90 mL, 11.68 mmol) in CH_2Cl_2 (15 mL) gave the crude hydroxy pyrrolidines (418, 80%) as a yellow oil, which contained a 60:40 mixture of *anti*-**221** and *syn*-**221** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 60:40 mixture of the crude hydroxy pyrrolidines *anti*-**221** and *syn*-**221** (418 mg, 2.35 mmol), benzaldehyde (0.48 mL, 2.59 mmol), sodium cyanoborohydride (311 mg, 4.70 mmol) and AcOH (0.43 mL, 7.05 mmol) in 1,2-dichloroethane (20 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**224** (183 mg, 23%) as a yellow oil and *N*-benzyl pyrrolidine *syn*-**224** (49 mg, 6%) as a yellow oil.

Lab book: chc/3/15A and chc/3/15BD

syn- and _anti_-1-Benzylpyrrolidin-2-yl)(pyridin-4-yl)methanol _syn_-225 and _anti_-225



syn-**208** + *anti*-**208** *syn*-**222** + *anti*-**222** *syn*-**225** *anti*-**225**

Table 3.6, entry 9

Using general procedure D, a 60:40 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**208** and *anti*-**208** (876 mg, 3.13 mmol) and TFA (2.0 mL, 12.53 mmol) in CH_2Cl_2 (10 mL) gave the crude hydroxy pyrrolidines (495, 88%) as a yellow oil, which contained a 65:35 mixture of *syn*-**222** and *anti*-**222** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 65:35 mixture of the crude hydroxy pyrrolidines *syn*-**222** and *anti*-**222** (495 mg, 2.78 mmol), benzaldehyde (0.60 mL, 3.06 mmol), sodium triacetoxyborohydride (1.24 g, 5.56 mmol) and AcOH (0.05 mL, 0.56 mmol) in 1,2-dichloroethane (15 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**225** (230 mg, 27%) as a yellow oil and *N*-benzyl pyrrolidine *syn*-**225** (228 mg, 27%) as a yellow oil.

Lab book: chc/3/45A and chc/3/45C

Table 3.6, entry 10

Using general procedure D, a 60:40 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**208** and *anti*-**208** (465 mg, 1.67 mmol) and TFA (1.05 mL, 6.68 mmol) in CH_2Cl_2 (8 mL) gave the crude hydroxy pyrrolidines (297, 99%) as a yellow oil, which contained a 65:35 mixture of *syn*-**222** and *anti*-**222** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 60:40 mixture of the crude hydroxy pyrrolidines *syn*-**222** and *anti*-**222** (297 mg, 1.67 mmol), benzaldehyde (0.35 mL, 1.84 mmol), sodium cyanoborohydride (221 mg, 3.34 mmol) and AcOH (0.20 mL, 3.34 mmol) in 1,2-dichloroethane (12 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**225** (94 mg, 21%) as a yellow oil, R_F (97:3 CH_2Cl_2-MeOH) 0.2; IR (ATR) 3232 (OH), 2973, 2881, 2813, 1390, 1165, 1114, 927, 828, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (br d, J = 4.5 Hz, 2H, Ar), 7.27-7.19 (m, 7H, Ar), 4.73 (d, J = 3.0 Hz, 1H, OCH), 4.20 (br s, 1H, OH), 4.05 (d, J = 13.0 Hz, 1H, NCH_AH$_B$Ph), 3.43 (d, J = 13.0 Hz, 1H, NCH$_A$$H_B$Ph), 2.97 (ddd, J =9.0, 4.5, 4.5 Hz, 1H, NCH), 2.84 (ddd, J =

9.0, 6.0, 3.0 Hz, 1H, NCH), 2.28 (ddd, *J* = 9.0, 9.0, 9.0 Hz, 1H, NCH), 1.67-1.57 (m, 3H, CH), 1.40-1.17 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.9 (*ipso*-Ar), 149.6 (Ar), 138.4 (*ipso*-Ar), 128.9 (Ar), 128.6 (Ar), 127.5 (Ar), 120.8 (Ar), 69.3 (OCH), 68.5 (NCH), 58.3 (Ph*C*H_2N), 54.7 (CH_2N), 24.2 (CH_2), 23.3 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1648, found 269.1647 (+0.5 ppm error) and *N*-benzyl pyrrolidine *syn*-**225** (55 mg, 12%) as a yellow oil, , R_F (97:3 CH_2Cl_2-MeOH) 0.1, IR (ATR) 3220 (OH), 3035, 2961, 2875, 2807, 1411, 1060, 920, 827, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br d, *J* = 6.0 Hz, 2H, Ar), 7.34-7.20 (m, 7H, Ar), 4.44 (d, *J* = 4.5 Hz, 1H, OCH), 4.11 (br s, 1H, OH), 3.56 (d, *J* = 13.0 Hz, 1H, NC$H_A$$H_B$Ph), 3.34 (d, *J* = 13.0 Hz, 1H, NC$H_A$$H_B$Ph), 3.09 (ddd, *J* = 8.0, 4.5, 4.5 Hz, 1H, NCH), 2.99 (ddd, *J* = 9.5, 6.0, 4.5 Hz, 1H, NCH), 2.41 (ddd, *J* = 9.5, 9.5, 7.0 Hz, NCH), 2.09-1.99 (m, 1H, CH), 1.86-1.71 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.0 (*ipso*-Ar), 149.6 (Ar), 138.1 (*ipso*-Ar), 128.7 (Ar), 128.5 (Ar), 127.4 (Ar), 121.2 (Ar), 73.5 (OCH), 69.5 (NCH), 60.8 (PhCH_2N), 54.3 (CH_2N), 29.7 (CH_2), 24.1 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1648, found 269.1655 (–2.3 ppm error).

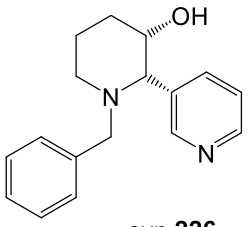
Lab book: chc/2/100B and chc/2/100D

Table 3.6, entry 11

Using general procedure D, a 60:40 mixture of *N*-Boc hydroxy pyrrolidines *syn*-**208** and *anti*-**208** (456 mg, 1.64 mmol) and TFA (1.10 mL, 6.56 mmol) in CH_2Cl_2 (8 mL) gave the crude hydroxy pyrrolidines (227, 78%) as a yellow oil, which contained a 65:35 mixture of *syn*-**222** and *anti*-**222** (by ^{1}H NMR spectroscopy). Then, using general procedure E, a 65:35 mixture of the crude hydroxy pyrrolidines *syn*-**222** and *anti*-**222** (227 mg, 1.28 mmol), benzaldehyde (0.26 mL, 1.41 mmol), sodium cyanoborohydride (169 mg, 2.56 mmol) and AcOH (0.24 mL, 3.84 mmol) in 1,2-dichloroethane (12 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**225** (38 mg, 9%) as a yellow oil and *N*-benzyl pyrrolidine *syn*-**225** (19 mg, 4%) as a yellow oil.

Lab book: chc/3/14E and chc/3/14F

syn-1-Benzyl-2-(pyridin-3-yl)piperidin-3-ol _syn_-226

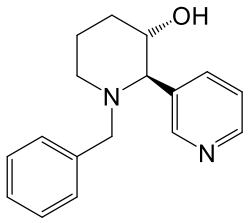


syn-**226**

Using general procedure F, *N*-benzyl pyrrolidine *syn*-**223** (86 mg, 0.32 mmol), trifluoroacetic anhydride (0.20 mL, 0.96 mmol), Et_3N (0.20 mL, 0.96 mmol) in THF (10 mL) and 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 CH_2Cl_2-EtOAc and then EtOAc as eluent gave 3-hydroxy piperidine *syn*-**226** (65 mg, 76%) as a yellow oil, R_F (EtOAc) 0.1; IR (ATR) 3277 (OH), 2924, 2858, 2804, 1422, 1134, 1028, 1015, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.5 Hz, 1H, Ar), 8.50 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar), 7.88 (br d, *J* = 8.0 Hz, 1H, Ar), 7.33-7.22 (m, 6H, Ar), 3.75 (d, *J* = 14.0 Hz, 1H, NCH_AH_BPh), 3.74 (br s, 1H, OCH), 3.39 (d, *J* = 1.5 Hz, 1H, NCH), 3.01 (br d, *J* = 11.5 Hz, 1H, NCH), 2.91 (d, *J* = 14.0 Hz, 1H, NCH_AH_BPh), 2.67 (br s, 1H, OH), 2.08-1.99 (m, 2H, CH), 1.93 (ddddd, *J* = 13.5, 13.5, 13.5, 4.0, 4.0 Hz, 1H, CH), 1.66 (dddd, *J* = 13.5, 13.5, 2.5, 2.5 Hz, 1H, CH), 1.56-1.53 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.9 (Ar), 148.9 (Ar), 138.5 (*ipso*-Ar), 136.8 (*ipso*-Ar), 136.4 (Ar), 128.7 (Ar), 128.4 (Ar), 127.1 (Ar), 123.4 (Ar), 70.2 (OCH or NCH), 69.8 (OCH or NCH), 59.5 (PhCH_2N), 53.4 (NCH_2), 31.7 (CH_2), 19.8 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1652, found 269.1648 (–1.4 ppm error).

Lab book: chc/2/94A.

***anti*- 1-Benzyl-2-(pyridin-3-yl)piperidin-3-ol *anti*-226**

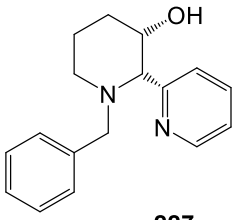


anti-**226**

Using general procedure F, *N*-benzyl pyrrolidine *anti*-**223** (123 mg, 0.46 mmol), trifluoroacetic anhydride (0.25 mL, 1.38 mmol), Et_3N (0.25 mL, 1.38 mmol) in THF (10 mL) and 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave 3-hydroxy piperidine *anti*-**226** (98 mg, 79%) as a yellow oil, R_F (EtOAc) 0.1; IR (ATR) 3164 (OH), 2931, 2854, 2792, 1429, 1253, 1110, 964, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H, Ar), 8.25 (d, *J* = 3.5 Hz, 1H, Ar), 7.85 (br d, *J* = 8.0 Hz, 1H, Ar), 7.28-7.18 (m, 6H, Ar), 3.65 (ddd, *J* = 11.5, 9.0, 5.0 Hz, 1H, OCH), 3.58 (d, *J* = 13.5 Hz, 1H, PhCH_AH_BN), 3.25 (br s, 1H, OH), 2.99 (d, *J* = 9.0 Hz, 1H, NCH), 2.92 (br d, *J* = 12.5 Hz, 1H, NCH), 2.88 (d, *J* = 13.5 Hz, 1H, PhCH_AH_BN), 2.17-2.13 (m, 1H, NCH), 1.97 (ddd, *J* = 11.5, 11.5, 3.5 Hz, 1H, CH), 1.71-1.63 (m, 2H, CH), 1.43 (dddd, *J* = 12.0, 12.0, 12.0, 5.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.5 (Ar), 148.8 (Ar), 139.0 (*ipso*-Ar), 137.7 (*ipso*-Ar), 136.5 (Ar), 128.5 (Ar), 128.3 (Ar), 126.9 (Ar), 123.8 (Ar), 73.7 (OCH or NCH), 73.6 (OCH or NCH), 59.5 (PhCH_2N), 52.5 (NCH_2), 33.3 (CH_2), 23.4 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1648, found 269.1651 (–1.1 ppm error).

Lab book: chc/2/93B

syn-1-Benzyl-2-(pyridin-2-yl)piperidin-3-ol _syn_-227

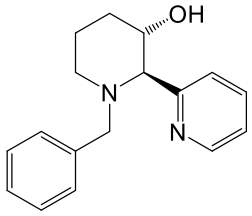


syn-**227**

Using general procedure F, *N*-benzyl pyrrolidine *syn*-**224** (159 mg, 0.59 mmol), trifluoroacetic anhydride (0.33 mL, 1.77 mmol), Et_3N (0.33 mL, 1.77 mmol) in THF (15 mL) and 20% $NaOH_{(aq)}$ (15 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 and 96:4 EtOAc-MeOH as eluent gave 3-hydroxy piperidine *syn*-**227** (72 mg, 46%) as a brown oil, R_F (95:5 EtOAc-MeOH) 0.3; IR (ATR) 3362 (OH), 3060, 3029, 2936, 2794, 1433, 1119, 1015, 749, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (br d, *J* = 5.5 Hz, 1H, Ar), 7.68 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H, Ar), 7.50 (d *J* = 7.5 Hz, 1H, Ar), 7.29-7.18 (m, 6H, Ar), 4.22 (br s, 1H, OH), 3.97 (br s, 1H, OCH), 3.70 (d, *J* = 14.0 Hz, 1H, NCH_AH_BPh), 3.56 (d, *J* = 2.0 Hz, 1H, NCH), 3.09 (d, *J* = 14.0 Hz, 1H, NCH_AH_BPh), 2.95 (dddd, *J* = 13.0, 3.5, 3.5, 1.5 Hz, 1H, NCH), 2.13 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.00-1.93 (m, 2H, CH), 1.67-1.62 (m, 1H, CH), 1.52-1.48 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.0 (*ipso*-Ar), 149.0 (Ar), 138.8 (*ipso*-Ar), 136.7 (Ar), 128.9 (Ar), 128.2 (Ar), 127.0 (Ar), 124.1 (Ar), 122.6 (Ar), 71.1 (OCH), 68.7 (NCH), 59.1 ($PhCH_2N$), 52.3 (NCH_2), 31.4 (CH_2), 19.8 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1648, found 269.1654 (–2.2 ppm error).

Lab book: chc/3/16D

***anti*-1-Benzyl-2-(pyridin-2-yl)piperidin-3-ol *anti*-227**

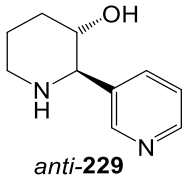


anti-**227**

Using general procedure F, *N*-benzyl pyrrolidine *anti*-**224** (168 mg, 0.63 mmol), trifluoroacetic anhydride (0.35 mL, 1.89 mmol), Et_3N (0.35 mL, 1.89 mmol) in THF (15 mL) and 20% $NaOH_{(aq)}$ (15 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-MeOH as eluent gave 3-hydroxy piperidine *anti*-**227** (116 mg, 69%) as a brown oil, R_F (95:5 CH_2Cl_2-MeOH) 0.3; IR (ATR) 3328 (OH), 2934, 2798, 1433, 1112, 1073, 969, 776, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (br d, *J* = 5.0 Hz, 1H, Ar), 7.71 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar), 7.67 (d, *J* = 8.0 Hz, 1H, Ar), 7.30-7.22 (m, 5H, Ar), 7.20 (ddd, *J* = 8.0, 5.0, 2.0 Hz, 1H, Ar), 3.75 (ddd, *J* = 11.0, 9.0, 4.5 Hz, 1H, OCH), 3.60 (d, *J* = 14.0 Hz, 1H, NC$H_A$$H_B$Ph), 3.23 (d, *J* = 9.0 Hz, 1H, NCH), 3.04 (br s, 1H, OH), 3.02 (d, *J* = 14.0 Hz, 1H, NC$H_A$$H_B$Ph), 2.93 (ddd, *J* = 12.0, 3.0, 3.0 Hz, 1H, NCH), 2.19-2.13 (m, 1H, NCH), 2.06-1.99 (m, 1H, NCH), 1.70-1.64 (m, 2H, CH), 1.49-1.39 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.0 (*ipso*-Ar), 148.9 (Ar), 138.9 (*ipso*-Ar), 137.1 (Ar), 128.6 (Ar), 128.2 (Ar), 126.8 (Ar), 122.8 (Ar), 122.6 (Ar), 75.9 (OCH), 73.0 (NCH), 59.3 ($PhCH_2N$), 52.0 (NCH_2), 33.3 (CH_2), 23.0 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1648, found 269.1655 (–2.5 ppm error).

Lab book: chc/3/9A

***anti*-2-(Pyridin-3-yl)piperidin-3-ol *anti*-229**

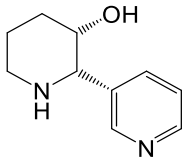


anti-**229**

$Pd(OH)_2/C$ (8 mg, 20 wt. %, 0.05 mmol.) and ammonium formate (96 mg, 1.50 mmol) were added to a stirred solution of *N*-benzyl hydroxy piperidine *anti*-**226** (40 mg, 0.15 mmol) in EtOH (10 mL) under Ar. The resulting mixture was stirred and heated at reflux for 16 h. Then, the reaction mixture was allowed to cool to rt and the solids were removed by filtration through a plug of Celite® and washed with EtOH (15 mL). The filtrate was evaporated under reduced pressure to give hydroxy piperidine *anti*-**229** (25 mg, 92% yield) as a yellow oil, IR (ATR) 3266 (OH or NH), 3130 (OH or NH), 2923, 2852, 1422, 1169, 1098, 1078, 799, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 2.0 Hz, 1H, Ar), 8.41 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar), 7.75 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1H, Ar), 7.23 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar), 3.54 (ddd, *J* = 10.5, 9.0, 4.5 Hz, 1H, OCH), 3.36 (d, *J* = 9.0 Hz, 1H, NCH), 3.10-3.06 (m, 1H, CH), 2.70 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H, CH), 2.24-2.15 (m, 1H, CH), 1.82-1.77 (m, 1H, CH), 1.69 (ddddd, *J* = 13.0, 13.0, 13.0, 4.0, 4.0 Hz, 1H, CH), 1.51-1.43 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.9 (Ar), 149.1 (Ar), 137.6 (*ipso*-Ar), 135.7 (Ar), 123.6 (Ar), 72.7 (OCH), 67.1 (NCH), 46.8 (NCH_2), 33.9 (CH_2), 25.4 (CH_2); MS (ESI) *m/z* 179 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_2O$ $(M + H)^+$ 179.1179, found 179.1176 (+1.6 ppm error).

Lab book: chc/4/7crude

***syn*-2-(Pyridin-3-yl)piperidin-3-ol *syn*-229**



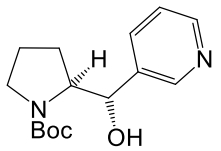
syn-**229**

$Pd(OH)_2/C$ (15 mg, 20 wt. %, 0.10 mmol.) and ammonium formate (144 mg, 2.28 mmol) were added to a stirred solution of *N*-benzyl hydroxy piperidine *syn*-**226** (40 mg, 0.15 mmol) in EtOH (10 mL) under Ar. The resulting mixture was stirred and heated at reflux for 16 h.

Then, the reaction mixture was allowed to cool to rt and the solids were removed by filtration through a plug of Celite® and washed with EtOH (15 mL). The filtrate was evaporated under reduced pressure to give hydroxy piperidine *syn*-**229** (22 mg, 82% yield) as a yellow oil, IR (ATR) 3235 (OH or NH), 2929, 2849, 1423, 1181, 1087, 997, 802, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H, Ar), 8.44 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar), 7.69 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar), 7.26-7.22 (m, 1H, Ar), 3.81 (s, 1H, OCH), 3.77 (s, 1H, NCH), 3.18 (dddd, *J* = 11.5, 2.0, 2.0, 2.0 Hz, 1H, NCH), 2.78 (ddd, *J* = 11.5, 11.5, 2.5 Hz, 1H, NCH), 2.01 (br d, *J* = 13.5 Hz, 1H, CH), 1.84 (dddd, *J* = 13.5, 13.5, 13.5, 3.5, 3.5 Hz, 1H, CH), 1.75-1.65 (m, 1H, CH), 1.50 (br d, *J* = 13.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.7 (Ar), 148.6 (Ar), 137.7 (*ipso*-Ar), 134.7 (Ar), 123.4 (Ar), 68.5 (OCH), 63.1 (NCH), 47.5 (NCH_2), 32.1 (CH_2), 19.8 (CH_2); MS (ESI) *m/z* 179 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_2O$ $(M + H)^+$ 179.1179, found 179.1178 (+0.6 ppm error).

Lab book: chc/4/8crude

tert-Butyl-2-(hydroxy(pyridine-3-yl)methyl)pyrrolidine-1-carboxylate _syn_-206



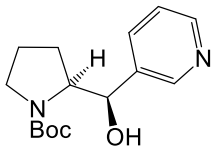
syn-**206**

Using general procedure G, palladium hydroxide on carbon (20 wt. %, 12 mg, 0.08 mmol), ammonium formate (145 mg, 2.30 mmol), *N*-benzyl hydroxy pyrrolidine *syn*-**223** (62 mg, 0.23 mmol) in EtOH (10 mL) and Boc_2O (55 mg, 0.25 mmol) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 50:50 CH_2Cl_2-MeCN as eluent gave *N*-Boc hydroxy pyrrolidine *syn*-**206** (26 mg, 41%) as a colourless oil, R_F (50:50 CH_2Cl_2-MeCN) 0.4; IR (ATR) 3332 (OH), 2974, 2931, 2886, 1687, 1668 (C=O), 1578, 1390, 1365, 1160, 1115, 772, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53-8.51 (m, 2H, Ar), 7.73 (d, *J* = 7.0 Hz, 1H, Ar), 7.28 (dd, *J* = 7.0, 5.0 Hz, 1H, Ar), 6.13 (br s, 1H, OH), 4.59 (d, *J* = 8.0 Hz, 1H, OCH), 4.08 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H, NCH), 3.48 (ddd, *J* = 7.5, 3.5, 3.5 Hz, 1H, NCH), 3.35-3.33 (m, 1H, NCH), 1.73-1.56 (m, 4H, CH), 1.50 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.3 (C=O), 149.3 (Ar), 149.0 (Ar), 138.1 (*ipso*-Ar), 134.8 (Ar), 123.7 (Ar), 81.2 (*C*Me_3), 76.9 (OCH), 64.1 (NCH), 47.9 (NCH_2), 28.8 (CH_2),

28.6 (C*Me*$_3$), 23.9 (CH_2); MS (ESI) *m/z* 279 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_2O_3$ $(M + H)^+$ 279.1703, found 279.1696 (+2.6 ppm error).

Lab book: chc/3/56A

tert-Butyl-2-(hydroxy(pyridine-3-yl)methyl)pyrrolidine-1-carboxylate _anti_-206

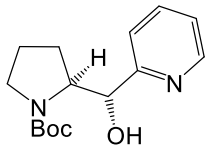


anti-**206**

Using general procedure G, palladium hydroxide on carbon (20 wt. %, 12 mg, 0.08 mmol), ammonium formate (217 mg, 3.45 mmol), *N*-benzyl hydroxy pyrrolidine *anti*-**223** (62 mg, 0.23 mmol) in EtOH (10 mL) and Boc_2O (55 mg, 0.25 mmol) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 50:50 CH_2Cl_2-MeCN as eluent gave *N*-Boc hydroxy pyrrolidine *anti*-**206** (24 mg, 37%) as a colourless oil, R_F (50:50 CH_2Cl_2-MeCN) 0.3; IR (ATR) 3332 (OH), 2973, 2926, 2878, 1668 (C=O), 1579, 1391, 1365, 1162, 1111, 771, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (80:20 mixture of rotamers) δ 8.55-8.49 (m, 2H, Ar), 7.71-7.63 (m, 1H, Ar), 7.27-7.24 (m, 1H, Ar), 5.95 (br s, 1H, OH), 5.16 (br s, 0.2H, OCH), 4.86 (br s, 0.8H, OCH), 4.33 (br s, 0.8H, NCH), 3.97 (br s, 0.2H, NCH), 3.54 (br s, 0.2H, NCH), 3.34-3.28 (m, 1H, NCH), 2.82-2.77 (m, 0.8H, NCH), 2.04-1.65 (m, 3H, CH), 1.49 (s, 9H, CMe_3), 1.20-1.08 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.6 (C=O), 148.9 (Ar), 148.6 (Ar), 136.8 (*ipso*-Ar), 134.9 (Ar), 123.3 (Ar), 80.9 (*C*Me$_3$), 75.2 (OCH), 63.2 (NCH), 48.0 (NCH_2), 28.6 (C*Me*$_3$), 27.7 (CH_2), 23.6 (CH_2); MS (ESI) *m/z* 279 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_2O_3$ $(M + H)^+$ 279.1703, found 279.1702 (+0.3 ppm error).

Lab book: chc/3/55A

tert-Butyl-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate _syn_-207

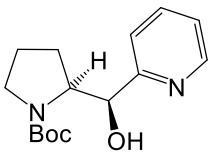


syn-**207**

Using general procedure G, palladium hydroxide on carbon (20 wt. %, 17 mg, 0.12 mmol), ammonium formate (107 mg, 1.70 mmol), *N*-benzyl hydroxy pyrrolidine *syn*-**224** (90 mg, 0.34 mmol) in EtOH (12 mL) and Boc_2O (81 mg, 0.37 mmol) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-MeOH as eluent gave *N*-Boc hydroxy pyrrolidine *syn*-**207** (64 mg, 68%) as a colourless oil, R_F (98:2 CH_2Cl_2-MeOH) 0.35; IR (ATR) 3384 (OH), 2974, 2931, 2882, 1687 (C=O), 1591, 1570, 1391, 1365, 1161, 1112, 1062, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 8.51 (br s, 1H, Ar), 7.65-7.63 (m, 1H, Ar), 7.42-7.40 (m, 0.6H, Ar), 7.18-7.12 (m, 1.4H, Ar), 5.76 (br s, 0.6H, OH), 5.05 (br s, 0.4H, OH), 4.87 (br s, 0.4H, OCH), 4.79 (br s, 0.6H, OCH), 4.19-4.14 (m, 1H, NCH), 3.35-3.25 (m, 1.6H, NCH), 2.95 (br s, 0.4H, NCH), 1.80 (br s, 1.6H, CH), 1.63 (br s, 2H, CH), 1.48 (s, 9H, CMe_3), 0.58 (br s, 0.4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.4 (*ipso*-Ar or C=O), 157.5 (*ipso*-Ar or C=O), 148.3 (Ar), 136.6 (Ar), 122.7 (Ar), 121.9 (Ar), 80.5 (CMe_3), 77.5 (OCH), 63.4 (NCH), 47.7 (NCH_2), 28.6 (CMe_3), 27.2 (CH_2), 23.9 (CH_2); MS (ESI) *m/z* 279 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_2O_3$ $(M + H)^+$ 279.1703, found 279.1694 (+3.5 ppm error).

Lab book: chc/3/54A

anti-tert-Butyl-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate _anti_-207



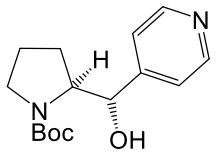
anti-**207**

Using general procedure G, palladium hydroxide on carbon (20 wt. %, 11 mg, 0.08 mmol), ammonium formate (69 mg, 1.10 mmol), *N*-benzyl hydroxy pyrrolidine *anti*-**224** (60 mg, 0.22 mmol) in EtOH (10 mL) and Boc_2O (53 mg, 0.24 mmol) gave the crude product as a

yellow oil. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-MeOH as eluent gave *N*-Boc hydroxy pyrrolidine *anti*-**207** (56 mg, 91%) as a colourless oil, R_F (98:2 CH_2Cl_2-MeOH) 0.3; IR (ATR) 3261 (OH), 2970, 2929, 2881, 1688 (C=O), 1593, 1569, 1394, 1365, 1162, 1100, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 8.53-8.50 (m, 1H, Ar), 7.65 (dd, *J* = 7.0, 7.0 Hz, 1H, Ar), 7.39 (d, *J* = 7.0 Hz, 0.65H, Ar), 7.22-7.16 (m, 1.35H, Ar), 5.15 (br s, 0.65H, OCH), 5.05 (br s, 0.35H, OCH), 4.64 (br s, 1H, OH), 4.19 (br s, 0.65H, NCH), 3.99 (br s, 0.35H, NCH), 3.55-3.29 (m, 1.35H, NCH), 3.14-3.08 (m, 0.65H, NCH), 2.02-1.59 (m, 4H, CH), 1.46 (s, 5.85H, CMe_3), 1.43 (s, 3.15H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 160.1 (*ipso*-Ar or C=O), 159.4 (*ipso*-Ar or C=O), 156.7 (*ipso*-Ar or C=O), 156.1 (*ipso*-Ar or C=O), 148.1 (Ar), 147.8 (Ar), 136.7 (Ar), 136.6 (Ar), 122.6 (Ar), 122.4 (Ar), 121.5 (Ar), 121.2 (Ar), 79.8 (*C*Me_3), 79.6 (*C*Me_3), 74.6 (OCH), 73.2 (OCH), 63.2 (NCH), 63.1 (NCH), 47.6 (NCH_2), 47.0 (NCH_2), 29.8 (CH_2), 28.7 (C*Me*$_3$), 28.3 (C*Me*$_3$), 25.8 (CH_2), 24.3 (CH_2), 23.7 (CH_2); MS (ESI) *m/z* 279 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_2O_3$ $(M + H)^+$ 279.1703, found 279.1692 (+4.2 ppm error).

Lab book: chc/3/52A

syn-tert-Butyl-2-(hydroxy(pyridin-4-yl)methyl)pyrrolidine-1-carboxylate _syn_-208



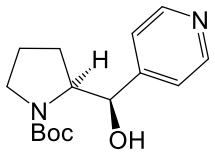
syn-**208**

Using general procedure G, palladium hydroxide on carbon (20 wt. %, 10 mg, 0.07 mmol), ammonium formate (60 mg, 0.95 mmol), *N*-benzyl hydroxy pyrrolidine *syn*-**225** (50 mg, 0.19 mmol) in EtOH (10 mL) and Boc_2O (98 mg, 0.42 mmol) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 50:50 CH_2Cl_2-MeCN as eluent gave *N*-Boc hydroxy pyrrolidine *syn*-**208** (18 mg, 35%) as a colourless oil, R_F (50:50 CH_2Cl_2-MeCN) 0.3; IR (ATR) 3345 (OH), 2974, 2934, 2881, 1672 (C=O), 1602, 1391, 1366, 1160, 1116, 1063, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (br s, 2H, Ar), 7.29 (d, *J* = 4.5 Hz, 2H, Ar), 5.71 (br s, 1H, OH), 4.55 (d, *J* = 7.0 Hz, 1H, OCH), 4.04 (ddd,

J = 7.0, 7.0, 4.0 Hz, 1H, NCH), 3.46 (ddd, *J* = 10.5, 7.5, 3.5 Hz, 1H, NCH), 3.32 (br s, 1H, NCH), 1.89-1.52 (m, 4H, CH), 1.51 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.7 (C=O), 151.5 (*ipso*-Ar), 149.7 (Ar), 149.3 (Ar), 122.6 (Ar), 122.5 (Ar), 81.2 (*C*Me_3), 77.8 (OCH), 63.7 (NCH), 47.9 (NCH_2), 28.6 (C*Me*$_3$), 23.9 (NCH_2); MS (ESI) *m/z* 301 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_2NaO_3$ $(M + H)^+$ 301.1523, found 301.1520 (+1.0 ppm error).

Lab book: chc/3/50A

anti-tert-Butyl-2-(hydroxy(pyridin-4-yl)methyl)pyrrolidine-1-carboxylate _anti_-208

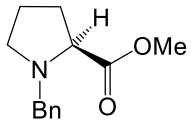


anti-**208**

Using general procedure G, palladium hydroxide on carbon (20 wt. %, 9 mg, 0.06 mmol), ammonium formate (54 mg, 0.85 mmol), *N*-benzyl hydroxy pyrrolidine *anti*-**225** (47 mg, 0.17 mmol) in EtOH (10 mL) and Boc_2O (41 mg, 0.19 mmol) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 40:60 CH_2Cl_2-MeCN as eluent gave *N*-Boc hydroxy pyrrolidine *anti*-**208** (24 mg, 50 %) as a colourless oil, R_F (40:60 CH_2Cl_2-MeCN) 0.4; IR (ATR) 3356 (OH), 2973, 2938, 2878, 1671 (C=O), 1602, 1391, 1365, 1162, 1112, 1064, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (80:20 mixture of rotamers) δ 8.53 (d, *J* = 4.5 Hz, 2H, Ar), 7.25 (br s, 2H, Ar), 5.59 (br s, 1H, OH), 5.16 (br s, 0.2H, OCH), 4.91 (br s, 0.8H, OCH), 4.26 (br s, 0.8H, NCH), 3.96 (br s, 0.2H, NCH), 3.57 (br s, 0.2H, NCH), 3.47 (br s, 1H, NCH), 2.86 (br s, 0.8H, NCH), 1.99-1.51 (m, 3H, CH), 1.50 (s, 9H, CMe_3), 1.49-1.33 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.1 (C=O), 150.7 (*ipso*-Ar), 149.8 (Ar), 149.5 (Ar), 122.2 (Ar), 121.0 (Ar), 80.8 (*C*Me_3), 75.4 (OCH), 63.2 (NCH), 48.0 (NCH_2), 28.5 (C*Me*$_3$), 27.3 (CH_2), 23.8 (CH_2); MS (ESI) *m/z* 279 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_2O_3$ $(M + H)^+$ 279.1703, found 279.1700 (+1.0 ppm error).

Lab book: chc/3/53A

(*S*)-Methyl 1-benzylpyrrolidine-2-carboxylate (*S*)-233

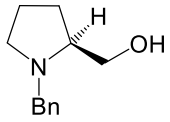


(*S*)-**233**

Acetyl chloride (1.90 mL, 26.07 mmol) was added to a stirred solution of (*S*)-proline (1.0 g, 8.69 mmol) in MeOH (20 mL) at rt under Ar. The resulting solution was stirred at rt for 15 h. Then, the solvent was evaporated under reduced pressure to give a colourless oil. MeCN (20 mL), benzyl bromide (1.30 mL, 10.43 mmol) and Et_3N (2.90 mL, 26.07 mmol) were added to the residue and the resulting suspension was stirred at rt for 12 h. Then, the solvent was evaporated under reduced pressure. Saturated $NH_4Cl_{(aq)}$ (50 mL) and Et_2O (50 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 92:8 hexane-EtOAc as eluent gave *N*-benzyl pyrrolidine (*S*)-**233** (1.21 g, 64%) as a colourless oil, $[\alpha]_D$ –82.8 (*c* 1.0 in $CHCl_3$) (lit.,[140] $[\alpha]_D$ –69.7 (*c* 1.05 in $CHCl_3$)); R_F (85:15 hexane-EtOAc) 0.2; IR (ATR) 2950, 2796, 1731 (C=O), 1434, 1196, 1169, 742, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H, Ph), 3.87 (d, *J* = 13.0 Hz, 1H, NCH_AH_BPh), 3.64 (s, 3H, OMe), 3.56 (d, *J* = 13.0 Hz, 1H, NCH_AH_BPh), 3.24 (dd, *J* = 9.0, 6.5 Hz, 1H, NCH), 3.08-3.03 (m, 1H, NCH), 2.38 (ddd, *J* = 9.0, 9.0, 9.0 Hz, 1H, CH), 2.18-2.07 (m, 1H, CH), 2.00-1.86 (m, 2H, CH), 1.84-1.73 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.7 (C=O), 138.4 (*ipso*-Ph), 129.4 (Ph), 128.3 (Ph), 127.2 (Ph), 65.4 (NCH), 58.9 (NCH_2Ph), 53.4 (NCH_2), 51.8 (OMe), 29.5 (CH_2), 23.0 (CH_2); MS (ESI) *m/z* 220 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}NO_2$ $(M + H)^+$ 220.1332, found 220.1336 (–2.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[140]

Lab book: chc/3/85B

(*S*)-(1-Benzylpyrrolidin-2-yl)methanol (*S*)-161

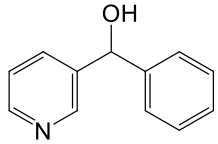


(*S*)-**161**

$LiAlH_4$ (382 mg, 10.04 mmol) was added to a stirred solution of *N*-benzyl ester (*S*)-**233** (2.0 g, 9.13 mmol) in THF (35 mL) at 0 ˚C under Ar. The resulting mixture was allowed to warm to rt and stirred at rt for 16 h. After cooling to 0 ˚C, 20% $NaOH_{(aq)}$ (30 mL) and Et_2O (30 mL) were added and the resulting mixture was stirred for 15 min. The solids were removed by filtration through Celite[@] and the filtrate was extracted wih Et_2O (3 × 30 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:1:1 CH_2Cl_2-EtOAc-MeOH as eluent gave *N*-benzyl hydroxy pyrrolidine (*S*)-**161** (1.01 g, 58%) as a colourless oil, R_F (3:1:1 CH_2Cl_2-EtOAc-MeOH) 0.3; IR (ATR) 3383 (OH), 2958, 2872, 2796, 1495, 1493, 1074, 1028, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H, Ph), 3.97 (d, *J* = 13.0 Hz, 1H, NC$H_A$$H_B$Ph), 3.66 (dd, *J* = 11.0, 3.5 Hz, 1H, OC$H_A$$H_B$), 3.43 (dd, *J* = 11.0, 2.5 Hz, 1H, OC$H_A$$H_B$), 3.36 (d, *J* = 13.0 Hz, 1H, NC$H_A$$H_B$Ph), 2.98 (ddd, *J* = 9.5, 6.0, 3.5 Hz, 1H, NCH), 2.89 (br s, 1H, OH), 2.77-2.72 (m, 1H, NCH), 2.30 (ddd, *J* = 9.5, 9.5, 8.0 Hz, 1H, NCH), 1.99-1.88 (m, 1H, CH), 1.86-1.80 (m, 1H, CH), 1.74-1.65 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.3 (*ipso*-Ph), 128.9 (Ph), 128.5 (Ph), 127.2 (Ph), 64.4 (NCH), 61.8 (OCH_2), 58.6 (NCH_2Ph), 54.6 (NCH_2), 27.9 (CH_2), 23.6 (CH_2); MS (ESI) *m/z* 192 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO$ $(M + H)^+$ 192.1383, found 192.1383 (+0.1 ppm error). Spectroscopic data are consistent with those reported in the literature.[141]

Lab book: chc/4/1B

Phenyl(pyridin-3-yl)methanol 234



234

Table 3.7, entry 1

n-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) was added dropwise to a stirred solution of 3-bromopyridine (316 mg, 2.0 mmol) in THF (14 mL) at −78 ˚C under Ar. The resulting solution was stirred at −78 ˚C for 30 min. Then, a solution of benzaldehyde (212 mg, 0.20 mL, 4.71 mmol) in THF (2 mL) was added dropwise at −78 ˚C and the resulting solution was allowed to warm to rt and stirred at rt for 2 h. Water (30 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave alcohol **234** (217 mg, 59%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.0 Hz, 1H, Ar), 8.20 (br d, *J* = 5.0 Hz, 1H, Ar), 7.66 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1H, Ar), 7.32-7.29 (m, 4H, Ar), 7.28-7.22 (m, 1H, Ar), 7.15 (dd, *J* = 8.0, 5.0 Hz), 5.75 (s, 1H, OCH), 5.43 (br s, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.9 (Ar), 147.8 (Ar), 143.5 (*ipso*-Ar), 140.3 (*ipso*-Ar), 134.7 (Ar), 128.6 (Ar), 127.8 (Ar), 126.6 (Ar), 123.6 (Ar), 73.6 (OCH). Spectroscopic data are consistent with those reported in the literature.[144]

Lab book: chc/3/66B

Table 3.7, entry 2

i-PrMgCl (1.0 mL of a 2.0 M solution in THF, 2.0 mmol) was added to a stirred solution of 3-bromopyridine (316 mg, 2.0 mmol) in THF (14 mL) at rt under Ar. The resulting solution was stirred at rt for 1 h. Then, benzaldehyde (212 mg, 0.20 mL, 2.0 mmol) was added and the resulting solution was stirred at rt for 2 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 4:1-1: 4 hexane-EtOAc as eluent gave alcohol **234** (240 mg, 65%) as a colourless oil.

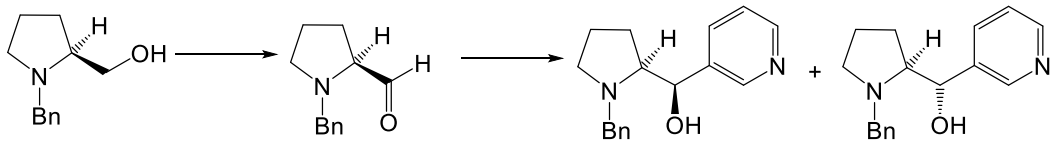
Lab book: chc/3/63B

Table 3.7, entry 3

i-PrMgCl•LiCl (1.65 mL of a 1.3 M solution in THF, 2.1 mmol) was added to a stirred solution of 3-bromopyridine (316 mg, 2.0 mmol) in THF (14 mL) at 0 ˚C under Ar. The resulting solution was stirred at 0 ˚C for 1 h. Then, benzaldehyde (223 mg, 0.25 mL, 2.1 mmol) was added at 0 ˚C and the resulting solution was allowed to warm to rt and stirred at rt for 1 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 3:7-4: 1 hexane-EtOAc as eluent gave alcohol **234** (227 mg, 61%) as a colourless oil.

Lab book: chc/3/64B

anti-and _syn_-1-Benzylpyrrolidin-2-yl)(pyridin-3-yl)methanol _anti_-and _syn_-223



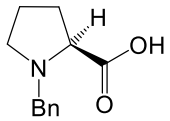
A solution of $(COCl)_2$ (0.14 mL, 1.58 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of DMSO (0.21 mL, 3.15 mmol) in CH_2Cl_2 (5 mL) at −78 ˚C under Ar. The resulting solution was stirred at −78 ˚C for 10 min and a solution of *N*-benzyl pyrrolidine alcohol (*S*)-**161** (200 mg, 1.05 mmol) in CH_2Cl_2 (10 mL) was added. The resulting solution was stirred at −78 ˚C for 20 min and Et_3N (0.60 mL, 4.20 mmol) was added. Then, the resulting solution was allowed to warm to 0 ˚C and stirred at 0 ˚C for 2 h. A 2:1 mixture of saturated $NH_4Cl_{(aq)}$ and 35% NH_3 (20 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give crude *N*-benzyl pyrrolidine aldehyde (*S*)-**230** which was used in the next step without further purification, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 4.0 Hz, 1H, CHO), 7.33-7.21 (m, 5H, Ph), 3.75 (d, *J* = 13.0 Hz, 1H, NCH_AH$_B$Ph), 3.64 (d, *J* = 13.0 Hz, 1H, NCH$_A$$H_B$Ph), 3.11-3.07 (m, 1H, NCH), 2.99-2.94 (m, 1H, NCH), 2.36 (ddd, *J* = 8.5, 8.5, 8.5 Hz, 1H, NCH), 2.00-1.78 (m, 4H, CH). The

^{1}H NMR spectroscopic data are consistent with those reported in the literature.[142] Attempted purification by flash chromatography led to compound decomposition.

n-BuLi (0.84 mL of a 2.5 M solution in hexanes, 2.10 mmol) was added dropwise to a stirred solution of 3-bromopyridine (332 mg, 2.10 mmol) in THF (10 mL) at −78 ˚C under Ar. The resulting yellow solution was stirred at −78 ˚C for 30 min. Then, a solution of crude aldehyde (*S*)-**230** in THF (5 mL) was added dropwise and the resulting solution was stirred at −78 ˚C for 10 min and allowed to warm to rt over 16 h. Water (20 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark brown oil which contained 60:40 *syn*-**223** and *anti*-**223**. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl hydroxy pyrrolidine *anti*-**223** (56 mg, 20%) as a brown oil and hydroxy pyrrolidine *syn*-**223** (41 mg, 15%) as a brown oil.

Lab book: chc/4/6C and chc/4/6E

(*S*)-1-Benzylpyrrolidine-2-carboxylic acid (*S*)-238



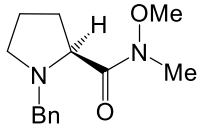
(*S*)-**238**

(*S*)-Proline (1.00 g, 8.69 mmol) was added to a stirred solution of KOH (1.46 g, 31.02 mmol) in *i*-PrOH (20 mL) at 40 ˚C under Ar. The suspension was stirred until the suspension became transparent. Then, benzyl chloride (1.15 mL, 10.0 mmol) was added dropwise to the resulting solution and the cloudy reaction mixture was stirred at 40 ˚C for 6 h. The resulting mixture was allowed to cool to 0 ˚C and 12 M $HCl_{(aq)}$ (2 mL) was added dropwise until the pH was 4-5. $CHCl_3$ (30 mL) was added and the suspension was stirred at rt for 18 h. The solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product. Purification by recrystallisation from acetone gave *N*-benzyl proline (*S*)-**238** (1.18 g, 66%) as a white solid, mp 155.158 ˚C (lit.,[148] mp 174-175 ˚C); $[\alpha]_D$ −27.6 (*c* 1.0 in EtOH) (lit.,[148] $[\alpha]_D$ −25.8 (*c* 1.0 in EtOH)); R_F (9:1 CH_2Cl_2-MeOH) 0.1; IR (ATR) 3352 (OH), 2992, 2822, 1649 (C=O), 1615, 1454, 1372, 1160, 751, 700, 484 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.45-7.41 (m, 2H, Ph), 7.39-7.36 (m, 3H, Ph), 4.33 (d, *J* = 13.0 Hz, NCH_AH_BPh), 4.16 (d, *J* = 13.0 Hz, NCH_AH_BPh), 3.80 (dd, *J* = 9.0, 6.0 Hz, NCH), 3.63 (ddd, *J* = 11.0, 7.5, 3.5 Hz, NCH), 2.87 (dd, *J* = 18.0, 9.0 Hz, NCH), 2.37-2.22 (m, 2H, CH), 2.05-1.88 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.3 (C=O), 131.4 (*ipso*-Ph), 130.5 (Ph), 129.6 (Ph), 129.3 (Ph), 67.5 (NCH), 58.1 (NCH_2Ph), 53.6 (NCH_2), 29.2 (CH_2), 23.2 (CH_2); MS (ESI) *m/z* 206 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_2$ $(M + H)^+$ 206.1176, found 206.1183 (–3.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[148]

Lab book: chc/3/28A

(*S*)-1-Benzyl-*N*-methoxy-*N*-methylpyrrolidine-2-carboxamide (*S*)-235



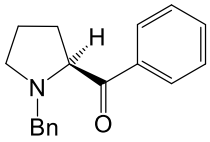
(*S*)-**235**

N,*O*-dimethylhydroxylamine hydrochloride (279 mg, 2.86 mmol) was added to a stirred solution of *N*-benzylproline (*S*)-**238** (553 mg, 2.60 mmol), *i*-Pr_2NEt (1.35 mL, 7.80 mmol) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred for 10 min. Then, T3P (2.48 g, of a 50% w/v solution in THF, 3.90 mmol) was added dropwise and the resulting solution was stirred at rt for 2 h. 1 M $HCl_{(aq)}$ (5 mL) was added to the resulting solution and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). 20% $NaOH_{(aq)}$ was added to the combined organics and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organics were washed with brine (10 mL), 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-MeOH as eluent gave *N*-benzyl Weinreb amide (*S*)-**235** (384 mg, 59%) as a colourless oil, $[\alpha]_D$ –141.8 (*c* 1.0 in $CHCl_3$); R_F (98:2 CH_2Cl_2-MeOH) 0.2; IR (ATR) 2962, 2870, 2800, 1662 (C=O), 1453, 1384, 1307, 1173, 997, 740, 699, 618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (m, 2H, Ph), 7.30-7.26 (m, 2H, Ph), 7.21 (tt, *J* = 7.5, 1.5 Hz, 1H, Ph), 3.92 (d, *J* = 13.0 Hz, 1H, NCH_AH_BPh), 3.63-3.57 (m, 1H, NCH), 3.54 (s, 3H, OMe), 3.54-3.52 (m, 1H, NCH_AH_BPh), 3.15 (s, 3H, NMe), 3.09 (ddd, *J* = 9.5, 6.0, 3.5 Hz, 1H, CH), 2.43 (ddd, *J* =

7.5, 7.5, 7.5 Hz, 1H, CH), 2.17-2.08 (m, 1H, CH), 1.94-1.76 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.9 (C=O), 138.7 (*ipso*-Ph), 129.4 (Ph), 128.2 (Ph), 127.1 (Ph), 62.1 (OMe), 61.3 (NCH), 58.0 (NCH_2Ph), 53.0 (NCH_2), 32.5 (NMe), 29.1 (CH_2), 23.0 (CH_2); MS (ESI) *m/z* 249 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}N_2O_2$ $(M + H)^+$ 249.1598, found 249.1611 (–5.5 ppm error). Spectroscopic data are consistent with those reported in the literature.[155]

Lab book: chc/3/29A

(*S*)-1-Benzylpyrrolidin-2-yl(phenyl)methanone (*S*)-239

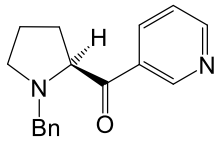


(*S*)-**239**

n-BuLi (0.85 mL of a 2.5 M solution in hexanes, 2.06 mmol) was added dropwise to a stirred solution of 3-bromobenzene (323 mg, 2.06 mmol) in THF (10 mL) at –78 ˚C under Ar. The resulting yellow solution was stirred at –78 ˚C for 30 min. Then, a solution of *N*-benzyl Weinreb amide (*S*)-**235** (255 mg, 1.03 mmol) in THF (2 mL) was added dropwise and the resulting solution was stirred at –78 ˚C for 2 h and allowed to warm to rt over 16 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 98.5:1.5-98:2 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidinone (*S*)-**239** (41 mg, 15%) as a yellow oil, R_F (98:2 CH_2Cl_2-MeOH) 0.3; IR (ATR) 3054, 2948, 2867, 1714 (C=O), 1468, 1193, 915, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 2H, Ph), 7.61-7.54 (m, 1H, Ph), 7.49-7.41 (m, 2H, Ph), 7.33-7.21 (m, 5H, Ph), 4.25 (dd, *J* = 9.5, 6.5 Hz, 1H, NCH), 4.08 (d, *J* = 12.5 Hz, 1H, NCH_AH_BPh), 3.67 (d, *J* = 12.5 Hz, 1H, NCH_AH_BPh), 3.28-323 (m, 1H, NCH), 2.68 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 1H, NCH), 2.40-2.31 (m, 1H, CH), 2.04-1.88 (m, 3H, CH). The ^{1}H NMR spectroscopic data are consistent with those reported in the literature.[149] On standing at rt, this compound decomposed within 48 h, as shown by ^{1}H NMR spectroscopy.

Lab book: chc/3/73D

(*S*)-1-Benzylpyrrolidin-2-yl(pyridin-3-yl)methanone (*S*)-240

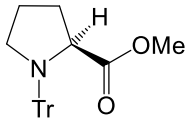


(*S*)-**240**

n-BuLi (0.90 mL of a 2.5 M solution in hexanes, 2.18 mmol) was added dropwise to a stirred solution of 3-bromopyridine (345 mg, 2.18 mmol) in THF (10 mL) at −78 ˚C under Ar. The resulting yellow solution was stirred at −78 ˚C for 30 min. Then, a solution of *N*-benzyl Weinreb amide (*S*)-**235** (271 mg, 1.09 mmol) in THF (2 mL) was added dropwise and the resulting solution was stirred at −78 ˚C for 2 h and allowed to warm to rt over 16 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidinone (*S*)-**240** (65 mg, 22%) as a yellow oil, R_F (98:2 CH_2Cl_2-MeOH) 0.3; IR (ATR) 2997, 2802, 1726 (C=O), 1477, 1189, 1106, 1084, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.27-9.26 (m, 1H, Ar), 8.73-8.71 (m, 1H, Ar), 8.26-8.23 (m, 1H, Ar), 7.37-7.33 (m, 1H, Ar), 7.21-7.16 (m, 5H, Ar), 3.85 (dd, *J* = 9.0, 7.0 Hz, 1H, NCH), 3.83 (d, *J* = 12.5 Hz, 1H, NC$H_A$$H_B$Ph), 3.51 (d, *J* = 12.5 Hz, 1H, NCH$_A$$H_B$Ph), 3.16 (ddd, *J* = 8.0, 8.0, 2.5 Hz, 1H, NCH), 2.43 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 1H, NCH), 2.31-2.23 (m, 1H, CH), 2.03-1.84 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.0 (C=O), 153.2 (Ar), 150.2 (Ar), 138.1 (*ipso*-Ar), 136.2 (Ar), 131.2 (*ipso*-Ar), 129.3 (Ar), 128.3 (Ar), 127.3 (Ar), 123.5 (Ar), 70.5 (NCH), 59.0 (NCH_2Ph), 53.7 (NCH_2), 29.7 (CH_2), 23.3 (CH_2); MS (ESI) *m/z* 267 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}N_2O$ $(M + H)^+$ 267.1492, found 267.1491 (+0.3 ppm error). On standing at rt, this compound decomposed within 24 h, as shown by ^1H NMR spectroscopy.

Lab book: chc/3/72C

(*S*)-Methyl-1-tritylpyrrolidine-2-carboxylate (*S*)-254

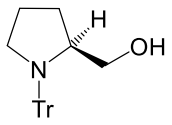


(*S*)-**254**

Thionyl chloride (7.25 mL, 100.0 mmol) was added to a solution of (*S*)-proline (5.8 g, 50.0 mmol) in MeOH (50 mL) at −10 ˚C under Ar. The resulting mixture was allowed to warm to rt and stirred at rt for 18 h. Then, the solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (60 mL). Et_3N (21.0 mL, 150.0 mmol) and trityl chloride (14.0 g, 50.0 mmol) were added and the resulting solution was stirred at rt for 18 h. A 2:1 mixture of saturated $NH_4Cl_{(aq)}$ and 35% $NH_{3(aq)}$ (60 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallization from Et_2O (40 mL) gave *N*-trityl pyrrolidine (*S*)-**254** (11.4 g, 62%) as a white solid, mp 45-48 ˚C (lit.,[ref] mp 55-56 ˚C); $[\alpha]_D$ −31.7 (*c* 1.0 in $CHCl_3$) (lit.,[ref] $[\alpha]_D$ −42.0 (*c* 2.70 in $CHCl_3$)); IR (ATR) 2992, 2970, 2951, 2875, 1733 (C=O), 1488, 1280, 1189, 1161, 774, 712, 628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.57 (m, 6H, Ph), 7.28-7.24 (m, 6H, Ph), 7.17 (tt, *J* = 8.5, 1.5 Hz, 3H, Ph), 3.91 (dd, *J* = 9.0, 2.5 Hz, 1H, NCH), 3.70 (s, 3H, OMe), 3.43 (ddd, *J* = 11.5, 8.0, 6.0 Hz, 1H, NCH), 2.86 (ddd, *J* = 11.5, 6.0, 6.0 Hz, 1H, NCH), 1.64-1.48 (m, 2H, CH), 1.08-0.91 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.3 (C=O), 144.8 (*ipso*-Ph), 129.4 (Ph), 127.8 (Ph), 126.3 (Ph), 77.5 (*C*Ph_3), 62.9 (NCH), 51.7 (OMe), 50.0 (NCH_2), 31.3 (CH_2), 24.4 (CH_2); MS (ESI) *m/z* 394 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}NO_2$ $(M + Na)^+$ 394.1778, found 394.1762 (+3.9 ppm error). Spectroscopic data are consistent with those reported in the literature.[150]

Lab book: chc/4/11A

(2*S*)-(1-Tritylpyrrolidin-2-yl)methanol (*S*)-255

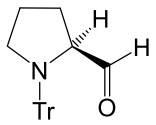


(*S*)-**255**

$LiAlH_4$ (571 mg, 15.1 mmol) was added to a stirred solution of *N*-tritylpyrrolidine ester (*S*)-**254** (7.0 g, 18.9 mmol) in THF (25 mL) at rt under Ar. The resulting mixture was stirred at rt for 2 h. Then, 20% $NaOH_{(aq)}$ (40 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash chromatography on silica with 85:15 hexane-EtOAc as eluent gave hydroxy *N*-trityl pyrrolidine (*S*)-**255** (4.59 g, 70%) as a colourless oil, $[\alpha]_D$ +35.8 (*c* 1.0 in $CHCl_3$) (lit.,[150] $[\alpha]_D$ +44.0 (*c* 2.20 in $CHCl_3$)); R_F (4:1 hexane-EtOAc) 0.3; IR (ATR) 3355 (OH), 3054, 2954, 2875, 1487, 1446, 1030, 900, 743, 706, 698 cm^{-1}; ^1H NMR (400, $CDCl_3$) δ 7.65 (dd, *J* = 8.0, 1.5 Hz, 6H, Ph), 7.33 (br t, *J* = 8.0 Hz, 6H, Ph), 7.24 (tt, *J* = 8.0, 1.5 Hz, 3H, Ph), 3.68 (dd, *J* = 10.0, 4.0 Hz, 1H, OC$H_A$$H_B$), 3.62 (dd, *J* = 10.0, 7.0 Hz, 1H, OC$H_A$$H_B$), 3.58-3.53 (m, 1H, NCH), 3.25 (ddd, *J* = 12.5, 8.0, 8.0 Hz, 1H, NC$H_A$$H_B$), 3.05 (ddd, *J* = 12.5, 8.5, 3.5 Hz, 1H, C$H_A$$H_B$N), 2.34 (br s, 1H, OH), 1.51-1.43 (m, 2H, CH), 1.07-1.01 (m, 1H, CH), 0.68-0.62 (m, 1H, CH); ^{13}C NMR (100.6, $CDCl_3$) δ 145.2 (*ipso*-Ph), 129.7 (Ph), 127.7 (Ph), 126.3 (Ph), 77.7 (*C*Ph_3), 65.9 (OCH_2), 61.2 (NCH), 51.1 (NCH_2), 29.3 (CH_2), 24.2 (CH_2); MS (ESI) *m/z* 366 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{24}H_{25}NO$ $(M + Na)^+$ 366.1828, found 366.1832 (–1.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[150]

Lab book: chc/4/13AA

(*S*)-1-Tritylpyrrolidine-2-carbaldehyde (*S*)-195

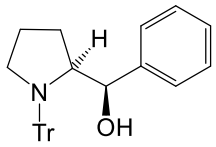


(*S*)-**195**

A solution of $(COCl)_2$ (1.20 mL, 13.73 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a stirred solution of DMSO (1.96 mL, 27.46 mmol) in CH_2Cl_2 (15 mL) at −78 ˚C under Ar. The resulting solution was stirred at −78 ˚C for 10 min and a solution of *N*-trityl pyrrolidine alcohol (*S*)-**255** (4.58 g, 13.33 mmol) in CH_2Cl_2 (20 mL) was added. The resulting solution was stirred at −78 ˚C for 1.5 h and Et_3N (7.73 mL, 54.92 mmol) was added. Then, the resulting solution was stirred at −78 ˚C for 1.5 h. A 2:1 mixture of saturated $NH_4Cl_{(aq)}$ and 35% $NH_{3(aq)}$ (20 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave *N*-trityl aldehyde (*S*)-**195** (2.15 g, 47%) as a white solid, mp 119-122 ˚C (lit.,[150] mp 140-141 ˚C); $[\alpha]_D$ −11.3 (*c* 1.0 in $CHCl_3$) (lit.,[ref] $[\alpha]_D$ −15.2 (*c* 2.54 in $CHCl_3$)); R_F (4:1 hexane-EtOAc) 0.7; IR (ATR) 3054, 3029, 2960, 1724 (C=O), 1594, 1487, 1446, 1177, 1031, 746, 707, 629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, *J* = 3.0 Hz, 1H, CHO), 7.55 (d, *J* = 7.5 Hz, 6H, Ph), 7.26 (d, *J* = 7.5 Hz, 6H, Ph), 7.17 (t, *J* = 7.5 Hz, 3H, Ph), 3.75 (ddd, *J* = 9.5, 3.0, 3.0 Hz, 1H, NCH), 3.27 (ddd, *J* = 11.5, 7.5, 7.5 Hz, 1H, NCH), 2.91 (ddd, *J* = 11.5, 5.5, 5.5 Hz, 1H, NCH), 1.64-1.54 (m, 1H, CH), 1.46-1.34 (m, 1H, CH), 1.16-1.07 (m, 1H, CH), 0.84-0.74 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.6 (C=O), 144.5 (*ipso*-Ph), 129.5 (Ph), 127.9 (Ph), 126.5 (Ph), 77.0 (*C*Ph_3), 68.6 (NCH), 50.7 (NCH_2), 28.1 (CH_2), 24.4 (CH_2); MS (ESI) *m/z* 364 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}NO$ $(M + H)^+$ 364.1672, found 364.1657 (+4.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[150]

Lab book: chc/4/15C

anti-Phenyl(1-tritylpyrrolidin-2-yl)methanol _anti_-256

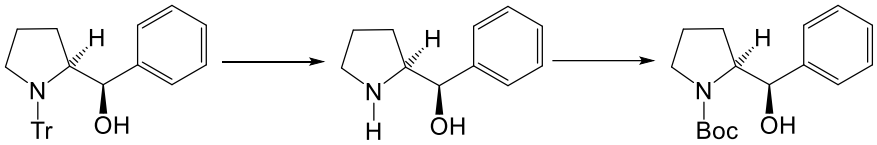


anti-**256**

PhMgBr (0.30 mL of a 3.0 M solution in Et_2O, 1.0 mmol) was added dropwise to a stirred solution of *N*-trityl aldehyde (*S*)-**195** (170 mg, 0.50 mmol) in Et_2O (5 mL) at −78 ˚C under Ar. The resulting yellow solution was allowed to warm to rt over 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) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil which contained a >98:2 mixture of *anti*-**256** and *syn*-**256** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-trityl pyrrolidine *anti*-**256** (200 mg, 95%) as a white solid, mp 67-69 ˚C (lit.,[150] mp 71-72 ˚C); $[\alpha]_D$ −56.4 (*c* 1.0 in $CHCl_3$) (lit.[150] $[\alpha]_D$ −77.8 (*c* 2.29 in $CHCl_3$)), R_F (9:1 hexane-EtOAc) 0.3; IR (ATR) 3327 (OH), 3024, 2941, 1452, 1296, 1163, 1017, 712, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (m, 5H, Ph), 7.30-7.13 (m, 13H, Ph), 7.06 (d, *J* = 7.5 Hz, 2H, Ph), 3.71 (ddd, *J* = 8.5, 5.5, 3.5 Hz, 1H, NCH), 3.30-3.23 (m, 2H, OCH and NCH), 3.03 (ddd, *J* = 12.0, 8.5, 4.0 Hz, 1H, NCH), 1.41 (dddd, *J* = 11.0, 8.5, 8.5, 3.0 Hz, 1H, CH), 1.33-1.23 (m, 1H, CH), 0.78 (dddd, *J* = 13.0, 8.5, 8.5, 4.5 Hz, 1H, CH), 0.24-0.12 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.7 (*ipso*-Ph), 142.3 (*ipso*-Ph), 130.0 (Ph), 128.1 (Ph), 127.7 (Ph), 126.6 (Ph), 126.5 (Ph), 125.5 (Ph), 78.3 (*C*Ph_3), 75.6 (OCH), 66.1 (NCH), 53.5 (NCH_2), 25.9 (CH_2), 24.9 (CH_2); MS (ESI) *m/z* 420 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{30}H_{29}NO$ $(M + H)^+$ 420.2321, found 420.2322 (+2.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[150]

Lab book: chc/4/17B

***anti-tert*-Butyl 2-(hydroxy(phenyl)methyl)pyrrolidine-1-carboxylate *anti*-30**

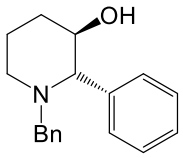


anti-**256** *anti*-**219** *anti*-**30**

Using general procedure H, *N*-trityl hydroxy pyrrolidine *anti*-**256** (300 mg, 0.72 mmol) and 5 M $HCl_{(aq)}$ (5 mL) in CH_2Cl_2 (2 mL) for 3 h gave the crude hydroxy pyrrolidine *anti*-**219** (172 mg) as a colourless oil. Then, Boc_2O (156 mg, 0.72 mmol) was added to a stirred solution of the crude hydroxy pyrrolidine in CH_2Cl_2 (7 mL) *anti*-**219** at 0 ˚C. The resulting solution was allowed to warm to rt and stirred for 16 h. Water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-MeOH as eluent gave *N*-trityl pyrrolidine *anti*-**30** (38 mg, 20%, 92:8 er) as a colourless oil. R_F (98:2 CH_2Cl_2-MeOH) 0.2; CSP-HPLC: Daicel Chiracel OD, 98:2 v/v hexane-*i*-PrOH, 1.0 mL min^{-1}, 10.8 min (1*R*,2*R*)-**30**, 14.9 min (1*S*,2*S*)-**30**.

Lab book reference: chc/4/70A

***anti*-1-Benzyl-2-phenylpiperidin-3-ol *anti*-172**

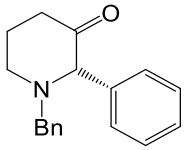


anti-**172**

Using general procedure J, *N*-benzyl pyrrolidine *anti*-**171** (130 mg, 0.49 mmol), trifluoroacetic anhydride (0.27 mL, 1.47 mmol), Et_3N (0.27 mL, 1.47 mmol) in THF (10 mL) and 20% $NaOH_{(aq)}$ (15 mL) gave the dark brown oil as a crude product as a dark brown oil. Purification by flash column chromatography on silica with 3:7 hexane-EtOAc as eluent gave 3-hydroxy piperidine *anti*-**172** (84 mg, 64%) as a yellow oil.

Lab book: chc/4/64A

1-Benzyl-2-phenylpiperidin-3-one (*S*)-173

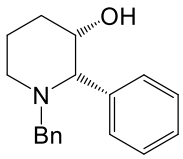


(*S*)-**173**

Dess-Martin periodinane (70 mg, 0.16 mmol) was added to a stirred solution of hydroxyl *N*-benzyl piperidine *anti*-**171** (40 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) at 0 ˚C under Ar. The resulting suspension was allowed to warm to rt and stirred at rt for 30 min. Then, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the resulting suspension was stirred for 16 h. CH_2Cl_2 (10 mL) was added to the resulting mixture and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave *N*-benzyl pyrrolidinone (*S*)-**173** (18 mg, 46%) as a white solid, mp 119-122 ˚C (lit.[156] mp 129-130 ˚C), $[\alpha]_D$ –2.5 (*c* 0.75 in CH_2Cl_2) (lit.,[156] $[\alpha]_D$ +7.0 (*c* 0.8 in CH_2Cl_2) for (*R*)-**173**); R_F (7:3 hexane-EtOAc) 0.55; IR (ATR) 2797, 1714 (C=O), 1493, 1153, 1132, 752, 738, 695, 550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.22 (m, 10H, Ph), 3.94 (s, 1H, NCH), 3.79 (d, *J* = 13.5 Hz, 1H, NC$H_A$$H_B$Ph), 3.21 (d, *J* = 13.5 Hz, 1H, NCH$_A$$H_B$Ph), 3.13 (ddd, *J* = 12.5, 4.5, 4.5 Hz, 1H, CH), 2.70 (ddd, *J* = 15.0, 6.0, 6.0 Hz, 1H, CH), 2.48-2.36 (m, 2H, CH), 2.10-1.95 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.2 (C=O), 138.6 (*ipso*-Ph), 137.6 (*ipso*-Ph), 128.9 (Ph), 128.8 (Ph), 128.7 (Ph), 128.4 (Ph), 128.0 (Ph), 127.2 (Ph), 77.9 (NCH), 59.4 (NCH_2Ph), 49.2 (NCH_2), 38.3 (CH_2), 23.5 (CH_2); MS (ESI) *m/z* 266 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO$ $(M + H)^+$ 266.1539, found 266.1540 (–0.3 ppm error). Spectroscopic data are consistent with those reported in the literature.[157]

Lab book: chc/4/65B

***syn*-1-Benzyl-2-phenylpiperidin-3-ol *syn*-172**

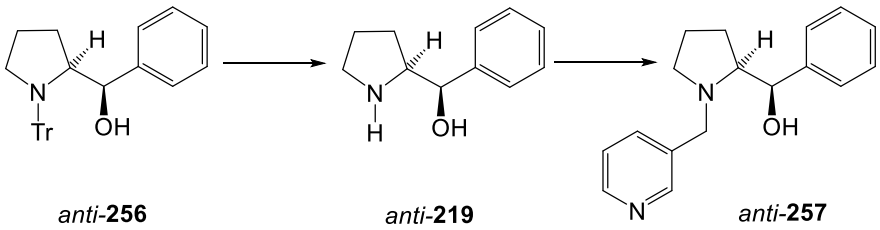


syn-**172**

L-Selectride (0.09 mL of a 1.0 M solution in THF, 0.09 mmol) was added to a solution of *N*-benzyl phenyl piperidinone (*S*)-**173** (15 mg, 0.06 mmol) in THF (2 mL) at −78 ˚C under Ar. The resulting solution was stirred at −78 for 1 h. Then, MeOH (5 mL) was added dropwise (caution: vigorous effervescence). 20% Rochelle's $salt_{(aq)}$ (10 mL) and Et_2O (10 mL) were added and the resulting mixture was allowed to warm to rt and stirred vigorously for 2 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were washed with water (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 hexane-EtOAc as eluent gave *N*-benzyl phenyl pyrrolidine *syn*-**172** (14 mg, 90%) as a yellow oil.

Lab book: chc/4/66B

***anti*-Phenyl(1-(pyridin-3-ylmethyl)pyrrolidin-2-yl)methanol *anti*-257**



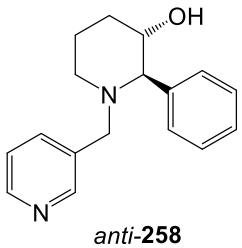
anti-**256** *anti*-**219** *anti*-**257**

Using general procedure H, *N*-trityl hydroxy pyrrolidine *anti*-**256** (280 mg, 0.67 mmol) and 5 M $HCl_{(aq)}$ (5 mL) in CH_2Cl_2 (2 mL) for 3 h gave the crude hydroxy pyrrolidine *anti*-**219** (188 mg) as a colourless oil. Then, using general procedure I, the crude hydroxy pyrrolidine *anti*-**219**, 3-pyridine carboxaldehyde (0.07 mL, 0.73 mmol), sodium triacetoxyborohydride (268 mg, 1.33 mmol) and AcOH (0.01 mL, 0.13 mmol) in 1,2-dichloroethane (10 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 99:1-95:5 CH_2Cl_2-MeOH as eluent gave *N*-trityl pyrrolidine *anti*-**257** (129 mg, 80% over 2 steps) as a yellow oil, R_F (95:5 CH_2Cl_2-MeOH) 0.4; IR (ATR) 3207 (OH), 2958,

2819, 1429, 1177, 1108, 1062, 728, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 1.0 Hz, 1H, Ar), 8.51 (dd, *J* = 4.5, 1.0 Hz, 1H, Ar), 7.67 (br d, *J* = 8.0 Hz, 1H, Ar), 7.38-7.21 (m, 6H, Ar), 4.90 (d, *J* = 3.5 Hz, 1H, OCH), 4.16 (d, *J* = 13.5 Hz, 1H, NCH_AH_BAr), 3.62 (br s, 1H, OH), 3.44 (d, *J* = 13.5 Hz, 1H, NCH_AH_BAr), 2.98 (ddd, *J* = 9.0, 4.5, 4.5 Hz, 1H, NCH), 2.90 (ddd, *J* = 9.0, 6.0, 3.5 Hz, 1H, NCH), 2.30 (ddd, *J* = 9.0, 9.0, 9.0 Hz, 1H, NCH), 1.77 (ddd, *J* = 13.5, 7.0, 6.5 Hz, 1H, CH), 1.66-1.59 (m, 2H, CH), 1.36 (dddd, *J* = 13.0, 9.0, 9.0, 9.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.1 (Ar), 148.8 (Ar), 141.3 (*ipso*-Ar), 136.5 (Ar), 134.3 (*ipso*-Ar), 128.2 (Ar), 127.0 (Ar), 125.6 (Ar), 123.5 (Ar), 70.4 (OCH), 69.5 (NCH), 55.6 (NCH_2Ar), 54.7 (NCH_2), 24.1 (CH_2), 23.2 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1529, found 269.1534 (–5.8 ppm error).

Lab book: chc/4/28C

anti-2-Phenyl-1-(pyridin-3-ylmethyl)piperidin-3-ol _anti_-258



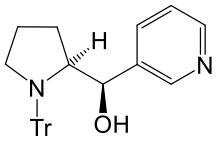
anti-**258**

Using general procedure J, *N*-pyridin-3-ylmethyl pyrrolidine *anti*-**257** (128 mg, 0.48 mmol), trifluoroacetic anhydride (0.26 mL, 1.44 mmol), Et_3N (0.26 mL, 1.44 mmol) in THF (12 mL) and 20% $NaOH_{(aq)}$ (12 mL) gave the crude product as a dark brown oil. Purification by flash column chromatography on silica with 3:7 hexane-EtOAc as eluent gave 3-hydroxy piperidine *anti*-**258** (70 mg, 54%) as a yellow oil, $[\alpha]_D$ −17.9 (*c* 1.0 in $CHCl_3$); R_F (3:7 hexane-EtOAc) 0.3; IR (ATR) 3160 (OH), 2938, 2783, 1445, 1261, 1096, 966, 760, 703, 540 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44-8.43 (m, 2H, Ar), 7.54 (br d, *J* = 7.5 Hz, 1H, Ar), 7.52 (br d, *J* = 7.0 Hz, 2H, Ar), 7.40 (t, *J* = 7.0 Hz, 2H, Ar), 7.32 (tt, *J* = 7.0, 1.5 Hz, 1H, Ar), 7.20 (dd, *J* = 7.5, 5.0 Hz, 1H, Ar), 3.65 (d, *J* = `14.0 Hz, 1H, NCH_AH_BAr), 3.64 (ddd, *J* = 8.5, 7.0, 5.0 Hz, 1H, OCH), 2.95 (d, *J* = 8.5 Hz, 1H, NCH), 2.90 (d, *J* = 14.0 Hz, 1H, NCH_AH_BAr), 2.85 (br d, *J* = 11.5 Hz, 1H, NCH), 2.15-2.11 (m, 1H, CH), 2.00 (ddd, *J* = 11.5, 11.5, 3.5 Hz, 1H, CH), 1.73-1.68 (m, 1H, CH), 1.62 (ddddd, *J* = 12.5, 12.5, 12.5, 3.5, 3.5 Hz, 1H, CH), 1.42 (dddd, *J* = 12.5, 12.5, 12.5, 5.0 Hz, 1H, CH); ^{13}C NMR (100.6

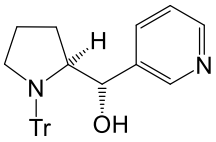
MHz, $CDCl_3$) δ 150.1 (Ar), 148.3 (Ar), 140.8 (*ipso*-Ar), 136.3 (Ar), 135.0 (*ipso*-Ar), 129.1 (Ar), 128.9 (Ar), 128.3 (Ar), 123.3 (Ar), 76.0 (OCH or NCH), 74.0 (OCH or NCH), 56.7 (NCH_2Ar), 52.6 (NCH_2), 32.5 (CH_2), 23.4 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N_2O$ $(M + H)^+$ 269.1648, found 269.1643 (+2.0 ppm error).

Lab book: chc/4/32B

anti- and _syn_-Pyridin-3-yl-1-tritylpyrrolidin-2-yl methanol _anti_- and _syn_-259



anti-**259**



syn-**259**

n-BuLi (1.33 mL of a 2.2 M solution in hexanes, 2.92 mmol) was added dropwise to a stirred solution of 3-bromopyridine (462 mg, 2.92 mmol) in Et_2O (15 mL) at −78 ˚C under Ar. The resulting yellow solution was stirred at −78 ˚C for 30 min. Then, a solution of *N*-trityl pyrrolidine aldehyde (*S*)-**195** (500 mg, 1.46 mmol) in Et_2O (10 mL) was added dropwise and the resulting solution was allowed to warm to rt over 16 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark brown oil. Purification by flash column chromatography on silica with 3:2 to 1:1 hexane-EtOAc as eluent gave *N*-trityl pyrrolidine *anti*-**259** (206 mg, 34%) as a colourless oil, $[\alpha]_D$ −38.9 (*c* 1.0 in $CHCl_3$); R_F (1:1 hexane-EtOAc) 0.45; IR (ATR) 3229 (OH), 3055, 2953, 1594, 1487, 1446, 1011, 744, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar), 8.24 (d, *J* = 1.5 Hz, 1H, Ar), 7.60-7.57 (m, 6H, Ar), 7.49 (ddd, *J* = 8.0, 1.5, 1.5 Hz, 1H, Ar), 7.31-7.17 (m, 10H, Ar), 5.10 (d, *J* = 3.5 Hz, 1H, OCH), 3.73 (ddd, *J* = 9.0, 5.5, 3.5 Hz, 1H, NCH), 3.43 (br s, 1H, OH), 3.27 (ddd, *J* = 12.0, 9.0, 7.0 Hz, 1H, NCH), 3.06 (ddd, *J* = 12.0, 9.0, 4.0 Hz, 1H, NCH), 1.42-1.24 (m, 2H, CH), 0.88-0.79 (m, 1H, CH), 0.26-0.13 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.1 (Ar), 147.7 (Ar), 144.5 (*ipso*-Ar), 137.6 (*ipso*-Ar), 133.3 (Ar), 130.0 (Ar), 127.8 (Ar), 126.6 (Ar), 123.2 (Ar), 78.2 (CPh_3), 73.9 (OCH), 65.9 (NCH), 53.6 (NCH_2), 26.1 (CH_2), 24.8 (CH_2); MS (ESI) 421 *m/z* [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{29}H_{28}N_2O$ $(M + H)^+$ 421.2274, found 421.2293 (−4.5 ppm error) and *N*-trityl pyrrolidine *syn*-**259** (77 mg, 12%)

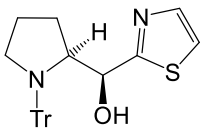
as a colourless oil, $[\alpha]_D$ –42.8 (*c* 1.0 in $CHCl_3$); R_F (1:1 hexane-EtOAc) 0.35; IR (ATR) 3228 (OH), 3065, 2924, 1592, 1486, 1447, 1060, 1026, 736, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.5 Hz, 1H, Ar), 8.50 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar), 7.74 (ddd, *J* = 8.0, 1.5, 1.5 Hz, 1H, Ar), 7.60-7.57 (m, 6H, Ar), 7.31-7.18 (m, 10H, Ar), 5.24 (br s, 1H, OH), 4.33 (d, *J* = 8.0 Hz, 1H, OCH), 3.70 (dd, *J* = 8.0, 8.0 Hz, 1H, NCH), 3.21-3.10 (m, 2H, CH), 1.36-1.27 (m, 1H, CH), 0.92-0.84 (m, 2H, CH), 0.59-0.52 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.2 (Ar), 149.0 (Ar), 145.1 (*ipso*-Ar), 138.4 (*ipso*-Ar), 135.0 (Ar), 129.9 (Ar), 127.8 (Ar), 126.7 (Ar), 123.6 (Ar), 78.0 (CPh_3), 73.6 (OCH), 67.4 (NCH), 49.7 (NCH_2), 28.2 (CH_2), 23.8 (CH_2); MS (ESI) 421 *m/z* [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{29}H_{28}N_2O$ $(M + H)^+$ 421.2274, found 421.2278 (–0.9 ppm error).

Lab book: chc/4/31D and chc/4/31E

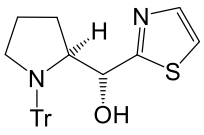
n-BuLi (1.22 mL of a 2.4 M solution in hexanes, 2.92 mmol) was added dropwise to a stirred solution of 3-bromopyridine (462 mg, 2.92 mmol) in THF (15 mL) at –78 ˚C under Ar. The resulting yellow solution was stirred at –78 ˚C for 30 min. Then, a solution of *N*-trityl pyrrolidine aldehyde (*S*)-**195** (500 mg, 1.46 mmol) in Et_2O (10 mL) was added dropwise and the resulting solution was allowed to warm to rt over 16 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark brown oil. Purification by flash column chromatography on silica with 1:1 then 2:3 hexane-EtOAc as eluent gave *N*-trityl pyrrolidine *anti*-**259** (250 mg, 41%) as a colourless oil and *N*-trityl pyrrolidine *syn*-**259** (54 mg, 9%) as a colourless oil.

Lab book: chc/4/37C and chc/4/37D

anti- and *syn*-Thiazol-2-yl(1-tritylpyrrolidin-2-yl)methanol *anti*- and *syn*-260



anti-**260**



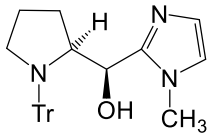
syn-**260**

n-BuLi (1.22 mL of a 2.4 M solution in hexanes, 2.92 mmol) was added dropwise to a stirred solution of 2-bromothiazole (479 mg, 2.92 mmol) in THF (15 mL) at –78 ˚C under Ar. The resulting yellow solution was stirred at –78 ˚C for 30 min. Then, a solution of *N*-trityl

aldehyde (*S*)-**195** (500 mg, 1.46 mmol) in Et_2O (10 mL) was added dropwise and the resulting solution was allowed to warm to rt over 16 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark brown oil which contained a 60:40 mixture of *anti*-**260** and *syn*-**260** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave *N*-trityl pyrrolidine *anti*-**260** (192 mg, 31%) as a colourless oil, $[\alpha]_D$ –2.7 (*c* 1.0 in $CHCl_3$); R_F (4:1 hexane-EtOAc) 0.4; IR (ATR) 3316 (OH), 3059, 2950, 2874, 1488, 1446, 1106, 904, 743, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 3.5 Hz, 1H, Ar), 7.59 (br d, *J* = 7.5 Hz, 6H, Ar), 7.30-7.25 (m, 6H, Ar), 7.21-7.17 (m, 4H, Ar), 5.25 (d, *J* = 4.5 Hz, 1H, OCH), 4.31 (br s, 1H, OH), 4.08 (ddd, *J* = 9.5, 4.5, 4.5 Hz, 1H, NCH), 3.27 (ddd, *J* = 12.0, 9.0, 6.5 Hz, 1H, NCH), 3.06 (d, *J* = 12.0, 8.0, 3.5, 1H, NCH), 1.35-1.20 (m, 2H, CH), 1.04-0.92 (m, 1H, CH), 0.28-0.16 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.7 (*ipso*-Ar), 144.4 (*ipso*-Ar), 142.6 (Ar), 129.8 (Ar), 127.8 (Ar), 126.6 (Ar), 118.1 (Ar), 78.3 (*C*Ph_3), 74.5 (OCH), 64.7 (NCH), 53.3 (NCH_2), 27.1 (CH_2), 24.7 (CH_2); MS (ESI) *m/z* 449 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}N_2OS$ (M + Na)$^+$ 449.1658, found 449.1643 (+3.5 ppm error) and *N*-trityl pyrrolidine *syn*-**260** (134 mg, 21%) as a colourless oil, $[\alpha]_D$ –1.7 (*c* 1.0 in $CHCl_3$); R_F (4:1 hexane-EtOAc) 0.3; IR (ATR) 3175 (OH), 3082, 2946, 1486, 1446, 1005, 906, 707, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 3.5 Hz, 1H, Ar), 7.56 (br d, *J* = 7.5 Hz, 6H, Ar), 7.31 (d, *J* = 3.5 Hz, 1H, Ar), 7.25 (t, *J* = 7.5 Hz, 6H, Ar), 7.20-7.15 (m, 3H, Ar), 5.54 (br s, 1H, OH), 4.76 (d, *J* = 7.5 Hz, 1H, OCH), 3.88 (ddd, *J* = 7.5, 7.5, 1.5 Hz, NCH), 3.13-3.00 (m, 2H, NCH), 1.64 (dddd, *J* = 13.5, 9.0, 4.0, 1.5 Hz, 1H, CH), 1.30-1.21 (m, 1H, CH), 1.03-0.96 (m, 1H, CH), 0.65-0.53 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.2 (*ipso*-Ar), 144.9 (*ipso*-Ar), 142.1 (Ar), 129.8 (Ar), 127.8 (Ar), 126.6 (Ar), 119.3 (Ar), 78.1 (*C*Ph_3), 73.8 (OCH), 65.9 (NCH), 50.5 (NCH_2), 29.1 (CH_2), 23.7 (CH_2); MS (ESI) *m/z* 449 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}N_2OS$ (M + Na)$^+$ 449.1658, found 449.1642 (+3.3 ppm error).

Lab book: chc/4/39C and chc/4/39D

anti-1-Methyl-1H-imidazol-2-yl(1-tritylpyrrolidin-2-yl)methanol _anti_-261

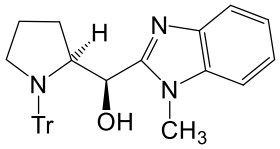


anti-**261**

n-BuLi (1.22 mL of a 2.4 M solution in hexanes, 2.92 mmol) was added dropwise to a stirred solution of 1-methyl imidazole (240 mg, 2.92 mmol) in THF (15 mL) at −78 ˚C under Ar. The resulting yellow solution was stirred at −78 ˚C for 30 min. Then, a solution of *N*-trityl aldehyde (*S*)-**195** (500 mg, 1.46 mmol) in Et_2O (10 mL) was added dropwise and the resulting solution was allowed to warm to rt over 16 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil which contained a >98:2 mixture of *anti*-**261** and *syn*-**261** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 6:2:2 hexane-EtOAc-acetone as eluent gave *N*-trityl pyrrolidine *anti*-**261** (467 mg, 76%) as a colourless oil, $[\alpha]_D$ −54.3 (*c* 1.0 in $CHCl_3$); R_F (6:2:2 hexane-EtOAc-acetone) 0.3; IR (ATR) 3055 (OH), 2950, 2877, 1488, 1446, 1011, 743, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (br d, *J* = 7.5 Hz, 6H, Ar), 7.26 (t, *J* = 7.0 Hz, 6H, Ar), 7.17 (tt, *J* = 7.5, 2.0 Hz, 3H, Ar), 6.89 (d, *J* = 1.5 Hz, 1H, Ar), 6.71 (d, *J* = 1.5 Hz, 1H, Ar), 5.26 (d, *J* = 2.5 Hz, 1H, OCH), 3.63 (ddd, *J* = 9.0, 3.5, 3.5 Hz, 1H, NCH), 3.47 (ddd, *J* = 12.5, 9.0, 9.0 Hz, 1H, NCH), 3.06 (s, 3H, NMe), 3.09-3.03 (m, 1H, NCH), 1.64-1.57 (m, 1H, CH), 1.43-1.38 (m, 1H, CH), 0.88-0.77 (m, 1H, CH), 0.33-0.24 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.6 (*ipso*-Ar), 145.1 (*ipso*-Ar), 129.8 (Ar), 127.7 (Ar), 126.9 (Ar), 126.2 (Ar), 121.5 (Ar), 78.1 (*C*Ph_3), 71.5 (OCH), 64.2 (NCH), 52.3 (NCH_2), 32.3 (NMe), 25.2 (CH_2), 25.0 (CH_2); MS (ESI) *m/z* 424 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{28}H_{29}N_3O$ $(M + H)^+$ 424.2383, found 424.2389 (–1.3 ppm error).

Lab book: chc/4/43A

anti-(1-Methyl-1H-benzo[d]imidazol-2-yl)(1-tritylpyrrolidin-2-yl)methanol _anti_-262

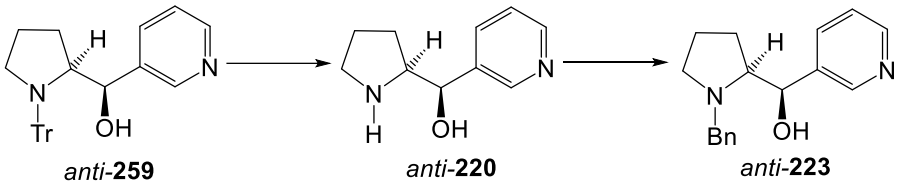


anti-**262**

n-BuLi (1.22 mL of a 2.4 M solution in hexanes, 2.92 mmol) was added dropwise to a stirred solution of 1-methyl benzimidazole (386 mg, 2.92 mmol) in THF (15 mL) at −78 ˚C under Ar. The resulting yellow solution was stirred at −78 ˚C for 30 min. Then, a solution of *N*-trityl aldehyde (*S*)-**195** (500 mg, 1.46 mmol) in Et_2O (10 mL) was added dropwise and the resulting solution was allowed to warm to rt over 16 h. Water (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as dark brown oil which contained a >98:2 mixture of *anti*-**262** and *syn*-**262** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 3:2 hexane-EtOAc as eluent gave *N*-trityl pyrrolidine *anti*-**262** (386 mg, 56%) as a colourless oil, $[\alpha]_D$ −21.4 (*c* 1.0 in $CHCl_3$); R_F (3:2 hexane-EtOAc) 0.4; IR (ATR) 3380 (OH), 3057, 2943, 2869, 1446, 1236, 1010, 901, 741, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 6H, Ar), 7.30-7.17 (m, 13H, Ar), 5.51 (br s, 1H, OCH), 4.04 (br s, 1H, OH), 3.81 (br s, 1H, NCH), 3.60-3.54 (m, 1H, NCH), 3.11 (br s, 4H, NMe and CH), 1.68 (br s, 1H, CH), 1.48 (br s, 1H, CH), 0.73 (br s, 1H, CH), 0.39-0.27 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.4 (*ipso*-Ar), 145.0 (*ipso*-Ar), 141.8 (*ipso*-Ar), 136.4 (*ipso*-Ar), 129.9 (Ar), 127.8 (Ar), 126.4 (Ar), 122.6 (Ar), 122.2 (Ar), 119.5 (Ar), 109.2 (Ar), 77.5 (*C*Ph_3), 71.8 (OCH), 64.3 (NCH), 52.5 (NCH_2), 29.4 (NMe), 25.4 (CH_2), 25.0 (CH_2); MS (ESI) *m/z* 496 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{32}H_{31}N_3O$ $(M + Na)^+$ 496.2359, found 496.2331 (+5.7 ppm error).

Lab book: chc/4/44A

anti-1-Benzylpyrrolidin-2-yl)(pyridin-3-yl)methanol _anti_-223

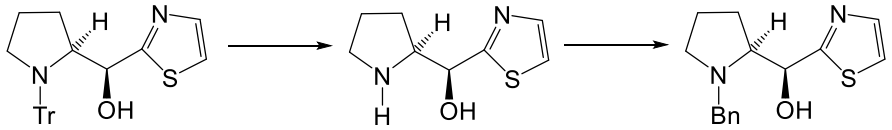


anti-**259** *anti*-**220** *anti*-**223**

Using general procedure H, *N*-trityl hydroxy pyrrolidine *anti*-**259** (200 mg, 0.48 mmol) and 5 M $HCl_{(aq)}$ (2 mL) in CH_2Cl_2 (2 mL) gave crude hydroxy pyrrolidine *anti*-**220** (338 mg) as a yellow oil. Then, using general procedure I, the crude hydroxy pyrrolidine *anti*-**220**, benzaldehyde (0.11 mL, 0.53 mmol), sodium triacetoxyborohydride (214 mg, 0.96 mmol) and AcOH (0.01 mL, 0.10 mmol) in 1,2-dichloroethane (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**223** (67 mg, 52%) as a colourless oil, $[\alpha]_D$ −78.4 (*c* 1.0 in $CHCl_3$).

Lab book: chc/4/48A

anti-1-Benzylpyrrolidin-2-yl(thiazol-2-yl)methanol _anti_-267



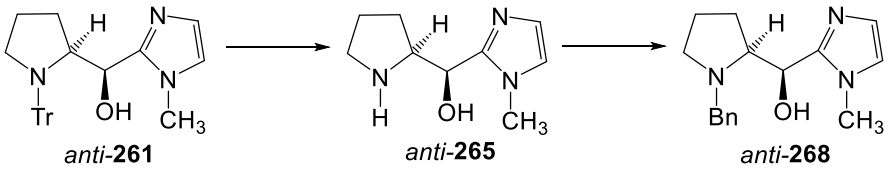
anti-**260** *anti*-**264** *anti*-**267**

Using general procedure H, *N*-trityl hydroxy pyrrolidine *anti*-**260** (200 mg, 0.47 mmol) and 5 M $HCl_{(aq)}$ (2 mL) in CH_2Cl_2 (2 mL) for 4 h gave the crude hydroxy pyrrolidine *anti*-**264** (167 mg) as a yellow oil. Then, using general procedure I, the crude hydroxy pyrrolidine *anti*-**264**, benzaldehyde (0.11 mL, 0.53 mmol), sodium triacetoxyborohydride (214 mg, 0.96 mmol) and AcOH (0.01 mL, 0.10 mmol) in 1,2-dichloroethane (5 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-MeOH as eluent gave *N*-benzyl pyrrolidine *anti*-**267** (62 mg, 48% over 2 steps) as a colourless oil, $[\alpha]_D$ −28.6 (*c* 1.0 in $CHCl_3$); R_F (98:2 CH_2Cl_2-MeOH) 0.25; IR (ATR) 3326 (OH), 3034, 2871, 2804, 1452, 1106, 1025, 731, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 3.5 Hz, 1H, Ar), 7.37-7.32 (m, 4H, Ar), 7.30-7.26 (m, 1H, Ar), 7.27 (d, *J* = 3.5 Hz, 1H, Ar), 5.13 (d, *J* = 3.5 Hz, 1H, OCH), 4.15 (d, *J* = 13.5 Hz, 1H, NCH_AH_BPh), 3.81

(br s, 1H, OH), 3.53 (d, J = 13.5 Hz, 1H, NCH_AH_BPh), 3.33-3.29 (m, 1H, NCH), 3.08-3.03 (m, 1H, NCH), 2.39 (ddd, J = 9.5, 9.5, 9.5 Hz, NCH), 1.73-1.62 (m, 3H, CH), 1.57-1.48 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (*ipso*-Ar), 142.7 (Ar), 138.6 (*ipso*-Ar), 128.9 (Ar), 128.6 (Ar), 127.5 (Ar), 118.3 (Ar), 70.2 (OCH), 67.8 (NCH), 58.4 (NCH_2Ph), 54.6 (NCH_2), 24.6 (CH_2), 23.5 (CH_2); MS (ESI) *m/z* 269 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{18}N_2OS$ $(M + H)^+$ 275.1213, found 275.1223 (–3.8 ppm error).

Lab book: chc/4/52C

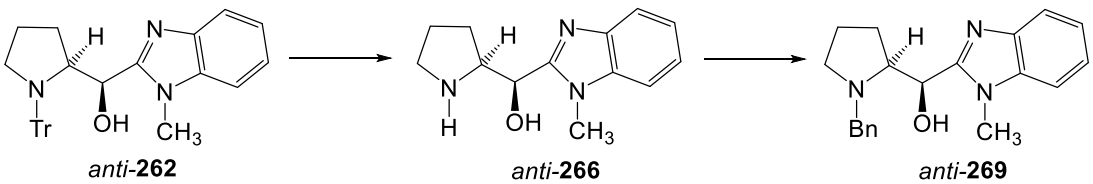
anti-1-Benzylpyrrolidin-2-yl)(1-methyl-1H-imidazol-2-yl)methanol _anti_-268



Using general procedure H, *N*-trityl hydroxy pyrrolidine *anti*-**261** (200 mg, 0.47 mmol) and 5 M $HCl_{(aq)}$ (2 mL) in CH_2Cl_2 (2 mL) for 4 h gave the crude hydroxy pyrrolidine *anti*-**265** (147 mg) as a yellow oil. Then, using general procedure I, the crude hydroxy pyrrolidine *anti*-**265**, benzaldehyde (0.11 mL, 0.53 mmol), sodium triacetoxyborohydride (214 mg, 0.96 mmol) and AcOH (0.01 mL, 0.10 mmol) in 1,2-dichloroethane (5 mL) gave the crude as a yellow oil, which contained none of alcohol *anti*-**268** (by ^1H NMR spectroscopy).

Lab book: chc/4/50

anti-1-Benzylpyrrolidin-2-yl(1-methyl-1H-benzo[d]imidazol-2-yl)methanol _anti_-269

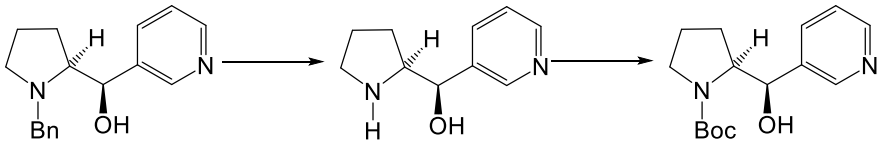


Using general procedure H, *N*-trityl hydroxy pyrrolidine *anti*-**262** (200 mg, 0.42 mmol) and 5 M $HCl_{(aq)}$ (2 mL) in CH_2Cl_2 (2 mL) for 4 h gave the crude hydroxy pyrrolidine *anti*-**266** (338 mg) as a yellow oil. Then, using general procedure I, the crude hydroxy pyrrolidine *anti*-**266**, benzaldehyde (0.10 mL, 0.46 mmol), sodium triacetoxyborohydride (188 mg, 0.84

mmol) and AcOH (0.01 mL, 0.08 mmol) in 1,2-dichloroethane (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 91:9 hexane-EtOAc as eluent gave *N*-benzyl pyrrolidine *anti*-**269** (93 mg, 68%) as a colourless oil, $[\alpha]_D$ –1.2 (*c* 1.0 in $CHCl_3$); R_F (9:1 hexane-EtOAc) 0.2; IR (ATR) 3277 (OH), 3055, 2897, 2802, 1475, 1072, 907, 745, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.74 (m, 1H, Ar), 7.32-7.22 (m, 8H, Ar), 4.97 (d, *J* = 4.5 Hz, 1H, OCH), 4.25 (br s, 1H, OH), 3.88 (d, *J* = 13.5 Hz, 1H, NCH_AH_BPh), 3.81 (s, 3H, NMe), 3.49 (d, *J* = 13.5 Hz, 1H, NCH_AH_BPh), 3.39 (ddd, *J* = 9.5, 4.5, 4.5 Hz, 1H, NCH), 3.06 (d, *J* = 9.5, 4.0, 4.0 Hz, 1H, NCH), 2.41 (ddd, *J* = 9.5, 9.5, 9.5 Hz, 1H, CH), 2.13-2.03 (m, 1H, CH), 2.01-1.93 (m, 1H, CH), 1.79-1.71 (m, 1H, CH) ; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.0 (*ipso*-Ar), 142.1 (*ipso*-Ar), 139.0 (*ipso*-Ar), 136.0 (*ipso*-Ar), 128.8 (Ar), 128.4 (Ar), 127.2 (Ar), 122.5 (Ar), 122.0 (Ar), 119.6 (Ar), 109.2 (Ar), 67.9 (OCH or NCH), 67.6 (OCH or NCH), 59.2 (NCH_2Ph), 54.9 (NCH_2), 30.7 (NMe), 26.6 (CH_2), 24.1 (CH_2); MS (ESI) *m/z* 322 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}N_2O$ $(M + H)^+$ 322.1914, found 322.1920 (–1.8 ppm error).

Lab book: chc/4/54B

anti-tert-Butyl 2-((*R*)-hydroxy(pyridin-3-yl)methyl)pyrrolidine-1-carboxylate _anti_-206



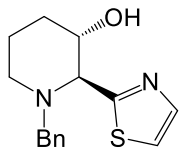
anti-**223** *anti*-**220** *anti*-**206**

Using general procedure H, *N*-benzyl hydroxy pyrrolidine *anti*-**223** (100 mg, 0.24 mmol) and 5 M $HCl_{(aq)}$ (5 mL) in CH_2Cl_2 (2 mL) for 6 h gave the crude hydroxy pyrrolidine *anti*-**220** (117 mg) as a colourless oil. Then, Boc_2O (52 mg, 0.24 mmol) was added to a stirred solution of the crude hydroxy pyrrolidine in CH_2Cl_2 (7 mL) *anti*-**220** at 0 ˚C. The resulting solution was allowed to warm to rt and stirred for 16 h. Water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 3:2 CH_2Cl_2-MeCN as eluent gave *N*-trityl pyrrolidine *anti*-**206** (15 mg, 22%, ≥90:10

er) as a colourless oil, R_F (3:2 CH_2Cl_2-MeCN) 0.2; CSP-HPLC: Daicel Chiracel IB, 97:3 v/v hexane-*i*-PrOH, 1.0 mL min^{-1}, 27.5 min (1*S*,2*R*)-**206**, 30.8 min (1*R*,2*S*)-**206**.

Lab book reference: chc/4/72A

anti-1-Benzyl-2-(thiazol-2-yl)piperidin-3-ol *anti*-270

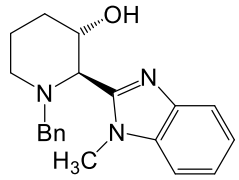


anti-**270**

Using general procedure J, *N*-benzyl pyrrolidine *anti*-**267** (55 mg, 0.20 mmol), trifluoroacetic anhydride (0.11 mL, 0.60 mmol), Et_3N (0.11 mL, 0.60 mmol) in THF (7 mL) and 20% $NaOH_{(aq)}$ (15 mL) gave the crude product as a dark brown oil. Purification by flash column chromatography on silica with 7:3-1:1 CH_2Cl_2-EtOAc as eluent gave 3-hydroxy piperidine *anti*-**270** (31 mg, 55%) as a yellow oil, $[\alpha]_D$ –4.6 (*c* 1.0 in $CHCl_3$); R_F (7:3 CH_2Cl_2-EtOAc) 0.15; IR (ATR) 3217 (OH), 3077, 2925, 2792, 1511, 1444, 1152, 1100, 742, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 3.5 Hz, 1H, Ar), 7.38 (d, *J* = 3.5 Hz, 1H, Ar), 7.35-7.22 (m, 5H, Ar), 3.85 (d, *J* = 13.5 Hz, 1H, NC$H_A$$H_B$Ph), 3.71-3.63 (m, 2H, OCH and NCH), 3.18 (d, *J* = 13.5 Hz, 1H, NC$H_A$$H_B$Ph), 2.95 (br d, *J* = 10.5 Hz, 1H, CH), 2.61 (br s, 1H, OH), 2.15 (dddd, *J* = 12.5, 3.5, 3.5, 3.5 Hz, 1H, CH), 2.12-2.04 (m, 1H, CH), 1.78-1.59 (m, 2H, CH), 1.47 (dddd, *J* = 12.5, 12.5, 12.5, 5.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.9 (*ipso*-Ar), 142.0 (Ar), 138.5 (*ipso*-Ar), 128.7 (Ar), 128.4 (Ar), 127.2 (Ar), 120.1 (Ar), 73.5 (OCH), 71.9 (NCH), 59.6 (NCH_2Ph), 51.6 (NCH_2), 32.0 (CH_2), 22.4 (CH_2); MS (ESI) *m/z* 275 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{18}N_2OS$ $(M + H)^+$ 275.1213, found 275.1209 (+1.2 ppm error)

Lab book: chc/4/57AA

anti-1-Benzyl-2-(1-methyl-1H-benzo[d]imidazol-2-yl)piperidin-3-ol _anti_-271



anti-**271**

Using general procedure J, *N*-benzyl pyrrolidine *anti*-**269** (90 mg, 0.28 mmol), trifluoroacetic anhydride (0.15 mL, 0.84 mmol), Et_3N (0.15 mL, 0.84 mmol) in THF (10 mL) and 20% $NaOH_{(aq)}$ (15 mL) gave the crude product as a dark brown oil. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-MeOH as eluent gave 3-hydroxy piperidine *anti*-**271** (56 mg, 63%) as a yellow oil, $[\alpha]_D$ −4.3 (*c* 1.0 in $CHCl_3$); R_F (98:2 CH_2Cl_2-MeOH) 0.5; IR (ATR) 3231 (OH), 2931, 2798, 1453, 1331, 1097, 1074, 742, 717, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-72 (m, 1H, Ar), 7.33-7.14 (m, 8H, Ar), 4.24-4.22 (m, 1H, OCH), 3.99 (s, 3H, NMe), 3.75 (d, *J* = 9.5 Hz, 1H, NCH), 3.63 (d, *J* = 13.5 Hz, 1H, NCH_AH_BPh), 3.39 (br s, 1H, OH), 3.26 (d, *J* = 13.5 Hz, 1H, NCH$_A$$H_B$Ph), 2.99 (br d, *J* = 12.0 Hz, 1H, NCH), 2.54-2.15 (m, 2H, CH), 1.78 (ddddd, *J* = 13.5, 13.5, 13.5, 3.5, 3.5 Hz, 1H, NCH), 1.67-1.64 (m, 1H, CH), 1.49 (dddd, *J* = 12.0, 12.0, 12.0, 3.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.9 (*ipso*-Ar), 142.1 (*ipso*-Ar), 138.4 (*ipso*-Ar), 136.3 (*ipso*-Ar), 128.6 (Ar), 128.3 (Ar), 127.0 (Ar), 122.8 (Ar), 122.3 (Ar), 119.6 (Ar), 109.4 (Ar), 68.6 (OCH and NCH), 57.3 (NCH_2Ph), 51.3 (NCH_2), 33.1 (CH_2), 30.6 (NMe), 22.0 (CH_2); MS (ESI) *m/z* 322 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}N_3O$ $(M + H)^+$ 322.1914, found 322.1920 (−1.9 ppm error).

Lab book: chc/4/60A

Abbreviations

$[\alpha]_D$	optical rotation
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
Boc	*t*-butoxycarbonyl
Bn	benzyl
br	broad
BSA	*N*,*O*-bis(trimethylsilyl)-acetamide
Bz	benzoyl
calcd	calculated
Cbz	carboxybenzyl
cm^{-1}	wavenumber
CSP	chiral stationary phase
d	doublet
dd	double doublet
ddd	double double doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCAD	di-(4-chlorobenzyl)azodicarboxylate
DCE	1,2-dichloroethane
DCM	dichloromethane

DIEA	*N*,*N*-diisopropylethylamine
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dd	double doublet
ddd	double double doublet
dddd	double double double doublet
ddddd	double double double double doublet
dr	diastereomeric ratio
dt	doublet of triplet
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
eq.	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
g	grams
h	hours

HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
IR	infra-red
J	coupling constant in Hz
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
m	meta
M	molar (mol dm^{-3})
m/z	mass to charge ratio
M^+	molecular ion
Me	methyl
MeCN	acetonitrile
mg	milligrams
min	minutes
mL	millilitre
mmol	millimole
mol%	percent by mole
MOM	methoxymethyl

mp	melting point
Ms	mesyl
MS	mass spectrometry
n	normal
NMR	nuclear magnetic resonance
o	ortho
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
PMDETA	*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
q	quartet
R	alkyl group
R_F	retention factor
rt	room temperature (18-25 ˚C)
s	*sec*, secondary
s	singlet
(−)-sp	(−)-sparteine
t	triplet
TBAI	tetrabutylammonium iodide

TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TfOH	trifluoromethanesulfonic acid
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TPP	triphenyl phosphine
Tr	trityl
Ts	tosyl
p-TsCl	*para*-toluenesulfonyl chloride
p-TsOH	*para*-toluenesulfonic acid
tt	triplet of triplets

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