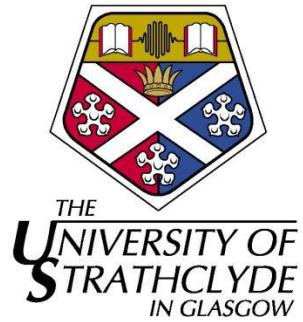
Probing the mechanism of diastereoselectivity of pseudoephedrine amide enolate alkylations

By Caroline Lory



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Abbreviations

Bn	Benzyl
Boc	*tert*-butoxycarbonyl
cat	Catalyst
Cbz	Carboxybenzyl
conc.	Concentrated
COD	1,5-Cyclooctadiene
^{t}Bu	*tert*-Butyl
DCM	Dichloromethane
de	Diastereomeric excess
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
ee	Enantiomeric excess
equiv.	Equivalent
HPMA	Hexamethylphosphoric triamide
^{i}Pr	Isopropyl
LDA	Lithium diisopropylamide
lk	like
Me	Methyl
NMR	Nuclear Magnetic Resonance

Ph	Phenyl
S_Ni	Substitution nucleophilic internal
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TRIBAL	Triisobutylaluminium

Summary

Pseudoephedrine was first used by Myers as a practical auxiliary for the asymmetric alkylation of amide enolates. The pseudoephedrine amide enolate intermediate is proposed by Myers *et al.* to adopt a staggered conformation that is supposed to be responsible for the high diastereoselectivity outcome. This reactive conformation involves a lithium alkoxide that is thought to create a steric screening which forces the attack onto one face. However, Procter and his group carried out several experiments on the alkylation using immobilized pseudoephedrine that may contradict the Myers' proposed mechanism. DFT calculations suggested that a π-cation interaction between the aromatic ring and the lithium cation may account for the diastereoselectivity of the alkylation. Modification of this interaction by either adding electron donating or withdrawing groups onto the aromatic ring was expected to respectively lead to higher or lower diastereoselectivity. Based on this last hypothesis, investigation of the mechanism of action of the pseudoephedrine chiral auxiliary by synthesising selected analogues of pseudoephedrine was the basis for this project. A route to synthesise analogues of pseudoephedrine involved the reduction/alkylation of protected L-alanine derivatives. This reaction necessitated much investigation to obtain analogues of pseudoephedrine amino alcohol bearing electron donating group in the aromatic ring. Five analogues of this type has been successfully synthesised with high diastereoselectivity.

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I. Introduction

A. Importance of asymmetric synthesis

The world around us is composed of chiral compounds. From the twenty amino acids that form proteins, excluding the achiral glycine, to the alkaloids and terpenes,[1] Nature offers a varied source of chiral material useful in asymmetric synthesis. Within nature, most of the macromolecules (DNA, polypeptides and carbohydrates…) are made up of building blocks in one specific enantiomeric form. Thus, the interaction between a chiral compound such as a drug and its chiral receptor is stereoselective. The other enantiomer can either be inactive, inhibit the activity of the other or possesses toxic biological effects.

The need for enantiomerically pure compounds is particularly true for pharmaceutical industries: there are many cases where chiral molecules have radically different bioactivities between two enantiomers. The interesting case of DOPA **1** (**Figure I.1**) illustrates the importance to introduce one of the enantiomer to the other. The decarboxylation of **1** gives the achiral dopamine that is active against Parkinson's disease, but this compound cannot cross the blood-brain barrier to reach the active site.[2] The prodrug **1** has the ability to do so and can be decarboxylated by the enzyme dopamine decarboxylase in a specific manner. Indeed, only the *S* form of DOPA can be decarboxylated by the enzyme, thus it is important to administer the right enantiomer of DOPA as the undesired enantiomeric form can be accumulated in the body and be metabolised by other enzymes.

There are a number of desirable reasons to produce enantiomerically pure compounds. For pharmaceutical companies, producing inert isomers is a waste of starting materials and resources. Inactive enantiomers are often not toxic. However, when they accumulate due to a lack of metabolism, they can cause toxic side effects. This perfectly highlights the need for an asymmetric synthetic approach to drug design.

The need for enantiopure bioactive drugs is of relevant importance in terms of pharmacodynamic, environmental and economic factors.[3] The demand for enantiomerically pure compounds is continuing to increase in the field of organic chemistry and asymmetric synthesis remains a real challenge for synthetic chemists.

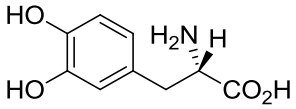

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Figure I.1

B. Various methods

The principle of asymmetric synthesis is to create one or more stereogenic centres within the substrate. This is carried out by the action of a chiral reagent, auxiliary or catalyst on heterotopic faces, atoms or groups within the substrate. This can be achieved in an enantioselective or diastereoselective way to form stereoisomers in unequal amounts. The goal is to form the desired stereoisomer in high proportions to maximize the enantioselectivity or diastereoselectivity. To quantify the ratio between the desired and the undesired enantiomers or diastereoisomers, one can measure the enantioselective or diastereoselective excess (ee or de) of the reaction.[4]

Nowadays, there are four known methods used to synthesis chiral non-racemic compounds:

- The "chiron" approach or first generation method directs the reaction in an intramolecular fashion. The formation of a new chiral centre is controlled by a stereogenic unit (G*) within the substrate and gives rise to diastereoselective reactions (**Figure I.2**).

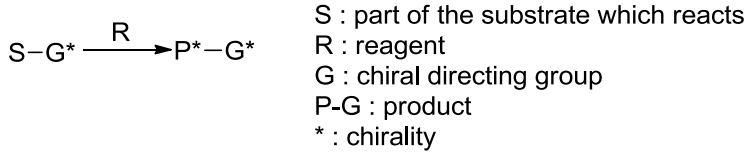


Figure I.2

An enantiomerically pure compound (referred to as a chiron) is needed and it represents the main drawback for this type of approach. Indeed, the chiral product is not formed from an achiral substrate but from an already enantiomerically pure starting material. The chiral starting materials are usually found in amino acids, carbohydrates, hydroxyl acids, terpenes and alkaloids.[5-7]

- The second generation method or auxiliary-controlled approach is similar to the "chiron" approach as the reaction is also directed in an intramolecular fashion. Here, an enantiomerically pure auxiliary (A*) is covalently attached to the substrate (S) and acts as directing group. An achiral reagent (R) is then introduced and the diastereoselective reaction gives rise to diastereoisomers in unequal amounts (**Figure I.3**). This procedure presents significant advantages because the substrate can be achiral. The chiral auxiliary can be removed and recycled with usually no racemisation and the undesired diastereoisomer can be removed by recrystallisation or chromatography.

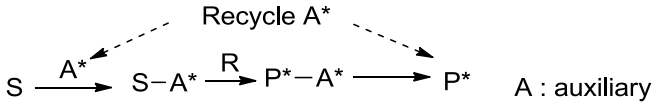


Figure I.3

- In the third generation or reagent-controlled methods, a chiral reagent (R*) converts an achiral substrate (S) into a chiral product (P*) using intermolecular control. Compared to the auxiliary approach, the two extra steps to attach and remove the auxiliary are avoided (**Figure I.4**). The control is intermolecular with enantioselective reactions but presently the range of reactions for which effective chiral reagents exist is limited.

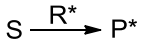


Figure I.4

- Fourth generation or catalyst-controlled methods are considered as the catalytic version of the third generation method. (**Figure I.5**). Instead of using a stoichiometric amount of an enantiomerically pure compound, only a catalytic amount is necessary. Despite the obvious advantages in terms of cost and recyclability, the purification of such reactions is a challenge because the products are enantiomers and hence difficult to separate. Although this approach is currently the subject of many investigations by academics and pharmaceutical companies, only a few catalysts give high enantiomeric excess on a wide range of substrates.

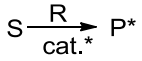


Figure I.5

Choosing the most appropriate method is key to synthesising compounds in high enantioselectivity, but when no general method can be assigned, the most reliable alternative is usually the auxiliary-controlled approach. The determination of the absolute configuration of the product is straightforward because it relies on the known configuration of the chiral auxiliary and may be determined by X-ray crystallography.[8, 9] The main drawback of this method is the two extra steps that are required to attach and remove the auxiliary. It can be similarly associated with the problem of protecting groups, thus the introduction of a chiral auxiliary in a synthesis must be high yielding. However, when a chiral auxiliary can be attached to a suitable functional group, it can sometimes act as protecting group and be used to shorten and optimize synthetic sequences. [10]

Some important requirements for chiral auxiliaries to be practically used are listed in **Table 1** but presently, only a few auxiliaries fulfill these demands.[11]

Requirements for chiral auxiliaries:
Enantiomerically pure
Available in both enantiomeric forms
Straightforward attachment to substrate
High and predictable control of stereoselectivity
Readily available and inexpensive
Purification of major diastereoisomer needs to be easy
Removal without loss of diastereoselectivity or enantioselectivity purity
Easily separated from product and recycled

Table 1 – Auxiliary features for high diastereocontrol

There are several factors that direct the attack onto one face of a double bond preferably over the other: steric effects certainly play an important role but also, metal cation chelation, hydrogen bonding and electrostatic interactions have an important role too. A transition state with many contacts between reacting partners is essential to obtain high diastereoselectivity.

The substrate that bears a chiral auxiliary can act either as a nucleophile, electrophile or be involved in concerted reactions. A range of asymmetric reactions using chiral auxiliaries is the topic of the following discussions.

C. Chiral azaenolates and enolates

The formation of new carbon-carbon bond is one of the more popular uses for a chiral auxiliary in asymmetric synthesis. The reaction of amide enolates, azaenolates and enolates through alkylation reactions is an important feature for C-C bond formation. The chiral auxiliary can be covalently attached to the C^1 of the enolate, to the *N* of the azaenolate or to the *N* of the amide (see **Figure I.6**).

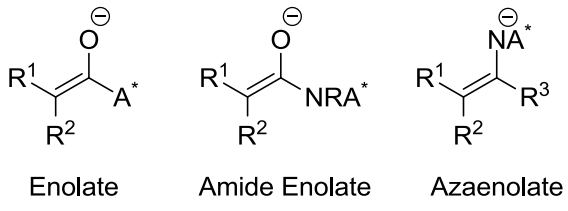


Figure I.6

1. Azaenolates: RAMP and SAMP

Developed by Enders and his group,[12] the hydrazine SAMP **2** derived from (*S*)-proline and its enantiomer RAMP **3**, are used for asymmetric alkylation of cyclic and acyclic ketones and aldehydes[13] (**Figure I.7**).

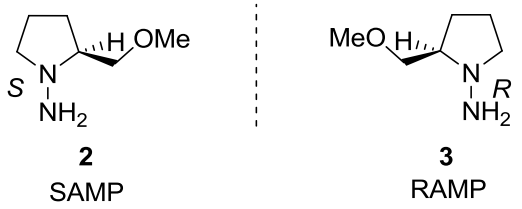


Figure I.7

In **Figure I.8**, the synthesis shows the excellent selectivity outcome for the conversion of 3-pentanone **4** into an ant alarm pheromone **8** using SAMP **2**.[13]

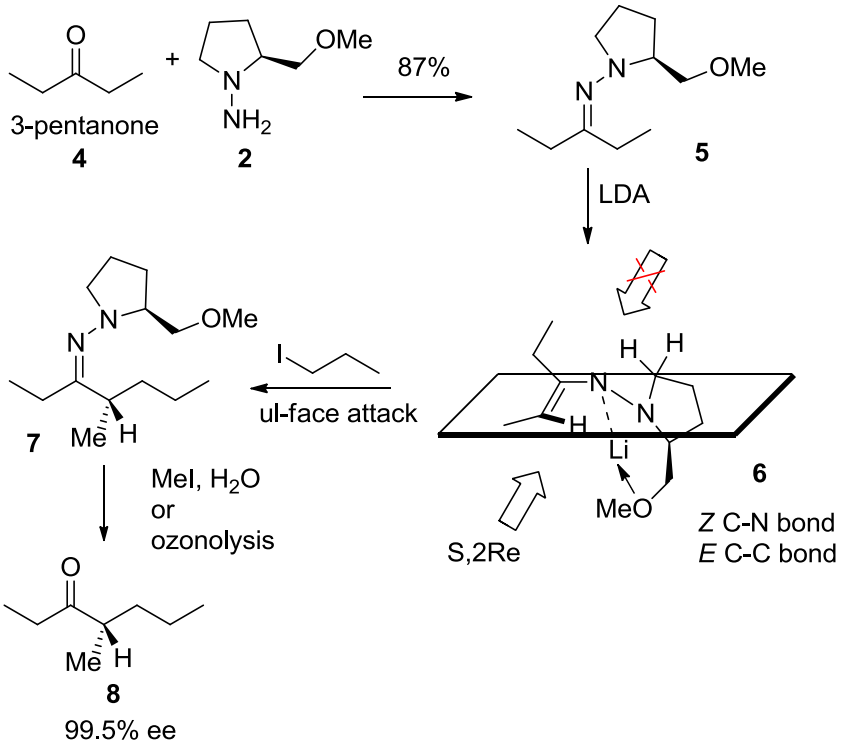


Figure I.8

In the mechanism proposed by Enders *et al.*, only the $E_{CC}Z_{CN}$ isomer of the azaenolate **6** is formed and the lithium ion is intramolecularly chelated to the

methoxy group.[12] The lithium coordinates the methoxy oxygen and below the C-C-N-N plane. The electrophile cannot attack the (*S*,2*Si*) face because of steric repulsion with the C-5 methylene of the auxiliary. The approach of the electrophile is then forced to approach from the opposite face (*S*,2*Re*). Removal of the auxiliary is done by methylation followed by acid hydrolysis or ozonolysis and usually no loss of stereochemical purity is observed.

2. Oxazolidinones

The Evans oxazolidinone methodology[14-16] may be the most widely used approach for aldol reactions and the synthesis of carboxylic acids substituted in the α-position with oxygen, nitrogen, and carbon (**Figure I.9**):

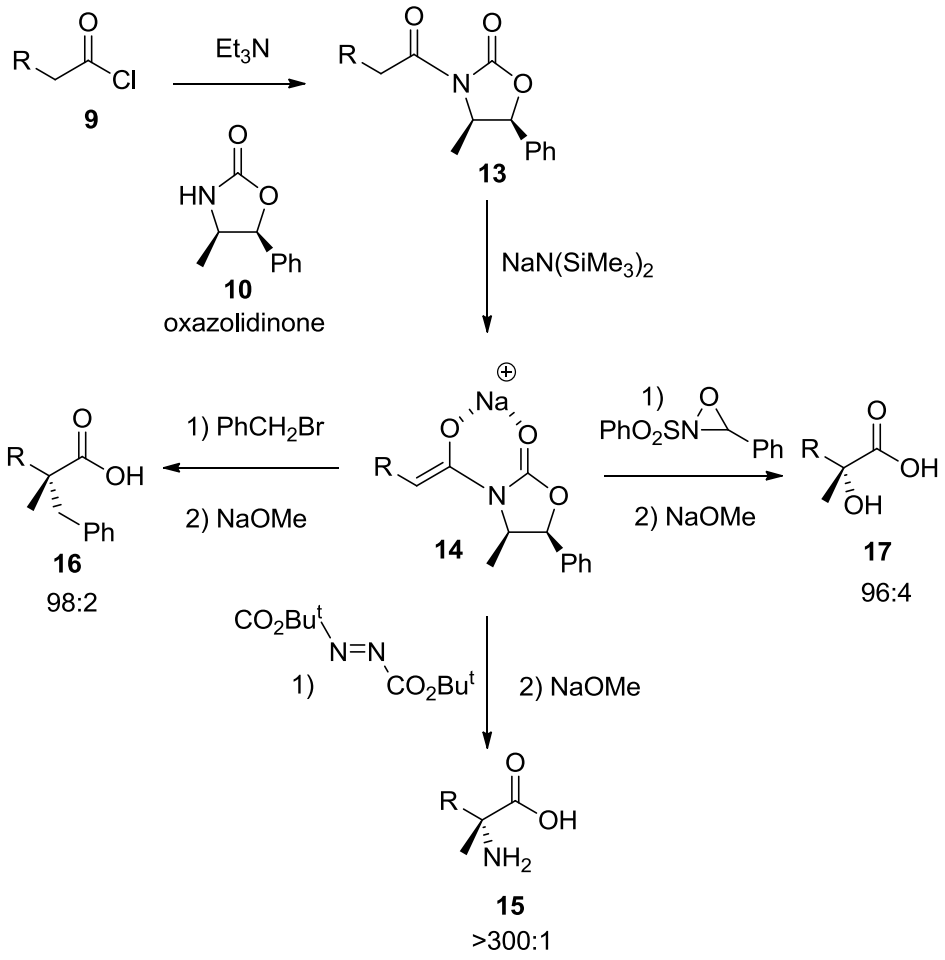
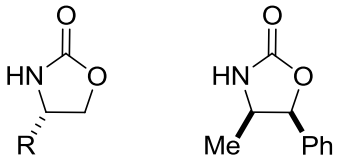


Figure I.9

The formation of the chelated *Z*-enolate **14** is caused by the deprotonation of the acylated oxazolidinone **13**. Indeed, the *Z*-enolate is formed because of repulsion between the enolate R group and the oxazolidinone ring and allows the electrophile to approach the face distant from the substituents of the oxazolidinone (methyl and phenyl group: the *Re* face in the example above **Figure I.9**). Removal of the auxiliary and purification can be done by hydrolysis, alcoholysis[17] or reduction. The main drawback of the Evans oxazolidinone is that it cannot be sufficiently used for non-activated alkyl halides and the removal of the auxiliary when the C-2 position is sterically hindered is difficult and cannot be done by hydrolysis.[18]

Evans' oxazolidinones can also be useful and highly effective for diastereoselective alkylations.[19] Oxazolidinone **10**, **11** and **12** (**Figure I.10**) can be prepared from amino acids including phenylalanine but usually they are derived from (*S*)-valine and (1*S*,2*R*)-norephedrine respectively.[14]



11 R = Bn
12 R = Pr^i

10

Figure I.10

When acylated oxazolidinones, e.g. **18** and **22** in **Figure I.11**, are treated with a base (usually LDA), chelate enolates are formed with a selectivity greater than 99:1 for the isomer **19** and **23** (**Figure I.11**). The chelation of the lithium to the carbonyl group of the oxazolidinone forms the rigid conformation of the enolate **19** and **23**. In this conformation, for the intermediate **23**, the *Re* face of the enolate is hindered by the isopropyl substituent so the attack proceeds through the *Si* face. Similar arguments predict that the oxazolidine intermediate **19** should direct alkylation to the *Re* face of the enolate.

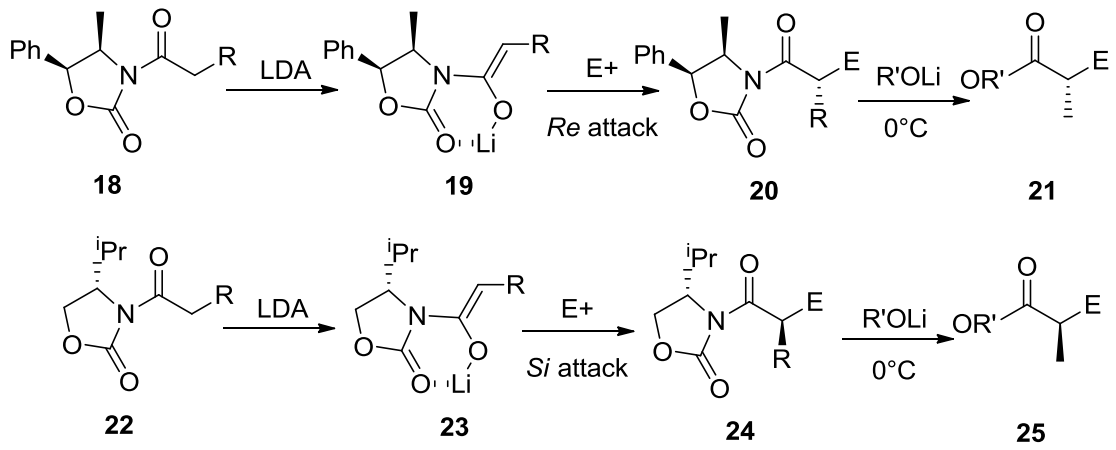


Figure I.11

Reaction with an electrophile such as activated alkyl halides (benzyl, allyl) gives both high selectivity (de > 90%) in good yield (**Table 2**, **entries 3**, **4**, **7** and **8**). However, when an unreactive halide (alkyl halide) is used, the selectivity is diminished and the yield is reduced (**Table 2**, **entries 1**, **5** and **6**).

Entry	Oxazolidinone	Electrophile	de of crude **20** or **24** (%)	Yield of **21** and **25** (%)
1	**18** (R=Me)	EtI	76	82
2	**22** (R=Me)	EtI	92	79
3	**18** (R=Me)	BnBr	96	78
4	**22** (R=Me)	BnBr	98	92
5	**18** (R=Et)	MeI	74	82
6	**22** (R=Et)	MeI	80	79
7	**18** (R=Me)	CH_2=$CHCH_2Br$	96	75
8	**22** (R=Me)	CH_2=$CHCH_2Br$	96	71

Table 2 – diastereoselectivity outcome for the alkylation of enolates using oxazolidinones 18 and 22

Another approach developed by Myers involves pseudoephedrine as a practical chiral auxiliary to introduce a new C-C bond, diastereoselectively, but this will be discussed later (see part **I.F.**)

D. Asymmetric aldol reactions

The aldol reaction is referred to as the addition of an enolate to an aldehyde. It has great value for asymmetric synthesis as it gives good methods for stereochemical control. The reaction generates a new C-C bond with two new stereocentres. The general scheme is shown in **Figure I.12**:

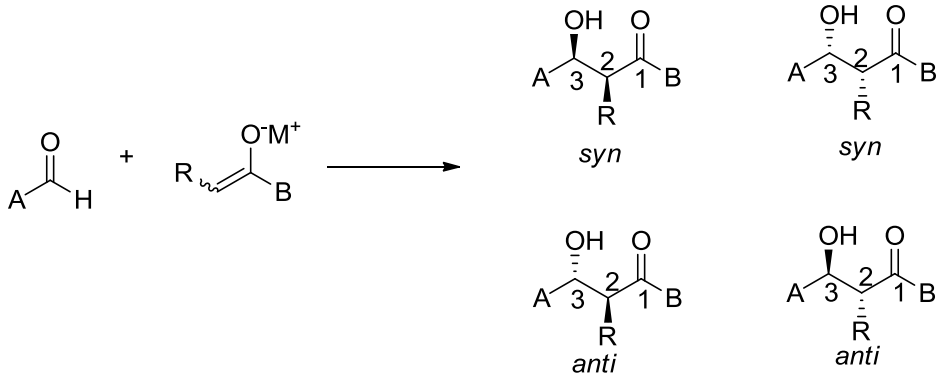


Figure I.12

The reaction engenders two stereocentres so a maximum of four isomers are possible.

In order to predict the stereochemical outcome, we need to predict:

- the relative stereochemistry at C-2 and C-3
- the influence of asymmetry within the aldehyde (A)
- the influence of asymmetry within the enolate (B)

Firstly, to determine the *anti*/*syn* **27**/**29** outcome, we need to refer to the Zimmerman-Traxler model based on a six-membered cyclic transition state system (**Figure I.13**):

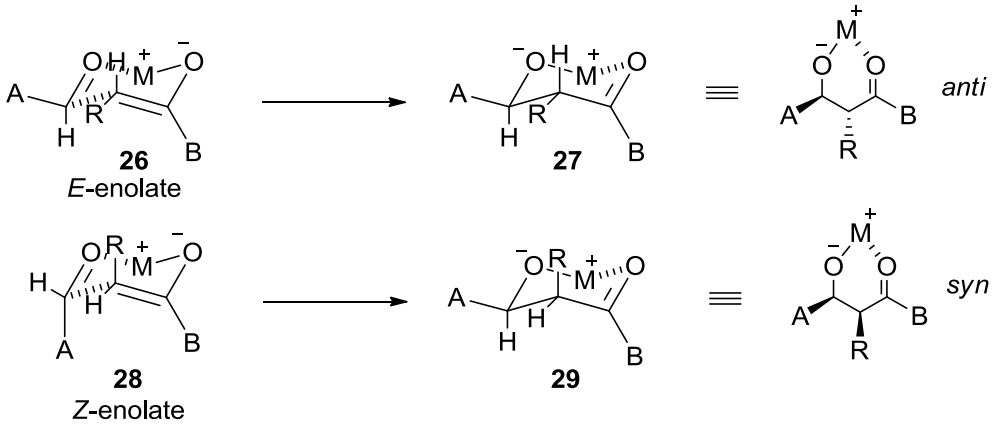


Figure I.13

The reaction is under kinetic control with the enolate, and the metal M is chelating to the aldehyde **26** or **28**. The chair-like transition state favours the equatorial position for the bulky A group in **26** and usually the best selectivity is observed when the metal M is Li^{+} or Mg^{2+} and chelates to both oxygen (in the absence of a Lewis acid). Under those conditions, the *E*-enolate **26** gives rise to the *anti*-aldol whereas the *Z*-enolate **28** gives rise to the *syn*.

However, the influence of chirality within the aldehyde (A in **26** or **28**) or the enolate (B in **26** or **28**) has not been yet considered. If the aldehyde faces become diastereotopic,[20] the diastereoselection is predicted by the Felkin-Ahn model (**Figure I.14**). [21, 22] The carbon adjacent to the carbonyl group is the stereogenic centre and carries three different groups with different steric bulk: a large (L), a medium (M) and a small (S). In this model, the favoured conformation results from the division of the small and medium sector by the carbonyl. The commonly accepted model is when the larger group is perpendicular to the C=O bond. The nucleophile attacks from the least hindered trajectory, the Bürgi-Dunitz trajectory, that is *trans* coplanar to the C-L bond. This minimizes steric interaction within the molecule and allows the attack of the nucleophile from the less hindered face (*Re* in **Figure I.14**).

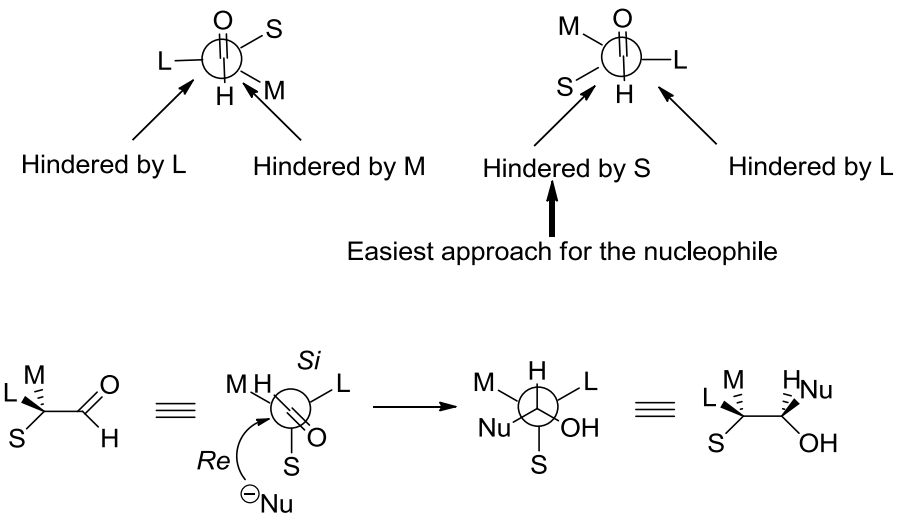


Figure I.14

Unfortunately, the *syn*/*anti* diastereocontrol of the Felkin-Ahn model is no better than 5:1 whilst Zimmerman-Traxler gives usually 100% of diastereoselection as reported in **Figure I.15**:[23]

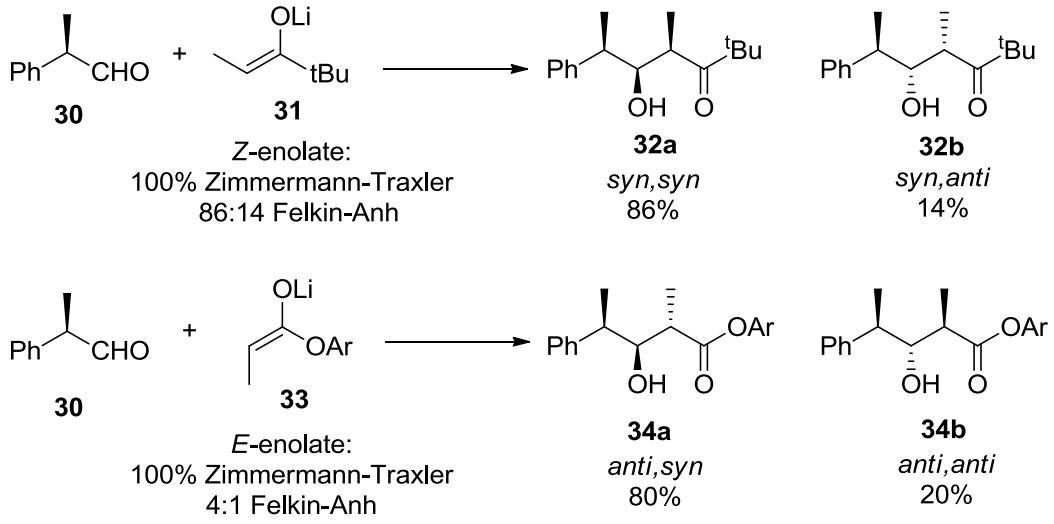


Figure I.15

The reaction of the aldehyde **30** with the *Z*-enolate **31** gives the *syn*,*syn* product **32a** as major diastereoisomer (while the addition of the *E*-enolate **33** with the aldehyde **30** gives the *anti*,*syn* product **34a** as major diastereoisomer).

However, when one of the groups at the sterocentre (X) is capable of chelating a metal cation, the chelation model for the nucleophile addition to the carbonyl group applies (**Figure I.16**). A rigid 5-membered (or 6-membered) chelated ring is formed between the oxygen, the metal and X, and can lead to high 1,2-diastereoselectivity.

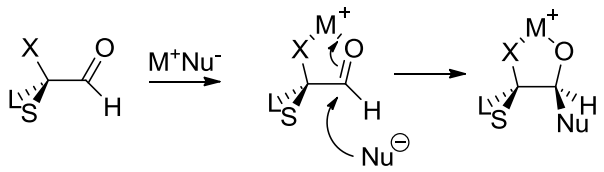


Figure I.16

In the case where the enalote is chiral and the aldehyde achiral, two major auxiliaries can be employed: the oxazolidinones of Evans[15, 16] and the (*S*)- or (*R*)-mandelic acid derived ketone of Masamune.[24, 25] Both approaches gained extensive use as they lead to high diastereoselectivity, but only the Evans' auxiliary will be described. Masamune's mandelic acid auxiliaries have the drawback that they are not recycled after the cleavage of the auxiliary.

The high stereochemical control of the aldol reaction using oxazolidinones is principally due to the formation of boron enolates (**Figure I.17**). The *Z*-enolate **35** is exclusively formed by reaction of the acylated oxazolidinone **22** with dibutylboron triflate and reacts with the aldehyde to give essentially only one aldol product **39**. The high stereochemical control is principally due to the formation of boron enolates (**Figure I.17**).

The boron is first co-ordinating to the enolate oxygen and the oxazolidinone carbonyl group but then switches to the aldehyde carbonyl group instead of the oxazolidinone C=O. The co-ordination of the boron to the aldehyde carbonyl group activates the aldehyde. The oxazolidinone group is now free to adopt two possible amide rotamers **36a** and **36b** and each of them reacts through an unlike transition state (from the Zimmerman-Traxler prediction).

The bulky group on the auxiliary is used to force the diastereoselective attack from the opposite face. When the attack proceeds through the *Si* face of the enolate **36a** (*Re* face of aldehyde), the transition state is disfavoured. The steric repulsion between the enolate substituent (methyl in the case of **36a**) and the isopropyl substituent (in this case) is believed to destabilise this transition state. However, when the *Re* face of the enolate **36b** is attacked the transition state does not involve this interaction as the two substituents are *anti*. The reaction is kinetically controlled and gives principally one diastereoisomer.[15]

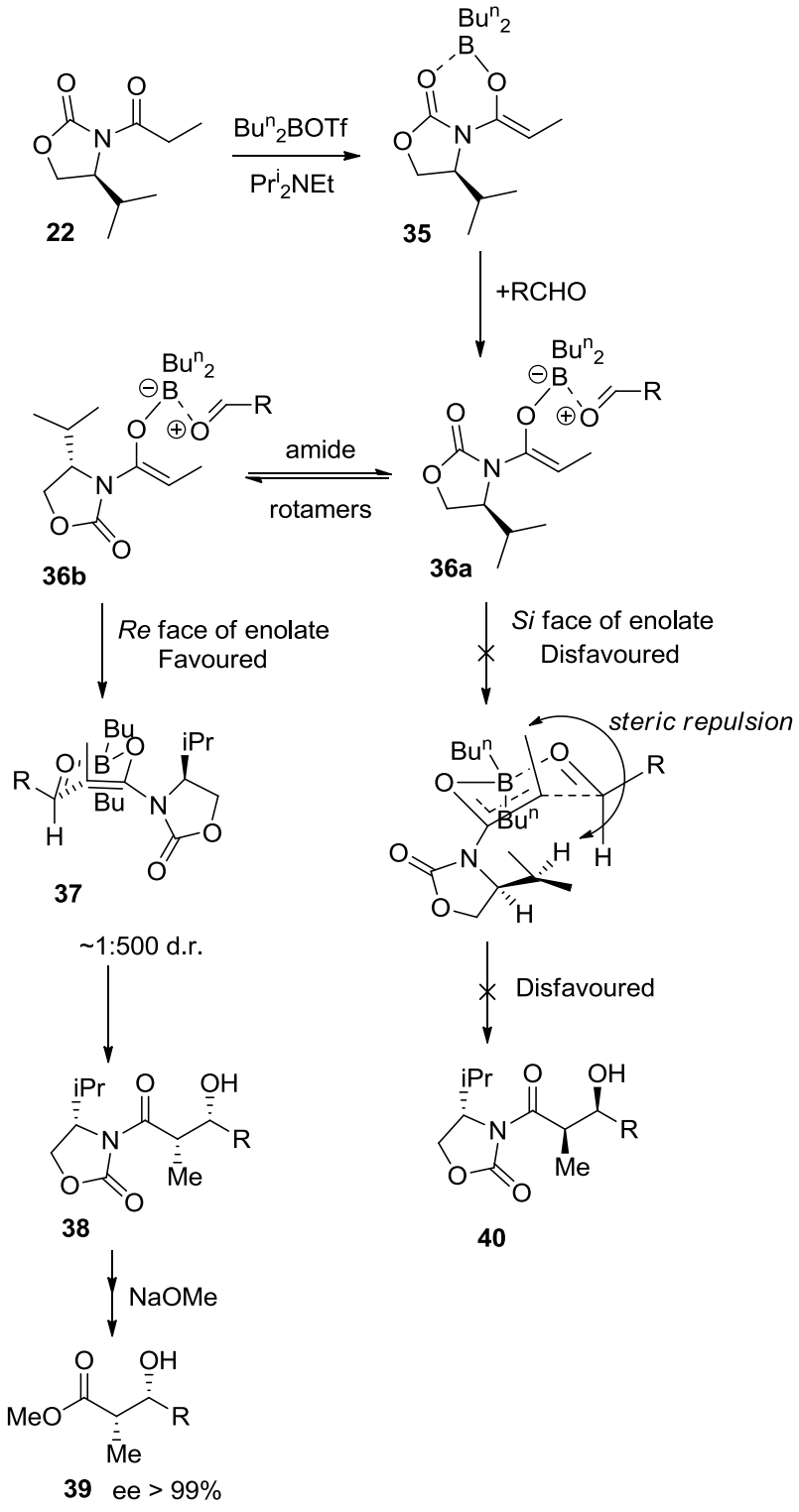

Bu$^n_2$BOTf
Pr$^i_2$NEt
22
35
+RCHO
amide
rotamers
36b
36a
Re face of enolate
Favoured
Si face of enolate
Disfavoured
steric repulsion
37
~1:500 d.r.
Disfavoured
38
40
NaOMe
39 ee > 99%

Figure I.17

E. The chiral Sultam auxiliary

Oxazolidinone enolates show some problems with alkylation of unreactive alkyl halides (*vide supra*, see **Table 2**), that is why other chiral auxiliaries have been developed.

Oppolzer and his group have been the first to develop a chiral auxiliary for acyclic systems.[20,21,23,24] The auxiliary sultam **41** and its enantiomer, are derived from both camphorsulfonyl chloride enantiomers (**Figure I.18**). Acyl derivatives **42** of the auxiliary can be prepared by treatment with base and an acid chloride. This acylated sultam **42** is then treated with BuLi (NaHMDS can also be employed), and the lithium chelates to the amide enolate oxygen and one of the sultam oxygens to produce the enolate **43**. Alkylation reactions with a variety of electrophiles give highly enriched diastereoisomers **45** and **46** even when an unreactive alkyl halide is employed (**Table 3**, **entries 4**, **5** and **6**). The auxiliary is removed either by hydrolysis to give alkylated carboxylic acids, or by reduction to the alcohol and in both cases without any loss of stereochemical purity.

For the stereochemical outcome, it can be explained by the *pro-S* bridgehead methyl group (Me^*) that hinders the 2*Si* face of enolate **43** (or upper face) forcing the alkylation of this enolate to take place from the 2*Re* face (lower face). [26]

Camphor sultam **41** can be employed for alkylation of alkyl halides with high yield and selective. However, the selectivity and the yield are dropping if HPMA is not used with the alkyl halide (**Table 3**, **entries 7** and **8**).[26]

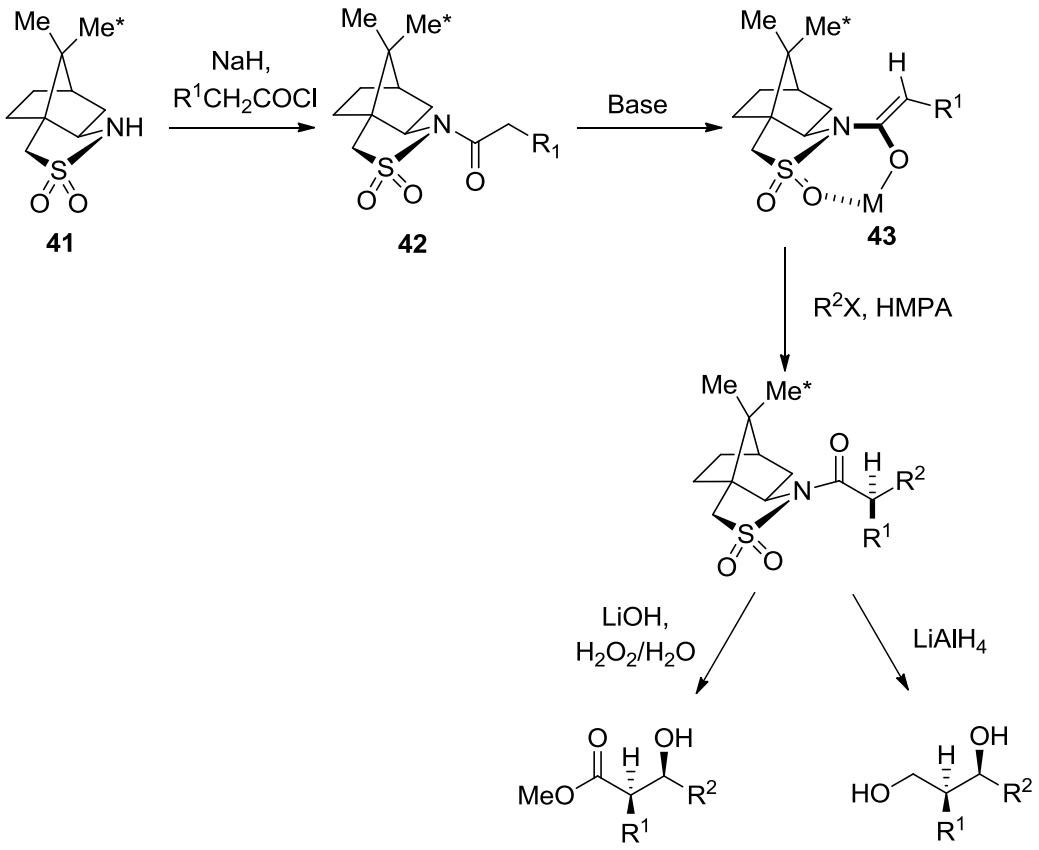


Figure I.18

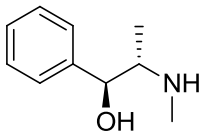
Entry	R^1	Electrophile R^2X	Use of HMPA	de of crude (%)	Yield (%)
1	Me	$PhCH_2I$	Yes	96.5	89
2	Me	$^tBuOCOCH_2Br$	Yes	98.5	77
3	Me	$Me_2CH(CH_2)_3$	Yes	99	81
4	$PhCH_2$	MeI	Yes	94.5	88
5	Me	$C_5H_{11}I$	Yes	97.7	81
6	CH_2= CH_2CH	MeI	Yes	98	-
7	Me	$CbzNMeCH_2Cl$	No	72.7	58
8	Me	$MeOCH_2$	No	74	67

Table 3 – Diastereoselectivity obtained for the alkylation of enolates using sultam auxiliary 41

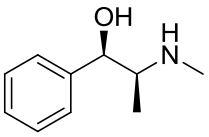
F. Pseudoephedrine as a chiral auxiliary

1. Asymmetric alkylation using pseudoephedrine

Pseudoephedrine **44** is a diastereomer of ephedrine **45** that was first discovered in 1924 (**Figure I.19**).[27] It naturally occurs as an alkaloid in ephedra species and is also known as Ma Huang, in which it occurs together with other isomers of ephedrine. Nowadays, the pseudoephedrine **44** produced for commercial use is derived from yeast fermentation of dextrose in the presence of benzaldehyde. Pseudoephedrine **44** is used as a decongestant and stimulant that can be purchased as an over the counter drug (Sudafed). It is usually dispensed in combination with antihistamines, paracetamol (acetaminophen), and/or nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen, etc.).



44
(1*R*,2*R*)-(-)-Pseudoephedrine



45
(1*R*,2*S*)-(-)-Ephedrine

Figure I.19

Myers and his co-workers reported in 1994 that pseudoephedrine **44** can be used as an efficient chiral auxiliary for asymmetric alkylation reactions of carboxylic acids.[24, 25] The *N*-acylation of pseudoephedrine **44** delivers tertiary amide **46** and the enolate derived from the pseudoephedrine amides undergo alkylation using lithium chloride to afford highly diastereoselective products **47** (**Figure I.20**). The alkylated products are often crystalline and can be easily enriched to >99% de upon recrystallization.[28]

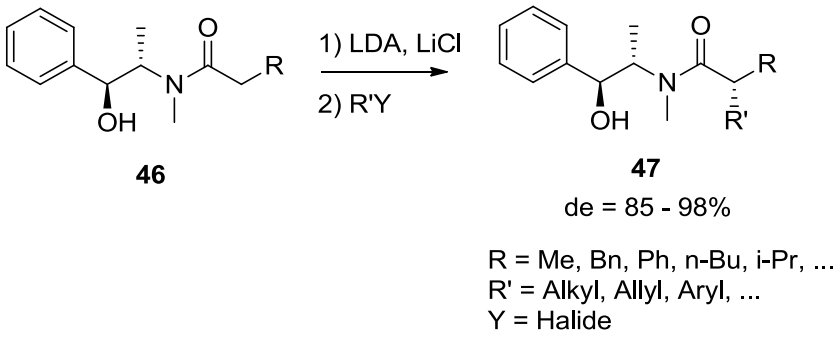


Figure I.20

Myers proposes the formation of the reactive *Z*-enolate conformer of pseudoephedrine side chain to explain the mechanistic rationale. He based his proposal on the mechanism suggested by Askin *et al.* in 1988 for the alkylation of prolinol amide enolates with epoxide electrophiles.[29] Askin postulated that a steric shielding effect resulting from the alkoxy group of the prolinol amide enolate **49** was the source of the diasteroselectivity of the alkylation. By analogy, Myers suggested that the alkoxy group of pseudoephedrine amide enolates **48** would have the same effect. The pseudoephedrine amide enolate **48** is postulated to adopt a staggered conformation where the alkoxide is positioned on the 1*Si*,2*Re* face of the enolate. The lithium alkoxide and perhaps some solvent molecules chelate to the lithium cation and block the 1*Si*,2*Re* face, therefore the attack by the electrophile is forced on the 1*Re*,2*Si* face (**Figure I.21**).

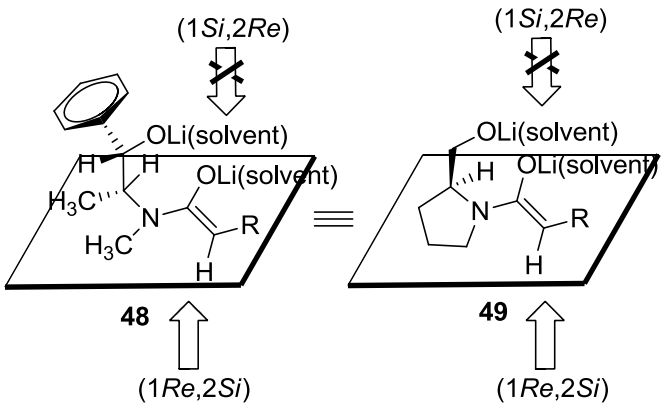
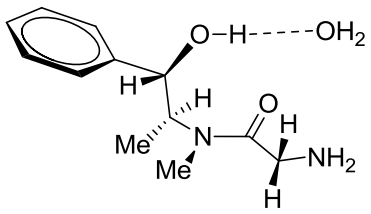


Figure I.21

Such a conformation of the enolate is confirmed by X-ray crystal structure of pseudoephedrine glycinamide hydrate **50** (**Figure I.22**).[28, 30] However, several

important features such as aggregation state, rotameric distribution, bond-breaking and bond-forming trajectories have not been considered for the proposed model.



50

Figure I.22

2. Hypothesis around the mechanism

In an evaluation of the pseudoephedrine amides for asymmetric synthesis, Procter and his group developed a new solid-phase technique using Merrifield resin to immobilise pseudoephedrine amides (e.g. **54**) through the pseudoephedrine alcohol group and control the stereochemistry of the alkylation.[31, 32] The reaction was carried out on pseudoephedrine derivatives (e.g. **54**). The strategy aimed to compare the stereoselectivity outcome of the asymmetric alkylation of amide enolates with Myers' pseudoephedrine auxiliary approach explained above (**Figure I.23**). The asymmetric enolate alkylation was carried out with benzyl derivative **51** of pseudoephedrine as a model to assess the polymer-supported systems and also with Myers' type-substrate **46**. Deprotonation with LDA/LiCl of *O*-benzyl ether **51** followed by alkylation with benzyl bromide, subsequent auxiliary removal gave the product **53** in 91% ee while the same reaction conditions with the underivatised **46** afforded **47** in 94% de (before removal of the auxiliary). Similar deprotonation and alkylation of the polymer-supported acylated auxiliary **54** gave the alkylated product **55**. In this case the polymer-support was attached to the pseudoephedrine through the hydroxyl group, which Myers had suggested controls the stereoselectivity of the reaction, and does not allow the formation of the dianion proposed by Myers. The resulting primary alcohol **53** was obtained in good yield and in slightly lower stereoselectivity

(87% ee) than either of the solution state reactions with **46** (95 % ee of **53**) or benzyl ether **54** (91 % ee of **53**).

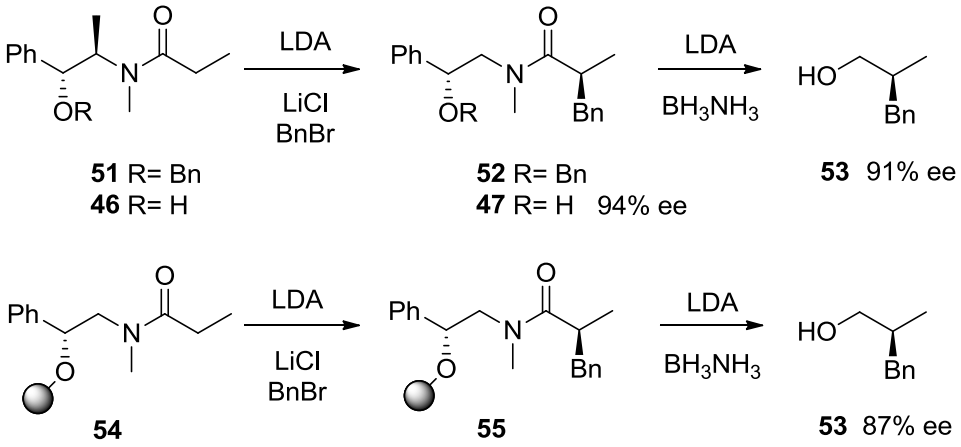


Figure I.23

This study reveals that the selectivity of the alkylation is not significantly affected when applied on the *O*-benzylpseudoephedrine **51** or on the immobilized pseudoephedrine amide **54** in comparison to the pseudoephedrine amides. Therefore, Myers' hypothesis of a steric screen created by the lithium alkoxide of the amide enolate **46**, may not necessarily be required to obtain good stereoselectivity.

In this context, computational conformational analyses experiments carried out by Gibson[33] also question the hypothesis of Myers proposed mechanism. Calculation of single point energies by DFT methods with the B3LYP 6-31G** basis set of the molecular mechanics derived conformers of the *Z*-enolate of **46**, indicated that the lowest conformer was not that resulting from Myers reactive conformation **48** but from a π-Li^+ interacting between the aromatic ring and the enolate lithium cation (**Figure I.24**).

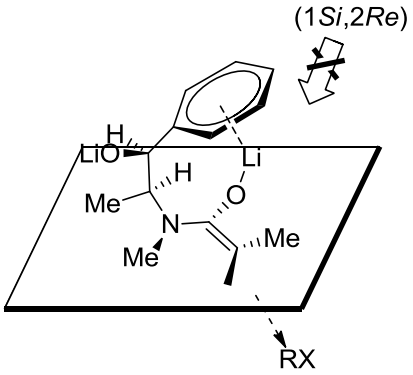
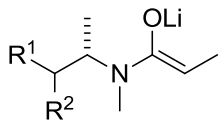


Figure I.24

Computational modelling experiments were completed on a number of *Z*-enolates of derivatives of pseudoephedrine **48**. The difference of energy between the π-Li interaction and Myer's conformation for the enolate is shown in **Table 4** (**Figure I.25)**. The most stable conformer results either from Myers conformation (M) or from the π-stacked conformation (P).



56

Entry	R^1 in **56**	R^2 in **56**	ΔE for π-Li vs Myers (kJ/mol)	Lowest energy conformation
1	Phenyl	OMe	13.6	P
2	Phenyl	OBn	0.29	P
3	2,6-dimethylphenyl	OLi	-2.55	M
4	3,5-dimethylphenyl	OLi	-1.2	M
5	9-anthracenyl	OLi	6.29	P
6	*p*-anisole	OLi	1.26	P
7	pentafluorophenyl	OLi	-13.68	M

Table 4 – Data for the DFT B3LYPT 631G calculations of enolates 56**
(P = π-Li lowest energy conformation, M= Myers as the lowest energy conformation)

Figure I.25

However in these calculations (**Table 4**), the solvation of the molecules is not taken into account and the compounds are supposed to be in gas phase. Albeit the accuracy of these values may be questioned, it allows us to wonder whether the conformation proposed by Myers is actually involved in the alkylation mechanism of the amide enolate derivatives of pseudoephedrine or not.

As a result of these observations, modifying the election density on the aromatic ring in pseudoephedrine amide enolates **56** (e.g **entry 4**) would have an impact on this electrostatic interaction between the lithium cation and the aromatic ring. Consequently this may affect the stereoselectivity of the reaction. For instance, increasing the electron density of the aromatic ring would strengthen the electrostatic interaction between the aromatic ring and the lithium cation. The ring would be closer to the plane of the lithium enolate which would give a more rigid transition state and may improve the de. On the contrary, the addition of

electron withdrawing groups on the aromatic ring would be expected to weaken the π-Li interaction and could therefore reduce the selectivity.

In order to verify this hypothesis, analogues bearing either electron donating or withdrawing groups on the aromatic ring in pseudoephedrine derivatives have been selected (**Figure I.26**). Besides of the increase of the electron density, the 9-anthracenyl analogue **57** adds steric hindrance to the blocked face and the selectivity here is expected to be greatly improved. Also the addition of two methyl groups in *meta* (e.g. **56**), or a methoxy group (e.g. **58**), may increase the electron density of the aromatic ring. In opposition, electron withdrawing group as fluorine (e.g. **59**), decrease the electron density and if a cyclohexyl group (e.g. **60**) replaces the phenyl ring then the π-Li^+ interaction would not be possible. The non aromatic nature of the cyclohexyl ring in **60** would remove the possibility of the π-Li^+ interaction; consequently a significant reduction of the selectivity might be expected if the π-Li^+ postulation is correct.

Compounds bearing electron donating group will be referred as "positive targets" (**56**, **57** and **58**) while compounds bearing electron withdrawing group will be referred as "negative targets" (**59** and **60**).

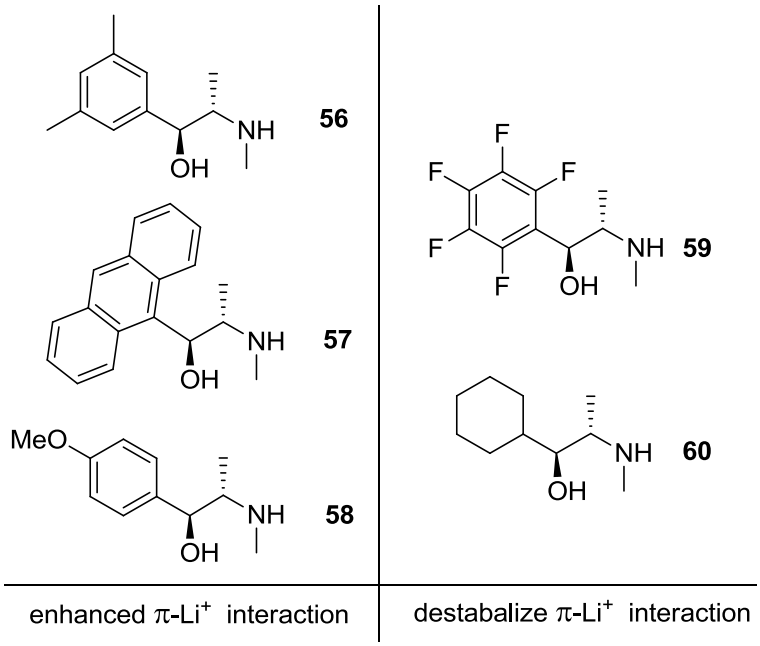


Figure I.26

3. The synthesis of analogues of pseudoephedrine

A practical synthesis to form analogues of pseudoephedrine had been developed by Coti and Gibson.[34] The synthesis of the analogue **56** can be achieved in 4 steps (**Figure I.27**).

The esterification of L-alanine **61** afforded the hydrochloride salt of the amino ester **62** by using thionyl chloride and ethanol in a 94% yield. The Boc protection of **62** led to the Boc-alanine-ester **63** in a 97% yield. Reductive alkylation of **63** using Zhao's and Polt's conditions[35, 36] afforded the secondary alcohol **65**. The other undesired diastereoisomer was not observed and the only side product is the corresponding aldehyde (can go up to 1:1 ratio). Reduction of the Boc amino alcohol using $LiAlH_4$ gave the pseudoephedrine analogue **56** in 38% yield.

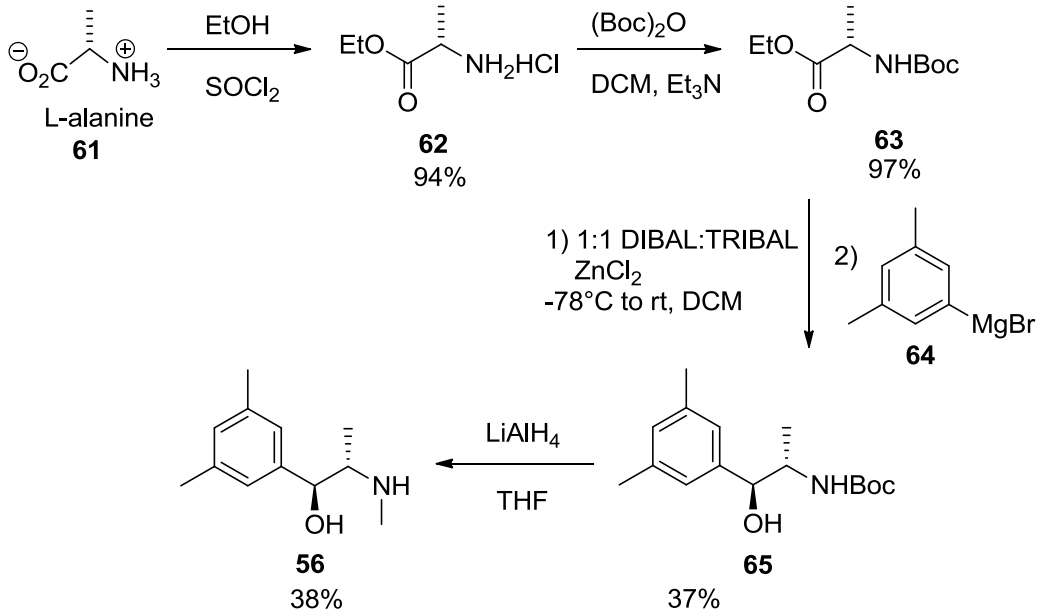


Figure I.27

The selectivity of the new chiral auxiliary **56** was then tested and compared with Myer's pseudoephedrine auxiliary **44** for the diastereoselective alkylayion of the propionamide with benzyl bromide (**Figure I.28**). The selective *N*-acylation of **56** using Myer's conditions[28] with propionic anhydride **66** and dry triethylamine afforded **67** in 52% yield. Subsequent addition of 4 equivalents of lithium diisopropylamide and alkylation with benzyl bromide gave the derivative **68a**. However, the de of the reaction to form **68a** could not be readily determined because of the presence of amide rotamers. The NMR of these acylated amides rotamers are complex and access to both epimers of the acyl side chain are needed to determine the de. Chiral HPLC analysis of **68a** also could not establish the de and access to the epimeric product would aid the determination of the de. Therefore synthesis of the other diastereoisomer **68b** is required to determine the de either by NMR or HPLC methods or cyclisation methods.[37]

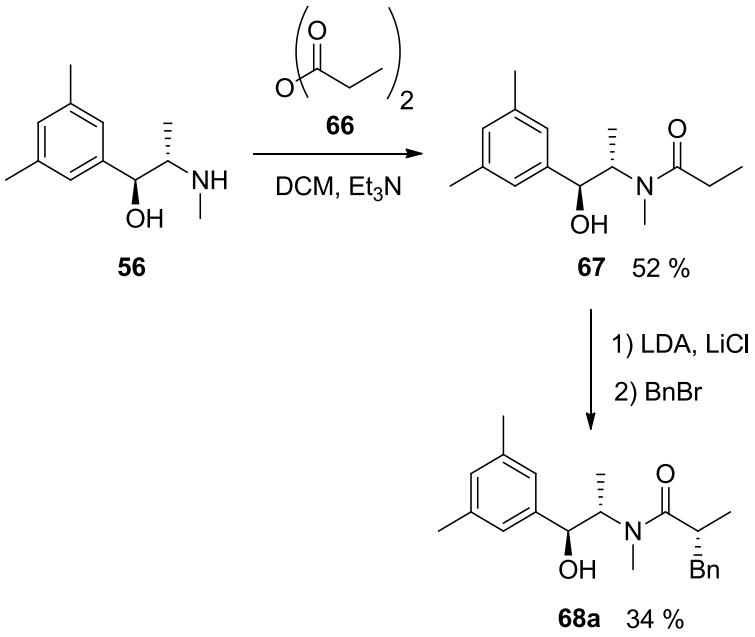


Figure I.28

4. The reductive alkylation of *N*-protected alanine ester to diastereoselectively generate alcohol

The addition of Grignard reagents to DIBAL reduction adducts of α-amino ester derivatives to generate β-amino secondary alcohols, diastereoselectively, has been studied by several groups including Taguchi[38] and Ibuka.[39] There are several ways to prepare α-amino secondary alcohols diastereoselectively:

- In the first method the chiral α-amino acid is first protected to give an amino acid ester and then reduced to its corresponding aldehyde. This chiral protected aminoaldehyde can then undergo alkylation with a range of different carbon nucleophiles.[39-42] This method is efficient but racemisation is often observed under certain reaction conditions and the selectivities of the reaction with nucleophiles are usually not high.[43, 44]

- Another way to selectively synthesis β-amino alcohols involves the use of DIBAL to reduce amino acid ester generating an aluminoxy acetal intermediate. This method significantly reduces the epimerization

problem observed with the route proceeding via the α-amino aldehydes. The addition of an organometallic reagent (usually Grignard type) to the DIBAL reduced intermediate gives good selectivity under specific conditions.[45] An example of this method is reported by Polt *et al.* in 1992 (**Figure I.29**).[36] The reduction of the enantiomerically pure imine-protected amino esters **69** with a mixture of DIBAL/TRIBAL followed by the addition of an organometallic reagent afforded *syn*-2-amino alcohols **70a** in high yield (73 to 85%) and good *syn* stereoselectivity (8:1 to 11:1 *syn* or *lk* product preferred).

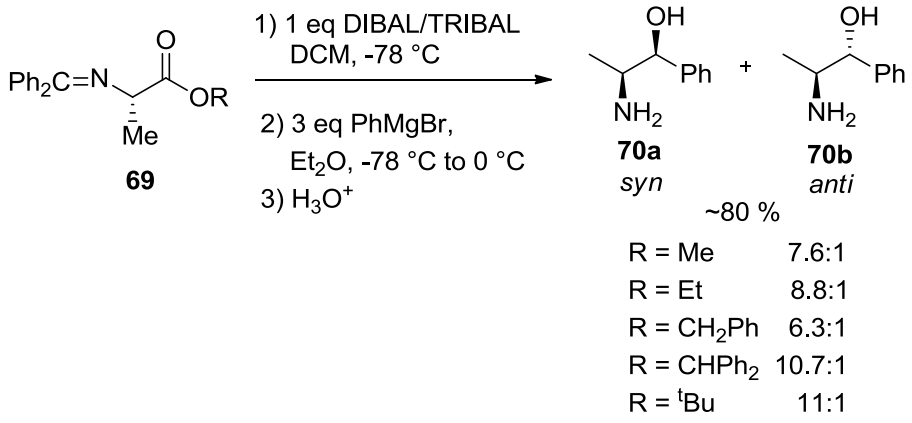


Figure I.29

- The addition of reducing reagent is usually carried out at low temperature (≤ -70 °C), directly followed by the addition of the nucleophilic reagent. Ibuka and co-workers were the first to introduce a warm-up step before the alkylation and it led to an important improvement in the stereoselectivity outcome of the reaction.[39] Indeed, when DIBAL along with the warm up step was utilized, the reductive alkylation of the *N*-Boc-(*S*)-methylalaninate **50** gave an excellent diastereoisomer ratio of 29:2 for the expected *syn* compound **51a** in good yield (60%) (**Figure I.30**). However, the alkylation of Boc-(*S*)-alaninal **52** using THF and without the warm-up step, gave a much lower selectivity of 7:3 (53%). The reductive alkylation of Cbz-protected alanine ester **73** without a warm-up step was carried out by Kano and co-workers.[46] The diastereoselectivity

of the reaction couldn't be precisely measured at this stage but after the addition of a base to **75** to form the oxazolidinone **76a** as major product in good yield. Nonetheless, the diastereoselectivity of this reaction (7:1) is not as high as when the warm-up step was utilized.

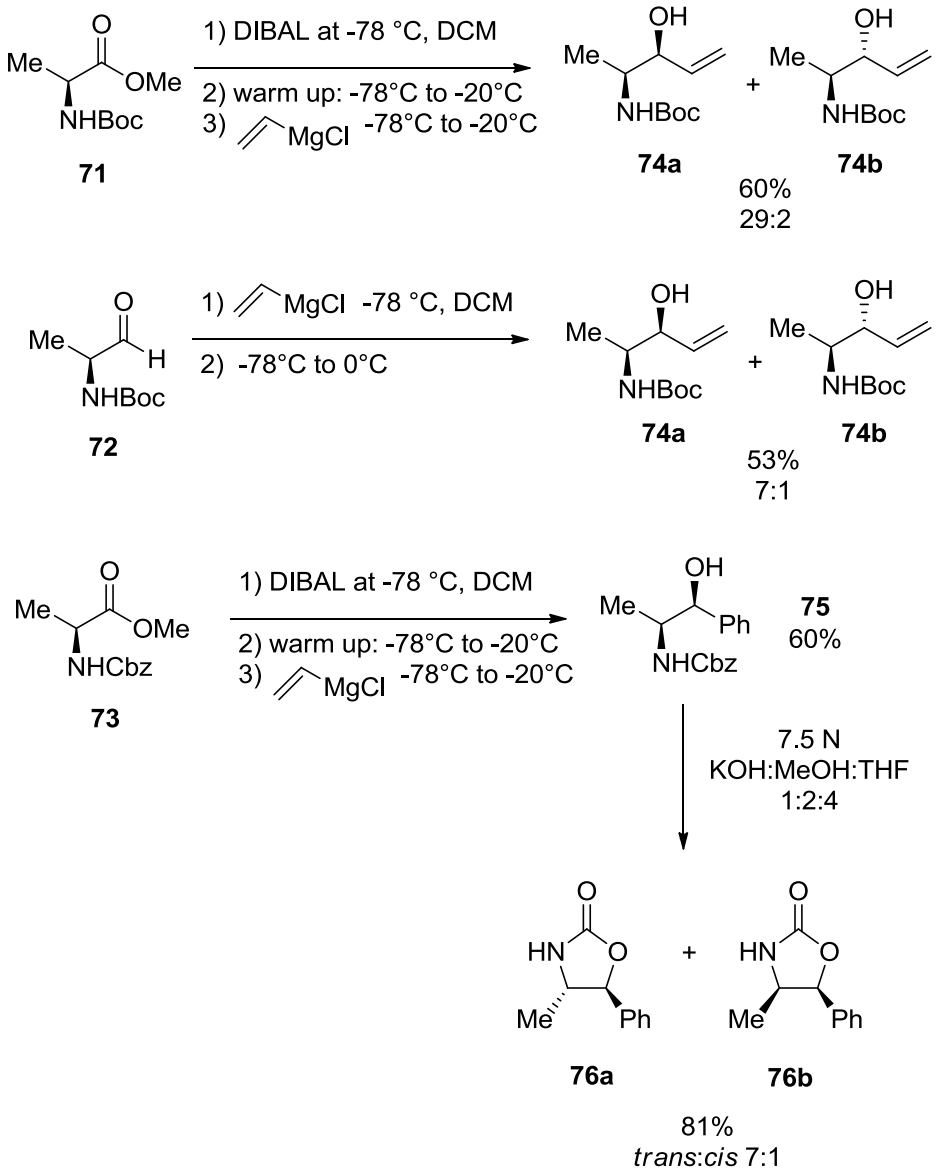


Figure I.30

Another example was reported by Angle and co-workers[47] where they applied the warm-up step procedure on the *N*-Boc protected amino ester after observing moderate selectivity (7:1 to 3:1) in Grignard addition to aldehyde **72**. As illustrated in **Figure I.31**, the aldehydes **72** and **77** were reacted with vinylmagnesium bromide at -78 °C to respectively afford the

major *syn* alcohols **74a** in a 3:1 ratio and **78a** in a 7:1 ratio. However, when the warm-up step procedure was adopted for the conversion of the amino esters **71** and **79** to the alcohol **74** and **80**, the stereoselectivity of the reaction significantly increased. The allyl alcohol **74a** and **80a** are produced as major diastereoisomer in good ratios and moderate yields. This one-pot synthesis is therefore a method of choice to form alcohols from amino ester in high stereoselectivity.

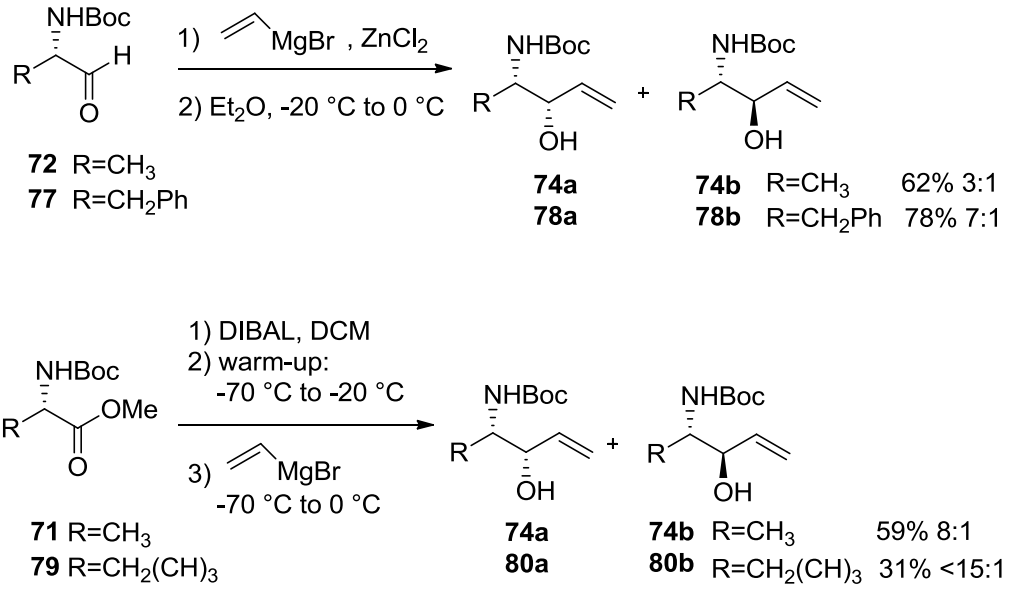


Figure I.31

At present, the mechanism of the addition of a hydride followed by the alkylation to a protected α-amino ester is not totally understood. The work reported by Polt and co-workers brought a better understanding of the reductive alkylation of ketamine esters e.g. **81** (**Figure I.32**).[36] During the reduction process, the addition of one hydride to the chelated imino ester forms an aluminoxy acetal **A** that is believed to be the reactive species. The chelating-Cram chelate model is proposed to direct the sense of stereocontrol in which the DIBAL acts as a chelating reagent. Inversion of configuration during the displacement of the methoxide ion by the incoming nucleophile leads to the intermediate **B**. Subsequent hydrolysis affords the *syn* secondary alcohol **82**.

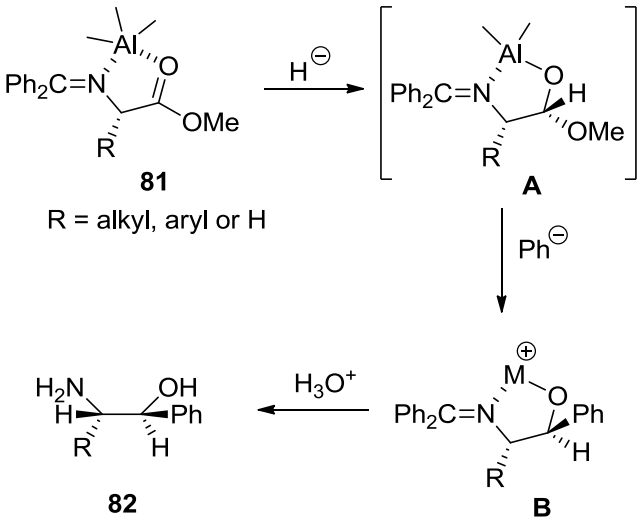


Figure I.32

In the case of the reductive alkylation of Boc esters of amino acids, it is thought that the *syn* diastereoselectivity observed is influenced by the presence of the NH group.[39, 42] Based on the Cram chelate model (**Figure I.33**) the attack of the vinylmagnesium bromide occurs from the less hindered face of the transition state **C** to give the *syn* alcohol as the major product.

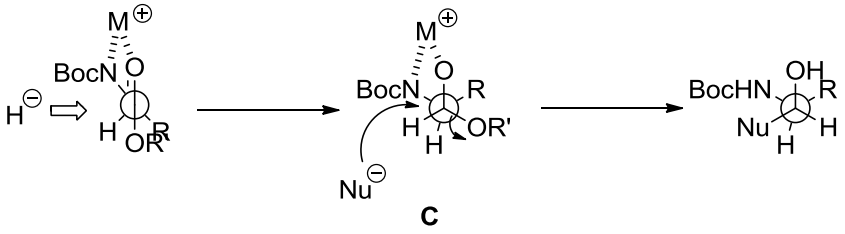


Figure I.33

Another approach carried out by Zhao on the L-proline-*N*-Boc methyl ester **83**, brought interesting selectivity results and increased mechanistic understanding of this specific reaction.[35] The Boc protected L-proline methyl ester **83** was reduced using DIBAL and alkylation using an allylmagnesiium bromide gave the major alcohol **84a** with excellent selectivity (> 32:1) and good yield (80%) (**Figure I.34**).

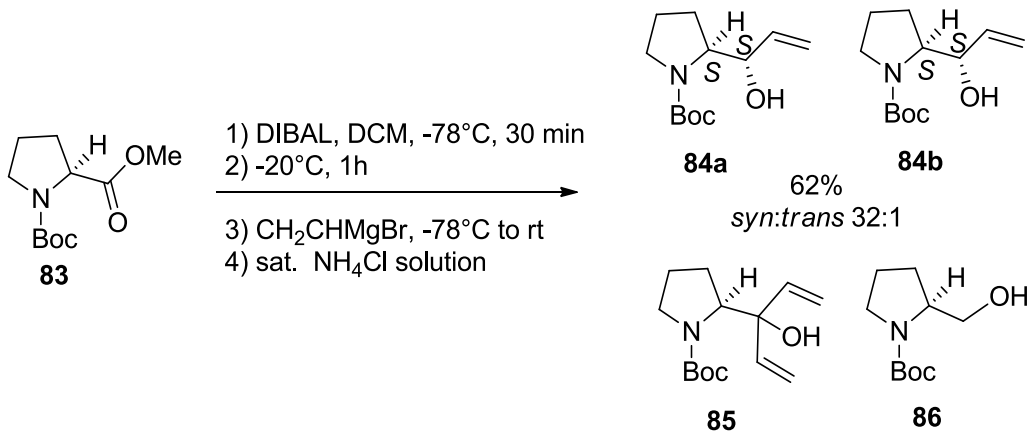


Figure I.34

In terms of mechanistic understanding, the high diasteroselectivity can be justified by the role of the DIBAL that coordinates to one of the oxygen atom of the Boc group. The procedure involves a warm-up step that is believed to be responsible for the formation of the favourable intermediate during the reaction. After addition of DIBAL at -78 °C, the aluminoxy-acetals **R1** and **R2** (**Figure I.35**) were suggested to be formed. The solution was then warmed to -20 °C which allows the equilibration of minor acetal **R1** into the major **R2** diastereoisomer in a very high ratio. Zhao postulated that the epimerisation of **R1** into **R2** was due to steric hindrance in the minor diastereoisomer **R1**. The Grignard reagent then reacts with **R2** in a S_Ni process with retention of configuration to afford **84a**. This mechanistic hypothesis was also confirmed by DFT calculation carried out by Zhao that showed that the minor aluminoxy acetal **R1** is higher in energy than **R2**.

The main side-products observed included the over-reduced primary alcohol **86** that was generated by the DIBAL reduction and the tertiary alcohol **85** resulting from the reaction of one molecule of **83** with two molecules of Grignard reagent.

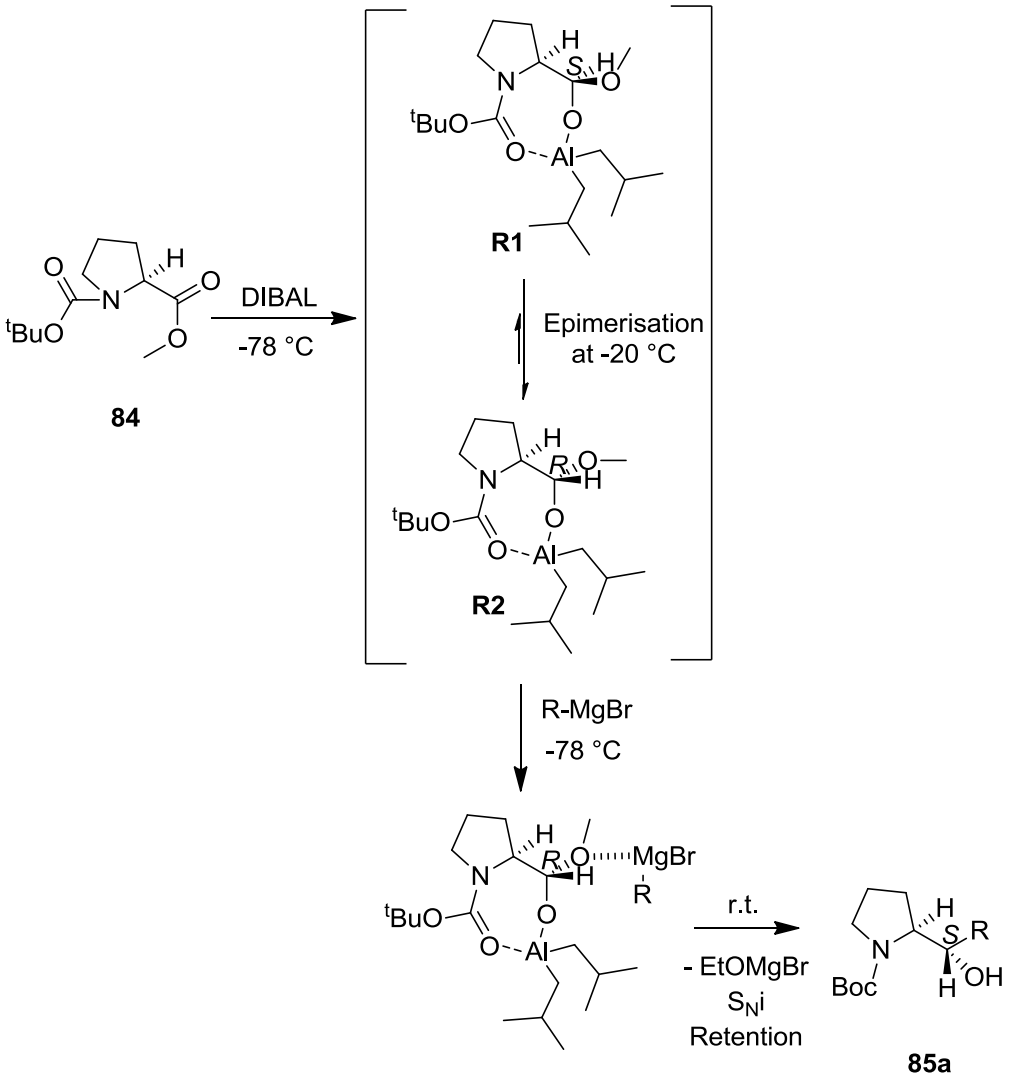


Figure I.35

In summary, as explained earlier, Myers' suggestion for the mechanistic rational of the alkylation of enolates derived from *N*-acylated pseudoephedrine is questioned. When the *O*-benzyl or *O*-polymer pseudoephedrine amides undergo the same asymmetric alkylation, the very high selectivity is maintained. In addition, DFT calculations suggest that the lowest energy conformer comes from a π-cation interaction within the auxiliary derivative and not from the dianion suggested by Myers. Therefore, this project was designed to synthesis derivatives of pseudoephedrine with a variety of functionalised aromatic ring bearing electron donating groups (**56**, **57**, **58** in **Figures I.25**) in order to investigate the impact of this interaction on the selectivity outcome of the enolate alkylation.

II. Results and discussion

A. Synthesis of 3,5-dimethylphenyl pseudoephedrine analogue

In a previous study, Coti synthesised the enantiomer (2*S*)-3,5-dimethylphenyl pseudoephedrine **68a** as a positive target for the alkylation of propionic acid derivatives.[34] However, in order to determine the de of the alkylation with benzyl bromide, the other diastereomer **68b** needed to be synthesised (**Figure II.1**). The first part of this project was concerned with the synthesis of the analogue (2*S*)-3,5-dimethylphenyl pseudoephedrine **56** using the synthesis developed by Gibson and Coti.[34] Subsequent reaction with hydrocinnamoyl chloride **86** followed by alkylation with methyl iodide would then afford the diasteromeric product **68b** (**Figure II.2**).

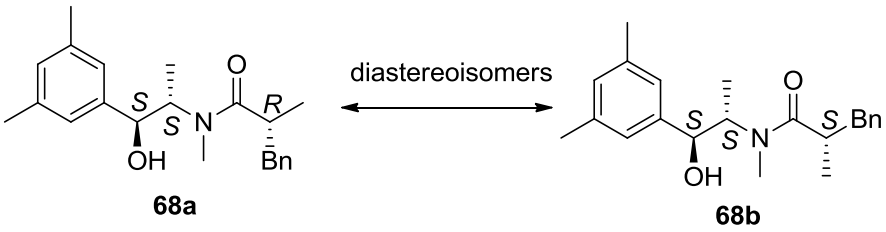


Figure II.1

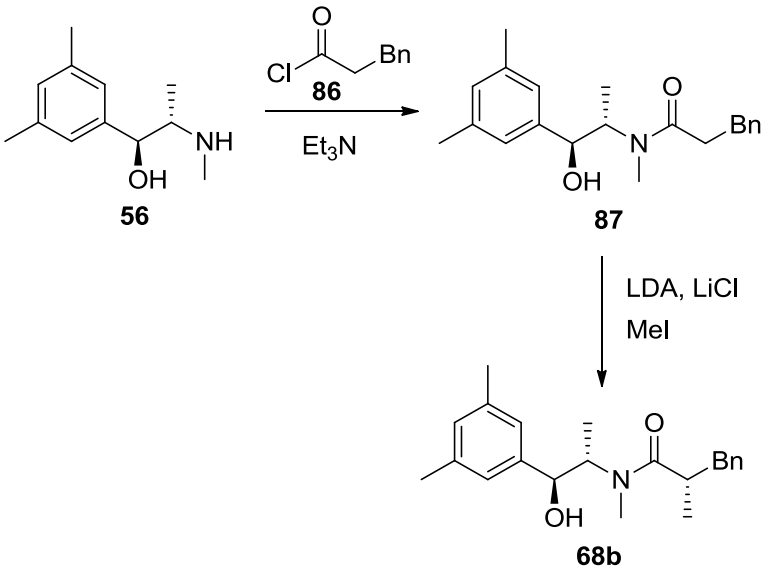
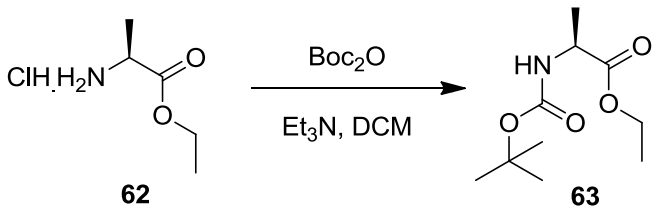


Figure II.2

1. Formation of the Boc protected alanine ester 63

The ethyl (2*S*)-2-aminopropionate hydrochloride **62** was available in the laboratory, therefore the first step was the protection of **62** by a Boc protecting group using standard conditions.[41, 42] Two equivalents of triethylamine were required to generate the free base and trap the acid that was generated as a result of the coupling. Subsequently, 1.4 equivalents of Boc anhydride were added after the formation of the precipitate resulting from the salt formation (**Figure II.3**). After purification by distillation compound **63** was obtained in 88% yield on a 10g scale.



62 **63**

Figure II.3

2. Preparation of 1-bromo-3,5-dimethylphenyl magnesium 64

To synthesise the 3,5-dimethyl pseudoephedrine derivative **56**, we needed access to the Grignard reagent **64** in ether. The only commercially available Grignard reagent was in THF. The use of THF as cosolvent for the reductive alkylation of Boc amino acid esters causes the *syn* stereoselectivity to drop. A possible explanation of this result suggested by Polt *et al.*[36] is that the chelated ring of the initial DIBAL:TRIBAL complex e.g **R2** (**Figure I.34**) is opened by THF which gives a greater percentage of the minor aluminoxy acetal e.g. **R1**. Thus, it was necessary to synthesis 3,5-dimethylphenylmagnesium bromide **64** from 1-bromo-3,5-dimethylbenzene **88** using magnesium turnings and anhydrous diethyl ether (**Figure II.4**).

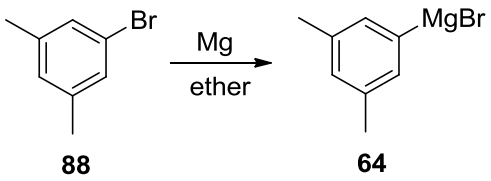


Figure II.4

Grignard reagents are highly reactive organometallic reagents generated by treating alkyl or aryl halides with magnesium metal in the presence of anhydrous ethereal solvent. The Grignard reaction is a heterogeneous reaction at the magnesium surface. The dryness of the solvent, the reactivity of the magnesium and the absence of oxygen are primary factors of concern[48, 49] and the reaction usually necessitates an induction time after which the reaction proceeds exothermically.

In the laboratory, the general procedure to prepare Grignard reagent was followed.[50] Experiments of the reaction are summarised in **Table 5**. The substrate was distilled prior to use, anhydrous diethyl ether was used as solvent and magnesium turnings were flame dried under a nitrogen atmosphere. To obtain the conversion by ^{1}H NMR, an aliquot of the reaction was taken and quenched with water. The peak of the *m*-xylene obtained from the quenching was compared to the starting bromide **88** and biphenyl by-product.

Entry	Mmol of aryl bromide **88**	Equivalents of Mg turnings	Changes	Conversion (%)
1	5	1.2	Substrate distilled, 2h reflux	0
2	2	2	Same as entry **1** + crystal of I_2	0
3	8.7	1.2	Same as entry **1** + iodomethane	73
4	19.7	1.2	Same as entry **3**	72
5	5	2	Mechanical activation of Mg	0
6	6.3	6.5	Same as entry **5** using dilute solution of dimethylbenzene bromide **88**	0
7	6.3	6.5	Same as entry **5** and enough solvent to cover Mg	90
8	53	6.5	Same as **7**	94

Table 5 – Conditions for the synthesis of 3,5-dimethylphenylmagnesium boromide 64

The first experiments (**entries 1** and **2**) didn't show any conversion of the 3,5-dimethylbenzene bromide **88** into the Grignard reagent **64**. In a second experiment, an excess of magnesium turnings was used and a crystal of iodine was added to the solution to initiate the reaction. This was followed by a change of colour (from uncoloured to brown solution). Iodine is thought to help the initiation by activating the magnesium surface.[51] The reaction was then refluxed for 2 hours but NMR analysis did not show any product formation. The conversion was determined by ^{1}H NMR by comparison of the integration

between the two methyl groups of the substrate **88** (detected at 2.28 ppm) and the methyl groups of *m*-xylene (detected at 2.38 ppm). For the concentration of the solution, this was determined by No-D NMR spectroscopy of the solution with 1,5-cyclooctadiene (COD) as an internal standard (see experimental).[52] In the third experiment, 2-3 drops of iodomethane were added instead of a crystal of iodine. This change resulted in a conversion of 1-bromo-3,5-dimethylbenzene into the Grignard reagent **64** in 73 % yield. The reaction was also carried out on a larger scale and gave 72 % conversion (**entry 4**).

Although the reaction worked, it was typically difficult to reproduce. At times the conversion was low and the NMR spectrum showed the formation of other products. Most of them were formed by dimerisation between two molecules of Grignard reagent.

Another literature procedure involving the mechanical activation of the magnesium turnings was found.[53] When dry magnesium turnings were vigorously stirred under nitrogen, it causes fragmentations and cleavages of the turnings to form microcrystalline magnesium particles. The surface area of oxide free magnesium was enhanced and magnesium particles become more reactive towards the aryl bromide. Several experiments were necessary to master this technique. The amount of solvent to cover the magnesium turnings was also crucial because if the solution is too dilute, the reaction will not initiate (**entries 5** and **6**). However, when all the reagents are dry and an appropriate amount of anhydrous diethyl ether is used, the reaction proceeds smoothly and is reproducible. The conversion of 1-bromo-3,5-dimethylbenzene to **88** was never lower than 90 % (**entry 7**). A conversion of 90% was observed on small scale reactions. On larger scale the conversion was very good (**entry 8**, 94 %). It is important to note that Grignard solutions were synthesised as dilute solutions as degradation of the Grignard was generally observed, within 2 days, with a concentration higher than 1 M.

3. Study of the reductive alkylation of the Boc-protected amino ester 63

The formation of compound **65** required 3,5-dimethylphenyl magnesium bromide **64** and a powerful reducing agent to provide the hydride source (**Figure II.5**).

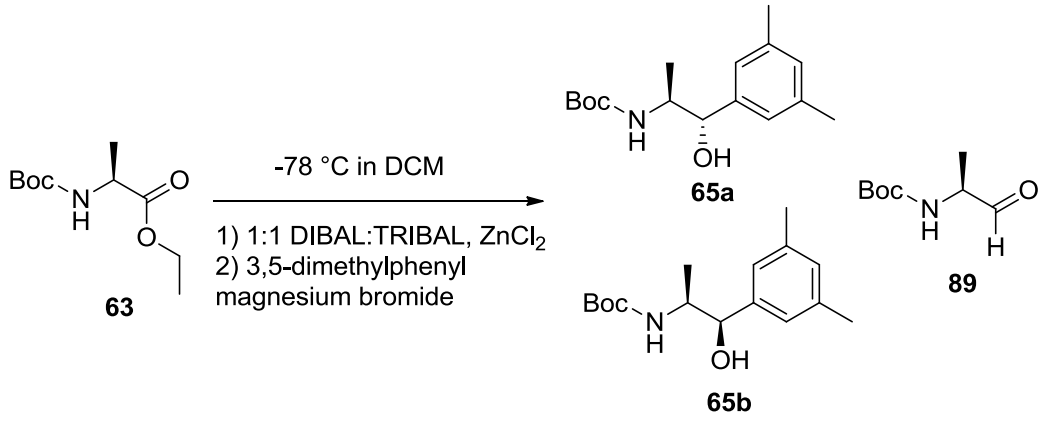


Figure II.5

The procedure chosen for the ester reduction/alkylation was based on experiments carried out by Coti.[34] A solution of 1:1 DIBAL:TRIBAL in hexane was used as a Lewis acidic mixture to reduce the ester.[36] A zinc chloride solution (10 % molar equivalent) in hexane was then added at -78 °C. Several attempts were necessary to obtain the desired secondary alcohol and many of them showed the importance in the use of fresh and anhydrous reagents (experiments summarised in **Table 6**). Anhydrous conditions also appeared to be crucial for the reaction to take place and all glassware was flame dried under nitrogen.

The first experiments did not show any conversion and only the starting material was recovered (**Table 6**, **entries 1** and **2**). The change between the Grignard solution in ether (**II.A.2**) with a commercially available solution in THF also did not give any conversion (**Table 6**, **entry 2**). During the first experiments only the starting ester **63** was recovered, so the reduction of the ester by formation of the aluminoxy acetal intermediate was not successful. A fresh bottle of DIBAL was then used and the TLC showed the appearance of some product (**entry 4**). The crude NMR spectra showed a 2:1 ratio of product **65** to starting material **63**. Purification of the crude mixture was not achieved at this time as separation of

the component parts was difficult. Repeating the reaction on a larger scale failed as a 3:7 ratio of product **65** to starting material **63** was recovered. At this stage it was assumed that the main problem was the formation of the aluminoxy acetal intermediate (see **Figures I.33**) as no aldehyde **89** was recovered. Moreover, only the small amount of aluminoxy acetal formed was reacting with the Grignard reagent to deliver the product.

Entry	Reducing Agent	Lewis acid (%mol)	Grignard reagent **64**	Conversion (%)	Comments
1	1:1 DIBAL: TRIBAL	10 mol% $ZnCl_2$	3 equiv. in ether	0	Starting material **63** recovered
2	1:1 DIBAL: TRIBAL	10 mol% $ZnCl_2$	3 equiv. in THF	0	Starting material **63** recovered
3	1:1 DIBAL: TRIBAL	10 mol% $ZnCl_2$	3 equiv. of fresh Grignard in ether	0	Starting material **63** (96%) and aldehyde **89** (4%) recovered
4	1:1 DIBAL: TRIBAL Using fresh bottle of DIBAL	10 mol% $ZnCl_2$	3 equiv. in ether	TLC shows product	Problem of purifications. 2:1 product to starting material
5	1:1 DIBAL: TRIBAL	10 mol% $ZnCl_2$	3 equiv. in ether	7.4	Difficulties during purification either by chromatography or distillation. 3:7 product to starting material

Table 6 – Experimental results for the reductive alkylation of alanine derivative 63

It was then decided to change of procedure for the reduction of the amino ester. Zhao conducted several experiments on the reduction/alkylation of *N*-Boc proline esters **83** with a warm-up step that provided high diastereoselectivity (see

above).[35] The DIBAL solution was added at -78 °C to the Boc ester **63** and the reaction mixture was warmed to -20 °C for 1 h (warm-up step). The reaction solution was then re-cooled to -78 °C before the addition of the Grignard reagent **64**. Adaptation of Zhao's postulated mechanism, that the higher temperature step allows the equilibrium of the aluminoxy acetals **R1**/**R2** intermediates to produce the major diastereomer **R2** (see **Figure I.35**) may be extended to ester **63**. The intermediate presented in **Figure I.33** can be adapted for the Boc-protected alanine ester **63** where the major aluminoxy acetal **E2** delivers, after alkylation, the alcohol **65** (**Figure II.6**).

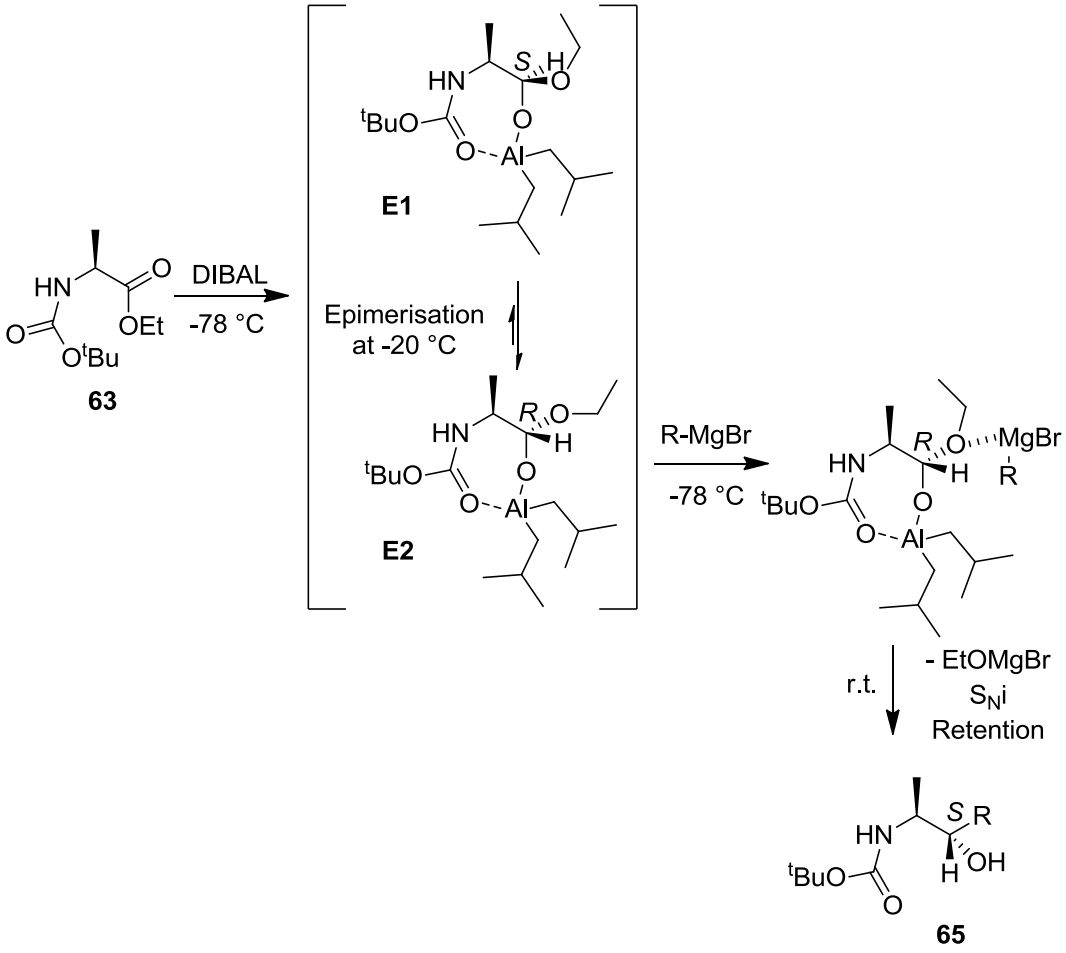


Figure II.6

In our case, this procedure was tested first with phenylmagnesium bromide and phenyllithium for the reductive alkylation of the Boc alanine ester **63** (**Figures II.7**, **Table 7**). Although the phenyllithium in solution in THF didn't give any

product (**entry 1**), the phenylmagnesium bromide in solution in THF gave the alcohol **90** in a moderate but promising yield (34 %).

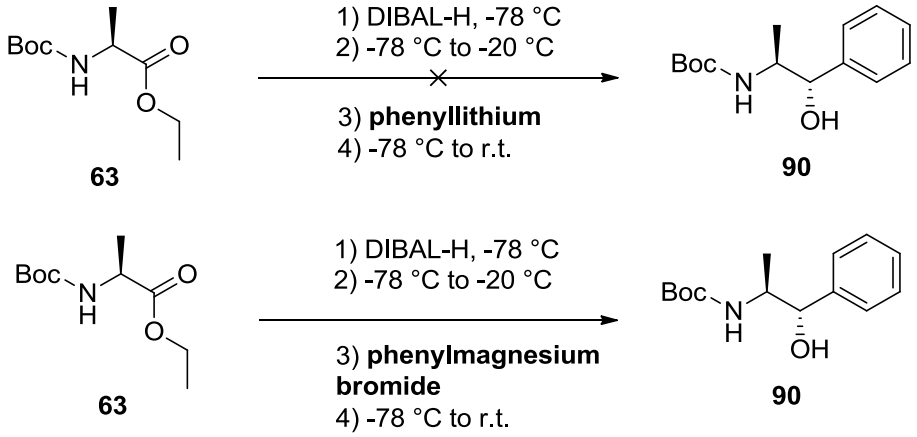


Figure II.7

Entry	Reducing Agent	Alkylating reagent	Conversion to **90** (%)	Comments
1	2 equiv. DIBAL	3 equiv. phenyllithium in THF	0	Starting material recovered
2	2 equiv. DIBAL	3 equiv. phenylmagnesium bromide in THF	34	7:2:1 ratio of product **90** :aldehyde **89** :starting material **63**

Table 7 – Reductive alkyltion of ester 63 using a warm up step with DIBAL

Zhao's procedure was then tested with the Boc alanine ester **63** and Grignard reagent **64** (**Table 8**). Experiments showed that when the solution of DIBAL:TRIBAL in hexane was used, only the aldehyde **89** could be recovered (**entry 1**). However, when 2 equivalents of DIBALH along with the warm-up step procedure were carried out, the reaction gave the alcohol **65** as major product (**entries 3-7**). It was also discovered that the concentration of commercially available DIBAL and TRIBAL solution in hexane could not be trusted. It was found that only 1.2 equivalents were actually being added when it

was originally thought to be 2. This may explain why the majority of the starting material was recovered. The titration of each new purchased bottle was therefore required to obtain the correct concentration of the reducing agents (see experimental).[54]

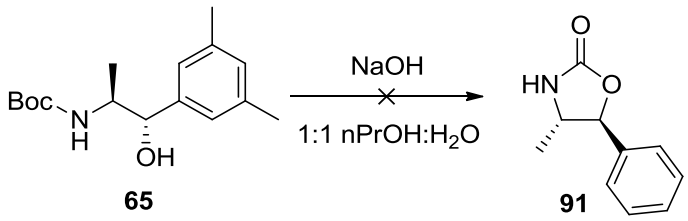
By adopting the procedure with the correct equivalents of reducing agent, all the starting material was converted into the aldehyde **89** but the product **65** couldn't be detected by ^{1}H NMR. This showed that the aluminoxy acetal intermediate was formed but the alkylation step was not optimal. As a general observation, the reaction gave a better conversion when the Grignard reagent **64** was in diethyl ether instead of THF and has been confirmed by experiments carried out by Polt.[36] The addition of 5 equivalents of Grignard reagent in diethyl ether allowed a conversion of 35 % (**Table 8**, **entry 7**).

Entry	Reducing Agent	Grignard reagent **64**	Conversion to **65** (%)	Comments
1	1:1 DIBAL:TRIBAL	3 equiv in THF	0	Aldehyde **89** is recovered
2	1.2 equiv DIBAL	3 equiv in THF	-	1:2 product **65** to starting material **63** but could not be purified
3	2 equiv DIBAL	3 equiv in THF	-	2:1 product **65** to starting material **63** but could not be purified
4	2 equiv DIBAL	3 equiv in ether	-	3:2 product **65** to starting material **63** but could not be purified
5	2 equiv DIBAL	3 equiv in ether	23	7:2:1 product **65** :aldehyde **89** :starting material **63**
6	2 equiv DIBAL	3 equiv in ether	18	9.7:0.3 product **65** to aldehyde **68**
7	2 equiv DIBAL	5 equiv in ether	35	9.9:0.1 product **65** to aldehyde **89**

Table 8 – Reduction/alkylation conditions for ester 63

The NMR spectra of the crude mixture showed the aldehyde **89**, the starting material **63** along with many aromatic impurities. The purification of this reaction was then not easy to achieve. Vacuum distillation of the crude mixture did not give a satisfying purification as the boiling point of most of the impurities were close to the product. To assist the purification, an attempt to cyclise the amino alcohol **65** into its corresponding oxazolidinone **91** was carried out, but only starting material was recovered (**Figure II.8**).[55] Finally, at least two purifications by flash column chromatography were necessary to obtain the desired product **65**.

However, this reaction gave a moderate yield and it is believed that some material was lost during work up as an aluminium complex.



65 **91**

Figure II.8

The selectivity of the reaction was determined by ^{1}H NMR of the crude reaction mixture. The proton α to the OH group in **65** couples with H_β and has a doublet at 4.44 ppm. A spinning side band effect was observed on each side of the peak and one of them was twice the integration as the other (downfield: 0.04 ppm at 4.48 ppm, upfield: 0.02 ppm at 4.40 ppm). It was thought that the doublet from the other (1*R*,2*S*) diastereoisomer of **65** was underneath this spinning side band. However, this cannot be confirmed spectroscopically but no other appropriate signals were apparent in the ^{1}H NMR. The best diastereoselectivity obtained was a 50:1 ratio of product **65** and undesired diastereoisomer (**Table 8**, **entry 8**).

Finally, the reductive alkylation of Boc alanine ester **63** to the Boc-protected amino alcohol **65** was possible using the warm-up step procedure and required fresh DIBAL solution in hexane and 3,5-dimethylphenyl magnesium bromide in diethyl ether. At this stage, the decision was taken to proceed with the synthesis as an adequate yield had been achieved and time was of the essence.

4. Reduction of Boc protected amino alcohol 65

The reduction of the Boc group within **65** was performed using $LiAlH_4$ as the reducing agent in THF (**Figure II.9**). The reaction was carried out on the pure **65** using 3 equivalents of $LiAlH_4$ and refluxed for 10 hours. Unfortunately the starting material was recovered. In order to test the batch of $LiAlH_4$, the reduction was then tried on the Boc-alanine ester **63** which should easily be reduced. The reaction didn't work and the starting material was recovered. The reaction was

also carried out on *N*-Boc-L-alanilol **92** with a new batch of $LiAlH_4$ but only starting material was recovered.

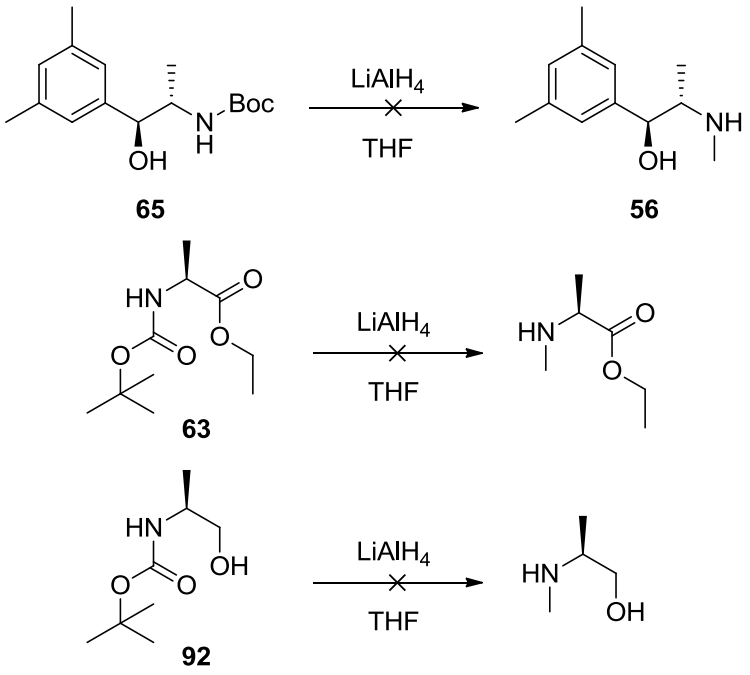


Figure II.9

Another procedure found in the literature involved the reduction of the pyrrolidine carbamate **93** into the tertiary amine **94** using 6 equivalents of DIBAL and reflux of 15 hours (**Figure II.10**).[56] However, when the reaction was carried out in the laboratory, it didn't work and only the Boc amino alcohol **65** was recovered.

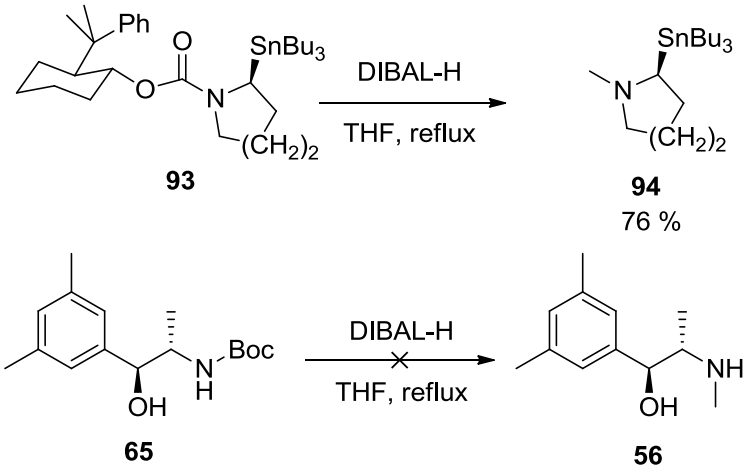


Figure II.10

B. Synthesis of analogues of 56

To investigate the mechanism of the alkylation of pseudoephedrine, it was necessary to synthesise analogues of **56**. The preparation of Grignard reagents was then required.

4-Methoxyphenylmagnesium bromide **96**, 4-*tert*-butylphenylmagnesium bromide **98** and 9-anthrylmagnesium bromide **101** were synthesised using the method described earlier for the formation of **64** (**Figure II.11**).[53] The results are summarised in **Table 9**. For the formation of the Grignard **101** the microcrystalline oxide-free particles of magnesium were not enough to initiate the reaction. Furthermore, the substrate **100** is minimally soluble in diethyl ether and the amount of solvent is a critical point for the initiation of this reaction (**II.2, entry 6** in **Table 5**). When the substrate was dissolved in ether and added directly to the magnesium particles, the reaction didn't initiate. Ultimately, addition of iodomethane (*ca.* 0.1 ml) after the injection of the substrate was enough to initiate the reaction. A reflux of 6 hours was also needed to convert all the substrate into the Grignard reagent **101**.

To obtain the conversion by ^{1}H NMR, an aliquot of each reaction was taken and quenched with water. For the conversion of **95** to **96**, the peak of the anisole obtained was compared to the starting bromide **95** and biphenyl by-product. For the conversion of **97** to **98**, the peak of the *tert*-butylbenzene obtained was compared to the starting bromide **97** and biphenyl by-product. For the conversion of **100** to **101**, the peak of the anthracene obtained was compared to the starting bromide **100** and bianthracene by-product.

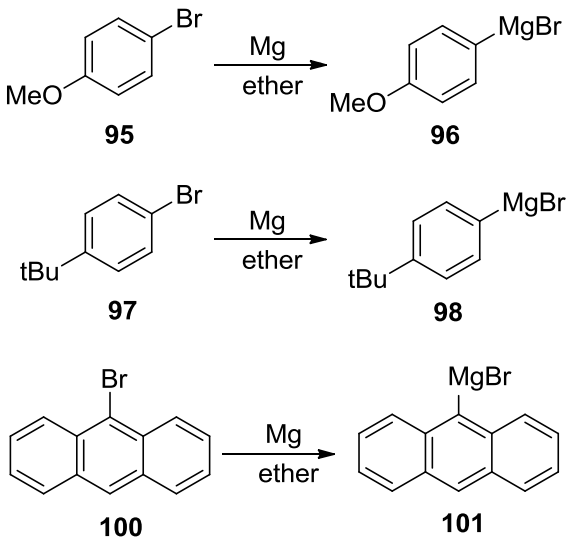


Figure II.11

Entry	Substrate	Mmol of aryl halide	Equivalents of Mg	Conversion (%)
1	**95**	16.1	6.5	82
2	**97**	16.1	5	91
3	**100**	5.83	5	99

Table 9

The Grignard reagents were then used for the reductive alkylation of Boc-alanine ester **63**. These reactions were carried out with four different organomagnesium reagents to afford four different analogues of the protected alcohol **65** (**Table 10**, **Figure II.12**). The yields were moderate to low and no sign of the other diastereoisomer was detected by NMR of the crude reaction mixtures for the **entries 1**, **3** and **4**. For the **entry 2**, the alcohol **103** was synthesised in high diastereomeric ratio and in moderate yield. For entries **1**, **3** and **4** the other diastereoisomer could not be detected by ^{1}H NMR neither by COSY.

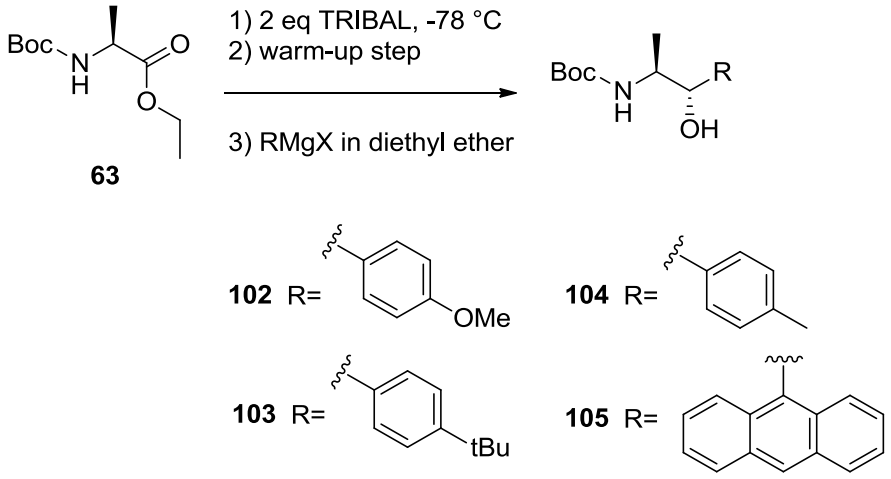


Figure II.12

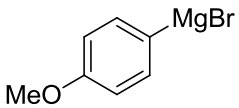
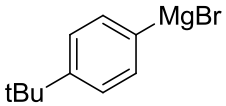
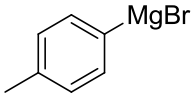
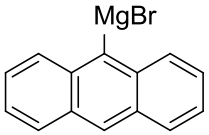
Entry	Grignard reagent	Product	Conversion (%)	dr
1	 **96**	**102**	11	-
2	 **98**	**103**	30	98:2
3	 **99**	**104**	30	-
4	 **101**	**105**	10	-

Table 10 – Reduction/alkylation of ester 63 with various Grignard reagents

Five Boc-protected analogues of pseudoephedrine were synthesized and they all bear electron donating groups onto the phenyl ring. The synthesis of Grignard reagents was achieved with a high conversion and then utilised for the reductive alkylation of the ester **63** to form alcohols in moderate yield and with high selectivity when measurable.

Conclusion

During this project, the synthesis of five different analogues of Boc-protected pseudoephedrine has been carried out in moderate yield and high diastereoisomeric ratio (**Figure II.13**). The reductive alkylation reaction was performed on the Boc-alanine ester **63** and has necessitated intensive investigations to improve the conditions.

Several modifications of the reagents and conditions were necessary to force the reaction to completion. Measuring the concentration of DIBAL solution and of Grignard reagents by No-D NMR method[52, 54] was vital to force the reaction to completion. The best conditions for the reduction alkylation involved an epimerization step by warming the reduction mixture to – 20 ˚C before addition of the Grignard reagent.

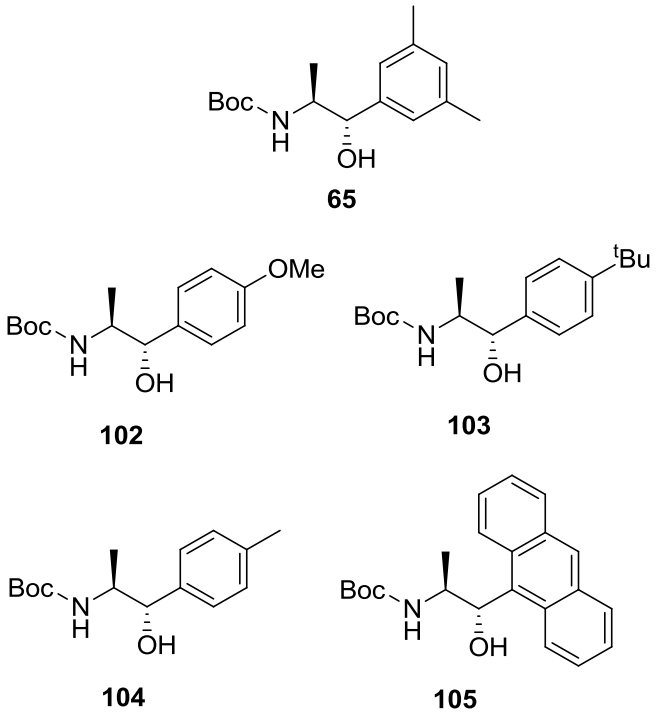


Figure II.13 – Boc-protected analogues of Pseudoephedrine 44

The Boc-protected pseudoephedrine analogues **65**, **102**, **103**, **104** and **105** synthesised all bear electron donating group onto the phenyl ring. The reduction of the Boc group would allow access to direct analogues of pseudoephedrine. Two different methods were tested to reduce the Boc alcohol **65**. The first method utilised $LiAlH_4$[57] and the other one required DIBAL[56] as reducing agents. Unfortunately, none of these methods reduced the Boc-protected amine into secondary amine.

Future Work

In order to avoid the issue of the Boc deprotection using $LiAlH_4$ or DIBAL, the commercially available *N*-methyl-L-alanine **107** could be used as starting material instead of the L-alanine **61** (see **Figure I.26**). The reaction of ethanol with thionylchloride would generate ethylchlorosulfite[58] to react with **107** and produce the ester **108** (**Figure II.14**). Boc protection followed by reductive alkylation using a phenyl magnesium bromide reagent bearing EDG (e.g. **64**) would then afford the Boc-protected alcohol **108**. Treatment with TFA[59] would remove the Boc group and afford the pseudoephedrine analogue **56**.

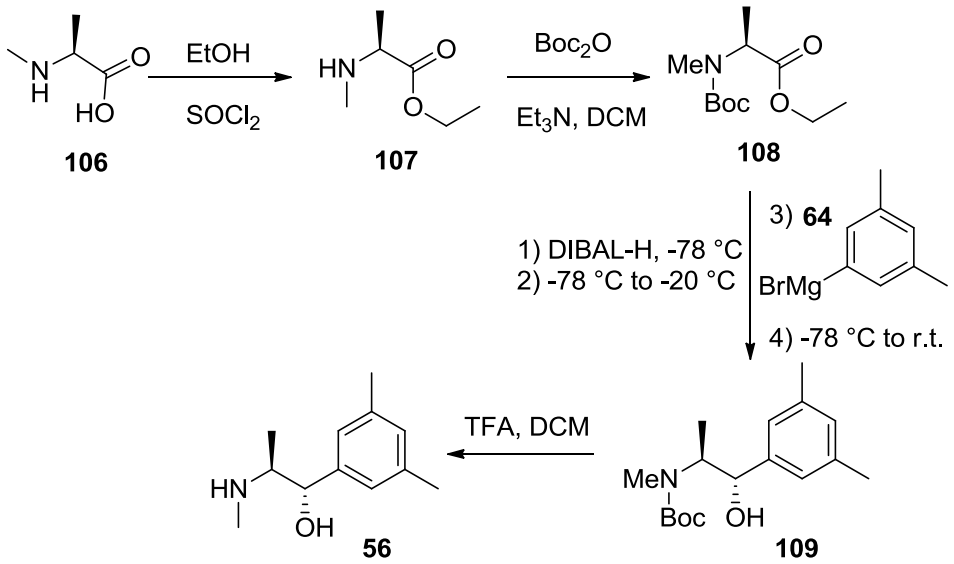


Figure II.14 – Other route to synthesis analogues of pseudoephedrine 44

Another approach to synthesis analogues of pseudoephedrine from the Boc-protected analogue **65** is presented in **Figure II.15**. First, protection of the alcohol would deliver the *O*-benzyl product **110** and subsequent *N*-methylation of the amine would afford the tertiary amide **111**. Removal of the benzyl protecting group by a naphthalene-catalysed lithiation[60] followed by deprotection of the amine would give the alcohol **56**, analogue of pseudoephedrine.

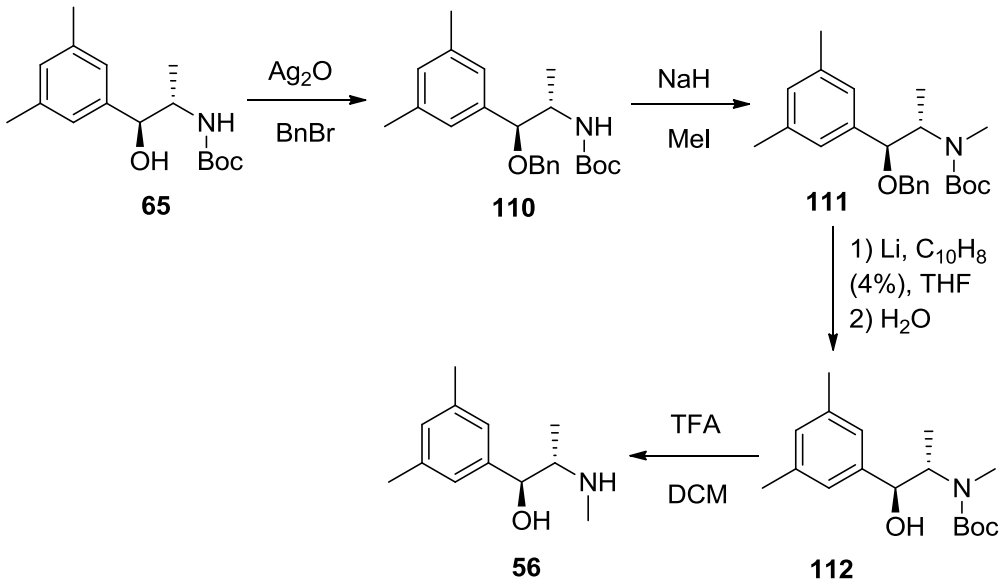


Figure II.15 – Suggestion to synthesis analogues of pseudoephedrine from their Boc-protected form

After building a library of pseudoephedrine analogues (e.g. **56**, **57** and **58** in **Figure I.25**), these compounds can undergo the acylation using hydrocinnamoyl chloride. The acylated derivatives will then be alkylated using Myers' conditions to afford the diastereoisomers (**Figure II.16**).[28] Access to both diastereoisomers will then allow the determination of the de of the reaction. For the analogue **68**, the diasteroisomeric ratio of the reaction will then be determined by NMR or by chiral HPLC[28] or by a cyclisation method[37] (**Figure II.17**). This value would therefore be of interest for a comparison with Myer's results. Indeed, if the diastereoisomeric ratio of the asymmetric alkylation reactions is higher than what

Myers obtained, the hypothesis for which the electron density of the phenyl ring has an impact on the selectivity of the reaction would be verified. On the other hand, if the diastereoisomeric ratio is similar to Myers, an alternative hypothesis is needed.

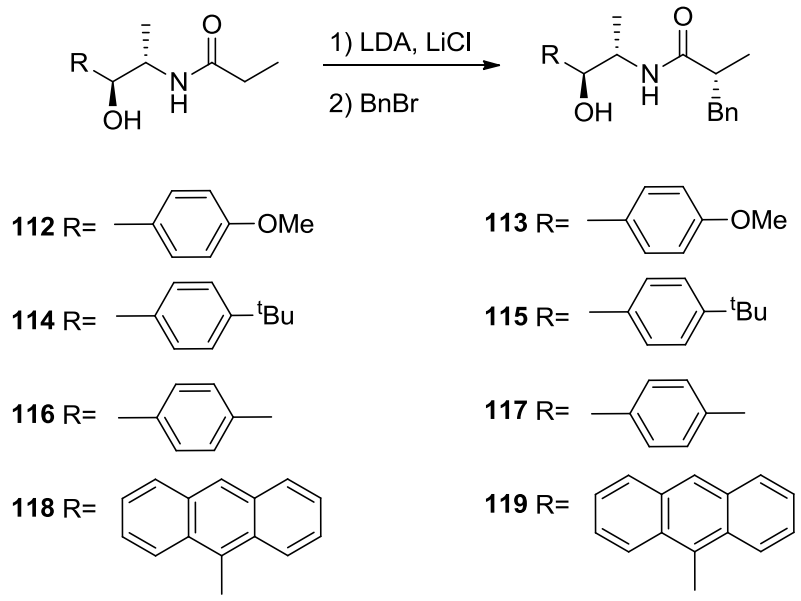


Figure II.16

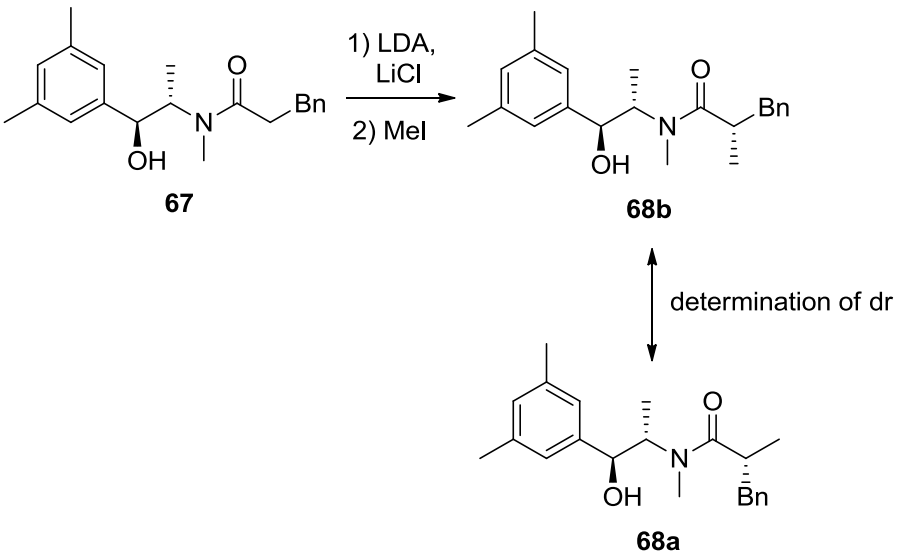


Figure II.17

Experimental Procedures

Instrumental

NMR ^{1}H and ^{13}C NMR nuclei were carried out on Brüker DPX-400 Spectrometer. The Chemical Shift δ are quoted in ppm and measured relative to residual proton from the deuterio solvent for ^{1}H and relative to solvent for ^{13}C NMR. Coupling constants, *J*, are given in Hz.

IR Mattson 1000 FTIR spectrometer (Unicam Analytical Systems). Breeze software. KBr discs were used for solid compounds and NaCl plates for oils. Frequencies are quoted in cm^{-1}.

HR-MS-FAB Recorded on a Joel JMS-700 M STATION high resolution magnetic sector spectrometer. Samples were analysed by the technical staff at the University of Strathclyde.

Chromatography

TLC Merck 0.25 mm silica gel 60 F_{254}. Visualisation using UV radiation at 254 nm, 366 nm.

TLC Visualisation Vanillin: 15g of vanillin in ethanol with 2.5 mL of conc. sulfuric acid.
Phosphomolybdic acid: 12g of phosphomolybdic acid in ethanol.

Column Silica gel mesh size 230-400 (40-60 μm). Flash column chromatography was carried out using standard procedures.[61]

Solvent Drying Procedure

DCM **Et_2O** **THF**	Provided by standard operating procedure for Innovative Technology Solvent Purification System.
NEt_3	Distilled from sodium hydroxide

Reagent drying

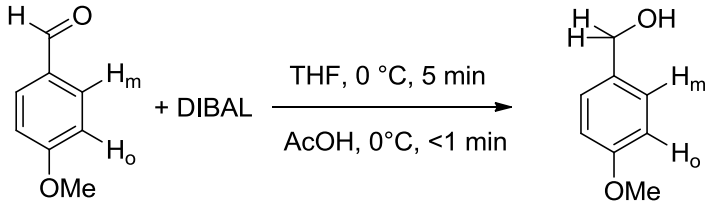
Drying of aryl halide reagents was done by distillation using a high vacuum pump. 1-bromo-3,5-dimethylbenzene was distilled under reduced pressure (2 mmHg) at 55 °C, 4-Methoxyphenyl bromide distilled under reduced pressure (2 mmHg) at 67 °C, 4-*tert* Butylphenyl bromide distilled under reduced pressure (2 mmHg) at 35 °C and 9-Bromoanthracene distilled under reduced pressure (1 mmHg) at 150 °C.

Experimental

Method for analysis or titrating Grignard reagents:

The method used for measurement of the concentration of the Grignard solution employs COD as a non-deuterium-enriched solvent for reference.[52] 100 µl of the COD standard was added to a tared 5 mm NMR tube previously flushed with nitrogen. The mass of COD added was recorded. A precise volume of the Grignard solution was added (600 µl) and the NMR tube was capped with a standard plastic NMR tube. The tube was then agitated to homogenize the solution and the ^{1}H NMR data was recorded. The NMR instrument was run in an unlocked mode and shimming was performed. The concentration is determined from the integral ratios between the Grignard reagent and the COD. To assess integration, the vinylic proton resonance of COD at 5.56 ppm is used as an internal integration standard for all Grignard reagents.

Titration procedure for DIBAL:



120 **121**

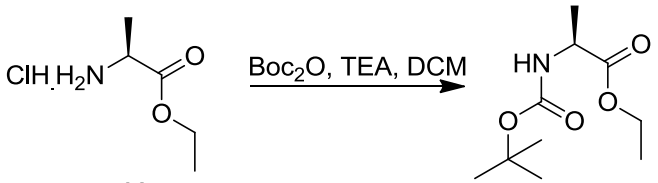
p-Anisaldehyde **120** (ca. 300 mg, ca. 2.5 mmol) was dissolved in THF (3 ml) and cooled to 0 °C under nitrogen. A precise volume of DIBAL (ca. 1.25 mmol) was added dropwise over 1 min and the solution was stirred for 5 min. Glacial acetic acid (ca. 2 ml) was added dropwise with vigorous stirring (protonolysis of Al-C bonds was sometimes exothermic and accompanied by some gas evolution). An aliquot of the homogeneous solution was transferred to a 5 mm NMR tube and capped in the normal fashion. The spectrum was recorded and the calculation of the concentration was based on the integration of the aromatic protons. The conversion of *p*-anisaldehyde **120** into neutral *p*-methoxybenzyl alcohol **121** was

determined by integration of the proton H_m in **120** (at 7.0 ppm) and **121** (at 6.8 ppm). The number of mmol of **120** and the volume of DIBAL being precisely known, the concentration of the DIBAL solution is given by the following equation:

[DIBAL] = (mmol **120**) * (%conversion) / (volume of DIBAL solution in mL)

where (%conversion) = (integral of **121**) / [(integral of **120**) + (integral of **121**)].

Synthesis of Ethyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]propanoate 63:



62 **63**

Ethyl (2*S*)-2-aminopropanoate hydrochloride **62** (65.1 mmol, 10g) was dissolved in anhydrous DCM (10 ml) under nitrogen. Triethylamine (2 equiv., 18 ml, 130.2 mmol) was added very slowly at the beginning. A slight reflux was observed in the flask and was controlled with an ice/water bath. The solution was stirred for 15 min at room temperature until all the triethylamine hydrochloride salt had precipitated. After the addition was completed, *tert*-butyloxycarbonyl anhydride (20 g, 91.1 mmol) was added dropwise using a syringe pump over a period of 15 min. The reaction was stirred overnight at room temperature and the reaction was monitored by TLC. If the reaction showed that some starting material remained, a further 0.2 equiv. of *tert*-butyloxycarbonyl anhydride (2.8 g, 13 mmol) was added until the disappearance of the spot of the starting material. The reaction was then quenched with saturated aqueous solution of $NaHCO_3$ (50 ml) followed by extraction using DCM (3 × 20 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure (53 mmHg) to afford 23.4 g of crude bright yellow oil. Distillation at 30 °C using a high vacuum pump (2 mmHg) removed most of the excess of *tert*-butyloxycarbonyl anhydride but a final chromatography (EtOAc (30%) : hexane (70%)) afforded 8.8 g (40.5 mmol, 88%) of a bright yellow oil.

HRMS: M+Na=240.1206 calculated for $C_{10}H_{19}NO_4$+Na=240.1204

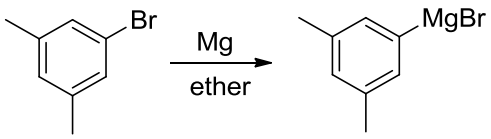
^{1}H NMR δ (400 MHz, $CDCl_3$): 5.06 (br. s, 1H), 4.24-4.32 (m, 1H), 4.19 (q, 2H, *J* = 7.2 Hz), 1.44 (s, 9H), 1.37 (d, 3H, *J* = 7.2 Hz), 1.27 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR δ (500 MHz, $CDCl_3$): 172.9 (C=O), 154.62 (C=O of Boc), 79.27, 60.79, 48.74, 27.9, 27.82, 27.67, 18.21

FTIR (neat, cm^{-1}): 3366 (br. s, NH), 2981, 2937, 1718 (br., 2 x C=O), 1517, 1455;

$[\alpha]_D$ = -41.8 (c = 1, MeOH) (lit. [α]D = -42 (c = 1, MeOH))[62]

Preparation of Grignard reagent bromo(3,5-dimethylphenyl)magnesium 64:



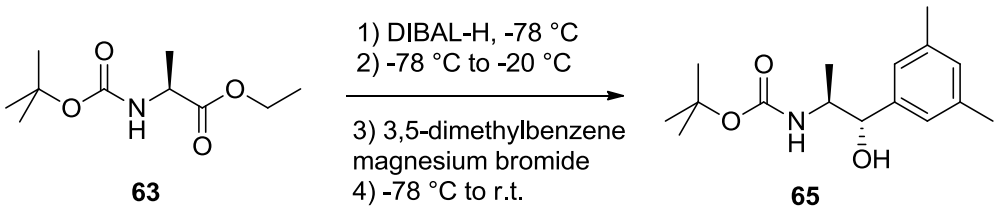
88 **64**

Magnesium turnings (5 equiv., 0.105 mol, 2.54 g) were flame dried under reduced pressure (53 mmHg) then allowed to cool and stirred at room temperature for 16 h under nitrogen. All junctions were sealed with parafilm to prevent any leaks. Anhydrous diethyl ether (5 ml) was then added to cover the surface of the fine magnesium particles and freshly distilled 1-bromo-3,5-dimethylbenzene **88** (16.1 mmol, 2.18 ml) was added via syringe pump to the solution mixture. A reflux of the solution started itself during the addition of the halide and was controlled by cooling the solution with an ice/water bath. Once all the substrate was added, the reaction was refluxed for 2 h. The reaction solution was then cooled to r.t. and transferred via cannula under nitrogen to a flame dried conical flask.

An aliquot (0.1 ml) of the solution was taken and quenched with water (1 ml) and analyzed by ^{1}H NMR. The comparison of the *m*-xylene peaks at 2.38 ppm to the starting bromide at 2.28 ppm and biphenyl by-product at 2.35 ppm gave the

conversion of the reaction and No-D NMR using COD was run for titrating the Grignard reagent. The concentration was usually maintained between 0.3 and 1.2 M.

Preparation of *tert*-butyl (1*S*,2*S*)-1-(3,5-Dimethylphenyl)-2-hydroxy-1-methylethylcarbamate 65:



Dry ethyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]propanoate **63** (4.67 mmol, 1.019 g) was dissolved in anhydrous DCM (50 ml) in a flame dried 3-necked flask under nitrogen. The reaction was cooled to -78 °C and stirred for 30 min. A 1 M solution of DIBAL in hexane (2 equiv., 9.34 mmol, 9.34 ml) was then added dropwise via a pressure-equalizing dropping funnel. The reaction was stirred at -78 °C for 3 h and then in a -20 °C ethyl acetate bath for 1 h. After the warm-up step, the reaction was cooled to -78 °C for 1 h and the Grignard solution in diethyl ether (3 eq, 14.01 mmol) was added dropwise via the same pressure-equalizing dropping funnel. After the addition was completed, the reaction was warmed to r.t. overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 ml) at 0 °C followed by DCM (3 × 30 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure (53 mmHg). Purification by chromatography (EtOAc (3%) : DCM (97%)) afforded 457 mg (35 %) of a thick and sticky light yellow oil. The undesired diastereoisomer was observed in the ^1H NMR of the crude mixture. Spinning sideband effects were observed for the ^1H in the methine doublet at 4.44 ppm but one of the most deshielded doublets (4.55 ppm) integrates as twice as the other (0.04:0.02). Thus, it is believed that the other diastereoisomer doublet was overlapping so the ratio of the desired and undesired diastereoisomer is 50:1. No

other evidence for the methine doublet of the minor diasteromer was evident in the ^{1}H NMR.

HRMS: M+H = 280.1904, calculated for $C_{14}H_{21}NO_3^+$ M+H = 280.1907

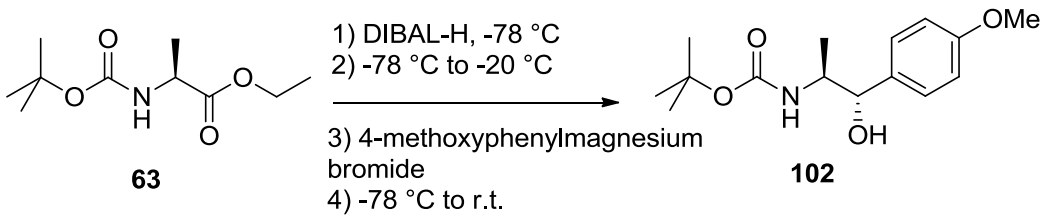
^{1}H NMR δ (400 MHz, $CDCl_3$): 6.95 (s, 2H), 6.92 (s, 1H), 4.72 (br. s, 1H), 4.44 (d, 1H, *J* = 6.5 Hz), 3.88-3.81 (m, 1H), 2.31 (s, 6H), 1.46 (s, 9H), 1.07 (d, 3H, *J* = 7 Hz)

^{13}C NMR δ (500 MHz, $CDCl_3$): 156.7 (C=O), 139.3, 137.8, 129.5, 124.5, 79.7, 78.7, 52.5, 28.5, 21.4, 17.8;

FTIR (neat, cm^{-1}): 3410 (br. s, OH), 1687 (m, C=O), 1452-1504 (m, C=C aromatic)

$[\alpha]_D$ = 28 (c=1.2, $CHCl_3$)

Preparation of *tert*-butyl (1*S*,2*S*)-2-hydroxy-2-(4-methoxyphenyl)-1-methylethylcarbamate 102:



63 **102**

The same procedure as above for *tert*-butyl (1*S*,2*S*)-1-(3,5-dimethylphenyl)-2-hydroxy-1-methylethylcarbamate **65** was followed. 4-Methoxyphenyl bromide **95** was used for the synthesis of the Grignard reagent 4-methoxyphenylmagnesium bromide **96** (82 % conversion by ^{1}H NMR) and the general procedure described above was followed. The reaction was carried out on 2.29 mmol (500 mg) of substrate **63** and thick bright yellow oil was recovered in 14% yield (70 mg, 0.25 mmol). The dr was calculated by ^{1}H NMR as previously and gave 50:1 of *anti* and *syn* diastereoisomers.

HRMS: M+H = 282.1698, calculated for $C_{15}H_{23}NO_4^+$ M+H = 282.1700

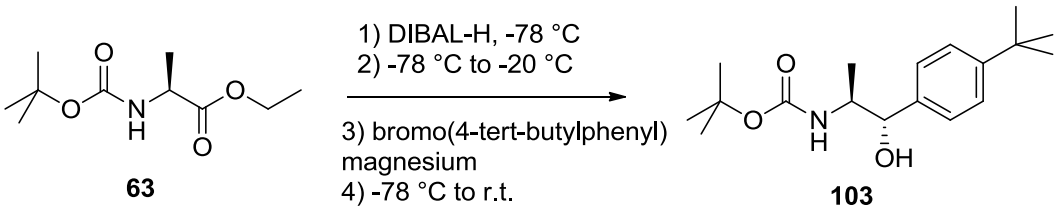
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.25 (d, 2H, *J* = 8.3 Hz), 6.87 (d, 2H, *J* = 8.3 Hz), 4.49 (d, 1H, *J* = 4.8 Hz), 3.9-3.78 (m, 1H), 3.82 (s, 3H), 3.17 (s br., OH), 1.42 (s, 9H), 1.05 (d, 3H, *J* = 8 Hz)

^{13}C NMR δ (500 MHz, $CDCl_3$): 159.5 (C-O), 157.1 (C=O), 134.1, 128.5, 114.03, 80.01, 78.8, 55.4, 52.9, 28.6, 17.9;

FTIR (neat, cm^{-1}): 3200-3549 (br. s, OH), 1662 (m, C=O), 1367-1507 (m, C=C aromatic)

$[\alpha]_D$ = 19.4 (c=0.95, $CHCl_3$)

Preparation of *tert*-butyl (1*S*,2*S*)-2-(4-tert-butylphenyl)-2-hydroxy-1-methylethylcarbamate 103:



63 **103**

The same procedure as above for *tert*-butyl (1*S*,2*S*)-1-(3,5-dimethylphenyl)-2-hydroxy-1-methylethylcarbamate **65** was followed. 4-*tert*-Butylphenyl bromide **97** was used for the synthesis of the Grignard reagent 4-*tert*-butylphenyl magnesium bromide **98** (91 % conversion by ^{1}H NMR) and the general procedure described above was followed. The reaction was carried out on 2.29 mmol (500 mg) of substrate **63** and thick bright yellow oil was recovered in 43% yield (213 mg). The dr was calculated by ^{1}H NMR as previously and gave 98:2 of *anti* and *syn* diastereoisomers.

HRMS: M+H = 308.2221, calculated for $C_{18}H_{30}NO_3^+$ M+H = 308.2220

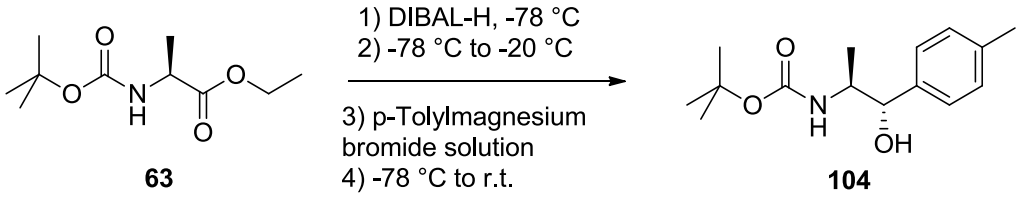
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.36 (d, 2H, 8.4 Hz), 7.27 (d, 2H, 8.4 Hz), 4.67 (br. s, 1H), 4.57 (d, 1H, *J* = 6 Hz), 3.93-3.86 (m, 1H), 1.41 (s, 9H), 1.32 (s, 9H), 1.08 (d, 3H, 6.8 Hz)

^{13}C NMR δ (500 MHz, $CDCl_3$): 156.3 (C=O), 150.5, 138.6, 126.0, 125.1, 79.5, 77.6, 52.2, 34.4, 31.3, 28.2, 17.6;

FTIR (neat, cm^{-1}): 3250-3500 (br. s, OH), 1684 (m, C=O), 1388-1507 (m, C=C aromatic)

$[\alpha]_D$ = 10.6 (c=0.85, $CHCl_3$)

Preparation of *tert*-butyl (1*S*,2*S*)-2-hydroxy-1-methyl-2-(4-methylphenyl)ethylcarbamate 104:



63 **104**

The same procedure as above for *tert*-butyl (1*S*,2*S*)-1-(3,5-dimethylphenyl)-2-hydroxy-1-methylethylcarbamate **65** was followed. *p*-Tolylmagnesium bromide **99** was purchased in solution in ether (Aldrich, 0.4 M). The reaction was carried out on 2.29 mmol (500 mg) of substrate **63** and a thick bright yellow oil was recovered in 36% yield (180 mg, 0.68 mmol). The dr was calculated by ^{1}H NMR as previously and gave 98:2 of *anti* and *syn* diastereoisomers.

HRMS: M+H = 266.1751, calculated for $C_{15}H_{23}NO_3^+$ M+H = 266.1751

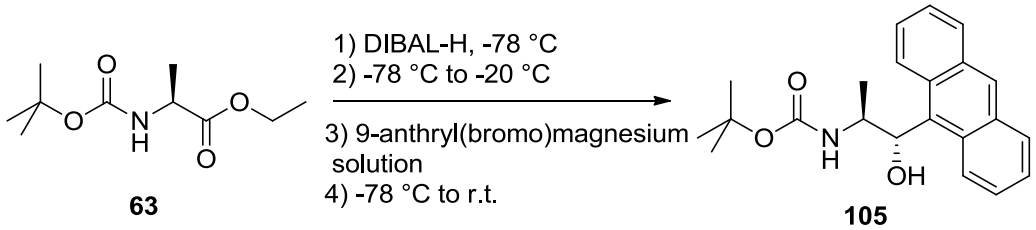
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.21 (d, 2H, *J* = 8 Hz), 7.14 (d, 2H, *J* = 8 Hz), 4.51 (d, 1H, *J* = 3.6 Hz), 3.89-3.81 (m, 1H), 3.1 (s, OH), 2.34 (s, 3H), 1.42 (s, 9H), 1.06 (d, 3H, *J* = 6.8 Hz)

^{13}C NMR δ (500 MHz, $CDCl_3$): 156.7 (C=O), 138.9, 137.5, 129.1, 126.7, 79.8, 78, 52.7, 28.5, 21.3, 17.7;

FTIR (neat, cm^{-1}): 3250-3500 (br. s, OH), 1684 (m, C=O), 1366-1500 (m, C=C aromatic)

$[\alpha]_D$ = 11.3 (c=0.85, $CHCl_3$)

Preparation of *tert*-butyl (1*S*,2*R*)-2-(9-anthryl)-2-hydroxy-1-methylethylcarbamate 105:



The same procedure as above for *tert*-butyl (1*S*,2*S*)-1-(3,5-dimethylphenyl)-2-hydroxy-1-methylethylcarbamate **65** was followed. 9-Bromoanthracene **100** was used for the synthesis of the Grignard reagent 9-anthrylmagnesium bromide **101** (99 % conversion by ^{1}H NMR) and the general procedure described above was followed. The initiation of the reaction required 0.1 ml of iodomethane. The reaction was carried out on 1.21 mmol (262 mg) of substrate **63** and a thick dark yellow oil was recovered in 10 % yield (40 mg, 0.11 mmol). No evidence of a minor diastereomer was observed in the ^{1}H NMR.

HRMS: M+H = 352.1905, calculated for $C_{22}H_{25}NO_3^+$ M+H = 352.1834

^{1}H NMR δ (400 MHz, $CDCl_3$): 8.44 (s, 1H), 8.02 (d, 2H, *J* = 0.8 Hz), 8.0 (d, 2H, *J* = 0.8 Hz), 7.54-7.48 (m, 2H), 7.48-4.44 (m, 2H), 6.07 (d, 1H, J = 8 Hz), 4.83-4.72 (m, 1H), 1.54 (s, 9H), 0.8 (d, 3H, *J* =6.8 Hz)

^{13}C NMR δ (500 MHz, $CDCl_3$): 156.75 (C=O), 139.3, 132.1, 130.5, 129.7, 129.5, 128.9, 125.2, 124.4, 80.6, 76.2, 53, 28.5, 18.6;

FTIR (neat, cm^{-1}): 3170-3520 (br. s, OH), 2977, 1694 (m, C=O), 1367-1505 (m, C=C aromatic)

$[\alpha]_D$ = 36.1 (c=0.9, $CHCl_3$)

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