Probing the mechanism of the asymmetric alkylation of pseudoephedrine amides

By

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Table of Contents

Abstract

One of the most significant issues in organic chemistry today is to create enantiomerically pure compounds. Racemic products, containing both enantiomers in equal quantities, can result is tragic consequences as in the notorious example of the thalidomide drug.

A widely used method to synthesize enantiomerically pure compounds is to utilise a chiral auxiliary. A.G. Myers developed a synthetic route using pseudoephedrine, which is an efficient auxiliary to produce enantiomeric enriched ketones, aldehydes and carboxylic acids. Myers and his co-workers proposed a mechanism for this asymmetric alkylation which assumes that a dianion is formed with the alcohol and the enolate that prevents the formation of the undesired diastereomer.

Results by D.J. Procter and his co-workers using immobilized pseudoephedrine amides on a Merrifield resin as chiral auxiliaries, when analysed, throw into question Myers' mechanistic model. Procter and his co-workers observed that the polymer-supported systems gave similar diastereomeric excess as the solution-state pseudoephedrine amides.

Dr. Gibson from the University of Strathclyde suggested that the mechanism proposed by Myers might be wrong because of Procter's results. Some DFT calculations were carried out which suggested that an alternative π-Li^+ transition state might predominate rather than an alkoxide acting as a steric screen. There are two possible routes to try find out which is the correct mechanism: improve the π-Li^+ interaction by using more electron-rich aromatic rings or avoid any possible chelation of the lithium with the oxygen of the alkoxide and see how it affects the diastereomeric outcome.

This research project focuses on the second route. Therefore, some silyl-protected pseudoephedrine amides were synthesized because they are supposed to prevent lithium chelation. Two silyl ether systems have been investigated: *tert*-butyldimethylsilyl and triisopropylsilyl. The alkylation has been carried out on the silylated derivatives in two different ways (using benzyl bromide or methyl iodide) and the resulting diastereomeric excess were oberved:

- For the TBDMS derivative: 42 % for the benzylation and 17 % for the methylation
- For the TIPS derivative: 34 % for the benzylation and 18 % for the methylation

These results led us to think that the π-Li^+ transition state is the correct one, but more experiments need to be carried out to confirm this result.

Abbreviations

$[\alpha]_D^{20}$: Specific rotation

DCM: Dichloromethane

de: Diastereomeric excess

DFT: Density functional theory

DMAP: 4-Dimethylaminopyridine

DMF: Dimethylformamide

dr: Diastereomeric ratio

ee: Enantiomeric excess

eq: Equivalent

EtOAc: Ethyl acetate

Et_2O: Diethyl ether

FMO: Frontier molecular orbitals

IR: Infra-red spectrometry

HMPA: Hexamethylphosphoramide

HRMS: High resolution mass spectrometry

LDA: Lithium diisopropylamide

NMR: Nuclear magnetic resonance

RAMP: (*R*)- 1-amino-2-methoxymethylpyrrolidine

rt: Room temperature

TBAF: Tetra-*n*-butylammonium fluoride

TBDMS: *tert*-Butyldimethylsilyl

TBDPS: *tert*-Butyldiphenylsilyl

TFA: Trifluoroacetic acid

Tf_2O: Trifluoromethanesulfonic anhydride

THF: Tetrahydrofuran

TIPS: Triisopropylsilyl

TMS: Trimethylsilyl

Ts: Transition state

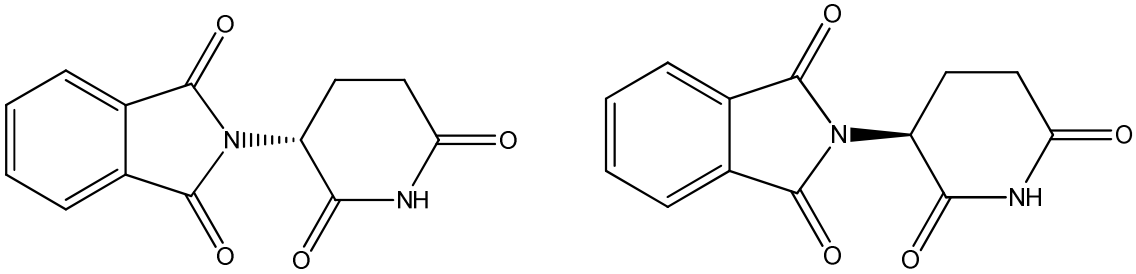
Introduction

The demand for enantiomerically pure compounds is continually increasing, especially in the pharmaceutical, food and agrochemical industries.[1] The industry often prefers enantiopure compounds for the following reasons: activity of the active enantiomer, registration and economic considerations. The enantiopure compound can sometimes be twice as active as the racemate because the undesired enantiomer can be an antagonist. Regarding the registration of drugs, the unwanted enantiomer is considered as an impurity so a full toxicity test is needed, and for economical reasons because the unwanted enantiomer is a waste of starting material.

Asymmetric synthesis remains the best way to produce enantiomerically pure compounds, but synthetic chemists still find these reactions challenging. The two enantiomers of one molecule can have very different bioactivities and different biological responses. In the best case, only one of the enantiomers is active. In the worse case, one enantiomer has the desired activity and the other one has a toxic effect.

This can result in tragic consequences, as in the well-known case of thalidomide drug sold in the 1950s.[2] It is a racemic compound that was prescribed to pregnant women to prevent morning sickness. Unfortunately, (*R*)-thalidomide **1a** is a sedative, but (*S*)-thalidomide **1b** is a teratogen that led to the birth of more than 10,000 deformed babies worldwide (**Figure 1.1**). The most problematic effect is that the two enantiomers are interconverted in the body: even if enantiomerically pure thalidomide had been administered racemisation *in vivo* would have still resulted in the same teratogenic effects. Therefore, this drug was removed from the market in 1961 to treat pregnant women. It is still used today to treat leprosy.

This example shows the importance of asymmetric synthesis and the need to produce enantiomerically pure compounds and to understand the influence of each enantiomer.



(*R*)-thalidomide **1.1 a** (*S*)-thalidomide **1.1 b**

Figure 1.1: The two enantiomers of thalidomide

1 - Asymmetric synthesis

1.1 Definition

An asymmetric synthesis is a "reaction or reaction sequence that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on a heterotopic face, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate."[3] The aim of an asymmetric synthesis is to get the best possible enantioselectivity or diastereoselectivity so as to obtain the highest proportion of the desired compound.

1.2 Principle of stereoselectivity

The stereoselectivity is almost always kinetically controlled, which means that the two stereoisomers must be formed through two diastereomeric transition states which differ in Gibb's free energy of activation (**Figure 1.2**).

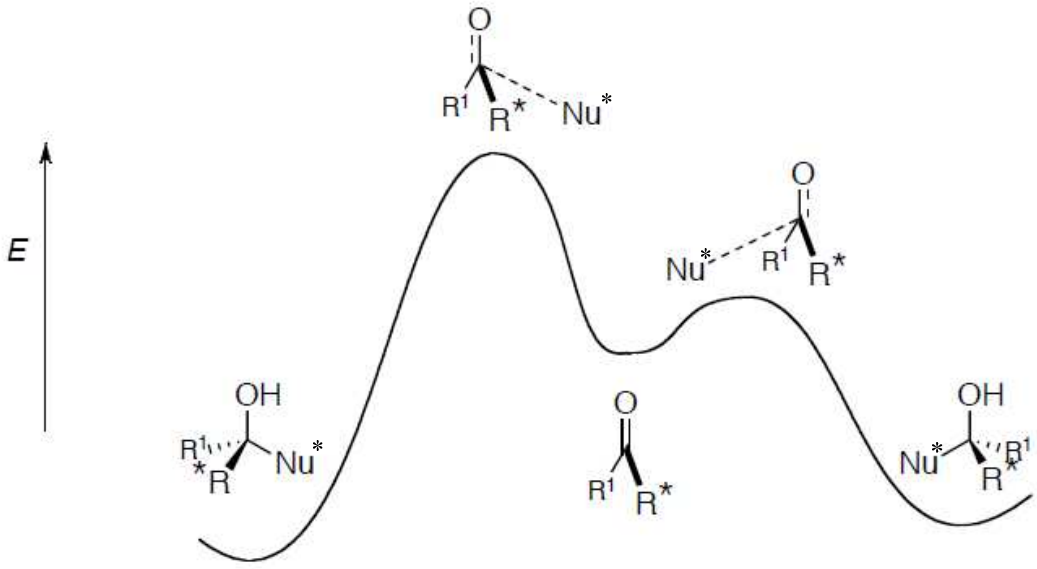
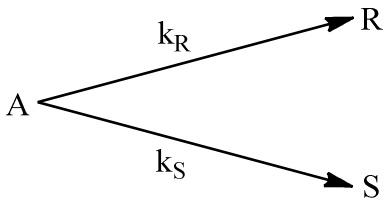


Figure 1.2: Different transition states of the formation of diastereomers in asymmetric synthesis[4]

These transition states will result from the reaction between:

- diastereoselective process: diastereotopic face, atoms or groups with achiral reagents
- diastereoselective process: diastereotopic face, atoms or groups with a chiral reagent
- enantioselective process: enantiotopic face, atoms or groups with chiral reagents or catalysts

Considering an asymmetric synthesis, the starting material A can react to give two possible stereoisomers *R* or *S*.



$$K = Ae^{\frac{-\Delta G^{\ddagger}}{RT}}$$

Arrhenius equation which gives the relationship between the rate constant (k) and the free energy of activation ($\Delta G^{\ddagger}$).

The enantiomereic or diastereomeric ratio is just the ratio of the rate constants:

$$\frac{[R]}{[S]} = \text{enantiomeric/diastereomeric ratio} = \frac{k_R}{k_S} = e^{\frac{-(\Delta G_R^{\ddagger} - \Delta G_S^{\ddagger})}{RT}} = e^{\frac{-\Delta\Delta G^{\ddagger}}{RT}}$$

Rearranged in $$-R\text{Tln}\left(\frac{[R]}{[S]}\right) = \Delta\Delta G^{\ddagger} = -R\text{Tln}(\text{stereoisomer ratio})$$

The selectivity is increased by the difference in the free energy of activation between the two stereo isomers e.g. *R* and *S*. But the difference does not need to be very high to obtain a high selectivity.

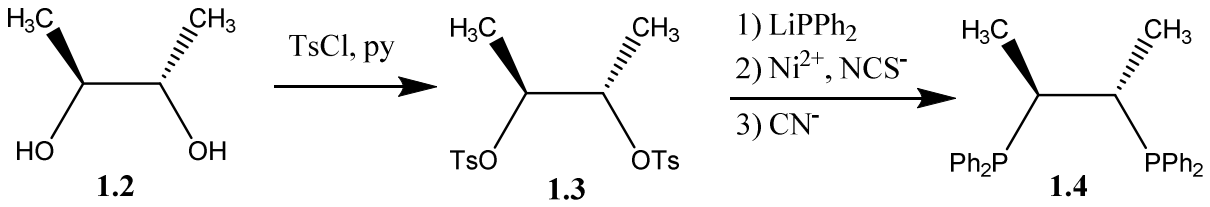
Racemic mixture of *R* and *S*	99.9% enantiomeric excess
$\Delta G_R^{\ddagger} = \Delta G_S^{\ddagger}$ then $\Delta\Delta G^{\ddagger} = 0$ and $\frac{k_R}{k_S} = 1 = \frac{[R]}{[S]}$	$\frac{[R]}{[S]} = \frac{99.95}{0.05}$ $\Delta\Delta G^{\ddagger} = -R\text{Tln}\left(\frac{99.95}{0.05}\right) = 10.9 \text{ kJ mol}^{-1}$ at −100 °C

1.3 Methods of asymmetric synthesis

Asymmetric syntheses can be divided in four categories[1] and each subset shows a different way to produce the new stereogenic elements:

First generation method or Chiron approach: this reaction is diastereoselective and the formation of the new stereocentre is controlled by stereogenic units present in the substrate.

It uses an enantiomerically pure starting material (a chiron), which is usually a natural product (the chiral pool).



Scheme 1.1: Example of first generation synthesis, preparation of (*S*,*S*)-chiraphos[5]

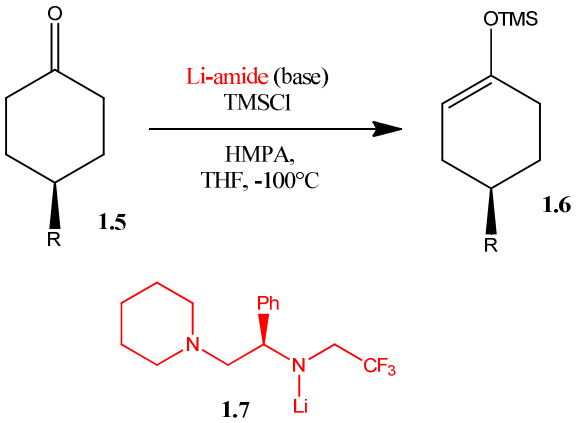
Second generation method or auxiliary control: a stoichiometric chiral auxiliary is covalently attached to the substrate to control the diastereoselective reaction. The auxiliary is removed and can be recycled once the new stereocentre is built.

There are three steps needed for the second-generation method:

- the enantomerically pure chiral auxiliary is covalently attached onto the substrate;
- the diastereoselective reaction with an achiral reagent is carried out to create diastereomers in unequal quantities;
- the chiral auxiliary is removed without racemisation and provides an enantiomerically pure or enriched product.

Many well known syntheses use the second generation method, like the aldol reaction or the Diels-Alder reaction. This will be discussed in more detail at the end of the section.

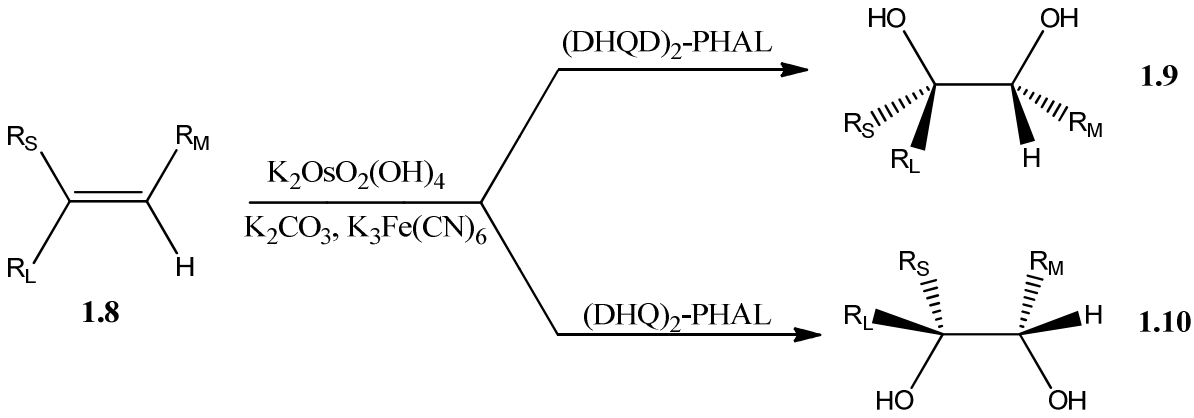
Third generation method: conversion of an achiral starting material in a chiral product using a chiral reagent (in stoichiometric quantity). The advantage of this method over second generation methods is that it does not require the two extra steps of the attachment and the subsequent removal of the chiral auxiliary.



R	Yield (%)	ee (%)
Me	78	94
i-Pr	92	95
t-Bu	88	93
Ph	95	93

Figure 1.3: Example of a third generation method (deprotonation using a chiral base)[6]

Fourth generation method: in this method a chiral catalyst is used to convert the achiral starting material into a chiral product with an achiral reagent. The advantage of this method is that the enatiomerically pure compound is used in catalytic quantity, which is preferred regarding the costs and the recyclability.



R_L = Largest substituent; R_M = Medium-sized substituent; R_S = Smallest substituent

Scheme 1.2: Example of a fourth generation synthesis, the Sharpless dihydroxylation[7]

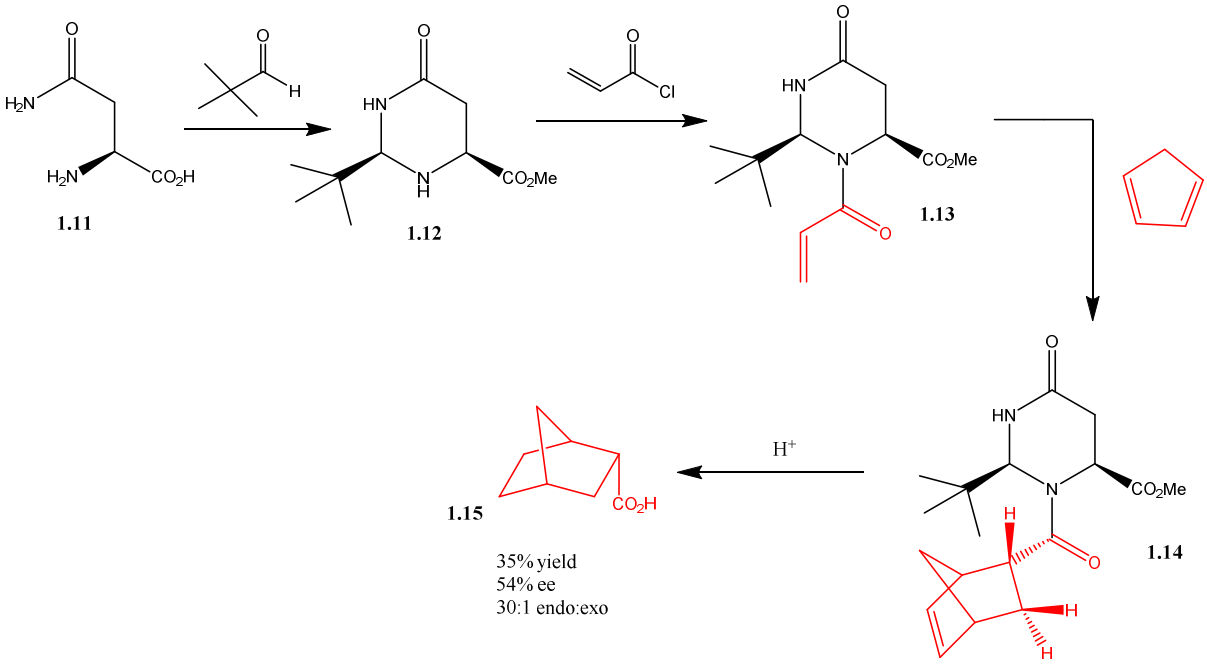
In the Sharpless dihydroxylation example (**Scheme 1.2**) the catalyst is the osmium tetroxide which is regenerated by the potassium ferricyanide at the end of the reaction. This allows the quantity of osmium tetroxide to be reduced, which is convenient as this reagent is very toxic and expensive. Commercially, you can find a mix of all four reagents called "AD-mix" where the "AD-mix-α" mixture contains the $(DHQ)_2PHAL$ and the "AD-mix-β" mixture contains the $(DHQD)_2PHAL$.

The advantage of the third and fourth generation methods is that they allow the use of a much wider range of starting materials. In fact the starting materials do not need to be a natural product (from the chiral pool) or to have a functional group to attach the auxiliary. The fourth generation method is the most elegant and desirable one, because it uses sub-stoichiometric amounts of expensive chiral materials. The problem is that there are only a limited number of catalytic methods available. Second generation methods are still very widely used, particularly those involving enolate reactions.

1.4 Second generation reactions

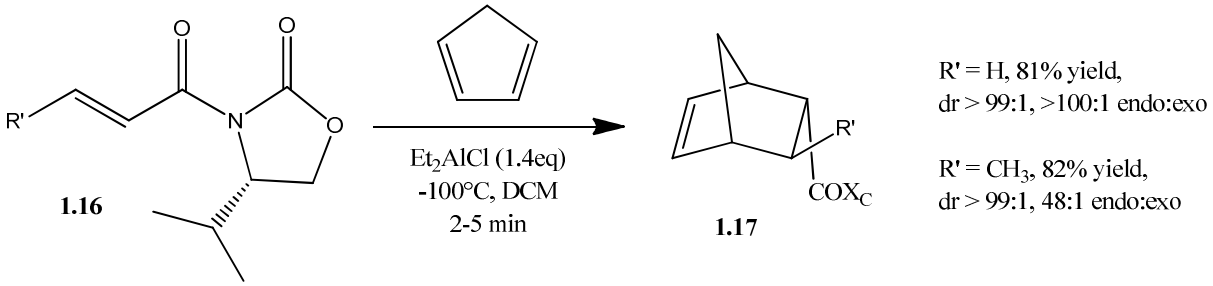
1.4.1 Diels-Alder reaction

Asymmetric Diels-Alder reactions[8,9,10] have frequently been carried out using a second generation asymmetric synthesis. In that case the dienophile or the diene can carry the chiral auxiliary. In general, it is the dienophile which bears the auxiliary. The majority of examples use a chiral auxiliary of acrylic acid amides or esters (**Scheme 1.3**). In the example shown[8] the auxiliary is a derivative of L-asparagine **1.12**.



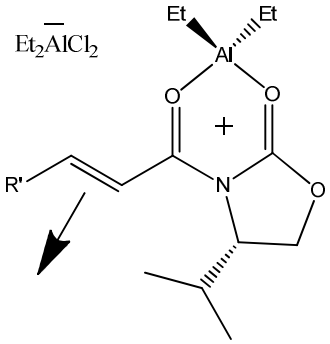
Scheme 1.3: Diels-Alder reaction using a chiral auxiliary[8]

Evans and his co-workers also developed a method for asymmetric Diels-Alder reactions using a *N*-acycloxazolidinone (**Scheme 1.4**).[11] In this reaction an achiral Lewis acid (Et_2AlCl) was used as a catalyst by coordinating to the dienophile.



Scheme 1.4: Evans use of oxazolidinone in an asymmetric Diels-alder reaction[11]

The stereochemical outcome of the reaction is consistent with the following transition state model and rules[11]:

	-the cycloaddition occurs on the less sterically hindered face (2*Si*,3*Re*) of the dienophile double bond. -the reactive dienophile is a chelated cationic species. -the favoured conformation of the chelated acyl oxazolidinone is the *s-cis* conformation.

1.4.2. Aldol reaction

The aldol reaction is a reaction between an enolate and an aldehyde providing a new C-C bond and two new stereogenic centres (**Figure 1.4**). This can lead to the formation of four different stereoisomers.

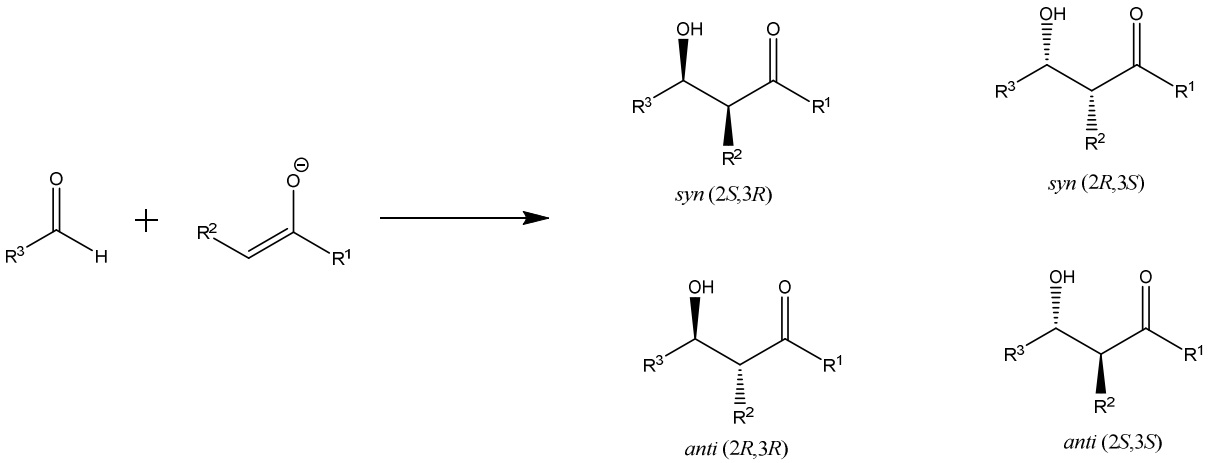
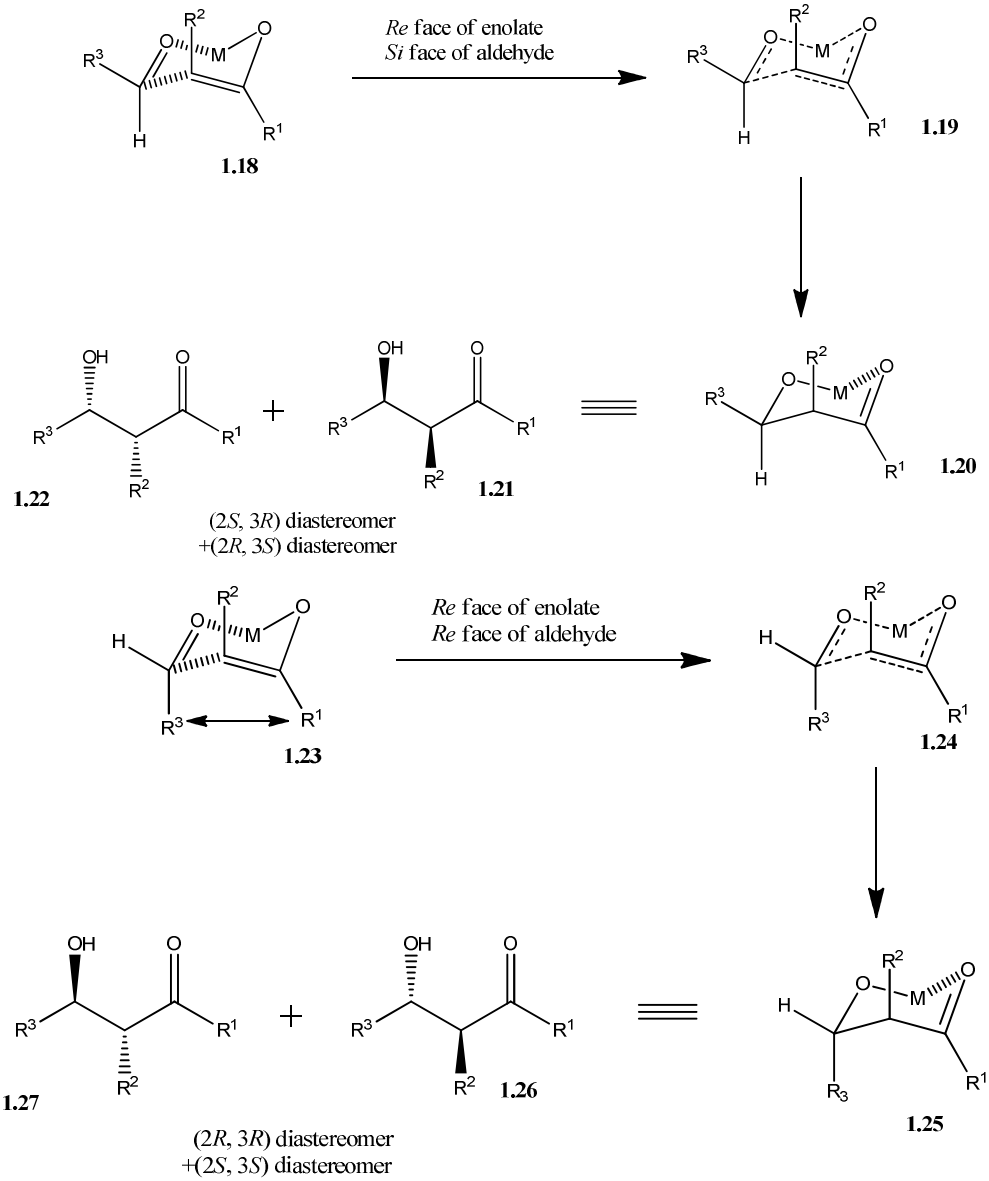


Figure 1.4: Four possible diastereomers of the aldol reaction

In order to predict the stereochemical outcome of the reaction we have to address three questions:

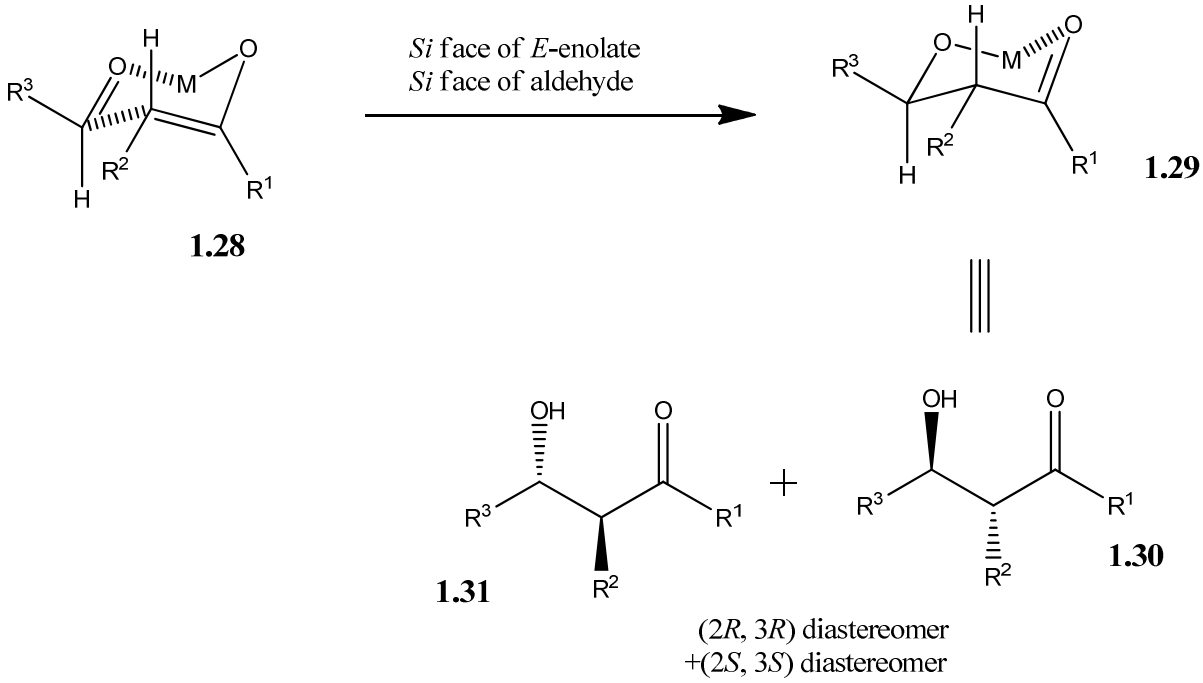
- the relative stereochemistry of the new stereocentres at C-2 and C-3
- the influence of chirality within the aldehyde
- the influence of stereochemistry within the enolate

The diastereomeric outcome of the reaction can be predicted using the Zimmermann-Traxler model which is based on six membered cyclic transition state.[12] This model is based on whether the enolate has a *Z* or *E* geometry (**Scheme 1.5**). This model is valid provided the reaction is under kinetic control, the aldehyde is chelated to the metal, and the transition state is chair-like.



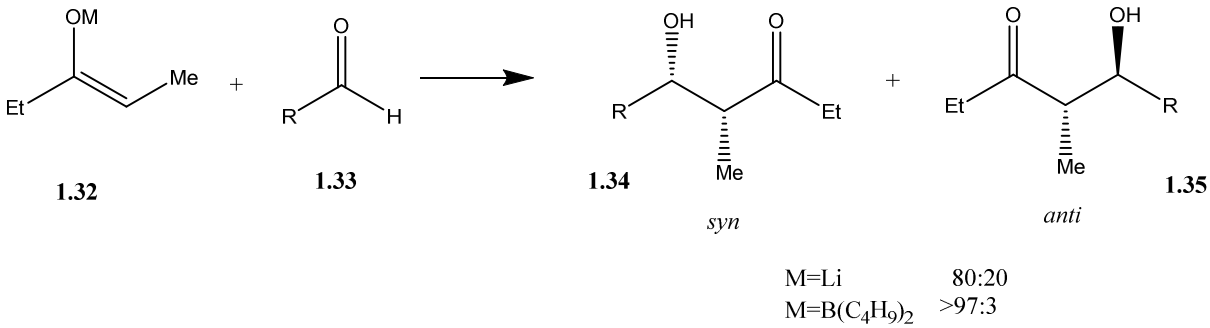
Scheme 1.5: Zimmermann-Traxler model of aldol additions with the *Z*-enolate

As we can see from the model in **Scheme 1.5**, the *anti* products **1.26** & **1.27** for the complex **1.23** is disfavoured because R^1 and R^3 are quite large groups and so there is a 1,3-diaxial repulsion in the transition state **1.23**. The favoured transition state **1.20** has the two R^1 and R^3 *anti* to each other and therefore there is no repulsion. A similar model can be applied for the complex **1.28** and so the *anti* product **1.30** & **1.31** is the major one (**Scheme 1.7**).



Scheme 1.7: Favoured transition state for aldol reaction of the *E*-enolate **1.28**

The enolate metal cation also plays an important part in the stereochemical outcome of the reaction. Boron is often used because boron-oxygen bond-length is significantly shorter than for other metals resulting in a more compact transition state which makes the reaction more stereoselective.[13] The use of boron rather than a metal gives greater selectivity because it "tightens" the transition state.[14] Also, boron only coordinates to two Lewis basic oxygens, important in auxiliary controlled processes (**Scheme 1.8**).

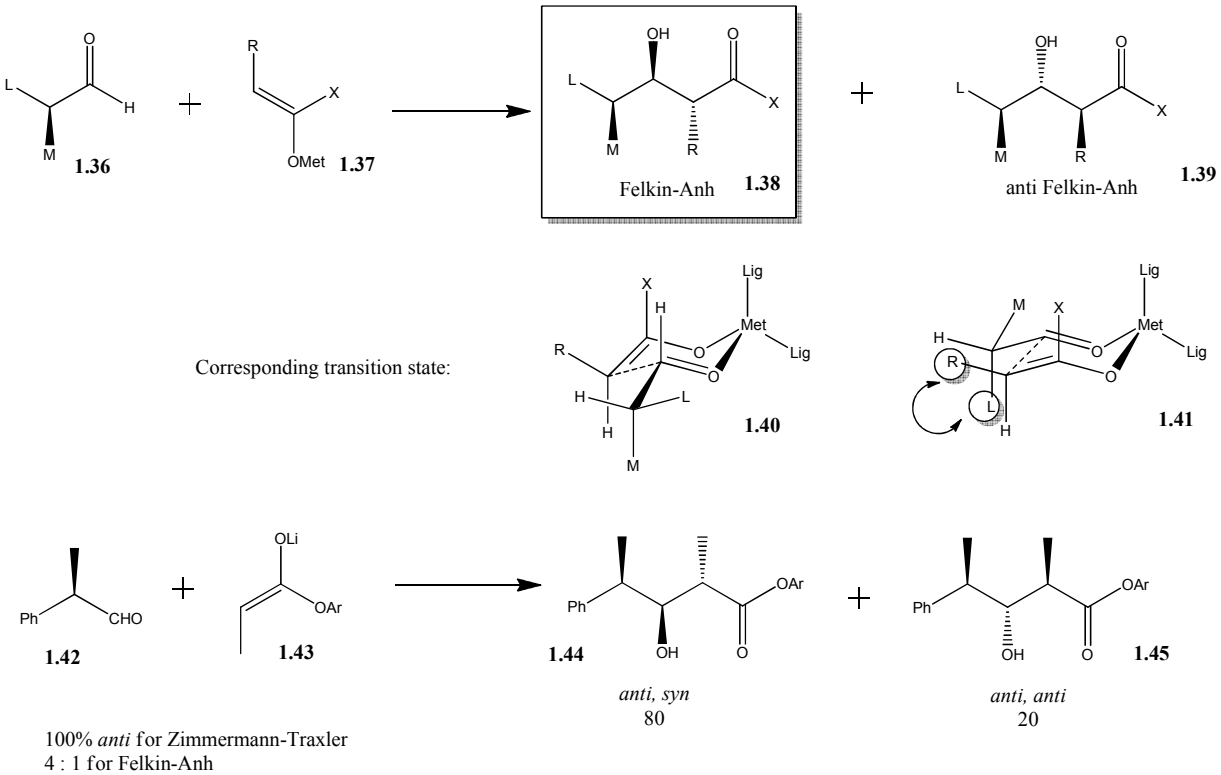


Scheme 1.8: Influence of the metal cation on *syn:anti* outcome in aldol reactions

In the above model (**Schemes 1.6** & **1.7**) the chirality of the enolate or the aldehyde is not considered. We will consider the case of a chiral enolate reacting with a chiral aldehyde. The carbonyl group of the aldehyde generally reacts in a stereoselective way with nucleophiles regarding the Felkin-Anh model or chelation model.[15] The Zimmermann-Traxler model can once again be used to determine the relative configuration of the new C-2-C-3 bond. Both models influence the stereochemical outcome of the reaction[16] (**Scheme 1.9**):

- the *Z*-enolate gives predominantly the *syn,syn* product
- the *E*-enolate gives predominantly the *anti,syn* product

The enolate **1.37** is a *Z*-enolate so the major product is the *syn,syn* compound **1.38**. **1.39** is disfavoured because of the steric repulsion in the transition state **1.41** between the two bulky groups R and L. As we can see for products **1.44** & **1.45**, the Felkin-Anh model does not give 100 % selectivity as the Zimmermann-Traxler model, but only a 4:1 ratio.[16]

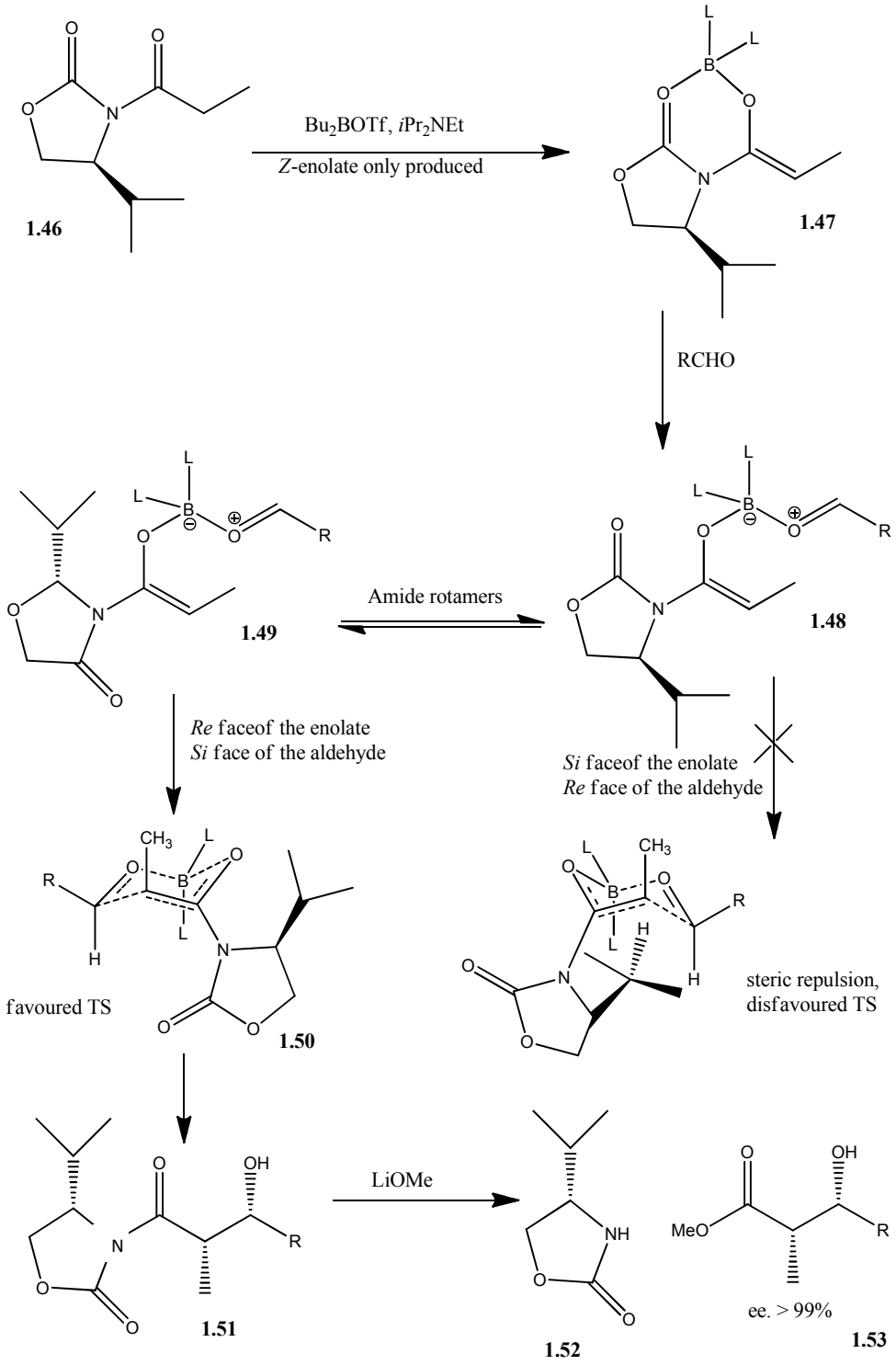


Scheme 1.9: Reaction outcome of a chiral aldehyde and a chiral enolate[16]

There are also reactions where a chiral enolate reacts with an achiral aldehyde which allows one to control the diastereofacial selectivity of the asymmetric aldol reaction.[17] In that area, Evans' chiral oxazolidinones are the most used because they generally give very good stereoselectivity with a predictable stereochemical outcome (**Scheme 1.10**).

In these reactions, only the *Z*-enolate **1.47** is generated by reaction of the oxazolidinone **1.46** with dibutylboron triflate. The aldol reaction has a high degree of selectivity and the *syn* isomer **1.51** is predominant. This stereochemical outcome can be explained by considering the transition states of the two amides rotamers **1.48** & **1.49**. In the disfavoured case **1.48**, there is a steric repulsion between the oxazolidinone substituent (*i*Pr) and the enolate substituent (Me in this case).

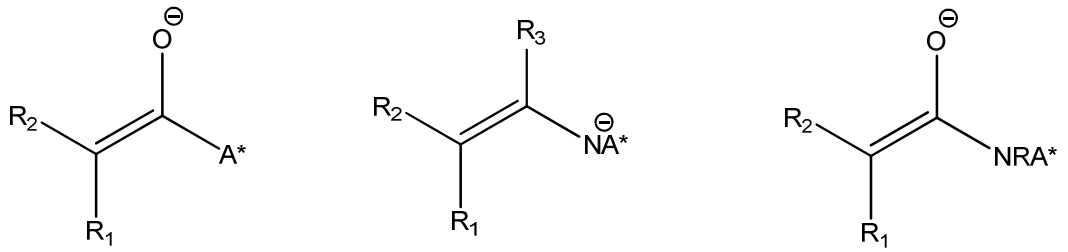
The major product is the *syn* compound **1.51** because the boron retains the chair-like transition state and the disfavoured transition state presents a steric repulsion between the oxazolidinone and the enolate substituent.



Scheme 1.10: Reaction of a chiral enolate with an achiral aldehyde[18]

1.4.3 Chiral azaenolates/enolates

The enolate is a well suited to the use of a chiral auxiliary especially for the formation of carbon-carbon bond reactions. There are three situations where enolates may be used with chiral auxiliaries (A*) in asymmetric synthesis (**Figure 1.5**).[2] The azaenolates **1.55** and amide enolates **1.56** equivalent have been most widely used so we will detail only these approaches.

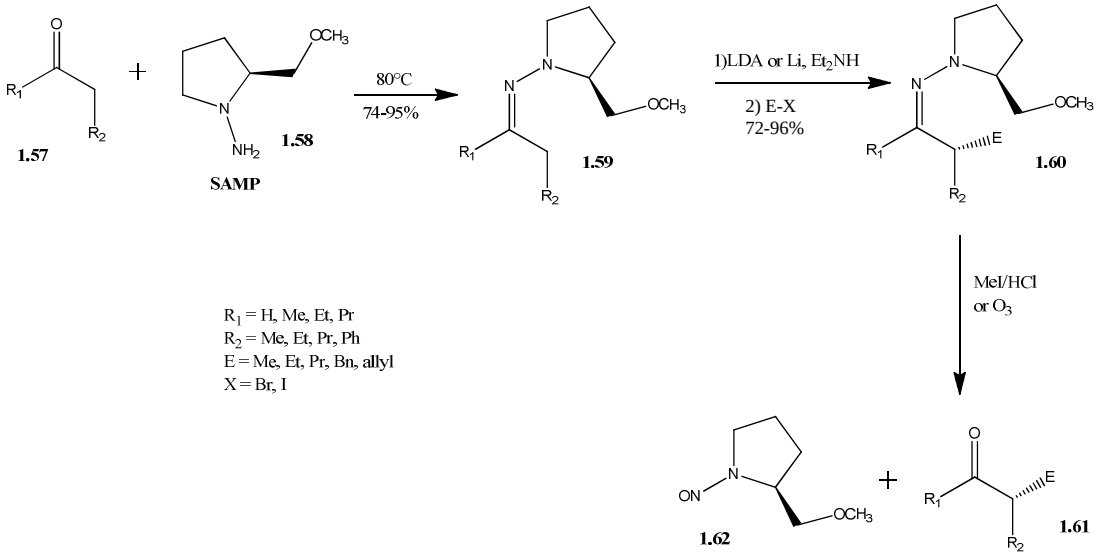


Enolate **1.54** Azaenolate **1.55** Amide enolate **1.56**

Figure 1.5: Different types of enolates

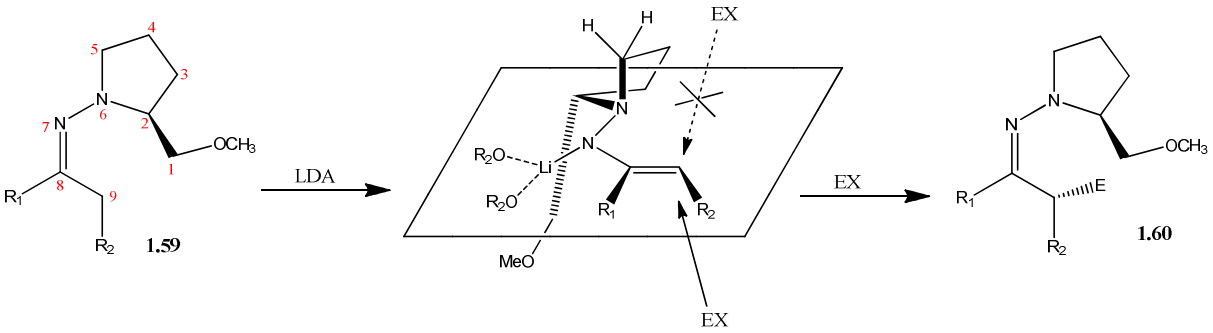
a) Azaenolates: use of RAMP and SAMP

Enders and his co-workers[19] have used RAMP derived from (*R*)-proline and SAMP **1.58** derived from (*S*)-proline for the α-alkylation of aldehydes and ketones *via* chiral azaenolates (**Scheme 1.11**).



Scheme 1.11: Reaction using SAMP as chiral auxiliary[14]

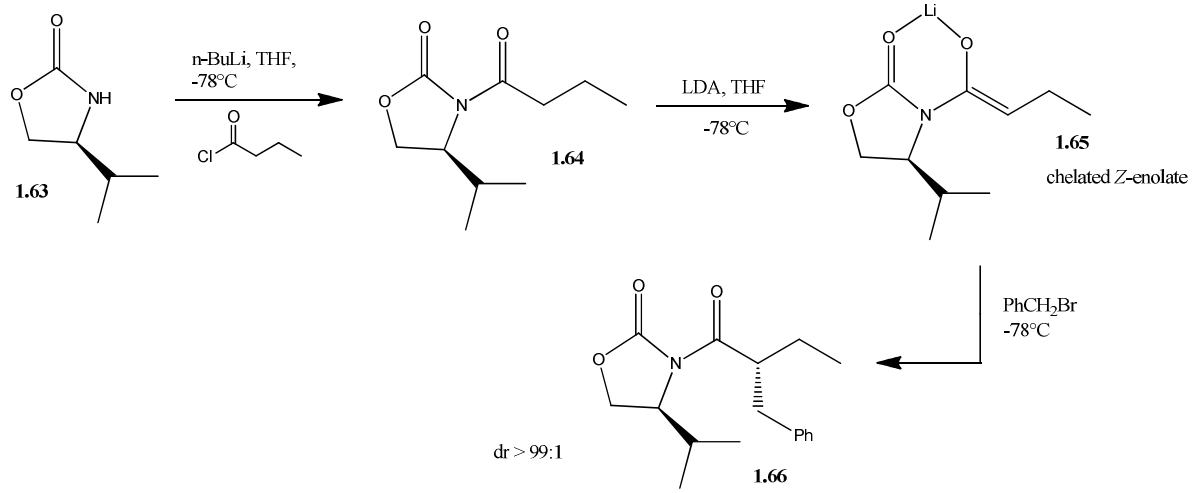
Regarding the mechanism of the reaction, the deprotonation of the SAMP hydrazones e.g. **1.59** can normally lead to four isomeric azaenolates, but it has been proved by X-ray, MNDO calculations and spectroscopy that only $E_{CC}Z_{CN}$ (in **1.59** the C_8-C_9 bond is in an *E* configuration and the C_8-N_7 bond is in an *Z* configuration) species is formed (**Scheme 1.12**). In this conformation, the pyrrolidine ring methylene hinders the approach of the electrophile (EX) on the (*S*,2*Si*) face and so the attack is from the (*S*,2*Re*) face.[19]



Scheme 1.12: Transition state of the SAMP alkylation reaction

b) Amide enolate equivalents

Chiral amide enolate equivalents is the most developed chemistry in this area. The most widely used compounds are the chiral oxazolidinones developed by Evans and his co-workers in 1982.[20] An example of an asymmetric alkylation using Evans' oxazolidinone is shown in **Scheme 1.13**.



Scheme 1.13: Evans' oxazolidinone in an asymmetric alkylation

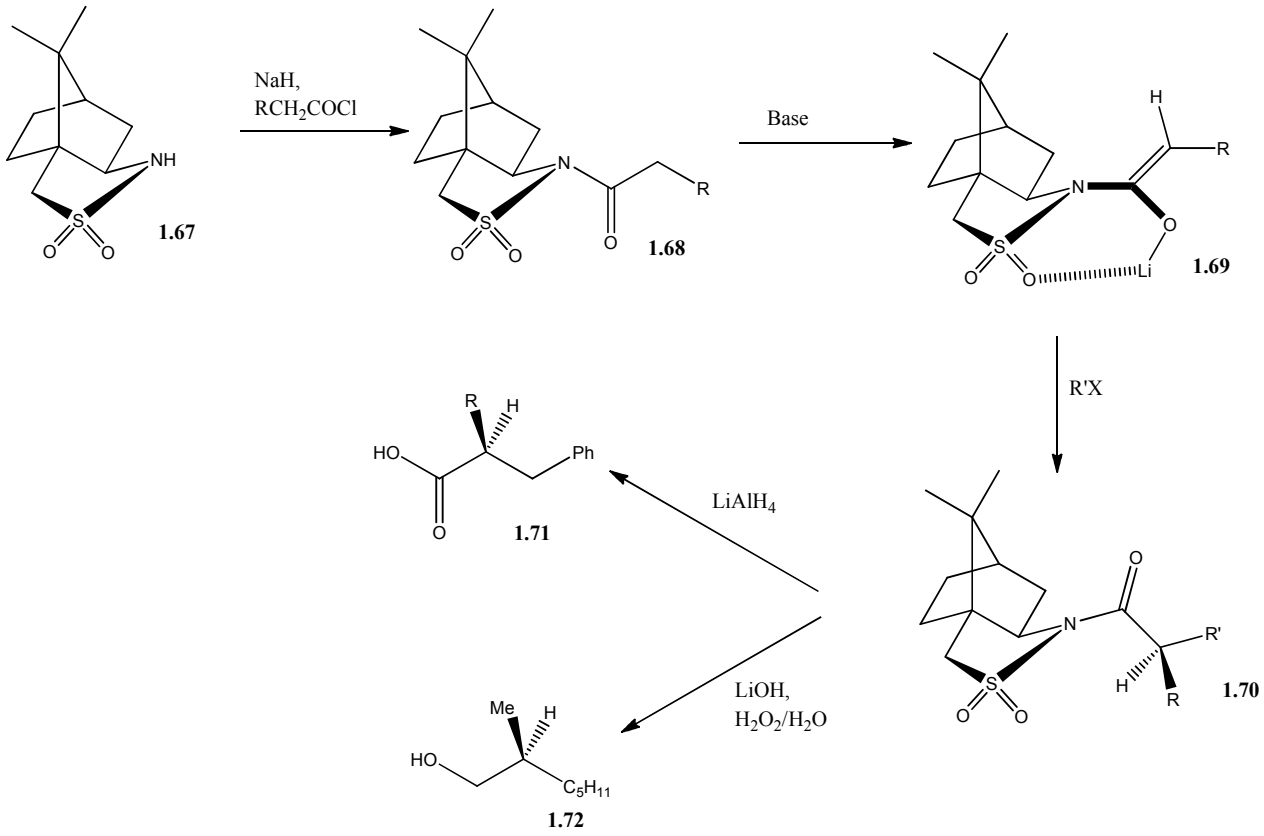
The deprotonation of the acylated oxazolidinone **1.64** gives predominantly the Z-enolate **1.65** (99 % selectivity) because this minimises the steric repulsion between the enolate C-2 subsituent and the oxazolidinone ring. The alkyl halide then approaches from the face remote from the substituent on the oxazolidinone ring. The last step is the removal of the chiral auxiliary which can be achieved by hydrolysis, reduction or alcoholysis.

The alkylation of oxazolidinone enolates can be problematic for non-activated alkyl halides like EtI (which gives 36% yield), so a number of alternative auxiliaries have been developed. Oppolzer's sultam chiral auxiliaries were developed in the 1980's and will be

detailed in section 1.4.4. Myers and his co-workers have developed, more recently (1994), the use of pseudoephedrine as a chiral auxiliary. The case of pseudoephedrine will be discussed in more detail in the next chapter as it is the basis of this research reported.

1.4.4 Oppolzer's sultam chiral auxiliary

Oppolzer and his group developed in 1984 a new group of chiral auxiliaries: the chiral sultams e.g. **1.67**.[21] The sultams have been widely used for dipolar cycloadditions, Diels-Alder reactions, annulations with metals, hydrogenation, and oxidation using osmium tetroxide.[22] Oppolzer and his co-workers have also used the sultams for asymmetric alkylations of acyclic carboxylic acid derivatives[23] (**Scheme 1.14**). The sultam auxiliary **1.67** is derived from the camphorsulfonyl chloride. The sultams e.g. **1.67** were acylated and treated with a base (BuLi or NaHMDS). An enolate **1.69** was produced by the chelation of the lithium to the amide and the sultam oxygen. The alkylation reaction can be carried out with a variety of electrophiles in order to give highly enriched diastereomers even with an unreactive alkyl halide ($PhCH_2I$) (**Table 1.1**).



Scheme 1.14: Asymmetric alkylation using Oppolzer's sultam auxiliary[23]

Entry	R	R'X	Base	Yield (%) cryst.	**1.70** de of crude mixture (%)
1	Me	$PhCH_2I$	NHMDS	89	96.5
2	Me	*t*-$BuOCOCH_2Br$	NHMDS	77	98.5
3	Me	Me_2CHMe_3	NHMDS	81	99
4	$PhCH_2$	MeI	NHMDS	83	94.5
5	$H_2C=CHCH_2$	MeI	BuLi	--	95.4
6	OCH_2Ph	MeI	LHMDS	68	98

Table 1.1: Diastereomeric excess obtained for the alkylation of acyl sultams **1.70** with alkyl halides[23]

2 - Pseudoephedrine, an efficient chiral auxiliary

2.1 Presentation and uses

Pseudoephedrine **2.1** (**Figure 2.1**) is a biologically active compound that is used as a nasal decongestant and stimulant and can be purchased in a pharmacy (Sudafed). The salts pseudoephedrine hydrochloride and pseudoephedrine sulfate are found in many drug preparations.

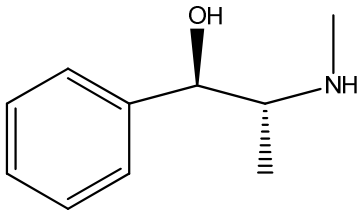
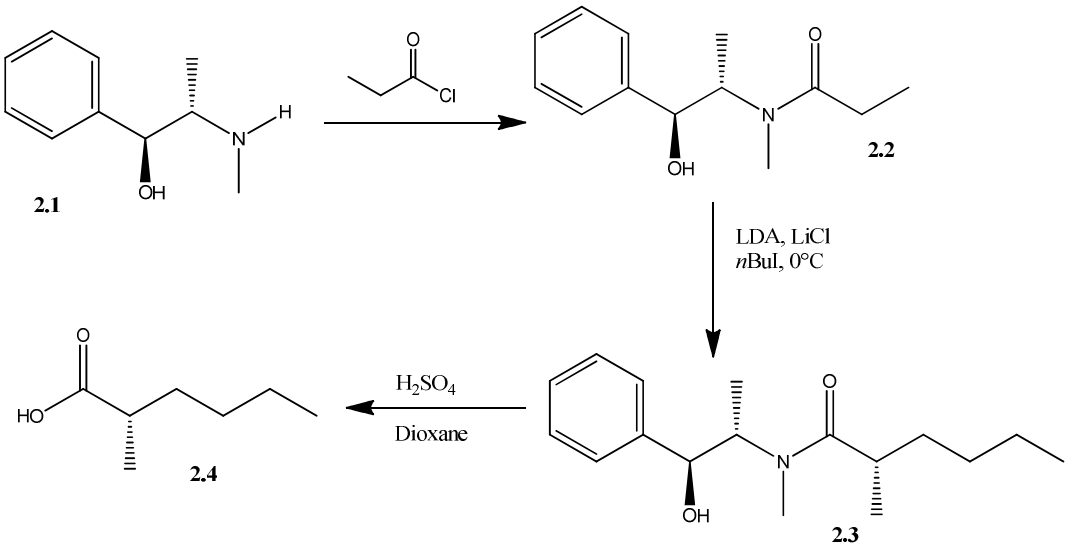


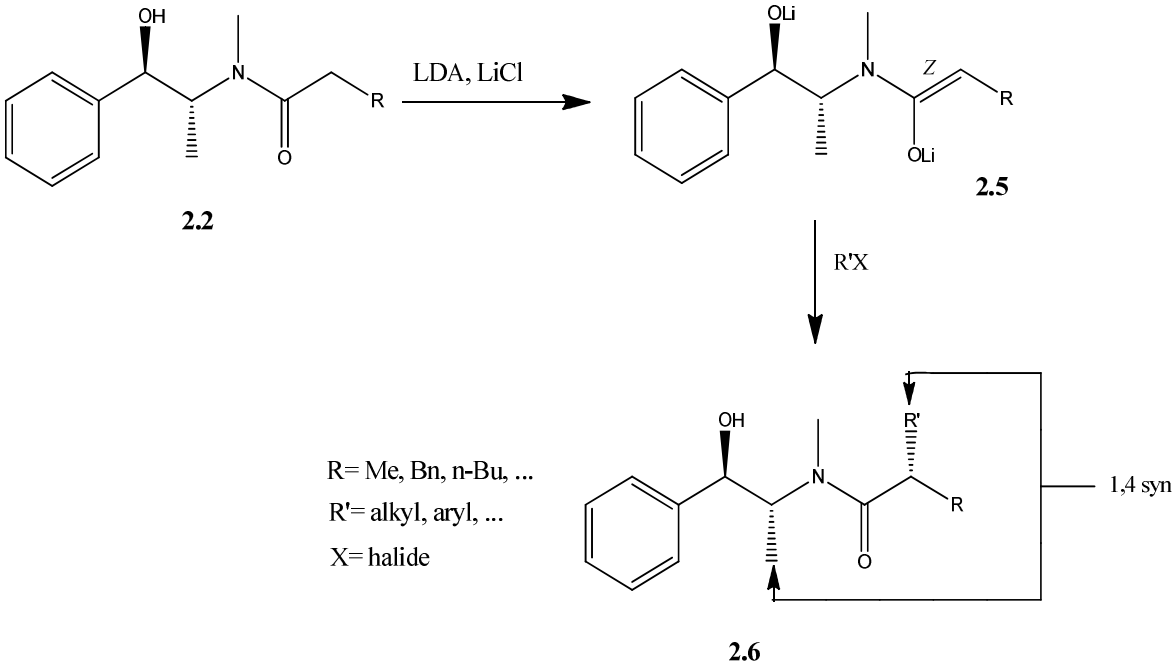
Figure 2.1: (1*R*,2*R*)-(-)-Pseudoephedrine **2.1**

Myers and his co-workers reported in 1994 the use of pseudoephedrine **2.1** as a highly effective chiral auxiliary for asymmetric alkylation reactions[24,25] in order to create α-substituted alcohols, aldehydes and carboxylic acids.



Scheme 2.1: Myers' first reaction using pseudoephedrine as a chiral auxiliary[24,25]

Each enantiomer of pseudoephedrine can be *N*-acylated, e.g. **2.1**, to form the tertiary amide derivative **2.2**. Alkylation of pseudoephedrine amides can be executed by using lithium diisopropylamide in THF in the presence of lithium chloride, followed by the addition of an alkylating agent (**Scheme 2.2**). These reactions are highly efficient (80-95% yield) and diastereoselective (96-99% de) as reported in **Table 2.1**. The role of lithium chloride is not known, but Myers proposes that it modifies the aggregation state and so the reactivity of the enolate.[25]

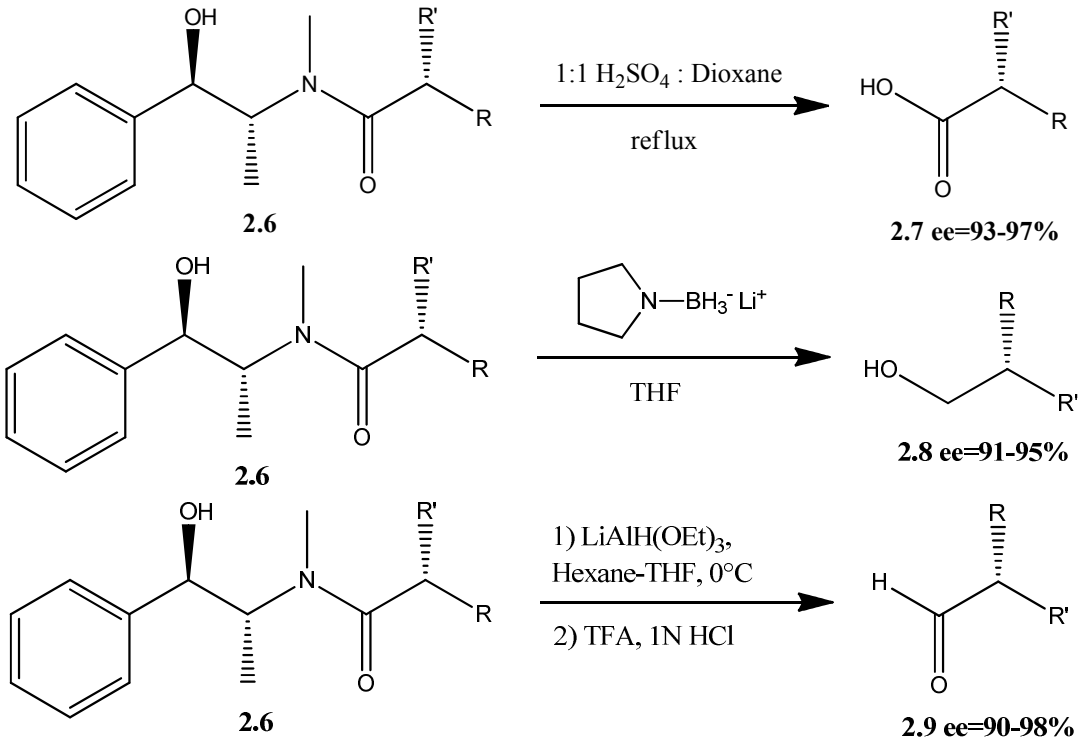


Scheme 2.2: The alkylation reaction

R	R'X	Temperature (°C)	Yield of **2.6** (%)	Isolated de of **2.6** (%)
CH_3	BnBr	0	90	≥ 99
CH_3	*n*-BuI	0	80	≥ 99
Bn	CH_3I	0	99	94
Bn	CH_3I	-78	95	97
Ph	EtI	0	92	≥ 99
i-Pr	BnBr	0	83	≥ 99
t-Bu	BnBr	0	84	≥ 99

Table 2.1: The yield and de of **2.6** with different groups[25]

In all the examples explored by Myers the electrophilic reacts with the (*Z*)-enolate **2.5** on the 1*Si*,2*Re* face (for amides of **2.2**) to set up a 1,4-*syn* stereochemistry **(Scheme 2.2**). Compound **2.6** can then be transformed into useful material like carboxylic acids **2.7**, primary alcohols **2.8** or aldehydes **2.9** with high enantiomeric excesses (**Scheme 2.3**).



Scheme 2.3: Possible transformations of compound **2.6** [25]

2.2 Mechanistic hypothesis

Myers had difficulties crystallising the pseudoephedrine amide enolate **2.10** or to obtain good ^{1}(H) NMR spectroscopy of it. Therefore, to explain the selectivity of pseudoephedrine amide enolate, he used a similar model to the one proposed by Askin *et al.* in 1988. Here Askin *et al.* suggested that the alkoxy group from the prolinol amide enolate **2.11** directed the alkylation as it provided a steric shielding of the (1*Si*,2*Re*) face (**Figure 2.2**).[26] This model was used by Myers to explain the pseudoephedrine amide enolate alkylations because there are structural similarities between pseudoephedrine amides and prolinol amides: both are amides of 2-amino alcohols. Myers, therefore, suggested an open chain conformation **2.10** where the lithium alkoxide cation and perhaps the associated solvent molecules block the (1*Si*,2*Re*) face of the Z-enolate **2.10** and forces the alkylation to occur on the (1*Re*,2*Si*) face.

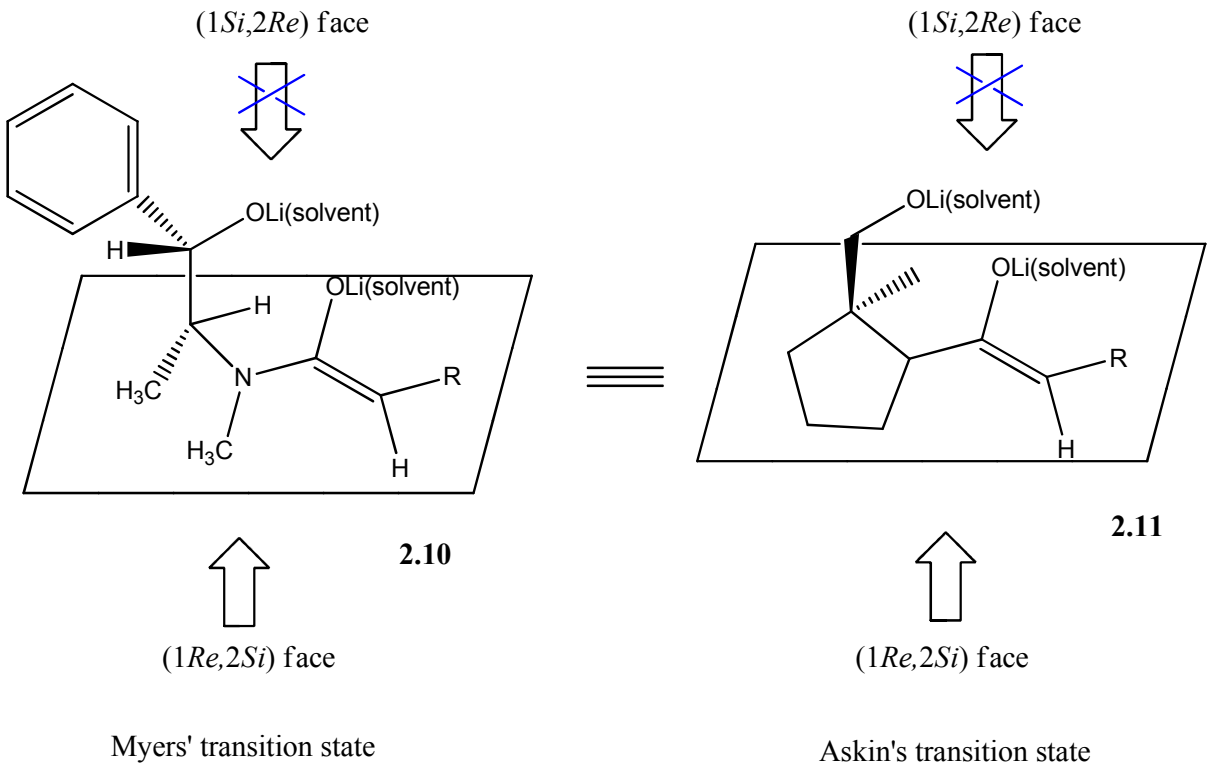


Figure 2.2: Myers mechanistic hypothesis[26]

This conformation of the reactive conformation of the enolate **2.10** was supported by the examination of the X-ray crystal structure of pseudoephedrine glycinamide hydrate **2.12** (**Figure 2.3**).[27] However, this model does not take into account important features like rotameric distribution, bond-forming and breaking trajectories, and aggregation state.

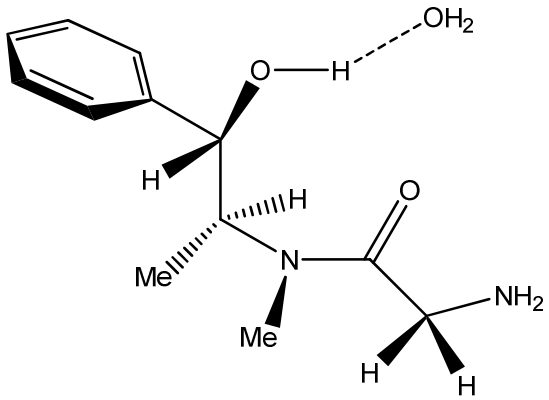
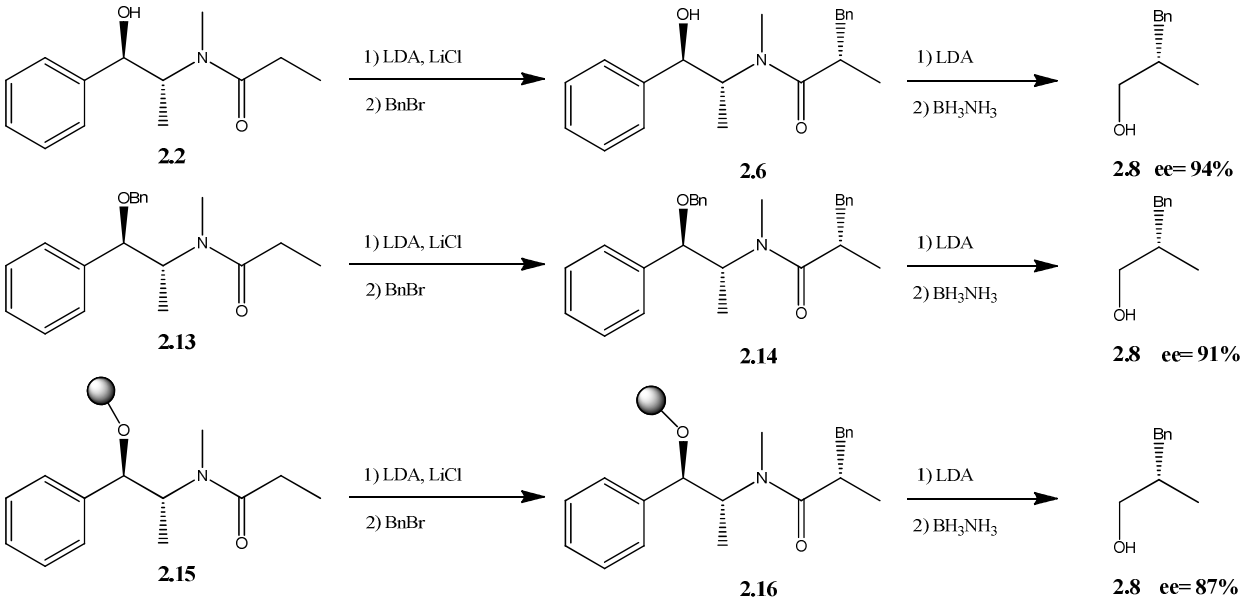


Figure 2.3: Representation of the solid state structure of pseudoephedrine glycinamide hydrate[27]

Procter and his group developed in 2002[28,29] a method to immobilize pseudoephedrine amides on a Merrifield resin. They were investigating if polymer-supported systems were viable in order to carry out asymmetric syntheses on a solid phase support. It was important to attach the chiral auxiliary in a one-step reaction by either an ether or an amine linkage. To assess the viability of the solid phase approach Procter and co-workers investigated solid-supported analogues **2.15** in comparison to solution phase derivatives **2.13** as well as the Myers' amides **2.2**. Therefore, the alkylation was carried out with the pseudoephedrine amide **2.2**, an *O*-benzyl derivative **2.13** (solution phase analogue of proposed polymer-supported derivatives) and the resin-attached compound **2.15** (**Scheme 2.4**).

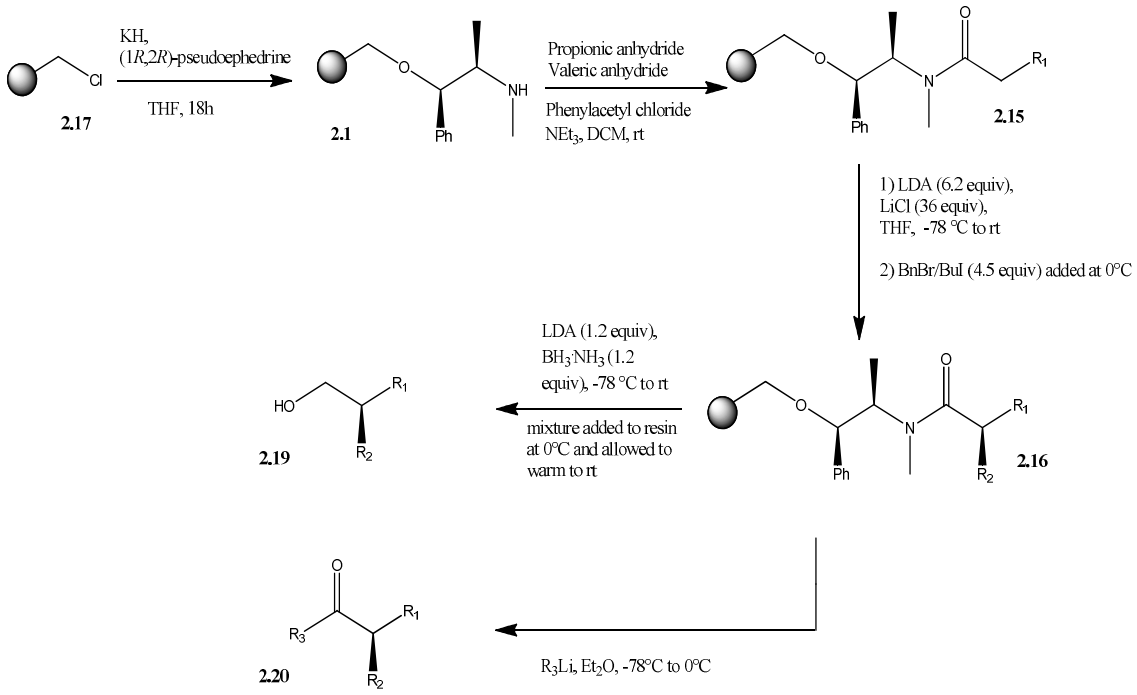


Scheme 2.4: Procter's group reactions on pseudoephedrine[28,29]

No significant drops in the ee were noted in the ether derivatives **2.13** and **2.15:** using Myers' **2.2** enolate alkylation and auxiliary removal gave the alcohol **2.8** in 94% ee, benzyl ether derivative **2.13** afforded **2.8** in 91% ee without significant depreciation in the selectivity and the polymer supported **2.15** gave **2.8** in 87% ee. It may be concluded that the dianion **2.10** is not needed in order to get a good selectivity.

Procter's group found that the diastereoselective alkylation was viable on the solid phase and developed the following method shown in **Scheme 2.5**. First of all the pseudoephedrine **2.1** was covalently attached to the resin by deprotonation of the alcohol functionality to obtain compound **2.18**. Then the acylation and the alkylation were carried

out with the pseudoephedrine still attached to the resin. The compounds of interest (alcohol **2.19** or ketone **2.20**) was detached from the pseudoephedrine and consequently from the resin. At the end of the process **2.1** was re-isolated and could be reused.



Scheme 2.5: Procter's asymmetric synthesis using pseudoephedrine on a solid phase[28,29]

The above results of Procter *et al.* where similar selectivity of the diastereoselective alkylations of **2.2** (hydroxyl), **2.13** (benzyl ether) and **2.15** (polymer-supported) might raise concerns over the validity of the suggested selectivity mechanism of Myers *et al.* Consequently, modelling studies were initiated here at Strathclyde to explore possible reactive conformations in the Myers' and Proctor alkylations (unpublished results from Dr. C.L. Gibson, private communication). Using single energy DFT (B3LYP 6-31G*) calculations of molecular mechanics generated conformations of enolate **2.10** and derivatives, indicated that the Myers' extended conformation (see **Figure 2.2**) was not always the lowest energy conformation. Instead, the conformers **2.21** with a π-Li^+ stabilizing interaction were often lower in energy. The major enolate is still the (Z)-enolate and the 1,4-*syn* electrophilic attack would be through the (1*Re*,2*Si*) with the aromatic ring providing a steric bias.

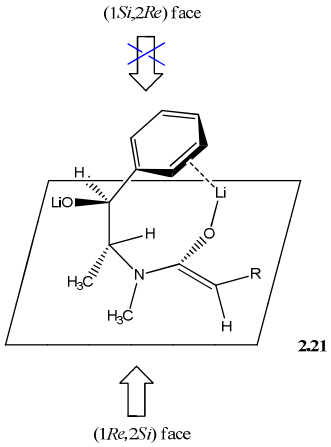


Figure 2.4: Gibson's mechanistic hypothesis

The calculations could only be done in a gas phase and, unfortunately, all calculations done in the presence of solvent failed (calculations were attempted using THF using the SM8 model). This is why some experimental data is needed to confirm the results of the calculations. In these calculations, the lithium coordination is not filled. The lowest energy transition state found was the π-Li^+ conformer, then a second π-Li^+ state was calculated. Only after these two first conformers a first Myers' transition state was found at +0.68 kJ mol^{-1}, followed by a second one at +6.97 kJ mol^{-1}. Some calculations on analogues have also been conducted and gave the following outcome (see **Table 2.2**).

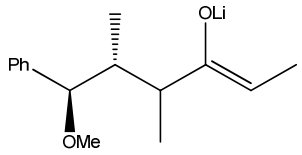
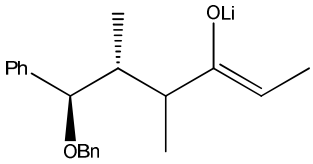
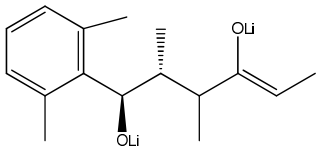
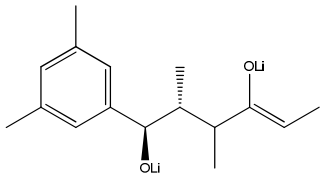
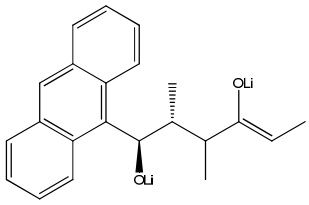
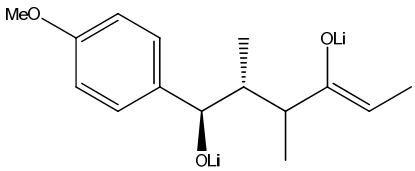
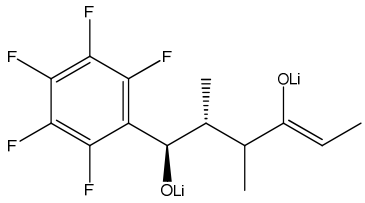
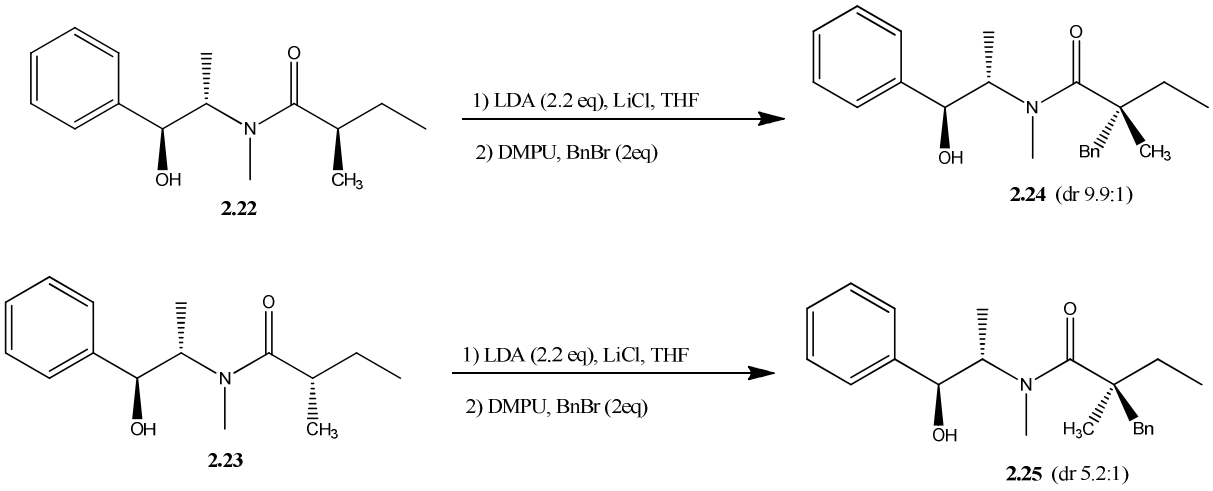
Entry	Tested analogue	Favoured intermediates
1		π-Li^+ favoured by 13.6 kJ mol^{-1} over Myers'
2		π-Li^+ favoured by 0.29 kJ mol^{-1}
3		Myers' favoured by 2.55 kJ mol^{-1}
4		More stable than the 2,6-derivative (Entry n° 3) by 26 kJ mol^{-1}; Myers' favoured by 1.2 kJ mol^{-1}
5		π-Li^+ is more stable by 6.29 kJ mol^{-1}
6		2 identical π-Li^+ minima more stable then Myers' by 1.26 kJ mol^{-1}
7		Myers' type by 13. 68 kJ mol^{-1}

Table 2.2: Calculations of the lowest energy intermediate of analogues of pseudoephedrine enolate

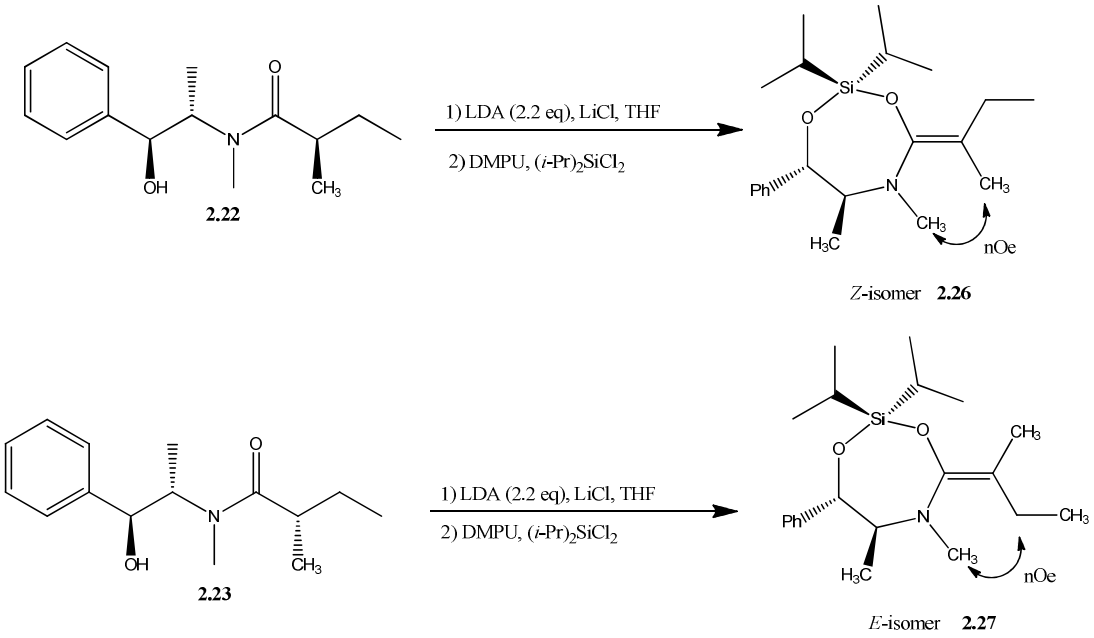
2.3 Myers' further work on pseudoephedrine and derivatives

Myers and his co-workers have now developed a method[30] to synthesize quaternary carbon centres in a stereocontrolled way using pseudoephedrine derivatives. Deprotonation of α-methylbutyramides **2.22** and **2.23** in a stereospecific way with lithium diisopropylamide (LDA) and lithium chloride at 0 °C gave, respectively, the *Z*- or *E*-enolate (**Scheme 2.6**). The enolates were then alkylated using an excess of benzyl bromide (2 equiv) in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and the compounds **2.24** and **2.25** were obtained with a moderate diastereomeric ratio (9.9:1 and 5.2:1 respectively).



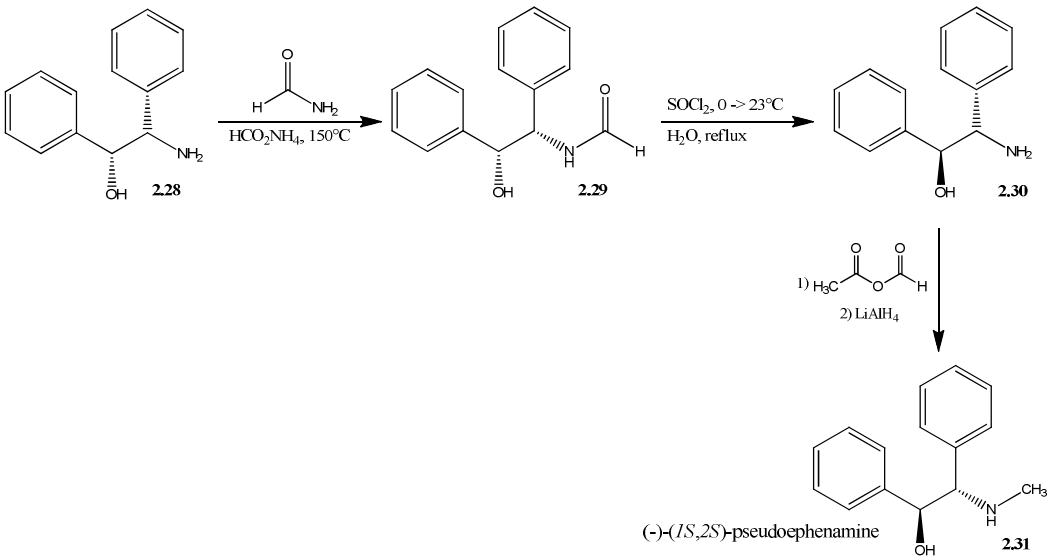
Scheme 2.6: Synthesis of quaternary carbon derivatives using Myers' pseudoephedrine auxiliaries

To prove that the enolization was stereospecific the reaction was also carried out using dichlorodiisopropylsilane instead of benzyl bromide. This way, the *Z*-isomer (**2.26**) and *E*-isomer (**2.27**) were trapped and allowed the determination of the configuration of the precursor enolate **2.26** (**Scheme 2.7**). This pre-transition state **2.26** was shown through ^{1}H-NMR analysis: the base and the alkoxide chain are positioned opposite to the receiving enolate.

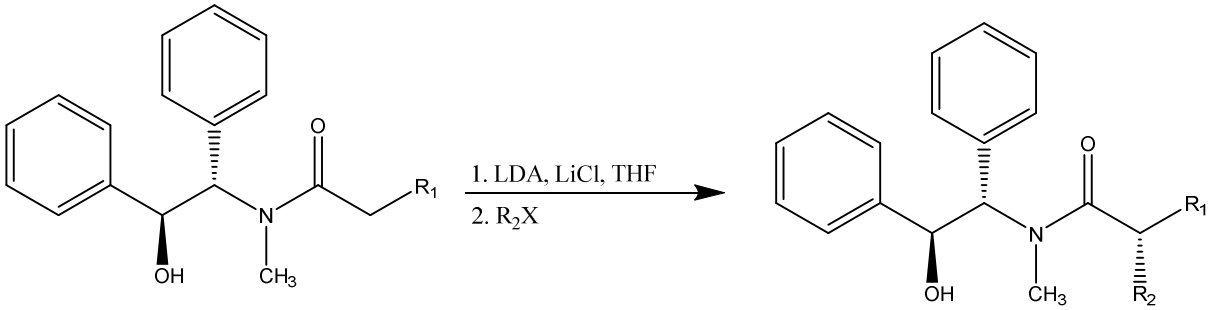


Scheme 2.7: Trapping of the *Z*- and *E*- isomers of the enolates from **2.22** and **2.23**

Myers published[31] also another paper on (-)-(*1S,2S*)-Pseudoephenamine **2.31** as a replacement for Pseudoephedrine **2.1** (**Scheme 2.8**). In fact, Pseudoephedrine **2.1** can be transformed into methamphetamine amongst other substances and therefore restrictions and bans exist in some countries about its use. This is why Myers was looking for a replacement in order to use it in industrial applications. (-)-(*1S,2S*)-Pseudoephenamine **2.31** is free from regulatory restriction, the asymmetric reactions using it have an equal or greater diastereoselectivity than the same reactions using Pseudoephedrine (**Table 2.3**). The third advantage is that the amides derivatives crystallise more often and give sharp and well-defined signals in NMR spectra.



Scheme 2.8: Synthesis of (-)-(1S,2S)-Pseudoephenamine starting from (-)-(1R,2S)-1,2-diphenyl-2-aminoethanol[31]



Entry	R_1	R_2	d.r. of crude product	d.r. of isolated product	Yield (%)
1	Me	Bn	95 :5	≥ 99 :1	85
2	Me	*n*Bu	95 :5	98 :2	97
3	Me	Et	≥ 94 :6	98 :2	96
4	Et	Me	≥ 96 :4	≥ 99 :1	87
5	*n*Bu	Bn	≥ 98 :2	≥ 99 :1	99
6	*n*Bu	Me	95 :5	98 :2	84
7	Bn	Me	98 :2	98 :2	92
8	Bn	*n*Bu	≥ 99 :1	≥ 99 :1	99

Table 2.3: Diastereoselective outcome of the alkylation reaction using Pseudoephenamine[31]

3 - Research project

The aim of this research project was to try and probe the mechanism of the asymmetric synthesis using pseudoephedrine. There are two possible directions to do so: try to favour the π-Li^+ cation by introducing more electronrich aromatic rings, or try to substitute the alcohol next to the aromatic ring to see if it affects the stereoselectivity. The latter was the chosen route to investigate the mechanistic possibilities.

The idea was to substitute the alcohol by silyl ethers because the alkyl ether does not prevent the chelation of the oxygen to the lithium as potentially shown in the work of Procter (see above). There are many criteria which led us to choose a silyl protecting group:

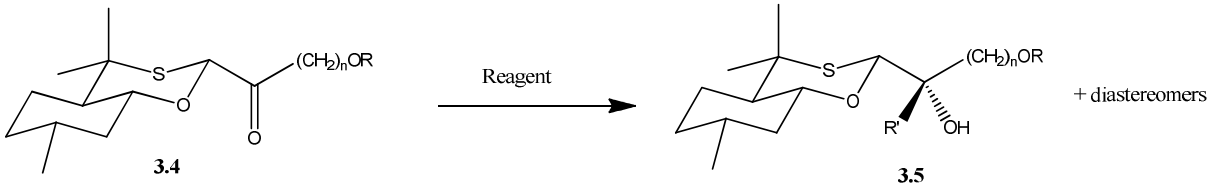
J. D. White and R. G. Carter said in their publication[32]:

"There is a considerable debate as to whether silyl ethers are more[33] or less[34] basic than alkyl ethers but it is generally agreed that the oxygen of a silyl ether is less strongly coordinating, for example with a Lewis acid, than the oxygen of an alkyl ether."[35]

This has been explained by Schreiber *et al.*[36] with a study of the FMO's:

- mixing of some lone pair orbitals of the oxygen with the relatively low lying π*(SiR_3) group orbitals.
- the π(SiR_3) orbital is higher in energy then π*(CR_3) orbital and there is a poorer mixing of the π(SiR_3) orbitals with the oxygen lone pairs due to the required 2p-3p overlap.

Therefore, the oxygen of silyl ether should be less prone to chelate with the lithium than the oxygen of the alkyl ether. But all silyl ethers do not completely prevent the chelation with powerful Lewis acids. The TIPS group is supposed to completely prevent the chelation (**Scheme 3.1** & **Table 3.1**) as shown by Frye *et al.*[37] In this paper these workers showed that the TIPS group prevented the chelation using Grignard reagents and selectride and afforded better diastereoselectivity than a benzyl ether (see Entry n° 1 to 4). They suggest that this result can be explained by a steric effect and not an electronic effect, because the TMS and TBDMS ethers did not give as good selectivity (see Entries 5 to 7).

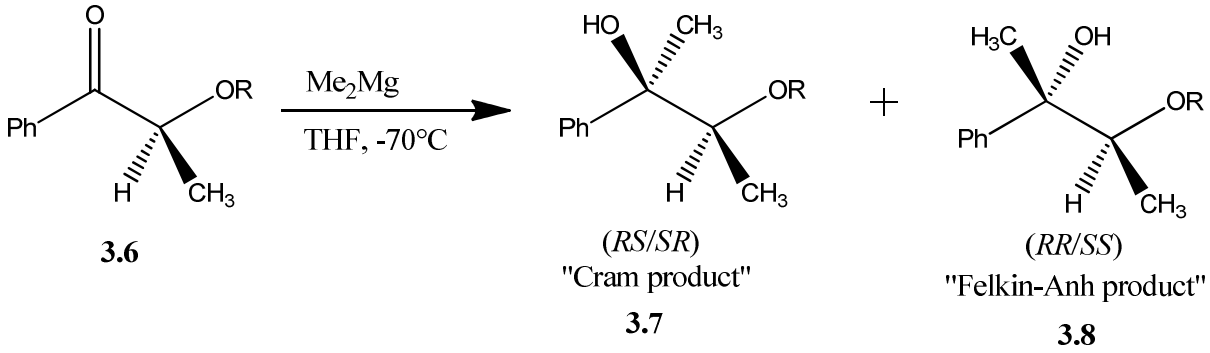


Scheme 3.1: Nucleophilic addition to 2-acyl-1,3-oxathianes

Entry	n =	R =	Reagent	de (%)
1	1	Bn	CH_3MgBr	33
2	1	Si(*i*Pr)$_3$	CH_3MgBr	95
3	2	Bn	CH_3MgBr	17
4	2	Si(*i*Pr)$_3$	CH_3MgBr	95
5	2	Si(*i*Pr)$_3$	L-Selectride®	76
6	2	$SiMe_3$	L-Selectride®	33
7	2	Si(*t*Bu)Me_2	L-Selectride®	13

Table 3.1: Diastereomeric excess of the different nucleophilic attacks[37]

Frye and his co-workers published another paper in 1992[33] in which they showed that the diastereoselectivity of the reaction of a protected ketone with Me_2Mg (**Scheme 3.2** & **Table 3.2**) is affected by some of the bulky silyl protecting groups (Entries 4 & 5), and even that in the case of TIPS the major stereoisomer is not the same: they obtained, predominantly, the Felkin-Anh product **3.8** and not the chelation compound **3.7**. This again shows that a TIPS group can prevent reagent chelation.



3.6

(*RS/SR*)
"Cram product"
3.7

(*RR/SS*)
"Felkin-Anh product"
3.8

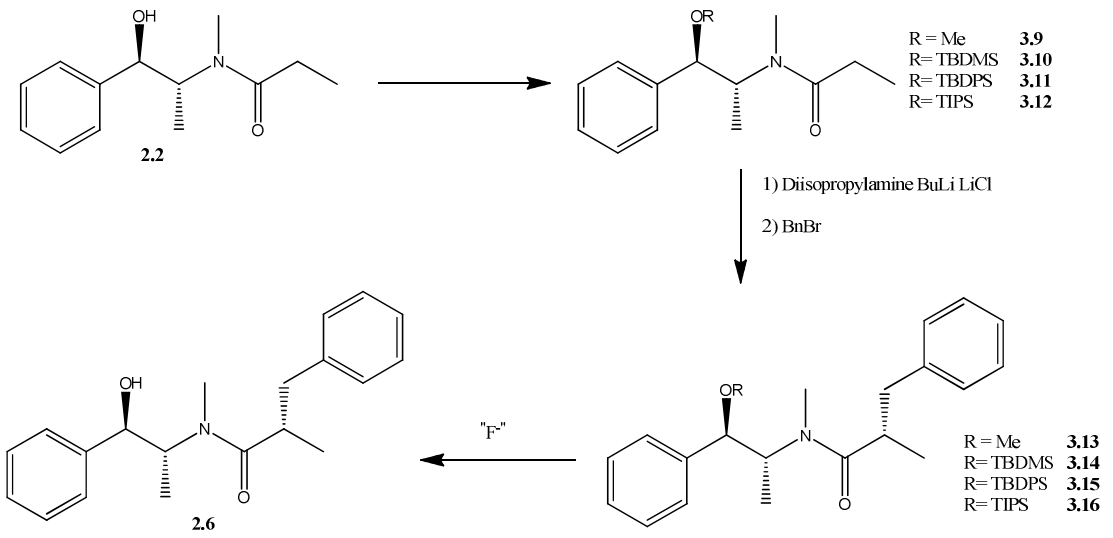
Scheme 3.2: Reaction of protected ketone **3.6** with Me_2Mg[33]

Entry	R =	Chelation / Felkin-Anh product
1	Me	99 / 1
2	$SiMe_3$	99 / 1
3	$SiEt_3$	96 / 4
4	$Si(tBu)Me_2$	88 / 12
5	$Si(tBu)Ph_2$	63 / 37
6	$Si(iPr)_3$	42 / 58

Table 3.2: Frye's reaction and diastereoselective outcome

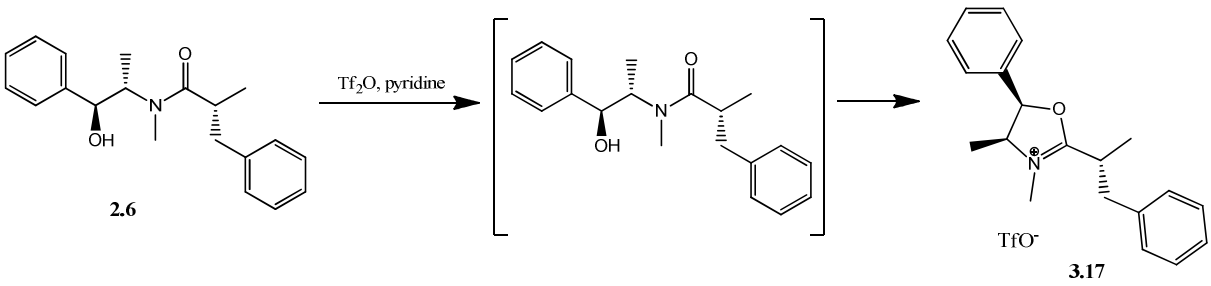
For the above reasons, it was decided to use different silyl protecting groups which should give us explicit information about the mechanism of the diastereoselective alkylation of pseudoephedrine amides. The use of silyl ether protecting groups in **3.11**-**3.13** would be expected to prevent lithium ion coordination to the pseudoephedrine side chain as required in the Myers' reactive conformation **2.10**. It was anticipated that complete loss of diastereocontrol in the alkylation of the enolates of silyl ethers **3.11**-**3.13** would be observed if the Myers' mechanism is in operation. On the other hand, if the π-Li^+ reactive conformation is operational, we might expect to observe diastereocontrol in the alkylation of the corresponding enolates. However, since the conformations of the pseudoephedrine sidechain may be disturbed by introducing bulky silyl ether groups, the high diastereocontrol observed in the Myers' hydroxyl analogues may not be observed in these cases.

So the plan was to first protect the alcohol of pseudoephedrine amide **2.2** with different silyl protecting groups, then carry out the asymmetric alkylation and, finally, remove the protecting group (**Scheme 3.3**) and determine the diastereomeric ratio of products in **2.6**.



Scheme 3.3: Proposed synthetic project

A final step is required in order to obtain a good measurement of the diastereoselective excess of the products e.g. **3.13-3.16**. Indeed, we have a sterically hindered system in molecules **3.9-3.16**, so would expect two amide rotamers to be problematic in determining the diastereomeric ratio of the diastereomers **3.13-3.16** formed during the alkylation. Therefore the analysis will utilize Myers' method published in 2006 to form the 4,5-dihydro-3,4-dimethyl-5-phenyl-1,3-oxazolium triflate derivative **3.17** (**Scheme 3.4**).[38] This will remove the amide rotamers and gave sharp and well-defined peaks in the ^{1}H NMR to measure the diastereoselective excess.

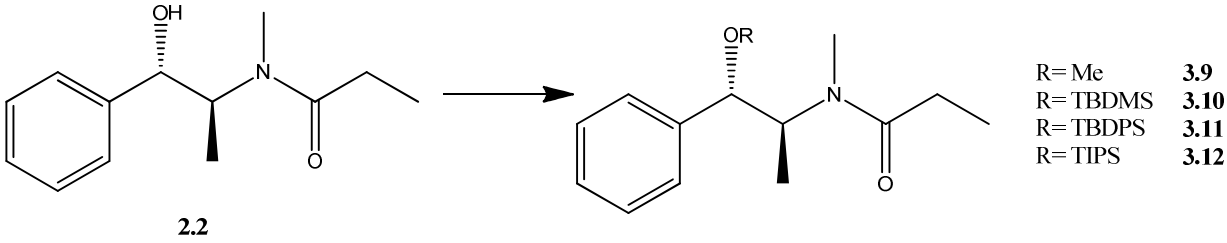


Scheme 3.4: Cyclization of the alkylation product from Myers' auxiliary based alkylation[39]

4 - Results and discussion

4.1 Preparation of silyl-protected or methyl-protected pseudoephedrine amides

The first step required was to protect the alcohol of pseudoephedrine amide **2.2**. It was decided to use in total 4 different protecting groups: methyl **3.9**, *tert*-butyldimethylsilyl **3.10**, *tert*-butyldiphenylsilyl **3.11** and triisopropylsilyl **3.12** (**Scheme 4.1**).



2.2

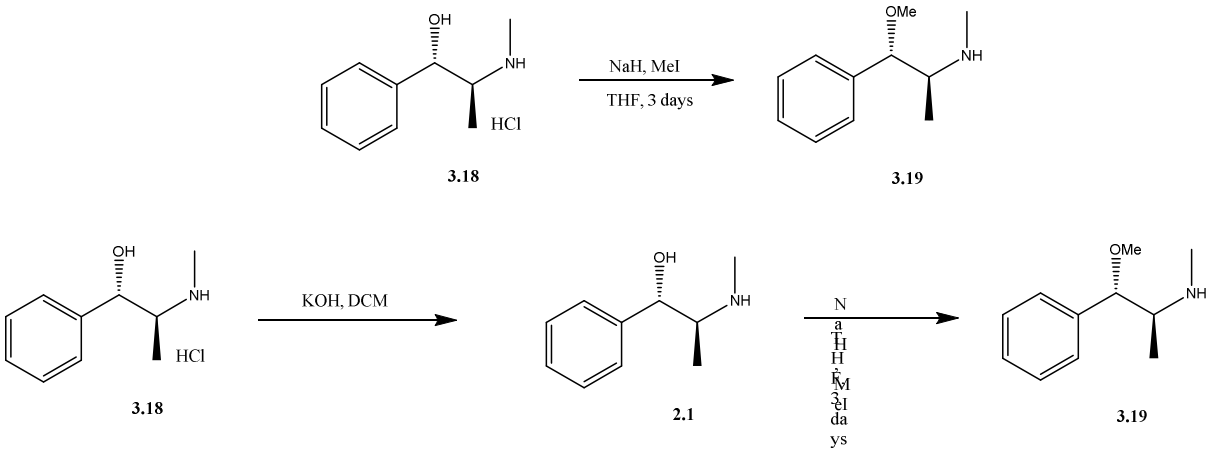
Scheme 4.1: Protection of pseudoephedrine amide[29,32,39,40]

Accordingly, methylation of commercially available (1*S*,2*S*)-(+)-pseudoephedrine amide **2.2** was investigated (**Table 4.1** entries 1-3 & 6). No indication of the formation of the required methyl ether **3.9** was observed. Analysis of the material recovered from the reaction by NMR indicated the decomposition of **2.2**. The silylation of the starting amide **2.2** was then tried with two different silyl groups (**Table 4.1** entries 4, 5, 7 & 8) but once again only the decomposition of **2.2** was observed.

Entry	Compound	Reagents	Reaction conditions	Yield
1	**3.9** (R= Me)	CH_3I (1.2 equiv), NaH, THF	Room temperature, 24 h	0%
2	**3.9** (R= Me)	CH_3I (4 equiv), NaH, THF	Room temperature, 24 h	0%
3	**3.9** (R= Me)	NaH, Me_2SO_4, THF	Room temperature, 19 h then 40 °C for 1 h 15	0%
4	**3.10** (R= TBDMS)	TBDMSCl, DMAP, DMF	rt, 3 days 21 h	0%
5	**3.10** (R= TBDMS)	TBDMSCl, DMAP, DMF	rt, 5 days	0%
6	**3.9** (R= Me)	NaH, Me_2SO_4, THF	rt, 19 h then 40 °C for 3 h	0%
7	**3.10** (R= TBDMS)	TBDMSCl, DMAP, THF	rt, 7 days	0%
8	**3.11** (R= TBDPS)	TBDPSCl, Pyridine, DMAP, THF	rt, 6 days	0%

Table 4.1: Reaction conditions for the protection of pseudoephedrine amide **2.2**

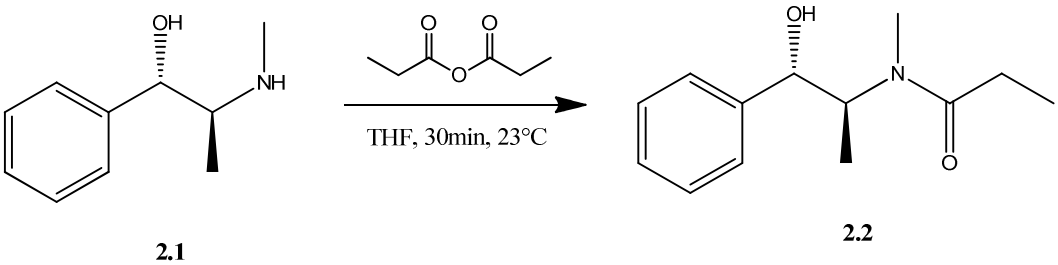
In view of the above decomposition upon attempted methylation of **2.2** it was decided to investigate the methylation of pseudoephedrine hydrochloride **3.18** and of the free base pseudoephedrine **2.1** with methyl iodide (**Scheme 4.2**). However, no evidence for the formation of methyl ether **3.19** was observed, and again NMR analysis indicated decomposition of starting material **2.1** or **3.18**.



Scheme 4.2: Methylation of pseudoephedrine hydrochloride and the free base

In view of the above difficulties which may have suggested that the starting amide **2.2** was impure, it was decided to synthesize the pseudoephedrine amide **2.2** starting from pseudoephedrine hydrochloride **3.18** (**Scheme 4.3**). The free base **2.1** of the pseudoephedrine salt **3.18** was made prior to the reaction (**Table 4.2**, entries 2 - 7). This way we would be sure of the quality and purity of the starting material, however some experimentation was necessary to obtain a good yield on a large scale (**Table 4.2**).

Initially pseudoephedrine hydrochloride salt **3.18** (commercially available) was used with triethylamine as the base but this did not afford the amide **2.2** (**Table 4.2**, entry 1).[25] Repeating the process with the free base **2.1** with triethylamine for extended periods gave no product and no starting material was recovered (**Table 4.2**, entries 2 & 3). For the next attempt (**Table 4.2**, entry 4) it was decided to stop the reaction after a much shorter stirring period (30 minutes) to see if any starting material **2.1** would be recovered and the desired product **2.2** (74%) was finally obtained. A large scale synthesis provided the product in poor yield (**Table 4.2**, entries 5 & 6, ≤ 5 %) so that it was decided to change the protocol[41]: no base was used and THF was preferred to DCM. These changes provided the product **2.2** with a good yield at reasonable scale (**Table 4.2**, entry 7, 52 %).



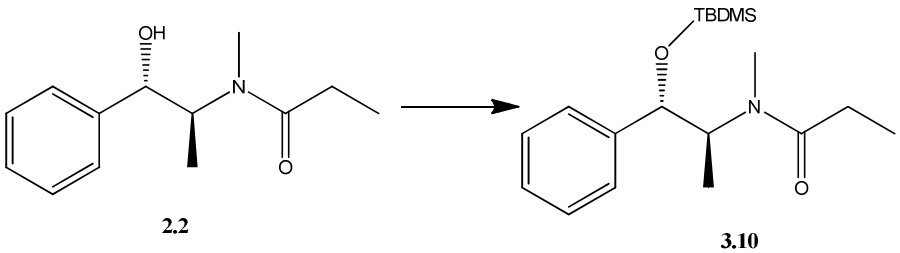
2.1 **2.2**

Scheme 4.3: Preparation of pseudoephedrine propionamide

Entry	Starting material: Pseudoephedrine	Base	Solvent	Stirring time	Yield
1	120 mg (HCl salt)	Et_3N	THF	1h 20	0%
2	127 mg	Et_3N	DCM	3 days	0%
3	142 mg	Et_3N	DCM	24 h	0%
4	123 mg	Et_3N	DCM	35 min	74 %
5	828 mg	Et_3N	DCM	50 min	5 %
6	773 mg	Et_3N	DCM	50 min	4 %
7	539 mg	No base	THF	40 min	52 %

Table 4.2: Reaction conditions for the synthesis of pseudoephedrine propionamide

With the in-house prepared pseudoephedrine propionamide **2.2** in hand, the silyl protection was attempted using *tert*-butyldimethylsilyl chloride (**Scheme 4.4** & **Table 4.3**)[42,43] However, this was unsuccessful and the NMR analysis showed the decomposition of the starting material **2.2**.



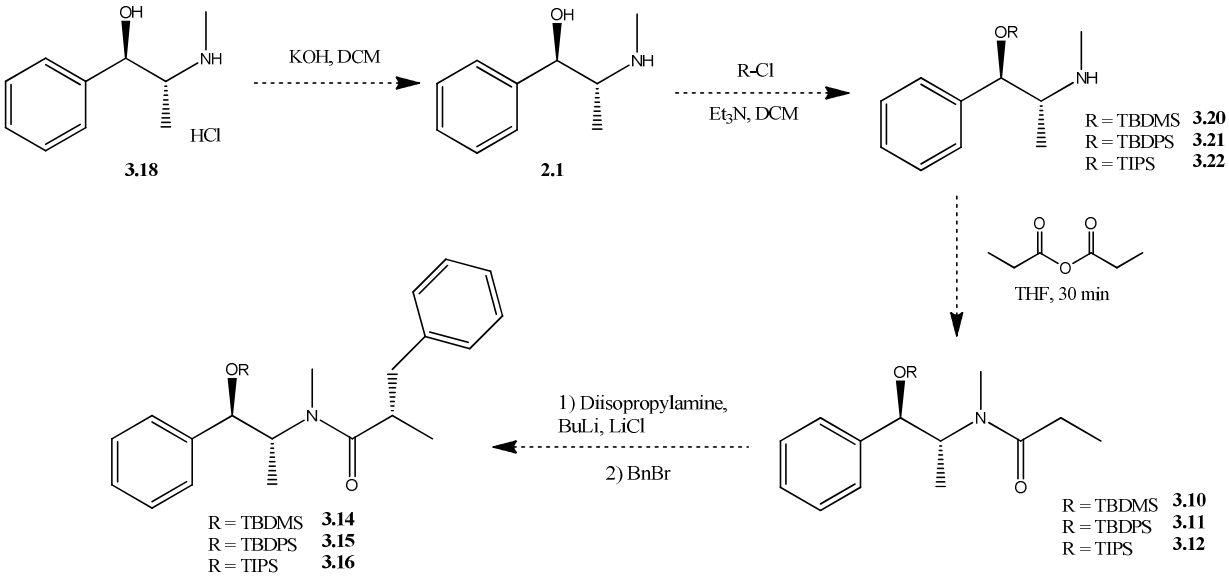
2.2 **3.10**

Scheme 4.4: Silylation with TBDMSCl of pseudoephedrine propionamide **2.2**

Essay	Compound	Reagents	Reaction conditions	Yield
1	**3.10** (R= TBDMS)	TBDMSCl, DMAP, DMF	rt, 1 day	0%
2	**3.10** (R= TBDMS)	TBDMSCl, DMAP, DMF	rt, 3h	0%
3	**3.10** (R= TBDPS)	TBDPSCl, Pyridine, DMAP, THF	rt, 3 days	0%

Table 4.3: Protection with silyl groups of the in-house pseudoephedrine propionamide **2.2**

Because of the lack of success in the silyl protection of pseudoephedrine propionamide **2.2**, it was decided to alter the sequence of the process: protect the hydroxyl group in **2.1** with a silyl protecting group followed by *N*-acylation of the silyl ethers **3.20-3.22** (**Scheme 4.5**):



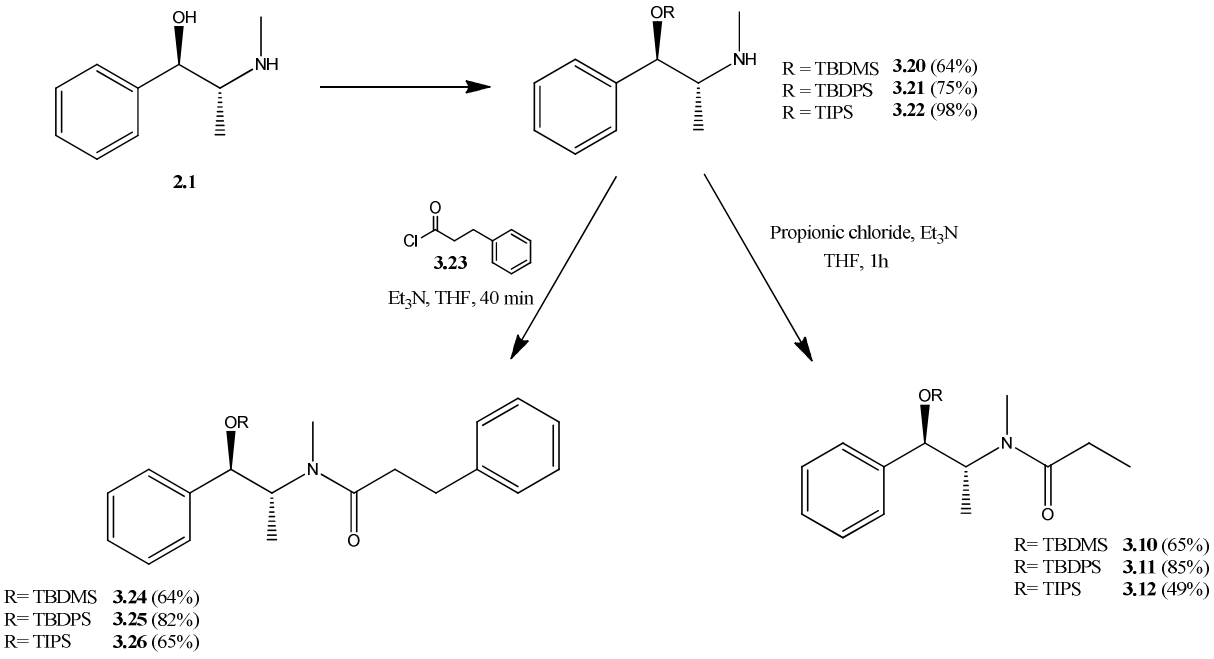
Scheme 4.5: New synthetic route to silyl ether amides **3.10-3.12**

Initial attempts at the silyl protection of **2.1** to afford ethers **3.20-3.22** were not successful. In this case the decomposition of the starting material was still observed by NMR. However, after a survey of the literature it was discovered that ephedrine solutions are sensitive to sunlight.[44] Carrying out reactions in the absence of light (flasks wrapped in aluminium foil) led to the successful silylation of the free base pseudoephedrine **2.1**. This gave silyl ethers **3.20**, **3.21** and **3.22** in 64%, 75% and 98% yields, respectively.

In view of this observation regarding the light sensitivity of pseudoephedrine **2.1** the protection of the pseudoephedrine propionamide **2.2** was investigated in reactions protected from direct sunlight. The protection of pseudoephedrine propionamide **2.2** with any silyl or methyl group was tried in the absence of light but led to no product formation. Consequently, approaches involving silyl ether protection of pseudoephedrine followed by *N*-acylation were deemed to be an attractive way forward.

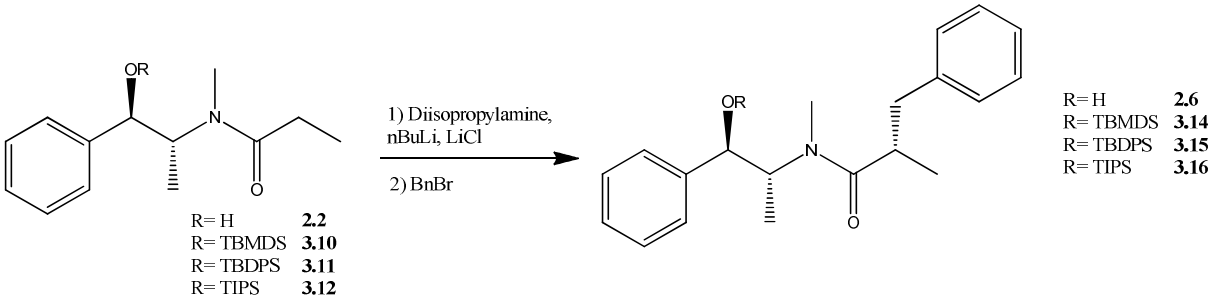
The *N*-acylation of ethers **3.20** & **3.21** was first carried out using propionic anhydride in the presence of different bases (Et_3N or DMAP), however, only starting material was recovered. Consequently, the acylation of ethers **3.20** & **3.21** using hydrocinnamoyl chloride **3.23** in the presence of triethyamine (**Scheme 4.6**) were carried out and afforded the corresponding amides **3.24-3.26** in yields of 64-82%. Application of this protocol to the TBDMS ether **3.20** with propionyl chloride gave the ether amide **3.10** in 65% yield. The other amides **3.11** and **3.12** have also been successfully synthesized following the same protocol and gave, respectively, 85% and 49% yields. The drop in yield for TIPS ether **3.12** can be explained by the size of the protecting group and a longer stirring time would have been needed (only one hour stirring at room temperature for **3.10-3.12**).

Finally, after a few months of trials, the following reactions with the corresponding yields in brackets were successfully carried out:



Scheme 4.6: Protection and acylation reactions on pseudoephedrine **2.1** [42, 43, 44, 45]

4.2 Benzylation of pseudoephedrine propionamide and the silyl protected derivatives

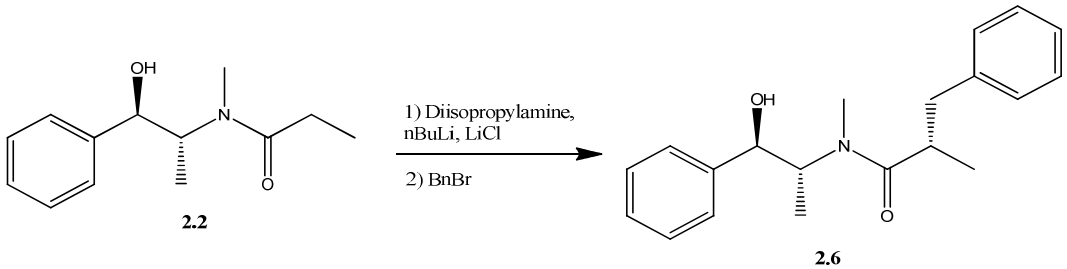


Scheme 4.7: Asymmetric alkylation[25]

As a model for the enolate alkylation of silyl ethers **3.10-3.12** it was decided to investigate the alkylation on the non-protected pseudoephedrine propionamide **2.2** commercially available (**Scheme 4.7**). This would give a comparison point to the synthesized molecules regarding the diastereomeric excess.

For this reaction, the base (LDA) was formed at -78 °C where *n*BuLi was added to diisopropylamine in anhydrous THF, in the presence of LiCl. After a short stirring at 0 °C, the mixture was cooled again to -78 °C and a solution of the amide **2.2** in anhydrous THF was added to the base. This mixture was stirred for 1h at -78 °C, 1h at 0 °C and then 40 min at room temperature. The solution was brought back to 0 °C for the addition of benzyl bromide to obtain the alkylated product **2.6**.

This reaction is air- and water-sensitive, so the glassware needed to be completely dry and only glass syringes were used. The starting material **2.2** and LiCl needed to be dried over night in a drying pistol at 40 °C and 2 mbar. Diisopropylamine and benzyl bromide were distilled from calcium hydride before use. Finally *n*BuLi was titrated prior to use, because of slow decomposition. A few attempts were necessary to obtain appropriate conditions to carry out this reaction (**Table 4.4**).



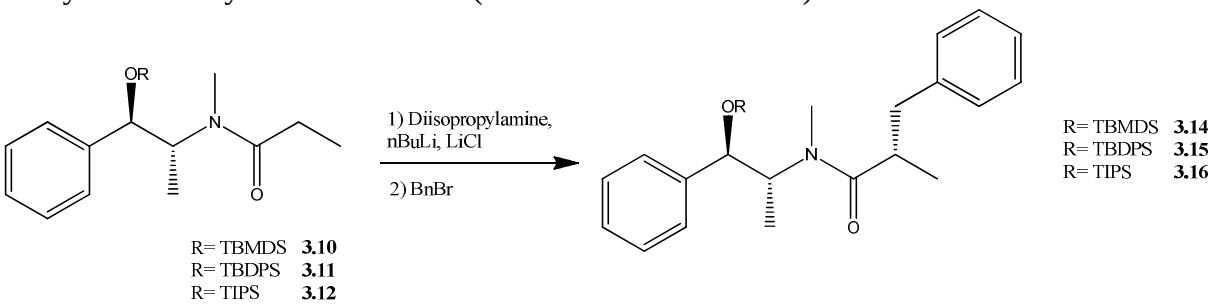
Scheme 4.8: Asymmetric alkylation of commercially available **2.2**

Entry	Diisopropyl amine	Equivalents of nBuLi (Molarity)	Time before addition of BnBr	Time and temperature of stirring after BnBr addition	Yield
1	2.25 eq	2.1 eq, titrated at 1.59 M	1h at -78 °C, 35 min at 0 °C, 15 min at rt	1h at 0 °C	9%
2	2.25 eq	2.1 eq, titrated at 1.59 M	Ditto	1h at rt	7%
3	2.25 eq	2.1 eq, titrated at 1.59 M	1h at -78 °C, 1h at 0 °C, 40 min at rt	1 h 20 at 0 °C	0%
4	2.25 eq, distilled	2.1 eq, new bottle (2.5 M)	ditto	ditto	0 %
5	4.5 eq, distilled	4.2 eq, new bottle (2.5 M)	ditto	ditto	53 %

Table 4.4: Reaction conditions for the asymmetric alkylation of amide **2.2**

For the first two entries (**Table 4.4**) most of the starting material **2.2** was recovered. Therefore it was decided to let the reaction stir longer for the next attempts in order to be sure to form the enolate. In the last assay (**Table 4.4**, entry 5) the quantities of diisopropylamine and butyllithium used were doubled, because only the starting material was still recovered in entries 3 & 4, which gave 53% of product **2.6**. Although this is lower than literature, these reactions were carried out on a much smaller scale where problems with moisture are more pronounced.

Successful alkylation of amide **2.2** allowed this procedure to be applied to the benzylation of silyl ethers **3.10**-**3.12** (**Scheme 4.8** & **Table 4.5**).



Scheme 4.8: Benzylation of the silyl derivatives

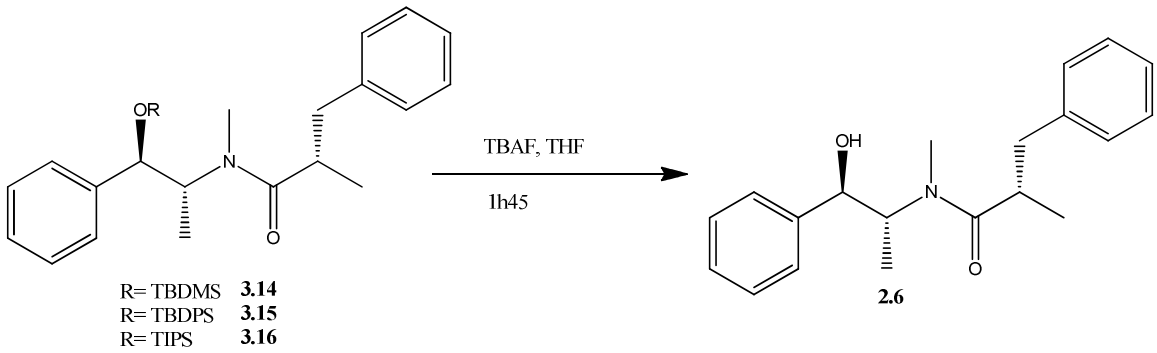
Essay	Starting material	Quantity of starting material used	Yield of the alkylated product
1	**3.10**	3.13 mmol	63 %
2	**3.11**	2.94 mmol	0 %
3	**3.11**	2.94 mmol	0 %
4	**3.12**	5.30 mmol	63 %
5	**3.10**	4.77 mmol	55 %

Table 4.5: Yields of the benzylation of the protected pseudoephedrine proponamide

Using the above conditions allowed the successful alkylation of TBDMS and TIPS amides **3.14** & **3.16** (**Table 4.5**, entries 1, 4 & 5). However, the TBDPS ether failed to alkylate under these conditions (**Table 4.5,** entries 2 & 3), possibly due to the large steric requirements of this silyl group preventing the enolate formation or the alkylation.

4.3 Deprotection of the alcohol functionality

To be able to carry out the cyclization and form oxazolium triflate derivatives **3.17** (**Scheme 4.10**) the silyl ether functionality of the alkylated products **3.14-3.16** needed to be deprotected. Therefore, the compound (**3.14**, **3.15** or **3.16**) was dissolved in anhydrous THF, the solution was cooled to 0 °C, and TBAF was slowly added (**Scheme 4.9**). The obtained yields for the deprotection are summarized in **Table 4.6**. The deprotection of compound **3.15** was never tried as **3.15** could not be obtained.



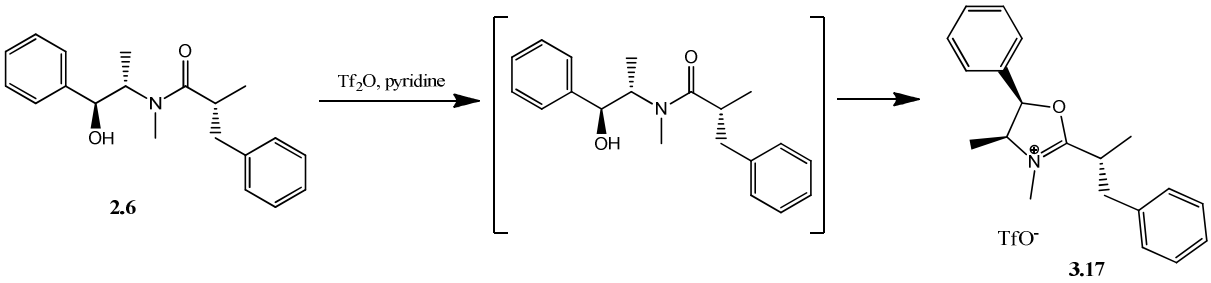
Scheme 4.9: Deprotection of the alcohol functionality of the alkylated products **3.14** & **3.16**[45]

Essay	Starting material used	Yield for product **2.6**
1	**3.14**	58 %
2	**3.16**	80 %
3	**3.14**	76 %

Table 4.6: Yields of the different deprotection reactions

4.4 Cyclization into oxazolium triflate derivatives

In order to determine the diastereomeric ratios, Myers' method was used to cyclise the amide alcohols **2.6** with triflic anhydride. In this assay, Myers[38] utilised recrystallised material and it was found that similarly purified material was vital to achieve smooth cyclization.

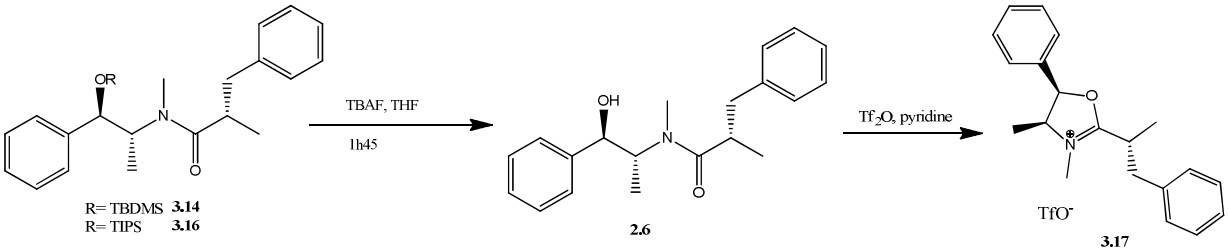


Scheme 4.10: Cyclization of alkylated pseudoephedrine propionamide[38]

Using the method of Myers, the substrate **2.6** was dissolved in DCM to a concentration of 0.04 M and the solution was cooled to 0 °C. Triflic anhydride (2 eq) and pyridine (3 eq) were added (**Scheme 4.8**). After stirring for 5 min the suspension was concentrated and the residue was held *in vacuo* (1 mmHg) for 1h.

This reaction was firstly tried on the alkylated compound which had not been previously silyl protected (**Scheme 4.10**). The first time the reaction was carried out, it did not give a good enough result to measure the diastereomeric excess with precision. The proton NMR of **3.17** showed traces of unalkylated material, so the starting material has to be very pure for a successful cyclisation and analysis. The reaction time was also increased to 30 minutes and monitored by TLC to make sure all the starting material was consumed. The second attempt using these improved conditions was a success and a diastereomeric excess of 92% was measured.

Then the reaction was carried out on the compounds which had been silylated previous to the benzylation (**Scheme 4.11**). Unfortunately the NMR did not always give workable NMRs (**Table 4.7**, entries 1 & 2), because of the non-sufficient purity of the starting material i.e. **2.6**. The attempts on repurified material allowed measuring the diastereomeric excess on the proton NMR (**Table 4.7**, entries 3 & 4).



Scheme 4.11: Deprotection and cyclization of alkylated products **3.14-3.16**

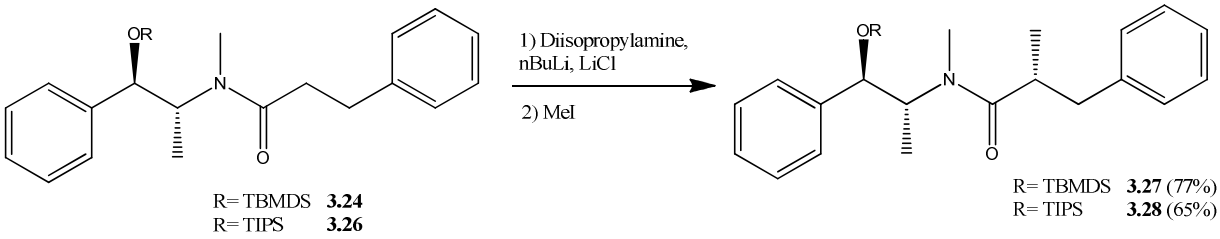
Entry	Silyl protecting product used	Diastereomeric excess measured on ^{1}H NMR
1	**3.14**	not usable NMR[1]
2	**3.16**	not usable NMR[1]
3	**3.16**	34 %
4	**3.14**	42 %

[1] Use of non high purity amide **2.6**

Table 4.7: Measured diastereomeric excess for the deprotected silyl derivatives

4.5 Methylation of the silyl derivatives

Because the *N*-acylation of the silyl protected pseudoephedrine using hydrocinnamoyl chloride **3.23** was successful it was important to apply these procedures to the formation of the corresponding diastereomers **3.27** & **3.28** by methylation of the dihydrocinnamyl amides **3.24** & **3.26** (**Scheme 4.12**). This reaction should give us the diastereomer of the benzylation reaction, because of the 1,4-*syn* product formed. This should give us more information on the mechanism of the alkylation. This reaction was carried out following the same protocol as for the benzylation except that methyl iodide was used instead of benzyl bromide.



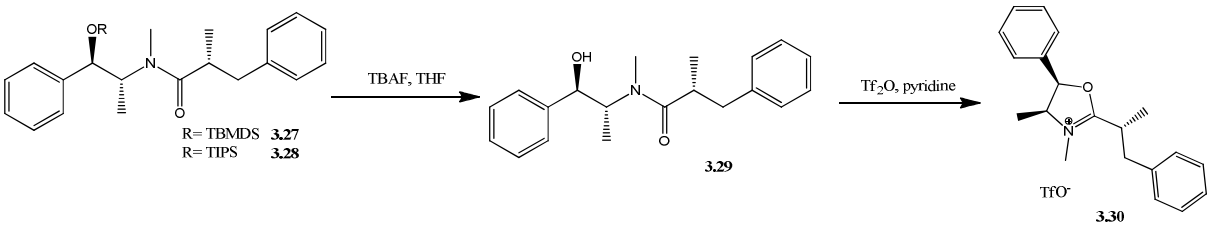
Scheme 4.12: Methyl of the silyl derivatives **3.24** & **3.26**

The methylation product **3.27** was obtained in 77% yield (about 10% more than all the other alkylations) because a larger amount of starting material **3.24** was used (400 mg instead of 150 mg): on a larger scale, moisture problems will be less and recovery will be better. Methylated TIPS ether **3.28** was prepared by methylation using 150 mg of starting material **3.26** and obtained with a yield of 65% (in the same range as for the benzylations).

The alkylated products **3.27** & **3.28** were then deprotected using again TBAF to obtain the alcohol **3.29** (**Scheme 4.13**). The TIPS starting material **3.27** gave a 41% yield of **3.29** and this low yield made the product hard to purify for the cyclization into **3.30** and a good NMR was not always obtained (**Table 4.8**). The product was, therefore, purified by

flash chromatography, then recrystallization was attempted but failed and finally a second small flash column was undertaken to obtain a pure enough compound **3.29**. The cyclization into **3.30** was successful after all these purifications and gave a diasteromeric excess of 18%. Even if the selectivity is lower then for the benzylation, we do observe the expected major diastereoisomer.

The deprotection of **3.28** gave a 69% yield and because the reaction process was carried out on a larger scale, only one purification by flash chromatography was necessary to obtain a pure product **3.29**. The cyclization showed by NMR a diastereomeric excess of 17% with the expected major diastereomer.



Scheme 4.13: Deprotection and cyclization of the methylated compounds **3.27** & **3.28**

Entry	Silyl protecting product used	Diastereomeric excess measured on ^{1}H NMR of **3.30**
1	**3.27**	not usable NMR
2	**3.28**	17 %
3	**3.27**	18 %

Table 4.8: Diastereomeric excess of the asymmetric methylation of amides **3.27** & **3.28**

4.6 Mechanistic conclusions

How do we practically measure the diastereomeric excess? We need to have a well-defined proton NMR spectrum of the cyclised compound **3.17** and then we compare it to Myers' spectra of his cyclization. The major differences between the two spectra are on the two methyl groups F and C (**Figure 4.1**).

For the benzylation, the major diastereomer **3.17** has a doublet for protons C at 0.98 ppm and a doublet for protons F at 1.43 ppm approximately. For the methylation, the major diastereoisomer **3.30** has a doublet for protons C at 0.81 ppm and a doublet for protons F at 1.50 ppm approximately. To measure the diastereomeric excess, we compare the integrals for the major and the minor peak on each NMR and we get the value of interest.

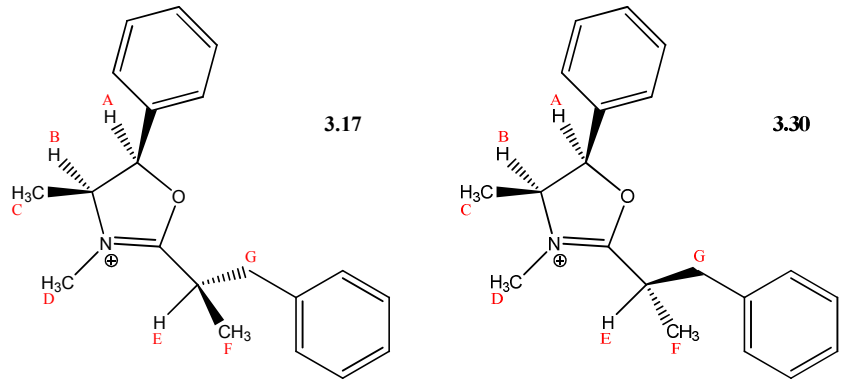


Figure 4.1: The cyclised compounds **3.17** & **3.30**[39]

What can be concluded about the mechanism? The question was to see which of the two supposed transition state, Myers' dianion **2.10** or the π-Li^+ interaction **2.21,** was the real pathway of the asymmetric alkylation.

Because we used silyl ethers that are supposed to affect the possible chelation of the lithium, we would expect a diastereomeric excess of 0% in the case of Myers' mechanism. We suppose that an open-chain mechanism would occur and that the large silyl group is far enough from the alkylation site so as not to create any steric shielding.

If the correct transition state is the π-Li^+ one, we would instead expect to have a very good diastereomeric excess not affected by the silyl ether as it does not interact in the mechanism.

In fact we are in neither of these two cases. We do see the expected major diastereomer in each case (so no 50:50 mixtures), but the ratio has dropped from over 90% to 42-17%. If, the silyl ethers **3.14**-**3.16**-**3.27**-**3.28** do, indeed, prevent Li+ coordination with the ether oxygen then an open conformation would be predicted where there would be little diastereofacial control. Under these circumstances we would expect that the 1*Si*,2*Re* and 1*Re*,2*Si* faces would be equally encumbered. We concluded therefore that the transition state is the π-Li^+ one but that the large silyl ether will conformationally disturb the low energy conformation of the side chain carrying the aromatic group. This affects the formation of the interaction between the aromatic ring and the lithium cation (**Figure 4.2**). The silyl ether group possibly interacts with the pseudoephedrine C-2 methyl group. Of course, it may be that the silyl ethers are still able to chelate the enolate lithium but with reduced capacity and so, reduced diastereoselectivity.

Some calculations were carried out on the TIPS Z-enolate. While the global minimum was the π-Li+ conformer, there were only two π-Li+ and two Myers' conformations within 20 $kJmol^{-1}$ of the global minimum. From the minimum (π-Li^+) there

are 8 extended conformations (i.e. not π-Li^+ nor Myers') between 3.44 and 11.35 $kJmol^{-1}$ less stable than the global minimum. Then follows the two Myers conformations (11.5 & 13.63 $kJmol^{-1}$) which are less stable than the global minimum. The second π-Li^+ is less stable at 15.04 $kJmol^{-1}$ and there are a further 4 extended conformations 13.78-19.19 $kJmol^{-1}$ less stable than the global minimum. The π-Li^+ looks like the aromatic ring is rotated away from the TIPS isopropyl groups. So, with so many extended conformations, we may have destabilized both the Myers' and π-Li^+ conformations. So, there is not much difference between the faces of the carbon atom of the enolate.

There is a significant difference between the benzylation and the methylation. The explanation could be that the size of the alkyl halide is important when working with silyl ether. We could imagine that the small methyl iodide can more easily attack each side of the molecule because the transition state which should provide the steric shielding on the (1*Si*,2*Re*) face is harder to form.

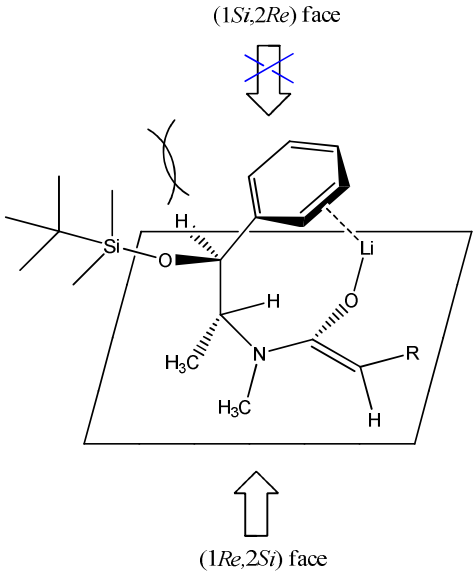


Figure 4.2: π-Li+ interaction affected by the silyl ether

Conclusion

The aim of this project was to synthesize silyl protected derivatives of pseudoephedrine amides and to proceed to an asymmetric alkylation using these compounds as chiral auxiliaries. By doing this we should obtain more information about the transition state and so the mechanism of this asymmetric alkylation of pseudoephedrine amide enolates.

At the beginning, difficulties were encountered to obtain the silyl protected derivatives **3.20 - 3.22** but, after discovering the light-sensitivity of the ephedrine solutions and changing the synthetic pathway, these molecules were obtained in good yields.

The pseudoephedrine silyl ethers **3.20 - 3.22** were prepared and acylated in two different ways: one using propionic chloride and another using hydrocinnamoyl chloride to give the corresponding amides **3.10-3.12** and **3.24-3.26**.

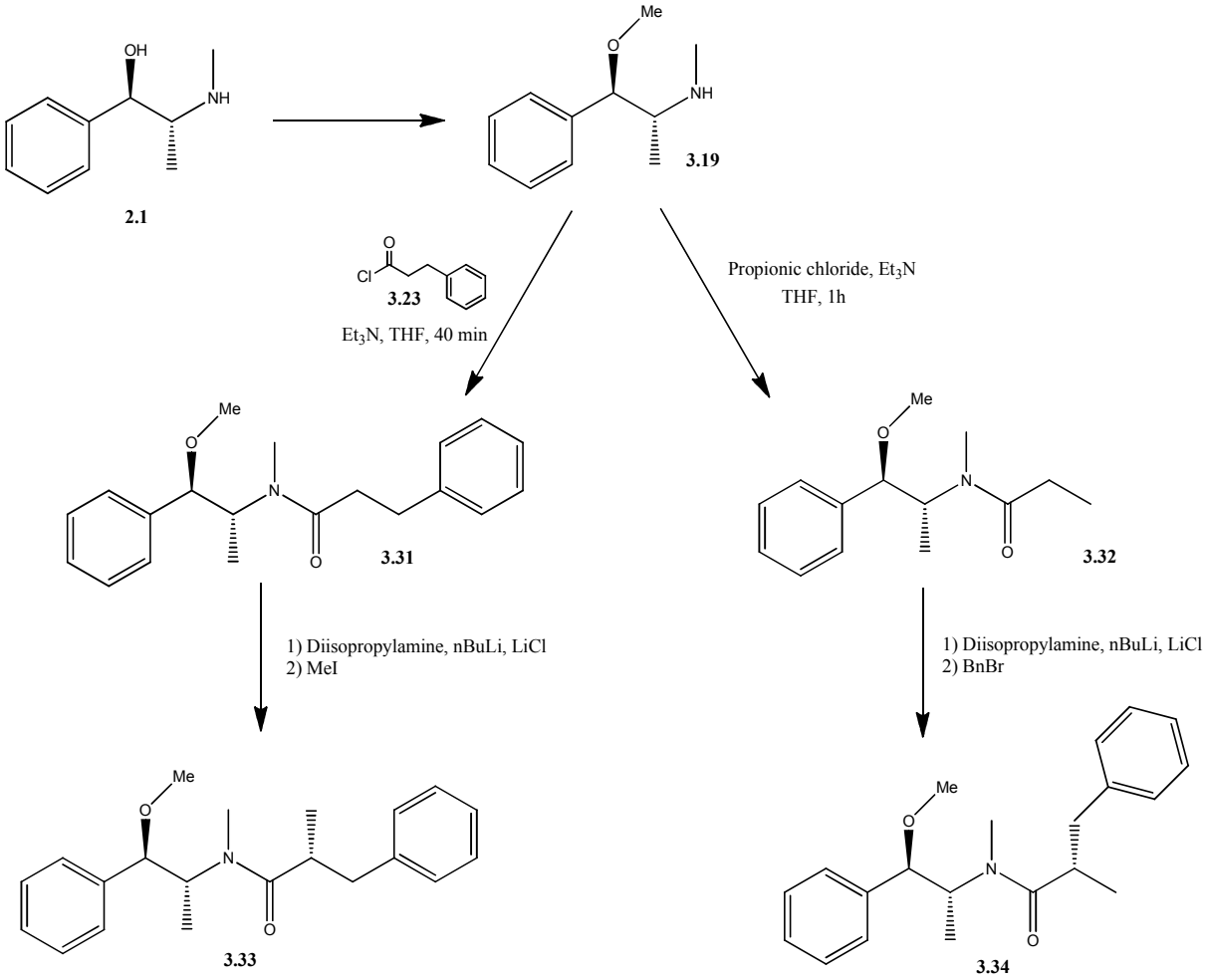
Then the actual asymmetric alkylation was carried out by either benzylating or methylating the enolates of the silyl ether amides. Finally the compounds **3.14-3.16** & **3.27-3.28** were deprotected and cyclised in order to be able to measure with accuracy the diastereomeric excess of the different molecules. The following diastereomeric excesses were measured:

- For the TBDMS derivatives **3.14** and **3.28**: 42 % for the benzylation and 17 % for the methylation
- For the TIPS derivative **3.16** and **3.27**: 34 % for the benzylation and 18 % for the methylation

It was concluded that the real transition state is the π-Li^+ interaction but some further explorations are necessary, especially after the calculations made on the TIPS compound.

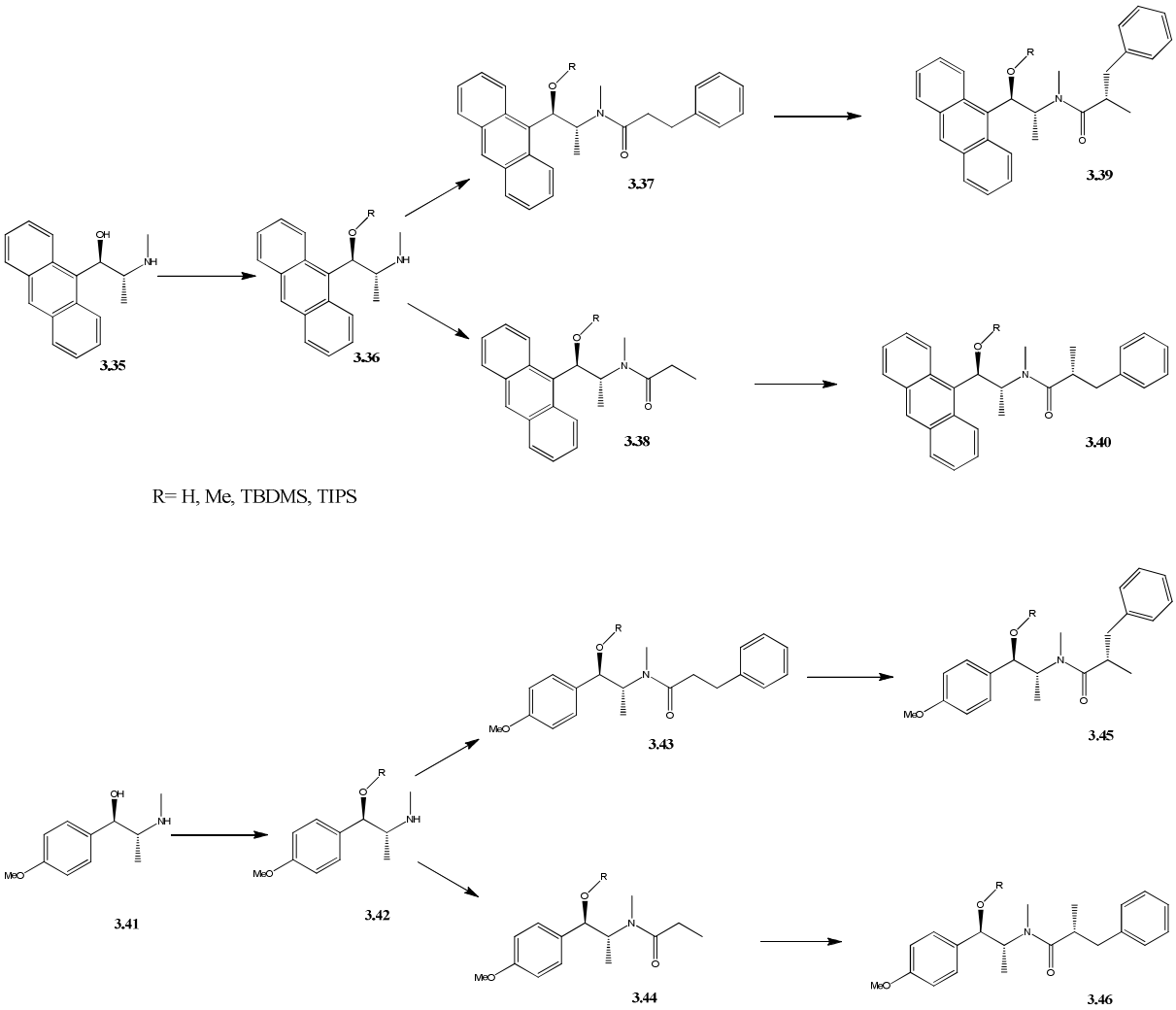
Future work

A first possibility would be to investigate the use of an *O*-methyl ether (**3.19**) instead of silyl ethers (**Scheme 4.14**). In fact, a methyl group is much smaller and should less affect the diastereomeric ratio of the alkylation. This could give us more information to confirm our mechanistic hypothesis. Doing the two different alkylations should show if the size of the alkyl halide has any importance or if it is only because of the presence of the large silyl group. However, the methyl ether could operate through the chelate suggested by Myers or through a π-Li^+ interaction.



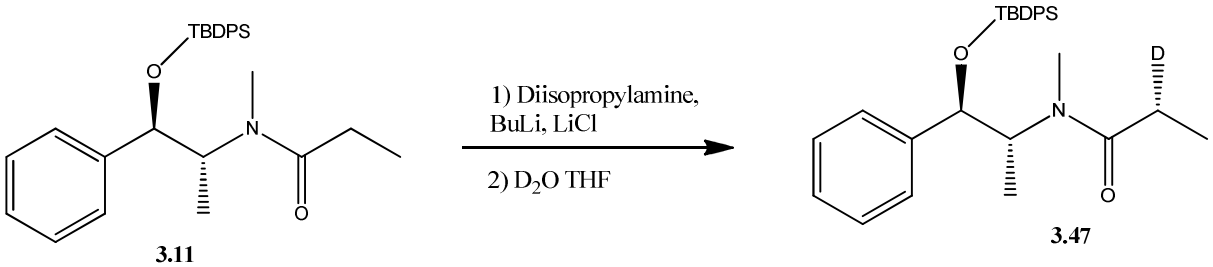
Scheme 4.14: Two alkylation routes using an O-methyl ether

Another option would be to work on more electron-rich aromatic rings with or without the silyl ether to see how the diastereomeric excess is affected: we would expect to improve it, as an electron rich aromatic ring would want to interact more with the lithium cation. Calculations have indicated that the anthracenyl pseudoepephedrine auxiliary 3.35 or 4-methoxy derivative 3.41 might provide enhanced π-Li^+ interactions (**Scheme 4.15**).



Scheme 4.15: Possible alkylations done with more electron-rich aromatic groups with or without silyl ethers

A third area of exploration could be to see if the *tert*-butyldiphenylsilyl group is too big for the enolate to be formed or if it is the alkyl halide which cannot reach the alkylation site. We could check this by adding some deuterated water instead of the alkyl halide which will show if the enolate is formed or not (**Scheme 4.16**).



Scheme 4.16: Alkylation of **3.11** with D_2O

Experimental

NMR: ^{1}H and ^{13}C NMR were recorded on Bruker AV 300 or DPX 500 spectrometer. The chemical shifts are given in ppm (δ values) relative to the residual proton resonances in deuteriated solvents for ^{1}H NMR and relative to solvent in ^{13}C NMR. The proton signals were reported as: multiplet (m), broad (br), quartet (q), quintuplet (quin), triplet (t), doublet (d), singlet (s) and the constant values *J* were recorded in Hertz.

IR spectroscopy: FT-IR Spectrometer from Shimadzu, the IR Affinity-1 machine was used. ATR analyses were carried out as liquid or solid films.

HRMS: High resolution mass spectra were obtained on a Jeol JMS AX505 using fast atom bombardment or electrospray ionisation.

$[\alpha]_D^{20}$: Specific rotations were recorded using a Perkin Elmer 341 polarimeter using the sodium D line with a 1 cm^3 10 dm cell at 20 °C with a wavelength of 589 nm. The $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^2 g^{-1} and the concentrations are given in g/100 mL.

Melting points were measured on a Reichert hot stage microscope and are uncorrected.

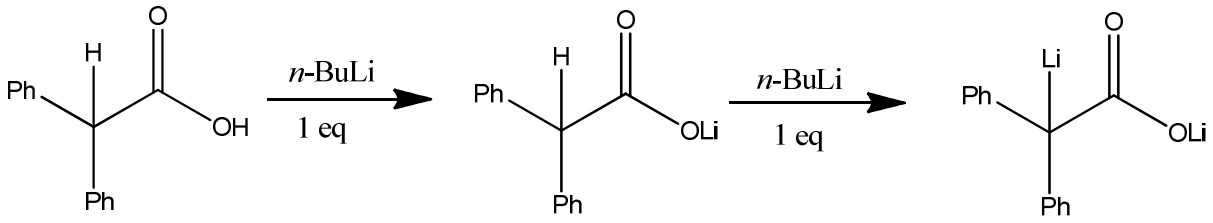
Flash chromatography was carried out using 200-400 mesh silica gel following standard procedures.[46]

All the silylation, acylation and deprotection reactions were carried out in the absence of light: the flasks were wrapped in aluminium foil.

All the glassware and glass syringes used for the reaction were previously dried in an oven at 140 °C. The flasks were also flame dried under inert atmosphere prior to use.

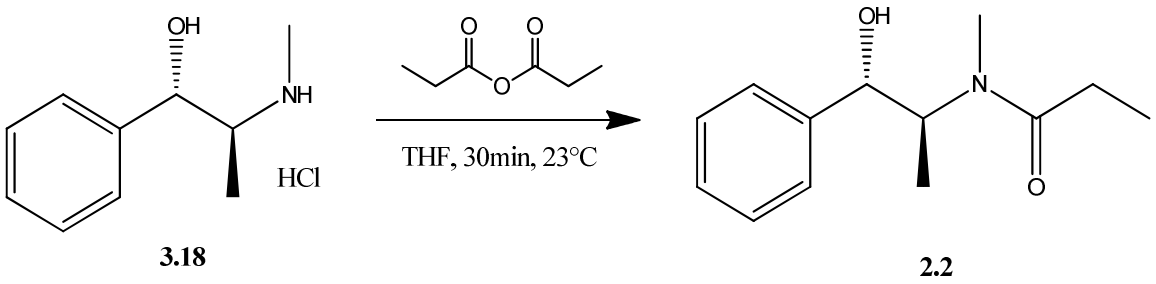
Prior to a reaction, solid starting materials were dried in a drying pistol at 40°C and 100 mmbar for at least 2h. Liquid reagents were distilled and kept in a dry box.
Solvents (DCM, THF, ether …) were taken from a dry solvent distribution machine. These solvents were dried over molecular sieves.

Titration of n-BuLi[47]:



Diphenylacetic acid (0.20g, 0.95 mmol) was added to a flask as well as dry THF (5 mL) under inert atmosphere. n-BuLi was added dropwise *via* syringe. The yellow colour of the solution indicates that the end point is reached because the lithium lithiodiphenylacetate has been formed. By knowing the exact volume on n-Buli added (0.60 mL) to reach the end point, it was possible to deduce the concentration of the titrated solution (1.59 mol.L^{-1} = 0.95 mmol/0.60 mL).

Preparation of *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide 2.2:



3.18 **2.2**

(1*R*,2*R*)-(-)-Pseudoephedrine hydrochloride **3.18** (0.22 g, 0.72 mmol, 1 eq) was dissolved in water (2 mL). Solid potassium hydroxide was added up to pH 11 and the precipitation of a white solid was observed. DCM (3 mL) was added and the precipitate re-dissolved. The layers were separated and the organic phase was washed with brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo* in order to obtain the free base material as a white solid (0.15 g, 84%). This reaction was carried out again in order to obtain finally 0.54 g of the free base material **2.1**. This reaction was repeated multiple times to obtain the needed amount of **2.1**.

The resulting free base **2.1** was dried overnight in a drying pistol (40 °C, 2 mbar). The resulting free base starting material (0.54 g, 3.26 mmol, 1 eq) was dissolved in dry THF (10 mL). The solution was heated to 23 °C and freshly distilled propionic anhydride (0.47 mL, 3.59 mmol, 1.1 eq) was slowly added. After 15 minutes, a saturated solution of

$NaHCO_3$ (10 mL) was added to quench the reaction. The aqueous layer was extracted three times with EtOAc (20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by recrystallization from hot toluene which gave *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide **2.2** as a white solid (0.38 g, 52%).

^{1}H NMR: (5:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.4 – 7.2 (m, 5H), 4.60 (m, 1H), 4.02 (quin, 1H, *J*=6.5 Hz), 2.94* (s, 3H), 2.82 (s, 3H), 2.55* (m, 2H), 2.32 (m, 2H), 1.18* (t, 3H, *J*=5.6 Hz), 1.15 (t, 3H, *J*=5.6 Hz), 0.97 (d, 3H, *J*=5.6 Hz), 0.91* (d, 3H, *J*=5.6 Hz)

^{13}C NMR: (5:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 175.74 (C=O), 142.02 (quaternary phenyl C), 128.53*, 128.24, 127.96, 127.72*, 126.42*, 125.89, 76.83, 75.07*, 58.25*, 57.75, 32.29, 27.09, 26.35*, 14.73*, 13.97, 9.09*, 8.69

IR Spectroscopy (cm^{-1}): 3375 (broad OH band), 2991-2822 (Csp^3-H), 1610 (C=O)

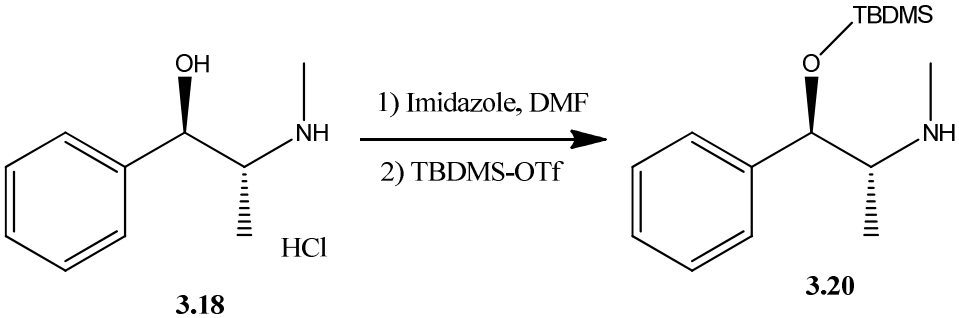
HRMS: found M+H = 312.1960 (calculated for $C_{20}H_{26}O_2N$ M+H= 312.1958)

$[\alpha]_D^{20}$ = -108.8 (c=1, $CHCl_3$), (lit.: $[\alpha]_D^{20}$ = -101.8 (c=1, $CHCl_3$))[48]

Melting point: 115-118 °C (lit.: 114-115 °C)[49]

Silylations of pseudoephedrine:

Preparation of (1*R*,2*R*)-1-((tert-butyldimethylsilyl)oxy)-N-methyl-1-phenylpropan-2-amine 3.20:



3.18 **3.20**

The free base starting material **3.18** was prepared the same way as in **2.2**. This starting material (1.70 g, 10.29 mmol, 1 eq) was dissolved, protected from light, in dry DMF (15 mL) and imidazole (1.40 g, 20.58 mmol, 2 eq) was added at room temperature. The solution was cooled to 0 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.31 mL,

14.41 mmol, 1.4 eq) was added. The reaction was stirred for 30 minutes at 0 °C and 23 h at room temperature. Then the DMF was removed *in vacuo* (1 mmHg) and the residue was dissolved in saturated aqueous $NaHCO_3$ (20 mL). The mixture was stirred for 10 minutes and then Et_2O (20 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (30% EtOAc / 70% DCM) in order to obtain (1*R*,2*R*)-1-((tert-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylpropan-2-amine **3.20** as a yellow oil (1.85 g, 64%).

^{1}H NMR: (9:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.4-7.2 (m, 5H), 4.57*(d, 1H, *J*=8.0 Hz), 4.49 (d, 1H, *J*=8.0 Hz), 3.62 (quin, 1H, *J*=6.5 Hz), 2.88* (s, 3H), 2.51 (s, 3H), 1.09* (d, 3H, *J*=5.6 Hz), 0.94 (d, 3H, *J*=5.6 Hz), 0.88 (s, 9H), 0.87* (s, 9H), 0.07 (s, 3H), 0.06* (s, 3H), -0.23* (s, 3H), -0.024 (s, 3H),

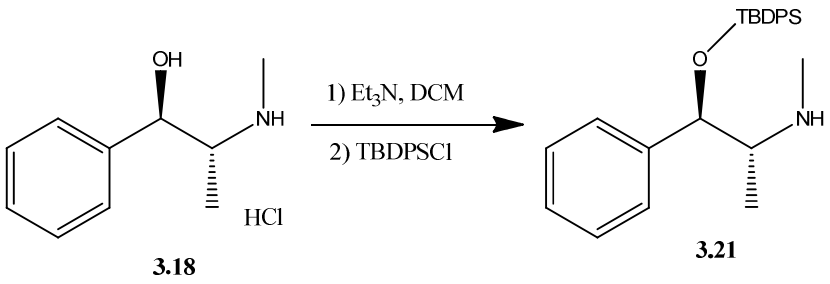
^{13}C NMR: δ 140.64 (quaternary phenyl C), 127.82, 127.63, 126.80, 77.63, 61.35, 32.17, 25.27, 17.57, 13.33, -5.04, -5.55

IR Spectroscopy (cm^{-1}): 2953-2856 (Csp^3-H), 835 (Si-O bond), no OH broad band around 3300

HRMS: found M+H = 280.2093 (calculated for $C_{16}H_{30}ONSi$ M+H= 280.2091)

$[\alpha]_D^{20}$ = -78.1 (c=1, $CHCl_3$)

Preparation of (1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-*N*-methyl-1-phenylpropan-2-amine 3.21 :



3.18 **3.21**

A mixture of pseudoephedrine hydrochloride **3.18** (0.20 g, 0.89 mmol, 1 eq), Et_3N (0.26 mL, 1.88 mmol, 2.1 eq) and DCM (5 mL) were stirred for 50 minutes (under nitrogen and with the flask wrapped in aluminium foil). *Tert*-butyldiphenylchlorosilane (0.24 mL,

0.94 mmol, 1.05 eq) was added and the reaction was left to stir for 6 h before Et_2O (5 mL) was added. The solution was filtered over celite and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (50% EtOAc / 50% DCM) to give (1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-*N*-methyl-1-phenylpropan-2-amine **3.21** as a transparent oil (0.15 g, 75 %).

^{1}H NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.7 – 7.1 (m, 15H), 4.62 (d, 1H, *J*=8.0 Hz), 4.42* (d, 1H, *J*=8.0 Hz), 3.56* (quin, 1H, *J*=6.5 Hz), 3.48 (quin, 1H, *J*=6.5 Hz), 2.57* (s, 3H), 2.26 (s, 3H), 1.08 (s, 9H), 1.03* (s, 9H), 0.79 (d, 3H, *J*=5.6 Hz)

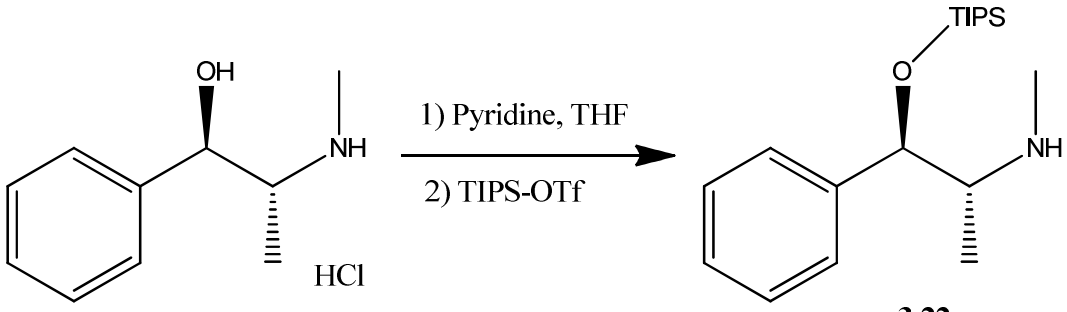
^{13}C NMR: δ 140.52 (quaternary phenyl C), 133.50 (quaternary phenyl C), 132.89 (quaternary phenyl C), 129.15 (CH), 129.04 (CH), 127.32 (CH), 127.23 (2 CH), 127.05 (2 CH), 126.88 (2 CH), 126.82 (2 CH), 126.74 (2 CH), 126.68 (2 CH), 77.55, 60.40, 32.99, 26.59, 18.91, 14.14

IR Spectroscopy (cm^{-1}): 2997-2856 (Csp^3-H), 819 (Si-O bond), no OH broad band around 3300

HRMS: found M+H = 404.2408 (calculated for $C_{26}H_{34}ONSi$ M+H= 404.2404)

$[\alpha]_D^{20}$ = -69.6 (c=1, $CHCl_3$)

Preparation of (1*R*,2*R*)-*N*-methyl-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-amine 3.22:



3.18 **3.22**

The free base starting material **2.1** (0.50 g, 3.03 mmol, 1 eq) was dissolved in anhydrous THF (5 mL) and the solution was cooled to 0 °C. Pyridine (0.32 mL, 4.24 mmol, 1.4 eq) was added and after 5 minutes triisopropylsilyl triflate (0.90 mL, 3.33 mmol, 1.1 eq) was also added. The reaction was left to stir at room temperature for 24 h. A saturated solution of aqueous NH_4Cl (10 mL) was added to quench the reaction. The product was

extracted with DCM (3 × 10 mL), the organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (60% EtOAC / 40% DCM) which gave (1*R*,2*R*)-*N*-methyl-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-amine **3.22** as a white solid (0.95 g, 98%).

^{1}H NMR: δ 7.3 – 7.4 (m, 5H), 4.85 (d, 1H, *J*=8.0 Hz), 3.31 (quin, 1H, *J*=6.5 Hz), 2.87 (s, 3H), 1.19 (d, 3H, J=5.6 Hz), 1.03 (s, 18H), 0.95 (m, 3H)

^{13}C NMR: δ 138.21 (quaternary phenyl C), 129.53 (CH), 129.02 (2CH), 127.32 (2CH), 75.97, 62.82, 31.59, 17.94, 12.33, 11.48

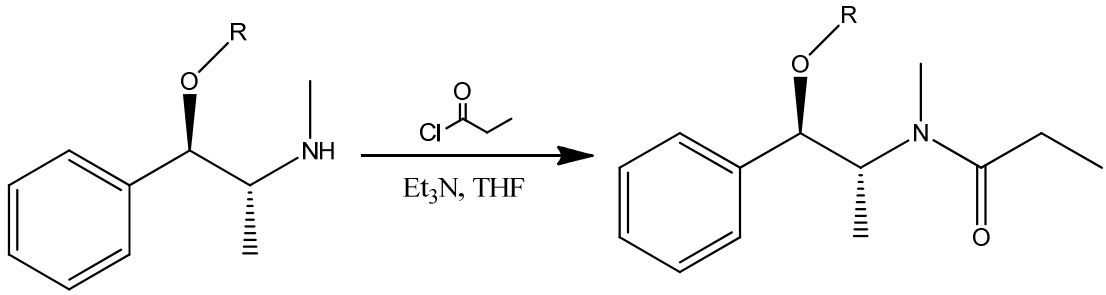
IR Spectroscopy (cm^{-1}): 2943-2866 (Csp^3-H), 885 (Si-O bond), no OH broad band around 3300

HRMS: found M+H = 322.2562 (calculated for $C_{19}H_{36}ONSi$ M+H= 322.2561)

$[\alpha]_D^{20}$ = -47.6 (c=1, $CHCl_3$)

Melting point: 151-154 °C

Acylation using propionic chloride:



R= TBDMS **3.20**
R= TBDPS **3.21**
R= TIPS **3.22**

R= TBDMS **3.10**
R= TBDPS **3.11**
R= TIPS **3.12**

Preparation of *N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methylpropionamide 3.10:

(1*R*,2*R*)-1-((*Tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylpropan-2-amine **3.20** (0.32 g, 1.13 mmol, 1eq) was dissolved in THF (7 mL) and Et_3N (0.21 mL, 1.47 mmol, 1.30 eq) was added. The solution was cooled at 0 °C and a solution of propionyl chloride (0.11 mL, 1.30 mmol, 1.15 eq) in THF (1 mL) was slowly added. The reaction was stirred for 50

minutes at room temperature and 5 mL of water were slowly added to quench the reaction. The mixture was partitioned between EtOAc (15 mL) and brine (5 mL). The organic layer was separated, washed twice with brine (2 × 5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash chromatography (7% EtOAc / 93% DCM) and gave *N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methylpropionamide **3.10** as a transparent oil (0.24 g, 65%).

^{1}H NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.4 – 7.2 (m, 5H), 4.47 (d, 1H, *J*=8.0 Hz), 3.99 (quin, 1H, *J*=6.5 Hz), 2.88 (s, 3H), 2.80* (s, 3H), 2.2 (q, 2H, *J*=7.4 Hz), 1.12 (t, 3H, *J*= 7.4 Hz), 0.95 (d, 3H, *J*=6.5 Hz), 0.87* (s, 9H), 0.81 (s, 9H), 0.04* (s, 3H), -0.01 (s, 3H), -0.26* (s, 3H), -0.32 (s, 3H)

^{13}C NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 173.96 (C=O), 141.75 (quaternary phenyl C), 127.93 (2 CH), 127.40 (CH), 126.47 (2 CH), 76.83, 75.82*, 57.76, 26.71*, 26.25, 25.11*, 25.04, 17.47*, 17.33, 15.03, 13.22, 9.00, 8.67*, -5.19, -5.86

IR Spectroscopy (cm^{-1}): no NH band around 3600, 2954-2856 (Csp^3-H), 1639 (amide C=O), 833 (Si-O bond)

HRMS: found M+H = 336.2352 (calculated for $C_{19}H_{34}O_2NSi$ M+H= 336.2353)

$[\alpha]_D^{20}$ = -93.1 (c=1, $CHCl_3$)

Preparation of *N*-((1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methylpropionamide 3.11:

The *N*-((1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methylpropionamide **3.11** was prepared in the same way as compound **3.10**. 0.35 g of starting material (1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-*N*-methyl-1-phenylpropan-2-amine **3.21** was used and **3.11** was obtained as a transparent oil (0.37 g, 85%).

^{1}H NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.7 – 7.1 (m, 15H), 4.59* (d, 1H, *J*=8.0 Hz), 4.46 (d, 1H, *J*=8.0 Hz), 4.05 (quin, 1H, J= 6.5 Hz), 2.49 (s, 3H), 2.40* (s, 3H), 2.15 (quart., 2H, *J*=7.4 Hz), 1.27 (t, 3H, *J*=7.4 Hz), 0.97 (s, 9H), 0.92* (s, 9H), 0.86 (d, 3H, *J*=5.6 Hz), 0.75* (d, 3H, *J*=5.6 Hz)

^{13}C NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 173.76 (C=O), 173.48* (C=O), 141.38 (quaternary phenyl C), 140.66 (quaternary phenyl C), 135.65 (quaternary phenyl C), 129.36 (CH), 129.04* (CH), 128.98* (CH), 128.95 (CH), 127.72 (2CH), 127.53* (2CH), 127.39 (2CH), 127.15* (2CH),127.10* (2CH) , 126.93 (2CH), 126.72* (2CH),

126.69 (2CH) , 76.85*, 76.22, 59.91*, 57.33, 26.97*, 26.81, 26.39, 26.14*, 20.57, 18.86*, 18.64, 14.46, 13.71*, 13.62, 13.45*, 9.08, 8.85*

IR Spectroscopy (cm^{-1}): no NH band around 3600, 2931-2856 (Csp^3-H), 1641 (C=O), 815 (Si-O bond)

HRMS: found M+H = 460.2665 (calculated for $C_{29}H_{38}O_2NSi$ M+H= 460.2666)

$[\alpha]_D^{20}$ = -73.8 (c=1, $CHCl_3$)

Preparation of *N*-methyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propionamide 3.12:

N-Methyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propionamide **3.12** was prepared using the same protocol as for compound **3.10**. 0.50 g of starting material (1*R*,2*R*)-*N*-methyl-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-amine **3.22** was used and **3.12** was obtained as a transparent oil (0.29 g, 49%).

^{1}H NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.2 – 7.4 (m, 5H), 4.68 (d, 1H, J=8.0 Hz), 4.01 (quin, 1H, J=6.5 Hz), 2.85 (s, 3H), 2.46* (s, 3H), 2.25 (q, 2H, J=7.4 Hz), 1.16 (t, 3H, J=7.4 Hz), 1.13 – 1.01 (m, 18H+3H)

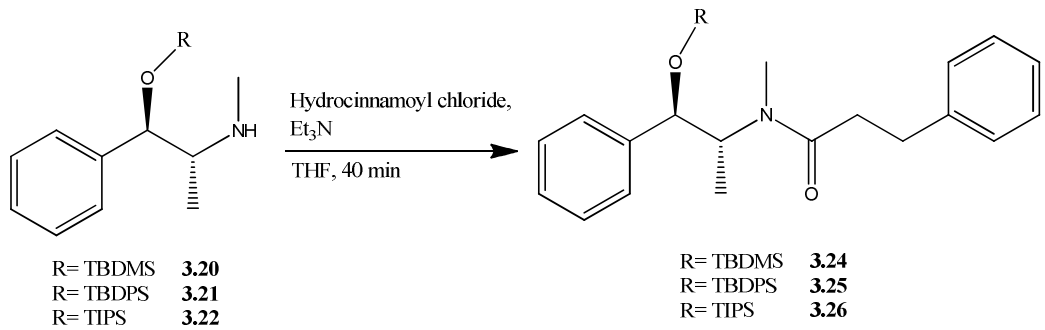
^{13}C NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 173.98, 173.60*, 141.84 (quaternary phenyl C), 141.49* (quaternary phenyl C), 127.87 (CH), 127.62* (CH), 127.27 (2CH), 126.96* (2CH), 126.90* (2CH), 126.69 (2CH), 76.84, 74.51*, 59.34*, 58.00, 27.40*, 26.92, 26.53*, 26.11, 17.42, 17.35*, 15.09, 11.99*, 11.52, 8.94*, 8.67

IR Spectroscopy (cm^{-1}): no NH band around 3600, 2939-2866 (Csp^3-H), 1643 (C=O), 881 (Si-O bond)

HRMS: found M+H = 378.2822 (calculated for $C_{22}H_{40}O_2NSi$ M+H= 378.2823)

$[\alpha]_D^{20}$ = -29.4 (c=1, $CHCl_3$)

Acylation using hydrocinnamoyl chloride:



R= TBDMS **3.20**
R= TBDPS **3.21**
R= TIPS **3.22**

R= TBDMS **3.24**
R= TBDPS **3.25**
R= TIPS **3.26**

Preparation of *N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methyl-3-phenylpropanamide 3.24:

To an ice-cooled solution of starting material (1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylpropan-2-amine **3.20** (0.10 g, 0.34 mmol, 1eq) and Et_3N (0.06 mL, 0.44 mmol, 1.3 eq) in THF (4 mL), hydrocinnamoyl chloride (0.06 mL, 0.39 mmol, 1.15 eq) in THF (1 mL) was slowly added. The mixture was stirred for 40 min at room temperature and water (1 mL) was added to quench the reaction. The solution was partitioned between EtOAc (10 mL) and brine (4 mL). The organic layer was washed twice with brine (2 × 4 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (90% DCM / 10% EtOAc) and *N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methyl-3-phenylpropanamide **3.24** was obtained as a transparent oil (0.09 g, 64%).

^{1}H NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.4 – 7.1 (m, 10H), 4.47 (d, 1H, *J*=8.0 Hz), 3.95 (quin, 1H, *J*=6.5 Hz), 3.0 – 2.8 (m, 2H), 2.91 (s, 3H), 2.78* (s, 3H), 2.5 (m, 2H), 1.03* (d, 3H, J=5.6 Hz), 0.91 (d, 3H, J=5.6 Hz), 0.88 (s, 9H), 0.83* (s, 9H), 0.08* (s, 3H), 0.02 (s, 3H), -0.25* (s, 3H), -0.31 (s, 3H)

^{13}C NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 172.33 (C=O), 171.45* (C=O), 141.75 (quaternary phenyl C),141.59* (quaternary phenyl C), 141.37 (quaternary phenyl C) 141.25* (quaternary phenyl C), 127.96 (2CH), 127.93* (2CH), 127.53 (CH), 127.49* (CH), 127.44 (CH), 127.37* (CH), 126.96 (CH), 126.84* (CH), 126.44 (2CH), 126.13* (2CH), 125.44 (CH), 125.07* (CH), 76.83*, 75.91, 58.64*, 57.83, 35.60*, 35.19, 31.10, 30.74*, 26.85, 25.26*, 25.10, 17.50*, 17.38, 14.98, 13.27*, -5.17, -5.23

IR Spectroscopy (cm^{-1}): no NH band around 3600, 2953-2852 (Csp^3-H), 1618 (C=O), 835 (Si-O bond)

HRMS: found M+H = 412.2666 (calculated for $C_{25}H_{38}O_2NSi$ M+H= 412.2666)

$[\alpha]_D^{20}$ = -75.3 (c=1, $CHCl_3$)

Melting point: 61-63 °C

Preparation of *N*-((1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methyl-3-phenylpropanamide 3.25:

The compound *N*-((1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methyl-3-phenylpropanamide **3.25** was prepared using the same procedure as **3.24**. 0.08 g of starting material **3.21** was used and **3.25** was obtained as a transparent oil (0.09 g, 82%).

^{1}H NMR: (3:2 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.7 – 7 (m, 20H), 4.45* (d, 1H, *J*=8.0 Hz), 4.15 (d, 1H, *J*=8.0 Hz), 4.03 (quin, 1H, J=6.5 Hz), 2.93 (m, 2H), 2.55 (s, 3H), 2.42 (m, 2H), 2.36* (s, 3H), 0.99 (s, 9H), 0.94* (s, 9H), 0.77 (d, 3H, J=5.6 Hz)

^{13}C NMR: (3:2 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 172.03 (C=O) , 171.96* (C=O) , 141.31 (quaternary phenyl C), 141.23 (quaternary phenyl C), 140.60 (quaternary phenyl C), 139.97 (quaternary phenyl C), 135.64* (2CH), 135.56 (2CH), 135.49 (CH), 135.17* (CH), 132.58 (CH), 132.03* (CH), 129.33 (CH), 129.06* (CH), 128.98* (CH), 128.94 (CH), 128.04 (2CH), 127.93* (2CH), 127.69 (2CH), 127.53* (2CH), 127.35 (2CH), 127.16* (2CH), 127.13* (2CH), 127.10 (2CH), 126.96* (2CH), 126.87 (2CH), 126.73 (2CH), 126.68* (2CH), 125.95 (2CH), 125.47* (2CH), 76.82, 76.07*, 59.88*, 57.46, 35.72*, 35.04, 31.10, 30.73*, 27.04, 26.48, 26.37*, 21.33, 18.87*, 18.67, 14.54, 13.52*

IR Spectroscopy (cm^{-1}): no NH band around 3600, 2995-2856 (Csp^3-H), 1643 (C=O), 821 (Si-O bond)

HRMS: found M+H = 536.2980 (calculated for $C_{35}H_{42}O_2NSi$ M+H= 536.2979)

$[\alpha]_D^{20}$ = -52.4 (c=1, $CHCl_3$)

Preparation of *N*-methyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide 3.26:

The compound *N*-methyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide **3.26** was prepared the same way as compound **3.24**. Starting material **3.22** (0.36 g) was used and 0.33 g of *N*-methyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide **3.26** was obtained as a transparent oil (65%).

^{1}H NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 7.35 – 7.2 (m, 10H), 4.67 (d, 1H, *J*=8.0 Hz), 3.95 (quin, 1H, *J*=6.5 Hz), 2.94 (m, 2H), 2.86 (s, 3H), 2.57 (m, 2H), 2.44* (s, 3H), 1.08 (d, 3H, J=5.6 Hz), 1.09 – 0.97 (m, 18H + 3H)

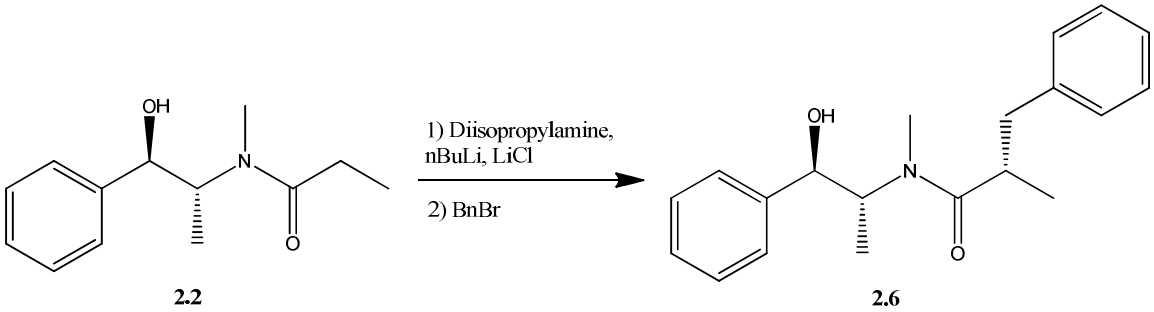
^{13}C NMR: (3:1 rotamer ratio, asterisk denotes minor rotamer peaks) **δ** 172.74, 172.42*, 142.20 (quaternary phenyl C), 141.95* (quaternary phenyl C), 141.78 (quaternary phenyl C), 141.66* (quaternary phenyl C), 128.47 (2CH), 128.41* (2CH), 128.37 (CH), 128.13* (CH), 127.79 (2CH), 127.49* (2CH), 127.41* (CH), 127.19 (CH), 127.01* (2CH), 126.46 (2CH) 126.07* (2CH), 125.95 (2CH), 77.45, 75.20*, 60.40*, 58.51, 36.23*, 35.50, 31.57, 31.35*, 28.07, 17.99*, 17.87, 15.45, 14.32*, 12.46, 12.33*

IR Spectroscopy (cm^{-1}): no NH band around 3600, 2941-2864 (Csp^3-H), 1643 (C=O), 881 (Si-O bond)

HRMS: found M+H = 454.3136 (calculated for $C_{28}H_{44}O_2NSi$ M+H=454.3136)

$[\alpha]_D^{20}$ = -15.03 (c=1, $CHCl_3$)

Preparation of *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethyl-3 phenylpropanamide 2.6:



2.2 **2.6**

A 3-necked-flask was charged with LiCl (0.14 g, 3.26 mmol, 6 eq), which was dried overnight in the drying pistol (40 °C, 2 mbar), and subsequently flame-dried. The flask was allowed to cool down under nitrogen and then anhydrous THF (5 mL) and freshly distilled diisopropylamine (0.34 mL, 2.44 mmol, 4.5 eq) was added. The reaction vessel was cooled to -78 °C and a solution of nBuLi (0.99 mL, 2.28 mmol, 4.2 eq) was added, (titrated at 2.3 M). Shortly after the addition, the solution was briefly warmed to 0 °C for 15 minutes and then cooled back to -78 °C. An ice cooled solution of the starting material **2.2** (0.10 g, 0.54 mmol, 1 eq) in THF (10 mL) was added to the reaction mixture. The solution was left to stir for 1 h at -78 °C, 1 h at 0 °C, then 40 minutes at room temperature and finally cooled back to 0 °C. Freshly distilled benzyl bromide (0.10 mL, 0.82 mmol, 1.5 eq) was then added and the reaction stirred for another $1^1/_2$ h at 0 °C. Then a saturated solution of aqueous NH_4Cl (10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 8 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by

flash chromatography (40% EtOAc / 60% DCM) gave *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-N,2-dimethyl-3-phenylpropanamide **2.6** as a white solid (0.09 g, 53%).

^{1}H NMR: (7:1 asterisk denotes minor rotamer or minor diastereoisomer peaks) **δ** 7.3 - 7.1 (m, 10H), 4.51 (d, 2H, *J*=8.0 Hz), 3.98 (quin, 1H, *J*=6.5 Hz), 2.91 (m, 2H), 2.84* (s, 3H), 2.65 (s, 3H), 2.58 (m, 1H), 1.13 (d, 3H, *J*=5.6 Hz), 1.09* (d, 3H, *J*=5.6 Hz), 0.97* (d, 3H, *J*=5.6 Hz), 0.93 (d, 3H, *J*=5.6 Hz)

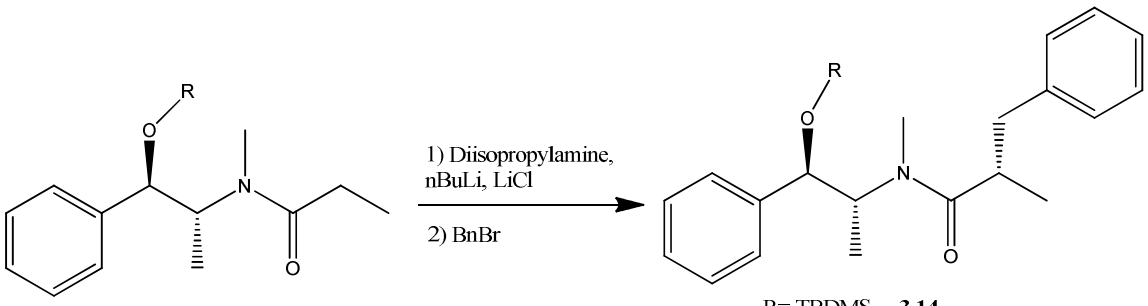
^{13}C NMR: (7:1 asterisk denotes minor rotamer or minor diastereoisomer peaks) **δ** 177.89 (C=O), 170.70* (C=O), 141.87 (quaternary phenyl C), 139.48 (quaternary phenyl C), 128.71* (2CH), 128.50 (2CH), 128.20* (2CH), 127.93 (2CH), 127.85 (CH), 127.73* (CH), 127.34 (2CH), 127.15* (2CH), 126.41 (CH), 126.12* (CH), 125.95* (2CH), 125.76 (2CH), 76.07, 74.82*, 59.92, 57.65*, 39.88, 39.65*, 38.47, 37.74*, 32.05, 17.35*, 17.00, 13.85, 13.71*

IR Spectroscopy (cm^{-1}): 3313 (broad OH band), 2966-2852 (Csp^{3}-H), 1610 (C=O)

HRMS: found M+H = 312.1960 (calculated for $C_{20}H_{26}O_2N$ M+H= 312.1958)

Melting point: 114-117 °C

Benzylation of the silyl ether propionyl derivatives 3.14-3.16:



R= TBDMS **3.10**
R= TBDPS **3.11**
R= TIPS **3.12**

R= TBDMS **3.14**
R= TBDPS **3.15**
R= TIPS **3.16**

Preparation of (*S*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide 3.14:

Using the procedure described above for the benzylation of pseudoephedrine propionamide **2.6** with *N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methylpropionamide **3.10** (0.11 g, 0.31 mmol) gave a transparent oil of (*S*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.14** (0.06 g, 63%).

^{1}H NMR: (1.3:1 asterisk denotes minor rotamer or diastereomer) **δ** 7.4 – 7 (m, 10H), 4.54 (d, 1H, *J*=8.0 Hz), 4.46* (d, 1H, *J*=8.0 Hz), 4.05 (quin, 1H, *J*=6.5 Hz), 3.9* (quin, 1H, *J*=6.5 Hz), 2.95-2.7 (m, 2H), 2.85 (s, 3H), 2.61* (s, 3H), 2.6-2.5 (m, 1H), 1.10 (d, 3H, J=6.5 Hz), 0.88 (s, 9H), 0.85* (s, 9H), 0.62 (d, 3H, *J*=5.6 Hz), 0.03 (s, 3H), -0.03* (s, 3H), -0.2 (s, 3H), -0.3* (s, 3H)
^{13}C NMR: (1.3:1 asterisk denotes minor rotamer) **δ** 176.62* (C=O), 175.85 (C=O), 142.20* (quaternary phenyl C), 142.00 (quaternary phenyl C), 140.41 (quaternary phenyl C), 140.13* (quaternary phenyl C), 129.27 (CH), 129.02* (CH), 128.95* (2CH), 128.46 (2CH), 128.35 (CH), 128.31* (CH), 128.18* (2CH), 128.06 (2CH), 127.81 (2CH), 127.26* (2CH), 126.89* (2CH), 126.04 (2CH), 76.71, 75.91*, 58.02*, 57.74, 41.28*, 40.42, 38.15, 38.01*, 28.15, 27.97*, 25.72, 25.68*, 18.08, 17.68*, 17.42, 15.45, 15.19*, -4.68*, -4.73, -5.16, -5.19*
IR Spectroscopy (cm^{-1}): no NH or OH band, 2954-2856 (Csp^3-H), 1635 (C=O), 833 (Si-O)

HRMS: found M+H = 426.2824 (calculated for $C_{26}H_{40}O_2NSi$ M+H= 426.2823)

Preparation of (*S*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide 3.15:

Using the procedure described above for *tert*-butyldimethylsilyl ether **3.14** with *N*-((1*R*,2*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methylpropionamide **3.11** only gave recovered starting material **3.11**.

Preparation of (*S*)-*N*-2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide 3.16:

Using the procedure described above for *tert*-butyldimethylsilyl ether **3.14** the (*S*)-*N*-2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide compound **3.16** was prepared. After the purification flash chromatography (3% EtOAc / 97% DCM) two fractions were obtained which might be two diastereomers of the same product **3.16**. The first fraction was obtained as a yellow oil (0.13 g) and the second fraction was obtained as a yellow solid (0.03 g). 200 mg of the starting material **3.12** was used in order to obtain (*S*)-*N*,2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl) propanamide **3.16** with an overall yield of 63% (0.16 g, 63% combined fractions).

Analysis of the first fraction:

^{1}H NMR: (1.2:1 asterisk denotes minor rotamer) **δ** 7.1 – 7.3 (m, 10H), 4.65* (d, 1H, *J*=8.0 Hz), 4.62 (d, 1H, *J*=8.0 Hz), 4.05* (quin, 1H, *J*=6.5 Hz), 3.85 (quin, 1H, *J*=6.5 Hz) 3.1 – 2.8

(m, 2H), 2.70 (s, 3H), 2.68 – 2.58 (m, 1H), 2.56* (s, 3H), 1.15* (d, 3H, *J*=5.6 Hz), 1.13 (d, 3H, *J*=5.6 Hz), 1.08 – 0.91 (m, 18H+3H), 0.62 (s, 3H, J=5.6 Hz)

^{13}C NMR: (1.2:1 asterisk denotes minor rotamer) **δ** 176.53* (C=O), 175.92 (C=O), 142.54 (quaternary phenyl C), 141.76* (quaternary phenyl C), 141.12 (quaternary phenyl C), 140.70* (quaternary phenyl C), 129.45* (2CH), 129.03 (2CH), 128.93 (CH), 128.30* (CH), 128.25 (2CH), 128.20* (2CH), 128.15* (CH), 127.99 (CH), 127.61* (2CH), 127.50 (2CH), 126.20 (2CH), 126.04* (2CH), 75.56, 74.45*, 58.09, 57.48*, 41.41, 40.39*, 39.10, 38.45*, 38.33*, 37.92, 28.74, 28.52*, 18.02, 17.98*, 14.73, 14.24*, 12.34, 12.29*

IR Spectroscopy (cm^{-1}): no NH band around 3600, 2960-2864 (Csp^3-H), 1639 (C=O), 881 (Si-O bond)

HRMS: found M+H = 468.3294 (calculated for $C_{29}H_{46}O_2NSi$ M+H= 468.3292)

Analysis of the second fraction:

^{1}H NMR: (9:1 asterisk denotes minor rotamer) **δ** 7.1 – 7.3 (m, 10H), 4.65* (d, 1H, *J*=8.0 Hz), 4.63 (d, 1H, *J*=8.0 Hz), 3.85 (quin, 1H, *J*=6.5 Hz) 3.1 – 2.8 (m, 2H), 2.74 (s, 3H), 2.63 – 2.53 (m, 1H), 2.23* (s, 3H), 1.13* (d, 3H, *J*=5.6 Hz), 1.07 (d, 3H, *J*=5.6 Hz), 1.04 – 0.91 (m, 18H+3H), 0.63 (s, 3H, J=5.6 Hz)

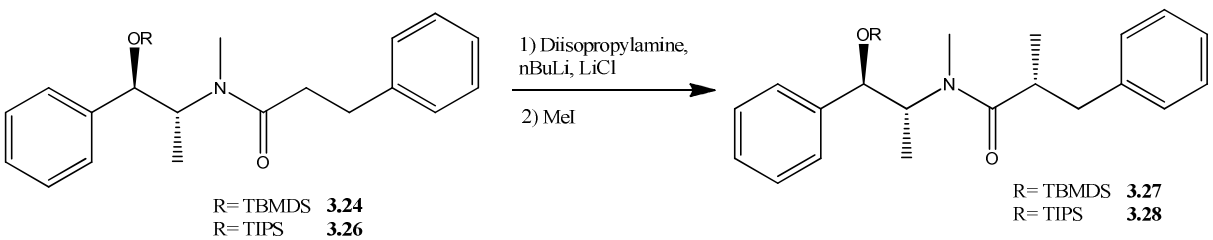
^{13}C NMR: δ 175.86 (C=O), 142.52 (quaternary phenyl C), 140.69 (quaternary phenyl C), 129.45 (2CH), 128.93 (CH), 128.30 (2CH), 127.98 (CH), 127.50 (2CH), 127.15 (2CH), 74.46, 58.08, 40.26, 39.09, 37.91, 28.51, 18.02, 14.73, 12.47

IR Spectroscopy (cm^{-1}): no NH band around 3600, 2960-2864 (Csp^3-H), 1633 (C=O), 883 (Si-O bond)

HRMS: found M+H = 468.3297 (calculated for $C_{29}H_{46}O_2NSi$ M+H= 468.3292)

Melting point: 52-55 °C

Methylation of the silyl-derivatives:



R= TBMDS **3.24**
R= TIPS **3.26**

R= TBMDS **3.27**
R= TIPS **3.28**

Preparation of (*R*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide 3.27:

The preparation of compound (*R*)-*N*-((1*R*,2*R*)-1-((tert-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.27** followed the same procedure as the benzylation of *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethyl-3 phenylpropanamide **2.6**, except that methyl iodide was used instead of benzyl bromide. 0.40 g of starting material *N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methyl-3-phenylpropanamide **3.24** were used in order to obtain (*R*)-*N*-((1*R*,2*R*)-1-((tert-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.27** as a yellow oil (0.32 g, 77%).

^{1}H NMR: (3:1 asterisk denotes minor rotamer) **δ** 7.4 – 7.1 (m, 10H), 4.54* (d, 1H, *J*=8.0 Hz), 4.47 (d, 1H, *J*=8.0 Hz), 4.01* (quin, 1H, *J*=6.5 Hz), 3.87 (quin, 1H, *J*=6.5 Hz), 2.9 – 2.8 (m, 2H), 2.82 (s, 3H), 2.69* (s, 3H), 2.6 – 2.4 (m, 1H), 1.07* (d, 3H, *J*=5.6 Hz), 0.89 (d, 3H, *J*=5.6 Hz), 0.85* (s, 9H), 0.80 (s, 9H), 0.62 (d, 3H, *J*=5.6 Hz), 0.03* (s, 3H), -0.03 (s, 3H), -0.25* (s, 3H), -0.30 (s, 3H)

^{13}C NMR: (3:1 asterisk denotes minor rotamer) **δ** 175.77 (C=O), 174.85* (C=O), 141.79 (quaternary phenyl C), 141.56*(quaternary phenyl C), 140.13* (quaternary phenyl C), 139.78 (quaternary phenyl C), 128.91* (CH), 128.51 (CH), 127.92 (2CH), 127.84* (2CH), 127.80* (CH), 127.73 (CH), 127.41 (2CH), 127.30* (2CH), 126.72* (2CH), 126.53 (2CH), 126.15 (2CH), 125.63* (2CH), 76.85, 75.41*, 58.22*, 57.52, 40.78, 39.43*, 38.00*, 37.65, 27.56*, 27.44, 25.22*, 25.17, 17.48, 17.18*, 16.91*, 16.30, -5.24, -5.58*, -5.66*, -5.70

IR Spectroscopy (cm^{-1}): no NH or OH band, 2956-2856 (Csp^{3}-H), 1631 (C=O), 833 (Si-O bond)

HRMS: found M+H= 426.2817 (calculated for $C_{26}H_{40}O_2NSi$ M+H= 426.2823)

Preparation of (*R*)-*N*,2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide 3.28:

Using the procedure described above for (*R*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.27** compound **3.28** was prepared. 0.15 g of starting material *N*-methyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide **3.26** was used in order to obtain the product (*R*)-*N*,2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2 yl)propanamide **3.28** as a yellow oil (0.12 g, 65%).

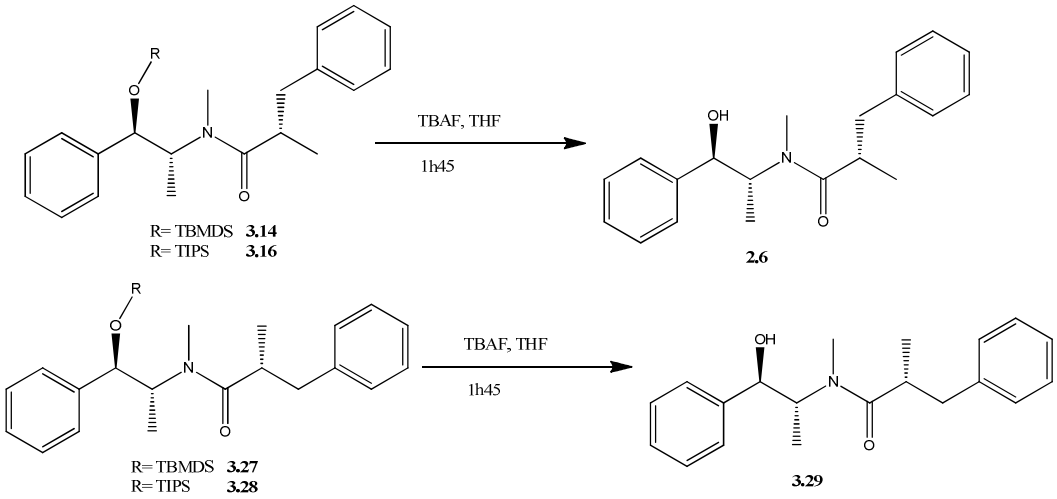
^{1}H NMR: (2:1 asterisk denotes minor rotamer) **δ** 7.4 – 7 (m, 10H), 4.61 (d, 1H, *J*=8.0 Hz), 4.47* (d, 1H, *J*=8.0 Hz), 4.05* (quin, 1H, *J*=6.5 Hz), 3.93 (quin, 1H, *J*=6.5 Hz), 3.1 – 2.9 (m, 2H), 2.85 (s, 3H), 2.64* (s, 3H), 2.6 – 2.5 (m, 1H), 1.15* (d, 3H, *J*=5.6 Hz), 1.10 (d, 3H, *J*=5.6 Hz), 1 – 0.8 (m, 18H+3H), 0.62 (d, 3H, *J*=5.6 Hz)

^{13}C NMR: (2:1 asterisk denotes minor rotamer) **δ** 176.51 (C=O), 175.85* (C=O), 142.53* (quaternary phenyl C), 141.83 (quaternary phenyl C), 141.24* (quaternary phenyl C), 140.81 (quaternary phenyl C), 129.45 (2CH), 129.22* (2CH), 128.47* (CH), 128.42 (CH), 128.26* (2CH), 128.14 (2CH), 127.71 (CH), 127.61* (CH), 127.50 (2CH), 127.40* (2CH), 126.65* (2CH), 126.07 (2CH), 75.20, 69.26*, 58.29*, 58.08, 40.27*, 39.10, 36.23, 35.48*, 33.33, 31.57*, 18.02*, 17.86, 15.45*, 14.73, 12.50*, 12.47, -5.18, -5.24*, -5.66, -5.70*

IR Spectroscopy (cm^{-1}): no NH or OH band, 2941-2864 (Csp^{3}-H), 1639 (C=O), 881 (Si-O bond)

HRMS: found M+H= 468.3289 (calculated for $C_{29}H_{46}O_2NSi$ M+H= 468.3292)

Deprotection reactions:



Deprotection of (*S*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide 3.14:

The starting material (*S*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.14** (0.95 g, 0.22 mmol, 1 eq) was dissolved in THF (6 mL) under inert atmosphere and the solution was cooled to 0 °C. TBAF (0.47 mL, 0.47 mmol, 2.1 eq) wad added to the reaction mixture and the reaction was stirred for 1^{3}/$_{4}$ h at room temperature. Water (5 mL) was added to quench the reaction and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined

organic extracts were washed with brine (3 × 8 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was first purified by flash chromatography (30% EtOAc / 70% DCM) and then recrystallised from hot toluene in order to obtain *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **2.6** as a white solid (0.05 g, 76%).

^{1}H NMR: (5:1 asterisk denotes minor rotamer) **δ** 7.4 – 7.1 (m, 10H), 4.57 (d, 1H, *J*=8.0 Hz), 4.48* (d, 1H, *J*=8.0 Hz), 4.03 (quin, 1H, *J*=6.5 Hz), 3.89* (quin, 1H, *J*=6.5 Hz), 3.2 – 3.1* (m, 2H), 3.0 - 2.8 (m, 2H), 2.68 (s, 3H), 2.65 – 2.60 (m, 1H), 2.58* (s, 3H), 1.16 (d, 3H, *J*=5.6 Hz), 1.10* (d, 3H, *J*=5.6 Hz), 0.95 (d, 3H, J=5.6 Hz), 0.52* (d, 3H, J=5.6 Hz)
^{13}C NMR: (5:1 asterisk denotes minor rotamer) **δ** 177.90 (C=O), 175.85* (C=O), 142.40 (quaternary phenyl C), 141.87* (quaternary phenyl C), 140.02* (quaternary phenyl C), 139.48 (quaternary phenyl C), 128.71* (CH), 128.56 (CH), 128.41* (2CH), 127.91 (2CH), 127.87 (CH), 127.74* (CH), 127.15 (2CH), 126.99* (2CH), 126.40 (2CH), 126.30* (2CH), 125.86* (2CH), 125.76 (2CH), 75.74, 74.83*, 58.01*, 57.66, 39.89, 39.82*, 38.48, 37.76*, 17.38*, 17.01, 15.02, 13.85, 13.79*
IR Spectroscopy (cm^{-1}): broad OH band around 3300, 2983-2852 (Csp^3-H), 1610 (C=O), no Si-O band

HRMS: found M+H= 312.1951 (calculated for $C_{20}H_{26}O_2N$ M+H= 312.1958)
Melting point: 92-95 °C

Deprotection of (*S*)-*N*,2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide 3.16:

The deprotection of (*S*)-*N*,2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide **3.16** followed the same protocol as for **3.14**. Starting material **3.16** (0.12 g) was used and *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **2.6** as a white solid (0.06 g, 80%).

^{1}H NMR: (5:1 asterisk denotes minor rotamer) **δ** 7.4 – 7.1 (m, 10H), 4.56 (d, 1H, *J*=8.0 Hz), 4.47* (d, 1H, *J*=8.0 Hz), 4.03* (quin, 1H, *J*=6.5 Hz), 3.87 (quin, 1H, *J*=6.5 Hz), 3.17 – 3.1* (m, 2H), 3.0 - 2.87 (m, 2H), 2.68* (s, 3H), 2.65 – 2.58 (m, 1H), 2.58 (s, 3H), 1.16 (d, 3H, *J*=5.6 Hz), 1.10* (d, 3H, *J*=5.6 Hz), 0.97 (d, 3H, J=5.6 Hz), 0.53* (d, 3H, J=5.6 Hz)
^{13}C NMR: (5:1 asterisk denotes minor rotamer) **δ** 178.35* (C=O), 177.19 (C=O), 142.38 (quaternary phenyl C), 140.22* (quaternary phenyl C), 140.00* (quaternary phenyl C), 139.94 (quaternary phenyl C), 129.22* (CH), 129.00 (CH), 128.92* (2CH), 128.71 (2CH), 128.40 (CH), 128.35* (CH), 127.64* (2CH), 127.49 (2CH), 126.46* (2CH), 126.35 (2CH), 126.28* (2CH), 126.18 (2CH), 76.20, 75.34*, 60.40, 58.16*, 41.29*, 40.39, 39.05, 38.32*, 21.04, 18.20*, 17.61, 15.51*, 15.05

IR Spectroscopy (cm^{-1}): 3307 (broad OH band), 2983-2850 (Csp^3-H), 1637 (C=O), no Si-O band

HRMS: found M+H= 312.1951 (calculated for $C_{20}H_{26}O_2N$ M+H= 312.1958)

Melting point: 55-58 °C

Deprotection of (*R*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide 3.27:

Using the procedure described above for the deprotection of (*S*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.14** compound **3.27** was deprotected. Starting material (*R*)-*N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.27** (0.20 g) was used and product (*R*)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.29** was obtained as a transparent oil (0.10 g, 69%).

^{1}H NMR: (3:1 asterisk denotes minor rotamer) **δ** 7.4 – 7.1 (m, 10H), 4.57 (d, 1H, *J*=8.0 Hz), 4.48* (d, 1H, *J*=8.0 Hz), 4.01* (quin, 1H, *J*=6.5 Hz), 3.86 (quin, 1H, *J*=6.5 Hz), 3.20 – 3.12* (m, 2H), 3.0 - 2.8 (m, 2H), 2.68 (s, 3H), 2.65 – 2.58 (m, 1H), 2.58* (s, 3H), 1.25* (d, 3H, *J*=5.6 Hz), 1.17 (d, 3H, *J*=5.6 Hz), 0.84 (d, 3H, J=5.6 Hz), 0.52* (d, 3H, J=5.6 Hz)

^{13}C NMR: (3:1 asterisk denotes minor rotamer) **δ** 178.38* (C=O), 178.16 (C=O), 142.39* (quaternary phenyl C), 141.58 (quaternary phenyl C), 139.99 (quaternary phenyl C), 139.94* (quaternary phenyl C), 129.21 (CH), 129.00* (CH), 128.92 (2CH), 128.73* (2CH), 128.41* (CH), 128.36 (CH), 128.24 (2CH), 127.65* (2CH), 127.49 (2CH), 126.80* (2CH), 126.45 (2CH), 126.27* (2CH), 77.03*, 76.77, 60.40*, 58.17, 41.28*, 40.32, 40.14*, 39.06, 25.26, 25.10*, 18.21*, 17.50, 14.84, 14.34*, 14.21

IR Spectroscopy (cm^{-1}): 3329 (broad OH band), 2968-2872 (Csp^3-H), 1602 (C=O), no Si-O band

HRMS: found M+H= 312.1950 (calculated for $C_{20}H_{26}O_2N$ M+H= 312.1958)

Deprotection of (*R*)-*N*,2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide 3.28:

The deprotection of (*R*)-*N*,2-dimethyl-3-phenyl-*N*-((1*R*,2*R*)-1-phenyl-1-((triisopropylsilyl)oxy)propan-2-yl)propanamide **3.28** followed the same protocol as the deprotection of **3.14**. Starting material **3.28** (0.10 g) gave (*R*)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-phenylpropanamide **3.29** as a transparent oil (0.30 g, 41%).

^{1}H NMR: (1.2:1 asterisk denotes minor rotamer) **δ** 7.4 – 7.1 (m, 10H), 4.59 (d, 1H, *J*=8.0 Hz), 4.53* (d, 1H, *J*=8.0 Hz), 4.01 (quin, 1H, *J*=6.5 Hz), 3.89* (quin, 1H, *J*=6.5 Hz), 3.20 – 3.11* (m, 2H), 3.0 - 2.85 (m, 2H), 2.70 (s, 3H), 2.68 – 2.55 (m, 1H), 2.60* (s, 3H), 1.18* (d, 3H, *J*=5.6 Hz), 1.12 (d, 3H, *J*=5.6 Hz), 0.96 (d, 3H, J=5.6 Hz), 0.54* (d, 3H, J=5.6 Hz)

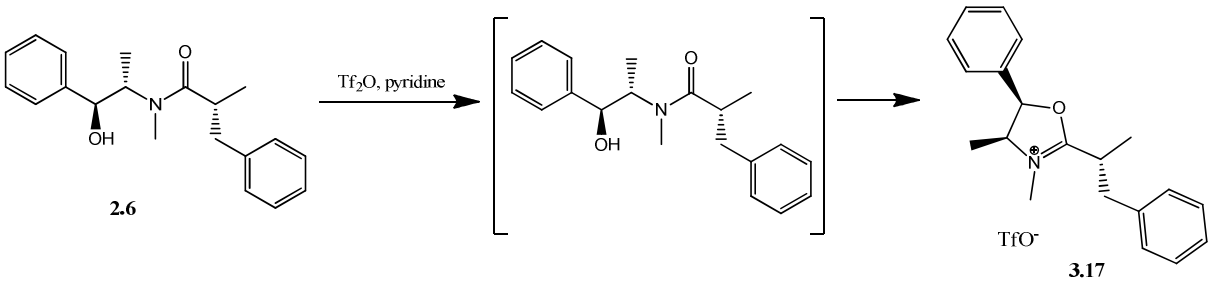
^{13}C NMR: (1.2:1 asterisk denotes minor rotamer) **δ** 177.88* (C=O), 178.84 (C=O), 141.88* (quaternary phenyl C), 141.52 (quaternary phenyl C), 140.71 (quaternary phenyl C), 140.03* (quaternary phenyl C), 128.49 (CH), 128.23* (CH), 127.92 (2CH), 127.85* (2CH), 127.73* (CH), 127.14 (CH), 126.38 (2CH), 126.30* (2CH), 125.94 (2CH), 125.84* (2CH), 125.76 (2CH), 125.69* (2CH), 76.83*, 76.19, 60.40*, 58.18, 39.89*, 38.82, 38.47*, 35.69, 17.11*, 17.00, 15.44, 14.73*, 13.96, 13.83*, 13.77

IR Spectroscopy (cm^{-1}): 3352 (broad OH band), 2970-2897 (Csp^{3}-H), 1612 (C=O), no Si-O band

HRMS: found M+H= 312.1951 (calculated for $C_{20}H_{26}O_2N$ M+H= 312.1958)

Cyclization for diastereomeric excess measurement:

Preparation of (4*S*,5*R*)-3,4-dimethyl-5-phenyl-2-((*R*)-1-phenylpropan-2-yl)-4,5-dihydrooxazol-3-ium trifluoromethanesulfonate 3.17:



N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethyl-3 phenylpropanamide **2.6** (0.03 g, 0.10 mmol, 1 eq) was dissolved in dry DCM to a concentration of 0.04 M (2.5 mL) and the solution was cooled to 0 °C. Triflic anhydride (0.03 mL, 0.19 mmol, 2 eq) and pyridine (0.02 mL, 0.29 mmol, 3 eq) were sequentially added. The reaction was stirred for 30 min at 0 °C. The solution was concentrated on the rotary evaporator and then on the high vacuum rotary evaporator for 1h (1 mmHg, 23 °C). Deuterated chloroform was added to the residue, the solution was hand-mixed and the supernatant was removed by pipette for a proton NMR analysis.

The analysis of the proton NMR was carried out for alcohol **2.6** which had not been silylated and this gave a diastereomeric excess of 92%.

^{1}H NMR determination of de: (asterisk denotes diasteromer) **δ** 1.55* (d, 0.122 H, de=91.9%), 1.45 (d, 2.88 H, de=91.9%), 0.97 (d, 2.887 H de=92.5%), 0.65* (d, 0.113 H de=92.47%)

The same reaction and analysis have been done for the TBDMS ans TIPS derivatives that have been synthesized. Here the ^{1}H NMR data used for the de determination:

Derivative used for the de measure	^{1}H NMR data (asterisk denotes diasteromer)
3.14	**δ** 6.49* (d, 1H, de=41.8%), 6.42 (d, 1H, de=41.8%), 0.98 (d, 3H, de=43%), 0.66* (d, 3H, de=43%)
3.28	**δ** 6.46 (d, 1H, de=17.95%), 6.42* (d, 1H, de=17.95%), 0.97* (d, 3H, de=17.0%), 0.66 (d, 3H, de=17.0%)
3.16	**δ** 6.50* (d, 1H, de=33%), 6.44 (d, 1H, de=33%), 0.99 (d, 3H, de=35.4%), 0.67* (d, 3H, de=35.4%)
3.27	**δ** 6.45 (d, 1H, de=18.7%), 6.43* (d, 1H, de=18.7%), 0.96* (d, 3H, de=17.8%), 0.65 (d, 3H, de=17.8%)

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