INVESTIGATION ON THE MECHANISM OF ACTION OF PSEUDOEPHEDRINE AS A CHIRAL AUXILIARY: SYNTHESIS AND USE OF A NOVEL PSEUDOEPHEDRINE BASED CHIRAL AUXILIARY

By

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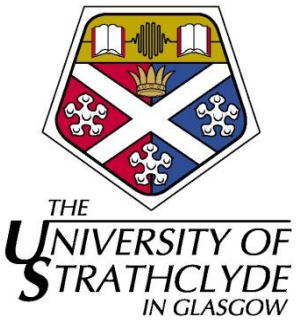

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Signed: Ghjuvanni Coti

Date: 01/02/2011

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Summary

In 1997, Myers reported pseudoephedrine to be a highly selective chiral auxiliary for alkylation of amide enolates. To account for the diasteroselectivity a reactive conformation was postulated. This reactive conformation was suggested to benefit from steric screening by a lithium alkoxide that may be further linked to the lithium enolate. However, later studies threw into question Myers' postulated mechanism of action of pseudoephedrine as an auxiliary. The purpose of this project was to explore the mechanism of action of the pseudoephedrine chiral auxiliary in order to get a better understanding of the origin of the diasteroselectivity and, therefore, to increase the steroslectivity by synthesizing appropriate analogues. DFT calculations suggest that the aromatic ring of the auxiliary may interact with the enolate lithium cation. Our hypothesis postulates that increasing the electron density of the aromatic ring of the pseudoephedrine will increase its selectivity. Thus, a route of synthesis of analogues of pseudoephedrine allowing us to modify the electron density of the benzyl ring was designed. An analogue, the 3,5-dimethylphenyl pseudoephedrine analogue, was synthesized with high diastereopurity which was confirmed by X-ray analysis. Comparison of the selectivity of acylated derivatives of this new analogue against the pseudoephedrine's using a standard enolate alkylation reaction was investigated.

Abbreviations:

Bn	Benzyl
Boc	*Tert*-butoxycarbonyl
cat	Catalyst
Cbz	Carboxybenzyl
Bu	Butyl
DCM	Dichloromethane
de	Diastereomeric excess
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
DIEA	Diisopropylethylamine
ee	Enantiomeric excess
HMPA	Hexamethylphosphoric triamide
HRMS	High resolution mass spectroscopy
iPr	Isopropyl
LDA	Lithium diisopropylamide
Me	Methyl
MMFF	Molecular mechanics force field
NMR	Nuclear magnetic resonance
Ph	Phenyl
PTSA	*Para*-toluenesulfonic acid
S_Ni	Substitution nucleophilic internal
TEA	Triethylamine
THF	Tetrahydrofuran

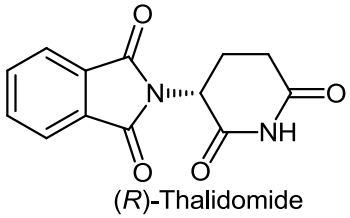
TLC	Thin layer chromatography
TRIBAL	Triisobutylaluminium

Index:

I) Introduction :

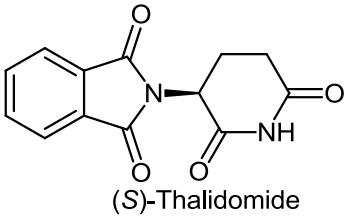
1) Basis of asymmetric synthesis:

Chirality is certainly one of the most important features of both chemistry and biology, as all known living organisms rely on it with 21 of the amino acids available to build proteins being in their *L* configuration. Only one, glycine, is achiral.[1] Although biological activity is based upon chirality, the pharmaceutical industry has not yet matched Nature's ability to control the stereochemistry of chemical reactions. As two stereoisomers (either enantiomers or diastereoisomers) usually have different pharmacokinetic properties, the undesired one shall be considered as an impurity. Therefore, the unwanted stereoisomer becomes potentially environmentally and economically damaging. In the best case scenario, that undesired stereoisomer will be inactive and won't have any effect on the overall activity of a drug. However, in most cases, it can either lower the drug activity or, worse, be toxic. The most well-known example of such a case would be the infamous thalidomide disaster during which the importance of the absolute configuration of an stereogenic carbon in a molecule has been highlighted: this drug, removed from the market in 1961, is the perfect example of the difference of biological activity between two enantiomers: whereas (*R*)-thalidomide **67a** is a sedative, (*S*)-thalidomide **67b**, has teratogenic properties.[2,3] Therefore, it is now crucial to perfectly control the stereochemistry of a reaction using asymmetric synthesis.



(*R*)-Thalidomide

67a



(*S*)-Thalidomide

67b

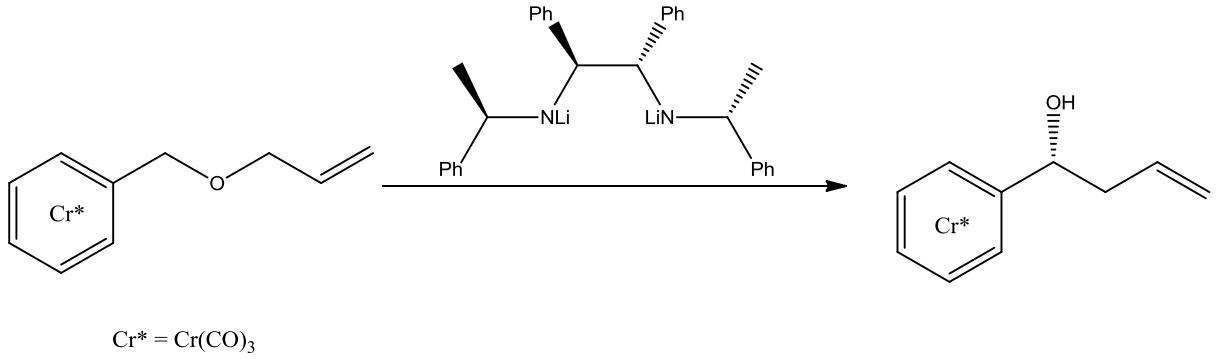
By definition, "asymmetric synthesis is a reaction or reaction sequence that selectively creates one configuration at one or more stereogenic elements by the action of a chiral reagent,

auxiliary or catalyst, acting on heterotopic faces, atoms or group within a substrate. The stereoselectivity is primarily influenced by the chiral reagent, auxiliary or catalyst, despite any stereogenic elements that may be present in the substrate".[4] The purpose of asymmetric synthesis is to maximise the ratio between the desired stereoisomer and the unwanted isomer, also called enantiomeric or diastereomeric excess. To do so, four different methods have been developed so far: the chiron approach, the chiral auxiliary method, and the chiral reagent or catalyst approaches.[5] They all rely on the same basic thermodynamic idea: in order to increase the selectivity of the process, a diastereomeric transition state shall be achieved in order to differentiate the two resulting enantiomers: unlike enantiomers, diastereoisomers have different physical properties, thus the transition state with the lowest Gibbs free energy barrier will lead to the major isomer through a kinetically controlled resolution.

The first method, known as the chiron approach,[6] consists of using enantiopure chiral starting material with the desired stereochemistry, usually derived from the chiral pool, and conserving the stereochemical information while building the rest of the molecule. Also, the chiral pool offers only a limited number of enantiomerically pure starting materials. Some of the commonly used chiron includes amino acids, terpenes, hydroxy acids and carbohydrates.

The second method is the use of chiral auxiliaries: this involves a chiral group (also called an auxiliary) which is covalently bound to the substrate. Here, the selectivity of the reaction comes from the auxiliary which will direct the process through a favoured diastereomeric transition state. The chiral auxiliary is then removed without racemisation and can be recycled. This method is very efficient but necessitates extra steps (attachment and cleavage of the auxiliary) and a stoichiometric equivalent of the chiral auxiliary. This method will be discussed further later on.

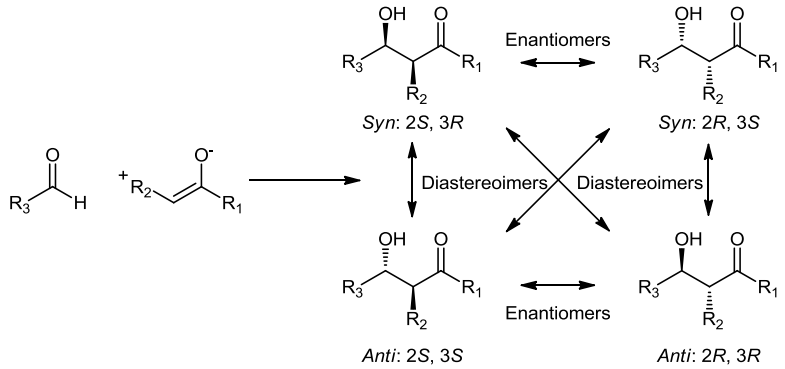
The third method, unlike the chiral auxiliary, does not necessitate the two extra steps. It is done by using a chiral reagent on an achiral substrate. However, a stoichiometric equivalent of such a reagent is still required. An example of this type of reaction would be the asymmetric [2,3]-Wittig rearrangement using a chiral base as described in scheme 1.1.[7]



Scheme 1.1[7]

The fourth method refers to substoichiometric use of chiral reagent i.e. catalysts. As enantiomerically pure reagents are essential to the success of these methods and considering the price of such compounds, using them as chiral catalyst (cat* < 10 mol%) will greatly improve the cost effectiveness of the process. Moreover, a catalyst is not consumed by the reaction and can be retrieved afterward.

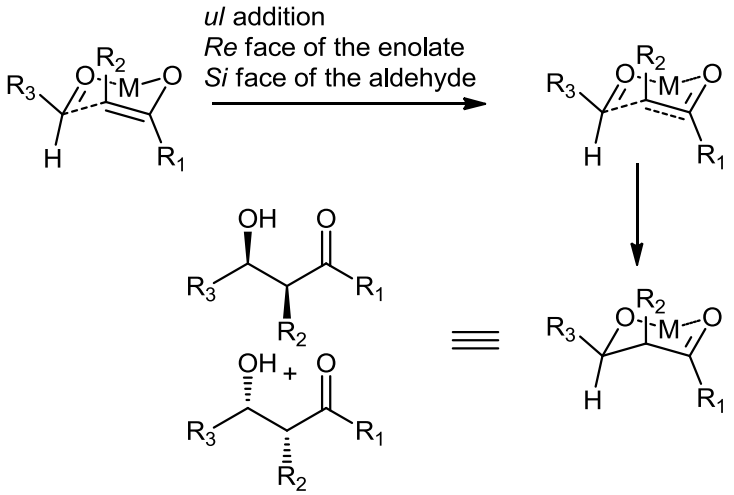
In modern synthetic organic chemistry, one of the most important reactions is the aldol reaction. Not only does it allow a C-C bond to form, but it introduces two new stereocentres in the molecule in one single step. Therefore, using asymmetric chemistry to control the stereocentre is crucial in achieving efficient synthesis as four isomers may be produced in the process (see Scheme 1.2).



Scheme 1.2

The Zimmerman-Traxler model allows us to predict the diastereomeric outcome of the reaction, in other words, whether the *syn* or the *anti* products will be the major diastereoisomer, based on a six membered cyclic transition state.[8] In fact, the *syn/anti* outcome depends on the geometry (*E* or *Z*) of the enolate. For instance, if the *Z*-enolate is considered, the enolate can be approached by the aldehyde by two different ways, these will give rise to the two different diastereoisomers:

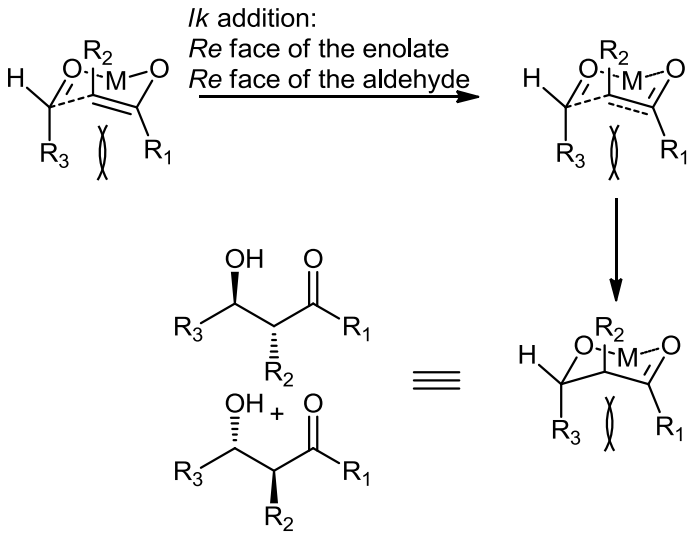
- The *syn* product may be obtained via addition to the *Re* face of the *Z*-enolate on the *Si* face of the aldehyde, as shown in scheme 1.3:



Scheme 1.3

The same outcome would be obtained by addition to the *Si* face of *Z*-enolate on *Re* face of the aldehyde.

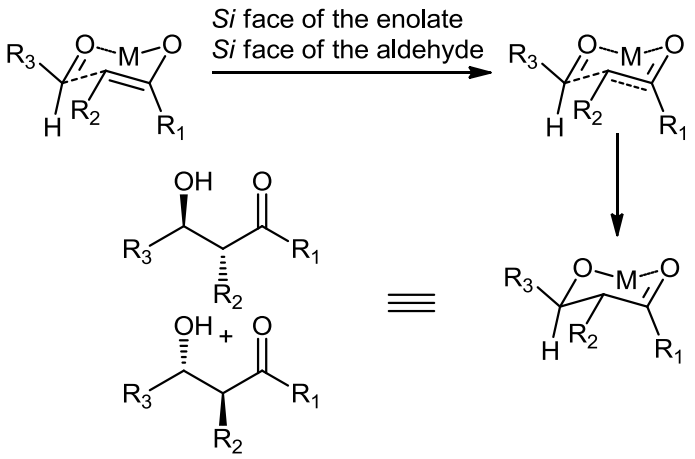
- The *anti* product could be obtained via addition of the *Re* face of the *Z*-enolate on the *Si* face of the aldehyde, as shown in scheme 1.4:



Scheme 1.4

The same outcome would be obtained by the addition to the *Si* face of *Z*-enolate on the *Re* face of the aldehyde.

This model predicts that if the substituent R^1 and R^3 are moderately large, a 1,3-diaxial repulsion in the transition state would disfavour the *anti* diastereoisomers for the *Z*-enolate. Thus, the Zimmerman-Traxler model would predict that the *Z*-enolate would favour the formation of the *syn* products. Similarly, when considering the *E*-enolate, that analysis predicts that the predominant product would be the *anti* stereoisomers (see scheme 1.5).



Scheme 1.5

In summary, those predictions are based on the following facts:

- the reactions are under kinetic control
- the enolate and the aldehyde are chelated to the metal
- the transition state is chair-like
- the metal is coordinated to both oxygens (in absence of Lewis acids)

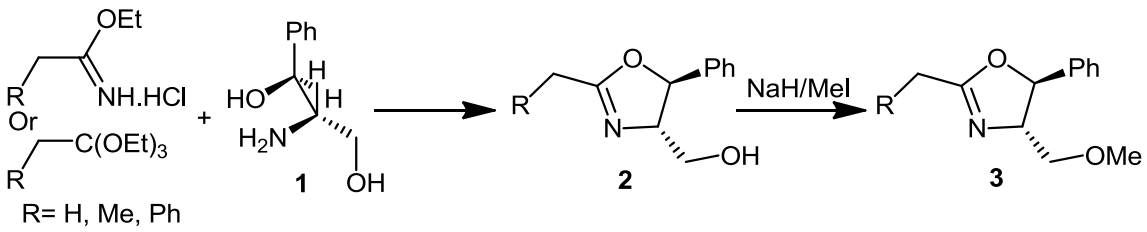
This type of prediction can also be applied to amide enolate as well as azaenolate. Therefore, preparing chiral amide enolates or azaenolates and coupling them with electrophiles will allow us to create carbon-carbon bonds and control the stereocentre induced in the process. This is the essence of the most widely used method in asymmetric chemistry: the chiral auxiliary method.[5]

2) The chiral auxiliary method

a) Meyers' chiral oxazolines

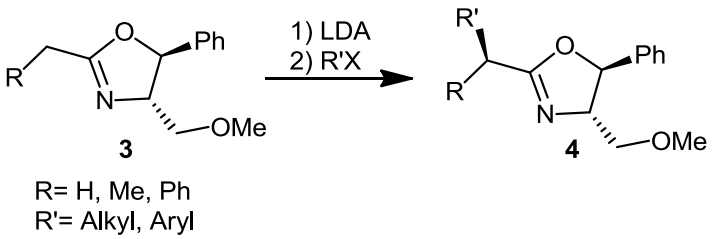
This method was first successfully reported by Meyers and co-workers in 1976.[9] They used oxazolines which were prepared by condensation of (l*S*,2*S*)-(+)-1-phenyl-2-amino-1,3-

propanediol **1** with imino ethers or orthoesters followed by reaction with NaH/MeI to obtain the corresponding methyl ether **3** (scheme 1.6).



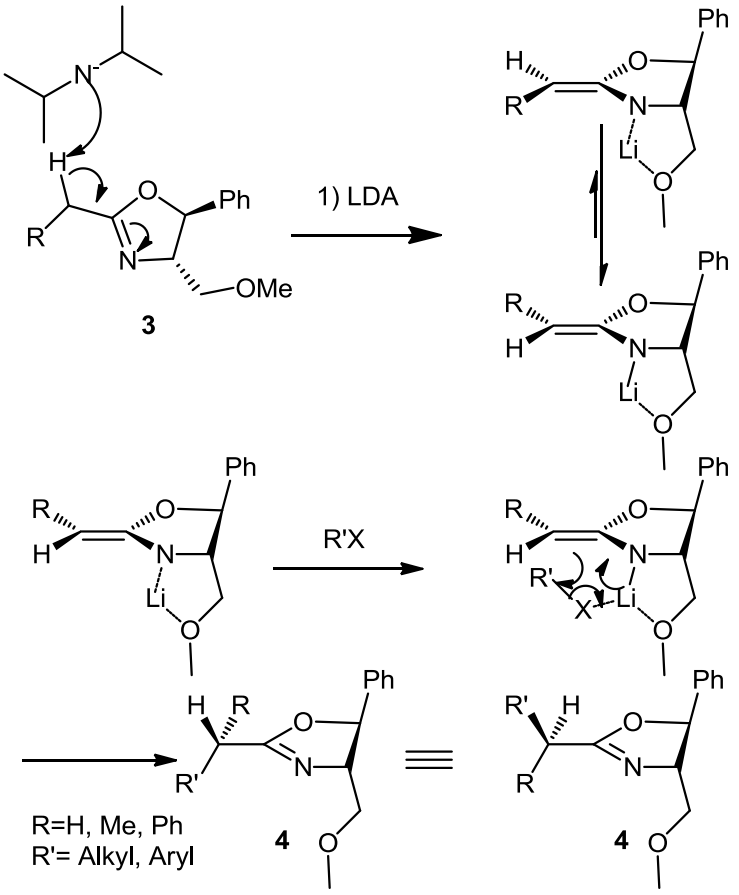
Scheme 1.6

Treatment of compound **3** with lithium diisopropylamide (LDA) and an alkyl halide led to diastereoselective alkylation (scheme 1.7).



Scheme 1.7

It is believed that the LDA removes the proton leading to the formation of a *Z*-enolate[10]. The lithium is then chelated by both the nitrogen and the oxygen of the methoxy group, forming a 5-membered ring. With addition of the halide, the lithium can also chelate with the halide to enhance its attack on the (1*Si*,2*Re*) face of the enolate. This process, leading mainly to the formation of the (*S*)-**4** compound (supposing that R'>R using the Cahn-Ingold-Prelog rule[11]), is illustrated by Scheme 1.8.



Scheme 1.8

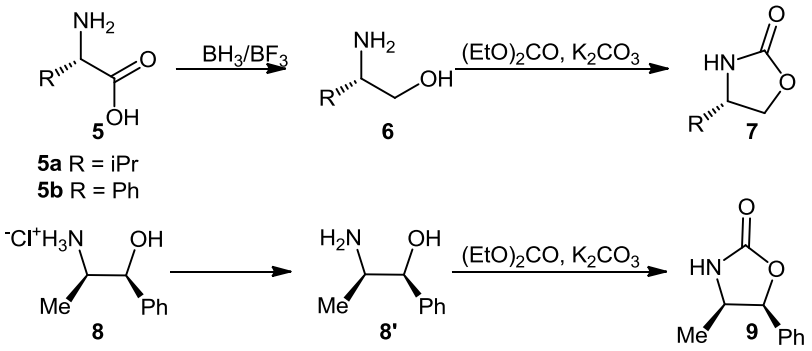
These oxazolines **4** can easily be cleaved without racemisation by reflux in aqueous 3-6 N HCl or H_2SO_4 to obtain the carboxylic acid and the methoxyamino alcohol which can be reused.

Meyers' oxazolines didn't provide great selectivity and the enantiomeric excess after cleavage was rather average: only 70-85% ees were reported. The yield was decent (between 60-85%) but, again, could also be improved.

However, as in any new aspect of sciences, it led the way to original synthesis, and many different chiral auxiliaries were developed in the 1980's. The most famous are the oxazolidinone reported by Evans[12] along with Oppolzer's[13] camphor sultam.

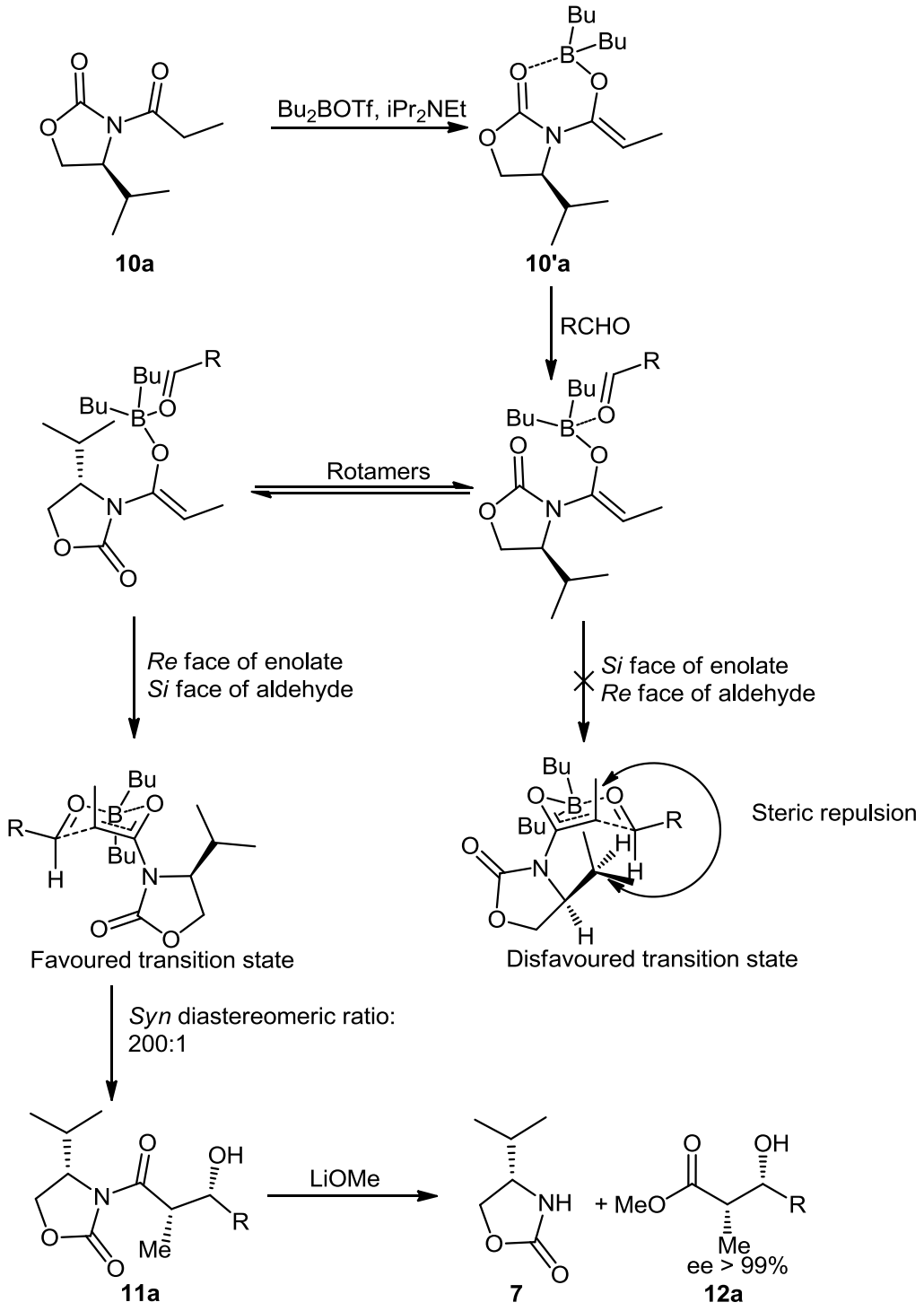
b) Evans' auxiliary: the oxazolidinone

Evans' chiral auxiliary is an oxazolidinone which can be obtained from the corresponding amino acid **5** in two steps or from norephedrine **8** in one step, as reported in scheme 1.9.[12]



Scheme 1.9[12]

The mechanism of action is as follows: the *Z*-enolate is exclusively formed using dibutylboron triflate to deprotonate the acylated auxiliary **10a**. The *Z*-boron enolate may be used in an aldol reaction with a very high degree of *syn* selectivity to produce essentially a single *syn*-isomer (see scheme 1.10).

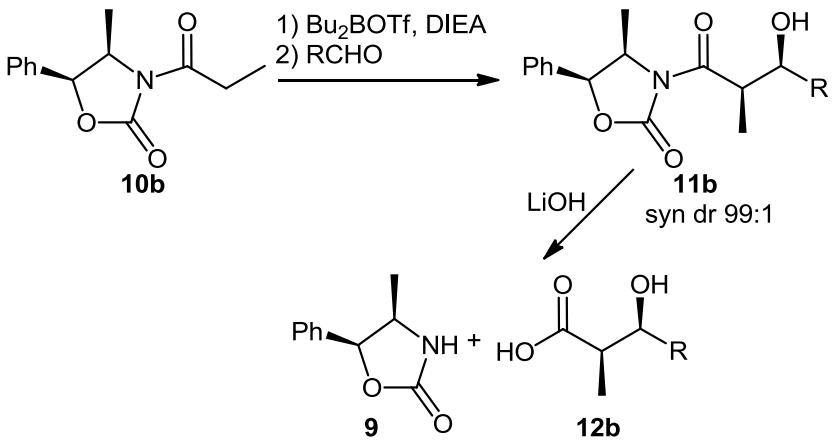


Scheme 1.10

In the *Z*-enolate **10'a**, the boron is coordinated to the oxazolidinone carbonyl group. However, in order to activate the aldehyde, the boron switches and coordinates the aldehyde carbonyl group instead. The oxazolidinone is now free to adopt two possible amide rotamer

conformations. Each amide rotamer can react through an *ul* transition state (as seen in the Zimmerman-Traxler analysis of the *Z*-enolate, *vide supra*). In the disfavoured transition state (*Si* face of the enolate, *Re* face of the aldehyde), a steric repulsion is observed between the enolate substituent (a methyl group in this case) and the oxazolidinone substituent (an isopropyl group in this case).

The other aldol product enantiomer **12b** can be obtained in an analogous way using the norephedrine based oxazolidinone **10b** (see scheme 1.11).



Scheme 1.11

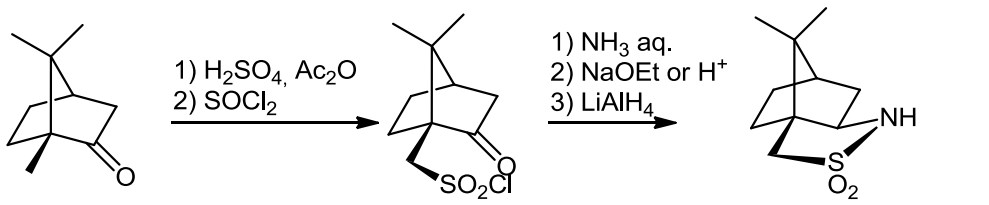
Evans' oxazolidinone enolate, when deprotonated with LDA, also reacts with electrophiles in order to perform diastereoselective alkylations.[14] It has been reported, when using activated alkyl halides (benzyl, allyl), both high selectivity (de > 90%) and good yield (>70%) (Table 1.1 entries 1 & 2) are obtained. However, the use of unreactive halide (alkyl halide) led to less selective alkylation along with a considerable decrease of the yield (Table 1.1 entry 3).[14]

Entry	Electrophile	Crude de (%)	isolated yield (%)
1	BnBr	96	78
2	CH_2=$CHCH_2Br$	96	75
3	EtI	88	53

Table 1.1[14]

c) The Camphor sultam auxiliary

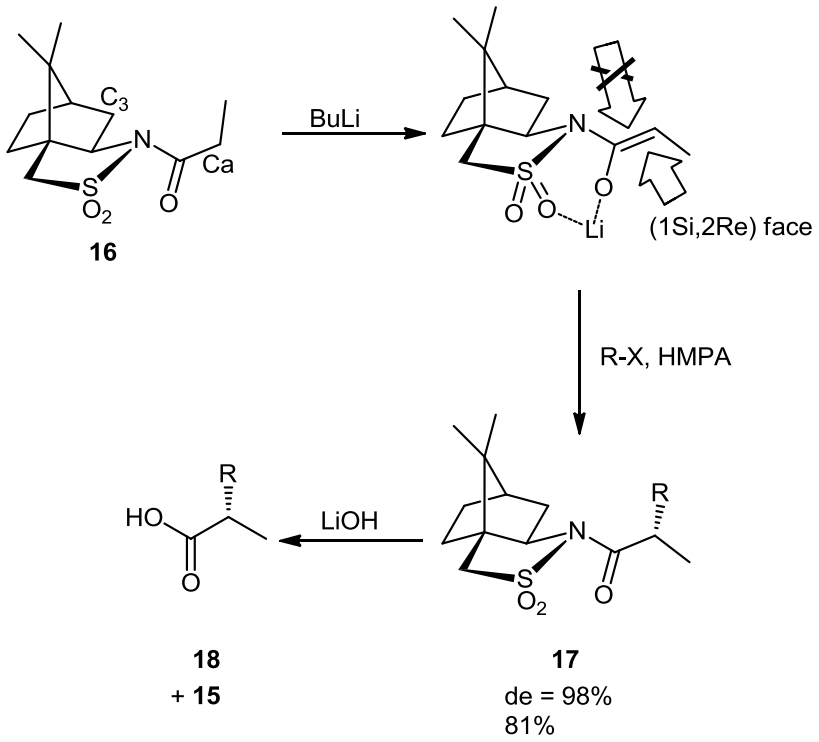
Because of the problems of alkylation of oxazolidinone enolates with unreactive alkyl halides, other chiral auxiliaries have been developed. These include derivatives of the camphor sultam **15**, reported by Oppolzer in 1990.[13] Camphor is a terpenoid compound isolated from a tree, the camphor Laurel. Camphor sultam **15** can be obtained in two steps (see scheme 1.12) by first functionalising the C-10 methyl group of camphor **13** with sulfuric acid in acetic anhydride[15] and then with thionyl chloride[16] which afforded the sulfonyl chloride derivative **14**. The ring closure was subsequently achieved using ammonia and the intermediate can then be reduced by lithium aluminium hydride to obtain the (-)-camphorsultam (-)-**15**.



Scheme 1.12

Acylation of sultam **15** gives access to sultam imides **16**. In that case, after deprotonation using strong base, both oxygen from the carbonyl and the sulfonyl will be chelated to the metal in a six membered ring.[13] The *Z*-enolate formed during the process can thus react with

an electrophile through an attack of the (1*Si*,2*Re*) face as the two bridgehead methyl groups provide shielding of the (1*Re*,2*Si*) face as shown in scheme 1.13.[13]



Scheme 1.13[13]

Entry	R	X	Use of HMPA	Crude de (%)	Yield (%)
1	$PhCH_2$	I	Yes	96.5	89
2	CH_2CHCH_2	I	Yes	94.2	94
3	Me_2CHCH_2	Br	Yes	98.8	70
4	C_5H_{11}	I	Yes	97.7	81
5	$Me_2CH(CH_2)_3$	I	Yes	99	81
6	$CbzNMeCH_2$	Cl	No	72.7	58
7	$MeOCH_2$	I	No	74	67

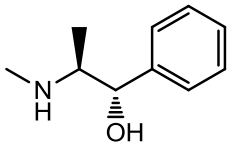
Table 1.2: Stereoselective synthesis of 17 by alkylation of 16[18]

Camphor sultam **14** has been reported to be highly selective for alkylation of alkyl (Table 1.2) halides with high yield (70-94%). However a considerable loss of both selectivity and yield has been observed when not using HMPA (entry 6-7), a carcinogenic solvent[17] (see table 1.2).[18]

Although both oxazolidinones and camphorsultams are commercially available, their prices remain high and can be prohibitive.[19]

d) Pseudoephedrine

In 1994, Myers and his group reported that a well known and inexpensive drug, pseudoephedrine **19a** (scheme 1.14), could be used as an efficient chiral auxiliary.[20] Pseudoephedrine **19a** has been used for decades as an over-the-counter nasal decongestant (e.g. Sudafed).[21]

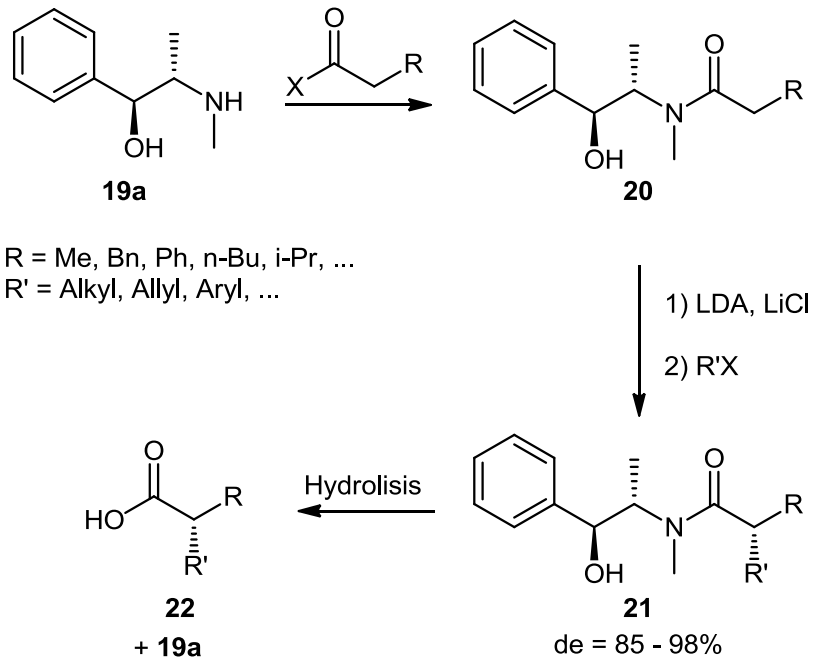


Pseudoephedrine

19a

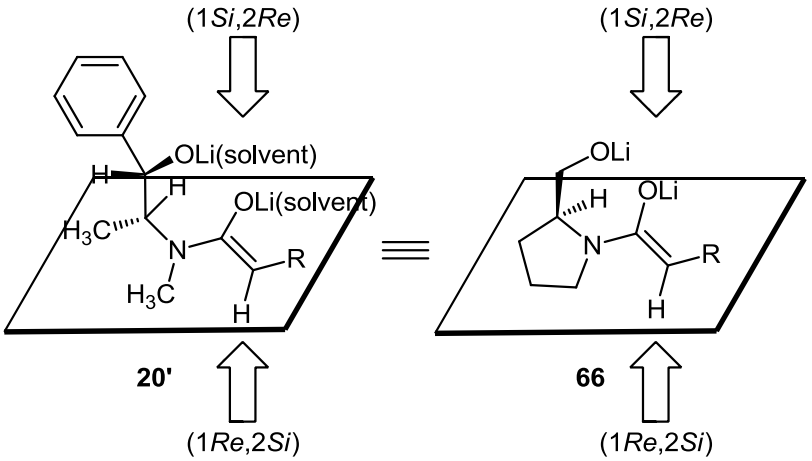
Scheme 1.14

Pseudoephedrine **19a** is commercially available in both enantiomeric forms ((1*S*,2*S*) and (1*R*,2*R*)) and is inexpensive.[22] Even if, overall, its selectivity is slightly lower than Evans' auxiliaries in enolate alkylations, it can be applied to a wider range of compounds, including non-activated alkyl halides. Generally the yield of alkylations of pseudoephedrine-derived amide enolates are usually very good without the need to use excessively toxic additives (see scheme1.15).



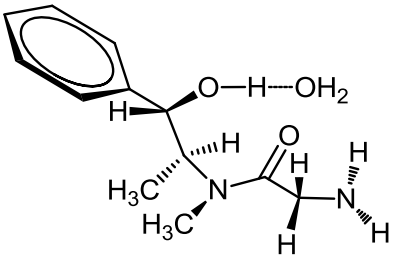
Scheme 1.15

Myers has postulated a mechanism for the alkylation of the enolates derived from **20.** The proposed mechanism is based on the mechanism suggested in the alkylation of prolinol amide enolates with epoxides as reported by Askin and his group in 1988.[23] Askin postulated that the alkoxy group of the prolinol amide enolate **66** may be directing the alkylation by providing a steric shielding effect (Scheme 1.16). By analogy, Myers thought that the alkoxy group of the pseudoephedrine would have the same effect as shown on scheme 1.16.



Scheme 1.16

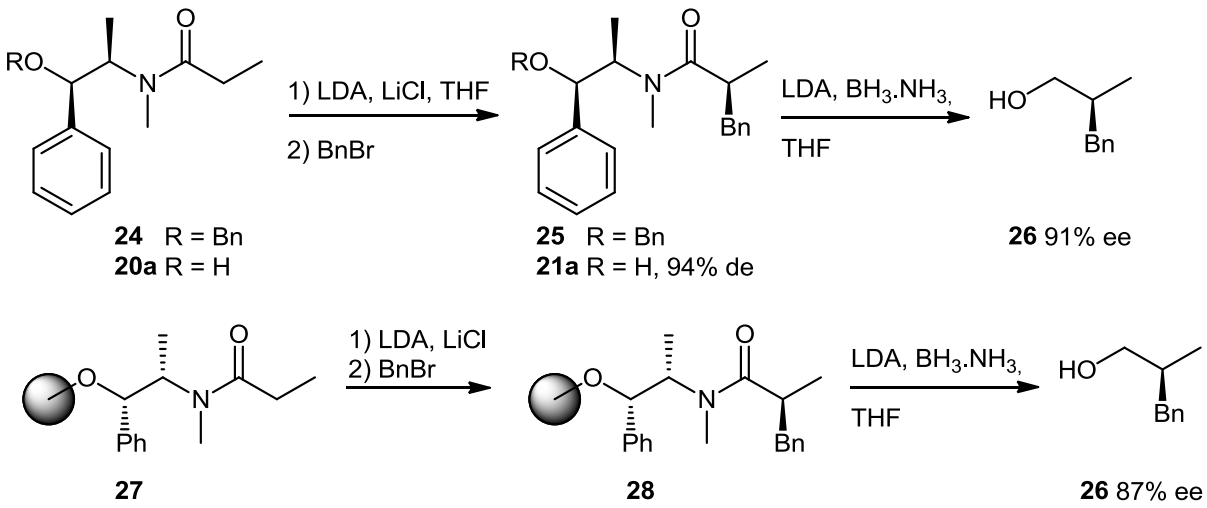
Myers suggested that for the *Z*-enolate **20'**, a reactive conformation is adopted (Scheme 1.16). In such a conformation, the lithium alkoxide and, perhaps, solvent molecules (tetrahydrofuran and possibly diisopropylamine) chelated to the lithium cation. These chelated cations were thought to block the (1*Si*,2*Re*) face of the *Z*-enolate, forcing the attack of the halide through the (1*Re*,2*Si*) face. The reactive conformation was suggested based on the X-ray structure of the pseudoephedrine glycinamide monohydrate **23**, which presents a similar conformation (see scheme 1.17).[20b,24]



23

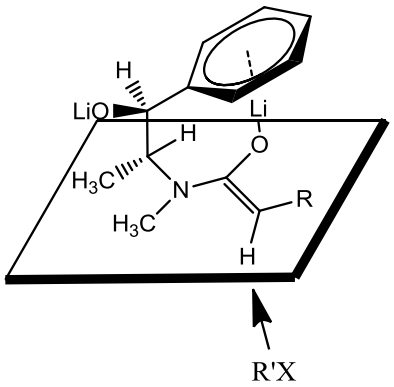
Scheme 1.17[20b,24]

Nonetheless, in 2003, Procter and his group had the idea to immobilise pseudoephedrine **19a** on a resin in order to facilitate its recovery and reuse the auxiliary readily[25]. Concerned about whether or not the selectivity of the auxiliary would be conserved in the process, they prepared the benzyl ether derivative **24** of the pseudoephedrine and tested it in asymmetric enolate alkylations (Scheme 1.18). Thus, deprotonation of **20a** with LDA/LiCl and alkylation with benzyl bromide gave the alkylated product **21a** in 94 % de, whereas the same reaction on **24** followed by reductive deprotection of **25** gave the benzylated alcohol **26** in 91 % ee. Indeed, similar deprotonation and alkylation of *O*-polymer-supported pseudoephedrine amides **27** gave products with the same absolute configuration in good enantioselectivity (87 %). These data show, surprisingly, that the selectivity of the auxiliary was not significantly affected in the cases of the *O*-benzyl or *O*-polymer-supported analogues, with respect to the pseudoephedrine amides (scheme 1.18).



Scheme 1.18

This experiment shows that the dianion **20'** proposed in Scheme 1.16 is not essential in obtaining good selectivity. This would suggest that the mechanism of enolate alkylation of the pseudoephedrine based enolates might not involve the reactive enolate proposed by Myers. With this possibility in mind, computational conformational analysis experiments were carried out in these laboratories.[27] Single point energy calculation using DFT B3LYP with the 6-31G** basis sets on the conformers generated by molecular mechanics methods of the enolate derived from **20** (**20a** R = Me) suggested that Myers' reactive conformation **20'** may not be the minimum energy conformation. Thus, the two lowest energy conformations involved an interaction between the enolate lithium cation and the aromatic ring (Scheme 1.19). That is a Li^{+}-π-interaction, which was *ca* 0.7 kJ mol^{-1} more stable than the Myers reactive conformation **20'**.



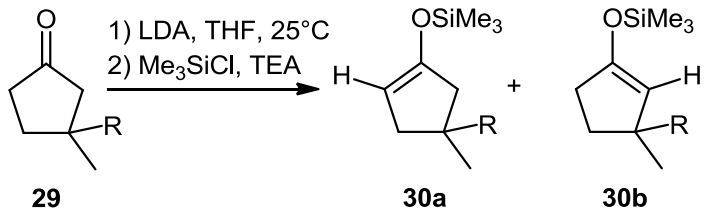
Scheme 1.19

Such a cation-π- interaction might result in the aromatic ring being the steric screen by blocking the (1*Si*,2*Re*) face to attack by electrophiles (Scheme 1.19).

If our hypothesis is correct, as a consequence, the electron density of the phenyl group of the pseudoephedrine plays a key role in the selectivity of the auxiliary. Thus, it is believed that increasing the electron density of the aromatic ring would strengthen the interaction between the lithium and the phenyl ring, bringing the ring closer to the metal cation, increasing the bulk over the (1*Si*,2*Re*) face and consequently, the selectivity of the chiral auxiliary. On the other hand, decreasing the electron density should also decrease the selectivity of the auxiliary by disfavouring this Li-π interaction.

As it happens, evidence of such a chelation has been reported by Posner and his group in 1979.[26] Posner postulated that lithium enolates could direct an alkylation or a bromination by chelating with the π-electron of a neighbouring benzyl ring to explain the selectivity observed while forming various β-aralkylcyclopentanone lithium enolates. The major enolate (later trapped with trimethylsilyl chloride) appeared to be the one where the lithium cation could interact with the aromatic ring. Adding an electron withdrawing group to the aromatic ring, such as a nitro group decreased the selectivity (1:0.9) (Table 1.3, entry 4). In contrast, an

electron donor substituent on the aromatic ring such as a methoxy, which would enhance a Li+-π interaction, led to an improved selectivity (1:7.4) (Table 1.3, entry 3). See scheme 1.20.



29 **30a** **30b**

Scheme 1.20

Entry	R	30a	30b
1	Ph	1.0	3.3
2	*p*-MePh	1.0	4.3
3	*p*-MeOPh	1.0	7.4
4	*p*-O_2NPh	1.0	0.9
5	$PhCH_2$	1.0	6.9
6	$PhCH_2CH_2$	1.0	2.5
7	CH_2=CH	1.0	0.9
8	*n*-Bu	1.0	0.3

Table 1.3 Stereoselective synthesis of 30 by trapping formed enolate from 29[26]

This tends to confirm that the lithium cation of an enolate can, indeed, interact with the π-electrons of the benzyl ring.

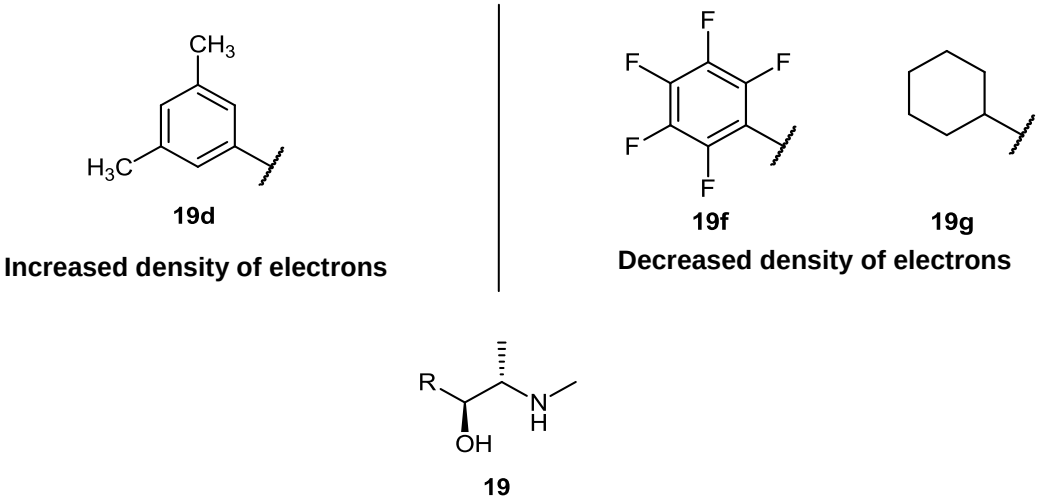
In the light of the observations of Posner *et al.* the molecular modelling experiments were extended to a number of Z-enolates of derivatives of pseudoephedrine **19a, b, c, d, e, f**. Each system gave between 70-100 conformers from molecular mechanics based conformational searching. As before, single point energy calculations using DFT using the B3LYP model with the 6-31G** basis set. The most stable conformers within a 15 $kJ.mol^{-1}$ range were then compared and classed between the Myers conformation (M) and the π-stacked conformation (P). Results are reported in Table 1.4[27] below.

Pseudoephedrine analogue	Lowest energy conformation	Order of conformers	ΔE for π vs Myers (kJ/mol)
Pseudoephedrine **19a**	P	P, P, M, M,	-0,68
Methoxy ether **19b**	P	P, M, P, P,	-13,6
2,6-Dimethylphenyl **19c**	M	M,M,P, M, P, M	1,99
3,5-Dimethylphenyl **19d**	M	M, P, P, M, M, M	1,20
9-Anthracene **19e**	P	P,P,P, M, P, M, M	-2,76
Pentafluorophenyl **19f**	M	M, M, M, P, P	13,68

Table 1.4[27]

One will notice that for the *Z*-enolate for the pseudoephedrine derivative **19a** and the 3,5-dimethylphenyl analogue **19d** as well as the 2,6-dimethylphenyl counterpart **19c**, the difference of energy between the Myers and the π-stacked conformation is very low, less than 2 $kJmol^{-1}$. Moreover, those calculations do not take into account the solvation of the molecules and suppose that the compounds are in gas phase. Although the accuracy of these values may not be realistic, it allows us to question whether the conformation proposed by Myers is actually involved in the mechanism of the alkylation of the enolates of the amide derivatives of pseudoephedrine or not.

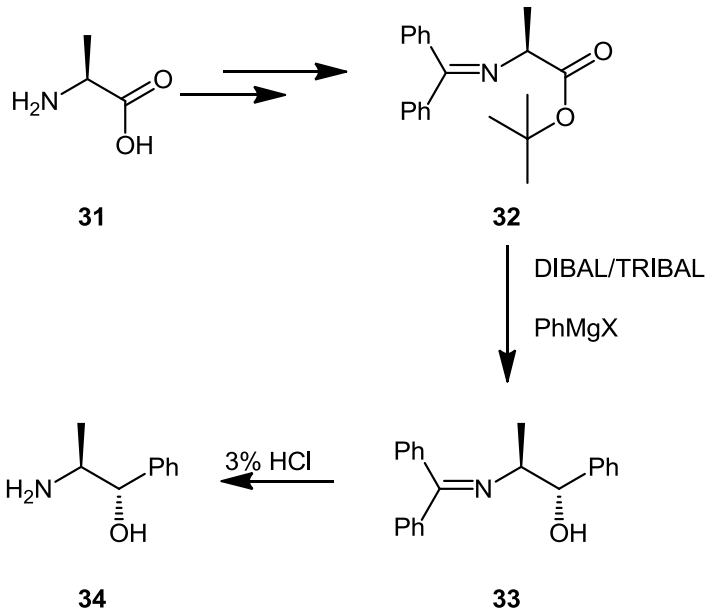
To verify this hypothesis, modifying the electron density of this phenyl group has been investigated by synthesising analogues of the pseudoephedrine with appropriate substituents on the phenyl group. The following analogues have been selected to verify that hypothesis (scheme 1.21): adding methyl groups on the positions 3 and 5 of the phenyl will increase the electron density of the phenyl group. In contrast, adding electronegative heteroatoms will withdraw electrons from the benzyl ring and decrease the electron density on the phenyl group. Moreover, using a non-aromatic group such as cyclohexyl might decrease considerably, if not entirely, the selectivity of the auxiliary if our hypothesis is correct. On the other hand, if the Myers' proposed mechanism is correct then a cyclohexyl group may not affect the diastereoselectivity of enolate alkylations.



Scheme 1.21

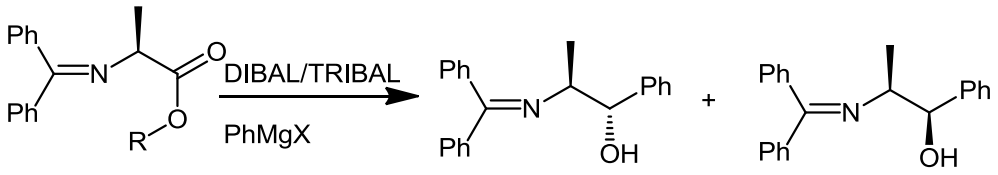
e) Synthesis of novel analogues

In 1992, Polt and his group reported a synthesis of pseudonorephedrine **34** through a stereoselective reductive alkylation of an inexpensive derivative of L-alanine **31**[28] (See scheme 1.22). This route offered the possibility to introduce functionalised aromatic groups of pseudoephedrine derivatives.



Scheme 1.22

The acid group of the alanine **31** was first protected as a *t*-butyl ester and then, the amino group was protected as a Schiff's base using benzophenone ketimine. The resulting compound **32** was partially reduced using a 1:1 mixture of diisobutylaluminium hydride (DIBAL) and triisobutylaluminium (TRIBAL) in hexanes. The complex formed provides good stereoselectivity when reacted with a Grignard reagent. Interestingly, the bulkier the ester is, the better the selectivity is, the *t*-butyl ester derivative **32** offered the best selectivity for that particular example with a ratio of 11:1 (Table 1.5, entry 5) in favour of the *threo* compound **33**.

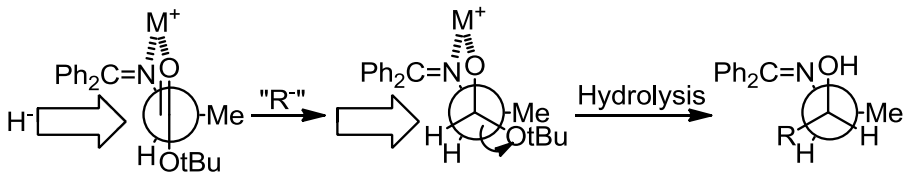


32 **33** **33'**

Entry	R	*Threo : Erythro*
1	Me	7.6 : 1
2	Et	8.8 : 1
3	CH_2Ph	6.3 : 1
4	$CHPh_2$	10.7 : 1
5	tBu	11.0 : 1

Table 1.5 : Stereoselective reductive alkylation of 32

The selectivity was explained by the Felkin-Ahn chelated model[29,30,31] (see scheme 1.23).



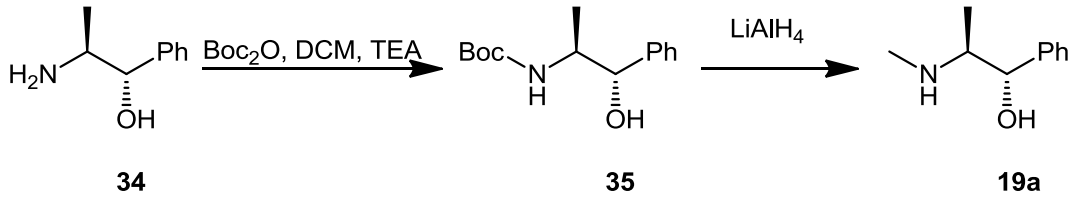
32 **32'** **33**

Scheme 1.23

The hydride first attacks the less hindered *Re* face of the ester **32**, accordingly to the Felkin-Ahn model. Then, the nucleophile attack occurs on the less hindered side of the resulting acetal **32'**, displacing the *tert*-butoxide leaving group to obtain the desired stereochemistry.

Deprotection of the imino alcohol **33** leads to pseudonorephedrine **34**.

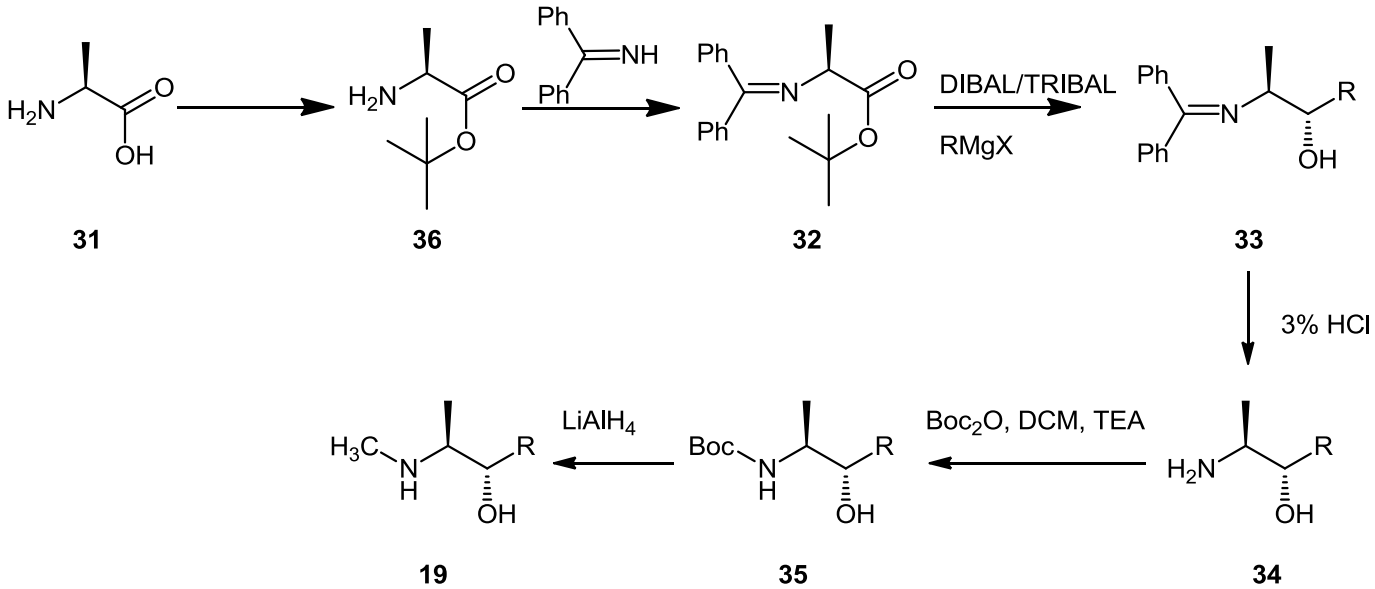
Pseudoephedrine **19a** could then possibly be obtained in two steps by reduction of the Boc protected amino alcohol **35** by lithium aluminium hydride (LAH) (Scheme 1.24).



34 **35** **19a**

Scheme 1.24

This work of Polt *et al.*[28] suggested that application of this methodology might provide a synthetic route to prepare analogues of pseudoephedrine starting from L-alanine **31** (see scheme 1.25).

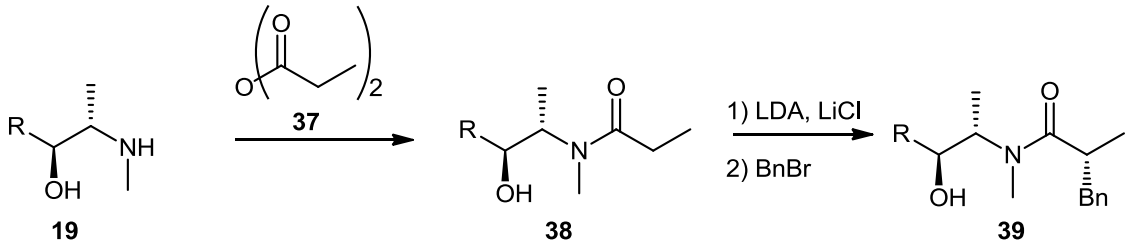


31 **36** **32** **33** **34** **35** **19**

d R = 3,5-dimethylphenyl
f R = 2,3,4,5,6-pentafluorophenyl
g R = cyclohexyl

Scheme 1.25

A standard reaction had to be defined as a reference for our study, once modified auxiliaries had been prepared. The following sequence was chosen to investigate the efficacy of new auxiliaries and was based on Myers' studies on pseudoephedrine[20] as a chiral auxiliary (scheme 1.26). Thus propionic anhydride **37** could be used to acylate the auxiliary **19** and form the propionamide **38**. Then lithium diisopropylamide should form the *Z*-enolate in the presence of lithium chloride; a de of 94% has been obtained with pseudoephedrine using benzyl bromide as the alkyl halide.



d R = 3,5-dimethylphenyl
f R = 2,3,4,5,6-pentafluorophenyl
g R = cyclohexyl

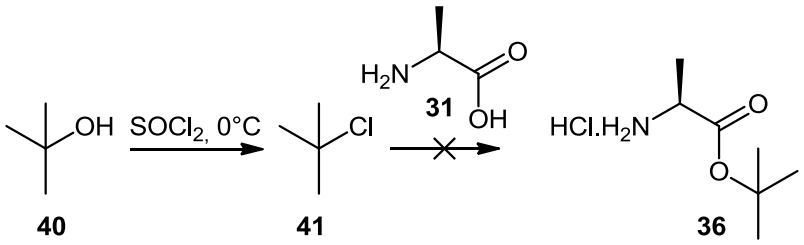
Scheme 1.26

In summary, as seen earlier, Myers' pseudoephedrine is a highly efficient chiral auxiliary, the diastereoselectivity mechanism of which remains unknown. O-Benzyl and O-polymer supported derivative have been reported to maintain a high selectivity toward enolate alkylation, throwing into question the commonly accepted mechanism postulated by Myers. A possible mechanism involving cation-π interaction, based on DFT calculations, is postulated here. Therefore, it was proposed to synthesize pseudoephedrine derivatives with tunable aromatic ring electron density in order to study the impact of such interactions on the outcome of enolate alkylation, using Myers' chemistry as a reference in our study.

II) Results and discussion:

1) Synthesis of the 3,5 dimethylphenyl pseudoephedrine analogue

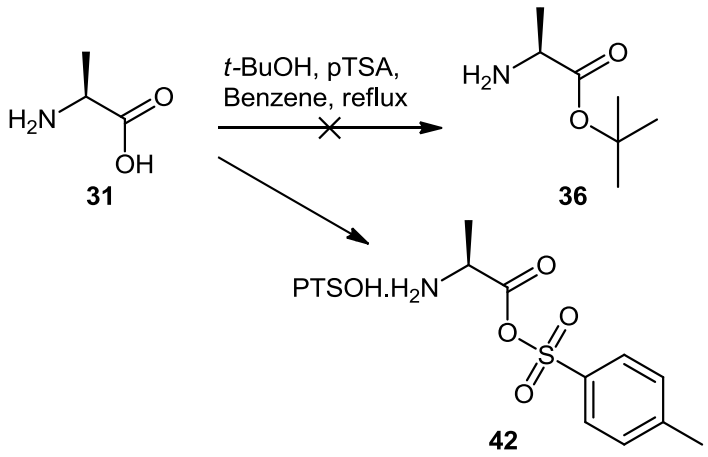
The first part of the project was, of course, to establish a robust route to prepare the various analogues of the pseudoephedrine (e.g. **19d**). To do so, as mentioned above, we were inspired by the synthesis of pseudonorephedrine **34** published by Polt and his group (see scheme 1.22).[28] The first step consisted of the preparation of the alanine *t*-butylester **36**. This step was crucial as *t*-butyl esters are not easy to synthesise, yet the *t*-butyl group offered the best potential selectivity during the reductive alkylation (see Table 1.5). Unfortunately, despite numerous efforts to prepare ester **36**, every single attempt failed or had an unacceptable yield. Those various attempts include the use of freshly distilled $SOCl_2$ on t-butanol at 0 °C in order to produce the corresponding chlorinated compound by nucleophilic substitution[32] on which was added L-alanine (see Scheme 2.1). The procedure was adapted from literature precedent.[40]



Scheme 2.1

This method might sound odd as the standard procedure of making ester would suggest adding the thionyl chloride to the acid, forming the acyl chloride, and then adding the alcohol. However, the stereocenter of the L-alanine **31** has to be taken into account and it is believed that such a classic procedure would inevitably lead to racemisation of the amino acid derivative. Every attempt using this method ended up with retrieving the alanine unmodified.

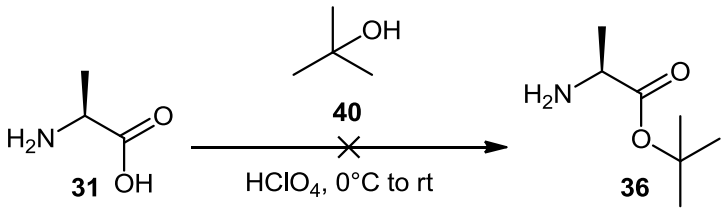
A second method was then investigated.[33] This time, the *t*-butyl cation is generated by dehydration with *p*-toluenesulfonic acid in refluxing benzene while the generated water is trapped in a Dean-Stark apparatus containing calcium chloride (see scheme 2.2).



Scheme 2.2

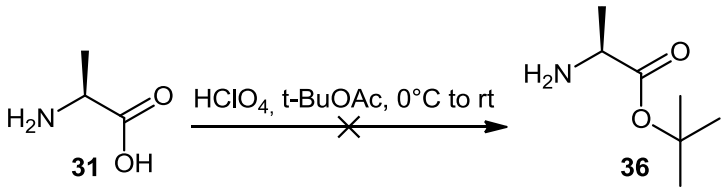
Again, the reaction failed and the only retrieved material was the tosylate salt of the tosylate ester **42**.

It was then decided to try generating isobutene gas by mixing *t*-butanol **40** and perchloric acid in the presence of L-alanine **31** in a sealed tube (scheme 2.3)[34] but the yield of the ester **36** obtained was very low (less than 30%) and the reproducibility of the reaction was very poor.



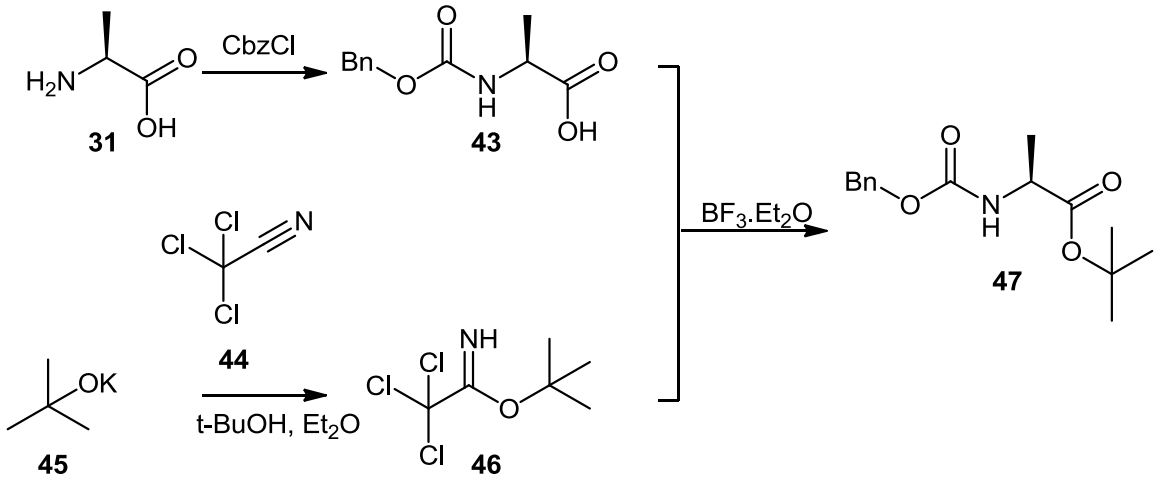
Scheme 2.3

In view of the low yields for the formation of ester **36**, the conditions were slightly modified, adapting a published procedure on the valine substrate: *t*-butanol **40** was replaced with a better source of carbocation: *t*-butyl acetate (Scheme 2.4).[35] This reaction failed as only a very complex mixture of unknown material was afforded.



Scheme 2.4

Literature precedent led us to attempt using *t*-butyl trichloroacetamidate **46** as a source of the *t*-butyl group[36] and coupling it with the benzyl carbamate derivative of the L-alanine[37] **43** (see Scheme 2.5) to obtain the Cbz-Ala-t-Butyl ester **47**. Deprotection of the Cbz group by hydrogenation would provide the desired amino ester **36**.



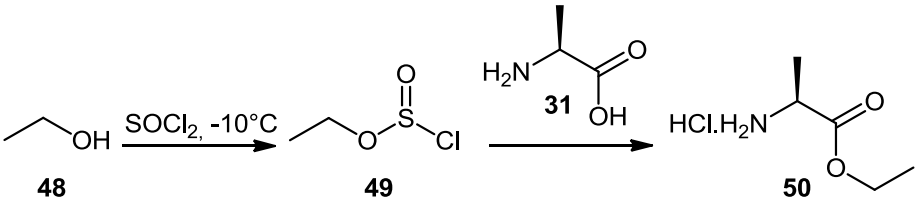
Scheme 2.5

In order to prepare the carbamate **43**, a general procedure[38] was used: the alanine **31** was reacted in aqueous sodium hydroxide with benzyl chloroformate in toluene but this led to only a 1% yield of carbamate **43**. However, using the method described by Kruse and her group,[39] which consists of refluxing the alanine **31** and the chloroformate in ethyl acetate overnight, afforded the required carbamate **43** in a much better yield (40%).

Several attempts to synthesise the *t*-butyl trichloroacetamidate **46** using the method provided by Armstrong[36] were unsuccessful. Even though freshly prepared potassium *t*-butoxide **45** and fresh trichloroacetonitrile **44** were used, the *t*-butyl trichloroacetamidate **46** was never obtained.

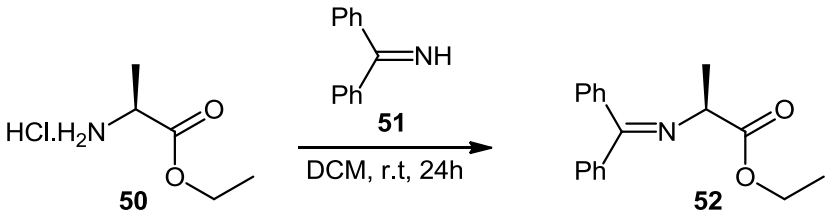
In the light of the difficulties in forming alaninine t-butyl ester **36,** it was then decided that alanine ethyl ester **50** would suffice. Polt[28], had observed good selectivity during the reductive alkylation of ethyl ester **50** (8.8:1 *threo:erytho* versus 11:1 from t-butyl ester **36**, see Table 1.5).

Thus, the first requirement was the formation of the ethyl ester **50**. This was achieved using a literature method[40] by reacting ethanol with thionyl chloride at -10 °C in order to generate the ethyl chlorosulfite **49**[32,41], followed by treatment with L-alanine **36** (scheme 2.6). This procedure afforded the ester hydrochloride salt **50** in 96 % yield that was enantiomerically pure, as judged by the $[\alpha]_D$. This method proved robust enough to use on a multi gram scale (*ca* 50g)



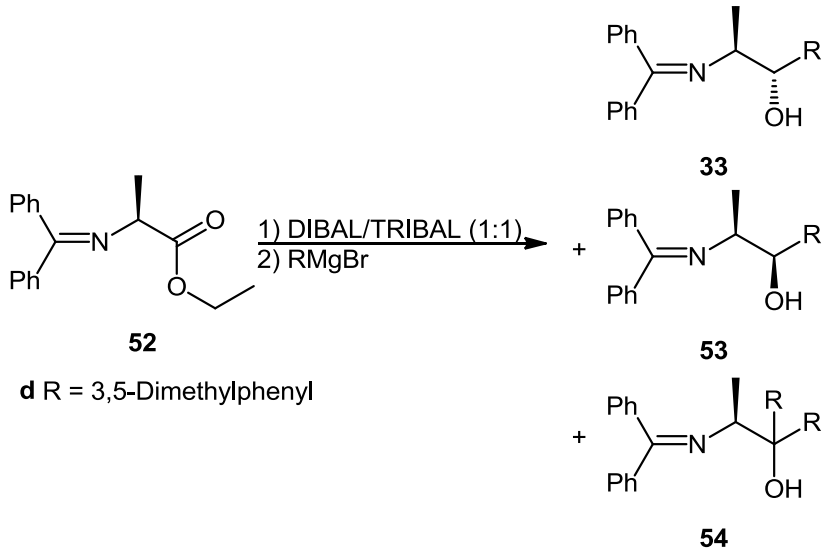
Scheme 2.6

The amino ester hydrochloride **50** was then reacted with benzophenone ketimine **51** using the literature of O'Donnel and Polt[42] which afforded the protected L-alanine derivative **52** (see scheme 2.6). The imine ester **52** was obtained enantiomerically pure upon trituration with hexane.



Scheme 2.6

The imine ester **52** was then submitted to reductive alkylation analogous to the method reported by Polt and co-workers[28] but using 3,5-dimethylphenylmagnesium bromide instead of phenylmagnesium bromide (See scheme 2.7).

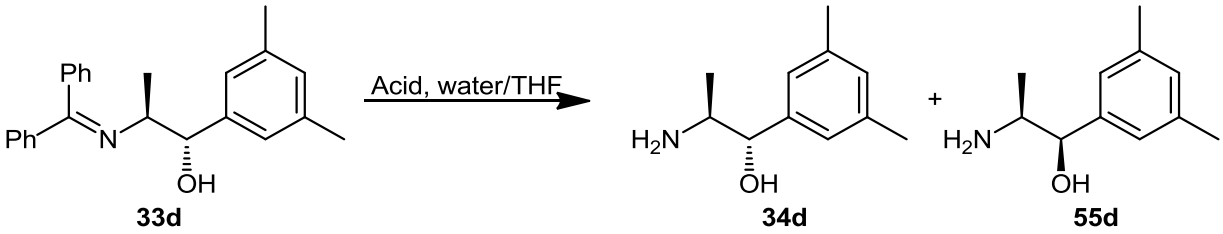


Scheme 2.7

Several attempts were necessary to fully master the reaction and obtain the best results. First of all, a mixture of DIBAL and TRIBAL in a 1:1 ratio was prepared and then added to the mixture. Initial attempts to add the DIBAL and TRIBAL consecutively were unsuccessful and the bisaddition by-product **54d** (see Scheme) was the main product. Also, the Grignard reagent needed to be prepared in diethyl ether. Polt *et al.* had shown that the use of tetrahydrofuran led to a considerable loss of selectivity in the reductive alkylation with phenylmagnesium bromide. In our case, only a THF solution of the 3,5-

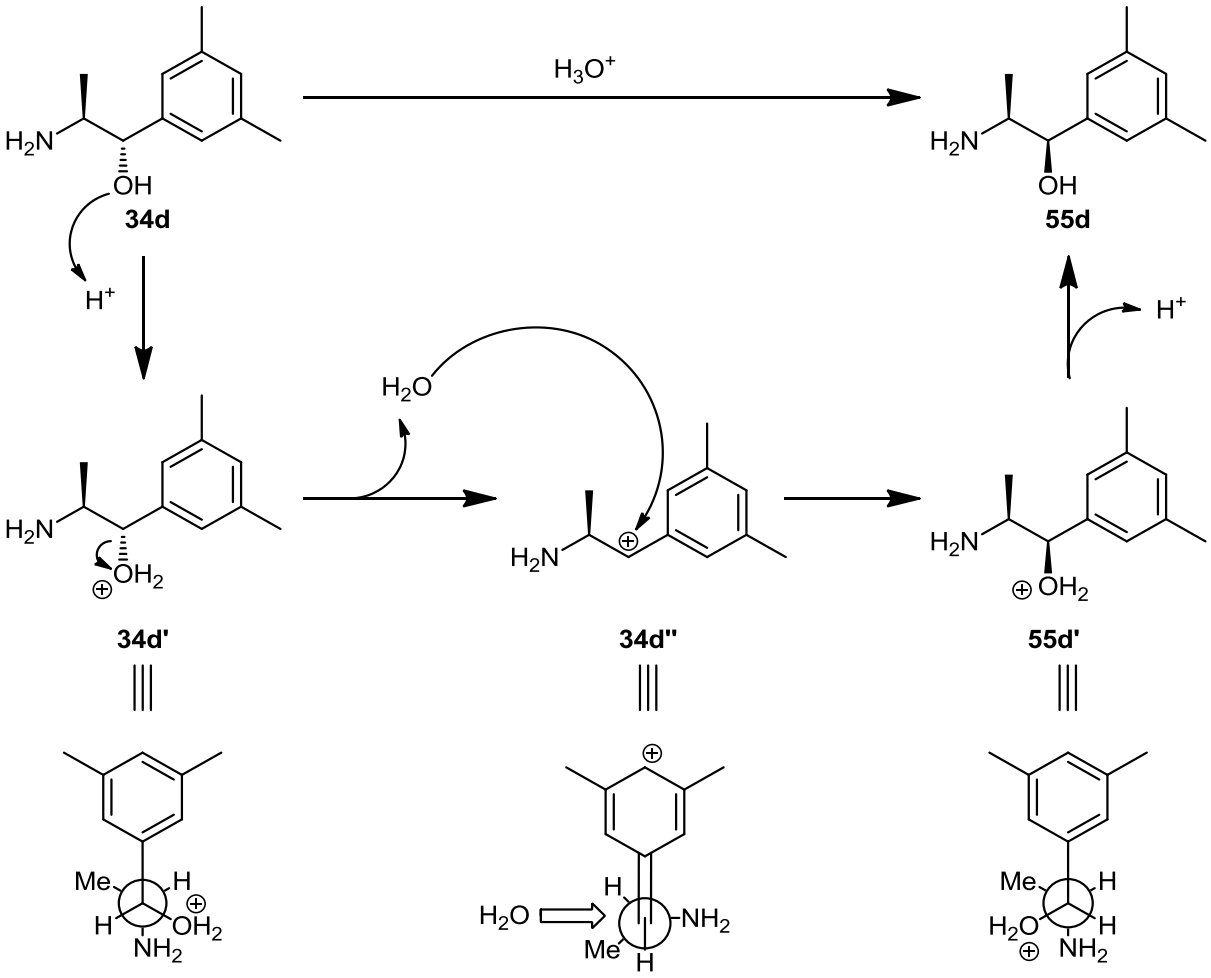
dimethylphenylmagnesium bromide was commercially available. A batch of the required Grignard reagent was thus prepared in Et_2O prior to use. Conversion of imine ester **52** into imine alcohol **33d** also seemed to be an issue as starting material or the bis-addition by-product **54d** was always observed in the crude NMR. It is believed that complexation of the starting material by the reducing agent is sluggish and, therefore, a longer delay is required before addition of the Grignard reagent. Waiting an hour between the two additions led to cleaner reactions with no sign of the bis-addition by-product **54d**. Crude NMR analysis showed a moderate selectivity with a ratio of 6.7:1 in favour of the desired (1*S*,2*S*) diastereoisomer **33d**. The ratio was obtained by comparing by NMR the integration of the signal of the H_α of both diastereoisomers showing as a doublet at 4.38 ppm for the *threo* compound **33d** and at 4.98 ppm for the *erythro* compound **53d** (^{1}H NMR spectras are available in annexe B). Attempts to separate those diastereoisomers by chromatography led to several fractions of mixed compound at various ratios (6.7:1, 16:1 and up to 67:1 in favour of the threo compound **33d**). Although it is also believed that the ketimine protective group is cleaved by the silica as a considerable amount of material was systematically lost during chromatography (only 38% recovery). Neutral alumina was considered as an alternative but no appropriate system of eluant was found to separate the compounds effectively. Effort to crystallise the imine alcohols **33d** and **53d** were also unsuccessful.

In the meantime, the cleavage of the ketimine protective group in imine alcohols **33d** and **53d** was investigated using a mixture of acidified water and tetrahydrofuran. However, NMR analysis indicated that epimerisation of the hydroxy group had occurred (see scheme 2.8).



Scheme 2.8

This epimerisation is believed to occur via a loss of water followed by a rehydratation of **34d** to convert into compound **55d** as described in scheme 2.8 bis.



Scheme 2.8 bis

The hydroxyl group of compound **34d** is first protonated, which leads to the loss of water in compound **34d'** and to the formation of the carbocation **34d''.** This carbocation is stabilised by the aromatic ring. A molecule of water then attacks the carbocation in a similar way that a

nucleophile would attack on a carbonyl, providing compound **55d** after release of a proton, resulting in an epimerisation of the newly designed stereocenter of compound **34d**. Note that deprotection of the ketimine protecting group has been successfully achieved without epimerisation after adding a phenyl ring by Polt and his group.[28] However, in our case, we have a more potent electron rich aromatic ring due to the two methyl groups which, by increasing the stabilisation of carbocation **34''**, may favour the epimerisation process as well.

Various conditions were used in an attempt to minimise the epimerisation (Table 2.1).

Entry	Scale (mg of 33d)	Acid	Temperature	Retrieved 34d (mg)	Ratio observed by NMR (34d : 55d)
1	86 mg (unpurified)	aq. HCl (3%)	r.t	None	no reaction
2	100 mg of 16:1 mixture	aq. HCl (3%)	r.t	25 (48%)	ratio of 10:1
3	500 mg of 6.7:1 mixture	aq. HCl (3%)	r.t	104 (40%)	ratio of 3:1
4	500 mg of 6.7:1 mixture	aq. Citric acid (10%)	r.t	108 (42%)	ratio of 3:1
5	500 mg of 6.7:1 mixture	aq. Citric acid (10%)	0°C	40 (15%)	ratio of 3:1

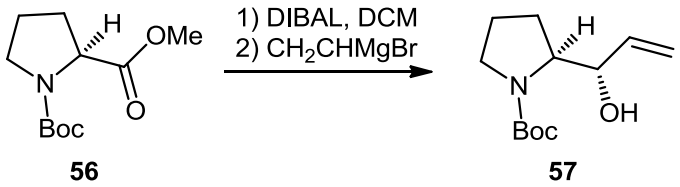
Table 2.1 : Deprotection of ketimine 33d

An attempt to deprotect crude material **33d** was carried out in order to see if the purification of **33d** by chromatography could be avoided. Unfortunately, use of 3% aqueous hydrochloric acid failed to remove the imine protecting group (Table 2.1, entry 1). Using these conditions on purified material did yield the amine alcohols **34d** and **55d** (40-48%) but NMR analysis indicated that some epimerisation of the benzylic stereocentre had occurred (Table 2.1, Entries 2 and 3). The use of 10% aqueous citric acid did not prevent this epimerisation (Table 2.1, entry 4) nor did the use of these conditions at 0 ˚C (Table 2.1, entry 5). Again, the ratio between compounds **34d** and **55d** was determined by ^{1}H NMR by comparing the integration

of the H_α. This signal shows as a clear doublet at 4.19 ppm for compound **34d** and at 4.44 ppm for compound **55d** (spectra available as Appendix C).

The inability to avoid epimerisation in the conversion of imine alcohol **33d** into pseudonorephedrine analogue **34d** was a major stumbling block in this route. Accordingly, instead of attempting to separate the two diastereoisomers, it was decided to reassess methods of synthesising **19d**.

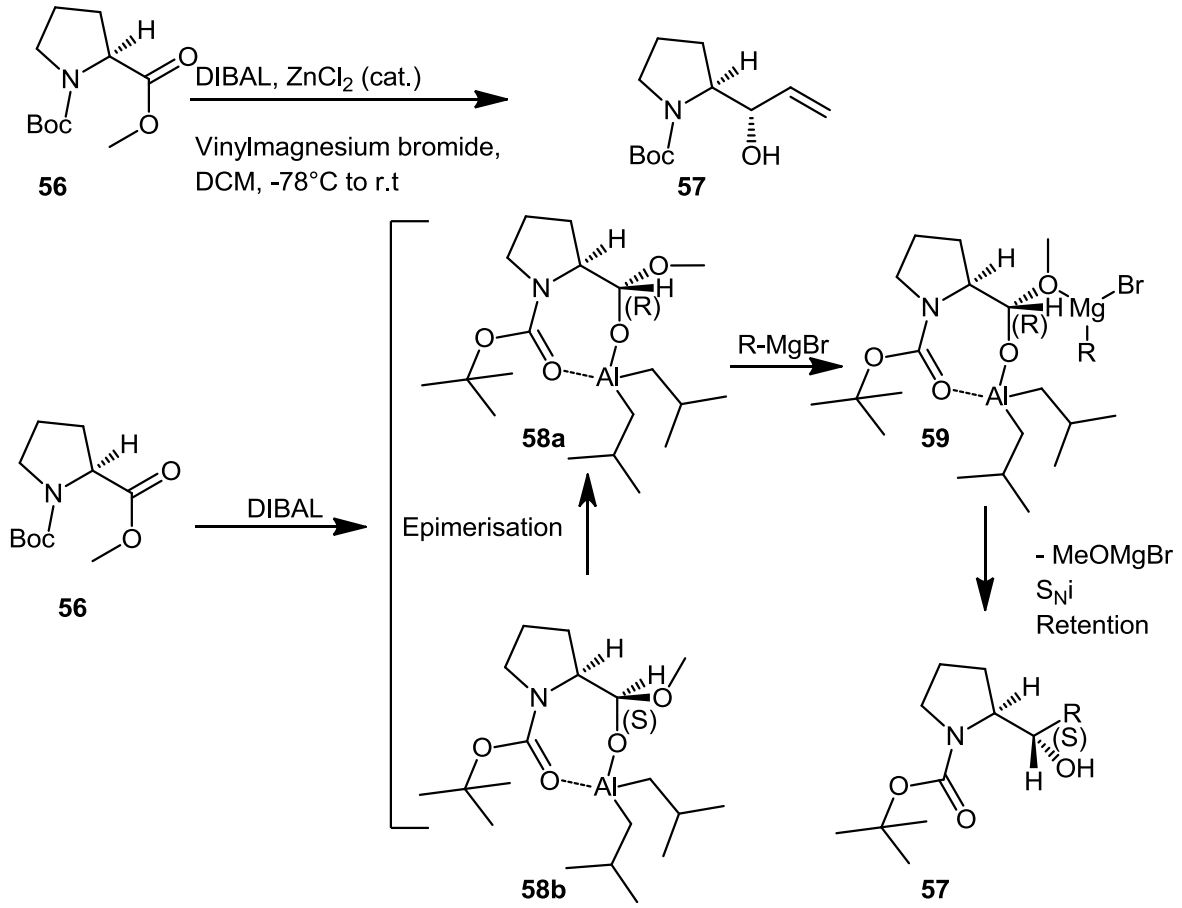
Interesting results reported by Zhao[43] attracted our attention. Thus, Zhao performed reductive alkylation on Boc protected L-proline methyl ester **56** using DIBAL and an allyl Grignard reagent which gave the alcohol **57** with excellent selectivity (> 32:1) (see Scheme 2.9).



56 **57**

Scheme 2.9

Zhao reported a ratio greater than 32:1 in favour of the desired diastereoisomer **57** by warming up the reaction mixture up to -20 °C after addition of DIBAL. Addition of the Grignard reagent still occurs at -78 °C. The high selectivity of the reaction is claimed to be due to a seven member ring transition state **58** between the aluminium and both carbonyl of the carbamate and the ester group as described in scheme 2.10.

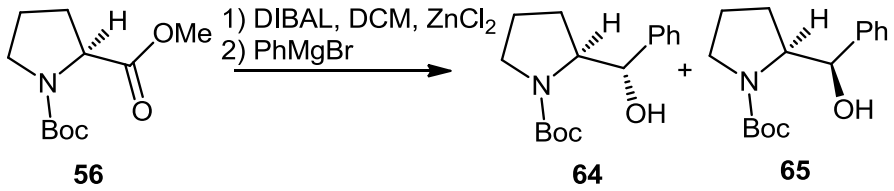


Scheme 2.10

Based on DFT calculations Zhao suggested that in the reaction of ester carbamate **56,** warming to -20 °C leads to epimerisation of the minor (*S*)-aluminoxyacetal diastereoisomer **58b** toward the major (*R*)-aluminoxyacetal diastereoisomer **58a** due to steric hindrance in the minor diastereoisomer **58b**. The Grignard reagent then displaces the methoxy group in the (*R*)-aluminoxyacetal **59** through an S_Ni process with retention of configuration.

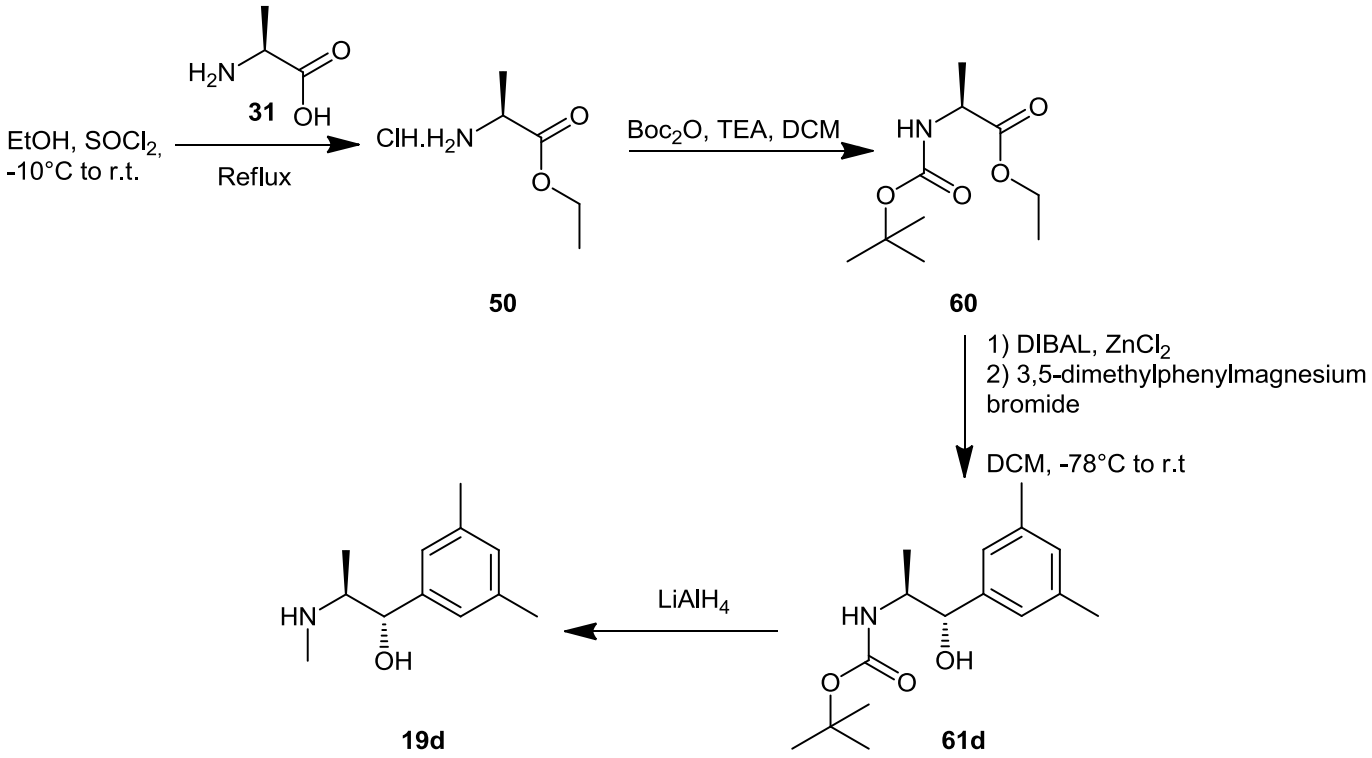
Moreover, Zhao also reported that using a Lewis acid such as zinc chloride in catalytic amounts both enhances the selectivity without the need for the warm up step. Although the role of the zinc chloride is still unclear, it is believed to be involved in the epimerisation process.

This reductive alkylation has been recently extended to the DIBAL phenylmagnesium bromide treatment of ester **56** which gave **64** and **65** in 99:1 ratio and 57% yield (see scheme 2.11).[44]



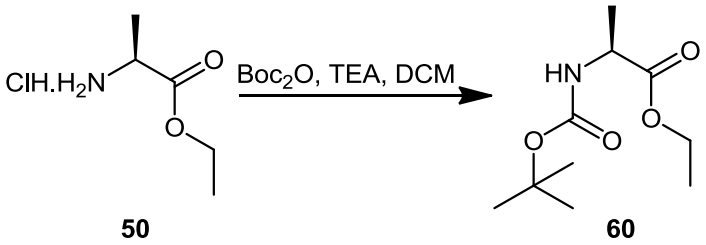
Scheme 2.11

Based on these results of Zhao and Cochi *et al.* for the reduction-Grignard addition to Boc proline ethyl ester **56** a new route to the synthesis of pseudoephedrine derivative **19d** was designed (see scheme 2.12). Thus, using Zhao's reductive alkylation of Boc alanine ethyl ester **60** with 3,5-dimethylphenylmagnesium bromide would be expected to afford the alcohol **61d** as the major diastereoisomer. Subsequent reduction of the amino alcohol **61d** with lithium aluminium hydride should provide the desired pseudoephedrine analogue **19d**.



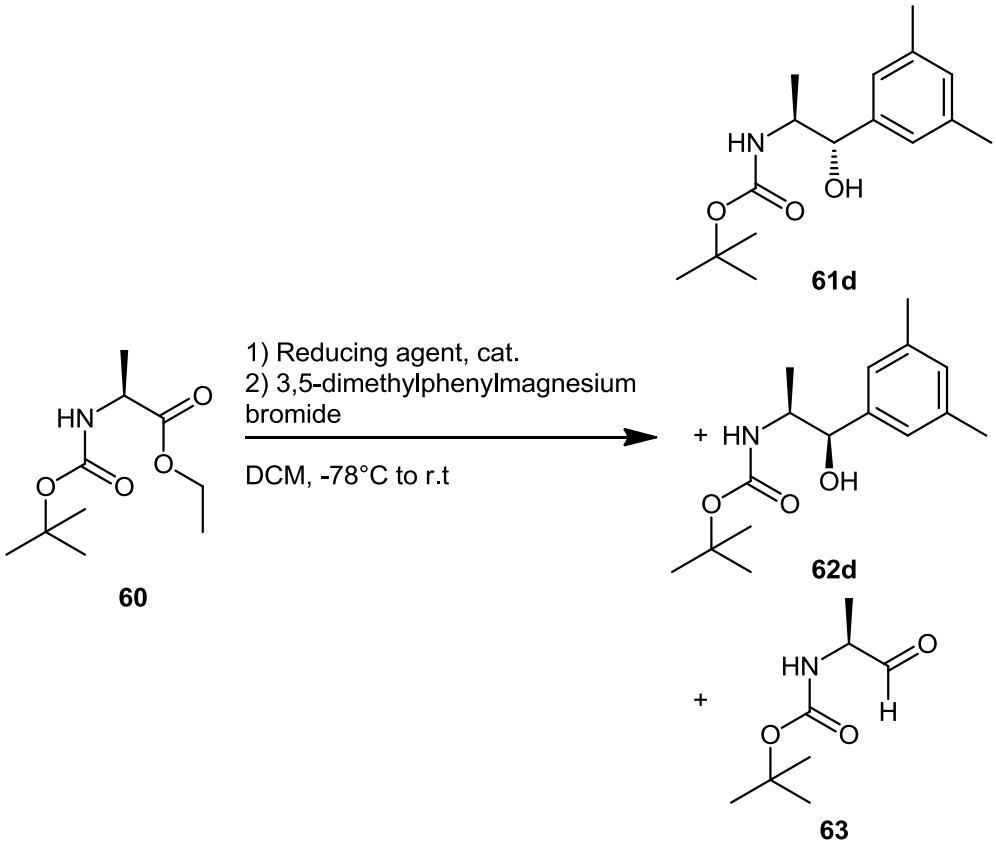
Scheme 2.12: Proposed route to pseudoephedrine analogue 19d

The proposed route to pseudoephedrine analogue **19d** required access to Boc alanine ethyl ester **60**. Standard conditions were used to perform the Boc protection of alanine ethyl ester hydrochloride **50** using an excess of Boc anhydride and triethylamine to free the amine from the HCl salt (scheme 2.13). Compound **60** was afforded in 96% yield and maintained its optical purity and could be carried out on a 10 g scale.



Scheme 2.13

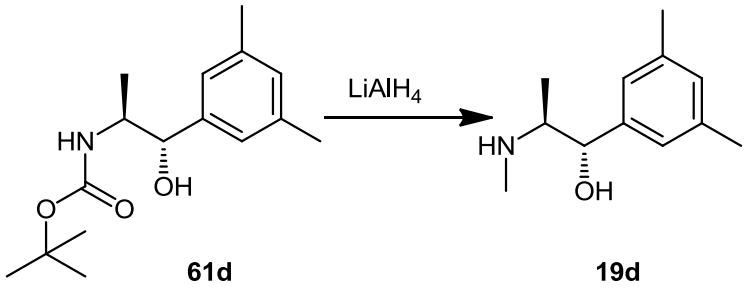
Several attempts were necessary to obtain the amino alcohol **61d** in a decent yield. A first attempt using DIBAL at -78 °C followed by addition of the Grignard reagent after six hours was unsuccessful (Table 2.2, Entry 1). NMR analysis of the crude reaction material showed mainly starting Boc alanine ester **60**. A second attempt adding DIBAL at -78 °C followed by warming to -20 °C for two hours before adding the Grignard reagent showed very little conversion (13%) by NMR analysis (Table 2.2, Entry 2) with no sign of undesired diastereoisomer **62d**. Adding 10% molar equivalent of zinc chloride after addition of DIBAL at -78 °C followed by addition of the Grignard reagent led to an increase of the conversion (25%) without the warm up step (Table 2.2, Entry 3). Those results were encouraging but we hoped to improve those conditions by using a DIBAL/TRIBAL (1:1) mixture. Using this mixture, we managed to increase the conversion up to 70% by also increasing the time delay between the addition of the reducing agent and the zinc chloride catalyst and then delaying addition of the Grignard reagent for 20 hours (Table 2.2, Entry 6). The use of 2 equivalent of DIBAL/TRIBAL in an attempt to reduce the overall reaction time, led to 50% conversion with a time lapse of 20 minutes between the additions of the DIBAL/TRIBAL mixture and the Grignard reagent. However, the overall yield decreased as the corresponding amino aldehyde **63** was formed as a by-product in a 1:1 ratio with the desired alcohol **61d** (Table 2.2, Entry 7) (data are reported in Table 2.2). In all cases, no sign of the undesired diastereoisomer **62d** was detected.



Entry	Reducing agent	Catalyst	Warm up step	Time between additions	Conversion
1	DIBAL (1.1 eq)	None	None	6 h	None
2	DIBAL (1.1 eq)	None	-20 °C (2h)	None	10%
3	DIBAL (1.1 eq)	$ZnCl_2$	None	20 mn	25%
4	DIBAL/TRIBAL (1.1 eq)	$ZnCl_2$	None	20 mn	50%
5	DIBAL/TRIBAL (1.1 eq)	$ZnCl_2$	None	6h	60%
6	DIBAL/TRIBAL (1.1 eq)	$ZnCl_2$	None	20h	70%
7	DIBAL/TRIBAL (2 eq)	$ZnCl_2$	None	20 mn	50% (Aldehyde/product : 1:1)

Table 2.2 Conversion of Boc alanine ethyl ester 60 to alcohol 61d

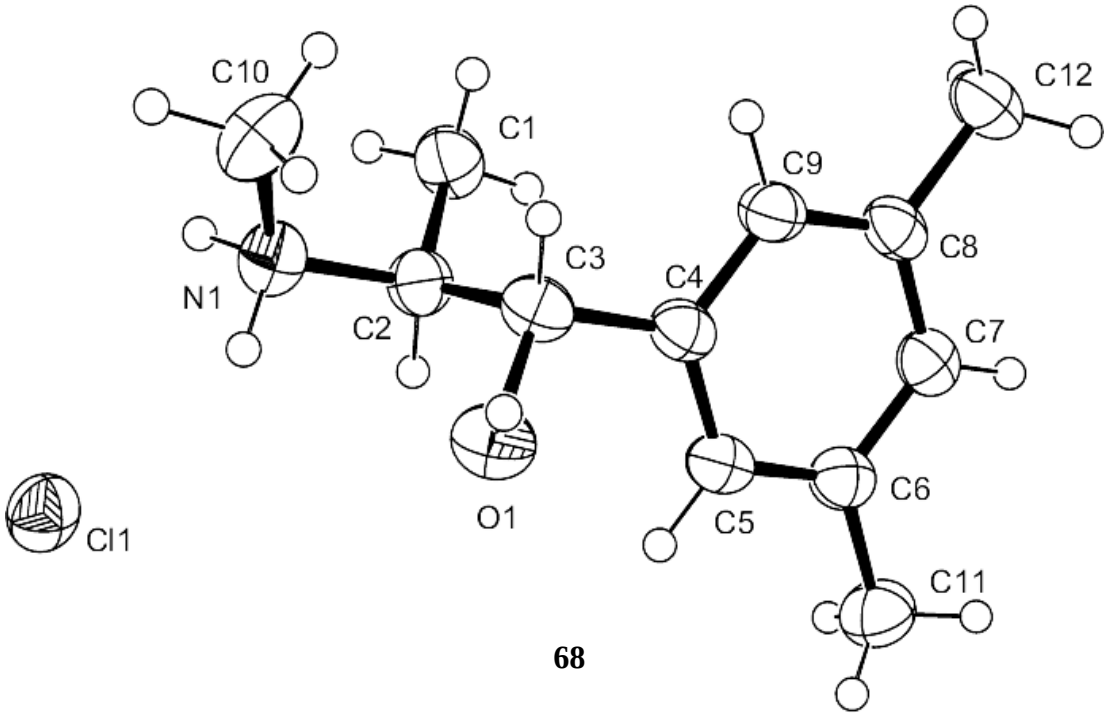
Purification by chromatography gives the Boc amino alcohol **61d** in moderate yield (up to 37%). It is believed that some material was lost during work up as an aluminium complex. Attempts to recover more material using Rochelle's reagent or acid/base treatment were unsuccessful.



61d **19d**

Scheme 2.14

Reduction of the Boc group of **61d** to give the *N*-methyl pseudoephedrine analogue **19d** was conducted using lithium aluminium hydride in tetrahydrofuran.[45] The reaction worked perfectly and no epimerisation occurred during the acidic work up as judged by subsequent NMR analysis. However, the yield was a moderate 38%, and again, it is believed that material was lost due to complexation with aluminium. Attempts to retrieve more material from the salts were unsuccessful. Interestingly, purification at this stage was much easier than after the reductive alkylation; therefore, reduction of the crude material from the reductive alkylation was investigated and found to be successful. Compound **19d** was easily purified and obtained with the same yield and purity as when conducting the reduction on purified amino alcohol **61d**. The expected stereochemistry of **19d** was confirmed by X-ray analysis of a crystal of the HCl salt **68** grown in toluene as reported in scheme 2.15.

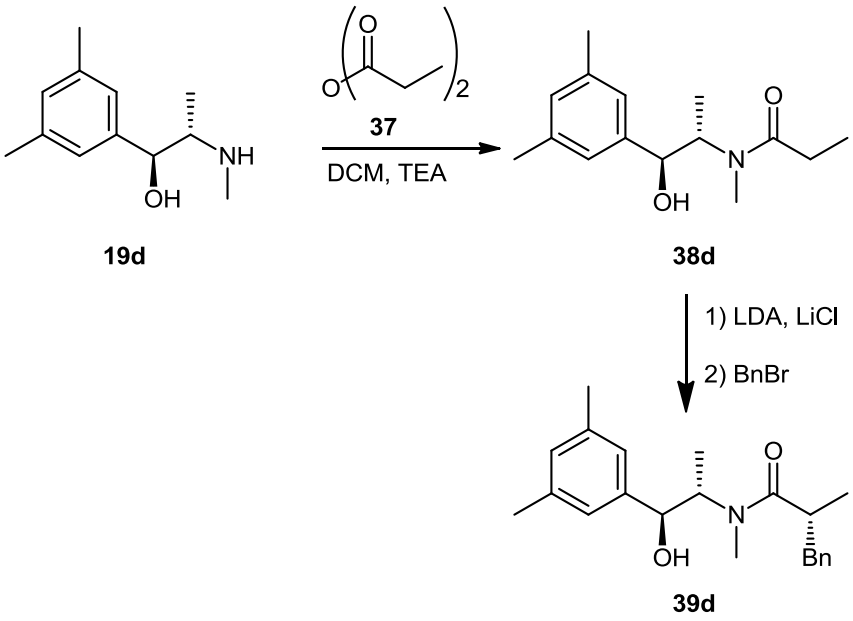


68

Scheme 2.15: Crystal structure of 68

2) Selectivity of the 3,5-dimethylphenyl pseudoephedrine analogue:

In order to test the selectivity of this novel chiral auxiliary **19d**, it was decided to compare it with the use of Myers' pseudoephedrine auxiliary **19a** (94% de)[20] in the diastereoselective alkylation of the corresponding propionamide **38d** with benzyl bromide (see scheme 2.16).



Scheme 2.16

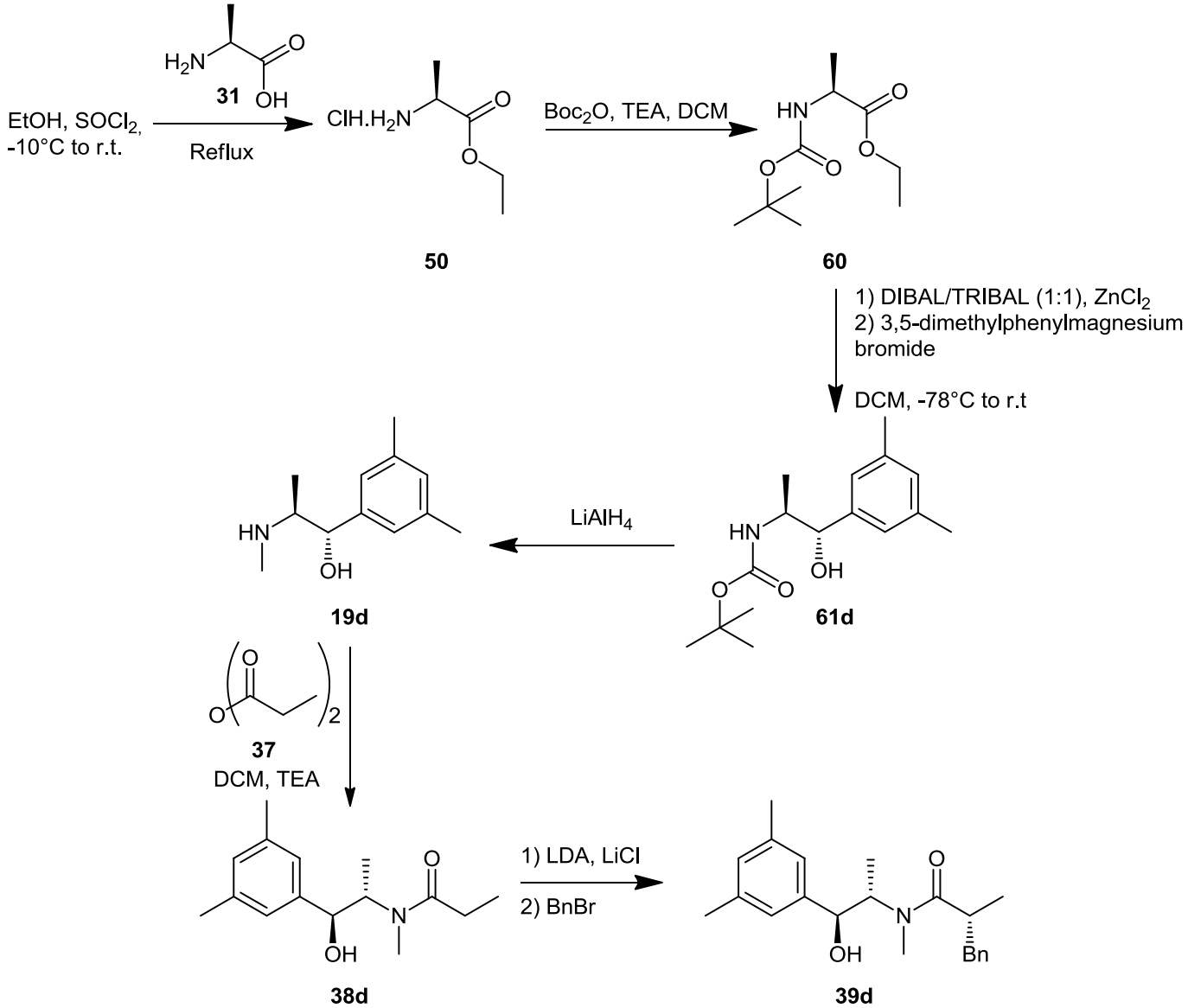
Amide **38d** was prepared according to Myers' procedure[20] using propionic anhydride in dry DCM and anhydrous triethylamine. The reaction succeeded in affording a 52% yield of an oil. Evidence of amide rotamers were supported by NMR analysis of 38d. Running the ^{1}H NMR in deuterated toluene at 95 °C showed only one set of peaks for some protons whereas two sets were observed at room temperature.

The propionamide **38d** was then treated with lithium diisopropylamide in order to form the *Z*-enolate. Addition of benzyl bromide to the enolate did not give the expected product. Crude NMR analysis only showed presence of benzyl bromide and starting material. Therefore, it was uncertain whether the *Z*-enolate was formed or if it did not react with benzyl bromide. Repeating the LDA deprotonation of amide **38d** and subsequent treatment with benzyl bromide and following the reaction by TLC did not indicate the formation of product. Consequently, enolate formation and quenching with D_2O was carried to investigate whether enolate formation had been successful. NMR analysis could not detect the incorporation of deuterium in the recovered propionamide **38d**, nor did high resolution mass spectrometric

analysis. From these observations it was assumed that the enolate of amide **38d** was not formed. The starting material **38d** was then suspected of being a monohydrate. Attempts to dry it with K_2CO_3 and azeotropic removal of toluene along with use of 4 equivalent of LDA led to alkylation of **38d** with benzyl bromide. Alkylated amide **39d** was then purified by chromatography to afford 38% of the desired compound. However, chiral HPLC analysis failed to unequivocally detect the minor isomer (Chiralcel OD 2.5% IP-hexane, 1 $ml.min^{-1}$, major peak at 31 min, chromatograms available in Appendix D): two experiments were run, one on the purified, isolated compound **39d** in order to determine the isolated de of the reaction. The second experiment was run on the crude material from the reaction in order to prevent any resolution during the purification process and to determine the actual de of the reaction. In both cases, even though the UV trace revealed several peaks, there was only one peak response in the chiral detector. It was therefore decided to synthesize the minor isomer as a reference sample to accurately determine its retention time under those conditions. The same method of synthesis of pseudoephedrine analogues is being investigated using D-Alanine as starting material.

Conclusions and future work:

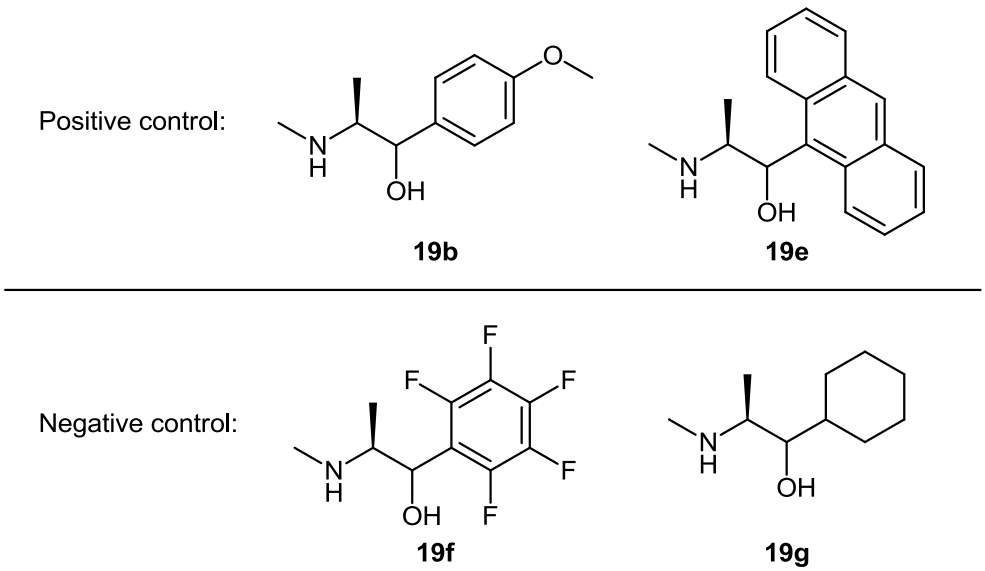
During this project, a new route of synthesis allowing the modification of the electron density of the aromatic ring of pseudoephedrine has been designed. An analogue of pseudoephedrine, the 3,5-dimethylphenyl pseudoephedrine **19d**, has been successfully prepared and tested via a standard alkylation of its propionamide derivative with benzyl bromide (see Scheme 3.1). The determination of the selectivity of this reaction is still in progress.



Scheme 3.1

In order to facilitate the determination of the selectivity of the alkylation of the pseudoephedrine substrate, the synthesis of the minor diastereoisomer is being carried out via the method described here but starting with D-Alanine instead of L-Alanine.

To continue this project, more analogues of the pseudoephedrine will be prepared and a library of diastereoselective alkylation will be investigated for each one of them in order to study the impact of the electron density of the aromatic ring on the selectivity of the pseudoephedrine chiral auxiliary. Among those analogues, the 4-methoxyphenyl pseudoephedrine **19b**, the 9-anthracene pseudoephedrine **19e** will be synthesized as a positive control, the electron density of the aromatic ring being increased. The 2,3,4,5,6-pentafluorophenyl pseudoephedrine **19f** and the cyclohexyl pseudoephedrine **19g** will be synthesized as a negative control to verify our original hypothesis: compound **19f** should show a decrease of selectivity due to a decrease of the electron density of the aromatic ring whereas compound **19g** should not show any difference of selectivity if Myers' mechanism applies but would should show an important decrease of selectivity if the π-Li interactions are present (see scheme 3.2).



Scheme 3.2 : Future work

Experimental:

^{1}H, and ^{13}C-NMR were carried out on a Bruker DPX-400 spectrometer with chemical shifts given in ppm (δ values), relative to the residual proton resonances in deuterio solvents for ^{1}H NMR and relative to solvent in ^{13}C NMR. The ^{1}H nmr signals are reported m (multiplet), d (doublet), s (singlet), t (triplet) etc and *J* values are recorded in Hz. IR spectra were recorded on a Perkin Elmer 1 FT-IR spectrometer as KBr discs (1mg of product per 100mg of KBr) or neat for oils. Elemental analysis was carried out on a Perkin Elmer 2400, analyser series 2 in house at the University of Strathclyde. Mass spectra were obtained on a Jeol JMS AX505 using fast atom bombardment or electrospray ionisation.

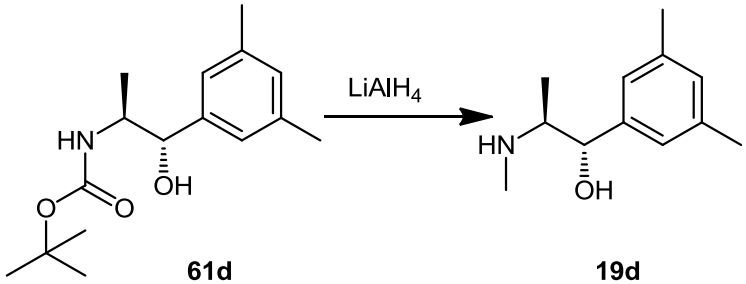
Melting points were recorded on a Reichert hot stage microscope, and are uncorrected. Chromatography was carried out using 200-400 mesh silica gels following standard procedure.[46]

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

Chiral HPLC analysis was conducted using an ACS 351 isocratic pump, Jasco UV-975 at 254 nm and Jasco OR-2090plus chiral detector with a Daicel Chiralcel OD (4.6 × 250 mm) column and guard column (4.6 × 50 mm). Data were processed using Azur software.

X-ray analysis were conducted by the UK synchrotron services.

Anhydrous solvents were obtained using a Puresolv purification system, from Innovative Technologies, or purchased as such from Aldrich and used as provided. Ethanol was dried over All other reagents were used as provided from Sigma-Aldrich



61d **19d**

(1*S*,2*S*)-1-(3,5-Dimethylphenyl)-2-(methylamino)-1-propanol (19d):

To a stirred suspension of $LiAlH_4$ (48 mg, 1.25 mmol, 3 eq) in anhydrous THF (5 ml) at 0 °C under an inert atmosphere was added, dropwise, a solution of *tert*-butyl (1*S*,2*S*)-2-(3,5-dimethylphenyl)-2-hydroxy-1-methylethylcarbamate (**61d**) (100 mg, 0.36 mmol) in anhydrous THF (5 ml). The resulting suspension was refluxed for 10 hours. The reaction mixture was then cooled to 0 °C and water (200 µl, 10 mmol) was added followed by 1.2 N aqueous HCl (1.1 ml, 1.32 mmol). The organic layer was decanted from the solids. The solids were washed with DCM (3 × 15 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by chromatography using MeOH (15%)/DCM (85%) gave 25 mg (38%) of light brown hygroscopic gum.

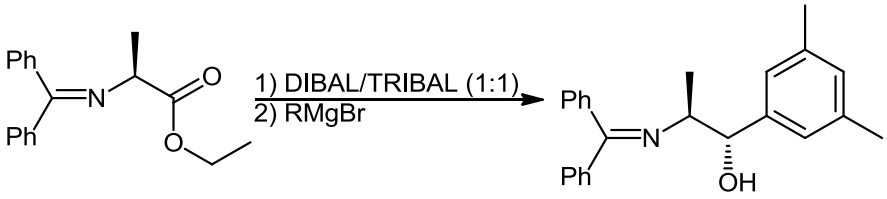
HRMS: M+H = 194.1539, calculated data for $C_{12}H_{19}NO^+$ M+H = 194.1539;

^{1}H NMR δ (400 MHz, $CDCl_3$) : 6.98 (s, 2H), 6.92 (s,1H), 4.72 (d, 1H, *J* = 10 Hz), 3.30-3.40 (m, 1H), 2.77 (s, 3H), 2.26 (s, 6H), 1.13 (d, 3H, *J* = 7 Hz);

^{13}C NMR δ (100 MHz, $CDCl_3$) : 139.8, 138.3, 130.2, 124.9, 74.8, 61.1, 30.5, 21.2, 12.4;

FTIR (CH_2Cl_2, cm^{-1}): 3320 (s, N-H), 1472-1586 (s, C=C), 1116 (s, C-OH);

$[\alpha]_D$ = 37.7 ° (c = 0.497, $CHCl_3$);



52
R = dimethylphenyl

33d

(1*S*,2*S*)-1-(3,5-Dimethylphenyl)-2-[(diphenylmethylene)amino]-1-propanol (33d)

Ethyl (2*S*)-2-[(diphenylmethylene)amino]propanoate (**50**) (2.84 g, 10.1 mmol) was dissolved in dry DCM (100 ml) in a flame dried flask under inert atmosphere. The solution was cooled to -78 °C and a solution of DIBAL/TRIBAL (1:1) (20.2 ml, 0.5 M in hexanes, 10.1 mmol) was added dropwise using a syringe pump. The mixture was stirred for 1 h at -78 °C before addition of 3,5-dimethylphenylmagnesium bromide in ether (0.2 M, 152 ml, 30.3 mmol, 3 equivalent, the Grignard reagent was prepared as follows: 1-bromo-3,5-dimethylbenzene (25 g, 0.13 mol, 1 eq) were added dropwise upon a stirred suspension of anhydrous magnesium powder (1.62 g, 0.13 mol, 1 eq) in anhydrous diethyl ether (200 ml) under inert atmosphere. One crystal of iodine was necessary to initiate the reaction and the mixture was gently refluxed for 2 hours. Conversion was confirmed by NMR analysis of an aliquot quenched with water by comparing the integral of the m-xylene peaks to starting bromide and biphenyl by-product. The crude reaction was transferred via cannula into a flame dried conical flask and the concentration was adjusted by adding enough anhydrous solvent to reach 500 ml, NMR showed 20% of biphenyl impurities) was added. The reaction was then stirred at room temperature for 6 h. The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (150 ml) and the product was extracted from the aqueous layer with DCM (3 × 50 ml). The combined organic layers were dried over K_2CO_3, filtered through celite and evaporated under vacuum which gave a crude oil. The crude material was purified by chromatography (EtOAc

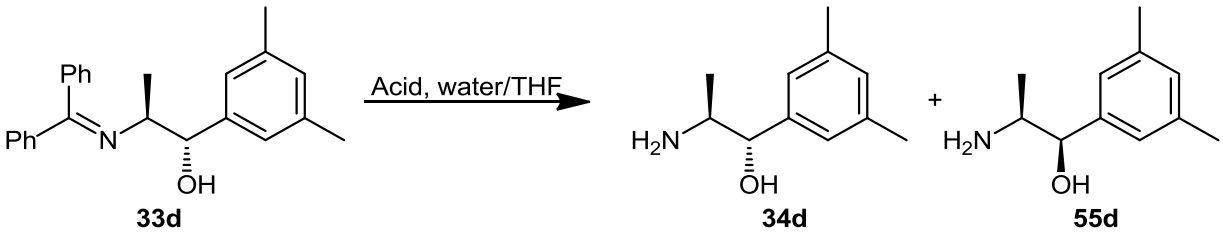
(5%)/DCM (5%)/hexane (90%)) to afford 1.78 g (52%) of yellow oil containing both diastereoisomers in a ratio of 6.7:1 in favour of the *threo* compound **33d** as judged by ^{1}H nmr. Further purification on a 100 mg by chromatography using ether (7%)/DCM (7%)/hexane (84%) increased the ratio up to 67:1.

HRMS: M+H = 344.2006, calculated data for $C_{24}H_{25}NO^{+}$ M+H = 344.2009;

^{1}H NMR δ (100 MHz, $CDCl_3$) : 7.24-7.85 (m, 10H), 6.90 (s, 1H), 6.77 (s, 2H), 4.38 (d, 1H, *J* = 8 Hz), 3.16 (dq, 1H, *J* = 8, 6 Hz), 2.24 (s, 6H), 1.23 (d, 3H, *J* = 6 Hz);

^{13}C NMR δ (400 MHz, $CDCl_3$) : 145.6, 139.8, 137.8, 132.4, 130.1, 129.4, 128.3, 128.1, 127.5, 127.2, 126.5, 125.6, 124.7, 124.3, 88.6, 62.8, 21.3, 15.9;

FTIR (neat, cm^{-1}): 3298, 3059, 3026, 2964, 2920, 2869, 1727, 1661, 1600, 1449, 1277, 702;



33d **34d** **55d**

(1*S*,2*S*)-2-Amino-1-(3,5-dimethylphenyl)-1-propanol (34d)

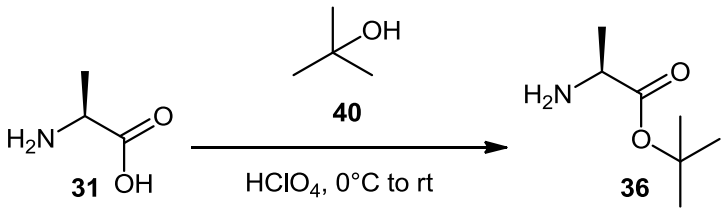
(1*S*,2*S*)-1-(3,5-Dimethylphenyl)-2-[(diphenylmethylene)amino]-1-propanol (**33d**) (500 mg, 1.46 mmol) was dissolved in THF (3 ml), acid (either 3% aq. HCl or 10% aq. citric acid, 3 eq) was added and the solution is stirred for 30 min at room temperature. The mixture was then extracted with DCM (3 × 15 ml) in order to remove the generated benzophenone. The aqueous layer was basified to pH 11 using NaOH pellets and the free base was extracted with DCM (3 × 20 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 104 mg (40%) of gum of a mixture of **34d** and **55d** in a 3:1 ratio in favour of **34d** when starting with 6.7:1 ratio in favour of **33d** or in a 10:1 ratio in favour of **34d** when starting with a 16:1 ratio in favour of **33d**.

HRMS: M+H = 180.1382, calculated for $C_{11}H_{17}NO^+$ M+H = 180.1383;

^{1}H NMR δ (400 MHz, $CDCl_3$) : 6.94 (s, 2H), 6.91 (s, 1H), 4.19 (d, 1H, *J* = 6 Hz), 3.05 (qd (appears as a pentat), 1H, *J* = 6, 6 Hz), 2.47 (br, 2H), 2.31 (s, 6H), 1.02 (d, 3H, *J* = 6 Hz);

^{13}C NMR δ (100 MHz, $CDCl_3$) : 142.6, 137.8, 129.2, 124.3, 78.6, 52.9, 21.3, 20.6;

FTIR on a 10:1 ratio mixture (KBr disc, cm^{-1}): 3353, 1607, 1456, 1379, 844;

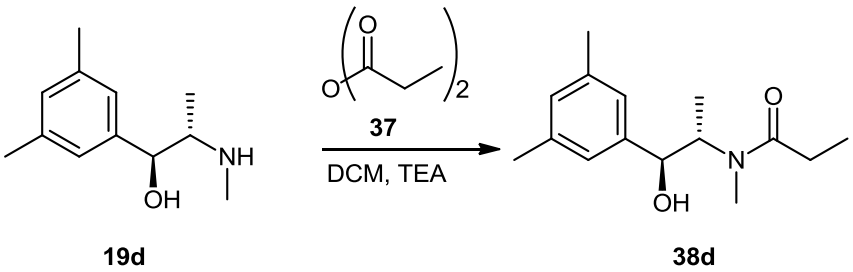


***tert*-Butyl (2*S*)-2-aminopropanoate (36)**[34]

L-Alanine (500 mg, 5.62 mmol) was suspended in *tert*-butanol (15 ml), aqueous perchloric acid (70%, 1.2 ml) was added. The mixture was sealed in a tube and stirred at room temperature overnight. It was then quenched with 10% aqueous Na_2CO_3 (100 ml) and the compound was extracted with EtOAc (3 x 20ml). The combined organic layer was dried over $MgSO_4$, filtered and evaporated on rotavap to afford oil (248 mg, 27%).

^{1}H NMR δ (400 MHz, $CDCl_3$): 3.77 (q, 1H, *J* = 7 Hz,), 1.41 (s, 9H), 1.36 (d, 3H, *J* = 7 Hz);

FTIR (neat, cm^{-1}): 3550-2930 (br. s), 1735 (m), 1150 (s), 1110 (s), 1100 (s);



19d 38d

***N*-[(1*S*,2*S*)-2-(3,5-Dimethylphenyl)-2-hydroxy-1-methylethyl]-*N*-methylpropanamide (38d)**

(1*S*,2*S*)-1-(3,5-Dimethylphenyl)-2-(methylamino)-1-propanol (**19d**) (100 mg, 0.52 mmol) and anhydrous triethylamine (95 µl, 0.68 mmol) were dissolved in dry DCM (20 ml) under an inert atmosphere. Propionic anhydride (75 µl, 0.57 mmol) was added and the mixture was stirred at room temperature for 2 h. Water (20 ml) was then added and the layers were separated. The organic layer was extracted with 5% aqueous $NaHCO_3$ (20 ml) and then with 1.2 N HCl (2 × 20 ml). The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by chromatography (first EtOAc (30%)/hexane (70%) to remove the remaining anhydride, then 100% EtOAc) gave 65 mg (50%) of very visquous oil.

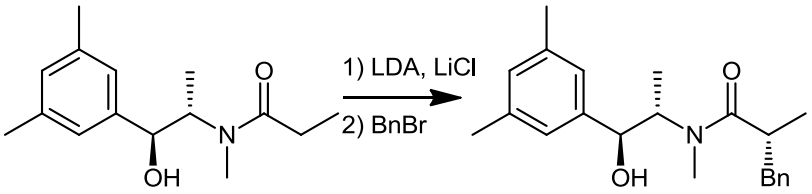
HRMS: M+H = 250.1800, calculated for $C_{15}H_{23}NO_2^+$ M+H = 250.1802;

^{1}H NMR δ (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, $CDCl_3$) : 6.96 (s, 2H), 6.91 (s, 1H), 4.52-4.60 (m, 1H), 4.47 (d, 1H, *J* = 8 Hz), 3.98-4.02* (m, 1H), 2.91* (s, 3H), 2.85 (s, 3H), 2.32-2.40 (m, 2H), 2.34* (s, 6H), 2.33 (s, 6H), 1.11-1.22 (m, 3H), 1.05 (s, 3H), 0.97* (d, 3H, *J* = 7 Hz);

^{13}C NMR δ (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 100 MHz, $CDCl_3$) : 175.8, 174.8*, 141.7, 140.6*, 137.7*, 137.4, 129.4*, 128.9, 124.3*, 123.9, 76.0, 74.9*, 57.8, 57.1*, 31.8*, 27.0, 26,9*, 26.7, 20.8, 14.8*, 14.0, 9.1*, 8.7;

FTIR (neat, cm^{-1}): 3391 (br. s, -OH), 1622 (s, C=O), 1464, 1064;

$[\alpha]_D$ = 86.1 ° (c = 0.10, $CHCl_3$);



38d **39d**

(*R*)-N-((1*S*,2*S*)-1-(3,5-dimethylphenyl)-1-hydroxypropan-2-yl)-N,2-dimethyl-3-phenylpropanamide (39d)

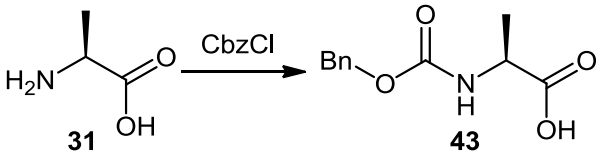
Lithium chloride (132 mg, 3.12 mmol, 6 eq) and diisopropylamine (0.4 ml, 2.8 mmol, 5.6 eq) were added to anhydrous tetrahydrofuran (20 ml) under inert atmosphere and the mixture was cooled to -78 °C. n-Butyllithium (2.0 M in hexane, 1 ml, 2 mmol, 4 eq) was added and the solution was briefly warmed to 0 °C. An ice cold solution of *N*-[(1*S*,2*S*)-2-(3,5-dimethylphenyl)-2-hydroxy-1-methylethyl]-*N*-methylpropanamide (**38d**), dried over K_2CO_3 along with azeotropic removal of water using anhydrous toluene under vacuum (ca 3 mm Hg), (130 mg, 0.52 mmol, 1 eq) in THF (3 ml) was added at -78 °C and the mixture was stirred at -78 °C for 1 h and then 2 h at 0 °C. Benzyl bromide (0.93 ml, 0.78 mmol, 1.5 eq) was then added and the reaction was stirred for 15 min. TLC showed a total conversion and the reaction was quenched with saturated aqueous ammonium chloride (30 ml). The mixture was then extracted with EtOAc (3 × 20 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated at rotavap to afford 274 mg of crude oil. Purification by flash chromatography using EtOAc (15%)/hexane to remove polar impurities and excess benzyl bromide followed by EtOAc (40%)/hexane yielded 64 mg of oil (34%).

^{1}H NMR δ (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, $CDCl_3$) : 7.17-7.33 (m, 5H), 6.98 (s, 2H), 6.93* (s, 2H), 6.88 (s, 1H), 4.54-4.63 (m, 1H), 4.45 (d, 1H, *J* = 9 Hz), 4.42* (d, 1H, *J* = 9 Hz), 3.99-4.09* (m, 1H), 3.66 (br. s, 1H), 3.10-3.19* (m, 2H), 2.92-3.06 (m, 2H), 2.89* (s, 3H), 2.73 (s, 3H), 2.62-2.74 (m, 1H), 2.35* (s, 6H), 2.32 (s, 6H), 1.20 (d, 3H, J = 6Hz), 1.12* (d, 3H, *J* = 6 Hz), 1.02* (d, 3H, *J* = 7 Hz), 0.88 (d, 3H, *J* = 7 Hz);

^{13}C NMR δ (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 100 MHz, $CDCl_3$) : 177.8, 176.7*, 141.7, 140.6*, 140.1*, 139.5, 137.7*, 137.1. 129.5*, 128.9, 128.7*, 128.5, 127.9*, 127.8, 125.8, 124.2*, 124.0, 123.6*, 76.0, 75.0*, 57.5, 56.5*, 40.0, 39.9*, 38.4, 37.6*, 30.9*, 26.7, 20.8, 17.2*, 17.0, 15.1*, 13.9;

FTIR (neat, cm^{-1}): 3391 (br. s, -OH), 1635 (s, C=O), 1453, 1081;

$[\alpha]_D$ = 2.6 ° (c = 0.363, $CHCl_3$);



(2*S*)-2-{[(Benzyloxy)carbonyl]amino}propanoic acid (43)[39]

L-Alanine (0.5 g, 5.62 mmol, 1 eq) was suspended in EtOAc (50 ml). The mixture was stirred and heated at reflux for 30 min to fully saturate the solvent with the amino acid. The refluxing suspension was then treated with benzyl chloroformate (802 µl, 5.62 mmol, 1 eq) and was allowed to continue refluxing overnight. After cooling the reaction mixture to room temperature, the solid amino acid hydrochloride was removed by filtration and the filtrate was concentrated at reduced pressure (10-20 mbar). Purification of the resulting solid by crystallization from Et_2O/hexane led to 493 mg (39%) of a white solid.

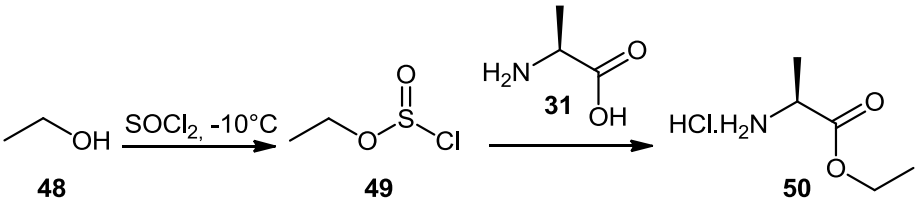
m.p = 88-91 °C (lit. m.p =90-91 °C[47]);

HRMS: M-H = 222.0773; calculated for $C_{11}H_{13}NO_4^-$ M-H = 222.0772;

^{1}H NMR δ (400 MHz, $CDCl_3$) : 7.32-7.41 (m, 5H), 5.30 (q, 1H, *J* = 7 Hz, 1H), 5.14 (s, 2H), 4.41-4.49 (m, 1H), 1.48 (d, 3H, *J* = 7 Hz, 3H);

^{13}C NMR δ (100 MHz, $CDCl_3$): 177.7, 155.8, 136.1, 128.5, 128.3, 128.1, 67.2, 49.4, 18.4;

FTIR (KBr, cm^{-1}): 3335 (s, N-H), 1696 (br. s, C=O), 1537 (s, aromatic C=C);



Ethyl (2*S*)-2-aminopropanoate hydrochloride (50)[40]

Freshly distilled thionyl chloride (12.5 ml, 172 mmol, 3.4 eq) was added dropwise to stirred and cooled (-10 °C) dried ethanol (50 ml), followed by the addition of L-alanine (4.46 g, 50 mmol, 1 eq). The mixture was allowed to warm to room temperature and then gently heated at 40 °C for 4 h. The solvent was then removed *in vacuo* and the resulting solid was crystallized using methanol (0.5 ml) and Et_2O to afford a white solid (7.2 g, 94%).

m.p = 76 °C; (lit. mp = 76 °C)[40]

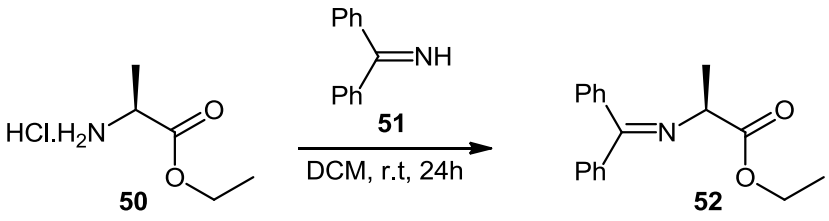
HRMS: M+H = 118.0862, calculated $C_5H_{11}NO_2^+$ M+H = 118.0863;

^{1}H NMR δ (400 MHz, DMSO): 8.61 (s, 3H), 4.18 (q, 2H, *J* = 7 Hz), 4.01 (q, 1H, *J* = 7 Hz), 1.40 (d, 3H, *J* = 7 Hz), 1.22 (t, 3H, *J* = 7 Hz);

^{13}C NMR δ (100 MHz, DMSO): 169.9, 61.7, 47.7, 15.7, 13.9;

FTIR (KBr disc, cm^{-1}): 3429 (s, N-H), 1743 (s, C=O), 1210-1237 (s, C-O).

$[\alpha]_D$ = +3.00 ° (c = 2.5, H_2O) (lit. $[\alpha]_D$ = +3.1 ° (c = 2.5, H_20);[48]



Ethyl (2*S*)-2-[(diphenylmethylene)amino]propanoate (52)[42]

Ethyl (2*S*)-2-aminopropanoate hydrochloride (**50**) (3.0 g, 19.5 mmol) was dissolved in DCM (20 ml) under an inert atmosphere. Benzophenone ketimine (3.56 g, 19.6 mmol) was then added and the mixture was stirred overnight. The resulting ammonium chloride salt was filtered and the crude solid product was dissolved in ether (20 ml) and filtered. The filtrate was washed with water (20 ml) and the organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to afford orange oil. Trituration with cold hexane gave the product as a white powder (3.64 g, 67%).

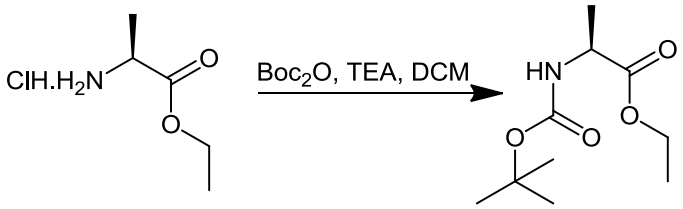
m.p = 51–53 °C (lit. m.p: 52–53 °C)[28];

HRMS: M+H = 282.1487, calculated for $C_{18}H_{19}NO_2^+$ M+H = 182.1489;

^{1}H NMR δ (400 MHz, $CDCl_3$) : 7.19-7.48 (m, 10H), 4.15-4-26 (m, 3H, -CH_2- and H_α), 1.43 (d, 3H, *J* = 7 Hz), 1.27 (t, 3H, *J* = 7 Hz);

^{13}C NMR δ (100 MHz, $CDCl_3$): 173.0, 169.7, 139.8, 136.5, 130.3, 128.8, 128.6, 128.5, 128.0, 127.7, 60.9, 60.7, 19.2, 14.2;

$[\alpha]_D$ = -95.4 ° (c = 2, $CHCl_3$) (lit. $[\alpha]_D$ = -90 ° (c = 2, $CHCl_3$)[28]);



50 **60**

Ethyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]propanoate (60)

Ethyl (2*S*)-2-aminopropanoate hydrochloride (50) (10g, 65.4 mmol) was dissolved in dry DCM (100 ml) and anhydrous triethylamine (18.2 ml, 130.8 mmol, 2 eq) was added. The mixture was stirred for 10 min at room temperature until all the triethylamine hydrochloride salt had precipitated. Then another 2 equivalent of anhydrous triethylamine (18.2 ml, 130.8 mmol) were added followed by the *tert*-butyloxycarbonyl anhydride (28.34 g, 130.8 mmol, 2

eq). The reaction was stirred at room temperature overnight. It was then quenched with saturated aqueous solution of $NaHCO_3$ (150 ml) and then extracted with DCM (3 × 50 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by chromatography (EtOAc (30%)/hexane (70%)) gave 13.56 g (96%) of orange oil.

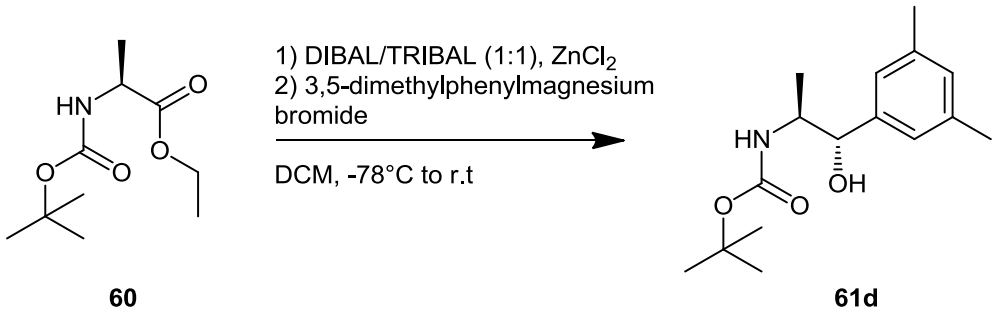
HRMS: M+H = 218.1387, calculated for $C_{10}H_{20}NO_4^+$ M+H = 218.1387;

^{1}H NMR δ (400 MHz, $CDCl_3$) : 5.10 (br. s, 1H), 4.25-4.35 (m, 1H), 4.20 (q, 2H, *J* = 7 Hz), 1.46 (s, 9H), 1.40 (d, 3H, *J* = 7 Hz), 1.29 (t, 3H, *J* = 7 Hz);

^{13}C NMR δ (100 MHz, $CDCl_3$) : 186.0, 181.6, 173.3, 171.8, 155.1, 79.5, 61.3, 49.2, 28.2, 18.4, 14.2;

FTIR (neat, cm^{-1}): 3367, 2981, 2936, 1717 (br. s, 2 × C=O), 1517, 1166;

$[\alpha]_D$ = -44.4 ° (c = 1, MeOH) (lit. $[\alpha]_D$ = -42 ° (c = 1, MeOH)[49]);



60 **61d**

***tert*-Butyl (1*S*,2*S*)-2-(3,5-dimethylphenyl)-2-hydroxy-1-methylethylcarbamate (61d):**

Ethyl (2*S*)-2-[(tert-butoxycarbonyl)amino]propanoate (**60**) (1 g, 4.61 mmol) was dissolved in dry DCM (50 ml) in a flame dried 3-necked flask under an inert atmosphere and the solution was cooled to -78 °C. A solution of DIBAL/TRIBAL (1:1) (0.5 M in hexane, 9.22 ml) was added dropwise using a syringe pump. Zinc chloride (0.46 ml, 1.0 M in hexane, 0.1 eq) was added and the mixture was stirred for 20 h at -78 °C. Thereupon, a solution of 3,5-dimethylphenylmagnesium bromide in ether (69 ml, 0.2 M, 13.83 mmol, 3 eq) was then added in one portion and the reaction was allowed to stir at room temperature for 3 h. The reaction

was then quenched using saturated aqueous $NaHCO_3$ (50 ml) and then with DCM (3 × 20 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by chromatography (EtOAc (25%)/hexane (75%) and 1% Et_3N) gave 470 mg (37%) of a very thick oil.

HRMS: M+H = 280.1906, calculated for $C_{16}H_{25}NO_3$ M+H = 280.1907;

^{1}H NMR δ (400 MHz, $CDCl_3$) : 6.97 (s, 2H), 6.94 (s, 1H), 4.68 (br. s, 1H), 4.46 (d, 1H, *J* = 7 Hz), 3.82-3.92 (m, 1H), 2.32 (s, 6H), 1.43 (br. s, 9H), 1.03 (d, 3H, *J* = 7 Hz);

^{13}C NMR δ (100 MHz, $CDCl_3$) : 156.8, 141.7, 137.8, 129.5, 124.5, 79.7, 52.5, 45.9, 28.4, 21.3, 17.7;

FTIR (neat, cm^{-1}): 3401 (br. s, OH), 1694 (m, C=O), 1455-1505 (m, C=C aromatic);

Appendix A: X-ray data of compound 19d

Table 1. Crystal data and structure refinement for gibsonsrs1.

Identification code	gibsonsrs1	
Empirical formula	$C_{12}H_{20}ClNO$	
Formula weight	229.74	
Temperature	120(2) K	
Wavelength	0.68890 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.243(5) Å	α= 90°.
	b = 7.989(5) Å	β= 90°.
	c = 21.898(14) Å	γ = 90°.
Volume	1267.0(14) $Å^3$	
Z	4	
Density (calculated)	1.204 Mg/m^3	
Absorption coefficient	0.278 mm^{-1}	
F(000)	496	
Crystal size	0.04 × 0.04 × 0.01 mm^3	
Theta range for data collection	2.87 to 26.85°.	
Index ranges	-9<=h<=9, -10<=k<=10, -28<=l<=28	
Reflections collected	12603	
Independent reflections	2965 [R(int) = 0.1073]	
Completeness to theta = 26.85°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.446	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2965 / 3 / 150	
Goodness-of-fit on F^2	1.079	
Final R indices [I>2sigma(I)]	R1 = 0.0563, wR2 = 0.1303	
R indices (all data)	R1 = 0.0719, wR2 = 0.1441	
Absolute structure parameter	0.07(9)	
Largest diff. peak and hole	0.445 and -0.357 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$)
for gibsonsrs1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	5585(1)	603(1)	4904(1)	44(1)
O(1)	7984(3)	4297(3)	3980(1)	48(1)
N(1)	4660(3)	4410(3)	4627(1)	43(1)
C(1)	3588(4)	6784(4)	3998(1)	48(1)
C(2)	4932(4)	5343(3)	4032(1)	40(1)
C(3)	6956(4)	5828(3)	3968(1)	40(1)
C(4)	7279(4)	6786(3)	3379(1)	37(1)
C(5)	7558(3)	5952(3)	2833(1)	39(1)
C(6)	7775(4)	6831(3)	2288(1)	40(1)
C(7)	7755(4)	8575(3)	2305(1)	40(1)
C(8)	7441(3)	9440(3)	2849(1)	39(1)
C(9)	7205(4)	8527(3)	3380(1)	40(1)
C(10)	5336(4)	5236(4)	5187(1)	51(1)
C(11)	8025(5)	5940(4)	1691(1)	53(1)
C(12)	7330(5)	11322(3)	2849(2)	50(1)

Table 3. Bond lengths [Å] and angles [°] for gibsonsrs1.

O(1)-C(3)	1.432(3)
O(1)-H(1H)	0.845(18)
N(1)-C(10)	1.476(4)
N(1)-C(2)	1.513(3)
N(1)-H(1N)	0.907(18)
N(1)-H(2N)	0.925(18)
C(1)-C(2)	1.510(4)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(3)	1.522(4)
C(2)-H(2)	1.0000
C(3)-C(4)	1.518(4)
C(3)-H(3)	1.0000
C(4)-C(5)	1.385(4)
C(4)-C(9)	1.391(4)
C(5)-C(6)	1.393(4)
C(5)-H(5)	0.9500
C(6)-C(7)	1.394(4)
C(6)-C(11)	1.498(4)
C(7)-C(8)	1.395(4)
C(7)-H(7)	0.9500
C(8)-C(9)	1.383(4)
C(8)-C(12)	1.505(4)
C(9)-H(9)	0.9500
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800

C(3)-O(1)-H(1H)	101(2)

C(10)-N(1)-C(2)	116.9(2)
C(10)-N(1)-H(1N)	111.7(19)
C(2)-N(1)-H(1N)	105.7(19)
C(10)-N(1)-H(2N)	103(2)
C(2)-N(1)-H(2N)	115.7(19)
H(1N)-N(1)-H(2N)	104(3)
C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
C(1)-C(2)-N(1)	109.6(2)
C(1)-C(2)-C(3)	115.0(2)
N(1)-C(2)-C(3)	109.3(2)
C(1)-C(2)-H(2)	107.6
N(1)-C(2)-H(2)	107.6
C(3)-C(2)-H(2)	107.6
O(1)-C(3)-C(4)	111.5(2)
O(1)-C(3)-C(2)	106.4(2)
C(4)-C(3)-C(2)	110.8(2)
O(1)-C(3)-H(3)	109.4
C(4)-C(3)-H(3)	109.4
C(2)-C(3)-H(3)	109.4
C(5)-C(4)-C(9)	119.2(3)
C(5)-C(4)-C(3)	120.9(2)
C(9)-C(4)-C(3)	119.8(2)
C(4)-C(5)-C(6)	120.9(2)
C(4)-C(5)-H(5)	119.5
C(6)-C(5)-H(5)	119.5
C(5)-C(6)-C(7)	118.6(3)
C(5)-C(6)-C(11)	121.3(3)
C(7)-C(6)-C(11)	120.0(3)
C(6)-C(7)-C(8)	121.3(3)
C(6)-C(7)-H(7)	119.3
C(8)-C(7)-H(7)	119.3
C(9)-C(8)-C(7)	118.4(2)
C(9)-C(8)-C(12)	121.4(3)

C(7)-C(8)-C(12)	120.2(3)
C(8)-C(9)-C(4)	121.4(2)
C(8)-C(9)-H(9)	119.3
C(4)-C(9)-H(9)	119.3
N(1)-C(10)-H(10A)	109.5
N(1)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
N(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(6)-C(11)-H(11A)	109.5
C(6)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(6)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(8)-C(12)-H(12A)	109.5
C(8)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(8)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$)for gibsonsrs1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	35(1)	49(1)	48(1)	4(1)	4(1)	1(1)
O(1)	47(1)	46(1)	50(1)	-1(1)	-10(1)	9(1)
N(1)	37(1)	48(1)	43(1)	5(1)	0(1)	2(1)
C(1)	40(2)	43(1)	60(2)	5(1)	1(1)	4(1)
C(2)	44(2)	40(1)	38(1)	2(1)	0(1)	2(1)
C(3)	40(1)	36(1)	43(1)	-2(1)	-6(1)	3(1)
C(4)	36(1)	33(1)	42(1)	-4(1)	-2(1)	-2(1)
C(5)	39(2)	34(1)	44(2)	-5(1)	-2(1)	2(1)
C(6)	37(2)	40(1)	43(2)	-4(1)	-2(1)	0(1)
C(7)	33(2)	40(1)	47(2)	1(1)	-4(1)	-2(1)
C(8)	31(1)	32(1)	53(2)	-3(1)	-4(1)	-3(1)
C(9)	39(2)	35(1)	45(2)	-8(1)	1(1)	-1(1)
C(10)	39(2)	78(2)	36(1)	-1(1)	-5(1)	1(2)
C(11)	60(2)	57(2)	43(2)	-10(1)	4(2)	0(2)
C(12)	51(2)	33(1)	66(2)	-1(1)	-3(2)	1(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for gibsonsrs1.

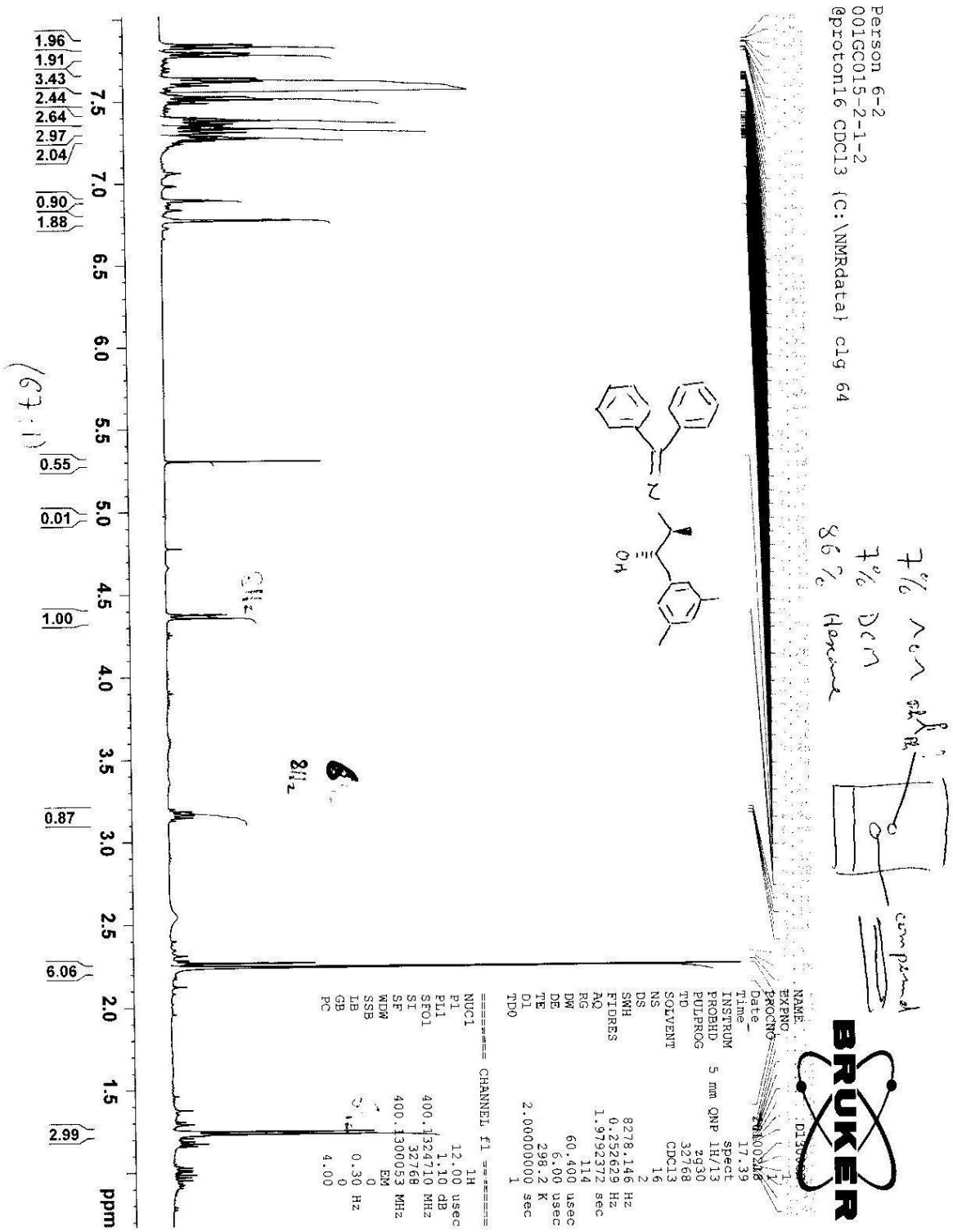
	x	y	z	U(eq)
H(1H)	8800(40)	4530(40)	4241(12)	57
H(1N)	5190(40)	3390(30)	4571(13)	51
H(2N)	3450(30)	4150(40)	4725(14)	51
H(1A)	3572	7233	3581	71
H(1B)	3969	7664	4282	71
H(1C)	2350	6390	4106	71
H(2)	4630	4554	3692	48
H(3)	7327	6540	4323	48
H(5)	7602	4764	2829	47
H(7)	7960	9188	1940	48
H(9)	6988	9100	3753	48
H(10A)	5038	6432	5171	77
H(10B)	6677	5093	5218	77
H(10C)	4741	4730	5544	77
H(11A)	6814	5630	1527	80
H(11B)	8765	4928	1755	80
H(11C)	8658	6679	1402	80
H(12A)	7526	11741	3264	75
H(12B)	6109	11672	2704	75
H(12C)	8282	11777	2577	75

Table 6. Torsion angles [°] for gibsonsrs1.

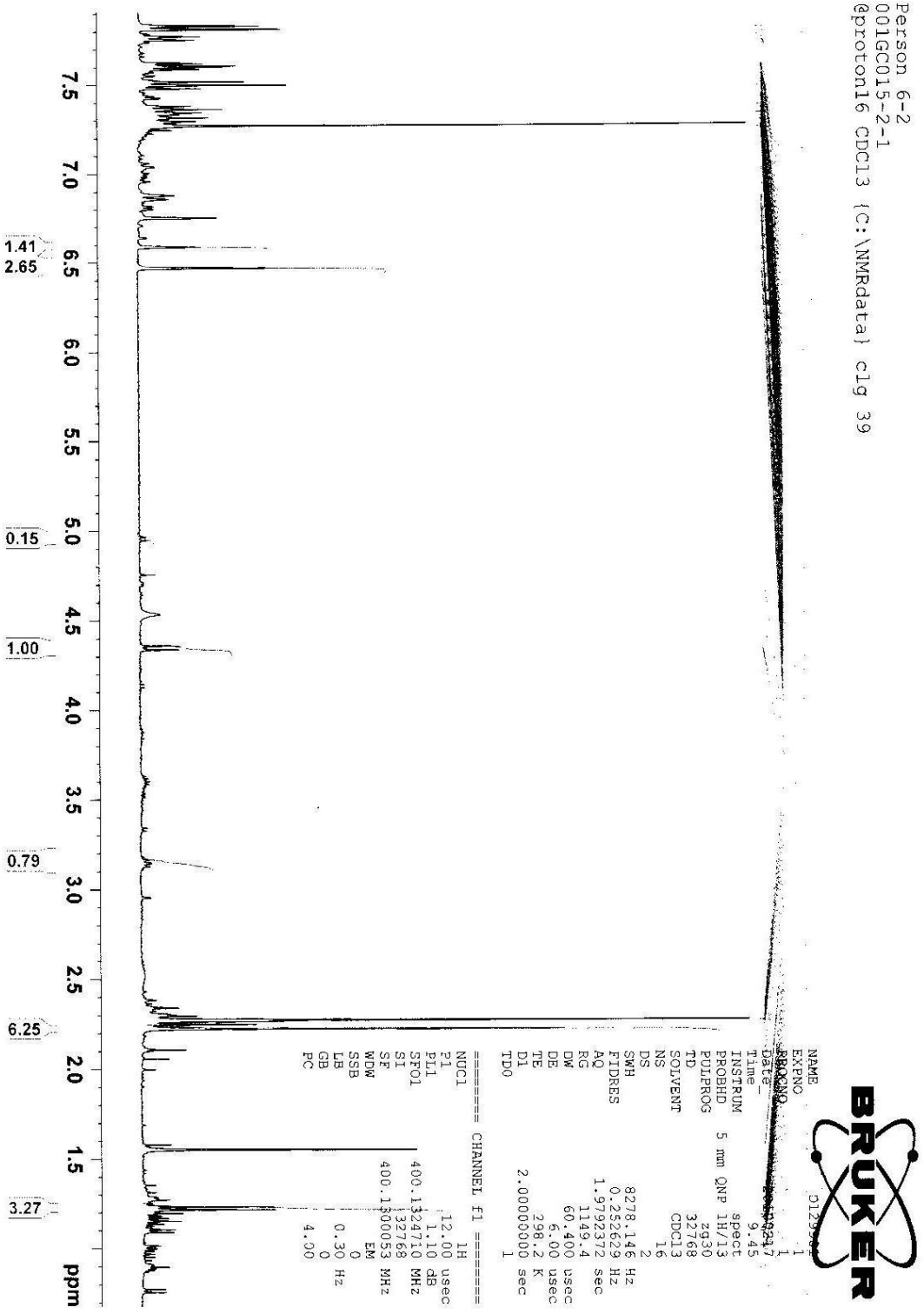
C(10)-N(1)-C(2)-C(1)	-73.7(3)
C(10)-N(1)-C(2)-C(3)	53.1(3)
C(1)-C(2)-C(3)-O(1)	-176.9(2)
N(1)-C(2)-C(3)-O(1)	59.4(3)
C(1)-C(2)-C(3)-C(4)	-55.6(3)
N(1)-C(2)-C(3)-C(4)	-179.3(2)
O(1)-C(3)-C(4)-C(5)	34.3(3)
C(2)-C(3)-C(4)-C(5)	-83.9(3)
O(1)-C(3)-C(4)-C(9)	-148.9(2)
C(2)-C(3)-C(4)-C(9)	92.9(3)
C(9)-C(4)-C(5)-C(6)	0.4(4)
C(3)-C(4)-C(5)-C(6)	177.2(3)
C(4)-C(5)-C(6)-C(7)	1.7(4)
C(4)-C(5)-C(6)-C(11)	-178.3(3)
C(5)-C(6)-C(7)-C(8)	-2.9(4)
C(11)-C(6)-C(7)-C(8)	177.0(3)
C(6)-C(7)-C(8)-C(9)	2.1(4)
C(6)-C(7)-C(8)-C(12)	-176.9(3)
C(7)-C(8)-C(9)-C(4)	0.1(4)
C(12)-C(8)-C(9)-C(4)	179.0(3)
C(5)-C(4)-C(9)-C(8)	-1.3(4)
C(3)-C(4)-C(9)-C(8)	-178.2(2)

Symmetry transformations used to generate equivalent atoms:

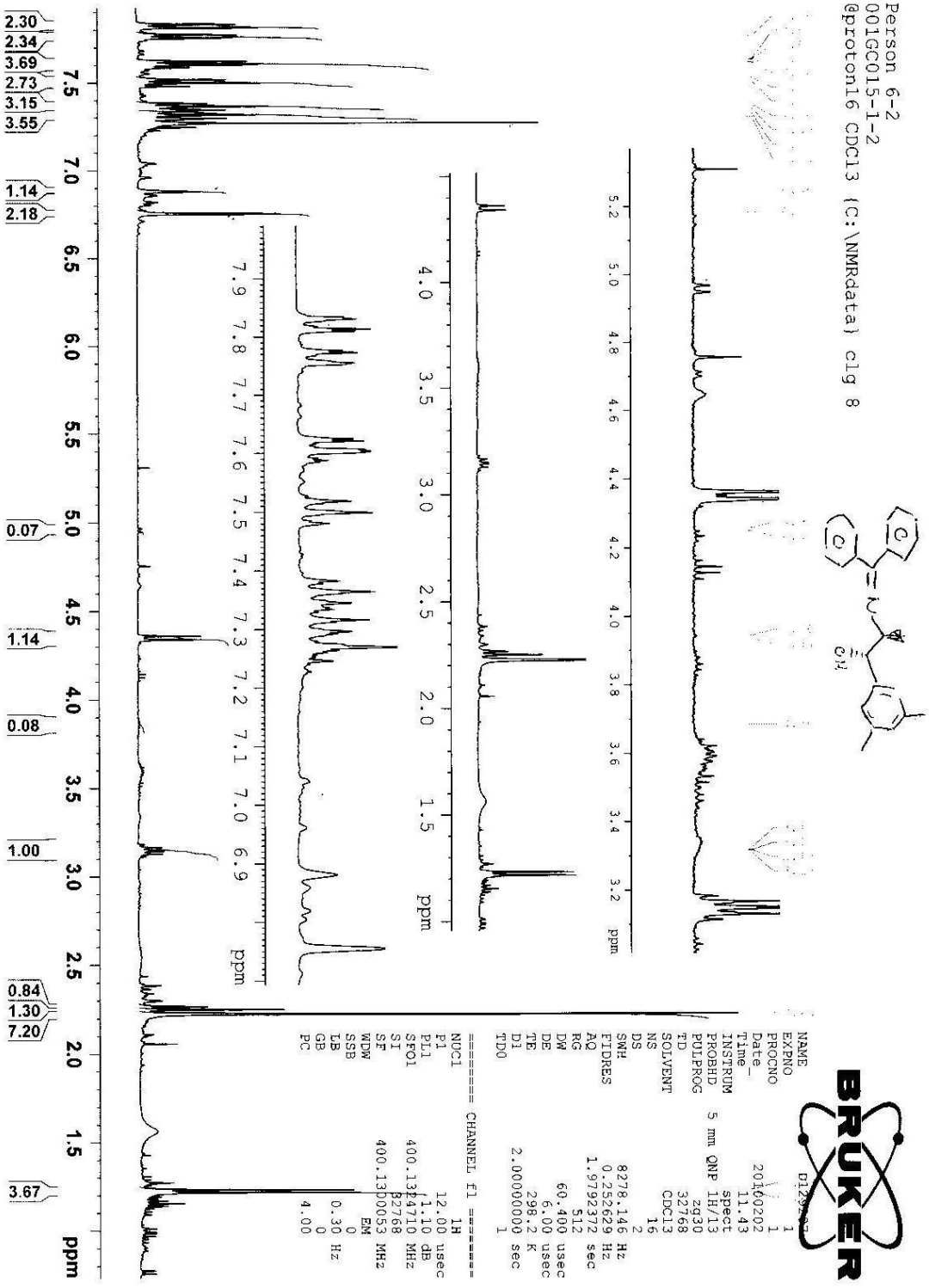
Appendix B: NMR Spectra of compound 33d



^{1}H NMR Spectra of compound 33d with a 67:1 ratio between diastereoisomers

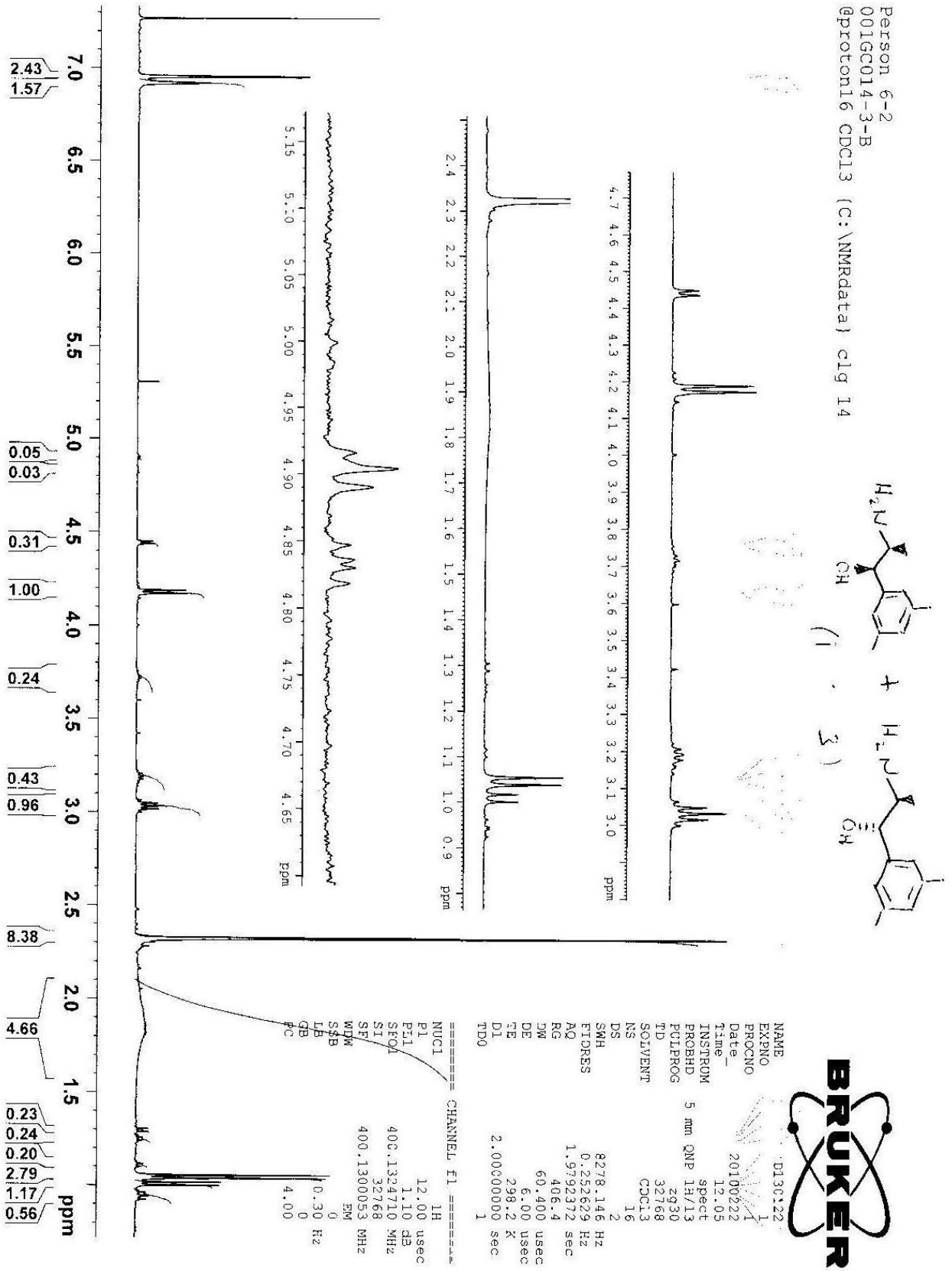


^{1}H NMR Spectra of compound 33d with a ratio of 6.7:1 between diastereoisomers

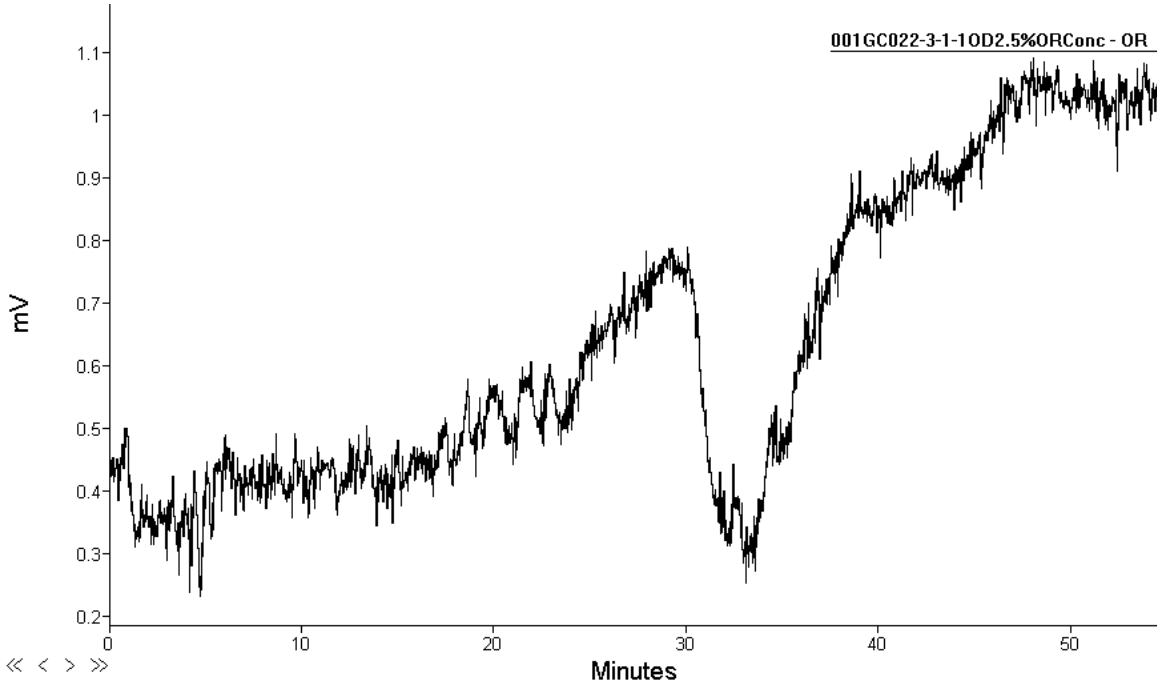


^{1}H NMR Spectra of compound 33d with a 16:1 ratio between diastereoisomers

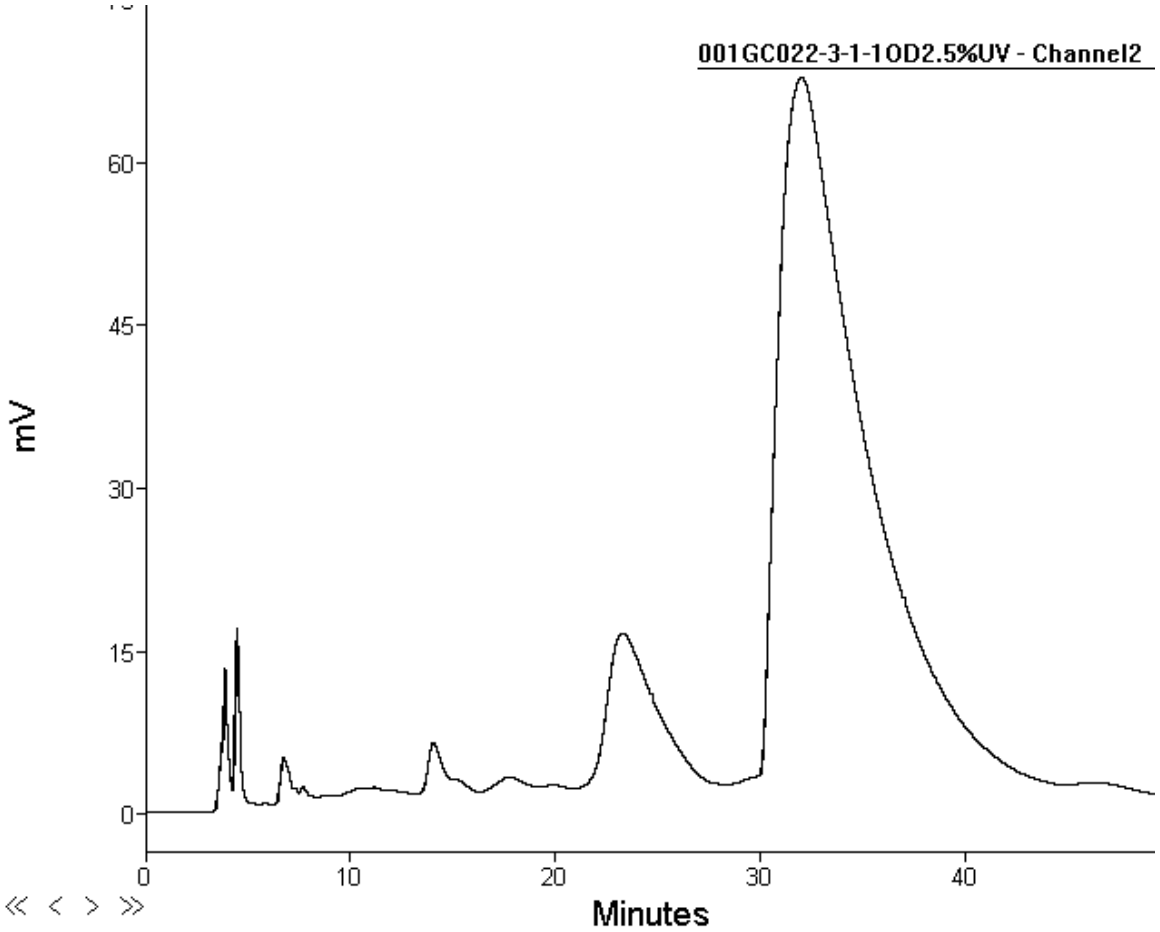
Appendix C: 1H NMR Spectra of 3:1 ratio between compounds 34d and 55d



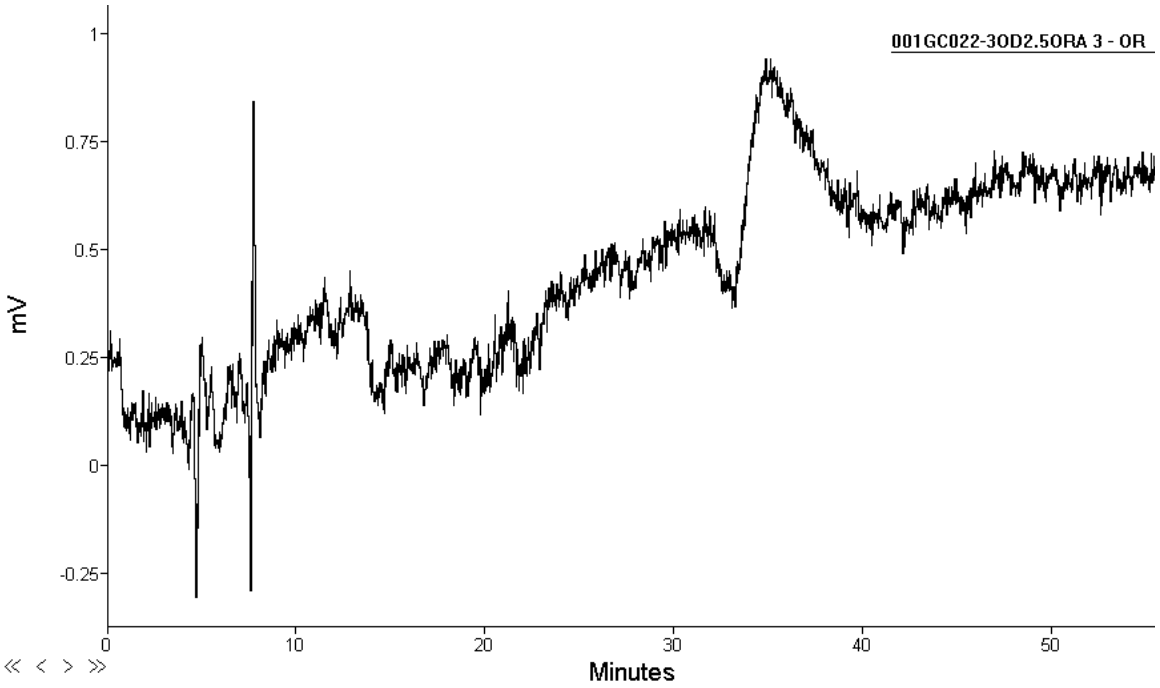
Appendix D: NMR Spectra and Chiral HPLC Chromatogram of compound 39d



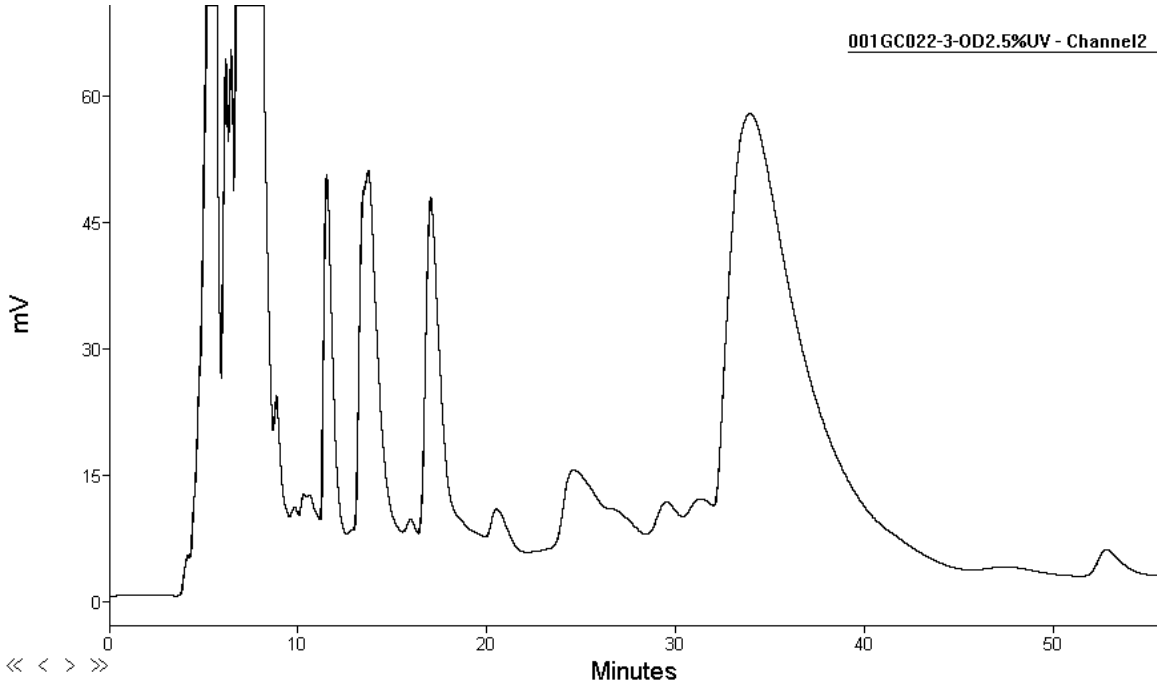
Chiral chromatogram of purified compound 39d



UV Chromatogram of purified compound 39d

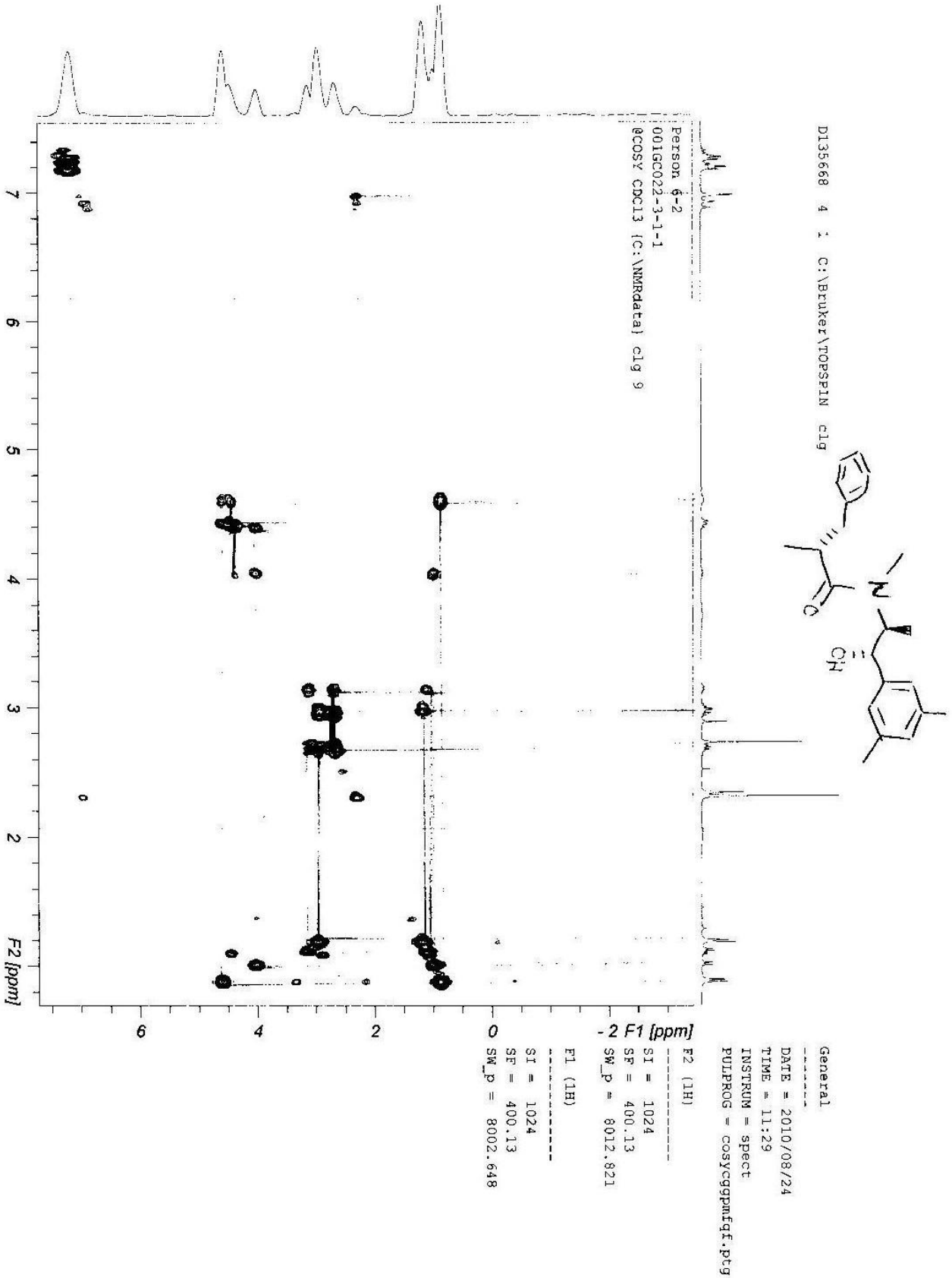


Chiral chromatogram of crude compound 39d



UV Chromatogram of crude compound 39d

^{1}H NMR Spectra of purified compound 33d



COSY Spectra of purified compound 39d

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