Boron-BINOL catalysed asymmetric Mannich and aldol type reaction: Novel boronate esters

Yeste, Sonia Lozano

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Sonia Lozano Yeste

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I would like to thanks to the past and the present members of SDB and TDJ groups. A truly appreciation to my current lab mates; Phil, Iwan and Gan for being there in bad and good moments, for having that much fun altogether and for their natural personality. Thanks to Dr. Matt Cheesman for all the chemistry knowledge he transfers to me and Dr. Piers Taylor for providing me some laboratory useful tools. Thanks to my friend Haniti who I am sure I will name, remember and miss a lot. I can not name everybody, but thanks to Ewan for all those big laughs together and evenings out, I liked them! Though more recently, still important, thanks to Carsten for having those interesting perspectives, Matthi for her help and humour, and in the very last moment Damien for help with word, etc.

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and I will keep remembering you all the time. All of you "Spanish people" have replaced my family who is miles away... thank you very much!

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Finally, I thank Roger for his support, help and belief in me since the very beginning. Thanks for all those happy moments together and fun conversations. I have experienced that "absence makes the heart grow fonder". I am very glad I met you one random day and extremely happy because we both have overcome this absence.

LIST OF ABBREVIATIONS

(DHQD)PYR	hydroquinidine2,5-diphenyl-4,6-pyrimidinedicyl diether
$(DHQH)_2$-PHAL	hydroquinidine 1,4-phthalazinediyl diether
(*R*)-BINOL	*R* (+)-1, 1´-Bi (2-naphthol)
(*S*)-BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl mono-oxide
[enim]OTf	ethylmethylimidazolium triflate
$[\alpha]_D$	specific rotation
9-AMA	(*R*)- 9-anthranylmethoxyacetic acid
Å	angstrom
AC	absolute configuration
Ac	acetyl
aq.	aqueous
Ar	aryl
$B(MeO)_3$	trimethyl borate
BH_3DMS	borane dimethyl sulphide
BLA	brönsted Lewis acid
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bis-oxazoline
br s	broad singlet
BTF	benzotrifluoride
BTF	trifluorotoluene
Bu	Butyl
CAN	cerium amonium nitrate
cat	catalytic quantity
CBS	reducting agent, oxaborolidine
CBz	carbobenzyloxy
CD	cicular dichroism

CDAs	chiral derivatising agents
$CDCl_3$	chloroform-d
CI	chemical ionization
CLSRs	chiral lanthanide shift reagents
cm	centimetre
COD	1,5-cyclooctadiene
Conv.	conversion
COSY	correlation spectroscopy
CSAs	chiral solvating agents
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublets of doublets
de	diastereomeric excess
DMF	dimethylformamide
DMFu	2,5-Dimethylfuran
DMI	demethylase inhibitor
DMS	dimethylsilyl enolates
DMSO	dimethyl sulfoxide
Dpp	diphenylphosphionyl
Dpp	diphenylphosphionyl
ee	enantiomeric excess
EI	electron impact
eq.	equivalent
equiv.	equivalent
Et	ethyl
EtOAc	ethyl acetate
exc.	excess
g	gram
GC	gas chromatography
h	hour
HFIP	1, 1, 1, 3, 3, 3-hexafluoroisopropanol

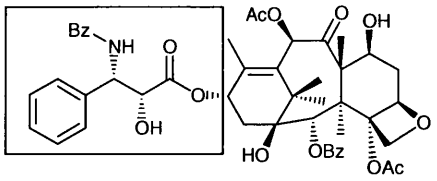
HFIPA	1, 1, 1, 3, 3, 3-hexafluoroisopropyl acrylate
HPA	2-hydroxypropyl acrylate
HPA-12	(1R,3R)-N-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide
HPLC	High Performance Liquid Chromatography
hrs	hours
IPA	*iso*-propanol
^{i}Pr	*iso*-propyl
IR	infrared
J	coupling constant
L	ligand
lit.	literature
m/z	mass to charge ratio
Me	methyl
mg	milligrams
MHz	megahertz
min.	minute
mL	millilitre
mmol	millimole
Mosher´s reagent	α-Methoxy-α-trifluoromethyl
mp	melting point
MS	molecular sieves, mass
MTPA	α-Methoxy-α-trifluoromethyl phenyl acetic acid (Moshers's reagent)
MW	molecular weight
Nap	naphthalene
^{n}BuLi	^{n}Butyllithium
NHPMP	*p*-methoxybenzylamine
NMI	*N*-methylimidazole
NMP	*N*-methylpyrrolidinone

NMR	nuclear magnetic resonante
NOESY	Nuclear Overhauser Effect spectroscopy (NMR technique)
° C	degrees celsius
o-	*ortho*
ORD	optical rotatory dispersion
p-	*para*
$P(O)Ph_2$	diphenylphosphinonyl
Petrol	petroleum ether
PGA	phosphoglyceric acid
Ph	phenyl
PHN	phthalazine ligand
PMA	phosphomolybdic acid
PMB	*p*-methoxybenzyl
PMHS	polymethylhydroxysilane
PMP	*p*-methoxyphenyl
ppm	parts per million
Pr	Propyl
p-TsOH	*para*-toluene sulfonic acid
q	quartet
R	generic substituent
r.t	room temperature
rac-	racemic
Rf	retention time
s	singlet
sat.	saturated
SDS	sodium dodecyl sulfate
SPE	solid phase extraction
t	triplet
TaDiAs	tartrate-derived diammonium
TBAF	tetrabutylamonium fluoride
TBDMSCl	*t*-Butyldimethylsilyl Chloride
TBSCl	*t*-Butyldimethylsilyl Chloride
^{t}Bu	*tert*-Butyl

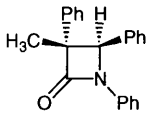
td	triplet of doublets
Tf	trifluromethane sulfonyl (trilyl)
TFA	trifluoroacetic acid
TfOH	trifluoro methane sulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethyl silane
TMS	trimethylsilyl Chloride
TMSCN	Trimethylsilyl cyanide
TMSOTf	trimethylsilyl triflate
Ts	*p*-Toluenesulfonyl (tosyl)
X	generic halide substituent
β-ICD	β-isocupreidine
Δ	chemical shift in parts per million
λ	wavelength

ABSTRACT

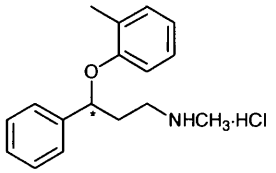
Enantiopure β-amino acids and their derivatives are components of a variety of important natural products and are valuable for pharmaceutical research such as a the prominent antitumor agent taxol [1-3] or the potential antibiotic component β-lactams.[4] β-Hydroxy esters are also a class of compounds of synthetic and biological importance for the synthesis of natural products such as the anti-depressant (*R*)-tomoxetine [5] as well as pinostrobin for gastrointestinal treatment.[6]



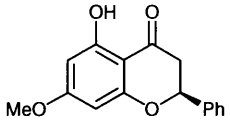
TAXOL



ß-lactams



(R)-tomoxetine hypodrochloride



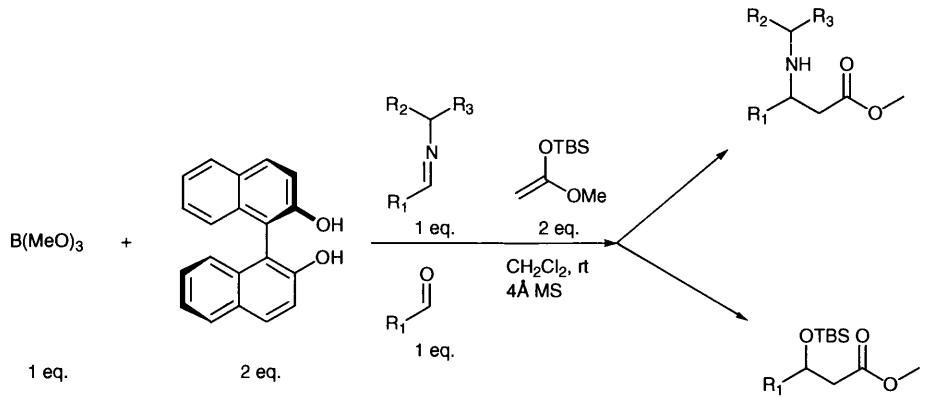
(-)-pinostrobin

Scheme 1: Natural products containing enantiopure β-amino acid fragments.

1. J. D. Bourzat and A. Commerçon, *Tetrahedron Lett.*, 1993, **34**, 6049.
2. G. Cardillo, L. Centilucci, A. Tolomelli and C. Tomasini, *J. Org. Chem.*, 1998, **63**, 2351.
3. S. H. Kang, C. M. Kim and J. H. Youn, *Tetrahedron Lett.*, 1999, **40**, 3581.
4. C. Gluchowski, L. Cooper, D. E. Bergbreiter and M. Newcomb, *J. Org. Chem.*, 1980, **45**, 3413.
5. X. Cheng-Fu and Y. Cheng-Ye, *Chinese J. Chem.*, 2004, **22**, 775.
6. K. J. Hodgetts, *Tetrahedron Lett.*, 2001, **42**, 3763.

A literature review of Mannich and aldol type reactions for the synthesis of chiral β-amino esters and aldol adducts has been documented in chapter 2.

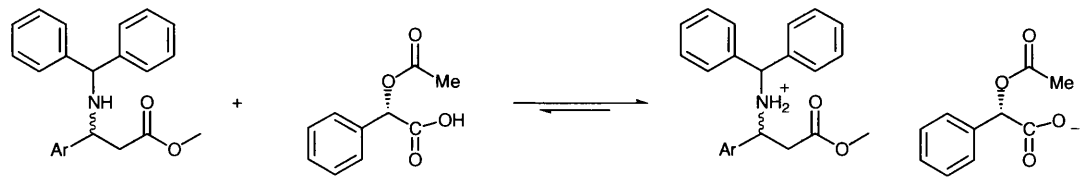
The purpose of chapter 3 is to describe my three years work developing methodology for the asymmetric synthesis of chiral β-amino esters and aldol adducts, using a BINOL-boron catalyst to catalyse Mannich-type reactions between silylketene acetals and *N*-benzyl imines.[7-12]



Scheme 2: BINOL-boron complex for the synthesis for the Mannich and aldol-type reaction.

Optimisation of the reaction and purification conditions, eventually led us to build up a table of promising results, mainly due to the diphenylmethylamine used as protecting group. Determination of enantiopurity of β-amino esters requires the intervention of chiral acetyl mandelic acid to form their two corresponding diastereomeric salts distinguished by ^{1}H NMR analysis.

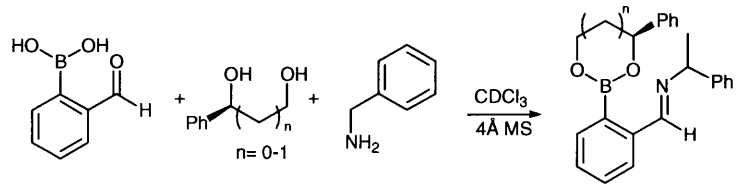
7. J. P. Cros, Y. Perez-Fuertes, M. J. Thatcher, S. Arimori, S. D. Bull and T. D. James, *Tetrahedron: Asymmetry*, 2003, **14**, 1965.
8. K. Ishihara, M. Funahashi, N. Hanaki, M. Miyata and H. Yamamoto, *Synlett*, 1994, 963.
9. S. Thormeier, B. Carboni and D. E. Kaufmann, *J. Organomet. Chem.*, 2002, **657**, 136.
10. K. Ishihara, Y. Kuroki and H. Yamamoto, *Synlett*, 1995, 41.
11. Y. Kuroki, K. Ishihara, N. Hanaki, S. Ohara and H. and Yamamoto, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1221.
12. K. Hattori, M. Miyata and H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 1151.



(*rac*)-)-*β*-amino ester (S)-(+)-*O*-Acetylmandelic acid

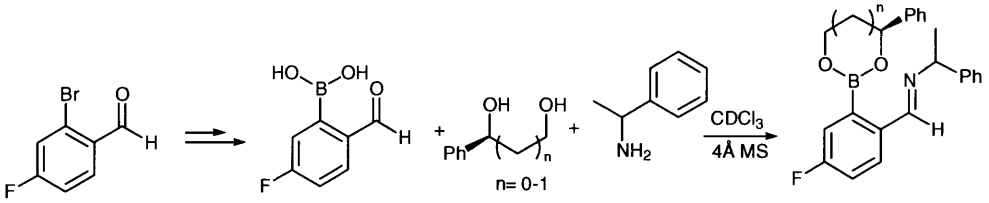
Scheme 3: Formation of the salt derived from *(rac)*-β-amino ester and (*S*)-(+)-*O*-acetylmandelic acid.

Reduction of the aldol adducts to their corresponding diols and posterior reaction in a practical simple three-component chiral derivatization protocol seemed to give the best enantiopurity determination by an accurate ^{1}H NMR spectroscopically analysis recently reported in our goup.[6]



Scheme 4: Derivatisation of enantiopure diols by a simple three-component chiral protocol.

Additionally, we have described in Chapter 4 a novel ^{19}F NMR spectroscopic analysis with the same three component protocol for determining the ee of a wide range of enantiomerically pure 1,2 and 1,3 diols. The method requires pre-synthesis of the 4-fluoro-2-formylphenylboronic from commercially available 4-fluoro-2-bromophenyl aldehyde.



Scheme 5: Synthesis of 4-fluoro-2-formylphenylboronic and posterior derivatisation of enantiopure diols by a simple three-component chiral protocol.

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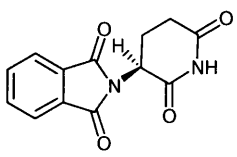
1 INTRODUCTION TO ASYMMETRY

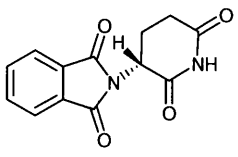
1.1 GENERAL INTRODUCTION

In just over 30 years organic chemists have transformed the virtually unknown area of asymmetric synthesis into a viable approach to virtually every class of chiral organic compound in greater than 90% enantiomeric purity. [1-4] The world of Nature around us is chiral and most of the important building blocks which make up the biological macromolecules of living systems are present in one enantiomeric form only. Thus, the enzymes in our cells are chiral, as are other receptors and structural biomolecules that play an important part in cell machinery. This has important consequences since biomolecules can bind to one enantiomer in the same way that a key fits a lock. Most drugs that are in use today are chiral molecules, many of which are natural products or their derivatives. A natural product is a compound that is isolated from a plant or an animal that exhibits biological activity, and as a consequence, we get a lot of inspiration for drug design from mother Nature. Conventional syntheses of chiral molecules often result in the formation of racemic mixtures, whereas natural products are normally found in enantiopure form. Therefore, when a biologically active chiral compound, such as a drug, interacts with a receptor site which is chiral, it comes as no surprise that the two enantiomers of the drug can interact differently and can lead to different effects.

One good example is the drug thalidomide for which one enantiomer has a sedative effect (calming or tranquilizing), whilst the (-)-enantiomer causes foetal deformities. In the 1960s, foetal deaths and malformations occurred due to its use by pregnant women. Unfortunately even if the pure (+)-enantiomer had been employed problems would still have arisen because the two enantiomers interconvert under physiological conditions.[1-4]



(-)-thalidomide



(+)-thalidomide

Figure 1. 1: The 1960's drug thalidomide was prescribed as a racemic mixture

There are other, less catastrophic examples of how two enantiomers can interact with biomolecules within our cells. Limonene, for example, is chiral, whilst the receptors in our nose are also chiral, which results in the (*S*)-enantiomer of limonene smelling of lemons, whilst the (*R*)-enantiomer smells of oranges. Therefore, our senses of tastes and smell are also highly sensitive to subtle stereochemical differences in molecules that stimulate them.[5]

Figure 1. 2: Two enantiomers of limonene

1.2 ASYMMETRIC SYNTHESIS

Asymmetric synthesis may be defined as a process in which an achiral fragment in a molecule is converted to a chiral group so that the possible stereoisomers are formed in unequal amounts. The aim in carrying out any asymmetric transformation is to achieve the highest degree of stereoselectivity possible.[1-4] If reagents and reaction conditions are all achiral, then the resultant product will be a racemic mixture, since no enantiomerically pure material can be created in the absence of a chiral molecule. Consequently, all current approaches to asymmetric synthesis require the intervention of a chiral entity, such as a chiral auxiliary or chiral catalyst.

Asymmetric synthesis has been widely used to prepare many classes of chiral compound, and its practise is based on four fundamentally different approaches involving:

- Chiral pool strategy
- Resolution of a racemate
- The use of chiral auxiliaries
- Asymmetric catalysts

1.2.1 Chiral pool strategy

This approach to preparing compounds as a single enantiomer involves using an enantiomerically pure natural product as a chiral starting material for synthesis.[5] The chiral pool is a collection of cheap, readily available natural products, usually amino acids or sugars, from which fragments containing the required chiral fragment can be incorporated into a chiral product.

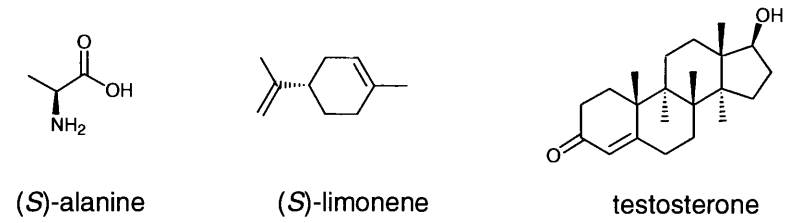
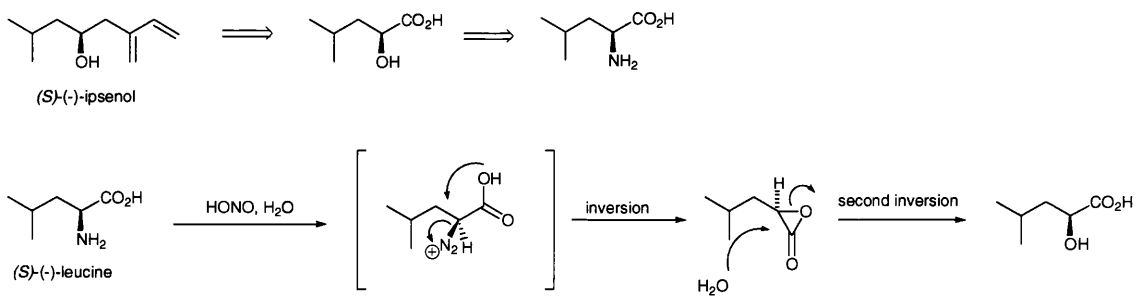


Figure 1. 3: (*S*)-Alanine, (*S*)-limonene, and testosterone: amino acid, terpene, and steroid buildings blocks.

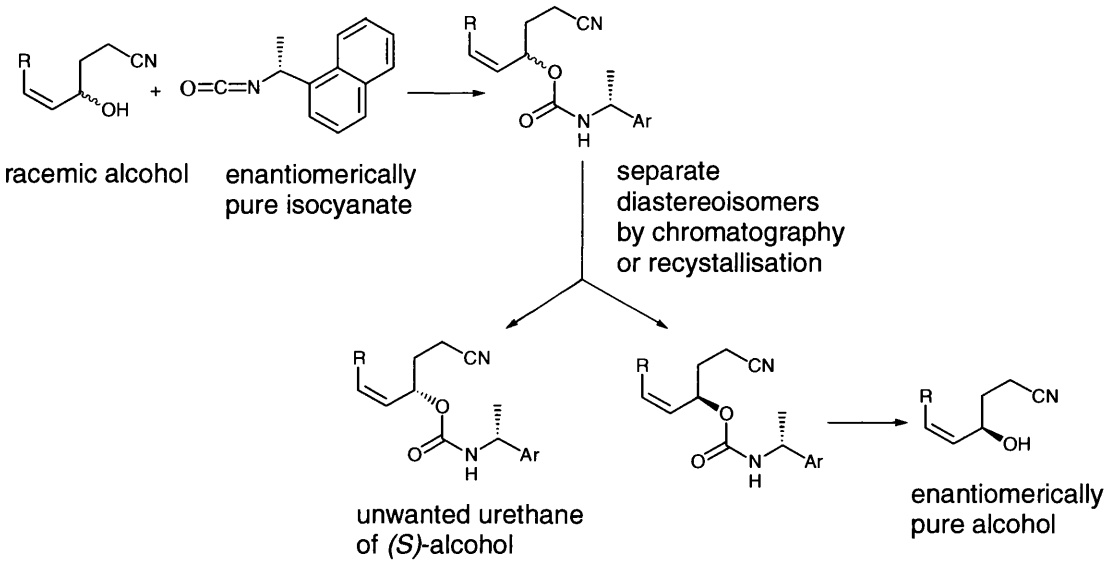
The difficulty with the chiral pool approach is that the compound needs to be closely related to the structure of the natural product, or the synthetic route can become extremely tortuous due to the need to remove reduntant functionality. The second major drawback is the lack of availability of both enantiomers of many natural products, though this inconvenience can often be solved using stereoselective reaction procedures to invert or transform selected stereocentres.[5]



Scheme 1. 1: Chiral pool strategy to provide a chiral α-hydroxyacid.

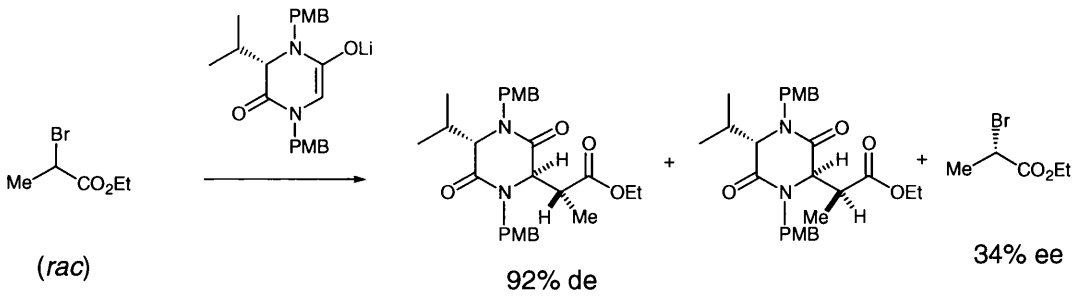
1.2.2 Resolution of a racemate

Resolution via formation of diastereoisomers. This approach consists of reacting a racemic compound with an enantiomerically pure resolving reagent to make a mixture of two diastereoisomers which exhibit different chemical properties, that can then be separated by fractional recrystallisation or chromatography.[5] Afterwards, the resolving reagent is removed from one of the pure diastereomers to afford a single enantiomer. This method is often used industrially, but it is wasteful because one enantiomer ends up being discarded. The major drawback with this approach is the need to use stoichiometric amounts of an often expensive resolving reagent.



Scheme 1. 2: Resolution of a racemic alcohol.

Kinetic resolution. This often exploited technique involves treatment of a racemic compound with an enantiomerically pure reagent or catalyst. In the best case scenario, one enantiomer reacts much faster with the chiral reagent/catalyst, yielding a mixture of chiral product and resolved starting material in enantiopure form. Afterwards, the two chiral products can be easily separated by flash chromatography, or fractional recrystallisation. For example, treatment of a racemic mixture of an α-bromo ester with a chiral enolate results in selective reaction of the (*R*)-enantiomer to afford a major diastereoisomer in 92% de, with the unreacted (*S*)-enantiomer being recovered in 34% ee.[6]



Scheme 1. 3: Kinetic resolution using an enantiopure enolate.

A less attractive feature of this approach is the fact that the maximum possible yield of chiral product obtainable in a standard kinetic resolution is 50%. Additionally, there may come a point in the resolution reaction where the concentration of the major enantiomer is sufficiently low that the rate of reaction of the kinetically less favourable enantiomer can begin to compete, hence leading to a lowering of the overall enantiomeric excess of the chiral product.

Dynamic kinetic resolution. This technique is a more powerful approach than standard kinetic resolution for the diastereoselective and enantioselective syntheses of organic compounds. Dynamic kinetic resolution processes require the presence of a rapidly equilibrating racemic starting material, which must occur in the presence of a kinetic resolution event where the enantiomers react at different rates ($K_R > K_S$).[7-9] Dynamic kinetic resolution (as shown in Figure 1.4), in its most favourable outcome results in greater than 50% conversion of a racemic substrate into a chiral product enriched in one enantiomer or diastereoisomer. Indeed, dynamic kinetic resolution reactions are known that enable 100% conversion of a racemic substrate to an enantiomerically pure product.[10]

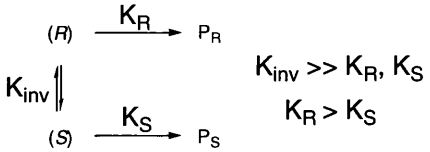
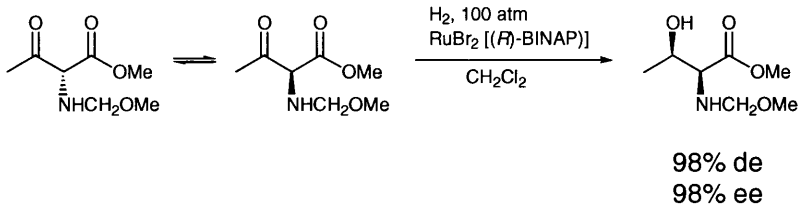


Figure 1. 4: Dynamic kinetic resolution with enantiomers of the starting materials

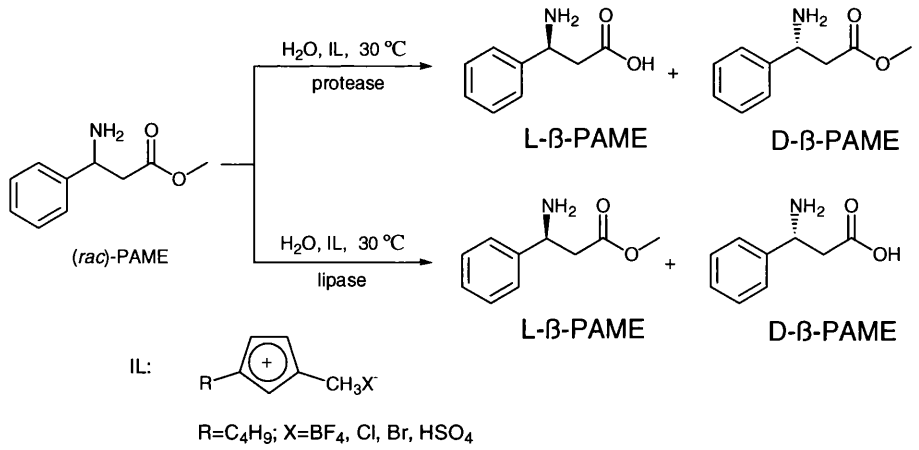
One of the most powerful examples of dynamic kinetic resolution was reported by Noyori in 1989 using a chiral Ru-BINAP hydrogenation catalyst to catalyse the

dynamic kinetic resolution of a racemic *N*-protected-α-amino-β-keto ester to afford a chiral β-hydroxy-ester containing two stereogenic centres as a single stereoisomer (Scheme 1.4);[11]



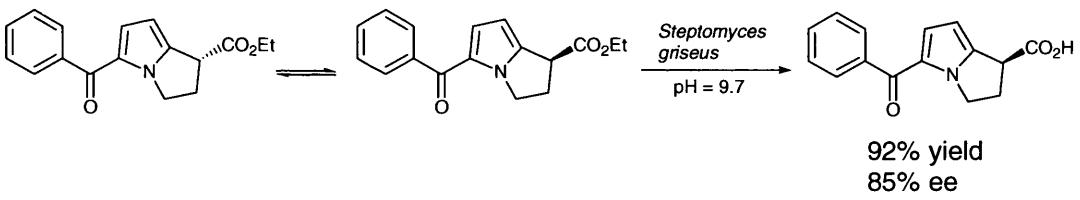
Scheme 1. 4: Dynamic kinetic resolution caused by Ru-BINAP catalyst

Enzymatic resolution. Enzymes are Nature´s catalysts that are very effective at affording chiral products in very high ee. Kinetic resolution and dynamic kinetic resolution processes using enzymes have been developed that provide enantiopure alcohols, acetals, carboxylic acids, esters and β-hydroxy esters. However, to avoid enzymatic denaturation, an aqueous environment at ambient temperature is normally required for reactions to proceed. Most organic reactants are only soluble in organic solvents, thus biphasic systems are often required, with cosolvents often complicating the reaction process. Nevertheless, enzymatic resolutions represent an important route to chiral products, particularly for the preparation of enantiopure unnatural amino acids and their derivatives. For example, lipases or proteases may be used to catalyse enantioselective hydrolysis reactions of racemic β-amino esters, thus providing a simple and convenient method to prepare this type of enantiopure amino acid. In this approach, the enzyme converts one of the enantiomers of the racemic β-amino ester into an enantiopure β-amino acid that can then be separated from its remaining β-amino ester antipode.[12]



Scheme 1. 5: Enzymatic asymmetric hydrolysis of β-amino esters in an ionic liquid solvent.

It is possible to perform dynamic kinetic resolutions using enzymes under conditions where the two enantiomers of the substrate are racemizing continuously. For example, Sin has reported the dynamic kinetic resolution of a pyrrole ester with the protease from *Steptomyces griseous* in alkaline solution to produce the corresponding acid in 92% yield and 85% ee.[13]



Scheme 1. 6: Dynamic kinetic resolution of ethyl ester with *Steptomyces griseous.*

1.2.3 Chiral auxiliary strategy

In this approach an enantiomerically pure compound called a chiral auxiliary is first attached to a prochiral starting material. [5] Then, a diastereoselective reaction is carried out at a prochiral centre to afford a new stereogenic centre, which because of the presence of the chiral auxiliary fragment, should ideally afford only one diastereoisomer. The major diastereoisomer is then purified to homogeneity via either chromatography or recrystallisation, before the chiral auxiliary is removed to afford a chiral product as a single enantiomer. The best protocols regenerate the chiral auxilary

so that it can be recycled, although if it is inexpensive, it can be destroyed in the cleavage step. Therefore, although stoichiometric quantities of the chiral auxiliary are needed, there is often less waste than in the case of resolution. The main disadvantage to this methodology is the necessity to carry out two extra reaction steps in order to introduce and remove the chiral auxiliary.

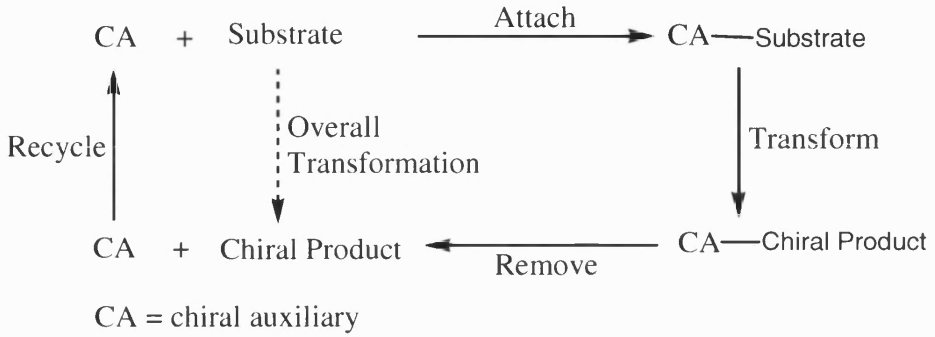
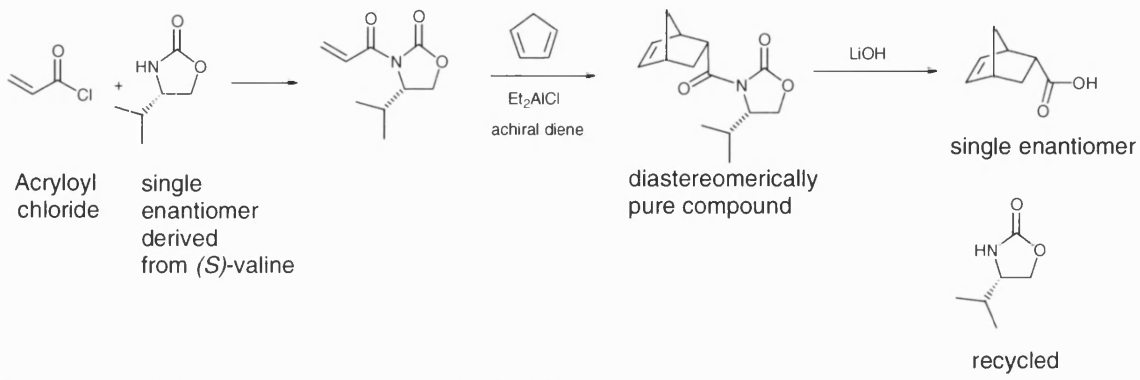


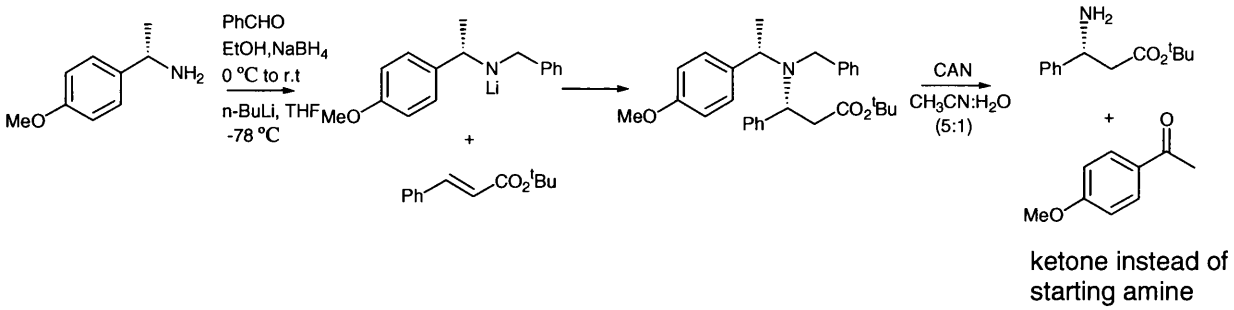
Figure 1. 5: Principle of using chiral auxiliaries for asymmetric synthesis.

This principle of using a chiral auxiliary for asymmetric synthesis can be illustrated by considering the Diels-Alder reaction of cyclopentadiene with benzyl acrylate, which in the absence of a chiral source affords an *endo* product in high de as a 50:50 mixture of enantiomers. If the acryloyl dienophile is attached to a chiral oxazolidin-2-one, the diastereoselectivity of the Diels-Alder reaction remains uncharged; however the presence of the chiral auxiliary fragment results can be used to prepare a single enantiomer of the chiral acid product. In this case, the chiral auxiliary functions to create two possible diastereomeric transition states of sufficient different energy that only one diastereoisomer is formed. In this particular case, the chiral auxiliary is recycled by hydrolytic cleavage, which makes this strategy extremely attractive.[5]



Scheme 1. 7: Chiral auxiliary strategy for a Diels-Alder reaction.

Another efficient chiral auxiliary approach that has been used for the asymmetric synthesis of many different types of β-amino acids is shown in Scheme 1.8,[14] involving stereoselective conjugate addition of a chiral lithium amide to α,β-unsaturated esters. This approach affords *N,N*-dibenzyl-β-amino esters that may be deprotected under oxidative conditions using ceric ammonium nitrate (CAN) to afford the desired enantiopure β-amino ester. It should be noted that this approach results in the destruction of the chiral auxiliary fragment and is therefore inherently more wasteful that the Evan's oxazolidinone example described in Scheme 1.7.



Scheme 1. 8: Asymmetric synthesis of β-amino esters

1.2.4 Asymmetric catalysis

A *catalyst* is a substance that modifies the rate of the reaction without being consumed in the process. The catalyst facilitates the reaction by lowering the activation energy of the reaction, but is not incorporated into the product, so it can be used at sub-stochiometric levels and recovered for recycling as required.[i] They function by providing an alternative pathway for the reaction to occur, thus reducing the activation energy and increasing the reaction rate.

Chiral catalysts can be employed for stereoselective synthesis and represents the best option for preparing chiral molecules in enantiopure form since only a small amount of an often expensive chiral catalyst is required.[15] Asymmetric catalysed reactions lead to the formation of diastereomeric transitions states which differ in energy, thus enabling chiral products to be formed in high enantiomeric excess. This can be best understood if we consider the transition state that arises during reduction of a prochiral ketone with an achiral reducing agent. In this case, the achiral reducing agent $NaBH_4$ provides a

[i] An exception is the process of autocatalysis where the product of a reaction can accelerate its own reaction.

hydride source that cannot distinguish between the *Re*- and *Si*- faces of the carbonyl compound, which leads to enantiomeric transition states of the same energy, that consequently afford a racemic alcohol.[5]

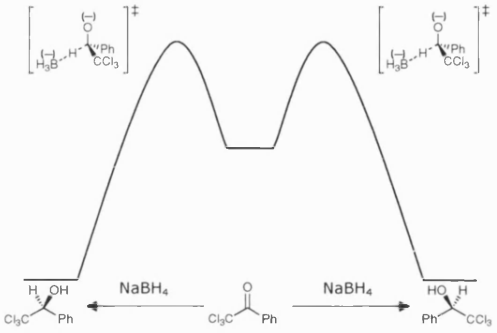


Figure 1. 6: Reduction in an achiral environment.

When this prochiral ketone is reduced with a chiral catalyst, it can potentially lead to two diastereomeric transition states of different energies, and as a consequence the transition state with the smallest energy barrier can lead to formation of the kinetically favoured enantiomer in high ee. For example, CBS reduction of 2,2,2-trichloro-1-phenylethanone, with the CBS oxazaborolidine catalyst is highly stereoselective affording a chiral secondary alcohol in 98% ee. [5, 16]

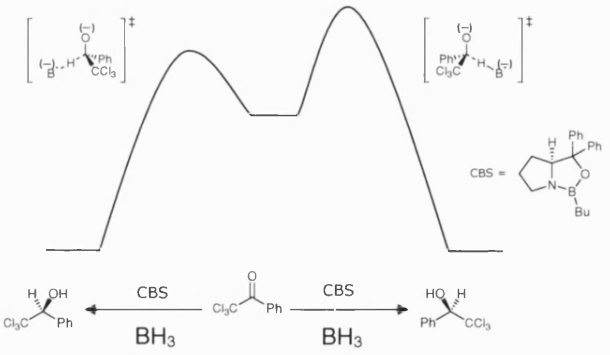


Figure 1. 7: Reduction using a chiral catalyst.

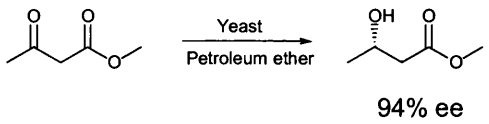
The main drawback with using chiral catalysts is the fact that small changes in the structure of the substrate can lead to big losses in enantiocontrol. This often means that

the catalytic conditions have to be reoptimised, which can prove an extremely frustrating and time-consuming process.

There are three fundamentally different types of asymmetric catalyst that can be used for asymmetric synthesis:

- Biocatalysis
- Organocatalysis
- Organometallic catalysis

Biocatalysis is the utilization of enzymes or whole cells to perform asymmetric transformations on organic compounds. A major advantage of biocatalysts are that they are environmentally acceptable, being completely degraded in the environment, and they are considered to be "green" catalysts that normally function in water. Furthermore, enzymes act under mild conditions, which often minimize problems caused by undesired side-reactions of structurally complex substrates such as decomposition, isomerisation, racemisation and rearrangement. However, enzymes often have narrow specificity profiles that restrict their use to a small group of substrates. There are numerous examples where whole cells or enzymes have been used for asymmetric catalysis, with one famous example being the use of yeast as a whole cell system for the asymmetric reduction of β-keto esters. In this system an alcohol dehydrogenase within the cell uses NADH as a stoichiometric reductant to reduce the β-keto functionality in high ee.[17]

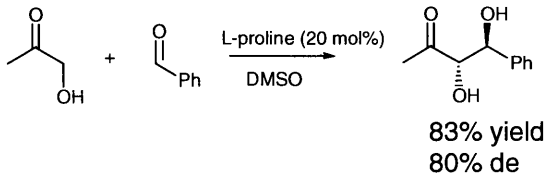


94% ee

Scheme 1. 9: Yeast biocatalyst for the enantioselective reduction of ketones.

Organocatalysis is the catalysis of chemical reactions using a pure organic compound that is formed from carbon, nitrogen, hydrogen, suphur or phosphorus atoms which does not contain any metal atoms. Organocatalysts are normally small chiral molecules that are stable to moisturise and oxygen, that often function in a biomimetry manner without the need for air sensitive techniques. For example, a commonly described

organocatalyst is L-proline, which relies on iminium/enamine chemistry to facilitate stereoselective aldol reactions in high ee.[18]



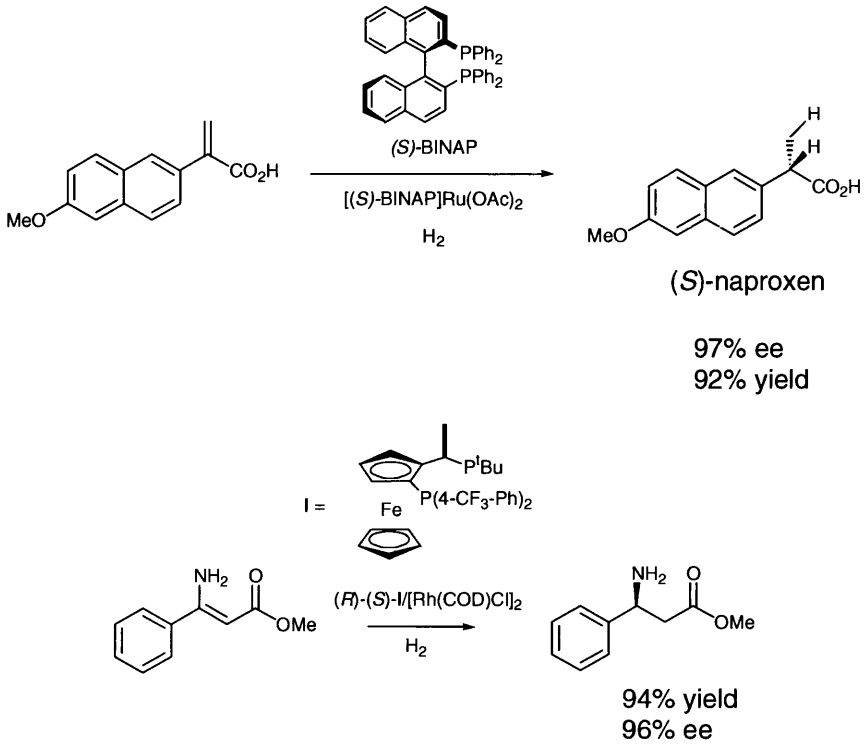
Scheme 1. 10: Direct asymmetric aldol reaction of hydroxyacetone catalysed by L-Proline.

Organocatalysts are generally more tolerant of water than their corresponding organometallic counterparts, and they can be used in many common organic solvents with their mechanism of action often being reminiscent of enzyme catalysed reactions. Nevertheless, as this field of research is still relatively new, more investigations need to be done to reduce catalyst loadings and increase reaction rates if they are to rival the efficiency of chiral organometallic or enzymatic reactions.

Organometallic catalysis. Transition metal complexes of chiral ligands have proven to afford homogeneous or heterogeneous catalysts with very high rates and levels of stereocontrol that approach and sometimes exceed those observed in enzymatic reactions. Typically, complexation of a chiral ligand to a transition metal affords a chiral complex that can induce chirality into the transition state of a reaction. In the best cases, < 1 mol% of a chiral transition metal catalyst are enough to achieve good catalyst turnover of >10000 molecules of substrate.

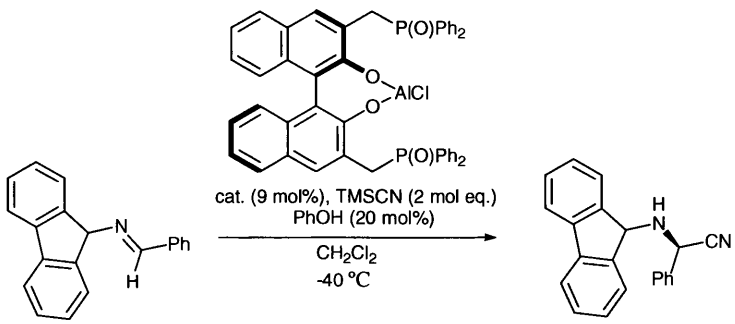
A number of chiral hydrogenation catalysts have been developed for the enantioselective reduction of alkenes, particularly for substrates containing oxygen or nitrogen heteratoms that can coordinate to metal complexes that direct the facial selectivity of the reduction process, with the Nobel prize being awarded to Knowles and Noyori for " *their work on chirally catalyzed hydrogenation reactions*" in 2001. For example, in 1980 Noyori *et al.* developed a chiral diphosphine ligand, BINAP (Scheme 1.11), which was found to be an excellent ligand for rhodium catalyzed hydrogenation reactions. Hydrogenation of the alkene functionality of α,β-unsaturated carboxylic acid with a ruthenium-BINAP catalyst gave the anti-inflammatory agent (*S*)-naproxen with high enantioselectivity and excellent yield (97% ee, 92% yield).[18] Since then, many

other chiral hydrogenation catalysts have been developed such as Rh-ferrophosphine ligand complex that can be used for the hydrogenation of β-amino α,β-unsaturated esters,[19] (Scheme 1.11).



Scheme 1. 11: Chiral catalysts for asymmetric reduction of alkenes.

A review of the literature reveals a wide range of metal-ligand complexes that have been used for organometallic asymmetric catalysis, whose efficiency is influenced by the electronic and steric demands of the chiral ligand responsible for asymmetric induction. Of particular note are C_2-symmetric ligands that have been widely used to achieve high levels of stereocontrol. This can be explained by considering the reduction in number of diastereomeric transition states available to such substrate-metal-ligand complexes, which leads to a decrease in the number of diastereomeric coordination sites available to the substrate. Consequently, a wide range of transformations using C_2-symmetrical ligands are known that have afforded extraordinary levels of enantioselectivity. For example, aluminium-BINOL Lewis acids have been employed for the asymmetric addition of TMSCN to imine substrates (Strecker reaction) to afford (*R*)-aminonitriles in high yields and with excellent levels of enantiocontrol (Scheme 1.12).[20]



95% ee
92% yield

Scheme 1. 12: Asymmetric Strecker reaction using a novel C_2-symmetric ligand

1.3 CONCLUSIONS

Inspired by the world of Nature around us, organic chemists are continuing to develop methods for the asymmetric synthesis of chiral organic compounds which are important building blocks for natural product synthesis, and drug discovery applications. In view of this, asymmetric catalysis is one of the most important fields of science, that will continue to contribute greatly to developments in the life science area. This thesis describes my attempts to develop an asymmetric Mannich and Mukaiyama aldol reactions using chiral boron-BINOL catalysts and as a consequence a review of current methodology for carrying out these asymmetric transformations now follows.

1.4 REFERENCES

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2 REVIEW OF MANNICH AND ALDOL TYPE REACTION

2.1 SYNOPSIS OF THE CHAPTER

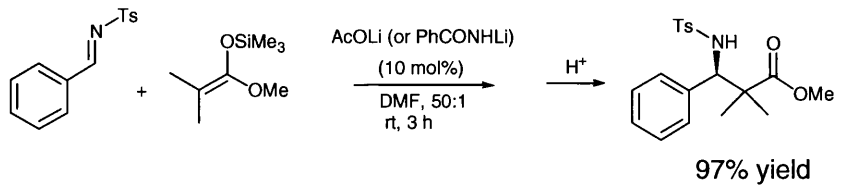
Mannich-type reactions between imines and silyl ketene acetals may be catalysed by Lewis acids or Lewis bases leading to the formation of either chiral or racemic β-amino esters. Consequently, the first part of this chapter now describes general aspects of achiral Mannich-type reactions using both types of catalysts, followed by a detailed review of asymmetric Mannich reactions that have been carried out to date. Secondly, a brief introduction of the Mukaiyama aldol reaction is given for the synthesis of chiral β-hydroxy esters derived from unsubstituted or symmetrically substituted silyl ketene acetals.

2.2 ACHIRAL MANNICH-TYPE REACTION OF IMINES

2.2.1 Lewis base catalysed Mannich-type reaction

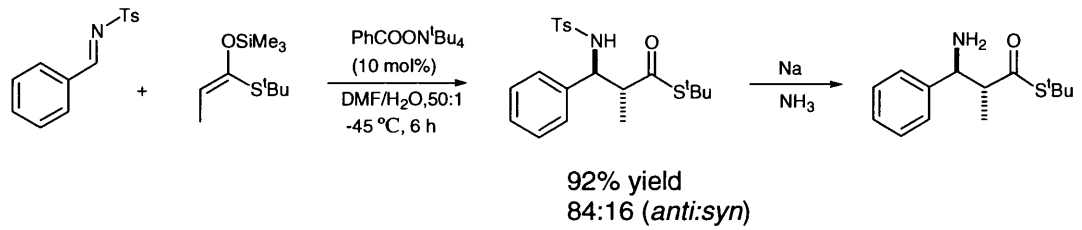
There are a number of other Mannich-type reactions reported involving nucleophilic activation of a silyl ketene acetal for addition to imine substrates. Investigations reported by Nakamura and cooworker between 1977 and 1988 revealed that Lewis bases such as fluoride could accelerate the aldol reactions of silyl ketene acetals by nucleophilic activation of silyl enolates due to the strong F-Si bond.[1]

The most recent example involves Lewis base catalysed Mannich-type reaction between a trimethyl silyl ketene acetal and *N*-tosylaldimines using lithium benzamide or potassium pthalimide as a nucleophile in DMF at room temperature [2] with a related lithium acetate-catalysed Mannich-type reaction affording β-amino esters in excellent yield. Further research within the Fujisawa group extended this methodology to the three component Mannich-type reaction of trimethyl silyl ketene acetal, tosylamide, and aromatic imines.[2]



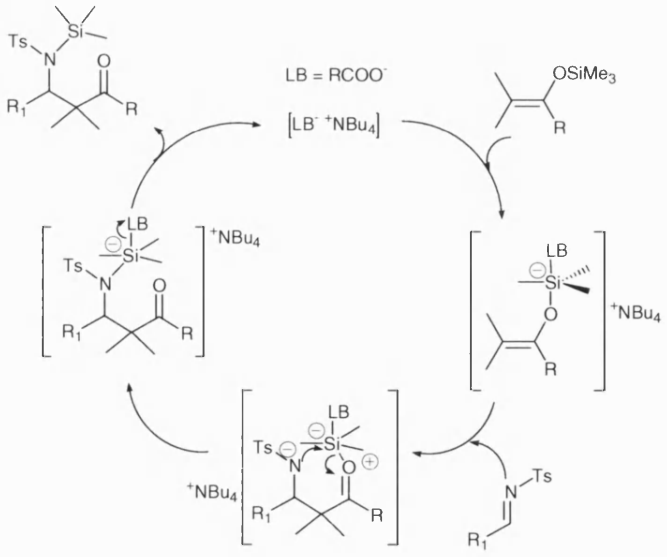
Scheme 2. 1: Mannich-type reaction between *N*-tosylaldimine and trimethyl silyl enol ester using lithium acetate.

However, the most effective Lewis base catalyst found for these type of Mannich-type reactions were ammonium carboxylates such as tetrabutyl ammonium acetate or tetrabutyl ammonium benzoate in DMF.[2] In terms of diastereoselectivity, excellent *anti*-selectivities and yields were obtained for the formation of β-amino ester products, irrespective of the (E)-/(Z)- geometries of the starting silylketene acetals. Reductive cleavage with Na or Li in liquid ammonia proved to be an effective method for cleaving the *N*-tosylamide protecting groups of these (*anti*)-α-alkyl β-amino esters.[3]



Scheme 2. 2: Mannich-type reaction between *N*-tosylaldimine and trimethyl silyl enol ester using tetrabutyl ammonium benzoate.

The mechanism of the Lewis base catalysed Mukaiyama Mannich reaction is shown in Scheme 2.3 involving formation of a silicon "ate" intermediate that triggers the Mannich reaction which proceeds with O→N silyl migration, to give on *N*-silyl-β-amino ester that is often hydrolysed during the reaction work-up.



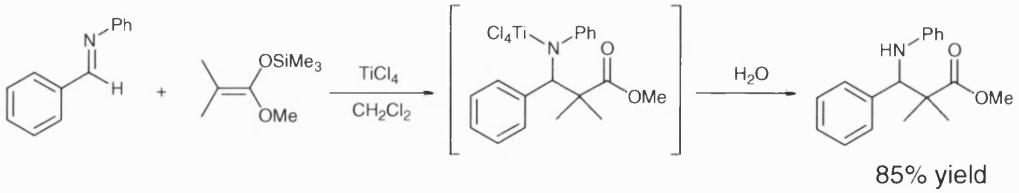
Scheme 2. 3: Assumed catalytic cycle of ammonium carboxylate-catalysed Mannich-type reaction.

2.2.2 Lewis acid catalysed Mannich-type reaction

Whilst the use of the Lewis base approach to catalyse Mukaiyama-Mannich reactions is still relatively unexplored, Lewis acids have been widely used to catalyse the same reaction.

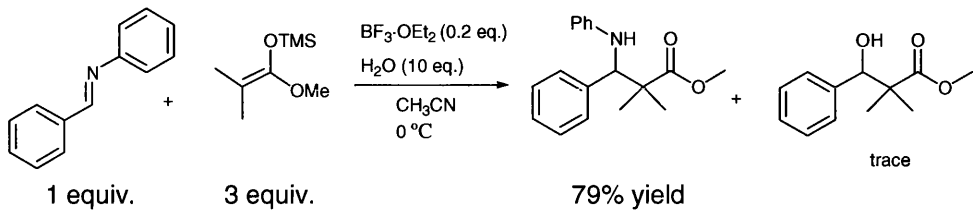
2.2.2.1 Two components Mukaiyama Mannich-type reaction

Initial studies into Mukaiyama Mannich-type reactions were reported using stochiometric amounts of conventional Lewis acids such as $TiCl_4$,[4] with more recent reports on the use of trimethylsilyltriflate,[5] diphosphonium salts,[6] iron iodide,[7] trityl hexafluoroantimonate [7] and clay montmorillonite [8] having been succesfully applied to this reaction.



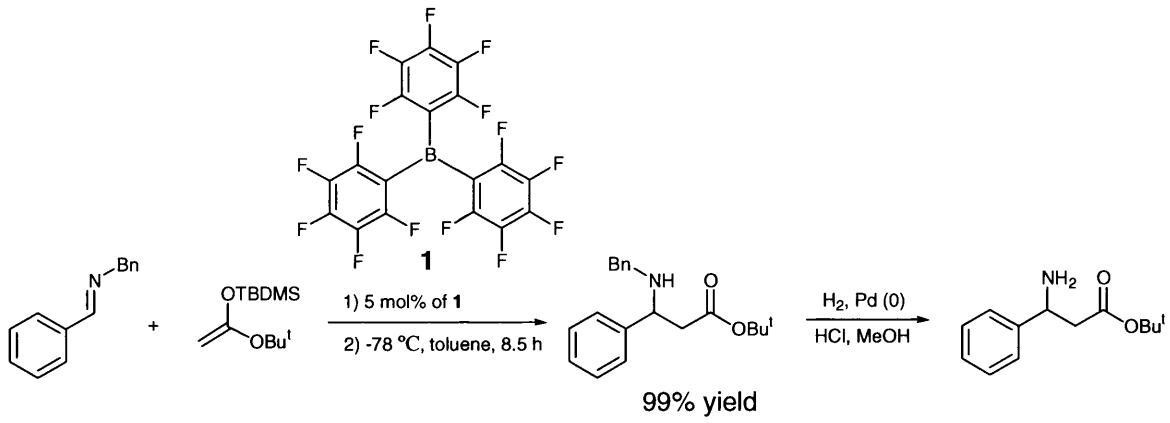
Scheme 2. 4: Mukaiyama Mannich-type reaction using stoichiometric amounts of $TiCl_4$.

Catalytic amounts of conventional Lewis acids, such as $BF_3 \cdot OEt_2$ and $SnCl_4$ in water have been documented to activate *N*-aryl-aldimines chemoselectively in the presence of aldehydes to afford β-amino-esters in high yield. Alternatively, chemoselective activation towards aldehyde substrate in the presence of the aldimine could be achieved using stoichiometric amounts of $BF_3 \cdot OEt_2$ or $SnCl_4$ to preferentially afford aldol adducts.[9]



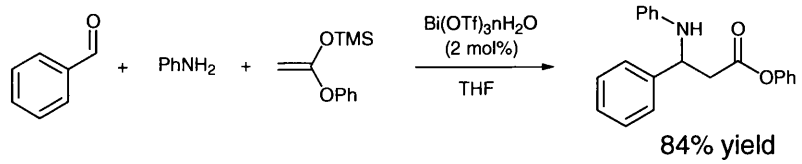
Scheme 2. 5: Chemioselective Mannich-type reaction of imine.

Ishihara and co-workers have reported the use of tris(pentafluorophenyl)boron **1** as a catalyst in the Mannich-type which resulted in smooth reaction between ketene silyl acetals and imines to give their corresponding β-amino esters in good yields.[10, 11]



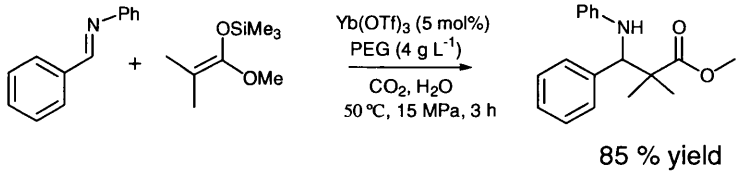
Scheme 2. 6: Boron-Lewis acid catalyst for Mannich-type reaction.

In the course of their investigations, Ollevier *et al.* developed a one pot bismuth catalysed Mannich-type reaction that combines an aldehyde, aniline and silyl ketene acetal at -78 °C.[12] $Bi(OTf)_3$ is particularly attractive, with phenyl-3-phenyl-3-(phenylamino)propanoate being obtained in a good 84% yield.[12]



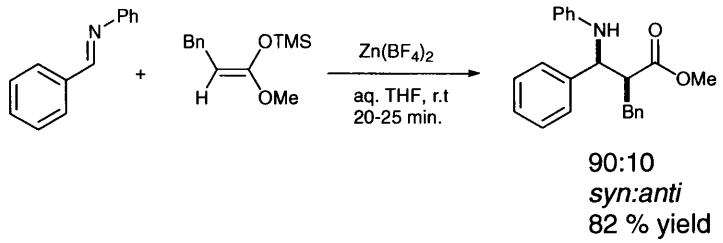
Scheme 2. 7: Bismuth catalysed Mannich-type reaction.

From an environmental and economical perspective, the development of Mannich-Type reactions in water is highly desirable. However many organic substrates are not soluble in water, and so it is difficult to obtain good reactivity. Komoto *et. al.* has attempted to solve this problem using surfactant molecules to create micelles that were found to accelerate the resultant Mannich-type reactions. Thus, the use of poly(ethylene glycol) derivatives (PEGs) [13-15] as an additive in supercritical carbon dioxide (sCO_2) resulted in emulsion formation leading to Lewis acid catalysed reaction of silyl ketene acetals with aldehydes and imines in aqueous solution. It is noteworthy that imines derived from aromatic, heterocyclic and aliphatic aldehydes could be used as substrates, with silylenolates derived from esters, thioesters and ketones also being employed using this system.



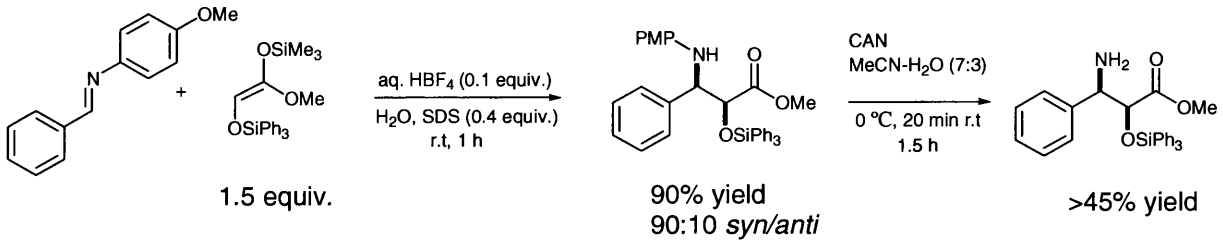
Scheme 2. 8: Mannich-type reaction in water with the use of surfactants.

Other Mannich reactions in aqueous medium have employed the cheap commercially available reagent, zinc tetrafluoroborate which catalysed the addition of ketene silyl acetals to aldimines in aqueous THF to provide β-amino esters in high yields, with the *syn* addition product being produced in these reactions.[16]



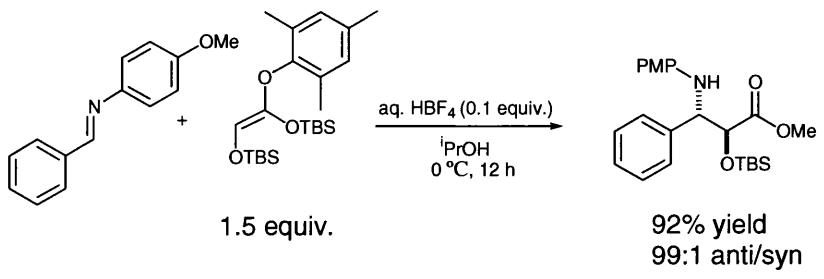
Scheme 2. 9: Major *syn* product using zinc tetrafluoroborate as a Lewis acid catalyst.

Recent investigations involving Brönsted acids in aqueous media have been reported to catalyse Mannich type reactions with good diastereocontrol.[17] A ketene silyl acetal was treated with an imine using the Brönsted acid, HBF_4 in the presence of sodium dodecyl sulphate (SDS) in water, to afford the *syn*-β-amino ester in good de and in high yield.[17, 18] CAN was subsequently used to deprotect the *p*-methoxyphenyl group of the resultant β-amino ester.[3]



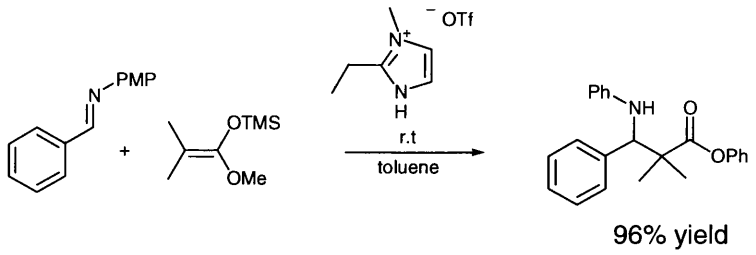
Scheme 2. 10: *Syn*-selective Mannich-type reaction.

It is interesting to note the importance of the surfactant (SDS) in these reactions since this type of Mannich-type reaction in aqueous 2-propanol led to preferential formation of the corresponding *anti*-β-amino-α-siloxy ester. [19]



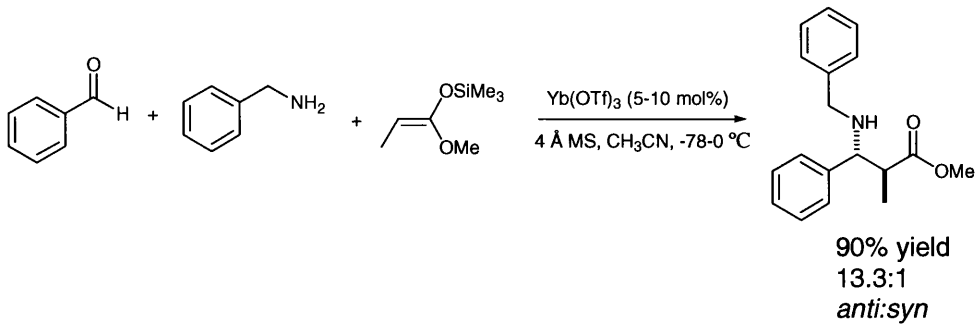
Scheme 2. 11: *Anti*-selective Mannich-type reaction.

Ionic liquids have attracted much recent attention because of their low vapour pressure and excellent recycling potential. Encouraged by the physical properties of these solvents, the Akiyama group published the Mannich-type reactions of silyl ketene acetals with aldimines in ethylmethylimidazolium triflate ([enim]OTf)/toluene to afford β-amino esters in up to 96% yield (Scheme 2.13).[19] This suggests that [enim]OTf may act as a Lewis acid to promote the Mannich-type reaction effectively, whilst it was shown that the ionic liquid could be recycled at least 5 times before any significant decrease in the yield of β-amino ester product was observed. Alternatively, a one-pot three component Mannich condensation of aldehyde, amines and silyl enolate was also found to proceed efficiently in [enim]OTf.[19]



Scheme 2. 12: Mannich-type reaction performed in ionic liquids.

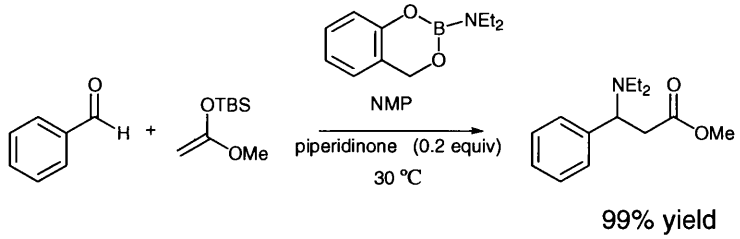
Many imines are hydroscopic, unstable at high temperature, and difficult to purify by distillation or column chromatography. Therefore, it is desirable that procedures are developed that enable imines to be generated *in situ* from aldehydes and amines, before being reacted with silyl ketene acetals *in situ*. One pot syntheses of β-amino esters from aldehydes and amines using a catalytic amount of lanthanide triflates ($Yb(OTf)_3$, $Er(OTf)_3$, $Tm(OTf)_3$, etc.) have been published by Kobayashi and Cozzi.[20-22] These Lewis-acid catalysed three component reactions proceed under strictly anhydrous conditions because water was shown to shut down the catalytic process, and as a consequence it was essential that either $MgSO_4$ or 4 Å molecular sieves were present to remove water during imine formation. Enolizable imines derived from aliphatic aldehydes gave poor results, however arylaldehydes generally gave the desired Mannich adducts in excellent yields. A*nti*-adducts were produced preferentially in the Mannich reactions of imines of benzaldehyde, whilst *syn*-adducts were obtained with high selectivities from reactions of aliphatic aldehydes.[20, 21]



Scheme 2. 13: Reaction of imines generated *in situ* with silyl ketene acetals using ytterbium triflate.

2.2.2.2 Three component Mannich-type reaction

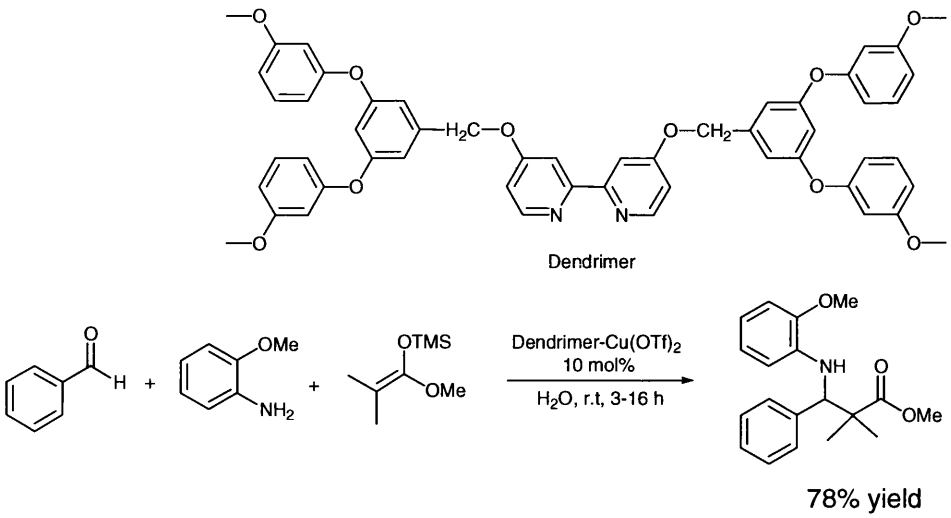
The Suginome group also found that reaction of 1 equiv. of silyl ketene acetal and 2 equiv. of benzaldehyde in *N*-methylpyrrolidinone (NMP) at 30 °C gave Mannich-type products in up to 99% yield.[23] It was found that the presence of the boron reagent was crucial for the generation of iminium intermediates under mild conditions, which facilitated nucleophilic addition of the silyl ketene acetal to generate the β-amino ester. Moreover, the presence of sub-stochiometric amount of piperidinone (0.2 equiv) served to further accelerate the reaction which allowed the temperature of the reaction to be lowered to 30 °C.[23] Whilst a chiral version of this reaction has not been developed to date, its potential for catalytic asymmetric synthesis clearly merits further investigation.[23]



Scheme 2. 14: Preparation of β-amino ester by a three component system.

Very recently, a novel catalytic system has been reported by the Takahito group. They described a three-component Mannich-type reaction catalysed by Lewis-acid containing metallodendrimers prepared from 2,2′-bipyridine ligands and $Cu(OTf)_2$ in water.[24] Although the reason for the positive dendritic effect on the chemical yield remains unclear, it was hypothesized that the hydrophobic environment constructed by the

dendritic $Cu(OTf)_2$ catalyst was responsible for the observed rate enhancement. In addition, it was shown that the reactivity or selectivity was enhanced by increasing the generation number of these type dendrimeric catalyst.[24]



Scheme 2. 15: Mannich-type reaction catalysed by Lewis-acid core metallodendrimers.

2.3 ASYMMETRIC MUKAIYAMA MANNICH-TYPE REACTION

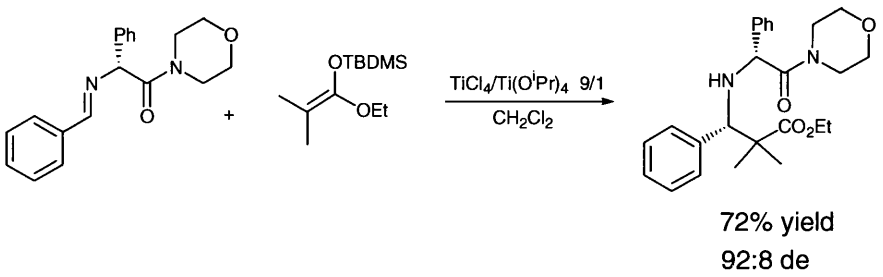
Given the biological importance of the β-amino esters, a wide range of efforts have been devoted to developing asymmetric Mukaiyama Mannich reactions. These approaches may be conveniently classified into these protocols that rely on the use of chiral auxiliaries or on chiral catalysts.

2.3.1 Chiral auxiliary based approaches for the asymmetric synthesis of β-amino esters

Chiral auxiliaries are powerful molecules for creating enantiomerically pure compounds in the Mannich condensation reaction with the chiral auxiliary fragment most often being attached to the nitrogen atom of the imine component.[25-28]

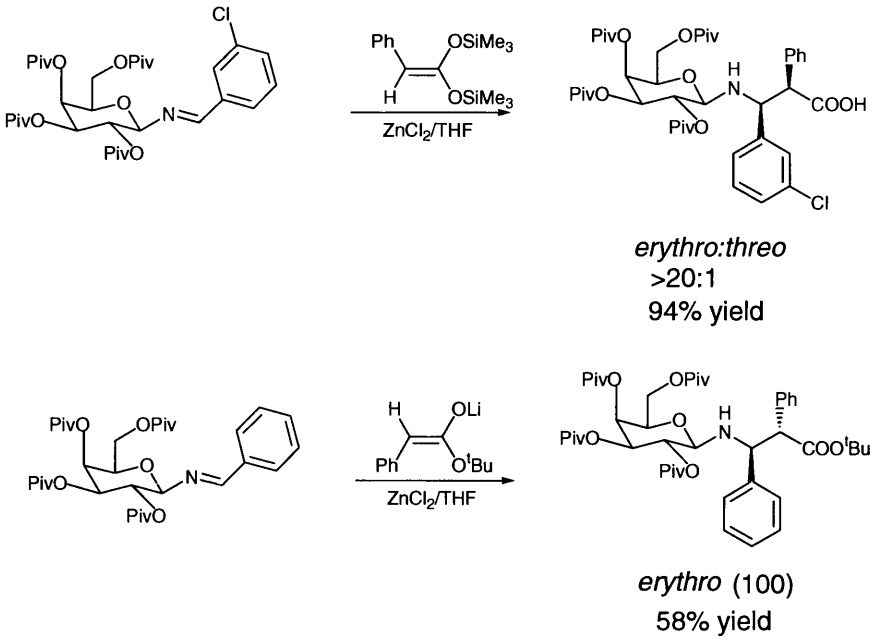
2.3.1.1 Two components Mannich-type reaction

Shimizu *et al.* have developed efficient steroselective methodology for the construction of β-lactam skeletons from condensations of silyl ketene acetals with an imine containing a phenylglycine derived stereocentre. Among the Lewis acids examined, $TiCl_4$ afforded the best diastereo-isomeric ratio of 92:8 (*R*:*S*).[29] Importantly, it was noted that the *tert*-butyldimethyl silyl fragment in the silyl ketene acetal gave better diastereoselectivity than using a trimethyl silyl group. Interestingly, the product yields were improved using $Ti(O^iPr)_4$ as an additive, with a 9:1 mixture of $TiCl_4$/ $Ti(O^iPr)_4$ affording the desired (*R*) Mannich type product in 72% yield. [29]



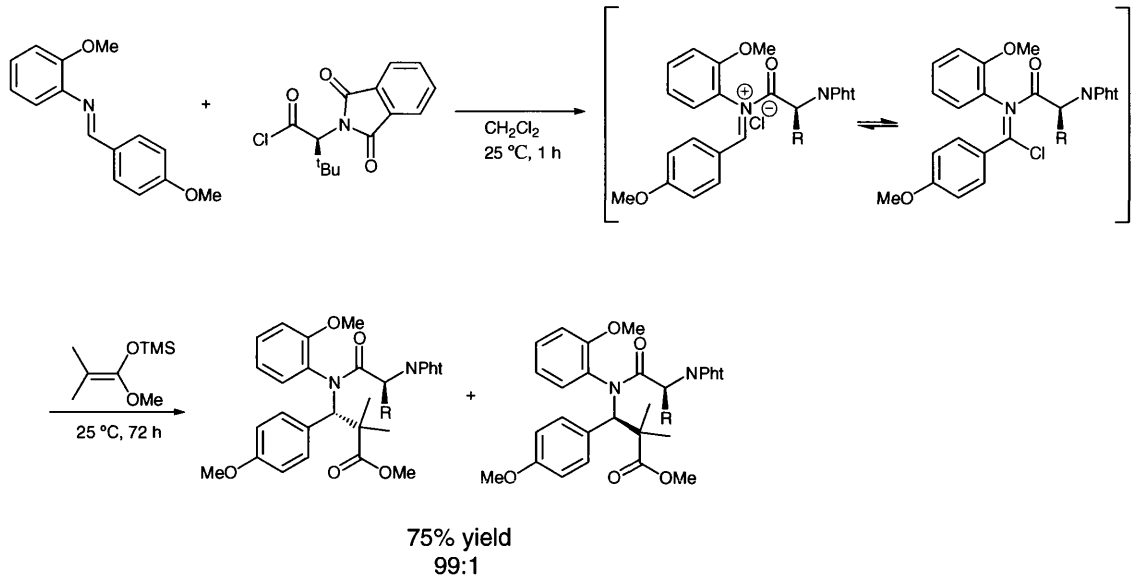
Scheme 2. 16: Diastereoselective Mannich-type reaction.

In 1997, Kunz and co-workers found that the zinc chloride-catalysed Mannich addition of 2,2-disubstituted silyl ketene acetals to *N*-galactosyl derived aldimines furnished β-amino acid esters in high yield and with good diastereoselectivity.[25, 26] Interestingly using a bis-silyl-ketene acetal as nucleophile resulted a *syn*-selective Mannich reaction, whilst employing the corresponding lithium enolate afforded the corresponding *anti*-β-amino ester. Afterwards, the auxiliary fragment could be cleaved from the purified major diastereoisomer by simple hydrolysis of the *N*-glycosidic bond using Bu_4NOH in THF.

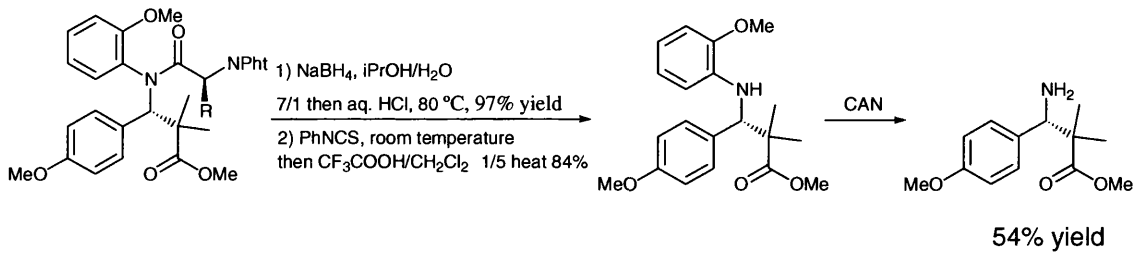


Scheme 2. 17: Asymmetric Mannich synthesis of α-branched β-amino acids.

Ongoing research within the Müller group into the Mannich-type reaction of *N,N*-phthaloylamino acids has reported that treatment of *N*-acyl-iminium species with *N,N*-phthaloyl-protected amino acid chlorides and a silyl ketene acetal gave *N*-acyl-β-amino acids in good yields and excellent diastereoisomeric ratios.[30] Surprisingly, the best results were obtained if the reaction was performed in the absence of a Lewis acid, whilst a remarkable dependence on temperature was observed with lower temperatures resulting in lower levels of stereocontrol! It is important to note that the presence of the phthaloyl protecting group was of paramount importance to achieve high levels of diastereoselection. X-ray crystal structure analysis of the resultant Mannich-adduct was used to assign the configuration of the newly formed stereocentre of the major diastereoisomer as (*S*). Finally, successfully cleavage of the phthaloyl group was carried out by partial reduction with $NaBH_4$ in 2-propanol/water mixture followed by acidic hydrolysis. The *N*-deprotected amino acid amide gave the desired *N*-acylated β-amino acid ester in high yield after carrying out Edman degradation (PhNCS, room temp, then CF_3COOH/CH_2Cl_2, 1/5, heat, 84% yield).[30, 31] Then, the *ortho* methoxy-substituted *N*-aryl group was cleaved off by treatment with cerium ammonium nitrate to give the desired *N*-deprotected β-amino acid methyl ester in 52% yield.

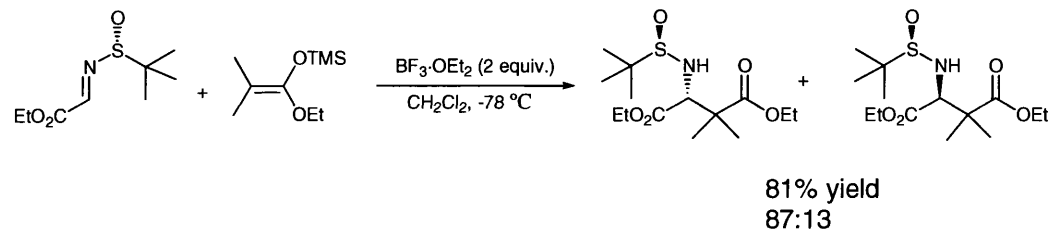


Scheme 2. 18: Asymmetric Mannich reactions using *N,N*-phthaloylamino acids as chiral auxiliaries.



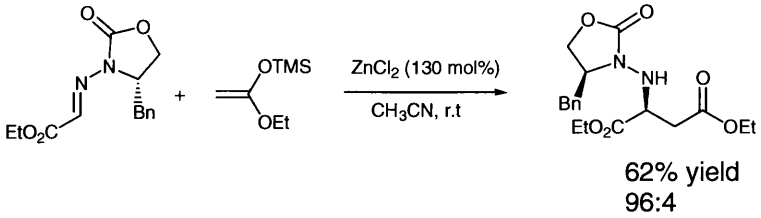
Scheme 2. 19: Cleavage of the chiral auxiliary.

Motivated by the fact that aspartic acid derivatives are excellent precursors of C4-functionalized β-lactams, Jacobsen and co-workers reacted a silyl ketene acetal with a enantiomerically pure glyoxylate imine containing an *N-tert*-butanesulfinyl auxiliary. The chiral auxiliary fragment served to activate the C=N bond of the glyoxylate imine towards nucleophilic attack in a stereoselective manner (*Re*-face is attacked), and was easily removed under acidic conditions using HCl in MeOH.[32] The reaction required the presence of a Lewis acid with best results obtained by precomplexing $BF_3 \cdot OEt_2$ to the imine for 20 minutes prior to addition of silyl ketene acetal at -78 °C in CH_2Cl_2.



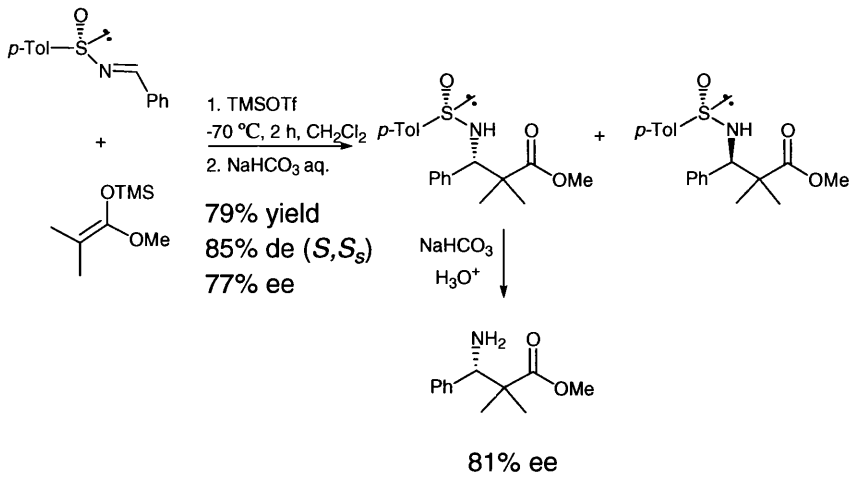
Scheme 2. 20: Asymmetric Mannich-type reactions for the synthesis of aspartic acid derivatives.

The Mannich-type reaction of chiral *N*-acylhydrazones and silyl enolates with $ZnCl_2$ at room temperature also affords Mannich-type adduct in consistently high diastereoselectivities, albeit in moderate yields.[33] The resultant diastereoselectivity was explained by preferential attack of the enolate nucleophile on the less shielded *Si* face of the chiral hydrazones which was confirmed by single crystal X-ray crystallography. Facile SmI_2-mediated cleavage of *N-N* bond of the diastereisomerically pure hydrazines was easily carried out to afford the parent β-amino acid derivative.[34]



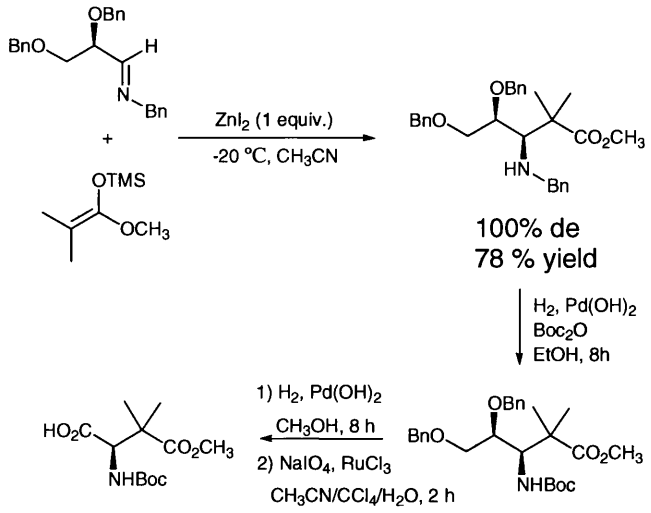
Scheme 2. 21: Highly diastereoselective Mannich-Type Reactions of Chiral *N*-acylhydrazones.

Another approach to the synthesis of β-amino acids was developed by Kawecki *et al.* who reacted sulfinimines with ketene silyl acetals in the presence of TMSOTf as a Lewis acid.[35] After creation of the new stereogenic center, the sulfinyl auxliary could be easily removed by acid treatment with TFA in MeOH. Aromatic sufinimiines gave their expected β-amino ester products in good yields as opposed to aliphatic sulfinimides which gave only traces of the desired Mannich products. For example, *N*-benzylidene *p*-tolylsufinimine was reacted with silyl ketene acetal in the presence of Lewis acid to afford an *N*-protected β-amino ester with high enantiomeric excess and good yields. The diastereoselection observed was dependent on the Lewis acid chosen with $BF_3 \cdot Et_2O$ and TMSOTf proving to be the most effective. The silyl ketene acetal chosen for reaction also played an important role in controlling the stereoselectivity of the reaction with the silyl ketene acetal derived from methyl acetate affording the major *(3S,S_s)* diastereoisomer in 85%.[35] Interestingly, the use of lithium enolates in this Mannich reaction once again gave the opposing (3*R*,*S*)-diastereoisomer. Basic work up of the sulphonamide product afforded the desired deprotected β-amino ester in 81% ee.[35]



Scheme 2. 22: *N*-Benzylidene *p*-tolylsufinamide reaction with enol silyl ketene acetals in the presence of TMSOTf.

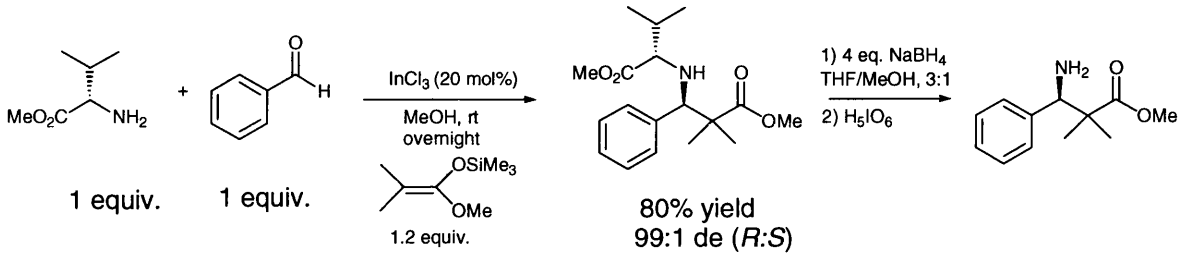
The Bandorrey group found that chiral benzyl imides derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde reacted with dimethyl silylketeneacetal in the presence of ZnI_2 at -20 °C in acetonitrile, to afford the corresponding β-amino ester with outstanding diastereoselectivity.[36] Selective benzylamine hydrogenolysis of the Mannich adduct in the presence of $(Boc)_2O$ using $Pd(OH)_2$ on carbon as a catalyst, afforded *N*-Boc derivative in 87% overall yield. As a consequence a range of Mannich adducts were deprotected to afford precursors of β,β-dimethyl aspartic acid which is a building block for many natural products and pharmaceutical agents.



Scheme 2. 23: Asymmetric Mannich reaction of chiral imine with a silyl dimethylketeneacetal.

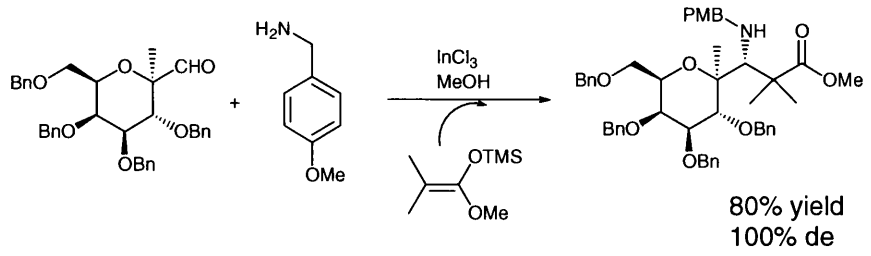
2.3.1.2 Three component Mannich-type reaction

In 2002, Loh *et al.* reported a one-pot $InCl_3$-catalysed Mannich reactions using an imine derived from aldehydes and valine methyl ester, with reactions carried out in MeOH giving good yields and high de for imines derived from enolizable aldehydes. The high diastereoselectivity obtained was explained using a transition state model in which the nitrogen atom of the imine and the carbonyl group of the ester were chelated by the indium catalyst to form a rigid transition state. The bulky isopropyl group of the L-valine methyl ester then selectively shields the *Re* face of imine with nucleophilic attack taking place from the more available *Si* face. For example, reaction of the imine of L-valine methyl ester and benzaldehyde gave a β-amino ester in 80% yield and 99:1 (*R/S*) diastereomeric ratio. [37-39] It was found that the ester group on the chiral auxiliary could be selectively reduced with $NaBH_4$ in THF/MeOH, followed by further oxidative chiral auxiliary cleavage with H_5IO_6.[38]



Scheme 2. 24: Diastereoselective Mannich-type reaction using L-valine methyl ester as a chiral auxiliary.

The interest in developing efficient routes to C-glucosyl β-amino acids within the Dondoni research group was inspired by their potential as glycopeptide-based drugs for the control of a wide range of biological processes. Thus, three component reaction of β-linked C-galactosyl formaldehyde, *p*-methoxybenzylamine and 2-methyl-1-trimethyl silyloxypropene in the presence of $InCl_3$ afforded a single diastereoisomer after 12 hrs.[40] Subsequent deprotection of the PMB group into their corresponding *N*-Boc derivatives was achieved via oxidative cleavage with ceric ammonium nitrate followed by treatment with di-*tert*-butyl dicarbonate (Boc_2O).[3]



Scheme 2. 25: Synthesis of a C-glycosyl β-amino ester *via* the one-pot three-component Mannich approach.

2.3.2 Lewis acidic chiral catalyst for the asymmetric Mukaiyama-Mannich reactions

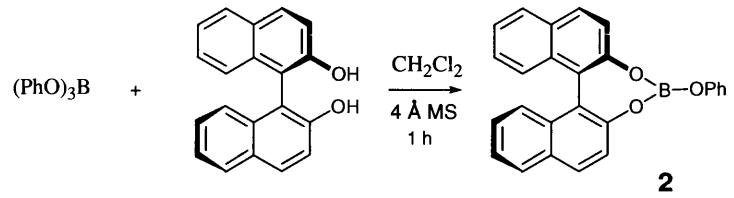
The vast majority of catalytic asymmetric Mukaiyama Mannich reactions have been catalysed by chiral transition metal complexes derived from different chiral ligands.

2.3.2.1 Chiral organometallic complexes

A number of outstanding examples of chiral Lewis acids that catalyse enantioselective reactions of imines with silyl ketene acetals have appeared in the last few years,[41-53] however these reactions are not without their problems. Some of the difficulties associated with Lewis acid catalysed Mannich reactions can be ascribed to the presence of the basic nitrogen atom, which can serve to irreversibly coordinate to the Lewis acid and shut down the catalytic process.[41] Alternatively, imine-chiral Lewis acid complexes are often insufficiently rigid for high levels of stereocontrol to occur due to the existence of structural isomers arising from lack of control of the *E/Z* geometry of the imine bond,[41] which can result in more than one accesible transition state, leading to decreased stereoselectivities. Furthermore, since Lewis acids can be deactivated when they coordinate to the basic nitrogen of the imine (or amine product) stoichiometric amounts of Lewis acid are often required for the reaction to reach completion. Therefore, Lewis acid catalysed reactions using imines are often more difficult to control than the corresponding aldol reactions of aldehydes or ketones.[41]

Nevertheless, asymmetric Mukaiyama Mannich reactions of silyl ketene acetals with imines in the presence of a chiral catalyst have provided useful methodology for the asymmetric synthesis of enantiomerically pure active β-amino esters. In this regard, Brönsted acid-assisted chiral Lewis acids (BLA) were one of the first catalysts used for

the enantioselective synthesis of chiral β-amino esters from reaction of achiral imines and ketene silyl acetals. The Yamamoto group first reported in 1993 the use of boron-BINOL complexes for the diastereoselective synthesis of β-aryl-β-amino acids in enantiomerically pure form as important fragments of spermine alkaloids.[53] The chiral boron Lewis acid **2** was originally reported to catalyse the diastereoselective reaction of aliphatic or aromatic imines derived from enantiopure α-methylbenzylamine **3** with silyl ketene acetal **4** to afford β-amino esters **5** in excellent de.[53]



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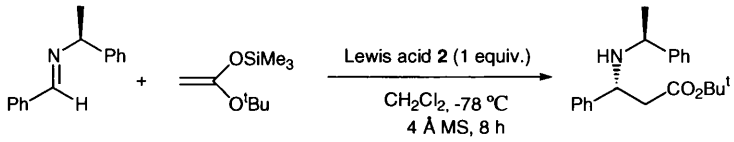
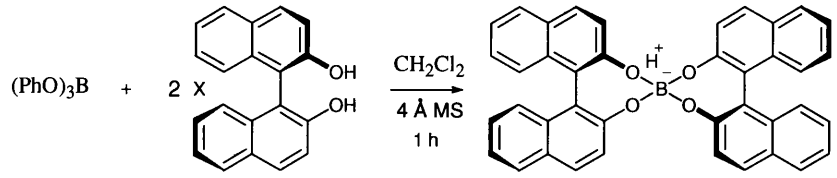
Scheme 2. 26: Preparation of the catalyst **2.**



3 **4** **5**

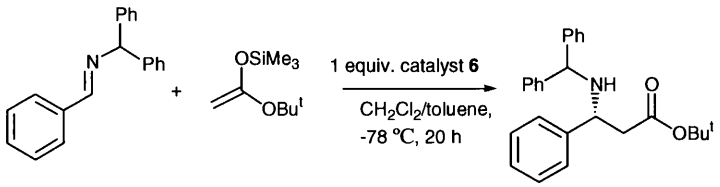
Scheme 2. 27: Diastereoselective Mannich-type reaction.

Other methods of preparing the boron-BINOL Lewis acid **6** were investigated involving stirring a 2:1 molar ratio of *(R)*-binaphthol and $B(OMe)_3$ in CH_2Cl_2, which was shown to catalyse an enantioselective reaction of *N*-benzylidenebenzhydrylamine and a ketene silyl acetal to afford the *tert*-butyl amino ester **8** in 96% ee. This catalytic enantioselective methodology will be discussed in more detail in Chapter 3 of this thesis.[42]



6

Scheme 2. 28: Preparation of boron-BINOL catalyst **6.**

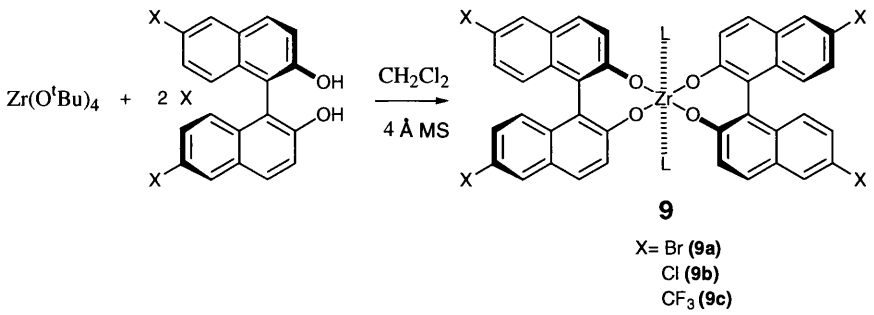


1 equiv. 2 equiv. 96% e.e
58% yield

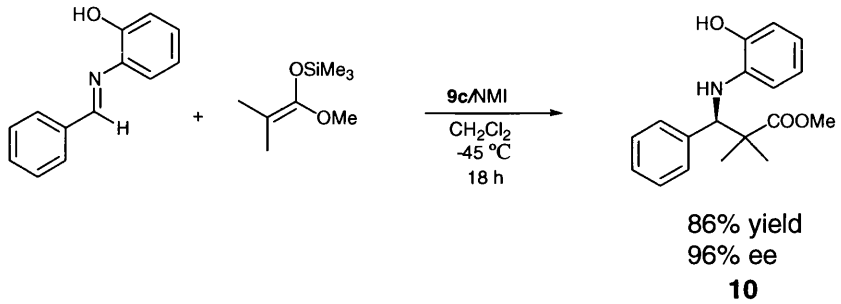
7 **8**

Scheme 2. 29: Enantioselective Mannich-type reaction.

In 1997, Kobayashi and co-workers reported the reaction of imines with silyl ketene acetals, using a chiral catalyst **9** that was prepared *in situ* from 1 equiv. of $Zr(O^tBu)_4$ and 2 equiv. of (*R*)-BINOL in dichloromethane at room temperature, before carrying out the Mannich reaction at -45 °C.[45, 47-51] The use of achiral additives such as *N*-methylimidazole (NMI) or 1,2-dimethylimidazole (DMI) were demonstrated to be necessary for good levels of stereocontrol.[48, 50] The Lewis acidity of the zirconium metal was found to increase when electron-withdrawing groups were introduced at the 6,6′-positions of the chiral BINOL ligand. When a trifluoromethyl group was used as the electron-withdrawing group in the presence of NMI as an additive, β-amino esters were produced in up to 96% ee using only 0.5 mol % of catalyst. In order to avoid potential problems associated with the conformational flexibility of the imine-metal complex, Kobayashi chose to employ an *o*-hydroxyphenyl *N*-protected group on the imine which proved essential for controlling reaction selectivity. It was proposed that both the nitrogen atom of the imine and the oxygen atom of the hydroxyl aryl group coordinated to Zr to form a rigid intermediate complex. The group demonstrated that imines from heterocyclic and aliphatic aldehydes worked well in this reaction, affording β-amino esters in good to high yields and excellent enantiomeric excesses. In addition, the 2-hydroxyphenylimine moiety facilitated the easy oxidative removal of the nitrogen protecting group to generate primary amines containing a free nitrogen functionality.[48, 50, 51]



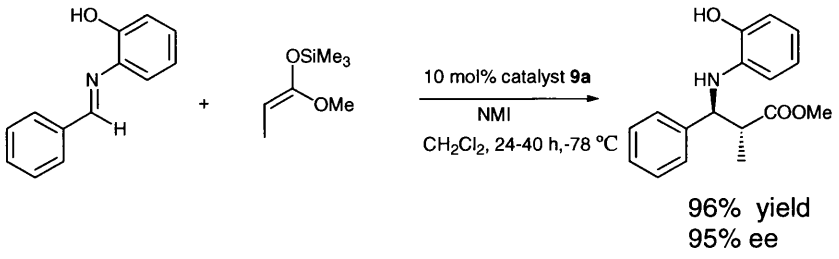
Scheme 2. 30: Preparation of zirconium catalyst **9.**



Scheme 2. 31: Enantioselective Mannich-type reaction of imines with silyl ketene acetal.

Additonal studies reported last year for the same Mannich-type reaction by the Kobayashi and Mouthtady groups have extended the scope of the remarkably stable chiral zirconium catalyst **9**.[46] Kobayashi and co-workers carried out their studies using 10 mol% (*S*)-6,6´-(C_2F_5)$_2$-BINOL-Zr which afforded β-amino ester **10** in 93% yield and 87% ee. On the other hand, Mouthtady described that 2 mol% (*S*)-6,6´-bis(trifluoromethanesulfonyl)-2,2´-dihydroxy-1,1´-binapthyl-Zr catalysed the Mannich-type reaction of an imine derived from 1-naphthalenecarboxaldehyde and trimethylsilyl ketene acetal at -95°C in dichloromethane to afford the corresponding Mannich-adduct after 4 hours in a 50% modest yield and good 80% enantiomeric excess.[46]

Further investigations demonstrated the synthetic utility of this type of Mannich type reaction to obtain enantiomerically pure *anti*-α-methyl-β-amino acids and β-lactam derivatives. As shown in Scheme 2.32 addition of propionate derived silyl ketene acetals to imines using 10 mol% of chiral zirconium complex **9a** and NMI at -78°C in CH_2Cl_2 afforded the desired *anti* adduct in 96 % yield and 95% ee.[54]



Scheme 2. 32: Asymmetric synthesis of anti-α-methyl β-amino ester using chiral zirconium catalyst **9a**.

In order to explain the sense of enantioselection, the authors postulated the transition state shown in Figure 2.1, in which the *Re* face of the imine is shielded by one of the napthyl rings of the BINOL ligand, which forces the ketene silyl acetal to attack from the *Si* face of the aldimine. Deactivation of the Lewis acid catalyst by imine or amine was not observed under these reaction conditions enabling substoichiometric amounts of the zirconium catalyst to be employed. In spite of the high rates of ligand exchange observed for zirconium alkoxides, it was shown that the phenolic functionality of the imine protecting group of the imine/amine did not appear to exchange with the BINOL ligand of these complexes.[48]

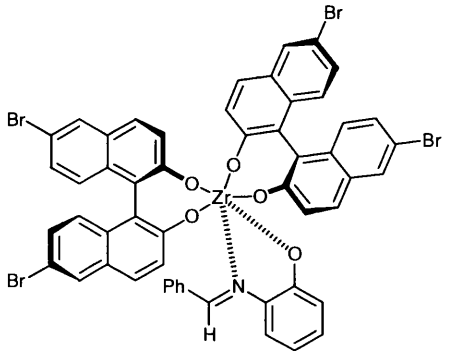
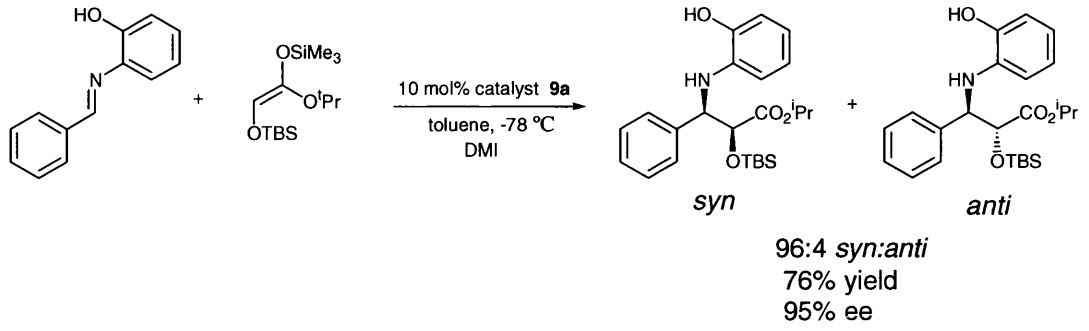


Figure 2. 1: Complex of the zirconium catalyst with an imine.

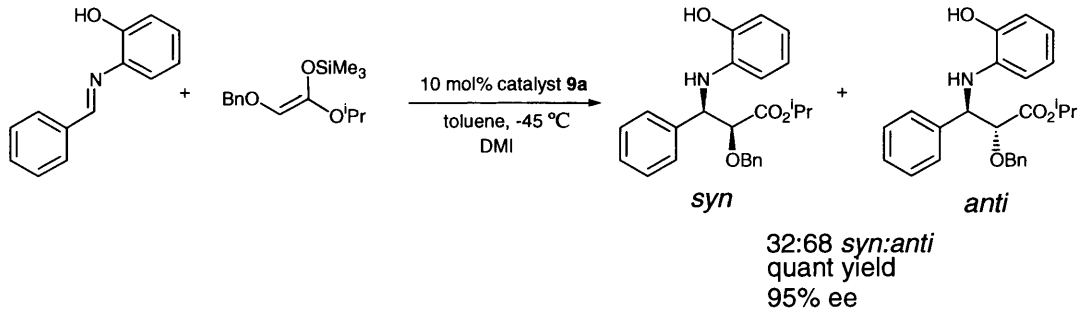
Catalytic diastereo- and enantioselective Mannich type reactions of (*E*) α-alkoxy silyl enol esters with imines have also been developed for the asymmetric synthesis of α-hydroxy-β-amino esters. After screening several conditions Kobayashi *et al.* described that the best results were obtained when imines were reacted with α-TBSO-ketene silyl acetal in toluene at -78 °C using 10 mol% of (*R*)-6, 6´-dibromo-BINOL-Zr catalyst **9a** and NMI. The reactions proceeded smoothly to afford the corresponding α-alkoxy-β-amino ester in 76% yield in a 96/4 *syn/anti* ratio, with the *syn* diastereoisomer being formed in 95% ee. Interestingly, better selectivities were found in the presence of DMI,

while the enantioselectivity of the β-amino ester product produced was highly dependent on the structure of the enolate used in the reaction. [47, 54]



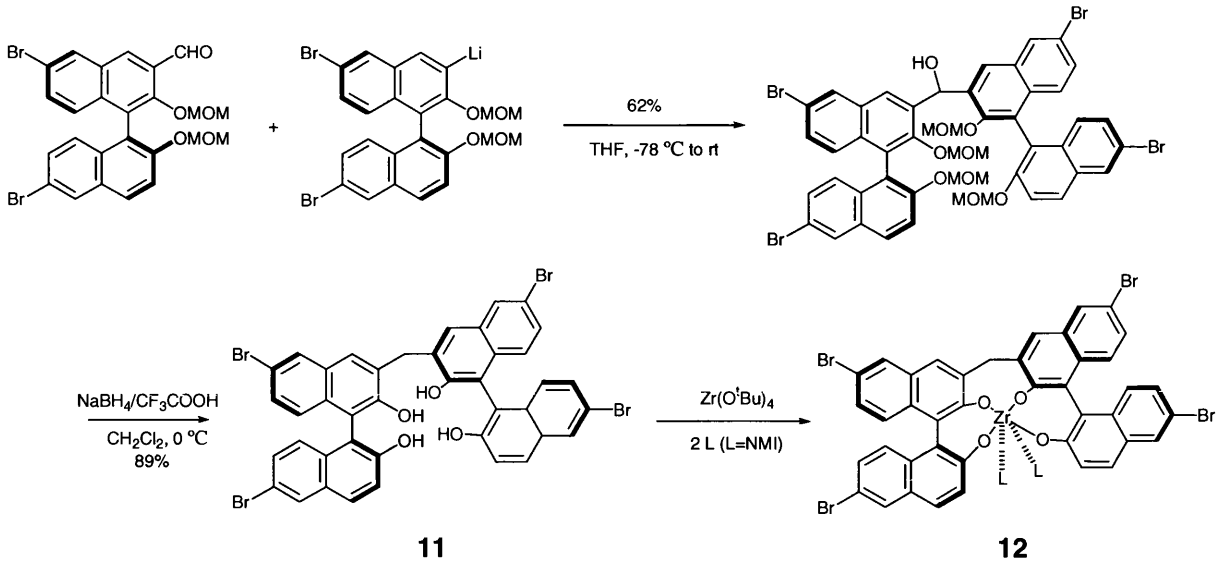
Scheme 2. 33: Mannich-type reaction for enantioselective synthesis of *syn*-β-amino alcohols.

Therefore, Kobayashi described that both *syn*- and *anti*- amino alcohol units could be prepared by judicious choice of the protecting group on the α-alkoxy fragment of the silyl ketene acetals. For example, when the Mannich reaction was carried out using an α-OBn-ketene silyl acetal in CH_2Cl_2 at -45°C under the same reaction conditions it gave an *anti* β-amino ester as the major product with an enantiomeric excess of 95% (Scheme 2.34). [47, 54]



Scheme 2. 34: Mannich-type reaction for enantioselective synthesis of *anti*-β-amino alcohols.

In 1999, Ishitani and co-workers reported the use of Shibasaki's bridged *bis*-BINOL ligand **11** to prepare another chiral zirconium catalyst **12**, which they proposed would coordinate to an imine substrate to afford the transition state described in Figure 2.2.[48]



Scheme 2. 35: Preparation of novel chiral zirconium catalyst **12**.

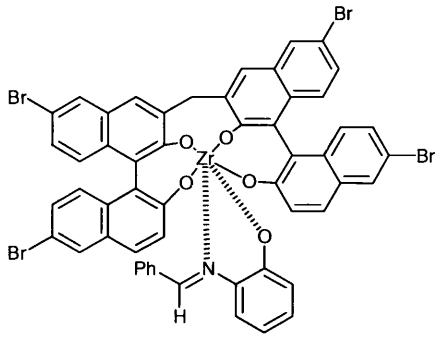
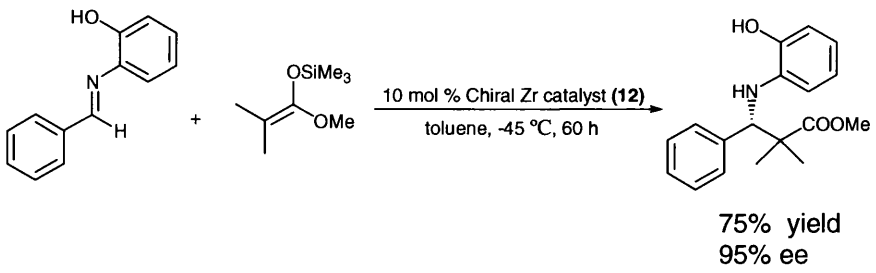


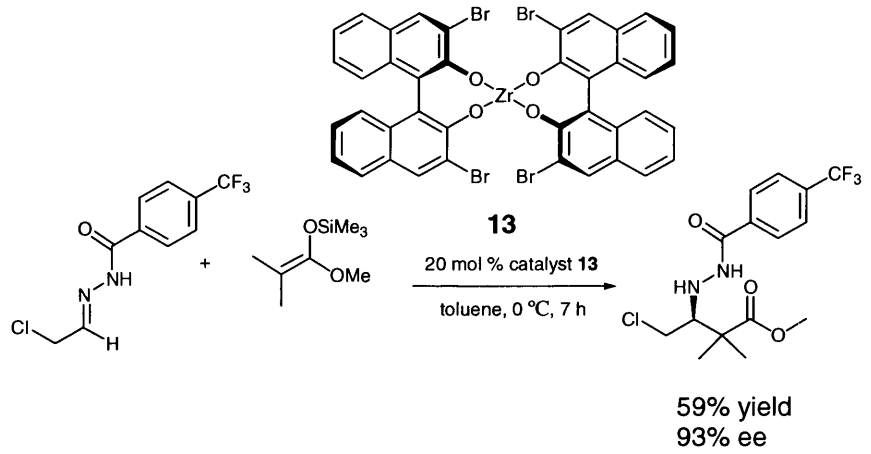
Figure 2. 2: Complex of the catalyst with the imine.

Thus, when 10 mol% of zirconium catalyst was used to catalyse the Mukaiyama Mannich reaction of an imine with a ketene silyl acetal derived from methyl isobutyrate at -45 °C in toluene, it gave the corresponding β-amino ester in quantitative yield and in a satisfactory enantiomeric excess of 95%.[48]



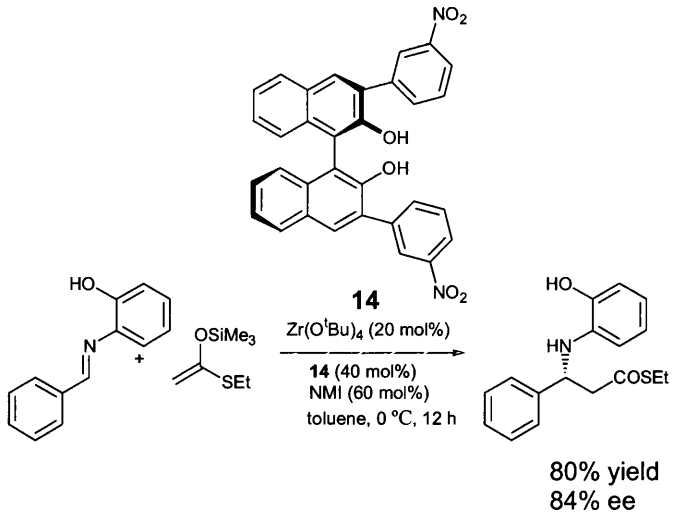
Scheme 2. 36: Enantioselective Mannich-type reaction of imines with silyl enol ether.

The Kobayashi group have also described the use of *N*-acylhydrazones as imine equivalents, which have the advantage that they are easy substrates to handle at room temperature, and afford chiral products that are readily deprotected to afford their corresponding β-amino esters. Best results were obtained in the presence of a catalytic amount of the new *ortho*-substituted zirconium catalyst **13**, with trifluoromethylbenzoylhydrazones reacting with silyl ketene acetals in toluene to afford β-*N*-acylhydrazinocarbonyl compounds in good yield and high enantiomeric excess. For example, reaction of the *N*-acylhydrazone derived from chloroacetaldehyde gave its *N*-protected β-amino ester in 93% ee.[54]



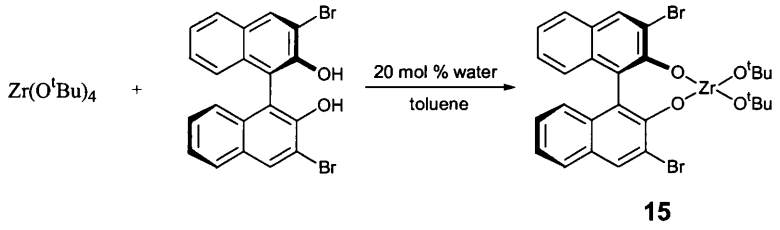
Scheme 2. 37: Zirconium catalyst for the Mannich-type reaction of acylhydrazones.

Two years later, Kobayashi group investigated the use of (*R*)-3,3′-di-(3-nitrophenyl)-binapthol-zirconium as a chiral catalyst, for the reaction of *S*-ethylthio-(trimethylsiloxy)ethene with imines. *N*-protected β-amino thioester products were obtained in up to 84% ee and 80% yield using 20 mol% of zirconium catalyst **14**.[54]

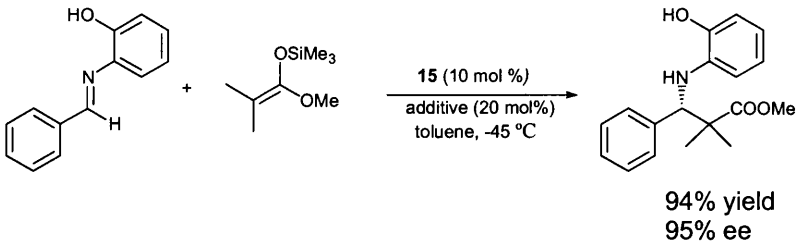


Scheme 2. 38: Mannich-type reaction for synthesis of β-amino *S*-ethyl esters.

In the same year, Kobayashi *et al.* developed improved conditions for the asymmetric Mukaiyama Mannich reactions of imines with silyl enolates. Thus, in the presence of 10 mol% of chiral zirconium catalyst **15**, prepared from 1 equiv. of $Zr(O^tBu)_4$ and 1 equiv. of (*R*)-3,3'-Br_2-BINOL and water, imine reacted with 1-trimethyl silyloxy-1-methoxy-2-methoxypropene at -45 °C in toluene to afford the desired β-amino ester adduct in 94% yield and 95% ee.[43]



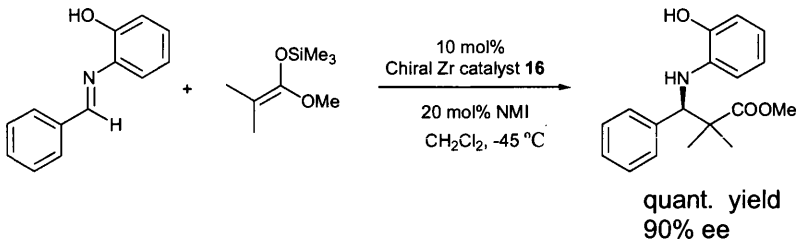
Scheme 2. 39: Zirconium catalyst **15**.



Scheme 2. 40: Asymmetric Mannich reaction using zirconium catalyst **15**.

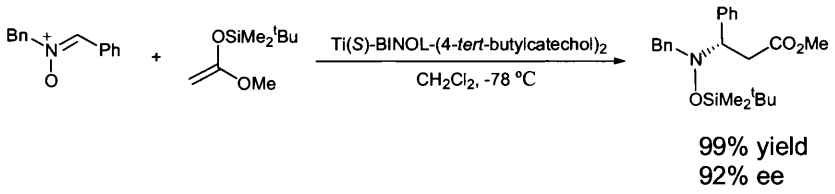
The following year, they also reported an air-stable, highly selective chiral zirconium Lewis acid catalyst **16**, (*R*)-6,6'-C_2F_5-Zr-MS (molecular sieves), whose structure was not determined. Its use as a catalyst in asymmetric Mannich reactions afforded β-amino

esters in quantitative yield and with excellent stereocontrol of 90% ee. The catalyst had the advantage that it could be stored for more than 3 months in air at room temperature without loss of activity, enabling it to be readily recovered and reused.[52]



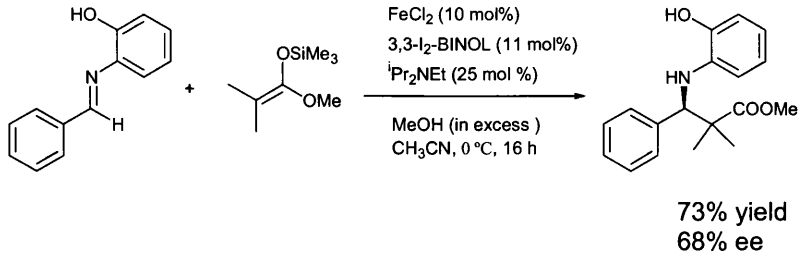
Scheme 2. 41: Asymmetric Mannich reaction using the novel zirconium catalyst **16**.

The first catalytic, enantioselective synthesis of enantiomerically pure *N*-hydroxy-*β*-amino acid derivatives using imines derivatives from hydroxylamines were carried out within the Maruhashi group. Ti-(*S*)-BINOL-(4-*tert*-butyl catechol)$_2$ was used to catalyse the reaction of *N*-benzylidenebenzylamine *N*-oxide with 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene in CH_2Cl_2 at -78 °C to give a *N*-hydroxyl-β-amino ester in 92% ee. The cleavage of the nitrogen-oxygen bond with Zn/H_2SO_4 and recrystrallisation of the resultant oxalic acid salt gave enantiomerically pure *N*-benzyl-*β*-phenylalanine methyl ester.[55]



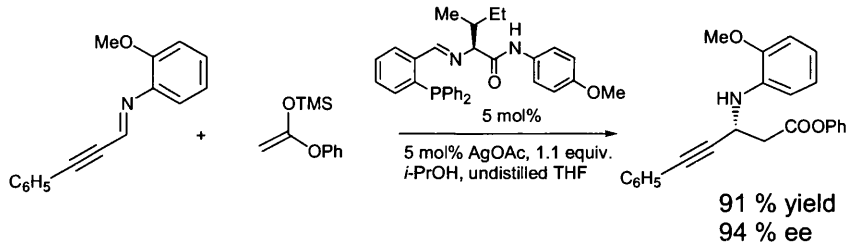
Scheme 2. 42: Enantioselective synthesis of optically active *N*-hydroxy-*β*-amino acid derivatives.

In 2002, Yamashita *et al.* developed a novel chiral iron complex **17** derived from $FeCl_2$, (*R*)-3,3'-diiodo-1,1'-binapthalene-2,2'-diol, diisopropylethylamine ($^iPr_2NEt$) and an excess of MeOH in acetonitrile at 0 °C. This complex catalysed reaction of an imine and ketene silyl acetal to give the desired β-amino ester in a good yield of 83% with a modest enantiomeric excess of 68%.[56]



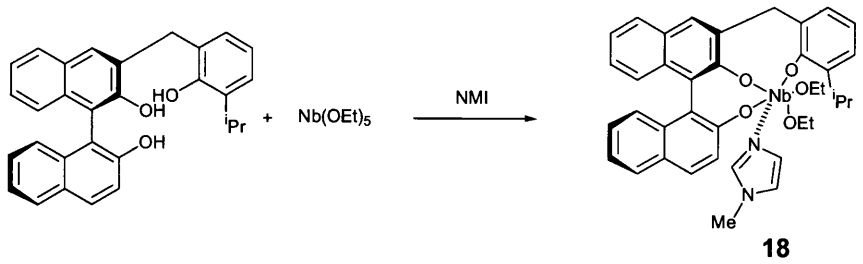
Scheme 2. 43: Asymmetric Mannich reaction using the novel iron complex **17**.

The reaction between α,β-alkynyl imines and silylketene acetal proceeds smoothly at -60 °C in the presence of a readily available *iso*-leucine derived phosphine ligand which promote Ag-catalysed Mannich reactions in THF. It was found that with 5 mol% catalyst loading, an excellent yield of 91% yield and 94% ee for β-amino ester formation were obtained.[57]

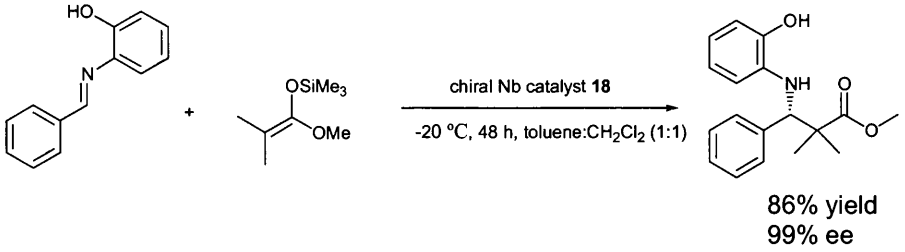


Scheme 2. 44: Ag-catalysed enantioselective Mannich reaction of silylketene acetal to alkynyl imines.

Very recent studies within the Kobayashi group have described the use of niobium catalysts derived from tridentate BINOL ligands and niobium alkoxides, Nb $(OEt)_5$. The novel catalyst (10 mol%) in the presence of the achiral ligand NMI, were employed in the Mannich-type reaction of imines with silyl enolates in toluene:CH_2Cl_2 (1:1) in the presence of 4 Å molecular sieves at -20 °C to afford the desired Mannich-type adduct in 86% yield and 99% ee.[44]

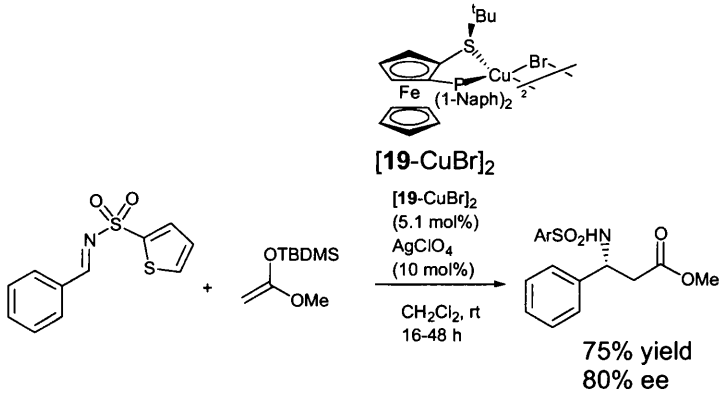


Scheme 2. 45: Novel dinuclear chiral niobium catalyst **18**.



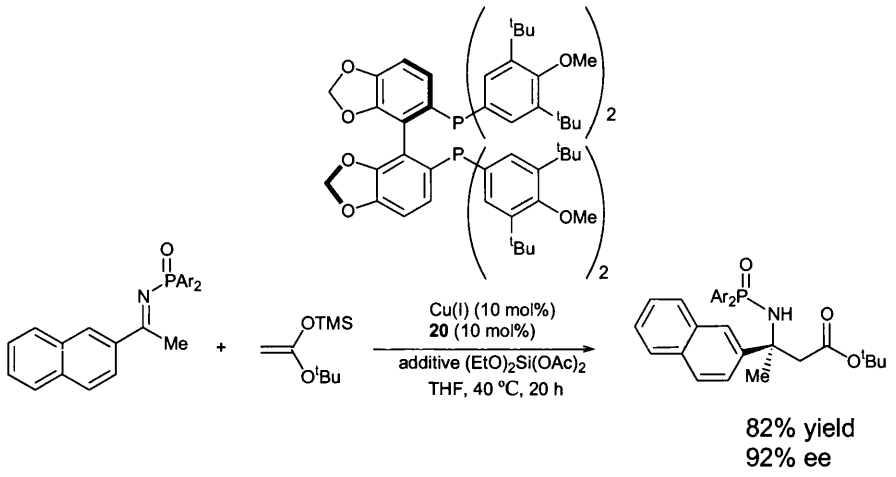
Scheme 2. 46: Mannich-type reaction catalysed by a novel dinuclear niobium catalyst **18**.

It has been shown within the Salvador González group that a combination of Cu^{I}-Fe-sulphos as catalyst and 2-thienylsulfunyl imines as a substrate affords a stereoselective route to β-amino esters for a series of silyl ketene acetal nucleophiles. From a synthetic perspective, it is important to note that the resulting 2-thienylsulfonyl-protected β-amino ester derivative can be easily removed with no loss of enantioselectivity by treatment with magnesium methoxide in methanol.[58]



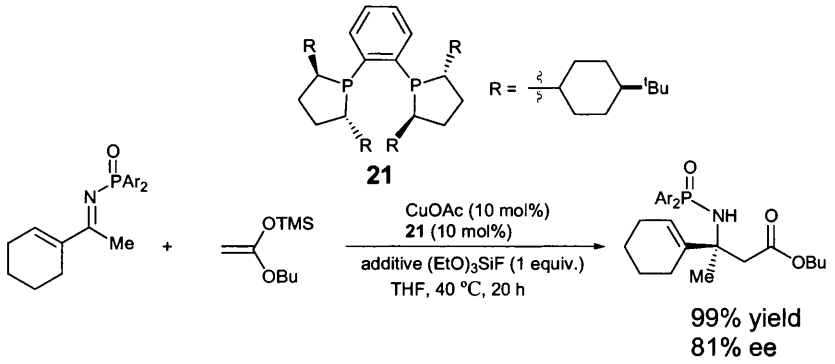
Scheme 2. 47: Mannich-type reaction of *N*-sulfonylimines catalysed using Cu^{I}-Fesulphos as catalyst.

Suto *et al.* have recently described the first catalytic enantioselective Mannich reaction of simple ketoimines by applying optimized conditions previously developed for aldimines. The reaction between ketoimine and silyl ketene acetal produced the Mannich-adduct in 82% yield and 92% ee, when 10 mol% CuOAc3PPh_3·2EtOH complex **20** was used as a catalyst. In this reaction, a highly nucleophilic copper enolate was generated through transmetallation of the corresponding silyl enolate which then functions as the incipient nucleophile. The catalyst regeneration step from the intermediate copper aldolate is the rate- limiting step, and it was found that using a stoichiometric amount of $(EtO)_2Si(OAc)_2$ as additive was essential to facilitate this turnover step.[58]



Scheme 2. 48: Catalytic enantioselective Mannich reaction of aromatic ketoimines.

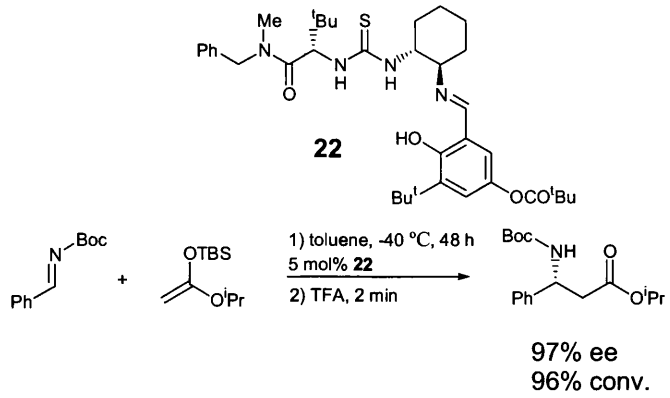
It was found that aliphatic ketoimines isomerised to their corresponding enamines under the reaction conditions thus lowering the yield of β-amino ester produced, however this undesired tautomerisation pathway could be suppressed by using $(EtO)_3SiF$ as a trapping reagent and DuPHOS derivatives as the chiral ligand.



Scheme 2. 49: Second generation catalytic enantioselective Mannich reaction of aromatic ketoimines.

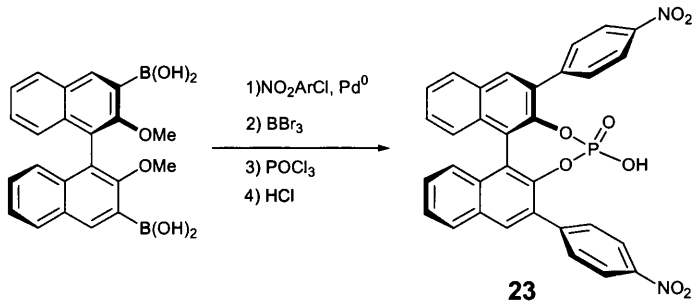
2.3.2.2 Organocatalysis

In 2003, it was reported that chiral thiourea catalysts could be used for the stereoselective addition of silyl ketene acetals to *N*-Boc-protected aldimines. A series of modifications to the structure of the peptidic fragment of the thiourea catalyst were carried out, resulting in an optimal catalyst derived from a tertiary amide. These Schiff base thiourea catalyst were shown to afford *N*-Boc-β-amino ester products in 97% ee at 96% conversion.[59]

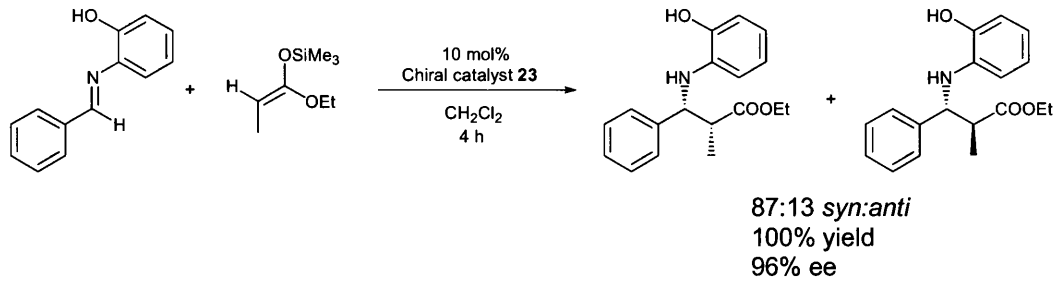


Scheme 2. 50: Thiourea catalysed Mannich-type reaction.

Further investigations into enantioselective Mukaiyama Mannich-type reactions catalysed by chiral Brönsted acid were reported last year by the Akiyama group.[60, 61] In this case, a chiral metal-free organocatalyst was prepared by Suzuki coupling of bis (boronic acid) with *p*-nitrophenyl chloride, followed by MeO-deprotection and formation of monophosphate **23**. It was shown that the introduction of aromatic groups at the 3, 3′-positions were essential for good enantioselectivities to be observed of up to 87% ee after 4 h at -78 °C. It was proposed that the 3, 3′-diaryl groups occupied a conformation perpendicular to the naphthalene groups which effectively shielded the phosphate moiety, leading to efficient asymmetric induction. Unsurprisingly, Akiyama and co-workers demonstrated that using aprotic non-polar aromatic solvents led to high enantioselectivity, whereas protic solvents gave racemic products.[60, 61]

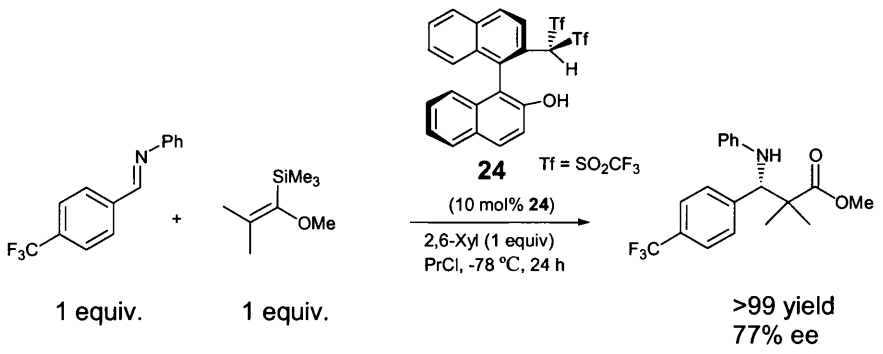


Scheme 2. 51: Preparation of the catalyst **23**.



Scheme 2. 52: Diastereoselective Mannich-type reaction.

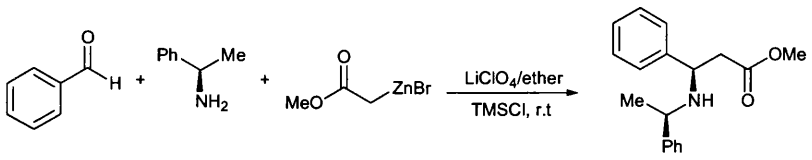
Early last year, Hasegawa reported the enantioselective Mannich-type reaction of *N*-arylaldimines with ketene acetals catalysed by a chiral Brönsted acid that acts through hydrogen bonding with the nitrogen imine. The novel Lewis Brönsted acid (LBA) was developed by replacing the hydroxy group of enantiopure 1,1′-bi(2-naphthol) with a stronger Brönsted acid group as a bis(trifluoromethanesulfonyl)hydroxymethyl group.[62] It was proposed that the conformation of the OH···N hydrogen bond was rotationally fixed with regard to the R*–O axis which facilitated an intramolecular OH···OH hydrogen bonding. Initial levels of enantioselectivity were low, but it was found that addition of sterically demanding 2,6-xylenol as an achiral additive resulted in improved levels of stereocontrol. A wide range of aldimines and silyl enol ethers were screened and the best result obtained for *p*-(trifluoromethyl)benzaldehyde using 2.5 mol% catalyst loading, which gave its corresponding β-amino ester in 77% ee.[62]



Scheme 2. 53: Enantioselective Mannich-type reaction catalysed with a novel Lewis Brönsted acid (BBA).

2.3.3 Direct Lewis acid chiral catalyst for asymmetric Mannich reactions

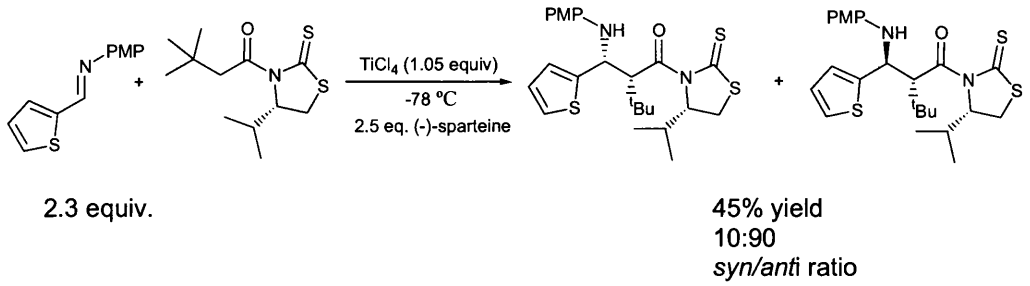
There has also been much interest in developing synthetic protocols that employ "unactivated" enolates nucleophiles for the asymmetric Mannich synthesis of β-amino esters. These protocols have the advantage of not having to use expensive silyl ketene acetals nucleophiles, and for completeness brief highlights of this area are now described here. In the chiral auxiliary area, a "one pot" diastereoselective β-amino ester synthesis has been reported by Saidi and Azidi, who described an efficient and straightforward method for aminoalkylation of aldehydes with chiral amines and zinc enolates using lithium perchlorate as a Lewis acid in diethyl ether.[63] The chiral imine substrate was first generated *in situ* at room temperature in a concentrated ethereal lithium perchlorate solution (5M), followed by addition of the zinc enolate ester to the reaction mixture, to afford the desired β-amino esters in 65-95% de.[63]



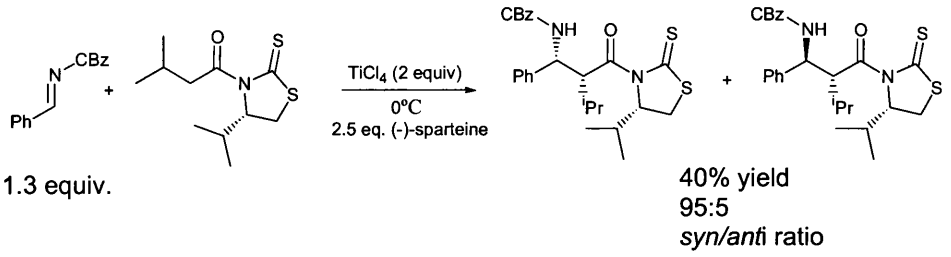
88% yield
95% de

Scheme 2. 54: Preparation of chiral β-amino ester using a three component chiral auxiliary strategy.

In 2002, the asymmetric synthesis of α-β-disubstituted β-amino ester derivatives was reported involving reaction of the titanium enolate of a chiral *N*-acyl-thiazolidine thione with non-enolizable imines. Variation of the substituent on the imine nitrogen enabled *syn-* or *anti-* β-amino derivatives to be obtained. Thus, in reactions involving PMB-substituted imines, transition state TS1 was proposed to explain the observed *anti* selectivity. In contrast, the use of CBZ-imines gave the *syn* adduct according to transition state TS2.[64] It was shown that an increase in stereoselectivity was obtained as the steric demand of the R group increased, whilst the presence of excess $TiCl_4$ also significantly increased both the yield and stereoselectivity.[64]



Scheme 2. 55: Thiazolidine-2-thione directed diastereoselective addition of chlorotitanium enolates to PMB-substituted imine.



Scheme 2. 56: Thiazolidine-2-thione directed diastereoselective addition of chlorotitanium enolates to CBz-substituted imine.

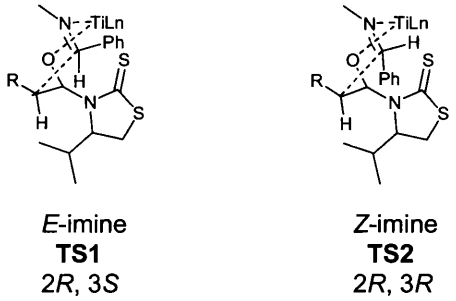
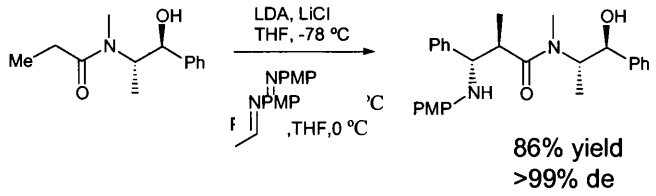


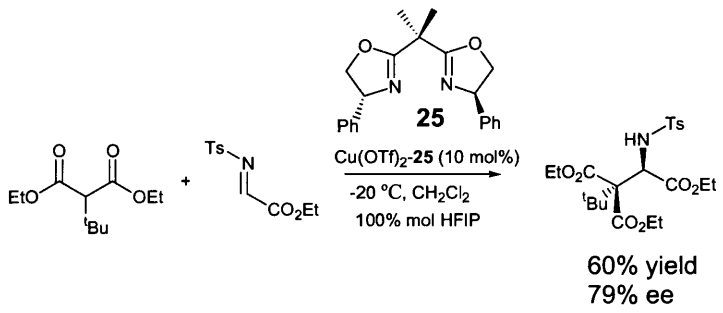
Figure 2. 3: Transition states TS1 and TS2.

Mannich reaction between the lithium enolates of substituted (*S,S*)-pseudophedrine amides with enolizable and non-enolizable imines afforded β-substituted α-alkyl-β-amino amides with excellent stereocontrol. For example, reaction of the enolates of *N*-4-methoxyphenyl-substituted imines in the presence of five equivalents of lithium chloride gave β-amino amide diastereoisomer in a good yield of 86% and >99% de. It must be noted that lithium chloride was an essential additive in these reactions for enhancing the reactivity of the poorly electrophilic imines, since in its absence only starting materials were recovered. Interestingly, enolizable imines required a different Lewis acid, $ZnCl_2$, for the reaction to proceed; the use of LiCl produced no product.



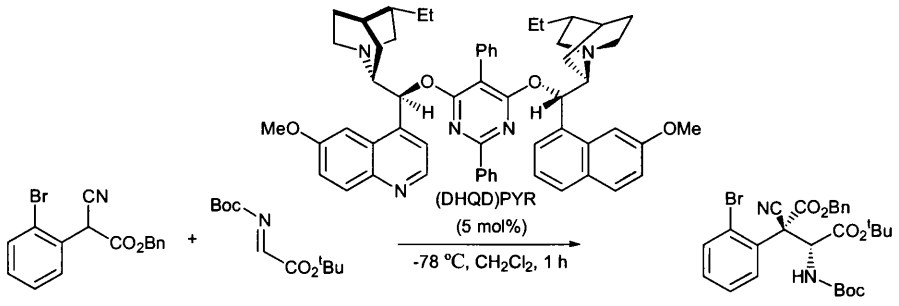
Scheme 2. 57: Asymmetric Mannich reaction using nonenolizable imines.

An investigation into direct catalytic asymmetric Mannich reactions of malonic esters and *N*-tosyl-α-imino-esters catalyzed by 10 mol% of the chiral copper (II) bisoxazoline complex $Cu(OTf)_2$/(R)-Ph-BOX gave the resultant β-carboxylic α-amino esters in moderate yield and good ee.[65] It is interesting to note that using additives such as hexafluoroisopropanol in this reaction gave a slight increase in enantioselectivity, without affecting the yield significantly.[65]



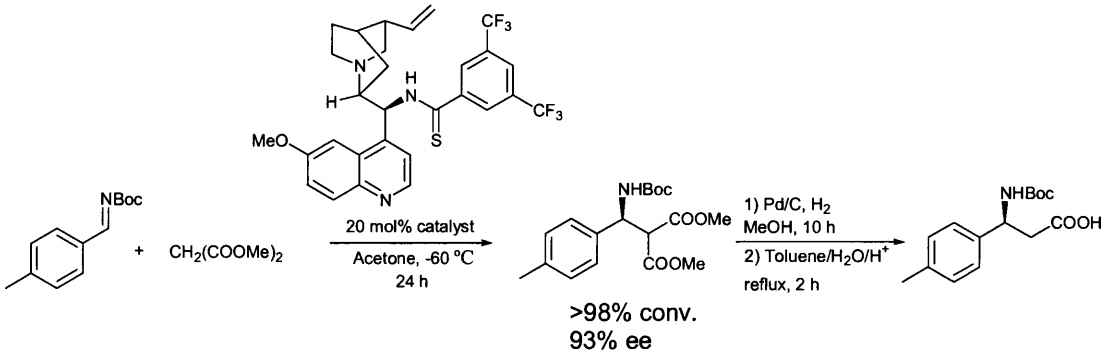
Scheme 2. 58: Direct catalytic asymmetric Mannich reactions of malonates and *N*-tosyl-imines.

Ongoing studies on highly enantio- and diastereoselective Mannich reactions catalyzed using commercially available (DHQD)PYR have also been reported by the Poulsen group.[66] This cinchona alkaloid catalyst mediates the addition of a α-aryl-cyano-malonate enolate to *N*-Boc-imines to afford highly functionalised β-amino ester products in 98% de, and 98% ee.



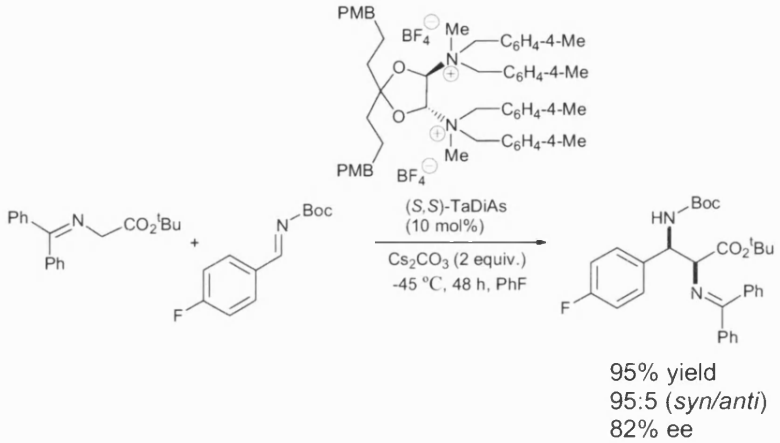
Scheme 2. 59: Distereoselective Mannich-type reaction of α-substituted α-cyanoacetates.

Further research lead the Song group to show that related cinchona alkaloid derivatives could also act as efficient bifunctional catalysts for the Mannich reaction of malonates with a variety of *N*-tosyl imines.[67] Excellent levels of enantioselectivity were observed for β-amino ester derivatives of dimethyl malonate in acetone at -60 °C. Subsequent hydrogenolysis of the Mannich-type adducts with Pd over C in MeOH, followed by reflux for 2 h in toluene lead to decarboxylation and efficient preparation of chiral *N*-Boc-β-amino acids.[67]



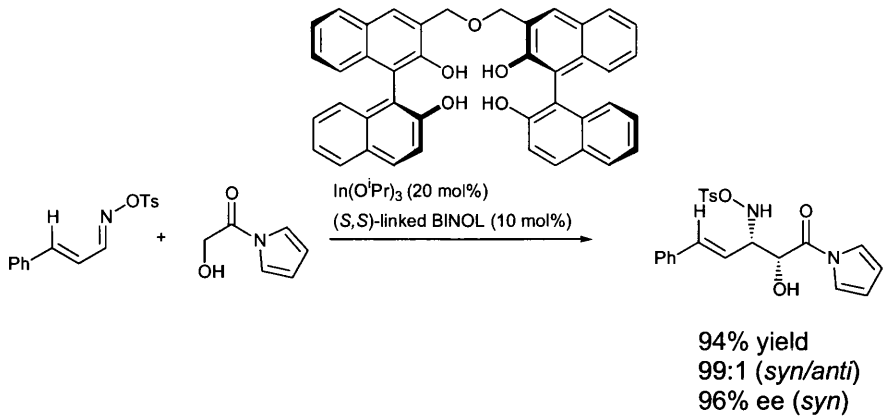
Scheme 2. 60: Enantioselective synthesis of malonates to *N*-Boc imine catalyzed by cinchona.

Additional studies within the Osaka group have resulted in the enantio- and diastereoselective synthesis of α,β-diamino acid derivatives, using a chiral two-center phase-transfer catalyst to control facial stereoselectivity.[68] The levels of asymmetric induction obtained were highly dependent on the structure of the phase transfer catalyst with best results being obtained using a 4-fluoro-phenyl-substituted aldehyde which suggesting that Л-Л interactions may be important for stereocontrol. Thus, the Mannich-type reaction of *N*-Boc imines with *N*-protected glycine enolates proceeded in good yield with high diastereoselectivity using 10 mol% of TaDiAs and Cs_2CO_3 in fluorobenzene at -45 °C for 48 °C.[68]



Scheme 2. 61: Mannich-type reaction by using a chiral two-center phase-transfer catalyst.

In 2005, an alternative ester-enolate-equivalent and new asymmetric catalyst were developed to induce high diastereselectivity and conversion into the Mannich-type reaction. The catalyst complex composed of $In(O^iPr)_3$ and (*S*,*S*)-linked BINOL and successfully catalyzed the Mannich reaction of *N*-(2-hydroxyacetyl)-pyrrole and *ortho*-tosylimines.[69] The *N*-acyl pyrrole reacted with the imine substrate in THF at room temperature to afford the Mannich adduct in 94% with good diastereoselectivity (*syn*/*anti*=91:9) and excellent enantioselectivity (96% ee). It was assumed that an alkoxide or phenoxide generated *in situ* functions as a Brönsted base to deprotonate the *N*-acyl pyrrole at its α-position thus afforded a chiral indium enolate *in situ* which then underwent the stereoselective Mannich reaction.[69]



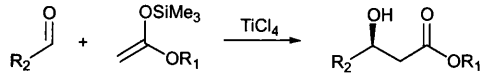
Scheme 2. 62: Asymmetric Mannich-type reactions of *N*-(2-hydroxyacetyl) pyrrole.

2.4 MUKAIYAMA ALDOL TYPE REACTION

Addition reactions of enolates to carbonyl are one of the most fundamental and important reactions in organic chemistry, and the aldol reaction of aldehydes with many enolate equivalents has been extensively studied. In this respect, the Mukaiyama aldol reaction has been shown to be a highly powerful method for stereoselective carbon-carbon bond formation,[70] and a brief review of this area now follows.

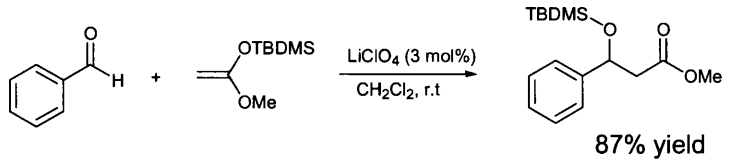
2.4.1 Lewis acid and Lewis base catalysed Mukaiyama aldol reactions

In the recent years, many reagents have been developed for the reaction of silylketene acetals with aldehydes using stoichiometric amounts of Lewis acid to mediate the reaction. The most common Lewis acids used are $TiCl_4$ [71] and $SnCl_4$, but a wide range of other Lewis acid catalysts such as ZnX_2 (X=I, Cl), $SnCl_2$, $AlCl_3$ and BF_3Et_2O [71-76] have also been shown to afford β-hydroxy-esters in good yield.[77]

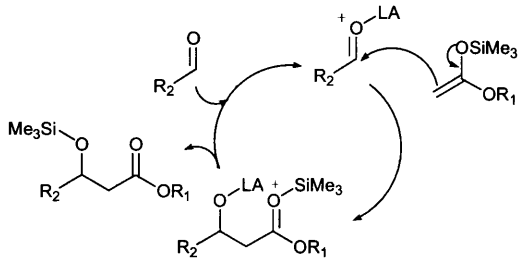


Scheme 2. 63: Aldol reaction catalysed with $TiCl_4$.

In 1992, Reetz reported that catalytic amounts (3 mol%) of lithium perchlorate suspended in dichloromethane provided a mild and effective medium to perform catalytic Mukaiyama aldol reactions in up to 87% yields.[78]

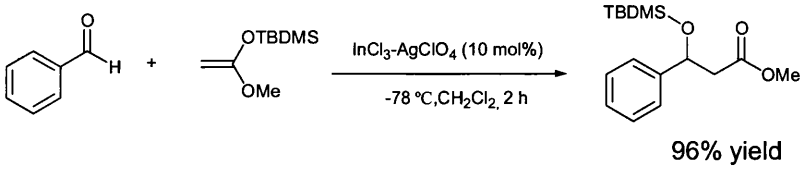


Scheme 2. 64: Aldol reaction catalysed by lithium perchlorate suspended in dichloromethane.



Scheme 2. 65: Mechanistic construction of the aldol reaction.

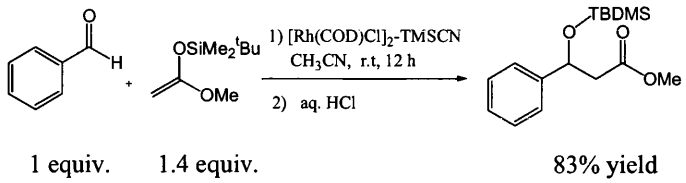
Efforts were also devoted to the development of new catalysts within the Silk Hah research group.[79] A series of weak Lewis acids and metal salts were screened such as $InCl_3$, $SnCl_4$, $ZrCl_4$, $SbCl_3$, $SiCl_4$, $AgClO_4$, LiOTf, AgOTf and $AgSbF_6$ as catalysts for the reaction of benzaldehyde and *tert*-butyl-(1-methoxy-vinyloxy)-dimethyl-silane. Although $InCl_3$ had poor activity, its combination with an equimolecular amount of $AgClO_4$ gave a rapid and clean reaction. Thus, reaction of benzaldehyde with silyl ketene acetals in the presence of 10 mol % $InCl_3$-$AgClO_4$ proceeded smoothly at low temperature to afford the corresponding aldol adduct in a good yield of 96%.[79]



Scheme 2. 66: Reaction of benzaldehyde with silyl enol ethers in the presence of 10 mol% $InCl_3$-$AgClO_4$.

Most Mukaiyama aldol reaction have been carried out under acidic conditions, nevertheless Tsunehiko *et. al* demonstrated in 1990 that these type of reactions could be

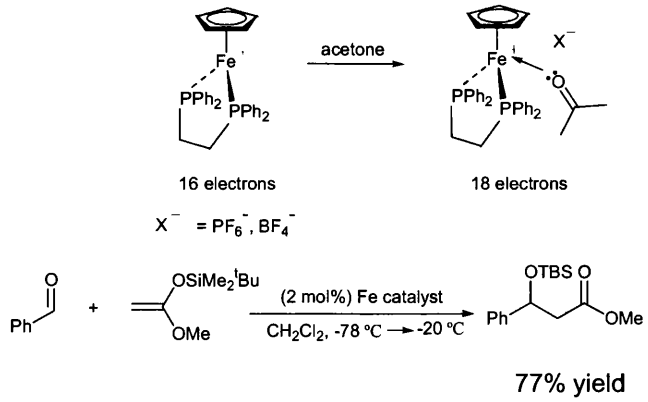
carried out under almost neutral conditions.[80] They found that the use of a catalytic amount of di-μ-chloro-bis(1,5-cyclooctadiene)-dirhodium $[Rh(COD)Cl]_2$ (0.01 equiv.) and TMS-CN (0.4 equv.), resulted in aldol reaction of silyl ketene acetals with aldehydes to furnish the corresponding β-hydroxy esters in good yields under almost neutral conditions. [80]



1 equiv. 1.4 equiv. 83% yield

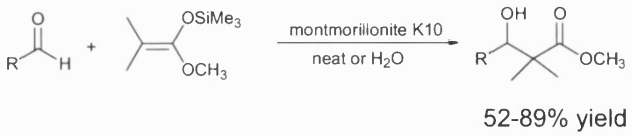
Scheme 2. 67: Efficient activation of aldehydes toward silylated nucleophiles under almost neutral conditions.

Furthermore, the Bach group have shown that an 18-electron cationic organometallic Lewis acids can mediate the Mukaiyama aldol reaction, using just 2 mol% of catalyst at -78 °C→-20 °C to afford an *O*-silyl aldol product in 77% yield.[81]



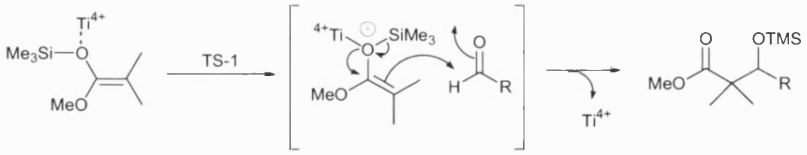
Scheme 2. 68: Mukaiyama aldol reaction catalysed by an iron complex.

In 1999, the Loh group used a zeolite for the aldol reaction of silyl keten acetal with various aldehydes using montmorillonite K10 as a catalyst under solvent free conditions resulting in rapid formation of the corresponding aldol products in good yield. Zeolites have often been proposed as environmentally benign catalysts because they minimise waste emission. The zeolite catalyst may be recovered by centrifugation and washing, followed by reactivation in an oven at 120-130 °C, which enables it to be reused for further synthesis.[82]



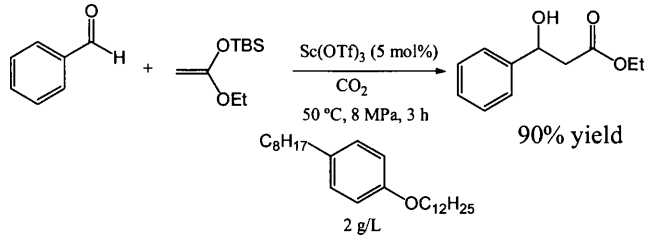
Scheme 2. 69: Aldol reaction of silyl keten acetal with various aldehydes using montmorillonite K10.

Remarkably, Sasidharan and Kumar reported that even titanium silicate molecular sieves TS-1 and Ti-β could promote the Mukaiyama-type aldol reaction in THF. Other metal containing also molecular sieves were also studied, but the activity per active site was consistently higher for titanium than for other metals such as Sn or Al, regardless of the pore size.[83] A wide range of aromatic aldehydes were screened and the results obtained suggested that an electron-withdrawing group on the aryl ring increased the electrophilicity of the carbonyl group in these aldol reactions. However, heteroaromatic aldehydes and aliphatic aldehydes were less reactive than their corresponding aromatic aldehydes.[83] A mechanism was proposed involving coordination of the encapsulated oxophilic Ti^{4+} species to one of the oxygen atoms of the silyl ketene acetal, which served to catalyse formation of the aldol adduct.[83]



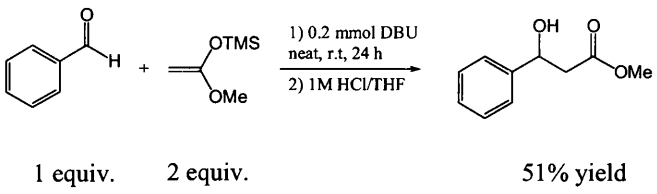
Scheme 2. 70: Titanium silicate molecular sieves TS-1 and Ti-β as promoters for Mukaiyama-type aldol condensation reactions.

Aldol reactions in aqueous solvent or pure water have received much attention in relation to the development of economical and enviromental benign methods.[84, 85] Kobayashi has focused on Lewis acid catalysis in supercritical carbon dioxide which has been proposed as a cheap and environmentally friendly solvent. The solubility of most organic substrates is low in SCO_2, but the presence of surfactants such as poly(ethylene glycol) derivatives (PEGs) or perfluoroalkyphenols enables them to dissolve, resulting in Mukaiyama aldol reactions proceeding smoothly.[13, 86, 87]



Scheme 2. 71: Surfactant molecules enable efficient catalysis in $ScCO_2$.

The interest in carrying out Mukaiyama aldol reactions under environmentally friendly conditions lead the *Shen group* to study the Mukaiyama reaction [88] in water [89] as well as in ionic liquids.[90] They reported that 20 mol % of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed the Mukaiyama aldol reaction of aromatic and aliphatic aldehydes under solvent-free conditions.[88] This reaction is proposed to proceed via activation of the trimethylsilyl enol ether to form a hypervalent silicon species via coordination of the nitrogen atom of DBU to the silicon atom of the silyl ketene nucleophile.

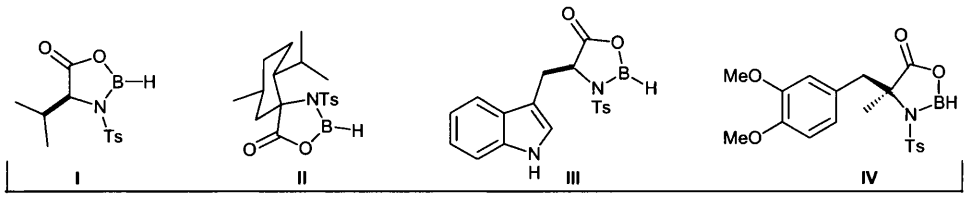


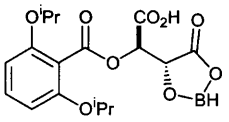
Scheme 2. 72: 20 mol% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed the Mukaiyama aldol reaction.

2.4.2 Asymmetric Mukaiyama reactions using chiral Lewis acids

Given the potential case with which achiral Lewis acids catalyse the Mukaiyama aldol reaction, it is unsurprising that a great deal of attention has been devoted to developing an asymmetric variant of this reaction.

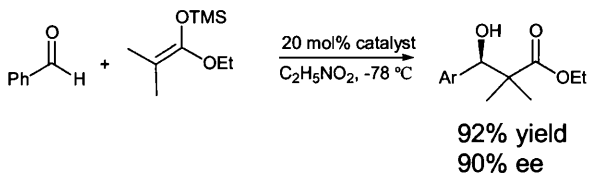
A range of oxa-*aza*-borilidines catalyst derived from β-amino alcohols or tartaric acid derivatives have been screened as catalyst for the asymmetric Mukaiyama aldol reaction.



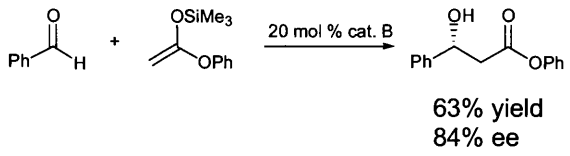


Scheme 2. 73: Chiral boron catalysts used as Lewis acids in asymmetric Mukaiyama aldol reaction.

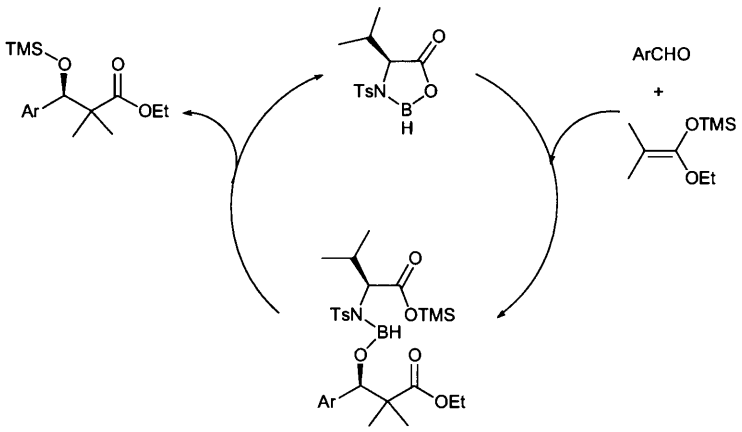
Studies on these chiral boron catalysts for the reaction of aldehydes with ketene silyl acetals have shown the need for the presence of an α-substituent in the ketene silyl acetal for high levels of enantioselectivity to be achieved.[74, 91]



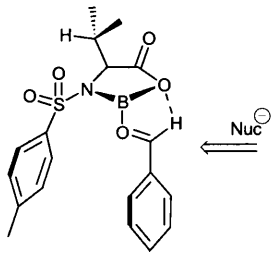
Scheme 2. 74: Use of chiral oxazaborolidines for Mukaiyama aldol type reaction



Scheme 2. 75: Use of acyloxoborane (B) for Mukaiyama aldol type reaction.

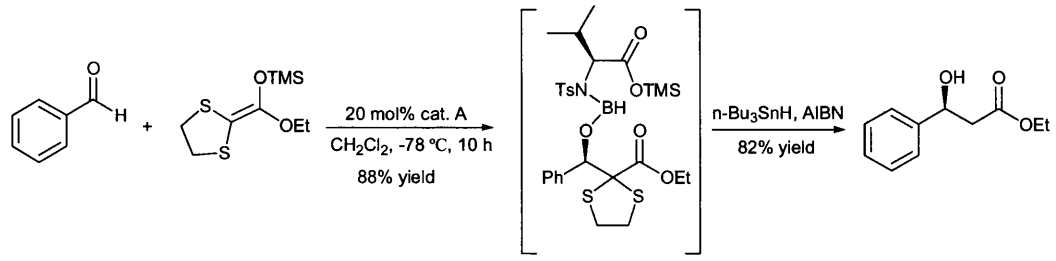


Scheme 2. 76: Proposed mechanism when oxazaborilidones (A) in the aldol type reaction



Scheme 2. 77: Three-dimensional structure of the aldehyde-oxazaborolidin complex.

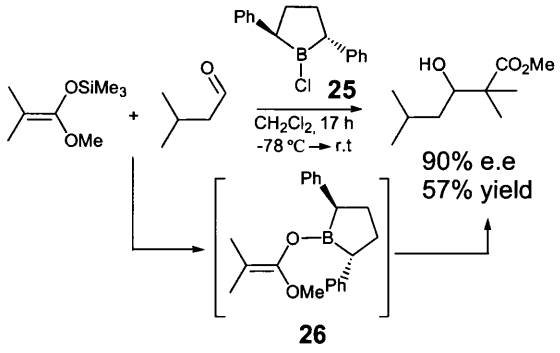
In order to prepare β-hydroxy esters that contain no α-substituents, a dithiaryl silylketene acetal nucleophile was employed to provide the steric bulk required for high levels of enantioselectivity to be obtained using this class of oxazaborilidine catalyst. The sulphur atoms of the resultant aldol product were then removed via treatment with *n*-Bu_3SnH/AIBN under free radical conditions to provide the corresponding unsubstituted aldol product in high yields and enantioselectivity ($[\alpha]_D^{24}$= -57.0 (c 1.0, $CHCl_3$)).[91]



Scheme 2. 78: Use of oxazaborolidine (A) as a catalyst for Mukaiyama aldol reaction with unsubstituted ketene silyl acetal.

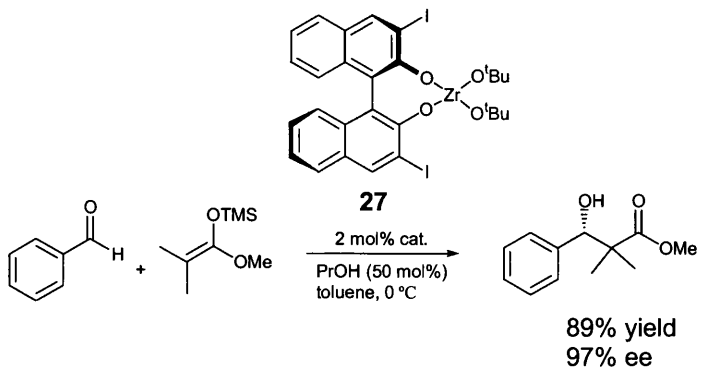
The catalytic mechanism proposed involves an intramolecular B-Si exchange reaction, that results in the aldehyde being bound to the oxazaborolidine by a hydrogen-bonding interaction to afford a transition state that induces high levels of enantioselectivity.[91, 92]

An enantiomerically pure C_2-symmetric Lewis acid has been used for the enantioselective addition of enolsilanes to aldehydes for 17 hrs. It was spectroscopically revealed that initially there is an Si/B exchange reaction to afford a boron enolate **26** which is the reactive species in this aldol addition, that then reacts with the aldehyde to afford the aldol product in a good 90% ee and a moderate 57% yield.[93]



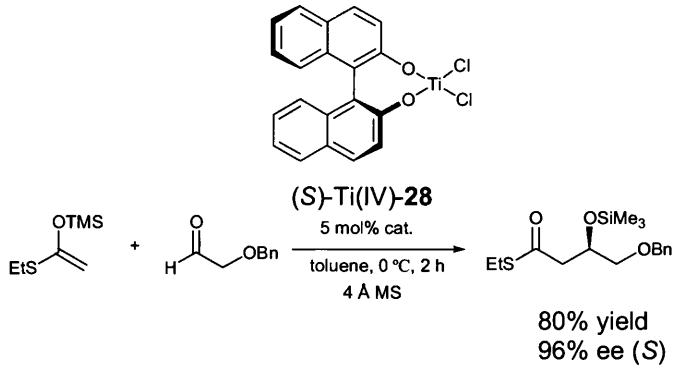
Scheme 2. 79: Other boron chiral catalyst for the aldol type reaction.

In 2002, Ishitani *et al.* described a Mukaiyama aldol reaction using a chiral zirconium complex **27** that initially gave unsatisfactory results, affording essentially racemic aldol products. However, it was found that mono-TMS-BINOL was being formed in these reactions from silyl transfer from the ketene silyl acetal, and as a consequence propanol was added to the reaction to regenerate BINOL. This modification resulted in the desired β-hydroxy ester being formed in 81% yield and in an excellent 92% ee when (*R*)-3,3-diiodo-1,1-bi-2-naphthol was used as a chiral ligand.[94]



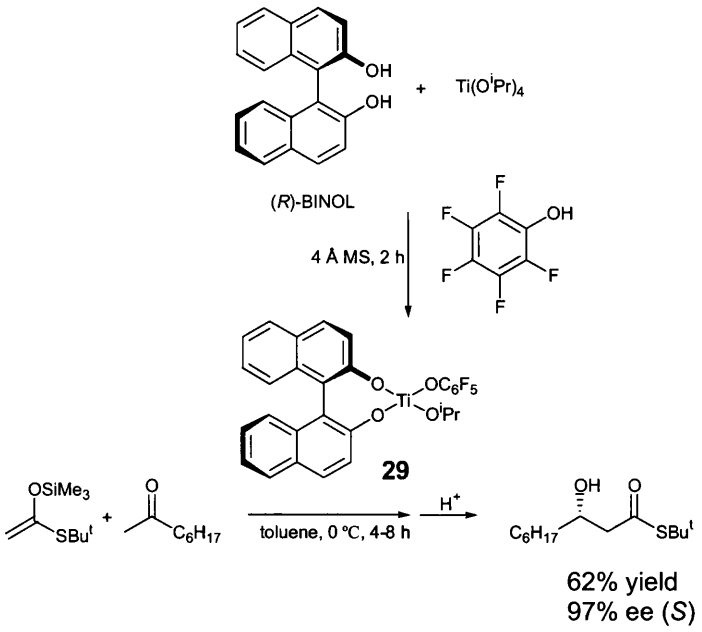
Scheme 2. 80: Mukaiyama aldol reaction using a chiral zirconium complex **27**.

Mikami first successfully used 5 mol% of titanium BINOL catalyst **28** for reaction of a broad range of functionalised aldehydes and thioester-derived ketene silyl acetal in the presence of molecular sieves to afford β-hydroxy-thio-esters in up to 96% ee.[95, 96]



Scheme 2. 81: Mukaiyama aldol reaction using a chiral titanium-BINOL catalyst

Moreover, the Mikiami group then prepared another Ti complex **29** derived from (*R*)-BINOL and Ti(^{i}OPr)$_4$, which in the presence of one equivalent of pentafluorophenol as an additive gave the corresponding β-hydroxy-thio-esters in 97% ee and 62% yield.

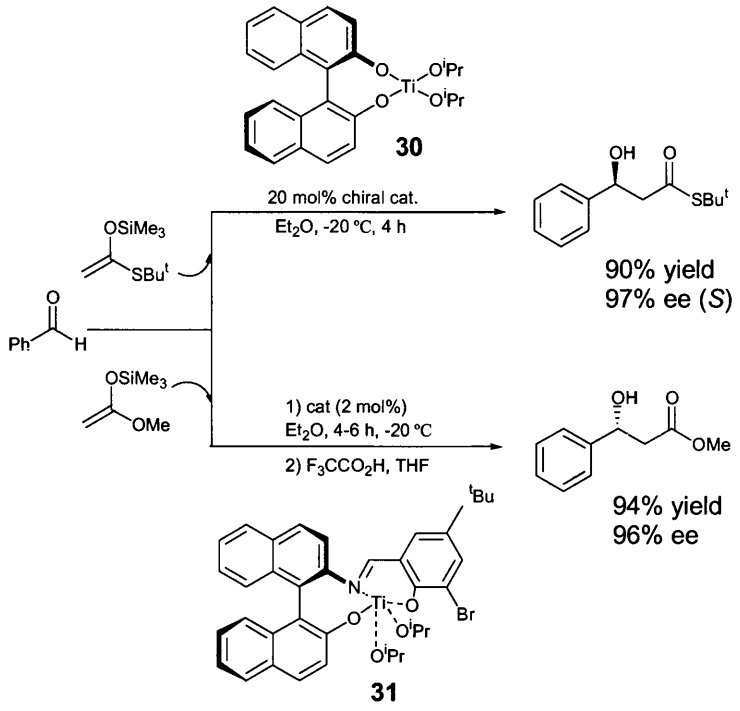


Scheme 2. 82: Mukaiyama aldol reaction and another chiral titanium-BINOL catalyst with pentafluoro phenol as chiral additive.

The same principle was employed by the Keck group who used Ti(^{i}OPr)$_4$ to prepare as chiral titanium complex **30** that catalysed Mukaiyama reactions to afford β-hydroxy-thio-esters in good ee.[95]

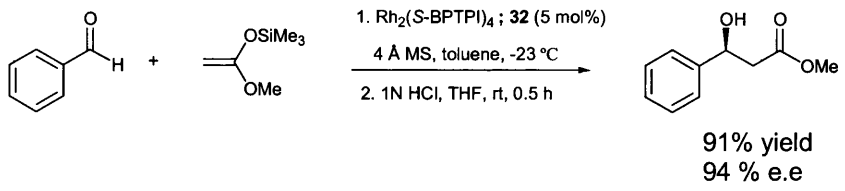
Carreira extended this scope of titianium aldol reactions using a chiral binaphthyl amino alcohol ligand and Ti(O^{i}Pr)$_4$ to form a chiral Ti(IV) catalyst, resulting in conventional aldol products being produced in 93-99% ee and 89-99% yield using only 2 mol % catalyst at -20 °C.[95, 97-99]

Interestingly, the presence of the 3,5-di-*tert*-butylsalicylate fragment was crucial for effective catalyst turnover of this potentially recyclable system.[95]



Scheme 2. 83: Mukaiyama aldol reaction using two titanium-BINOL catalysts.

Studies have recently reported within Washio group on Mukaiyama aldol reactions catalyzed by chiral dirhodium (II) complex **32** which gave levels of enantioselectivities up to 94%.[100] They found that the catalytic process was limited to aromatic aldehydes bearing strong electron-withdrawing groups as well as to non-substituted demanding silylketene acetals.[100] They also reported that the transition state of the reaction was controlled by a hydrogen bond between the formyl hydrogen atom and the carboxamidate oxygen atom in the transition state, which results in nucleophilic attack from the aldehyde *Si* face.[101]



Scheme 2. 84: Mukaiyama aldol reactions catalyzed by chiral dirhodium (II) complex **32**.

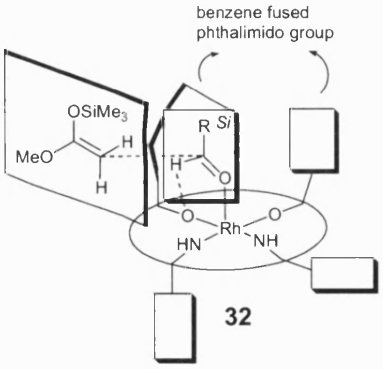
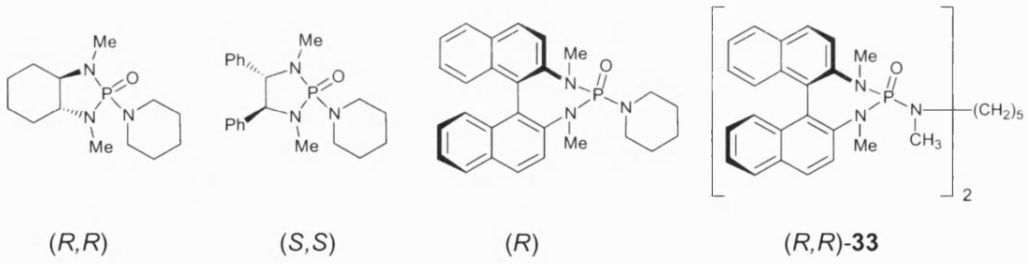


Figure 2. 4: Plausible stereochemical pathway.

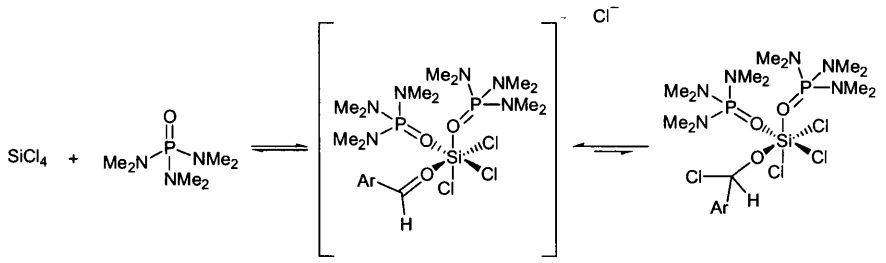
2.4.3 Lewis base activation of Lewis acid for the asymmetric aldol reaction

Chiral Lewis bases have also been screeed as catalytic promoters for asymmetric Mukaiyama aldol reaction. Phosphoramide bases have been the most widely used chiral catalysed used to promote this type of aldol reaction. [34,96, 102-106]



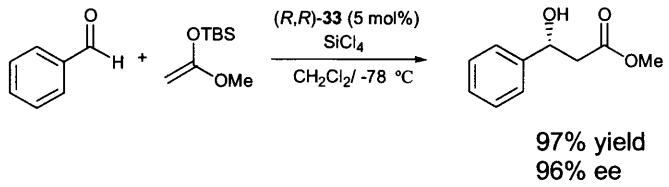
Scheme 2. 85: C_2-symmetric chiral phosphoramides used to promote Mukaiyama aldol reactions.

This phosphoramidate protocol involves binding of the weakly Lewis acid silicon tetrachloride species to the Lewis basic chiral phosphoramide resulting in formation of a chiral catalytic complex *in situ*. Subsequent binding of the lone pair of the aldehyde to the central silicon atom of this complex, carbonyl activation which facilitates results in nucleophilic attack of the silyl ketene acetal.[107-109]



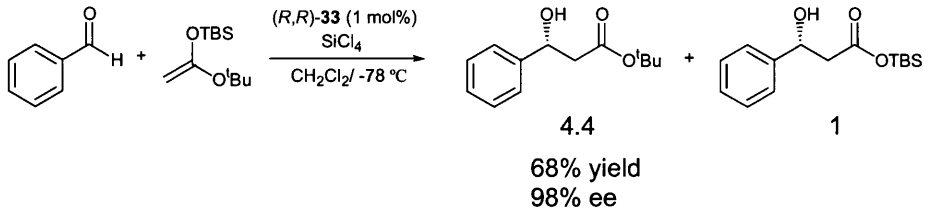
Scheme 2. 86: Ionization of a chloride by polarization of phosphoramide silicon-bonds.

For example, addition of bulky *tert*-butyl dimethylsilyl ketene acetal (1.2 equiv.) to benzaldehyde (1 equiv.) promoted by 5 mol % of dimeric phosphoramide (*R,R*)-**33** and $SiCl_4$ (1.1 equiv) at -78 °C gave the corresponding aldol product in high yield and ee in an extremely rapid reaction time of 30 seconds.[108, 109]



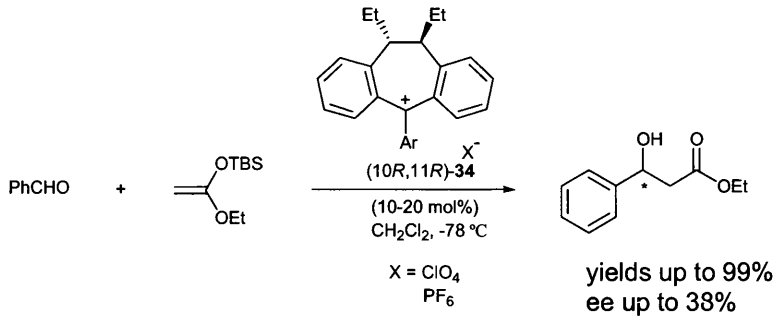
Scheme 2. 87: Lewis base activation by phosphoramides (*R,R*)-**33** for the Mukaiyama aldol type reaction.

The bulkier silyl ketene acetal that contains two *tert*-butyl groups provided the corresponding β-hydroxy ester products with even higher levels of enantioselectivity, but in lower isolated yields.[108, 109]



Scheme 2. 88: Lewis base Activation of Lewis acid by phosphoramides (*R, R*)-**33** for the aldol type reaction of a bulkier *tert*-butyl dimethylsilyl ketene acetal and benzaldehyde.

Recently, Denmark *et al.* have shown that asymmetric Mukaiyama aldol reactions do not always require the presence of transition metal. Lewis acid catalyst reporting a novel non-metallic, triarylcarbenium Lewis acid catalyst **34** lead to enantiomerically enriched aldol products according to Scheme 2.89.[110, 111]



Scheme 2. 89: Chiral non metallic Lewis acid for the Asymmetric aldol reaction.

Best results were obtained by using *tert*-butyldimethyl silyl TBS instead of trimethyl silyl TMS and perchlorate and hexafluorophosphate counteranions.[110, 111]

2.5 CONCLUSIONS

It is clear from this brief review that a range of asymmetric methodology has been developed for the asymmetric synthesis of β-amino esters and β-hydroxy esters using variants of the Mukaiyama Mannich and Mukaiyama aldol reactions. These different approaches have their differents merits and disadvantages, with chiral auxiliary approaches being inherently inefficient, but easy to optimise with many of the catalytic approaches being highly efficient but having poor substrate specificity profiles and requiring non-commercially available ligands that need to be prepared via multi-step synthesis. The development of a cheap and robust catalytic approach to the asymmetric synthesis of β-aryl-amino-acids and β-aryl-β-hydroxy esters using cheap commercially available reagents is therefore necessary, and I now described my investigations into optimising Yamamoto's boron-BINOL catalyst for this purpose.

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3 RESULTS AND DISCUSSION; MANNICH AND ALDOL TYPE REACTION

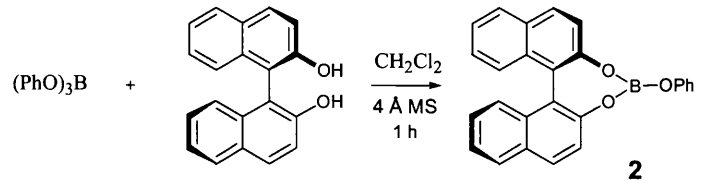
3.1 INTRODUCTION

In this chapter we will explore several modifications of Yamamoto's original procedure for carrying out boron-BINOL mediated Mukaiyama Mannich-type reaction between silyl ketene acetals and a range of imines.[1-4] The study includes optimization of levels of conversion and yields, as well as catalytic studies on model Mukaiyama Mannich-type reactions that lead to highly practical methodology for the enantioselective synthesis of β-amino acids and esters. Investigations into attempts to develop asymmetric Mukaiyama aldol reactions using this class of catalyst will also be described.

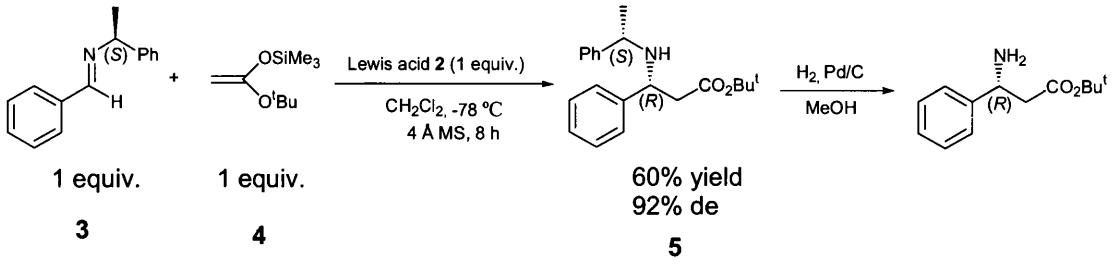
In order to set the scene for my studies, Yamamoto's previous research in this area is now reviewed in detail, as well as describing previous research carried out in our group using boron-BINOL catalysts for asymmetric *aza*-Diels-Alder reaction that are relevant to my studies into asymmetric β-amino ester synthesis.[1-4]

3.2 PRECEDENT USING YAMAMOTO'S CATALYST FOR MUKAIYAMA MANNICH AND *AZA*-DIELS ALDER REACTIONS

The Yamamoto group first reported,[1] the use of boron-BINOL complexes for the asymmetric synthesis of β-aryl-β-amino esters in 1993. The chiral reagent **2** (or its enantiomer) was prepared from equimolar amounts of enantiopure-BINOL and triphenyl borate in CH_2Cl_2 under an argon atmosphere in the presence of molecular sieves. This chiral boron Lewis acid (*R*)-**2** was initially used to convert an aromatic imine derived from enantiopure α-methylbenzylamine **3** into β-amino ester (*R,S*)-**5** in 92% de via reaction with silyl-ketene acetal **4** at -78 °C. Subsequently, the *(S)*-(+)-*N*-α-methylbenzylamine fragment could be cleaved via hydrogenolysis over palladium on carbon to afford the parent β-amino acid with no loss of enantiopurity.



Scheme 3. 1: Preparation of chiral boron-BINOL catalyst **2**.

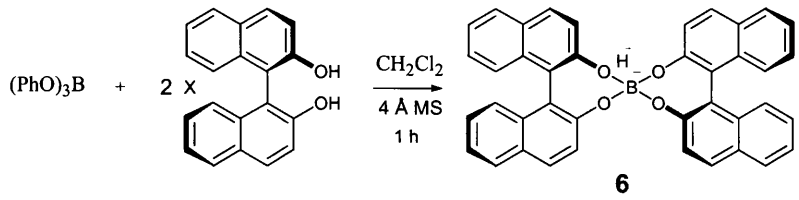


Scheme 3. 2: Diastereoselective Mukaiyama Mannich reaction.

The reaction of (*S*)-(+)-*N*-benzylidene-α-methylbenzylamine **3** with trimethylsilyl ketene acetal **4** (derived from *tert*-butyl acetate) in the presence of a new (*R*)-Lewis acid **6** (1 equiv) was also investigated. In a typical reaction, one equivalent of $B(OMe)_3$ was treated with two equivalents of (*S*)-BINOL in CH_2Cl_2 at reflux (50~60 °C) over 2~3 hrs with removal of methanol (4 Å molecular sieves in a Soxhlet thimble) to afford boron-BINOL complex **6**. This complex (*S*)-**6**, was then added to the corresponding (*S*)-(+)-*N*-benzylidene-α-methylbenzylamine **3** in CH_2Cl_2/toluene at 0 °C and the resultant suspension cooled to -78 °C before *tert*-butyl ketene silyl acetal **4** was added dropwise to afford β-amino ester **5** in 63% yield and 95% de.[2] This methodology was subsequently used for the stereoselective synthesis of the β-amino side chain of taxol,[1] and for the preparation of chiral β-lactam compounds.[5]

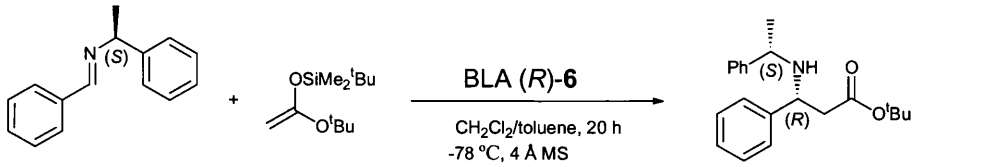
Other methods of preparing the boron-BINOL Lewis acid **6** were also investigated involving stirring a 2:1 molar ratio of *(R)*-binaphthol and $B(OMe)_3$ in the presence of excess 4 Å molecular sieves (drying agent) in CH_2Cl_2 under an argon atmosphere for 1 h, before addition of *(S)*-(+)-*N*-benzylidene-α-methylbenzylamine **3** (1 equivalent). Subsequent addition of *tert*-butyl ketene silyl acetal **4** (2 equivalent) afforded the desired β-amino ester **5**, in the same 63% yield and in an essentially identical 94% de. Alternatively, a chiral boron Lewis acid was also prepared by reacting 2 equivalents of BINOL with one equivalent of $B(OPh)_3$, under otherwise identical conditions, which catalysed the same Mukaiyama Mannich reaction in >99% de.[2] These similarities in de

suggested to us that the same catalytic species was probably operating in all these Mukaiyama Mannich reactions.



6

Scheme 3. 3: Preparation of boron-BINOL catalyst **6**.



1 equiv. 2 equiv.

3 **4** **5**

Method A: 63% yield, 94% de
Method B: 65% yield, >99% de
Method C: 63% yield, 95% de

Scheme 3. 4: Mukaiyama Mannich-type reaction using boron-BINOL complex **6**.

Yellow crystals of a boron-BINOL-imine complex could be obtained from recrystallisation from dichloromethane-hexane, which X-ray analysis showed was composed of a 1:1:1 molar ratio mixture of boron-*(S)*-binaphthol **6**, PhOH and *(S)*-(+)-*N*-benzylidene-α-methylbenzylamine **3**. Mannich-type reactions using these yellow crystals were shown to proceed with an excellent diastereoselectivity of more than 99.5% de. However, it should be noted that this borate anionic species **6** is unlikely to be acting as a Lewis acid in these reactions since it does not contain a vacant p orbital capable of binding the imine substrate, and we propose that it is likely to be acting as some form of precatalyst reservoir.[2, 6, 7]

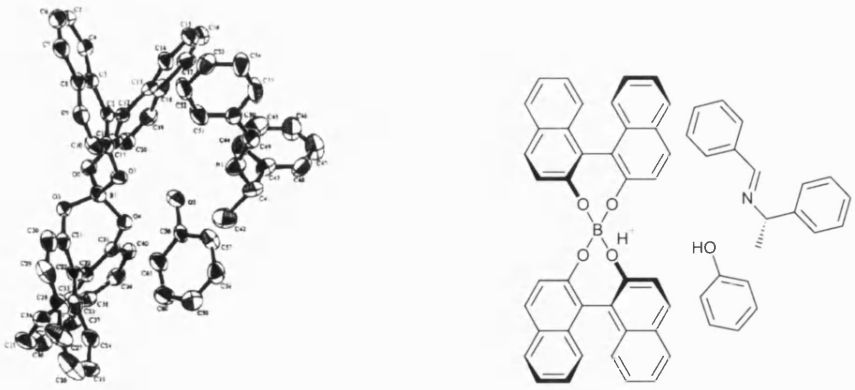
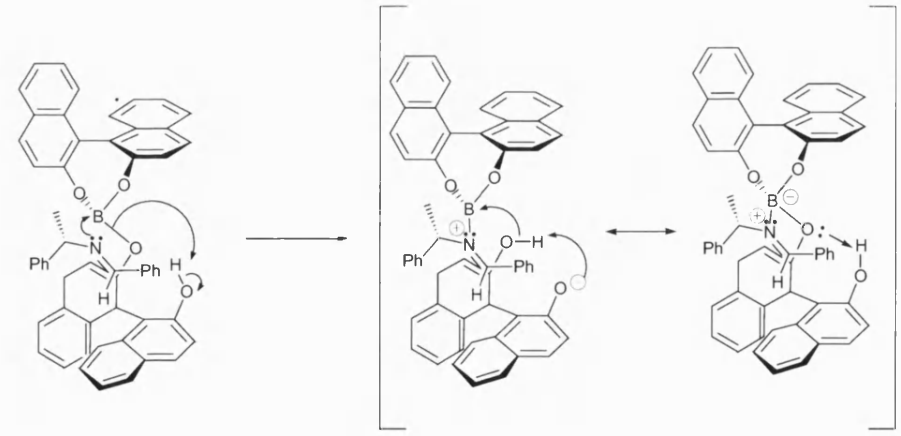


Figure 3. 1: Crystal structure of 1:1:1 molar ratio mixture of boron-*(S)*-binaphthol **6**, PhOH and *(S)*-(+)-*N*-benzylidene-α-methylbenzylamine **3**.

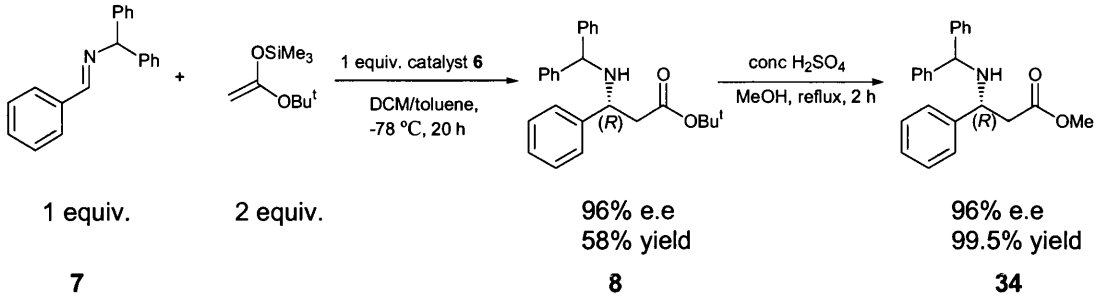
Yamamoto *et. al.* postulated a transition state to explain the stereoselectivity for these reactions involving a complex formed between the α-methyl-*N*-benzyl-imine substrate and boron-BINOL complex, in which the hydroxyl group of one of the BINOL fragments acts as an intramolecular proton source to catalyse the reaction.[2, 7]



Scheme 3. 5: Activation of imine by boron-BINOL complex **34**.

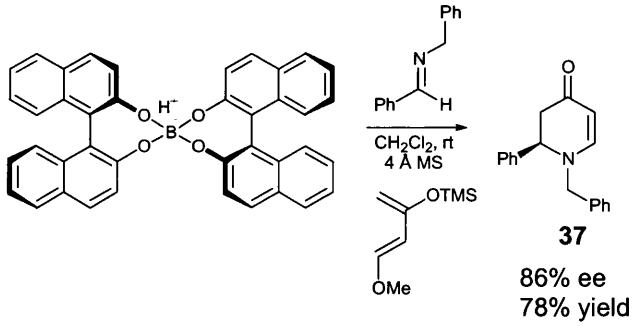
Four years later, Yamamoto and co-workers used this methodology to synthesise a range of spermine alkaloids,[4] which are natural products with important pharmaceutical properties.[8] Hence, boron-BINOL complex **6** was used to catalyse the enantioselective reaction of *N*-benzylidenebenzhydrylimine **7** and *tert*-butyl-ketene silyl acetal **4** to afford the *tert*-butyl amino ester **8** in 58% yield and 96% ee, whose subsequent transesterification gave methyl *(S)*-3-(benzhydrylamino)-3-phenylpropionate **34**. It was

shown that the *N*-benzhydryl protecting group could be cleaved by catalytic hydrogenation (10% Pd/C, H_2, MeOH) to afford the parent β-amino acid as required.[9]



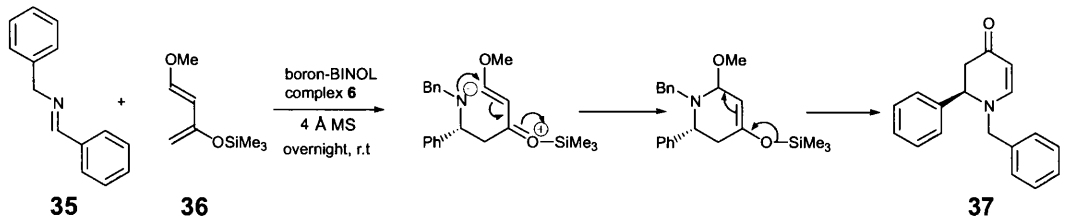
Scheme 3. 6: Asymmetric synthesis of *(S)*-3-(benzhydrylamino)-3-phenylpropionate **6**.

Yamamoto *et al.* also reported the use of these type of boron-BINOL catalysts for the related *aza*-Diels-Alder reaction of *N*-benzylidenebenzylamine **35** with Danishefsky diene **36**, using (*R*)-boron-BINOL complex **6** (1 equiv.) to afford a 78% yield of (*R*)-*N*-benzyl-2,3-dihydro-2-phenyl-4-pyridone **37** in 86% ee.[2]



Scheme 3. 7: Yamamoto's *aza*-Diels Alder reaction using boron-BINOL complex **6**.

It should be noted that whilst this reaction is often referred to as an *aza*-Diels-Alder reaction, the fact that these boron-BINOL catalysts **6** also catalyse Mukaiyama-Mannich reactions suggests that the reaction proceeds via a two-step Mannich/conjugate addition pathway, rather than a concerted pericyclic [4+2] cycloaddition pathway.



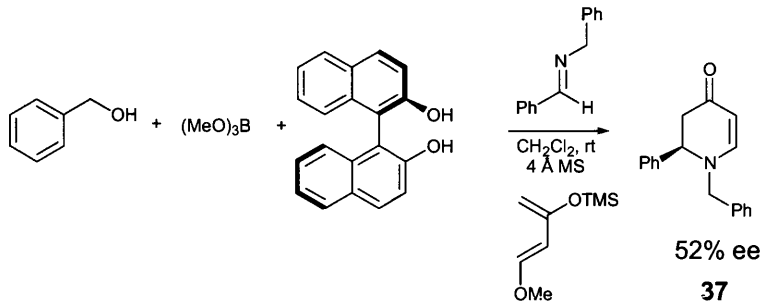
35 **36** **37**

Scheme 3. 8: Alternative two-step Mannich/conjugate addition mechanism for formation of dihydropyridines.

Further work in the SDB/TDJ group involving NMR spectroscopic analysis of this *aza*-Diels-Alder reaction has shown that no new species is formed on premixing a 1:2 molar ratio of trimethyl borate and (*R*)-binaphthol in dichloromethane at room temperature.[7] Therefore, it was proposed that formation of monomeric and dimeric boron-BINOL catalytic species must only occur on addition of the imine substrate. Moreover, it has also been shown that non-linear effects operate in these *aza*-Diels-Alder reactions, which implying that at least two equivalents of BINOL ligand are present in the boron-BINOL complex responsible for asymmetric induction. [6, 7]

Considerations of the Lewis acidity of this boron Lewis acids revealed that trimethyl borate was a weaker Lewis acid than the boron-BINOL catalyst generated in these reactions, whilst triphenyl borate was slightly more acidic. This lead to the conclusion that $B(OMe)_3$ was the best precursor for generating these type of BINOL-boron catalysts because the enhanced Lewis acidity of $B(OPh)_3$ was more likely to catalyse a competing background achiral reaction to afford racemic products. This increased Lewis acidity is because the sp^2 carbons of the phenoxy ligands of triphenyl borate are relatively electron withdrawing in comparison to the sp^2 carbons of the methoxy ligands of trimethyl borate, and as a consequence its boron center is more acidic.[7]

Unpublished studies within our group have also focused on developing an additive approach to tune the stereoselectivity of this type of *aza*-Diels-Alder reaction at room temperature. Initial experiments showed that the use of stoichiometric amounts of boron-BINOL complex for *aza*-Diels Alder reactions in CH_2Cl_2 at room temperature gave dihydropyridone **37** in 33% ee. However, in the presence of a stoichiometric amounts of an achiral alcohol additive such as benzyl alcohol, dihydropyridone **37** could be formed in an increased 52% ee.[7]

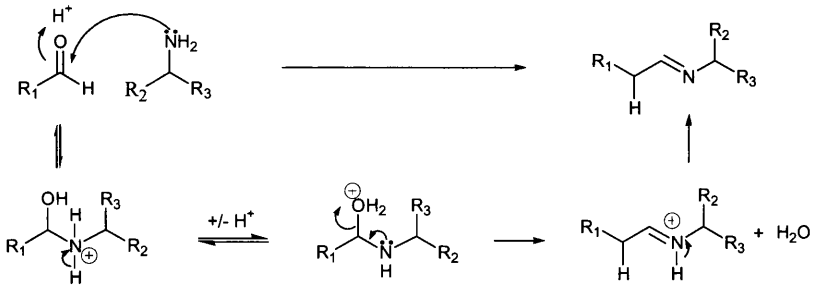


Scheme 3. 9: Additive approach for improving the enantioselectivity of *aza*-Diels-Alder reactions.

Therefore, to conclude there was significant precedent that chiral boron-BINOL complexes could be used in asymmetric *aza*-Mannich reactions for the enantioselective synthesis of β-amino esters. It was therefore decided to further explore this methodology in an attempt to develop a truly practical approach for the asymmetric synthesis of chiral β-amino esters.

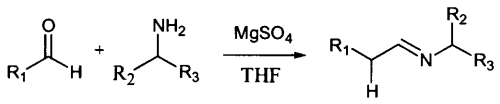
3.3 SYNTHESIS OF IMINES

In order to carry out our investigations into the asymmetric synthesis of β-amino esters, we needed to prepare a range of *N*-benzyl imines as substrates for the series of Mukaiyama Mannich reactions carried out in this thesis. These type of imines are normally formed via condensation of aldehydes and amines under anhydrous conditions. The rate of imine formation clearly depends on the nature of substituents of the amino and aldehyde substrates, with aromatic imines being more stable than aliphatic imine by virtue of their added conjugation. Imines are normally formed as a mixture of (*E*)- and (*Z*)- isomers, however for the *N*-benzyl-imines used in this study the (*E*)-isomer normally predominates due to its thermodynamic stability.[10, 11] The mechanism of imines formation is shown in Scheme 3.10, involving reversible addition of the amine to an aldehyde, to afford an aminol intermediate that then undergoes reversible elimination of water in the presence of an acid catalyst (pH = 4-6).



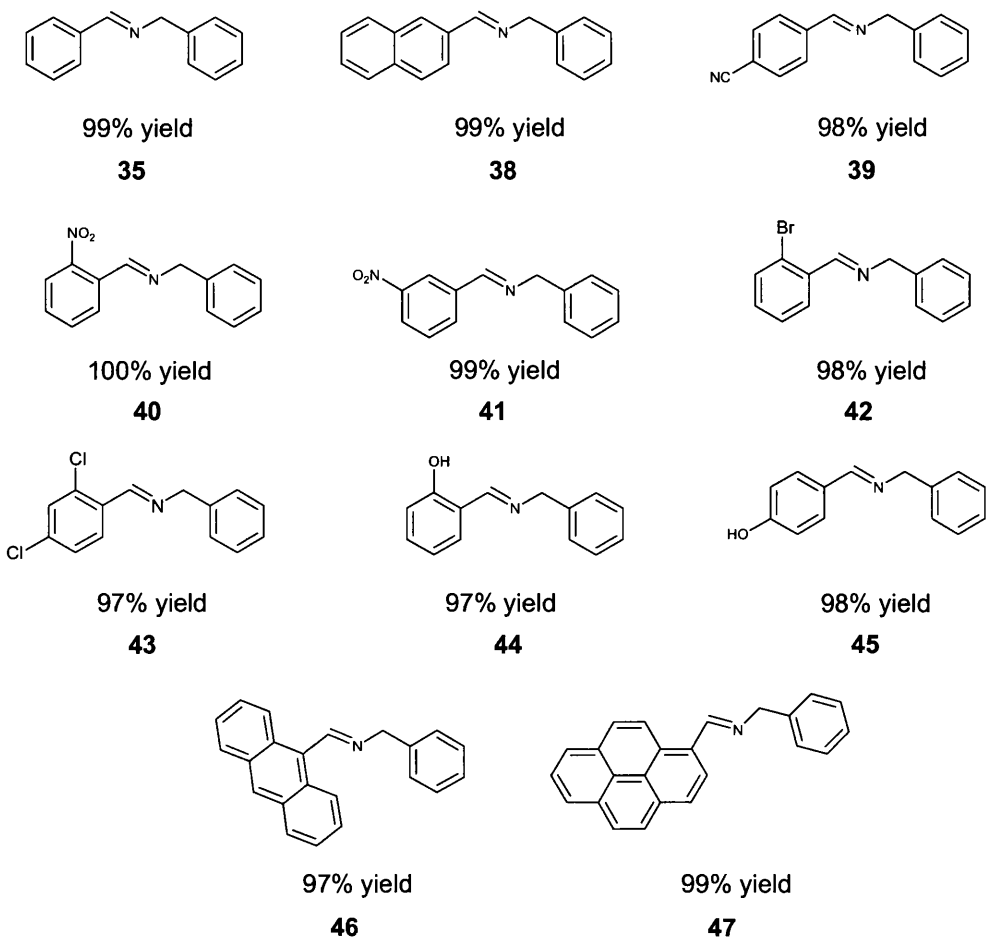
Scheme 3. 10: Mechanism of imine formation.

A range of imines were therefore synthesised by stirring a mixture of the corresponding aldehyde (1 equiv.) and primary amine (1 equiv.) in THF at room temperature overnight, with water being removed using $MgSO_4$ (5 equivalents) in order to drive the equilibrium in favour of imine formation. Occasionally, methylene chloride was used as an alternative solvent, which resulted in the target imine being produced over a longer period of time.



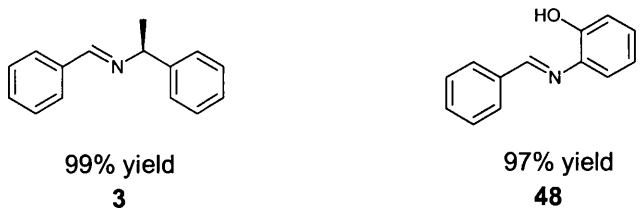
Scheme 3. 11: Synthesis of imines.

This robust methodology was used to prepare over twenty *N*-benzyl-imines as substrates for subsequent Mukaiyama Mannich reactions (vide supra), where filtration of $MgSO_4$ and removal of the solvent were sufficient to afford the desired imine in essentially pure form without any further purification being required. Therefore, a range of imines derived from benzylamine were prepared in 97-100% yields, a number of which contained electron withdrawing or mesomerically releasing substituents.



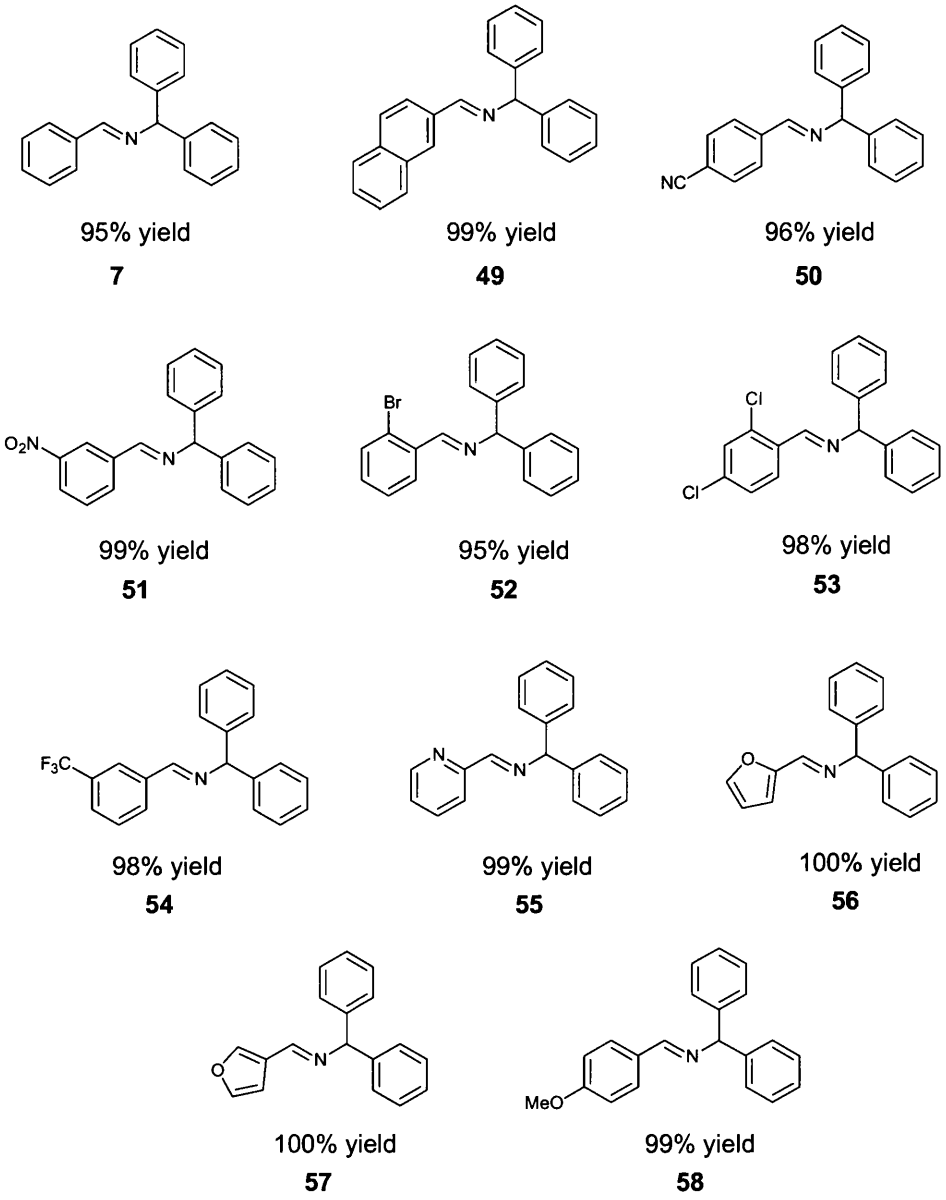
Scheme 3. 12: Yields of *N*-benzyl-imines.

Two other aromatic imines that had been used previously as substrates in related asymmetric Mannich reactions were also prepared.[12-16] These were a chiral imine **3** derived from *(S)*-α-methylbenzylamine and imine **48** derived from a 2-amino-phenol group, both of which were synthesised in excellent yield.



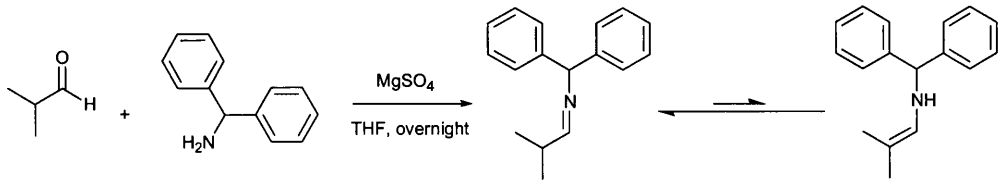
Scheme 3. 13: Imines derived from 2-amino-phenol and *(S)*-α-methylbenzylamine.

A second series of imines containing branching at their benzylic position were also prepared using this methodology using diphenylmethylamine as an amine substrate, which once again afforded the desired imines in excellent 95-99% yields.[2, 10, 15]



Scheme 3. 14: Yields of imines derived from diphenylmethylamine.

In addition, an imine **59** derived from isobutyraldehyde and diphenylmethylamine was also prepared. The imines of aliphatic aldehydes have the potential to exist in equilibrium with their enamine tautomer, however the predominance of the imine tautomer was revealed by the presence of a resonance at δ 7.60 in its ^{1}H NMR.[10, 11]



imine

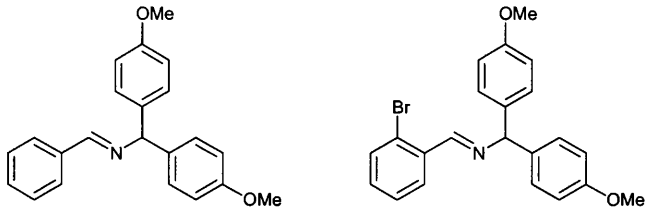
98 % yield

59

enamine

Scheme 3. 15: Tautomeric equilibrium between imine and enamine.

Finally, representative examples of a third class of *N*-benzyl-imines derived from 4, 4′-dimethoxybenzydrylamine was also prepared in good yield using this methodology.



>99% yield

60

>99% yield

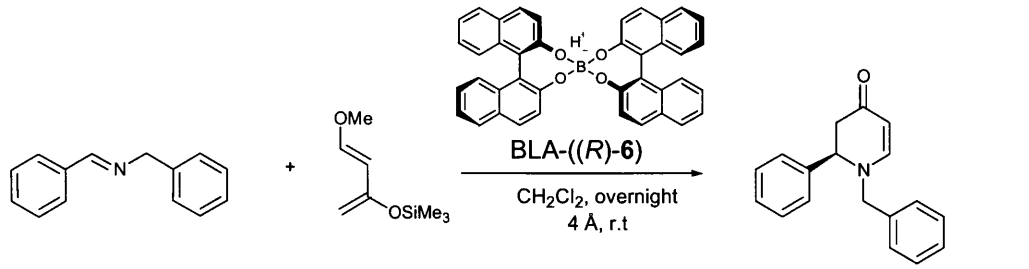
61

Scheme 3. 16: Imines derived from 4, 4′-dimethoxybenzydrylamine.

In all cases formation of the desired imine was evident from the presence of a singlet at δ 8-9 ppm in their ^{1}H NMR spectra corresponding to the resonance of the imine proton, as well as the presence of a strong $(C=N)_{str}$ absorption at between 1645-1650 cm^{-1} in their infra-red spectra. Because of their susceptibility to hydrolysis, these imines were used immediately to carry out their corresponding asymmetric *aza*-Diels-Alder or Mannich reactions. However, it was subsequently found that a number of these imines could be stored in a sealed flask for up to six months without any deterioration.

3.4 ASYMMETRIC *AZA*-DIELS ALDER REACTION OF IMINES

In order to gain experience of using chiral boron-BINOL complexes for asymmetric synthesis it was first decided to repeat an asymmetric *aza*-Diels-Alder reaction that had been carried out previously in our group. [1, 2, 4, 17] Therefore, reaction of imine **35** with a stoichiometric amount of Yamamoto's chiral boron complex (*R,R)*-**6** and Danishefsky diene **36** in dichloromethane was carried out under nitrogen at room temperature in the presence of 4 Å molecular sieves to give the desired *N*-benzyl-2-phenyl-2,3-dihydro-1H-pyridine-4-one **37** in 60% yield. The structure of dihydropyridone **37** was evident from its ^{1}H NMR spectrum that revealed alkene resonances at δ 5.1 and 7.1 ppm, ABX quartets at δ 2.60 and 2.80 ppm corresponding to the CH_AH_BCO resonances, and CH_AH_BPh benzylic protons at δ 4.05 and 4.25 ppm respectively. Furthermore, the ^{13}C NMR spectra of dihydropyridone **37** exhibited 14 resonances, whilst there was a strong absorption for the C=O group at 1664 cm^{-1} in the infra-red spectra. The enantiomeric excess of dihydropyridone **37** was determined as 40% ee by chiral HPLC analysis using an AD Chiralpack column that gave baseline resolution of its (*R*)- and (*S*)-enantiomers. A comparative sample of racemic pyridone **37** was prepared for analytical purposes using (*rac)*-BINOL as ligand for the *aza*-Diels-Alder reaction. The value of 40% ee produced using (*R*)-BINOL for catalyst formation at room temperature was found to be better than the 33% ee obtained previously under these conditions by another member of our research group. Repeating the reaction at -78°C resulted in formation of dihydropyridone **37** in 71% yield and 73% ee; values that were very close to the 70% yield and 74% ee obtained previously in our research group under identical conditions.[2, 7]



rt, 60% yield, 40% ee
-78 °C, 71% yield, 73% ee

35 **36** **37**

Scheme 3. 17: Preparation of (*R*)-*N*-benzyl-2-phenyl-2,3-dihydro-1H-pyridine-4-one **37** using chiral BINOL-boron catalyst **6**.

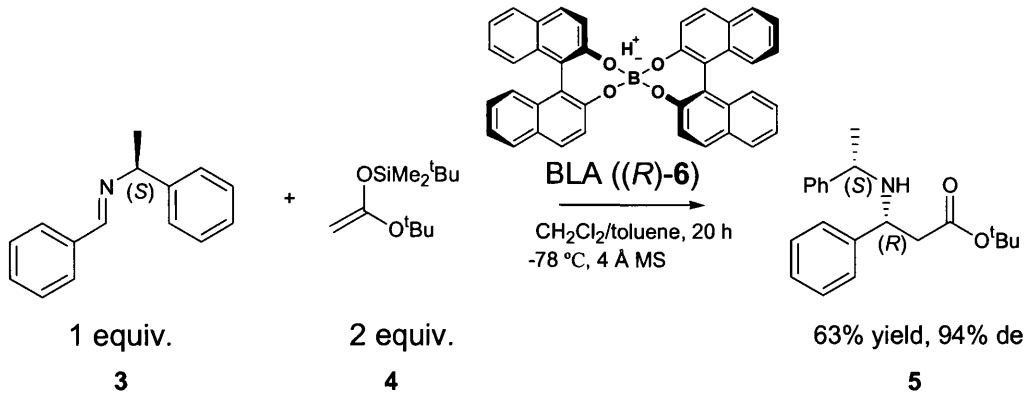
Since Yamamoto's complex had proven successful in inducing enantioselectivity into an asymmetric *aza*-Diels Alder reaction for formation of dihydropyridone **37** [2] my attention then turned to employing this chiral boron-BINOL complex as a catalyst for asymmetric Mannich reactions. [1-4]

3.5 MANNICH-TYPE REACTION

3.5.1 A diastereoselective Mannich reaction

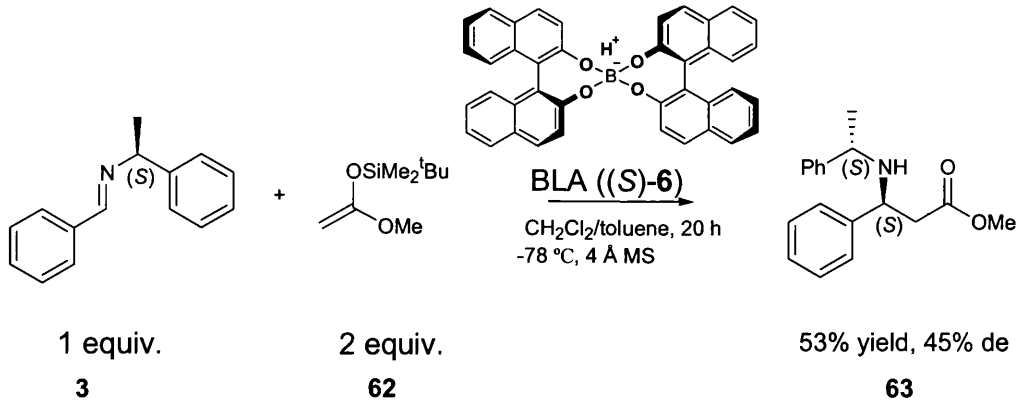
We next focused on the use of boron-BINOL catalyst for the asymmetric Mannich-type of silyl ketene acetals with aldimines at room temperature or at -78 °C to afford chiral β-amino esters. [1, 2] Bearing in mind Yamamoto's previous report, we initially decided to optimise these type of boron-BINOL catalysed Mannich-type reactions using *N*-α-methylbenzyl imine **3**, since this substrate would afford β-amino-esters whose diastereoisomeric excess could be easily determined by ^{1}H NMR spectroscopic analysis.

Yamamoto's original diastereoselective Mannich protocol for the preparation of chiral β-amino esters employed *tert*-butyl-silyl-ketene acetal **4** as a nucleophile that was prepared via treatment of *tert*-butyl-acetate with lithium diisopropylamide. Reaction of this silyl-ketene-acetal with (*S*)-α-methylbenzyl-imine **3** in the presence of BLA **6** was then reported to afford *tert*-butyl-β-amino-ester **5** in 63% yield and 94% de. [1, 2]



Scheme 3. 18: Yamamoto's diastereoselective synthesis of β-amino ester **5**.

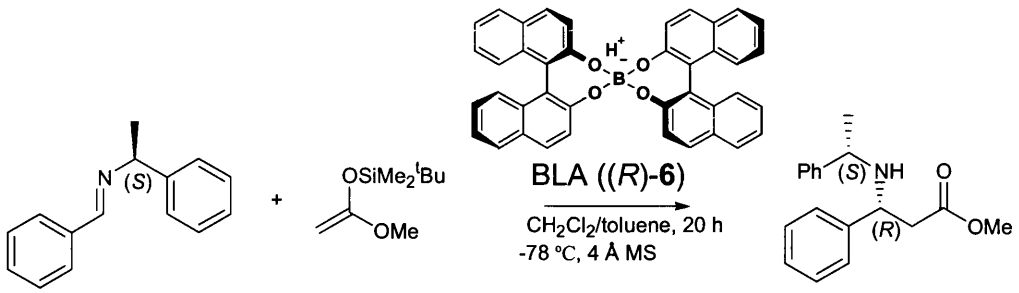
Unfortunately, despite repeated attempts, I and a number of other members of the SDB/TDJ research group were unable to prepare silyl-ketene-acetal **4** using Yamamoto's literature protocol.[ii] Consequently, a decision was made to employ commercially available 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** as an alternative enolate equivalent for carrying out these types of asymmetric Mannich reactions. Chiral boron complex **6** was therefore prepared by stirring a 1:2 molar ratio of $B(OMe)_3$ and (*S*)-binapthol in the presence of 4 Å molecular sieves (drying agent) in dichloromethane under argon for 1 hour. The reaction mixture was cooled to 0 °C and one equivalent of (*S*)-imine **3** added, followed by cooling to -78 °C, addition of the silyl ketene acetal, before stirring overnight to afford the corresponding β-amino ester (*S,S*)-**63** in 53% yield and 45% de. [1,2]



Scheme 3. 19: Mukaiyama Mannich reaction using (*S*)-boron-BINOL complex **6**.

[ii] Other methods of preparing this silyl ketene acetal require the use of the cancerogenic cosolvent HMPA and were therefore not pursued.

This Mannich reaction was then repeated using (*R*)-BINOL-boron catalyst **6** which gave the opposing β-amino ester diastereoisomer (*S,R*)-**63** in 65% yield and 72% de. Therefore, it was clear that the sense of asymmetric induction in these Mannich reactions is dominated by the configuration of the BINOL ligand, with a combination of (*S*)-imine substrate and (*R*)-BINOL catalyst resulting in 'matched' stereocontrol. [1,2]



Scheme 3. 20: Mukaiyama Mannich reaction using (*R*)-boron-BINOL complex **6**.

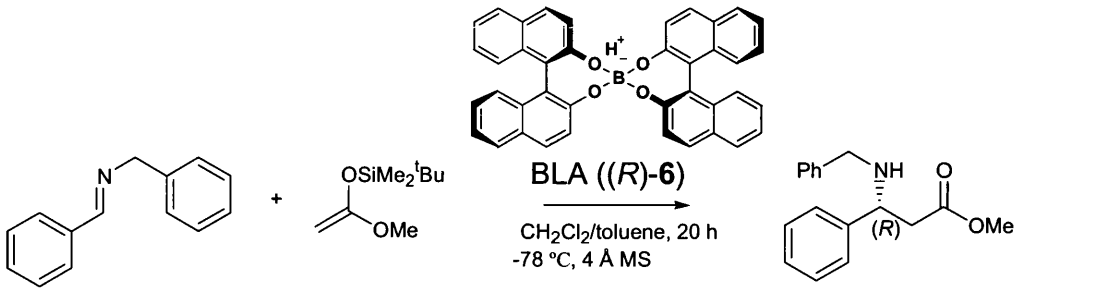
The configuration of the newly formed stereocentres of the two diastereoisomeric β-amino-esters (*S,S*)-**63** and (*S,R*)-**63** formed in these reactions were assigned by comparison of their ^{1}H NMR spectra with those previously reported for the corresponding *tert*-butyl-β-amino-ester diastereoisomer **5** previously reported by Yamamoto *et al.* [1,2]

Clearly, the levels of diastereoselectivity obtained using trimethyl-silyl-ketene acetal **62** (72% de) as a nucleophile in these Mannich reactions were inferior to those reported previously for the corresponding *tert*-butylsilyl-ketene acetal **4** of 94% de (Scheme 3.18). It was proposed that the poorer stereoselectivity produced in my Mannich reactions were likely to be due to the change of ester substituent from a bulky *tert*-butyl group to a less sterically demanding methyl group, which had resulted in a less stereoselective transition state. [1,2,7]

3.5.2 An enantioselective Mannich reaction

Attention then turned to using boron-BINOL complex **6** to catalyse the enantioselective reaction of ketene-silyl acetal **62** with *N*-benzyl-imine **35**; a reaction that had not been reported previously. Since there were no previous reports of any asymmetric Mannich

type reactions having being carried out at temperatures above -78 °C, [1-4] it was decided to carry out reactions at both room temperature and at -78 °C. Therefore, reaction of imine **35** with silyl ketene acetal **62** in the presence of BLA **(*R*)-6** was shown to afford (*R*)-*N*-benzyl-β-amino ester **64** as crude yellow oil in 50% yield and 26% ee at room temperature, and in 48% yield and 47% ee at -78°C.

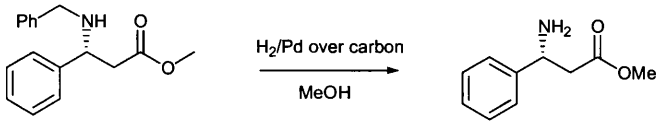


1 equiv. 1 equiv. **r.t,** 50% yield, 26% ee
-78°C, 48% yield, 47% ee

35 **62** **64**

Scheme 3. 21: Mukaiyama Mannich reaction using boron-(*S*)-BINOL complex **6**.

The structure of the (*R*)-*N*-benzyl-β-amino ester **64** was evident from its ^{1}H NMR spectra that revealed ABX quartets at δ 2.55 and δ 2.65 ppm corresponding to the CH_AH_BCO resonances and CH_AH_BPh benzylic protons at δ 3.45 and 3.68 ppm respectively. Furthemore, the ^{13}C NMR spectrum showed the presence of thirteen resonances, whilst IR analysis is revealed a strong absorption for the C=O of the ester group at 1732 cm^{-1}. The enantiomeric excess of β-amino ester **64** was determined by chiral HPLC analysis using an AD chiralpack column which resulted in baseline resolution of its (*R*)- and (*S*)- enantiomers. An authentic sample of (*rac*)-β-amino ester **64** was prepared for analytical purposes via repeating the Mannich reaction using (*rac*)-BINOL for catalyst generation. The β-amino ester **64** was then treated overnight at room temperature with methanol in the presence of palladium on carbon (10% by mass) under hydrogen atmosphere (5 atm) to furnish its corresponding (+)-(3*R*)-methyl-3-amino-3-phenylpropionate **65** in an isolated 84% yield, according to scheme 3.22. The (*R*)-absolute configuration of β-amino-ester **65** was assigned via comparison of the positive sign of its specific rotation of **65** ($[\alpha]_D^{20}$ +11.9 (c 1.00, $CHCl_3$)) with that previously reported for the (*R*)-β-amino ester in its enantiopure form ($[\alpha]_D^{20}$ +22.3 (c 1.99, $CHCl_3$)).[9, 18-20]



64 **65**

Scheme 3. 22: Deprotection of benzyl group by hydrogenation with palladium over carbon.

With these promising results in hand, it was decided to use the reaction of imine **35** and silyl-ketene-acetal **62** as a model reaction to optimise the yield and enantioselectivity of this asymmetric Mannich reaction. It was initially decided to carry out this optimisation process at room temperature, because this temperature was most likely to afford the largest improvements in enantioselectivity. Once optimal conditions had been stablished at room temperature they could then be applied to Mannich reactions at -78 °C to afford β-amino esters in higher ee.

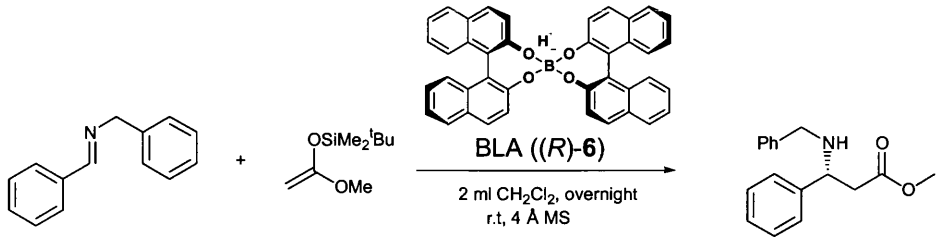
3.5.2.1 Solvent screen

Screening a range of solvents (THF, Et_2O, hexane, $CHCl_3$, MeCN, MeOH) at room temperature revealed that toluene (43%, 31% ee) and CH_2Cl_2 (81%, 26% ee) afforded the best levels of stereocontrol for the asymmetric synthesis of β-amino-ester **64**. The rate of reaction and overall yield of the reaction was much improved for the more polar solvent CH_2Cl_2 which afforded a truly homogeneous reaction mixture. Since the difference in enantioselectivity between these solvents was not large, it was therefore decided to use dichloromethane as a solvent in all further Mannich reactions.

3.5.2.2 Purification issues

Whilst these asymmetric Mannich reactions resulted in excellent conversions of reactants to products, attempts to purify the desired β-amino-ester **64** by chromatography were hampered by the presence of excess BINOL species in the crude reaction product. Bearing these purification difficulties in mind, a number of conditions were changed in an attempt to optimise the isolated yield of β-amino ester **64**. It was found that decreasing the amount of solvent used for the reaction, and using two

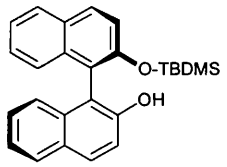
equivalents of silyl-enol ether **62** afforded a cleaner reaction product which could be purified by careful chromatography to afford the desired β-amino ester **64** in an excellent 81% isolated yield. The key to the efficient isolation of β-amino ester was the use of ninhydrin [21] as a stain to visualise the β-amino ester product that was revealed as an orange spot on the TLC plate. However, this purification process also enabled the isolation of a new compound with almost the same Rf as the β-amino ester product, which was identified as mono-TBDMS-BINOL **66**. (Figure 3.2).



1 equiv. 2 equiv. 81% yield
26% ee

35 **62** **64**

Scheme 3. 23: Preparation of β-amino ester **64** by using chiral BINOL-boron catalyst **6**.



TBDMS-protected BINOL

66

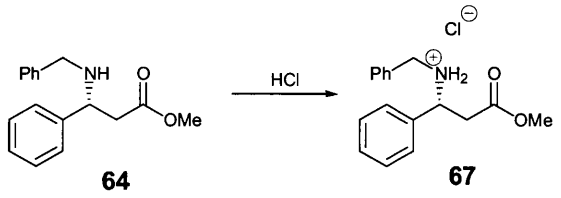
Figure 3. 2: Monoprotected *O*-TBDMS-BINOL **66**.

Due to the similar retention times observed for mono-silylated-BINOL **66** (Rf = 0.23) and the β-amino ester **64** (Rf = 0.20) on silica gel it was decided that an alternative to chromatography was desirable for purifying the wide range of β-amino esters that would be produced in this study. Therefore, it was decided to carry out further investigations into the best method of isolating pure β-amino esters from these crude reaction mixtures.

Attempts to purify crude reaction mixtures via fractional recrystallisation from different mixtures of solvents (CH_2Cl_2/petrol 40-60 °C) (ethyl acetate/petrol 40-60°C) proved

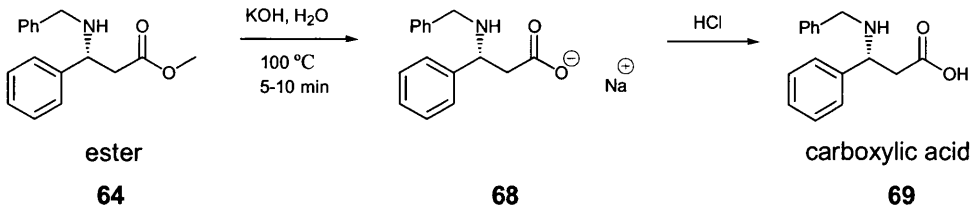
partially successful in removing crystalline BINOL, however the oily β-amino ester **64** obtained could never be isolated totally free of BINOL derivatives using this approach.

Alternatively, it was proposed that treating the crude β-amino ester products with HCl would result in conversion their corresponding hydrochloride salts which could then be extracted into water. Once again, attempts to employ this acidification strategy were only partially successful since the lipophilic β-amino ester hydrochloride salt **67** was found to partition itself between both the aqueous and organic phases, leading to a decreased yield.



Scheme 3. 24: Formation of the hydrochloride salt of β-amino ester **64**.

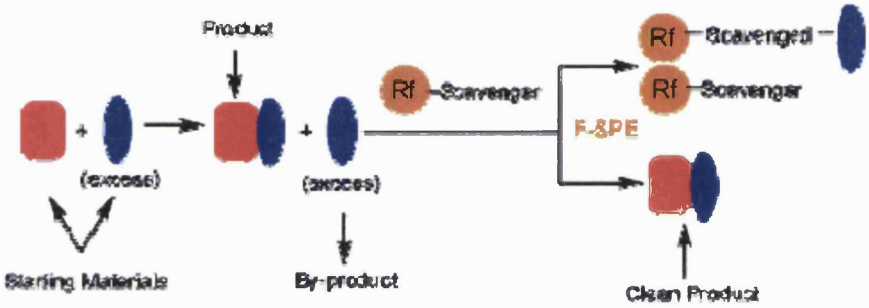
Finally, we converted the β-amino ester **64** into its corresponding carboxylic acid derivative **69** by refluxing with five equivalents of KOH in a mixture of acetone/water. Afterwards, the aqueous layer, containing β-amino acid hydrochloride salt **68,** was extracted three times with dichloromethane in an attempt to remove BINOL and the aqueous phase acidified with HCl to afford the corresponding carboxylic acid derivative **69**. However, once again ^{1}H NMR spectroscopic analysis revealed several peaks in the aromatic region corresponding to the presence of unwanted BINOL residues.



Scheme 3. 25: Base catalysed hydrolysis of β-amino ester **64**.

3.5.2.3 A scavenging polymer approach

There has recently been much interest in developing polymer supported scavenging agents for the rapid purification of crude reaction products for solution-phase chemical library synthesis. They are employed to remove or scavenge unwanted reagents or by-products from crude reaction products and thus aid the purification process. Typically, the polymeric scavengers are added to a reaction when it is complete, with the resultant polymer bound reactants then removed by simple filtration, leaving the purified target product in solution.



Scheme 3. 26: Polymer scavenging strategy.

Boronic acids are known to reversibly bind diols and polymer bound boronic acids [iii] have been used previously to scavenge diols.[22] For example, polystyrylboronic acid resin has been shown to selectively react with *cis*-1, 2-cyclohexanediol in the presence of *trans*-1, 2-cyclohexanediol in refluxing benzene/pyridine with azeotropic removal of water. Subsequent filtration and washing of the polymer results in separation of the stereoisomeric 1,2-cyclohexanediols, allowing pure *trans*-diol to be recovered from solution.[23]

[iii] Diols have also been scavenged previously using polymer supported aldehydes that afford polymer-supported acetals.

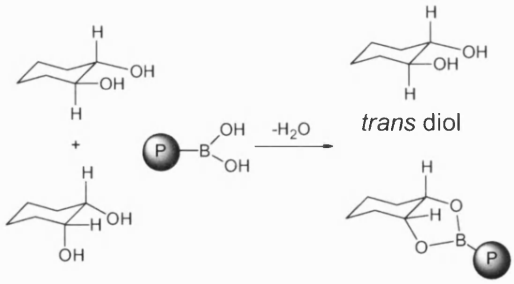
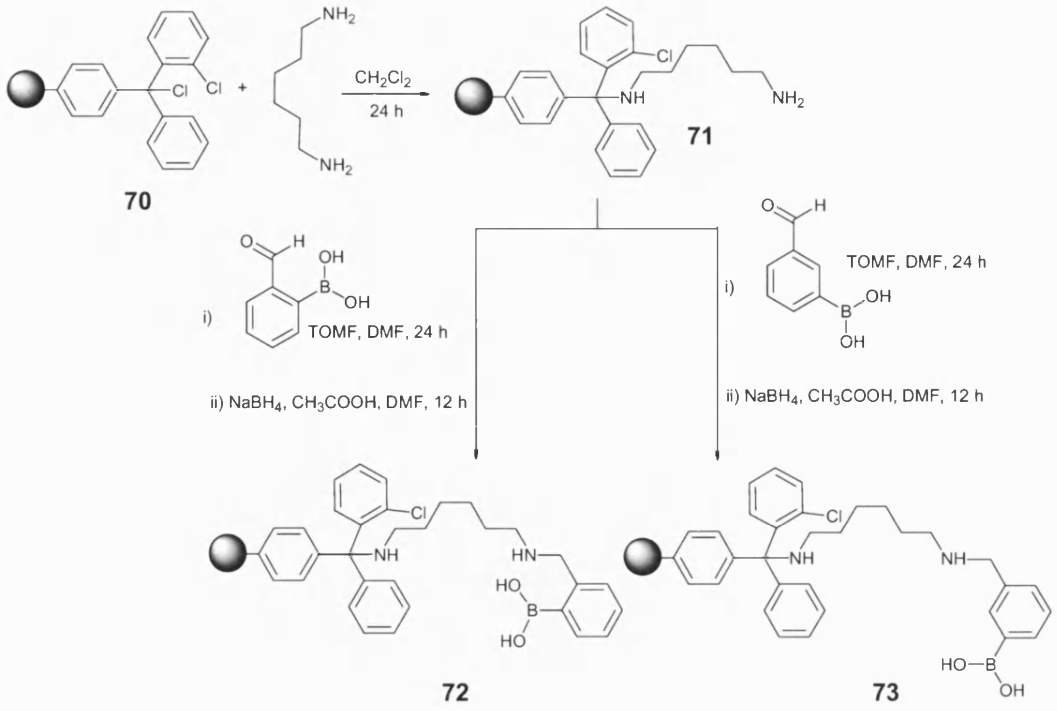


Figure 3. 3: Polymer scavenging scavenger of *cis*-1,2-cyclohexanediol in the presence of *trans*-1,2-cyclohexanediol.

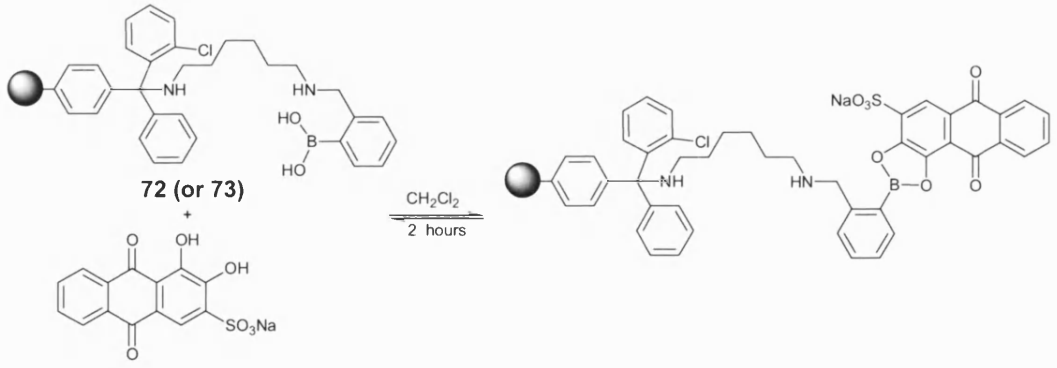
Previous investigations within the TDJ group have been directed towards developing stable boronic acid sensors for detecting monosaccharides, with a number of boronic acid containing polymers and dendrimers having been screened as polymer-supported glucose sensors.[24] It was reasoned that these type of boronic acid polymers might prove useful for scavenging BINOL from the crude reaction products of our Mannich reactions, and as a consequence two of these boronic acid polymers **72** and **73** were prepared using the following protocol.[24]

Boronic acid polymers **72** and **73** were prepared from a common polymer intermediate **71** obtained via nucleophilic fictionalisation of 2-chlorotrityl chloride resin (500 mg, 0.69 mmol) with 1,6-diaminohexane (1.6 g, 13.8 mmol) in dry CH_2Cl_2 at room temperature. The resultant polymer resin was then subjected to a reductive amination protocol involving treatment with either 2- or 3-formylphenyl boronic acid in dry DMF and trimethylorthoformate (TMOF) (1 mL), followed by reduction of the resultant imine with $NaBH_4$. These protocols afforded the respective boronic acid polymers **72** or **73**, which were dried under vacuum at 40 °C for 12 hours prior to use as scavenging agents for BINOL.



Scheme 3. 27: Preparation of boronic acid polymers **72** and **73.**

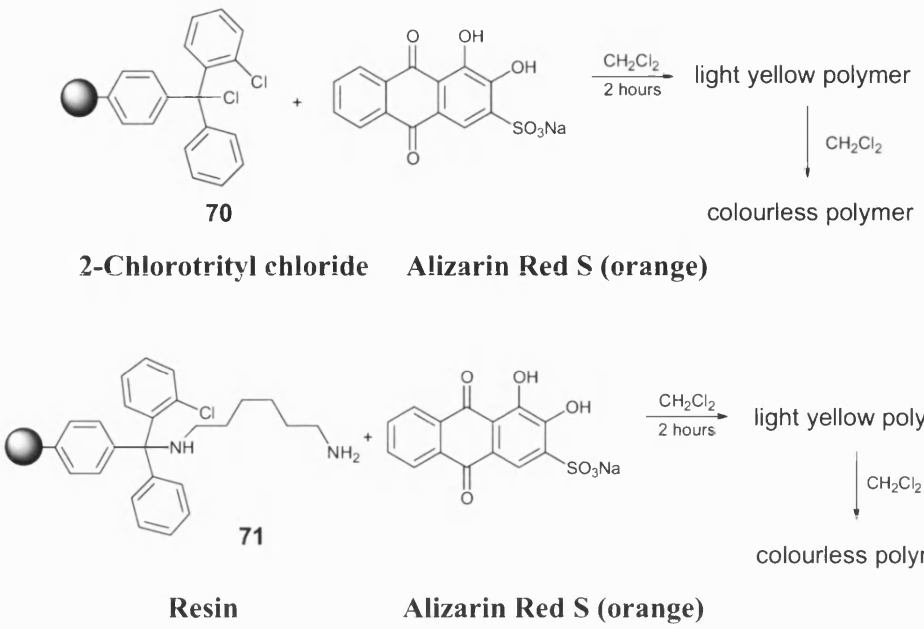
Boronic acids are known to react with Alizarin Red S to afford bright orange complexes in solution, and this complexation reaction was used to qualitatively determine whether our boronic acid polymers **72** and **73** had been prepared successfully.



Scheme 3. 28: Reaction of Alizarin with boronic acid polymer **72**.

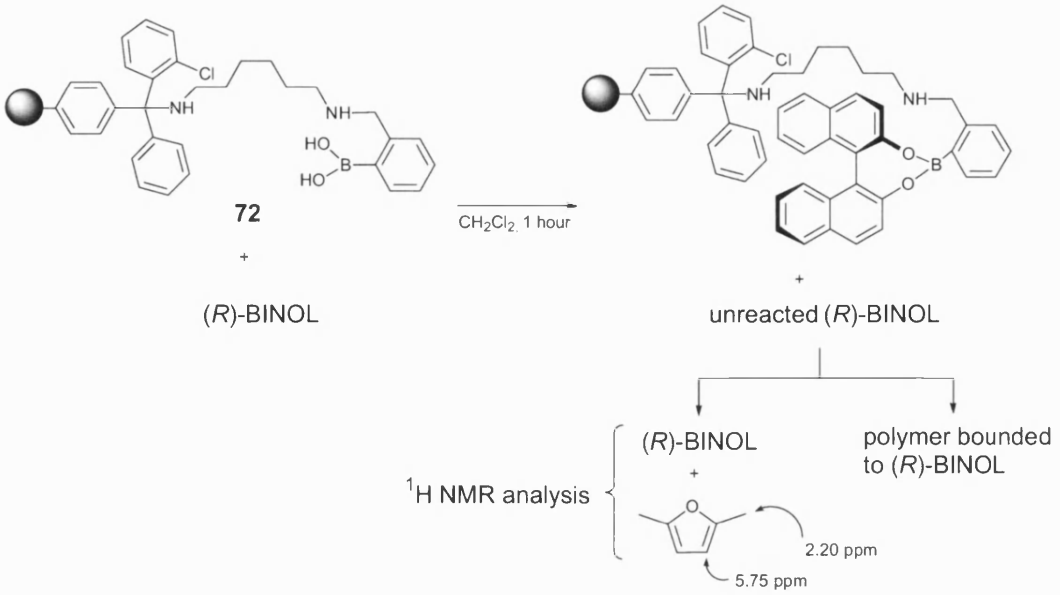
Therefore, each polymer **72** and **73** was treated with a solution of alizarin in dichloromethane for 2 hours which resulted in both resins being stained a persistent orange colour, even after repeated washing with DMF and CH_2Cl_2. In contrast, treatment of unfunctionalised 2-chloro-trityl resin **70**, or the amino-polymer

intermediate **71**, with Alizarin Red S lead to light orange resins whose colour was removed on washing with DMF or CH_2Cl_2.



Scheme 3. 29: Reaction of Alizarin with 2-chlorotrityl chloride resin **70** and amino resin **71**.

The loading of each polymer **72** and **73** was determined by the following procedure. A weighed amount of polymer was stirred in a 1.5 mmol solution of BINOL in CH_2Cl_2 for 1 hour. The polymer was then filtered off and the filtrate concentrated *in vacuum* to afford recovered BINOL that was redissolved in a solution of 1 mmol of 2,5-dimethylfuran in $CDCl_3$.[25] ^1H NMR spectroscopic analysis of the resultant solution allowed the concentration of recovered BINOL to be calculated via comparison of the relative intensities of the integrals of its phenolic hydroxyl groups (δ 5.2 ppm) with the methyl groups of the 2,5-dimethylfuran (δ 2.20 ppm). This comparison enabled us to determine that polymer **72** had been formed with a loading of 1.3 mmol/mg, and that polymer **73** had been formed with a loading of 1.5 mmol/mg.



Scheme 3. 30: Loading determination protocol.

We next determined whether these polymers could be recycled by treating them with excess methanol under conditions that were sufficient to remove all of the immobilised BINOL. Importantly, the amount of BINOL recovered from these decomplexation reactions was found to correspond well with the boronic acid loading previously calculated for each polymer using our ^{1}H NMR spectroscopic method. After filtration and drying, polymer **72** was dried and reused in a standard BINOL sequestration experiment, and shown to bind 1.08 mmol of BINOL (72% yield) thus indicating that each boronic acid polymer could potentially be recycled.

These polymers were then screened for their ability to scavenge BINOL from the crude reaction products of our asymmetric Mannich reactions.[iv] Therefore, three equivalents of each boronic acid polymer were added to the crude reaction product of a crude Mannich reaction (containing two equivalents of BINOL) in CH_2Cl_2, and the sequestration reaction allowed to stir for 12 hours. The polymer was then filtered off and the resultant crude reaction product concentrated *in vacuum* to afford a filtrate that was analysed by ^{1}H NMR spectroscopy using a known concentration of 2, 5-dimethylfuran as internal standard. This revealed that only 38-44% of the total amount of BINOL had been scavenged from these crude reaction products, and as a consequence this polymer scavenging was deemed unsuitable for rapidly purifying

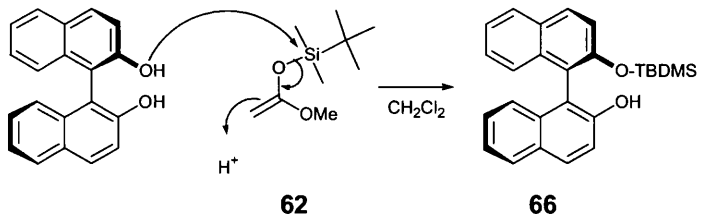
[iv] A series of other boronic acid polymers and dendrimers available from the TDJ group were also screened for their ability to scavenge BINOL from solution, however their performance was shown to be inferior to the scavenging ability of polymers **72** and **73**.

these types of asymmetric Mannich reactions. It was subsequently demonstrated that boronic acid polymers **72** and **73** did not sequester the mono-TBDMS-BINOL **66** that was being formed as a by-product in these Mannich reactions, thus explaining why BINOL species persisted in the crude reaction products.

Concurrent to this scavenging polymer work it was found that the β-amino esters produced in these Mannich type reactions were sufficiently volatile to be purified by distillation of the crude reaction product *in vacuum*. Therefore, careful bulb to bulb distillation of the crude reaction product of an asymmetric Mannich reaction using a Kugelrohr distillation apparatus at a reduced pressure of 1 mbar gave clean β-amino-ester products in 80-85% isolated yield that were free of any BINOL derived contaminants.

3.5.2.4 Stoichiometric of substrates used in Mannich reaction

Since ^{1}H NMR spectroscopic analysis had shown that Mannich reactions using these boron-BINOL catalysts produced up to one equivalent of monosilyl-BINOL **66** as a by-product it was proposed that using more than one equivalent of silyl- ketene acetal **62** might result in the yield of β-amino ester **64** being improved.



Scheme 3. 31: Mechanism of formation of *O*-silyl- BINOL **66.**

Therefore, our standard Mannich reaction was repeated using one equivalent of imine **35** and one, two or three equivalents of ketene-silyl-acetal **62** respectively at room temperature. This revealed that the use of two equivalents of ketene-silyl-acetal **62** was optimal in these reactions affording >99% conversion of imine **35** to β-amino-ester **64** over a period of 24 hours.

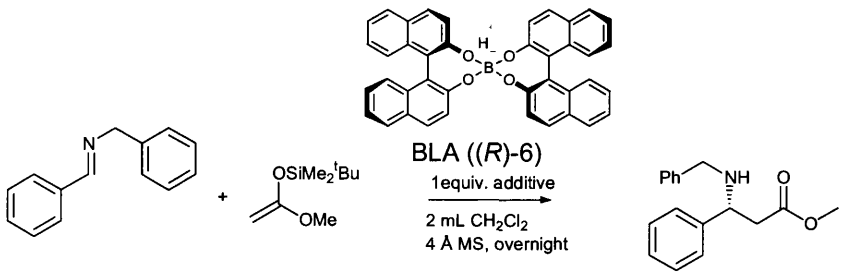
Table 3. 1: Optimizing the level of conversion of the standard Mannich reaction.

reaction time	silyl enol ethers	Conversion (%)
12 hrs	1 equiv.	50
12 hrs	3 equiv.	85
24 hrs	2 equiv.	>99

3.5.2.5 Attempts to employ achiral additives to increase enantioselectivity

As described earlier in this chapter, another member of the SDB/TDJ group had shown that addition of alcohol additives to *aza*-Diels-Alder reactions catalysed by boron-BINOL complex **6** at room temperature had resulted in formation of dihydropyridone **37** in enhanced ee.[7] [v] Given this precedent it was decided to explore whether the presence of achiral additives would also result in an improvement in the enantioselectivity of our Mannich reactions.

A series of Mannich reactions were carried out under standard conditions at room temperature in the presence of one equivalent of *N*-methyl-imidazole (NMI), propanol or benzyl alcohol as achiral additives. However, these experiments were unsuccessful in affording enhanced enantioselectivity resulting in the corresponding β-amino ester **64** being formed in only 25% ee and 27% ee respectively.



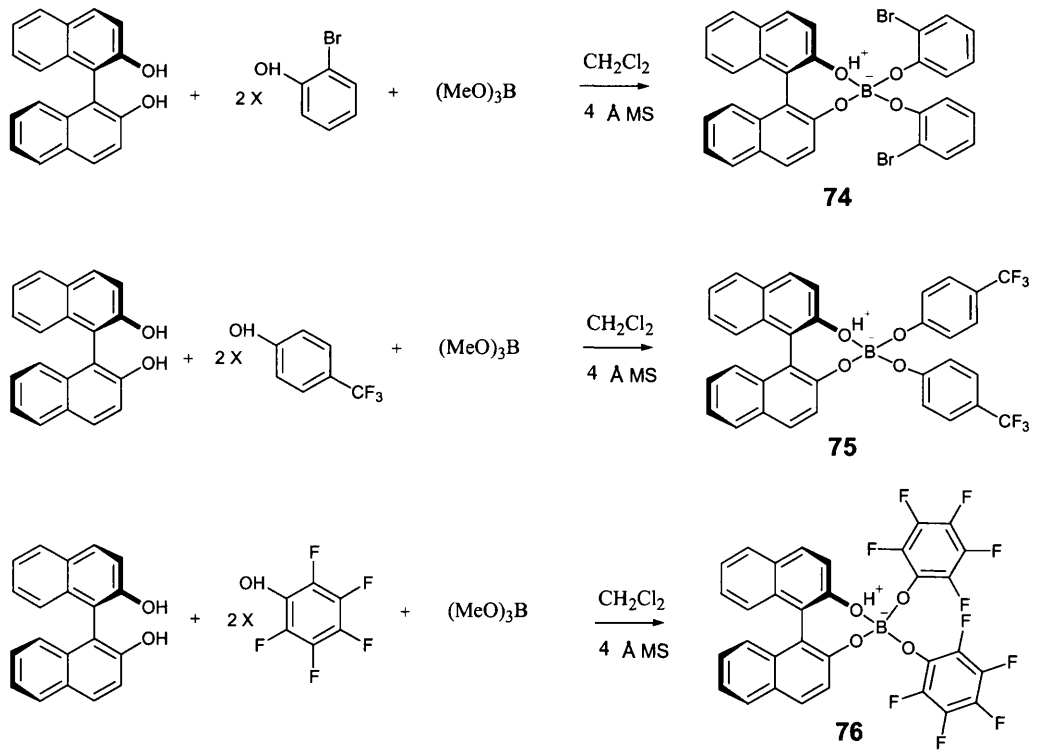
Scheme 3. 32: Mannich-type reaction with one equivalent of achiral additive.

[v] For other examples where the use of achiral additives have been reported to enhance the enantioselectivity of reactions catalysed by zirconium or niobium catalysts, see references 44 and 46 in chapter 2.

Table 3. 2: Results for β-amino ester **64** by using a wide range of additives.

Additive	Yield (%)	ee (%)
None	50	26
NMI	50	26
Propanol	40	25
Benzyl alcohol	43	27

We also attempted to carry out this Mannich reaction in the presence of a series of halo-phenol additives that we proposed had the potential to form mixed BINOL-phenol-boron complexes **74-76**. Unfortunately use of these ligand mixtures under our standard Mannich conditions did not afford any major improvements in stereocontrol, affording β-amino-ester **64** in 14-32% ee at room temperature.



Scheme 3. 33: Three new Lewis acid chiral catalysts for Mukaiyama Mannich reactions.

Table 3. 3: Three new approaches to increase the level of stereoselection of β-amino ester **64**.

entry	pre-catalyst	Yield (%)	ee (%)
1	74	40	24
2	75	69	14
3	76	36	32

3.5.2.6 Changing the imine protecting group

We next explored the use of imine **48** as a substrate in the Mannich reaction which had been used previously by Kobayashi *et al.* for zirconium-BINOL complex catalysed asymmetric Mannich reactions.[26] This imine substrate contains a phenolic protecting group capable of coordinating to the boron-BINOL catalyst which we thought might add structural rigidity to the transition state and hence afford better levels of stereocontrol at room temperature (see Figure 3.4).

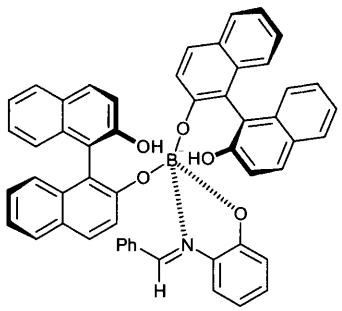
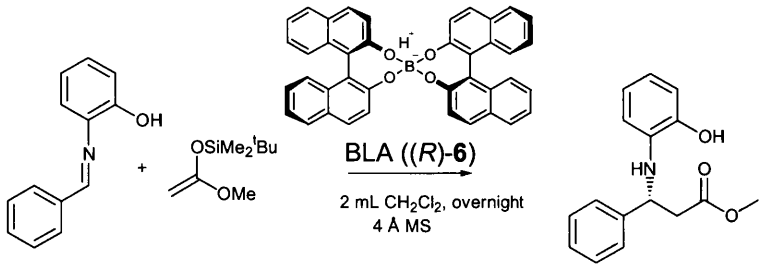


Figure 3. 4: Transition state proposed for the boron complex **6** of imine **48**.

Therefore, Mukaiyama Mannich reaction was carried out under standard conditions at room temperature which gave the desired β-amino ester **77** in an excellent 93% isolated yield, but in a disappointing 22% enantiomeric excess as determined by chiral HPLC analysis.



1 equiv. 1 equiv. 93% yield
22% ee

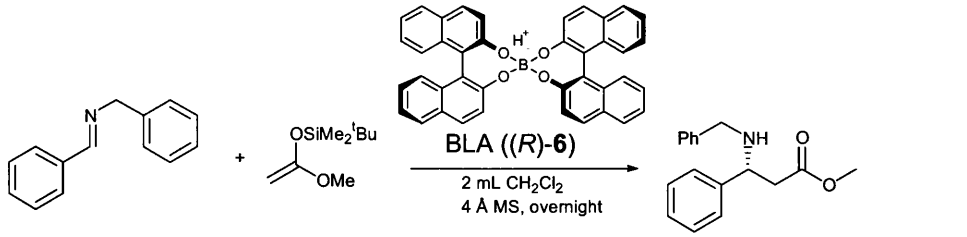
48 **62** **77**

Scheme 3. 34: Preparation of 2-phenol-phenyl β-amino ester **77** using stoichiometric amounts of chiral BINOL-boron catalyst **6**.

3.5.2.7 Changing the catalyst loading

All the boron-BINOL mediated *aza*-Mannich-type reactions between aldimines and silyl ketene acetals carried out to date had employed the BINOL-boron Lewis acid in stoichiometric amounts. One of the original aims of this research project was to attempt to develop a catalytic boron-BINOL catalysed *aza*-Mannich-type reaction that employed lower catalyst loadings, as described previously for catalytic Mannich-type reaction using chiral ligand complexes of zirconium, [26-30] palladium, phosphorus,[31] copper,[32, 33] zinc,[34, 35] titanium,[36] iron[37] and niobium.[38] Therefore, we decided to see whether the use of sub-stoichiometric amounts of boron-BINOL complexes in these asymmetric Mannich reactions would produce useful yields of chiral β-amino-esters.

We first investigated the use of 10 mol% of boron-BINOL complex **6** in the Mannich-type reaction between one equivalent of imine **35** and two equivalents of silyl enol ether **62** at room temperature which gave the desired β-amino ester **64** in only 16% yield and 27% ee after 24 hours. The same reaction was repeated at -78 °C over a period of two days which gave the β-amino ester **64** in 29% yield and 49% ee, clearly indicating that some catalyst turnover had occurred in the reaction.[2]



1equiv. 1 equiv.

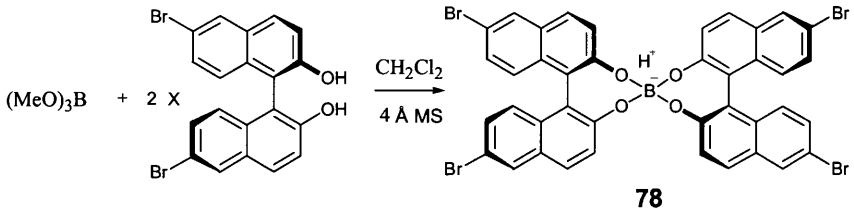
r.t, 24h; 16% yield, 27% e.e
-78 °C, 48h; 29% yield, 49% ee

35 **62** **64**

Scheme 3. 35: Preparation of β-amino ester **64** using catalytic amount of chiral BINOL-boron catalyst **6**.

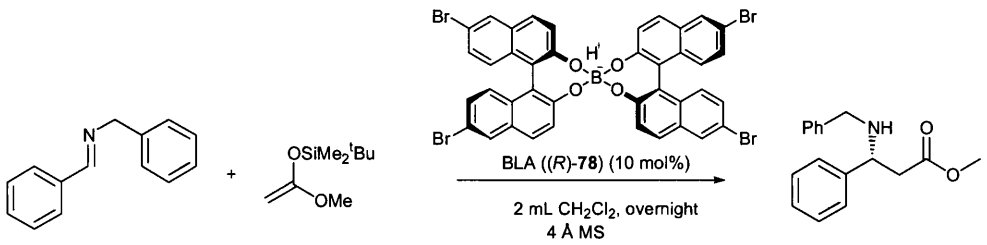
3.5.2.8 Changing the BINOL ligand and the catalyst loading

A number of structural analogues of BINOL containing electron withdrawing groups at their 6,6′-positions have been developed that were known to afford enhanced levels of stereocontrol in enantioselective Mannich-type reactions.[26-29] Therefore, 6,6′-dibromo-BINOL was used as an alternative ligand to prepare a new chiral boron catalyst which was used at 10 mol% to afford the β-amino ester **64** in a poor 15% yield but in an improved 65% ee when a catalytic amount of complex **78** was used at room temperature. However the yield of this Mannich type reaction was decreased due to the precatalyst being used in catalytic amounts because of the expense of the 6, 6′-dibromo-BINOL ligand (£155.0/500 mg). Repeating this substoichiometric catalytic Mannich reaction at -78 °C unfortunately did not result in any β-amino ester being formed. This catalytic system is currently being explored further by members of the SDB/TDJ group.



78

Scheme 3. 36: Preparation of proposed boron-6,6′-dibromo-binaphthol complex, 78.



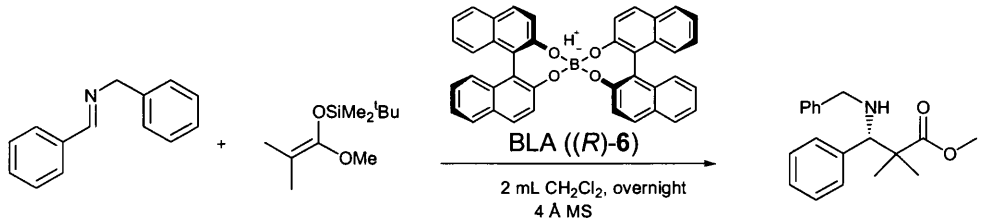
1 equiv. 1 equiv. 15% yield
65% e.e

35 **62** **64**

Scheme 3. 37: Promising enantioselectivity obtained using chiral 6, 6′dibromo-BINOL-boron catalyst **78**.

3.5.2.9 An alternative silyl-ketene-acetal [39, 40]

We next screened the use of chiral boron-BINOL complex **6** as a catalyst for the asymmetric Mannich reaction of 1-methoxy-2-methyl-propenyloxy-trimethyl-silane **79** with imine **35** under our standard conditions.[2] Unfortunately, this Mannich reaction afforded its corresponding β-amino ester **80** in 71% yield but in highly disappointing 6% ee as determined by chiral HPLC analysis.



71% yield
6% ee

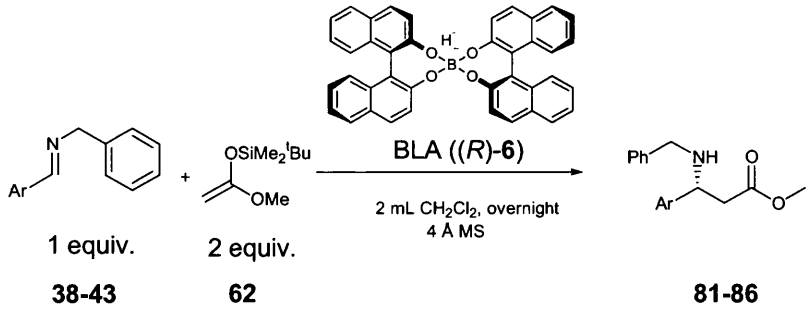
35 **79** **80**

Scheme 3. 38: Preparation of β-amino ester **80** using a stoichiometric amount of chiral BINOL-boron catalyst **6**.

3.5.2.10 Asymmetric Mannich reactions using BINOL-boron catalyst

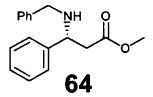
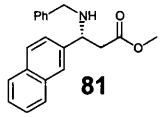
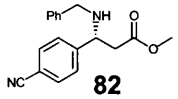
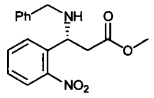
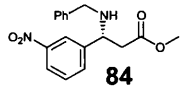
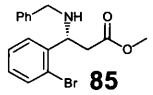
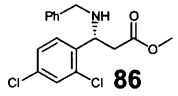
The optimal conditions for using these boron-BINOL catalysts were then established to catalyse a range of asymmetric Mannich reactions using different imine substrates at room temperature and at -78 °C. Therefore, a BINOL-boron catalyst was prepared by

mixing one equivalent of trimethyl borate with two equivalents of (*R*)-BINOL in dichloromethane in the presence of 4 Å molecular sieves.[1-3] This precatalyst was then added to a solution of one equivalent of imine in dichloromethane, followed by addition of two equivalents of silyl ketene acetal **62**. These Mannich reactions gave their corresponding β-amino esters **81-86** in 74-95% yield and 22-34% ee at room temperature, and in 73-92% yield and 32-62% ee at -78 °C. These results clearly revealed that the enantiomeric excesses of the β-amino-esters **81-86** formed at room temperature of <35% ee were generally unsatisfactory. However, the asymmetric Mannich reactions carried out at -78 °C were more promising, affording a number of β-amino esters containing electron withdrawing groups in their aryl rings in >50% ee. The enantiomeric excesses of all the β-amino esters produced in these Mannich reaction were determined via chiral HPLC analysis (using either AD or OD Chiralpack columns), in comparison with authentic racemic standards prepared separately using racemic boron-BINOL complexes or trimethyl borate as a Lewis acid. Their configuration was assigned as (*R*) from to the precedent previously established for β-amino ester **64**.



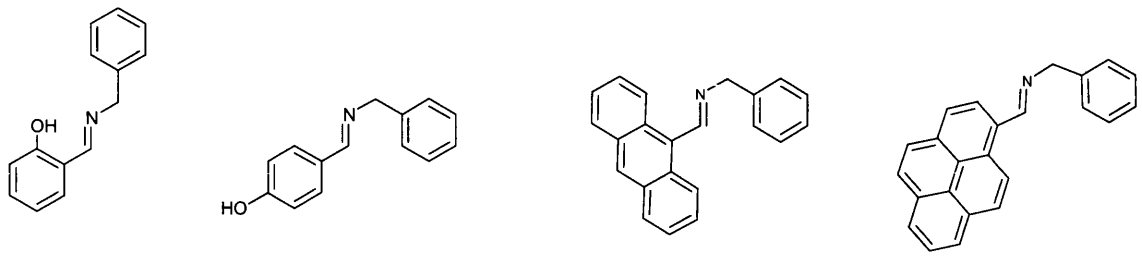
Scheme 3. 39: Mannich-type reaction derived from benzylimines at room temperature and -78 °C.

Table 3. 4: Seven β-amino esters prepared using BINOL-boron complex **6**.

imine	β-amino acid ester	% yield (rt)	% e.e. (rt)%	% yield (-78°C)	% e.e. (-78°C)
35	 **64**	81	26	77	50
38	 **81**	87	22	73	32
39	 **82**	89	33	68	64
40	 **83**	74	30	66	52
41	 **84**	90	31	75	54
42	 **85**	95	34	82	62
43	 **86**	84	26	92	60

Attempts to employ imines **44-47** as substrates in these asymmetric Mannich reactions were unsuccessful however, affording no more than trace amounts of their respective β-amino esters at either room temperature, or at -78 °C. It is proposed that the failure of imines **44** and **45** to afford β-amino-esters in these reactions may be a result of their

unprotected phenolic groups interfering with boron-BINOL catalyst formation. Alternatively, it is proposed that imines **46-47** may fail to react due to steric hindrance which may prevent efficient catalyst-substrate complexation, and/or steric blocking of the trajectory of approach of the incipient silyl-ketene-acetal **62**.



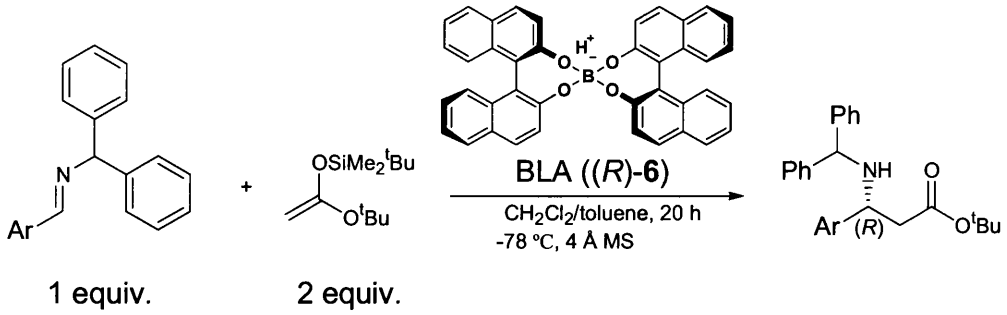
44 **45** **46** **47**

Scheme 3. 40: Failed Mukaiyama Mannich reactions of imines **44-47**.

With these promising results in hand our attention then turned to the use of imines derived from diphenylmethylamine, since Yamamoto has reported better results for this class of imine in asymmetric Mukaiyama Mannich reactions.

3.5.3 Diphenyl protecting group

Previous investigations within Yamamoto's research group had described the enantioselective synthesis of three β-amino esters **8, 87** and **88**.[1-3] derived from reaction of *tert*-butyl-silyl ketene acetal **4** with imines **7, 49** and **53** containing an *N*-diphenylmethyl protecting group.



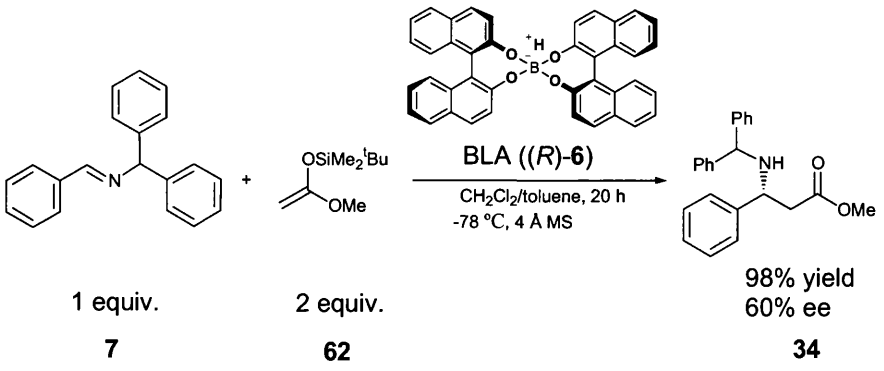
1 equiv. 2 equiv.

Scheme 3. 41: Yamamoto Mannich-type reaction using (*R*)-boron-BINOL complex **6**.

Table 3. 5: Three different β-amino esters reported by Yamamoto's.

β-amino ester	Ar	yield (%)	ee (%)
8	C_6H_5	58	96
87	2-naphthyl	43	96
88	2,4-$Cl_2C_6H_5$	49	95

As the *tert*-butyl silyl ketene acetal **4** previously employed by Yamamoto was not available to us, it was decided to repeat this reaction using commercially available 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** as an alternative nucleophile. Therefore, chiral boron-BINOL Lewis acid (BLA) **6** was prepared *in situ* by mixing a 1:2 molar ratio of trimethyl borate with (*R*)-binaphthol in dichloromethane at room temperature for 1 hour, in the presence of 4 Å molecular sieves under a nitrogen atmosphere.[2] A solution of the corresponding imine **7** in dichloromethane/toluene was then added dropwise to the solution of the boron-BINOL complex, and the resulting yellow solution stirred at 0 °C for 10 minutes. The reaction mixture was then cooled down to -78 °C before addition of *tert*-butyldimethylsilyloxy-1-methoxy ethene **62,** followed by stirring overnight. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding β-amino ester **34** in 60% ee and 98% yield.

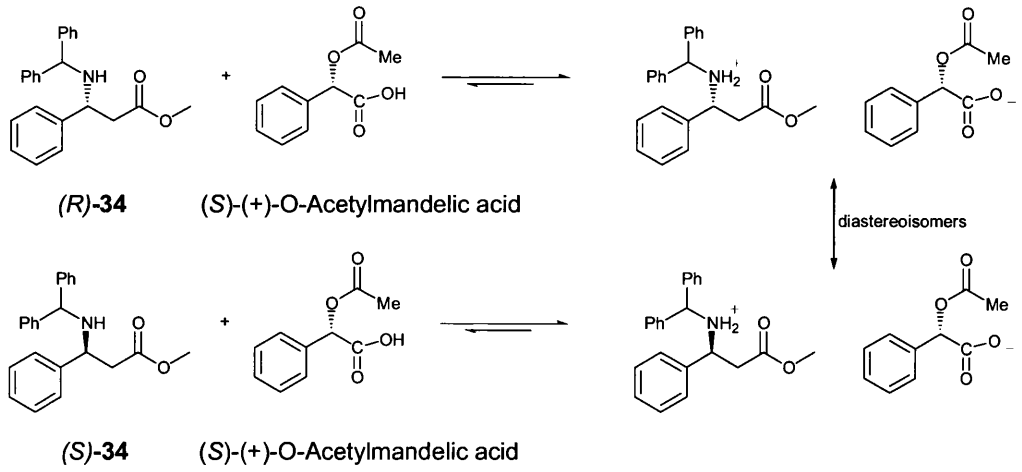


Scheme 3. 42: Yamamoto Mannich-type reaction using (*R*)-boron-BINOL complex **6**.

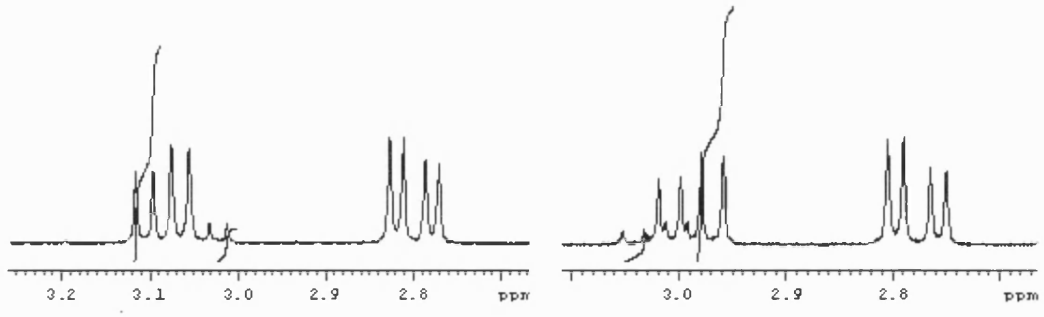
3.5.3.1 Determining the enantiomeric excess*

Attempts to determine the enantiomeric excess of β-amino ester **34** via chiral HPLC analysis proved unsuccessful because of the presence of impurities with similar retention times that we were concerned could cause erroneous results and as a consequence an alternative NMR method was developed to determine its ee using (*S*)-(+)-*O*-acetylmandelic acid as a chiral solvating agent.

Reasonably good splitting of the diastereotopic protons H_2A and H_2B of the β-amino ester **34** were observed when an NMR sample was treated with one, two or three equivalents of (*S*)-(+)-*O*-acetylmandelic acid.[41] Selected regions of the ^1H NMR spectra of samples of (*R*)- and (*S*)-β-amino ester **34,** that were produced in Mannich reactions using opposite enantiomers of BINOL for catalyst generation, are shown in Scheme 3.43. The ee of the β-amino ester was assigned as 60% ee from comparison of the height of integral of the left hand doublet at δ 3.15 with height of the integral of the right hand doublet at δ 3.02. In order to confirm this ee value, the Mannich reaction was repeated using (*S*)-BINOL, which gave a complementary ^1H NMR spectra for (*S*)-β-amino ester **34** in the presence of (*S*)-*O*-acetyl-mandelic acid, which gave an ee of 60%.



Scheme 3. 43: Formation of the salt derived from *(R)*-**34** and (*S*)-**34** β-amino ester and (*S*)-(+)-*O*-acetylmandelic acid.

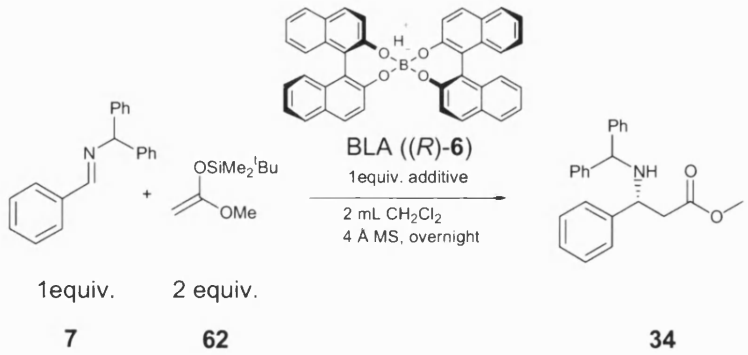


Spectra A (H_A and H_B) Spectra B (H_A and H_B)

Figure 3. 5: 400 MHz ^{1}H NMRs spectra of β-amino ester *(R)*-34 (Spectra A) and (*S*)-34 (Spectra B) with *(S)*-(+)-*O*-acetylmandelic acid.

3.5.3.2 Use of additives to increase the stereoselectivity

Although results described for *N*-benzylimines had shown that addition of alcohol additives did not increase the steroselection of the asymmetric Mannich reaction, it was considered worth screening whether additives might result in enhancement of the enantioselectivity of Mannich-type reaction of *N*-benzylidenebenzhydrylamine **7**. A series of reactions were performed under the optimized conditions in the presence of five different achiral additives at room temperature. However, once again no significant enhancement in enantioselectivity was observed for the β-amino ester **34** formed in these reactions.



Scheme 3. 44: Mukaiyama Mannich reaction using achiral additives.

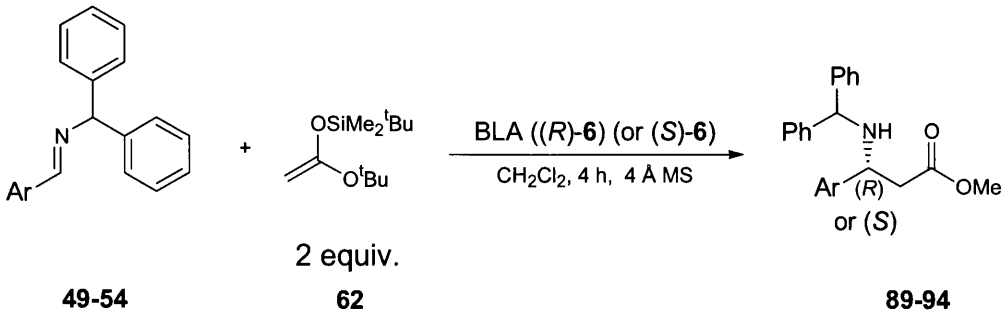
Table 3. 6: Results for β-amino ester **34** by using a wide range of additives.

Additive	Yield (%)	ee (%)
None	97	56
NMI	none	none
DMI	none	none
Propanol	85	63
MeOH	85	60
Benzyl alcohol	>99	53

3.5.3.3 Synthesis of a wide range of β-amino esters

The optimised Mannich-type reaction conditions were then applied for the asymmetric synthesis of seven new β-amino esters at room temperature and at -78 °C. The reactions at room temperature resulted in excellent yields of β-amino esters **89-94** in useful 82-97% ee. Lowering the temperature to -78 °C resulted in a decreased 47-80% yield of β-amino ester products **89-94**, however their enantioselectivity was much improved from 79-97% ee. All enantiomeric excesses were calculated using *(S)*-(+)-*O*-acetylmandelic acid as achiral solvating agent for ^{1}H NMR spectroscopic analysis.

These levels of stereoselectivity were much better than those obtained previously for *N*-benzyl-imine substrates, possibly due to more favourable Π-Π-interaction between the aryl ring of the naphthyl unit of the BINOL ligand and the diphenyl ring of the imines *N*-substituent (Table 3.4). This type of interaction may produce a more ordered transition state that more efficiently blocks one face of the imine from nucleophilic attack. It is clear that imines contain electron-withdrawing substituents afforded much better levels of stereocontrol in these asymmetric Mukaiyama Mannich reactions, once again suggesting that more efficient Π-Π-stacking may occur for these electron deficient arenes in their transition states.

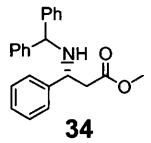
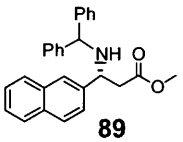
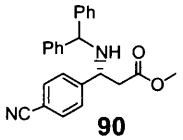
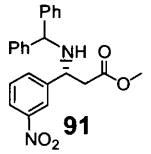
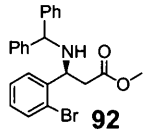
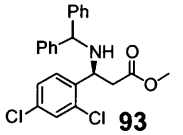
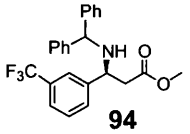


2 equiv.

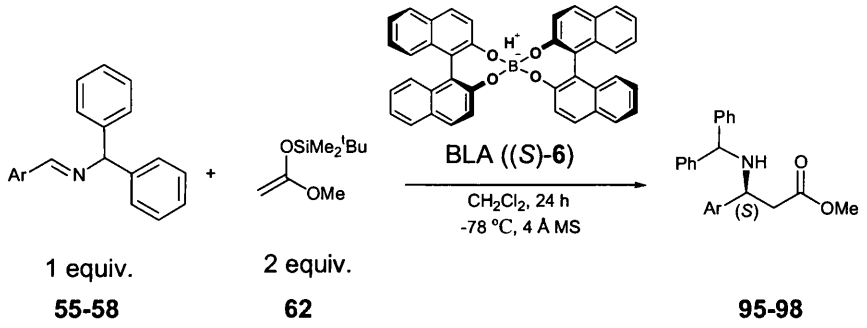
49-54 **62** **89-94**

Scheme 3. 45: Mukaiyama Mannich reaction of imines containing and N-diphenylmethine protecting group.

Table 3. 7: Preparation of chiral β-amino esters containing a diphenylmethine protecting group. Enantiomeric excess was determined using (*S*)-(+)-*O*-acetylmandelic acid.*

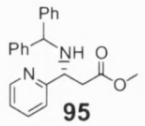
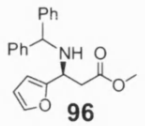
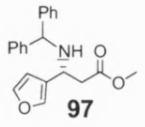
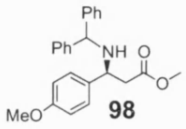
imine	β-amino acid ester	% yield (rt)	% e.e (rt)*	% yield (-78 °C)	% e.e (-78 °C)*
7	 **34**	97	56	80	75
49	 **89**	93	53	47	79
50	 **90**	91	65	61	88
51	 **91**	82	67	64	91
52	 **92**	92	73	49	97
53	 **93**	87	77	74	94
54	 **94**	84	63	-	-

These conditions were then applied to three heteroaryl imines **55-58** containing a diphenylmethine protecting group that were derived from pyridine or furyl aldehydes. The pyridine derived imine **55** afforded its corresponding β-amino ester **95** in a good 75% yield, but poor 25% ee, and it was proposed that this significantly lower ee might have been a result of the basic pyridinyl nitrogen atom interfering with boron-BINOL complexation. However, Mannich reaction of the 2-furyl **56** and 3-furyl-imines **57** afforded their corresponding β-amino esters **96** and **97** in reduced 53-56% yields and acceptable 61-69% ee. Whilst, Mannich-type reaction of imine **58**, containing a methoxy group in the aryl ring did not give the desired β-amino ester **98**, presumably because the imine **58** is not reactive enough.



Scheme 3. 46: Mukaiyama Mannich reaction of diphenylbenzylimines.

Table 3. 8: Other β-amino ester obtained under the same experimental conditions at room temperature.

Imine	β-amino ester	yield (%)	ee (%)
55	 **95**	75	25
56	 **96**	53	69
57	 **97**	56	61
58	 **98**	failed	-

The enantiomeric excess of these β-amino esters **97** were determined in the usual manner via derivatisation with (*S*)-acetyl mandelic acid. Surprisingly, the methyl ester group of the corresponding diastereomeric salts of compound **97** displayed different different chemical shifts which enabled their integrals to be used for ee determination.

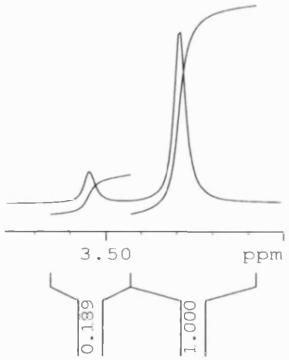
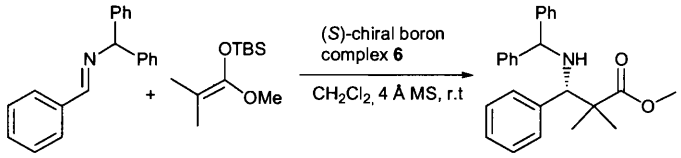


Figure 3. 6: Spectra of the diastereomeric salts derived from of compound **97** and (*S*)-acetylmandelic acid.

3.5.3.4 Alternative silyl ketene acetal

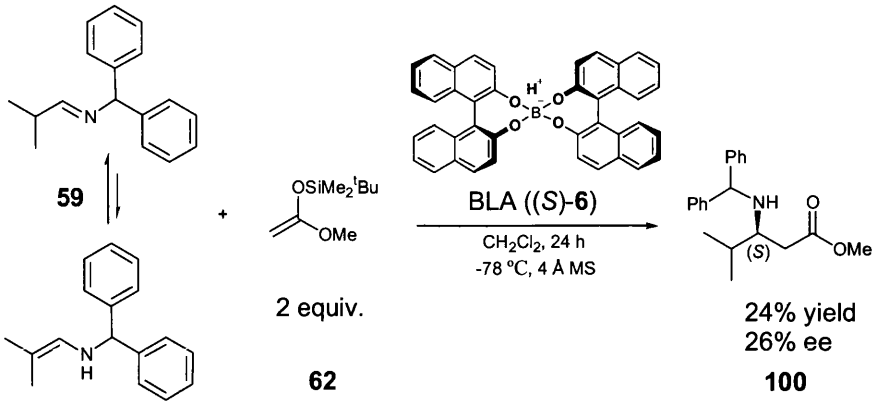
It was then decided to determine wether boron-BINOL complex could be used to catalyse the Mannich reaction of imine **7** with the alternative 1-methoxy-2-methyl-propenyloxy-trimethyl-silane **79** as nucleophile, however reaction at room temperature gave its corresponding β-amino ester **99** in 69% yield but with a dramatic decrease of 4% enantiomeric excess. Therefore, it appears that introduction of steric bulk at the α-position of the silyl ketene acetal of **79** is not compatible with the formation of β-amino esters in high ee.



Scheme 3. 47: Preparation of β-amino ester **99** using 1-methoxy-2-methyl-propenyloxy-trimethyl-silane **79** as a nucleophile.

3.5.3.5 Mukaiyama Mannich reaction of aliphatic imine 59

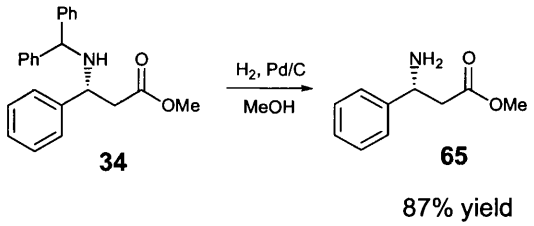
Carrying out the asymmetric Mukaiyama Mannich reactions of aliphatic imine **59** under standard conditions at -78 °C, afforded its corresponding β-amino ester **100** in 24% yield and 28% ee. It is proposed that the lower ee in this reaction is a result of the absence of an aryl substituent in the imine substrate. Aliphatic imine **59** is also presumably in equilibrium with its corresponding enamine tautomer and therefore may explain the much lower level of conversion obtained when compared with aryl imine substrates under identical conditions.



Scheme 3. 48: Synthesis of β-amino ester **100** derived from an aliphatic imine.

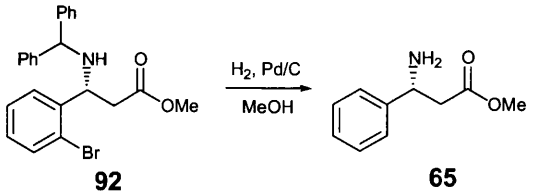
3.5.3.6 Deprotection of β-amino esters

In order to demonstrate that the nitrogen protecting group could be deprotected, *N*-benzhydryl-β-amino-ester **34** was treated with hydrogen in the presence of palladium on carbon methanol. This resulted in formation of β-amino ester **65** in 87% yield. It had been shown previously that this hydrogenolytic deprotection strategy does not cause racemisation.



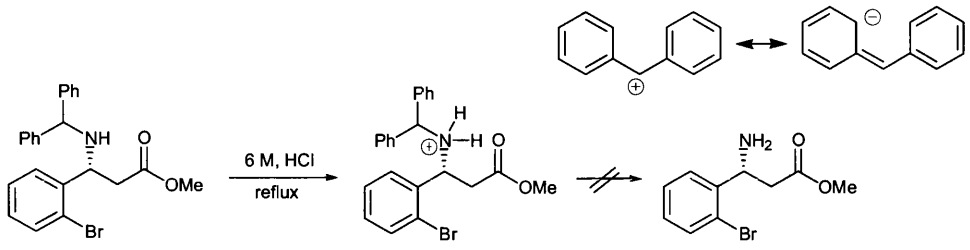
Scheme 3. 49: Deprotection of *N*-benzhydryl group by hydrogenation with palladium over carbon.

However, this hydrogenolytic approach was clearly not suited to deprotection of the β-amino esters **92-94** that contained aryl halo functionality that would also be removed via hydrogenolysis.



Scheme 3. 50: Deprotection of *N*-benzhydryl group of β-amino esters **92** by hydrogenation with palladium over carbon.

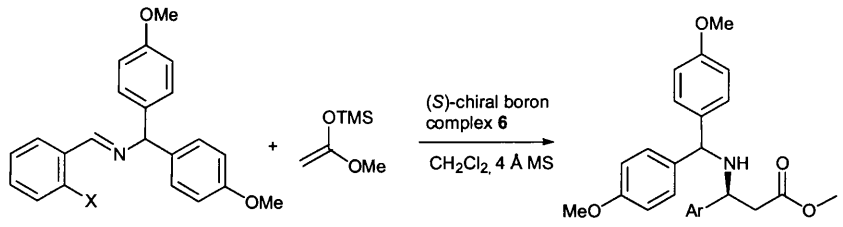
It was thought that the bis benzylic position of β-amino ester **92** might allow for hydrolytic *N*-deprotection using strong acid, with the phenyl groups of the diphenylimine group serving to stabilise the resultant benzylic carbocation.



Scheme 3. 51: Hydrolytic deprotection of β-amino ester **92** under acidic conditions does not occur.

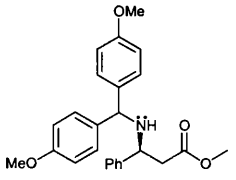
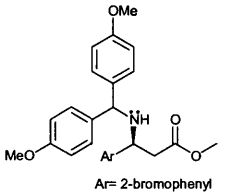
However, treatment of *N*-protected β-amino ester **92** with refluxing HCl (aq.) only resulted in the recovery of starting material and as a consequence it was decided to change the *N*-protecting group to incorporate two *p*-methoxybenzyl groups.

Therefore, Mannich reaction of bis-*p*-methoxyphenylmethine imine **60** with silyl ketene acetal **62** was carried out using our standard boron-BINOL conditions at room temperature to afford β-amino ester **101** in 60% yield and 51% ee at room temperature and in >98% yield and 89% ee at -78 °C. Furthermore, Mannich reaction of *o*-chloro-imine under identical conditions, but using 3 equivalents of silyl ketene acetal, afforded the resultant β-amino ester **102** in >99% and 70% ee at room temperature and 89% yield and 76% ee at -78°C.



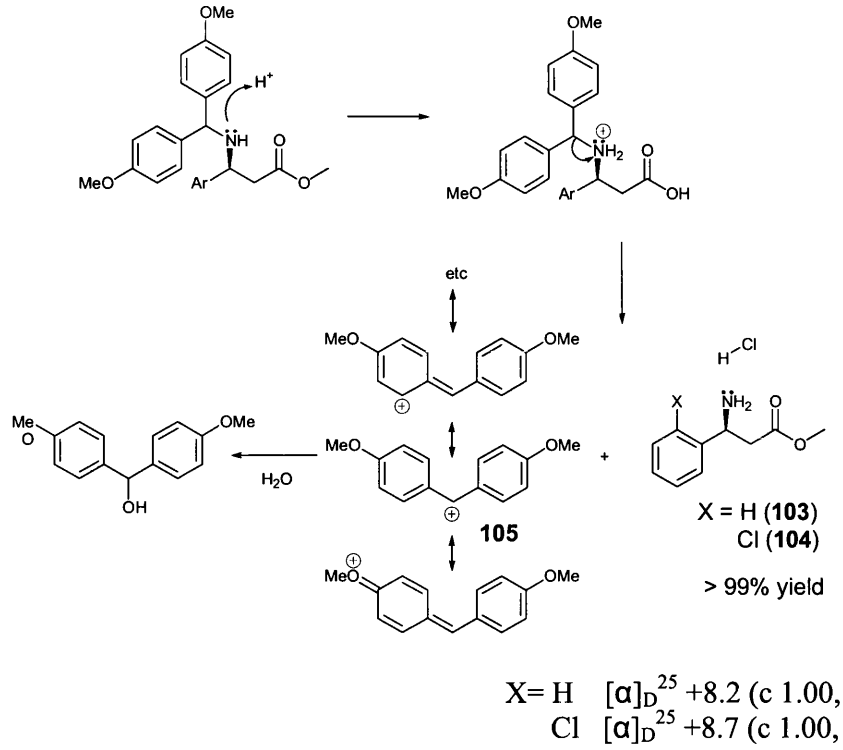
Scheme 3. 52: Preparation of novel β-amino esters containing bis-(4-methoxyphenyl)-methine protecting group

Table 3. 9: Results obtained for formation of β-amino esters **101** and **102** derived from bis-(4-methoxyphenyl)-methyl *N*-protecting group.

β-amino ester	R	r.t	-78°C
 **101**	H	60% yield* 51% ee	>98% yield 89% ee
 Ar= 2-bromophenyl **102**	Cl	>99 yield 70% ee	89% yield 76% ee

*The yield was achieved by using 2 equivalents of silyl ketene acetal

Subsequent deprotection of β-amino esters **101** and **102** were carried out under reflux using 6M HCl (aq) for 24 h at 96°C to afford the corresponding hydrochloric salt in essentially quantitative yield. This facile hydrolytic cleavage reaction is likely to proceed due to the presence of the *p*-methoxy substituents that facilitate formation of carbocation **105** via resonance stabilisation.



X= H $[\alpha]_D^{25}$ +8.2 (c 1.00, H_2O)
Cl $[\alpha]_D^{25}$ +8.7 (c 1.00, H_2O)

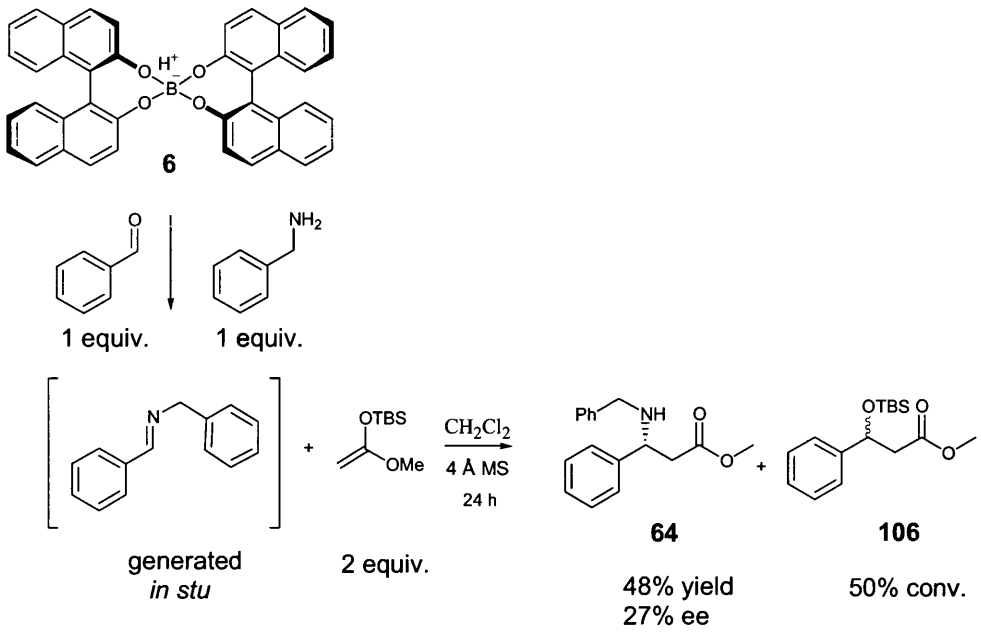
Scheme 3. 53: Successful deprotection of diphenylmethine protecting group using reflux HCl (aq.).

The optical rotation obtained for the sample of β-amino ester **104** ($[\alpha]_D$ = +8.7 (c 1.00, H_2O)) was compared with the literature values of $[\alpha]_D$ = +8.2 (c 1.00, H_2O).[42] This indicates that no racemisation had occurred in this hydrolytic deprotection step.

3.5.4 Three component Mannich-type reaction

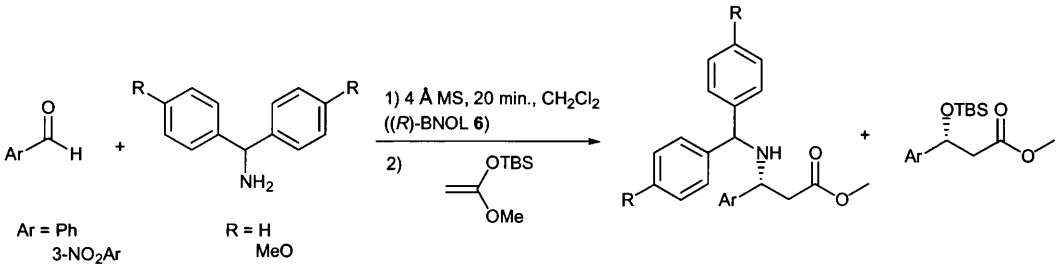
Having developed useful methodology for the asymmetric Mannich reaction of imines with silyl ketene acetals it was decided to attempt to develop an efficient "one pot three-component Mannich reaction" of aldehydes, amines and ketene silyl acetals.[43-45] Imine condensation reactions were known to work very well in the presence of a Lewis acid, so we first treated benzaldehyde and benzylamine with boron-BINOL complex **6** in dichloromethane at room temperature, followed by addition of ketene silyl acetal which gave β-amino ester **64** in 48% yield and 27% ee, which was comparable to the 26% ee previously obtained using preformed imine. It was proposed that the water given off in this reaction was rapiddly absorbed by the 4 Å molecular sieves. This methodology would allow further substrate screening without the need to synthesise the desired imine substrate separately. Closer explanation of the ^1H NMR spectrum of the crude reaction product of this three component Mannich-type reaction revealed the presence of a

second major component with a distinctive resonance at δ 5.10. Purification of the crude reaction product revealed that this product was *O*-silyl-β-hydroxy ester **106** formed from a competing Mukaiyama aldol reaction.

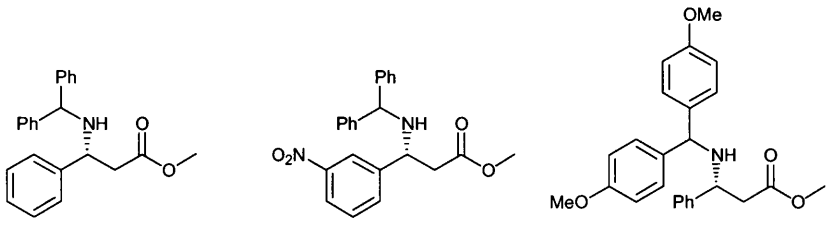


Scheme 3. 54: One pot Mukaiyama Mannich reaction for the synthesis of β-amino ester.

This three-component methodology was then repeated for reaction of two aldehydes and two imines generated *in situ* and the silyl ketene acetal **62** which also gave a mixture the desired β-amino ester and the resultant aldol adduct, indicating that the aldehydes reacted with silyl ketene acetal despite leaving amine and aldehyde to premix for up to four hours.[45]



Scheme 3. 55: Three-component methodology to prepare β-amino esters and as a by products; aldol adducts.

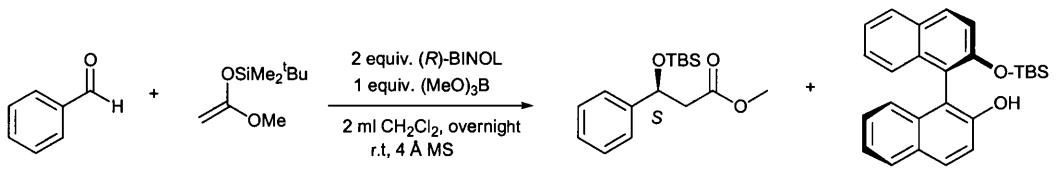


34 30% conv. **91** 50% conv. **101** 50% conv.

Scheme 3. 56: Three β-amino esters prepared with a three-component methodology.

3.6 STOICHIOMETRIC BORON-BINOL COMPLEX CATALYSED MUKAIYAMA ALDOL-TYPE REACTION

Since our attempts to develop a three-component Mannich reaction had resulted in competing formation of silylated aldol products it was decided to investigate whether we could optimise the yield of this aldol product and determine its enantiomeric excess. Therefore, addition of three equivalents of silyl ketene acetal to benzaldehyde in the presence of stoichiometric amounts of Yamamoto's boron-BINOL complex **6** and 4 Å molecular sieves in dichloromethane at room temperature,[2] cleanly afforded *O*-silylated aldol adduct **106** in 65% isolated yield. This type of *O*-silylated aldol adducts are formed in all Mukaiyama aldol reactions, however many previously reported protocols involve an acidic reaction work-up that results in the parent desilylated aldol product being isolated.

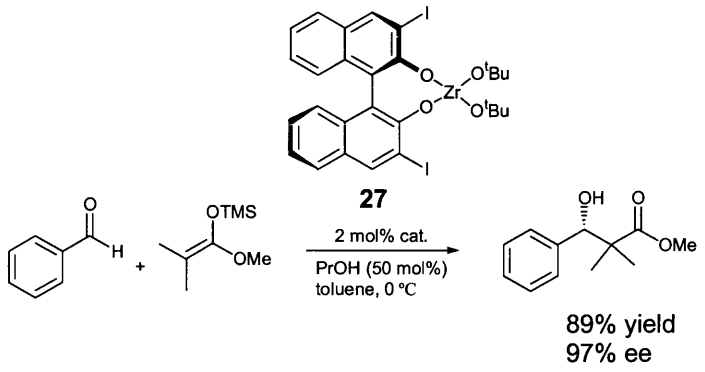


62 3 equiv. **106** 65% yield **66** 35% yield

Scheme 3. 57: Simultaneous protection of BINOL and silylated aldol adducts formation.

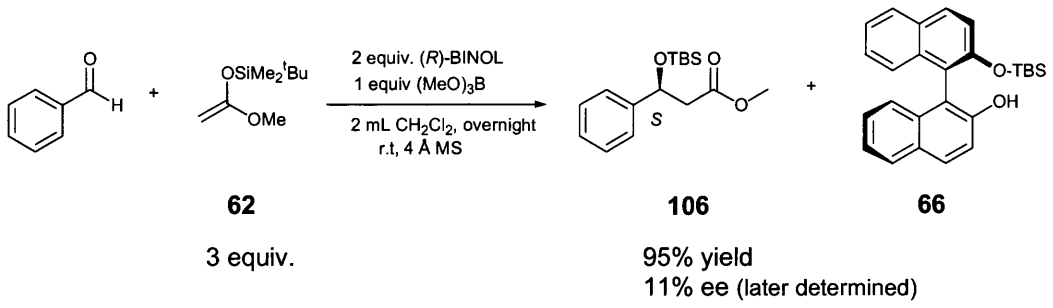
Careful examination of the ^{1}H NMR spectrum of our crude aldol Mukaiyama reaction product once again revealed the presence of mono-silyl-BINOL **66** in our crude reaction

product. Despite the fact that many publications have previously employed BINOL as a chiral ligand in Mukaiyama aldol reactions, there is only one previous report of the formation of monosilylated BINOL in this type of reaction.[46] In this report, the authors described they employed propanol as a sacrificial nucleophile to convert the monosilyl-BINOL formed back into BINOL, which enabled the chiral catalyst to be continuously regenerated.



Scheme 3. 58: Mukaiyama aldol reaction using a chiral zirconium complex **27**.

Consequently, the Mukaiyama aldol reaction was optimised using three equivalents of silyl-ketene-acetal **62** which gave the corresponding aldol product in 95% isolated yield after purification by Kugelrohr distillation under reduced pressure (1 mbar) at ~180-190 °C. In this respect, it was important to ensure that the temperature of the distillation remained below 200 °C to ensure that the mono-silyl-BINOL **66** by-product formed in this reaction did not co-distil.



Scheme 3. 59: Preparation of aldol adduct 106 using chiral BINOL-boron catalyst **6**.

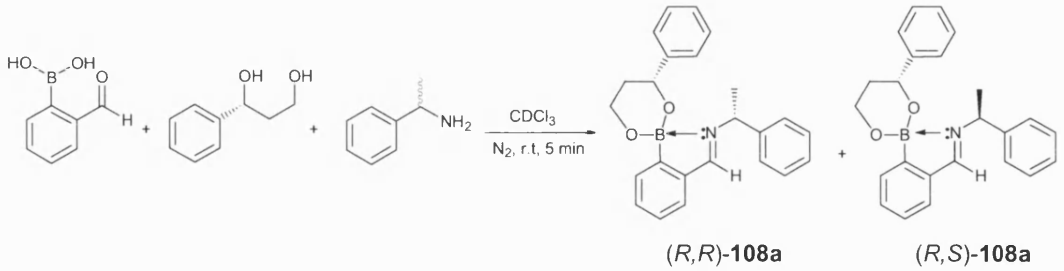
The structure of the aldol product produced in this reaction was confirmed from its ^{1}H NMR spectrum from the presence of five C-H aryl protons at δ 7.20-7.30, the C*H* (OH) proton at δ 5.10 ($J_{(2a,3)}$ = 4.0 Hz, $J_{(2b,3)}$ = 4.0 Hz), and the presence of two

diastereoisomeric H_{2a} and H_{2b} protons at δ 2.50 and δ 2.70 with a $J_{(gem)}$ = 3.8 Hz. The ^{13}C NMR spectrum of the aldol product revealed the presence of eleven carbon atoms, whilst the HRMS revealed the presence of a molecular ion for [M+Na] at 317.1550.

3.6.1 Determining the ee of the aldol product by a chiral derivatisation approach

We next turned out attention to determining the enantiomeric excess of the aldol product produced in this Mukaiyama aldol reaction, which we initially attempted using chiral HPLC analysis. An authentic sample of the racemic silyl aldol adduct **106** was prepared using a Mukaiyama aldol reaction employing (*rac*)-BINOL as a ligand, with optimal HPLC conditions being established for splitting their enantiomers using Chiralpack AD or OD column. This HPLC protocol could be used to determine the enantiomeric excess of aldol products prepared in our asymmetric Mukaiyama reactions, however on a significant number of occasions co-running impurities produced in these reactions led to incorrect values being determined for the ee of the aldol products. Therefore, it was decided that these HPLC analytical methods were not totally trustworthy and as a consequence an alternative ^1H NMR spectrosocopic method using a novel chiral derivatisation agent previously developed within the SDB/TDJ groups was employed to determine their ee.

A new chiral derivatisation agent had been developed for derivatisation of 1,2- and 1,3-diols involving treatment of a diol with 2-formylboronic acid and (*S*)-α-methylbenzylamine in $CDCl_3$.[6, 47-49] This reaction results in a three-component self-assembly reaction occurring to afford a mixture of diastereoisomeric imino-boronate-ester derivatives whose ratio is an accurate reflection of the enantiomeric excess of the parent diol. This chiral derivatisation approach had previously been demonstrated to be applicable for determining the ee of (*R*)-1-phenyl-propane-1,3-diol, as can be seen from the ^1H NMR spectrum of a 1:1 mixture of the diastereoiomeric imino-boronate ester complexes (*R,R*)-**108a** and (*R,S*)-**108a** derived from racemic phenylethylamine shown in Figure 3.7.



Scheme 3. 60: Synthesis of diastereomeric stable imino-boronate ester complexes (*R,R*)-**108a** and (*R,S*)-**108a.**

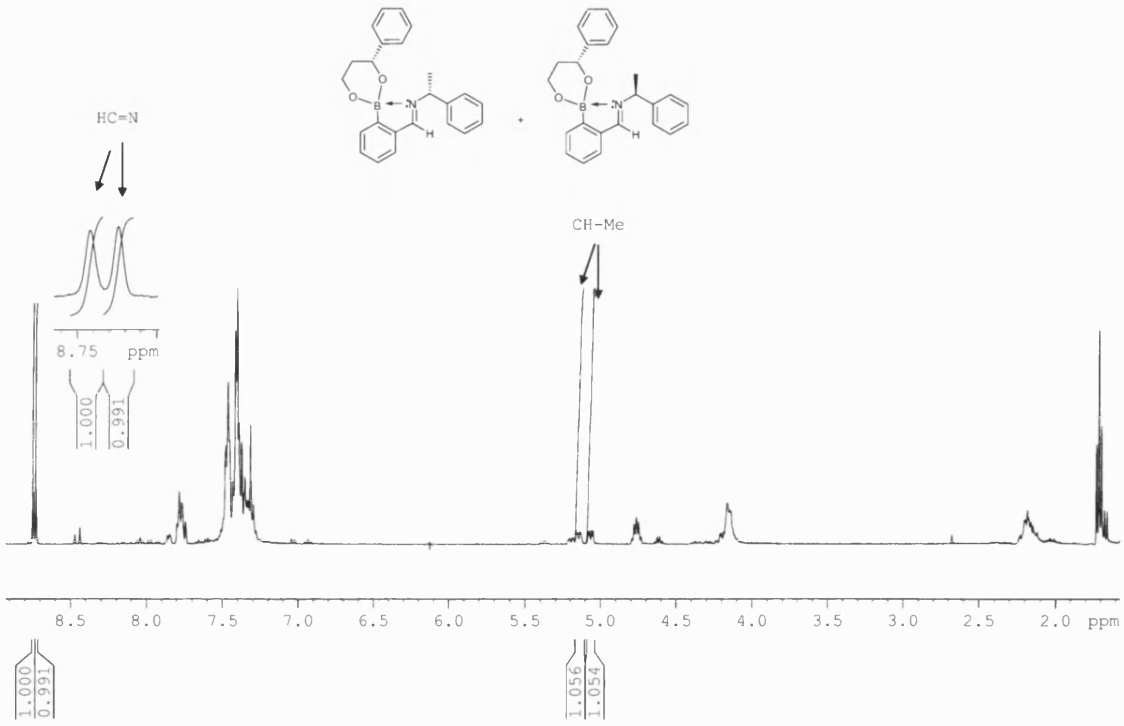
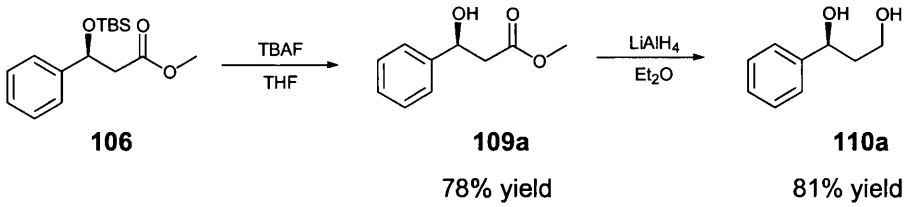


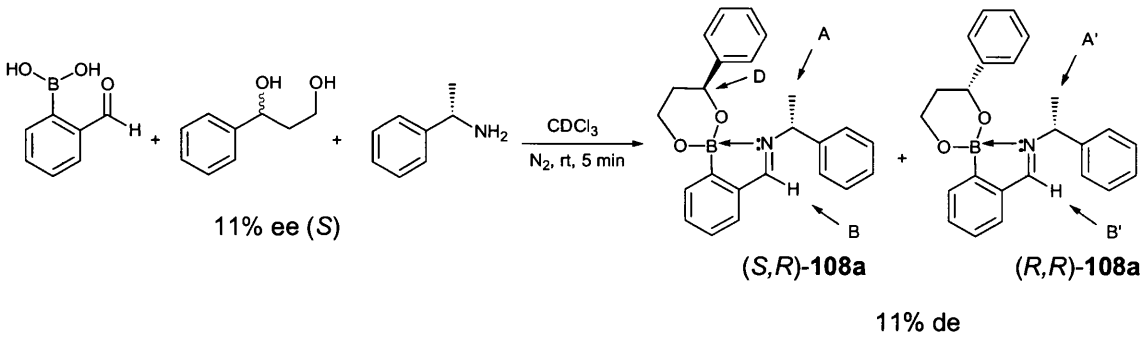
Figure 3. 7: ^{1}H NMR spectrum of an aliquot of the reaction mixture of *o*-formyl-phenyl-boronic acid, (*rac*)-α-methyl-benzylamine and (*R*)-1-phenyl-propane-1,3-diols in $CDCl_3$ taken after a reaction time of 5 minutes.

Therefore, the silyl-aldol product **106** obtained from our chiral Mukaiyama reaction was treated with 1M TBAF solution in THF to furnish its parent desilylated aldol product **109a** in 78% yield.[50] The resultant β-hydroxy ester **109a** was then reduced to its corresponding 1-phenyl-propane-1,3-diol **110a** in 81% yield, which was then used as a substrate for our three-component CDA protocol



Scheme 3. 61: Silyl deprotection and ester reduction.

This sample of diol was then derivatised via treatment with 2-formyl-phenyl-boronic acid to afford a mixture of chiral imino-boronate esters (*S,S*)-**108** and (*R,S*)-**108** in 11% de as determined via integration of the diastereoisomeric imine peaks at δ 8.60 and δ 8.75, and the methylene peaks at δ 5.05 and δ 5.15 ppm.[6, 47-49] The absolute configuration of the aldol product was established as (*S*)- via comparision of its optical rotation of $[\alpha]_D^{20}$ = -13.6° (c 1.00, $CDCl_3$, (*S*)) with the known specific rotation of $[\alpha]_D^{22}$ = 54.5° (c 1.00, $CDCl_3$, (*R*)) for enantiomerically pure (*R*)-1-phenyl-propane-1,3-diol.[51] In view of this, the aldol type reaction catalysed with boron-(*R*)-BINOL complex provides the resultant aldol adduct with (*S*)-configuration.



Scheme 3. 62: Chiral boronate formation.

Comparison with the Mannich-type adduct reveals that the boron-BINOL complex **6** gives opposite configurations in the Mukaiyama aldol reaction since β-amino esters with (*R*) configuration are derived from (*R*)-BINOL and vice versa.

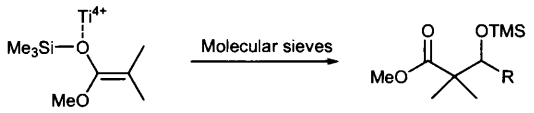
This chiral derivatisation approach was used to determine the enantiomeric excess of all the β-hydroxy-esters produced in subsequent investigations in these asymmetric Mukaiyama reactions.

3.6.2 Investigations of other potential catalytic species present in the asymmetric Mukaiyama aldol reaction

Given the poor level of stereocontrol obtained in this Mukaiyama aldol reaction compared to those obtained previously in our asymmetric Mukaiyama Mannich reactions it was decided to investigate whether other species present in this reaction might be catalysing the reaction.

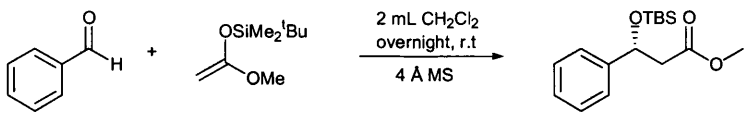
3.6.2.1 Molecular sieves as Lewis acids

It had been reported previously that titanium silicate molecular sieves could catalyse achiral Mukaiyama reactions between ketene-silyl-acetals and aldehydes to afford aldol products,[52] with the d^0 configuration of Ti^{4+} being sufficiently "oxophilic" to activate the O-Si bond and increase the nucleophilicity of the silyl enol ethers.[52]



Scheme 3. 63: Titanium silicate molecular sieves TS-1 and Ti-β as promoters for Mukaiyama-type aldol condensation.

It was proposed that the presence of 4 Å molecular sieves in our Mukaiyama reactions might be catalysing an achiral background that was responsible for the low ee in our boron-BINOL complex catalysed reactions. Consequently, we investigated reaction of one equivalent of benzaldehyde with one equivalent of silyl ketene acetal in CH_2Cl_2 in the presence of 4 Å molecular sieves at room temperature which afforded silyl-aldol product **106** in 54% yield. Therefore, it was clear that all subsequent asymmetric Mukaiyama aldol reactions would need to be carried out in the absence of molecular sieves.

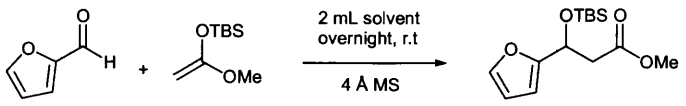


62 **106**

1 equiv. 54% yield

Scheme 3. 64: 4 Å molecular sieves as promoters of Mukaiyama aldol reactions.

The unexpected result that simple 4 Å molecular sieves acted as catalysts for achiral Mukaiyama aldol reaction led us to explore the scope and limitation of this methodology for the synthesis of a range of achiral *O*-silyl-β-hydroxy esters. We first carried out a solvent screen for the reaction of 2-furaldehyde (0.63 mmol) with silyl ketene acetal **62** (1.27 mmol) in the presence of 0.25 g of 4 Å molecular sieves. This revealed that best yields of aldol product were obtained using dichloromethane, tetrahydrofuran or hexane as solvents.



66 **111**

2 equiv.

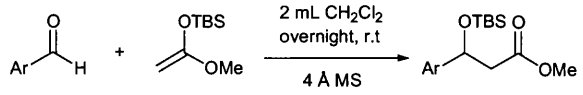
Scheme 3. 65: Screen of different solvents in the presence 4 Å molecular sieves as promoters for Mukaiyama-type aldol reaction.

Table 3. 10: Solvent screen **for** the Mukaiyama-type aldol reaction from scheme 3.65.

Solvent (1.5 mL)	Yield (%)
CH_2Cl_2	**88**
THF	**>99**
H_2O	25
MeOH	26
Toluene	84
Hexane	**>99**

Consequently, these conditions were employed for the aldol reaction of a wide range of aromatic aldehydes (1 equiv., 0.63 mmol) and silyl ketene acetal **62** (2 equiv., 0.28 mL,

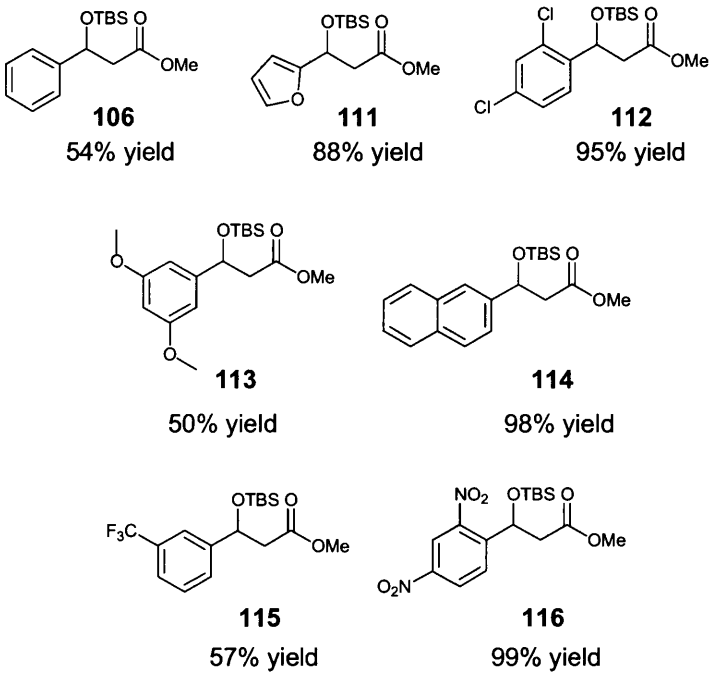
1.27 mmol) in the presence of 4 Å molecular sieves, which successfully gave monoprotected silyl-aldol adducts **111-116** in 50-99% yields.



2 equiv.

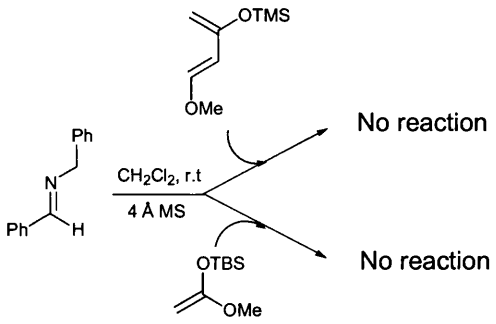
62 **111-116**

Scheme 3. 66: 4 Å molecular sieves as promoters for Mukaiyama-type aldol reactions.



Scheme 3. 67: Racemic silylated aldol products.

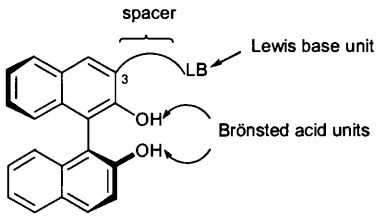
Importantly, the discovery of the catalytic activity of molecular sieves towards silyl-ketene acetals in these Mukaiyama aldol reactions led us to reinvestigate whether achiral background reactions were also operating to lower the ee of the *aza*-Diels Alder and Mannich-type reaction previously investigated in this thesis. However, using 4 Å molecular sieves to catalyse reaction of Danishefsky's diene or silyl-ketene acetal with imine **35** did not produce any of the expected dihydropyridone or β-amino ester products.



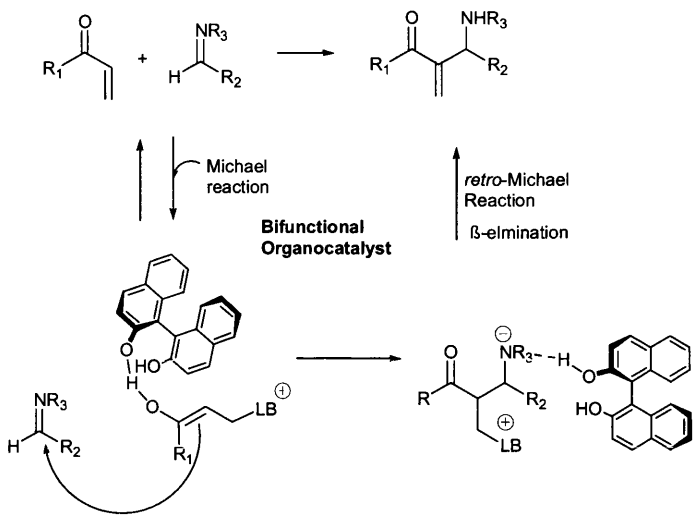
Scheme 3. 68: Failed Mannich and *Aza* Diels Alder type reactions in the presence of molecular sieves.

3.6.2.2 Attempting to catalyse asymmetric Mukaiyama aldol reactions by monosilyl-BINOL species 66

There have been great developments in the area of organocatalysis over the last ten years for the asymmetric synthesis of chiral compounds.[53] One class of organocatalysts relies on hydrogen bonding interactions between the catalyst and substrate to induce both catalytic activity and stereocontrol, with chiral BINOL derived catalysts currently proving extremely effective at catalysing aldol reactions. For example, a modified BINOL derivative has been developed as a bifunctional organocatalyst for the Morita-Baylis-Hilman reaction. In this catalytic system the phenolic proton of the BINOL acts as an acid to protonate the carbonyl at the α,β-unsaturated ketone, whilst the Lewis basic side-chain undergoes simultaneous conjugate addition at the β-carbon. The resultant enolate the undergoes a Mannich type reaction to afford β-amino ketone whose retro Michael reaction to afforded the observed product.

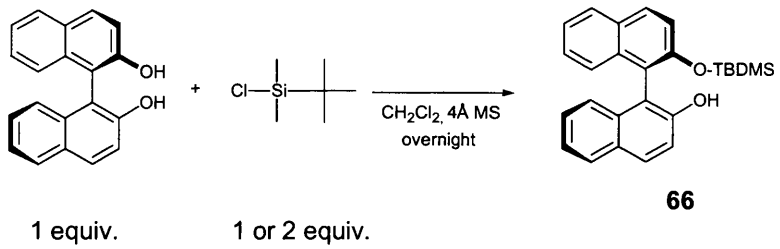


Scheme 3. 69: Concept of novel chiral bifunctional organocatalysis for *aza* Marita-Baylis-Hilman reaction.



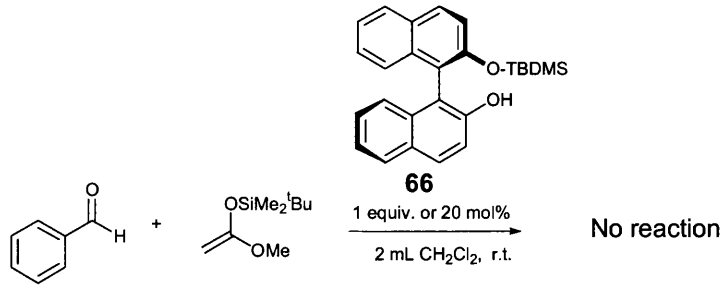
Scheme 3. 70: Proposed catalytic cycle for the bifunctional organocatalyst-mediated *aza*-MBH reaction.

Therefore, it was proposed that mono-silyl-BINOL **66** might be acting as a competing Lewis acid-Lewis base organocatalyst in this reaction and as a consequence we wished to screen it as a catalyst in Mukaiyama aldol reactions. Therefore, an authentic sample of monosilyl-BINOL **66** was prepared in 60% yield via treatment of BINOL with one equivalent of *tert*-butyl-dimethylsilyl chloride in CH_2Cl_2 in the presence of 4 Å molecular sieves.



Scheme 3. 71: Synthesis of monosilyl-BINOL **66**.

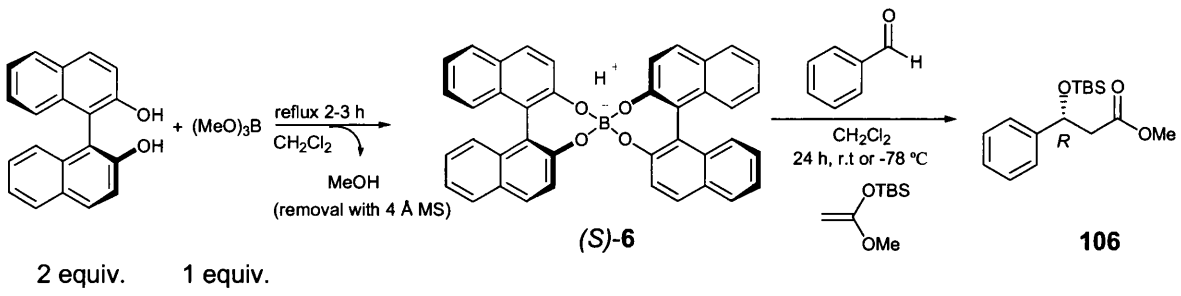
This sample of monosilyl-BINOL **66** was then employed as a potential catalyst for the Mukaiyama aldol reaction of silyl-ketene-acetal **62** with benzaldehyde; however no aldol product was obtained in this reaction, indicating that mono-silyl-BINOL **66** is acting solely as a spectator in these reactions.



Scheme 2. 90: Failed Mukaiyama reaction of mono-TBDMS-BINOL **66**.

3.6.3 Mukaiyama reactions without molecular sieves

The fact that molecular sieves catalysed a background achiral Mukaiyama aldol reaction lead us to modify the reaction conditions used to prepare the boron-BINOL catalyst in an attempt to achieve higher levels of stereoselectivity. Therefore, the boron-BINOL complex was prepared by reacting one equivalent of $B(OMe)_3$ and (*S*)-BINOL in CH_2Cl_2 at reflux (50-60 °C) over 2-3 hours with removal of methanol being achieved using 4 Å molecular sieves suspended in a Soxhlet thimble (Method C).[2] Benzaldehyde was then added to this complex (*S*)-**6** in CH_2Cl_2, before dropwise addition of *tert*-butyl ketene silyl acetal **62** to give the aldol adduct in 95% yield. Subsequent silyl deprotection and reduction of the resultant ester with $LiAlH_4$ afforded the corresponding aldol product **106** that was shown to have a 22% ee using our previously described CDA protocol (Scheme 3.61 and 3.62). Repeating this reaction at -78 °C resulted in the formation of *O*-TBS-aldol **106** in an improved 45% ee.



Scheme 3. 72: Mukaiyama aldol type reaction catalysed by boron-BINOL complex (S)-**6** (Method C).

Table 3. 11: Results obtained for the reaction from scheme 3.67.

temperature (°C)	yield (%)	ee (%)
r.t	95	22
-78°C	86	45

3.7 CONCLUSIONS

In this chapter we have described our investigations into the use of boron-BINOL complex **6** for the diastereoselective and enantioselective Mukaiyama Mannich reaction of imines with silyl-ketene acetal **62** that a wide range of gave *N*-benzyl-β-amino esters in acceptable yields with moderate to good levels of stereocontrol. We have shown that the best yields of reaction are obtained using stoichiometric amounts of boron-BINOL catalyst and two equivalent of silyl-ketene acetal **62** at -78°C. Experiments employing 10 mol% of the chiral boron-BINOL complex were only partially successful, affording lower yields of β-amino ester with poorer levels of enantioselectivity.

Attempts to develop a three-component Mukaiyama reaction were only partially successful, however these investigations led to the discovery of a boron-BINOL complex catalysed Mukaiyama aldol reaction. The discovery that 4 Å molecular sieves catalysed an achiral background Mukaiyama aldol condensation reaction led us to optimize the reaction conditions to afford silyl protected-β-hydroxy-ester in 45% ee at -78°C.[52]

3.8 REFERENCES

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4 NOVEL IMINO BORONATE ESTERS

4.1 AIMS AND OBJECTIVES OF THE CHAPTER

This chapter initially describes the four most commonly used analytical methods for determination of the enantiopurity of chiral compounds, including a discussion of the range of chiral derivatising agents that have been developed for determining the enantiomeric purity of chiral diols. The chemistry of boronate complexes that contain stable intramolecular imino N→B coordinate bonds is then discussed including a discussion of how they may be applied for determining the enantiomeric excess of primary chiral amines or 1,2- and 1,3- diols by ^{1}H NMR spectroscopy. We will then describe the development of a series of a second generation chiral derivatising agents which contain a fluorine atom that enables the enantiomeric purity of scalemic amines and diols to be determined by ^{19}F NMR spectroscopy.

4.2 ANALYTICAL METHODS: DETERMINATION OF ENANTIOMERIC PURITY

The development of accurate methods for the determination of enantiomeric purity, has been critical to the development of asymmetric synthesis, allowing precise and reliable assessment of the degree of enantioselectivity and the absolute configuration of chiral compounds. The four most commonly employed methods are described below.[3, 4]

4.2.1 Polarimetric methods

Polarimetric methods are based on the optical activity of the chiral substance under investigation. Optically active materials are asymmetric with their enantiomers rotating the plane of polarized light in equal but opposite directions. Measurement of the extent of this rotation is performed using a polarimeter. However, in order to accurately measure a compounds optical rotation it must be pure and devoid of trace chiral impurities whilst errors in measuring rotations are normally considered to be at least ±

4%. The rotation obtained for a chiral compound is either clockwise (+) or counter clockwise (-), depending on the enantiomer being analysed, whilst its magnitude is dependent on its enantiomer excess.

If a chiral compound contains a suitable chromophore then powerful polarimetric techniques based on optical dispersion (ORD) and circular dichroism (CD) can be used to analyze their absolute configuration. X-ray crystallographic analysis can also be used to assign the absolute configuration (AC) of an optically pure compound and is often used to confirm stereochemical assignments obtained from detailed NMR spectroscopic analysis.[5, 6] Although these optical methods are convenient, they are often unsatisfactory for accurately determining enantiomeric purities of chiral compounds, because the presence of trace chiral impurities can result in erroneous results. Consequently, the use of optical rotation measurements to assign the ee of chiral compounds is increasingly discouraged.

4.2.2 Liquid chromatographic methods

Chiral high performance liquid chromatography (HPLC) techniques are able to separate enantiomers, either indirectly via derivatisation of the analyte with chiral derivatising reagents, or directly using chiral stationary phases or in the use of chiral mobile additives.[7, 8] The principle of direct methods used for HPLC analysis involves chiral molecules making different interactions with chiral stationary phases due to the reversible formation of transient diastereomeric interactions. Enantiomeric separation is normally achieved through hydrogen bonding, dipole-dipole, or Л-acceptor and Л-donor interactions, all of which rely on the formation of temporary diastereomeric interactions.

One approach to carrying out HPLC is to carry out derivatisation with a chiral derivatising agent to give chromatographically separable diastereoisomers. For example, the reversible complexation of metal ions (usually Cu^{2+} or Ni^{2+}) to amino acids can be explored to afford diastereomeric complexes that can be resolved on achiral HPLC supports. Therefore, a solution of a Cu^{2+}-proline complex in sodium acetate buffer can be used as an eluant on a non-chiral support to resolve the enantiomers of another chiral amino acid, due to the transient formation of diastereomeric complexes.[8]

Alternatively, chiral stationary phases that contain covalently bonded chiral selectors may be used to directly separate the enantiomers of a chiral compound. These are preformed by grafting or copolymerising chiral monomers onto/into conventional stationary phases, and have met with widespread success for the resolution of a wide range of chiral compounds.

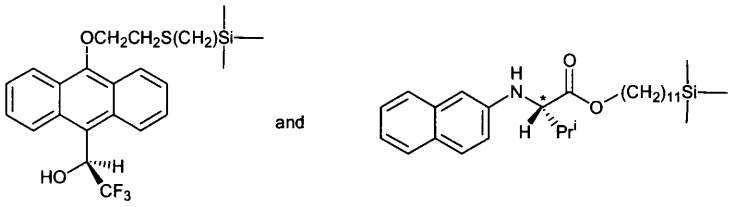


Figure 4. 1: Chiral stationary phases for HPLC.

4.2.3 Gas chromatographic methods

The principle of using chiral gas chromatography for determining the ee of chiral compounds is the same for that of chiral HPLC, except the carrier phase is now a gas rather than a liquid. This sensitive method is particularly accurate (±0.05%), often unaffected by trace impurities, and is particularly useful for analysing mixtures which are highly enriched (>95% ee), or close to the racemic limit (<5% ee). The sample needs to be sufficiently volatile and thermally stable to be analysed by chiral GC and should be baseline resolved on a chiral stationary phase.[8] Examples of chiral stationary phases that are widely employed include chiral cyclodextrins, as well as a range of *O*-silyl stationary phases similar to that depicted in figure 4.2.

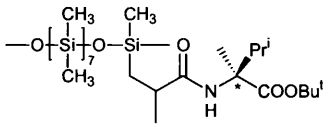


Figure 4. 2: Chiral stationary phase for GC.

The major problem associated with analysing ee by chiral GC (or chiral HPLC) is the potential of co-eluting compounds serving to distort the enantiomeric excess values that are determined. This is particularly problematic if minor trace impurities are particularly well ionized (for GC), or have a large UV chromophore (for HPLC).[8]

4.2.4 NMR spectroscopy

Methods for determining the enantiomeric excess of compounds via NMR spectroscopy continue to attract great interest due to the practicality of the methodology, and general availability of NMR spectrometers.[6, 9] Although enantiomers cannot be distinguished in an achiral medium by NMR spectroscopy because the resonances of enantiotopic protons are isochronous (equivalent chemical shifts), diastereoisomers may be distinguished because the resonances of certain diastereotopic nuclei are anisochronous. Thus, determination of the enantiomeric purity of a chiral compound using NMR requires the intervention of a chiral auxiliary to convert an enantiomeric mixture into a mixture of diastereoisomers without racemisation occurring. As long as signals corresponding to the two diastereoisomers baseline are resolved, then integration of the appropriate signals can be used to give a measure of the diastereomeric composition. Therefore, as long as no resolution occurs in the derivatisation process then this diastereomeric excess value can be directly related to the enantiomeric composition of the original mixture.[5]

Three types of approach have been developed for this purpose.[6, 10] Chiral derivatising agents (CDAs) [9, 11-14] are used to form permanent diastereoisomers prior to NMR analysis, whilst chiral solvating agents (CSAs) [6, 9, 15] and chiral lanthanide shift reagents (CLSRs) [6, 9, 16] react reversibly to afford diastereoisomers *in situ*.

The magnitude of the chemical shift non-equivalence of the diastereoisomers is proportional to the size of the applied magnetic field. Lowering the temperature at which the spectrum is recorded can also accentuate the anisochronicity between diastereoisomers. The use of relatively non-polar solvents such as d-chloroform, d_6-benzene and d_9-toluene offer considerable advantages, but numerous chiral compounds are only soluble in polar solvents such as d_6-DMSO. Finally. the measured integrals are only reliable for determining diastereomeric excesses if fully relaxed spectra free from any saturation effects are acquired.

- *Chiral solvents or chiral solvating agents* (CSAs), [6, 9, 11-15, 17] form diastereomeric complexes with the enantiomeric mixture under analysis forming noncovalent diastereomeric interactions. There is a rapid reversible equilibrium between the diastereomeric complexes and the uncomplexed substrate enantiomers in the bulk achiral deuterated solvent. The advantage of the CSA technique is that it is quick and simple to carry out, whilst accidental resolution of a scalemic sample hardly ever occurs. The enantiopurity of the CSA is not essential since a CSA with less than 100% ee will still give an averaged signal intensity, resulting in chemical shift non-equivalences albeit with a reduced chemical shift difference. Some of the more commonly used CSAs include 1-aryl-2, 2, 2-trifluoroethanols, quinine and mandelic acid.

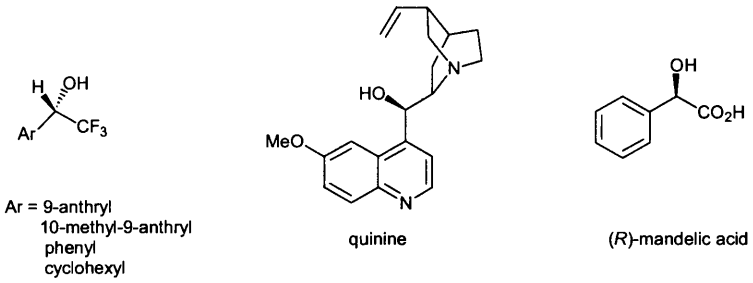


Figure 4. 3: Some examples of chiral compounds used as chiral solvating agents.

Other chiral solvating agents that have been used to determine the ee of chiral amines and amino acids include (*R*)-acetyl mandelic acid, and (*S*)-1,1′-binaphthyl-diphosphoric acid.

- *Chiral lanthanide shift reagents* (CLSRs) [6, 16] are formed from complexation of chiral ligands with lanthanides such Eu^{3+}, Pr^{3+}, or Yb^{3+}. These labile lanthanide metal nuclei are able to expand their coordination number beyond six by accepting electron density from donor functionalities to give a complex which is in rapid equilibrium with uncomplexed substrate. This complexation induces a large shift in the NMR spectra of certain nuclei within the substrate, the magnitude of which is dependent on the distance of the atom from the site of interaction with the lanthanide metal. Though larger chemical shift differences are often observed with CLSRs when compared with CSAs, signal broadening often limits their use, especially at higher magnetic fields where the paramagnetism of the lanthanide metal is more significant. The structure of one

of the most widely used CLSRs is given below [eg tris(t-butyl-hydroxy-methylene-(1*R*)-camphorato)europium(III)], which is suitable for substrates containing hydroxy or carbonyl functionalities.

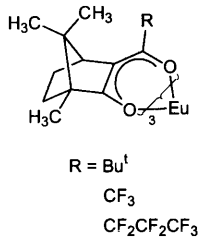


Figure 4. 4: Example of common chiral lanthanide shift reagents.

- *Chiral derivatising agents* (CDAs) [6, 9-14, 17-22] form permanent long-lived diastereomeric complexes when they react with a chiral compound that are either covalent derivatives or diastereomeric salts. The resultant diastereoisomers are normally well resolved, with chemical shift non-equivalence being up to five times larger than normally observed for chiral solvating agents (CSA). There are a number of disadvantages in the use of CDAs such as the need to use enantiomerically pure derivatising agents, and the need to carry out an additional chemical reaction prior to NMR analysis. It is also important to ensure that no kinetic resolution or racemisation occurs during the derivatisation process. Two of the most commonly used CDAs currently employed are depicted in Figure 4.5 with Mosher's reagent (MTPA) still the most popular CDA currently employed for determining the enantiopurity of chiral alcohols and amines.

(*R*)-MTPA (*R*)-MPA

MTPA: α-methoxy-alpha-trifluoromethylphenylacetic acid (Mosher's reagent)

MPA: α-methoxyphenylacetic acid

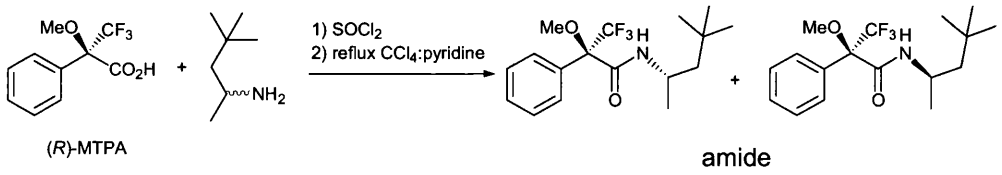
Figure 4. 5: Two of the most common chiral derivatising reagents.

4.3 LITERATURE PRECEDENTS

My research into the asymmetric synthesis of chiral amines and 1,2-diols had revealed that the methodology available for determining their ee was far from ideal and we decided to develop a new CDA for this purpose.

4.3.1 Chiral derivating agents for determining the enantiomeric excess of amines

Mosher's acid was first used as a chiral derivatising agent for determining the enantiomeric excess of amines in 1969 using either ^{1}H or ^{19}F NMR spectroscopy.[12, 13] The reagent was proven to work for a series of chiral amines and secondary alcohols, and may be used to determine the absolute configuration of many classes of chiral amine. The chemical shift differences observed for the resultant diastereoisomeric amides are usually in the range of 0.3-0.7 ppm in ^{19}F NMR analysis.[13] In contrast signals in their ^{1}H NMR spectra normally exhibit a smaller range of 0.1-0.2 ppm for their diastereomeric methoxy resonances. Nevertheless, there have been several unsuccessful reports where no chemical shift differences between the amide diastereoisomers of chiral amines have been observed, particularly for compounds containing remote stereocenters. Therefore Mosher's reagent is not a universal chiral derivatising reagent for every chiral amine or alcohol.[9, 12, 13]



Scheme 4. 1: Mosher's acid reacts easily with scalemic amines to give mixtures of diastereomeric amides.

In view of these limitations, other CDA's have been developed to determine the enantiomeric excess of chiral amines containing remote stereocentres.[12, 13, 23] Unfortunately, none of these CDA's are commercially available, and therefore often require laborious multi-step synthesis and purification by flash chromatography, and as a consequence they are not widely used.

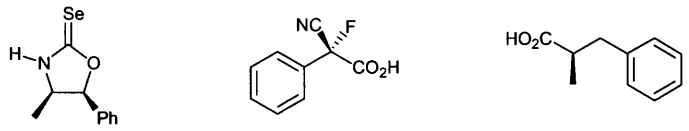


Figure 4. 6: Examples of chiral derivatising agents capable of detecting remote stereocenters.

For example, one-pot coupling of a chiral selone derivatising agent to chiral amines, affords urea-like adducts whose diastereomeric excess can be determined by ^{77}Se NMR spectroscopy.[23]

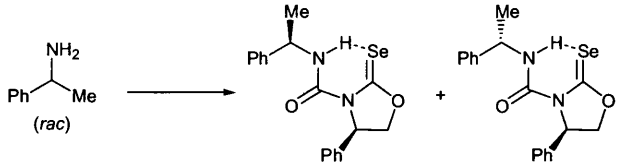
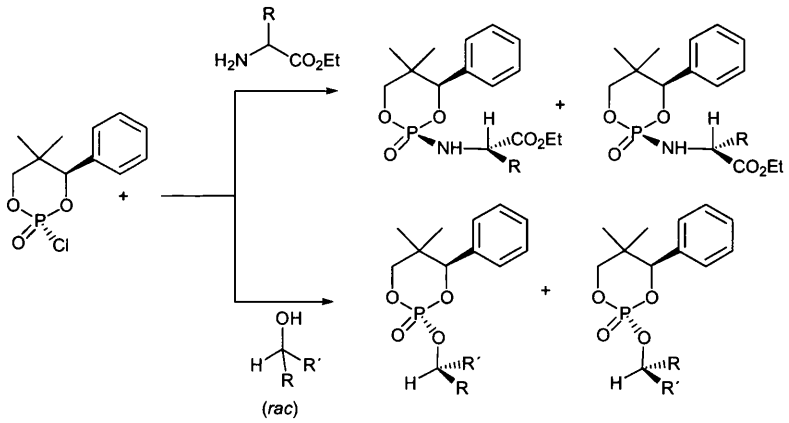


Figure 4. 7: One-pot coupling of a chiral selone derivatising agent.

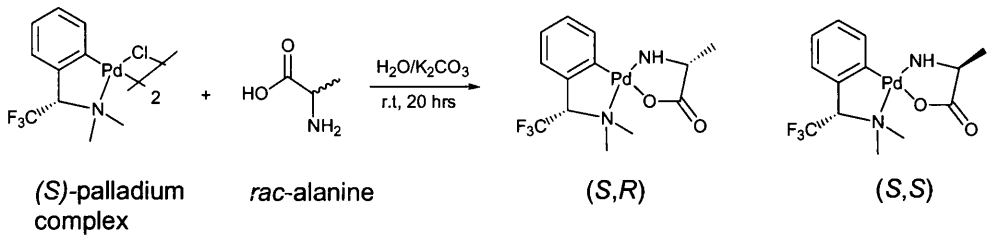
In 1993, Hulst *et al.* found that diastereomeric ester and amide derivatives of phosphoryl chloride gave well resolved signals in their ^{31}P NMR spectra allowing accurate determination of ee for chiral alcohols, esters of amino acids and amines.[24]



Scheme 4. 2: Chiral phosphoric acid chloride gives well resolved signals for diastereomeric amides and esters in its ^{31}P NMR spectra.

The Levrat group demonstrated that ^{19}F NMR is a reliable spectroscopic method for the enantiomeric excess determination of α-amino acids by analysis of their corresponding

N,N-dimethyl-(2,2,2-trifluoro-1-phenylethyl)-amine-C,N) palladium complexes according to Scheme 4.3.[25]

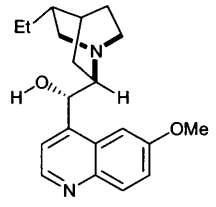


(S)-palladium complex | *rac*-alanine | (*S,R*) | (*S,S*)

Scheme 4. 3: Determination of enantiomeric excess of α-amino acids by ^{19}F NMR spectroscopic analysis.

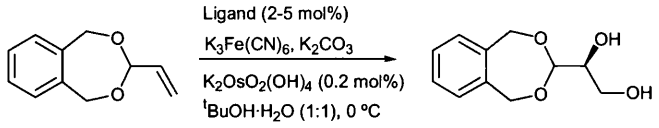
4.3.2 Chiral derivatising agents for determining the enantiomeric excess of diols

Diols are important synthetic intemediates that have been used as important chiral buildings blocks for the synthesis of natural products and biologically active compounds. There are many ways to prepare chiral diols in enantiomerically pure form, most notably via Sharpless asymmetric dihydroxylation of alkenes.[26] For example, dihydroxylation of acrolein acetonide using a $(DHQD)_2PHAL$ ligand affords the corresponding diol in 86% ee.



Dihydroquinidine (DHQD)

Figure 4. 8: Phthalazine ligand (PHAL).



DHQD-PHN 86% ee (97% ee, 60% yield after recristallisation)

Scheme 4. 4: Dihydroxylation of acrolein derivative.

Many natural products are derived from the polypropionate biosynthetic pathway that contain repeating diol subunits of different absolute and relative configuration, and attempts have been made to develop NMR models to assign the absolute configuration of their stereogenic centers. For example, the configurations of the diol fragment of onchitriols have been established from comparison of the $\Delta\delta^{RS}$ values of their bis-MPA esters, with those of the bisMPA esters of diastereomerically pure pentane diols of known absolute configuration.[9]

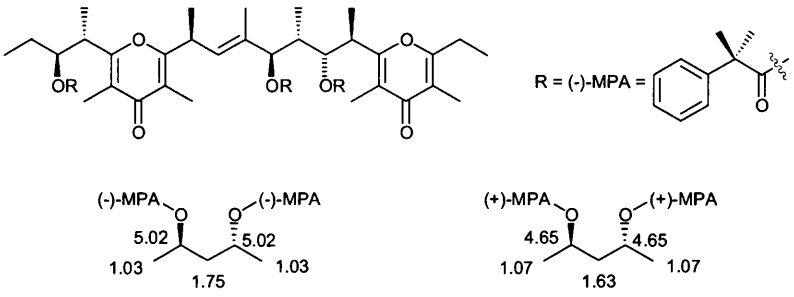
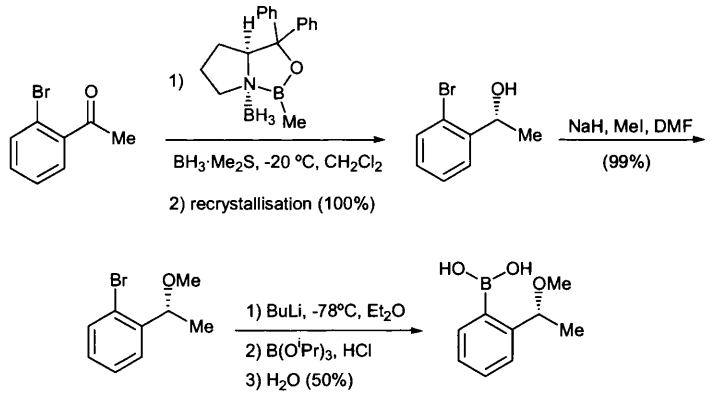


Figure 4. 9: Comparison of ^{1}H NMR chemical shifts of chiral bis-MPA esters of onchitriol with (2*R*, 4*R*)-(-)-pentanediol, indicating the different shielding caused by the auxiliary reagents for each diastereoisomer.

The most widely employed approach to determining the enantiomeric purity of chiral diols is to use CDA's such as MPA or 9-AMA to prepare bis esters. The resultant chemical shift differences between the diastereoisomers are a consequence of the additivity of the shielding/deshielding effects of both CDA fragments within the resultant bis-ester. However, non C_2-symmetric diols with inequivalent hydroxyl functionalities afford esters whose diagnostic resonances often occur in narrow regions of the ^{1}H NMR spectra causing problems with assignment. Furthermore, some of the commercially available derivatising agents are not enantiomerically pure (97.9-99.7% for Mosher's acid),[9, 12, 13] affording the potential for introducing further additional errors

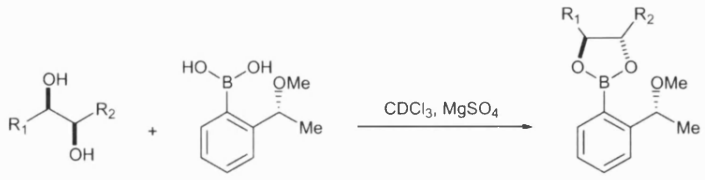
when two hydroxyl groups are derivatised. Further disadvantages include the need to use two equivalents of expensive CDA, as well as the possibility of forming monoester intermediates that can cause inaccurate ee determination due to resolution events occurring.

In order to overcame this problem, Burgess and co-workers devised an alternative enantiomerically pure derivatising agent for chiral diols that posses a single functional group capable of quantitatively reacting with both hydroxyl functionalities.[27, 28] Therefore, they introduced the boronic acid shown is scheme 4.5 as a new chiral derivatising agent for determining the enantiomeric excess of 1, 2- and 1, 3 diols. This protocol required the pre-synthesis of an enantiomerically pure aromatic boronic acid via asymmetric reduction of *ortho*-bromoacetophenone using the CBS catalyst and BH_3 as a stoichiometric reductant, which gave a chiral benzylic alcohol in 85% ee. The corresponding alcohol was then *O*-methylated with MeI, followed by lithiation of the aryl bromide and introduction of the boronic acid fragment.[27]



Scheme 4. 5: Asymmetric synthesis of (*S*)-boronic acid.

It was found that derivatization of a slight excess of chiral diol in the presence of a dehydratating agent ($MgSO_4$) gave the corresponding ester in good yield whose diastereomeric excess could be determined by ^1H NMR spectroscopy.[27] The resultant diastereoisomers gave sufficient resolution of their methoxy resonances in a 400 MHz ^1H NMR ($\Delta\delta$ = 5-20 ppb), for a wide range of 1, 2- and 1, 3- diols to be assayed. The main advantage of this approach is that kinetic resolution of the parent diol is avoided because both alcohol functionalities are complexed to the central boron atom.



Scheme 4. 6: Derivatization of diols using arylboronic acid.

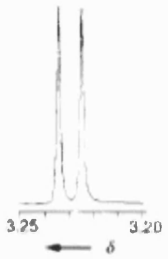
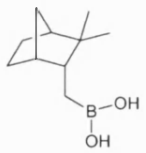
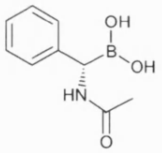


Figure 4. 10: Selected region of the ^{1}H NMR spectrum showing the OCH_3 signals of diastereomeric boronate esters from arylboronic ester derivatives of racemic 2,3-butanediol (at 400 MHz in $CDCl_3$).

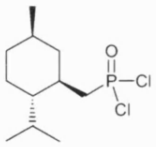
Three other important chiral derivatising agents have been reported for determining the enantiomeric excess of chiral diols.[29, 30]



campanylboronic acid



(*S*)-*N*-acetylphenylglycineboronic acid



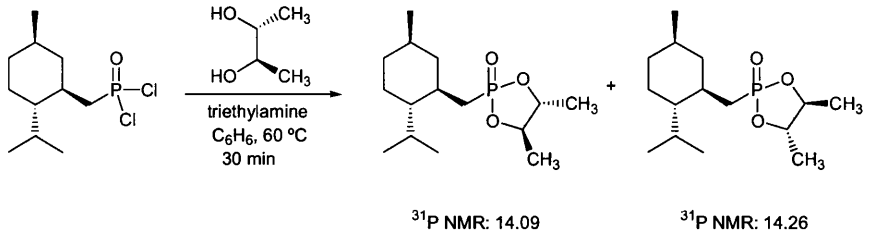
menthyldichlorophosphate

Figure 4. 11: Three more chiral derivatising agents for chiral diols.

These include a related campanylboronic acid reagent developed within the Tokles group which was used to derivatise chiral diols to afford diastereomeric boronate esters whose de was determined by ^{13}C NMR spectroscopy.[31]

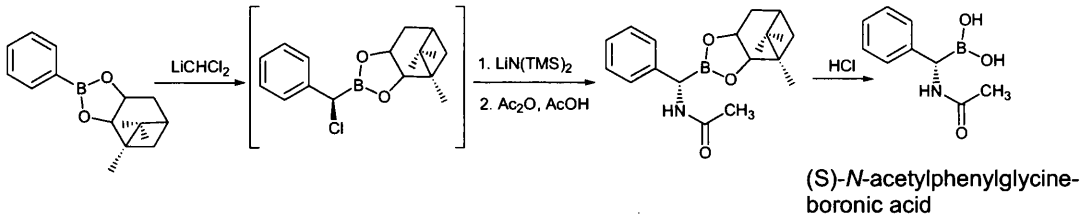
On the other hand, the compound menthyldichlorophosphate was easily prepared on a multigram scale by reaction of (-)-menthol with phosphorous oxychloride and triethylamine, and has been reported to act as an efficient chiral derivatising agent for a wide range of 1,2-diols. In general, the chemical shift differences of the resultant diastereomeric phosphonates in the ^{31}P NMR spectra were well resolved, with

diastereomeric 1,3-diols affording very good separation of $\Delta\delta$= 4 ppm in their ^{31}P NMR spectrum.[30]



Scheme 4. 7: Menthyldichlorophosphate: a chiral derivatising agent for symmetrical diols

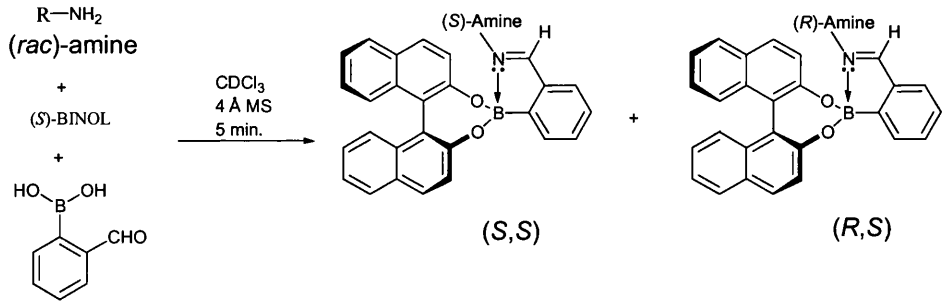
In 2003, (*S*)-*N*-acetylphenylglycineboronic acid was published as an alternative boronic acid derived CDA for the derivatisation of chiral diols with the advantage that both enantiomers were easily accessible. Its use for derivatisation of diols was reported to be quantitative and the resultant diastereomeric boronate esters were shown to be well resolved ($\Delta\delta$ = 70-220 ppb) enabling their diastereomeric excess to be readily determined.[29]



Scheme 4. 8: Synthesis of chiral derivatising agent (*S*)-*N*-acetylphenylglycineboronic acid.

4.3.3 A novel three-component CDA for determining the enantiomeric excess of chiral primary amines and diols

Recent work within the SDB/TDJ group has resulted in the development of a new chiral derivatising agent for determining the enantiopurity of chiral amines and diols by ^{1}H NMR spectroscopic analysis.[1,2] For chiral amines, the novel protocol utilizes stoichiometric amounts of 2-formyl phenylboronic as a template to simultaneously coordinate one equivalent of enantiomerically pure BINOL and one equivalent of chiral amine substrate in $CDCl_3$ in the presence of 4 Å molecular sieves. This results in a quantitative complexation reaction occurring to afford diastereomeric boronate esters whose ratio can be determined using ^{1}H NMR spectroscopy. The presence of the aryl substituents within these complexes exerts significantly different anisotropic effect for each diastereoisomer, resulting in different chemical shifts for a large number of resonances of the resultant diastereomers. This new derivatising approach has been validated for a wide range of chiral primary amines, including α-arylethylamines, α-methylalkylamines, β-amino ethers, α-amino esters, and β-amino esters, with baseline resolution of at least three sets of diastereomeric resonances being observed in all cases. This derivatisation protocol could also be used to predict the absolute configuration of α-arylethyl amines, and was shown to proceed with no kinetic resolution even for sterically hindered amines.[1, 2, 32, 33]

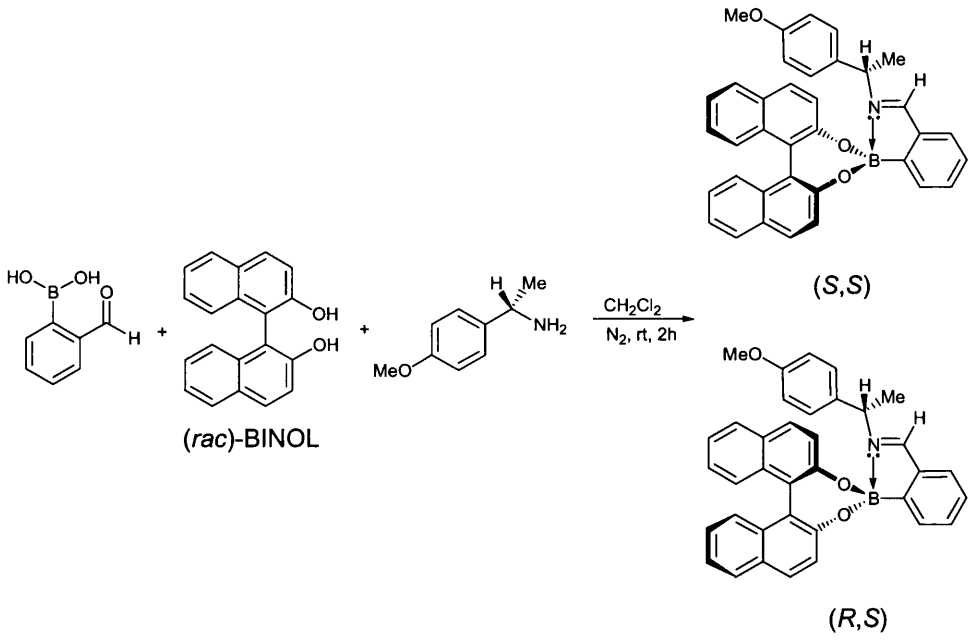


Scheme 4. 9: Three-component coupling reaction that affords diastereomeric imino-boronate esters.

The structure of a number of these diastereomerically pure boronate esters have been confirmed by X-ray crystallography which showed the existence of an internal B→N coordinate bond as revealed by the sp^3 character of the central boron atom. This was

confirmed from the ^{11}B NMR spectrum of these complexes which displayed a resonance at δ_B 14.1 ppm inferring an intramolecular nitrogen boron bond.

Since this chiral derivatising strategy had been shown to be effective for determining the enantiopurity of chiral amines, this three component self-assembling approach was then applied to determine the enantiopurity of chiral diols. With this aim in mind, the roles of the reactive components were reversed with (*S*)-*p*-methoxybenzylamine being used as a chiral auxiliary to determine the ee of a range of chiral diols. For example, stirring equimolar amounts of (*rac*)-BINOL, 2-formylboronic acid and (*S*)-1-(4-methoxyphenyl)ethanamine in CH_2Cl_2 afforded two diastereoisomeric boronate esters with multiple resonances that could be integrated to determine their de.[1, 2, 32, 33]



Scheme 4. 10: Synthesis of diastereomeric BINOL-complexes (*S*,*S*) and (*R*,*S*).

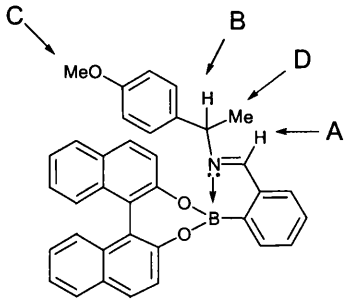


Figure 4. 12: Iminoboronic acid BINOL-complexes.

Table 4. 1: Chemical shift differences between (S,S) and (R,S)-imino boronate esters as detemined spectroscopy.

Protons	$\Delta\delta$ (δ_R- δ_S) (ppm)
A	0.189
B	-0.1223
C	-0.152
D	0.203

Extended studies within the Bull and James group have shown that this derivatisation methodology could be applied to determine the ee of a wide range of 1,2, 1,3 and 1, 4-diols.[1, 32]

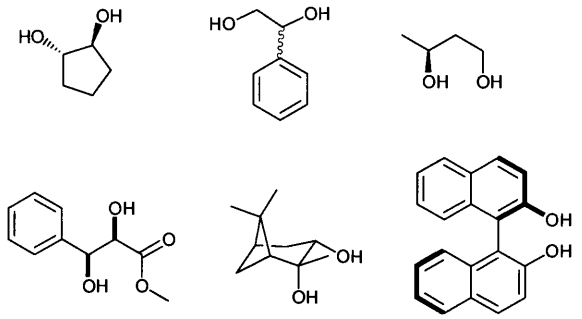
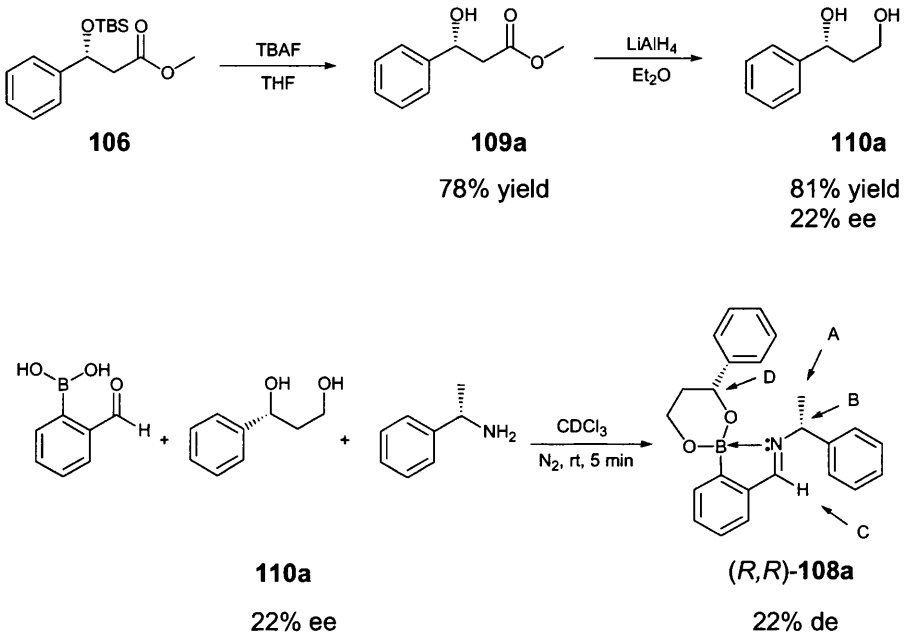


Figure 4. 13: Symmetrical and unsymmetrical diols successfully resolved using our new boronic acid three-component chiral derivatising agent.

4.4 RESULTS AND DISCUSSION

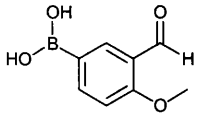
4.4.1 Aims and objectives

The chiral derivatisation protocol previously developed within our group is clearly a powerful way to determine the enantiomeric excess of chiral amines and diols by ^{1}H or ^{13}C NMR spectroscopy. Indeed, it was previously employed in this thesis to determine the enantiomeric excess of chiral diols produced using asymmetric Mukaiyama aldol protocols.[1, 32]



Scheme 4. 11: Methodology used for determining the ee of the β-hydroxyesters produced in asymmetric Mukaiyama aldol reactions.

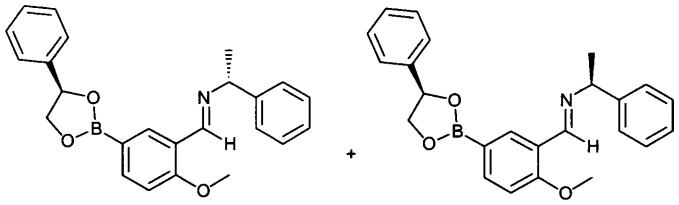
Given its usefulness it was decided to carry out a series of mechanistic investigations into the use of this CDA methodology that we hoped might lead to an even better chiral derivatising agent for determining the enantiomeric excess of chiral amines and diols. In the first instance we first wished to explore whether a commercially available 3-formyl-boronic acid **117** containing a 2-methoxy substituent could be used as a template for complex formation with amines or diols.



117

Scheme 4. 12: 3-formyl-boronic acid **117**.

This would enable us to determine whether the presence of an intramolecular B-N bond was necessary for the resultant diastereoisomers to exhibit different ^{1}H NMR spectra. Furthermore, if splitting occurred then the presence of a methoxy singlet in the ^{1}H NMR spectra of the resultant imino-boronate esters **(*S,R*)-118** and **(*S,S*)-118** would function as ideal reporter resonances for determining their de.

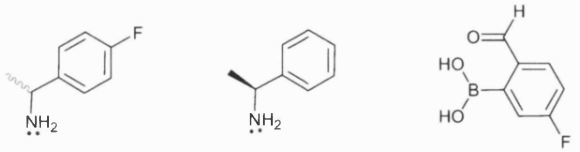


(*S,R*)-118 **(*S,S*)-118**

Scheme 4. 13: Imino boronate complexes derived from 3-formyl-2-methoxy boronic acid **117**.

One of the advantages of using the Mosher's acid derivatisation methodology for determining the ee of chiral amines (or alcohols) is the possibility of using ^{19}F NMR spectroscopy as a technique for analysis.[9, 12, 13] We reasoned that we might be able to adapt our three-component methodology to develop second generation chiral derivatising agents which contained fluorine atoms that would enable the de of their resultant imino-boronate ester complexes to be determined by ^{19}F NMR spectroscopy. It was proposed that this could be achieved by one of two different approaches, by either incorporating the fluorine atom into the chiral auxiliary fragment, or a more flexible approach involving the use of a fluorous 2-formyl-aryl-boronic acid template for complexation. In the first case, a review of the literature revealed that enantiopure *p*-fluoro-α-methylbenzylamine **119** was commercially available, which appeared well suited for devising a CDA approach for determining the enantiomeric excess of diols by ^{19}F NMR spectroscopy. Since 2-formyl-fluoroboronic acid **121** was not commercially available, it was identified as a synthetic target that could then be used as a versatile

template for our self-assembly methodology to enable the ee of both amines and diols to be determined by ^{19}F NMR spectroscopy.

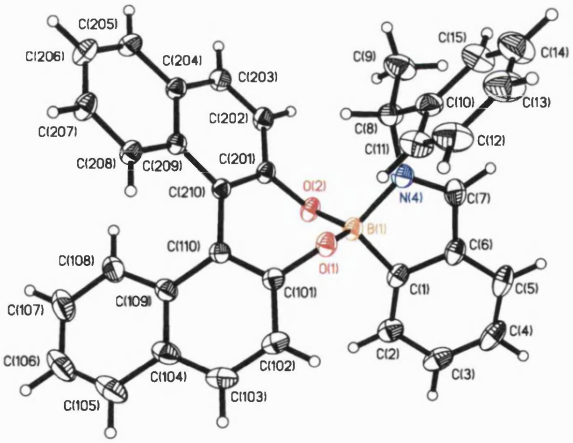


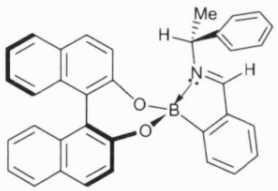
119 **(*S*)-120** **121**

Scheme 4. 14: racemic *p*-fluoro-α-methylbenzylamine **119**, chiral amine **(*S*)-120** and 2-formyl-fluoroboronic acid **121**.

4.4.2 Exploring the role of the intramolecular B-N bond

It had been proposed that the ability of 2-formyl-phenyl-boronic acid to afford diastereoisomeric imino-boronate ester complexes that exhibited significantly different NMR spectra was a consequence of the presence of intramolecular B-N bonds providing structural rigidity to each complex, thus creating different diastereoisomeric environments in each case.[33]



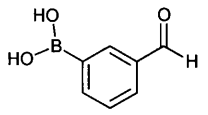


(*S*,*R*)-**108c**

Figure 4. 14: ORTEP view of (*S*, *R*)-108a with ellipsoids drawn at 30% probability level.

In order to probe this hypothesis we decided to probe whether an intramolecular B-N bond was necessary for efficient splitting of the diastereoisomers of imino-boronate

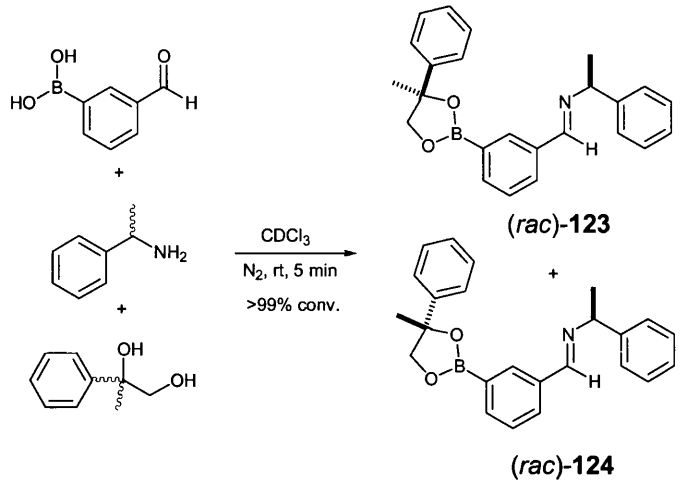
esters and as a consequence it was decided to explore whether 3-formylphenyl boronic acids could be used as a template for our three-component CDA methodology. It was proposed that derivatisation of 3-formyl boronic acid **122** with a chiral amine and a chiral diol would afford diastereoisomeric imino-boronate ester complexes that did not contain an intramolecular B-N bond and therefore it was predicted that they should display almost identical ^{1}H NMR spectra.



122

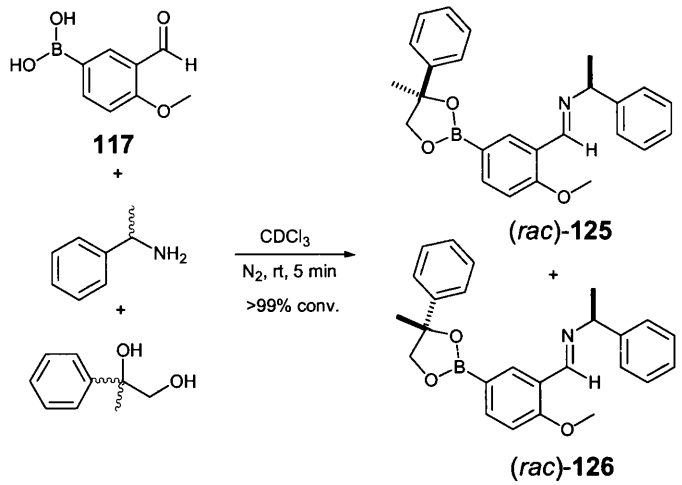
Figure 4. 15: 2-formyl-phenyl-boronic acid and 3-formyl-phenyl-boronic acids.

A 1:1 mixture of chiral imino-boronate ester complexes (*rac*)-**123** and (*rac*)-**124** were therefore prepared by reacting 3-formyl-phenylboronic acid **122** with (*rac*)-2-phenyl-1,2-propane diol and (*R*)-phenylethylamine in $CDCl_3$. Analysis of the resultant ^{1}H NMR spectrum revealed a single set of resonances corresponding to the apparent formation of a single compound. Since the complexation reaction had clearly proceeded to completion, it was therefore clear that the diastereoisomeric imino-boronate esters formed in this complexation reaction exhibit identical superimposable ^{1}H NMR spectra with no distinguishable resonances. The fact that (*E*)-boronate ester complexes had been formed was confirmed by NOESY spectroscopic analysis of the mixture of stereoisomers which revealed a crosspeak between the N-α-CH(Ph) proton and the imine proton. The absence of any *intermolecular* N→B interaction was confirmed from analysis of the ^{11}B NMR spectrum which revealed a resonance at δ 31.46 ppm consistent with the boron atom being sp^2 hybridised.



Scheme 4. 15: Diastereomeric boronate complexes **(*rac*)-123** and **(*rac*)-124** derived from 3-formylboronic acids.

A sample of 2-methoxy-3-formylphenylboronic acid **117** was also available in our laboratory and as a consequence it was also employed as a substrate to confirm the intramolecular B-N hypothesis. Therefore, equimolar amounts of 2-methoxy-3-formylphenylboronic acid **117**, (*rac*)-2-phenyl-1,2-propane diol and (*rac*)-phenylethylamine were stirred in $CDCl_3$ for five minutes to afford a 1:1 mixture of (*rac*)-**125**, and (*rac*)-**126.** However, in this case the ^1H NMR spectra revealed some evidence of two diastereoisomeric complexes having been formed, with the presence of two resolved CH_3CH doublets appearing in a 1:1 ratio at δ_H 1.55 and 1.56 ppm, corresponding to the presence of the diastereoisoemeric α-methyl benzyl fragments. NOESY analysis on this mixture revealed (*rac*)-**125**, and (*rac*)-**126** had once again been formed as their expected (*E*)- geometric isomers, whilst ^{11}B NMR analysis revealed that their boron atoms were sp^2 hybridised, with a chemical shift of 29.45 ppm.



Scheme 4. 16: Diastereomeric boronate complexes derived from 2-methoxy-3-formylphenylboronic acid **122**.

It was found that crystals suitable for X-ray analysis could be obtained via slow recrystallisation of the mixture of boronate ester complexes (*rac*)-**125** and (*rac*)-**126** from a 1:1 mixture of CH_2Cl_2/petrol 40-60 which ^1H NMR analysis revealed were formed as a single diastereoisomer. X-Ray crystallographic analysis of these crystals revealed that (*rac*)-**125** had preferentially crystallised from solution with its imine functionality clearly adopting an (*E*)- geometry (Figure 4.16). However, consideration of the extended structure of (*rac*)-**125**, which positions the methyl substituent of the chiral amine fragment remote to the chiral diol fragment, means it is difficult to rationalise the nonequivalence observed of the methyl protons of diastereoisomeric complexes (*rac*)-**125** and (*rac*)-**126** in their ^1H NMR spectra.

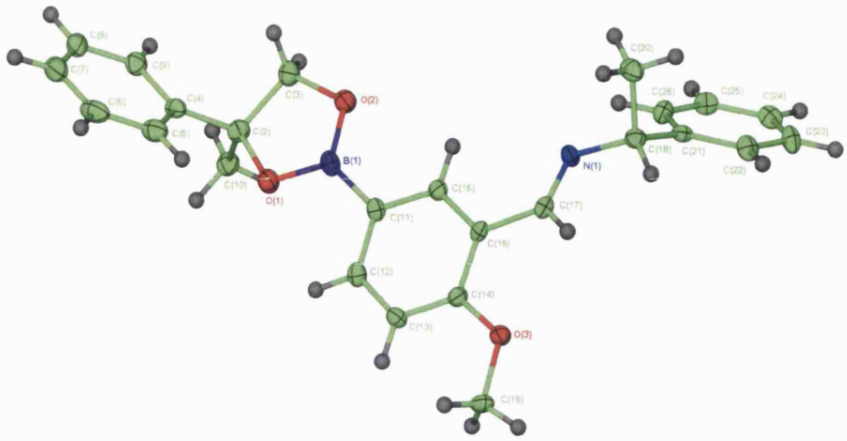
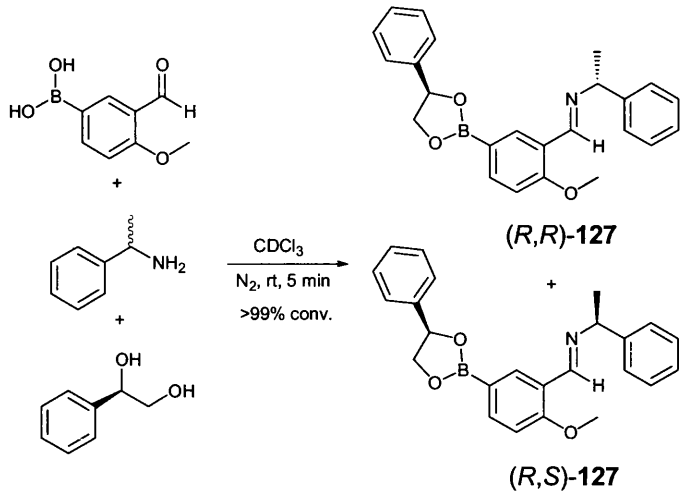


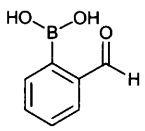
Figure 4. 16: ORTEP view of (*rac)*-**125.**

In order to demonstrate that 3-formyl-2-methoxy-boronic acid **117** could potentially be used as a template to develop a general CDA for determining the enantiomeric excess of amines (or diols), it was treated with stoichiometric amounts of (*rac*)-α-methylbenzylamine, and enantiomerically pure (*R*)-1-phenyl-1, 2-ethanediol in $CDCl_3$ to afford a 1:1 diastereomeric mixture of (*R*,*R*)-**127** and (*R*,*S*)-**127**. Analysis of the resultant ^{1}H NMR spectrum once again revealed the presence of two sets of doublets for the methyl groups at δ 1.60 and δ 1.61 that were resolved using a 500 MHz spectrometer. Diastereomerically pure complexes (*R*, *R*)-**127** and (*R*, *S*)-**127** were then prepared using the individual (*R*) - and (*S*) - enantiomers of α-methylbenzylamine for complexation, which allowed us to identify the resonances corresponding to each diastereoisomer. NOESY experiments on these individual diastereoisomerically pure complexes once again confirmed the presence of an (*E*)-configured imine functionality (see appendix) with the ^{11}B NMR spectrum revealing resonances at δ_B at 31.89 and 31.61 ppm respectively, consistent with the presence of sp^2 boron atoms.



Scheme 4. 17: Diastereomeric imino boronate complexes (*R,R*)-127 and (*R,S*)-127 derived from 2-methoxy-3-formylphenylboronic acid.

Therefore, the use of 3-formyl-2-methoxy-boronic acid **117** as a template for CDA development with sufficiently different NMR spectra to enable diastereoisomeric excess analysis to be carried out. However, whilst it is possible to use this boronic acid as a template for CDA formation at high field strengths, the difference in chemical shifts of comparative resonances between each diastereoisomer, and the number of resonances split were significantly inferior to those previously obtained using 2-formyl-phenylboronic acid **128**, and as a consequence it was not pursued for further study. This involved the use of α-methyl-*p*-fluorobenzylamine instead of α-methylbenzylamine which enabled ^{19}F NMR spectroscopy analyses for determining the ee of diols.



128

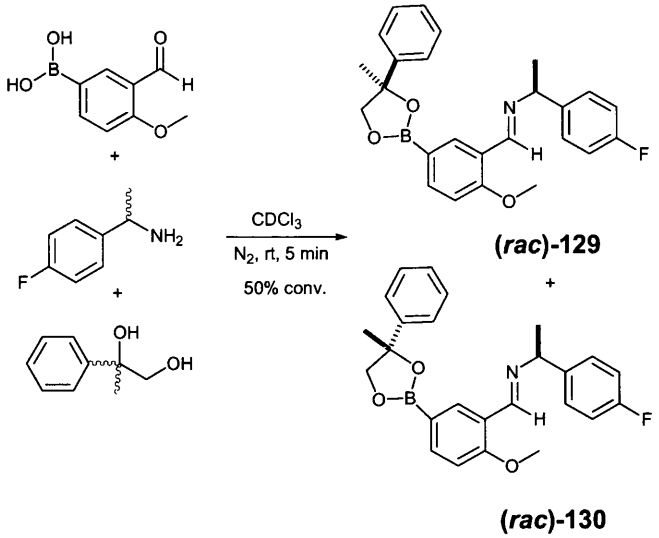
Scheme 4. 18: 2-formyl-phenylboronic acid **128**.

4.4.3 Using α-methyl-*p*-fluorobenzylamine as a chiral auxiliary for CDA development

In comparing our three-component boronic acid methodology with the most commonly used Mosher's acid derivatisation approach,[9, 12, 13] it was clear that our boronic acid

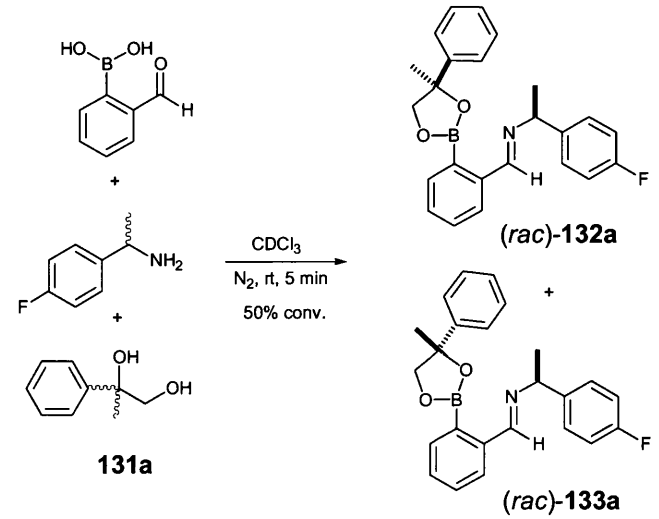
templating approach had many practical advantages. These include the ability to carry out derivatisation without kinetic resolution occurring, splitting of more than one set of diastereomeric protons with good resolution, and the ability to determine de using ^{13}C NMR spectroscopy. However, an advantage of using Mosher's acid for derivatisation of diols was the ability to use ^{19}F NMR spectroscopy to determine diastereomeric excess,[9, 12, 13] and as a consequence we decided to generate a second generation CDA that would also enable us to use this technique for de determination.

A review of commercially available amines revealed that enantiopure α-methyl-*p*-fluorobenzylamine was available that could potentially be employed to develop a CDA for determining the ee of diols, since it would result in a mixture of diastereoisomeric imino-boronate esters that could be discriminated by ^{19}F NMR spectroscopy. In order to probe this hypothesis, it was decided to investigate whether diastereoisomeric mixtures of imino-boronate ester complexes **(*rac*)-129** and **(*rac*)-130** would show well resolved peaks in their ^{19}F NMR spectra. Therefore, 2-methoxy-3-formylphenylboronic acid **117**, (*rac*)-2-phenyl-1,2-propane diol and (*rac*)-4-fluoro-phenylethylamine were reacted in $CDCl_3$ for five minutes which gave a 1:1 mixture of diastereoisomeric imino-boronate esters ***(rac)*-129** and ***(rac)*-130**. The ^{1}H NMR spectrum analysis of both diastereoisomers provided two sets of well resolved signals for the diastereoisomeric methyl resonances at δ 1.55 and δ 1.56 in a 1:1 ratio. In addition, the ^{11}B NMR spectrum showed a peak at δ 30.75 ppm, indicating the sp^2 hybridisation of boron atom as a consequence of the distance between boron and nitrogen. ^{19}F NMR spectrosocopy of the resultant mixture of imino-boronate ester complexes **(*rac*)-129** and **(*rac*)-130** showed one set of resonances corresponding to each diastereoisomer at δ -116.60 and -116.64 in 1:1 ratio. In view of this, it has been clearly demonstrated that the presence of an intramolecular N→B bond is not an absolute requirement for the formation of diastereoisomeric imino-boronate esters to alow distinction between diastereoisomers.



Scheme 4. 19: Diastereoisomeric imino-boronate ester complexes (*rac*)-**129** and (*rac*)-**130** containing fluorine.

Expanded work in this area revealed that this amine can be used as a CDA for determining the diastereomeric excess of a range of chiral diols. A representative example is the imino boronate esters **(*rac*)-132a** and **(*rac*)-133a** whose ^{1}H NMR spectrum analysis provided two sets of signals for the diastereomeric imine resonances at δ 8.10 and 8.19, and the methylene protons at δ 1.10 and 1.15 in 1:1 ratio. Moreover, the ^{11}B NMR spectra showed a peak at δ 16.11 ppm, consistent with the formation of an sp^3 boron atom, and a C=N strech in the IR spectrum at 1692 cm^{-1}.



Scheme 4. 20: Diastereoisomeric imino-boronate ester complexes (*rac*)-**132a** and (*rac*)-**133a** containing fluorine.

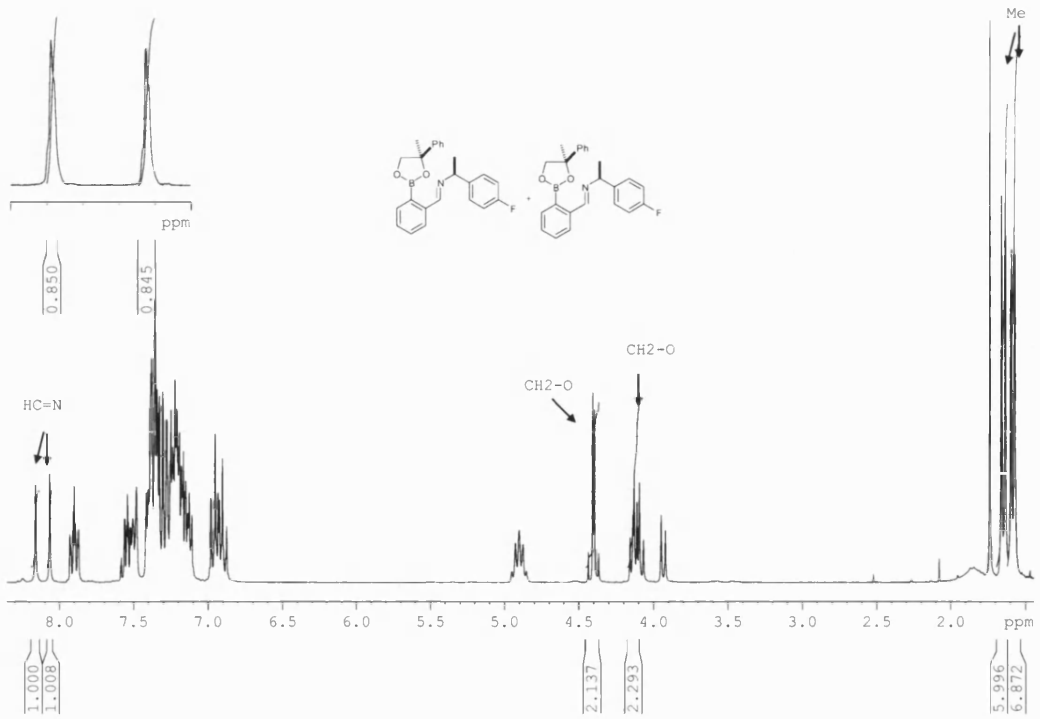


Figure 4. 17: ^{1}H NMR spectrum of an aliquot of the reaction mixture of 3-formylphenylboronic acid, (*rac*)-2-phenyl-1,2-propane diol and (*rac*)-4-fluoro-phenylethylamine in $CDCl_3$ taken after a reaction time of 5 minutes.

^{19}F NMR spectrosocopy of the resultant 1:1 mixture of imino-boronate ester complexes (*rac*)-**132a** and (*rac*)-**133a** showed two sets of resonances corresponding to each diastereoisomer. However, these broad ^{1}H-^{19}F coupled signals were not sufficiently well resolved to enable them to be well-resolved since they appeared as partially overlapping multiplets. Consequently, a fluorine-proton decoupling NMR experiment was carried out which resulted in the appearance of two sets of well-resolved singlets at at δ_F -113.40 and -114.10 in a 1:1 ratio.

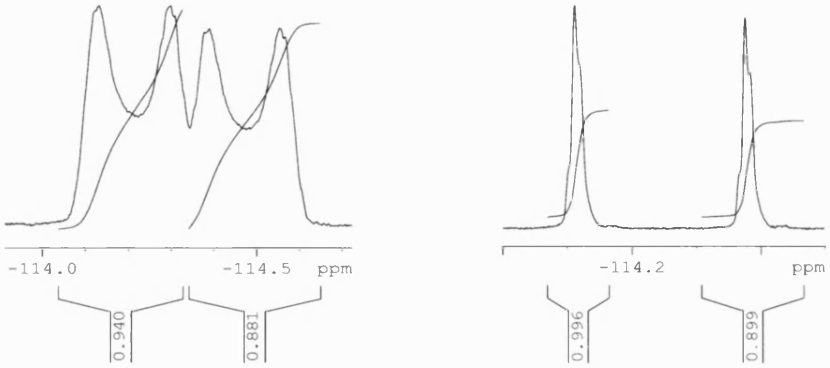
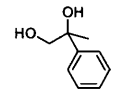
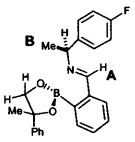
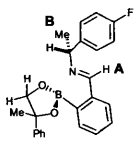
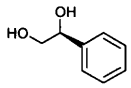
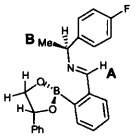
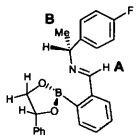
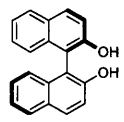
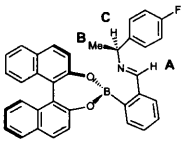
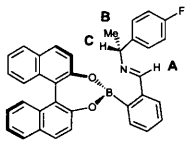
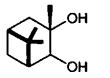
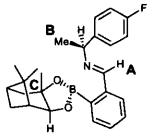
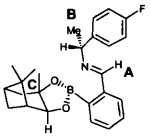
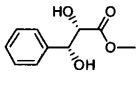
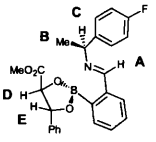
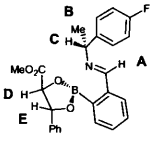
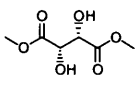
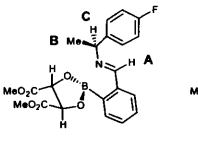
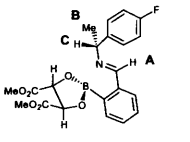


Figure 4. 18: Coupled and decoupled ^{19}F NMR spectra of diastereoisomeric imino-boronate ester complexes (*rac*)-**132a** and (*rac*)-**133a**.

Since these results clearly demonstrated that this amine could be used as a CDA we screened it for determining the diastereoisomeric excess of a range of chiral diols **131a-f**, the results of which are shown in Table 4.2. These results revealed that a 50:50 mixture of two diastereoisomers complexes **132a-e** and **133a-e** were formed in moderate yields with baseline resolution being observed for at least the imine protons and methyl protons of each pair of diastereoisomers. Moreover, nonequivalent fluorine resonances were observed for these diastereoisomers complexes in their ^{19}F NMR spectra, with a $\Delta\delta$ = 0.05-0.75 ppm. These observations were very promising since we now had a CDA that enabled comparison of the integrals of diastereomeric protons in the ^{1}H NMR or diastereomeric fluorine atoms in the ^{19}F NMR spectra to be used for the accurate determination of the enantiopurity of a scalemic sample of this diol by both spectroscopic methods.

Table 4. 2: Chemical shift differences (Δδ) in the 300 MHz ^{1}H NMR and 400 MHz ^{19}F NMR spectra of 50:50 mixtures of **132a-f** and **133a-f** derived from chiral diols **131a-f** and α-methyl-*p*-fluorobenzylamine.

(*chiral*)-diol	boronate complexes*		Δδ (δ2-δ3ppm)	Δδ ^{19}F NMR (ppm)
			0.05 (A) 0.05 (B)	0.300
(*rac*)-**131a**	(*rac*)-**132a**	(*rac*)-**133a**		
			0.10 (A) 0.01 (B)	0.200
(*S*)-**131b**	(*S*,α-*S*)-**132b**	(*S*,α-*R*)-**133b**		
			0.15 (A) 0.30 (B) 0.10 (C)	0.550
(*R*)-**131c**	(*R*, α-*S*)-**132c**	(*R*, α-*R*)-**133c**		
			0.10 (A) 0.15 (B) 0.20 (C)	0.05
(*R,R,R,S*)-**131d**	(*RRRS*,α-*S*)-**132d**	(*RRRS*,α-*R*)-**133d**		
			0.30 (A) 0.10 (C) 0.15 (D) 0.50 (E)	0.750
(*R,S*)-**131e**	(3*R*,2*S*,α-*S*)-**132e**	(3*R*,2*S*,α-*R*)-**133e**		
			0.35 (A) 0.25 (B) 0.10 (C)	0.750
(*S,S*)-**131f**	(2*S*,3*S*,α-*S*)-**132f**	(2*S*,3*S*,α-*R*)-**133f**		

* Sterochemistry assignment of the boronate complexes has been done arbitrarily.

Although enantiopure α-methyl-*p*-fluorobenzylamine was not used in this study because of its expense (£33/1g ApolloScientific), the results obtained using the racemic amine clearly demonstrate that it is well suited to determining the enantiomeric excess of diols via ^{1}H and ^{19}F NMR spectroscopy. However, given developments described in the following chapter, complexation reactions using chiral amine α-methyl-*p*-fluorobenzylamine to afford pure diastereoisomeric imino-boronate esters, and determination of the de detection limits of this CDA were not carried out.

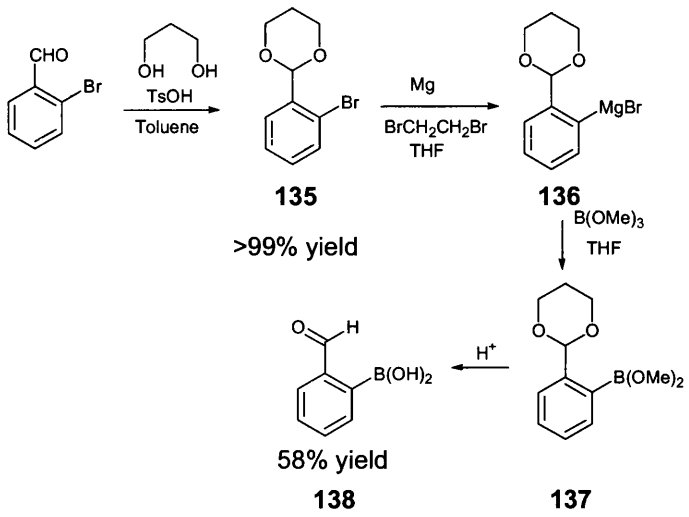
4.4.4 A new chiral fluorous boronic acid for determining the enantiopurity of primary amines or diols

The results described using α-methyl-*p*-fluorobenzylamine clearly demonstrated it could potentially be used as a useful chiral auxiliary to develop a CDA for determining the enantiomeric purity of chiral diols by ^{19}F NMR spectroscopy. However, it was decided to target an alternative fluorous containing boronic acid as a template for complexation, since this would allow the enantiopurity of both chiral diols and amines to be determined. In this regard, it was necessary to prepare 4-fluoro-2-formylphenylboronic acid **134** which was not commercially available.

4.4.4.1 Optimised synthesis of 4-fluoro-2-formylphenylboronic acid

It was decided to establish conditions for the synthesis of 4-fluoro-2-formylphenyl boronic acid **134** using the cheaper 2-formyl-bromo-benzene as a model substrate according to the protocol described in scheme 4.21.[34] Therefore, the aldehyde functionality of commercially available 2-formyl-bromobenzene was treated with propane-1,3-diol in the presence of a catalytic amount of *p*-toluensulphonic acid to afford the cyclic acetal **135** in 99% yield. The resultant acetal **141** was then treated with magnesium turnings in THF in the presence of a catalytic amount of 1,2-dibromoethane, and the resultant reaction refluxed for 1 h to afford the corresponding Grignard reagent **136**. This solution of Grignard agent was then cooled to room temperature before being quenched via addition to a solution of trimethylborate in THF at -78°C which gave the corresponding arylboronic ester **137**. Subsequent hydrolysis of boronic ester by

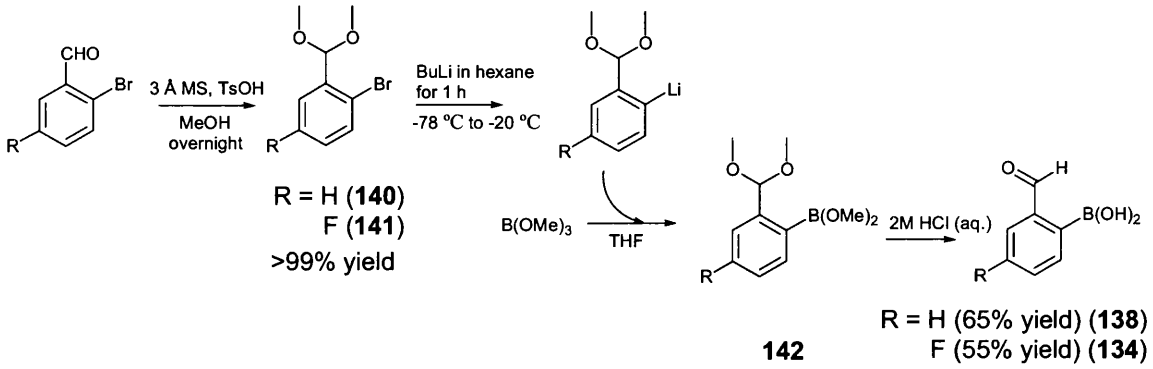
treatment with 10 mol% sulphuric acid solution resulted in formation of the corresponding crystalline boronic acid **138** in 58% overall yield after a final recrystallisation from petrol/ether (95:5).



Scheme 4. 21: Synthesis of *o*-formylbenzeneboronic acid.

The synthesis of 4-fluoro-2-formylbenzeneboronic acid **134** was then carried out in an analogous manner. After carrying out a range of optimisation reactions,[34, 35] a modified version of this protocol was then used for the preparation of 4-fluoro-2-formylphenylboronic acid **134** using 4-fluoro-2-formyl-bromobenzene **139** as a starting material. Therefore, the required aldehyde and a catalytic amount of *p*-toluene sulphonic acid were dissolved in methanol in the presence of 3 Å molecular sieves to remove water.[7, 36-41] After stirring overnight, the reaction was worked-up to afford the corresponding highly crystalline dimethoxy acetal **141** in 99% yield. Attempts to generate the Grignard reagent of **142** proved unsuccessful leading to recovery of starting material, therefore an alternative directed lithiation strategy was developed for introducing the boronic acid functionality. Selective transmetalation of the bromo functionality of fluorobenzene **141** was achieved via treatment with *n*-BuLi in hexane at -78°C followed by warming to -20°C, which resulted in formation of the corresponding lithium anion that was quenched via addition to a solution of trimethylborate in THF at -78°C to afford boronic ester **134**. Presumably, the inherent selectivity for lithiation of the bromo over the fluoro functionality of **141** is enhanced by coordination of one of the oxygen atoms of the dimethyl acetal functionality to the lithium counter ion of butyl-lithium which would kinetically favour *trans*-metallation at the *o*-bromo position.

Subsequent hydrolysis of the acetal functionality of fluoro-boronic acid **142** via treatment with 2M HCl (aq) afforded the desired crystalline 4-fluoro-2-formylphenylboronic acid **134** in an overall 55% yield. Full characterisation of the resultant 4-fluoro-2-formylphenylboronic acid confirms its satisfactory formation. Thus, the ^{1}H NMR spectrum revealed the presence of two hydroxyl groups for the boronic acid fragment at 1.60 ppm, the CHO aldehyde peak at 9.80 ppm and the corresponding aromatic protons within 7.50 and 8.30 ppm. As a consequence of 1H-19F coupling constants, ^{19}F NMR spectra gave a doublet of doublets of doublets. Furthermore, the ^{11}B NMR spectra of δ_B = 28.70 revealed the presence of a sp^2 hybridatised boron atom. Finally, mass spectroscopic data verified the successful formation of 4-fluoro-2-formylboronic acid, with a HRMS peak for $[M+Na]^+$ found at 191.0286 in comparison with the calculated $[M+Na]^+$ of 191.0286.

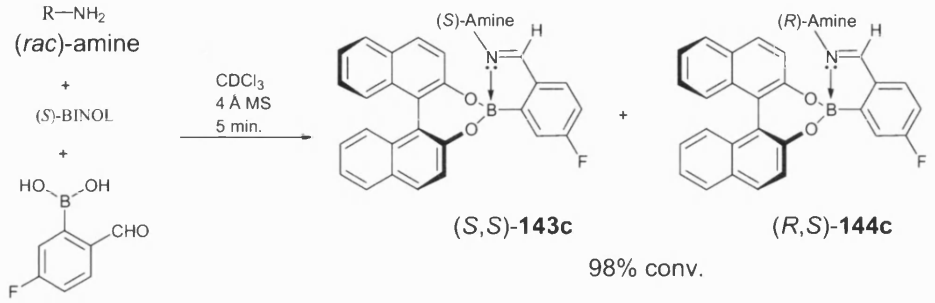


Scheme 4. 22: Synthesis of o-formylbenzeneboronic acid **145** and *p*-fluoro-*o*-formylbenzeneboronic acid **140**.

4.4.4.2 Three-component chiral derivatising protocol for determining the ee of primary amines or diols

Having devised a high-yielding synthesis of enantiopure *p*-fluoro-*o*-formyl-phenyl-boronic acid **134**, our next aim was to employ it as a template to develop a CDA for determining the enantiopurity of chiral amines and diols.[1, 2, 32, 33] We first decided to demonstrate that this boronic acid could be used as a template for a three-component reaction between racemic α-methyl-benzylamine and (*S*)-BINOL. Therefore, equimolar amounts of *p*-fluoro-*o*-formylbenzeneboronic acid **134**, (*S*)-BINOL and (*rac*)-1-α-methylbenzylamine were dissolved in $CDCl_3$ and a ^{1}H NMR spectrum acquired after 5 minutes. This spectrum revealed that a clean 'self-assembly' reaction had occurred to

afford a 1:1 mixture of diastereoisomeric boronate esters (*S,S*)-**143c** and (*R,S*)-**144c** with three sets of protons showing nonequivalence; the methyl protons at 1.40 and 1.60 ppm, the methylene protons at 4.80 and 4.90 ppm and imine protons at 8.00 ppm and 8.15 ppm. The tetrahedral sp^3 character of the boron atoms of these complexes was demonstrated from ^{11}B NMR spectrum which revealed a peak at 12.68 ppm.



Scheme 4. 23: Chiral boronate complex containing fluorine in the formylboronic acid ring.

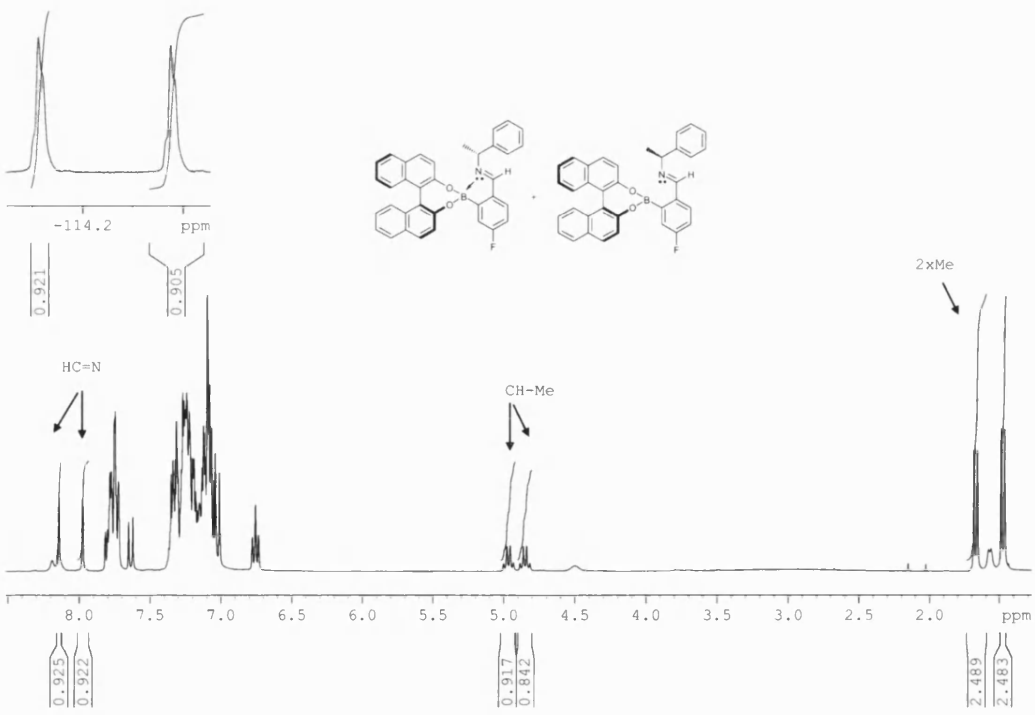
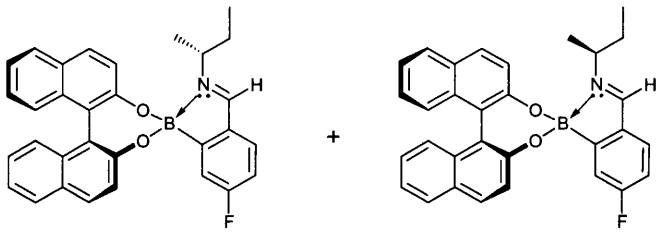


Figure 4. 19: ^1H NMR and ^{19}F NMR spectrum of an aliquot of the reaction mixture of *p*-fluoro-*o*-formyl-phenyl-boronic acid, α-methyl-benzylamine and (*S*)-BINOL in $CDCl_3$ taken after a reaction time of 5 minutes.

We then acquired the ^{19}F NMR spectrum of the mixture of diastereoisomeric boronate esters (*S,S*)-**143c** and (*R,S*)-**144c** which clearly revealed the presence of two well-resolved peaks in a 1: 1 ratio δ_F -114.10 and -114.40 corresponding to the aryl-fluoride residue of each diastereoisomer.

In order to demonstrate the broad applicability of this derivatisation protocol it was decided to apply it to the aliphatic chiral amine (*rac*)-butylamine. [32, 33] Therefore, the ^1H NMR spectrum of a stoichiometric amount of (*S*)-BINOL and 4-fluoro-2-formylphenyl boronic acid in $CDCl_3$ revealed a clean 1:1 mixture of diastereoisomeric imino-boronate esters (*S,R*)-**145** + (*S,S*)-**146** with two sets of diastereoisomeric resonaces fully resolved. Furthermore, the ^{19}F NMR spectra revealed two singlets at -114.55 and -114.75, confirming the asynchronous environment of the two fluoro atoms of each of the diastereoisomers.

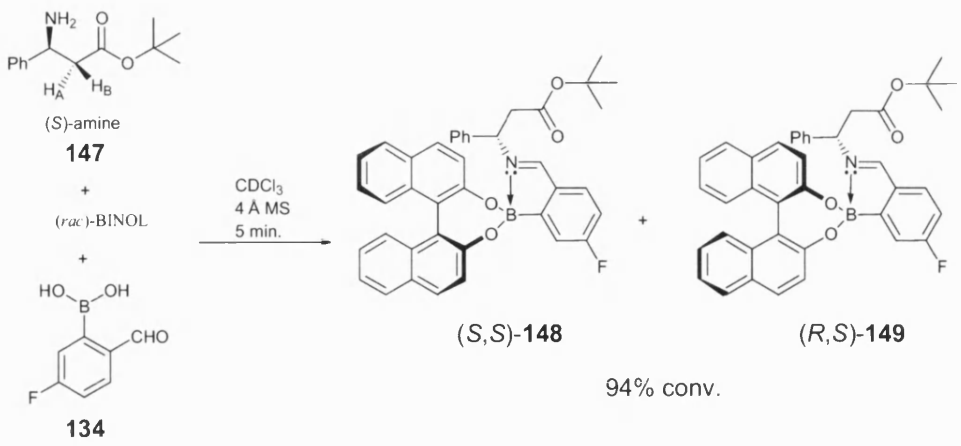


(*S, R*)-**145** + (*S, S*)-**146**

>99% conv.

Scheme 4. 24: Mixture of imino boronate esters derived from α-methyl-benzylamine, (*S*)-BINOL and 4-fluoro-2-formylphenyl boronic acid.

We demonstrated the potential three component derivatisation protocol for the analysis of *tert*-butyl-(3*S*)-3-amino-3-phenylpropanoate.[33] Thus, stoichiometric amounts of chiral amine **147,** (*rac*)-BINOL and 4-fluoro-2-formylphenyl boronic acid **134** were reacted in $CDCl_3$ for 5 minutes. The resultant mixture of diastereomeric imino boronate esters (*S,S*)-**148** + (*R,S*)-**149** was obtained in 1:1 mixture indicating that kinetic resolution had not occurred. The ^1H NMR spectra revealed good baseline resolution with two sets of resonances for H_A and H_B at 2.8 ppm and 3.4 ppm. The individual resonances of one diastereoisomer was assigned by comparison of the ^1H NMR spectra of authentic sample of (*S,S*)-**148** prepared from a separate reaction of (*S*)-amine with (*S*)-BINOL.



Scheme 4. 25: Chiral boronate complex containing fluorine in the formylboronic acid ring.

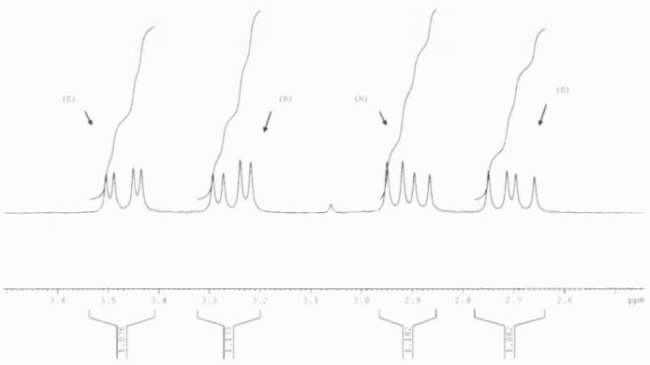
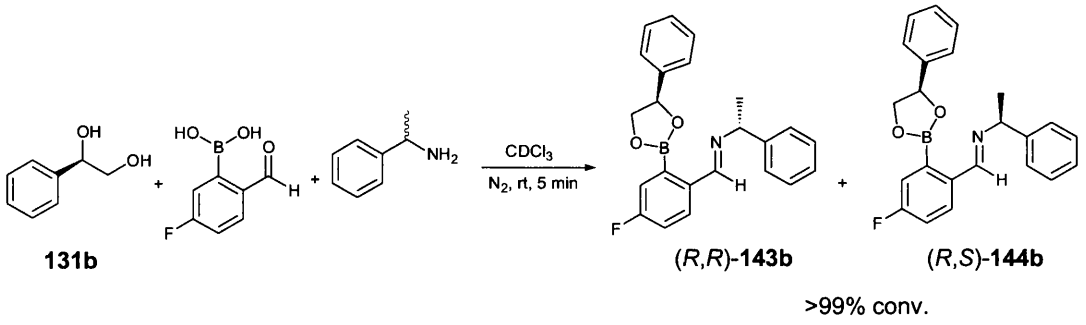


Figure 4. 20: ^{1}H NMR spectra of imino boronate complexes (*S, S*)-**148** and (*R, S*)-**149**.

4.4.4.3 Determining the enantiomeric excess of chiral diols by ^{1}H and ^{19}F NMR spectroscopy

Our attention then turned to demonstrating that our new second-generation fluorine containing CDA could be used to determine the enantiomeric excess of a wide range of structurally diverse diols.[1, 32] Initially, 1.0 equiv of (*R*)-1-phenyl-1,2-ethanediol **131b**, 1.0 equiv of 4-fluoro-2-formylphenyl boronic acid **134**, and 1.0 equiv of (*rac*)-α-methyl-benzylamine were dissolved in $CDCl_3$ and the ^{1}H NMR spectra of an aliquot acquired after 5 min. The resultant ^{1}H NMR spectrum revealed that a 50:50 mixture of two diastereoisomeric complexes (*S*,*R*)-**143b** and (*S*,*S*)-**144b** had been formed quantitatively with baseline resolution being observed for both the imine protons and the diol benzylic proton of each diastereoisomer (Scheme 4.26).



Scheme 4. 26: A 50:50 mixture of two diastereoisomeric complexes (*S*, *R*)-**143b** and (*S*, *S*)-**144b**.

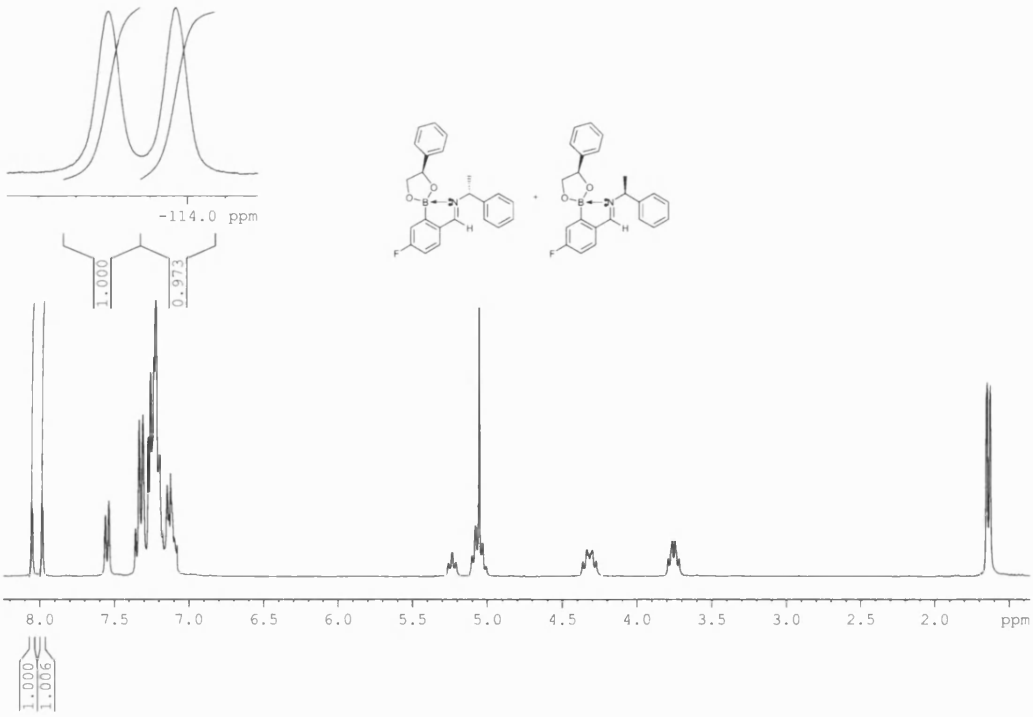


Figure 4. 21: 300 MHz ^{1}H NMR spectrum of an aliquot of the reaction mixture of 4-fluoro-2-formylphenylboronic acid, α-methyl-benzylamine and (*R*)-1-phenyl-1,2-ethanediol in $CDCl_3$ taken after a reaction time of 5 minutes.

This observation was highly promising because it meant that comparison of the relative intensities of the integrals of their imine protons could be used to accurately confirm the enantiopurity of a scalemic sample of this diol by ^{1}H NMR spectroscopy. To investigate the scope and limitation of this chiral derivatization protocol, a range of seven further racemic diols **131a-g** containing primary, secondary, and tertiary hydroxyl groups were then investigated. Analysis of the 400 MHz ^{1}H NMR spectra of the resultant 50:50 mixture of diastereoisomeric iminoboronate esters **143a-g** and **143a-g** revealed that baseline resolution had been achieved for at least one set of resonances in all cases, with up to five distinct resonances being observed in some instances. For example, analysis of the 400 MHz ^{1}H NMR spectra of a 50:50 mixture of iminoboronate esters **143e** and **144e** revealed that baseline resolution had been achieved for five distinct sets of signals.

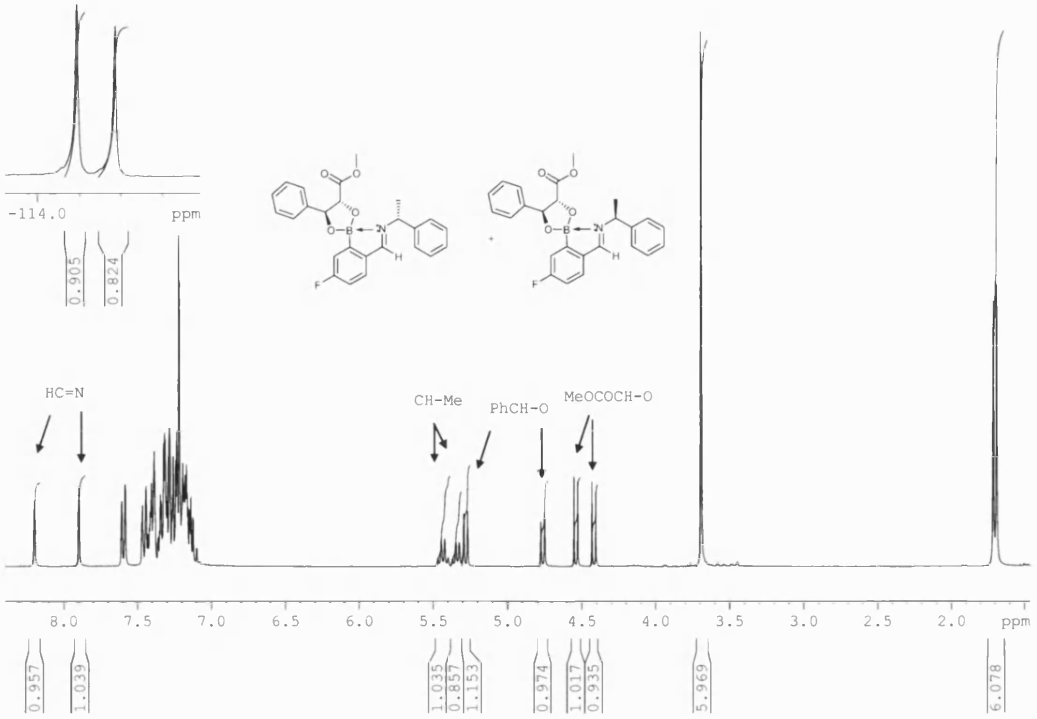


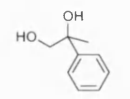
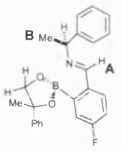
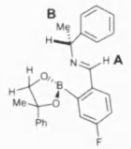
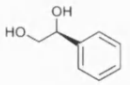
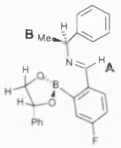
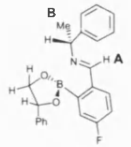
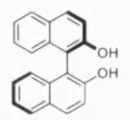
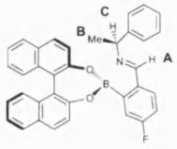
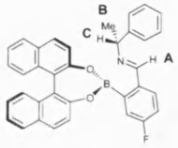
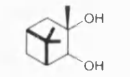
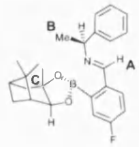
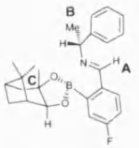
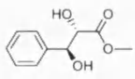
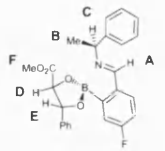
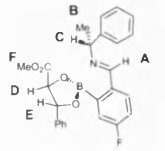
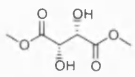
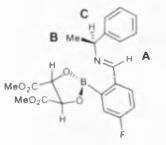
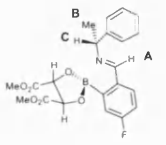
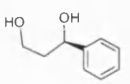
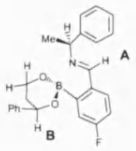
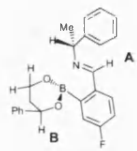
Figure 4. 22: 400 MHz ^{1}H NMR spectrum of an aliquot of the reaction mixture of 4-fluoro-2-formylphenylboronic acid, α-methyl-benzylamine and diol **131e** in $CDCl_3$ taken after a reaction time of 5 minutes.

Importantly, in all cases splitting of the imine signal was observed (0.05-0.35 ppm) in a region of the ^{1}H NMR spectra that was free of any other resonances. This feature is highly desirable since the imine resonances are removed from any other resonances associated with the diol fragment, thus providing diagnostic resonances for integration that are independent of the diol being derivatized. Importantly, it was found that derivatization of every diol **131a-h** gave two sets of diastereoisomeric iminoboronate ester resonances in their ^{1}H NMR spectra clearly indicating that free rotation was occuring around the aryl-boron bond on the NMR time scale. Of important note is that 1,2-diol **131d** and 1,3-diol **131g** give the corresponding imino boronate esters with an sp^2 hydridatisation for the boron atom. This is potentially due to an existing steric restriction of boron atom to approach to the nitrogen atom and as a consequence imino boronate esters **143** and **144** derived from larger diols **131d** and **131g** have a planar sp^2 boron atom with δ_B 30.45 and 27.68 ppm respectively. Therefore, these results clearly demonstrate that this chiral derivatization protocol is well suited for determination of

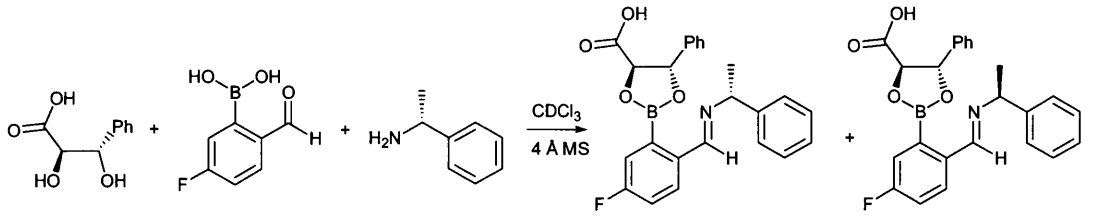
the enantiopurity of a wide range of chiral 1,2-, 1,3-, or 1,4-diols by ^{1}H NMR spectroscopy.

We then investigated whether ^{19}F NMR spectroscopic analysis could also be used to distinguish between the diastereoisomeric imino-boronate ester derivatives of diols **143-144a-g** as originally envisaged. Therefore, acquiring proton decoupled ^{19}F NMR spectra for the mixtures of diasteroisomeric boronate esters **143a-g** and **144a-g** revealed the presence of two well resolved peaks in a 1:1 ratio in each case, with a $\Delta\delta F$ splitting of their aryl-fluorine resonances for each diastereomeric pair ranging from 0.30 – 0.26 ppm. Therefore, these results clearly demonstrate that this new second generation CDA would enable both ^{1}H and ^{19}F NMR spectroscopic analysis to be used to determine the enantiomeric excess of the range of chiral diols assayed in a highly practical manner.

Table 4. 3: Chemical shift differences (Δδ) in the 300 MHz ^{1}H NMR and 400 MHz ^{19}F NMR spectra of 50:50 mixtures of **143a-g** and **144a-g** derived from chiral diols and amine **134**.

(*chiral*)-diol	boronate complexes		Δδ (δ 2- δ 3ppm)	δ ^{11}B NMR (ppm)	Δδ^{19}F NMR (ppm)
 (*rac*)-**131a**	 (*rac*,α-*S*)-**143a**	 (*rac*,α-*R*)-**144a**	0.05 (A) 0.10 (B)	17.31	0.260
 (*S*)-**131b**	 (*S* ,α-*S*)-**143b**	 (*S* ,α-*R*)-**144b**	0.10 (A) 0.01 (B)	17.91	0.200
 (*R*)-**131c**	 (*R* ,α-*S*)-**143c**	 (*R* ,α-*R*)-**144c**	0.15 (A) 0.20 (B) 0.10 (C)	12.68	0.300
 (*R,R,R,S*)-**131d**	 (*RRRS*,α-*S*)-**143d**	 (*RRRS*,α-*R*)-**144d**	0.10 (A) 0.15 (B) 0.20 (C)	30.45	0.030
 (*R,S*)-**131e**	 (3*R*,2*S*,α-*S*)-**143e**	 (3*R*,2*S*,α-*R*)-**144e**	0.30 (A) 0.05 (C) 0.15 (D) 0.55 (E) 0.01 (F)	15.05	0.110
 (*S,S*)-**131f**	 (2*S*,3*S*,α-*S*)-**143f**	 (2*S*,3*S*,α-*R*)-**144f**	0.35 (A) 0.15 (C)	13.82	0.160
 (*R*)-**131g**	 (*R* ,α-*S*)-**143g**	 (*R* ,α-*R*)-**144g**	0.12 (A) 0.05 (B)	27.68	0.080

We next investigated the detection limits of our new second generation CDA reagent for determining the enantiopurity of scalemic samples of diol **131e** using 2-formyl-4-fluorophenylboronic acid **134** as a complexing template and (*R*)-1-phenylethylamine as a chiral auxiliary.[2, 33] Therefore, samples of diol 2,3-dihydroxy-3-phenyl-propionic acid **131e** of 80%, 90% and 98% ee respectively, were treated with enantiopure (*R*)-1-phenylethylamine and 2-formyl-4-fluorophenylboronic acid **134** to afford three samples of their corresponding imino-boronate ester complexes (*S,R*)-**143e** and (*S,S*)-**144e**.



131e **134** **(*R*)-120** (3*R*,2*S*,*R*)-**143e** (3*R*,2*R*,*R*)-**144e**

Scheme 4. 27: Imino boronate complex derived from 2-formyl-4-fluorophenylboronic acid and (*R*)-1-phenylethylamine and scalemic diol **131e** of 80% ee, 90% ee and 98% ee.

Analysis of the ^{1}H NMR spectra of each sample revealed that the calculated diastereomeric excess for the resultant mixtures of (3*R*,2*S*,α-*R*)-**143e** and (2*R*,3*S*,α-*R*)-**144e** of 80%, 90% and 98% de were in excellent agreement with the known enantiomeric purity of the starting **131e** of 80%, 90% and 98% ee respectively (Figure 4.24). For example, the ^{1}H NMR resonances corresponding to proton A and A′ of the diols fragment of both diastereomers is shown in Figure 4.24, which clearly shows the decrease in intensity of A′ in going from 80% ee to 98% ee.

The values calculated are well within the accepted 5% error limit normally accepted for CDA analysis with NMR spectroscopy and indicated that no kinetic resolution had occurred in the derivatisation process. In view of this, de′s were in agreement with the known enantiomeric purities of the parent scalemic diol.

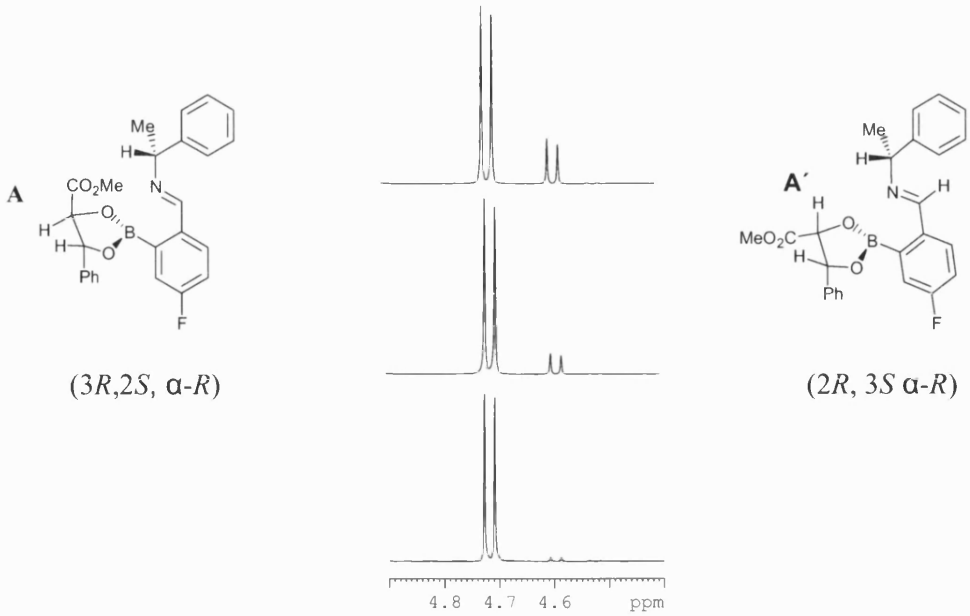
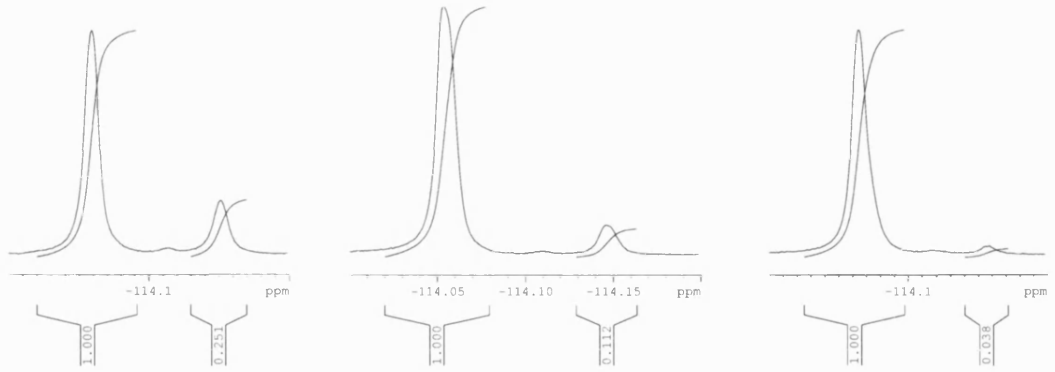


Figure 4. 23: ^{1}H NMR expansion of a mixture of (3*R*,2*S*,α-*R*)-2e and (2*R*,3*S*,α-*R*)-3e prepared from (3*R*,2*S*)-**136c** of 80%, 90% and 98% e.e.

We then analysed the diastereoisomeric excess of the same three samples of diasteroisomeric imino-boronate esters **143e** and **144e** using ^{19}F NMR spectroscopy which revealed values of 80%, 90% and 96% de respectively, These values were once again in excellent agreement with the 80%, 90% and 98% de values previously determined by ^{1}H NMR spectroscopic analysis, and the known 80%, 90% and 96% ee of the samples of scalemic diols originally used for derivatisation.



(a) 80% de (b) 90% de (c) 96% de

Figure 4. 24: ^{19}F NMR spectra and integrals of the diastereoisomers formed when 1 equivalent of enantiopure (*R*)-1-phenylethylamine and 1 equivalent of 2-formyl-4-fluorophenylboronic acid were 1 equivalent of **136c** of (a) 80% ee, (b) 90% ee, (c) 98% ee.

Therefore, these results clearly demonstrate that we had proven successful in our aim of developing a new CDA that enables the ee of chiral diols (and chiral amines) to be determined by both ^{1}H and ^{19}F NMR spectroscopic analysis.[1, 2, 32, 33]

4.5 CONCLUSIONS

This chapter has described the development of a simple and practically useful chiral derivatising agent for determining the ee of a wide range chiral amines and diols using ^{1}H and/or ^{19}F NMR spectroscopic analysis. We believe that the simplicity and speed of this approach and the wide range of substrates that it is capable of resolving warrants its consideration as a versatile method for determining the enantiomeric excess of amines and diols produced in asymmetric protocols. For diols, in the unlikely event that (*R*)-α-methylbenzylamine failed as a chiral auxiliary, we anticipate that substituting an alternative chiral amine in this three-component derivatization protocol would enable its ee to be determined.

4.6 REFERENCES

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Chiral high-performance liquid chromatography (chiral HPLC) analyses were done on a Schimazu 6A or 9A instrument using 4, 6 mm × 25 cm Daicel CHIRALPACK AD or OD columns.
Crystallographic measurements were recorded on a Nonius KappaCCD difractometer with MO-K_α radiation (λ = 0.71074 Å). All structures were solved by direct methods and refined on all F_2 data using the SHELX-97 suite of programmes.

For thin-layer chromatography (TLC) analysis, Macherey-Nagel TLC plates (silica gel 60 GF^{254}, 0.20 mm) were used to monitor all the reactions. Visualisation of these plates was by 254 nm UV light and/or $KMnO_4$, ninhydrin or PMA dips followed by gentle warming.

Flash chromatography was carried out using Davisil LC 60A silica gel (35-70 micron) purchased from Fluorochem. Samples were either pre-absorbed onto silica or loaded as saturated solutions in an appropriate solvent.

Mass spectra including high resolution spectra were recorded by the EPSRC national mass spectrometry service centre from Swansea, and University of Bath, using electron impact (EI), chemical ionization (CI), or electrospray (ES). A Micromass Quattro II triple quadrupole was used for low resolution measurements using ammonia as the CI reagent gas. A MAT900 high resolution spectrometer was used for high resolution measurements.

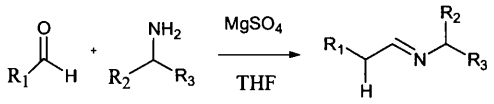
Melting points were recorded using a Büchi 535 melting point apparatus and the readings were taken from a mercury-in-glass thermometer and were reported uncorrected.

Optical rotations were performed on an Optical Activity LYD: AA-10 automatic polarimeter (c= 1.00).

Diastereomeric (de) and enantiomeric (ee) excesses values were determined by ^{1}H-NMR and HPLC unless stated otherwise.

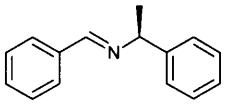
5.2 GENERAL PROCEDURE 1: Preparation of imines

General procedure 1: The required aldehyde (1 equiv.) was added dropwise to a stirred mixture of amine (1 equiv.) and $MgSO_4$ (1g) in anhydrous tetrahydrofuran at room temperature and was stirred for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated *in vacuum* to yield the product which was carried forward without the need for further purification.[1]



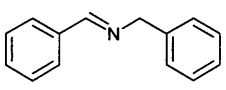
Scheme 5. 1: Preparation of imines.

(*S*)-*N*-Benzylidene-(1-phenyl-ethyl)-amine, 3 [2-8]



According to general procedure 1, benzaldehyde (0.23 mL, 2.33 mmol) and (*R*)-(+)-phenylethylamine (0.30 mL, 2.33 mmol) in THF after 12 hrs afforded yellowish oil in 99% yield (482 mg, 2.30 mmol). $[\alpha]_D^{22}$ = +72 (c 1.00 (Lit. data $[\alpha]_D^{25}$ = +74 (c 0.80, $CHCl_3$)). ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, *J* 6.8 Hz, 3H, C*H*$_3$), 4.40 (q, *J* 6.4 Hz, 1H, C*H*Me), 7.0-7.40 (m, 8H, Ar*H*), 7.80 (m, 2H, Ar*H*), 8.25 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.1 (*C*H_3), 70.2 (*C*HCH_3), 126.7, 128.1, 128.8, 128.9, 129.0, 130.1, 145.7, 160.0; IR ($CDCl_3$): ν 1630 (C=N) cm^{-1}; MS (*m/z*): Calc. $[M+ H]^+$; 210.1277, Found; $[M+ H]^+$; 210.1277, 210.1 (7) 129 (20), 167 (5), 165 (5), 147 (9), 105 (100), 79 (11), 77 (20), 51 (10) %.

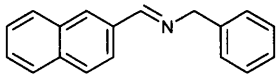
***N*-Benzylidenebenzylamine, 35**



According to general procedure 1, benzaldehyde (4.79 mL, 47 mmol) and benzylamine (5.13 mL, 47 mmol) in THF after 12 hrs afforded a yellow oil in 99% yield (9.01 g, 47 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 2H, NC*H*$_2$), 7.30-

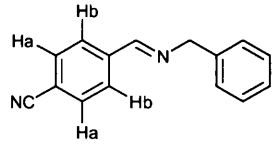
7.55 (m, 8H, Ph*H*), 7.95 (dd, *J* 2.6, 6.8 Hz, 2H, Ph*H*), 8.45 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.5 (*C*H_2Ph), 127.6, 129.0, 129.2, 129.5, 130.2, 136.7, 136.9, 162.6 (*C*=N); IR (neat) ν 1645 (C=N) cm^{-1}.

_N_-(2-naphthalenylmethylene)benzyl amine, 38



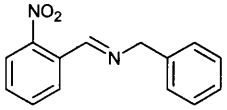
According to general procedure 1, 2-naphthaldehyde (364 mg, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a yellow solid in 99% yield (565 mg, 2.30 mmol), m.p: 78-82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (s, 2H, NCH_2), 7.00-7.30 (m, 5H, Ph*H*), 7.38 (t, *J* 4.7 Hz, 2H, Nap*H*), 7.80 (m, 3H, Nap*H*), 7.90 (d, *J* 6.8 Hz, 2H, Nap*H*), 8.40 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.6 (Ph*C*H_2), 124.4, 126.9, 127.3, 127.5, 127.5, 127.6, 128.4, 128.5, 128.9, 129.1, 130.6, 133.6, 135.2, 139.8, 162.47 (*C*=N); IR (KBr disk): ν 1636 (C=N) cm^{-1}; MS (*m/z*): Calc.; $[M+H]^+$: 246.1277, Found; $[M+H]^+$: 246.1276 (Cl^+), 246.2 [M+H] (100%).

_N_-(4-cyanobenzylidene)benzyl amine, 39



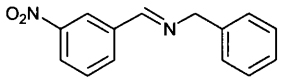
According to general procedure 1, 4-cyanbenzaldehyde (205 mg, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a yellow solid in 98% yield (493 mg, 2.28 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 2H, NCH_2), 7.10-7.30 (m, 5H, Ph*H*), 7.50 (dd, *J* 1.9, 6.4 Hz, 2PhH_a), 7.70 (dd, *J* 1.9, 6.4 Hz, 2PhH_b), 8.20 (s, 1H, *H*C=C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.4 (Ph*C*H_2), 114.6, 118.9 (*C*N), 127.1, 128.4, 129.0, 129.4, 132.4, 139.2, 139.9, 162.2 (*C*=N); IR (KBr disk): ν 2214 (C≡N), 1637 (C=N) cm^{-1}.

_N_-(2-nitrobenzylidene)benzyl amine, 40



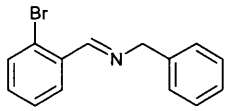
According to general procedure 1, 2-nitrobenzaldehyde (352 mg, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a yellow oil in quantitative (559 mg, 2.33 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (s, 2H, NC*H*$_2$), 7.10-7.33 (m, 5H, Ph*H*), 7.50 (dt, *J* 1.9, 8.3 Hz, 2H, Ar*H*), 7.95 (dd, *J* 1.1, 8.3 Hz, Ar*H*), 8.80 (t, *J* 1.1 Hz, 1H, *H*C=C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.7 (Ph*C*H$_2$), 124.8, 127.4, 128.4, 126.9, 129.1, 129.2, 131.2, 134.0, 136.5, 138.9, 162.5 (*C*=N); IR (neat): ν 1638 (C=N), 1523 (NO_2) cm^{-1}.

N-(3-nitrobenzylidene)benzyl amine, 41



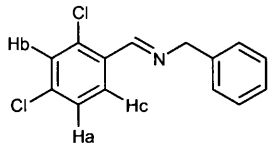
According to general procedure 1, 3-nitrobenzaldehyde (352 mg, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a pale yellow solid in 99% yield (554 mg, 2.30 mmol), m.p: 64-65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (s, 2H, NC*H*$_2$), 7.00-7.20 (m, 5H, Ph*H*), 7.30 (t, *J* 7.9 Hz, 1H, Ar*H*), 7.85 (d, *J* 7.5 Hz, 1H, Ar*H*), 7.99 (dd, *J* 2.3, 7.9 Hz, 1H, Ar*H*), 8.25 (s, 1H, *H*C=N), 8.40 (t, *J* 1.9 Hz, 1H, ArC*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.4 (Ph*C*H$_2$), 123.5, 125.6, 127.3, 128.5, 129.1, 130.1, 134.1, 138.2, 138.9, 149.0, 159.60 (*C*=N); IR (KBr disk): ν 1643 (C=N), 1554 (NO_2) cm^{-1}.

N-(2-bromobenzylidene)benzyl amine, 42



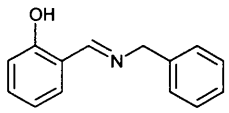
According to general procedure 1, 2-bromobenzaldehyde (0.27 mL, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a yellow solid in 98% yield (626 mg, 2.28 mmol). m.p: 37-39 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (s, 2H, C*H*$_2$Ph), 7.20-7.60 (m, 6H, Ar*H*), 7.33 (d, *J* 1.9 Hz, 1H, Ar*H*) 7.65 (d, *J* 7.9 Hz 1H, Ar*H*), 8.20 (d, *J* 7.7 Hz, 1H, Ar*H*), 8.90 (s, 1H, *H*C=C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.5 (Ph*C*H$_2$), 125.6, 127.5, 128.5, 129.0, 129.4, 130.3, 132.3, 135.7, 139.4, 161.4 (*C*=N); IR (KBr disk): ν 1638 (C=N conjugated) cm^{-1}.

N-(2,4-dichlorobenzylidene)benzyl amine, 43



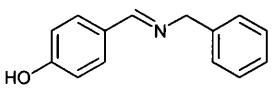
According to general procedure 1, 2,4-clorobenzaldehyde (408 mg, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a pale yellow solid isolated in 97% yield (596 mg, 2.26 mmol). m.p: 42-45 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (s, 1H, 2H, CH_2Ph), 7.15-7.30 (m, 5H, Ph*H*), 7.15-7.3 (m, 1H_a, PhH_a), 7.95 (d, *J* 8.5 Hz, 1H_b, PhH_b), 8.33 (d, *J* 1.9 Hz, 1H_c, PhH_c), 8.70 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.7 (Ph*C*H_2), 127.6, 127.9, 128.4, 128.70, 129.0, 130.0, 132.2, 136.1, 137.4, 139.3, 157.9 (*C*=N); IR (KBr disk): ν 1628 (C=N), 1095 (*p*-ClC_6H_4), 1047 (*o*-ClC_6H_4) cm^{-1}.

N-(2-hydroxybenzylidene)benzyl amine, 44



According to general procedure 1, salicylaldehyde (0.25 mL, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a yellow oil in 97% yield (477 mg, 2.27 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (s, 2H, NCH_2), 6.7 (t, *J* 7.5, 14.7 Hz, 2H, Ar*H*), 6.85 (d, *J* 8.3 Hz, 2H, Ar*H*), 7.10-7.35 (m, 5H, Ph*H*), 8.30 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 63.6 (Ph*C*H_2), 117.5, 119.3, 127.8 128.2, 129.0, 131.9, 132.8, 138.6, 161.7, 166.1 (*C*=N); IR (neat): ν ~3500 (OH), 1525 (C=N) cm^{-1}.

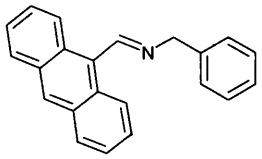
N-(4-hydroxybenzylidene)benzyl amine, 45



According to general procedure 1, 4-hydroxybenzaldehyde (284 mg, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a light yellow solid obtained in 98% yield (482 mg, 2.28 mmol), m.p: 200 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (s, 2H, NCH_2), 7.00-7.40 (m, 5H, Ph*H*), 6.75 (d, *J* 8.7 Hz, 2H, Ar*H*), 7.45 (dd, *J* 8.6 Hz, 2H, Ar*H*), 8.33 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ

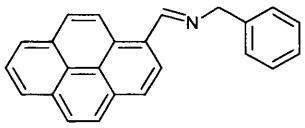
65.4 (Ph*C*H_2), 127.4, 128.4, 128.7, 128.9, 129.0, 131.2, 136.48, 139.61, 162.49 (*C*=N); IR (KBr disk): ν 3500-3700 (OH), 1644 (C=N), 1260-1180 (ArC) cm^{-1}.

_N_-(9-anthracenylmethylene)benzyl amine, 46



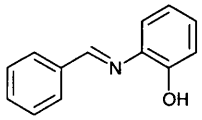
According to general procedure 1, 9-antracenaldehyde (480 mg, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a yellow-green solid isolated in 97% yield (667 mg, 2.26 mmol), m.p: 85-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 2H, NCH_2), 7.00-7.50 (m, 9H, Ar*H*), 7.90 (dd, *J* 2.2, 7.5 Hz, 2H, anthracen*H*), 8.45 (td, *J* 1.4, 9.4 Hz, 3H, anthracen*H*), 9.50 (s, 1H, *H*C=N); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.2 (Ph*C*H_2), 125.2, 125.7, 127.2, 127.6, 128.5, 128.6, 128.8, 129.1, 129.3, 129.9, 130.5, 131.7, 139.6, 161.6 (*C*=N); IR (KBr disk): ν 1635 (C=N) cm^{-1}.

_N_-(1-pyrenylmethylene)benzyl amine, 47



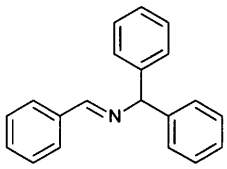
According to general procedure 1, 1-pyrenecarboxaldehyde (536 mg, 2.33 mmol) and benzylamine (0.25 mL, 2.33 mmol) in THF after 12 hrs afforded a light yellow solid obtained in 99% yield (744 mg, 2.30 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 2H, NCH_2), 7.20-7.60 (m, 5H, Ph*H*), 7.90-8.20 (m, 7H, pyren*H*), 8.55 (d, *J* 8.3 Hz, 1H, pyren*H*), 8.90 (d, *J* 9.0 Hz, 1H, pyren*H*), 9.20 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 66.5 (Ph*C*H_2), 123.0, 125.0, 125.4, 126.1, 126.3, 126.5, 127.0, 127.5, 127.9, 128.5, 128.9, 129.0, 129.2, 130.4, 131.0 , 131.7 , 133.3 , 140.0 , 161.2 (*C*=N); IR (KBr disk): ν 1631 (C=N) cm^{-1}.

_N_-2-(Benzylidene-amino)-phenol, 48



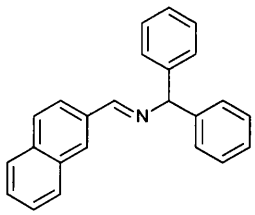
According to general procedure 1, benzaldehyde (0.23 mL, 2.33 mmol) and 2-hydroxyanilin (254 mg, 2.33 mmol) in THF after 12 hrs afforded a brown solid in 97% yield (450 mg, 2.28 mmol). m.p: 171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5 (s, 1H, O*H*), 6.85 (t, *J* 1.3 Hz, 1H, Ar*H*), 6.95 (d, *J* 1.5 Hz, 1H, Ar*H*), 7.2 (d, *J* 1.5 Hz, 1H, Ar*H*), 7.25 (m, 1H, Ar*H*), 7.35-7.40 (m, 3H, Ph*H*), 7.85 (m, 2H, Ph*H*), 8.65 (s, 1H, *H*C=N);^{13}C NMR (75.5 MHz, $CDCl_3$) δ 115.4, 120.5, 128.9, 129.2, 129.3, 129.4, 130.6, 135.9 , 136.3 , 152.7 , 157.5 (*C*=N); IR (neat): ν 1694 (C=N) cm^{-1}.

N-Benzylidenebenzhydrylamine, 7 [7, 9-11]



According to general procedure 1, benzaldehyde (1.10 mL, 10.91 mmol) and diphenylmethylamine (1.88 mL, 10.91 mmol) in THF after 12 hrs afforded a yellow solid in 95% yield (2.81 g, 10.36 mmol), m.p: 95-97 °C (Lit data 94-95 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H, Ph_2CH), 7.20-7.50 (m, 13H, Ar*H*), 7.80-7.90 (m, 2H, Ar*H*), 8.43 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 127.9 (*C*HPh), 128.9, 128.9, 129.0, 129.1, 130.5, 136.7, 144.3, 161.3 (*C*=N); IR (KBr disk): ν 1625 (C=N) cm^{-1}; MS (*m/z*): 271 (M^+, 44), 194 ([M-C_6H_5]$^+$, 12), 167 ([M-C_6H_4CH=N]$^+$, 100) %.

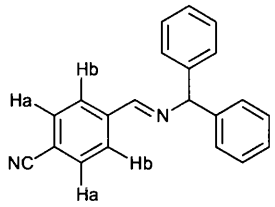
N-(2-naphthalenylmethylene)benzhydrylamine, 49 [7, 12]



According to general procedure 1, 2-naphthalenbenzaldehyde (748 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a pale yellow solid in 99% yield (738 mg, 2.30 mmol), m.p: 139-144 °C (Lit data 151-152 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (s, 1H, Ph_2CH), 7.10-8.00 (m, 12H, Ph*H*), 7.8-7.9 (m, 3H, Ar*H*), 8.1 (s, 1H, Ar*H*), 8.2 (dd, *J* 1.5, 8.5 Hz, 1H, Ar*H*), 8.60 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 64.0 (C*H*Ph_2), 126.0, 125.9, 128.0,

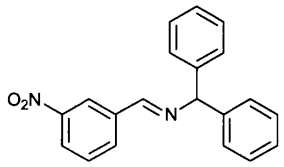
128.4, 125.9, 129.0, 133.5, 134.8, 135.9, 144.0, 163.7 (*C*=N); IR (KBr disk): ν 1954 cm^{-1}.

_N_-(4-cyano-benzylidene)benzhydrylamine, 50 [11]



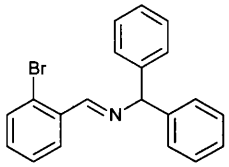
According to general procedure 1, 4-cyanbenzaldehyde (205 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a pale yellow solid in 96% yield (654 mg, 2.24 mmol), m.p: 113-115 °C (Lit data 117-118°C).[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H, *H*C=N), 7.10-7.50 (m, 10H, Ph*H*), 7.60 (dd, *J* 1.9, 8.3 Hz, 2H, 2PhH_a), 7.85 (dd, *J* 1.9, 8.3 Hz, 2H, 2PhH_b), 8.40 (s, 1H, N=C*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 78.5 (Ph_2*C*H), 114.4, 119.0 (*C*N), 127.7, 128.0, 128.8, 129.0, 129.2, 140.5, 143.7, 159.4 (*C*=N); IR (KBr disk): ν 2220 (Ar-C≡N), 1644 (C=N) cm^{-1}; MS (*m/z*): Calc. $[M+H]^+$; 297.1386, Found $[M+H]^+$; 297.1383, 296.3 (1), 219.2 (1), 190.1 (1), 168.2 (18), 167.0 (100), 165.0 (44), 152.0 (23), 139.0 (4), 128.0 (12), 115.1 (12), 89.1 (12), 77.2 (18), 63.1 (7), 51.2 (10) %.

_N_-(3-nitro-benzylidene)benzhydrylamine, 51 [11]



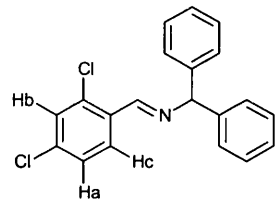
According to general procedure 1, 3-nitrobenzaldehyde (352 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a pale yellow solid in 99% yield (729 mg, 2.30 mmol), m.p: 139-142 °C (Lit data 136-137 °C).[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H, Ph_2C*H*), 7.10-7.45 (m, 10H, Ph*H*), 7.50 (m, 1H, Ar*H*), 8.10 (d, *J* 8.6 Hz, 1H, Ar*H*), 8.20 (d, *J* 8.2 Hz, 1H, Ar*H*), 8.40 (s, 1H, Ar*H*), 8.60 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 77.9 (Ph_2*C*H), 125.6, 127.69, 128.0, 128.7, 129.0, 130.0, 134.4, 138.3, 143.7, 149.0, 158.7 (*C*=N); IR (KBr disk): ν 1646 (C=N), 1524 (NO_2) cm^{-1}; MS (*m/z*): Calc. $[M^+]$; 316.1212, Found $[M^+]$; 316.1211.

N-(2-bromobenzylidene)benzhydrylamine, 52



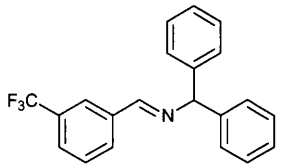
According to general procedure 1, 2-bromobenzaldehyde (0.27 mL, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a pale yellow solid in 95% yield (774 mg, 2.21 mmol), m.p: 104-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (s, 1H, Ph_2CH), 7.20-7.60 (m, 12H, Ph*H*), 7.70 (dd, *J* 1.3, 8.1 Hz, 1H, Ar*H*), 8.40 (dd, *J* 1.9, 7.9 Hz, 1H, Ar*H*), 9.0 (s, 1H, *H*C=C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 68.1 (Ph_2CH), 127.7, 128.1, 128.4, 129.1, 129.8, 132.5, 133.0, 133.5, 144.2, 145.4, 160.4 (*C*=N); IR (KBr disk): ν 1651 (C=N) cm^{-1}; M (*m/z*): Calc. [M^+]; 350.0539, Found [M^+]; 350.0540.

N-(2,4-dichlorobenzylidene)benzhydrylamine, 53 [7]



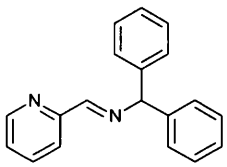
According to general procedure 1, 2,4-dichlorobenzaldehyde (408 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a pale brown solid obtained in 98% yield (785 mg, 2.28 mmol), m.p: 98-101 °C. (Lit data 101-102 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H, Ph_2CH), 7.10-7.40 (m, 12H, Ph*H* and ArH_a,H_b), 8.10 (d, *J* 8.5 Hz, 1H, ArH_c), 8.75 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 77.9 (Ph_2CH), 126.3, 126.8, 127.1, 127.9, 128.4, 129.3, 131.4, 135.4, 136.7, 143.1, 156.04 (*C*=N); IR (KBr disk): ν 1629 (C=N), 1098 (*p*-ClC_6H_4), 1051 (*o*-ClC_6H_4) cm^{-1}; MS (m/z): Calc. [M^+]; 340.0654, Found [M^+]; 340.0651.

N-(3-trifluoromethylbenzylidene)benzhydrylamine, 54



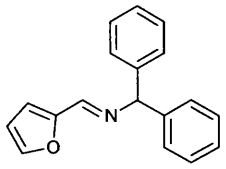
According to general procedure 1, 3-trifluorobenzaldehyde (408 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a pale orange solid in 98% yield (774 mg, 2.28 mmol), m.p: 74-75 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (s, 1H, Ph_2CH), 7.10-7.35 (m, 10H, Ph*H*), 7.45 (t, *J* 7.4 Hz, 1H, Ar*H*), 7.60 (d, *J* 8.3 Hz, 1H, Ar*H*), 7.95 (d, *J* 8.1 Hz, 1H, Ar*H*), 8.05 (s, 1H, Ar*H*), 8.4 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 78.3 (Ph_2CH), 125.5 (CF_3), 125.5, 127.4, 127.6, 128.0, 128.9, 129.0, 129.5, 132.0, 137.4, 143.8, 159.7 (*C*=N); IR (KBr disk): ν 1649 cm^{-1}; MS (*m/z*): Calc.$[M+H]^+$; 340.1308, Found; $[M+H]^+$; 340.1308.

N-(2-piridinylmethylene)benzhydrylamine, 55



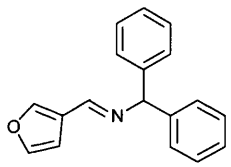
According to general procedure 1, 2-pyridinecarboxaldehyde (252 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a brown solid in 99% yield (628 mg, 2.30 mmol), m.p: 99-100 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H, Ph_2CH), 7.10-7.30 (m, 10H, Ph*H*), 7.40 (tdd, *J* 0.6, 1.7, 8.1 Hz, 1H, pyridine*H*), 7.7 (dt, *J* 1.1, 2.3 Hz, 1H, pyridine*H*), 8.2 (td, *J* 1.1, 2.1 Hz, pyridine*H*), 8.4 (s, 1H, *H*C=N), 8.5 (d, *J* 3.4 Hz, pyridine*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 78.1 (Ph_2CH), 121.7, 125.3, 127.6, 128.2, 128.9, 136.9, 143.7, 149.7, 155.1, 162.4 (*C*=N); IR (KBr disk): ν 1648 (C=N) cm^{-1}; M (*m/z*): Calc. $[M^+]$; 272.131349, Found $[M^+]$; 272.12569. 272.1 ($[M^+]$, 36), 254.0 ($[M^+$-18], 10) 195.1 ($[M^+$- $C_6H_5]$, 18), 193.0 ($[M^+$- $C_5H_5N]$, 64), 180.0 ($[M^+$- Ph-CH_2+H], 11), 168.1 ($[M^+$-104], 23), 167.1 ($[M^+$-PhCO], 100), 165.0 ($[M^+$- 107.1], 47) 152.0 ([M^+-120], 20) %.

N-(2-furanylmethylene)benzhydrylamine, 56



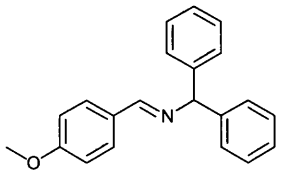
According to general procedure 1, 2-furaldehyde (223 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a brown solid in 100% yield (609 mg, 2.33 mmol), m.p: 97-100°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (s, 1H, Ph_2CH), 6.35 (q, *J* 1.7 Hz, 1H, 2-furan*H*), 6.60 (dd, *J* 0.7, 3.6 Hz, 1H, 2-furan*H*), 7.00-7.40 (m, 10H, Ph*H*), 7.40 (d, *J* 1.7 Hz, 1H, 2-furan*H*), 8.00 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 78.4 (Ph_2CH), 112.1, 115.0, 127.5, 128.2, 128.9, 143.7, 145.3, 150.1, 152.1 (*C*=N); IR (KBr disk): ν 1645.0 (CN) cm^{-1}; MS (*m/z*): Calc. [M$^+$]; 262.1226, Found [M$^+$]; 262.1229. 262.1 ([M$^+$], 100), 200.1 (1), 182.1 (13), 167.0 (16), 106.0 (3), 96.0 (19), 52.1 (39) %.

N-(3-furanylmethylene)benzhydrylamine, 57



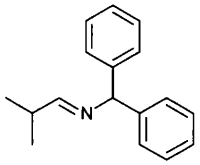
According to general procedure 1, 3-furaldehyde (223 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a light brown solid in 100% yield (609 mg, 2.33 mmol), m.p: 98-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (s, 1H, Ph_2CH), 6.80 (s, 1H, 3-furan*H*), 7.10-7.35 (m, 10H, Ph*H*), 7.40 (s, 1H, 3-furan*H*), 7.65 (s, 1H, 3-furan*H*), 8.30 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 78.3 (Ph_2CH), 108.7, 126.1, 127.3, 127.4, 128.1, 128.8, 144.1, 144.3, 145.8, 152.9 (*C*=N); IR (KBr disk): ν 1651.1 (CN) cm^{-1}; MS (*m/z*): Calc. [M+H]$^+$; 262.1266, Found [M+H]$^+$; 262.1266, 261.1 (8), 232.1 (1), 184.1 (1), 167.0 (100), 152.0 (29), 139.0 (5), 128.1 (9), 115.0 (7), 104.1 (2), 84.0 (8), 77.1 (9), 65.1 (5), 51.2 (7) %.

N-(4-methoxybenzylidene)benzhydrylamine, 58



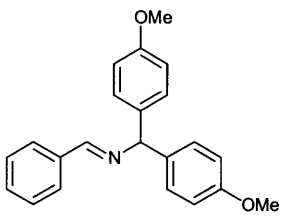
According to general procedure 1, 4-methoxybenzaldehyde (320 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded a pale yellow solid in 99% yield (693 mg, 2.30 mmol), m.p: 87-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H, CH_3O), 5.50 (s, 1H, Ph_2CH), 6.80 (m, 2H, Ar*H*), 7.00-7.04 (m, 10H, Ph*H*), 7.65 (m, 2H, Ar*H*), 8.20 (s, 1H, *HC*=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 56.0 (CH_3O), 68.1 (Ph_2CH), 114.1, 114.4, 127.2, 127.4, 128.4, 128.6, 128.9, 129.3, 129.8, 130.4, 130.6, 165.1 (*C*=N); IR (KBr disk): ν 1652 (C=N) cm^{-1}.

N-isobutylidenebenzhydrylamine, 59



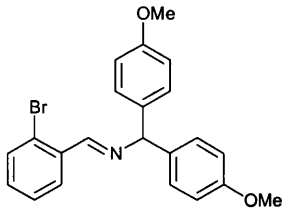
According to general procedure 1, *iso*-butyraldehyde (72 mg, 2.33 mmol) and diphenylmethylamine (0.40 mL, 2.33 mmol) in THF after 12 hrs afforded an orange oil in 98% yield (541 mg, 2.28 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (q, *J* 2.8 Hz, 6H, $2CH_3$), 2.5 (m, 1H, Me_2CH), 5.20 (s, 1H, Ph_2CH), 7.10-7.30 (m, 10H, Ph*H*), 7.6 (d, *J* 2.4 Hz, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.7 (isobutyl*C*H), 78.3 (Ph_2CH), 126.6, 128.3, 129.0, 143.5, 168.4 (*C*=N); IR (KBr disk): ν 1689 (C=N) cm^{-1}.

N-benzylidene-bis(4-methoxyphenyl)-methylamine, 60



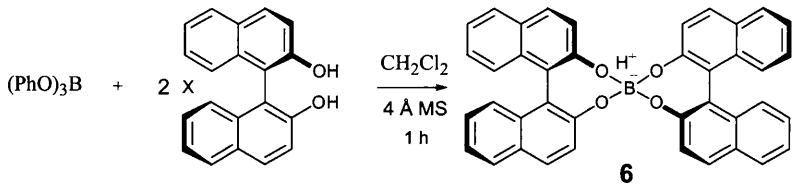
According to general procedure 1, benzaldehyde (0.13 mL, 1.27 mmol) and bis-(4-methoxyphenyl)-methylamine (308 mg, 1.27 mmol) in THF afford a yellow oil in >99% (415 mg, 1.25 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 6H, CH_3O), 5.45 (s, 1H, Ph_2CH), 6.80 (d, *J* 7.9 Hz, 4H, Ar*H*), 7.20 (d, *J* 7. 4 Hz, 4H, Ar*H*), 7.30 (t, *J* 3.7 Hz, 3H, Ar*H*), 7.75 (t, *J* 3.4 Hz, 2H, Ar*H*), 8.3 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.7 (CH_3O), 77.0 (*C*H), 114.2, 114.3, 128.9, 128.9, 129.1, 130.2, 131.1, 136.8, 136.8, 158.9, 160.8 (*C*=N); IR (nujol): ν 1649 (C=N) cm^{-1}.

N-(2-bromobenzylidene)- bis(4-methoxyphenyl)-methylamine, 61



According to general procedure 1, 2-bromobenzaldehyde (0.07 mL, 0.63 mmol) and bis-(4-methoxyphenyl)-methylamine (154 mg, 0.63 mmol) in THF afford a yellow oil in >99% (257 mg, 0.63 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 6H, CH_3O), 5.50 (s, 1H, Ph_2CH), 6.80 (d, *J* 8.8 Hz, 4H, Ar*H*), 7.10-7.30 (d, *J* 7. 4 Hz, 6H, Ar*H*), 7.50 (dd, *J* 1.3, 7.9 Hz, 3H, Ar*H*), 8.15 (dd, *J* 1.7, 7.7 Hz, 2H, Ar*H*), 8.7 (s, 1H, *H*C=N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.7 (CH_3O), 77.0 (*C*H), 114.3, 114.4, 125.6, 127.9, 128.8, 129.1, 129.6, 132.2, 133.4, 135.1, 136.5, 159.0, 159.7 (*C*=N).

5.3 PROCEDURE 2: Preparation of (*R*) or (*S*)-Lewis acid chiral boron complex 6 [7, 13]



Scheme 5. 2: Preparation of chiral boron complex **6**.

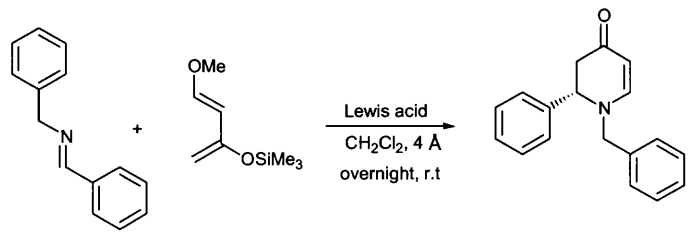
Procedure 2-Method A: The chiral Bronsted acid-assisted Lewis acid (BLA) was prepared *in situ* by mixing a 1:2 molar ratio of trimethyl borate (0.07 mL $(MeO)_3B$, 0.63

mmol, 1eq.) with (*R*) or (*S*)-binaphthol (363 mg BINOL, 1.27 mmol, 2 eq.) in CH_2Cl_2 at room temperature for 1 h, in the presence of 4 Å molecular sieves (1g) under a nitrogen atmosphere.

Procedure 2-Method B: The chiral Brönsted acid-assisted Lewis acid (BLA) was prepared *in situ* by mixing a 1:2 molar ratio of trimethyl borate (0.07 mL $(MeO)_3B$, 0.63 mmol, 1eq.) with (*R*) or (*S*)-binaphthol (363 mg BINOL, 1.27 mmol, 2 eq.) in toluene at -78°C for 1 h, in the presence of 4 Å molecular sieves (1g) under a nitrogen atmosphere.

Procedure 2-Method C: A 2 neck round botton flask and 10 mL pressure-equalized addition funnel (containing a cotton plug with 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with (*S*)-binaphthol (363 mg, 0.63 mmol). After addition of 4 mL of dichloromethane and trimethyl borate (0.07 mL, 0.63 mmol), the solution was brought to reflux (bath temperature 40°C) under a nitrogen atmosphere for 2 hrs.

5.4 PROCEDURES 3 AND 4: Asymmetric *Aza* Diels- Alder reactions of imines promoted by chiral Lewis catalyst 6 at room temperature and -78°C



35 **36** **37**

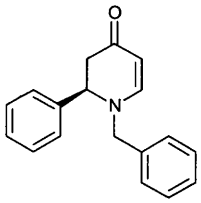
Scheme 5. 3: Preparation of benzyl-2-phenyl-2,3-dihydro-1H-pyridine-4-one **37** using chiral BINOL-boron catalyst **6**.

Procedure 3: The boron-BINOL catalyst prepared according to procedure 2-Method A was cooled down to 0 °C and Benzyl-benzylidene-amine **35** (0.12 mL, 0.63 mmol) was added and stirred at this temperature for 10 minutes. Then, the reaction mixture was warmed up to room temperature, and Danishefsky diene **36** (0.12 mL, 0.63 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature,

diluted with dichloromethane and filtered through Celite. The organic layer was washed twice with aqueous $NaHCO_3$ solution, and dried ($MgSO_4$). The solvent was then removed *in vacuum* to give a crude yellow oil.

Procedure 4: The boron-BINOL catalyst prepared according to procedure 2-Method A was cooled down to 0 °C and Benzyl-benzylidene-amine **35** (0.12 mL, 0.63 mmol) was added and stirred at this temperature for 10 minutes. Then, the mixture was cooled down to -78 °C, and Danishefsky diene **36** (0.12 mL, 0.63 mmol) was added dropwise. The reaction mixture was left to warm up overnight, diluted with dichloromethane and filtered through Celite. The organic layer was washed twice with aqueous $NaHCO_3$ solution, and dried ($MgSO_4$). The solvent was then removed *in vacuum* to give a crude yellow oil.

Benzyl-2-phenyl-2,3-dihydro-1H-pyridine-4-one, (*R*)-37 [7]



According to procedure 3, benzyl-2-phenyl-2,3-dihydro-1H-pyridine-4-one **37** was prepared at room temperature. Evaporation of the solvent and purification by column chromatography on silica gel (EtOAc: petroleum 40-60 °C, 1:1) gave the desired pyridone **37** in 60 % yield as a yellow oil (100 mg, 0.38 mmol) and 40% ee.

According to procedure 4, benzyl-2-phenyl-2,3-dihydro-1H-pyridine-4-one **37** was prepared at -78 °C to yield the desired benzyl-2-phenyl-2,3-dihydro-1H-pyridine-4-one **37** in 71% yield (118 mg, 0.45 mmol) and 73% ee.

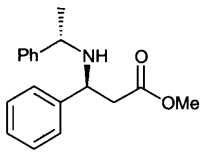
Separation of enantiomers with HPLC (Daicel Chiracel AD with 97:3, Hex:IPA, flow rate = 1mL/min) gave the major isomer with a t_r^R = 67.58 min and minor isomer with a t_r^S = 28.99 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (dd, *J* 8.3, 16.6 Hz, 1H, CH_AH_BCO), 2.80 (dd, *J* 7.2, 16.2 Hz, 1H, CH_AH_BCO), 4.05 (d, *J* 15.1 Hz, 1H, CH_AH_BPh), 4.25 (d, *J* 15.1 Hz, 1H, CH_AH_BPh), 4.40 (t, *J* 7.5 Hz, 1H, PhC*H*N), 5.00 (d, *J* 7.9 Hz, 1H, COC*H*=CH), 7.05 (d, *J* 1.9 Hz, 1H, COCH=C*H*), 7.10-7.40 (m, 10H,

Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 44.1 (*C*H_2CO), 57.7 (*C*HNH), 61.1 (*C*H_2Ph), 99.1 (*C*=C), 127.5, 128.1, 128.6, 128.8, 129.4, 129.5, 136.3, 139.0, 154.7 (C=*C*), 190.8 (*C*=O); MS (m/z): Calc. $[M+1]^+$; 264.1383, Found $[M+1]^+$; 264.1382. IR (neat): ν > 3000 (Csp^2-H), < 3000 (Csp^3-H), 2000-1600 (ArC-H), 1664.7 (C=O), 1351.6-1000 (C-N) cm^{-1}.

5.5 GENERAL PROCEDURE 5: Yamamoto enantioselective Mannich-Type reactions of imines promoted by chiral boron complex 6

General procedure 5: To the (*S*) or (*R*)-chiral boron complex **6** which prepared by procedure 2-Method A was added 2 mL of dichloromethane, 5 mL of toluene, and the corresponding imine (0.12 mL, 0.63 mmol) at 0 °C, and the yellow suspension was stirred at 0 °C for 10 min. After that, the suspension was cooled down to -78 °C. The mixture was stirred for a further 10 minutes at this temperature before *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) was added dropwise at -78 °C. After stirring for 20 hrs, the mixture was brought to r.t and the solution was washed with water (2 X 30 mL) and saturated $NaHCO_3$ (2 X 30 mL), and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding products (*S,S*)-**63** and (*R,S*)-**63**.

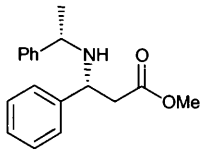
Methyl-3-(*S*)-((S)-phenylethylamino)- 3-phenylpropionate, (*S,S*)-63 [7, 14, 15]



According to procedure 5, (*S*)-*N*-Benzylidene-(1-phenyl-ethyl)-amine **3** (132 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 20 h in the presence of (*S*)-chiral boron complex **6** (363 mg, 1.27 mmol), at -78 °C to afford the crude β-amino ester (*S,S*)-**63.** Column chromatography (Et_2O: petroleum 40-60 °C, 2:8 ratio, Rf = 0.06) afforded the title compound (*S,S*)-**63** as a yellow oil in 53% yield (95.1 mg, 0.33 mmol) and 45% de. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* 6.5 Hz, 3H, CH_3), 2.65 (dd, *J* 6.6, 15.5 Hz, $CH_AH_BCO_2CH_3$), 2.75 (dd, *J* 7.7, 15.3 Hz, $CH_AH_BCO_2CH_3$), 3.55 (s, 3H, CH_3O), 3.70 (m, 1H, C*H*Me), 4.15 (q, *J*

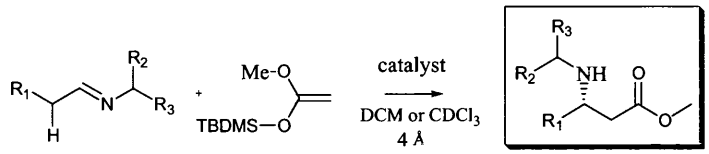
6.5, 6.6 Hz, 1H, C*H*NH), 7.00-7.40 (m, 10H, PhC*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 22.6 (*C*H_3), 42.8 (*C*H_2COOMe), 52.0 (*C*HNH), 55.1 (*C*H_3O), 57.0 (*C*HCH_3), 127.0, 127.2, 127.8, 128.7, 129.1, 131.1, 131.0, 143.0, 146.2, 172.4 (*C*=O); IR (CH_2Cl_2) ν 1733 (RCOOMe), 3407 (NH) cm^{-1}; MS (*m/z*): 283 (M^+), 268 (78), 210 (60), 178 (21), 121 (56), 106 (100), 77 (21).

Methyl-3-(*R*)-((S)-phenylethylamino)- 3-phenylpropionate, (*R,S*)-63 [7, 14, 15]



According to procedure 5, (*S*)-*N*-Benzylidene-(1-phenyl-ethyl)-amine **3** (132 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 20 h in the presence of (*R*)-chiral boron complex **6** (363 mg, 1.27 mmol) at -78 °C to afford the β-amino ester (*R,S*)-**63.** Evaporation of the solvent and isolation of the resultant crude by flash chromatography (Et_2O:petroleum 40-60 °C, 2:8 ratio, Rf = 0.06) afforded a yellow oil in 65% yield (116 mg, 0.41 mmol) and 72% de. Spectroscopic data is similar to **(*S,S*)-63**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, *J* 6.5 Hz, 3H, CH_3), 2.66 (dd, *J* 5.9, 14.5 Hz, CH_AH$_B$CO$_2$CH$_3$), 2.85 (dd, *J* 7.8, 15.7 Hz, CH$_A$H$_B$CO$_2$CH$_3$), 3.45 (s, 3H, C*H*$_3$O), 3.70 (m, 1H, C*H*Me), 4.20 (q, *J* 5.9, 7.8 Hz, 1H, C*H*NH), 7.00-7.40 (m, 10H, PhC*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 21.8 (*C*H_3), 41.0 (*C*H_2COOMe), 52.3 (*C*HNH), 55.7 (*C*H_3O), 57.8 (*C*HCH_3), 127.0, 127.3, 127.9, 129.0, 129.1, 131.0, 131.4, 143.5, 146.3, 172.5 (*C*=O); IR (CH_2Cl_2) ν 1732 (RCOOMe), 3406 (NH) cm^{-1}.

5.6 GENERAL PROCEDURES 6-9: Standard enantioselective Mannich-Type reactions of imines promoted by chiral boron complex 6



62

Scheme 5. 4: Preparation of β-amino acid ester.

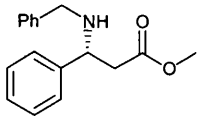
General procedure 6: To the chiral boron complex **6** prepared according to procedure 2-Method A, imine (0.63 mmol, 1eq.) was added. The mixture was stirred for a further 10 minutes at this temperature. To the reaction mixture 1-(*tert*-Butyldimethylsilyloxy)-1-methoxy ethene **62** (1 g.) was added dropwise. After stirring for 24 hrs at room temperature, the reaction mixture was diluted with dichloromethane and filtered through Celite. The organic layer were washed twice with 30 mL of aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was then removed *in vacuum* to give a crude yellow oil.

General procedure 7: To the chiral boron complex **6** prepared according to procedure 2-Method A, imine (0.63 mmol, 1eq.) was added. The mixture was stirred for a further 10 minutes at this temperature. The reaction mixture was cooled down to -78 °C, and then 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (1, 2 or 3 eq.) was added dropwise. After stirring for 24 hrs, the reaction mixture was diluted with dichloromethane and filtered into a separating funnel. The organic layer were washed twice with 30 mL of aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was then removed *in vaccum* to give a crude yellow oil.

General procedure 8: Racemic β-amino esters were derived from the overnight reaction at room temperature between imine (0.63 mmol) and *tert*-Butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) in the presence of trimethyl borate (0.07 mL, 0.63 mmol).

General procedure 9: To the chiral boron complex prepared according to procedure 2-Method B, imine (0.63 mmol, 1 eq.) was added. The mixture was stirred for further 10 minutes before the addition of *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (1.27 mmol, 2 eq.) and the *aza* Mannich-type reaction was performed in 24 hrs at room temperature.

(*R*)-Methyl 3-(benzylamino)-3-phenylpropanoate, (*R*)-64 [13]



According to general procedure 6, *N*-benzylidenebenzylamine 35 (0.12 mL, 0.63 mmol) and 1, 2 and 3 equivalents of *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** were reacted at room temperature to afford the title β-amino ester **(*R*)-64** as a colourless oil in;

- 50% yield (85 mg, 0.37 mmol) and 26% ee from 1 equivalent of *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** after stirring for 12 hrs.
- 81% yield (138 mg, 0.51 mmol) and 26% ee from 2 equivalents of *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** after stirring for 24 hrs.
- >99% yield (169 mg, 0.63 mmol) and 26% ee derived from 3 equivalents of *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** after stirring for 24 hrs.

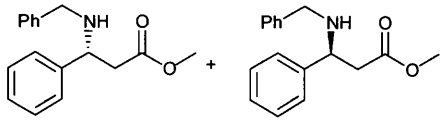
According to general procedure 7, the same β-amino acid ester **(*R*)-64** , derived from *N*-benzylidenebenzylamine **35** (0.12 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** was obtained in;

- 48% yield and 47% ee from 1 equivalent of *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** after stirring overnight at -78 °C.
- 77% yield and 50% ee from 2 equivalents of *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** after stirring for 24 hrs at -78 °C.

According to general procedure 9, the title compound **(*R*)-64** was obtained in 43% yield (73 mg, 0.27 mmol) and 31% ee. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.20) afforded the isolated title β-amino esters **(*R*)-64**. HPLC (Daicel Chiracel OD with 95:5 Hex:IPA, flow rate = 1 mL/min) t_r^R = 7.47 and t_r^S = 11.63 min; ($[\alpha]_D^{20}$ +11.9 (c 1.00, $CHCl_3$)), ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 1H, N*H*), 2.55

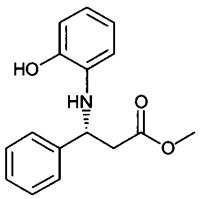
(dd, *J* 5.3, 15.6 Hz, 1H, C*H*$_A$H$_B$CO$_2$CH$_3$), 2.65 (dd, *J* 8.7, 15.6 Hz, 1H, CH$_A$*H*$_B$CO$_2$CH$_3$), 3.45 (d, *J* 13.2 Hz, 1H, C*H*$_A$H$_B$Ph), 3.60 (s, 3H, C*H*$_3$O), 3.68 (d, *J* 13.2 Hz, 1H, CH$_A$*H*$_B$Ph), 4.10 (dd, *J* 5.3, 8.7 Hz, 1H, C*H*NH), 7.00-7.40 (m, 10H, Ph*H*); ^{13}C (75.5 MHz, CDCl$_3$) δ 43.2 (*C*H$_2$COCH$_3$), 51.7 (*C*H$_3$O), 52.1 (*C*H$_2$Ph), 59.2 (*C*HNH), 127.3, 127.5, 128.0, 128.6, 128.8, 129.1, 140.6, 142.8, 1722.7 (*C*=O); IR (neat) ν 1732 cm $^{-1}$. MS (*m/z*): 270.3 (1), 239.2 (1), 226.2 (1), 211.2 (1), 197.3 (1), 196.2 (100), 194.0 (20), 179.2 (7), 178.1 (51), 165.1 (11), 153.2 (1), 145.9 (9), 139.1 (3), 131.1 (19) %.

(*rac*)-Methyl 3-(benzylamino)-3-phenylpropanoate, (*rac*)-64 [13]



According to general procedure 8, racemic Mannich-type adduct **(*rac*)-64** was prepared from *N*-benzylidenebenzylamine **35** (0.24 mL, 1.27 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.24 mL, 1.27 mmol) using trimethyl borate (0.14 mL, 1.27 mmol) as the Lewis acid, resulting in the formation of the title compound **(*rac*)-64** in 45% yield (115 mg, 0.43 mmol). Spectroscopic data is identical to **(*R*)-64.**

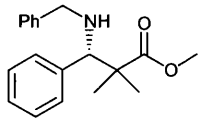
(*R*)-3-(2-Hydroxy-phenylamino)-3-phenyl-propanoate, (*R*)-77 [16]



According to general procedure 6, *N*-2-(Benzylidene-amino)-phenol **48** (81 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) were reacted overnight at room temperature to afford the title β-amino ester **(*R*)-77**. Column chromatography (Et$_2$O:petroleum, 2:3, Rf = 0.14) afforded the title β-amino ester **(*R*)-77** as a yellow oil in 93% yield (160 mg, 0.59 mmol) and 22% ee. HPLC (Column Chiralpack AD with 90:10, Hex:IPA, flow rate = 1mL/min) t_r^R = 15.71 and t_r^S = 13.32 min. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.60 (dd, *J* 5.6, 15.5 Hz, 1H, C*H*$_A$H$_B$CO$_2$CH$_3$), 2.70 (dd, *J* 8.5, 15.5 Hz, 1H, CH$_A$*H*$_B$CO$_2$CH$_3$), 3.50 (s, 3H, C*H*$_3$O), 4.55 (dd, *J* 5.6, 8.5 Hz, 1H, C*H*NH), 6.30 (m, 1H, ArC*H*), 6.50 (m, 2H, ArC*H*), 6.60 (m, 1H, ArC*H*), 7.00-7.40

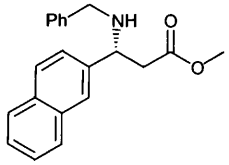
(m, 5H, ArC*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 42.1 (*C*H_2CO), 52.0 (*C*H_3O), 54.7 (*C*HNH), 127.5, 128.0, 128.5, 128.8, 129.7, 129.9, 133.8, 134.5, 138.4, 140.2, 172.3 (*C*=O); MS (*m/z*): Calc. $[M+H]^+$; 272.1281, Found $[M+1]^+$; 272.1266.

(*R*)-Methyl 3-(benzylamino)-2,2-dimethyl-3-phenylpropanoate, (*R*)-80 [17, 18]



According to general procedure 6, *N*-Benzylidenebenzylamine **35** (0.12 mL, 0.63 mmol) and 1-methoxy-2-methyl-1-trimethyl-1-(trimethylsiloxy)propene **79** (0.13 mL, 0.63 mmol) were reacted for 24 hrs at room temperature to afford the crude of β-amino ester **(*R*)-80**. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.20) afforded the title β-amino ester as a yellow oil in 71% yield (134 mg, 0.45 mmol) and 6% ee. HPLC (Column Chiralpack AD with 99:1, Hex:IPA, flow rate = 1mL/min) t_r^R = 6.62 and t_r^S = 8.46 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.80 (br s, 1H, N*H*), 3.35 (d, *J* 12.6 Hz, 1H, CH_AH$_B$Ph), 3.60 (s, 3H, CH_3O), 3.65 (d, *J* 12.6 Hz, 1H, CH$_A$$H_B$Ph), 3.80 (s, 1H, C*H*NH), 7.00-7.20 (m, 10H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 19.9 (*C*H_3), 24.5 (*C*H_3), 47.9 (*C*HMe_2), 51.9 (*C*H_3O), 52.2 (*C*HPh), 68.1 (*C*HNH), 127.2, 127.9, 128.3, 128.6, 128.7, 129.4, 139.6, 140.9 (*C*=O); IR (KBr disc): ν 1734 cm^{-1}; MS (*m/z*): Calc. $[M+1]^+$; 298.1802, Found $[M+1]^+$; 298.1790.

(*R*) -Methyl 3-(benzylamino)-3-(2-naphthalenyl)-propanoate, (*R*)-81

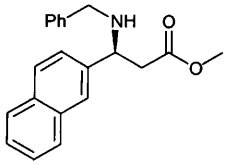


According to gereral procedure 6, *N*-(2-naphthelenylmethylene)benzylamine **38** (155 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-81** as a yellow oil in 87% yield (176 mg, 0.55 mmol) and 22% ee.

Column chromatography (Et_2O: petroleum, 3:7, Rf = 0.40) afforded the title β-amino ester **(*R*)-81** as a yellow oil. HPLC (Column Chiralpack OD with 95:5, Hex:IPA, flow rate = 1mL/min) t_r^R = 11.91 and t_r^S = 13.34 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s,

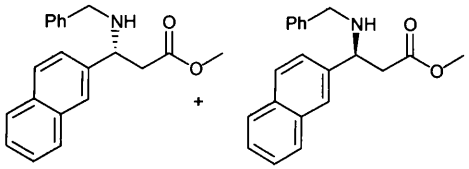
1H, N*H*), 2.65 (dd, *J* 5.3, 15.4 Hz, 1H, CH_AH$_B$CO$_2$CH$_3$), 2.78 (dd, *J* 8.7, 15.7 Hz, 1H, CH$_A$$H_BCO_2CH_3$), 3.48 (d, *J* 13.2 Hz, 1H, CH_AH$_B$Ph), 3.58 (s, 3H, CH_3O), 3.60 (d, *J* 13.2 Hz, CH$_A$$H_B$Ph), 4.20 (dd, *J* 5.3, 8.7 Hz, 1H, C*H*NH), 7.00-7.50 (m, 12H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.1 (*C*H$_2$COOMe), 51.7 (*C*H$_3$O), 52.1 (*C*H$_2$), 59.3 (*C*HNH), 123.2, 125.3, 126.2, 126.5, 126.7, 127.4, 127.5, 128.1, 128.3, 128.6, 128.8, 129.0, 129.5, 133.5, 133.8, 172.6 (*C*OOMe); IR (neat): ν 3500-3300 (NH), 1731 (RCOOMe), 850-700 (NH) cm^{-1}; MS (*m/z*): 319 ([M$^+$], 1), 287.2 ([M$^+$-CH$_3$O], 4), 286.2 ([O$_2$], 14), 257.2 ([M$^+$-CH$_3$COO+2H], 3), 246.2 ((M$^+$-52), [M$^+$-COOMe]), 244.2 ([M$^+$-CH$_2$COOCH$_3$+H], 4), 228.2 ([M$^+$-Ph-CH+H], 9), 226.2 ([M$^+$-Ph-CH$_2$+H], 3), 154.2 ([M$^+$-164.8], 28), 153.1 ([M$^+$-165.9], 14), 106.1 ([M$^+$-Ph-CH-NH$_2$] [M$^+$-Nap-CH$_2$COOMe], 41), 91.1 ([M$^+$-amine, C$_{14}$H$_{14}$O$_2$N], 100), 77.2 ([M$^+$-246.8], 12), 65.2 ([M$^+$-253.8], 18) %.

(*S*)-Methyl 3-(benzylamino)-3-(2-naphthalenyl)-propanoate, (*S*)-81



According to general procedure 7, *N*-(2-naphthelenylmethylene)benzylamine **38** (155 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester **(*S*)-81** as a yellow oil in 73% yield (148 mg, 0.46 mmol) and 32% ee (*S*). Spectroscopic data is identical to **(*R*)-81**.

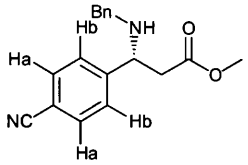
(*rac*)-Methyl 3-(benzylamino)-3-(2-naphthalenyl)-propanoate, (*rac*)-81



According to general procedure 9, racemic Mannich-type adduct was prepared from stoichiometric amounts of *N*-(2-naphthelenylmethylene)benzylamine **38** (155 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) using trimethyl borate (0.07 mL, 0.63 mmol), resulting in the formation of the title

compound ***(rac)*-81** in 56% yield (113 mg, 0.35 mmol). Spectroscopic data is identical to ***(R)*-81**.

(R) -Methyl 3-(benzylamino)-3-(4-cyanophenyl)-propanoate, *(R)*-82

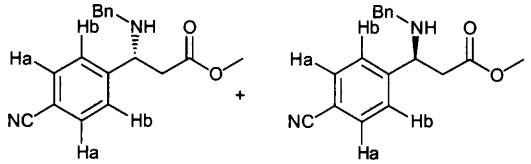


According to general procedure 6, *N*-(4-cyanobenzylidene)benzylamine **39** (139 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester ***(R)*-82** as a yellow oil in 89% yield (164 mg, 0.56 mmol) and 33% ee.

According to general procedure 7, *N*-(4-cyanobenzylidene)benzylamine **39** (139 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester ***(R)*-82** as a yellow oil in 68% yield (92 mg, 0.43 mmol) and 64% ee.

Column chromatography (Et_2O: petroleum 40-60°C, 3:7, Rf = 0.15) afforded the isolated title β-amino esters ***(R)*-82**. HPLC (Daicel Chiracel OD with 99:1 Hex:IPA, flow rate = 1 mL/min) t_r^R = 6.34 and t_r^S = 7.14 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 1H, N*H*), 2.50 (dd, *J* 5.7, 15.8 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.60 (dd, *J* 8.3, 15.8 Hz, 1H, $CH_AH_BCO_2CH_3$), 3.44 (d, *J* 13.2 Hz, 1H, CH_AH_BPh), 3.56 (s, 3H, CH_3O), 3.57 (d, *J* 13.2 Hz, 1H, CH_AH_BPh), 4.10 (dd, *J* 5.7, 8.3 Hz, 1H, C*H*NH), 7.15-7.30 (m, 5H, Ph*H*), 7.43 (d, *J* 8.3 Hz, 2ArH_a), 7.58 (d, *J* 8.3 Hz, 2ArH_b); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.2 (CH_2CO), 51.7 (CH_3O), 52.1 (CH_2Ph), 59.2 (*C*HNH), 118.2, 127.4, 127.9, 128.0, 128.8, 131.8, 140.5, 142.7, 172.69 (*C*=O); IR (KBr disk): ν 3300-3450 (NH), 3173 (RCOOMe) cm^{-1}; MS (*m/z*): Calc. $[M+1]^+$; 295.1441, Found; $[M+1]^+$; 295.1443.

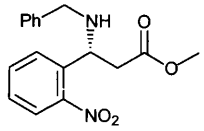
(rac)-Methyl 3-(benzylamino)-3-(4-cyanophenyl)-propanoate, *(rac)*-82



According to general procedure 8, racemic Mannich-type adduct ***(rac)*-82** was prepared from stoichiometric amounts of the required imine and *tert*-butyldimethylsilyloxy-1-

methoxy ethene **62** (0.14 mL, 0.63 mmol), using trimethyl borate (0.07 mL, 0.63 mmol), resulting in the formation of the title compound ***(rac)*-82** in 52% yield (96 mg, 0.33 mmol). Spectroscopic data is identical to ***(R)*-82**.

(R)-Methyl 3-(benzylamino)-3-(2-nitrophenyl)-propanoate, *(R)*-83

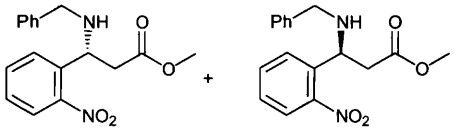


According to general procedure 6, *N*-(2-nitrobenzylidene)benzylamine **40** (152 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester ***(R)*-83** as a yellow oil in 74% yield (147 mg, 0.47 mmol) and 30% ee.

According to general procedure 7, *N*-(2-nitrobenzylidene)benzylamine **40** (152 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester ***(R)*-83** as a yellow oil in 66% yield (131 mmol, 0.42 mmol) and 52% ee.

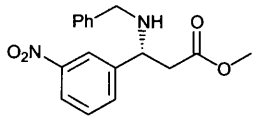
Column chromatography (Et_2O: petroleum 40-60° C, 2:3, Rf = 0.18) afforded the title isolated β-amino esters ***(R)*-83**. HPLC (Daicel Chiracel OD with 99:1 Hex:IPA, flow rate = 1 mL/min) t_r^R = 5.76 and t_r^S = 6.95 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 1H, N*H*), 2.64 (dd, *J* 8.7, 16.2 Hz, 1H, CH_AH$_B$CO$_2$CH$_3$), 2.82 (dd, *J* 4.1, 16.2 Hz, 1H, CH$_A$$H_B$ CO$_2$CH$_3$), 3.45 (d, *J* 12.8 Hz, 1H, CH_AH$_B$Ph), 3.60 (s, 3H, CH_3O), 3.51 (d, *J* 12.8 Hz, CH$_A$$H_B$Ph), 4.55 (dd, *J* 4.1, 8.7 Hz, 1H, C*H*NH), 7.10-7.30 (m, 5H, Ph*H*), 7.35 (td, *J* 1.5, 8.7 Hz, 1H, Ar*H*), 7.57 (td, *J* 1.5, 7.5 H, Ar*H*), 7.75 (dd, *J* 1.5, 8.3 Hz, 1H, Ar*H*), 7.85 (dd, 1.5, 7.9 Hz, 1H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 42.0 (*C*H$_2$COCH$_3$), 52.3 (*C*H$_3$O), 52.3 (*C*H$_2$NH), 54.4 (*C*HNH), 123.1, 124.6, 127.6, 127.9, 128.5, 128.8, 128.8, 129.3, 133.5, 133.8, 172.2 (*C*=O); MS (*m/z*): 315.2 (9), 304.2 (19), 284.2 (5), 270.2 (16), 253.2 (4), 211.1 (4), 196.1 (8), 180.0 (6), 163.1 (16), 146.0 (4), 125.1 (7), 108.0 (38), 91.1 (4), 84.2 (9), 52.2 (35), 44.2 (2) %.

(*rac*)-Methyl 3-(benzylamino)-3-(2-nitrophenyl)-propanoate, (*rac*)-83



According to general procedure 8, racemic Mannich-type adduct **(*rac*)-83** was prepared from stoichiometric amounts of the required imine and *tert*-butyldimethylsilyloxy-1-methoxy (0.14 mL, 0.63 mmol), using trimethyl borate (0.07 mL, 0.63 mmol) as the Lewis acid, resulting the formation of the title compound **(*rac*)-83** in 45% yield (89 mg, 0.28 mmol). Spectroscopic data is identical to **(*S*)-83**.

(*R*)-Methyl 3-(benzylamino)-3-(3-nitrophenyl)-propanoate, (*R*)-84.



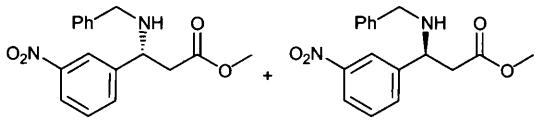
According to general procedure 6, *N*-(3-nitrobenzylidene)benzylamine **41** (152 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-84** as a yellow oil in 90% yield (179 mg, 0.57 mmol) and 31% ee.

According to general procedure 7, *N*-(3-nitrobenzylidene)benzylamine **41** (152 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-84** as a yellow oil in 75% yield (149 mg, 0.47 mmol) and 54% ee.

Column chromatography (Et_2O: petroleum 40-60 °C, 2:3, Rf = 0.18) afforded the title β-amino ester **(*R*)-84**. HPLC (Daicel Chiracel OD with 95:5 Hex:IPA, flow rate = 1 mL/min) t_r^R = 17.14 and t_r^S = 20.86 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 1H, N*H*), 2.63 (dd, *J* 5.3, 15.8 Hz, 1H, CH_AH$_B$CO$_2$CH$_3$), 2.60 (dd, *J* 8.3, 15.8 Hz, 1H, CH$_A$$H_BCO_2CH_3$), 3.54 (d, *J* 13.2 Hz, 1H, CH_AH$_B$Ph), 3.64 (d, *J* 13.2 Hz, 1H, CH$_A$$H_B$Ph), 3.64 (s, 3H, C$H_3$O), 4.24 (dd, *J* 5.3, 8.3 Hz, 1H, C*H*NH), 7.20-7.40 (m, 5H, Ph*H*), 7.52 (t, *J* 7.9, 15.8 Hz, Ar*H*), 7.72 (dt, *J* 1.1, 7.9 Hz, 1H, Ar*H*), 8.14 (q, *J* 1.13, 2.3 Hz, 1H, Ar*H*), 8.27 (t, *J* 1.9 Hz, 1H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 42.9 (*C*H$_2$CO), 51.8 (*C*H$_3$O), 52.3 (*C*H$_2$NH), 58.6 (*C*HNH), 122.7, 123.1, 127.6, 128.5, 128.9, 129.1, 134.0, 140.0, 145.3, 149.0, 172.0 (*C*=O); IR (KBr disk): ν 3237 (NH),

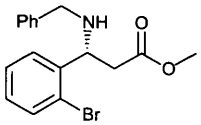
1742.7 (RCOOMe), 850-700 (N-H) cm^{-1}; MS (*m/z*): Calc. $[M+H]^+$; 315.1339, Found $[M+H]^+$; 315.1342.

(*rac*)-Methyl 3-(benzylamino)-3-(3-nitrophenyl)-propanoate, (*rac*)-84



According to general procedure 8, racemic Mannich-type adduct was prepared from the stoichiometric amounts of the required imine **41** (152 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy (0.14 mL, 0.63 mmol), using trimethyl borate (0.07 mL, 0.633 mmol) as the Lewis acid, resulting the formation of the title isolated compound in in 47% yield (95.5 mg, 0.30 mmol). Spectroscopic data is identical to **(*R*)-84**.

(*R*)-Methyl 3-(benzylamino)-3-(2-bromophenyl)-propanoate, (*R*)-85



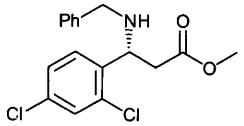
According to general procedure 6, *N*-(2-bromobenzylidene)benzylamine **42** (173 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-85** as a yellow oil in 95% yield (209 mg, 0.60 mmol) and 34% ee.

According to gereral procedure 6, *N*-(2-bromobenzylidene)benzylamine **42** (173 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester **(*R*)-85** as a yellow oil in 82% yield (181 mg, 0.52 mmol) and 66% ee (*R*).

Column chromatography (EtOAc: petroleum 40-60 °C, 2:3) afforded the title β-amino ester **(*R*)-85**. HPLC (Column Chiralpack OD-H with 99:1, Hex:IPA, flow rate = 1mL/min) t_r^R = 9.22 and t_r^S = 9.89 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 1H, N*H*), 2.52 (dd, *J* 9.2, 15.8 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.66 (dd, *J* 4.1, 20.0 Hz, 1H, $CH_AH_BCO_2CH_3$), 3.49 (d, *J* 13.2 Hz, 1H, CH_AH_BPh), 3.57 (d, *J* 13.2 Hz, 1H, CH_AH_BPh), 3.60 (s, 3H, CH_3O), 4.52 (dd, *J* 4.1, 9.2 Hz, 1H, C*H*NH), 7.06 (td, *J* 1.9, 7.5

Hz, 1H, ArC*H*), 7.15-7.30 (m, 6H, ArC*H*), 7.48 (dd, *J* 1.1, 7.9 Hz, 1H, ArC*H*), 7.55 (dd, *J* 1.9, 7.9 Hz, 1H, ArC*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 41.4 (*C*H_2CO), 51.8 (*C*HNH), 52.2 (*C*H_3O), 58.1 (*C*H_2Ph), 124.3, 127.4, 128.3, 128.6, 128.8, 129.2, 133.6, 140.4, 141.2, 172.5 (*C*=O).

(*R*)-Methyl 3-(benzylamino)-3-(2,4-dichlorophenyl)-propanoate, (*R*)-86

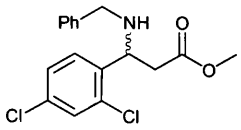


According to general procedure 6, *N*-(2,4-dichlorobenzylidene)benzylamine **43** (167 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-86** as a yellow oil in 84% yield (180 mg, 0.53 mmol) and 26% ee.

According to general procedure 7, *N*-(2,4-dichlorobenzylidene)benzylamine **43** (167 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester **(*S*)-86** as a yellow oil in 92% yield (197 mg, 0.58 mmol) and 60% ee.

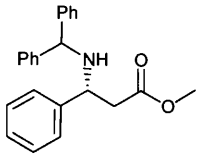
Column chromatography (EtOAc: petroleum 40-60 °C, 2:8, Rf = 0.34) afforded the title β-amino ester **(*S*)-86**. HPLC (Column Chiralpack OD with 99:1, Hex:IPA, flow rate = 1mL/min) t_r^R = 9.61 and t_r^S = 11.04 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 1H, N*H*), 2.55 (dd, *J* 8.6, 15.8 Hz, 1H, C$H_A$$H_B$$CO_2CH_3$), 2.62 (dd, *J* 4.1, 15.8 Hz, 1H, C$H_A$$H_B$$CO_2CH_3$), 3.45 (d, *J* 12.8 Hz, 1H, C$H_A$$H_B$Ph), 3.55 (d, J 12.8 Hz, 1H, C$H_A$$H_B$Ph), 3.6 (s, 3H, C$H_3$O), 4.43 (dd, *J* 4.1, 8.6 Hz, 1H, C*H*NH), 7.18-7.26 (m, 6H, Ar*H*), 7.30 (d, 1H, Ar*H*), 7.52 (d, 1H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 41.1 (*C*H_2CO), 51.8 (*C*H_3O), 52.2 (*C*H_2NH), 55.2 (*C*HNH), 127.5 (*C*H), 128.0, 128.5, 128.8, 129.7, 129.9, 133.8, 134.5, 138.4, 140.2, 172.3 (*C*=O); IR (KBr disk): ν 3300-3450 (NH), 1730 (RCOOMe), 816 (NH) cm^{-1}; MS (*m/z*): Calc. $[M+H]^+$; 338.0709, Found $[M+H]^+$; 338.0711.

(*rac*)-Methyl 3-(benzylamino)-3-(2,4-dichlorophenyl)-propanoate, (*rac*)-86



According to procedure 8, racemic Mannich-type adduct **(*rac*)-86** was prepared from stochiometric amounts of imine **43** and *tert*-butyldimethylsilyloxy-1-methoxy ethene (0.14 mL, 0.63 mmol) using trimethyl borate (0.07 mL, 0.63 mmol), resulting the formation of the title compound **(*rac*)-86** in 58% yield (124 mg, 0.37 mmol). Spectroscopic data is identical to **(*R*)-86**.

Methyl-3-(*R*)-(benzhydrylamino)-3-phenylpropionate, (*R*)-34 [7, 19]



According to general procedure 5, *N*-Benzylidenebenzhydrylamine **7** (171 mg, 0.63 mmol) and *tert*-Butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted in the presence of (*R*)-chiral boron complex **6** (363 mg, 1.27 mmol) at -78 °C for 20 hrs to afford β-amino ester **(*R*)-34** as a yellow oil in 98% (214 mg, 0.62 mmol) yield and 60% ee.

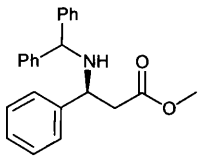
According to general procedure 6, *N*-(benzylidene)benzhydrylamine **7** (171 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-34** as a yellow oil in 97% yield (12 mg, 0.61 mmol) and 56% ee.

According to general procedure 7, *N*-(benzylidene)benzhydrylamine **7** (171 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester **(*R*)-34** as a yellow oil in 80% yield (175 mg, 0.51 mmol) and 75% ee.

The crude products were isolated by flash chromatography (Et_2O:petroleum 40-60 °C, 2:8 ratio, Rf = 0.36). Enantiomeric excess determination was carried out by stirring stochiometric amounts of (*S*)-(+)-*O*-acetylmandelic acid and β-amino ester (*R*)-34 in $CDCl_3$ for 5 minutes to give the corresponding diastereotopic salts with differences in

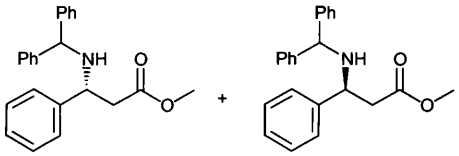
their ^{1}H NMR chemical shifs. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 1H, N*H*), 2.58 (dd, *J* 5.3, 15.1 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.64 (dd, *J* 9.0, 15.1 Hz, 1H, $CH_AH_BCO_2CH_3$), 3.58 (s, 3H, CH_3O), 3.94 (dd, *J* 5.3, 9.0 Hz, 1H, C*H*NH), 4.48 (s, 1H, C*H*Ph_2), 7.02-7.30 (m, 15H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.0 (*C*H_2CO), 52.0 (*C*H_3O), 51.2 (*C*HNH), 63.9 (*C*HPh_2), 127.4, 127.5, 127.7, 128.0, 128.2, 128.8, 128.9, 129.1, 172.5 (*C*=O); IR (neat) ν 1741 (RCOOMe); MS (*m/z*): Calc. $[M+H]^+$; 346.1802, Found $[M+H]^+$; 346.1803.

Methyl-3-(*R*)-(benzhydrylamino)-3-phenylpropionate, (*S*)-34



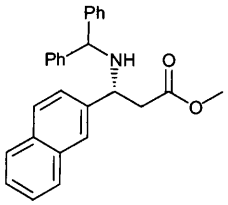
According to general procedure 5, *N*-Benzylidenebenzhydrylamine **7** (171 mg, 0.63 mmol) and *tert*-Butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted in the presence of (*S*)-chiral boron complex **6** (363 mg, 1.27 mmol) at -78 °C for 20 hrs to afford β-amino ester **(*S*)-34** as a yellow oil in 98% (214 mg, 0.62 mmol) yield and 60% ee.

Methyl-3- (*rac*)-(benzhydrylamino)-3-phenylpropionate, (*rac*)-34 [7, 19]



According to procedure 8, racemic β-amino ester was derived from reacting overnight reaction at room temperature *N*-(benzylidene)benzhydrylamine **7** (171 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) using trimethyl borate (0.07 mL, 0.63 mmol) to yield the Mannich-type adduct **(*rac*)-34** in >90% yield. Spectroscopic data is identical to **(*R*)-34**.

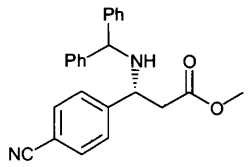
Methyl-3-(*R*)-(benzhydrylamino)-3-(3-naphthalen)propionate, (*R*)-89



According to general procedure 6, *N*-(3-naphthalen)benzhydrylamine **49** (203 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-89** as a yellow oil in 93% yield (223 mg, 0.59 mmol) and 53% ee.
According to general procedure 7, *N*-(3-naphthalen)benzhydrylamine **49** (203 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester **(*R*)-89** as a yellow oil in 47% yield (118 mg, 0.30 mmol) and 79% ee.

Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.28) afforded the title isolated β-amino ester **(*R*)-89**.(*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 1H, N*H*), 2.65 (dd, *J* 5.5, 15.5 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.75 (dd, *J* 8.5, 15.3 Hz, 1H, $CH_AH_BCO_2CH_3$), 3.60 (s, 3H, CH_3O), 4.15 (dd, *J* 5.5, 8.5 Hz, 1H, C*H*NH), 4.50 (s, 1H, C*H*Ph_2), 7.30-7.65 (m, 17H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.1 (CH_2COOMe), 51.7 (CH_3O), 58.0 (CH_2), 59.3 (*C*HNH), 123.2, 125.3, 126.2, 126.5, 126.7, 127.4, 127.5, 128.1, 128.3, 128.6, 128.8, 129.0, 129.1, 129.3, 129.5, 133.5, 133.8, 135.2, 135.5, 172.63 (*C*OOMe); MS (*m/z*): Calc. $[M+1]^+$; 396.1958, Found $[M+1]^+$; 396.1950.

Methyl-3-(*R*)-(benzhydrylamino)-3-(4-cyanophenyl) propionate, (*R*)-90

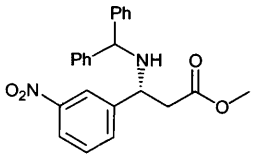


According to general procedure 6, *N*-(4-cyanobenzylidene)benzhydrylamine **50** (188 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-90** as a yellow oil in 91% yield (213 mg, 0.56 mmol) and 65% ee.

According to general procedure 7, *N*-(4-cyanobenzylidene)benzhydrylamine **50** (188 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester **(*R*)-90** as a yellow oil in 61% yield (143 mg, 0.34 mmol) and 88% ee (*R*).

Enantiomeric excess determination was carried out by stirring stoichiometric amounts of (*S*)-(+)-*O*-acetylmandelic acid and isolated β-amino ester **(*R*)-90** in $CDCl_3$ for 5 minutes to give the corresponding diastereotopic salts with non equivalent protons; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 1H, N*H*), 2.54 (dd, *J* 5.7, 15.4 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.66 (dd, *J* 8.7, 15.4 Hz, 1H, $CH_AH_BCO_2H_3$), 3.56 (s, 3H, CH_3O), 3.98 (dd, *J* 5.7, 8.7 Hz, 1H, C*H*NH), 4.42 (s, 1H, C*H*Ph_2), 7.30 (d, *J* 7.9 Hz, 1H, ArC*H*), 7.56 (d, *J* 8.7 Hz, 1H, ArC*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 52,2 (*C*HNH), 111.3, 118.0 (*C*N), 126.6, 128.5, 128.8, 129.0, 131.8, 134.3, 143.7 ; IR (KBr disk) ν 1735 (RCOOMe); MS (*m/z*): Calc. [M^+]; 370.2524, Found [M^+]; 370.2002.

Methyl-3-(*R*)-(benzhydrylamino)-3-(3-nitrophenyl)propionate, (*R*)-91

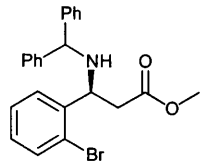


According to general procedure 6, *N*-(3-nitrobenzylidene)benzhydrylamine **51** (200 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*R*)-91** as a yellow oil in 82% yield (202 mg, 0.52 mmol) and 67% ee (*R*).
According to general procedure 7, *N*-(3-nitrobenzylidene)benzhydrylamine **51** (200 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester **(*R*)-91** as a yellow oil in 64% yield (158 mg, 0.40 mmol) and 91% ee.

Column chromatography (Et_2O: petroleum 40-60 °C, 2:8) afforded the title isolated β-amino ester **(*R*)-91**. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excesses; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 1H, N*H*), 2.85 (dd, *J* 5.3, 10.2 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.66 (dd, *J* 8.7, 16.8 Hz, 1H, $CH_AH_BCO_2CH_3$), 3.85 (s, 3H, CH_3O), 4.35 (dd, *J* 5.3, 8.7 Hz, 1H, C*H*NH), 4.42 (s, 1H, C*H*Ph_2), 7.30-7.65 (m, 10H, Ph*H*), 7.70 (t, *J* 7.5 Hz, 1H, Ph*H*), 7.80 (d, *J* 6.4 Hz, 1H, Ph*H*), 8.10 (d, *J* 7.9 Hz, 1H, *H*), 8.35 (s, 1H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 42.85 (CH_2COOMe), 52.19 (*C*HNH), 56.73 (CH_3O), 64.30 (*C*HPh_2), 122.5, 123.06, 124.91, 127.54, 127.63, 127.81, 128.02, 128.84, 128.99, 129.09, 129.99, 133.86, 142.65,

144.04, 145.20, 149.01, 171.75 (*C*OOMe); MS (*m/z*) : Calc. [M^+]; 390.5643, Found [M^+];390.3421

Methyl-3-(*S*) -(benzhydrylamino)-3-(2-bromophenyl)propionate, (*S*)-92

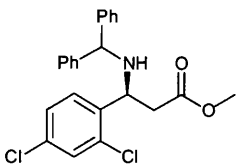


According to general procedure 6, *N*-(2-bromophenyl)benzhydrylamine **52** (222 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*S*)-92** as a yellow oil in 92% yield (247 mg, 0.58 mmol) and 73% ee.

According to general procedure 7, *N*-(2-bromophenyl)benzhydrylamine **52** (222 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs -78 °C to afford the title β-amino ester **(*S*)-92** as a yellow oil in 49% yield (132 mg, 0.31 mmol) and 97% ee.

Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.48) afforded the title isolated β-amino ester **(*R*)-92**. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (dd, *J* 9.0, 15.3 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.90 (dd, *J* 4.7, 15.3 Hz, 1H, $CH_AH_BCO_2CH_3$), 3.85 (s, 3H, CH_3O), 4.65 (dd, *J* 4.7, 9.1 Hz, 1H, C*H*NH), 4.80 (s, 1H, C*H*Ph_2), 7.30-7.65 (m, 14H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 41.0 (CH_2CO), 51.6 (*C*HNH), 51.9 (CH_3O), 58.9 (*C*HPh), 124.3, 127.4, 128.3, 128.6, 128.7, 128.8, 129.0, 129.1, 129.2, 133.6, 140.4, 141.2, 172.5 (*C*=O); MS (*m/z*): Calc. $[M+1]^+$; 424.0907, Found $[M+1]^+$; 424.0907.

Methyl-3-(*S*)-(benzhydrylamino)-3-(2,4-dichlorophenyl)propionate, (*S*)-93.



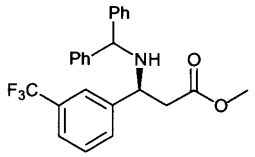
According to general procedure 6, *N*-(2,4-dichlorobenzylidene)benzhydrylamine **53** (213 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL,

1.27 mmol) were reacted for 24 hrs at room temperature the title β-amino ester **(*S*)-93** as a yellow oil in 87% yield (228 mg, 0.55 mmol) and 77% ee.

According to general procedure 7, *N*-(2,4-dichlorobenzylidene)benzhydrylamine **53** (213 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at -78 °C to afford the title β-amino ester **(*S*)-93** as a yellow oil in 74% yield (100 mg, 0.47 mmol) and 94% ee.

Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.30) afforded the title isolated β-amino ester **(*S*)-93**. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 1H, N*H*), 2.75 (dd, *J* 8.3, 15.1 Hz, 1H, CH_AH$_B$CO$_2$CH$_3$), 2.85 (dd, *J* 5.3, 15.4 Hz, 1H, CH$_A$$H_BCO_2CH_3$), 3.75 (s, 3H, C$H_3$O), 4.65 (dd, *J* 5.3, 8.6 Hz, 1H, C*H*NH), 4.75 (s, 1H, C*H*Ph$_2$), 7.25-7.70 (m, 13H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 39.8 (*C*H$_2$COOMe), 40.3 (*C*HNH), 50.6 (*C*H$_3$O), 62.8 (*C*HPh$_2$), 126.2, 126.4, 126.7, 127.1, 127.3, 128.1, 128.4, 129.3, 130.8, 133.1, 134.7, 136.0, 142.4, 142.9, 170.6 (*C*OOMe); MS (*m/z*): Calc. [M+1]$^+$; 414.1022, Found [M+1]$^+$; 414.1005.

Methyl-3-(*S*)-(benzhydrylamino)-3-(3-trifluorophenyl)propionate, (*S*)-94

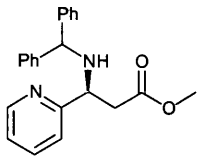


According to general procedure 6, *N*-(3-trifluorophenyl)benzhydrylamine **54** (215 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the title β-amino ester **(*S*)-94** as a yellow oil in 84% yield (220 mg, 0.53 mmol) and 63% ee.

Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.23) afforded the title β-amino ester **(*S*)-94**. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8 (br s, 1H, N*H*), 2.70 (dd, *J* 5.5, 15.6 Hz, CH_AH$_B$CO$_2$CH$_3$), 2.80 (dd, *J* 8.8, 15.1 Hz, CH$_A$$H_BCO_2CH_3$), 3.70 (s, 3H, C$H_3$O), 4.2 (dd, *J* 5.5, 8.8 MHz, C*H*NH), 4.6 (s, 1H, C*H*Ph$_2$), 7.00-7.40 (m, 14H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.1 (*C*H$_2$), 52.1 (*C*HNH),

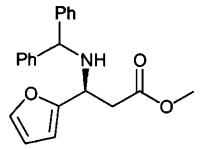
56.9 (CH_3O), 64.1 ($CHPh_2$), 127.5, 127.6, 127.7, 128.1, 128.8, 129.0, 129.5, 131.0, 142.7, 143.8, 144.3, 172.0 (*C*=N); MS (*m/z*): Calc. $[M+1]^+$; 414.1675, Found $[M+1]^+$; 414.166

Methyl-3-(*S*)-(benzhydrylamino)-3-(2-piridine)propionate, (*S*)-95



According to general procedure 6, *N*-(2-piridinylmethylene)benzhydrylamine **55** (291 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the crude β-amino ester **(*S*)-95**. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.15) afforded the title β-amino ester **(*S*)-95** as a yellow oil in 75% yield (164.46 mg, 0.4747 mmol) and 25% ee. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (dd, *J* 5.2, 16.0 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.85 (dd, *J* 7.9, 15.1 Hz, 1H, $CH_AH_BCO_2CH_3$), 3.60 (s, 3H, CH_3O), 4.10 (dd, *J* 5.2, 7.9 Hz, 1H, C*H*NH), 4.55 (s, 1H, C*H*Ph_2), 7.00-7.30 (m, 14H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 40.1 (CH_2COOMe), 41.2 (*C*HNH), 50.8 (CH_3O), 62.9 ($CHPh_2$), 126.1, 126.5, 126.8, 127.1, 127.4, 128.2, 128.3, 129.4, 130.9, 133.2, 134.8, 136.1, 142.5, 143.0, 171.2 (*C*OOMe); IR (neat) ν 1732 (RCOOMe); MS (*m/z*): Calc. $[M+1]^+$; 347.1754, Found $[M+1]^+$; 347.1801

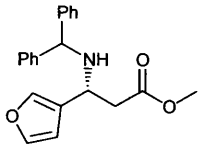
Methyl-3-(*S*)-(benzhydrylamino)-3-(2-furayl)propionate, (*S*)-96



According to general procedure 6, *N*-(2-furanyl)benzhydrylamine **56** (165 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the crude β-amino ester **(*S*)-96.** Column chromatography (Et_2O: petroleum 40-60 °C, 2:8) afforded the title β-amino ester **(*S*)-96** as a yellow oil in 53% yield (212 mg, 0.33 mmol) and 69% ee. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8 (br s, 1H, NH), 2.55 (dd, *J* 6.0,

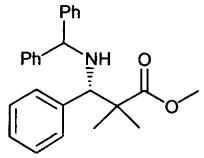
15.2 Hz, 1H, C*H*$_A$H$_B$CO$_2$CH$_3$), 2.65 (dd, *J* 8.4, 15.3 Hz, 1H, CH$_A$*H*$_B$CO$_2$CH$_3$), 3.55 (s, 3H, CH$_3$O), 3.90 (dd, *J* 6.0, 8.4 Hz, 1H, CHNH) , 4.6 (s, 1H, CHPh$_2$), 6.7 (s, 1H, furanH), 7.0 (s, 1H, furanH), 7.0-7.40 (m, 11H, CHAr); ^{13}C (75.5 MHz, CDCl$_3$) δ 42.2 (CH$_2$COOMe), 50.0 (CHNH), 52.5 (CH$_3$O), 65.1 (CHPh$_2$), 108.1, 126.4, 127.6, 127.9, 128.0, 128.8, 128.9, 140.0, 143.1, 144.4, 144.5, 172.0 (C=N); IR (neat) ν 1736 (RCOOMe); MS (m/z): Calc. [M+H]$^+$; 336.1594, Found [M+H]$^+$; 336.1596.

Methyl-3-(*R*)-(benzhydrylamino)-3-(3-furayl)propionate, (*R*)-97



According to general procedure 6, *N*-(3-furanyl)benzhydrylamine **57** (212 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the crude β-amino ester **(*R*)-97**. Column chromatography (Et$_2$O: petroleum 40-60 °C, 2:8) afforded the title β-amino ester **(*R*)-97** as a yellow oil in 56% yield (119 mg, 0.35 mmol) and 61% ee. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.8 (br s, 1H, N*H*), 2.55 (dd, *J* 5.8, 15.1 Hz, 1H, C*H*$_A$H$_B$CO$_2$CH$_3$), 2.65 (dd, *J* 8.1, 15.3 Hz, 1H, CH$_A$*H*$_B$CO$_2$CH$_3$), 3.55 (s, 3H, C*H*$_3$O), 3.90 (dd, *J* 5.8, 8.1 Hz, 1H, C*H*NH), 4.6 (s, 1H, C*H*Ph$_2$), 6.3 (s, 1H, furan*H*), 7.0-7.40 (m, 12H, C*H*Ar); ^{13}C (75.5 MHz, CDCl$_3$) δ 42.3 (*C*H$_2$COOMe), 48.4 (*C*HNH), 52.0 (*C*H$_3$O), 64.1 (*C*HPh$_2$), 108.9, 126.5, 127.4, 127.5, 127.7, 128.0, 128.8, 128.9, 140.4, 143.2, 144.0, 144.7, 172.5 (*C*=N); IR (neat) ν 1736 (RCOOMe).

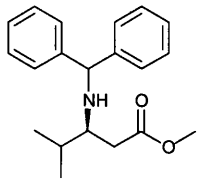
(*R*)-Methyl 3-(benzhydrylamino)-2,2-dimethyl-3-phenylpropanoate, (*R*)-99



According to general procedure 6, *N*-Benzylidenebenzylamine **7** (171 mg, 0.63 mmol) and 1-Methoxy-2-methyl-1-trimethyl-1-(trimethylsiloxy)propene **79** (0.26 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the crude β-amino ester **(*R*)-99**. Column chromatography (Et$_2$O: petroleum 40-60 °C, 2:8, Rf = 0.22) afforded the title β-amino ester as a yellow oil in 69% yield (163 mg, 0.44 mmol) and 4% ee. (*S*)-

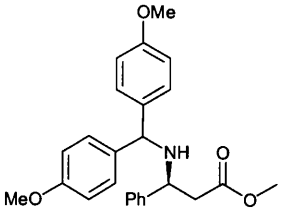
(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.20 (br s, 1H, N*H*), 3.56 (s, 3H, CH_3O), 3.70 (s, 1H, $CHPh_2$), 4.40 (s, 1H, C*H*NH), 7.00-7.20 (m, 15H, Ph*H*); ^{13}C (75 MHz, $CDCl_3$) δ 20.2 (CH_3), 24.6 (CH_3), 47.7 (CMe_2), 52.0 (CH_3O), 64.1 ($CHPh_2$), 66.2 (*C*HNH), 127.3, 127.4, 127.5, 127.8, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.4, 130.5, 131.1, 143.4, 144.3, 145.2, 177.9 (*C*=N); IR (neat) ν 1725 (RCOOMe), 1460, 1250, 1135, 700 cm^{-1}.

Methyl-3-(*S*)-(benzhydrylamino)-4-methylpentaionate, (*S*)-100



According to general procedure 6, *N*-isobutylidenebenzhydrylamine **59** (197 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted for 24 hrs at room temperature to afford the crude β-amino ester **(*S*)-100**. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.57) afforded the title β-amino ester **(*S*)-100** as a yellow oil in 24% yield (48.5 mg, 0.15 mmol) and 26% ee. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (m, 1H, $CHMe_2$), 2.25 (dd, *J* 7.7, 14.9 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.35 (dd, *J* 5.1, 14.5 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.70 (m, 1H, C*H*NH), 3.2 (s, 3H, CH_3O), 4.8 (s, 1H, $CHPh_2$), 7.10-7.30 (m, 10H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 16.3 (CH_3), 33.0 ($CH(CH_3)_3$), 39.8 (CH_2), 53.1 (*C*HNH), 555.7 (CH_3O), 64.1 ($CHPh_2$), 127.5, 127.6, 127.7, 128.1, 128.8, 129.0, 129.5, 143.8, 144.3, 172.0 (*C*=N); MS (*m/z*): Calc. $[M+1]^+$; 312.1960, Found $[M+1]^+$; 312.1958.

(*S*)-Methyl-3-[Bis-(4-methoxy-phenyl)amino]-3-phenylpropanoate, (*S*)-101



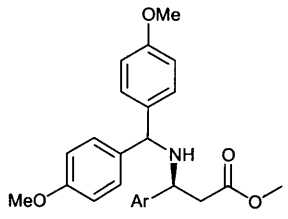
According to general procedure 6, *N*-benzylidene-bis(4-methoxyphenyl)-methylamine **60** (209 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL,

1.27 mmol) were reacted for 24 hrs at room temperature to afford a the title β-amino ester **(*S*)-101** as a colorless oil in 60% yield (154 mg, 0.38 mmol) and 51% ee.

According to general procedure 7, *N*-benzylidene-bis(4-methoxyphenyl)-methylamine **60** (209 mg, 0.63 mmol) and *tert*-Butyldimethylsilyloxy-1-methoxy ethene **62** (0.42 mL, 1.90 mmol) were reacted for 24 hrs at -78 °C to afford a the title β-amino ester **(*S*)-101** as a colourless oil in >98% yield (251 mg, 0.62 mmol) and 89% ee (*S*).

Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.07) afforded the title β-amino ester **(*S*)-101**. (*S*)-(+)-O-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (br s, 1H, N*H*), 2.55 (dd, *J* 5.1, 15.4 Hz, 1H, $CH_AH_BCO_2CH_3$), 2.65 (dd, *J* 9.0, 15.1 Hz, 1H, $CH_AH_BCO_2CH_3$), 3.60 (s, 3H, CH_3O), 3.70 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3O), 3.90 (q, *J* 5.1 Hz, 1H, C*H*NH), 4.40 (dd, *J* 5.1, 9.0 Hz, 1H, CHN*H*), 6.70 (d, *J* 8.8 Hz, 2H, Ar*H*), 6.80 (d, *J* 8.8 Hz, 2H, Ar*H*), 7.00-7.35 (m, 5H, Ar*H*), 7.80-9.00 (m, 4H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.4 (CH_2COOCH_3) , 51.9 (*C*HNH), 55.6 (CH_3O) , 57.1 (CH_3O), 62.6 (*C*H), 114.1, 114.2, 127.5, 127.8, 128.6, 129.0, 129.1, 159.0, 172.5 (C=O); MS (*m/z*): Calc. $[M+Na]^+$; 428.1832, Found $[M+1]^+$; 428.1830, neutral monoisotopic mass: 405.1940 Da.

(*S*)-Methyl-3-[Bis-(4-methoxy-phenyl)amino]-3-(2-bromo-phenyl)-propanoate, (*S*)-102



Ar = 2-bromophenyl

According to general procedure 6, *N*-(2-bromobenzylidene)- bis(4-methoxyphenyl)methylamine **61** (260 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.42 mL, 1.90 mmol) were reacted overnight at room temperature to afford the title β-amino ester **(*S*)-102** as a colourless oil in >99% yield (303 mg, 0.63 mmol) and 70% ee.

According to general procedure 7, *N*-(2-bromobenzylidene)- bis(4-methoxyphenyl)methylamine **61** (260 mg, 0.63 mmol) and *tert*-Butyldimethylsilyloxy-1-methoxy ethene **62** (0.42 mL, 1.90 mmol) were reacted overnight at -78 °C to afford the title β-amino ester **(*S*)-102** as a colorless oil in 89% yield (273 mg, 0.56 mmol) and 76% ee.

Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.07) afforded the title β-amino ester **(*S*)-102**. (*S*)-(+)-*O*-acetylmandelic acid was used as a chiral derivatising reagent for determining the enantiomeric excess. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (br s, 1H, N*H*), 2.65 (dd, *J* 5.3, 15.8 Hz, 1H, CH_AH$_B$CO$_2$CH$_3$), 2.80 (dd, *J* 8.8, 16.0 Hz, 1H, CH$_A$$H_BCO_2CH_3$), 3.60 (s, 3H, C$H_3$O), 3.70 (s, 3H, C$H_3$O), 3.75 (s, 3H, C$H_3$O), 4.50 (s, 1H, CHN*H*), 4.55 (dd, *J* 5.3, 8.8 Hz, 1H, C*H*NH), 6.65 (d, *J* 8.8 Hz, 2H, Ar*H*), 6.80 (d, *J* 8.8 Hz, 2H, Ar*H*), 7.00-7.35 (m, 4H, Ar*H*), 7.85 (d, 2H, *J* 8.8 Hz, Ar*H*), 7.95 (d, 2H, *J* 8.8 Hz, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.8 (*C*H$_2$COOCH$_3$), 52.4 (*C*HNH), 55.5 (*C*H$_3$O) , 57.0 (*C*H$_3$O), 62.8 (*C*H), 114.6, 114.8, 123.4, 127.8, 128.0, 128.6, 129.0, 129.1, 159.0, 172.6 (C=O).

5.7 VARIANTS FOR THE MANNICH-TYPE REACTION OF IMINES

5.7.1 General procedure 10 and 11: Addition of additives for the synthesis of β-amino esters 64 and 34

General Procedure 10A: [13]

To the chiral precatalyst **6** is formed according to procedure 2-Method A, 1 equivalent of additive is added. To the reaction mixture, *N*-Benzylidenebenzylamine **35** (0.06 mL, 0.63 mmol) is added and stirred for further 10 minutes, before 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) is added. After stirring 24 hrs at room temperature, the reaction mixtures were diluted with dichloromethane and filtered through celite. The organic layer was washed twice with 30 mL of aqueous $NaHCO_3$ solution, and then dried ($MgSO_4$). The solvent was then removed *in vacuum* to give a crude yellow oils of β-amino ester **64** with the results

shown in table 5.1. Spectroscopic data of compound **64** is shown previously in this chapter.

General Procedure 10B:

To the chiral precatalyst **6** is formed according to procedure 2-Method A, 1 equivalent of additive is added. To the reaction mixture, *N*-Benzylidenebenzhydrylamine (171 mg, 0.63 mmol) **7** is added and stirred for further 10 minutes, before 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) is added. The same work up followed in general procedure 10A was carried out for the extraction of compound **34**. Results are shown in table 5.1.Spectroscopic data of compound **34** is shown previously in this chapter.

Table 5. 1: Results obtained by using additives for compounds **64** and **34**.

	Compound 64		**Compound 34**	
Additive (0.633 mmol)	**yield (%)**	**ee (%)**	**yield (%)**	**ee (%)**
NMI (5 μL)	none	none	none	None
DMI (5.6 μL)	50	26	none	none
Propanol (4.8 μL)	40	25	85	63
MeOH (2.5 μL)			85	60
Benzyl alcohol (4.5 μL)	43	27	>99	53

General Procedure 11: Proposed halophenol additives

The proposed chiral Brönsted acid-assisted chiral Lewis acids (BLA) were prepared *in situ* by mixing a 1:1:2 molar ratio of trimethyl borate (0.07 mL, 0.63 mmol, 1eq.), (*R*)-binaphthol (363 mg BINOL, 1.26 mmol, 2 eq.) and substituted phenol (1.27 mmol) in CH_2Cl_2 at room temperature for 1 h in the presence of 4 Å molecular sieves (1g) under a nitrogen atmosphere. To the chiral boron complexes **74-76**, imine **35** (0.12 mL, 0.63 mmol) was added. The mixture was stirred for further 10 minutes before adding 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.14 mL, 0.63 mmol). After stirring overnight for 24 hrs at room temperature the reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The organic layer was washed twice with 30 mL of aqueous $NaHCO_3$ solution, and dried ($MgSO_4$). The solvent was then removed *in vacuum* to give a crude yellow oils of β-amino esters **64**. Evaporation of solvent and purification by

column chromatography (EtO_2:petroleum 40-60 °C, 2:3, Rf = 0.20) afforded the title β-amino ester **(*R*)-64** as a colourless oil with the results shown in table 5.2. Spectroscopic data for compound **(*R*)-64** is shown earlier in this chapter.

Table 5. 2: Three new approaches to increase the level of stereoselection of β-amino ester (*R*)-64.

substituted phenol (2 equiv, 1.27 mmol)	Pre-catalyst	Yield (%)	ee (%)
219 mg *o*-bromophenol	**74**	40	40
205 mg *p*-trifluorophenol	**75**	69	69
233 mg pentafluorophenol	**76**	36	36

5.7.2 Procedure 12-14: Catalytic Mannich-Type reaction of imines

Procedure 12: the chiral Brönsted acid-assisted chiral Lewis acid **6** (BLA) was prepared *in situ* by mixing a 1:2 molar ratio of trimethyl borate (0.71 µL $(MeO)_3B$, 10 mol%) with (*R*)-binaphthol (36 mg, 20 mol%) in CH_2Cl_2 at room temperature for 1 h, in the presence of 4 Å molecular sieves (1g) under a nitrogen atmosphere. To the chiral boron complex **6**, imine **35** (0.12 mL, 0.63 mmol) was added. The mixture was stirred for further 10 minutes before the 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.14 mL, 0.63 mmol, 1 eq.) was added dropwise and the mixture stirred for 24 hrs at room temperature. The organic layer was washed twice with 30 mL of aqueous $NaHCO_3$ solution, and dried ($MgSO_4$). The solvent was then removed *in vacuum* to give a crude yellow oil of β-amino ester **(*R*)-64**. Evaporation of solvent and purification by column chromatography (Et_2O:petroleum 40-60 °C, 2:8) afforded β-amino ester **(*R*)-64** as a colourless oil in 16% yield and 27% ee. Spectroscopic data of compound **(*R*)-64** is shown earlier in this chapter.

Procedure 13: the chiral Brönsted acid-assisted chiral Lewis acid **6** (BLA) was prepared *in situ* by mixing a 1:2 molar ratio of trimethyl borate (0.71 µL $(MeO)_3B$, 10 mol%) with (*R*)-binaphthol (36 mg, 20 mol%) in CH_2Cl_2 at room temperature for 1h, in the presence of 4 Å molecular sieves (1g) under a nitrogen atmosphere. The chiral boron complex **6** was cooled down to -78°C and imine **35** (0.12 mL, 0.63 mmol) was added. The mixture was stirred for further 10 minutes before the 1-(*tert*-

butyldimethylsilyloxy)-1-methoxy ethene **62** (0.14 mL, 0.63 mmol, 1 eq.) was added dropwise and mixture stirred for 48 hrs. The reaction mixture was brought to room temperature and then the organic layer was washed twice with 30 mL of aqueous $NaHCO_3$ solution, and dried ($MgSO_4$). The solvent was then removed *in vacuum* to give a crude yellow oil of β-amino ester **(*R*)-64**. Evaporation of solvent and purification by column chromatography (Et_2O:petroleum 40-60°C, 2:8) afforded β-amino ester **(*R*)-64** as a colourless oil in 29% yield and 49% ee. Spectroscopic data of compound **(*R*)-64** is shown previously in this chapter.

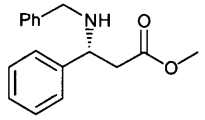
Procedure 14: The chiral Bronsted acid-assisted chiral Lewis acid **78** (BLA) was prepared *in situ* by mixing a 1:2 molar ratio of trimethyl borate (0.71 μL $(MeO)_3B$, 10 mol%) with (*R*)-(-)-6,6′-Dibromo-1,1′-bi-napthol (56 mg, 20 mol%) in CH_2Cl_2 at room temperature for 1 h in the presence of 4 Å molecular sieves (1g) under a nitrogen atmosphere. To the chiral boron complex **78**, imine **35** (0.12 mL, 0.63 mmol) was added. The mixture was stirred for further 10 minutes before the 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.14 mL, 0.63 mmol, 1 eq.) was added dropwise and the mixture stirred for 24 hrs at room temperature. The organic layer was washed twice with 30 mL of aqueous $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give a crude yellow oil of β-amino ester **(*R*)-64**. Evaporation of solvent and purification by column chromatography (Et_2O:petroleum 40-60°C, 2:8) afforded β-amino ester **(*R*)-64** as a colorless oil in 15% yield and 65% ee. Spectroscopic data of compound **(*R*)-64** is shown earlier in this chapter.

5.7.3 General procedure 15: β-amino esters derived from imines synthetised *in situ*

General Procedure 15: The chiral Brönsted acid-assisted chiral Lewis acid (BLA) **6** was prepared *in situ* by mixing a 1:2 molar ratio of trimethyl borate (0.07 mL $(MeO)_3B$, 0.63 mmol, 1eq.) with (*R*) or (*S*)-binaphthol (363 mg BINOL, 1.27 mmol, 2 eq.) in CH_2Cl_2 at room temperature for 1 h in the presence of 4 Å molecular sieves (1g) under a nitrogen atmosphere. The aldehyde (0.63 mmol) substrate and boron-BINOL complex **6** were stirred for 10 minuutes, and then 1 equivalent of amine was added. After 20 minutes, the reaction mixture change colour from white to yellow. Aldehyde and amine

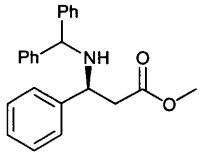
were left stirring for a certain period of time before the 1-(*tert*-butyldimethylsilyloxy)-1-methoxy (0.14 mL, 0.63 mmol, 1 eq.) was added dropwise into the reaction mixture. After stirring for 24 hrs stirring, the reaction mixture was diluted with dichloromethane and filtered through celite. The organic layer were washed twice with 30 mL of aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give a crude yellow oil.

(*R*)-Methyl 3-(benzylamino)-3-phenylpropanoate, (*R*)-64 [13]



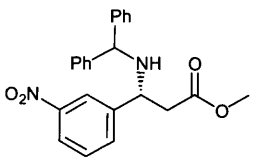
Acording to general procedure 15, benzaldehyde (0.06 mL, 0.63 mmol) and benylamine (0.11 mL, 0.63 mmol) were stirred for 20 minutes before addition of 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) to afford a mixture of the desired β-amino ester crude in 48% yield (81 mg, 0.30 mmol) and 27% ee. ^1H NMR analysis showed contamination by the resultant aldol condensation product **106**. Spectroscopic data of compound **(*R*)-64** is shown previously in this chapter.

Methyl-3-(*S*)-(benzhydrylamino)-3-phenylpropionate, (*S*)-34



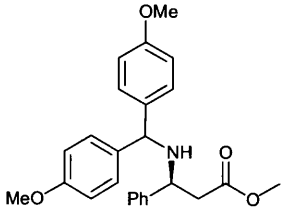
Acording to general procedure 15, benzaldehyde (0.06 mL, 0.63 mmol) and diphenylmethylamine (0.11 mL, 0.63 mmol) were stirred for 20 minutes before addition of 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) to afford a mixture of the desired β-amino ester **34** crude in 30% conv. and the resultant aldol condensation product **106** in 50% conv. Spectroscopic data of compound **(*S*)-34** is shown previously in this chapter.

Methyl-3-(*R*)-(benzhydrylamino)-3-(3-nitrophenyl)propionate, (*R*)-91



Acording to general procedure 15, 3-nitrobenzaldehyde (96 mg, 0.63 mmol) and diphenylmethylamine (0.11 mL, 0.63 mmol) were stirred for 4 hrs before addition of 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) to afford after 12 hrs a mixture of the desired β-amino ester **(*R*)-91** in 50% conversion and the resultant aldol condensation product **107** in 35% conv. Spectroscopic data of compound **(*R*)-91** is shown previously in this chapter.

(*S*)-Methyl-3-[Bis-(4-methoxy-phenyl)amino]-3-phenylpropanoate, (*S*)-101



Acording to general procedure 15, benzaldehyde (0.06 mL, 0.63 mmol) and bis-(4-methoxyphenyl)-methylamine (566 mg, 2.33 mmol) were stirred for 45 min before addition of 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **54** (0.42 mL, 1.90 mmol) to afford after 24 h a crude mixture of the desired β-amino ester **(*S*)-101** in 50% conv. and the resultant aldol adduct 106 in 40% conv. ^{1}H NMR analysis showed 50% conversion of the resultant aldol condensation product. Spectroscopic data of compound **(*S*)-101** is shown previously in this chapter.

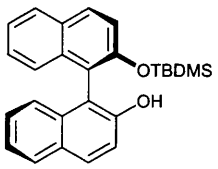
5.8 PROCEDURE 16-18: silylation of BINOL

Procedure 16: Monosilylation of BINOL. trimethyl borate (0.07 mL, 0.63 mmol) and (*R*)-binapthol (181 mg, 0.63 mmol) were reacted with 1-(*tert*-butyldimethylsilyloxy)-1-methoxy **62** ethene (0.14 mL, 0.63 mmol) or (0.28 mL, 1.27 mmol) overnight in the presence of 4 Å molecular sieves in CH_2Cl_2. After stirring overnight the reaction mixture was diluted with dichloromethane and filtered through celite. The organic layer was washed twice with 30 mL of aqueous $NaHCO_3$ solution, brine and then dried ($MgSO_4$). The solvent was then removed *in vacuo* to give the crude of the mono-silylated BINOL **66**. Column chromatography (from Et_2O:petroleum 40-60 °C, 2:8, Rf = 0.46), afforded the mono-silylated BINOL **66** as a sticky yellow oil in 50% yield (127 mg, 0.32 mmol).

Procedure 17: Monosilylation of BINOL. (*R*)-binapthol (600 mg, 1.7 mmol) was reacted overnight with *tert*-butyldimethyl chloride (263 mg, 1.7 mmol) in the presence of triethylamine (0.24 mL, 1.75 mmol) in CH_2Cl_2. The reaction mixture was diluted with dichloromethane and filtered through celite. The organic layer was worked up before column chromatography (from Et_2O:petroleum 40-60 °C, 2:8, Rf = 0.46) afforded the mono-silylated BINOL **66** in 60% yield (419 mg, 1.05 mmol).

Procedure 18: Attempted bisilylation of BINOL. (*R*)-mono-silylated binapthol **66** (135 mg, 0.34 mmol) was reacted for 24 hrs with *tert*-butyldimethyl chloride (101 mg, 0.67 mmol) in the presence of triethylamine in CH_2Cl_2. The reaction mixture was diluted with dichloromethane and filtered into a separating funnel. The organic layer was worked up as usually. The solvent was then removed *in vacuo* to give a mixture of 47% (*R*)-binapthol and 53% (72 mg, 0.18 mmol) of mono-silylated BINOL **66**.

2′-(tert-Butyl-dimethyl-silanyloxy)-[1,1′]binaphthalenyl-2-ol, 66



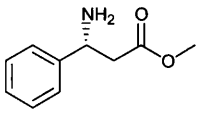
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H, C*H*$_3$Si), 0.20 (s, 3H, C*H*$_3$Si), 0.70 (s, 9H, ^{t}(C*H*$_3$)$_3$Si), 5.25 (s, 1H, O*H*), 7.2-8.2 (m, 12H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ -4.0 (*C*H$_3$Si), -4.2 (*C*H$_3$Si), 18.0 (Me$_3$*C*H), 25.4 (*C*H$_3$), 118.0, 118.8, 123.5, 125.7, 126.6, 127.5, 128.5, 129.6, 134.3, 151.8; MS (*m/z*): Calc [M$^+$]; 400.1853, Found [M$^+$]; 400.1849.

5.9 PROCEDURE 19 AND 20: Deprotection of benzylamino, diphenylmethine and bis-(4-methoxyphenyl)-methyl protecting groups

Procedure 19: Hydrogenation over palladium/carbon for deprotecting benzylamino and diphenylmethine groups. (*R*)-Methyl-3-(benzylamino)-3-phenylpropanoate **64** or methyl-3-(*R*)- benzhydrylamino)-3-phenylpropionate, **34** and palladium on carbon (10% by mass) in MeOH was placed in a round botton flask which

was flushed with H_2 (g) and stirred vigorously overnight. The reaction mixture was then filtered through a plug of celite washing through with methanol, and the filtrate concentrated to give a white solid. This residue was dissolved with saturated aqueous $NaHCO_3$ which was subsequently extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford the debenzylated product in quantitative yields.

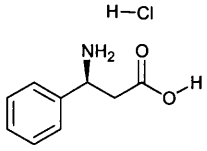
(+)-(3*R*)-Methyl 3-Amino-3-phenylpropionate, 65 [19-22]



According general procedure 19, β-amino ester **64** (26% ee) (138mg, 0.51 mmol) and **34** (56% ee) (176 mg, 0.51 mmol) were succesfully deprotected to yield the resultant deprotected β-amino ester in 84% yield (77 mg, 0.43 mmol) and 87% yield (76 mg, 0.44 mmol) respectively. ($[\alpha]_D^{20}$ +21.9 (c 1.00, $CHCl_3$). (Lit. data: $[\alpha]_D^{20}$ = +22.3 (c 1.99, $CHCl_3$). ^{1}H NMR (300 MHz, CDCl3) δ 2.07 (s, 2H, N*H*$_2$), 2.75 (d, *J* 7 Hz, 2H, C*H*$_2$), 3.76 (s, 3H, C*H*$_3$O), 4.50 (t, *J* 7 Hz, 1H, C*H*Ph), 7.41 (s, 5H); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.7 (*C*H$_2$COOCH$_3$), 51.0 (*C*HNH), 52.4 (*C*H$_3$O), 126.9, 128.2, 145.0, 171.9 (C=O); IR (neat) ν 3364, 1731 cm^{-1}; MS (*m/z*): Calc. [M$^+$]; 179.0946, Found [M$^+$]; 179.0952.[23]

General Procedure 20: Deprotection of 4,4′-Dimethoxybenzhydrylamine protecting group. [23] The β-amino ester **101** (154 mg, 0.38 mmol) and **102** (303 mg, 0.63 mmol) were refluxed with 6M HCl at 96°C for 24 hrs. The reaction mixture was allowed to cool down to room temperature and the aqueous solvent was concentrated in vacuo to dryness to give a white/yellowish solid in >99% yield.

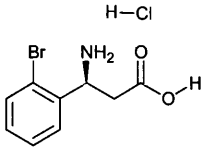
(+)-(3*S*)-3-Amino-3-phenylpropionic acid hydrochloride, 103 [24-26]



The resultant salt was formed according to general procedure 20 in >99% yield (62 mg, 0.38 mmol). $[\alpha]_D^{25}$ +8.2 (c 1.00, H_2O) for (*S*). ^{1}H NMR (300 MHz, D_2O) δ 3.0 (dd, *J* 7.16, 16.95 Hz, 1H, C*H*$_A$H$_B$COOH), 3.15 (dd, *J* 7.91, 17.14 Hz, 1H, CH$_A$*H*$_B$COH), 4.56

(q, *J* 7.35 Hz, C*H*NH_2), 7.30-7.50 (m, 5H, Ph*H*). ^{13}C (75.5 MHz, D_2O) δ 38.3 (*C*H_2COOCH_3), 52.0 (*C*HNH_3), 127.4, 129.8, 130.0, 135.6, 174.2 (C=O). MS (*m/z*): Calc. $[M+Na]^+$; 188.0682, Found $[M+Na]^+$; 188.0679.

(+)-(3*S*)-3-Amino-3-(2-bromo-phenyl)-propionic acid hydrochloride, 104 [27]



The resultant salt was formed according to general procedure 20 in >99% yield (151 mg, 0.62). $[\alpha]_D^{25}$ +8.7 (c 1.00, H_2O) for (*S*). (Lit value: $[\alpha]_D^{25}$ +8.2 (c 1.00, H_2O) for (*S*)). ^1H NMR (300 MHz, D_2O) δ 2.90 (dd, *J* 6.6, 17.5 Hz, 1H, C$H_A$$H_B$COOH), 3.10 (dd, *J* 3.3, 13.0 Hz, 1H, CH_AH_BCOH), 5.15 (q, *J* 7.5 Hz, C*H*NH_2), 7.20 (td, *J* 2.1, 7.2, 15.1 Hz, 1H, ArH), 7.40 (m, 2H, Ar*H*), 7.6 (d, *J* 1.1, 8.3 Hz, 1H, Ar*H*); ^{13}C (75.5 MHz, D_2O) δ 37.2 (*C*H_2COOCH_3), 50.7 (*C*HNH_3), 123.6, 127.7, 129.0, 131.5, 134.0, 134.4, 173.6 (C=O).

5.10 PROCEDURE 21-26: Mukaiyama aldol type reaction

General procedure 21: standard enantioselective aldol type reactions of aldehydes promoted by chiral boron complex 6 (prepared with procedure 2-Method A). To the chiral boron complex **6** prepared according to procedure 2-Method A, aldehyde (0.63 mmol, 1eq.) was added. The mixture was stirred for further 10 minutes before 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.14 mL, 0.63 mmol, 1 eq.) was added dropwise. After stirring overnight at room temperature, the reaction mixture was diluted with dichloromethane and filtered through celite. The organic layer were washed twice with 30 mL of aqueous $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give a crude yellow oil.

General procedure 22: racemic aldol type reaction promoted by trimethyl borate. Racemic aldol-type adduct was derived from the condensation of aldehyde (0.63 mmol) and 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) using

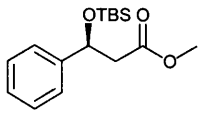
trimethylborate (0.07 mL, 0.63 mmol) and 4 Å molecular sieves in CH_2Cl_2. Filtration through celite of the molecular sieves and evaporation of the solvent afforded the corresponding racemic aldol-type adducts without further work-up.

Procedure 23: aldol type reaction promoted by chiral boron complex 6 at room temperature (prepared with procedure 2-Method C). To the chiral boron complex **6** prepared according to procedure 2-Method C, aldehyde (0.63 mmol, 1eq.) was added. The mixture was stirred for a further 10 minutes before 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.28 mL, 1.27 mmol, 1 eq.) was added dropwise. After stirring for 24 hrs at room temperature, the reaction mixture was diluted with dichloromethane and filtered through celite. The organic layer were washed twice with 30 mL of aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give a crude yellow oil.

Procedure 24: aldol type reaction promoted by chiral boron complex 6 at -78 °C (prepared with procedure 2-Method C). the chiral boron complex **6** prepared according to procedure 2-Method C, aldehyde (0.63 mmol, 1eq.) was added. The mixture was stirred for further 10 minutes before 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.28 mL, 1.27 mmol, 1 eq.) was added dropwise. After stirring for 24 hrs at -78 °C, the reaction mixture was diluted with dichloromethane and filtered through celite. The organic layer were washed twice with 30 mL of aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give a crude yellow oil.

General Procedure 25: racemic aldol type reaction promoted by 4 Å molecular sieves. Racemic silylated aldol-type adduct was derived from the condensation of aldehyde (0.06 mL, 0.63 mmol) and 1-(*tert*-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) in the presence of 4 Å molecular sieves and 1.5 mL of CH_2Cl_2.

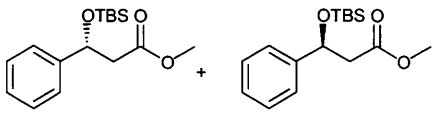
(*S*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-phenylpropanoate, (*S*)-106 [28-33]



According to gereral procedure 21, benzaldehyde (0.06 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.06 mmol) were reacted overnight at room temperature to afford a crude silylated aldol product **(*S*)-106**. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.51) afforded the title silylated aldol product **(*S*)-106** as a colourless oil in 65% yield (121 mg, 0.41 mmol) and 11% ee, $[\alpha]_D^{25}$ +10.5 (c 1.00, $CHCl_3$) for (*R*).

^{1}H NMR (300 MHz, $CDCl_3$) δ -0.20 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si), 0.80 (s, 9H, $^t(CH_3)_3Si$), 2.50 (dd, *J* 3.8, 14.5 Hz, 1H, CH_AH_BCOOMe), 2.70 (dd, *J* 10.0, 14.9 Hz, 1H, CH_AH_BCOOMe), 3.60 (s, 3H, CH_3O), 5.10 (q, *J* 4.0 Hz, 1H, *CH*OTBDMS), 7.20-7.30 (m, 5H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ -4.3 (CH_3Si), -4.4 (CH_3Si), 26.1 ($^t(CH_3)_3Si$), 46.7 (CH_2CO), 52.0 (CH_3O), 72.6 (*C*HOTBDMS), 126.2, 127.9, 128.7, 144.4, 172.0 (*C*=O); IR (neat) ν 1739 (RCOOMe) cm^{-1}; MS (*m/z*). Calc for $C_{12}H_{17}O_3Si$: 317.1550 $[M+Na]^+$, Found; 317.1543. 295 $[M+Na]^+$.

(*rac*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-phenylpropanoate, (*rac*)-106 [28-33]



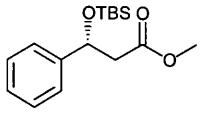
According to general procedure 22, racemic aldol-type adduct was derived from the condensation of benzaldehyde (0.06 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) in 62% isolated yield (115 mg, 0.39 mmol). Spectroscopic data is identical to **(*S*)-106**.

According to general procedure 25, racemic aldol-type adduct **(*rac*)-106** was derived from the condensation of benzaldehyde (0.06 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) in the presence of;

- 0.50 g of 4 Å MS to afford the title compound in 54% isolated yield (100 mg, 0.34 mmol). Spectroscopic data is identical to **(*S*)-106**.

- 0.76 g of 4 Å MS to afford the title compound in 28% isolated yield (52 mg, 0.18 mmol). Spectroscopic data is indentical to **(*S*)-106**.

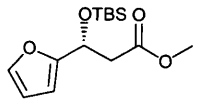
(*R*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-phenylpropanoate, (*R*)-106 [28-33]



According to procedure 23, benzaldehyde (0.06 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.42 mL, 1.90 mmol) were reacted for 24 hrs at room temperature to afford a crude silylated aldol type product. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.51) afforded the title silylated aldol type product **(*R*)-106** as a colourless oil in 95% yield (176 mg, 0.60 mmol) and 22% ee. Spectroscopic data is the same as for **(*S*)-106**.

According to procedure 24, benzaldehyde (0.06 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.42 mL, 1.90 mmol) were reacted for 24 hrs at room temperature to afford a crude silylated aldol type product **(*S*)-106**. Column chromatography (Et_2O: petroleum, 2:8, Rf = 0.51) afforded the title silylated aldol type product **(*S*)-106** as a colourless oil in 86% yield (159 mg, 0.54 mmol) and 45% ee. Spectroscopic data is identical to **(*S*)-106**.

(*R*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(2-furanyl)-propanoate, (*R*)-111

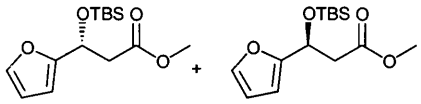


According to gereral procedure 21, 2-furaldehyde (0.04 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.06 mmol) were reacted overnight at room temperature to afford a crude silylated aldol type product. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.44) afforded the title silylated aldol adduct **(*R*)-111** as a colourless oil in >99% yield (178 mg, 0.63 mmol) and 8.7% ee, $[\alpha]_D^{25}$ +14.0 (c 1.00, $CHCl_3$) for (*R*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H, CH_3Si), 0.20 (s, 3H, CH_3Si), 0.90 (s, 9H, $^t(CH_3)_3$Si), 2.80 (dd, *J* 4.5, 14.9 Hz, 1H, CH_AH_BCOOMe), 2.90 (dd, *J* 9.0, 14.7 Hz, 1H, CH_AH_BCOOMe), 3.75 (s, 3H, CH_3O), 5.30 (q, *J* 5.1 Hz, 1H, CHOTBDMS), 6.30 (dd, *J*

0.7, 3.4 Hz, 1H, 2-furan*H*), 6.40 (dd, *J* 1.7, 3.2 Hz, 1H, 2-furan*H*), 7.40 (s, 1H, 2-furan*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ -5.0 (CH_3Si), -4.6 (CH_3Si), 26.0 ($^t(CH_3)_3Si$), 42.6 (CH_2CO), 52.0 (CH_3O), 64.9 (*C*HOTBDMS), 106.5, 110.5, 142.1, 148.4, 156.0, 178.3 (*C*=O); IR (neat) ν 1739 (RCOOMe); MS (*m/z*): Calc $[M+H]^+$; 285.0538, Found $[M+H]^+$; 285.1263.

(*rac*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(2-furanyl)-propanoate, (*rac*)-111

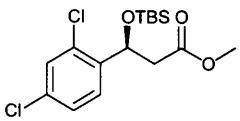


According to general procedure 22, racemic aldol-type adduct was derived from the condensation of 2-furaldehyde (0.04 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) in >99% yield (178 mg, 0.63 mmol).

According to general procedure 25, racemic aldol-type adduct was derived from the condensation of 2-furaldehyde (0.04 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) in the presence of;

- 0.25 g of 4 Å MS to afford the title compound in 88% isolated yield (158 mg, 0.55 mmol). Spectroscopic data is identical to **(*R*)-111**.
- 0.30 g of 4 Å MS to afford the title compound in 77% isolated yield (138 mg, 0.49 mmol). Spectroscopic data is identical to **(*R*)-111**.
- 0.50 g of 4 Å MS to afford the title compound in 76% isolated yield (131 mg, 0.46 mmol). Spectroscopic data is identical to **(*R*)-111**.

(*S*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(2,4-dichlorophenyl)-propanoate, (*S*)-112

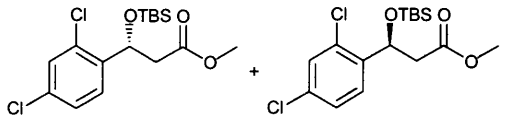


According to general procedure 21, 2,4-dichlorobenzaldehyde (111 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) were reacted overnight at room temperature to afford a crude silylated aldol type product. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.51) afforded the title silylated

aldol adduct **(*S*)-112** as a colourless oil in 46% yield (106 mg, 0.29 mmol), $[\alpha]_D^{25}$ +11.1 (c 1.00, $CHCl_3$) for (*S*).

^{1}H NMR (300 MHz, $CDCl_3$) δ -0.20 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si), 0.80 (s, 9H, $^t(CH_3)_3Si$), 2.45 (dd, *J* 9.2, 15.7 Hz, 1H, CH_AH_BCOOMe), 2.70 (dd, *J* 3.8, 14.5 Hz, 1H, CH_AH_BCOOMe), 3.65 (s, 3H, CH_3O), 5.45 (q, *J* 3.2 Hz, 1H, *CH*OTBDMS), 7.10-7.30 (m, 2H, Ar*H*), 7.5 (d, *J* 8.7 Hz, 1H, Ar*H*); ^{13}C (75 MHz, $CDCl_3$) δ -4.5 (CH_3Si), -4.4 (CH_3Si), 18.4 (*C*), 25.8 (CH_3C), 26.0 (CH_3C), 44.9 (CH_2COOMe), 52.0 (CH_3O), 70.0 (*C*HO), 123.0, 129.2, 129.4, 129.5, 145.5, 171.5 (*C*=O); IR (neat) ν 1741 (RCOOMe); MS (*m/z*): Calc. $[M]^+$; 363.0945, Found $[M]^+$; 363.0943.

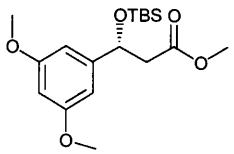
(*rac*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(2,4-dichlorophenyl)-propanoate, (*rac*)-112



According to general procedure 22, racemic aldol-type adduct was derived from the condensation of 2,4-dichlorobenzaldehyde (111 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) in 98% isolated yield (225 mg, 0.62 mmol). Spectroscopic data is identical to **(*S*)-112**.

According to general procedure 25, racemic aldol-type adduct was derived from the condensation of 2,4-dichlorobenzaldehyde (111 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) in the presence of an unknown amount of 4 Å MS to afford the title compound in 95% isolated yield (217 mg, 0.60 mmol). Spectroscopic data is identical to **(*S*)-112**.

(*R*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(3,5-dimethoxyphenyl)-propanoate, (*R*)-113

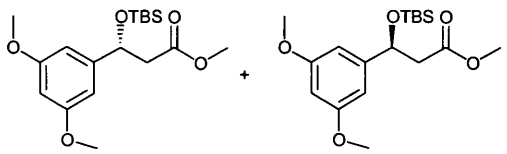


According to general procedure 21, 3,5-dimethoxybenzaldehyde (105 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.06 mmol) were

reacted overnight at room temperature to afford a crude silylated aldol type product. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.37) afforded the title aldol-type adduct **(*R*)-113** as a colourless oil in 53% yield (119 mg, 0.34 mmol), $[\alpha]_D^{25}$ +13.7 (c 1.00, $CHCl_3$) for (*R*).

^{1}H NMR (300 MHz, $CDCl_3$) δ -0.15 (s, 3H, C*H*$_3$Si), 0.00 (s, 3H, C*H*$_3$Si), 0.80 (s, 9H, ^{t}(C*H*$_3$)$_3$Si), 2.50 (dd, *J* 4.3, 15.1 Hz, 1H, C*H*$_A$H$_B$COOMe), 2.70 (dd, *J* 9.4, 14.5 Hz, 1H, CH$_A$*H*$_B$COOMe), 3.65 (s, 3H, C*H*$_3$O), 3.75 (s, 3H, C*H*$_3$O), 3.85 (s, 3H, C*H*$_3$O), 5.10 (q, *J* 3.8 Hz, 1H, C*H*OTBDMS), 6.30 (s, 1H, Ar*H*), 6.50 (s, 2H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ -4.94 (*C*H$_3$Si), -4.66 (*C*H$_3$Si), 17.96 (*C*), 18.41 (*C*H$_3$C), 18.60 (*C*H$_3$C), 18.85 (*C*H$_3$C), 46.71 (*C*H$_2$COOMe), 51.81 (*C*H$_3$O), 55.50 (*C*H$_3$O), 55.89 (*C*H$_3$O), 72.22 (*C*HO), 113.59, 114.01, 114.68, 136.60, 159.37, 171.94 (*C*=O); IR (CH_2Cl_2) ν 1739.8 (RCOOMe); MS (*m/z*): 353.2 (1), 255.0 (16), 223.0 (19), 191.0 (6), 164.0 (4), 131.0 (7), 89.0 (100), 73.0 (6), 1.3 (10).

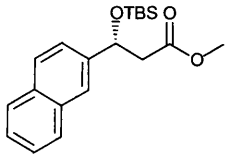
(*rac*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(3,5-dimethoxyphenyl)-propanoate, (*rac*)-113



According to general procedure 22, racemic aldol-type adduct was derived from the condensation of 3,5-dimethoxybenzaldehyde ethene **62** (105 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy (0.14 mL, 0.63 mmol) in >99% yield (221 mg, 0.63 mmol). Spectroscopic data is identical to **(*R*)-113**.

According to general procedure 22, racemic aldol-type adduct was derived from the condensation of 3,5-dimethoxybenzaldehyde ethene **62** (105 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy (0.14 mL, 0.63 mmol) in the presence of 0.5 g of 4 Å MS to afford the title compound in 50% isolated yield (112 mg, 0.31 mmol). Spectroscopic data is identical to **(*R*)-113**.

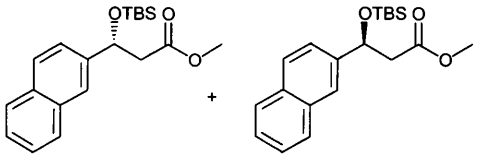
(*R*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(2-naphthalenyl)-propanoate, (*R*)-114



According to general procedure 21, 2-naphthaldehyde (99 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) were reacted overnight at room temperature to afford a crude silylated aldol type product. Evaporation of solvent and purification by column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.35) afforded the title silylated aldol type as a colourless oil in 50% yield (109 mg, 0.32 mmol), $[\alpha]_D^{25}$ +13.8 (c 1.00, $CHCl_3$) for (*R*).

^{1}H NMR (300 MHz, $CDCl_3$) δ -0.20 (s, 3H, C*H*$_3$Si), 0.00 (s, 3H, C*H*$_3$Si), 0.80 (s, 9H, ^{t}(C*H*$_3$)$_3$Si), 2.60 (dd, *J* 3.9, 14.5 Hz, 1H, C*H*$_A$H$_B$COOMe), 2.80 (dd, *J* 9.4, 14.7 Hz, 1H, CH$_A$*H*$_B$COOMe), 3.65 (s, 3H, C*H*$_3$O), 5.30 (q, *J* 4.1 Hz, 1H, C*H*OTBDMS), 7.4-7.8 (m, 7H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ -4.9 (*C*H$_3$Si), -4.2 (*C*H$_3$Si), 26.1 (*C*H$_3$C), 46.7 (*C*H$_2$COOMe), 52.0 (*C*H$_3$O), 72.8 (*C*HO), 124.4, 124.6, 124.9, 126.2, 126.5, 128.1, 128.4, 128.6, 133.4, 133.6, 141.9, 171.9 (*C*=O); MS (*m/z*): Calc. $[M]^+$; 345.1880, Found $[M]^+$; 345.1884.

(*rac*)- Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(2-naphthalenyl)-propanoate, (*rac*)-114

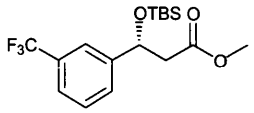


According to general procedure 22, racemic aldol-type adduct was derived from the condensation of 2-naphthaldehyde (99 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) in >99% isolated yield (216 mg, 0.63 mmol). Spectroscopic data is identical to **(*R*)-114**.

According to general procedure 25, racemic aldol-type adduct was derived from the condensation of 2-naphthaldehyde (99 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) in the presence of;

- an unknown amount of 4 Å MS to afford the title compound in 98% isolated yield (213 mg, 0.62 mmol). Spectroscopic data is identical to **(*R*)-114**.
- 0.50 g of 4 Å MS to afford the title compound in 57% isolated yield (124 mg, 0.36 mmol). Spectroscopic data is identical to **(*R*)-114**.

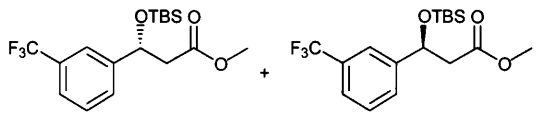
(*R*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(3-trifluorophenyl)-propanoate, (*R*)-115



According to general procedure 21, 3-tetrafluorobenzaldehyde (0.08 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) were reacted overnight at room temperature to afford a crude silylated aldol type product. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.44) afforded the title silylated aldol type product **(*R*)-115** as a colourless oil in 50% yield (115 mg, 0.32 mmol), $[\alpha]_D^{25}$ +20.5 (c 1.00, $CHCl_3$) for (*R*).

^{1}H NMR (300 MHz, $CDCl_3$) δ -0.20 (s, 3H, C*H*$_3$Si), 0.00 (s, 3H, C*H*$_3$Si), 0.80 (s, 9H, ^{t}(C*H*$_3$)$_3$Si), 2.50 (dd, *J* 4.1, 14.9 Hz, 1H, C*H*$_A$H$_B$COOMe), 2.70 (dd, *J* 9.0, 14.7 Hz, 1H, CH$_A$*H*$_B$COOMe), 3.65 (s, 3H, C*H*$_3$O), 5.20 (q, *J* 4.3 Hz, 1H, C*H*OTBDMS), 7.40-7.80 (m, 4H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ -4.97 (*C*H$_3$Si), -4.43 (*C*H$_3$Si), 17.93 (*C*), 18.22 (CH$_3$*C*), 18.37 (*C*H$_3$C), 44.97 (*C*H$_3$COOMe), 52.01 (*C*H$_3$O), 70.05 (CHO), 122.28 (*C*F$_3$), 124.72, 124.77, 129.19, 130.93, 131.36, 143.88, 173.08 (*C*=O); IR (neat) ν 1743 (RCOOMe); MS (*m/z*); 363.0 (1), 305.0 (42), 263.0 (45), 247.0 (37), 189.0 (11), 173.0 (22), 155.0 (49), 131.0 (27), 115.1 (11), 89.0 (63), 73.0 (100), 59.0 (12) %.

(*rac*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(3-trifluorophenyl)-propanoate, (*rac*)-115



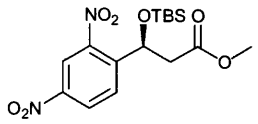
According to general procedure 22, racemic aldol-type adduct was derived from the condensation of 3-tetrafluorobenzaldehyde (0.08 mL, 0.63 mmol) and *tert*-

butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) in >99% isolated yield (227 mg, 0.63 mmol).

According to general procedure 25, racemic aldol-type adduct was derived from the condensation of 3-tetrafluorobenzaldehyde (0.08 mL, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy (0.28 mL, 1.27 mmol) in the presence of;

- 1.12 g of 4 Å MS to afford the title compound in 45% isolated yield (101 mg, 0.28 mmol). Spectroscopic data is identical to **(*R*)-115**.
- 0.56 g of 4 Å MS to afford the title compound in 57% isolated yield (130 mg, 0.36 mmol). Spectroscopic data is identical to **(*R*)-115**.

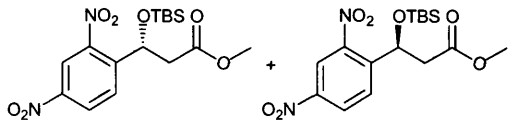
(*S*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(2,4-dinitrophenyl)-propanoate, (*S*)-116



According to general procedure 21, 2,4-dinitrobenzaldehyde (124 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy (0.14 mL, 0.63 mmol) were reacted overnight at room temperature to afford a crude silylated aldol type product. Column chromatography (Et_2O: petroleum 40-60 °C, 2:8, Rf = 0.06) afforded the title silylated aldol type product **(*S*)-116** as a yellow oil in 48% yield (115 mg, 0.32 mmol), $[\alpha]_D^{25}$ +21.9 (c 1.00, $CHCl_3$) for (*S*).

^{1}H NMR (300 MHz, $CDCl_3$) δ -0.20 (s, 3H, C*H*$_3$Si), 0.00 (s, 3H, C*H*$_3$Si), 0.80 (s, 9H, (C*H*$_3$)$_3$Si), 2.60 (dd, *J* 7.9, 15.1 Hz, 1H, C*H*$_A$H$_B$COOMe), 2.80 (dd, *J* 4.1, 15.1 Hz, 1H, CH$_A$*H*$_B$COOMe), 3.65 (s, 3H, C*H*$_3$O), 5.70 (q, *J* 3.9 Hz, 1H, C*H*OTBDMS), 8.0 (d, *J* 8.7 Hz, 1H, Ar*H*), 8.4 (dd, *J* 3.0, 9.0 Hz, 1H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ -4.4 (*C*H$_3$Si), -4.5 (*C*H$_3$Si), 18.3 (*C*), 25.5 (*C*H$_3$), 25.9 (*C*H$_3$), 45.0 (*C*H$_2$COOMe), 53.0 (*C*H$_3$O), 67.4 (*C*HO), 120.3, 127.7, 131.1, 146.7, 170.4 (*C*=O); IR (neat) ν 1741 (RCOOMe); MS (*m/z*): Calc. $[M+Na]^+$; 407.1245, Found $[M+Na]^+$; 407.1258 , neutral accurate mass: 384.1353 Da.

(*rac*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-3-(2,4-dinitrophenyl)-propanoate, (*rac*)-116



According to general procedure 22, racemic aldol-type adduct was derived from the condensation of 2,4-dinitrobenzaldehyde (124 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.14 mL, 0.63 mmol) in >99% isolated yield (241 mg, 0.63 mmol). Spectroscopic data is identical to **(*S*)-116**.

According to general procedure 25, racemic aldol-type adduct was derived from the condensation of 2,4-dinitrobenzaldehyde (124 mg, 0.63 mmol) and *tert*-butyldimethylsilyloxy-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) in the presence of an unknown amount of 4 Å MS to afford the title compound in 99% isolated yield (241 mg, 0.63 mmol). Spectroscopic data is identical to **(*S*)-116**.

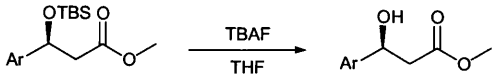
General Procedure 26: Racemic silylated aldol-type adduct **(*rac*)-111** was derived from the condensation of 2-furaldehyde (0.08 mL, 0.63 mmol) and 1-(tert-butyldimethylsilyloxy)-1-methoxy ethene **62** (0.28 mL, 1.27 mmol) in the presence of 4 Å molecular sieves (0.25g) and 1.5 mL of different solvents. Table 5.3 show the results obtained for each of the aldol-type adducts synthetised. Spectroscopic data is shown previously for compound **(*R*)-111**.

Table 5. 3: Solvent screen.

Solvent (1.5 mL)	Yield (%)
DCM	**88**
THF	**>99**
H_2O	25
MeOH	26
Toluene	84
Hexane	**>99**

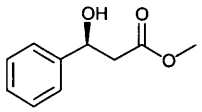
5.11 GENERAL PROCEDURE 27: *tert*-Butyl-dimethyl-silanyloxy deprotection

General procedure 27: *Tert*-butyl-dimethyl-silanyloxy protected aldol adduct (1 equiv.) was dissolved in THF and 3 equivalents of TBAF (1.0 M solution in THF) were added slowly via syringe with rigorous stirring. Addition of TBAF immediately resulted in appearance of characteristic yelow-greenish colour which remained unchanged thought the entire reaction. The mixture was then partioned between diethyl ether and aqueous 1M HCl. The organic layer was washed with saturated aq. $NaHCO_3$ and solution of NaCl. The organic extracts were dried over magnesium sulphate, followed by solvent reduction *in vacuum*. The crudes were purified by flash chromatographic column (EtO_2: Petroleum 40-60 °C, 2:3) to give the corresponding secondary alcohols.



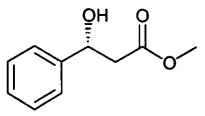
Scheme 5. 5: *tert*-butyl-dimethyl-silanyloxy deprotection.

(*S*)-3-Hydroxy-3-phenyl-propionic acid methyl ester, (*S*)-109a [34-39]



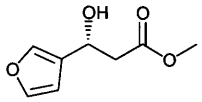
According to general procedure 27, deprotected aldol adduct was obtained from compound **(*S*)-106** (121 mg, 0.41 mmol) as a colourless oil in 78% yield (58 mg, 0.32 mmol). $[\alpha]_D^{20}$ = -13.6° (c 1.00, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (dd, *J* 4.3, 16.4 Hz, 1H, C*H*$_A$H$_B$COOMe), 2.75 (dd, *J* 8.3, 16.2 Hz, 1H, CH$_A$*H*$_B$COOMe), 3.10 (s, 1H, O*H*), 3.65 (s, 3H, C*H*$_3$O), 5.05 (q, *J* 4.3 Hz, 1H, C*H*OTBDMS), 7.2-7.4 (m, 7H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.5 (*C*H$_2$O), 52.3 (*C*H$_2$O), 70.7 (*C*HOH), 126.0, 128.3, 129.0, 142.8, 173.2 (*C*=O); IR (neat) ν 1605 (Ph), 1726 (RCOOMe), 3510 (br OH), 3601 (OH); MS (*m/z*) Calc. $[M+Na]^+$; 317.1543, Found $[M+Na]^+$; 317.1550, neutral accurate mass: 294.1651 Da.

(*R*)-3-Hydroxy-3-phenyl-propionic acid methyl ester, (*R*)-109a [34-39]



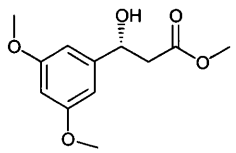
According to general procedure 27, deprotected aldol adduct was obtained from compound **(*R*)-106** (121 mg, 0.41 mmol) as a colourless oil in 75% yield (57 mg, 0.31 mmol). Spectroscopic data is identical to **(*S*)-109a**.

(*R*)-3-Hydroxy-2-furanyl-propionic acid methyl ester, (*R*)-109b



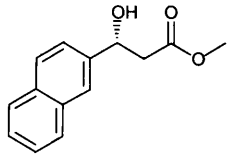
According to general procedure 27, deprotected aldol adduct **(*R*)-109b** was obtained from compound **(*R*)-111** (178 mg, 0.63 mmol) as a colourless oil in 72% yield (77 mg, 0.45 mmol), ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (dd, *J* 5.1, 16.6 Hz, 1H, CH_AH$_B$COOMe), 2.75 (dd, *J* 7.4, 16.2 Hz, 1H, CH$_A$$H_B$COOMe), 3.00 (s, 1H, O*H*), 3.80 (s, 3H, CH_3O), 5.05 (q, *J* 5.3 Hz, 1H, C*H*OTBDMS), 6.35 (dd, *J* 0.9 Hz, 1H, 3-furan*H*), 7.35 (m, 2H, C*H*-3-furan*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ -4.9 (*C*H$_3$Si), -4.3 (*C*H$_3$Si), 26.0 (^{t}(CH$_3$)$_3$Si), 45.3 (*C*H$_2$CO), 52.1 (*C*H$_3$O), 65.2 (*C*HOH), 108.9, 111.3, 139.1, 143.5, 178.1 (*C*=O); MS (*m/z*): Calc. [M$^+$]; 170.0574, Found. [M$^+$]; 170.0571.

(*R*)-3-Hydroxy-4-methoxyphenyl-propionic acid methyl ester, (*R*)-109c



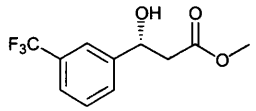
According to general procedure 27, deprotected aldol adduct was obtained from compound **(*R*)-113** (119 mg, 0.33 mmol) as a colourless oil in 85% yield (68 mg, 0.28 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (dd, *J* 8.9, 15.9 Hz, 1H, CH_AH$_B$COOMe), 2.70 (dd, *J* 4.3, 15.2 Hz, 1H, CH$_A$$H_B$COOMe), 3.05 (s, 1H, O*H*), 3.65 (s, 3H, CH_3O), 3.70 (s, 6H, 2CH_3O), 5.00 (q, *J* 3.8 Hz, 1H, C*H*OTBDMS), 6.45 (s, 1H, Ar*H*), 6.60 (s, 2H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 43.5 (CH$_2$COOMe), 52.3 (*C*H$_3$O), 55.76 (*C*H$_3$O), 70.76 (*C*HO), 100.19, 103.9, 145.4, 161.39, 173.16 (*C*=O); MS (*m/z*): Calc. [M+Na]$^+$; 263.0890, Found [M+Na]$^+$; 263.0885, neutral accurate mass: 240.0998 Da.

(*R*)-3-Hydroxy-2-naphthnyl-propionic acid methyl ester, (*R*)-109d [39, 40]



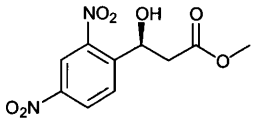
According to general procedure 27, deprotected aldol adduct was obtained from compound **(*R*)-114** (109 mg, 0.32 mmol) as a colourless oil in 74% yield (54 mg, 0.23 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (dd, *J* 4.1, 14.3 Hz, 1H, CH_AH$_B$COOMe), 2.96 (dd, *J* 9.3, 14.7 Hz, 1H, CH$_A$$H_B$COOMe), 3.43 (s, 1H, O*H*), 3.91 (s, 3H, CH_3O), 5.22-5.30 (q, *J* 3.9 Hz, 1H, C*H*OH), 7.57-8.27 (m, 7H, Ar*H*); ^{13}C (75 MHz, $CDCl_3$) δ 43.3 (CH_2COOMe), 52.8 (*C*H_3O), 71.3 (*C*HO), 122.5, 123.3, 131.9, 173.3 (*C*=O). MS (*m/z*) 230 ([M^+], 99), 157 (100), 129 (83), 77 (16), 43 (21). IR (KBr disk) ν 1751 (RCOOMe), 2830 (CH_2), 2949 (CH_3), 3422 (OH) cm^{-1}.

(*R*)-3-Hydroxy-4-trifluorophenyl-propionic acid methyl ester, (R)-109e



According to general procedure 27, deprotected aldol adduct was obtained from compound **(*R*)-115** (115 mg, 0.32 mmol) as a colourless oil in 83% yield (65 mg, 0.26 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (dd, *J* 4.0, 14.6 Hz, 1H, CH_AH$_B$COOMe), 2.70 (dd, *J* 9.0, 15.9 Hz, 1H, CH$_A$$H_B$COOMe), 3.30 (s, 1H, O*H*), 3.65 (s, 3H, CH_3O), 5.15 (q, *J* 4.0 Hz, 1H, C*H*OTBDMS), 7.3-7.7 (m, 4H, Ar*H*); ^{13}C (75 MHz, $CDCl_3$) δ 43.2 (CH_2COOMe), 51.9 (*C*H_3O), 71.6 (*C*HO), 119.1 (*C*F_3), 122.5, 123.3, 131.9, 136.5, 173.3 (*C*=O). MS (*m/z*) 248.1 ([M^+], 6), 225.1 (9), 199.0 (12), 173.0 (29), 144.9 (30), 127.0 (68), 143.1 (23), 89.0 (100), 74.1 (59), 57.1 (89).

(*S*)-3-Hydroxy-2,4-dinitrophenyl-propionic acid methyl ester, (*S*)-109f [41]

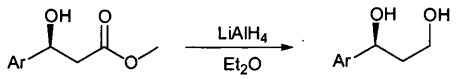


According to general procedure 27, deprotected aldol adduct was obtained from compound **(*R*)-116** (115 mg, 0.32 mmol) as a yellow oil in 88% yield (76 mg, 0.28 mmol), column chromatography (1:1 hexane/EtOAc) R_f = 0.34. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (dd, *J* 9.9, 16.5 Hz, 1H, CH_AH$_B$COOMe), 3.00 (dd, *J* 2.6, 16.5 Hz, 1H,

CH_AH_BCOOMe), 3.78 (s, 3H, CH_3O), 3.91 (d, *J* 3.3 Hz, 1H, O*H*), 5.78 (ddd, *J* 2.6, 3.3, 9.9 Hz, 1H, C*H*OH), 8.20 (d, *J* 8.6 Hz, 1H, Ph*H*), 8.51 (dd, *J* 2.6, 8.6 Hz, 1H, Ph*H*), 8.85 (d, *J* 2.6 Hz, 1H, Ph*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 41.9 (CH_2COOMe), 52.3 (CH_3O), 65.8 (*C*HO), 120.0, 127.6, 130.1, 144.6, 146.9, 147.0, 172.0 (*C*=O); IR (KBr) ν 1348, 1528, 1714, 1736, 3428 cm^{-1}; MS (*m/z*) Calc. for $C_{10}H_{11}N_2O_7$ $(M+H)^+$ 271.0566, Found 271.0565.

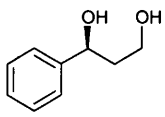
5.12 GENERAL PROCEDURE 28: reduction of the ester to alcohol [42-44]

General procedure 28: propionic acids methyl esters **109a** and **109b** were dissolved in diethyl ether and 1 equivalent of $LiAlH_4$ (1.0 M solution in Et_2O) was slowly added via syringe upon rigorous stirring. The mixture was reacted overnight and then it was quenched by dropwise addition of NH_4^+ Cl^- until no more hydrogen gas was released. After that, the mixture was dried ($MgSO_4$) and filtrated through Celite. The diethyl ether was evaporated under reduced pressure to give the crude diol. Flash chromatography (Et_2O:Petroleum 40-60 °C, 2:3) afforded the isolated diols.



Scheme 5. 6: reduction of the esters to aldohols.

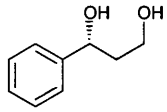
(*S*)-1-Phenyl-propane-1,3-diol, (*S*)-110a [40]



According to general procedure 28, 1,3-diol **(*S*)-110a** was obtained from compound **(*S*)-109a** (58 mg, 0.32 mmol) as a colourless oil in 81% yield (39 mg mg, 0.26 mmol) and 11% ee (*S*) (determined with a novel three components protocol-general procedure 29). $[\alpha]_D^{20}$ = -13.6 (c 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (m, 2H, CH_2COOMe), 2.30 (s, 2H, 2O*H*), 3.80 (t, *J* 5.6 Hz, 2H, CH_2OH), 4.90 (q, *J* 4.0 Hz, Ph*H*), 7.20-7.40 (m, 5H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) δ 40.9 (CH_2), 62.0 (CH_2O),

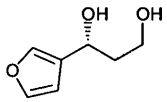
74.9 (*C*HO), 126.0, 128.0, 129.9; IR (neat): ν 3320 (OH), 3020 (CH_3), 2935 (CH_2), 1595 (C=C). MS (*m/z*): Calc $[M+Na]^+$; 175.0703, Found $[M+Na]^+$; 175.0722. monoisotopic accurate mass; 152.0837.

(*R*)-1-Phenyl-propane-1,3-diol, (*R*)-110a [40]



According to general procedure 28, 1,3-diol **(*R*)-110a** was obtained from compound **(*R*)-109a** (57 mg, 0.31 mmol) as a colourless oil in 81% yield (38 mg, 0.25 mmol) and 22% ee (*R*). (determined with a novel three components protocol-general procedure 29). $[\alpha]_D^{20}$ = +46.9 (c 1.00, $CHCl_3$) (Commercially available from acrossorganics: $[\alpha]_D^{22}$ = +54.5° (c 1.00, $CDCl_3$, (*R*)). Spectroscopic data are identical to **(*S*)-110a.**

(*R*)-1-3-Furanyl-propane-1,3-diol, (*R*)-110b

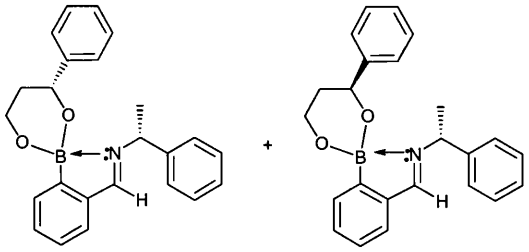


According to general procedure 28, 1,3-diol **(*R*)-114b** was obtained from compound **(*R*)-113b** (77 mg, 0.45 mmol) as a yellow oil in 63% yield (40 mg, 0.29 mmol) and 8.7% ee (*R*) (determined with a novel three components protocol-general procedure 29). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (m, 2H, C*H*$_2$COOMe), 2.30 (s, 1H, O*H*), 2.7 (s, 1H, O*H*), 4.00 (m, 2H, C*H*$_2$OH), 5.00 (q, *J* 3.8, 8.3, 13.2 Hz, furan*H*), 6.5 (s, 1H, Ar*H*), 7.5 (s, 2H, Ar*H*).

5.13 GENERAL PROCEDURE 29: Derivatisation of 1,3-diols

General procedure 29: The 1,3 diols were derivatised by stirring stoichiometric amounts of (*R*)-1-phenylethylamine, 2-formylphenylboronic acid, and the corresponding 1,3-diol in 1 mL $CDCl_3$ for 5 minutes.

(*E*,1*R*,*S*)-N-(2-(4-Phenyl-[1,3,2] dioxoborian-2-yl)benzylidene)-1-phenylethanamine (*R*,*R*)-108a + (*S*,*R*)-108a

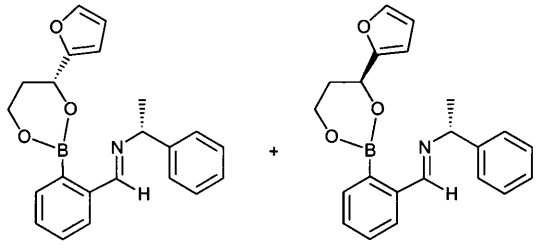


(*R*,*R*)-108a **(*R*,*S*)-108a**

The title mixture of imino esters **108a** was synthetised according the general procedure 29, using (*S*)-1-Phenyl-1,3-propanediol **(*S*)-110a** (39mg, 0.26 mmol). Evaporation of the solvent affords a yellow oil in 99% yield (96 mg, 0.26 mmol) and 11%.

The title mixture of imino esters **108a** was synthetised according the general procedure 29, using (*R*)-1-Phenyl-1,3-propanediol **(*S*)-110a** (40 mg, 0.29 mmol). Evaporation of the solvent affords a yellow oil in 99% yield (106 mg, 0.29 mmol) and 22%.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, *J* 4.90 Hz, 3H, C*H*$_3$), 1.55 (d, *J* 4.90 Hz, 3H, C*H*$_3$), 2.00 (m, 4H, 2XC*H*$_2$), 4.00 (s, 2H, 2XC*H*O), 4.60 (t, *J* 6.6 Hz, 2H, 2XC*H*CH$_3$), 5.00 (q, *J* 4.5 Hz, 2H, 2XC*H*-Ph), 7.20-7.70 (m, 14H, C*H*Ph), 8.59 (s,1H, *H*C=N), 8.60 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) δ 24.3 (*C*H$_3$), 36.1 (*C*H$_2$), 61.9 (*C*HMe), 67.6 (*C*HO), 62.7 (*C*HO), 73.6 (*C*HO), 125.9, 126.1, 127.2, 127.3, 127.8, 128.6, 128.7, 128.8, 128.9, 128.9, 129.6, 130.6, 133.3, 133.3, 140.3, 140.3, 143.6, 144.8, 144.8, 162.5 (*C*=N), 162.6 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 26.72; MS (m/z): Calc $[M+H]^+$; 370.1973, Found $[M+H]^+$; 370.1964, neutral monoisotopic mass: 369.1900.

(*E*,1*R*,*S*)-N-(2-(4-Furan-3-yl-[1,3,2] dioxoborian-2-yl)benzylidene)-1-phenylethanamine (*R*,*R*)-108b + (*S*,*R*)-108b



(*R*,*R*)-108b **(*R*,*S*)-108b**

The title mixture of imino boronate esters **108b** was synthetised according the general procedure 29, using 1-(*S*)-3-Furanyl-propane-1,3-diol (40mg, 0.29 mmol). Evaporation

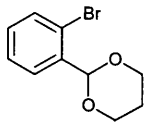
of the solvent affords imino boronate esters as a yellow oil in 95% yield (99 mg, 0.28 mmol) and 8.7% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, *J* 7.9 Hz, 3H, CH_3), 2.00 (m, 2H, CH_2), 4.00 (q, *J* 6.6 Hz, 1H, C*H*O), 4.60 (t, *J* 6.6 Hz, 1H, C*H*CH_3), 4.90 (t, *J* 4.3 Hz, 1H, Ph*H*), 6.40 (s, 1H, Ar*H*), 7.10-7.60 (m, 11H, Ar*H*), 8.55 (s, 1H, *H*C=N), 8.56 (s, 1H, *H*C=N).

5.14 PROCEDURE 30 AND 31: Protection of aldehydes [43, 45-55]

Procedure 30: A solution of *o*-bromo arylzaldehyde (54 mmol), 1,3-propanediol (81 mmol) and a catalytic amount *p*-toluenesulphonic acid in toluene (100 mL) was heated at reflux using a Dean-Stark trap for 2-3 hours.

The reaction mixture should be washed with water 3x100 mL and dried over magnesium sulphate. The organic phase was then be removed under reduced pressure. The clean ^{1}H NMR indicates the formation of the dioxanes with a 100% conversion.

2-(2-Bromo-phenyl)-[1,3]dioxane, 135

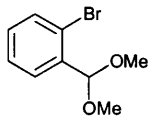


The title compound was derived from *o*-bromobenzaldehyde (1.00 mL, 8.64 mmol) and 1,3-propanediol (0.63 mL, 8.64 mmol) as a yellow oil in >99% yield (2.1 g, 8.55 mmol) according to procedure 30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3 (dm, *J* 13.6 Hz, 1H ax., CH_2), 2.10 (m, 1H eq., CH_2), 3.90 (td, *J* 2.5, 12.2 Hz, 2H, CH_2O), 4.20 (ddd, *J* 1.3, 5.0, 10.5 Hz, 2H, CH_2O), 5.70 (s, 1H, CHO_2), 7.10 (td, *J* 1.7, 7.9 Hz, 1H, Ar*H*), 7.30 (td, *J* 1.1, 7.7 Hz, 1H, Ar*H*), 7.45 (dd, *J* 1.1, 7.9 Hz, 1H, Ar*H*), 7.65 (dd, *J* 1.5, 7.7 Hz, 1H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) 26.1 (CH_2), 68.0 (CH_2O), 100.3 (CHO_2), 122.7, 127.9, 129.4, 130.3, 137.9; MS (*m/z*): Calc [M^+]; 243.0015 (^{79}Br), Found [M^+]; 243.0012.

Procedure 31: To a solution of dry MeOH containing 3 Å MS and a catalytic amount *p*-toluenesulphonic acid was added bromoarylbenzaldehyde. The mixture was stirred overnight under nitrogen. The solution was filtered through Celite and the solvent was removed *in vacuum*. The residue was dissolved with diethyl ether and washed three

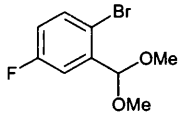
times with distilled water. The organic phase was dried over magnesium sulphate and the solvent removed under reduced pressure to give pure dimethoxymethyl.[45-57]

1-bromo-2-dimethoxymethyl-benzene, 140



The title compounds was derived from *o*-bromobenzaldehyde (1.14 mL, 9.8 mmol) and trimethyl orthoformate (1.08 mL, 9.8 mmol) in 2.5 mL of dry MeOH as a yellow oil in >99% yield (2.26 g, 9.8 mmol) according to procedure 31. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.4 (s, 6H, 2XCH_3O), 5.6 (s, 1H, C*H*O), 7.2 (td, *J* 1.9, 7.9 Hz, 2H, Ar*H*), 7.4 (td, *J* 1.1, 7.7 Hz, 1H, Ar*H*), 7.6 (qd, *J* 1.3, 8.3 Hz, 1H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) 54.3 (CH_3O), 103.4 (CHO_2), 123.4, 127.6, 128.7, 130.4, 133.3, 137.2; MS (*m/z*): Calc $[M+Na]^+$; 252.9835, Found $[M+Na]^+$; 252.9833. Calc [^{79}Br]; 229.0037, [^{79}Br]; 229.9940.

1-bromo-2-dimethoxymethyl-4-fluoro-benzene, 141



The title compounds was derived from *o*-bromo-*p*-fluorobenzaldehyde (15 g, 74 mmol) and trimethyl orthoformate (7.83 mL, 73.85 mmol) in 15 mL of dry MeOH as a yellow oil in >99% yield (18.4 g, 73.8 mmol) according to procedure 31. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (s, 6H, 2XCH_3O), 5.40 (s, 1H, C*H*O), 6.80 (tdd, *J* 1.1, 3.2, 7.7 Hz, 2H, Ar*H*), 7.20 (dd, *J*= 3.2, 9.6 Hz, 1H, Ar*H*), 7.40 (c, *J*= 5.1, 8.3 Hz, 1H, Ar*H*); ^{13}C (75.5 MHz, $CDCl_3$) 54.1 (CH_3O), 102.6 (CHO_2), 116.6, 117.1, 117.7, 134.5, 139.6, 160.6; MS (*m/z*): Calc $[M^+ + NH_4^+]$; 266.0186 (^{79}Br), Found $[M^+ + NH_4^+]$; 266.0185.

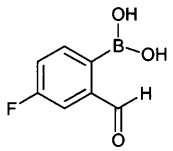
5.15 PROCEDURE 32 AND 33: General procedure for the preparation of arylboronic acids [57-59]

Procedure 32: To a solution of toluene (16 mL) and THF (4 mL) under nitrogen atmosphere, aryl halide (10 mmol) was added. The mixture was cooled to -78°C using a dry ice/acetone bath and *n*-Butyl-lithium (1.6M in hexane, 12 mmol) was added dropwise via a syringe pump over 1 h. The mixture was stirred for an additional 0.5h while the temperature was held at -78°C. The reaction mixture was then allowed to warm to -20°C and lithium halide solution was tranfered dropwise (slow rate) *via cannula* to a solution of trimethylborate (12 mmol in 1 mL toluene) at -78 °C. The mixture was stirred at -78° C for 1 h and the temperature was allowed to warm up to -20°C before 2M HCl solution (10 mL) was added. When the mixture reached room temperature, it was transferred to a 100 mL separatory funnel and the layers were separated. Both the organic and aqueous layers were assayed by ^{1}H NMR. The organic layer was evaporated *in vacuum* to provide an oil which was recrystallized (from petroleum ether 40-60°C and a small volume of diethyl ether) to give a white solid. The recrystallized products gave satisfactory ^{1}H NMR, ^{13}C NMR and ^{11}B NMR. The aqueous phase was concentrated and its ^{1}H NMR showed $B(OH)_3$ and desired boronic acid. The desired white precipitate was washed with CH_2Cl_2 several times to isolate the product.

Procedure 33: A solution of 2-(bromopehnyl)-[1,3]-dioxane (2.1 g, 8.6 mmol) in dry THF (6 mL) was added dropwise to a slurry of magnesium (0.25 g, 10 mmol) and 1,2-dibromoethane (catalytic-1-2 drops) in dry THF (6 mL). The reaction mixture is heated at reflux for 1 h. After cooling down to room temperature, the solution was added dropwise *via cannula* to a solution of trimethyl borate (1.52 mL, 13 mmol) in dry THF (6 mL) at -78°C under a nitrogen atmosphere. After the addition, the reaction mixture was stirred at -78°C for 2 hrs, and then stirred overnight at room temperature. After that 10% sulphuric acid aqueous solution (32 mL) was added to the reaction mixture, and stirred at room temperature for 1 h. The solution was extracted with diethyl ether (2x50 mL). The organic phase was then dried over magnesium sulphate and the solvent

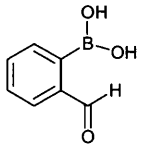
removed under reduced pressure. The residue was washed with petroleum ether and a small volume of diethyl ether to give the product as a white powder.

2-boronic acid-5-fluoro-benzaldehyde, 134



The title compound was prepared according the procedure 32 from 1-bromo-2-dimethoxymethyl-benzene (19 g, 74 mmol) using *n*-Butyl-lithium (1.6M in hexane, 56 mL, 89 mmol) and trimethyl borate (10 mL, 89 mmol) followed by quenching with HCl 2M (74 mL) to afford a recrystallised white precipitate in 55% yield (6.90 g, 41.00 mmol). m.p: 123-125°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6 (broad s, 2H, 2xO*H*), 7.5 (td, *J* 2.5, 8.1 Hz, 1H, Ar*H*), 7.7 (dd, *J* 2.6, 8,8 Hz, 1H, Ar*H*), 8.3 (q, *J* 6.4, 7.9 Hz, 1H, Ar*H*), 9.8 (s, 1H, C*H*O_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 121.4, 121.63, 124.72, 141.61, 197.45 (*C*=O); ^{11}B NMR (96 MHz, $CDCl_3$) δ 28.7 ($ArBOH_2$); ^{19}F NMR (400 MHz, $CDCl_3$) δ -108.2 (ddd, *J* 6.0, 8.4, 14.5 Hz, Ar-F); MS (*m/z*): Calc. $[M-H]^-$; 168.0400, Found $[M-H]^-$; 168.0400, 168.00, neutral monoisotopic mass: 168.0394 Da; MS (*m/z*): Calc. $[M+Na]^+$; 191.0286, Found $[M+Na]^+$; 191.0286.

2-boronic acid-benzaldehyde, 138



The title compound was prepared according the general procedure 32 from 1-bromo-2-dimethoxymethyl-benzene (500 mg, 2.25 mmol) using *n*-Butyl-lithium (1.6M in hexane, 1.70 mL, 2.70 mmol) and trimethyl botate (0.30 mL, 2.70 mmol) followed by quenching with HCl 2M (2.5 mL) to afford a recrystallised white precipitate in 65% yield (220 mg, 1.50 mmol).

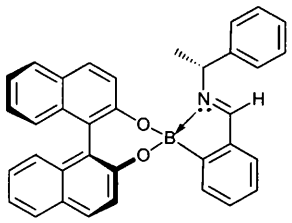
The title compound was also prepared according to the general procedure 33 to yield the desired 2-boronic acid-benzaldehyde in 58% yield (196 mg, 1.30 mmol). m.p = 115-120°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5 (br s, 2H, 2XO*H*), 7.6 (m, 2H, Ar*H*), 7.8 (q, *J* 2.5 Hz, 1H, Ar*H*), 8.3 (q, J 3.8, 3.9 Hz, 1H, Ar*H*), 9.8 (s, 1H, C*H*O_2); ^{13}C (75.5 MHz,

$CDCl_3$) 131.5, 134.7, 139.0, 197.45 (*C*=O); MS (*m/z*): 152.0, 151.0, 150.1 [M^+] (100), 149.0 (40), 134.2 (25), 133.2 (15), 124.2 (9), 106.0 (38), 58.2 (8); ^{11}B NMR (96 MHz, $CDCl_3$) δ 29.1 ($ArBOH_2$).

5.16 GENERAL PROCEDURE 34: general procedure for the derivatisation of chiral diol[60-64]

General procedure 34: the corresponding racemic amine (1 equiv.), chiral diol (1 equiv.) and formylphenylboronic acid (1 equiv.) were stirred in $CDCl_3$ under nitrogen atmosphere for 5 minutes. H NMR analysis was then directly taken from the solution. Subsequently the solvent was evaporated *in vacuum* to dryness to yield yellow oils or occasionally yellow precipitates.

(*E*,1*R*,*S*)-N-(2-((*S*)-Naphto[2,1,2,3-def][1,3,2]dioxaborepin-4-yl)benzylidene)-1-phenylethanamine (*S*,*R*)-108c [63, 64]

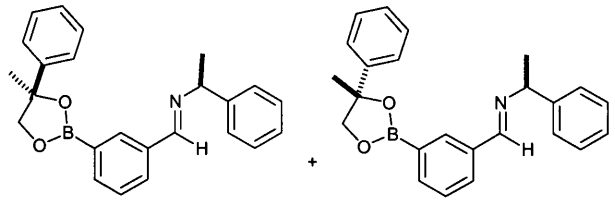


(*S*,*R*)-108c

The title compound was synthesised according to general procedure 34 using (*R*)-1-phenylethylamine (52 μL, 0.40 mmol), 2-formylphenylboronic acid (60 mg, 0.4 mmol), (*S*)-BINOL (114 mg, 0.40 mmol) and 1 mol $CDCl_3$. Evaporation of the solvent gave a yellow solid (201 mg, >99%), mp: 143-146°C (Lit data for one of the diastereoisomers: 195°C); IR ν_{max} (KBr)/cm^{-1} 1625 (C=N).^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, *J* 6.7 Hz, 3H, Me), 1.70 (d, *J* 6.8 Hz, 3H, C*H*$_3$CH), 4.80 (q, *J* 7.5 Hz, 1H, C*H*CH$_3$), 4.90 (q, *J* 7.2 Hz, 1H, C*H*CH$_3$), 6.80 (t, *J* 6.9 Hz, 1H, Ar*H*), 7.00-7.80 (m, 20H, Ar*H*), 8.00 (s, 1H, *H*C=N), 8.15 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 21.1 (*C*H$_3$), 21.5 (*C*H$_3$), 57.0 (*C*HCH$_3$), 59.0 (*C*HCH$_3$), 111.9, 118.3, 122.3, 122.3, 123.2, 123.4, 123.4, 123.6, 123.7, 123.7, 123.8, 123.8, 123.8, 124.3, 124.8, 125.7, 125.7, 125.8, 126.0, 126.9, 127.5, 127.6, 127.7, 127.8, 128.0, 128.2, 128.4, 128.6, 128.8, 129.0, 129.1, 129.2, 129.3,

129.4, 129.6, 129.8, 130.2, 130.6, 130.7, 130.8, 131.6, 133.7, 133.7, 133.8, 133.6, 133.7, 133.7, 133.8, 133.9, 134.0, 134.2, 137.1, 137.4, 139.7, 140.5, 153.2, 154.4, 154.6, 154.8, 155.1, 166.1, 169.3 (*C*=N), 169.7 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 12.06. MS (*m/z*): Calc [M^+]; 503.2129, Found [M^+]; 503.2053.

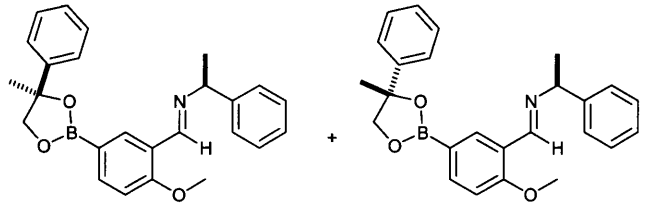
(*E*,1*R*)-N-[3-(4-Methyl-4-phenyl-[1,2,3]dioxaborolan-2-yl)benzylidene]-(1-phenyl-ethyl) –amine (*R*,α-*R*)-123 + (*S*,α-*R*)-124



(*rac*)-123 **(*rac*)-124**

This compound was synthesised according to general procedure 34 using (*R*)-1-phenylethylamine (52 μL, 0.40 mmol), 3-formylphenylboronic acid (60 mg, 0.40 mmol), (*rac*)-2-Phenyl-1,2-propanediol (61 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a yellow oil (146 mg, 99%). IR ν_{max} (neat)/cm^{-1} 1633 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, *J* 7.0 Hz, 3H, C*H*$_3$), 1.70 (s, 3H, C*H*$_3$), 4.25 (d, *J* 8.8 Hz, 1H, C*H*$_2$), 4.26 (d, *J* 8.7 Hz, 1H, C*H*$_2$), 4.44 (q, *J* 6.6 Hz, 1H, C*H*CH$_3$), 7.00-7.40 (m, 13H, Ar*H*), 7.90 (tt, *J* 1.1, 2.4 Hz, 1H, Ar*H*), 8.15 (s, 1H, Ar*H*) , 8.30 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) 25.3 (*C*H$_3$), 30.1 (*C*H$_3$), 70.2 (*C*H), 79.4 (*C*), 84,1 (*C*H$_2$), 124.7, 126.1, 127.1, 127.8, 128.6, 128.9, 128.9, 128.9, 131.3, 136.3, 137.6, 146.3, 160.0 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.46; NOESY (400 MHz): 100% *E* isomer; MS (*m/z*): Calc [M^+]; 370.1973, Found [M^+]; 370.1973, neutral monoisotopic mass: 369.1900 Da. 254.1348 (100) [M^+-diol].

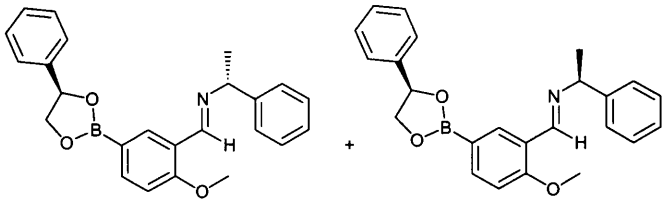
(*E*,1*R*,*S*)-N-[2-Methoxy-5-(4-methyl-4-phenyl-[1,3]dioxalan-2-yl)-benzylidene]-(1-phenyl-ethyl)-amine (*rac*)-125 + (*rac*)-126



(*rac*)-125 **(*rac*)-126**

The title compound was synthesised according to general procedure 34 using (*rac*)-1-phenylethylamine (52 μL, 0.40 mmol), 3-formyl-4-methyl phenylboronic acid (72 mg, 0.40 mmol), (*rac*)- 2-phenyl-1,2-propane diol (61 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a yellow solid (159 mg, >99%). m.p: 128-130°C. IR ν_{max} (neat)/cm^{-1} 1680 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, *J* 3.2 Hz, 3H, C*H*$_3$), 1.56 (d, *J* 3.2 Hz, 3H, C*H*$_3$), 1.65 (s, 6H, 2XC*H*$_3$), 3.70 (s, 3H, C*H*$_3$O), 4.25 (d, *J* 8.8 Hz, 1H, C*H*H), 4.26 (d, *J* 8.7 Hz, 1H, CH*H*), 4.44 (q, *J* 6.4 Hz, 2H, C*H*CH$_3$), 6.80 (d, *J* 8.5 Hz, 1H, Ar*H*), 7.00-7.40 (m, 10H, 2XPh*H*), 7.8 (dd, *J* 1.9, 8.3 Hz, 1H, Ar*H*), 8.50 (s, Ar*H*), 8.80 (s, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 25.4 (*C*H$_3$), 30.0 (*C*H$_3$), 55.9 (*C*H), 56.1 (*C*H$_3$O), 83.9 (*C*), 84,1 (*C*H$_2$), 111.6, 124.7, 124.8, 124.9, 126.2, 127.1, 127.7, 128.8, 128.9, 135.0, 139.3, 146.5, 161.8, 164.5 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 29.45; NOESY (400 MHz): 100% *E* isomer; MS (m/z): Calc [M^+]; 400.2079, Found [M^+]; 400.2072, neutral monoisotopic mass: 399.2006.

(*E*,1*R*,*S*)-N-[2-Methoxy-5-(4-phenyl-[1,3,2]dioxoborolan-2-yl)-benzylidene]-(1-phenyl-ethyl)-amine (*R*,α-*R*)-127 + (*R*,α-*S*)-127

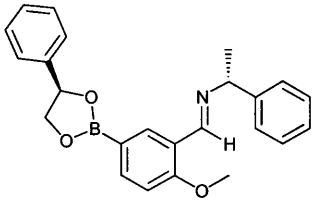


(*R*,*R*)-127 **(*R*,*S*)-127**

The title compound was synthesised according to general 34 procedure using (*rac*)-1-phenylethylamine (52 μL, 0.40 mmol), 3-formyl-4-methyl phenylboronic acid (72 mg, 0.40 mmol), (*R*)-1-Phenyl-1,2-ethanediol (55.3 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a pale yellow solid (154 mg, >99%). m.p: 137-139°C. IR ν_{max} (neat)/cm^{-1} 1683 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, *J* 1.7 Hz, 3H, C*H*$_3$), 1.61 (d, *J* 2.1 Hz, 3H, C*H*$_3$), 3.8 (s, 6H, 2XC*H*$_3$O), 4.25 (t, *J* 8.3 Hz, 2H, 2XC*H*O), 4.60 (q, *J* 6.6 Hz, 2H, 2XC*H*CH$_3$), 4.75 (t, *J* 8.5 Hz, 2H, 2XC*H*HO), 5.6 (t, *J* 7.9 Hz, 2H, 2XCHC*H*O), 6.80 (d, *J* 8.5 Hz, 1H, Ar*H*), 7.00-7.40 (m, 10H, Ph*H*), 7.9 (dd, *J* 1.9, 8.3 Hz, 1H, Ar*H*), 8.60 (s, 1H, Ar*H*), 8.75 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 25.4 (*C*H$_3$), 55.9 (*C*HCH$_3$), 56.1 (CH$_3$O), 70.8 (*C*H$_2$), 73.9 (*C*H$_2$), 79.4 (*C*HO), 111.6, 124.9, 126.0, 126.1, 127.1, 127. 2, 128.6, 128.9, 128.8, 129.2, 135.2, 136.9, 141.3, 141.5,

143.1, 145.8, 155.7, 161.8 (*C*=N), 164.5 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.55; NOESY (400 MHz): 100% *E* isomer; MS (*m/z*): Calc $[M-H]^+$; 385.1958 (^{10}B), Found $[M-H]^+$; 385.1963.

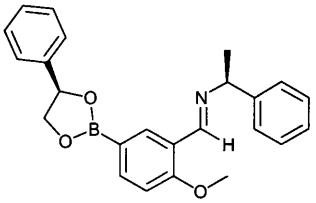
(*E*,1*R*)-N-[2-Methoxy-5-(4-phenyl-[1,3,2]dioxoborolan-2-yl)-benzylidene]-(1-phenyl-ethyl)-amine (*R*,α-*R*)-127



(*R,R*)-127

The title compound was synthesised according to general procedure 34 using (*R*)-1-phenylethylamine (52 μL, 0.40 mmol), 3-formyl-4-methyl phenylboronic acid (72 mg, 0.4 mmol), (*R*)-1-Phenyl-1,2-ethanediol (55 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a pale yellow solid (153 mg, >99%). m.p: 137-139°C. $[\alpha]_D^{25}$ -29.0 (c 1.01, $CHCl_3$). IR ν_{max} (neat)/cm^{-1} 1679 (C=N) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, *J* 2.1 Hz, 3H, C*H*$_3$), (s, 3H, C*H*$_3$O), 4.25 (t, *J* 8.3 Hz, H, C*H*O), 4.60 (q, *J* 6.6 Hz, H, C*H*CH$_3$), 4.75 (t, *J* 8.5 Hz, 1H, C*H*HO), 5.6 (t, *J* 7.9 Hz, 1H, CHC*H*O), 6.80 (d, *J* 8.5 Hz, 1H, Ar*H*), 7.00-7.40 (m, 10H, Ph*H*), 7.9 (dd, *J* 1.9, 8.3 Hz, 1H, Ar*H*), 8.60 (s, 1H, Ar*H*), 8.75 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) δ 25.4 (*C*H$_3$), 55.9 (*C*HCH$_3$), 56.1 (CH$_3$O), 70.8 (*C*H$_2$), 73.8 (*C*H$_2$), 79.4 (*C*HO), 110.8, 124.9, 126.2, 127.1, 127.4, 128.6, 128.8, 129.0, 129.2, 135.2, 139.4, 141.5, 143.1, 145.9, 155.7, 161.8 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.89; NOESY (400 MHz): 100% *E* isomer; MS (*m/z*): Calc $[M-H]^+$; 385.1958 (^{10}B), Found $[M-H]^+$; 385.1963.

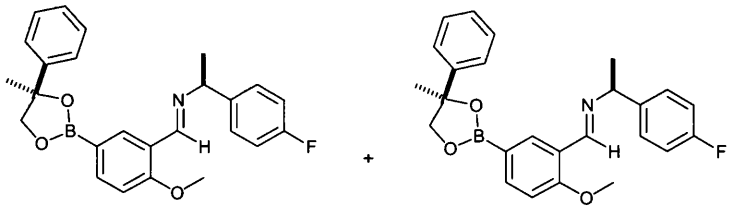
(*E*,1*R*)-N-[2-Methoxy-5-(4-phenyl-[1,3,2]dioxoborolan-2-yl)-benzylidene]-(1-phenyl-ethyl)-amine (*R*,*S*)-127



(*R,S*)-127

The title compound was synthesised according to general procedure 34 using (*R*)-1-phenylethylamine (51 μL, 0.40 mmol), 3-formyl-4-methyl phenylboronic acid (72 mg, 0.40 mmol), (*R*)-1-Phenyl-1,2-ethanediol (55 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a pale yellow solid (153 mg, >99%). m.p: 137-139°C. $[\alpha]_D^{25}$ -125.06 (c 1.010, $CHCl_3$). IR ν_{max} (neat)/cm^{-1} 1679 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, *J* 2.1 Hz, 3H, C*H*$_3$), (s, 3H, C*H*$_3$O), 4.25 (t, *J* 8.3 Hz, H, C*H*O), 4.60 (q, *J* 6.6 Hz, H, C*H*CH_3), 4.75 (t, *J* 8.5 Hz, 1H, C*H*HO), 5.6 (t, *J* 7.9 Hz, 1H, CHC*H*O), 6.80 (d, *J* 8.5 Hz, 1H, Ar*H*), 7.00-7.40 (m, 10H, Ph*H*), 7.9 (dd, *J* 1.9, 8.3 Hz, 1H, Ar*H*), 8.60 (s, 1H, Ar*H*), 8.75 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) δ 25.4 (*C*H_3), 55.9 (*C*HCH_3), 56.1 (CH_3O), 70.8 (*C*H_2), 73.8 (*C*H_2), 79.4 (*C*HO), 110.8, 124.9, 126.2, 127.1, 127.4, 128.6, 128.8, 129.0, 129.2, 135.2, 139.4, 141.5, 143.1, 145.9, 155.7, 161.8 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.61; NOESY (400 MHz): 100% *E* isomer; MS (*m/z*): Calc. $[M-H]^+$; 385.1958 (^{10}B), Found $[M-H]^+$; 385.1963.

(*E*,1*R*,*S*)-N-[1-(4-Fluoro-phenyl)-ethyl]-[2-Methoxy-5-(4-methyl-4-phenyl-[1,3,2]dioxaborolan-2-yl)-benzylidene]-amine (*rac*)-129 + (*rac*)-130

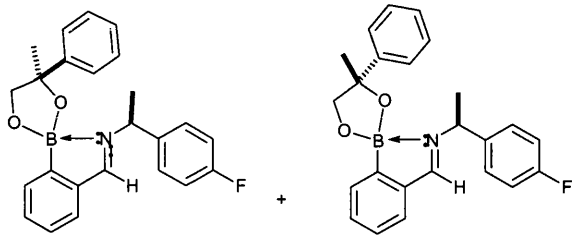


(*rac*)-129 **(*rac*)-130**

The title compound was synthesised according to general procedure 34 using (*rac*)-4-fluoro-1-phenylethylamine (37 μL, 0.40 mmol), 3-formyl-4-methyl phenylboronic acid (72 mg, 0.40 mmol), (*rac*)- 2-phenyl-1,2-propane diol (61 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a yellow solid (83 mg, 50%). IR ν_{max} (neat)/cm^{-1} 1683 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, *J* 3.4 Hz, 3H, C*H*$_3$), 1.56 (d, *J* 3.4 Hz, 3H, C*H*$_3$), 1.65 (s, 6H, 2XC*H*$_3$), 3.80 (s, 5H, 2XC*H*$_3$O), 4.29 (d, *J* 8.8 Hz, 1H, C*H*H), 4.30 (d, *J* 8.6 Hz, 1H, CH*H*), 4.45 (q, *J* 6.6 Hz, 2H, C*H*CH_3), 6.85 (d, *J* 8.3 Hz, 1H, Ar*H*), 7.00-7.40 (m, 9H, 2XAr*H*), 7.8 (dd, *J* 1.9, 8.5 Hz, 1H, Ar*H*), 8.50 (s, 1H, Ar*H*), 2 X 8.75 (s, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 25.5 (*C*H_3), 30.0 (*C*H_3), 55.9 (*C*H), 56.1 (*C*H_3O), 83.9 (*C*), 84.1 (*C*H_2), 115.3, 115.6, 124.6, 124.7, 125.5, 127.5, 127.7, 128.6, 128.7, 128.8, 128.9, 134.9, 136.7, 146.4, 155.9, 161.7, 163.7, 164.5

(*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.75; ^{19}F NMR (400 MHz, $CDCl_3$) δ -116.60 (s, F-Ar), -116.64 (s, F-Ar).

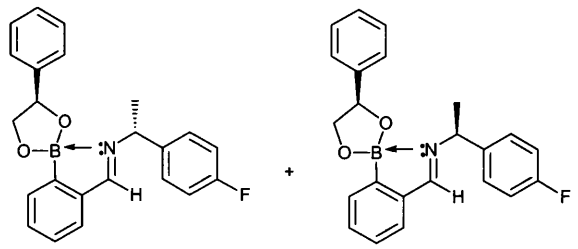
(*E*,1*R*,*S*)-N-(4-Methyl-(4-Phenyl-[1,3,2]dioxaborolan-2-yl)benzylidene)-4-fluoro-1-phenylethanamine (*rac*)-132a + (rac)-133a



(*rac*)-132a **(*rac*)-133a**

The compound was synthesised according to general procedure 34 using (*rac*)-4-fluoro-1-phenylethylamine (37 μL, 0.40 mmol), 2-formylphenylboronic acid (60 mg, 0.40 mmol), 2-phenyl-1,2-propanediol **131a** (61 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a yellow oil (77 mg, 50%). IR ν_{max} (neat)/cm^{-1} 1692 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, *J* 7.6 Hz, 3H, C*H*$_3$), 1.15 (d, *J* 8.3 Hz, 3H, C*H*$_3$), 1.70 (s, 6H, 2XC*H*$_3$), 4.10 (m, 4H, 2XC*H*$_2$), 4.80 (q, 2H, *J* 6.7, 2H, 2XC*H*Me), 6.90-7.90 (m, 13H, Ph*H*), 8.15 (s, 1H, *H*C=N), 8.20 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 20.51 (*C*H$_3$), 20.70 (*C*H$_3$), 29.79 (*C*H$_3$), 29.95 (*C*H$_3$), 56.95 (*C*H), 57.15 (*C*H), 80.38 (*C*H$_2$), 80.44 (*C*H$_2$), 114.82, 126.38, 127.05, 127.24, 127.29, 130.02, 130.28, 130.38, 131.96, 132.02, 135.58, 137.11, 147.31, 159.54, 164.69 (*C*=N), 164.81 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 16.11; ^{19}F NMR (400 MHz, $CDCl_3$) δ 114.10 (s, F-Ar), - 114.40 (s, F-Ar); MS (m/z): Calc [M$^+$]; 388.1806, Found [M$^+$]; 388.1897.

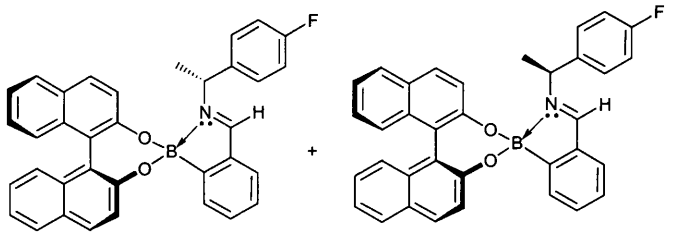
(*E*,1*R*,*S*)-N-(2-(4-Phenyl-[1,3,2]dioxaborolan-2-yl)benzylidene)-4-fluoro-1-phenylethanamine (*R*,α-*R*)-132b + (*R*,α-*S*)-133b



(*R*,*R*)-132b **(*R*,*S*)-133b**

The compound was synthesised according to general procedure 34 using (*rac*)-4-fluoro-1-phenylethylamine (37 μL, 0.4 mmol), 2-formylphenylboronic acid (60 mg, 0.4 mmol), (*R*)-1,2-phenylethanediol **131b** (55 mg, 0.4 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent gave a dark yellow solid (75 mg, 50%). IR ν_{max} (neat)/cm^{-1} 1689 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, *J* 2.3 Hz, 3H, CH_3), 1.71 (d, *J* 2.1 Hz, 3H, CH_3), 3.80 (br q, *J* 8.3 Hz, 2H, CH_AH$_B$O), 4.40 (br s, 2H, CH$_A$$H_B$O), 5.05 (q, *J* = 7.2 Hz, 2H, 2XC*H*CH$_3$), 5.30 (br s, 1H, C*H*CH$_3$), 5.60 (t, *J* = 7.7 Hz, 1H, C*H*CH$_3$), 7.00-7.90 (m, 13H, PhC*H*), 8.05 (s, 1H, *H*C=N), 8.15 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 21.8 (*C*H$_3$CH), 58.4 (*C*HMe), 72.8 (*C*H$_2$O), 79.7 (*C*HO), 116.0, 126.7, 127.6, 128.6, 128.8, 129.1, 129.2, 129.4, 129.5, 129.6, 131.5, 135.9, 136.5, 141.7, 143.4, 166.7 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 16.11; ^{19}F NMR (400 MHz, $CDCl_3$) δ -113.80 (s, F-Ar), -114.00 (s, F-Ar).

(*E*,1*R*,*S*)-N-(2-((*S*)-Naphto[2,1,2,3-def][1,3,2]dioxaborepin-4-yl)benzylidene)-4-fluoro-1-phenylethanamine (*S*,α-*R*)-132c + (*S*,α-*S*)-133c

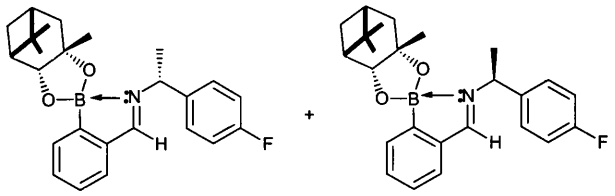


(*S*,*R*)-132c **(*S*,*S*)-133c**

The title compound was synthesised according to general procedure 34 using (*rac*)-4-fluoro-1-phenylethylamine (37 μL, 0.40 mmol), 2-formylphenylboronic acid (60 mg, 0.40 mmol), (*S*)-BINOL **131c** (114 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent gave a yellow solid (202 mg, 96%). m.p: 277-280°C. IR ν_{max} (neat)/cm^{-1} 1685 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, *J* 7.2 Hz, 3H, CH_3), 1.70 (d, *J* 7.2 Hz, 3H, CH_3), 4.80 (q, *J* 7.0 Hz, 1H, C*H*CH$_3$), 4.90 (q, *J* 6.6 Hz, 1H, C*H*CH$_3$), 6.80-7.80 (m, 20H, Ar*H*), 8.00 (s, 1H, *H*C=N), 8.15 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 20.18 (*C*H$_3$), 20.41 (*C*H$_3$), 54.86 (*C*HCH$_3$), 56.78 (*C*HCH$_3$), 110.2, 114.26, 114.5, 114.7, 114.9, 115.2, 116.7, 120.9, 121.6, 121.7, 121.8, 122.0, 122.2, 122.3, 122.4, 122.8, 123.2, 124.2, 124.3, 125.5, 125.9, 126.0, 126.1, 126.3, 126.8, 126.9, 127.1, 127.3, 127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 129.1, 129.2, 129.3, 130.1, 132.1, 132.1, 132.3, 132.4, 132.4, 132.9, 134.0, 134.8, 135.5, 135.7,

151.6, 152.7, 152.9, 153.1, 153.3, 159.6, 159.9, 162.8, 167.8, 167.8 (*C*=N), 168.0 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 11.79; ^{19}F NMR (400 MHz, $CDCl_3$) δ -113.20 (s, F-Ar), -113.75 (s, F-Ar). MS (m/z): Calc $[M]^+$; 521.1957 (^{11}B), Found $[M]^+$; 521.1961.

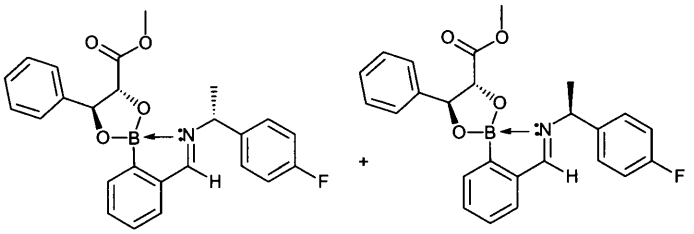
(*E*,1*R*,*S*)-N-(1-Phenyl-ethyl)-[2-(6, 9, 9-trimethyl-3,5-dioxa-4-bora-tricyclo[6. 1. 0^{2,6}] dec-4-yl)-bezylidene)-4-fluoro-1-phenylethanamine (*R*,*R*,*R*,*R*,α-*R*)-132d + (*R*,*R*,*R*,*R*,α-*S*)-133d



(*R*,*R*,*R*,*S*,*R*)-132d **(*R*,*R*,*R*,*S*,*S*)-133d**

The compound was synthesised according to general procedure 34 using (*rac*)-4-fluoro-1-phenylethylamine (37 μL, 0.40 mmol), 2-formylphenylboronic acid (60 mg, 0.40 mmol), 3,6,6-Trimethyl-bicyclo[3.1.1]-2,3-heptanediol **131d** (68 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a yellow oil (58 mg, 50%). IR ν_{max} (neat)/cm^{-1} 1733 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 6H, 2XC*H*$_3$), 1.25 (s, 6H, 2XC*H*$_3$), 1.40 (d, *J* 4.3 Hz, 3H, C*H*$_3$), 1.55 (d, *J* 6.6 Hz, 3H, C*H*$_3$), 1.90 (m, 6H, 3XC*H*$_2$), 2.10 (m, 2H, C*H*$_2$), 2.15 (m, 2H, 2XC*H*), 2.30 (m, 2H, 2XC*H*), 4.35 (dc, *J* 1.7, 3.4 Hz, 2H, 2XC*H*O), 4.45 (q, *J* 6.9 Hz, 2H, 2XC*H*CH$_3$), 7.00 (m, 1H, Ar*H*), 7.10-7.40 (m, 5H, Ar*H*), 7.70 (m, 2H, Ar*H*), 8.90 (s, 1H, *H*C=N), 9.00 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 23.0 (*C*H$_3$), 23.18 (*C*H$_3$), 23.2 (*C*H$_3$), 25.4 (*C*H$_3$), 25.5 (*C*H$_3$), 26.0 (*C*H$_3$), 26.1 (*C*H$_2$), 27.5 (*C*H$_2$), 27.6 (*C*H$_2$), 27.6 (*C*H$_2$), 34.4 (*C*H$_2$), 34.5 (*C*H$_2$), 34.6 (*C*H$_2$), 37.2 (*C*Me$_2$), 38.5 (*C*), 38.5 (*C*), 50.3 (*C*), 50.5 (*C*), 66.6 (*C*HCH$_3$), 66.7 (*C*HCH$_3$), 77.1 (*C*), 77.4 (*C*), 85.1 (*C*H), 85.8 (*C*H), 114.1, 114.7, 125.9, 126.9, 127.1, 127.2, 127.2, 127.3, 127.4, 128.6, 129.6, 129.7, 132.0, 134.1, 134.5, 139.5, 139.6, 139.6, 140.2, 140.4, 159.1, 160.6, 160.6 (*C*=N), 162.3 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.81; ^{19}F NMR (400 MHz, $CDCl_3$) δ -116.38 (s, F-Ar), -116.43 (m, F-Ar). MS (m/z): Calc $[M+1]^+$; 406.2353, Found $[M+1]^+$; 406.2383.

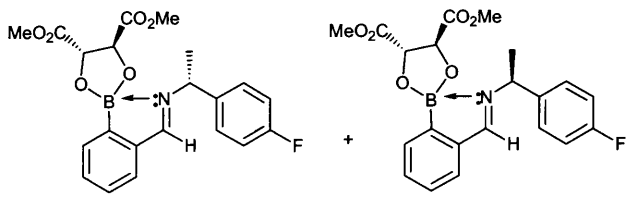
(*E*,1*R*,*S*)-N-2-(2-{[1-(4-Fluoro-phenyl)-ethylimino]-methyl]-phenyl}-5-phenyl-[1,2,3]dioxaborolane-4-carboxylic acid methyl ester (2*S*,3*R*,α-*R*)-132e + (2*S*,3*R*,α-*S*)-133e



(*S*,*R*,*R*)-132e **(*S*,*R*,*S*)-133e**

The compound was synthesised according to general procedure 34 using (*rac*)-4-fluoro-1-phenylethylamine (37 μL, 0.40 mmol), 2-formylphenylboronic acid (60 mg, 0.40 mmol), 2,3-dihydroxy-3-phenyl-propionic acid methyl ester **131e** (78 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a yellow oil (112 mg, 65%). IR ν_{max} (neat)/cm^{-1} 1746 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, *J* 6.8 Hz, 6H, 2XC*H*$_3$), 3.70 (s, 3H, 2XC*H*$_3$O), 4.40 (d, *J* 7.3 Hz, 1H, C*H*COOMe), 4.55 (d, *J* 7.7 Hz, 1H, C*H*COOMe), 4.75 (d, *J* 8.3 Hz, 1H, Ph*H*), 5.25 (d, *J* 7.7 Hz, 1H, PhC*H*), 5.35 (q, *J* 7.2 Hz, 1H, C*H*CH$_3$), 5.45 (q, *J* 6.8 Hz, 1H, C*H*CH$_3$), 6.90 (t, *J* 8.5 Hz, 2H, Ar*H*), 7.00 (t, *J* 9.0 Hz, 2H, Ar*H*), 7.00-7.60 (m, 9H, Ph*H*), 7.90 (s, 1H, *H*C=N), 8.20 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) δ 19.7 (*C*H$_3$), 20.7 (*C*H$_3$), 51.0 (*C*H$_3$O), 51.8 (*C*H$_3$O), 54.8 (*C*HMe), 55.4 (*C*HMe), 79.9 (*C*HO), 81.1 (*C*HO), 81.3 (*C*HCOOMe), 81.4 (*C*HCOOMe), 114.8, 115.0, 125.1, 125.2, 126.6, 126.6, 127.7, 127.8, 127.9, 128.0, 128.6, 128.7, 129.4, 129.5, 130.2, 132.4, 132.7, 132.9, 135.2, 136.2, 136.2, 138.8, 140.2, 141.3, 141.4, 159.6, 162.9 (*C*=N), 163.2 (*C*=N), 172.8 (*C*O), 172.9 (*C*O); ^1B NMR (96 MHz, $CDCl_3$) δ 14.47; ^{19}F NMR (400 MHz, $CDCl_3$) δ -113.30 (s, F-Ar), -114.05 (s, F-Ar).

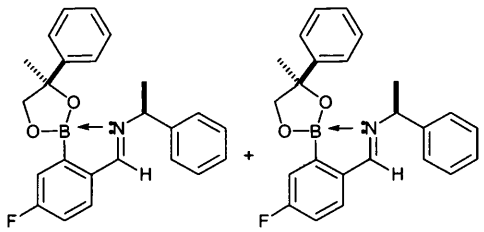
(4*S*, 5*S*)-Dimethyl 2-(2-((*E*)-((*R*,*S*)-1-phenylethylimino)methyl)-4-fluoro-phenyl)-1,3,2-dioxoborolane-4,5-dicarboxylate (2*S*3*S*,α-*R*)-132f + (2*S*3*S*,α-*S*)-133f



(2*S*3*S*,*R*)-132f **(2*S*3*S*,*S*)-133f**

The compound was synthesised according to general procedure 34 using (*rac*)-4-fluoro-1-phenylethylamine (37 μL, 0.40 mmol), 2-formylphenylboronic acid (60 mg, 0.40 mmol), (+)-Dimethyl-L-tartrate **131f** (71 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent gives the boronate (115 mg, 67%) as a yellow oil. IR ν_{max} (neat)/cm^{-1} 1687 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, *J* 4.9 Hz, 3H, C*H*$_3$), 1.71 (d, *J* 4.7 Hz, 3H, C*H*$_3$), 3.75 (s, 12H, 4XCH$_3$OCO), 4.55 (s, 1H, CHCOOMe), 4.85 (s, 1H, CHCOOMe), 5.30 (q, *J* 7.2 Hz, C*H*CH$_3$), 5.45 (q, *J* 6.8 Hz, C*H*CH$_3$), 7.00-7.60 (m, 8H, PhC*H*), 7.90 (s, 1H, *H*C=N), 8.25 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 19.6 (*C*H$_3$), 20.6 (*C*H$_3$), 51.4 (*C*H$_3$O), 51.4 (*C*H$_3$O), 54.3 (*C*H), 54.8 (*C*H), 76.3 (*C*HO), 76.5 (*C*HO), 115.0 (Ar*C*H), 127.8 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 129.6 (Ar*C*H), 129.7 (Ar*C*H), 133.0 (Ar*C*H), 135.1 (Ar*C*), 136.0 (Ar*C*), 167.4 (Ar*C*), 168.1 (*C*=N), 170.9 (*C*=N), 172.1 (*C*=O), 172.3 (*C*=O); ^{11}B NMR (96 MHz, $CDCl_3$) δ 14.36; ^{19}F NMR (400 MHz, $CDCl_3$) δ -113.25 (s, F-Ar), -114.00 (s, F-Ar). MS (*m/z*): Calc. $[M]^+$; 414.1519, Found $[M]^+$; 414.1522.

(*E*,1*R*,*S*)-N-(4-Methyl-(4-Phenyl-[1,3,2]dioxaborolan-2-yl)-4-fluoro-benzylidene)-1-phenylethanamine (*rac*)-143a + (*rac*)-144a

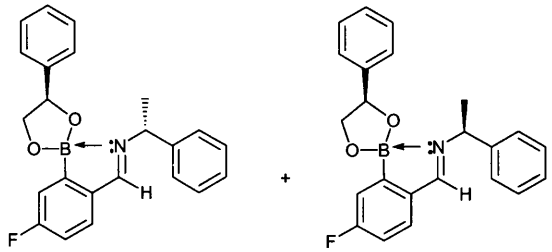


(*rac*)-143a **(rac)-144a**

The compound was synthesised according to general procedure 34 using (*rac*)-1-phenylethylamine (52 μL, 0.40 mmol), 4-fluoro-2-formylphenylboronic acid **134** (67 mg, 0.40 mmol), 2-phenyl-1,2-propanediol **131a** (61 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent gave a yellow oil (155 mg, >99%). IR ν_{max} (neat)/cm^{-1} 1690 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, *J* 7.16 Hz, 3H, C*H*$_3$), 1.65 (d, *J* 7.16 Hz, 3H, C*H*$_3$), 2.10 (s, 6H, 2XC*H*$_3$), 4.10 (m, 4H, 2XC*H*$_2$), 4.80 (q, 2H, J 6.9Hz, 2H, 2XC*H*CH$_3$), 7.00-7.60 (m, 9H, Ph*H*), 8.05 (s, 1H, *H*C=N), 8.15 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 21.6 (*C*H$_3$), 31.4 (*C*H$_3$), 58.6 (*C*H), 81.8 (*C*), 81.8 (*C*H$_2$), 125.0, 127.1, 127.5, 127.7, 128.3, 128.6, 129.1, 129.2, 129.3, 131.6, 138.5, 141.0, 149.0, 164.0 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 20.42; ^{19}F NMR (400 MHz, $CDCl_3$) δ -112.45

(d, F-Ar), -112.71 (d, F-Ar); NOE (^{19}F irradiation) δ 7.2 (ArH-F); MS (m/z): Calc [M^+]; 388.1879, Found [M^+]; 388.1886, neutral monoisotopic mass: 387.1806 Da.

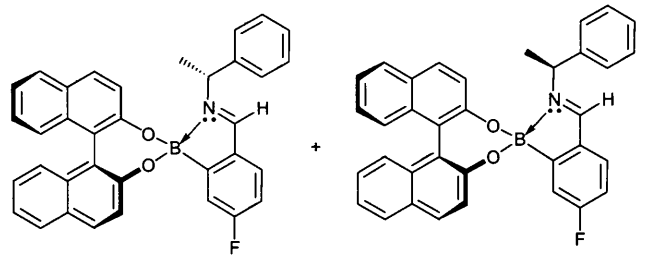
(*E*,1*R*,*S*)-N-(2-(4-Phenyl-[1,3,2]dioxaborolan-2-yl)-4-fluoro-benzylidene)-1-phenylethanamine (*R*,α-*R*)-143b + (*R*,α-*S*)-144b



(*R*,*R*)-143b **(*R*,*S*)-144b**

The compound was synthesised according to general procedure 34 using (*rac*)-1-phenylethylamine (51 μL, 0.40 mmol), 4-fluoro-2-formylphenylboronic acid **134** (68 mg, 0.40 mmol), (*R*)-1,2-phenylethanediol **131b** (55 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent gave a dark yellow solid (149 mg, 99%). IR ν_{max} (neat)/cm^{-1} 1646 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, *J* 6.97 Hz, 6H, 2XC*H*$_3$), 3.80 (q, *J* 7.9 Hz, 2H, C*H*$_A$H$_B$O), 4.40 (q, *J* 8.7 Hz, 2H, CH$_A$*H*$_B$O), 5.05 (q, *J* 7.5 Hz, 2H, 2XC*H*CH$_3$), 5.20 (t, *J* 7.7 Hz, 1H, C*H*CH$_3$), 5.30 (t, *J* 7.5 Hz, 1H, C*H*CH$_3$), 7.00-7.60 (m, 13H, Ph*H*), 8.15 (s, 1H, *H*C=N), 8.25 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) δ 21.9 (*C*H$_3$CH), 51.6 (*C*HCH$_3$), 72.9 (*C*H$_2$O), 80.0 (*C*HO), 119.7, 120.0, 126.0, 126.3, 127.8, 128.5, 128.8, 129.1, 129.4, 133.4, 140.3, 165.0 (*C*=N), 166.0 (Ar*C*). ^{11}B NMR (96 MHz, $CDCl_3$) δ 17.91; ^{19}F NMR (400 MHz, $CDCl_3$) δ -113.80 (s, F-Ar), -114.00 (s, F-Ar); MS (*m/z*): Calc [M+H]$^+$; 374.1722, Found [M+H]$^+$; 374.1722. neutral monoisotopic mass: 373.1648 Da.

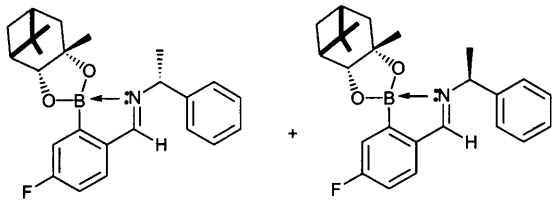
(*E*,1*R*,*S*)-N-(4-fluoro-2-((*S*)-Naphto[2,1,2,3-def][1,3,2]dioxaborepin-4-yl)benzylidene)-1-phenylethanamine (*S*,α-*R*)-143c + (*S*,α-*S*)-144c



(*S*,*R*)-143c **(*S*,*S*)-144c**

This compound was synthesised according to general procedure 34 using (*rac*)-1-phenylethylamine (51 μL, 0.40 mmol), 4-fluor-2-formylphenylboronic acid **134** (67 mg, 0.40 mmol), (*S*)-BINOL **131c** (114 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent gave a dark yellow oil (204 mg, 98%). IR ν_{max} (neat)/cm^{-1} 1684 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, *J* 7.7 Hz, 3H, CH_3), 1.60 (d, *J* 6.8 Hz, 3H, CH_3), 4.80 (q, *J* 6.8 Hz, 1H, $CHCH_3$), 4.90 (q, *J* 6.8 Hz, 1H, $CHCH_3$), 6.80-7.80 (m, 20H, Ar*H*), 8.00 (s, 1H, *H*C=N), 8.15 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 21.09 (CH_3), 21.35 (CH_3), 51.47 ($CHCH_3$), 57.45 ($CHCH_3$), 112.68, 113.5, 113.8, 118.6, 120.7, 120.9, 122.3, 123.1, 123.3, 123.5, 123.7, 123.8, 123.7, 123.9, 124.0, 124.2, 125.0, 125.8, 126.2, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.5, 128.7, 128.8, 129.1, 129.2, 129.3, 129.4, 128.6, 129.7, 129.8, 130.3, 130.3, 130.8, 130.9, 131.3, 132.0, 132.1, 133.7, 133.7, 133.8, 133.9, 134.2, 138.4, 138.5, 138.6, 138.7, 139.3, 140.2, 153.3, 154.2, 154.4, 154.6, 154.9, 161.4, 164.7, 168.3 (*C*=N), 168.7 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 12.68; ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.10 (m, F-Ar), -114.40 (m, F-Ar). MS (m/z): Calc $[M+H]^+$; 522.2035, Found $[M+H]^+$; 522.2029. monoisotopic mass: 521.1962.

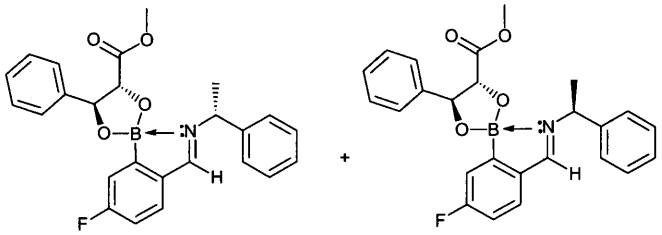
(*E*,1*R*,*S*)-N-(1-Phenyl-ethyl)-[2-(6, 9, 9-trimethyl-3,5-dioxa-4-bora-tricyclo[6. 1. $0^{2,6}$] dec-4-yl)-4-fluoro-bezylidene)-1-phenylethanamine (*R*,*R*,*R*,*R*,α-*R*)-143d + (*R*,*R*,*R*,*R*,α-*S*)-144d



(*R*,*R*,*R*,*S*,*R*)-143d **(*R*,*R*,*R*,*S*,*S*)-144d**

The compound was synthesised according to general procedure 34 using (*rac*)-1-phenylethylamine (36 μL, 0.30 mmol), 4-fluoro-2-formylphenylboronic acid **134** (42 mg, 0.30 mmol), 3,6,6-Trimethyl-bicyclo[3.1.1]-2,3-heptanediol **131d** (43 mg, 0.30 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a dark yellow oil (116 mg, >99%). IR ν_{max} (neat)/cm^{-1} 1654 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 6H, 2XC*H*$_3$), 1.25 (s, 6H, 2XC*H*$_3$), 1.40 (d, *J* 2.5 Hz, 3H, C*H*$_3$), 1.55 (d, *J* 6.8 Hz, 3H, C*H*$_3$), 1.90 (m, 6H, 3XC*H*$_2$), 2.10 (m, 2H, C*H*$_2$), 2.15 (m, 2H, 2XC*H*), 2.30 (m, 2H, 2XC*H*), 4.40 (dd, *J* 1.9, 3.4 Hz, 2H, 2XC*H*-O), 4.45 (c, *J* 6.6 Hz, 2H, 2XC*H*Me), 7.00 (td, *J* 2.64 Hz, 1H, Ar*H*), 7.10-7.40 (m, 5H, Ar*H*), 7.70 (m, 2H, Ar*H*), 8.90 (s, 1H, *H*C=N), 9.00 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 23.0 (*C*H$_3$), 25.4 (*C*H$_3$), 27.5 (*C*H$_3$), 27.6 (*C*H$_2$), 34.5 (*C*H$_2$), 34.6 (*C*H), 38.6 (*C*), 50.5 (*C*HMe), 67.2 (*C*), 85.0 (*C*HO), 124.8, 125.7, 127.3, 127.5, 128.5, 129.4, 134.0, 134.5, 160.4 (*C*=N); ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.45; ^{19}F NMR (400 MHz, $CDCl_3$) δ -109.11 (s, F-Ar), -109.14 (s, F-Ar); MS (m/z): Calc $[M+H]^+$; 406.2348, Found $[M+H]^+$; 406.2361, neutral monoisotopic mass: 405.2274 Da.

(*E*,1*R*,*S*)-N-2-{5-fluoro-2-[(1-phenyl-ethylimine)-methyl]-phenyl}-5-phenyl-[1,2,3]dioxaborolane-4-carboxylic acid methyl ester (2*S*,3*R*,α-*R*)-143e + (2*S*,3*R*,α-*S*)-144e

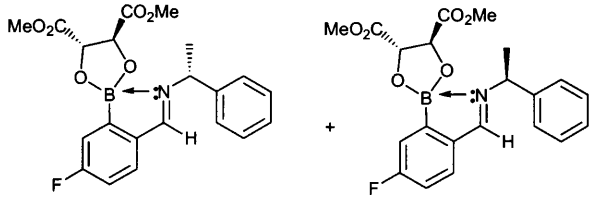


(*S*,*R*,*R*)-143e **(*S*,*R*,*S*)-144e**

The compound was synthesised according to general procedure 34 using (*rac*)-1-phenylethylamine (52 μL, 0.40 mmol), 4-fluoro-2-formylphenylboronic acid **134** (67 mg, 0.40 mmol), 2,3-dihydroxy-3-phenyl-propionic acid methyl ester **131e** (79 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a thick yellow oil (172 mg, >99%). m.p: 60°C. IR ν_{max} (neat)/cm^{-1} 1740 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, *J* 6.8 Hz, 6H, 2XCH$_3$), 3.70 (s, 3H, CH$_3$O), 3.71 (s, 3H, CH$_3$O), 4.40 (d, *J* 7.7 Hz, 1H, C*H*COOMe), 4.55 (d, *J* 7.7 Hz, 1H, C*H*COOMe), 4.75 (d, *J* 7.5 Hz, 1H, Ph*H*), 5.30 (d, *J* 7.9 Hz, 1H, PhC*H*), 5.35 (q, *J* 6.2 Hz, 1H, C*H*CH$_3$), 5.45 (q, *J* 6.2 Hz, 1H,

C*H*CH_3), 7.00-7.60 (m, 13H, Ph*H*), 7.90 (s, 1H, *H*C=N), 8.20 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 20.9 (*C*H_3), 22.1 (*C*H_3), 52.4 (*C*H_3O), 52.5 (*C*H_3O), 57.7 (*C*HMe), 58.1 (*C*HMe), 80.7 (*C*HPh), 81.3 (*C*HPh), 82.5 (*C*HCOOMe), 82.6 (*C*HCOOMe), 113.4, 113.7, 120.5, 126.3, 126.5, 126.6, 127.5, 126.6, 127.5, 128.1, 128.3, 128.5, 128.7, 128.8, 129.0, 129.2, 132.56, 132.4, 139.2, 139.6, 140.4, 140.6, 142.6, 166.6 (*C*=N), 167.18 (*C*=N), 173.6 (*C*=O), 174.2 (*C*=O); ^{1}B NMR (96 MHz, $CDCl_3$) δ 15.05; ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.08 (s, F-Ar), -114.19 (s, F-Ar); MS (m/z): Calc $[M+H]^+$; 432.2376, Found $[M+H]^+$; 432.2394.

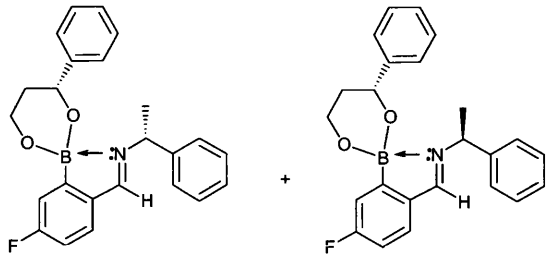
(4*S*, 5*S*)-Dimethyl 2-(2-((*E*)-((*R*,*S*)-4-fluoro-1-phenylethylimino)methyl)phenyl)-1,3,2-dioxoborolane-4,5-dicarboxylate (2*S*3*S*,α-*R*)-143f + (2*S*3*S*,α-*S*)-144f



(2*S*3*S*,*R*)-143f **(2*S*3*S*,*S*)-144f**

The compound was synthesised according to general procedure 34 using (*rac*)-1-phenylethylamine (51 μL, 0.40 mmol), 4-fluoro-2-formylphenylboronic acid **134** (67 mg, 0.4 mmol), (+)-Dimethyl-L-tartrate **131f** (71 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords the boronate (177 mg, >99%) as a yellow oil. IR ν_{max} (neat)/cm^{-1} 1740 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (t, *J* 6.8 Hz, 3H, 2XC*H*$_3$), 3.70 (s, 12H, 4XC*H*$_3$OCO), 4.55 (s, 1H, C*H*COOMe), 4.85 (s, 1H, C*H*COOMe), 5.30 (q, *J* 6.9 Hz, CH-Me), 5.4 (c, *J* 7.2 Hz, C*H*CH_3), 7.00-7.60 (m, 8H, Ph*H*), 7.85 (s, 1H, *H*C=N), 8.20 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) δ 19.36 (*C*H_3), 20.4 (*C*H_3), 51.3 (*C*H_3O), 51.4 (*C*H_3O), 55.6 (*C*H), 55.9 (*C*H), 76.2 (*C*HO), 76.3 (*C*HO), 76.4 (*C*HO), 76.6 (*C*HO), 111.8, 112.1, 119.3, 119.4, 125.6, 126.0, 126.6, 126.9, 127.1, 127.4, 127.6, 127.8, 128.1, 131.2, 137.4, 137.5, 138.8, 166.0 (*C*=N), 166.6 (*C*=N), 170.9 (*C*=O), 172.0 (*C*=O), 172.2 (*C*=O), 173.7 (*C*=O); ^{11}B NMR (96 MHz, $CDCl_3$) δ 13.82; ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.11 (s, F-Ar), -114.27 (s, F-Ar); MS (*m/z*): Calc $[M^+]$; 414.1519, Found $[M^+]$; 414.1515. neutral monoisotopic mass: 413.1446 Da.

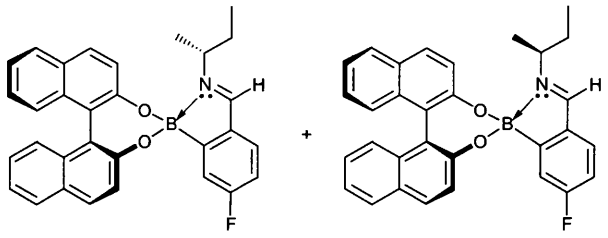
(*E*,1*R*,*S*)-N-(2-(4-Phenyl-[1,3,2] dioxoborian-2-yl)-4-fluoro-benzylidene)-1-phenylethanamine (*R*,α-*R*)-143g + (*R*,α-*S*)-144g



(*R*,*R*)-143g **(*R*,*S*)-144g**

The compound was synthesised according to general procedure 34 using (*rac*)-1-phenylethylamine (51 μL, 0.40 mmol), 4-fluoro-2-formylphenylboronic acid **134** (67 mg, 0.40 mmol), 1-Phenyl-1,3-propanediol **131g** (61 mg, 0.40 mmol) and 1 mL $CDCl_3$. Evaporation of the solvent affords a yellow oil (129 mg, 95%). IR ν_{max} (neat)/cm^{-1} 1689 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, *J* 6.40 Hz, 3H, CH_3), 1.55 (d, *J* 6.40 Hz, 3H, CH_3), 3.2 (m, 4H, 2XC*H*$_2$), 4.00 (s, 2H, 2XC*H*O), 4.50 (t, *J* 2.6, Hz, 2H, 2XC*H*CH_3), 5.00 (br s, 2H, 2XC*H*-Ph), 6.90 (td, *J* 2.6, 8.5Hz, 1H, Ar*H*), 7.10-7.35 (m, 10H, Ph*H*), 7.45 (td, *J* 2.6, 8.3, Hz, 1H, Ar*H*), 7.71 (td, *J* 3.0, 6.2 Hz, 1H, Ar*H*), 8.78 (s, 1H, *H*C=N), 8.90 (s, 1H, *H*C=N); ^{13}C (75.5 MHz, $CDCl_3$) δ 23.9 (*C*H_3), 24.5 (*C*H_3), 51.6 (*C*H_2), 61.76 (*C*HCH_3), 68.7 (*C*HO), 114.5, 114.6, 114.7, 114.8, 116.9, 125.8, 126.3, 127.2, 127.3, 128.0, 128.1, 128.9, 129.1, 129.4, 136.4, 136.5, 136.6, 143.9, 144.2, 144.9, 145.0, 161.16 (*C*=N), 166.0; ^{11}B NMR (96 MHz, $CDCl_3$) δ 27.68. ^{19}F NMR (400 MHz, $CDCl_3$) δ -111.12 (s, F-Ar), -111.20 (s, F-Ar); MS (m/z): Calc $[M+H]^+$; 388.1879, Found $[M+H]^+$; 388.1880, neutral monoisotopic mass: 387.1806.

(*E*,1*R*,*S*)-N-sec-Butyl-[2-(3,5-dioxa-4-bora-cyclohepta[2,1-α;3,4-α′]dinaphthalen-4-yl)-4-fluoro-benzylidene]-amine, (S,α-R)-145 + (S, α-S)-146

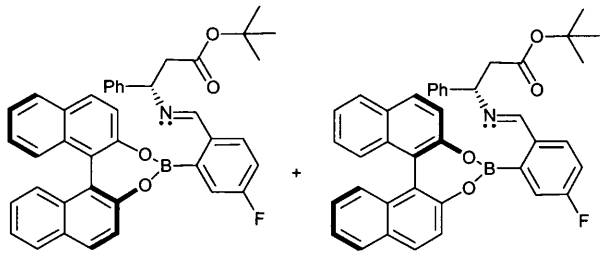


(*S*,*R*)-145 **(*S*,*S*)-146**

The title compound was prepared according to the general procedure 34 using (*rac*)-butylamine (42 μL, 0.40 mmol), 4-fluoro-2-formylphenylboronic acid (67 mg, 0.40

mmol), (*S*)-BINOL (114 mg, 0.40 mL) in 1 mL $CDCl_3$. Evaporation of the solvent gave a yellow oil (187 mg, 99%). IR ν_{max} ($CHCl_3$)/cm^{-1} 1684 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (m, 3H, C*H*$_3$), 1.15 (d, *J* 6.6 Hz, 3H, C*H*$_3$), 1.35 (d, *J* 7.4 Hz, 4H, 2xC*H*$_2$), 3.70 (m, 1H, C*H*CH_3), 3.80 (m, 1H, C*H*CH_3), 6.80 (dd, *J* 5.7, 7.9 Hz, 1H, Ar*H*), 6.85 (dd, *J* 5.6, 7.9 Hz, 1H, Ar*H*), 7.0–7.5 (m, 9H, Ar*H*), 7.8 (m, 1H, Ar*H*), 8.5 (s, 1H, *H*C=N), 8.6 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) 17.4 (*C*H_3), 18.8 (*C*H_3), 59.4 (*C*H), 59.7 (*C*H), 113.5, 113.8, 118.3, 120.5, 120.7, 122.1, 122.4, 122.8, 123.0, 123.5 123.6, 123.8, 123.9, 124.3, 124.8, 125.7, 125.8, 127.4, 127.6, 127.7, 128.3, 128.4, 128.5, 128.7, 129.2, 129.3, 129.5, 129.7, 130.1, 130.3, 130.7, 131.5, 131.9, 133.58, 133.7, 133.8, 134.0, 139.0, 139.1, 153.1, 154.3, 154.4, 154.6, 154.7, 161.5 (*C*=N), 168.7 (*C*F_3). ^{11}B NMR (96 MHz, $CDCl_3$) δ 11.95; ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.55 (s, F-Ar), -114.75 (s, F-Ar).

(*S,E*)-tert-Butyl 3-(2-((S)-naphthol[2,1,2,3-def][1,3,2]dioxaborepin-4-yl)-4-fluoro-benzylidene]-amine (*R,S*)-148 + (*S,S*)-149

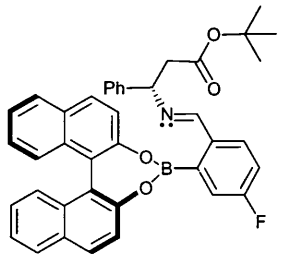


(*S,S*)-148 **(*R,S*)-149**

The title compound was prepared according to the general procedure 34 using *tert*-butyl(3S)-3-amino-3-phenylpropanoate (88 mg, 0.40 mmol), 4-fluoro-2-formylphenylboronic acid **134** (68 mg, 0.40 mmol), (*rac*)-BINOL (114 mg, 0.40 mL) in 2 mL $CDCl_3$. Evaporation of the solvent gave a yellow oil (233.68 mg, 94%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (9H, s, (*C*H_3)$_3$C), 2.70 (1H, dd, *J* 11.7, 17.2 Hz, C*H*$_A$H$_B$CO), 2.91 (1H, dd, *J* 4.9, 16.2 Hz, C*H*$_A$H$_B$CO), 3.25 (1H, dd, *J* 9.9, 16.0 Hz, CH$_A$*H*$_B$CO), 3.40 (1H, dd, *J* 5.8, 16.2 Hz, CH$_A$*H*$_B$CO), 5.30 (1H, dd, J 4.5, 11.1 Hz, C*H*CH_2), 7.0–7.9 (m, 15H, Ar*H*), 8.3 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) 27.7 ((*C*H_3)$_3$C), 28.0 (*C*H_2CH), 28.4 (*C*H_2CH), 44.0, 81.7 (O*C*(CH$_3$)$_3$, 111.7, 118.3, 123.9, 124.4, 124.7, 126.8, 127.3, 127.8, 128.5, 128.8, 129.0, 129.4, 129.5, 129.8, 129.9, 131.6, 133.9,

153.2, 170.4 (C=N). ^{11}B NMR (96 MHz, $CDCl_3$) δ 13.2 ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.16 (s, F-Ar), -110.14 (s, F-Ar).

(*S,E*)-tert-Butyl 3-(2-((S)-naphthol[2,1,2,3-def][1,3,2]dioxaborepin-4-yl)-4-fluoro-benzylidene]-amine (*S,S*)-148



(*S,S*)-148

The title compound was prepared according to the general procedure 34 using *tert*-butyl(3S)-3-amino-3-phenylpropanoate (88 mg, 0.4 mmol), 4-fluoro-2-formylphenylboronic acid (68 mg, 0.4 mmol), (*S*)-BINOL (114 mg, 0.4 mL) in 2 mL $CDCl_3$. Evaporation of the solvent gave a yellow oil (231.19 mg, 93% yield). $[\alpha]_D^{20}$= +437.0 (c 1.000, $CHCl_3$). IR ν_{max} (neat)/cm^{-1} 1718 (COO ^{t}Bu), 1653 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (9H, s, $(CH_3)_3C$), 2.80 (1H, dd, *J* 4.7, 14.9 Hz, CH_AH_BCO), 3.15 (1H, dd, *J* 9.8, 16.0 Hz, CH_AH_BCO), 5.30 (1H, dd, J 4.9, 11.1 Hz, $CHCH_2$), 7.0–7.9 (m, 15H, Ar*H*), 8.3 (s, 1H, *H*C=N). ^{13}C (75.5 MHz, $CDCl_3$) 27.8 ($(CH_3)_3C$), 28.4 (CH_2CH), 28.5 (CH_2CH), 45.4, 53.1 ($CHCH_2$), 81.2 ($OC(CH_3)_3$, 118.4, 124.3, 124.7, 126.7, 127.3, 127.8, 128.4, 128.7, 128.9, 129.4, 129.7, 131.5, 134.0, 144.7, 153.3, 171.7 (C=N). ^{11}B NMR (96 MHz, $CDCl_3$) δ 12.1 ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.16 (s, F-Ar).

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6 APPENDIX

6.1 APPENDIX 1: NMR spectra

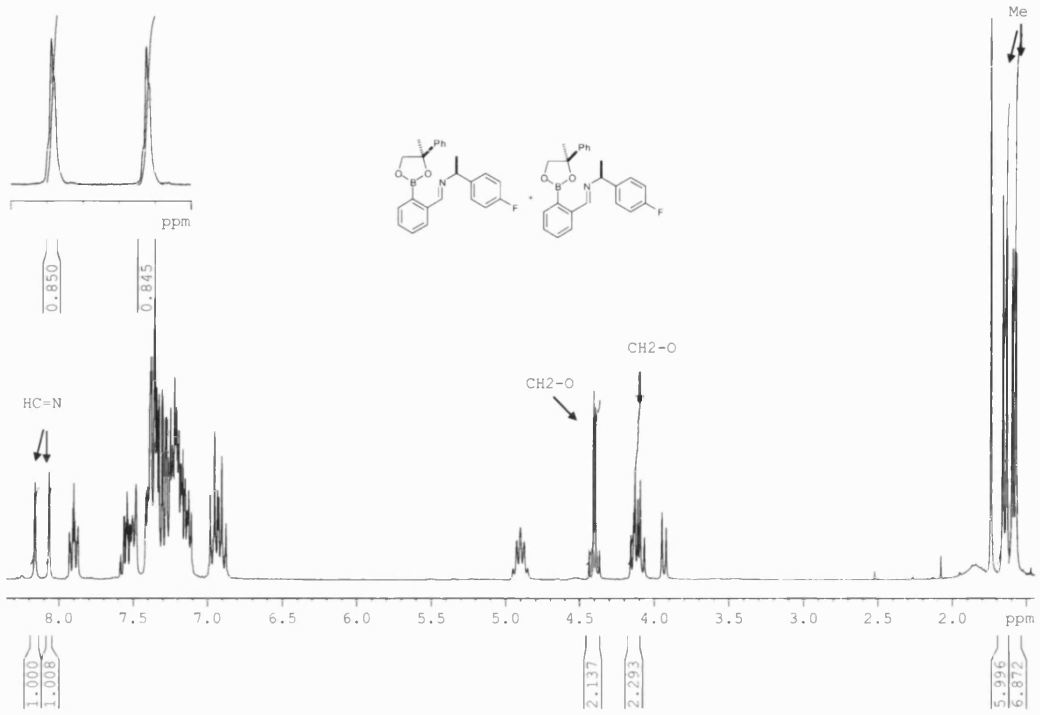


Figure 6. 1^{1}H and ^{19}F {H} NMR spectra of imino boronate esters (*rac*)-**132a** + (*rac*)-**133a**

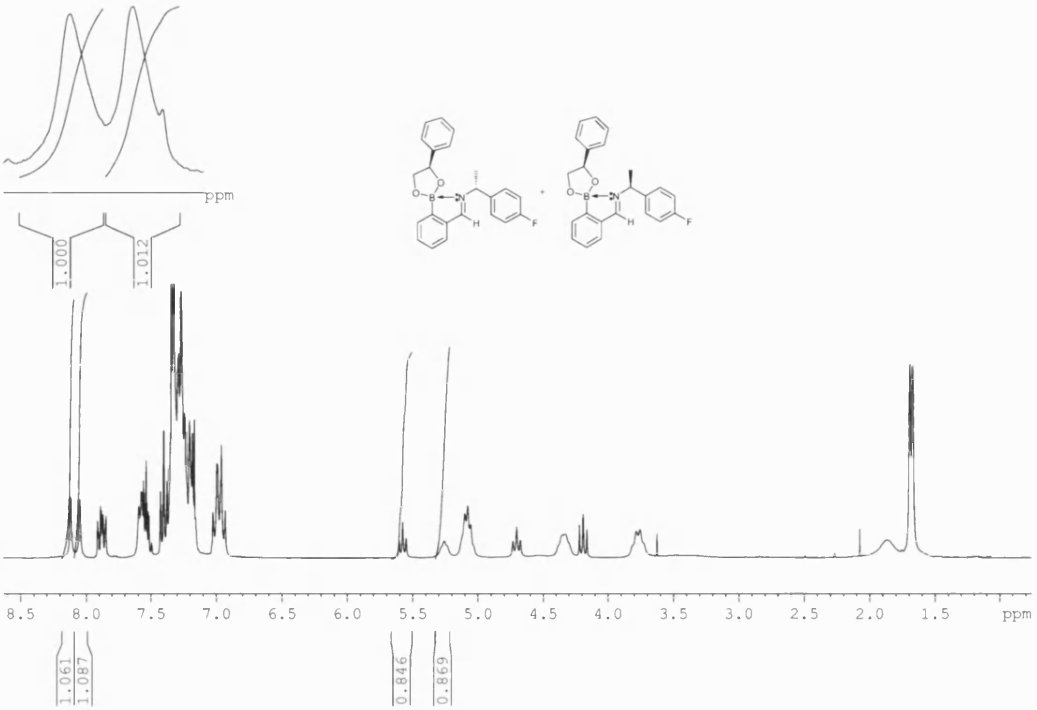


Figure 6. 2: ^{1}H and ^{19}F {H}NMR spectra of imino boronate esters (*R,R*)-**132b** + (*R,S*)-**133b**

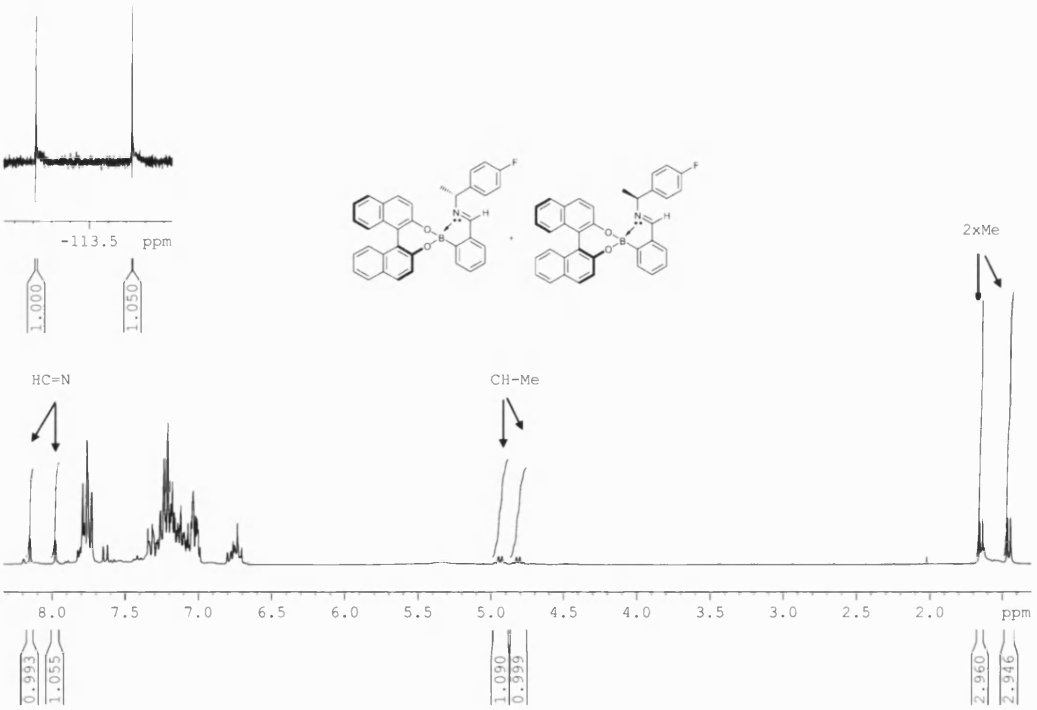


Figure 6. 3: ^{1}H and ^{19}F {H}NMR spectra of imino boronate esters (*S,R*)-**132c** + (*S,S*)-**133c**

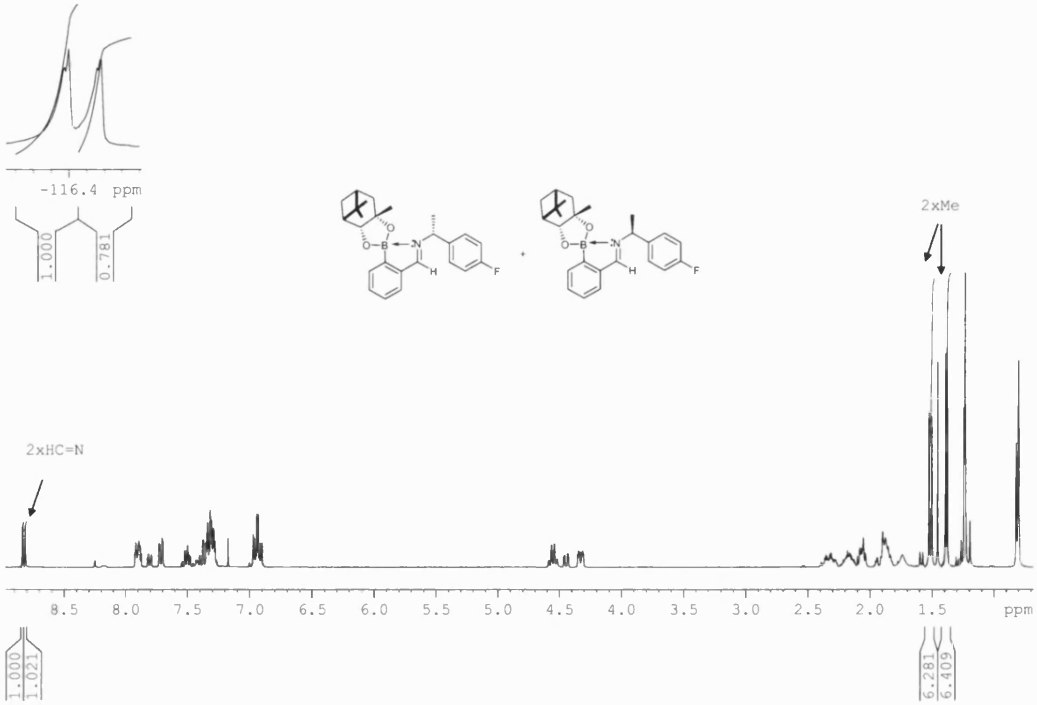


Figure 6. 4: ^{1}H and ^{19}F {H} NMR spectra of imino boronate esters (*R,R,R,S,R*)-**132d** + (*R,R,R,S,R*)-**133d**

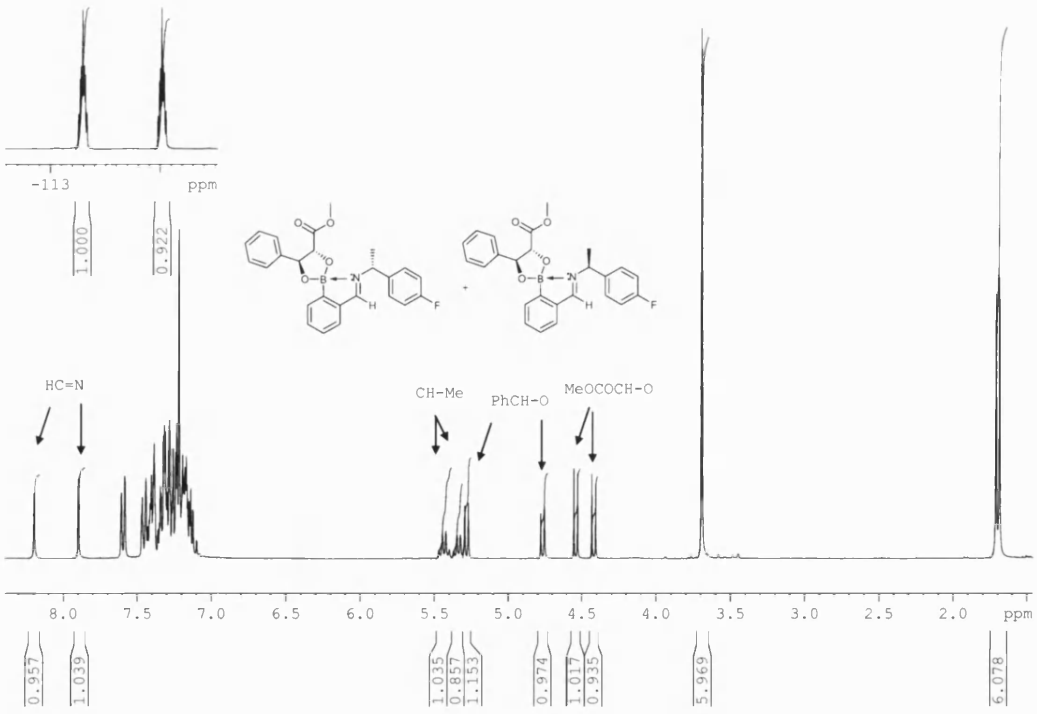


Figure 6. 5: ^{1}H and ^{19}F NMR spectra of imino boronate esters (*S,R,R*)-**132e** + (*S,R,S*)-**133e**

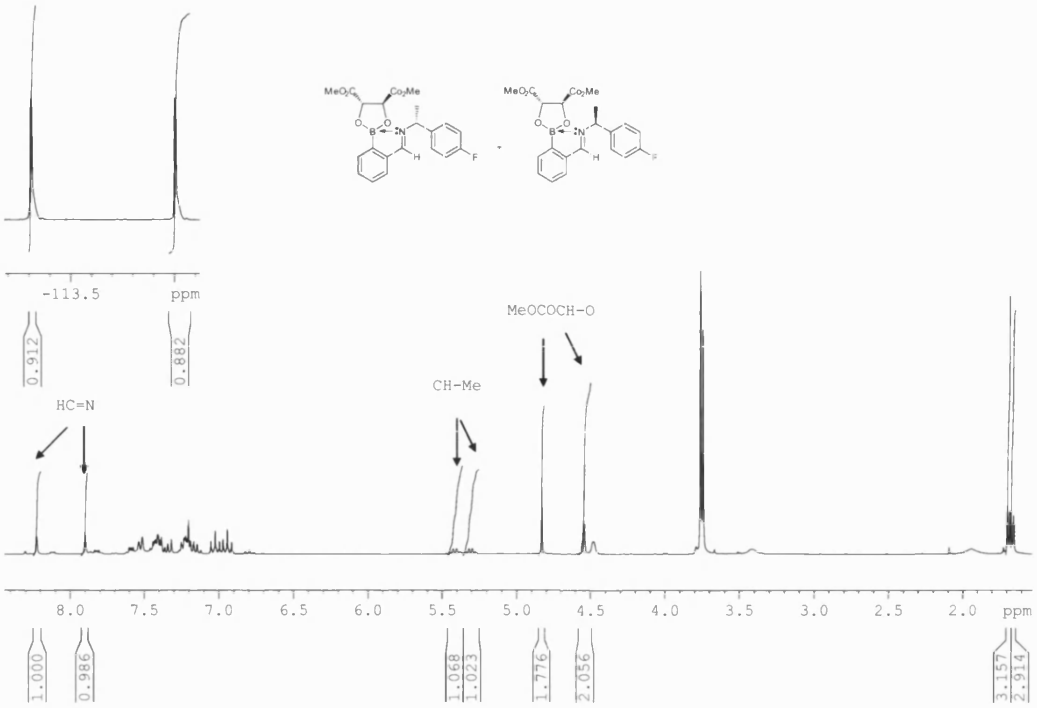


Figure 6. 6: ^{1}H and ^{19}F {H}NMR spectra of imino boronate esters (*S,S,R*)-**132f** + (*S,S,S*)-**133f**

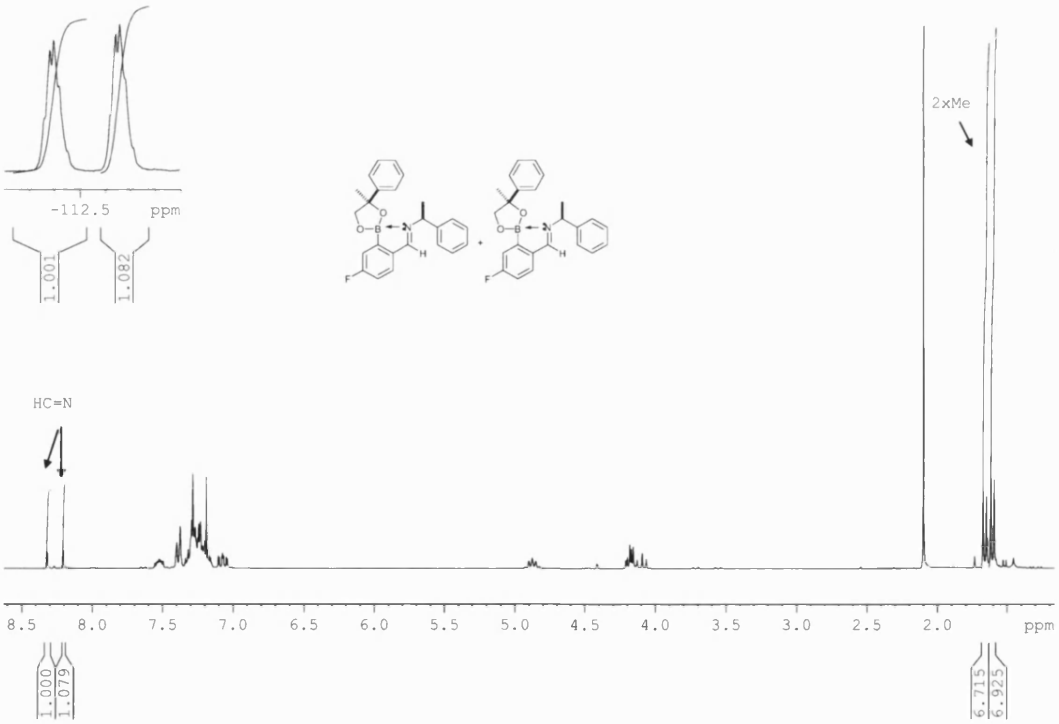


Figure 6. 7: ^{1}H and ^{19}F NMR spectra of imino boronate esters (*rac*)-**143a** + (*rac*)-**144a**

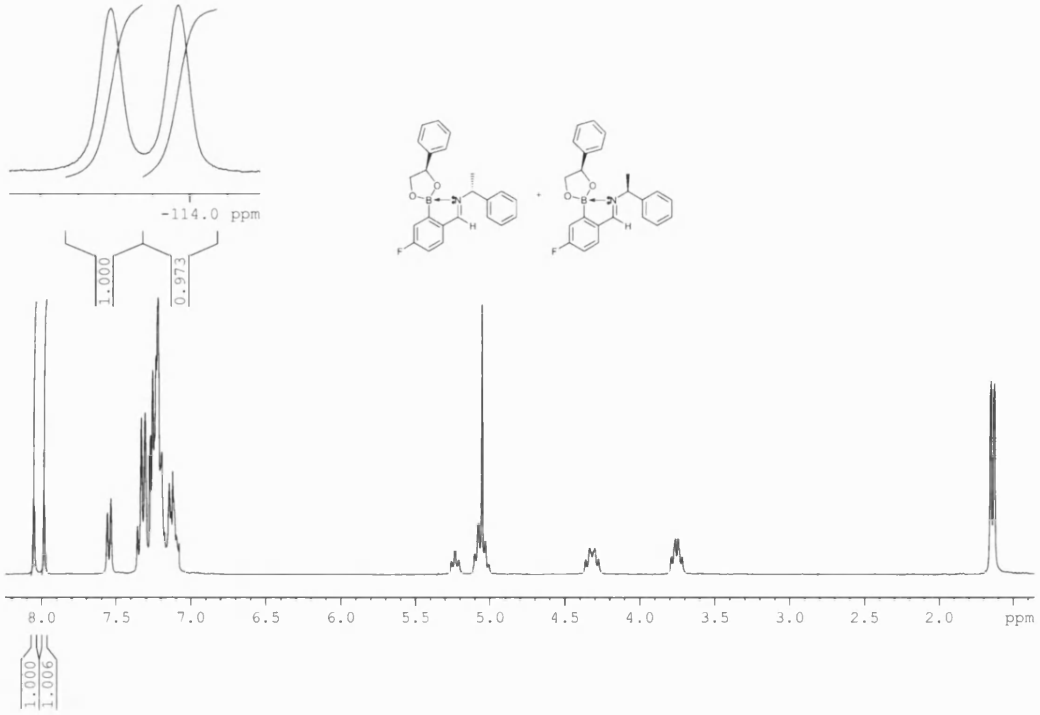


Figure 6. 8: ^{1}H and ^{19}F {H}NMR spectra of imino boronate esters (*R,R*)-**143b** + (*R,S*)-**144b**

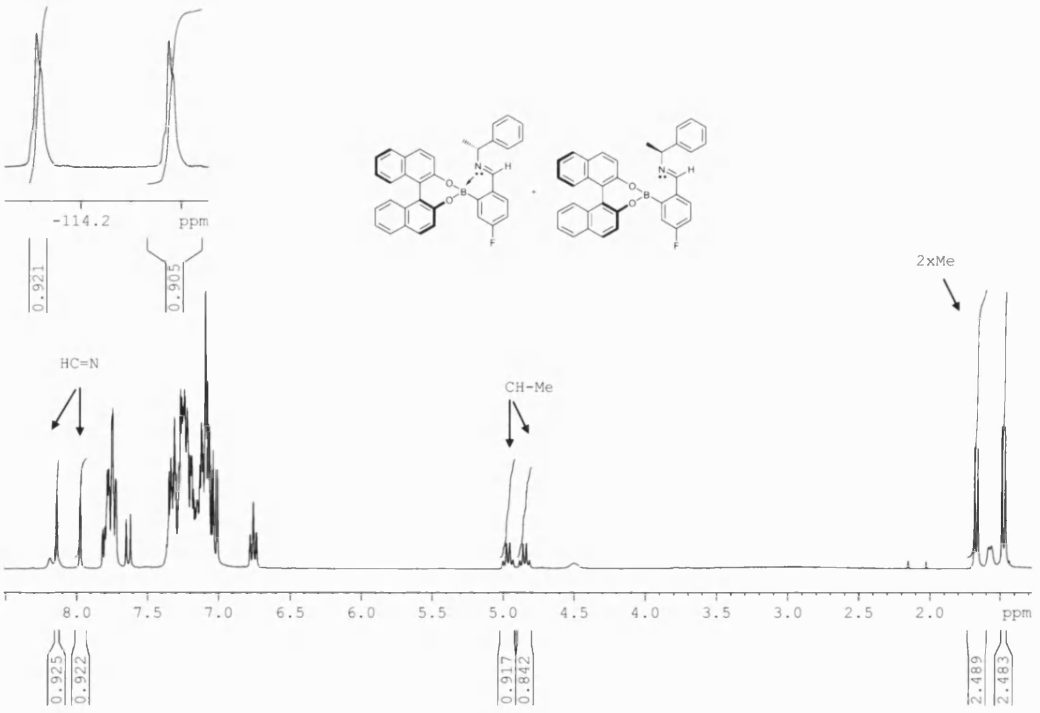


Figure 6. 9: ^{1}H and ^{19}F {H}NMR spectra of imino boronate esters (*S,R*)-**143c** + (*S,S*)-**144c**

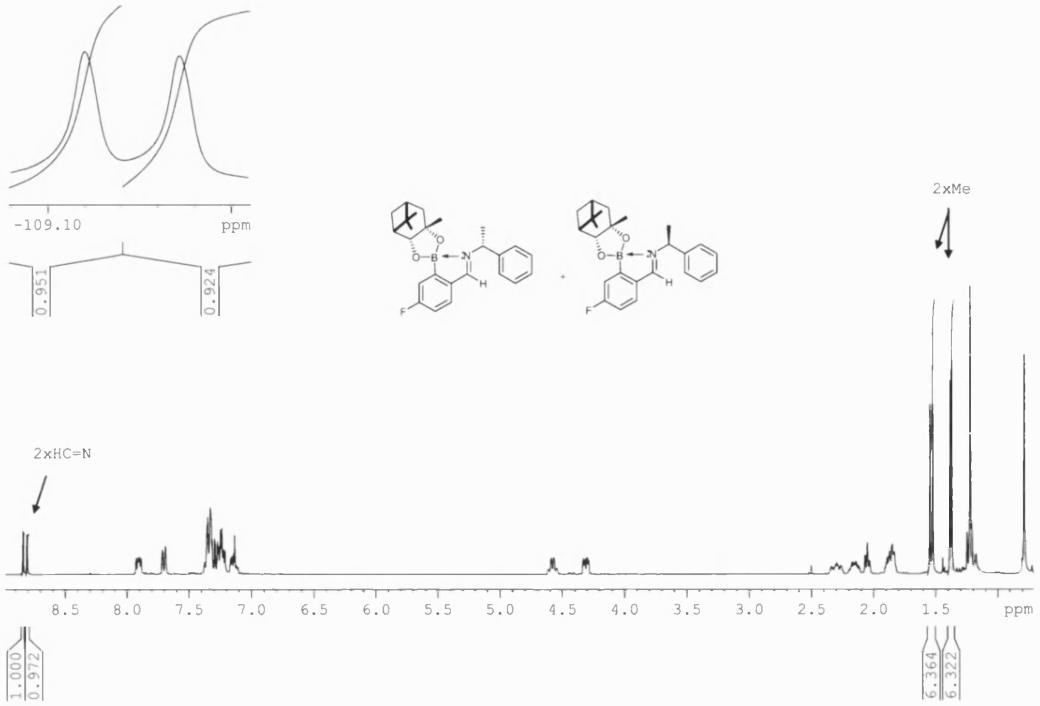


Figure 6. 10: ^{1}H and ^{19}F {H}NMR spectra of imino boronate esters (*R,R,R,S,R*)-**143d** + (*R,R,R,S,R*)-**144d**

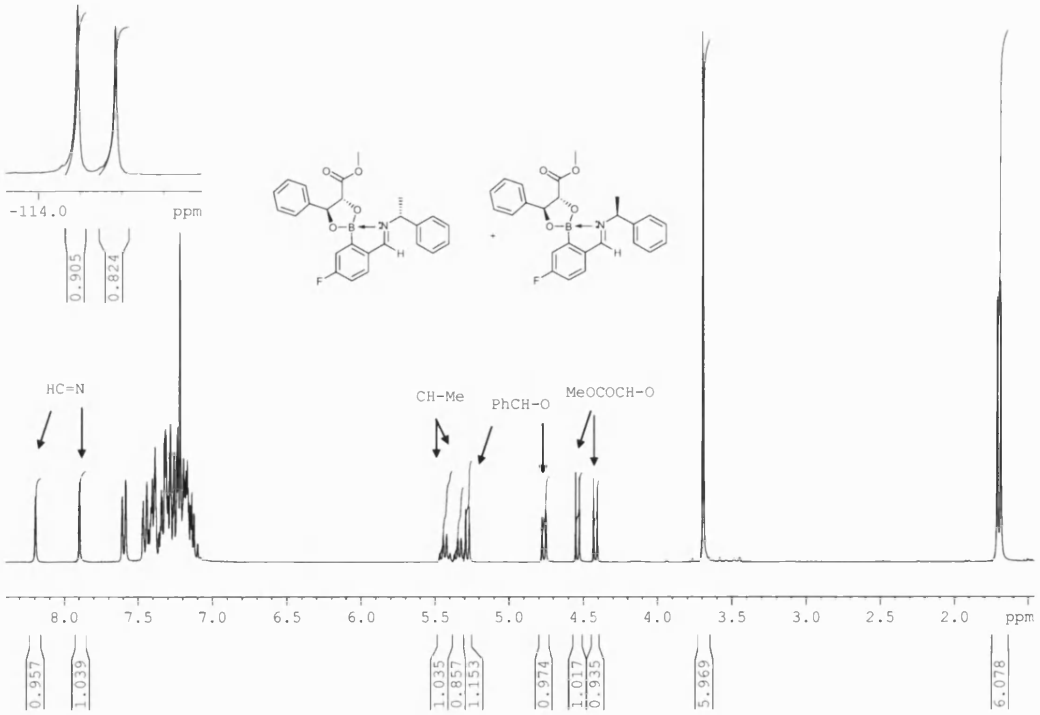


Figure 6. 11: ^{1}H and ^{19}F NMR {H}spectra of imino boronate esters (*S,R,R*)-**143e** + (*S,R,S*)-**144e**

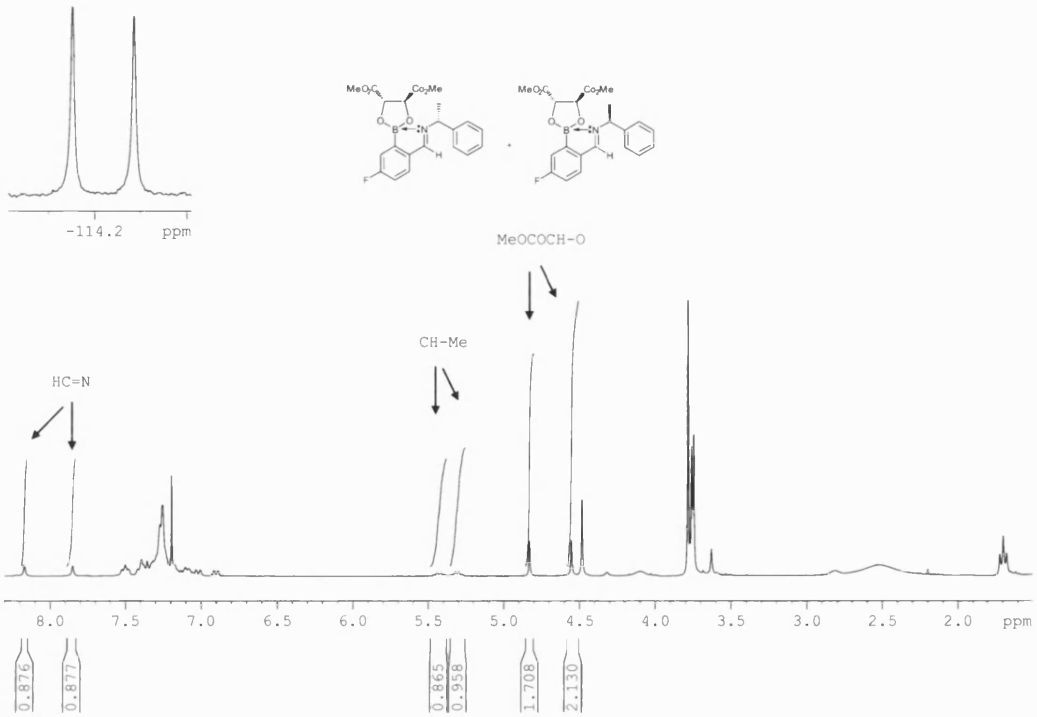


Figure 6. 12: H and ^{19}F {H}NMR spectra of imino boronate esters (*S,S,R*)-**143f** + (*S,S,S*)-**144f**

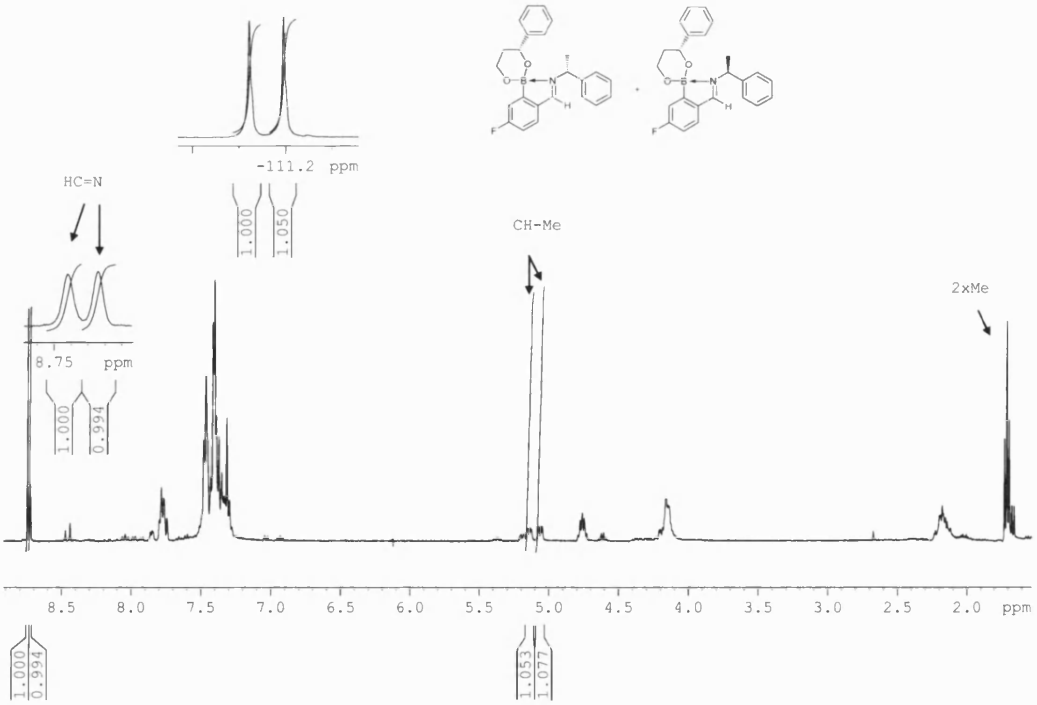


Figure 6. 13: ^{1}H and ^{19}F {H}NMR spectra of imino boronate esters (*R,R*)-**143g** + (*R,S*)-**144g**

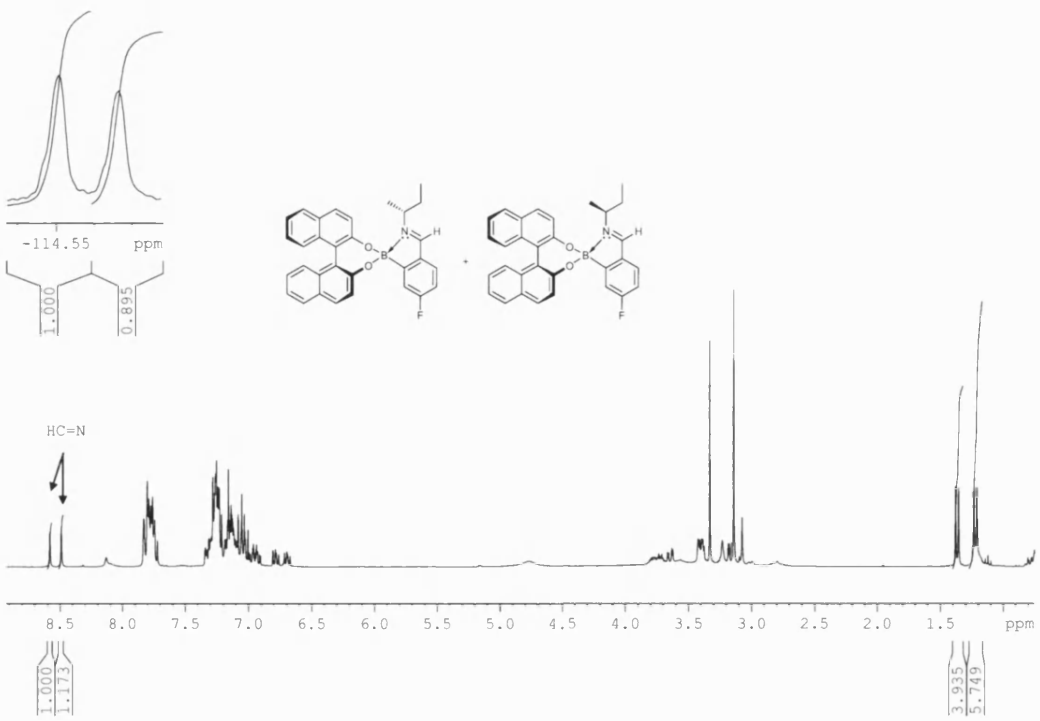
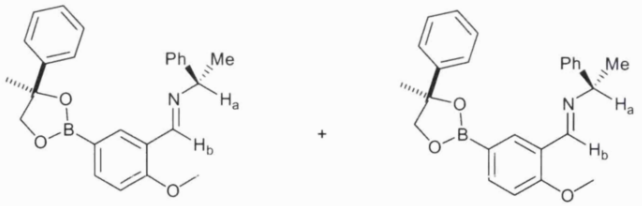
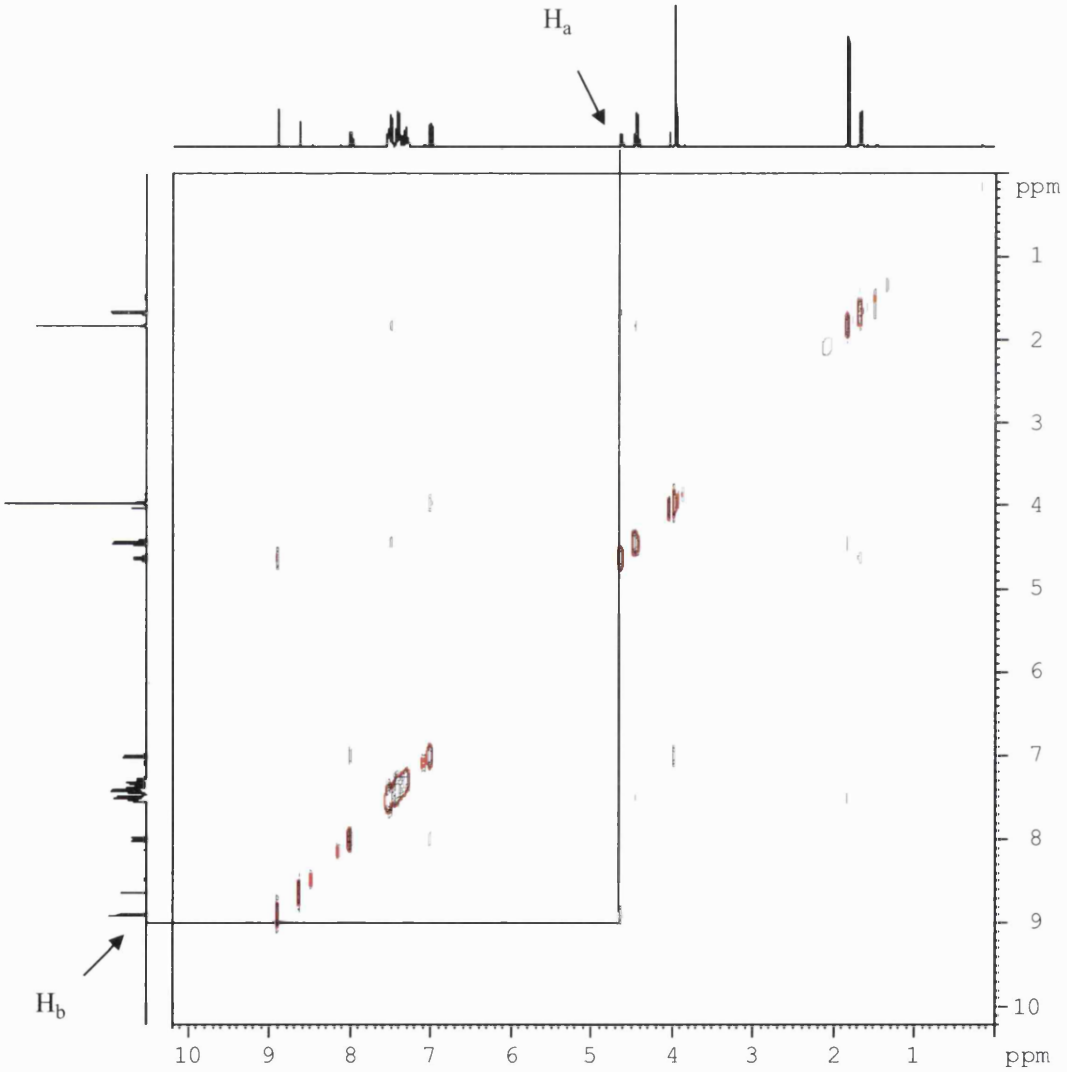


Figure 6. 14: ^{1}H and ^{19}F {H}NMR spectra of imino boronate esters (*S,R*)-**145** + (*S,R*)-**146**

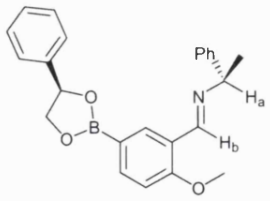
1.1 NOESY spectra of imino boronate ester **(*rac*)-125** + **(*rac*)-126**



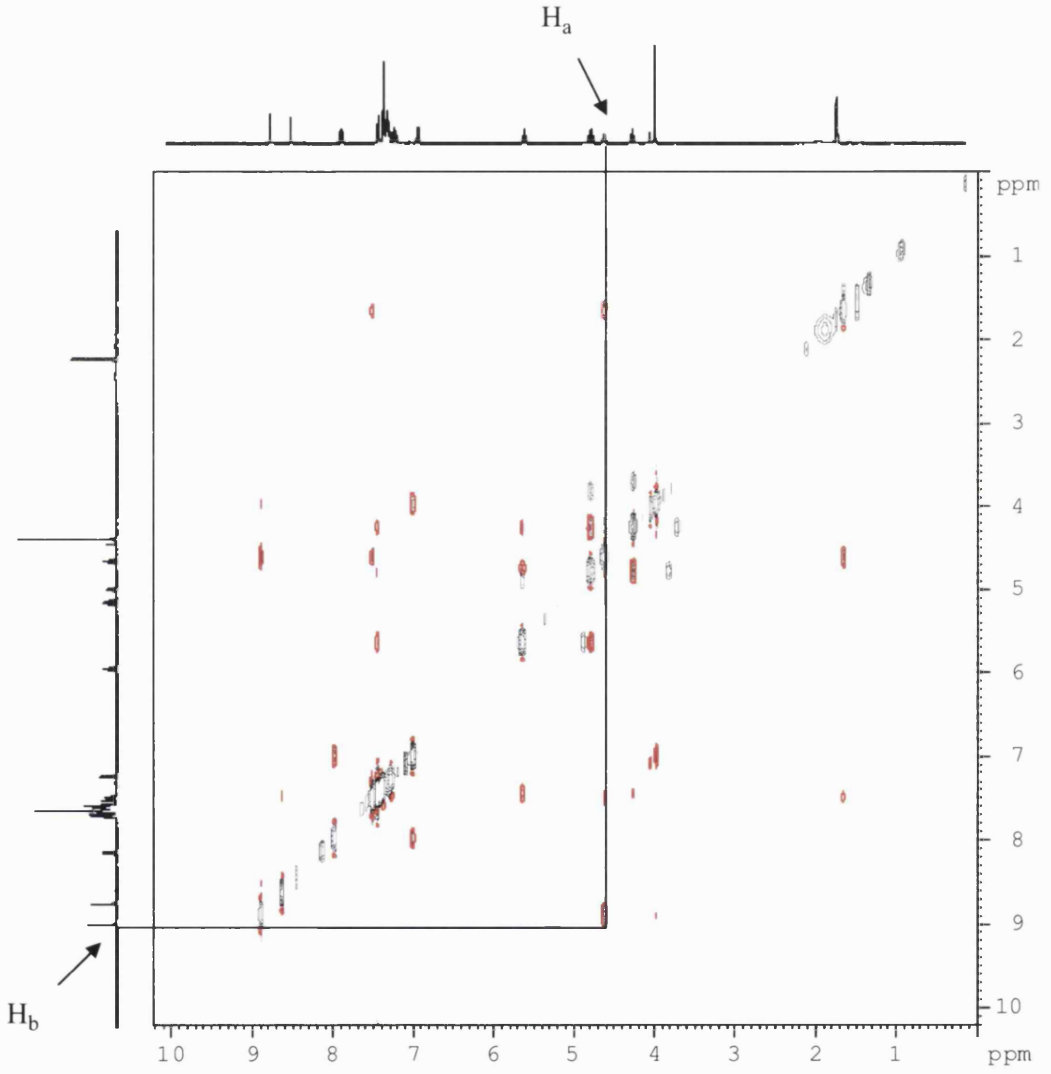
(*rac*)-125 **(*rac*)-126**



1.2 NOESY spectra of imino boronate ester **(*R*,*R*)-127**



(*R*,*R*)-127



6.2 APPENDIX II: X-ray crystal structure data for (*rac*)-125

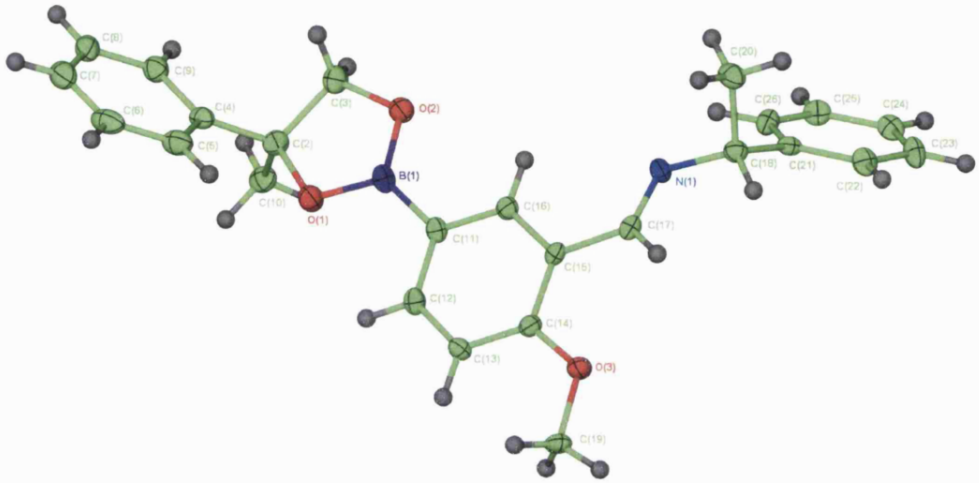


Table 6. 1: Crystal data and structure refinement for 1.

Identification code	k06tdj7
Empirical formula	C25 H26 B N O3
Formula weight	399.28
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.6800(7)Å α = 90°
	b = 8.4480(8)Å β = 90°
	c = 33.137(4)Å γ = 90°
Volume	2149.9(4) $Å^3$
Z	4
Density (calculated)	1.234 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	848
Crystal size	0.25 x 0.20 x 0.03 mm
Theta range for data collection	3.59 to 25.02°
Index ranges	-7<=h<=8; -9<=k<=9; -39<=l<=29
Reflections collected	4874
Independent reflections	2548 [R(int) = 0.0513]
Reflections observed (>2σ)	1637
Data Completeness	0.765
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2548 / 0 / 274
Goodness-of-fit on F^2	1.097
Final R indices [I>2σ(I)]	R^1 = 0.0644 wR_2 = 0.1192
R indices (all data)	R^1 = 0.1249 wR_2 = 0.1419
Absolute structure parameter	4(3)
Largest diff. peak and hole	0.204 and -0.201 $eÅ^{-3}$

Notes: Very thin xtal accounts for the fact that despite long exposure time, the completeness of the data are not quite as high as desirable

Table 6. 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	3097(5)	972(4)	1478(1)	50(1)
O(2)	3062(5)	2867(4)	1965(1)	49(1)
O(3)	1781(5)	-3684(4)	3024(1)	45(1)
N(1)	1870(6)	759(5)	3449(1)	38(1)
C(2)	3534(9)	2432(6)	1265(2)	44(2)
C(3)	3325(9)	3734(6)	1592(2)	51(2)
C(4)	2291(8)	2642(6)	913(2)	39(1)
C(5)	899(9)	1608(7)	842(2)	56(2)
C(6)	-155(9)	1790(8)	505(2)	65(2)
C(7)	143(10)	3013(9)	242(2)	66(2)
C(8)	1423(10)	4055(8)	317(2)	54(2)
C(9)	2501(8)	3891(6)	648(2)	47(2)
C(10)	5392(8)	2282(7)	1119(2)	49(2)
C(11)	2633(7)	-59(6)	2189(2)	38(2)
C(12)	2723(8)	-1633(7)	2070(2)	43(2)
C(13)	2454(7)	-2863(6)	2337(2)	42(2)
C(14)	2078(8)	-2553(6)	2738(2)	38(2)
C(15)	1970(7)	-981(6)	2873(1)	35(1)
C(16)	2279(7)	227(6)	2594(2)	37(2)
C(17)	1579(7)	-608(7)	3300(1)	36(2)
C(18)	1437(8)	953(7)	3877(2)	39(2)
C(19)	2026(8)	-5304(5)	2905(2)	47(2)
C(20)	-60(8)	2137(7)	3911(2)	50(2)
C(21)	2994(7)	1571(6)	4108(2)	34(1)
C(22)	3211(8)	1197(7)	4514(2)	46(2)
C(23)	4585(9)	1842(7)	4736(2)	49(2)
C(24)	5745(8)	2853(7)	4555(2)	46(2)
C(25)	5548(8)	3207(7)	4154(2)	45(2)
C(26)	4203(8)	2570(7)	3937(2)	44(2)
B(1)	2939(9)	1281(8)	1880(2)	42(2)

Table 6. 3: Bond lengths [Å] and angles [°] for 1.

O(1)-B(1)	1.361(6)	O(1)-C(2)	1.462(6)
O(2)-B(1)	1.373(7)	O(2)-C(3)	1.452(6)
O(3)-C(14)	1.364(6)	O(3)-C(19)	1.436(5)
N(1)-C(17)	1.275(6)	N(1)-C(18)	1.467(6)
C(2)-C(10)	1.512(8)	C(2)-C(4)	1.517(7)
C(2)-C(3)	1.553(7)	C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900	C(4)-C(9)	1.382(7)
C(4)-C(5)	1.400(8)	C(5)-C(6)	1.388(9)
C(5)-H(5)	0.9500	C(6)-C(7)	1.371(9)
C(6)-H(6)	0.9500	C(7)-C(8)	1.343(8)
C(7)-H(7)	0.9500	C(8)-C(9)	1.381(8)
C(8)-H(8)	0.9500	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)-C(12)	1.388(7)
C(11)-C(16)	1.392(7)	C(11)-B(1)	1.544(8)
C(12)-C(13)	1.381(6)	C(12)-H(12)	0.9500
C(13)-C(14)	1.386(7)	C(13)-H(13)	0.9500
C(14)-C(15)	1.403(7)	C(15)-C(16)	1.398(6)
C(15)-C(17)	1.481(7)	C(16)-H(16)	0.9500
C(17)-H(17)	0.9500	C(18)-C(21)	1.514(7)
C(18)-C(20)	1.528(7)	C(18)-H(18)	1.0000
C(19)-H(19A)	0.9800	C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800	C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800	C(20)-H(20C)	0.9800
C(21)-C(26)	1.377(7)	C(21)-C(22)	1.392(7)
C(22)-C(23)	1.396(8)	C(22)-H(22)	0.9500
C(23)-C(24)	1.372(7)	C(23)-H(23)	0.9500
C(24)-C(25)	1.369(8)	C(24)-H(24)	0.9500
C(25)-C(26)	1.369(8)	C(25)-H(25)	0.9500
C(26)-H(26)	0.9500		
B(1)-O(1)-C(2)	109.4(4)	B(1)-O(2)-C(3)	109.1(4)
C(14)-O(3)-C(19)	117.1(4)	C(17)-N(1)-C(18)	115.7(4)
O(1)-C(2)-C(10)	107.5(5)	O(1)-C(2)-C(4)	109.0(5)
C(10)-C(2)-C(4)	111.0(5)	O(1)-C(2)-C(3)	103.7(4)
C(10)-C(2)-C(3)	112.3(5)	C(4)-C(2)-C(3)	112.9(5)
O(2)-C(3)-C(2)	104.6(4)	O(2)-C(3)-H(3A)	110.8
C(2)-C(3)-H(3A)	110.8	O(2)-C(3)-H(3B)	110.8
C(2)-C(3)-H(3B)	110.8	H(3A)-C(3)-H(3B)	108.9
C(9)-C(4)-C(5)	117.3(6)	C(9)-C(4)-C(2)	120.2(6)
C(5)-C(4)-C(2)	122.5(5)	C(6)-C(5)-C(4)	120.8(6)
C(6)-C(5)-H(5)	119.6	C(4)-C(5)-H(5)	119.6
C(7)-C(6)-C(5)	119.8(7)	C(7)-C(6)-H(6)	120.1
C(5)-C(6)-H(6)	120.1	C(8)-C(7)-C(6)	119.9(6)
C(8)-C(7)-H(7)	120.0	C(6)-C(7)-H(7)	120.0
C(7)-C(8)-C(9)	121.4(6)	C(7)-C(8)-H(8)	119.3
C(9)-C(8)-H(8)	119.3	C(8)-C(9)-C(4)	120.7(6)
C(8)-C(9)-H(9)	119.6	C(4)-C(9)-H(9)	119.6
C(2)-C(10)-H(10A)	109.5	C(2)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5	C(2)-C(10)-H(10C)	109.5

H(10A)-C(10)-H(10C)	109.5	H(10B)-C(10)-H(10C)	109.5
C(12)-C(11)-C(16)	116.8(5)	C(12)-C(11)-B(1)	120.4(5)
C(16)-C(11)-B(1)	122.8(5)	C(13)-C(12)-C(11)	122.1(5)
C(13)-C(12)-H(12)	119.0	C(11)-C(12)-H(12)	119.0
C(12)-C(13)-C(14)	120.3(5)	C(12)-C(13)-H(13)	119.9
C(14)-C(13)-H(13)	119.9	O(3)-C(14)-C(13)	124.6(5)
O(3)-C(14)-C(15)	115.6(4)	C(13)-C(14)-C(15)	119.8(5)
C(16)-C(15)-C(14)	118.1(4)	C(16)-C(15)-C(17)	120.7(5)
C(14)-C(15)-C(17)	121.2(4)	C(11)-C(16)-C(15)	123.0(5)
C(11)-C(16)-H(16)	118.5	C(15)-C(16)-H(16)	118.5
N(1)-C(17)-C(15)	121.7(5)	N(1)-C(17)-H(17)	119.1
C(15)-C(17)-H(17)	119.1	N(1)-C(18)-C(21)	110.4(4)
N(1)-C(18)-C(20)	108.3(4)	C(21)-C(18)-C(20)	109.4(4)
N(1)-C(18)-H(18)	109.6	C(21)-C(18)-H(18)	109.6
C(20)-C(18)-H(18)	109.6	O(3)-C(19)-H(19A)	109.5
O(3)-C(19)-H(19B)	109.5	H(19A)-C(19)-H(19B)	109.5
O(3)-C(19)-H(19C)	109.5	H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5	C(18)-C(20)-H(20A)	109.5
C(18)-C(20)-H(20B)	109.5	H(20A)-C(20)-H(20B)	109.5
C(18)-C(20)-H(20C)	109.5	H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5	C(26)-C(21)-C(22)	117.2(5)
C(26)-C(21)-C(18)	122.4(5)	C(22)-C(21)-C(18)	120.4(5)
C(21)-C(22)-C(23)	120.6(6)	C(21)-C(22)-H(22)	119.7
C(23)-C(22)-H(22)	119.7	C(24)-C(23)-C(22)	120.2(6)
C(24)-C(23)-H(23)	119.9	C(22)-C(23)-H(23)	119.9
C(25)-C(24)-C(23)	119.3(6)	C(25)-C(24)-H(24)	120.4
C(23)-C(24)-H(24)	120.4	C(26)-C(25)-C(24)	120.4(6)
C(26)-C(25)-H(25)	119.8	C(24)-C(25)-H(25)	119.8
C(25)-C(26)-C(21)	122.3(5)	C(25)-C(26)-H(26)	118.9
C(21)-C(26)-H(26)	118.9	O(1)-B(1)-O(2)	112.5(5)
O(1)-B(1)-C(11)	121.4(5)	O(2)-B(1)-C(11)	126.1(5)

Symmetry transformations used to generate equivalent atoms:

Table 6. 4: Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U.

Atom	U11	U22	U33	U23	U13	U12
O(1)	69(3)	41(2)	41(2)	1(2)	6(2)	-8(2)
O(2)	64(3)	40(2)	42(2)	1(2)	5(2)	-3(2)
O(3)	64(3)	31(2)	40(2)	3(2)	5(2)	-2(2)
N(1)	43(4)	38(3)	32(2)	-5(2)	1(2)	-5(3)
C(2)	49(5)	37(3)	46(4)	6(3)	3(3)	-7(4)
C(3)	59(5)	54(4)	41(3)	6(3)	7(3)	-1(4)
C(4)	38(4)	36(3)	44(3)	-3(3)	-1(3)	4(3)
C(5)	58(5)	43(4)	67(5)	-6(3)	-5(4)	1(4)
C(6)	57(6)	49(4)	89(5)	-23(4)	-21(4)	8(4)
C(7)	65(6)	71(6)	60(5)	-17(4)	-21(4)	23(5)
C(8)	58(5)	64(4)	40(4)	-3(3)	3(3)	21(4)
C(9)	49(5)	46(4)	44(3)	-1(3)	4(3)	-2(4)
C(10)	45(5)	50(4)	52(4)	2(3)	-6(3)	1(3)
C(11)	38(4)	43(4)	33(3)	-3(2)	-1(3)	-5(3)
C(12)	46(5)	51(4)	32(3)	1(3)	5(3)	-3(4)
C(13)	47(5)	37(3)	41(3)	-8(3)	-2(3)	2(3)
C(14)	41(4)	33(3)	39(3)	1(3)	-6(3)	1(3)
C(15)	35(4)	38(3)	31(3)	6(2)	-6(3)	0(3)
C(16)	40(4)	35(3)	37(3)	-2(2)	-6(3)	-3(3)
C(17)	32(4)	43(4)	34(3)	7(3)	-2(3)	0(3)
C(18)	42(4)	33(3)	42(3)	0(3)	1(3)	-1(3)
C(19)	62(5)	25(3)	53(4)	1(2)	-5(3)	2(4)
C(20)	45(5)	51(4)	53(4)	-10(3)	-2(3)	6(4)
C(21)	36(4)	25(3)	40(3)	1(2)	11(3)	1(3)
C(22)	39(5)	58(4)	41(3)	-2(3)	12(3)	-2(4)
C(23)	41(5)	70(5)	36(4)	-9(3)	-4(3)	-4(4)
C(24)	29(5)	54(4)	55(4)	-11(3)	1(3)	5(4)
C(25)	38(5)	41(4)	55(4)	2(3)	4(3)	-6(3)
C(26)	46(5)	48(4)	38(3)	6(3)	-2(3)	2(4)
B(1)	36(5)	53(5)	36(4)	-5(3)	3(3)	-8(4)

Table 6. 5: Hydrogen coordinates (x 10^4) and isotropic displacemen parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(3A)	4383	4401	1608	62
H(3B)	2311	4419	1532	62
H(5)	674	773	1027	67
H(6)	-1081	1069	457	78
H(7)	-554	3123	7	79
H(8)	1591	4922	139	65
H(9)	3396	4646	694	56
H(10A)	6151	2023	1347	74
H(10B)	5766	3286	999	74
H(10C)	5465	1440	916	74
H(12)	2978	-1871	1796	52
H(13)	2526	-3927	2245	50
H(16)	2245	1293	2685	45
H(17)	1099	-1408	3468	44
H(18)	1068	-89	3992	46
H(19A)	1156	-5588	2701	70
H(19B)	1893	-5993	3141	70
H(19C)	3196	-5435	2791	70
H(20A)	281	3139	3784	75
H(20B)	-330	2319	4196	75
H(20C)	-1089	1712	3774	75
H(22)	2416	496	4642	55
H(23)	4718	1580	5013	59
H(24)	6674	3302	4705	55
H(25)	6350	3899	4025	54
H(26)	4099	2825	3659	53