The selective immobilisation of chiral intermediates in asymmetric synthesis.

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The Selective Immobilisation of Chiral Intermediates in Asymmetric Synthesis

A thesis submitted to the University of Wales in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry

by

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Abstract

The advantage of solid phase synthesis is that the products can be isolated and purified simply by filtration. However, the reaction conditions required often lead to different kinetic behaviour, differences in reactivity and solvation and other problems, not encountered in solution phase reactions. This thesis describes an approach at utilising the ease of purification associated with solid-phase synthesis without encountering the problems associated with two-phase reaction systems. It was achieved by selectively immobilising a bipyridyl-tagged chiral auxiliary and a bipyridyl-tagged oxazaborolidine catalyst by interaction by with a resin-bound transition metal upon completion of the solution-phase reaction.

Chapter one is a literature review detailing some of the different approaches that have been reported in exploiting the benefits of solid-phase purifications whilst avoiding the associated problems. Soluble polymeric supports, fluorous labelling and some more unusual methods are investigated.

Chapter two is a general introduction to how chiral auxiliaries can stereochemically influence reactions. Chiral auxiliary mediated alkylations, aldol reactions, conjugate additions and Diels-Alder reactions are focussed on.

Chapter three details the complete synthesis of (*R*,*R*)-4,4′-*bis*-[1-(4,5-diphenyl-3-propionyl-imidazolidinonyl)-*N*-methyl]-2,2′-bipyridine, a bipyridyl-tagged chiral auxiliary. An investigation into its ability to reversibly bind to a resin-bound transition metal is then reported.

Chapter four describes the extensive study on the reactivity of the tagged chiral auxiliary, concentrating on chiral alkylations, halogenations and aldol reactions.

Chapter five is an account of how the selective immobilisation approach was extended to include chiral oxazaborolidine catalysts. A general introduction to oxazaborolidine catalysts is provided. The total synthesis of the bipyridyl-tagged oxazaborolidine, (*S*,*S*)-4,4′-*bis*-[4-(2-amino-3-hydroxy-3,3-diphenyl-propyl)phenoxymethyl]-2,2'-bipyridine is reported and the investigation into its ability to reversibly bind to a resin-bound transition metal is described. The chiral reduction of acetophenone using the tagged catalyst and the subsequent recovery of the catalyst is then explored.

Abbreviations

AIBN	Azo*bis*isobutyronitrile
BBN	Borabicyclo[3.3.1]nonane
Boc-	*tert*-Butoxycarbonyl
BuLi	Butyllithium
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIA	Diisopropylamine
DIBAL	Diisobutylaluminium
DIEA	Diisopropylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
E-	*Entgegen*
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
FAB	Fast atom bombardment
f-moc	(9-fluorobenzyl)methoxycarbonyl
GC	Gas chromatography
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HOBT	1-Hydroxybenotriazole hydrate
HPLC	High performance liquid chromatography
LDA	Lithium diisopropylamide
MCPBA	*meta*-chloroperbenzoic acid
MeOPEG	Polyethyleneglycol-monomethylether
MS	Mass spectrometry
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
PAMAM	Polyamidoamine
Phe	Phenylanaline
$Pr^{i}_{2}NET$	Diisopropylethylamine
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
R-	*Rectus*
Rf	Retention factor
S-	*Sinister*
SEC	Size exclusion chromatography
Tbf	Tetrabenzofluorene
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Z-	*Zusammen*

Contents

Chapter One

Strategic Alternatives to Solid Phase Synthesis

1.1 Introduction

Since the preparation of oligopeptides by Merrifield using solid phase synthesis[1], the use of solid polymeric supports in organic synthesis[2,3] has increased. Following recent developments in combinatorial chemistry[4] the real potential of the technique has begun to be explored. The technique is particularly beneficial in the discovery of lead structures in the pharmaceutical industry. The ease of isolation of product after each step by simple filtration allows large libraries of organic molecules to be produced simultaneously by combinatorial methods. Another advantage is that excess reagents can be added to force reactions to completion without needing to remove the excess at the end of the reaction. Reactions can be directed by attachment of an appropriate component to the resin to increase the chemoselectivity of a reaction. The process can be easily automated and is useful when using toxic or hazardous chemicals, which can be handled safely when attached to the resin without risk to the user or the environment.

The process begins with the immobilization of a starting material onto the solid support. This requires a linking group to attach the molecule onto the polymeric resin. This linker needs to be stable in the reaction conditions required for synthesis but must be selectively cleaved at the end of the reaction to liberate the product from the resin. The use of a linker adds two synthetic steps to the solid phase route.

Once the resin and linker have been determined the next problem arises from how to monitor the reaction. Chromatographic techniques such as TLC will not work when the molecule is attached to the insoluble support. One option is to cleave the molecule before analysis but this usually takes too long. Infrared spectroscopy can give useful results from KBr discs although some resins can give weak absorption bands that complicate the spectra. Standard ^{13}C NMR can produce good spectra but specialised equipment is needed to give similar quality proton spectra. Some classical analytical techniques can give useful information on the progress of solid phase reactions such as the titration of functional groups, gravimetric analysis and colour tests.

Isolation of the product after each synthetic step and prior to cleavage is achieved by washing the solid support with a range of solvents. The accepted technique is to use

swelling solvents followed by non-swelling solvents with the final rinse involving a solvent that will fully swell the resin ready for the next step.

The two-phase system enables compounds to be easily isolated but it can lead to problems with reaction kinetics and the conversion of a solution phase synthesis to a solid phase synthesis takes extra time and labour. Another flaw is the need for extra linkage and cleavage steps as well as the limited spectroscopic and chromatographic methods available for analysis of the organic molecule whilst attached to the resin.

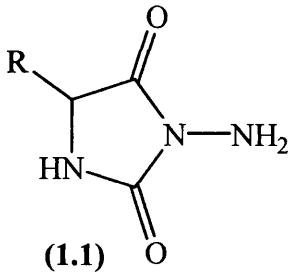
Recently research has moved into a new area of synthesis where the advantages of solid phase synthesis and the advantages of solution phase chemistry are combined. There are many different approaches to this problem and the most popular solutions are discussed below.

1.2 Soluble Polymeric Support Separation Strategy

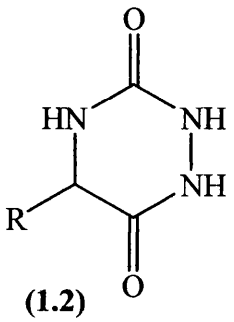
Soluble polymeric supports[5] have recently become popular as they offer all the benefits of solid phase synthesis but, as they form a one-phase reaction mixture, they cause less interference with reaction kinetics. They can be precipitated after the synthetic step has been completed to allow easy isolation. Soluble polymers can be used in a variety of different ways for organic synthesis and purification, for example: anchoring the substrate, ligand or reagent and polymer-supported scavengers.[6]

1.2.1 Soluble Polymer Supported Substrates

A soluble polymer methodology has been used by Janda *et al.*[7] to produce 3-aminoimidazoline-2,4-diones **(1.1)**. Heterocyclices bearing one or more nitrogen atoms have potential therapeutic value and the development of new strategies for their synthesis is of key interest. Previous attempts to produce 3-aminoimidazoline-2,4-diones have resulted in the production of racemic mixtures containing the isomeric hexahydro-1,2,4-triazine-3,6-dione **(1.2)**.

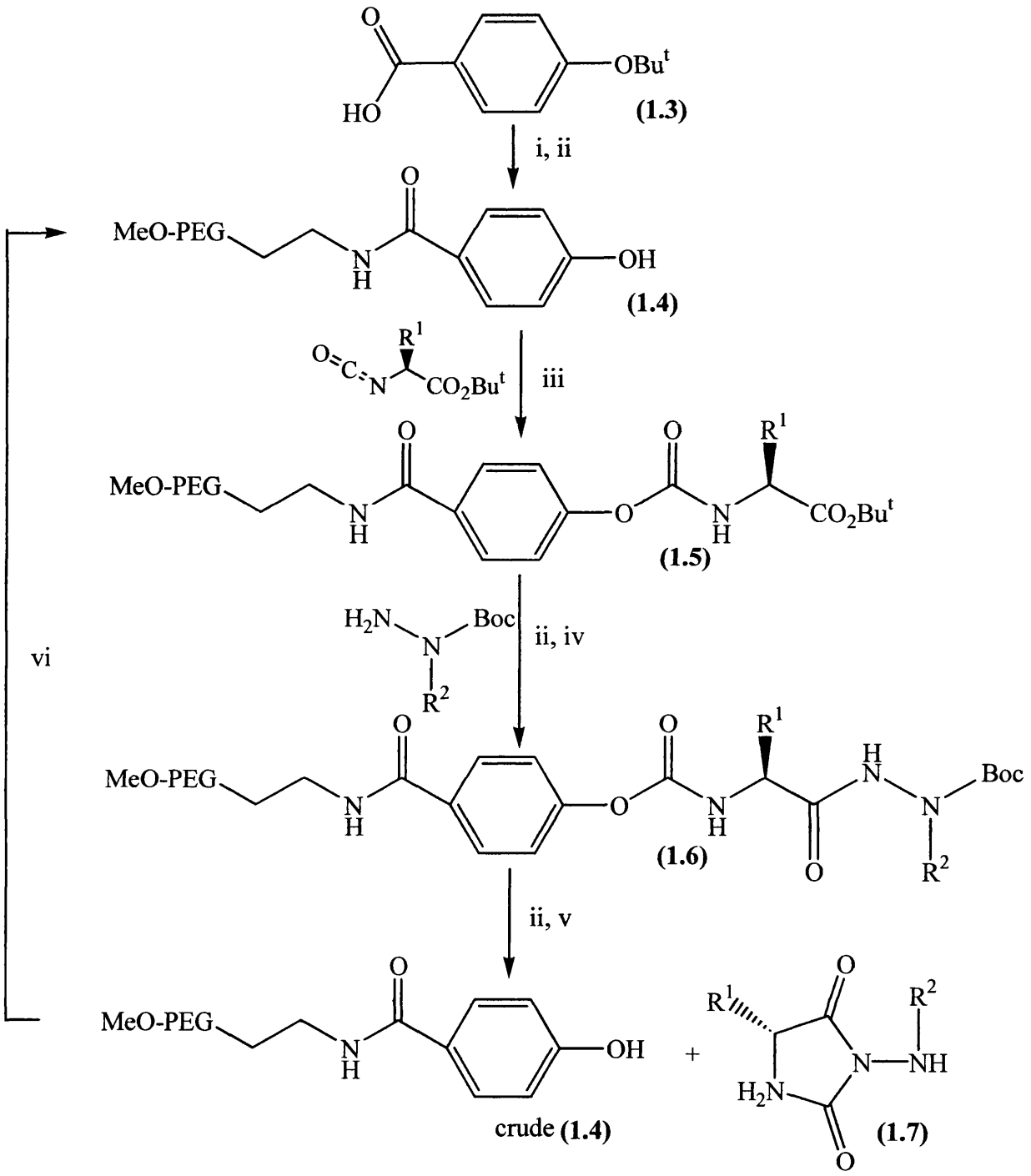


(1.1)



(1.2)

Janda's methodology made use of soluble polyethylene glycol monomethyl ether (MeO-PEG) support that enabled the reaction mixture to be purified after each step by precipitation of the polymer and filtration. The reaction proceeds as shown in Scheme 1.1.



Scheme 1.1

Reagents and Conditions: i. MeO-PEG-$CH_2CH_2NH_2$, DCC, DMAP; ii. TFA-CH_2Cl_2. iii. Et_3N; iv. DCC; v. dilution, Pr^i_2NEt (1.1 equiv.); vi. 1M NaOH.

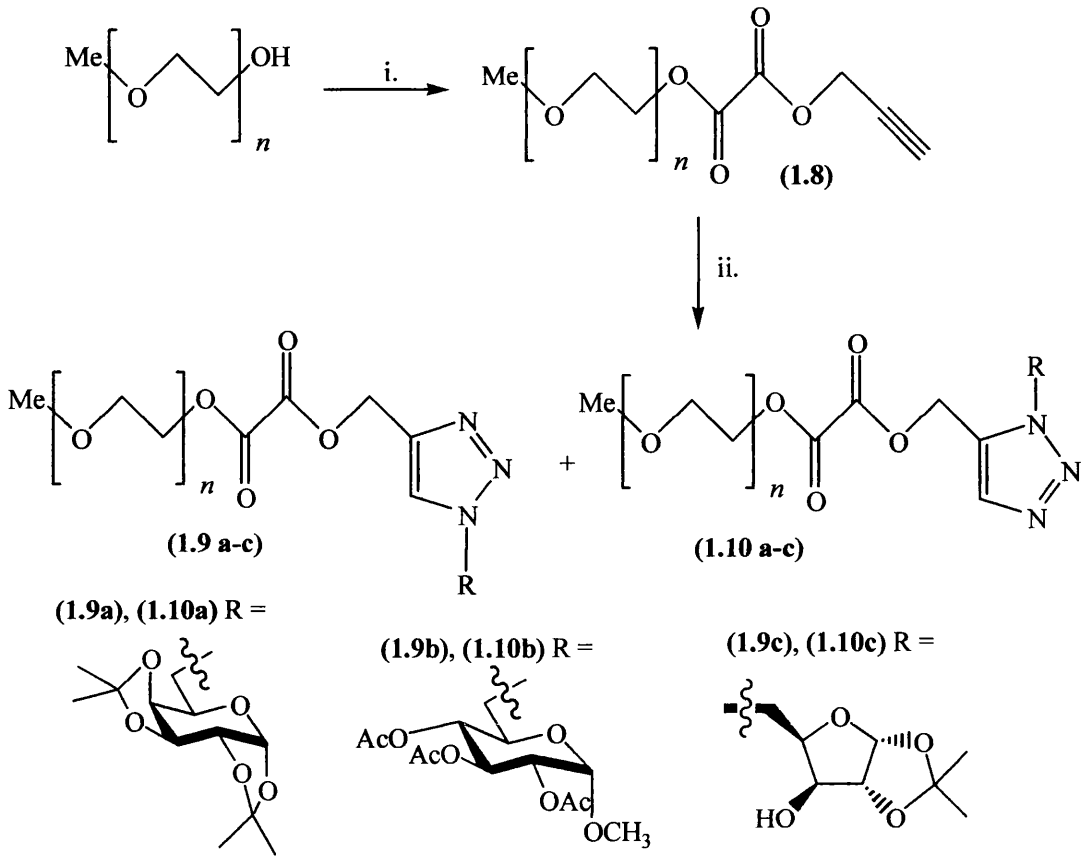
The linker group **(1.3)**, was coupled to MeO-PEG5000-amine to give the soluble polymer supported template **(1.4)**. An amino acid building block was added to form **(1.5)** followed by a Boc-aza-amino acid to form **(1.6)**. At the end of the reaction the product was Boc-deprotected and base-cyclized thus cleaving it from the support to produce a variety of 3-aminoimidazoline-2,4-diones **(1.7)** in greater than 90% purity and in 62-80% yield. The MeO-PEG **(1.4)** was regenerated by extraction with NaOH to remove any previously accumulated material and could be re-used without any significant reduction in loading or yield.

This method shows the controlled stepwise synthesis of 3-aminoimidazoline-2,4-diones. It allows the incorporation of two points of diversity and enables the reuse of the polymeric support.

Another example of the use of MeO-PEG as a soluble polymeric support attached to the substrate molecule in organic synthesis is provided by the work of Norris *et al.*[8] in the 1,3-dipolar cycloaddition reaction with azides. Dipolar cycloaddition to alkenes and alkynes is an established method for the synthesis of both aromatic and non-aromatic five-membered heterocycles. Solution phase methods for their preparation are well documented[9] and more recently the dipolar cycloaddition to insoluble polymer-supported dipolarophiles has been reported.[10, 11] These syntheses offer the advantages associated with solid phase synthesis but also cause problems such as lower reactivity at the polymer-solvent interface and difficult characterization of intermediates whilst still attached to the polymer. The use of a soluble polymer can overcome some of these problems.

The MeO-PEG 5000 monomethyl ether derivative of polyethylene glycol, which has a molecular weight of five thousand, was used as the polymeric support. It is soluble in many organic solvents with the exception of ethers including THF.

The polymer supported alkyne **(1.8)** was reacted *via* a 1,3-dipolar cycloaddition employing azidodeoxy carbohydrate derivatives to afford regioisomeric mixtures of polymer-supported triazoles **(1.9a-c)** and **(1.10a-c)** (Scheme 1.2). Isolation of the triazoles was achieved by precipitation of the polymer using cold ether followed by recrystallization using hot ethanol. Liberation of the triazole products from the polymer was achieved under mild conditions ($NaBH_4$ in ethanol) in yields of greater than 75%. The polymer could then be removed from the mixture of heterocyclic products by precipitation and filtration.



Scheme 1.2

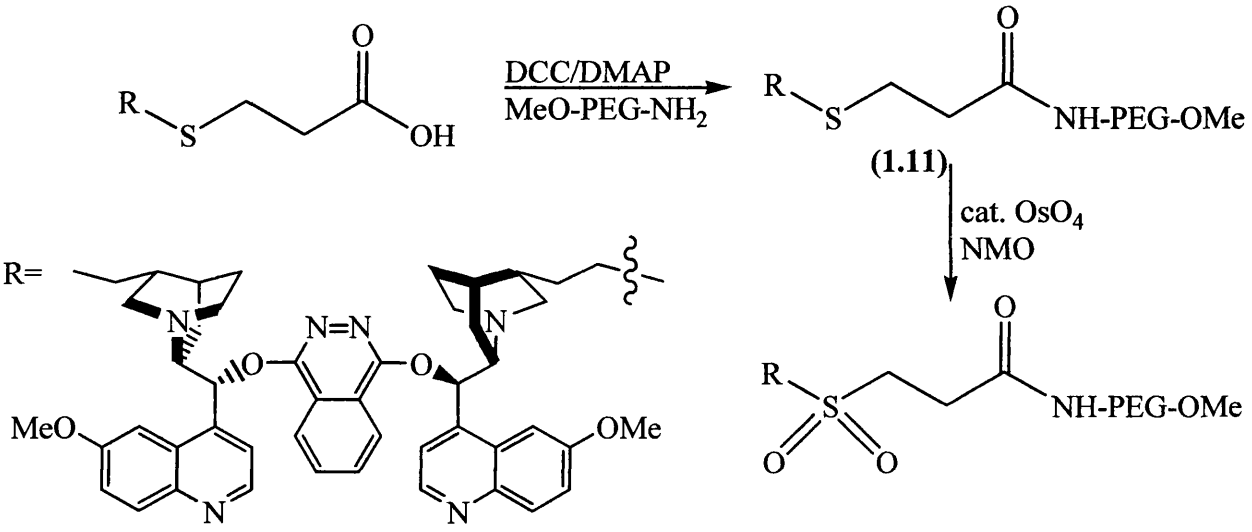
Reagents and Conditions: i. $(COCl)_2$, pyridine, CH_2Cl_2, 0°C, then propargyl alcohol; ii. R-N_3, toluene, reflux.

1.2.2 Soluble Polymer Supported Ligands and Reagents

A reaction that has attracted a lot of interest is Sharpless' asymmetric dihydroxylation (AD) of olefins. The ligand in this reaction is expensive therefore immobilization of the ligand onto an insoluble polymer support to aid its recovery is profitable. However this method has its limitations such as increased reaction times and a reduction in enantioselectivity. Recent research has been directed to carrying out the AD reaction using the soluble polymer MeO-PEG. This solution phase methodology provides all the advantages of a solid support while allowing the ligand to act as it would if unbound in terms of reactivity and enantioselectivity.

Janda *et al.*[12] proposed the synthesis of a soluble polymer-bound $(DHQD)_2PHAL$ ligand **(1.11)** and its successful application to the AD reaction. The ligand is coupled to MeO-PEG-NH_2 in the presence of DMAP and DCC (Scheme 1.3). After the reaction was complete the polymer supported ligand **(1.11)** was isolated by addition of

diethylether to afford precipitation and subsequent filtration. Polymer supported ligand **(1.11)** was found to be completely soluble in *t*-butanol/water solvent systems allowing the study of the AD reaction in homogenous reaction conditions with various olefins (Table 1.1). This method produced considerably higher enantiomeric excesses than previously reported[13,14,15,16,17,18] and the reaction times were similar to those of the free ligand suggesting that the MeO-PEG backbone does not interfere with the reaction kinetics or stereochemistry. Additionally, ligand **(1.11)** can be isolated almost quantitatively by precipitation using diethyl ether.



Scheme 1.3

Table 1.1 - Catalytic asymmetric dihydroxylations using ligand **(1.11)**

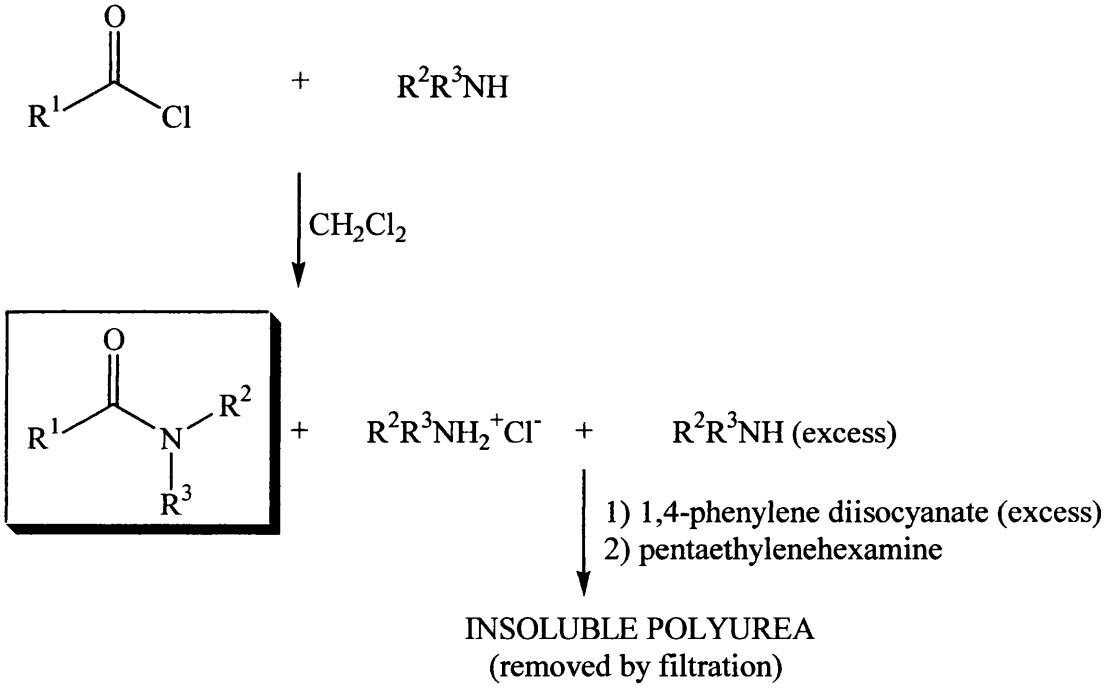
Entry	Olefin	Oxidant	Yield (%)	ee (%)
1	Ph	NMO	87	72
2		K_3FeCN_6	88	98 (97)*
3	Ph, Me	NMO	87	91
4		K_3FeCN_6	83	99 (99)*
5	Ph, Ph	NMO	98	94
6		K_3FeCN_6	95	99 (>97)*
7	n-Bu, n-Bu	NMO	84	80
8		K_3FeCN_6	80	97 (97)*

*Number in parenthesis represents results for free ligand[19]

1.3 Impurity Polymerisation Separation Strategy

A technique which makes use of polymerisation to clean up solution phase reactions has been investigated by Barrett *et al.*[20] The approach is based on the selective annihilation of the unwanted contaminants that are then removed from the reaction mixture by simple filtration as an insoluble product. A small amide library was generated to demonstrate the procedure.

Reaction of acid chloride with excess amine was used to prepare pure amides in the solution phase without the use of chromatography by polymerization of the excess amine and filtration (Scheme 1.4).

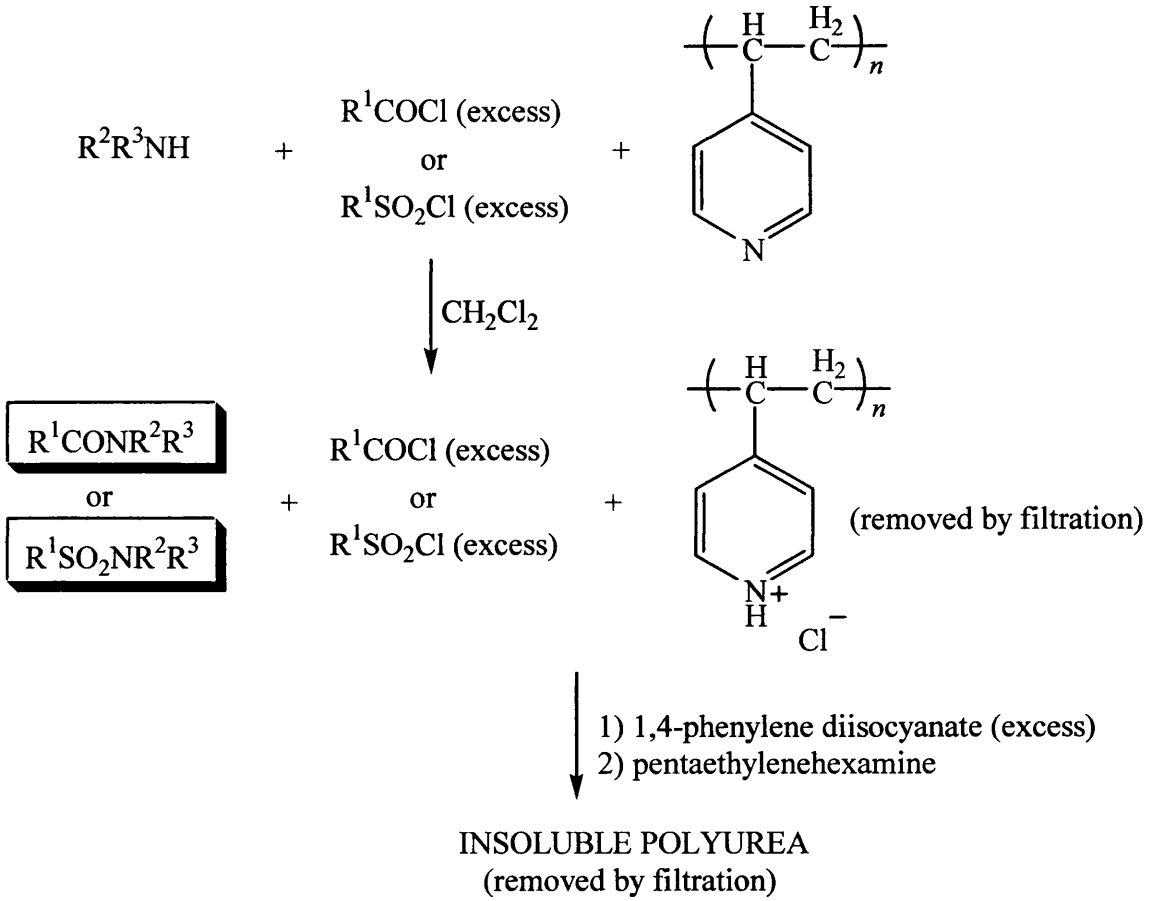


Scheme 1.4

Co-polymerization of 1,4-phenylene diisocyanate and pentaethylenehexamine was used to effectively remove the excess amine as a highly insoluble easily filtered polyurea. The procedure is reported to produce good yields and purities with both primary and secondary amines.

The same method was used to prepare sulfonamides by reacting a sulphonyl chloride with excess amine and removing the impurities in the same way. Amide and sulphonamide formation may also be accomplished by the reaction of amine with excess acyl or sulphonyl chloride respectively (Scheme 1.5). In these circumstances

an excess of poly(vinylpyridine) is added in order to capture liberated hydrogen chloride and enable the reaction to go to completion. The excess acyl or sulphonyl chloride is then scavenged by the addition of the polyamine followed by the diisocyanate to induce polymerization to a polyurea.



Scheme 1.5

The poly(vinylpyridine) and the polyurea are then removed by filtration and high yields and purities of the desired products are reported. This demonstrates that the method is suitable for removal of either excess electrophilic or excess nucleophilic components.

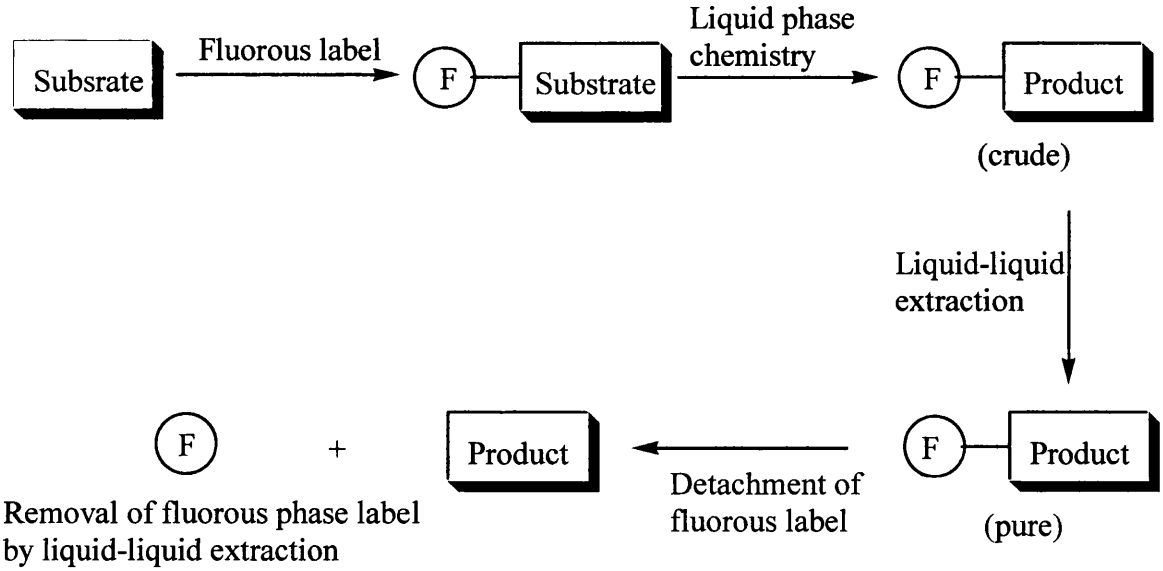
1.4 Fluorous Label Separation Strategy

A recent area of research in organic synthesis is the 'fluorous synthesis' approach to reactions. A molecule attached to a fluorous tag will selectively partition into a

fluorous solvent to allow easy separation. The fluorous synthesis technique offers advantages over solid phase synthesis. It is possible to follow fluorous-tagged reactions using standard techniques such as TLC and to characterize intermediates by standard spectroscopic methods. This is not possible with the polymer bound intermediates in solid phase synthesis. The fluorous synthesis method uses a one-phase reaction mixture that prevents problems occurring with the reaction kinetics as seen in the two-phase reaction mixtures of solid phase synthesis. 'Fluorous' molecules, which are rich in carbon-fluorine bonds, will partition out of an organic or aqueous phase and into a fluorinated phase. Fluorocarbon solvents are often immiscible with organic solvents making it easy to conduct 'fluorous'/organic extractions.

1.4.1 Fluorous Labelled Synthesis

A strategy making use of this property was proposed by Curran *et al.*[21] In this arrangement a 'fluorous phase label' is attached to an organic substrate to render it fluorous. Reactions are then conducted and the fluorous-labelled products are purified by extraction into a fluorinated solvent, leaving any excess reagents and side products in the organic or aqueous phases. The final step of the synthesis is to cleave the fluorous label from the organic product (Scheme 1.6).



Scheme 1.6

This general strategy was used to prepare a small isoxazole and isoxazoline library *via* the cycloaddition of nitrile oxides to alkenes and alkynes (Scheme 1.7), (Table 1.2). There are three stages to the process: attachment of the fluorous label, cycloaddition reaction and detachment. The products of each stage are purified by a three-phase extraction with an organic solvent, water and a fluorous solvent.

The labelling reagent, a highly fluorinated bromosilane is coupled to an allylalcohol in the attachment stage. The fluorous allyl silyl ether will partition into the fluorous phase of the three-phase extraction and can be isolated by evaporation. Any unreacted allylalcohol will be distributed in the organic phase and the inorganic salts formed in the reaction will move into the aqueous phase.

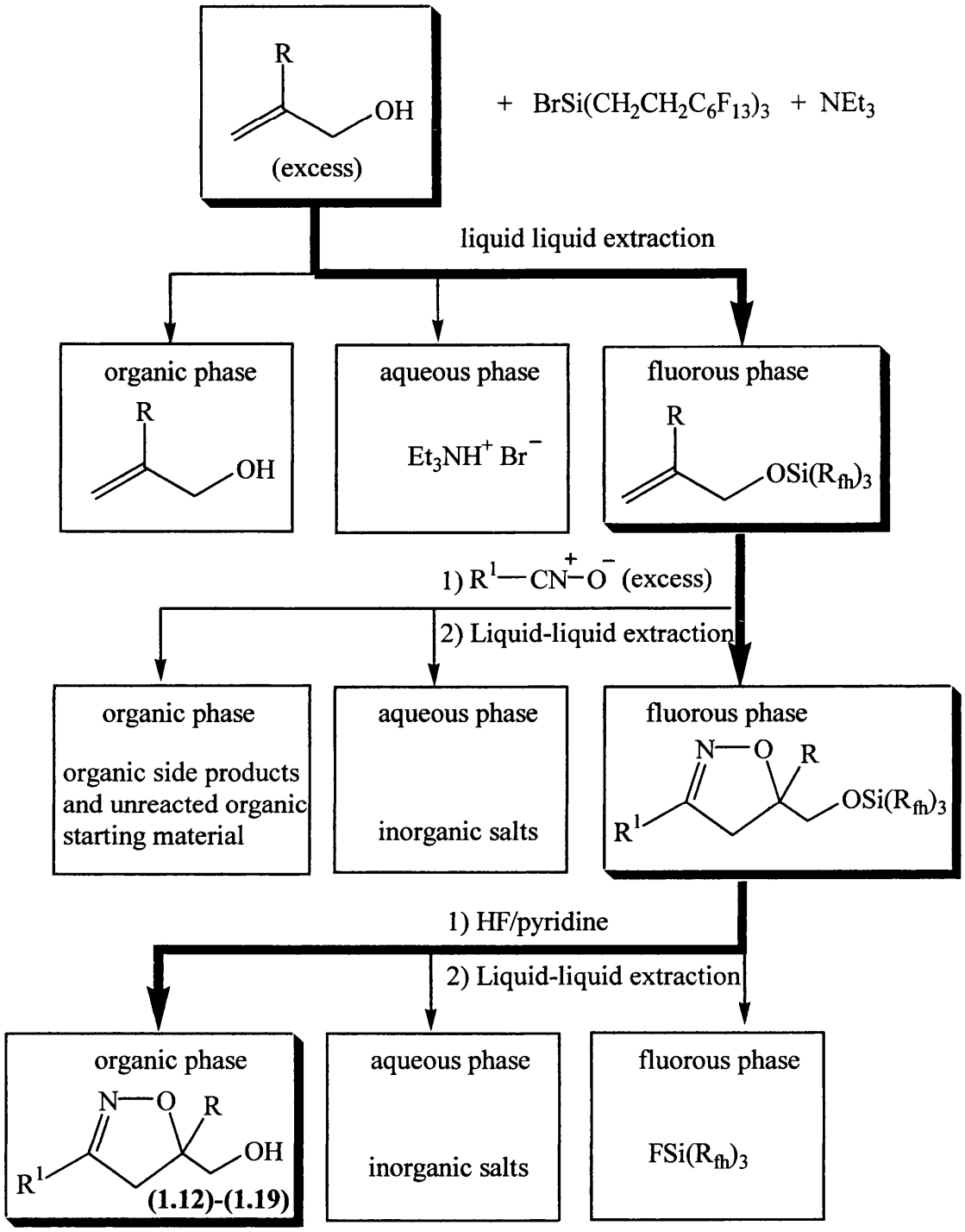
In the cycloaddition step, the fluorous-labelled ether reacts with a nitrile oxide to form the corresponding isoxazoline or isoxazole. After three-phase extraction the fluorous product can be separated from any unreacted organic material or side products and inorganic salts.

In the final detachment stage the fluorous silyl labelling group is cleaved to produce the final isoxazoline or isoxazole product which will partition into the organic phase of the three-stage extraction leaving the fluorous label in the fluorous phase.

Table 1.2 – Results of the synthesis of isoxazolines using the fluorous method

Compound	R	R^1	Yield (%)	Purity (%)
(1.12)	t-Bu	H	99	91
(1.13)	t-Bu	Me	99	99
(1.14)	Ph	H	99	95
(1.15)	Ph	Me	95	98
(1.16)	Me	H	29	93
(1.17)	Me	Me	31	99
(1.18)	Pr	H	48	94
(1.19)	Pr	Me	99	99

(purity determined by GC-analysis)



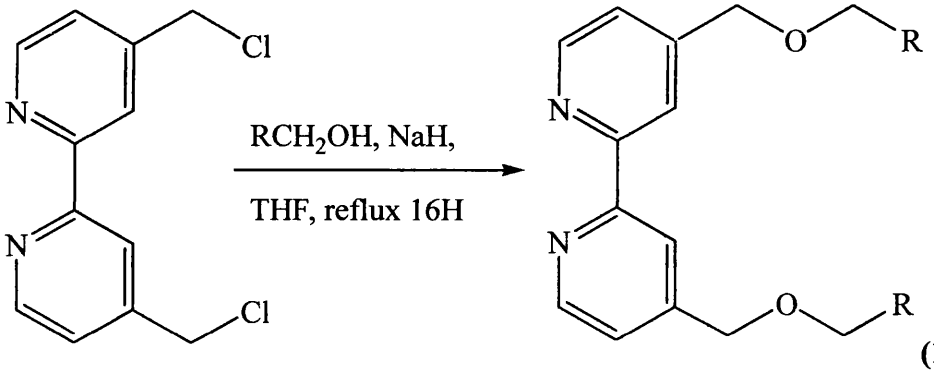
Scheme 1.7

The fluorous synthesis strategy appears to be promising at this early stage of development but its major limitations may have not yet become apparent. Solubility could be a concern since the fluorous label makes molecules 'less organic'. Success has so far been achieved by using 'hybrid' solvents that dissolve both organic and

fluorous compounds, such as benzotrifluoride. The steric or electronic effects of a fluorous label could also alter the reaction profile of an attached organic substrate. Another consideration is the size of the label needed in order to make an organic compound fluorous. Any increase in the molecular weight of the organic substrate will mean a label with a larger fluorine content is needed in order to render it fluorous.

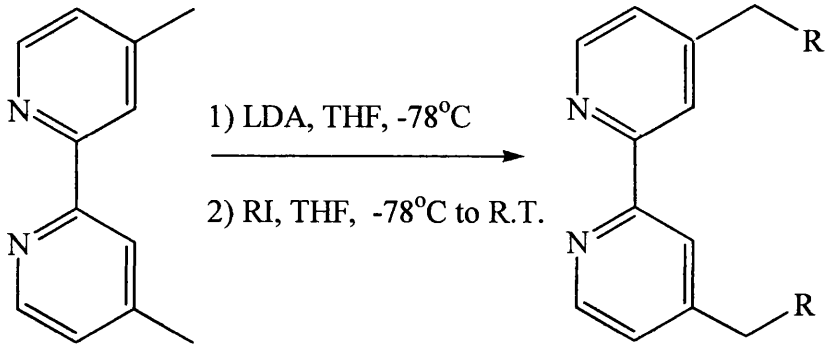
1.4.2 Fluorous Labelled Reagents

Another example of fluorous chemistry is the use of fluorous soluble bipyridines as ligands in catalytic oxidations.[22] Three perfluoroalkylated bipyridines **(1.20-1.22)** were synthesised (Scheme 1.8) and used in a ruthenium-catalysed epoxidation of *trans*-stilbene under the conditions described by Balavoine *et al.*[23] (Scheme 1.9).



(1.20-1.21)

(1.20) R = $C_{10}F_{21}$
(1.21) R = C_7F_{15}
(1.22) R = $C_{11}F_{13}$

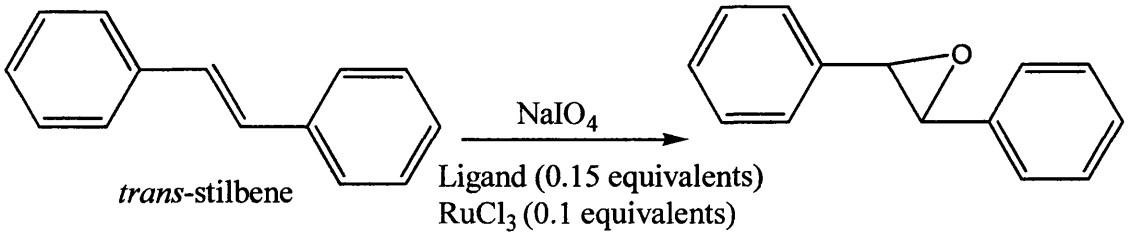


(1.22)

Scheme 1.8

The reaction was carried out in a three-phase system and upon completion the epoxide content of the organic phase was estimated by GC and the fluorous phase containing the ligand was re-used. The results compared to non-fluorinated 2,2'-bipyridine are

shown in Table 1.3. The results show that easily available ligands such as bipyridines can be conveniently used in fluorous chemistry and that fluorous triphasic systems can be applied to catalytic reactions.



Scheme 1.9

Table 1.3 – Ruthenium Catalysed Epoxidation of *trans*-stilbene with $NaIO_4$

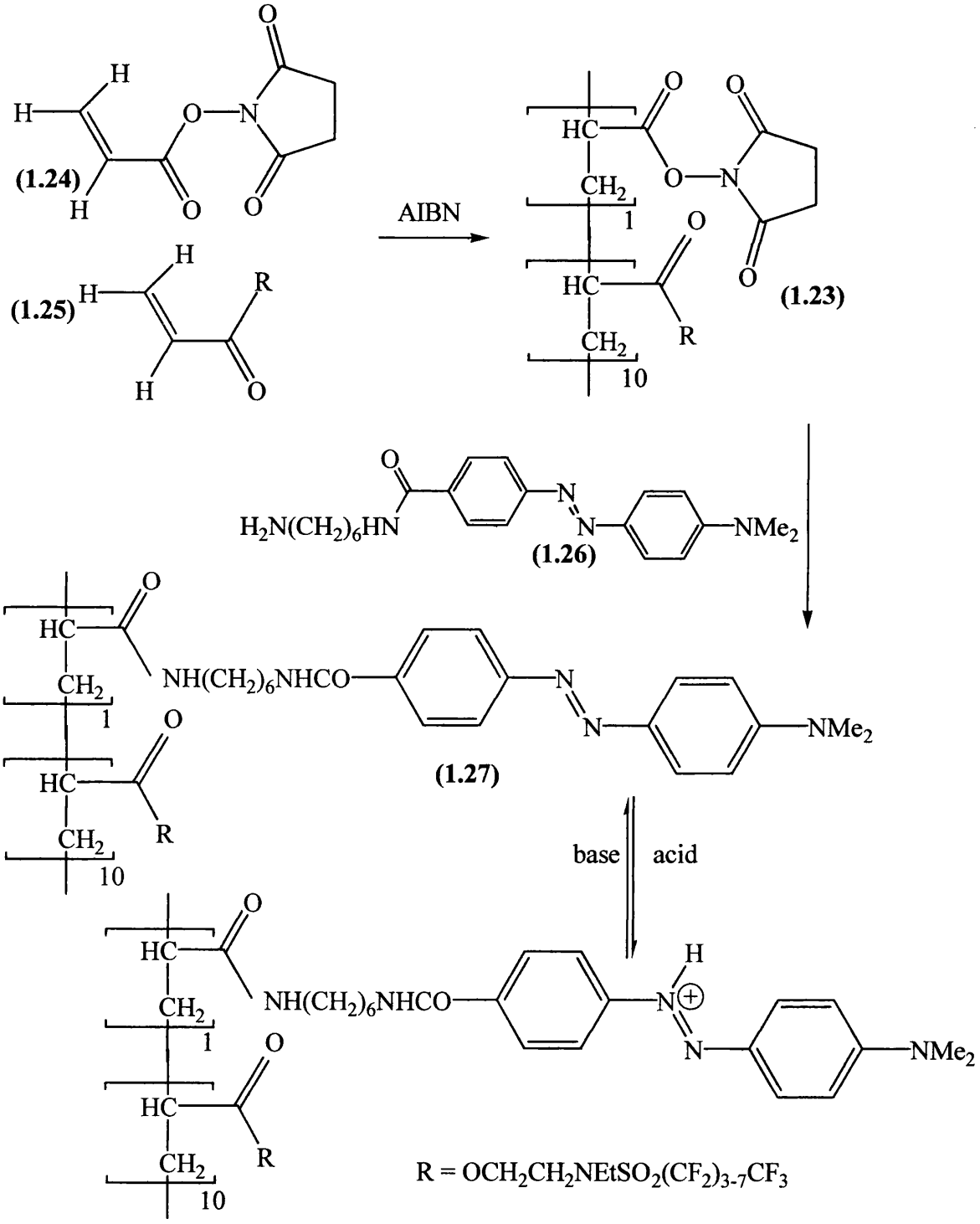
Entry	Ligand	t (min)	T (°C)	Epoxide Yield (%)
1	2,2'-Bipyridine	90	25	45
2	**(1.20)**	90	25	77
3	**(1.21)**	90	25	70
4	**(1.22)**	90	25	87
5	2,2'-Bipyridine	15	0	83
6	**(1.20)**	15	0	79
7	**(1.21)**	15	0	84
8	**(1.22)**	15	0	92

1.4.3 Fluorous Labelled Scavengers

Bergbreiter[24] describes an alternative use for fluorous labels in the sequestration of excess reagents from a reaction mixture. A soluble fluorocarbon polymer was prepared that has reactive sites that can be used to covalently bind amine-containing reagents and render them soluble in the fluorous phase as a fluoropolymer-bound reagent.

The fluorous polymer **(1.23)** was prepared from the co-polymerisation of *N*-acryloyloxysuccinimide **(1.24)** and a fluorinated acrylate **(1.25)** (Scheme 1.10). This fluoropolymer was selectively soluble in the fluorous phase, as opposed to an aqueous or organic solvent phase, and demonstrated facile attachment and removal of reagents

as well as reacting readily in the non-fluorous phase. As a test reaction, **(1.23)** was dissolved in a fluorocarbon solvent and mixed vigorously with a THF solution of the amine-containing methyl red derivative **(1.26)**. The product, **(1.27)**, was isolated by simple separation and removal of the fluorous phase and UV-visible spectroscopy showed no **(1.26)** in the THF layer. The polymer was estimated to have a loading of 0.075×10^{-3} equivalents of **(1.26)** per gram of polymer.



Scheme 1.10

Addition of HCl to **(1.27)** in an aqueous or immiscible THF phase produced immediate protonation of **(1.27)** observed by the colour change in the fluorous phase from yellow to red. Addition of base to the THF or water solution produced a change back to yellow.

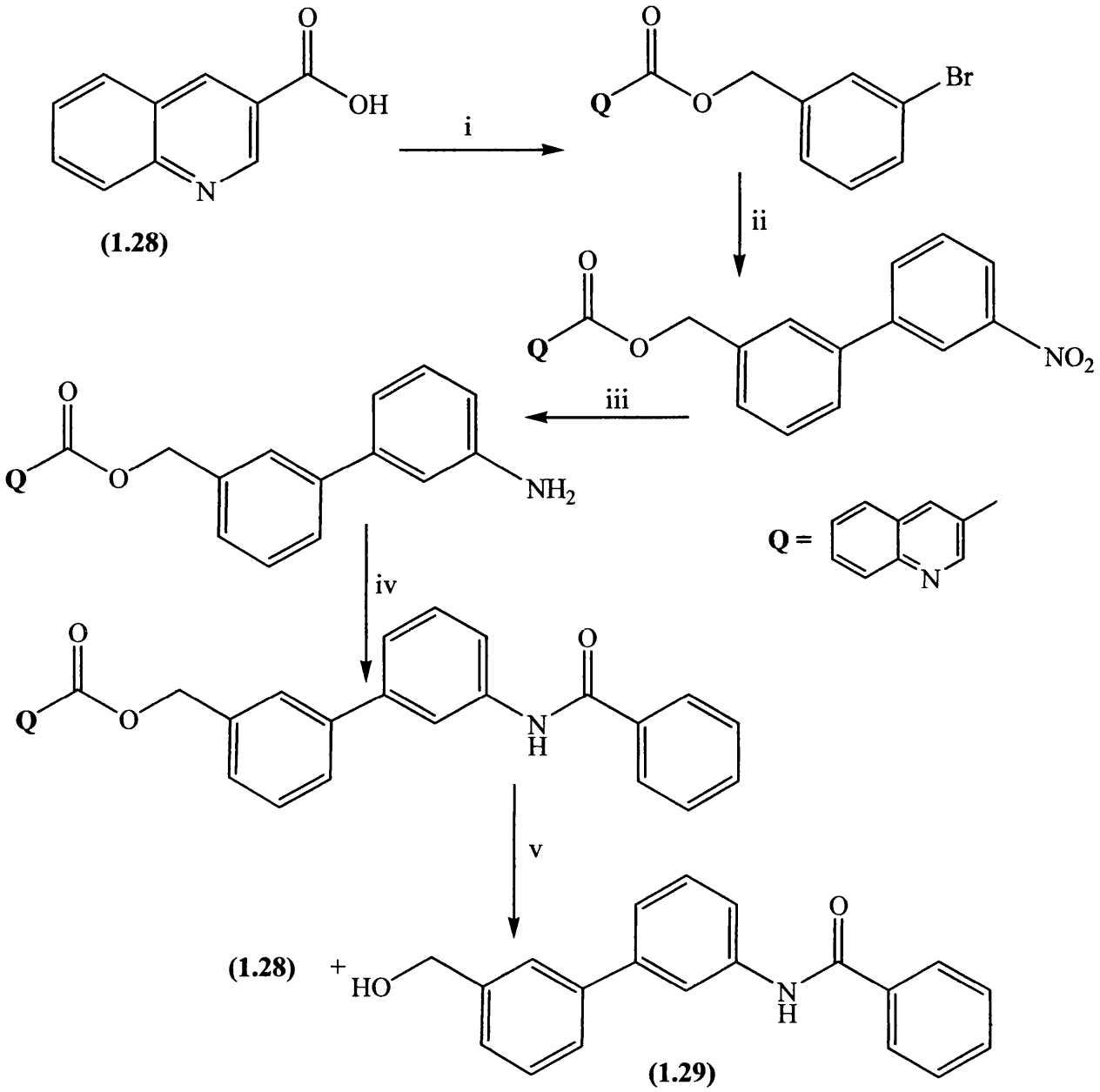
This evidence suggests that vinylfluoropolymers can be easily separated from organic or aqueous solutions using fluorous solvents and are reactive as demonstrated by the protonation/deprotonation experiments. Work is continuing to develop these fluoropolymer supports and exploit their reactivity in catalytic chemistry.

1.5 Acid Precipitation Separation Strategy

Perrier *et al.*[25] approached the problem in a similar way by seeking a low molecular weight group that has switchable solubility properties. This would allow separation on demand and permit reaction monitoring and intermediate characterisation by conventional methods.

The quinoline group was chosen as it is a stable, low molecular weight, neutral group with normal solution properties in standard reaction solvents. However, protonation of the nitrogen affects the solubility of the molecule. This means that a reacting molecule attached to a quinoline group can be isolated from the reaction mixture by precipitation with acid. The usefulness of the quinoline precipitation device was tested in a multistep synthesis (Scheme 1.11). The intermediates were purified after each step by sulphuric acid precipitation and subsequent filtration. The quinoline tag group **(1.28)** was separated from the final reaction mixture by sulphuric acid precipitation and was reused without further purification. Compound **(1.29)** was obtained in 53% yield and 98% purity.

The quinoline precipitation device enables the reaction to proceed as a single-phase organic reaction and standard techniques such as TLC and NMR can be used to monitor the reaction without needing to remove the quinoline group. Upon precipitation with H_2SO_4 the advantages of a solid phase work-up are available. Its usefulness has been demonstrated in a multistep and combinatorial synthesis but further investigation into the scope and limitations of this method are needed.



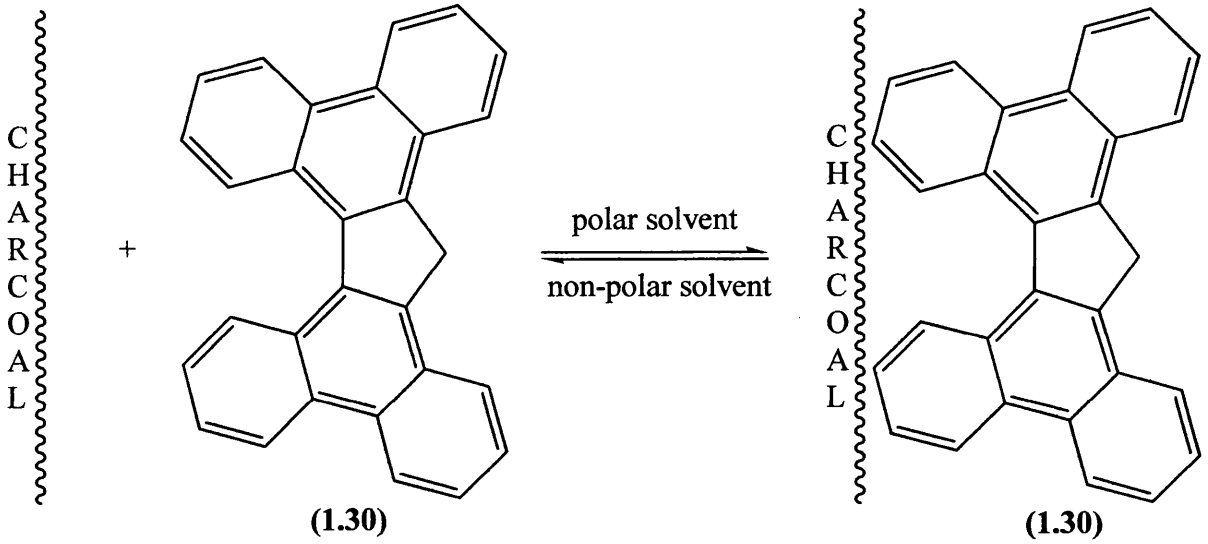
Scheme 1.11

Reagents and Conditions: i. 3-bromobenzyl alcohol, EDCI, CH_2Cl_2; ii. 3-nitrobenzeneboronic acid, $Pd(PPh_3)_4$, DME; iii. Fe, NH_4Cl, EtOH-H_2O 89%; iv. Benzoyl chloride, Et_3N, CH_2Cl_2, 91%; v. LiOH, THF-H_2O 85%.

1.6 Product Sequestration Separation Strategy

Ramage *et al.*[26] have concentrated on a method of purification that makes use of the affinity of tetrabenzo[a,c,g,i]fluorene (Tbf) **(1.30)** and charcoal. These molecules can

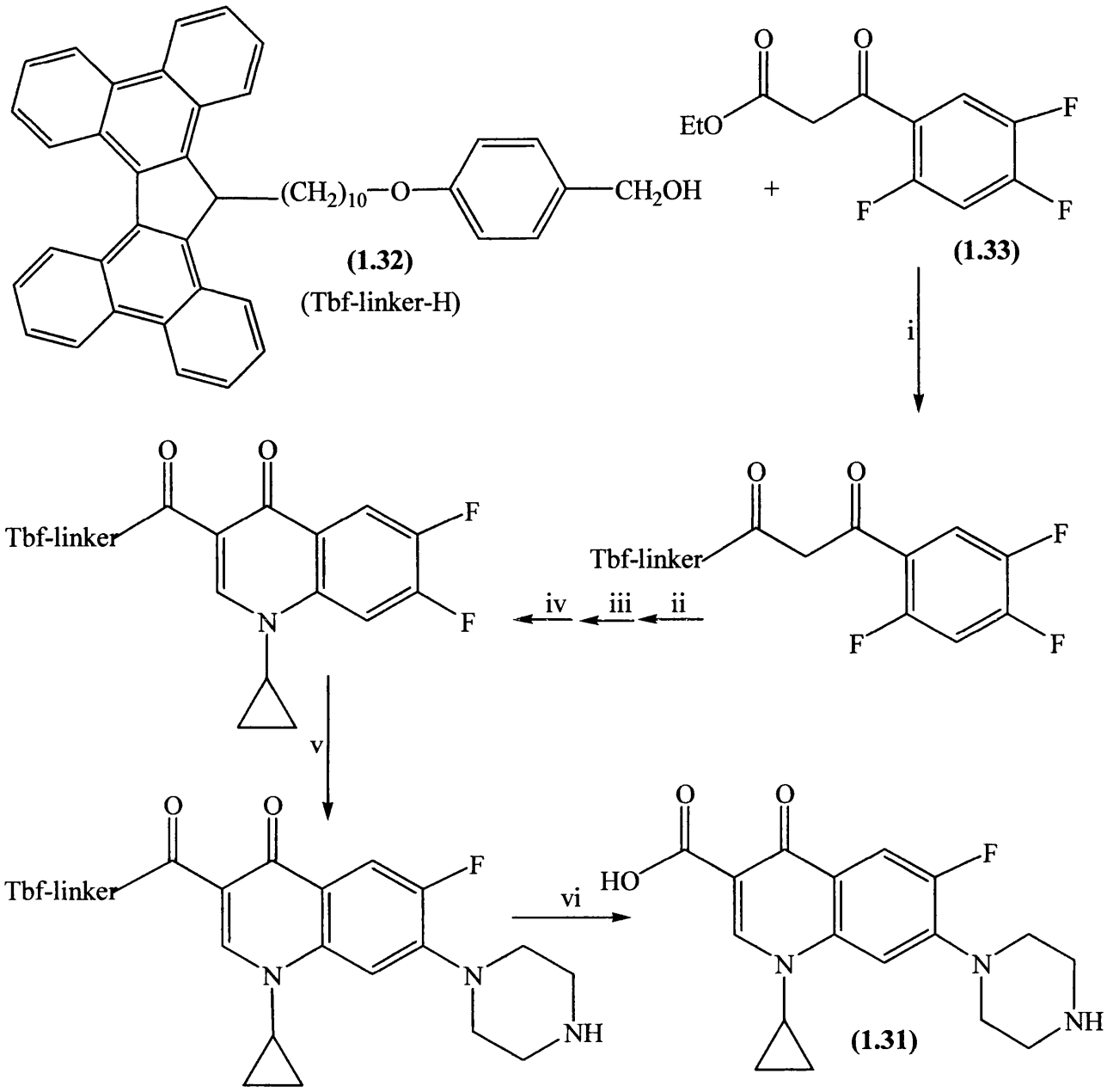
form non-covalent interactions with each other and the adsorption–desorption equilibrium is influenced by the polarity of the solvent (Scheme 1.12).



(1.30) **(1.30)**

Scheme 1.12

Organic compounds covalently bound to Tbf *via* a suitable linker group can be reacted using traditional solution phase chemistry and the product purified by absorption onto charcoal. Non-Tbf-bound compounds can be removed in the filtrate. As no covalent bonds are formed with the support, recovery of the Tbf-bound product can be achieved by desorption from the charcoal. This method has been used for the solution-phase synthesis of the antibacterial agent Ciprofloxacin® **(1.31)** (Scheme 1.13) which has previously been produced by a more conventional solid-phase synthesis.[27] The Tbf anchor group **(1.32)** contained a benzyl alcohol functionality to enable it to bind to the precursor in the quinoline synthesis **(1.33)** and included a *para*-alkoxy functionality to allow TFA cleavage from the final product. The successful synthesis of Ciprofloxacin (57% yield, >95% purity) has shown that traditional solution phase synthesis can be performed on molecules covalently bound to a Tbf anchor. The high affinity of Tbf for charcoal has enabled a *pseudo*-solid phase purification of organic molecules to be developed.



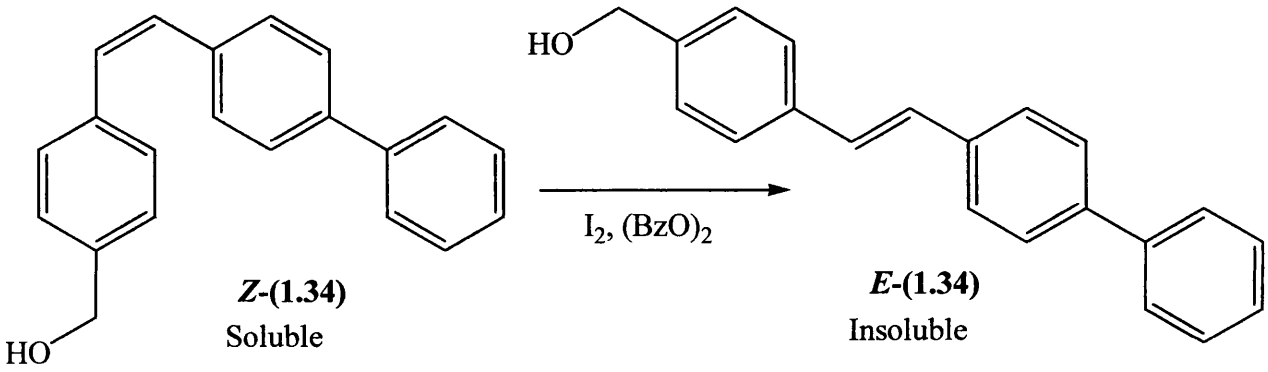
Scheme 1.13

Reagents and Conditions: i. DMAP, toluene, reflux, 40hr; ii. $(CH_3)_2NCH(OCH_3)_2$, 6eq., THF, RT., 24hr; iii. Cyclopropylamine, 12eq., THF, RT., 20hr; iv. Tetramethylguanidine, THF, 20eq., reflux, 20hr; v. Piperazine, pyridine, reflux, 6hr; vi. 90% TFA in DCM.

1.7 Precipitation by Isomerism Separation Strategy

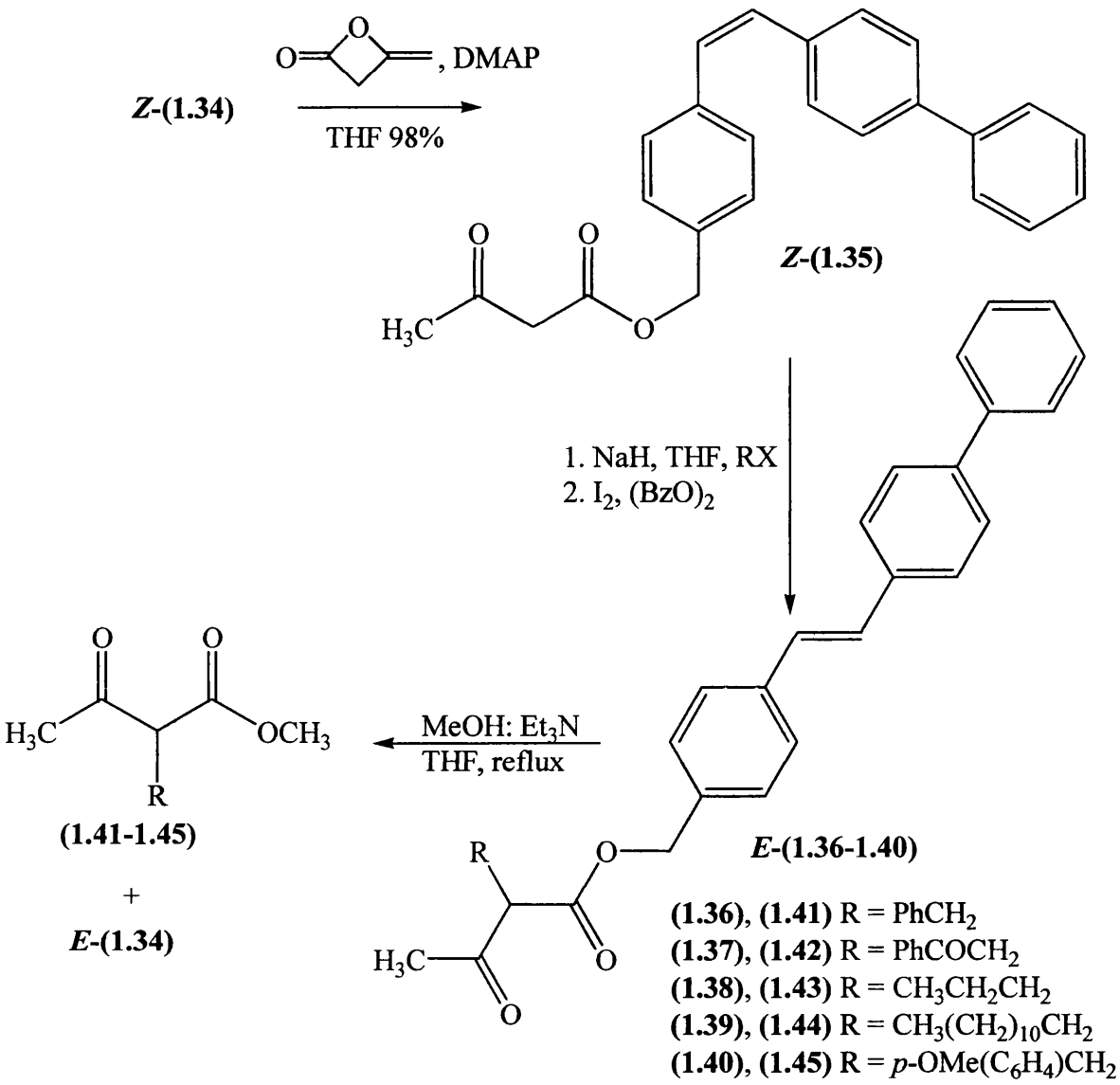
An approach by Wilcox *et al.*[28] utilizes the different solvation properties of the *E* and *Z* isomers of the diaryl alkene **(1.34)** (Scheme 1.14). The *Z*-isomer is soluble in ether,

hexanes and methanol but the *E*-isomer is insoluble in these solvents. By tagging a reacting molecule to **(1.34)** it is possible to precipitate the product by isomerization. This technique was used to prepare a series of α-substituted β-ketoesters (Scheme 1.15).



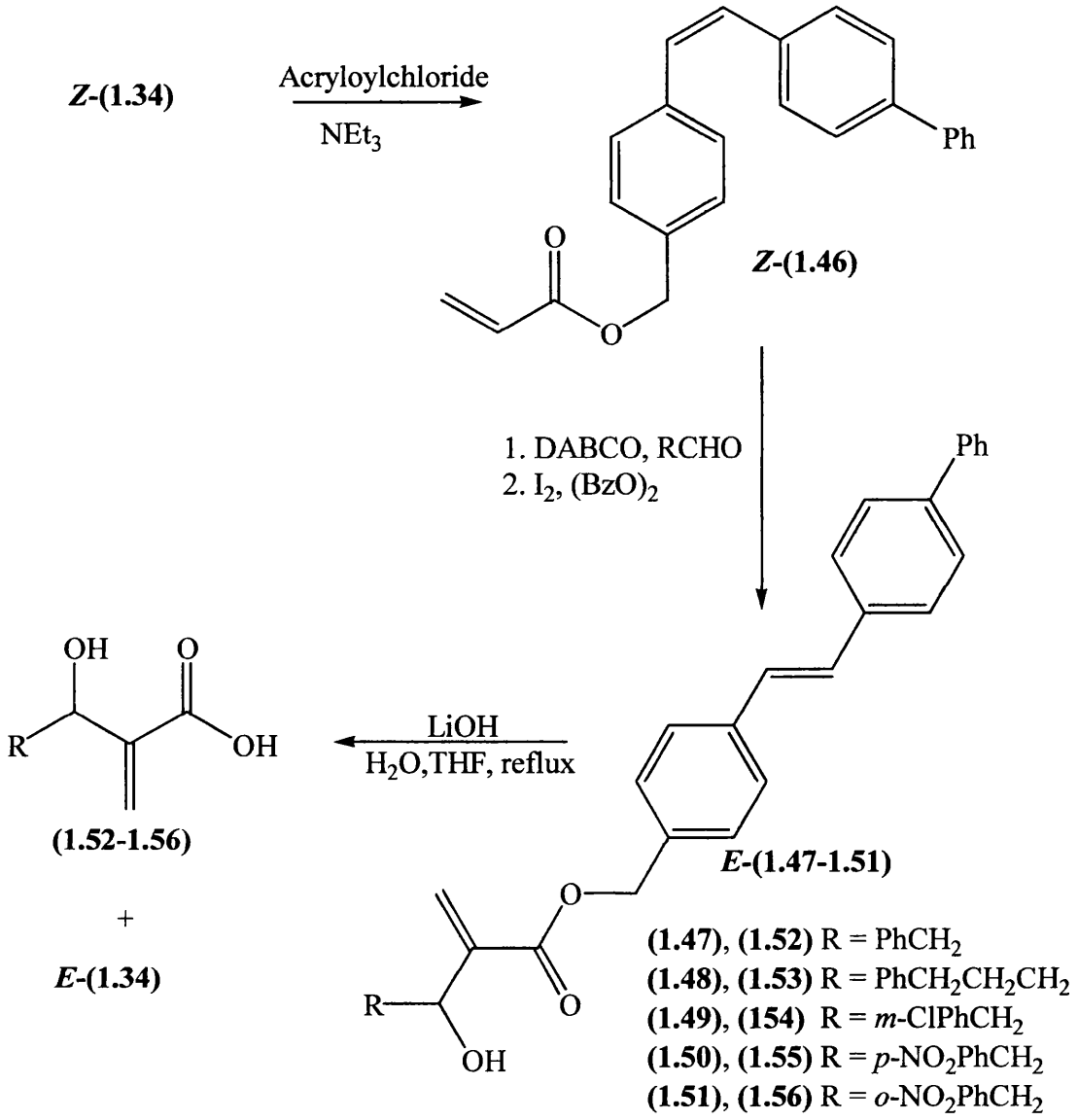
Scheme 1.14

Z-**(1.34)**-tagged acetoacetate ester, *Z*-**(1.35)**, was prepared from the reaction of *Z*-**(1.34)** with diketene using a catalytic amount of DMAP. *Z*-**(1.35)** was then deprotonated with sodium hydride to generate the enolate that was treated with an excess of the alkylating reagent, generally for 3 hours at 23°C, before partitioning the reaction mixture between EtOAc and aqueous NH_4Cl. The organic layer was isolated and evaporated. To achieve isomerization, the resulting residue was redissolved in a CCl_4 solution of iodine and benzoyl peroxide and stirred for 4-24 hours. The mixture was washed with an aqueous bisulfite solution and the organic layer was isolated and evaporated to give the crude product. Purification was achieved simply by trituration with ether, hexane and/or methanol, as all contaminants not bound to *Z*-**(1.34)** were soluble in these solvents. This afforded the tagged compounds *E*-**(1.36-1.40)** in good yields with purities over 95%. Cleavage of the products from the tag group was achieved by methanolysis. The ether insoluble *E*-**(1.34)** group was separated from the products by evaporation of the reaction mixture and washing with ether or methanol. Evaporation of the filtrate afforded the methyl β-ketoesters **(1.41-1.45)** in good yields and purities over 95%.



Scheme 1.15

This technique has also been used in the purification of Baylis-Hillman adducts[29] (Scheme 1.16). The *Z*-**(1.34)**-tagged acrylate, *Z*-**(1.46),** was prepared by treatment of *Z*-**(1.34)** with acryloyl chloride in the presence of NEt_3. The Baylis-Hillman reaction was then carried out and the resulting product isomerized to produce *E*-**(1.47-1.51).** The purification was achieved by trituration with ether, hexane or methanol to afford the Bayliss-Hillman adducts in good yields with purities greater than 95%. The products were cleaved from the tag group by hydrolysis and the acids were isolated by filtration of the insoluble *E*-**(1.34)** and acidification of the filtrate, followed by extraction with EtOAc. Removal of EtOAc produced the desired acids in good yields and purities over 95%.



Scheme 1.16

This method allows excess reagents to be used to increase reaction rates and product yields without the need to use chromatography or distillation to remove the excess. The loading of the resin is reported to be over 3mmol/g. The process can be automated and is cost effective so may be useful in large-scale preparations.

1.8 Acid/Base Extraction Separation Strategy

Boger *et al.*[30] exploited the acidic and basic properties of a template molecule in order to extract it from the reaction mixture. The template **(1.57)** contains three positions which can react with nucleophiles or an acylating agent enabling the synthesis of libraries with three variable regions (Figure 1.1)

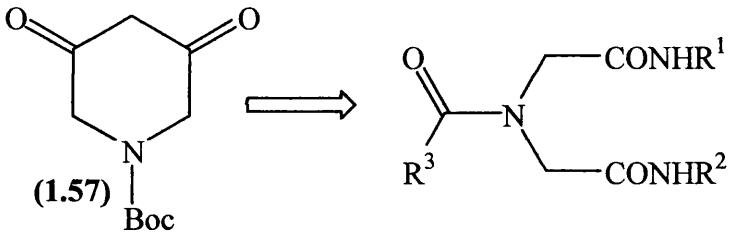
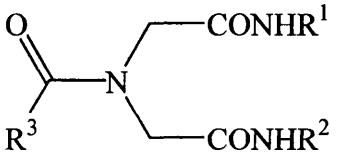


Figure 1.1

The reaction sequence is shown in Scheme 1.17. The template is activated by reaction with EDCI. Compound **(1.57)** then reacts with an amine to form a carboxylic acid group on the template. The excess amine, EDCI and byproducts can be removed from the mixture by extraction into an acidic solution. The pure compound then reacts with a second amine and is purified by acid/base washing. N-Boc deprotection and subsequent reaction with a carboxylic acid adds a third group. An example of a library produced in this way is shown in Figure 1.2. All compounds were at least 90% pure.



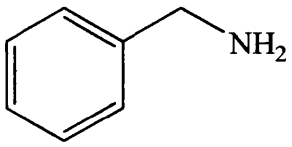
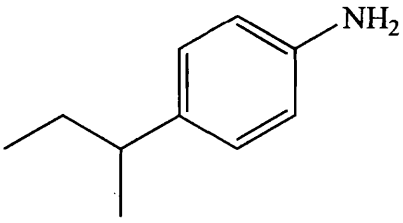
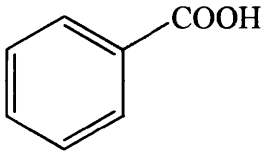
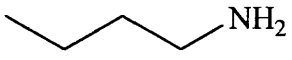
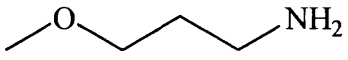
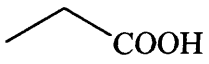
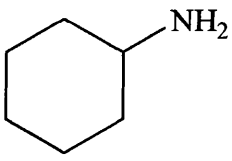
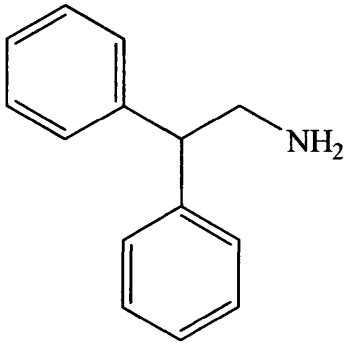
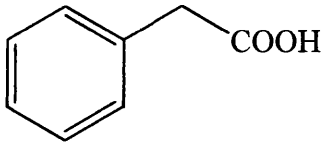
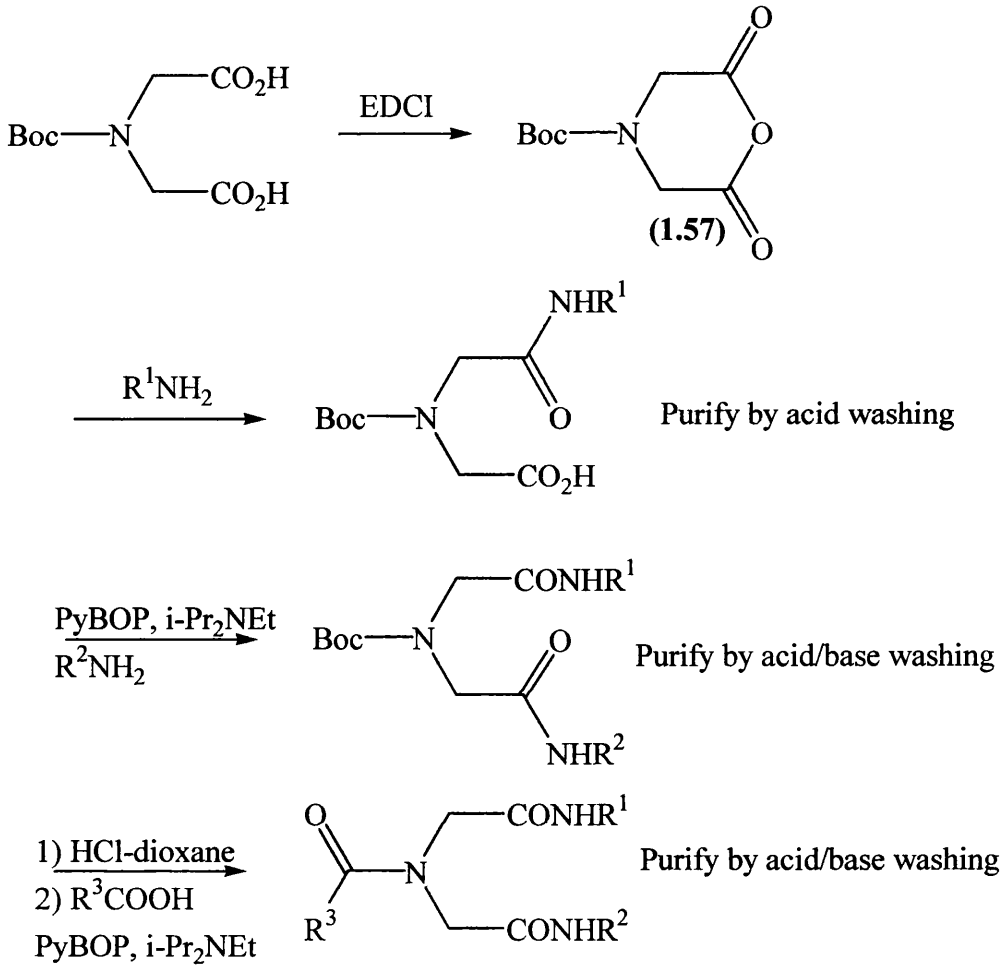
R^1NH_2	R^2NH_2	R^3COOH
		
		
		

Figure 1.2

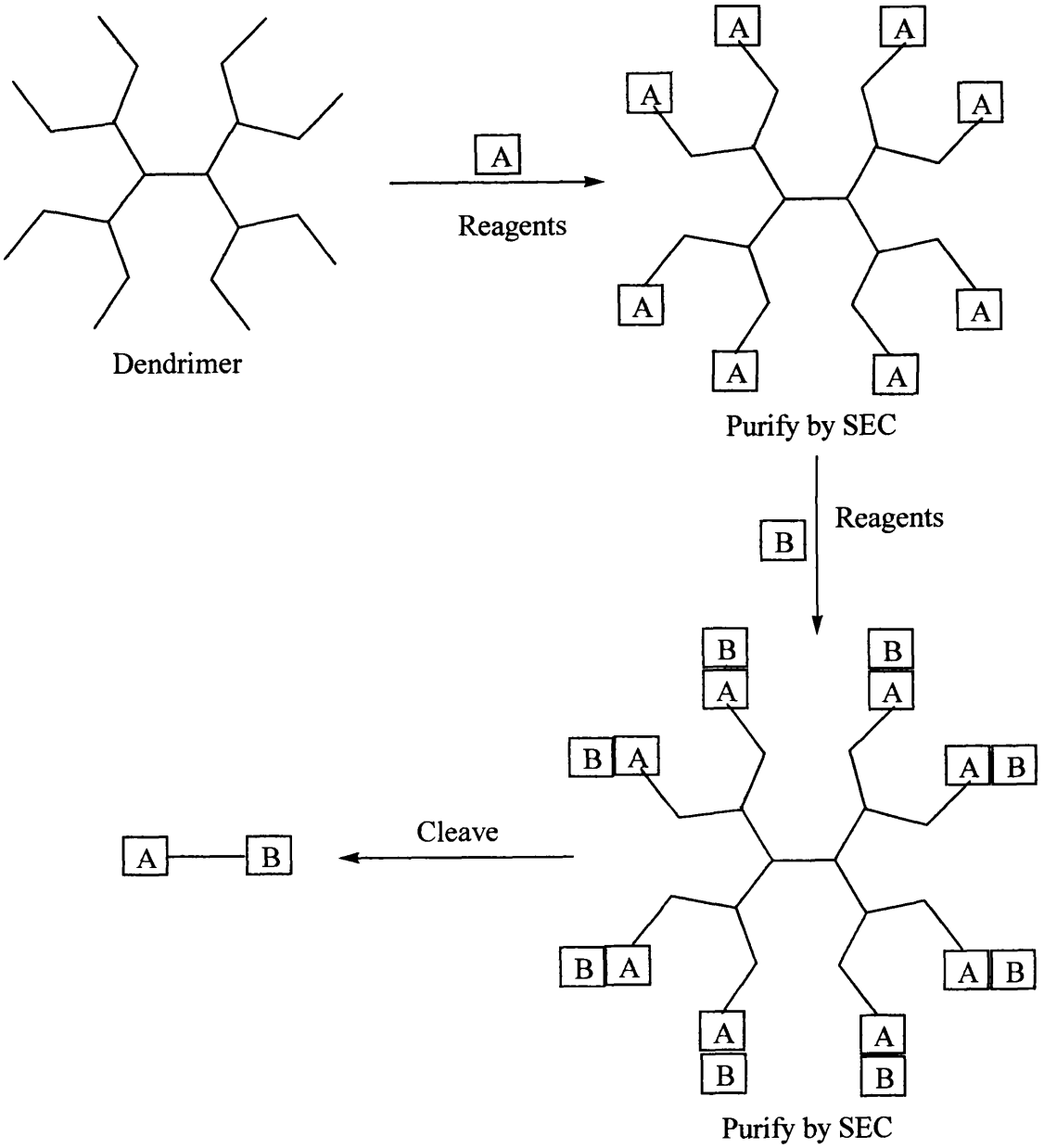


Scheme 1.17

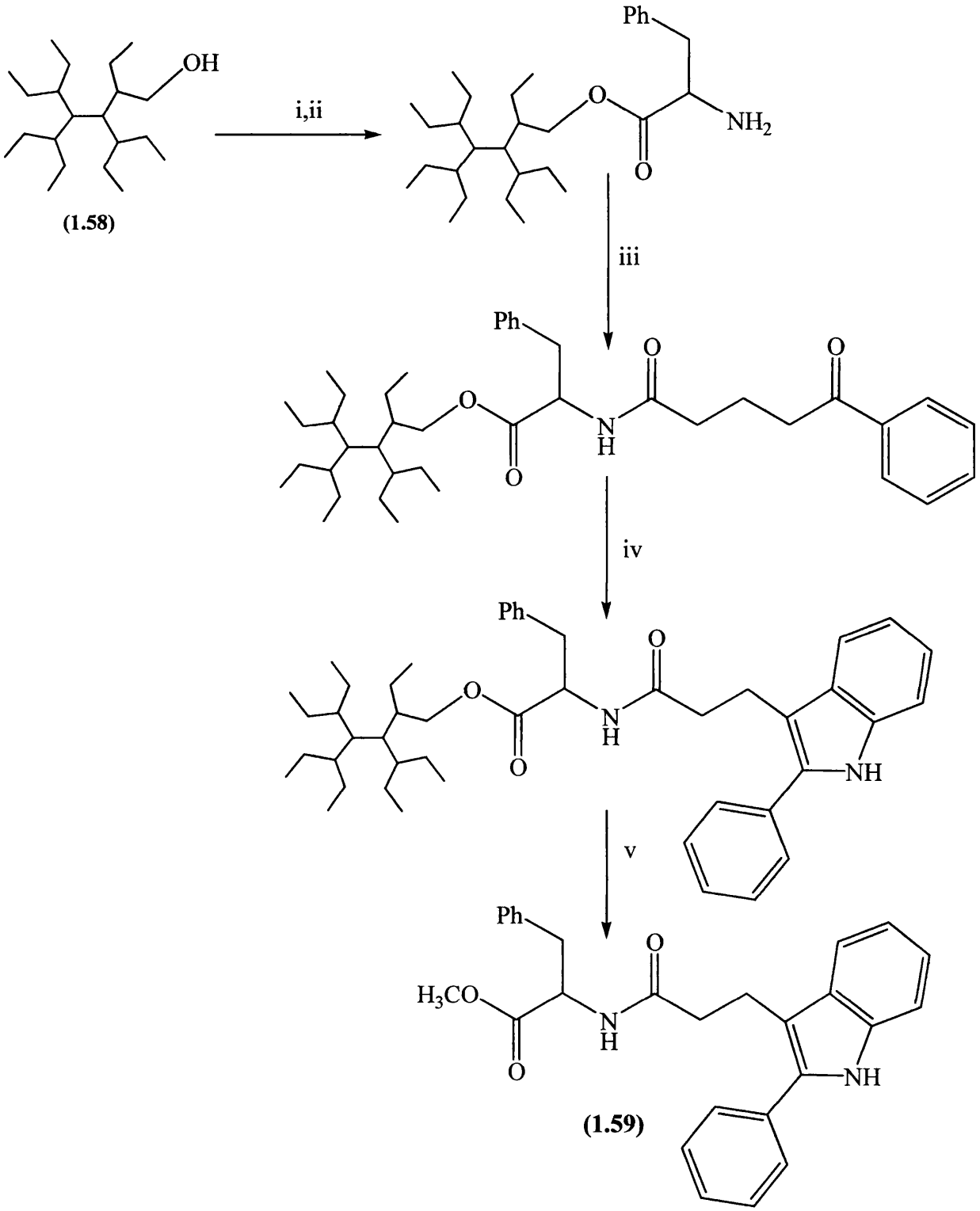
1.9 Soluble Dendrimer Support Separation Strategy

An approach by Kim *et al.*[31] uses dendrimers as soluble supports in solution phase synthesis as outlined schematically in Scheme 1.18. Dendrimers are branching oligomers and due to their large size can be purified from reagents by size exclusion chromatography (SEC) or ultrafiltration. The Fischer indole synthesis was used to demonstrate the feasibility of the approach (Scheme 1.19). The compounds were formed on a polyamidoamine (PAMAM) dendrimer which is commercially available and has eight amine-terminated 'arms' which can be readily functionalised. PAMAM was coupled to 4-hydroxymethylbenzoic acid to form **(1.58)** with a base-labile handle for anchoring compounds onto the dendrimer. A three-step reaction was then performed with the intermediates being purified by SEC. At the end of the sequence the dendrimer was cleaved to yield the methyl ester product **(1.59)** and **(1.58)** was regenerated. The cleaved product was isolated from the dendrimer by SEC affording

(1.59) in 90%yield and 99% purity. This method has been extended to the synthesis of a small indole library **(1.60a-f)** (Table 1.4).

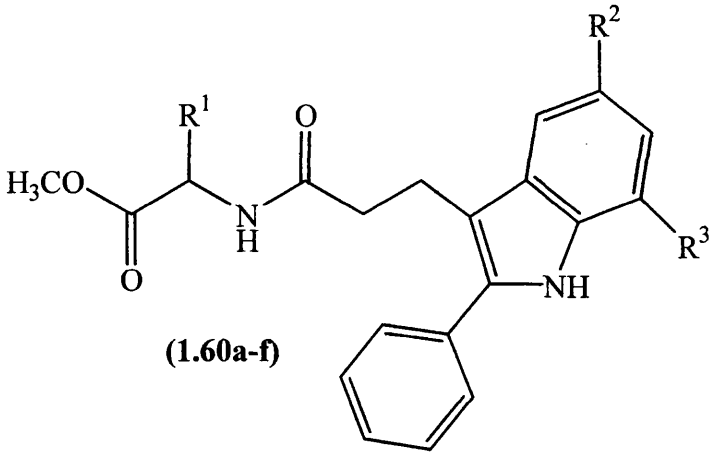


Scheme 1.18



Scheme 1.19

Reagents and Conditions: i. Fmoc-Phe-OH, EDCI, DMA, DMAP; ii. 25% piperidine/ DMF; iii. 4-benzoylbutyric acid, PyBOP, HOBT, DIEA, DMF; iv. Phenylhydrazine.HCl, $ZnCl_2$, HOAc, 70°C; v. 9:1 MeOH/Et_3N, 50°C.



(1.60a-f)

Table 1.4 – Indoles prepared from dendrimer-support methodology

Compound	R^1	R^2	R^3	Purity (%)*
(1.60a)	$-CH_2Ph$	H	H	99
(1.60b)	$-CH_2Ph$	t-Bu	H	96
(1.60c)	$-CH_2Ph$	Cl	H	99
(1.60d)	$-CH_2Ph$	Cl	Cl	84
(1.60e)	$-CH_2CH(CH_3)_2$	t-Bu	H	96
(1.60f)	$-CH_2CH(CH_3)_2$	Cl	Cl	91

*Determined by reverse-phase HPLC.

This method offers a general strategy by which a wide variety of compounds and libraries may be created.

1.10 Conclusion

The work described in this chapter provides an insight into the different and innovative strategies for incorporating the positive aspects of conventional solid phase synthesis into solution phase methodology.

1.11 References

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Chapter Two

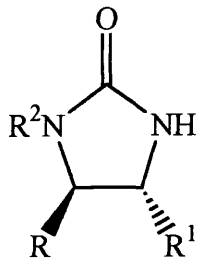
An Introduction to Chiral Auxiliary Mediated Asymmetric Enolate Reactions

2.1 Introduction to Chiral Auxiliaries

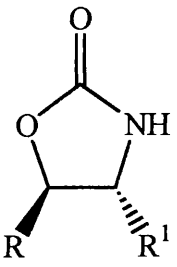
The use of chiral auxiliaries in enolate reactions has become increasingly popular. A good chiral auxiliary induces high diastereofacial selectivity in the reaction of the attached enolate group.

There are three stages involved in the use of a chiral auxiliary: - the attachment of the auxiliary, the asymmetric reaction, and the cleavage of the product from the auxiliary. Each stage must be completed easily and efficiently for the auxiliary to be useful.

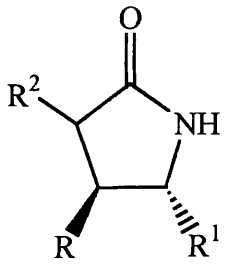
Early auxiliaries were derived from natural sources such as amino acids, carbohydrates and terpenes but since the early1990's many new chiral auxiliaries have been developed. There are many different types of auxiliary but this introduction will focus on the derivatives of imidazolidinones **(2.1)**, oxazolidinones **(2.2)** and pyrrolidinones **(2.3)**.



(2.1)

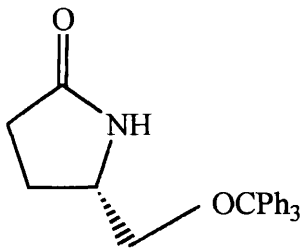


(2.2)

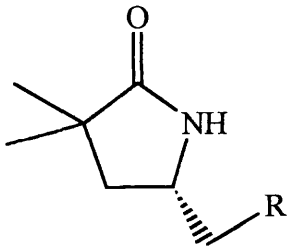


(2.3)

Koga and Tamioka have used the *O*-trityl-5-hydroxymethyl-2-pyrrolidinone **(2.4)** auxiliary in selective conjugate additions and Diels-Alder reactions of α,β-unsaturated *N*-acyl fragments.[1,2,3] However, this auxiliary is unsuitable for controlling the reactions of acyl enolates as the deprotonation of the α-position on the acyl fragment competes with the deprotonation of C-3 on the pyrrolidinone ring. A group of 5-substituted-3,3-dimethyl-2-pyrrolidinones, known as 'Quat' chiral auxiliaries **(2.5a-d)**, developed by Davies *et al.*[4], has been shown to induce high stereoselectivities in enolate alkylations of the attached acyl side chains. The dimethyl group on C-3 prevents deprotonation.

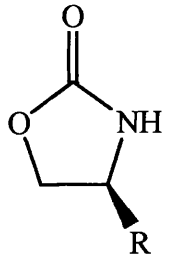


(2.4)

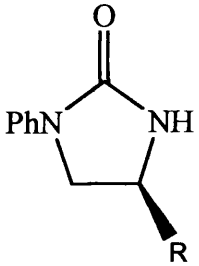


(2.5a) R=$OSiMe_2{}^tBu$ **(2.5c)** R=Me
(2.5b) R=$OCPh_3$ **(2.5d)** R=Et

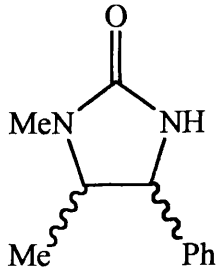
A useful group of chiral auxiliaries developed by Evans and co-workers is the oxazolidin-2-one auxiliaries, **(2.6-2.7)**. These compounds have been proved effective in inducing stereoselectivity in alkylation,[5] acylation,[6] bromination,[7] amination,[8] hydroxylation[9] and aldol reactions[10] of attached *N*-acyl enolates. They have an oxygen in the 3-position so that problems with competing deprotonation at this position do not exist.



(2.6) R=*i*Pr
(2.7) R=Bn



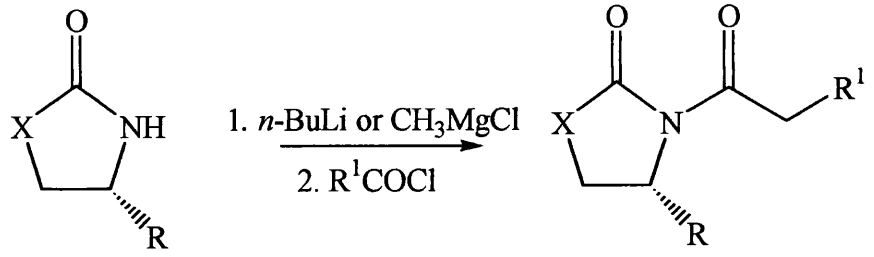
(2.8) R=*i*Pr
(2.9) R=Bn



(2.10)

The imidazolidinone-derived auxiliaries **(2.8-2.9)** are similar in structure to the oxazolidinones **(2.6-2.7)**. The phenyl chromophore present in the imidazolidinone ring facilitates reaction monitoring and product isolation by HPLC. It has been used successfully in asymmetric aldol reactions[11] and Michael additions.[12] 1,5-Dimethyl-4-phenylimidazolidinone **(2.10)** is a powerful auxiliary for many asymmetric reactions. It is easily and economically prepared from the fusion of ephidrine hydrochloride and urea as reported by Close in 1950.[13] The (4*R*,5*R*)-, (4*R*,5*S*)-, (4*S*,5*R*)- and (4*S*,5*S*)-isomers have all been used in asymmetric reactions such as aldol,[14] Diels-Alder,[15] conjugate addition of organometallics[16] reaction with phthalimide,[17] and asymmetric alkylation[18,19,20,21,22,23] reactions.

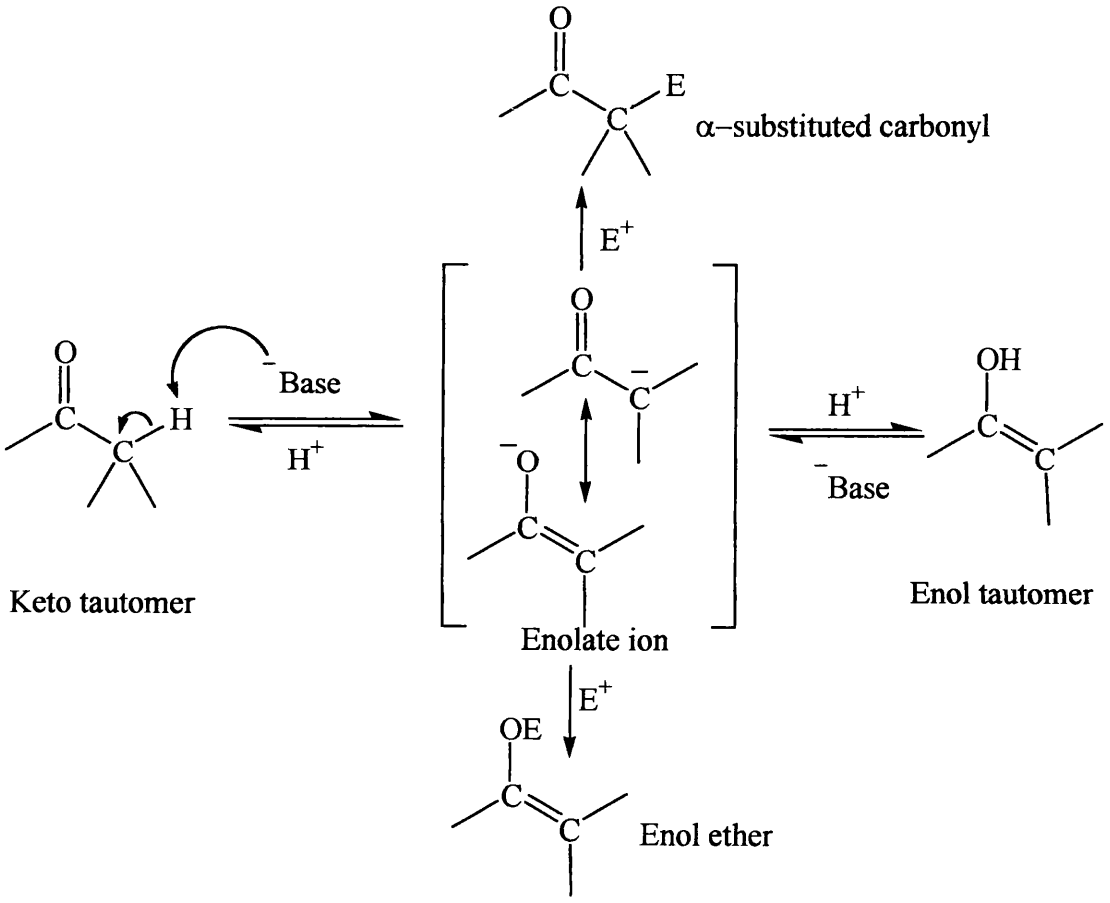
The acyl group is readily attached to the auxiliary using BuLi or methylmagnesium chloride[21,22] and the appropriate acyl chloride. (Scheme 2.1).



Scheme 2.1

2.2 Asymmetric Enolate Reactions

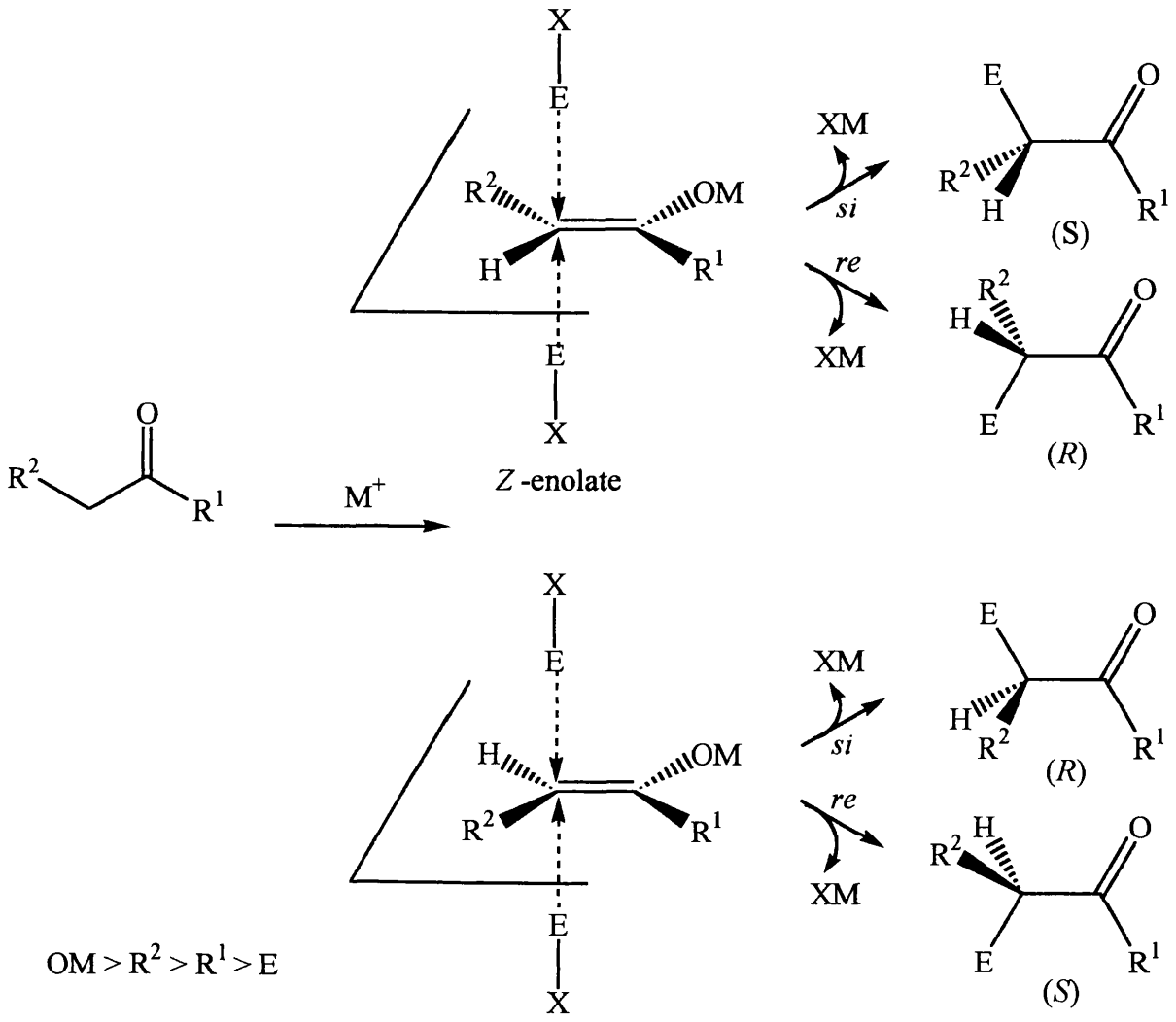
An enolate ion is formed by the base-catalysed abstraction of a α-hydrogen from a carbonyl compound (Scheme 2.2). Enolate ions are good nucleophiles and can react with electrophiles *via* the oxygen atom to yield an enol derivative, or, *via* the carbon atom to yield an α-substituted carbonyl compound.



Scheme 2.2

This use of chiral auxiliaries in enolate reactions is a broad topic of study and therefore this discussion concentrates on alkylation, aldol, conjugate addition and Diels Alder reactions.

Under kinetic conditions, two stereoisomers known as *Z*- and *E*-enolates are produced from the carbonyl compound assuming MO > R^1 (Scheme 2.3). Each isomer can then react with the electrophile (E) either from the top (*si*) or from the bottom (*re*) face to produce the (*R*) or (*S*) enantiomers respectively

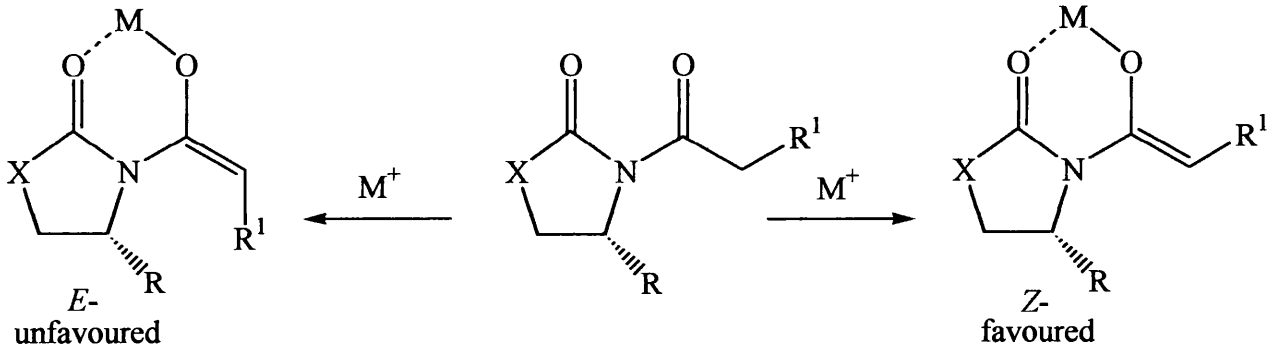


Scheme 2.3

By attaching a chiral auxiliary onto the carbonyl group the reactions can be selectively directed so that the product is enriched with one of the enantiomers.

2.2.1 Chiral Auxiliary Mediated Alkylation Reactions

Lithium or sodium amide bases such as $LiN(i\text{-}C_3H_7)_2$ or $NaN(SiMe_3)_2$ cleanly transform acylated, cyclic imides to their respective *Z*-metal enolates (Scheme 2.4). The *E*-isomer is disfavoured due to the steric interaction of the R^1 group with the R group.



Scheme 2.4

Stereoselection can then be achieved because one diastereotopic face of the enolate is shielded by the R-group (Figure 2.1).

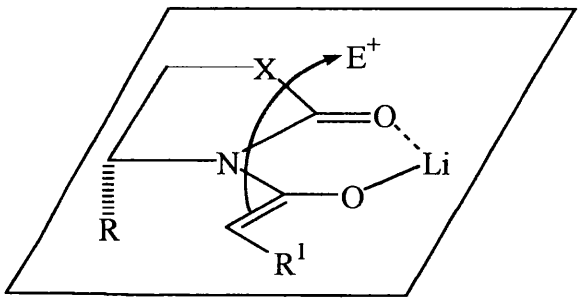
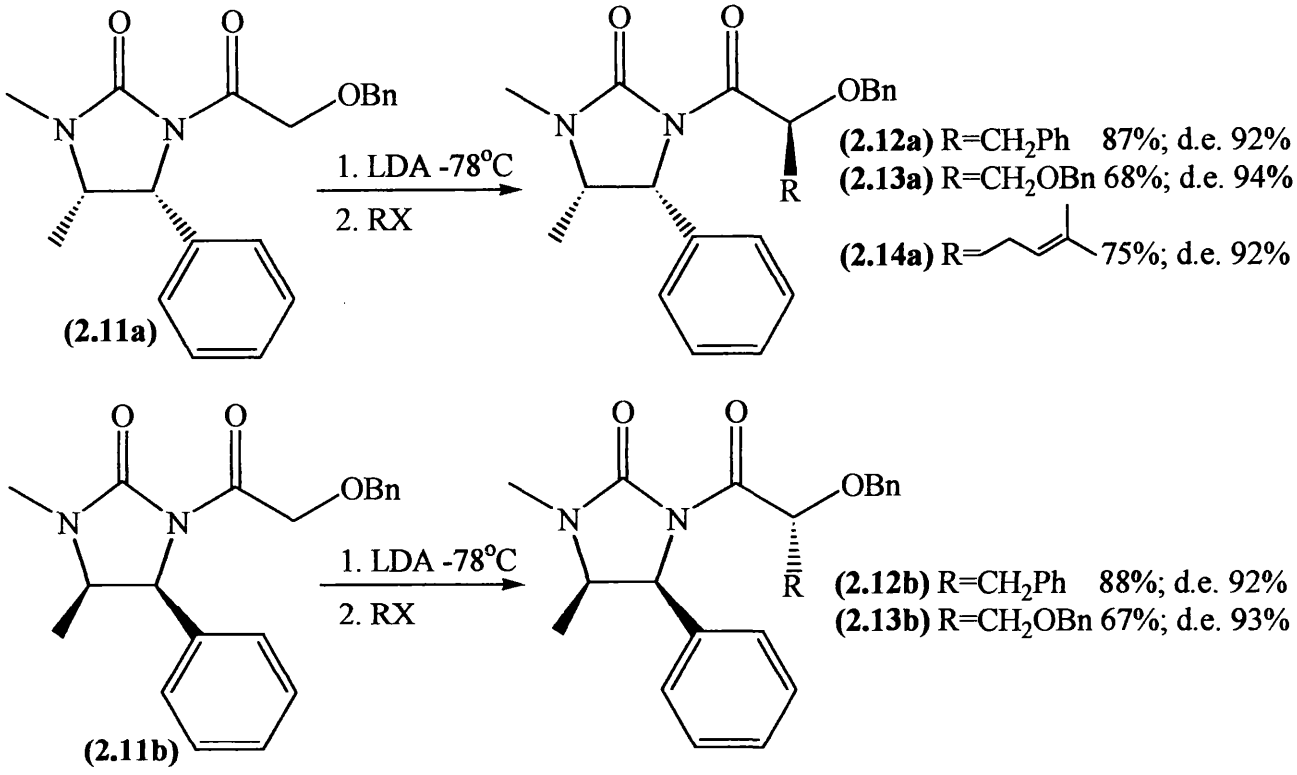


Figure 2.1

Cardillo *et al.*[24] have shown that using different diastereoisomers of the auxiliary **(2.10)** it is possible to obtain different isomers of the product (Scheme 2.5). Treatment of the *N*-glycolate derivative of the (4*R*,5*S*)-enantiomer **(2.11a)** with LDA and subsequent alkylation afforded **(2.12a-2.14a)**. The same reaction sequence starting with the (4*S*,5*R*)-enantiomer **(2.11b)** produced **(2.12b-2.13b)** in high yields and high diastereomeric excesses. The observed diastereoselection can be explained by the formation of a planar enolate which is shielded on the underside by the large

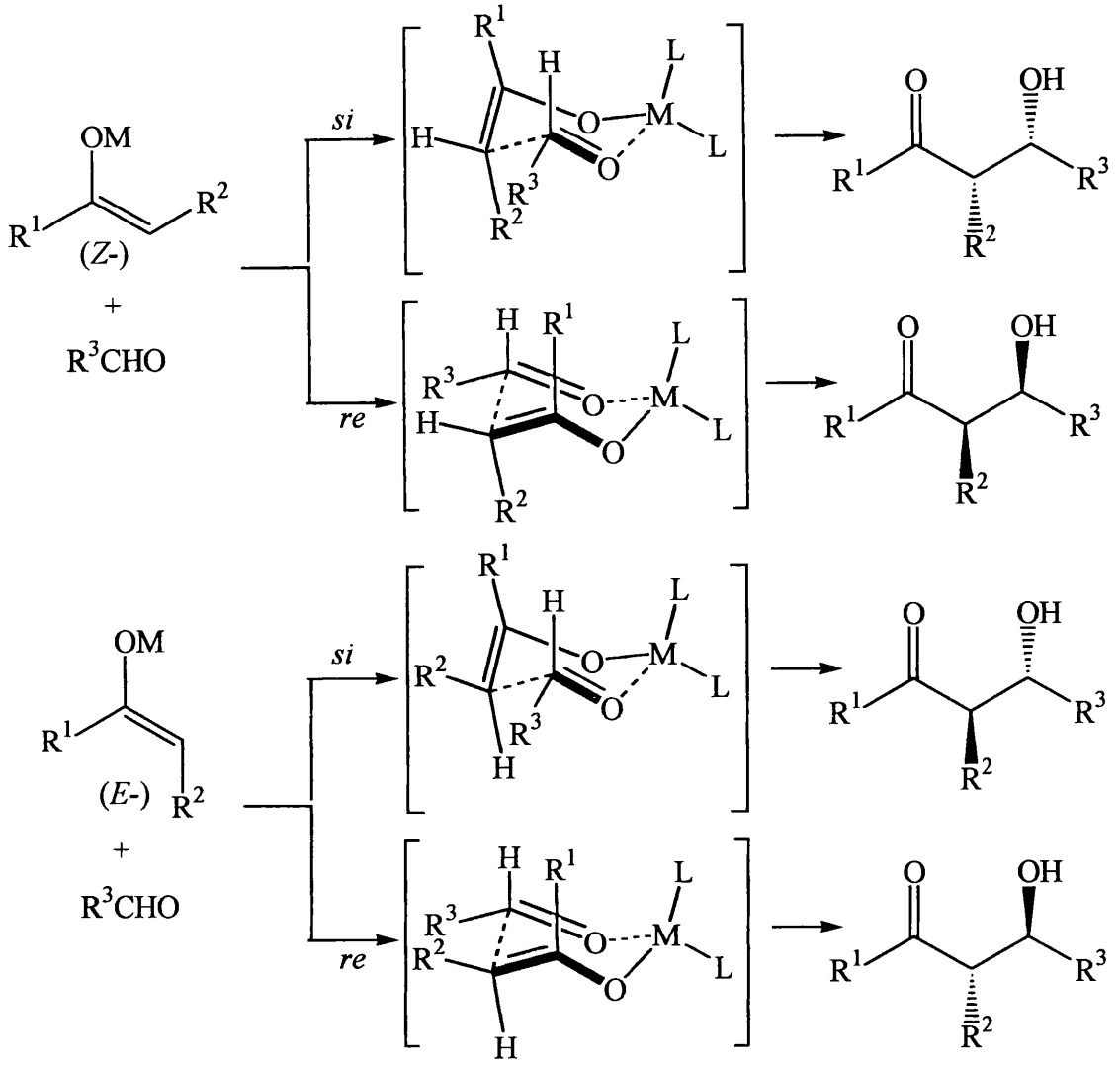
phenyl group. It therefore follows that each configuration can be obtained by using the correct enantiomer of the chiral auxiliary.



Scheme 2.5

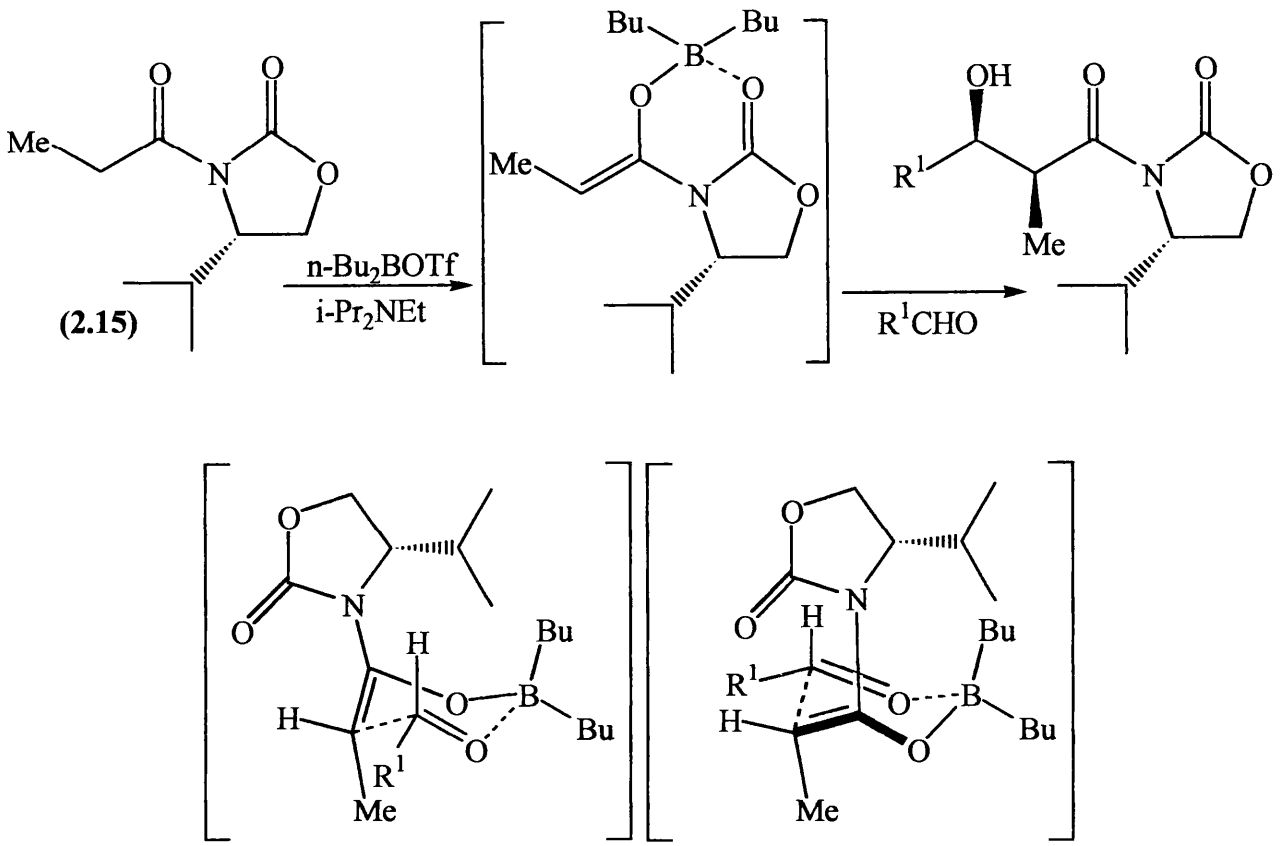
2.2.2 Chiral Auxiliary Mediated Aldol Reactions

Enolates react with aldehydes and ketones under neutral conditions to give aldol products. The reaction proceeds via a six membered cyclic, Zimmerman-Traxler-type transition state (Scheme 2.6). The reaction proceeds both regioselectively and stereoselectively to form 1,2-*syn* or 1,2-*anti* aldol products.



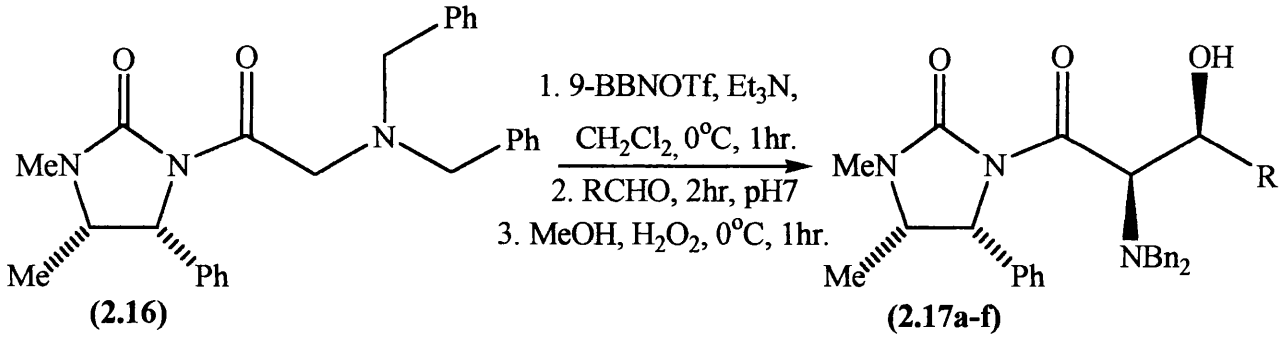
Scheme 2.6

The regioselectivity of the reaction can be influenced using different bases to form the enolate. For example, the reaction of a carbonyl compound with a boron reagent can selectively generate either the *Z*- or the *E*- enolate by choice of base and dialkylboryltriflate. The stereoselectivity of the reaction can be controlled by using a chiral auxiliary. An example of this is the reaction of the oxazolidinone derivative **(2.15)** (Scheme 2.7). Kinetic conditions using *n*-Bu_2BOTf and *i*-Pr_2NEt at −78°C generates the *Z*-enolate which reacts with an aldehyde to form the *syn*-aldol with high diastereofacial selectivity (>250:1, >99% d.e.).[25] The reaction is thought to proceed *via* the Zimmerman-Traxler transition state in which the *si*-face of the enolate is shielded by the auxiliary and therefore attack from the *re*-face is favoured to give the *syn* product.



Scheme 2.7

The imidazolidinone derived auxiliary **(2.10)** has also been used in a *syn*-selective boron mediated aldol condensation.[26] The 9-BBN-vinyloxy borane derivative reacts diastereoselectively with both aromatic and aliphatic aldehydes to produce *syn*-aldol derivatives (Scheme 2.8). The results are summarised in Table 2.1.



Scheme 2.8

Table 2.1 - Aldol products derived from **(2.16)**

Aldehyde	Prod.	Yield (%)	(2R,3S) : (2S,3R) : Other	d.e. (%)
Benzaldehyde	**(2.17a)**	84	1:0:0	>95
4-methoxybenzaldehyde	**(2.17b)**	66	32:1:0	94
4-fluorobenzaldehyde	**(2.17c)**	62	1:0:0	>95
4-nitrobenzaldehyde	**(2.17d)**	72	1:0:0	>95
Butyraldehyde	**(2.17e)**	69	1:0:0	>95
2-furaldehyde	**(2.17f)**	65	94:6:0	88

Assuming *Z*-boron enolate generation under the reaction conditions, the stereo-selectivity observed for the 9-BBN enolates can be explained by the chair-like transition state (Figure 2.2). In this conformation, the dipole-dipole repulsion between the two oxygen atoms of the enolate is minimised and the approach of the aldehyde from the *re*-face is hindered.

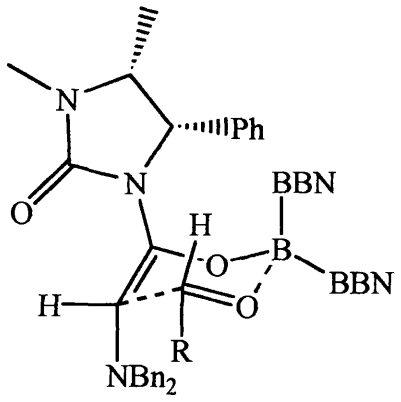
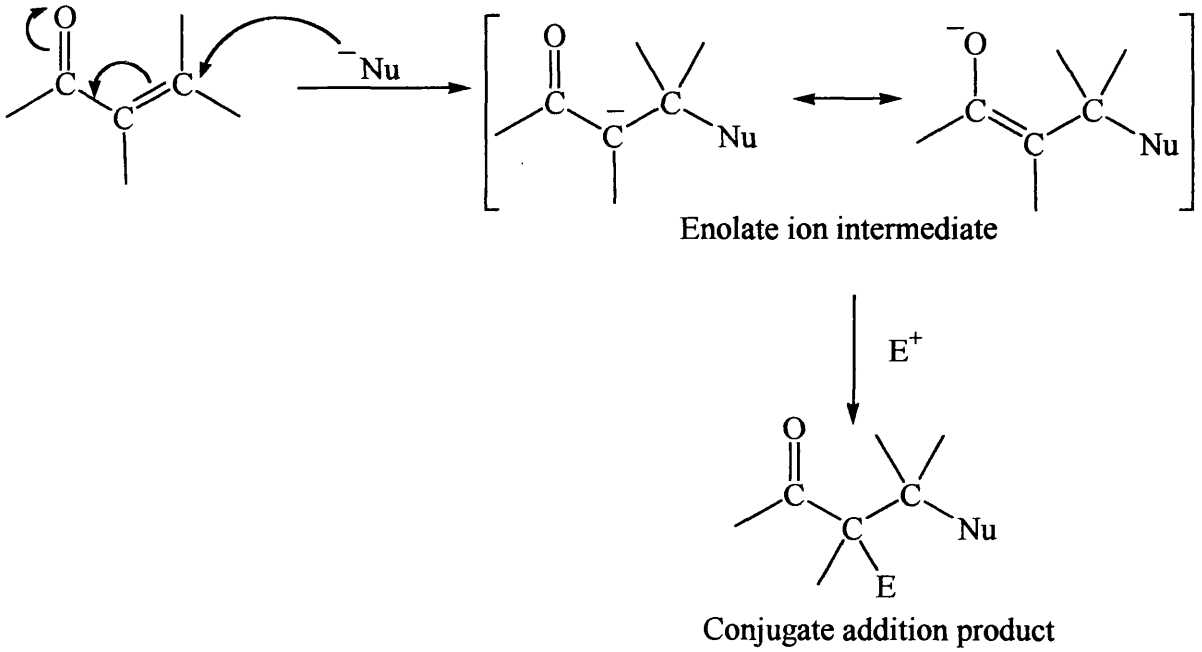


Figure 2.2

2.2.3 Chiral Auxiliary Mediated Conjugate Addition Reactions

α,β-Unsaturated carbonyl compounds can undergo either 1,2- or 1,4- addition reactions. 1,2-Additions involve only one of the π bonds of the conjugated system and form α,β-unsaturated alcohols. Reactions that produce the 1,4-addition products are called conjugate addition reactions or Michael-type additions. The reagent adds to the conjugated π system of the α,β-unsaturated carbonyl compound to form an enolate intermediate which can be trapped with an electrophile to produce an α,β-disubstituted carbonyl compound (Scheme 2.9). Primary and secondary amines, cyano compounds and organocuprate reagents all undergo 1,4-conjugate addition with α,β-unsaturated carbonyl compounds.

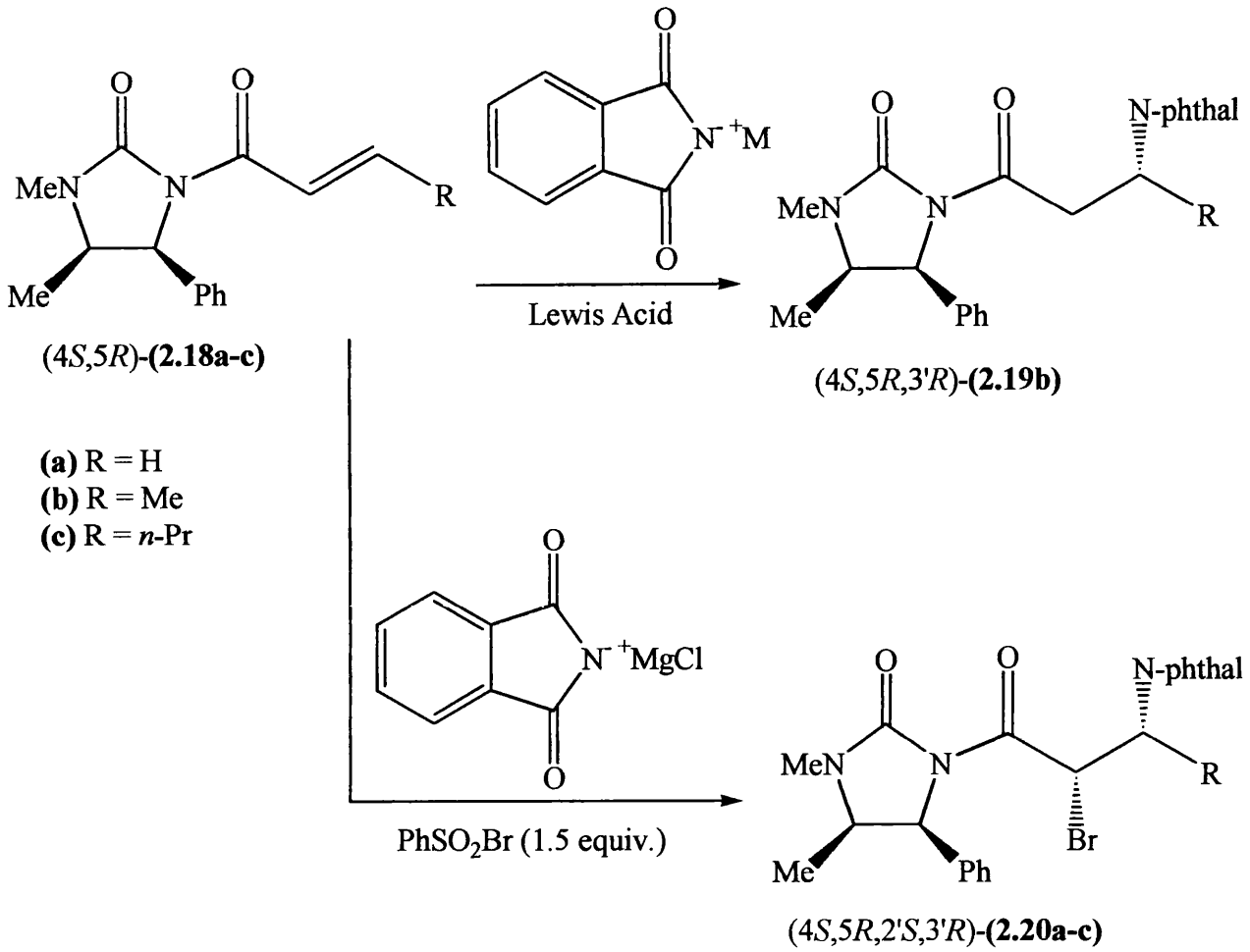


Scheme 2.9

The conjugate addition reaction provides an opportunity to introduce chiral centres at the α and β carbons. By attaching the unsaturated carbonyl to a chiral auxiliary it is possible to control the stereochemical outcome of the reaction.

Cardillo *et al.*[17] investigated the conjugate addition of phthalimido salts to the imidazolidinone derivative **(2.18)** to facilitate the successful synthesis of (*R*)-(-)-3-aminobutanoic acid (Scheme 2.10). They demonstrated that a Michael-like addition

followed by electrophilic bromination introduces two new chiral centres with *syn*-configuration.



Scheme 2.10

The conjugate addition occurs on the *re*-face of the Lewis acid-imide complex where the chloromagnesium phthalimide acts both as a Lewis acid and a nucleophile (Figure 2.3). In the presence of benzene sulphonyl bromide, the intermediate magnesium enolate is trapped and the corresponding 2-bromo-3-phthalimidoimides are obtained in high yields and good diastereomeric ratios.

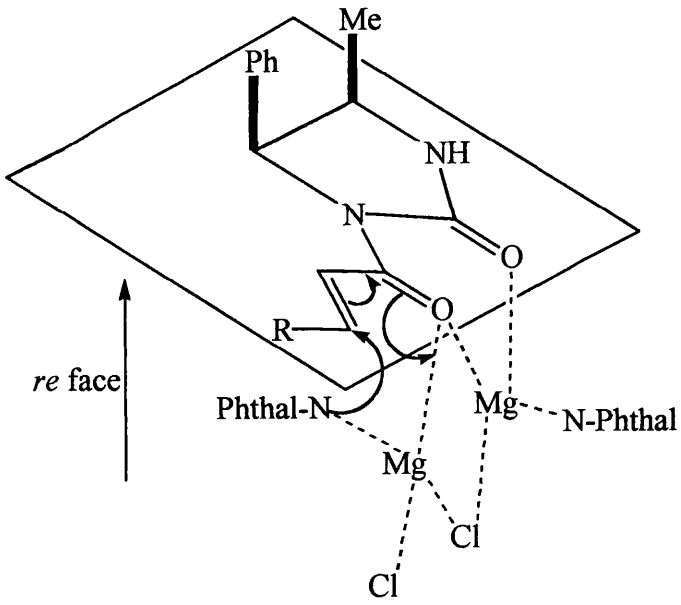


Figure 2.3

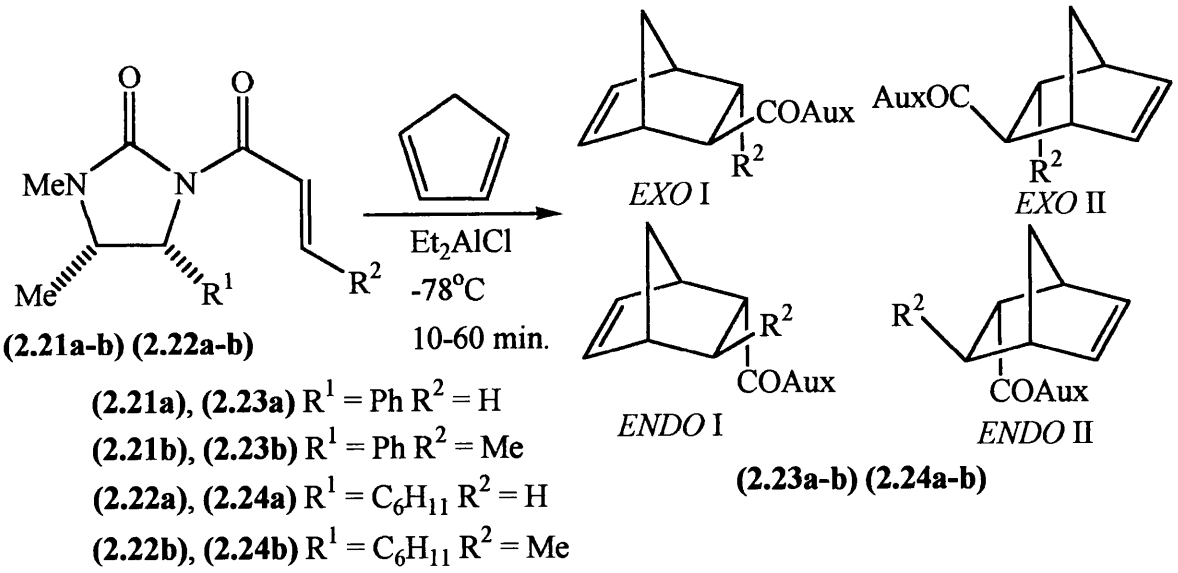
2.2.4 Chiral Auxiliary Mediated Diels Alder Rections

Roos *et al.*[15] investigated the use of imidazolidinone derived auxiliaries in asymmetric Diels-Alder reactions. The *N*-acyl derivatives **(2.21a-b)** and **(2.22a-b)** were prepared which were subjected to Lewis acid catalysed cycloaddition with cyclopentadiene (Scheme 2.11). This produced mixtures of two diastereoisomers of the *exo* product and two diastereoisomers of the *endo* product with *endo* I being the major product in each case. The diastereomeric ratios were determined by GC-MS (Table 2.2).

Table 2.2 – Reaction of **(2.21a-b)** and **(2.22a-b)** with cyclopentadiene

Auxiliary	Product	Endo:Exo	Endo d.e.
(2.21a)	**(2.23a)**	>6:1	6:1
(2.21b)	**(2.23b)**	15:1	9:1
(2.22a)	**(2.24a)**	>100:1	>100:1
(2.22b)	**(2.24b)**	99:1	>100:1

The results show that the 5-cyclohexyl derivative **(2.22)** is a superior diastereofacial director in this case, probably due to simple steric requirements.



(2.21a-b) (2.22a-b)

(2.21a), (2.23a) $R^1 = Ph$ $R^2 = H$
(2.21b), (2.23b) $R^1 = Ph$ $R^2 = Me$
(2.22a), (2.24a) $R^1 = C_6H_{11}$ $R^2 = H$
(2.22b), (2.24b) $R^1 = C_6H_{11}$ $R^2 = Me$

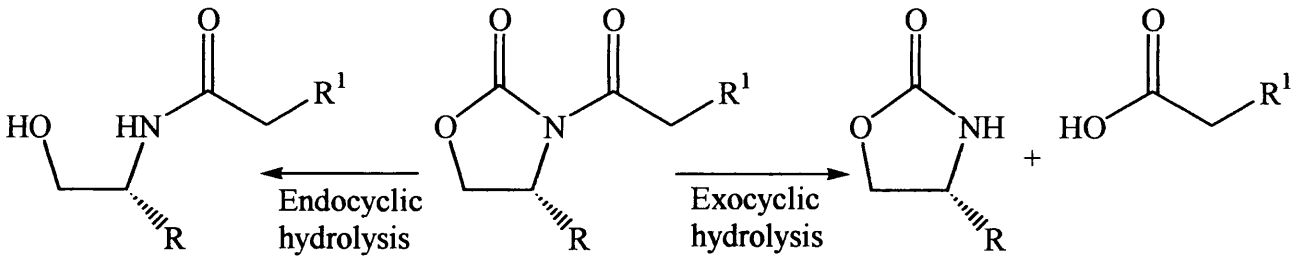
(2.23a-b) (2.24a-b)

Scheme 2.11

2.3 Cleavage of the Chiral Auxiliary

For a chiral auxiliary to be useful in a synthetic strategy it has to be easily and selectively cleaved from the chiral product without compromising the stereogenic centres in the system.

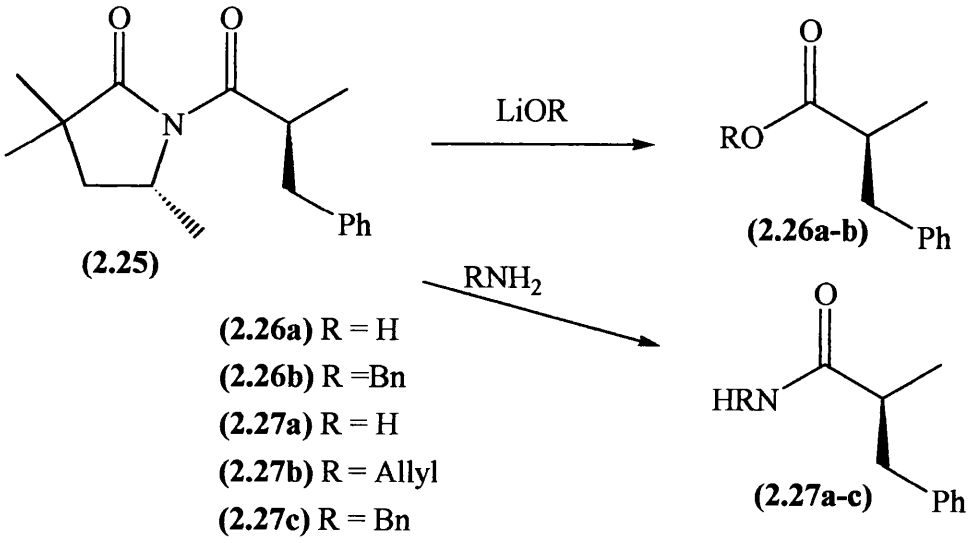
Oxazolidinone derived chiral auxiliaries can undergo either endocyclic or exocylic cleavage depending on the position of nucleophillic attack (Scheme 2.12). An unhindered auxiliary will be attacked at the exocyclic carbonyl to yield the required products. However, when the R group has a large steric bulk the exocyclic carbonyl is hindered and a nucleophile will preferentially attack the ring carbonyl resulting in unwanted ring cleavage. This can be overcome by using a nucleophile that is less susceptible to steric hindrance such as lithium hydroperoxide.[27]



Scheme 2.12

Nucleophillic attack on the pyrrolidinone derived Quat auxiliary favours exocyclic cleavage of the acyl side chain from the auxiliary.[4] This is because the ring carbonyl is sterically protected from nucleophilic attack by the geminal dimethyl group, which prevents endocyclic cleavage. Similarly, imidazolidinone derived auxiliaries do not suffer from endocyclic cleavage due to the electronic shielding effect of the *N*-R group.[14]

By using different nucleophiles to cleave the auxiliary, it is possible to generate different final products. The synthesis of chiral esters by the nucleophilic action of lithium or sodium alkoxides has been demonstrated using an imidazolidinone-derived auxiliary[27] and a pyrrolidinone derived Quat auxiliary **(2.25)** (Scheme 2.13).[28] The direct aminolysis of the Quat auxiliary **(2.25)** has been shown to produce chiral amides[29] (Scheme 2.13).



(2.25)

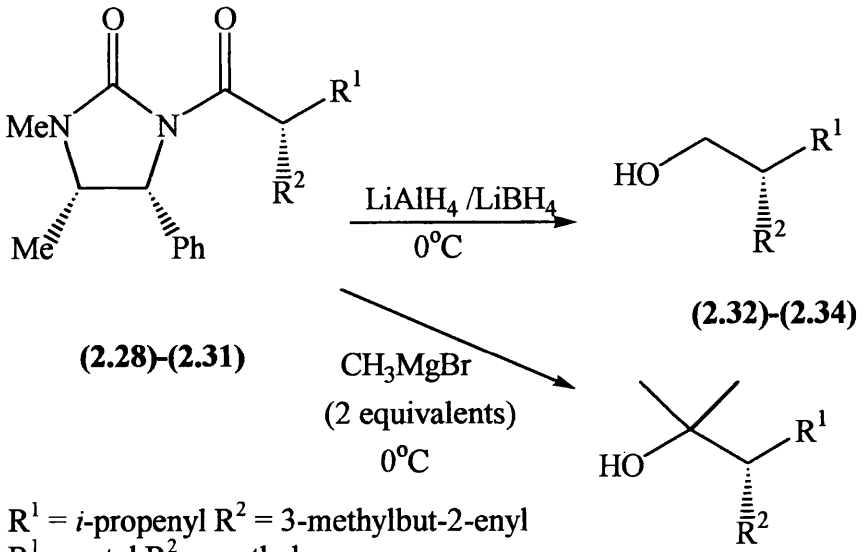
(2.26a-b)

(2.26a) R = H
(2.26b) R =Bn
(2.27a) R = H
(2.27b) R = Allyl
(2.27c) R = Bn

(2.27a-c)

Scheme 2.13

Reductive cleavage using $LiAlH$[18] or $LiBH_4$[24] enables chiral primary alcohols to be formed. It is also possible to form tertiary alcohols by using Grignard reagents[19] (Scheme 2.14).



(2.28)-(2.31)

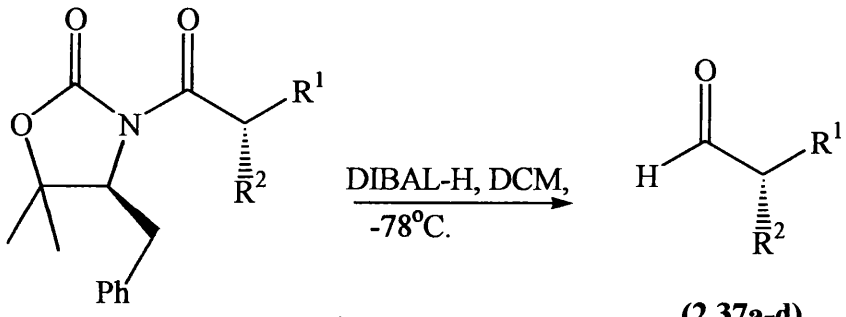
(2.32)-(2.34)

(2.35)

(2.28), **(2.32)** R^1 = *i*-propenyl R^2 = 3-methylbut-2-enyl
(2.29), **(2.33)** R^1 = octyl R^2 = methyl
(2.30), **(2.34)** R^1 = OBn R^2 = Bn
(2.31), **(2.35)** R^1 = SPh R^2 = 3-methylbut-2-enyl

Scheme 2.14

Bull *et al.* have demonstrated that by using DIBAL-H the aldehyde product can be recovered[30] (Scheme 2.15).



(2.36a-d)

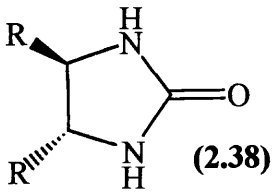
(2.37a-d)

a: R^1 = Bn R^2 = Me
b: R^1 = Bn R^2 = $CH_2CH{=}CH_2$
c: R^1 = *i*Pr R^2 = Bn
d: R^1 = Et R^2 = Bn

Scheme 2.15

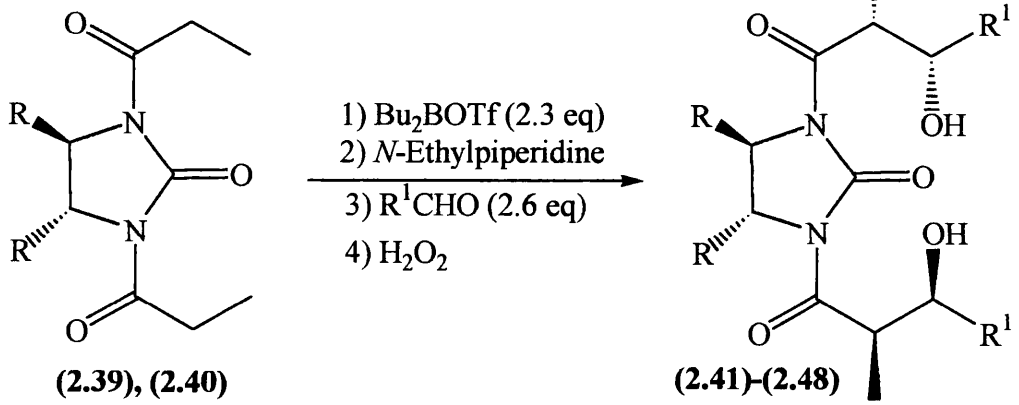
2.4 Bifunctional Chiral Auxiliaries

One of the disadvantages of using chiral auxiliaries is that a heavy chiral fragment has to be carried through a number of synthetic steps. The bifunctional approach effectively reduces the mass of the auxiliary by incorporating two chiral centres, into the auxiliary, each capable of independently controlling an asymmetric process. Davies and Mortlock[31] have done an extensive study on the imidazolidinone derived bifunctional auxiliary **(2.38)**.



(2.38)

It has been proved effective in controlling the stereochemical outcome of asymmetric aldol reactions.[31,32] The (1*R*,2*R*)-bifunctional compounds **(2.39)** and **(2.40)** were reacted with a range of aldehydes (Scheme 2.16). For all the examples listed only one diastereoisomer was detected by ^{1}H NMR and the diastereomeric excess of each reaction was estimated at >96%. Cleavage of products **(2.41)-(2.48)** was obtained using $LiAlH_4$ to produce the corresponding alcohols with (2*R*,3*S*)-stereochemistry.



(2.39), (2.40) **(2.41)-(2.48)**

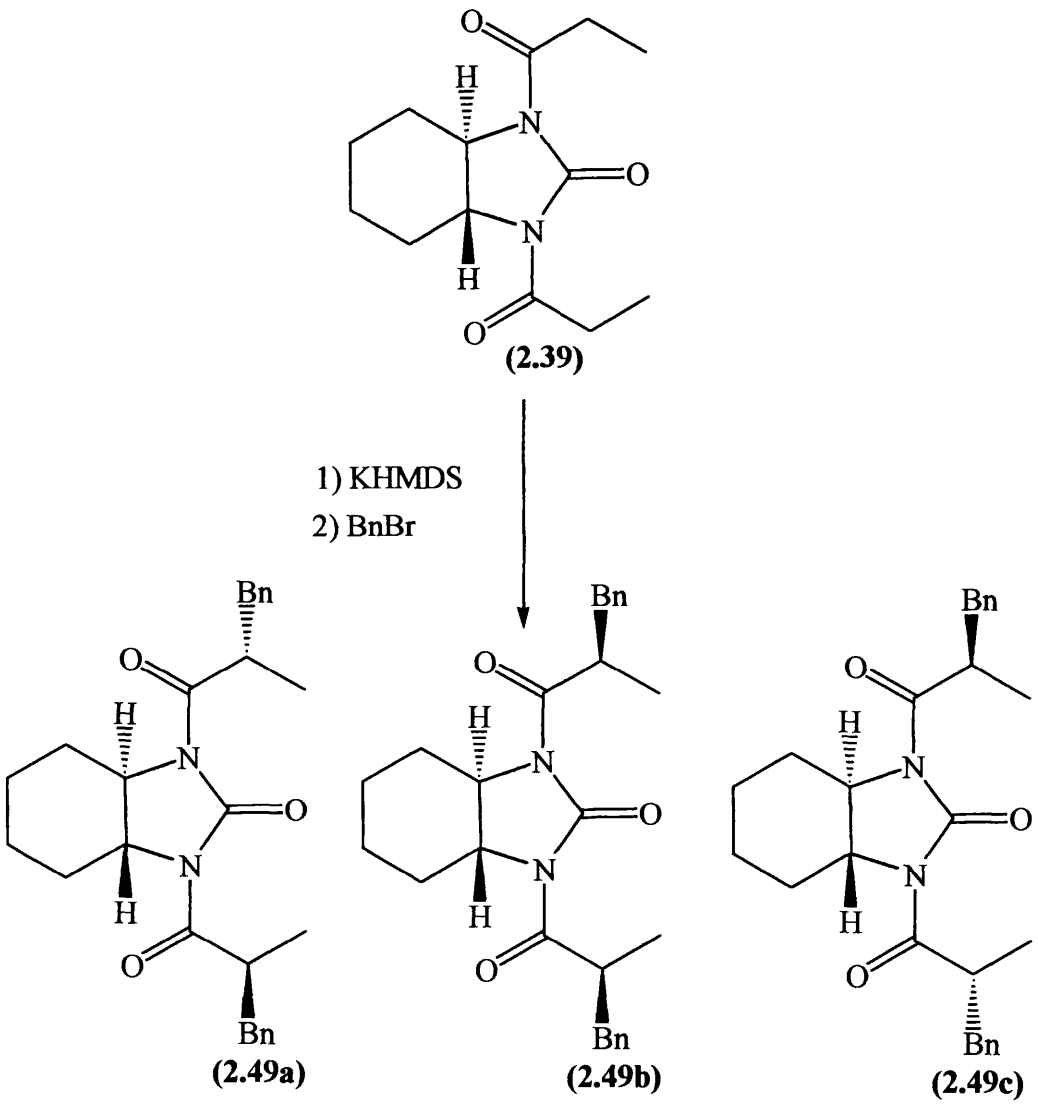
(2.39) R = -$(CH_2)_4$-
(2.40) R = Ph

(2.41) R = -$(CH_2)_4$- R^1= Me **(2.45)** R = -$(CH_2)_4$- R^1= Ph
(2.42) R = -$(CH_2)_4$- R^1= Et **(2.46)** R = Ph R^1= Ph
(2.43) R = -$(CH_2)_4$- R^1= *n*-Pr **(2.47)** R = Ph R^1= *i*-Pr
(2.44) R = -$(CH_2)_4$- R^1= *i*-Pr **(2.48)** R = Ph R^1= Me

Scheme 2.16

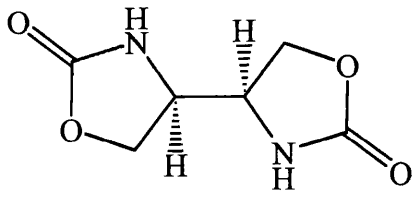
Compound **(2.39)** has also been used in asymmetric alkylation reactions with some success.[33] Alkylation of both acyl side chains of the substrate could in principle generate two different configurations, therefore three possible isomers could be

produced. In a representative reaction, the potassium enolate of compound **(2.39)** was quenched with benzyl bromide to give a mixture of products **(2.49a)**, **(2.49b)** and **(2.49c)** in a ratio of 94:5:1 respectively (Scheme 2.17), which corresponds to a facial selectivity of 97:3.

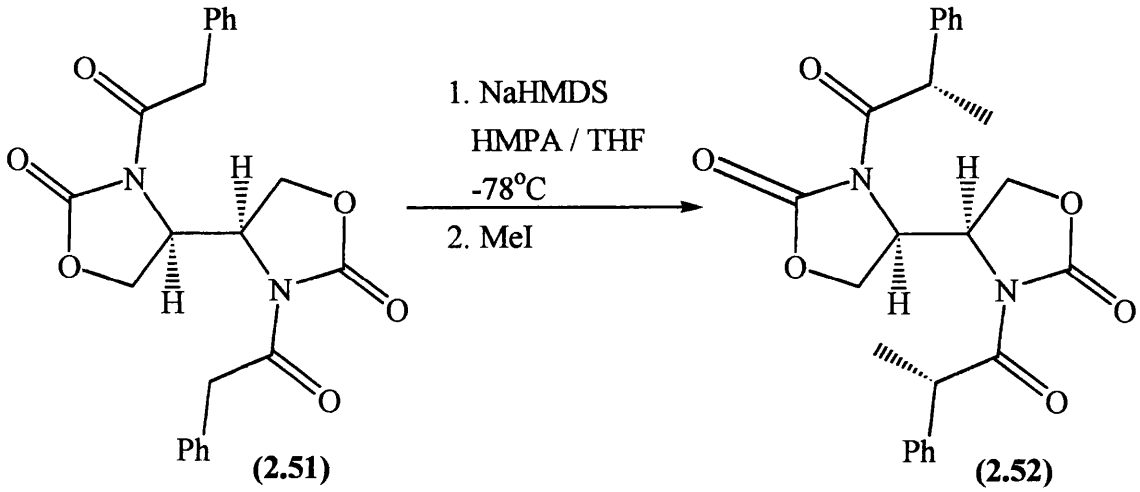


Scheme 2.17

Lee *et al.* have synthesised a water-soluble *bis*(oxazolidinone) bifunctional auxiliary **(2.50)** and demonstrated its use in a chiral alkylation reaction[34] (Scheme 2.18). The major isomer was formed with a facial selectivity of 95:5 and hydrolysis of **(2.52)** afforded (*S*)-α-methylphenylacetic acid.



(2.50)



(2.51) **(2.52)**

Scheme 2.18

2.5 Conclusion

The chiral auxiliary methodology has a wide range of applications in the synthesis of asymmetric compounds.

2.6 References

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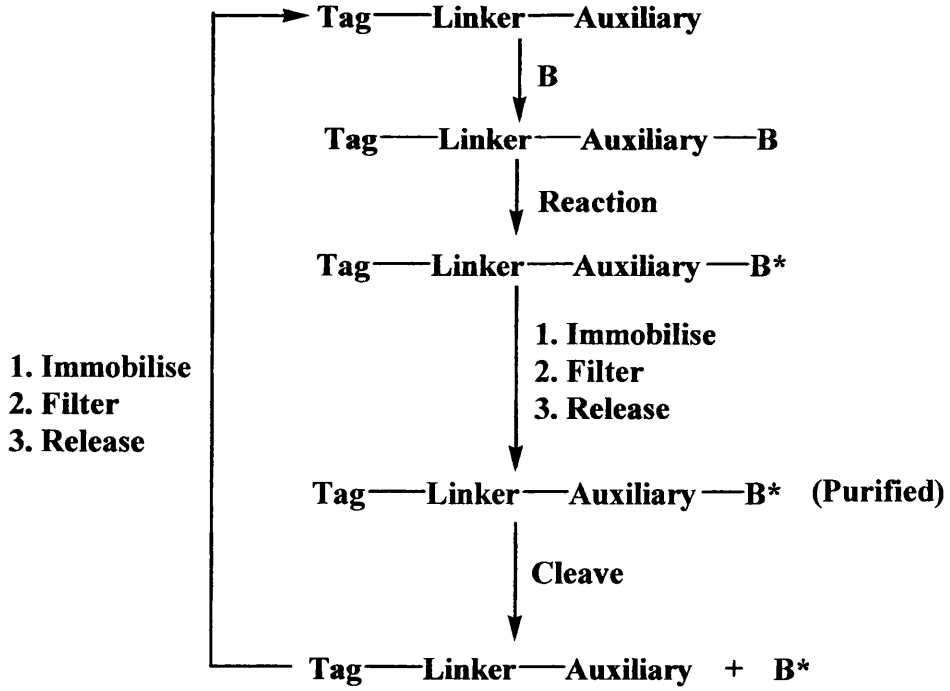
Chapter Three

The Design and Synthesis of a Chiral Auxiliary Capable of being Immobilised

3.1 Introduction

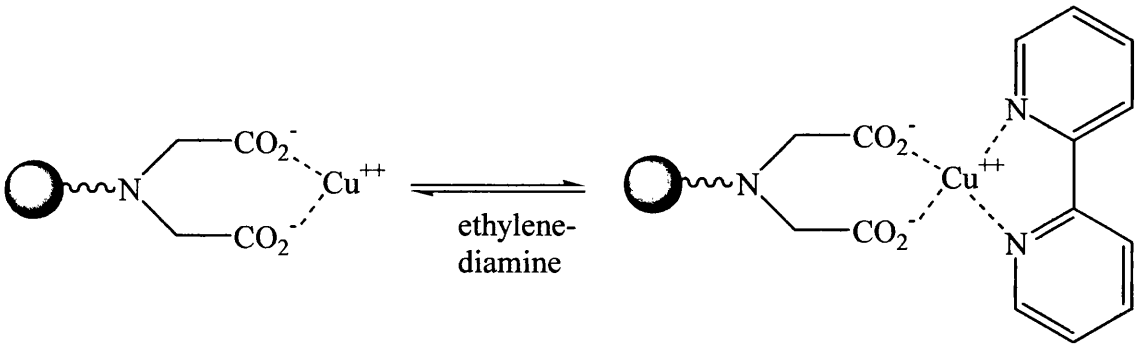
The aim of the work described in this chapter was to synthesise a new chiral auxiliary that would enable asymmetric enolate reactions to be carried out in solution as well as being capable of forming temporary bonds to a solid resin. This would enable the chiral auxiliary to be immobilised by complexation to a polymeric support after the solution phase asymmetric reaction was completed, thus combining the benefits of solution phase reactions and solid phase purification.

Scheme 1.1 shows the outline of the selective immobilisation approach. Molecule 'B' is reacted with the tagged auxiliary to form the substrate which undergoes reaction to form the chiral product 'B*' attached to the auxiliary. The tagged compound is then immobilised by addition of the solid support to the crude product. Any unwanted compounds not bearing a tag group are left in solution and removed by filtration. The purified auxiliary complex is then released from the resin and finally the chiral product B* is cleaved from the auxiliary. The tagged auxiliary can then be immobilised and separated from the product by filtration. The auxiliary is released from the solid support and recycled.



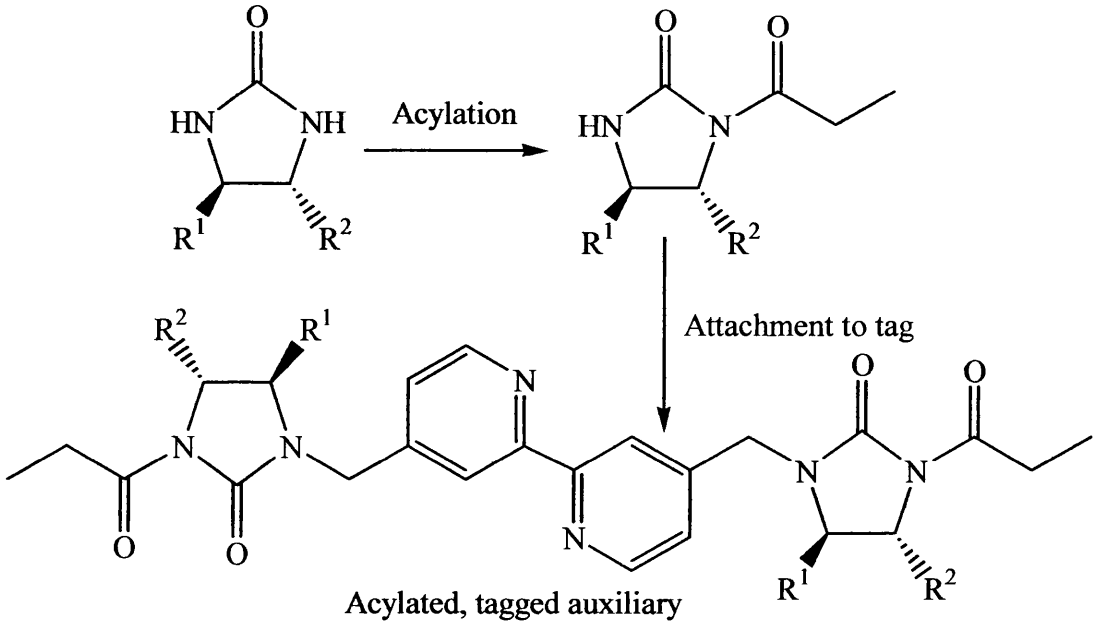
Scheme 1.1

The tag unit chosen was based on a bipyridine molecule, following the findings of Pritchard and co–workers.[1] They identified that bipyridine was able to form reversible non-covalent bonds to Cu^{2+} ions on iminodiacetic acid based resins, such as IRC-718, *via* the lone pairs of electrons on the nitrogen groups (Scheme 3.2). The bipyridine can be cleaved from the resin by ethylene diamine, which also changes the colour of the resin from light blue to dark blue. The stability of bipyridine under a number of reaction conditions also made it an ideal tag unit.



Scheme 3.2

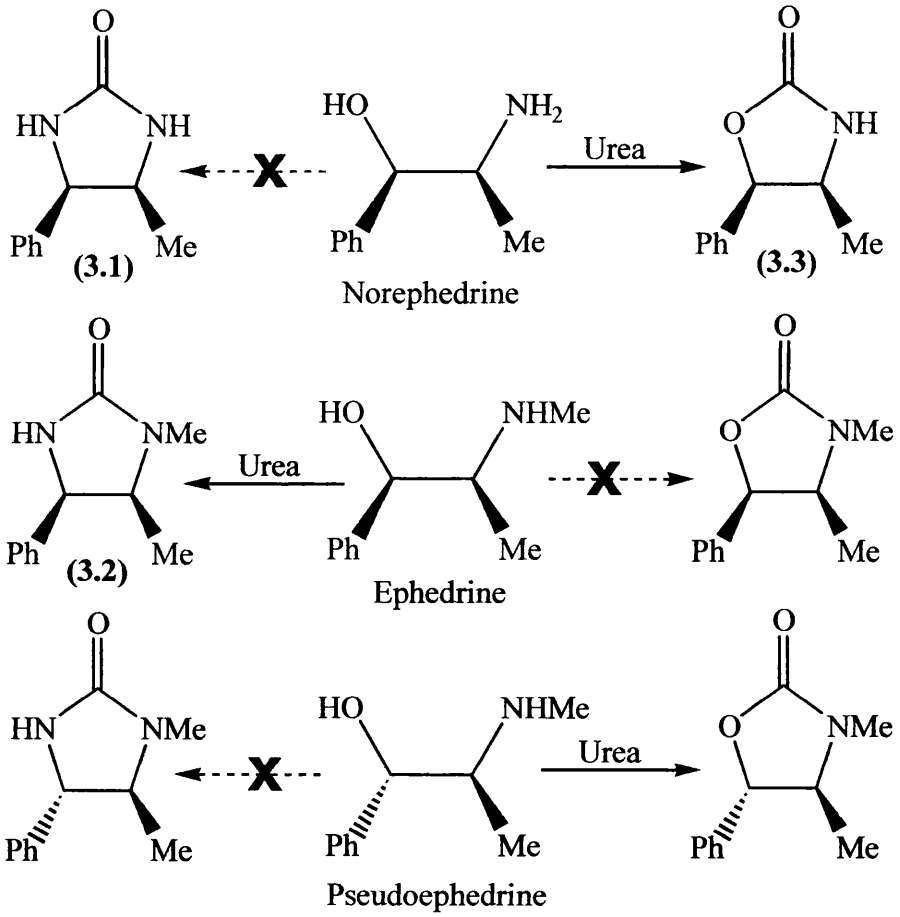
An imidazolidinone, a five membered heterocyclic ring containing two NH groups, was chosen as the auxiliary. One of the NH groups was acylated to form the template for the asymmetric synthesis. The link to the bipyridine molecule was achieved *via* the other NH group to form the acylated, tagged, C_2-symmetrical, bifunctional auxiliary.



Scheme 3.3

3.2 Attempted Preparation of (4*S*,5*R*)-4-methyl-5-phenyl-imidazolidinone (3.1)

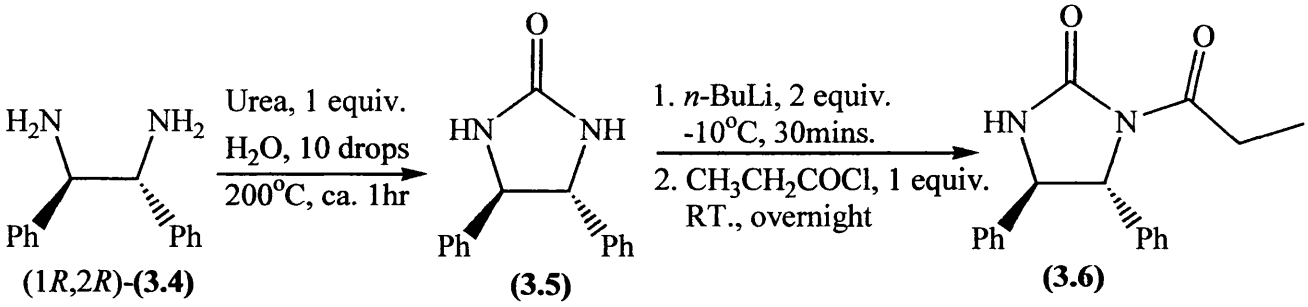
The original strategy was to use **(3.1)** as the chiral auxiliary but problems were encountered during its synthesis. It was envisaged that the method by Close[2] for the preparation of 3,4-dimethyl-5-phenylimidazolidinone **(3.2)** from ephedrine could be adapted. It seemed reasonable to presume that reacting norephedrine with urea would produce the corresponding imidazolidinone **(3.1)**. Unfortunately in practice, the only product formed was (4*S*,5*R*)-4-methyl-5-phenyloxazolidinone **(3.3)** (Scheme 3.4), identified by ^{1}H NMR as the broad NH peak at 5.65ppm intergrated to only one hydrogen instead of the expected two hydrogens. The structure was confirmed by mass spectrometry. In this respect, norephidrine reacts in the same way as pseudoephedrine.



Scheme 3.4

3.3 Preparation of (4*R*,5*R*)-4,5-diphenyl-1-propionylimidazolidinone (3.6)

The revised plan was to base the auxiliary on (4*R*,5*R*)-4,5-diphenylimidazolidinone **(3.5)** as seen in the work by Sankhavasi *et al.*[3] Compound **(3.5)** was prepared by heating (1*R*,2*R*)-1,2-diphenylethylene-1,2-diamine **(3.4)** with urea and a small amount of water as described in the literature procedure (Scheme 3.5). However, heating for two hours as suggested in the literature only produced 40% of the desired product. By monitoring the reaction by TLC it was possible to stop heating the reaction mixture when the starting material was no longer detected. This increased the yield to 75%. It was important to make sure the reaction had reached completion before removing the heat source as once the reaction had cooled the mixture would solidify and would not re-melt at 200°C. Compound **(3.5)** was identified by ^{13}C NMR from a characteristic carbonyl signal at 163.0 ppm.

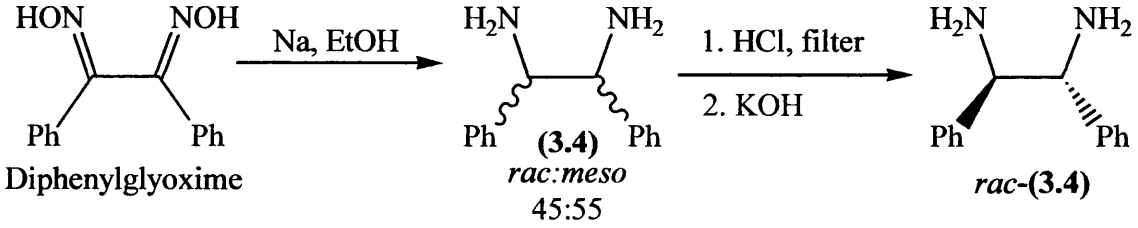


Scheme 3.5

The mono-acylation of **(3.5)** was achieved by using two equivalents of *n*-BuLi and one equivalent of propionyl chloride in THF affording **(3.6)** in an 81%yield. The product was identified by ^{1}H NMR, as the propionyl group displayed a characteristic triplet at 1.02 ppm, which was coupled to a quartet at 2.91 ppm, corresponding to the CH_3 and CH_2 group respectively. Additionally, by ^{13}C NMR, a second carbonyl signal was present at 174.0 ppm.

3.4 Preparation of *rac*-1,2-diphenylethylene-1,2-diamine (3.4)

The possibility of using racemic **(3.4)** instead of the expensive (*R*,*R*)-isomer was investigated, since to demonstrate the feasibility of the project it was not necessary to use enantiomerically pure material. It was prepared by the reduction of diphenylglyoxime using sodium as described by Pivintsky (Scheme 3.6).[4] It was observed that the reaction mixture frequently solidified after the addition of sodium and on these occasions, the yield was reduced. Although it was unclear why this happened it was found that it could be avoided by using larger amounts of ethanol and by adding the sodium as quickly and as safely as possible. The *meso*-isomer was separated from the *rac*-isomer by the precipitation of the *meso*-isomer as its hydrochloride salt and filtration. The remaining solution was neutralised and extracted into an organic solvent to isolate the *rac*-isomer. However, this step was found to be inefficient as, by ^{1}H NMR, 31% of the *meso*-isomer could still be detected. It was identified by the presence of two signals at 4.01 and 4.09, which corresponded to the CH groups of the *meso*- and *rac*-isomers respectively. The separation step was repeated but the ratio of isomers in the product was unaffected. The product was crystallised from hexane but again, the ratio of isomers was unaffected.

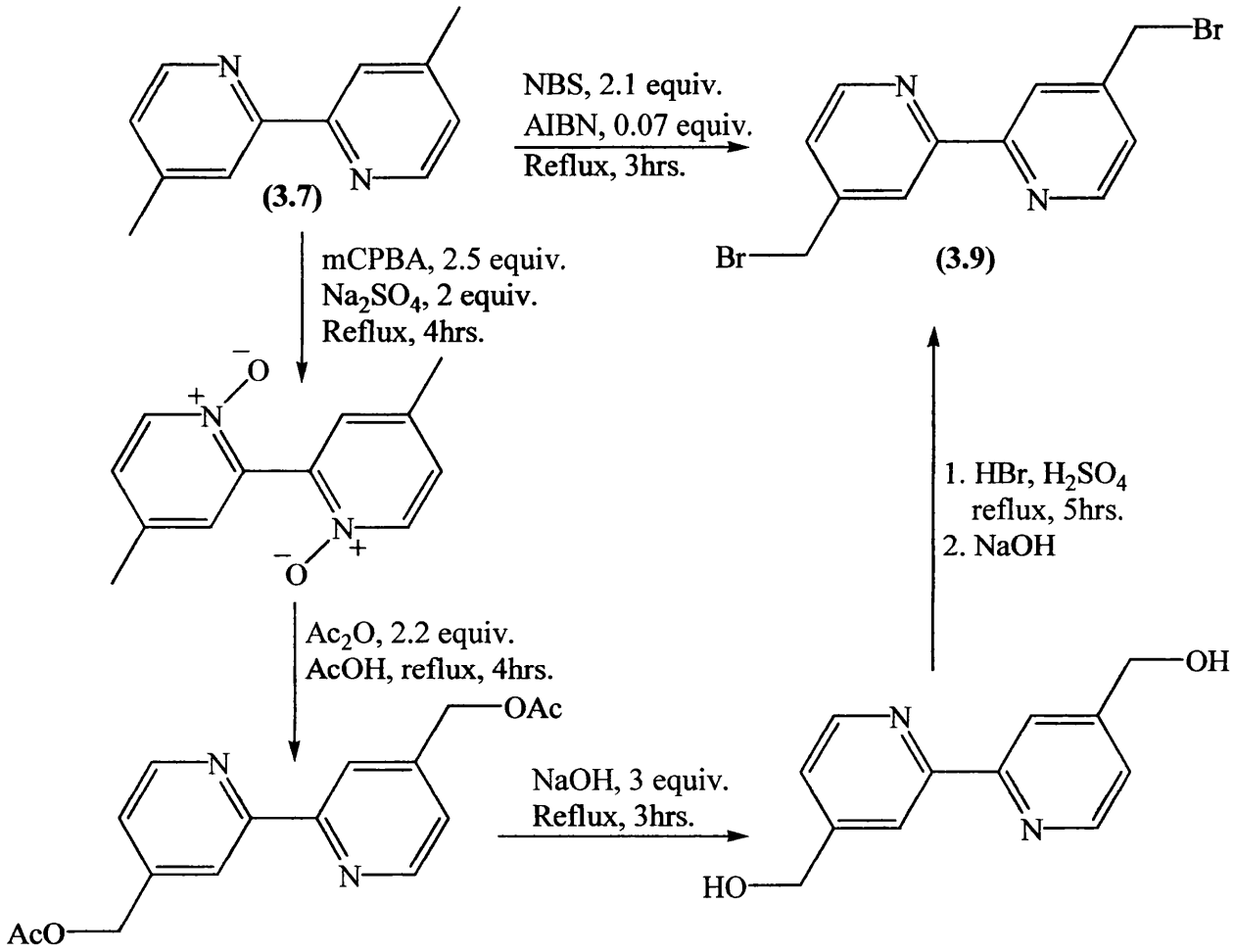


Scheme 3.6

The presence of the *meso*-isomer in the diamine greatly reduced the yield in the subsequent reactions and would obviously complicate any attempts to carry out asymmetric synthesis. Therefore, since the preparation of **(3.4)** was time consuming and produced poor results the commercially available homochiral material was used in future preparations.

3. 5 Preparation of 4,4′-*bis*-bromomethyl-2,2′-bipyridine (3.9)

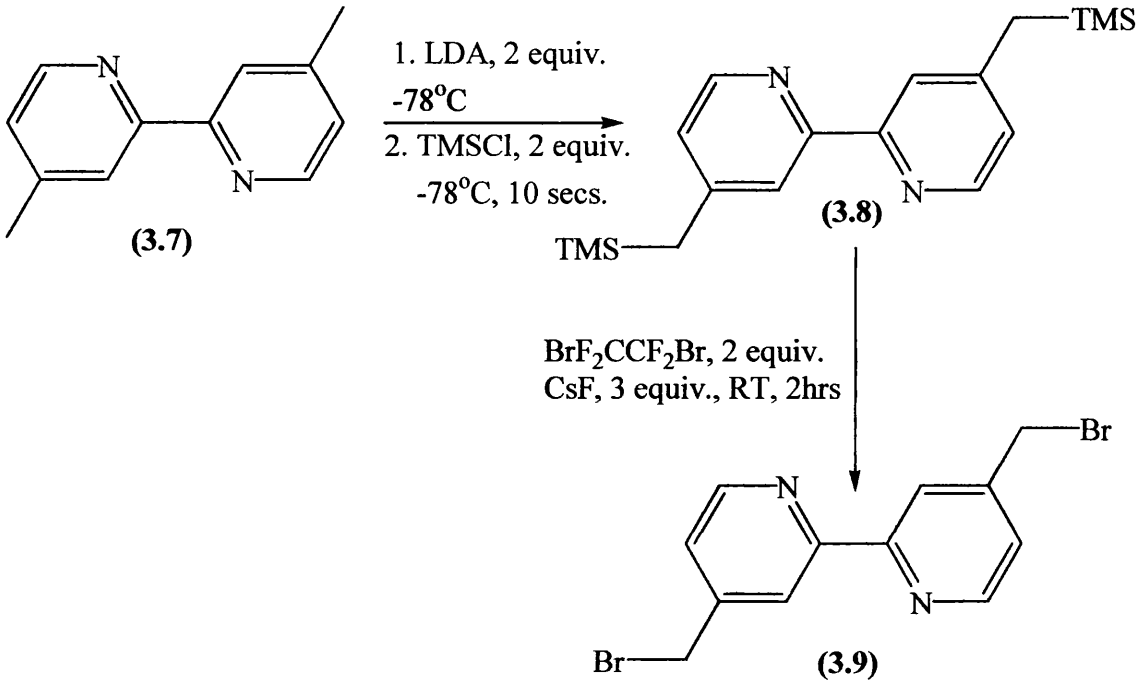
The literature describes three different methods for the preparation of compound **(3.9)** from commercially available 4,4′-dimethyl-2,2′-bipyridine **(3.7)**. Gould *et al.*[5] performed a one step reaction using *N*-bromosuccinimide (NBS) to obtain a 30% yield but the same reaction carried out by Kaes *et al.*[6] only yielded 5% of **(3.9)**. Kaes *et al.*[6] also describe a four step preparation of **(3.9)** with an overall yield of about 30% (Scheme 3.7).



Scheme 3.7

However, Fraser *et al.*[7] reported a two step reaction (Scheme 3.8) with a 96% overall yield and this was found to be the preferred method[8] for the synthesis of **(3.9)**. 4,4′-Dimethyl-2,2′-bipyridine was converted to the protected di-anion 4,4′-*bis*-[(trimethylsilyl)methyl]-2,2′-bipyridine **(3.8)** by deprotonation with LDA before the addition of TMSCl. Fraser *et al.* described a colour change shortly after the addition addition of TMSCl, and that this was the signal to quench the reaction. However, in

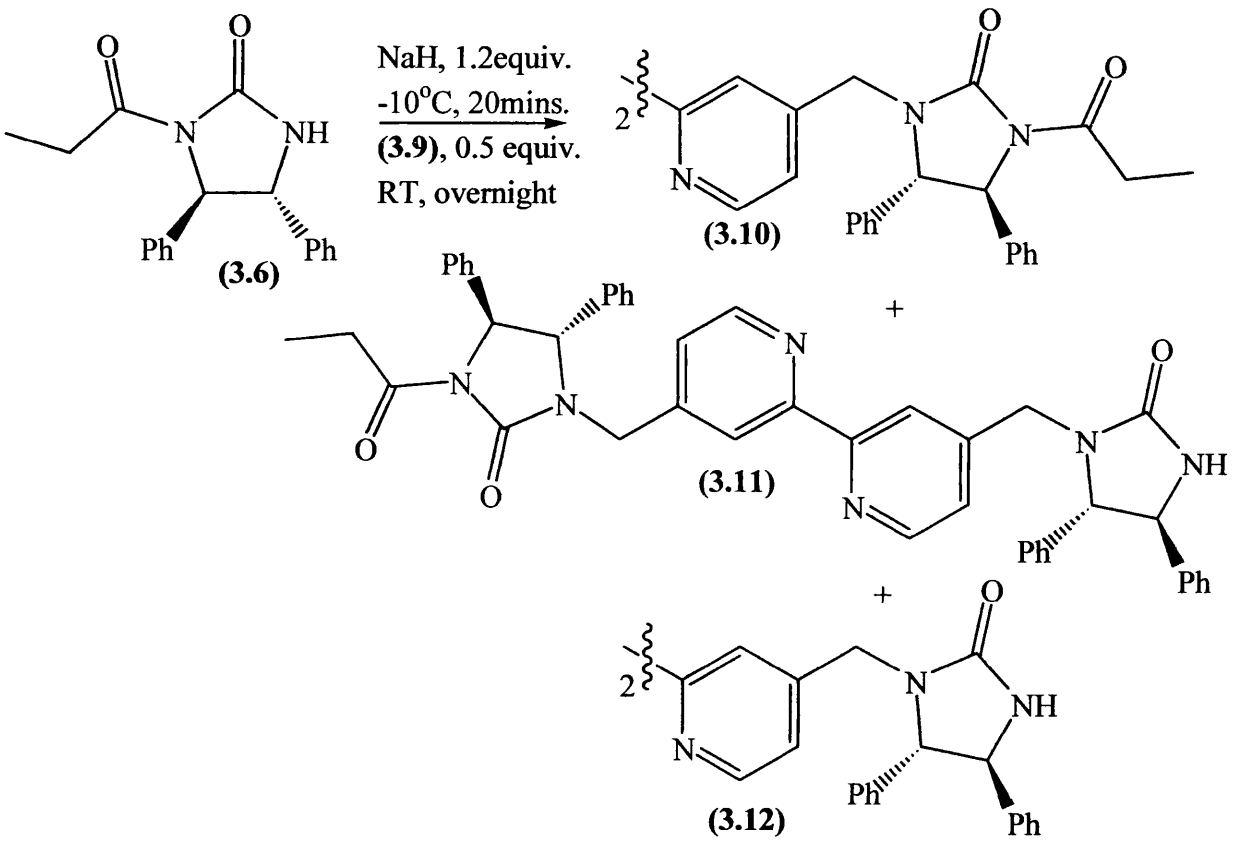
practice, a colour change was not observed and therefore the reaction was quenched after five to ten seconds. If the reaction mixture was left for longer than ten seconds over-silylation would occur and as a consequence, a loss of yield. Compound **(3.8)** was identified by ^{1}H NMR from a peak at 0.04 ppm, which integrated for eighteen hydrogens, corresponding to the six methyl-groups of the TMS-substituted compound. Compound **(3.9)** was formed by exchanging the TMS groups for bromine using CsF and dibromotetrafluoroethane. Identification of **(3.9)** was found from the absence of any methyl groups in the upfield section of the ^{1}H NMR spectrum, and by the downfield shift to 4.48 ppm of the CH_2 group. It was most important to use anhydrous conditions in the second step of the reaction as the presence of moisture in the reaction system caused the reformation of **(3.7)**. The attempted purification of **(3.9)** by crystallisation from THF also resulted in the reformation of **(3.7)** as observed by mass spectroscopy.



Scheme 3.8

3.6 Preparation of (4*R*,5*R*)-4,4′-*bis*-[1-(4,5-diphenyl-3-propionyl-imidazolidinonyl)-*N*-methyl]-2,2′-bipyridine (3.10)

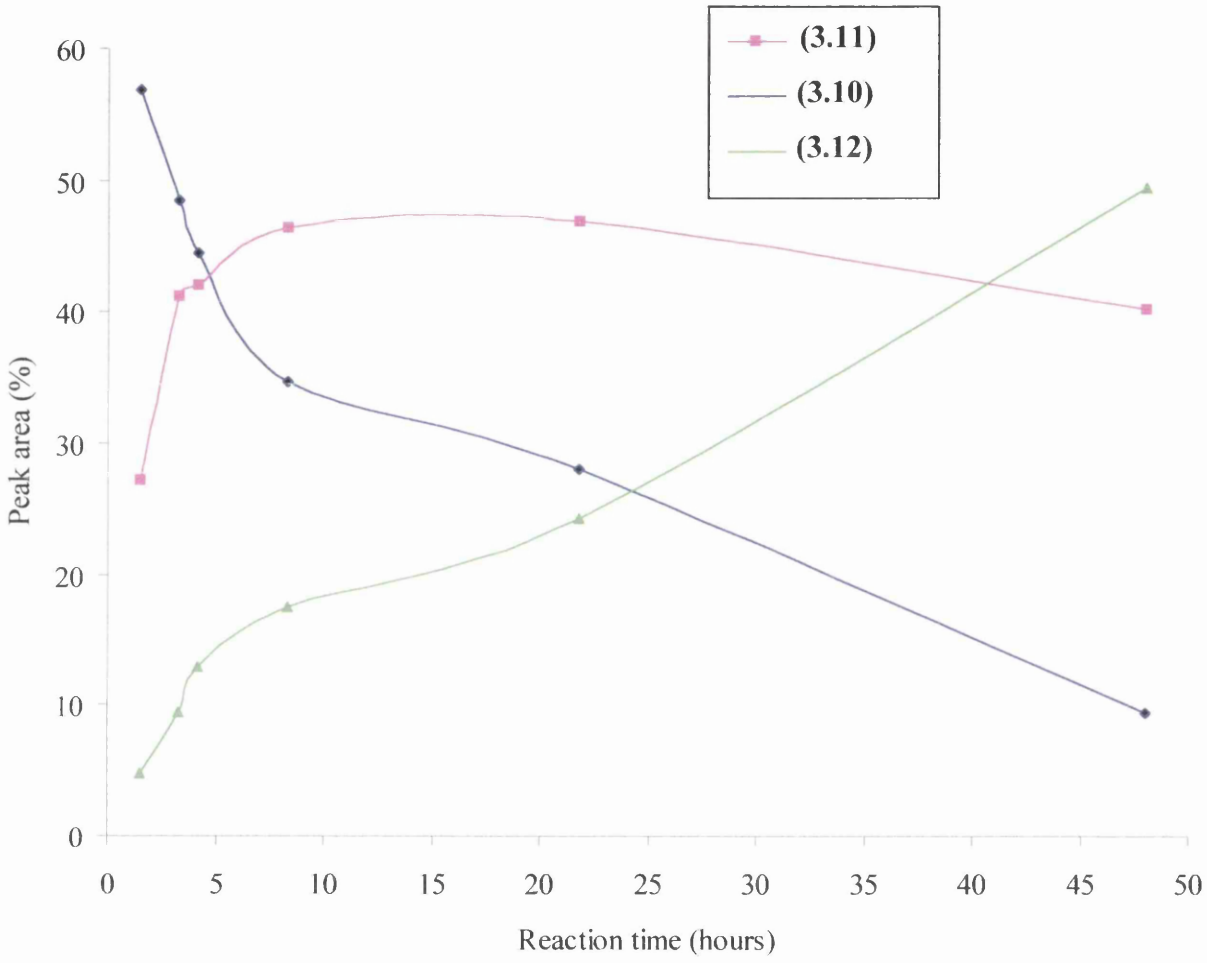
The tagged auxiliary derivative **(3.10)** was formed from the reaction of **(3.6)** with **(3.9)** (Scheme 3.9). NaH was employed to form the *N*-anion of **(3.6)**, which subsequently attacked both CH_2 positions of **(3.9)** to generate **(3.10)** with the loss of two bromide ions. The crude mixture was separated by reverse phase chromatography and three products were isolated, identified as the diacylated compound **(3.10)**, the monoacylated compound **(3.11)** and the deacylated compound **(3.12)**.



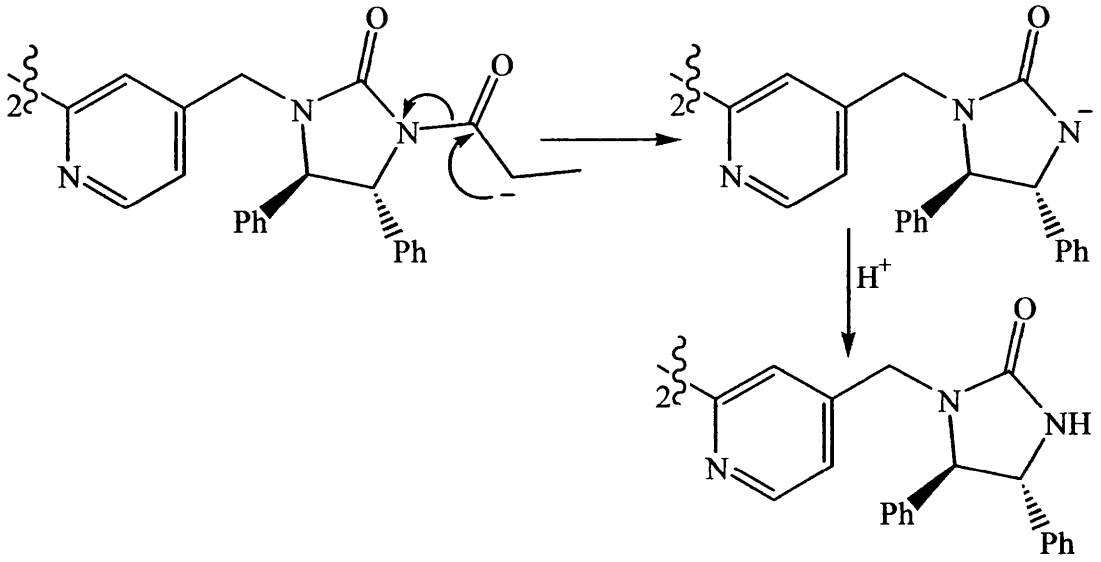
Scheme 3.9

The reaction was monitored by HPLC and a graph of the relative concentrations of **(3.10)**, **(3.11)** and **(3.12)** against reaction time was produced (Figure 3.1).

Figure 3.1 – Relative concentrations of compounds **(3.10)**, **(3.11)** and **(3.12)** during reaction at room temperature



From the graph it was observed that compound **(3.10)** was formed initially and then decomposed to compound **(3.11)** and subsequently to compound **(3.12)**. It was considered possible that unstable α-anions were being produced on the propionyl groups which, when left unquenched, caused the loss of the propionyl groups (Scheme 3.10). Evidence for this explanation was that the decomposition to **(3.12)** occurred faster if excess NaH was used in the reaction.

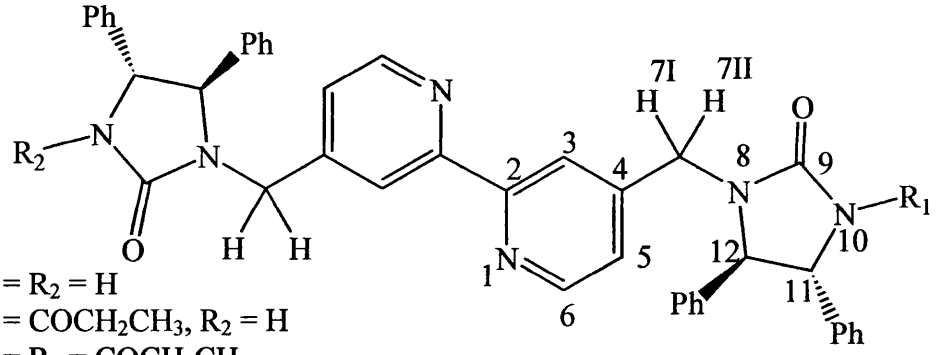


Scheme 3.10

By adjusting the conditions of the reaction, the yields of each compound could be maximised. A 51% yield of **(3.10)** was obtained by carrying out the reaction at −10°C and quenching after one hour. Quenching the reaction after stirring for nineteen hours at room temperature produced a 73% yield of **(3.11)** and quenching after forty-eight hours at room temperature produced a 48% yield of **(3.12)**. The reaction was also attempted using *n*-BuLi in THF but only starting materials were recovered, probably due to the reduced solubility of **(3.9)** in the less-polar solvent.

Evidence for the structures of **(3.10)**, **(3.12)** and **(3.13)** came from ^{1}H NMR. The spectrum of compound **(3.10)** revealed a triplet at 1.17ppm coupled to a quartet at 3.11ppm, which was known to be characteristic of a propionyl group. Integration of the peaks indicated two propionyl groups were present. The spectrum of compound **(3.11)** also contained peaks characteristic of a propionyl group and broad peak at 6.00 ppm indicated the presence of a NH group. The spectrum of compound **(3.12)** did not show any evidence of propionyl groups but did have two broad peaks at 6.00 ppm and 6.20 ppm indicating the presence of two NH groups (see Table 3.1 for ^{1}H NMR data and Table 3.2 for ^{13}C NMR data). The structures were confirmed by accurate mass spectrometry.

Table 3.1 - ^{1}H NMR data of compounds **(3.10)**, **(3.11)** and **(3.12)**



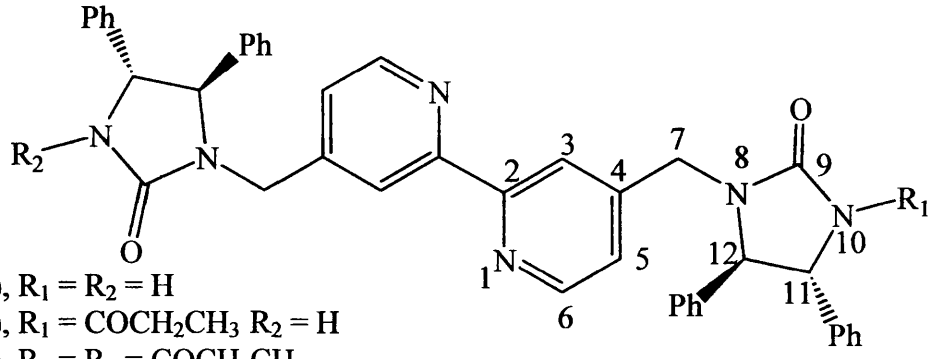
(3.12), $R_1 = R_2 = H$
(3.11), $R_1 = COCH_2CH_3$, $R_2 = H$
(3.10), $R_1 = R_2 = COCH_2CH_3$

Chemical Shift [a,b]

Proton No.	**(3.12)**	**(3.11)**	**(3.10)**
3	8.04, s, 2H	7.97, s, 1H 7.99, s, 1H	8.15, s, 2H
6	8.60, d, 2H, (5.1)	8.62, d, 1H, (5.6) 8.64, d, 1H, (5.5)	8.57, d, 2H, (4.4)
7I	3.98, d, 2H (16.2)	3.97, d, 1H, (16.5) 4.07, d, 1H, (16.3)	3.84, d, 2H, (15.9)
7II	4.70, d, 2H, (16.2)	4.61, d, 1H, (16.5) 4.85, d, 1H, (16.3)	5.04, d, 2H, (15.9)
11*	4.24, d, 2H, (7.4)	4.22, d, 1H, (3.1) 4.24 d 1H, (4.9)	4.24, d, 1H, (2.9)
12*	4.65, d, 2H, (7.4)	4.66, d, 1H, (4.9) 5.13, d, 1H, (3.1)	5.15, d, 2H, (2.9)
Ph & 5	7.15-7.40, 16H, m	7.00-7.40, 16H, m	7.13-7.40, 16H, m
14	-	3.02, q, 2H, (7.3)	3.11, q, 4H, (7.3)
15	-	1.00, t, 3H, (7.3)	1.17, t, 6H, (7.3)
NH	6.00 br, s, 1H 6.20 br, s, 1H	6.00, br, s, 1H	-

a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constants, Hz) *may be reversed

Table 3.2 - ^{13}C NMR data of compounds **(3.10)**, **(3.11)** and **(3.12)**



(3.12), $R_1 = R_2 = H$
(3.11), $R_1 = COCH_2CH_3$ $R_2 = H$
(3.10), $R_1 = R_2 = COCH_2CH_3$

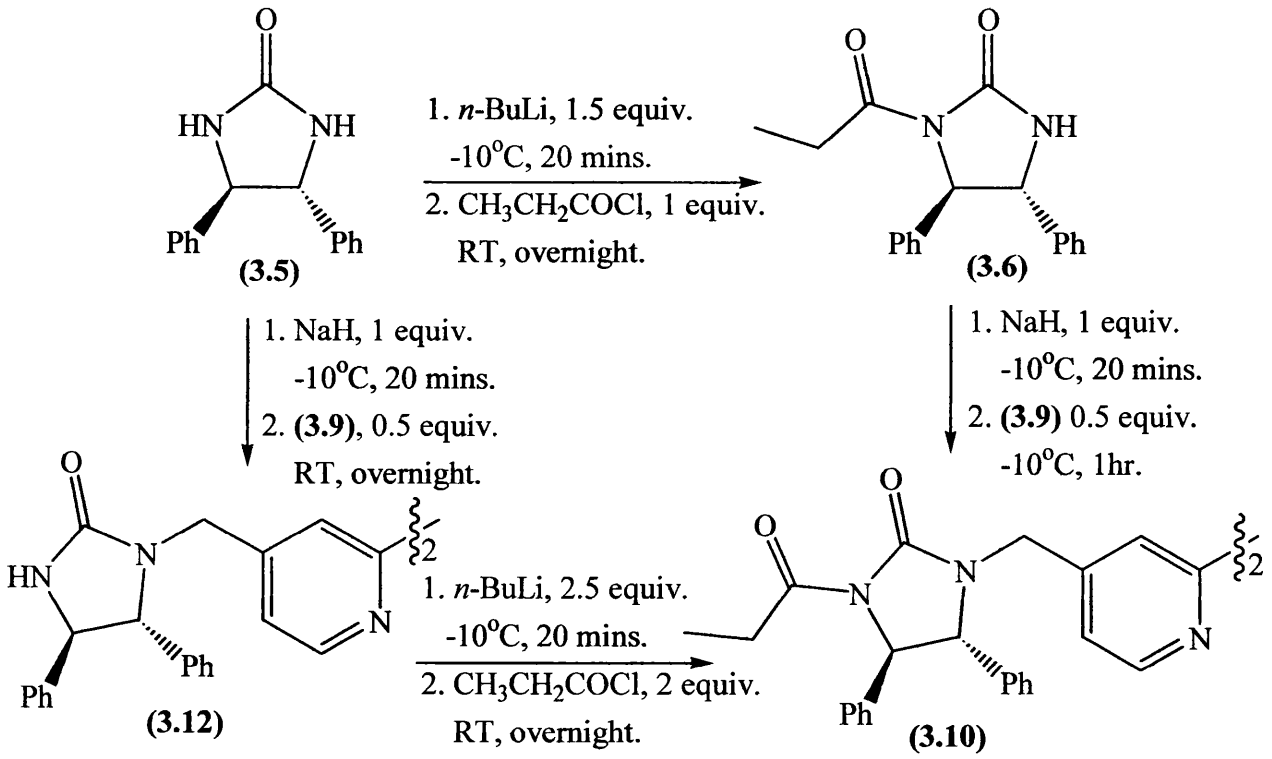
Chemical Shift [a,b]

Carbon No.	(3.12)	(3.11)	(3.10)
2	149.5	149.9	145.3
3	121.5	121.8	120.4
4	139.9	140.1	140.5
5	123.8	124.2	123.0
6	148.2	148.1	149.0
7	44.7	44.8	44.6
9	161.8	155.1 & 161.8	155.1
11*	69.6	63.5 & 69.9	63.6
12*	66.0	65.6	64.9
Ph	139.8, 137.3, 125.6, 127.6, 128.7, 128.9, 129.0, 129.2	139.0, 137.6, 136.7, 129.5, 129.3, 129.2, 129.1, 129.0, 128.6, 128.2, 127.5, 126.4, 125.9, 124.9, 124.4	137.9, 129.6, 129.2, 129.1, 128.2, 126.4, 125.2
13	-	173.8	173.9
14	-	29.4	29.5 & 29.7
15	-	8.4	8.5

a) Spectra run in $CDCl_3$ b) δ values, ppm *may be reversed

3.7 Alternative route to (3.10)

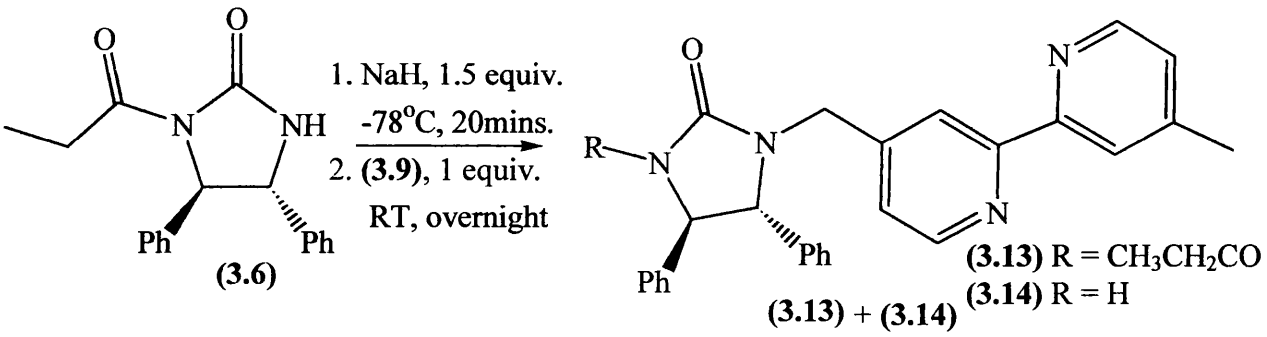
An alternative route to the formation of **(3.10)** was investigated *via* the preparation of **(3.12)** and subsequent acylation to **(3.10)** (Scheme 3.11). The unacylated imidazolidinone **(3.5)** was linked to **(3.9)** using NaH in DMF. Separation by reverse phase chromatography produced **(3.12)** in a 30% yield. The reaction was thought to be low yielding because the NaH could deprotonate either NH-group. Compound **(3.12)** was subsequently acylated using *n*-BuLi and propionyl chloride and stirred overnight to give a mixture of **(3.10)**, **(3.11)** and **(3.12)**. Separation by reverse phase chromatography gave **(3.10)** in a 31% yield. It is possible that this yield could have been increased by shortening the reaction time, which would minimise the production of the unwanted decomposition products **(3.11)** and **(3.12)**. The overall yield of **(3.10)** from **(3.5)** *via* this route was 9%, which, compared to a 41% overall yield from the previous route, clearly showed that this route was less efficient.



Scheme 3.11

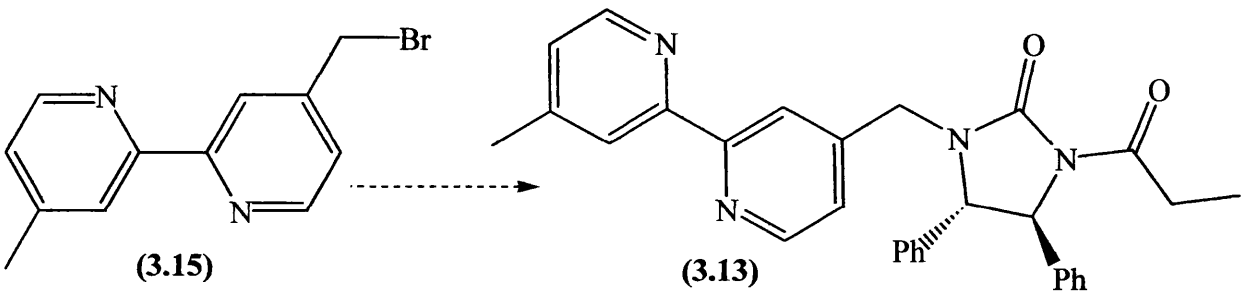
3.8 Preparation of (4*R*,5*R*)-4′-[1-(4,5-diphenyl-3-propionyl-imidazolidinone)-*N*-methyl]-4′-methyl-2,2′-bipyridine (3.13)

The preparation of the monosubstituted bipyridine **(3.13)**, was achieved using 1.5 equivalents of NaH and one equivalent of both **(3.6)** and **(3.9)** in DMF (Scheme 3.12). Separation by reverse phase chromatography gave **(3.13)** in 65% yield. Evidence for its structure came from ^{1}H NMR which revealed characteristic propionyl peaks as well as a signal at 2.62 which corresponded to a methyl group on one of the biyridine rings (see Table 3.3 for ^{1}H and ^{13}C NMR data). The structure was confirmed by accurate mass spectrometry. The de-acylated compound, **(3.14)** was also isolated in 10% yield, identified by a broad NH peak at 5.41ppm in the ^{1}H NMR spectrum.



Scheme 3.12

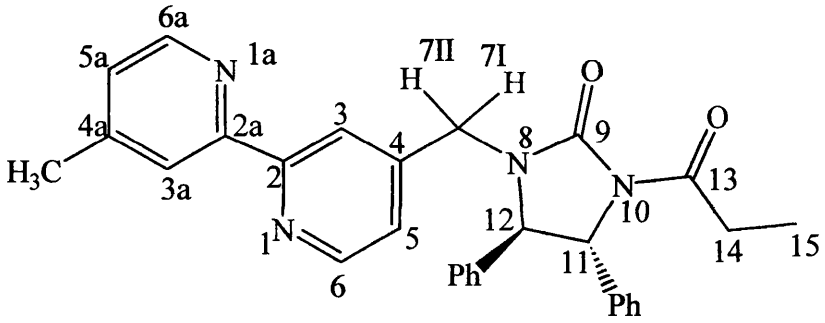
It was unclear how the unsubstituted bipyridine ring reacted to form the 4-methyl adduct and it was suggested that the starting material, **(3.9)**, may have broken down to the 4-methyl,4-bromomethyl-adduct **(3.15)** prior to the reaction (Scheme 3.13).



However, subsequent ^{1}H NMR of the **(3.9)** used in the reaction disproved this theory.

Scheme 3.13

Table 3.3 - ^{1}H and ^{13}C NMR data of compound **(3.13)**



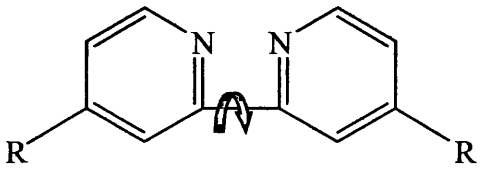
Chemical Shift [a,b]

Carbon/proton no.	**^{1}H**	**^{13}C**
2, 2a	-	149.5, 149.4
3, 3a	7.84, s, 1H, 8.02, s, 1H	121.5
4, 4a	-	140.1, 139.0
5, 5a	7.57, d, 2H, (5.1)	124.3, 124.8
6, 6a	8.59, d, 1H, (5.1) 8.75, d, 1H, (5.8)	149.4, 143.4
7I & 7II	4.03, d, 1H, (16.2) 4.80, d, 1H, (16.2)	44.8
9	-	158.1
11*	4.24, d, 1H, (3.1)	63.5
12*	5.15, d, 1H, (3.1)	65.8
Ph	7.06-7.38, m, 10H	33137.5, 129.6, 129.4, 129.2, 129.1, 129.0, 128.3, 127.2, 126.4, 125.4
13	-	173.9
14	3.03, q, 2H, (7.4)	29.4
15	1.09, t, 3H, (7.4)	8.4
CH_3	2.62, s, 3H	22.2

a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constant, Hz) *may be reversed

3.9 Molecular Modelling Investigation

A molecular modelling investigation was carried out to compare the energy profiles of **(3.10)** and bipyridine. Bipyridine-tagged molecules must adopt a *cis*-conformation in order to co-ordinate to the Cu^{2+} ions on the resin (Figure 3.2). The arrow represents the rotation around the relevant bond as executed during the systematic search procedures. It was expected that *cis*-conformer of **(3.10)** would be unstable due to its large side groups whereas bipyridine would easily adopt the *cis*-conformation.



Bipyridine R = H

Figure 3.2

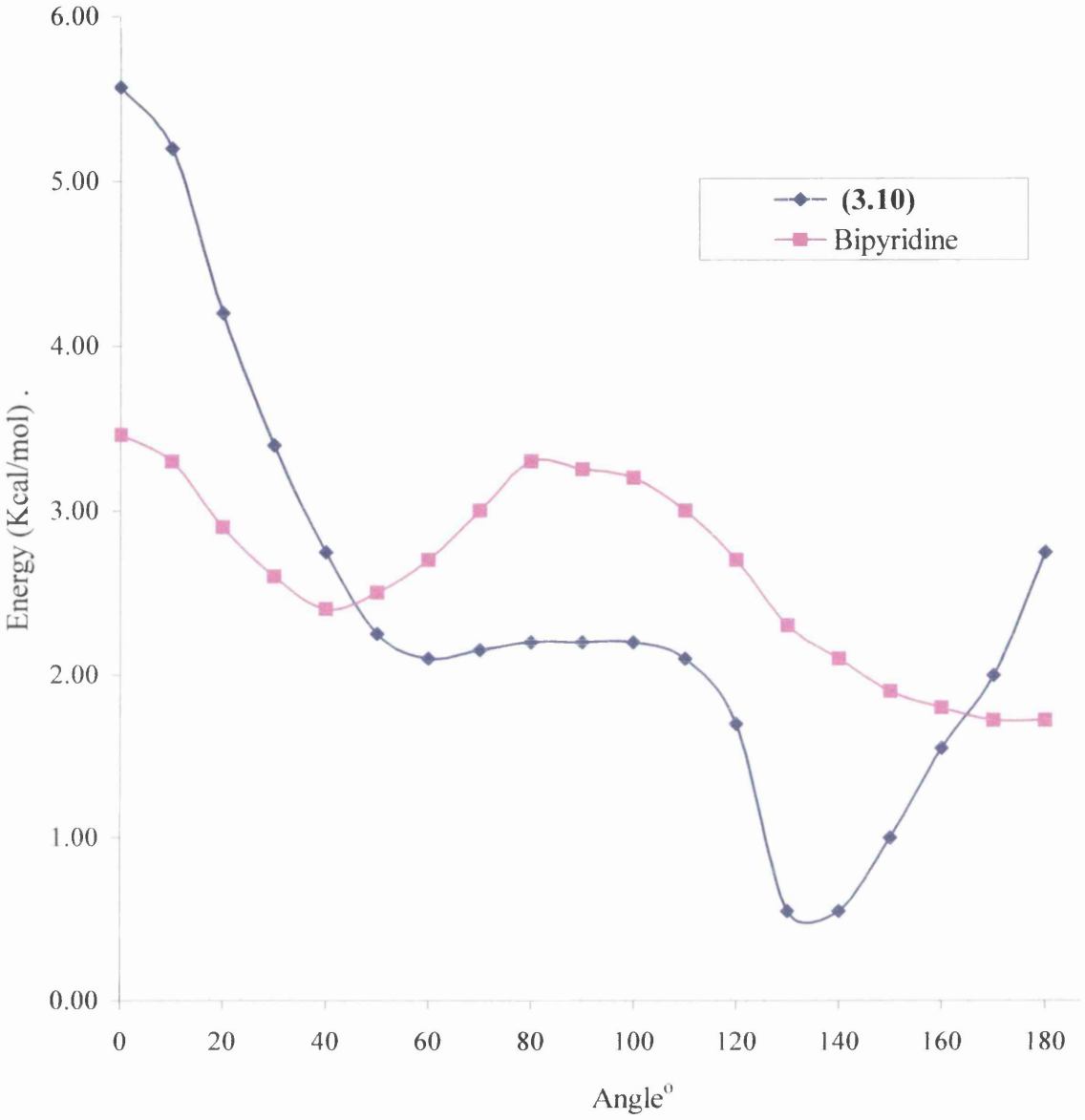
The compounds were drawn using Sybyl software and energetically optimised using Tripos Force Field. A systematic search procedure was applied in order to obtain the energy profile for each molecule. Rotation around the relevant bond was performed with 10° increments over a range of 0° (*cis*) to 180° (*trans*) and the energy at each step was calculated to produce an energy profile for each compound (Figure 3.3). The difference in energy between the *cis* conformation and the global minimum energy conformation for each compound was then determined (Table 3.4).

Table 3.4 - The calculated energy values for **(3.10)** and bipyridine

	(3.10)	Bipyridine
E_{min}	0.39	1.72
E_{cis}	3.94	3.46
$\Delta E_{cis\text{-}min}$	3.55	1.74

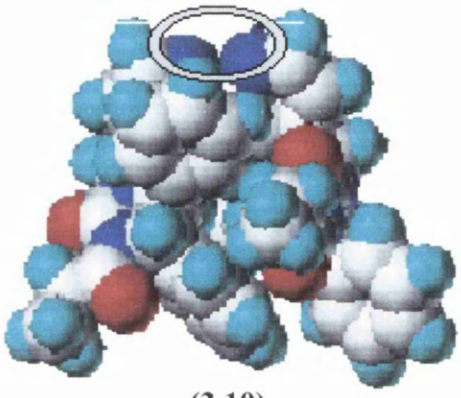
Energy values (Kcals/mol)

Figure 3.3 - The energies of conformations of **(3.10)** and bipyridine

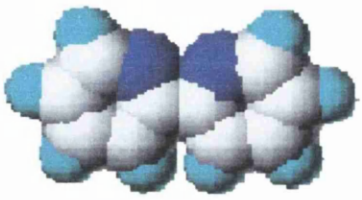


The low energy difference of 1.74 Kcals/mol for bipyridine showed it could readily exist in the *cis*-conformation, which is necessary for loading on to the resin. The energy difference between the *cis*-conformer of **(3.10)** and the global minimum conformer was moderate at 3.55 Kcals/mol. However, steric hindrance was observed on the space fill diagram (Figure 3.4) that could hinder **(3.10)** from adopting the *cis*-conformation and therefore from binding to the resin. The E_{cis}-E_{min} value for **(3.13)** was expected to be lower than the value for **(3.10)** as it contained only one large bulky

side group. However, the value was calculated to be 3.45 Kcals/mol which was similar to the value for **(3.10)**. This suggests that even a relatively small CH_3-group attached to the 4-position of the bipyridyl-ring will greatly affect the molecule's ability to adopt the *cis*-conformation.



(3.10)



Bipyridine

Figure 3.4

3.10 Solid Support Loading Investigation

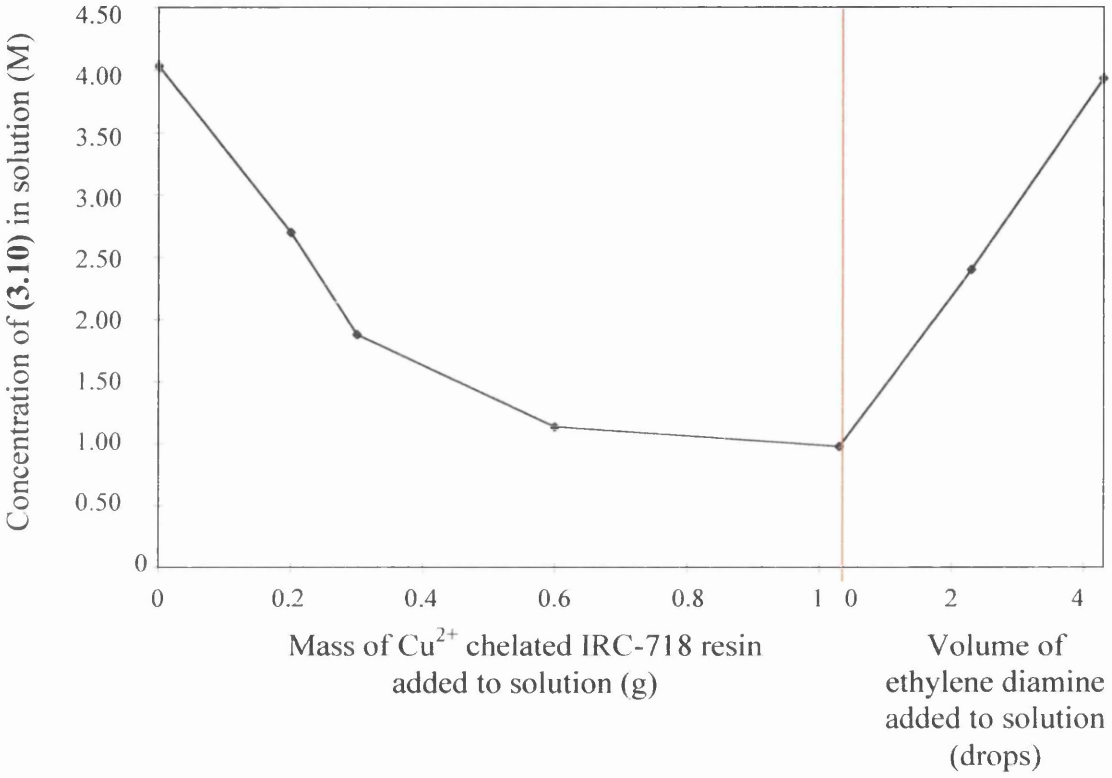
A simple investigation was performed to determine the approximate loading of **(3.10)** on to IRC-718 Cu^{2+} chelated resin. The resin was prepared by washing successively with water, DMF and DCM followed by repeated washing with 0.3M copper sulphate solution, until the resin became the same colour as the copper sulphate solution. This indicated that all the sites on the resin were saturated with Cu^{2+} ions. The loading was calculated by measuring, by HPLC, the peak area of **(3.10)** in a standard solution after the addition of measured amounts of resin and subsequent shaking for two hours. The peak area of an internal, non-binding standard was also measured and the concentration of **(3.10)** was calculated using the following formula:

Conc. (3.10) = (Peak area (3.10) / R.F) × Conc. (standard) / Peak area (standard)

Where R.F is the response factor of **(3.10)** calculated from solutions of known concentration.

The cleavage of **(3.10)** from the resin was also monitored by HPLC by calculating the concentration of **(3.10)** in solution after addition of measured amounts of ethylene diamine and subsequent shaking. The results are shown in Figure 3.5 and correspond to a loading of 0.04mmol of **(3.10)** per gram of resin. It should be noted that compound **(3.10)** could not be detected by NMR in concentrations less than 0.001M.

Figure 3.5 – A graph to show the loading and cleavage of **(3.10)** from the resin



The same methodology was used to determine the loading of bipyridine and the monosubstituted compound **(3.13)** (Figures 3.6 and 3.7 respectively). Bipyridine had a measured loading of 0.25mmol of per gram of resin, which was six times greater than the loading of **(3.10)**. A loading of 0.04moles/g of resin was calculated for **(3.13)**, which was equivalent to the loading of **(3.10)**. It was also found that the resin was unstable in the presence of **(3.13)**. After leaving the resin in a solution of **(3.13)** for a few hours a blue colouration of the solution was observed, presumably due to loss of Cu^{2+} ions from the resin, and this may have impaired the loading result. The blue colouration of the solution was not observed in the presence of the disubstituted compound **(3.10)**.

Figure 3.6 – A graph to show the loading of bipyridine on to the resin

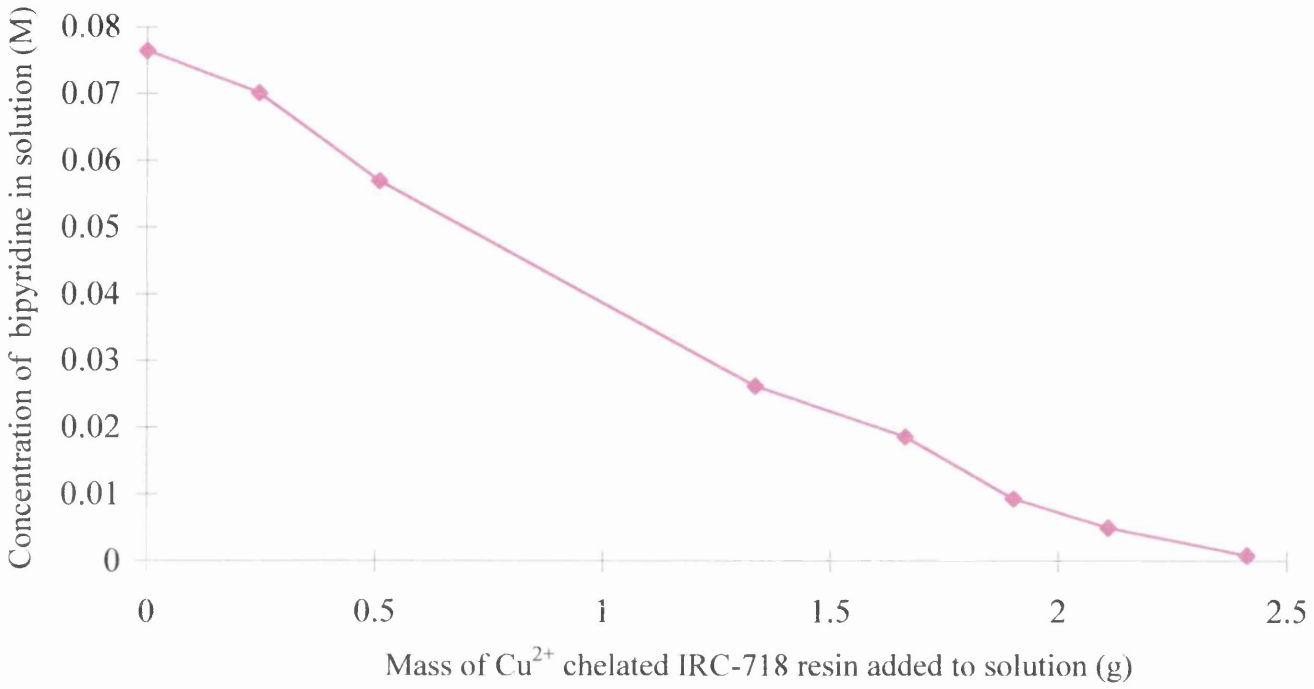
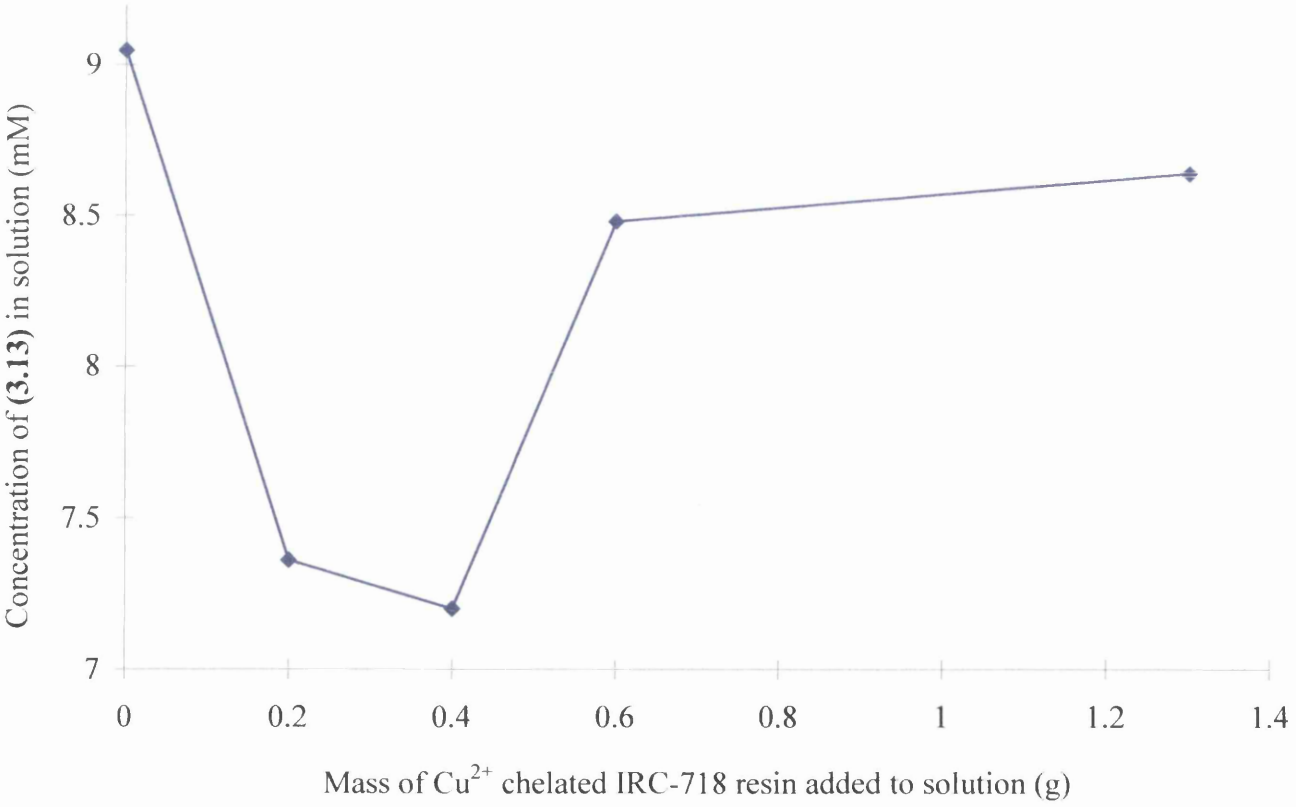


Figure 3.7 – A graph to show the loading of **(3.13)** on to the resin



3.11 Conclusion

This chapter illustrates the successful synthesis of a bipyridine-tagged, C_2-symmetrical, bifunctional chiral auxiliary. The acylated, tagged auxiliary derivative has been shown to be capable of co-ordinating to a solid-phase resin to facilitate isolation and purification.

3.12 Experimental

Instrumentation

^{1}H NMR spectra were recorded on a Bruker AC spectrometer at 400MHz. ^{13}C NMR spectra were recorded on a Bruker AC spectrometer at 100MHz. All spectra contained a tetramethylsilane internal standard. The mass spectra were recorded on a VG analytical Quattro II triple quadrupole mass spectrometer. The accurate mass measurements were obtained from a Finnigan MAT 900 XL mass spectrometer. Melting points were recorded using an electrothermal IA9100 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR 1725x spectrophotometer. HPLC results were obtained from a Hewlett Packard 1100 series. All retention times stated in the experimental data refer to elution time of compound from a Phenomenex Prodigy, 15cm, C18 column. The mobile phase was a gradient of 5% acetonitrile (0.1% TFA) increasing to 100% acetonitrile (0.1%TFA) over 11 minutes then held at that concentration. Products **(3.10)** to **(3.13)** were separated by reverse phase flash chromatography (starting with 50:50 acetonitrile:water and increasing to 80:20 acetonitrile:water) using a dry column method described by Harwood[9] and demonstrated by O'Neil.[10]

Reagents

Anhydrous reactions were carried out under an inert atmosphere and used argon or nitrogen from the cylinder passed through H_2SO_4 and $CaCl_2$. THF was dried by stirring overnight over CaH_2 and then distilled from sodium wire and benzophenone. Diisopropylamine was dried by distilling from KOH. DMF was bought dry from Fluka. Solutions of *n*-BuLi in hexane were bought from Aldrich and regularly estimated. Solid starting materials were dried *in vacuo* over P_2Cl_5 prior to use. Temperatures of –78° and –10°C were obtained from acetone/solid CO_2 and acetone/ice baths respectively.

Attempted preparation of (4*R*,5*R*)-4-methyl-5-phenylimidazolidin-2-one (3.1)

$[C_{16}H_{16}N_2O]$: F.W. = 252

Norephedrine hydrochloride (3.60g, 19.19mmol) and urea (5.30g, 88.35mmol 4.5mol. equiv.) were heated for 30 minutes at 175°C in an oil bath. The resultant melt was heated for 1 hour at 200°C with stirring. The mixture was then cooled to 100°C by lowering the bath temperature and water (50ml) was added. The flask was removed from the oil bath and the reaction mixture was filtered, washed with 5% HCl (100ml) and water (100ml) affording 2.61g (77%) of square white crystals, identified as **(3.3)**. M.pt.143-146°C (lit.[2] 213-214°C). ^{1}H NMR ($CDCl_3$) δ = 0.61 (d, 3 H, J = 5.8 Hz, CH_3), 4.12 (dd, 1H, J = 5.8 Hz and 7.4 Hz, CH), 5.67 (d, 1H, J = 7.5 Hz, CH), 6.83 (br, s, NH), 7.12-7.28 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ = 17.15, 51.15, 79.41, 125.99, 128.09, 128.33, 136.03, 158.29. *m/z*: (ei) 77 (47%), 79 (54%), 105 (18%), 107 (98%).

Preparation of (4*R*,5*R*)-4,5-diphenylimidazolidin-2-one (3.5)

$[C_{15}H_{14}N_2O]$: F.W. = 238

(1*R*,2*R*)-1,2-diphenylethylene-1,2-diamine **(3.4)** (3.02g, 14.24mmol), urea (0.91g, 15.10mmol, 1 mol. equiv.) and water (10 drops) were heated at 200°C for 1 hour or until no starting material could be observed by TLC. The resulting residue was purified by flash chromatography (ethyl acetate) affording 2.56g (75%) of **(3.5)** as a white solid. M.pt. 194-197°C (lit.[3] 196-197.5). ^{1}H NMR ($CDCl_3$) δ = 4.55 (s, 2H, 2 × CH), 5.85 (br s, 2H, 2 × NH) 7.33 (s, 10H, Ph). ^{13}C NMR ($CDCl_3$) δ = 66, 126.5, 128.3, 128.8, 140.2, 163.0

Preparation of (4*R*,5*R*)-4,5-diphenyl-1-propionylimidazolidin-2-one (3.6)

$[C_{18}H_{18}N_2O_2]$: F.W. = 294

To a solution of **(3.5)** (1.87g, 7.85mmol) in THF (30ml) was added *n*-BuLi (15.70mmol, 1.3M, 12ml, 2 mol. equiv.) dropwise at −10°C and stirred for 30 minutes before propionyl chloride (0.73g, 7.89mmol 1 mol. equiv.) was added. The reaction temperature was allowed to reach room temperature and stirring was continued

overnight. The reaction was quenched with sat. NH_4Cl (aq) (5ml), diluted with DCM (20ml) and the organic layer separated. The aqueous layer was extracted with DCM (2 × 50ml) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the crude material (hexane/ ethyl acetate, 80:20) afforded 1.87g (81%) of **(3.6)** as a white solid. M.pt. 119-122°C (lit.[3] 120-121°C). ^1H NMR ($CDCl_3$) δ = 1.02 (t, 3H, J = 7.6Hz, CH_3), 2.91 (q, 2H, J=7.6Hz, CH_2), 4.48 (d, 1H, J=3.4Hz, CH), 5.10 (d, 1H, J=3.4Hz, CH), 6.65 (br s, 1H, NH), 7.31(s, 10H, Ph). ^{13}C NMR ($CDCl_3$) δ = 8.4, 29.4, 61.0, 66.1, 125.5, 125.6, 128.2, 128.7, 129.1, 129.3, 140.7, 140.8, 156.6, 174.0.

Preparation of 1,2-diphenylethan-1,2-diamine (3.4)

$[C_{14}H_{16}N_2]$: F.W. = 212

Roughly cut metallic sodium (7.30g, 0.32mol) was added to a suspension of dioxime (2.39g, 9.96mmol) in anhydrous ethanol (100ml) in a 200ml round bottom flask equipped with an efficient reflux condenser. It was allowed to boil intensely until all the sodium had dissolved (40 minutes). Water was then added (50ml) and the ethanol was removed *in vacuo*. The suspension formed was extracted with ether (3 × 20ml) and the ether was removed *in vacuo* affording 3.03g (144%) of a mixture of *rac*- and *meso*-isomers (45:55). ^1H NMR ($CDCl_3$) *rac*-**(3.4)** δ = 1.59 (br, s, 4H, 2 × NH_2), 4.09 (s, 2H, 2 × CH), 7.26 (s, 10H, 2 × Ph); *meso*-**(3.4)** ^1H δ = 1.38 (br, s, 4H, 2 × NH_2), 4.01 (s, 2H, 2 × CH), 7.26-7.43 (m, 10H, 2 × Ph).

Separation of *rac*- and *meso*-(3.4)

The mixture of **(3.4)** was extracted with boiling water (3 × 15ml) until nearly all the resin had dissolved. Concentrated HCl was added (18ml) and the solution was cooled. The resulting suspension was filtered off to give the *meso*-hydrochloride. The filtrate was made alkaline with KOH (40%) and extracted with ether (4 × 50ml). The ether was removed *in vacuo* affording 1.52g (72%) of *rac*-diphenylethandiamine. Isomeric purity (by ^1H NMR) 69%. M.pt. 98-107°C (lit.[4] 113-114°C). NMR data as before.

Preparation of 4,4′-*bis*-[(trimethylsilyl)methyl]-2,2′-bipyridine (3.8)

$[C_{18}H_{28}N_2Si_2]$: F.W. = 328

To diisopropylamine (2.1ml, 15.00mmol, 2 mol. equiv.) in dry THF (18ml) at -78°C was added *n*-BuLi (5.75ml, 2.3M, 13.22mmol, 2 mol. equiv.). The solution was stirred at –78°C for 20 minutes. 4,4′-dimethylbipyridine (1.12g, 6.07mmol) was dissolved in dry THF (10ml) and transferred dropwise *via* cannula to the LDA solution. The mixture was stirred at –78°C for 20 minutes, warmed to –10°C for 25 minutes and recooled to –78°C before addition of TMSCl (2.0ml, 13.00mmol, 2 mol. equiv.). 5-10 seconds after the TMSCl addition the mixture was quenched with methanol (3ml). Sat. $NaHCO_3$ (aq) (20ml) was added and the product was extracted into ethyl acetate (3 × 250ml), washed with brine (50ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* affording **(3.8)** as an off-white powder (1.55g, 78%). M.pt. 87-89°C (Lit.[7] 90-92°C). ^{1}H NMR ($CDCl_3$): 0.04 (s, 18H, 6 × CH_3), 2.21 (s, 4H, 2 × CH_2), 6.94 (dd, 2H, J = 1.7 Hz and 5.0 Hz, 2 × Arom. CH), 8.05 (d, 2H, J = 1.2, 2 × Arom. CH), 8.46 (d, 2H, J = 5.0 Hz, 2 × Arom. CH). ^{13}C NMR ($CDCl_3$): -2.2, 27.2, 120.6, 123.3, 148.5, 151.1, 155.8.

Preparation of 4,4′-*bis*-bromomethyl-2,2′-bipyridine (3.9)

$[C_{12}H_{10}Br_2N_2]$: F.W. = 342

To a solution of **(3.8)** (1.31g, 3.98mmol) and BrF_2CCF_2Br (3.00g, 8.34mmol, 2 mol. equiv.) in dry DMF (8ml), was added anhydrous CsF (1.30g, 11.31mmol, 3 mol. equiv.). The reaction was stirred at room temperature for 2 hours. The reaction mixture was quenched with water (7ml) and extracted with ethyl acetate (3 × 100ml). The combined organic fractions were washed with brine (20ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* affording **(3.9)** as a pale brown powder (1.28g, 94%). M.pt. = 117-119°C (lit.[7] 116-117°C). ^{1}H NMR ($CDCl_3$): 4.48 (s, 4H, 2 × CH_2), 7.36 (dd, 2H, J = 1.7 Hz, J = 5.0 Hz, 2 × Arom. CH), 8.43 (d, 2H, J = 1.0, 2 × Arom. CH), 8.67 (d, 2H, J = 5.0 Hz, 2 × Arom. CH). ^{13}C NMR ($CDCl_3$): 30.65, 121.04, 123.86, 147.33, 149.75, 156.18.

Preparation of (4*R*,5*R*)-4,4'-*bis*-[(4,5-diphenyl-3-propionyl-imidazolidinonyl)-*N*-methyl]-2,2'-bipyridine (3.10)

$[C_{48}H_{44}N_6O_4]$: F.W. = 768

Method A

NaH (60% mineral oil suspension) (0.03g, 0.67mmol, 2 mol. equiv.) was washed 3 times with dry petroleum spirit (40-60°C) under a nitrogen atmosphere. Dry DMF (10ml) was added and the solution was cooled to -10°C before addition of a DMF solution of **(3.6)** (0.20g, 0.68mmol, 2 mol. equiv.). The reaction mixture was stirred at -10°C for 20 minutes before a solution of **(3.9)** (0.12g, 0.35mmol, 1 mol. equiv.) in DMF (5ml) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with water (5ml) and the DMF was removed *in vacuo*. The residue was extracted into DCM (3 x 40ml), washed with water (2 x 10ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* affording the crude product. Separation by reverse phase flash chromatography afforded **(3.10)** as a pink gum (0.13g, 51%) that did not crystallise from common solvents or their mixtures. Retention time = 12.2 mins. IR (ν, cm^{-1}): 1750 (urea C=O), 1625 (amide C=O) 1550 (pyridine). ^1H and ^{13}C NMR data – see Tables 3.1 and 3.2. *m/z*: (FAB, noba matirx) 792 (17%), 770 (81%), 476 (25%), 133 (98%). Calculated $M+H^+$ = 769.3502. Found $M+H^+$ = 769.3501.

Method B

To a solution of **(3.12)** (0.46g, 0.70mmol) in dry THF (10ml) was added *n*-BuLi (1.3ml, 1.3M, 1.74mmol, 2.5 mol. equiv.) dropwise at -10°C changing the colour of the solution from pink to brown. After stirring at -10°C for 30 minutes propionyl chloride (0.16g, 1.75mmol, 2.5 mol. equiv.) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq) (5ml), extracted into DCM (3 x 50ml), washed with water (50ml) and brine (50ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* affording the crude product. Separation by reverse phase flash chromatography afforded **(3.10)** as a pink gum (0.17g, 31%). Spectroscopic data as before.

Preparation of (4*R*,5*R*)-4-[(4,5-diphenyl-3-propionyl-imidazolidinonyl)-*N*-methyl]–4-[(4,5-diphenyl-imidazolidinonyl)-*N*-methyl]-2,2′-bipyridine (3.11)

$[C_{45}H_{40}N_6O_3]$: F.W. = 712

As Method A for the preparation of **(3.10)**, but with a longer reaction time. NaH (60% mineral oil suspension) (0.04g, 0.88mmol, 3 mol. equiv.), **(3.6)** (0.17g, 0.58mmol, 2 mol. equiv.), **(3.9)** (0.10g, 0.29mmol, 1 mol. equiv.). The final reaction mixture was stirred at room temperature for 19 hours before quenching. **(3.11)** was afforded as a pink gum (0.16g, 77%) that did not crystallise from common solvents or their mixtures.. Retention time = 10.7 mins. I.R (ν, cm^{-1}): 3300 (NH),1725 (urea C=O), 1625 (amide C=O) 1550 (pyridine). ^1H and ^{13}C NMR data – see Tables 3.1 and 3.2. *m/z*: (FAB, noba matrix) 714 (98%), 658 (47%), 420 (73%), 179 (58%). Calculated $M+H^+$ = 713.3240. Found $M+H^+$ = 713.3241.

Preparation of (4*R*,5*R*)-4,4′-*bis*-[(4,5-diphenyl-imidazolidinonyl)-*N*-methyl]-2,2′-bipyridine (3.12)

$[C_{42}H_{36}N_6O_2]$: F.W. = 656

As Method A for the preparation of **(3.10)**, but with a longer reaction time. NaH (60% mineral oil suspension) (0.02g, 0.50mmol, 2.5 mol. equiv.), **(3.6)** (0.10g, 0.34mmol, 2 mol. equiv.), **(3.9)** (0.06g, 0.17mmol, 1 mol. equiv.). The final reaction mixture was stirred at room temperature for 2 days before quenching. **(3.12)** was afforded as a pink gum (0.05g, 48%). Crystallised from ethyl acetate/ethanol. Mpt = 115-117°C. Retention time = 9.8 mins. I.R (ν, cm^{-1}): 3275 (NH), 1700 (urea C=O), 1625 (amide C=O) 1550 (pyridine). ^1H and ^{13}C NMR data – see Tables 3.1 and 3.2. *m/z* : (FAB, noba matrix) 421 (9%), 132 (95%), 104 (80%), 77 (60%); (ci) 658 (15%), 257 (17%), 240 (95%), 106 (48%). Calculated $M+H^+$ = 657.2978. Found $M+H^+$ = 657.2983.

Method B

As Method A for the preparation of **(3.10)**, but with **(3.5)** as the starting material. NaH (60% mineral oil suspension) (0.03g, 0.87mmol, 2.5 mol. equiv.), **(3.5)** (0.14g, 0.59mmol, 2 mol. equiv.), **(3.9)** (0.10g, 0.29mmol, 1 mol. equiv.). The reaction was

stirred at room temperature overnight. **(3.12)** was afforded as a pink gum (0.06g, 30%). Spectroscopic data as before.

Preparation of (*R,R*)-4-[1-(4,5-diphenyl-3-propionylimidazolidinonyl)-*N*-methyl]-4-methyl-2,2′-bipyridine (3.13)

$[C_{30}H_{28}N_4O_2]$: F.W. = 476

As Method A for the preparation of **(3.10)**, but with equivalent amounts of **(3.6)** and **(3.9)**. NaH (60% mineral oil suspension) (0.22g, 5.50mmol, 1.5 mol. equiv.), **(3.6)** (1.13g, 3.80mmol, 2 mol. equiv.), **(3.9)** (0.95g, 2.79mmol 1 mol. equiv.). The reaction was stirred at room temperature overnight. **(3.13)** was afforded as a pink gum (0.90g, 72%). Retention time = 8.9mins. I.R (ν, cm^{-1}): 1725 (urea C=O), 1625 (amide C=O) 1550 (pyridine). ^1H and ^{13}C NMR data – see Table 3.3. *m/z*: (ei) 57 (38%), 77 (41%), 132 (83%), 184 (98%). Calculated $M+H^+$ = 477.2290. Found $M+H^+$ = 477.2284.

Preparation of Cu^{2+} chelated IRC-718 resin

IRC-718 (Amberlite) resin (50g) was placed in a large sintered funnel and washed successively with water (3 × 250ml), DMF (3 × 60ml) and DCM (3 × 100ml) to remove the brown particles present in the resin. $CuS0_4$(aq) (0.3M, 250ml) was passed repeatedly through the clean resin until the filtrate was the same colour as the added solution. The resulting blue resin was washed successively with water (3 × 250ml), DMF (3 × 60ml) and DCM (3 × 100ml) to remove the excess $CuSO_4$. The chelated resin was stored under DCM.

Calculation of the Response Factor of (3.10)

A solution of **(3.10)** (0.08g, 0.10mmol) in THF (10ml) was prepared in a 10ml volumetric flask and was designated as Solution A. A solution of 2-nitrotoluene (1.51g, 11.02mmol) in THF was prepared in a 1000ml volumetric flask and was designated as Solution B. The solutions were pipetted into clean, dry sample tubes in the following ratios; 1A:1B, 1A:2B, 1A:3B, 2A:1B and 3A:1B, using a different 1ml pipette for each solution. Each solution was analysed in triplicate by HPLC. The results are shown in Table 3.5.

Table 3.5 – Calculation of the response factor for **(3.10)**

Volume A (ml)	Amount A (mM)	Peak Area A	Volume B (ml)	Amount B (mM)	Peak Area B	Response Factor
		9745			49788	4.95
1	5.14	9714	1	5.51	48438	4.83
		9805			48405	4.78
		6295			64117	4.93
1	3.43	6547	2	7.35	63967	4.72
		6274			61743	4.76
		5549			89339	5.20
1	2.57	5811	3	8.26	93868	5.21
		6106			90218	4.77
		7529			17923	4.61
2	6.85	6728	1	3.67	16822	4.84
		7010			17561	4.85
		7174			11934	4.83
3	7.71	6895	1	2.75	11756	4.95
		7236			12087	4.85
					Average Response Factor	4.87

Estimation of the Loading of (3.10)

To a solution of **(3.10)** (0.03g, 0.04mmol) and 2-nitrotoluene (0.01g, 0.01mmol) in THF (10ml) was added IRC-718 Cu^{2+} chelated resin (0.23g). The mixture was shaken for 2 hours before a 0.1ml sample was taken. The sample was filtered and diluted with acetonitrile (2ml) before analysis by HPLC. The sequence was repeated as shown in Table 3.6.

Table 3.6 – Estimation of the loading of **(3.10)**

Amount of Resin (g)	Peak Area (3.10)	Peak Area Nitrotoluene	Conc. of Nitrotoluene (mM)	Response Factor	Calculated Conc. of (3.10) (mM)	Average Conc. of (3.10)
0.23	743	12075			2.85	
	799	13720	9.48	4.90	2.70	2.7
	613	11133			2.56	
0.32	517	14594			1.65	
	620	16024	9.48	4.90	1.79	1.88
	934	19583			2.21	
0.61	186	12736			0.68	
	406	13181	9.48	4.90	1.43	1.14
	379	13521			1.30	
	548	22805			1.12	
1.03	-	-	9.48	4.90	undetectable	0.98
	386	21345			0.84	
1.03 + 2 drops $(CH_2NH_2)_2$	507	9824	9.48	4.90	2.40	2.40
1.03 + 4 drops $(CH_2NH_2)_2$	2190	25844	9.48	4.90	3.93	3.93

Calculation of the response factor for 2,2′-bipyridine

As the method used for the calculation of the response factor of **(3.10)**, but with bipyridine. Standard solution A = 2,2′-bipyridine (0.16g, 1.03mmol, 0.013mM) in THF (1000ml) then further diluted by taking 10ml of the solution using a 10ml pippette and making up to 100ml in THF in a volumetric flask. Standard solution B = 2-nitrotoluene (0.39g, 2.87mmol, 0.11mM) in THF (1000ml) then further diluted by taking 10ml of the solution using a 10ml pippette and making up to 250ml in THF in a volumetric flask. The results are shown in Table 3.7.

Table 3.7 – Calculation of the response factor for 2,2′-bipyridine

Volume A (ml)	Amount A (mM)	Peak Area A	Volume B (ml)	Amount B (mM)	Peak Area B	Response Factor
	0.05	11134			5521	0.44
1		10950	1	0.06	5495	0.45
		10929			5522	0.45
		7717			8029	
1	0.03	7673	2	0.08	7831	0.47
		7601			8028	
		5653			8971	
1	0.03	5628	3	0.09	8909	0.47
		5456			8754	
		14514			3451	0.43
2	0.07	15058	1	0.04	3582	0.43
		15117			3486	0.42
3	0.08	17895	1	0.03	2920	0.44
					Average Response Factor	0.45

Estimation of the Loading of Bipyridine

As the method used for the estimation of the loading of **(3.10)**, but with bipyridine. 2,2′-bipyride (0.117g, 0.75mmol), 2-nitrotoluene (0.161g, 0.12mmol) in THF (10ml). The results are shown in Table 3.8

Table 3.8 - Estimation of the loading of bipyridine

Amount of Resin (g)	Peak Area Bipyridine	Peak Area Nitrotoluene	Conc. of Nitrotoluene (M)	Response Factor	Calculated Conc. of Bipyridine (M)	Average Conc. of Bipyridine (M)
	7062	5358			0.07	
0.25	7346	5474	0.12	0.45	0.07	0.07
	7069	5443			0.07	
	8609	8110			0.06	
0.51	8718	8076	0.12	0.45	0.06	0.06
	8717	8118			0.06	
	2611	5383			0.03	
1.33	2815	5712	0.12	0.45	0.03	0.03
	2899	5786			0.03	
	2478	7018			0.02	
1.66	2472	6935	0.12	0.45	0.02	0.02
	2456	7124			0.02	
	3216	1809			0.01	
1.90	3124	1736	0.12	0.45	0.01	0.01
	2920	1734			0.01	
	1634	1662			0.01	
2.11	1434	1657	0.12	0.45	0.00	0.01
	4076	4117			0.01	
	903	5987			0.00	
2.41	906	5862	0.12	0.45	0.00	0.00
	802	5227			0.00	

Calculation of the response factor for (3.13)

As the method used for the calculation of the response factor of **(3.10)**, but with **(3.13)**. Standard solution A = **(3.13)** (0.04g, 0.1mmol, 0.1mM), THF (1000ml). Standard solution B = 2-nitrotoluene (0.01g, 0.01mmol, 0.1mM), THF (1000ml). The results are shown in Table 3.9.

Table 3.9 – Calculation of the response factor of compound **(3.13)**

Volume A (ml)	Amount A (mM)	Peak Area A	Volume B (ml)	Amount B (mM)	Peak Area B	Response Factor
		255			145	0.99
2	0.06	233	1	0.03	138	1.04
		250			137	0.95
		188			201	0.93
1	0.05	176	1	0.05	207	1.03
		183			213	1.01
		127			283	0.97
1	0.03	124	2	0.07	274	0.96
		136			280	0.90
		276			106	1.01
3	0.07	278	1	0.03	109	1.03
		277			98	0.93
		94			325	1.00
1	0.02	96	3	0.08	323	0.99
		96			321	0.97
					Average Response Factor	0.98

Estimation of the Loading of (3.13)

As the method used for the estimation of the loading of **(3.10)**, but with **(3.13)**. **(3.13)** (0.04g, 0.01mmol), nitrotoluene (0.01g, 0.10mmol), 10ml THF. The results are shown in Table 3.10.

Table 3.10 – Estimation of the loading of **(3.13)**

Amount of Resin (g)	Peak Area of (3.13)	Peak Area of Nitrotoluene	Conc. of Nitrotoluene (mM)	Response Factor	Calculated Conc. of (3.13) (mM)	Average Conc. of (3.13) (mM)
	7145	9959			6.91	
0.2	11993	15539	10.35	0.98	7.43	7.36
	13118	16319			7.74	
	12645	17101			7.12	
0.4	11881	15828	10.35	0.98	7.23	7.20
	11796	15668			7.25	
	4075	4839			8.11	
0.6	1302	1406	10.35	0.98	8.92	8.48
	8188	9386			8.40	
1.3	7838	8676	10.35	0.98	8.70	8.64
	5820	6527			8.59	
1.3	1279	1167			10.56	
more	3820	3787	10.35	0.98	9.71	10.24
shaking	530	489			10.44	

3.13 References

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Chapter Four

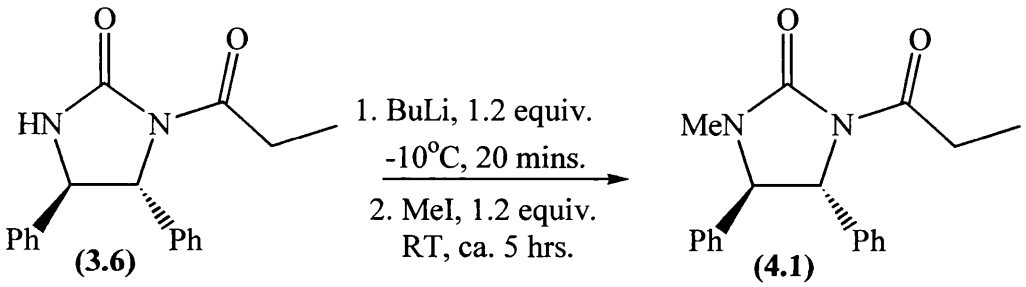
Investigation of the Reactivity of the Chiral Auxiliary

4.1 Introduction

The object of the work described in this chapter was to test the effectiveness of the tagged chiral auxiliary **(3.10)** in asymmetric enolate reactions. The strategy was to carry out a series of alkylations, halogenations and aldol reactions using the tagged auxiliary **(3.10)** and the known auxiliary **(4.1)** that would act as a model for the untagged auxiliary. The yields and diastereomeric excesses of the asymmetric products of the two auxiliaries would then be compared in order to see if the large bipyridyl group on tagged auxiliary **(3.10)** affected the chiral directing effect of the auxiliary moiety.

4.2 Preparation of (4*R*,5*R*)-4,5-diphenyl-1-methyl-3-propionyl-imidazolidinone (4.1)

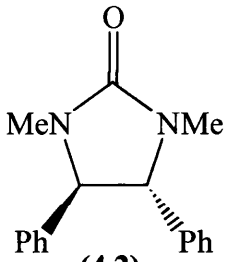
Chiral auxiliary derivative **(4.1)** was synthesised from compound **(3.6)** using *n*-BuLi and methyl iodide (Scheme 4.1) as reported by Sankhavasi *et al.*[1]



Scheme 4.1

The reaction mixture was stirred overnight at room temperature, as in the published procedure, to afford **(4.1)** in 20% yield. It was identified by ^{1}H NMR, from the appearance of a peak at 2.79 ppm which intergrated to three hydrogens, indicating the presence of a methyl group. In an effort to increase the yield the reaction was monitored by TLC and quenched once the starting material was no longer detectable (approximately five hours). This increased the yield to >90% by preventing unwanted products from being formed, especially the 1,3-dimethyl-adduct **(4.2)**, which was identified by ^{1}H NMR from the loss of the peaks which corresponded to the propionyl group. Also, the signal from the methyl group integrated to six hydrogens. It was

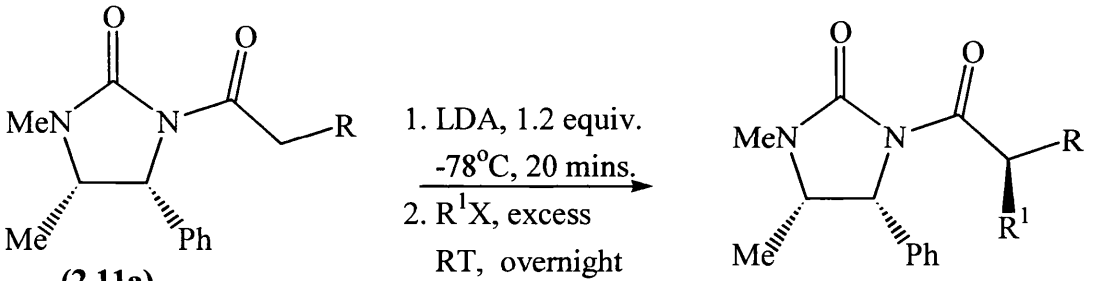
important to purify the crude product promptly, by flash chromatography, as it decomposed if left overnight.



(4.2)

4.3 Alkylation of (4.1)

The chiral auxiliary derivative **(4.1)** has been used in chiral aldol reactions[1] but no examples exist in the literature of its use in chiral enolate alkylations. However, the structurally similar (4*R*,5*S*)-1,5-dimethyl-4-phenyl-imidazolidinone derivatives **(2.11a)** and **(4.3)** have been shown to readily undergo enolate alkylations using LDA to form an α-anion on the propionyl group which is subsequently quenched using an alkyl halide (Scheme 4.2).[2,3,4]



(2.11a)
(4.3)

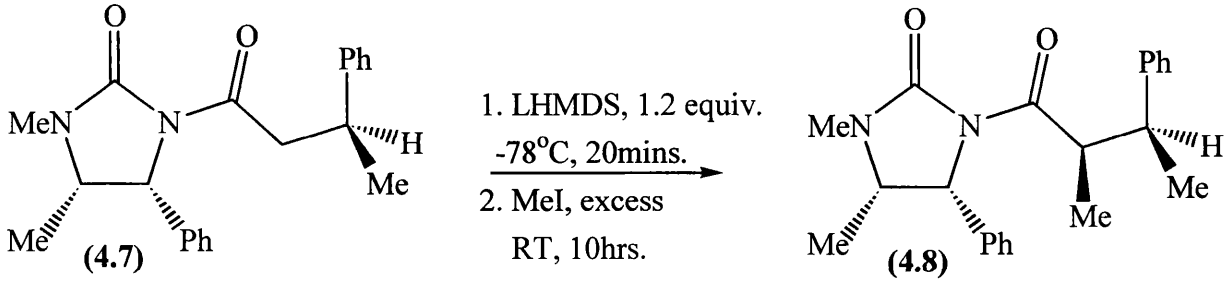
(2.12a)-(2.13a)
(4.4)-(4.6)

(2.11a) R=OBn
(4.3) R=CH_3

(2.12a) R=OBn, R^1=CH_2Ph
(2.13a) R=OBn, R^1=CH_2OBn
(4.4) R=CH_3, R^1=C_8H_{17}
(4.5) R= CH_3, R^1=CH_2Ph
(4.6) R= CH_3, R1=CH_2CHCH_2

Scheme 4.2

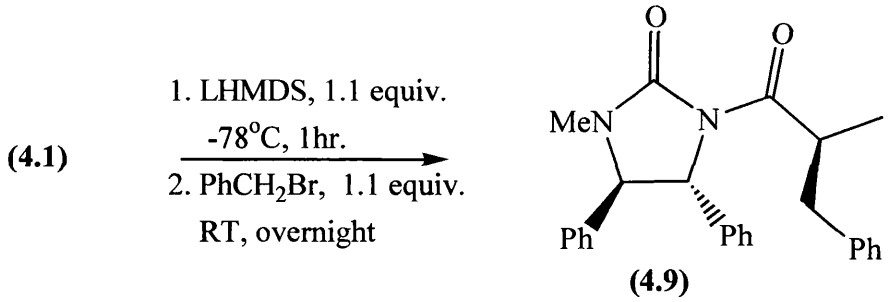
The use of lithiated 1,1,1-hexamethyldisilazane (LHMDS) in an alkylation of a similar imidazolidinone derivative **(4.7)** has also been reported (Scheme 4.3).[5] Due to the crowded structure of LHMDS it is a more selective base than LDA.



Scheme 4.3

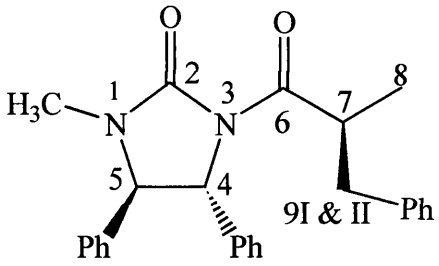
4.3.1 Benzylation of (4.1)

The synthesis of (4*R*,5*R*)-3-(2*S*-benzylpropionyl)-4,5-diphenyl-1-methyl-imidazolidinone **(4.9)** was initially attempted using LDA and excess benzyl bromide. However, no reaction was observed by TLC under these conditions and only starting materials were recovered. The reaction was however achieved by the addition of **(4.1)** to a solution of LHMDS followed by addition of benzyl bromide (Scheme 4.4). Compound **(4.9)** was identified by ^{1}H NMR, from the change in the signal of the CH_3 of the propionyl group which was present as a triplet at 1.13ppm in **(4.1)** but was a doublet in **(4.9)**. The structure was confirmed by ^{13}C NMR and accurate mass spectrometry (^{1}H and ^{13}C data are shown in Table 4.1). The diastereomeric excess of **(4.9)** was 90%, calculated by ^{1}H NMR from the ratio of peaks at 4.45ppm and 4.40ppm, which correspond to H-7 in the individual diastereoisomers.



Scheme 4.4

Table 4.1 – ^{1}H and ^{13}C NMR of compound **(4.9)**



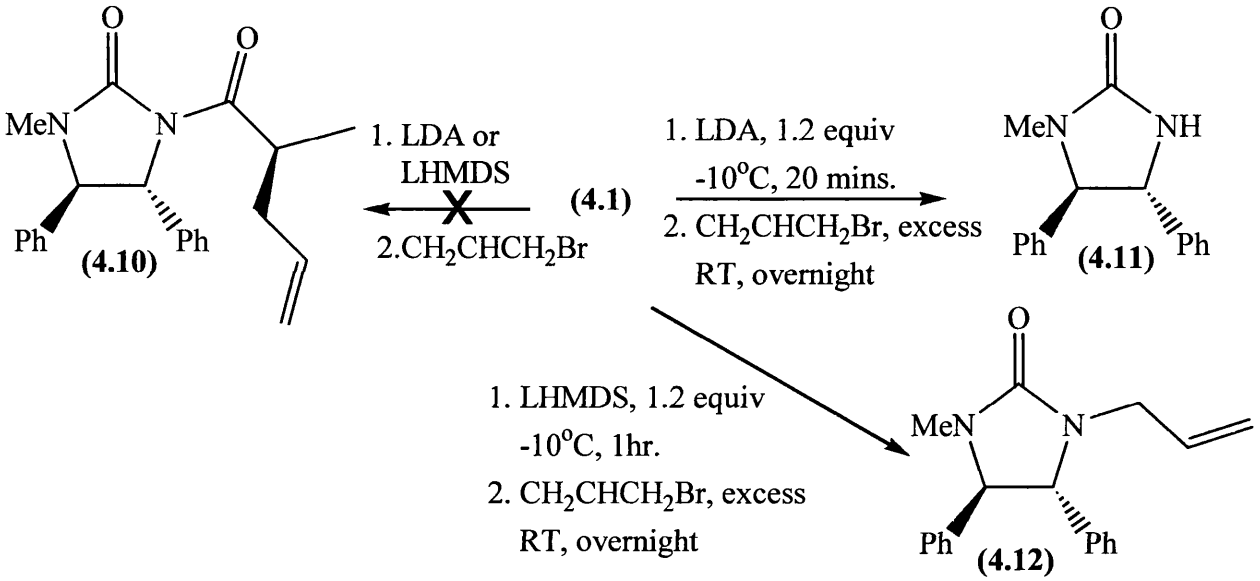
Chemical Shift [a,b]

Proton/carbon no.	**^{1}H**	**^{13}C**
2	-	176.8
4*	4.23, 2H, d (3.8)	64.0
5*	5.08, 2H, d (3.8)	67.6
6	-	154.9
7	4.45, 1H, m	29.5
8	1.16, 3H, d (6.8)	8.13
9I & II	3.17, 1H, dd (6.9, 13.2) 2.55, 1H, dd (7.8, 13.2)	16.9
CH_3	2.80, 3H, s	32.2
Ph	7.03, 5H, m	138.9, 129.7, 129.5, 129.3, 126.9, 125.6.
Ph	7.16-7.43, 10H, m	140.1, 140.9, 129.8, 129.8, 129.7, 129.6, 129.4, 129.4, 128.7, 128.3, 126.6, 126.4.

a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constants, Hz) *may be reversed

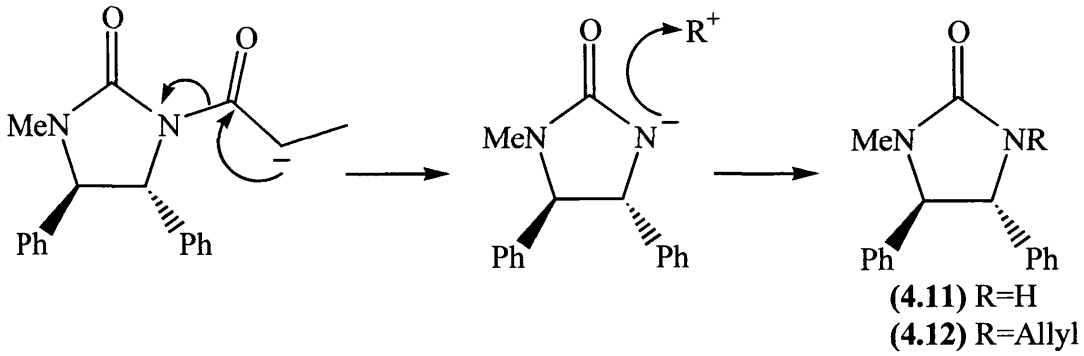
4.3.2 Attempted Allylation of (4.1)

The synthesis of **(4.10)** was undertaken in order to show another example of an alkylation mediated by chiral auxiliary derivative **(4.1)**. However, even after several attempts the desired product was not obtained (Scheme 4.5).



Scheme 4.5

The reaction was initially attempted using LDA but this resulted in the propionyl group being cleaved to produce compound **(4.11)** in 79% yield. It was thought that any excess negatively charged species could be responsible for this by attacking the carbonyl group. However, the same cleavage reaction was observed even when no excess of BuLi or diisopropylamine was present. It was therefore thought probable that an intramolecular reaction of the α-anion was causing the cleavage of the propionyl group from the auxiliary, which was subsequently quenched with a H^+ ion on work-up (Scheme 4.6). The reaction was repeated using LHMDS, under the same conditions as descibed in the benzylation of **(4.1)** (Section 4.3.1), but this only produced compound **(4.12)** in 52% yield, presumably as a result of cleavage of the propionyl group and subsequent attack by the allyl electrophile (Scheme 4.6).



(4.11) R=H
(4.12) R=Allyl

Scheme 4.6

The sequence was repeated using different reaction conditions. The reagents were cooled to –78°C before addition to the reaction mixture, the LHMDS/**(4.1)** mixture was left for shorter lengths of time and greater equivalents of allyl bromide were used. However, in each case, only **(4.12)** or **(4.1)** were recovered after work-up. The various conditions examined are summarised in Table 4.2.

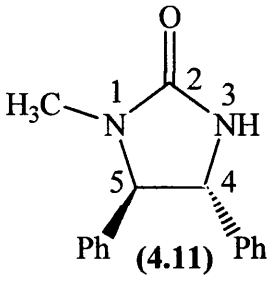
Table 4.2 – Conditions examined in the attempted preparation of **(4.10)**

Run	Base (equiv.)	Reaction Conditions after addition of **(4.1)**, before addition of allyl bromide	Allyl bromide equiv.s	Product
1	LDA (1.5)	-78°C, 1hr	1.5	**(4.11)**
2	LDA (1)	-78°C, 30mins	1.5	**(4.11)**
3	LHMDS (1)	-78°C, 1hr	2	**(4.12)**
4	LHMDS (1.2)	-78°C, 10mins	4 (cooled to –78°C before addition)	**(4.1)**
5	LHMDS (1.1)	-78°C, 30mins	4 (cooled to –78°C before addition)	**(4.12)**

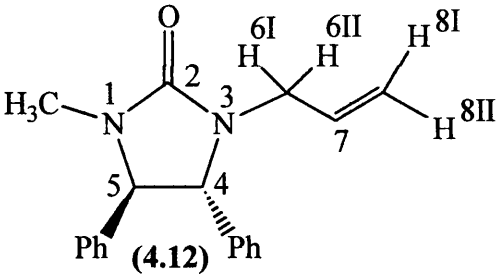
Compound **(4.11)** was identified by ^{1}H NMR, from the loss of signals corresponding to the propionyl group and from the appearance of a broad peak at 5.29 ppm which corresponded to the NH group (see Table 4.3 for ^{1}H NMR data and Table 4.4 for ^{13}C NMR data). Compound **(4.12)** was identified by ^{13}C NMR, from the appearance of peaks corresponding to an allyl group, but also from the disappearance of the carbonyl

signal of the propionyl group, which should have been around 170-190 ppm (see Table 4.3 for ^{1}H NMR data and Table 4.4 for ^{13}C NMR data). The structures were supported by accurate mass spectrometry.

Table 4.3 – ^{1}H NMR of compounds **(4.11)** and **(4.12)**



(4.11)



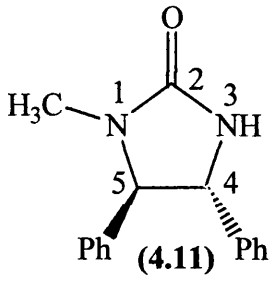
(4.12)

Chemical Shift [a,b]

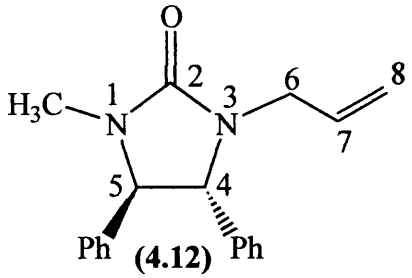
Proton no.	**(4.11)**	**(4.12)**
3	5.29, br s, 1H	-
4*	4.21, d, 1H (8.0)	4.06, d, 1H (8.4)
5*	4.40, d, 1H (8.0)	4.18, d, 1H (8.4)
6I	-	4.19, dd, 1H (4.5, 15.4)
6II	-	3.10, dd, 1H (8.0, 15.4)
7	-	5.58-5.68, dddd, 1H (4.5, 8.0, 10.1, 15.0)
8I	-	4.87, dd, 1H (1.0, 15.0)
8II	-	5.00, dd, 1H (1.0, 10.1)
CH_3	2.65, s, 3H	2.63, s, 3H
Ph	7.18-7.42, m, 10H	7.03-7.33, m, 10H

a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constants, Hz) *may be reversed

Table 4.4 – ^{13}C NMR of compounds **(4.11)** and **(4.12)**



(4.11)



(4.12)

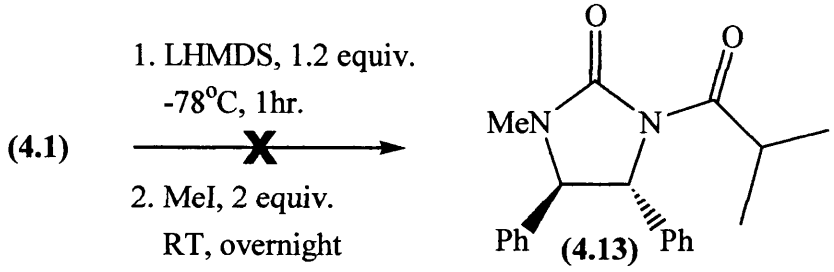
Chemical Shift[a,b]

Carbon no.	**(4.11)**	**(4.12)**
2	162.3	161.4
4*	63.9	67.1
5*	72.5	70.5
6	-	45.1
7	-	132.7
8	-	118.8
CH_3	29.5	30.3
Ph	126.9, 127.7, 128.8, 129.0, 129.2, 129.4	125.9, 127.5, 127.9, 128.8, 129.2, 129.7, 138.5, 138.7

a) Spectra run in $CDCl_3$ b) δ values, ppm *may be reversed

4.3.3 Attempted Methylation of (4.1)

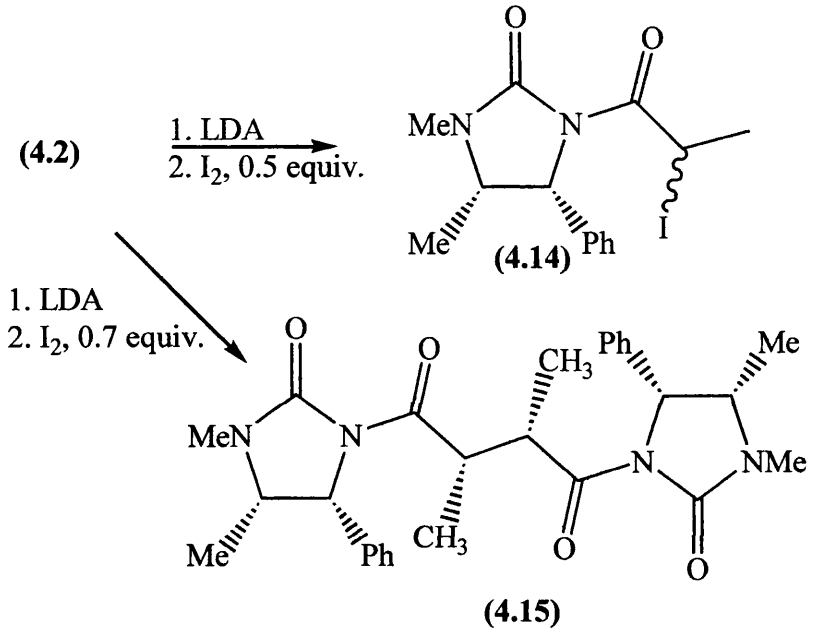
The preparation of **(4.13)** was attempted because it was thought that addition of a smaller alkyl group might occur more readily, although the product would not contain an additional chiral centre. The reaction was attempted with LHMDS (Scheme 4.7). The reaction mixture of LHMDS and **(4.1)** was stirred for one hour at –78°C before the addition of methyl iodide, which were the same conditions as in the benzylation of **(4.1)** (Section 4.3.1), but only starting materials were recovered. It was thought that the α-anion on the propionyl group was not being formed, so harsher conditions were used. The LHMDS/**(4.1)** mixture was allowed to warm to room temperature for thirty minutes before it was re-cooled to –78°C for the addition of methyl iodide. The reaction was monitored by TLC but no reaction was observed and after stirring at room temperature for 24 hours only starting materials were recovered.



Scheme 4.7

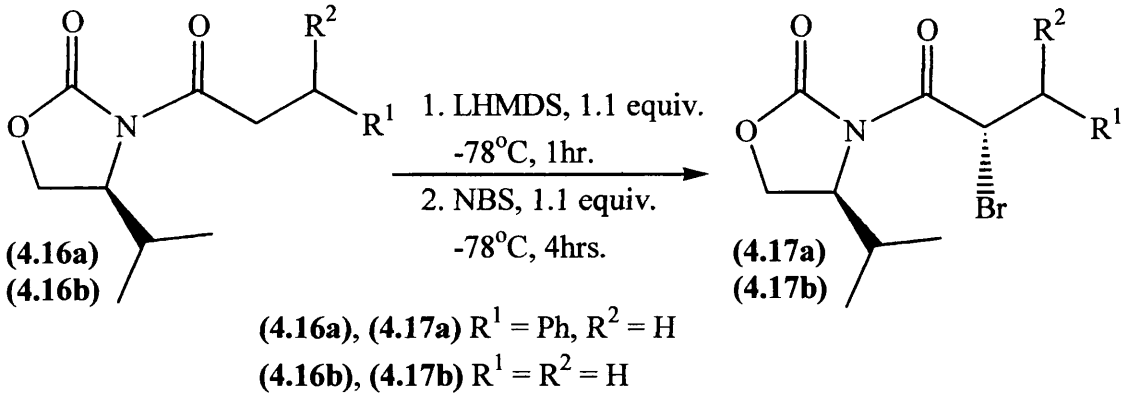
4.4 Attempted Halogenation of Chiral Auxiliary (4.1)

The halogenation of **(4.1)** has not been documented in the literature, but the non-selective α-iodination of **(4.2)** has been demonstrated by Helmchen *et al.*[6] using LDA and 0.5 equivalents of I_2 to form **(4.14)**. However, when more than 0.5 equivalents of I_2 were used an intermolecular oxidative coupling resulted to form dimer **(4.15)** (Scheme 4.8).



Scheme 4.8

The bromination of an oxazolidinone derivative **(4.16)** has been achieved using LHMDS and NBS (Scheme 4.9).[7]

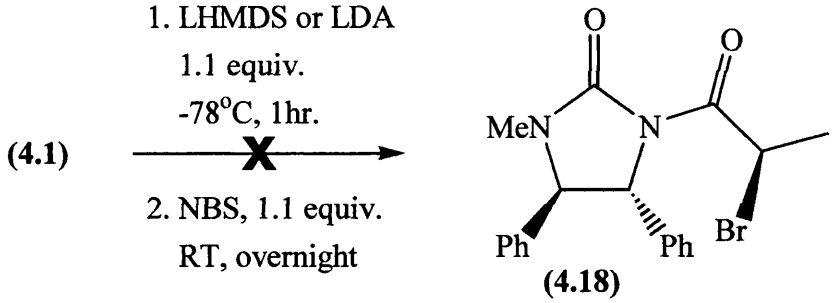


(4.16a), **(4.17a)** R^1 = Ph, R^2 = H

(4.16b), **(4.17b)** $R^1 = R^2$ = H

Scheme 4.9

The preparation of (4*R*,5*R*)-3-(2-bromopropionyl)-4,5-diphenyl-1-methyl-imidazolidinone **(4.18)** was therefore attempted using both LDA and LHMDS with NBS (Scheme 4.10). The various conditions examined are shown in Table 4.5. The reactions were monitored by TLC but no change was observed and after work up only starting materials were recovered.



Scheme 4.10

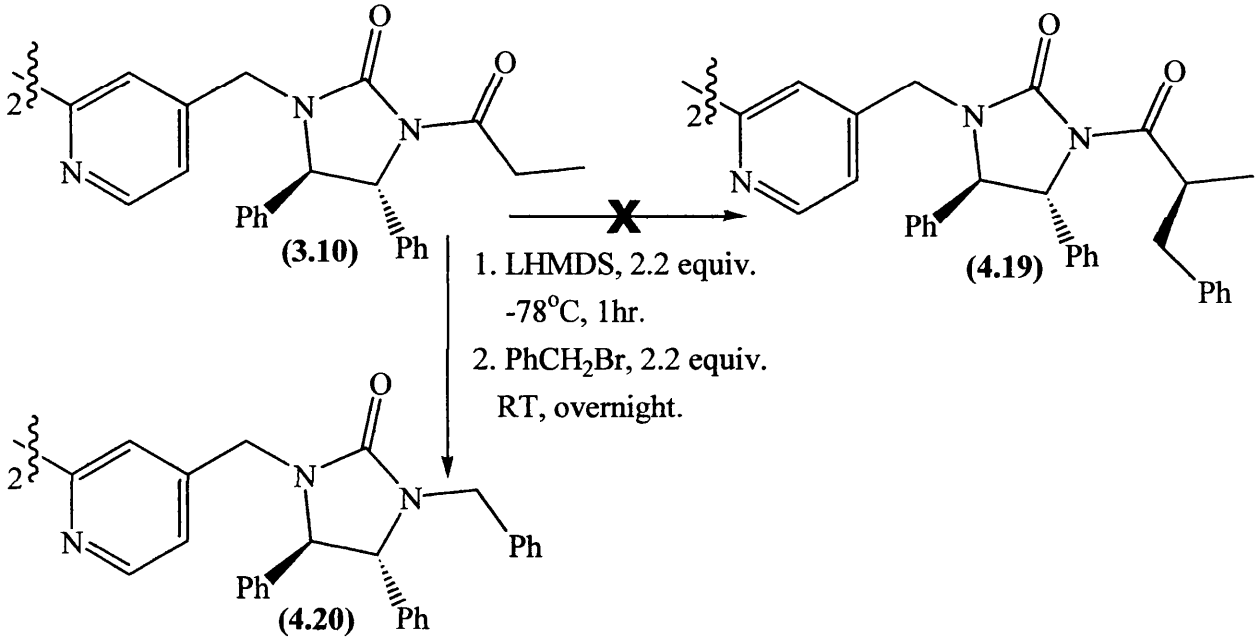
Table 4.5 – conditions examined in the attempted preparation of **(4.18)**

Run	Base	Reaction conditions after addition of **(4.1)**, before addition of NBS	Reaction conditions after addition of NBS	Product
1	LHMDS	-78°C, 1hr	-78°C, 4hrs	**(4.1)**
2	LHMDS	-78°C, 30mins	-78°C, 4hrs, RT overnight	**(4.1)**
3	LHMDS	-78°C, 20mins, 0°C, 20mins, -78°C, 20mins	-78°C, 4hrs, RT overnight	**(4.1)**
4	LDA	-78°C, 1hr	-78°C, 4hrs, RT overnight	**(4.1)**
5	LDA	-78°C, 20mins, 0°C, 20mins, -78°C, 20mins	-78°C, 4hrs, RT overnight	**(4.1)**

4.5 Attempted Alkylation of (3.10)

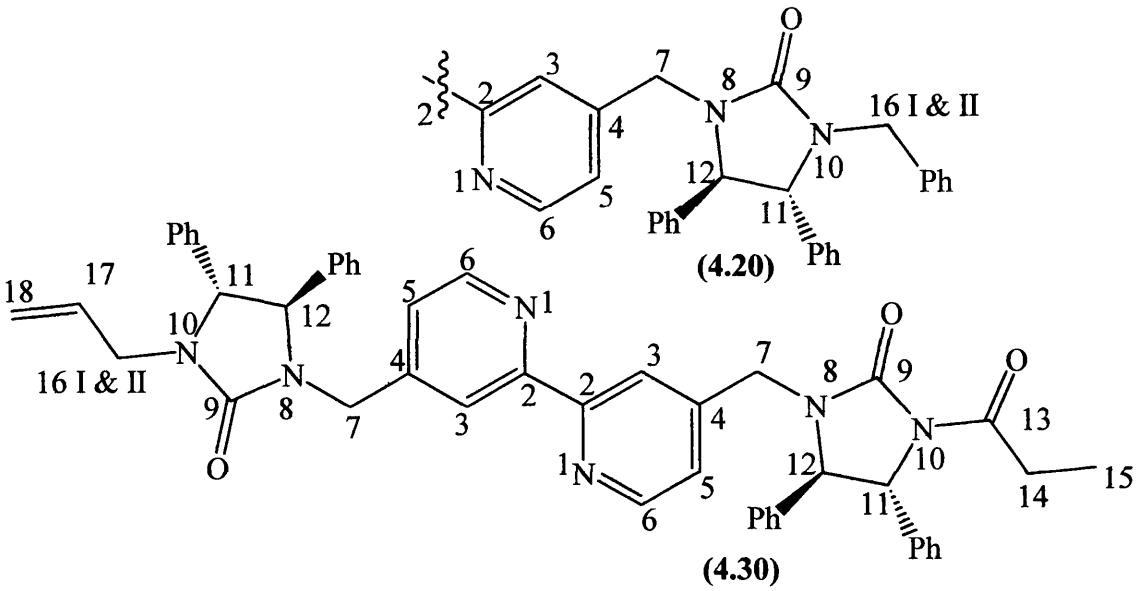
4.5.1 Attempted Benzylation of (3.10)

The preparation of (4*R*,5*R*)-4,4′-*bis*-[1-3-(2-benzylpropionyl)-4,5-diphenyl-imidazolidinonyl]-*N*-methyl-2,2′-bipyridine **(4.19)** was undertaken in an effort to compare the diasteromeric selectivity of the reaction to the benzylation of the untagged auxiliary derivative **(4.1)** (Section 4.3.1). The reaction was attempted using LHMDS and benzyl bromide but the main product of the reaction was identified as **(4.20)**, with the benzyl group attached directly to imidazolidinone ring (Scheme 4.11). This was again thought to be the result of an intramolecular reaction of the α-anion causing cleavage of the propionyl group and subsequent attack by the benzyl electrophile, similar to the reaction shown in Scheme 4.6. Compound **(4.20)** was identified by ^{1}H NMR from the loss of the peaks corresponding to the propionyl groups and by the appearance of two new doublets, which corresponded to the two diastereotopic protons on the benzyl-CH_2 group. The structure was confirmed by ^{13}C NMR and accurate mass spectrometry (see Table 4.6 for ^{1}H NMR data and Table 4.7 for ^{13}C NMR data).



Scheme 4.11

Table 4.6 – ^{1}H NMR spectra of compounds **(4.20)** and **(4.30)**



(4.20)

(4.30)

Chemical Shift [a,b]

Proton no.	(4.20)	(4.30)
3	8.06, 2H, s	8.02, 1H, s, 8.03, 1H, s
6	8.49, 2H, d (4.3)	8.45, 1H, d (5.2), 8.47, 1H, d (4.7)
7I	3.77, 2H, d (16.1)	3.75, 1H, d (15.8), 3.77, 1H, d (15.7)
7II	4.93, 2H, d (16.1)	4.82, 1H, d (15.8), 5.03, 1H, d (15.7)
11*	4.05, 2H, d (7.2)	4.12, 1H, d (7.2), 4.18, 1H, d (7.1)
12*	4.12, 2H, d (7.2)	4.30, 1H, d (7.2), 4.53, 1H, d (7.1)
14	-	3.04, 2H, q (7.3)
15	-	1.16, 3H, t (7.3)
16I	3.62, 2H, d (15.7)	3.19, 1H , dd (6.5, 16.0)
16II	5.01, 2H, d (15.7)	4.18, 1H, d (6.5)
17	-	6.8, 1H, m
18	-	4.89, 2H, d (16.0)
5 & Ph	7.01-7.34, 32H, m	6.99-7.31, 22H, m

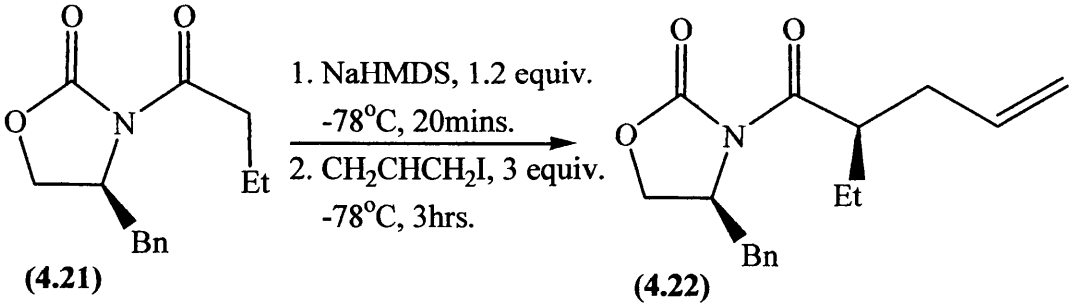
a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constants, Hz) *may be reversed

Table 4.7 – ^{13}C NMR data for compounds **(4.20)** and **(4.30)**

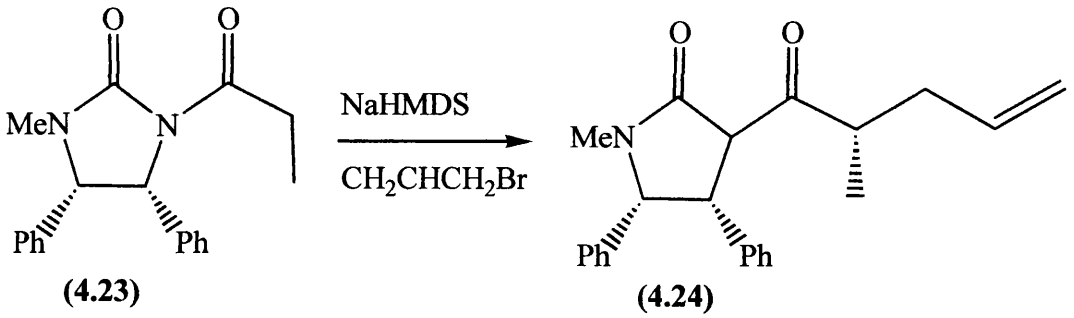
	Chemical Shift [a,b]	
Carbon no.	**(4.20)**	**(4.30)**
2	138.3	156.6,
3	120.7	120.7, 120.8
4	136.8	147.0, 147.2
5	123.30	123.3, 123.4
6	149.8	149.7
7	44.8	44.9, 45.1
9	161.6	160.5, 161.5
11*	63.7	63.7, 67.1
12 *	66.4	67.0, 69.4
13	-	173.9
14	-	29.9
15	-	8.9
16	30.1	30.0
17	-	132.7
18	-	118.9
Ph	130.0, 129.5, 129.3, 129.0, 128.9, 128.8, 128.5, 127.9, 127.6, 126.8, 126.7, 125.7	140.5, 138.8, 138.6, 138.2, 129.5, 129.4, 129.3, 129.3, 129.2, 129.0, 128.8, 128.7, 127.9, 127.7, 126.8, 126.6

a) Spectra run in $CDCl_3$ b) δ values, ppm *may be reversed

The use of NaHMDS as a base in the allylation of a chiral oxazolidinone derivative **(4.21)** has been reported by Evans *et al.*[8] and Maleczka *et al.*[9] adopted the same methodology for the allylation of a chiral imidazolidinone derivative **(4.23)** (Scheme 4.12). In both procedures, the reaction temperatures were kept at -78°C as it has been reported that Na-enolates are less stable at higher temperatures than their corresponding Li-enolates.[10]



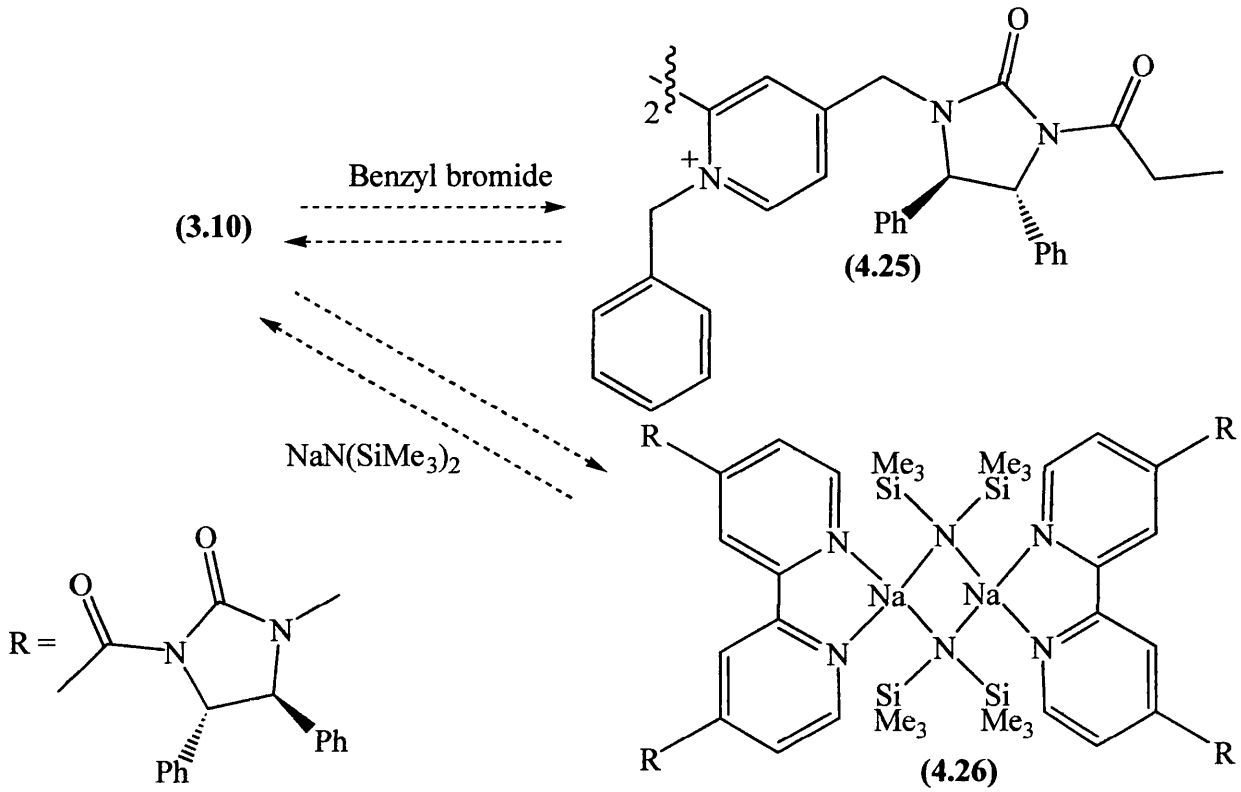
(4.21) **(4.22)**



(4.23) **(4.24)**

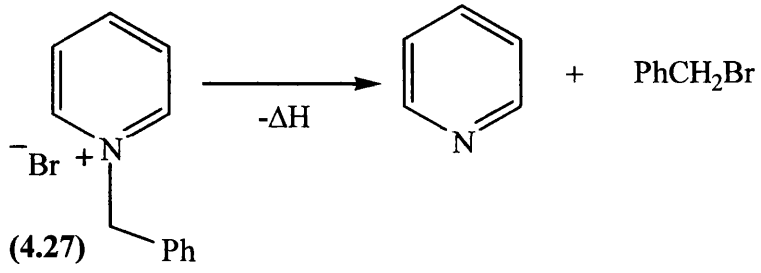
Scheme 4.12

Hence, NaHMDS was employed in the attempted preparation of **(4.19)**. A solution of **(3.10)** was cooled and added slowly to the NaHMDS solution at –78°C. The mixture was stirred for twenty minutes before the slow addition of cooled benzyl bromide. The reaction mixture was stirred at –78°C and monitored by HPLC. After one hour it was observed, by HPLC, that all of the starting material had disappeared and a new compound, less polar than the starting material had been formed. The reaction was quenched and purified by extraction. However, inspection of the ^{1}H NMR revealed only the presence of compound **(3.10)**, which meant the new compound must have decomposed after quenching the reaction, but was apparently stable enough to survive analysis by HPLC. Some consideration of the structure of this new compound was given (Scheme 4.13).



Scheme 4.13

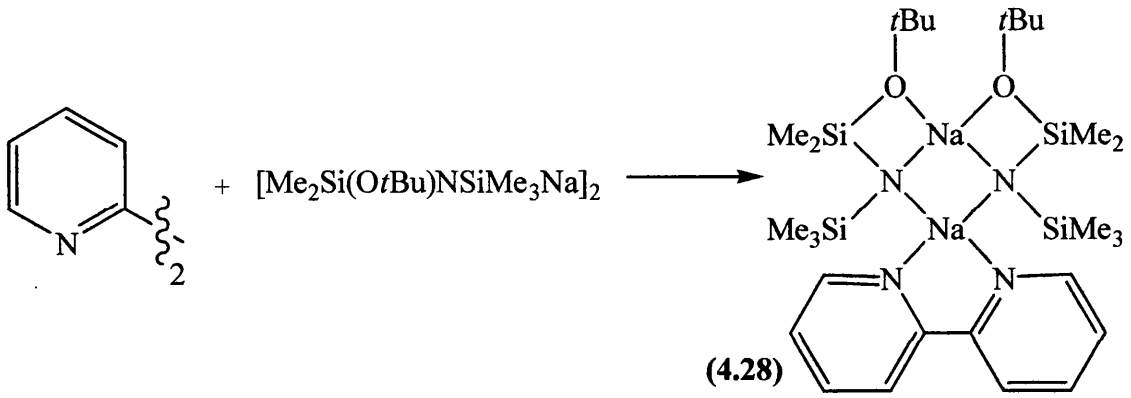
It was speculated that the unidentified compound was the *N,N*-dibenzyl bromine salt **(4.25)**, formed from the reaction of the lone pairs of electrons on the nitrogen atom of pyridine with benzyl bromide. *N*-Benzylpyridinium bromide **(4.27)** has been shown to readily dissociate to pyridine and benzyl bromide,[11] (Scheme 4.14) and therefore could explain the decomposition of the new compound to **(3.10)**.



Scheme 4.14

An alternative explanation is that the lone pairs of electrons on the nitrogen reacted with the NaHMDS to form a compound such as **(4.26)**, similar to the reaction of bipyridine with $[Me_2Si(O\textit{t}\text{-Bu})(NSiMe_3)Na]_2$, which occurs on contact to form an

acid-base complex **(4.28)** (Scheme 4.15).[12] This compound would also be unstable and could dissociate back to **(3.10)**.

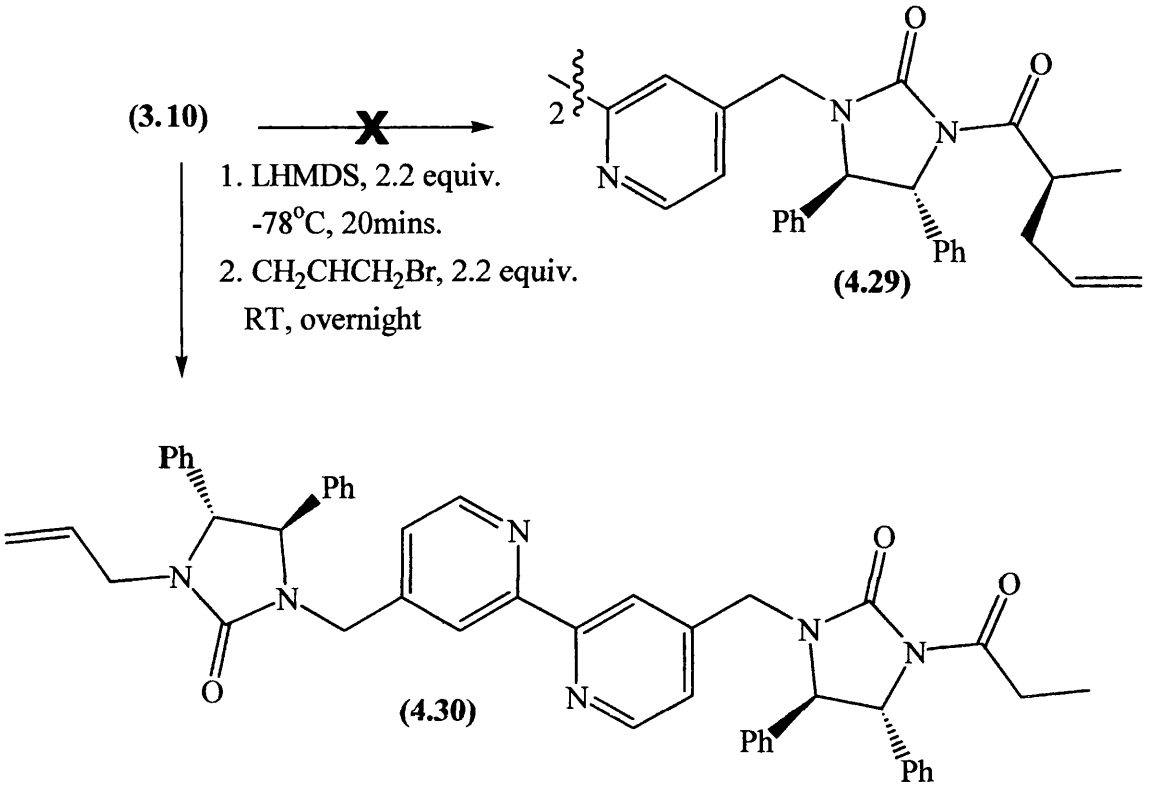


(4.28)

Scheme 4.15

4.5.2 Attempted Allylation of (3.10)

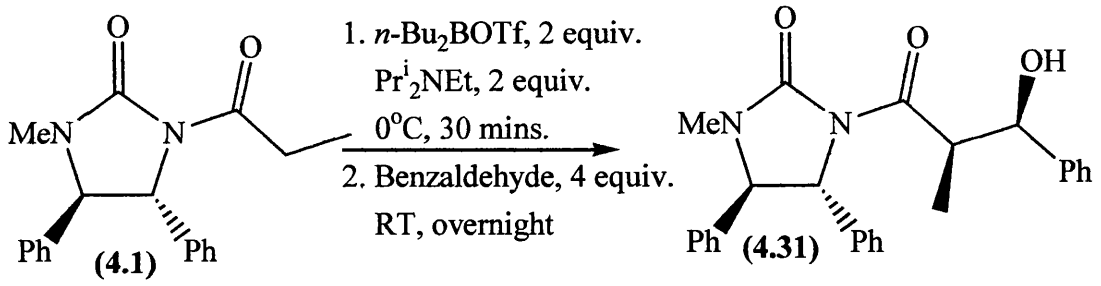
The preparation of (4*R*,5*R*)-4,4′-*bis*-[1-3-(2*S*-allylpropionyl)-4,5-diphenyl-imidazolidinonyl]-*N*-methyl-2,2′-bipyridine **(4.29)** was undertaken using LHMDS and allyl bromide (Scheme 4.16) to see if the same problems occurred as in the unsuccessful allylation of the untagged compound **(4.1)** (Section 4.3.2). Two equivalents of LHMDS were used to account for the two propionyl groups present in compound **(3.10)**. The solution was stirred for twenty minutes at –10°C before addition of excess allyl bromide followed by stirring overnight. The major product isolated after work-up and purification was **(4.30)** in 25% yield. It was identified by ^{1}H NMR, from the presence of peaks corresponding to both an *N*-propionyl group and an *N*-allyl group, which indicated that one of the propionyl groups had been cleaved and replaced by an allyl group, whilst the other propionyl group was unchanged. The structure was confirmed by accurate mass spectrometry and ^{13}C NMR (see Table 4.7 for ^{1}H NMR data and Table 4.8 for ^{13}C NMR data).



Scheme 4.16

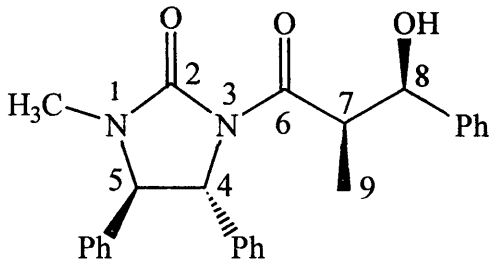
4.6 Aldol Reaction of (4.1)

(4*R*,5*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-1-oxo-3-phenyl-propionyl]-4,5-diphenyl-1-methylimidazolidinone **(4.31)** was prepared using the methodology reported by Sankhavasi *et al.* (Scheme 4.17).[1] The boron enolate of chiral auxiliary derivative **(4.1)** was formed by stirring with *n*-Bu_2BOTf and Pr^i_2NEt at 0°C for thirty minutes. Subsequent addition of excess benzaldehyde at –78°C followed by stirring at room temperature overnight generated the crude product, which was treated with 30% hydrogen peroxide solution to remove the boron moiety. Subsequent extraction produced the aldol product, **(4.31)** in 69% yield. It was identified by ^1H NMR, from the change in the signal of the CH_3 of the propionyl group. In the spectrum of the starting material **(4.1)**, it was present as a triplet at 1.13 ppm but it appeared as a doublet at 1.15 ppm in **(4.31)**. The structure was confirmed by ^{13}C NMR and accurate mass spectrometry (^1H and ^{13}C data are shown in Table 4.9). The ^1H NMR spectrum of the product indicated that only one diastereoisomer was present, which corresponded to the published diastereomeric excess of ≥99%.[1] According to the same reference, **(4.31)** could be assigned as the *syn*-aldol product.



Scheme 4.17

Table 4.8 – ^{1}H and ^{13}C NMR of compound **(4.31)**



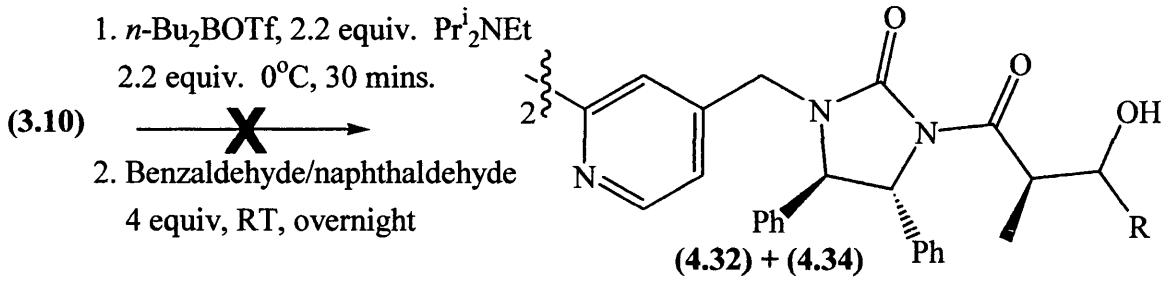
Chemical Shift [a,b]

Proton/carbon no.	**^{1}H**	**^{13}C**
2	-	154.3
4*	4.23, 1H, d (3.7)	63.4
5*	5.02, 1H, d (3.7)	67.2
6	-	177.2
7	4.42, 1H, dq (3.6, 7.2Hz)	44.4
8	5.14, 1H, m	73.3
9	1.15, 3H, d (7.2)	11.0
N-CH_3	2.77, 3H, s	29.1
OH	3.42, 1H, d (2.2)	-
Ph	7.08-7.44, 15H, m	124.9, 126.2, 127.1, 128.3, 129.0, 138.2, 140.4, 141.6

a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constants, Hz) *may be reversed

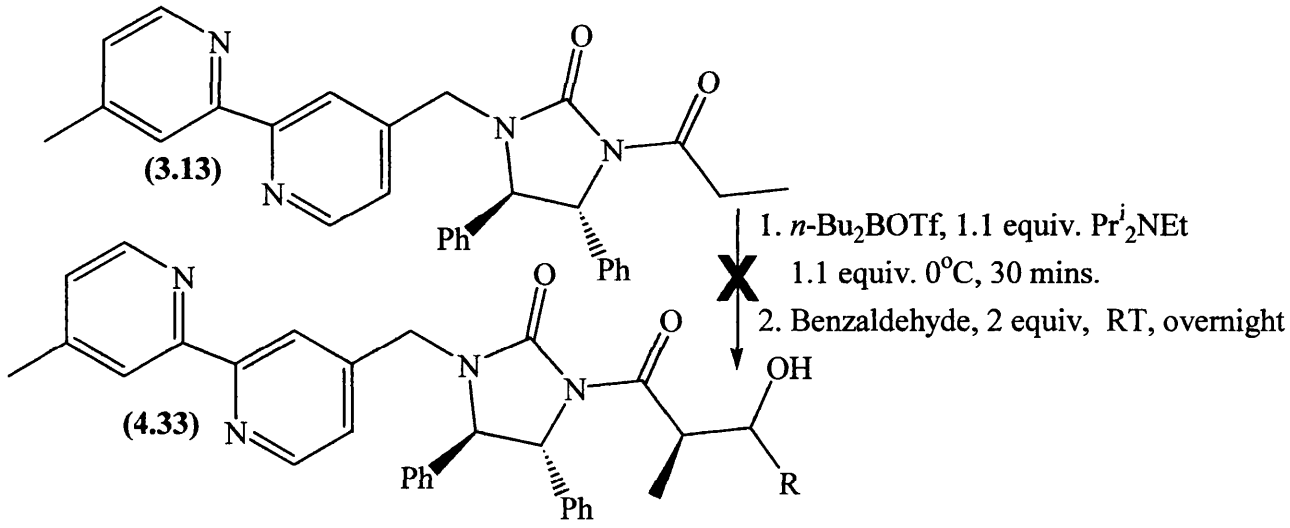
4.7 Attempted Aldol Reaction of (3.10)

Having confirmed that the aldol reaction worked on the model compound without any problems, the reaction was attempted on the tagged auxiliary derivative **(3.10)**, using double the equivalents of *n*-Bu_2BOTf, Pr^i_2NEt and benzaldehyde, to account for the two propionyl groups on **(3.10)** (Scheme 4.18). The reaction conditions were identical those used in Section 4.7. The ^1H and ^{13}C NMR spectra of the crude product were very complicated and became more confused after purification by reverse-phase chromatography, indicating decomposition of the product or products.



Scheme 4.18 **(4.32)** R = Ph **(4.34)** R = 2-Naphthyl

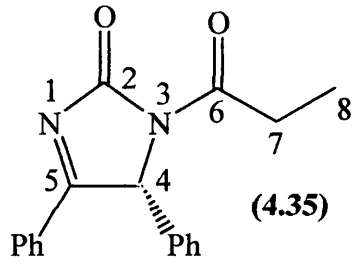
The reaction was repeated on the monosubstituted tagged auxiliary **(3.13)**. It was thought the spectral data of the product might be clearer as the molecule included only one propionyl moiety (Scheme 4.19). However, the only findings were that the bipyridyl part of the molecule could not be found on the ^1H or ^{13}C NMR spectra of the crude product.



Scheme 4.19

It was considered that the H_2O_2 employed in the work-up of the reaction could have broken down the bipyridyl part of the molecule, therefore the reaction was repeated, this time using a different aldehyde (naphthaldehyde) and with the omission of H_2O_2. Half of the reaction was quenched after one hour and the remainder was quenched after seventeen hours. This was done in order to assess if the molecule was breaking down as a result of reaction time. However, this was not found to be the case as the HPLC chromatograms of the two crude products were found to be identical. The compounds were purified by simple extraction into DCM and washing with sodium metabisulphite solution, to remove the excess aldehyde. This was done to eliminate any possibility that the compound was breaking down due to the reverse-phase purification procedure. The HPLC chromatograms of the product showed a new peak at 13.0 minutes.

Table 4.9 – ^{1}H and ^{13}C NMR of compound **(4.35)** and predicted ^{13}C NMR



(4.35)

Chemical Shift [a,b]

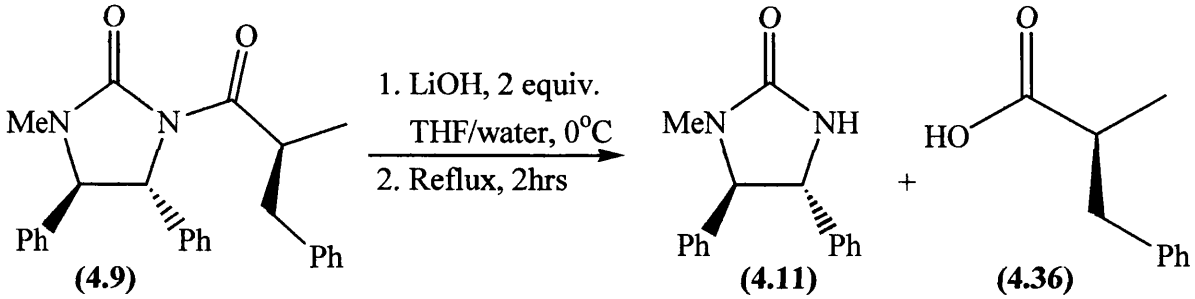
Proton/ Carbon no.	**^{1}H Spectrum**	**^{13}C Spectrum**	**^{13}C Prediction**
2	-	151.4	162.0
4	5.07, 1H, s	61.2	49.7
5	-	123.4	164.6
6	-	172.8	173.7
7	2.92, 2H, q (7.5)	29.0	24.2
8	1.04, 3H, t (7.5)	7.2	9.3
Ph	7.08-7.29, 10H, m	127.8, 128.0, 128.1, 128.2, 128.3, 133.5, 138.5	126.5, 127.1, 128.3, 128.6, 129.0, 130.8, 131.2

a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constants, Hz)

NMR spectra of the crude material revealed that the major product was a fragment of the auxiliary, identified as **(4.35)**, confirmed by comparison to ^{13}C NMR spectrum as predicted by Chemdraw (see Table 4.9 for ^{1}H and ^{13}C NMR data). It was characterised by the large upfield shift of C-5 in the ^{13}C spectrum and from the absence of a peak corresponding to H-5 in the ^{1}H spectrum. It was therefore evident that under the reaction conditions described, compound **(3.10)** was unstable and the bipyridyl part of the molecule was lost.

4.8 Hydrolysis of (4.9)

In order to determine the absolute stereochemical assignment of the alkylation product **(4.9)** it was necessary to cleave the side chain from the auxiliary. This was achieved by hydrolysis using lithium hydroxide in aqueous THF, to yield the auxiliary **(4.11)** (see Table 4.3 for ^{1}H NMR data and Table 4.4 for ^{13}C NMR data) and the carboxylic acid **(4.36)** (Scheme 4.20). Compound **(4.36)** was identified by ^{1}H NMR from the broad singlet at 2.09ppm, which corresponded to the OH group, and the structure was confirmed by ^{13}C NMR. Compound **(4.36)** had a positive specific rotation by polarimetry and was therefore designated the (*S*)-configuration by comparison to the literature.[13] It was consequently assumed that during the reaction a *Z*-enolate was formed (Figure 4.1). The observed stereoselectivity could then be explained by electrophilic attack preferentially from the top (*si*) face, as the bottom (*re*) face was protected by the 4-phenyl group. The enantiomeric excess of 81% was determined by HPLC using a chiral column. As the diastereomeric excess of **(4.9)** was 90%, it was proposed that the cleavage of **(4.36)** occurred without any significant racemization.



(4.9) **(4.11)** **(4.36)**

Scheme 4.20

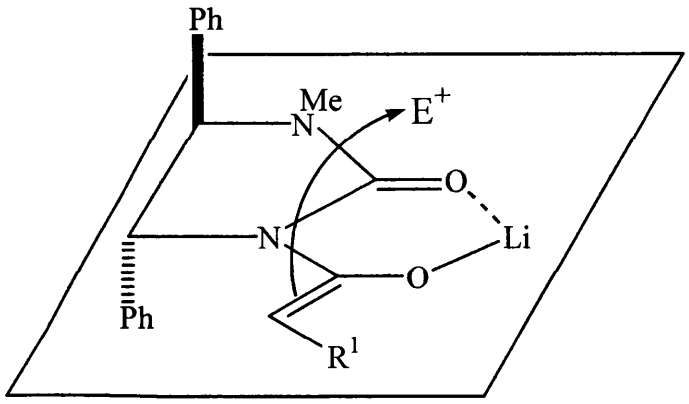


Figure 4.1

4.9 Conclusion

The results presented in this chapter have demonstrated that both the tagged auxilary derivative **(3.10)**, and the untagged auxiliary derivative **(4.1)**, are unstable with respect to the alkylation conditions described. However, it has been shown that it was possible to perform a benzylation reaction on compound **(4.1)** and that the reaction proceeded with high diastereoselectivity, as expected from the structure of the auxiliary. It is therefore realistic to think that other alkylations on both **(4.1)** and **(3.10)** could be possible by finding conditions that enable the α-anion to be stabilised long enough for it to react with the alkyl electrophile. The findings of the investigation also show that the tagged auxiliary derivative **(3.10)** does not undergo aldol reactions, unlike the untagged auxiliary derivative **(4.1)**, due to the instability of the bipyridyl part of the molecule under the reaction conditions described.

4.10 Experimental

Instrumentation

^{1}H NMR spectra were recorded on a Bruker AC spectrometer at 400MHz. ^{13}C NMR spectra were recorded on a Bruker AC spectrometer at 100MHz. All spectra contained a tetramethylsilane internal standard. The mass spectra were recorded on a VG analytical Quattro II triple quadrupole mass spectrometer. The accurate mass measurements were obtained from a Finnigan MAT 900 XL mass spectrometer. Melting points were recorded using an electrothermal IA9100 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR 1725x spectrophotometer. HPLC results were obtained from a Hewlett Packard 1100 series. All retention times stated in the experimental data refer to elution time of compound from a Phenomenex Prodidgy, 15cm, C18 column. The mobile phase was a gradient of 5% acetonitrile (0.1% TFA) increasing to 100% acetonitrile (0.1%TFA) over 11 minutes then held at that concentration. Purification by reverse phase chromatography refers to a mobile phase starting with 50:50 acetonitrile:water and increasing to 80:20 acetonitrile:water using a dry column method described by Harwood[14] and demonstrated by O'Neil.[15]

Reagents

Anhydrous reactions were carried out under an inert atmosphere and used argon or nitrogen from the cylinder passed through H_2SO_4 and $CaCl_2$. THF was dried by stirring overnight over CaH_2 and then distilled from sodium wire and benzophenone. Diisopropylamine, HMDS and $Pr^{i}_{2}NEt$ were dried by distillation from KOH. Solutions of *n*-BuLi in hexane were bought from Aldrich and regularly estimated. Benzyl bromide was fractionally distilled from $MgSO_4$, in the dark, under reduced pressure immediately prior to use. Allyl bromide was dried with $MgSO_4$ and fractionally distilled, and methyl iodide was dried with $CaCl_2$ and distilled. *N*-Bromosuccinimide was purified by recrystallisation from boiling water and dried in a vacuum oven over P_2O_5. Temperatures of –78°C, –10°C and 0°C were obtained from acetone/solid-CO_2, acetone/ice and salt-water/ice baths respectively.

Preparation of (4*R*,5*R*)-4,5-diphenyl-1-methyl-3-propionyl-imidazolidinone (4.1)

$[C_{19}H_{20}N_2O_2]$: F.W. = 308

To a solution of **(3.6)** (0.36g, 1.16mmol) in THF (10ml) at -10°C was added *n*-BuLi (0.95ml, 1.3M, 1.12mmol, 1 mol. equiv.). The solution was stirred at -10°C for 30 minutes before methyl iodide (0.19g, 1.31mmol, 1.5 mol.equiv.) was added dropwise. The solution was stirred until all the starting material had disappeared (about 5 hours). The THF was removed *in vacuo* and the remaining residue was extracted into DCM (2 × 100ml) and dried ($NaSO_4$). Flash chromatography (50: 50 ethyl acetate: hexane) of the crude product afforded **(4.1)** as a colourless gum which was further dried in a desiccator under vacuum with P_2O_5 for two days to form a white solid (0.34g, 92%). Mpt = 64-68°C (lit = 67.5-69.5°C.) Rf = 0.65 (50: 50 ethyl acetate: hexane). ^1H NMR ($CDCl_3$) δ = 1.13 (t, 3H, J = 7.3 Hz, CH_3), 2.79 (s, 3H, N-CH_3), 3.06 (q, 2H, J = 7.3 Hz, CH_2), 4.26 (d, 1H, J = 3.6 Hz, CH) 5.05 (d, 1H, J=3.6 Hz, CH) 7.16-7.43 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$) δ = 8.6, 29.1, 29.4, 63.5, 67.4, 125.4, 126.2, 128.1, 129.0, 129.1, 129.4, 138.6, 141.0, 155.0, 174.0.

General Procedure for the Alkylation of (4.1)

LDA method

To diisopropylamine in dry THF (5ml) at -78°C was added *n*-BuLi dropwise. The solution was stirred at -78°C for 20 minutes, heated to 0°C for 20 minutes then recooled to -78°C before addition of a solution of **(4.1)** in THF (5ml). The solution was stirred at –78°C for a further hour before the electrophile was added. The solution was warmed to room temperature and stirred overnight. The THF was removed *in vacuo* and the remaining residue was extracted into DCM (2 × 100ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product.

LHMDS method

To 4,4,4-hexamethyldisilazane in dry THF (5ml) at -78°C was added *n*-BuLi dropwise. The solution was stirred at -78°C for 20 minutes, heated to 0°C for 20 minutes then re-cooled to -78°C before addition of a solution of **(4.1)** in THF (5ml). The solution was stirred at -78°C for a further hour before the alkyl halide was added. The solution was warmed to room temperature and stirred overnight. The THF was removed *in vacuo* and the remaining residue was extracted into DCM (2 × 100ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product.

Attempted preparation of (4*R*,5*R*)-3-(2*S*-benzylpropionyl)-4,5-diphenyl-1-methyl-imidazolidinone (4.9)

$[C_{26}H_{26}N_2O_2]$: F.W. = 398

The LDA method was used. Diisopropylamine (0.02g, 0.24mmol, 1.2 mol. equiv.), *n*-BuLi (0.20ml, 1.3M, 0.26mmol, 1.2 mol. equiv.), **(4.1)** (0.06g, 0.20mmol) benzyl bromide (0.04g, 0.24mmol, 1.2 mol. equiv.). Afforded **(4.1)** (0.04g, 66%). Confirmed by ^1H NMR.

Preparation of (4*R*,5*R*)-3-(2*S*-benzylpropionyl)-4,5-diphenyl-1-methyl-imidazolidinone (4.9)

$[C_{26}H_{26}N_2O_2]$: F.W. = 398

The LHMDS method was used. 1,1,1-3,3,3-hexamethyldisilazane (0.11g, 0.69mmol, 1.1 mol. equiv.), *n*-BuLi (0.28ml, 2.5M, 0.70mmol, 1.1 equivalents), **(4.1)** (0.19g, 0.63mmol) benzyl bromide (0.43g, 2.5mmol, 1.2 mol. equiv.). Afforded **(4.9)** as a light brown gum (0.05g, 33%) that did not crystallise from common solvents or their mixtures. See Table 4.1 for NMR data. *m/z*: (Ei) 77 (30%), 91 (99%), 132 (37%), 251 (45%). Calculated M+H = 399.2072. Measured M+H = 399.2074.

Attempted Preparation of (4*R*,5*R*)-3-(2*S*-allylpropionyl)-4,5-diphenyl-1-methyl-imidazolidinone (4.10)

$[C_{23}H_{26}N_2O_2]$: F.W. = 362

The LDA method was used. Diisopropylamine (0.04g, 0.42mmol, 1 mol. equiv.), *n*-BuLi (0.20ml, 2.5M, 0.5mmol, 1.2 mol. equiv.), **(4.1)** (0.13g, 0.42mmol), allyl bromide (0.08g, 0.63mmol, 1.5 mol. equiv.). Filtration and concentration produced **(4.11)** as a colourless gum (0.08g, 79%). See Table 4.3 for ^{1}H NMR data and Table 4.4 for ^{13}C NMR data.

Attempted preparation of (4*R*,5*R*)-3-(2*S*-allylpropionyl)-4,5-diphenyl-1-methyl-imidazolidinone (4.10)

$[C_{23}H_{26}N_2O_2]$: F.W. = 362

The LHMDS method was used. 1,1,1-3,3,3-hexamethyldisilazane (0.09g, 0.56mmol, 1 mol. equiv.), *n*-BuLi (0.20ml, 2.5M, 0.51mmol, 1 mol. equiv.), **(4.1)** (0.16g, 0.52mmol), allyl bromide (0.24g, 2.02mmol, 4 mol. equiv.). The product was produced as a green gum and identified as **(4.12)** (52%). See Table 4.3 for ^{1}H NMR data and Table 4.4 for ^{13}C NMR data. *m/z*: (ei) 77 (98%), 91 (78%), 118, (89%), 132 (99%). Calculated M+H (293.1654). Measured M+H (293.1650).

Attempted preparation of (4*R*,5*R*)-4,5-diphenyl-3-(2-methylpropionyl)-1-methyl-imidazolidinone (4.13)

$[C_{21}H_{24}N_2O_2]$: F.W. = 336

The LHMDS method was used. 1,1,1-3,3,3-hexamethyldisilazane (0.07g, 0.33mmol, 1 mol. equiv.), *n*-BuLi (0.15ml, 2.5M, 0.37mmol, 1 mol. equiv.), **(4.1)** (0.10g, 0.32mmol), methyl iodide (0.10g, 0.49mmol, 5 mol. equiv.). Afforded **(4.1)** (0.06g, 59%). Confirmed by ^{1}H NMR.

Attempted preparation of (4*R*,5*R*)-3-(2*S*-bromo-propionyl)-4,5-diphenyl-1-methyl-imidazolidinone (4.18)

$[C_{20}H_{21}N_2O_2Br]$: F.W. = 401

The LHMDS method was used. 1,1,1-3,3,3-hexamethyldisilazane (0.06g, 0.32mmol, 1.1 equivalent), *n*-BuLi (0.15ml, 2.5M, 0.33mmol, 1.1 equivalent), **(4.1)** (0.12g, 0.32mmol) The reaction mixture was transferred via cannula, to a stirred solution of NBS (0.06g, 0.32mmol, 1.1 equivalents) in THF (10ml) at -78°C. The resulting yellow solution was stirred at -78°C for 4 hours, then quenched with 0.5M aq.$NaHCO_3$ (5ml). The THF was removed *in vacuo* and the remaining residue was extracted into dichloromethane (2 × 100ml), washed with $Na_2S_2O_3$ (0.5M, 2 × 10ml), sat. NaCl (aq) (20ml) and dried ($MgSO_4$). Afforded **(4.1)** (0.08g, 66%). Confirmed by ^1H NMR.

Attempted Preparation of (4*R*,5*R*)-4,4′-*bis*-[1-3-(2*S*-benzylpropionyl)-4,5-diphenyl-imidazolidinonyl]-*N*-methyl-2,2′-bipyridine (4.19)

$[C_{60}H_{58}N_6O_4]$: F.W. = 927

The LHMDS method was used. 1,1,1-3,3,3-hexamethyldisilazane (0.06g, 0.40mmol, 2.2 mol. equiv.) was added as 1ml of a solution of HMDS (0.75ml) in THF (9.25ml), *n*-BuLi (0.22ml, 1.8M, 0.40mmol, 2.2 mol. equiv.), **(3.10)** (0.14g, 0.182mmol) benzyl bromide (0.18g, 1.02mmol, 8 mol. equiv.). Produced a yellow gum identified as **(4.20)** (0.11g, 73%). See Table 4.6 for ^1H NMR data and Table 4.7 for ^{13}C NMR data. Retention time = 12.9 mins. *m/z*: (ci) 108 (31%), 132 (27%), 329, (99%), 837 (52%). Calculated M+H = 837.3917. Measured M+H = 837.3909

Attempted Preparation of (4*R*,5*R*)-4,4′-*bis*-[1-3-(2*S*-benzylpropionyl)-4,5-diphenyl-imidazolidinonyl]-*N*-methyl-2,2'bipyridine (4.19)

$[C_{60}H_{58}N_6O_4]$: F.W. = 927

NaH (60% suspension in mineral oil) (0.01g, 0.34mmol 2.2 mol. equiv.) was washed with dry petroleum spirit (3 × 1ml) and dried under a stream of nitrogen before THF (1ml) was added. The mixture was cooled to -78°C and 1,1,1-3,3,3-

hexamethyldisilazane (0.05g, 0.33mmol, 2.2 mol. equiv.) was added as 1ml of a solution of HMDS (0.7ml) in THF (9.3ml) at -78°C. The mixture was stirred at -78°C for 10 minutes before a cooled solution of **(3.10)** (0.12g, 0.16mmol) in THF (2ml) was slowly added dropwise. The mixture was stirred at -78°C for a further 30 minutes before benzyl bromide (0.19g, 1.09mmol, 7 mol. equiv.) was added slowly. The mixture was stirred for 1 hour at -78°C before quenching with sat. NH_4Cl (aq) (5ml). The THF was removed *in vacuo* and the mixture was extracted into diethylether (3 × 10ml), concentrated and dried *in vacuo* over P_2O_5. Retention time of product = 14.8mins. The compound decomposed overnight to **(3.10)**, (0.06g, 50%) confirmed by NMR and HPLC.

Attempted Preparation of (4*R*,5*R*)-4,4′-*bis*-[1-3-(2*S*-allylpropionyl)-4,5-diphenyl-imidazolidinonyl]-*N*-methyl-2,2′-bipyridine (4.29)

$[C_{54}H_{54}N_6O_4]$: F.W. = 850

The LHMDS method was used. 1,1,1-3,3,3-hexamethyldisilazane (0.06g, 0.37mmol, 2.2 mol. equiv.), added as a 1ml solution of HMDS (0.8ml) in THF (9.2ml), *n*-BuLi (0.15ml, 2.5M, 0.37mmol, 2.2 mol. equiv.), **(3.10)** (0.13g, 0.17mmol) allyl bromide (0.16g, 1.323mmol, 8 mol. equiv.). Produced a yellow gum identified as **(4.30)** (0.11g, 85%). See Table 4.6 for ^1H NMR data and Table 4.7 for ^{13}C NMR data. Retention time = 10.2mins. Calculated M+H = 752.3475. Measured M+H = 752.3483.

Preparation of (4*R*,5*R*)-3-[(2*R*,3*R*)-3-hydroxy-2-methyl-1-oxo-3-phenyl-propionyl]-4,5-diphenyl-1-methyl-imidazolidinone (4.31)[1]

$[C_{26}H_{26}N_2O_3]$: F.W. = 414

To a solution of **(4.1)** (0.10g, 0.32mmol) in DCM (3ml) at 0°C was added *n*-Bu_2BOTf (0.35ml, 1M, 0.35mmol, 1.1 mol. equiv.) and Pr^i_2NEt (0.05g, 0.39mmol, 1.2 mol. equiv.). The mixture was stirred at 0°C for 30 minutes before cooling to –78°C and subsequent addition of a solution of benzaldehyde (0.68g, 0.64mmol, 2 mol. equiv.) in DCM (3ml). The mixture was stirred at –78°C for 2 hours then overnight at room

temperature. The reaction was quenched with water (5ml) and the DCM was removed *in vacuo*. The crude product was extracted into diethylether (3 × 30ml) and concentrated *in vacuo*. The residue was dissolved into methanol (3ml) and cooled to 0°C before addition of 30% H_2O_2 (1ml). The mixture was stirred at 0°C for 1 hour before quenching with water (10ml). The methanol was removed *in vacuo* and the mixture was extracted into diethylether (3 × 30ml), washed with sat. $NaHCO_3$ (aq) (50ml) and brine (50ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford **(4.31)** as colourless glass, (0.093g, 69%). See Table 4.8 for ^1H and ^{13}C NMR data.

Attempted Preparation of (4*R*,5*R*)-4,4′-*bis*-[1-3-((2*R*,3*R*)-3-hydroxy-2-methyl-1-oxo-3-phenyl-propionyl)-4,5-diphenyl-imidazolidinonyl]-*N*-methyl-2,2′-bipyridine (4.32)

$[C_{62}H_{56}N_6O_6]$: F.W. = 980

As the preparation of **(4.31)** only using **(3.10)** as the starting material. **(3.10)** (0.06g, 0.08mmol), *n*-Bu_2BOTf (0.20ml, 1M, 0.20mmol, 2.5 mol. equiv.), Pr^i_2NEt (0.02g, 0.19mmol, 2.4 mol. equiv.), benzaldehyde (0.03g, 0.31mmol, 4 mol. equiv.). Afforded 0.34g of crude products unidentifiable by ^1H or ^{13}C NMR. Separation by reverse-phase chromatography did not afford any pure products.

Attempted Preparation of (4*R*,5*R*)-4-[1-3-((2*R*,3*R*)-3-hydroxy-2-methyl-1-oxo-3-phenyl-propionyl)-4,5-diphenyl-imidazolidinonyl]-*N*-methyl-4-methyl-2,2′-bipyridine (4.33)

$[C_{37}H_{34}N_4O_3]$: F.W. = 582

As the preparation of **(4.32)** only using **(3.13)**. **(3.13)** (0.06g, 0.13mmol) in dry DCM (1.25ml), *n*-Bu_2BOTf (0.14mmol, 1.1 mol. equiv.) added as 2ml of a solution of *n*-Bu_2BOTf (0.7ml, 1M) in DCM (9.3ml), Pr^i_2NEt (0.14mmol, 1.1 mol. equiv.) added as 0.3ml of a solution of Pr^i_2NEt (0.57ml) in DCM (9.43ml). Benzaldehyde (0.03g, 0.25mmol, 2 mol. equiv.) in dry DCM (2ml). Afforded 0.03g of crude products unidentifiable by ^1H or ^{13}C NMR.

Attempted Preparation of (4*R*,5*R*)-4,4′-*bis*-[1-3-((2*R*,3*R*)-3-hydroxy-2-methyl-3-(2-naphthyl)-1-oxo-propionyl)-4,5-diphenyl-imidazolidinonyl]-*N*-methyl-4-methyl-2,2′-bipyridine (4.34)

$[C_{70}H_{60}N_6O_6]$: F.W. = 1060

As the preparation of **(4.32)** only using naphthaldehyde and a different work-up proceedure. **(3.10)** (0.29g, 0.38mmol) in dry DCM (1.25ml), *n*-Bu_2BOTf (0.85ml, 1M, 0.85mmol, 2.2 mol. equiv.), Pr^i_2NEt (0.12g, 0.91mmol, 2.4 mol. equiv.), naphthaldehyde (0.23g, 1.51mmol, 4 mol. equiv.) in dry DCM (2ml). After 1 hour at room temperature 2ml of the reaction mixture was taken by syringe and quenched with water (5ml). The rest of the reaction mixture was quenched after 17 hours at room temperature with water (5ml). HPLC chromatagrams of the mixtures were identical therefore the mixtures were combined, extracted into DCM (2 × 30ml), washed sequentially with $Na_2S_2O_4$ (aq) (10ml) and water (10ml), concentrated and dried over P_2O_5 *in vacuo* to afford 0.10g of a mixture of naphthaldehyde and **(4.35)**. See Table 4.9 for ^1H and ^{13}C NMR data.

Preparation of (*S*)-3-phenylpropionoic acid (4.36)

$[C_{10}H_{12}O_2]$: F.W. = 164

To a solution of **(4.9)** (0.04g, 0.08mmol) in THF (2ml) at 0°C was added a solution of LiOH (0.1g, 0.17mmol, 2 mol. equiv.) in THF (4ml) and water (1ml). The mixture was stirred at room temperature for 2 hours before refluxing overnight. The mixture was then allowed to cool to room temperature and the THF was removed *in vacuo*. The resulting residue was extracted into DCM (60ml) and washed with water (2 × 60ml). The DCM layer was concentrated *in vacuo* and dried over P_2Cl_5 *in vacuo* to afford **(4.11)** as a white solid (0.02g, 80%). M.pt. = 213-215°C (lit[16] =214-215°C). Rf = 0.53 (50:50 DCM : Pet.ether 40-60° b.pt. fraction). See table 4.3 for ^1H NMR data and Table 4.4 for ^{13}C NMR data. Calculated M+H = 253.1341. Measured M+H = 253.1339. The water layer was acidified with concentrated HCl (3ml) and extracted into DCM (3 × 60ml). The organic layer was concentrated *in vacuo* and dried over P_2O_5 *in vacuo* to afford **(4.36)** as a light brown gum (0.01g, 88%) that did not crystallize from common solvents or their mixtures. Rf = 0.89. ^1H NMR ($CDCl_3$) δ =

1.10 (d, 3H, J = 6.8Hz, CH_3), 2.09 (br, s, 1H, OH), 2.59 (dd, 1H, J = 7.8 Hz and 13.4 Hz, CHH), 2.71 (m, 1H, CH), 3.02 (dd, 1H, J = 6.2 Hz and 13.3 Hz, CHH), 7.10-7.32 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$) δ = 14.4, 39.3, 41.2, 126.3, 127.6, 128.4, 129.0, 175.1 $[\alpha]_D^{27}$ = +20.9 (c 0.002,$CHCl_3$) (lit[17] = +28.6 (c 1.0, $CHCl_3$). Enantiomeric excess = 81% determined using a Dailcel Chiralcel OJ column with acetonitrile mobile phase detecting at 254nm.

4.11 References

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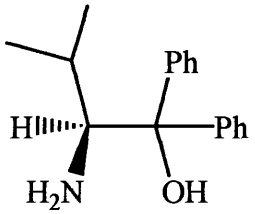
Chapter Five

The Selective Immobilisation of an Oxazaborolidine Catalyst

5.1 Introduction to the Reduction of Ketones with Oxazaborolidine Catalysts

Until the early 1980's, attempts at combining boron hydrides with chiral ligands to achieve efficient asymmetric reductions of carbonyl groups had proved disappointing. However, in 1983 Itsuno *et al.*[1] reported the reduction of aromatic ketones by use of borane and a chiral 1,2-amino alcohol **(5.1)**. They reported high selectivities when a 1:2 ratio of **(5.1)**:borane was used (Table 5.1). When a 1:1 ratio of **(5.1)**:borane was used (run 5) the selectivity was low. The results showed that (*S*)-**(5.1)** gave the (*R*)-alcohol whereas *R*-**(5.1)** gave the (*S*)-alcohol.



(5.1)

Table 5.1 - Asymmetric reduction of aromatic ketones with the reagent prepared from **(5.1)** and borane in THF at 30°C for 2 hours

			Alcohol Produced	
Run	**Aminoalcohol**	**Ketone**	**Optical Yield**	**Configuration**
1	(*S*)-**(5.1)**	MeCOPh	94	(*R*)
2	(*S*)-**(5.1)**	EtCOPh	94	(R)
3	(*S*)-**(5.1)**	Pr^nCOPh	96	(*R*)
4	(*S*)-**(5.1)**	Pr^nCOPh	95	(*R*)
5	(*S*)-**(5.1)**	Pr^nCOPh[a]	6.6	(*R*)
6	(*R*)-**(5.1)**	Pr^nCOPh	91	(*S*)
7	(*S*)-**(5.1)**	Bu^nCOPh	100	(*R*)

[a]Ratio of **(5.1)**:borane was 1:1

Itsuno then extended his research to include reduction of aliphatic ketones with (*S*)-**(5.1)** and borane with good enantioselectivity[2] (Table 5.2). The results showed that the selectivity increases with the steric bulk of the ketone. The optical yields of the straight chain alcohols (runs 1-3) are lower than those with a branched alkyl chain (runs 4 and 5) which are lower than the optical yields of the tertiary-butyl alcohols

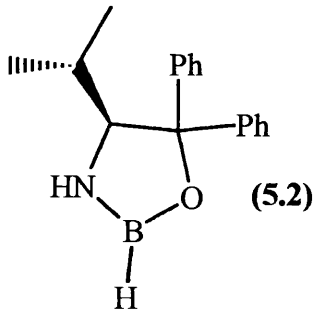
(runs 6 and 7). A higher enantioselectivity was shown to be achieved by lowering the reaction temperature from 30°C to 0°C (run 7).

Table 5.2 - Asymmetric reduction of aliphatic ketones with the reagent prepared from **(5.1)** and borane in THF at 30°C for 2 hours

			Alcohol Produced	
Run	**Aminoalcohol**	**Ketone**	**Optical Yield**	**Configuration**
1	*S*-**(5.1)**	$Me(CH_2)_3COMe$	55	(*R*)
2	*S*-**(5.1)**	$Me(CH_2)_4COMe$	56	(*R*)
3	*S*-**(5.1)**	$Me(CH_2)_5COMe$	58	(*R*)
4	*S*-**(5.1)**	$(Me)_2CHCOMe$	60	(*R*)
5	*S*-**(5.1)**	$(Me)_2CHCH_2COMe$	61	(*R*)
6	*S*-**(5.1)**	$(Me)_3CCOMe$	73	(*R*)
7	*S*-**(5.1)**	$(Me)_3CCOMe$[a]	78	(*R*)

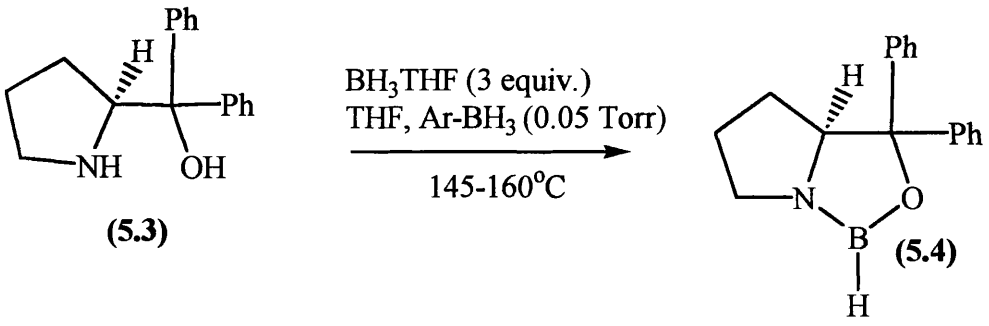
[a]Reaction carried out at 0°C

The structure of the product of **(5.1)** and borane was determined by Corey, Bakshi and Shibatta[3] using ^1H and ^{11}B NMR and mass spectrometry as an oxazoborolidine **(5.2)** and hence this reaction is sometimes known as the CBS reaction.



(5.2)

They also discovered that a catalytic amount of **(5.2)** (0.025-0.1 equivalents) and 1.2 equivalents of borane could reduce acetophenone to (*R*)-1-phenylethanol with 95% e.e. Corey *et al.*[3] then reported that oxazaborolidine **(5.4)** prepared from (*S*)-diphenylprolinol **(5.3)** (Scheme 5.1) was found to be an effective catalyst for the reduction of tertiary aliphatic and aromatic ketones in substoichiometric amounts (Table 5.3).

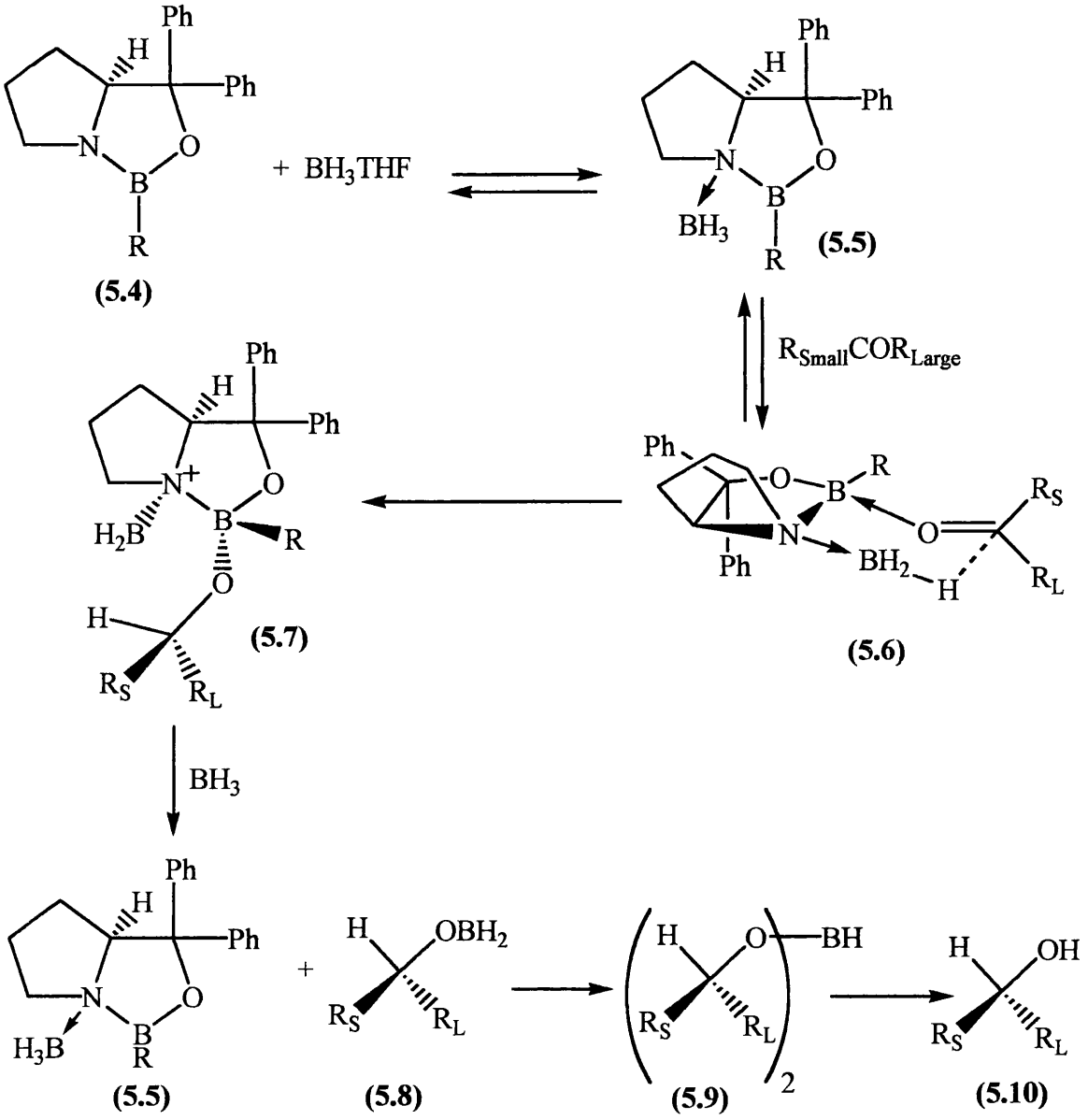


Scheme 5.1

Table 5.3 – (*S*)-**(5.4)** catalysed borane reduction of ketones

			Alcohol Produced	
Run	**Ketone**	**Equiv. BH_3**	**% ee**	**Configuration**
1	PhCOMe	2	97	(*R*)
2	PhCOMe	1	97	(*R*)
3	PhCOMe	1.2	95	(*R*)
4	PhCOMe	1.2	80	(*R*)
5	PhCOEt	1.2	86	(*R*)
6	PhCOEt	1	88	(*R*)
7	PhCOEt	0.6	90	(*R*)
8	t-BuCOMe	1	81	(*R*)
9	t-BuCOMe	0.6	88	(*R*)
10	t-BuCOMe	0.6	92	(*R*)

Corey *et al.*[4] proposed a mechanism for the enantioselective reductions. The ^{11}B NMR spectrum of a mixture of **(5.4)** and BH_3THF clearly indicated a 1:1 complex **(5.5)**. This strongly Lewis acidic complex readily binds to the ketone in an orientation which avoids unfavourable steric interactions **(5.6)**. A face-selective hydride transfer *via* a six membered transition state then occurs to form **(5.7)**, which subsequently dissociates to regenerate **(5.5)** and form the borinate **(5.8)**, which subsequently forms the chiral alcohol **(5.10)** (Scheme 5.2).

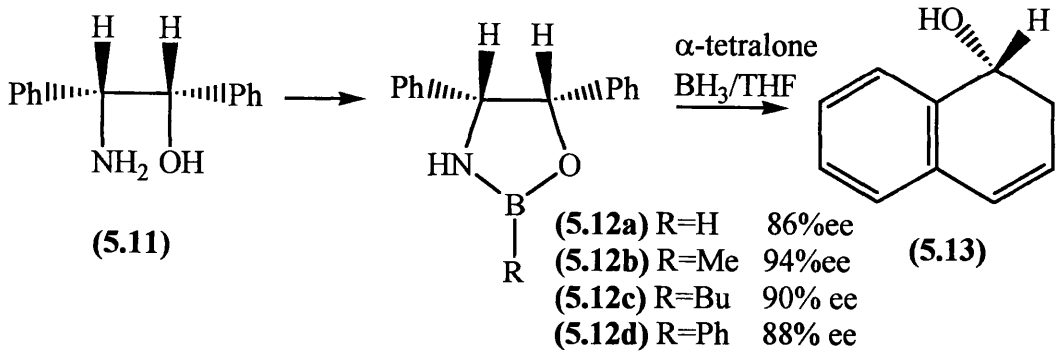


Scheme 5.2

This mechanism explains the effectiveness of catalyst **(5.4)**: -The rigid ring system of **(5.4)** means only co-ordination of BH_3 to the Lewis basic nitrogen atom below the plane is energetically favourable which in turn determines the positioning of the ketone so the unwanted enantiomer is not produced. -The co-ordination of BH_3 to the nitrogen atom intensifies the Lewis acidity of the boron atom in the heterocyclic ring. This facilitates co-ordination to the ketone and the subsequent hydride transfer, thus increasing the reaction rate.

Quallich *et al.*[5] proposed that an oxazoborolidine catalyst with one of its faces completely blocked would produce high enantioselectivities in prochiral ketone

reductions. To this end they produced catalyst **(5.12a)** prepared from (1*R*,2*S*)-2-amino-1,2-diphenylethanol **(5.11)** and trimethylboroxine which produced good results in the enantioselective reduction of tetralone (94% e.e) (Scheme 5.3). Further investigation into the optimal substituent on the heterocyclic boron atom was then carried out by reducing tetralone with catalysts **(5.12b-d)**.



Scheme 5.3

The best results were obtained from the *B*-methyl catalyst **(5.12b)** and it was proposed that this was due to an interaction between the methyl group and the small substituent on the ketone (see Figure 5.1)

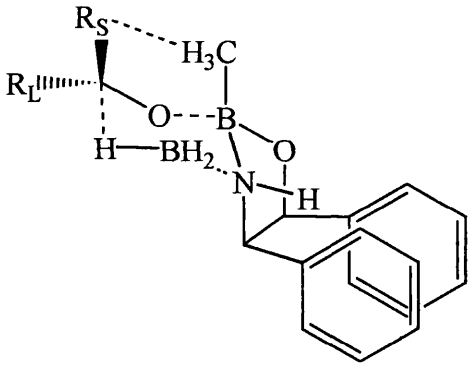
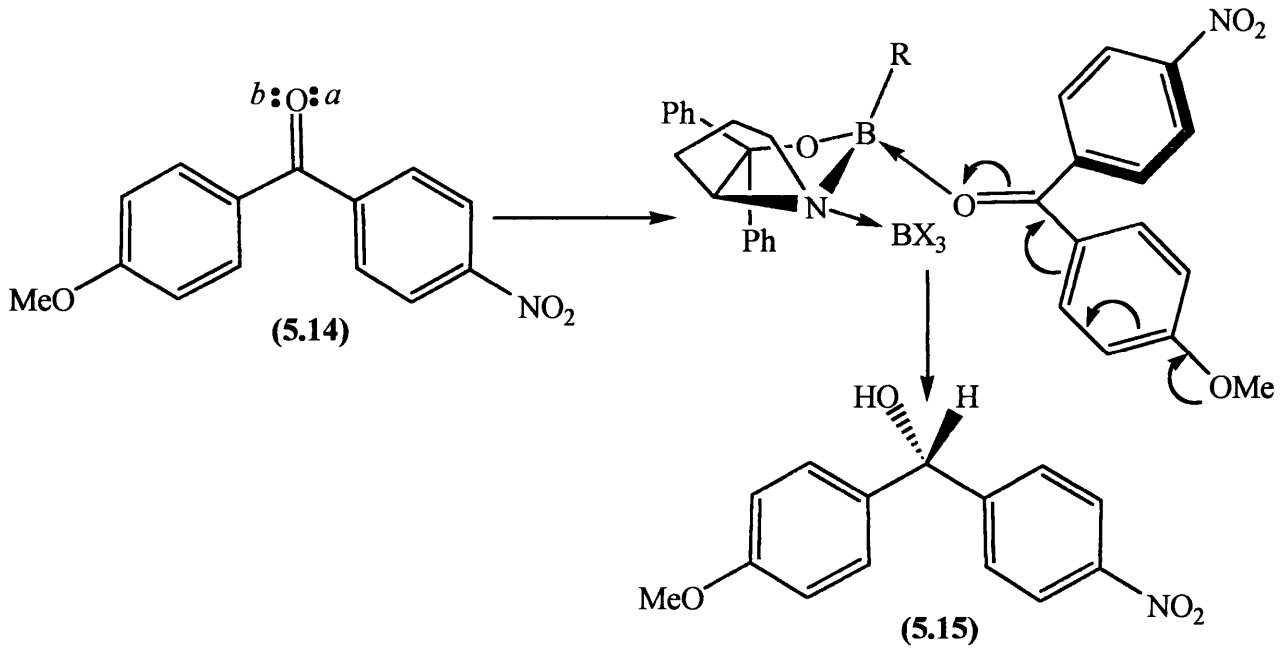


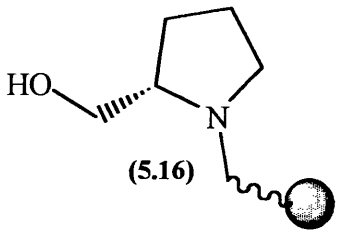
Figure 5.1 showing one face of the catalyst blocked by the phenyl groups and the possible interaction between the boron-methyl group and the small ketone substituent.

Corey *et al.*[6] proposed that the electronic effect of the remote ketone substituent could dictate the diastereoselectivity. The idea was illustrated using ketone **(5.14)**. They predicted that co-ordination of BX_3 would occur more strongly at lone pair *a* since the resulting complex with catalyst **(5.4)** allows maximum π-electron donation from the *p*-methoxyphenyl group to the electron deficient carbonyl carbon. The prediction was confirmed by the production of the (*R*)-alcohol **(5.15)** with 81% e.e (Scheme 5.4)



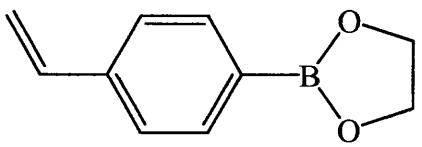
Scheme 5.4

The introduction of oxazoborolidine catalysts into solid phase methodology has been investigated. Itsuno *et al.* reported the asymmetric reduction of ketones using polymer bound (*S*)-prolinol **(5.16)** and borane.[7] They reported enantioselectivity comparable with the unbound reagent and easy separation of optically active reagent by filtration.



(5.16)

Wulff *et al.*[8] have investigated the use of soluble polymer supported oxazoborolidines by utilizing microgels as the catalyst carriers. The copolymerisation of the boronic acid **(5.17)** with styrene and divinylbenzene in low concentrations yields a stable solution of polymer. The addition of diphenylpropinol **(5.3)** afforded the polymer-bound oxazaborolidine analogue of **(5.4)**. The catalyst was employed in the enantioselective reduction of acetophenone with BH_3DMS to produce the (*R*) alcohol with 88% e.e.

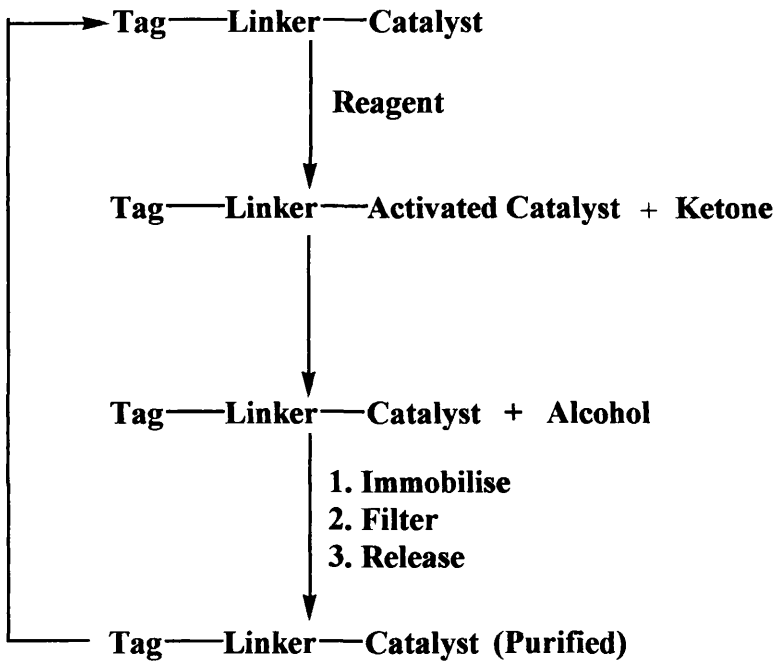


(5.17)

5.2 The Selective Immobilisation Approach to Oxazaborolidine Catalysed Reduction of Ketones

The selective immobilisation of an oxazaborolidine catalyst was undertaken in order to demonstrate the potential diversity of the approach. It was envisioned that tagging a chiral catalyst with a bipyridine molecule would enable isolation of the tagged catalyst by interaction with a resin bound transition metal upon completion of the solution phase reaction.

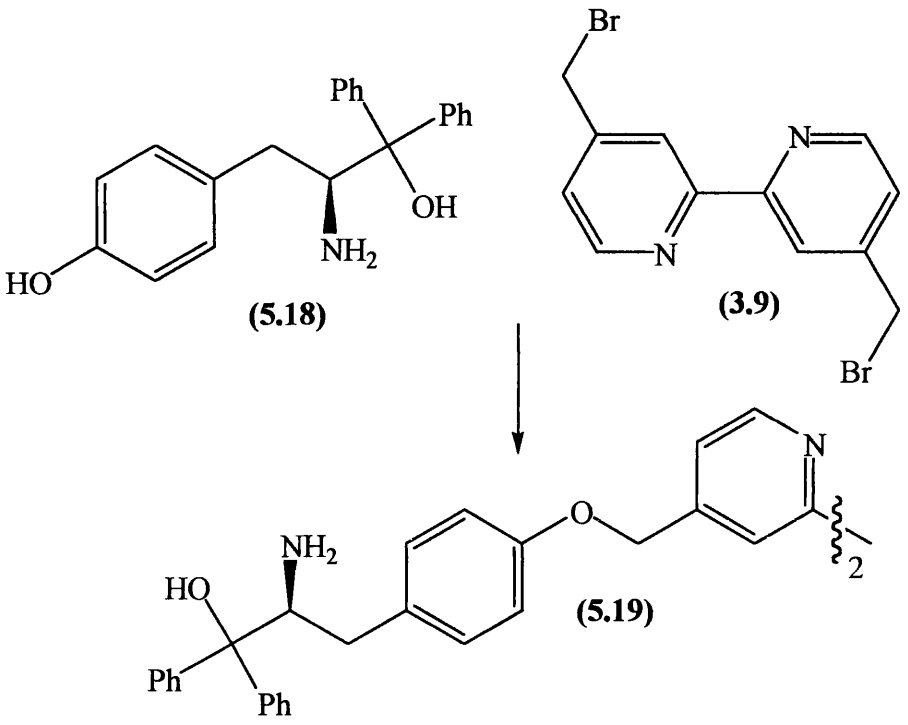
Scheme 5.5 shows the outline of the selective immobilisation approach. The tagged catalyst is activated and employed in the solution phase reduction of a ketone. Cu^{2+} chelated resin is then added to the reaction mixture in order to immobilise the chiral catalyst through a reversible non-covalent interaction between the tag and the Cu^{2+} ions. The reaction mixture is then filtered to isolate the alcohol in the filtrate. Treatment of the immobilised catalyst with ethylene diamine would cleave the linkage allowing the chiral catalyst to be recovered by filtration and recycled.



Scheme 5.5

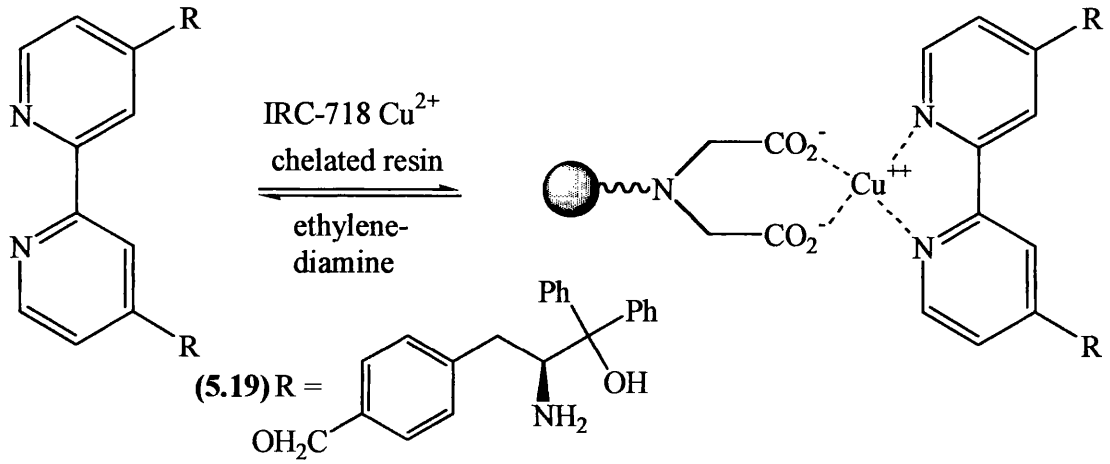
To prove this theory, the chiral catalyst (*S*)-2-amino-3-(4-hydroxy)phenyl-1,1-diphenylpropan-1-ol **(5.18)** was linked to the tag molecule, 4,4′-*bis*-(bromomethyl)-

2,2′-bipyridine **(3.9)**,[9] to form the tagged catalyst, (*S*,*S*)-4,4′-*bis*-[4-(2-amino-3-hydroxy-3,3-diphenylpropyl)phenoxymethyl]-2,2′-bipyridine **(5.19)** (Scheme 5.6).



Scheme 5.6

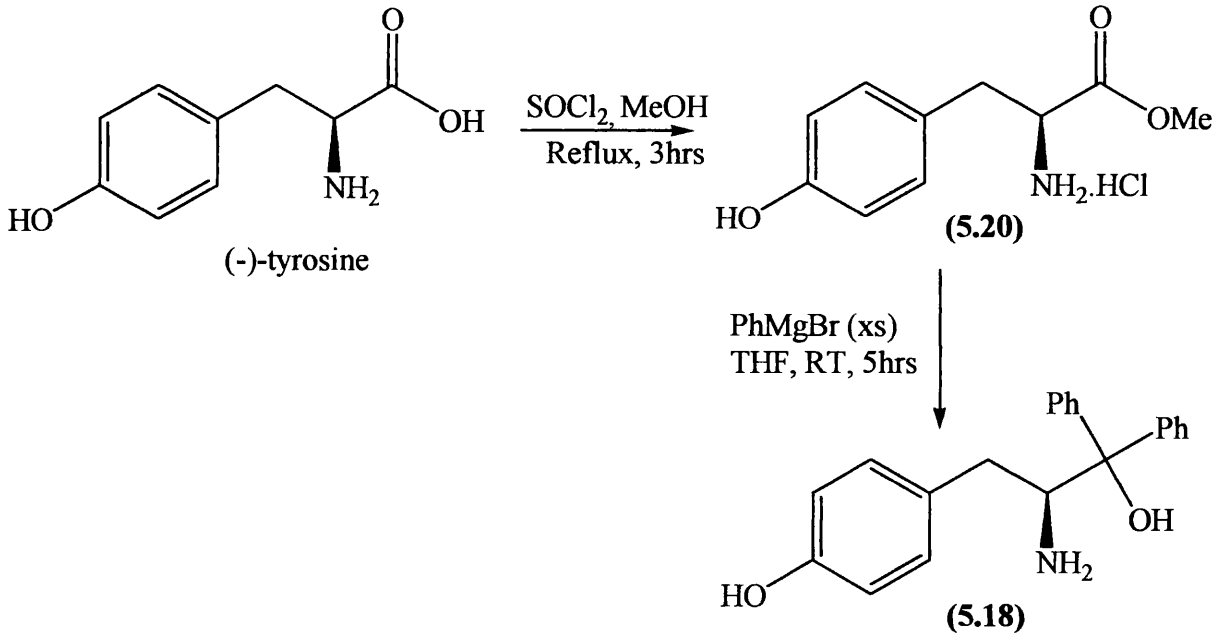
It was envisioned that the tagged catalyst would function in the same way as if unbound but would be able to be reversibly precipitated by co-ordination of the nitrogen atoms in the bipyridyl group to the Cu^{2+} ions on IRC-718 Cu^{2+} chelated resin (Scheme 5.7).



Scheme 5.7

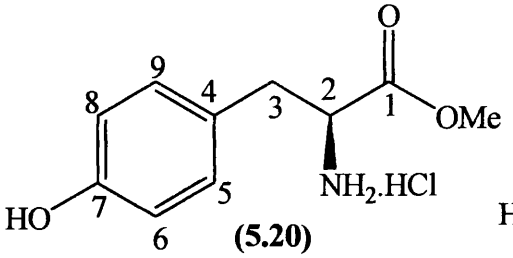
5.3 Preparation of (*S*)-2-amino-3-(4-hydroxyphenyl)-1,1-diphenyl-propan-1-ol (5.18)

The chiral catalyst was synthesised from the commercially available (-)-tyrosine in two steps (Scheme 5.8).[10] In the first step the (-)-tyrosine was esterified to the (-)-tyrosine methyl ester hydrochloride **(5.20)**. It was characterised by ^{1}H NMR, which showed an additional singlet at 3.67ppm corresponding to the methyl ester group (see Table 5.4 for the ^{1}H NMR data and Table 5.5 for the ^{13}C NMR data). In the second step a Grignard reagent was used to form **(5.18)** in 65% yield. It was characterised by its ^{1}H NMR spectrum, which contained additional peaks in the aromatic region, which intergrated for 10 hydrogens, indicating the presence of two phenyl groups. Also, the ^{13}C NMR revealed the disappearance of the carbonyl group at 169.9ppm present in the starting material **(5.20)** (see Table 5.4 for the ^{1}H NMR data and Table 5.5 for the ^{13}C NMR data).

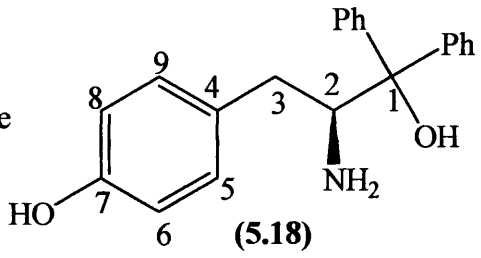


Scheme 5.8

Table 5.4 – ^{1}H NMR data of **(5.20)** and **(5.18)**



(5.20)



(5.18)

Chemical Shift [a,b]

Proton no.	**(5.20)**	**(5.18)**
2	4.16, 1H, t (6.6)	4.06, 1H, dd (10.6, 2.3)
3I	3.02, 2H, m	2.31, 1H, dd (14.0, 10.6)
3II		2.63, 1H, dd (14.0, 2.0)
5,9	7.00, 2H, d (8.5)	7.00, 2H, d (8.4)
6,8	6.72, 2H, d (8.5)	6.70, 2H, d (8.5)
OMe	3.67, 3H, s	-
Ph	-	7.16-7.61, 10H, m

a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constants, Hz)

Table 5.5 – ^{13}C NMR data of **(5.20)** and **(5.18)**

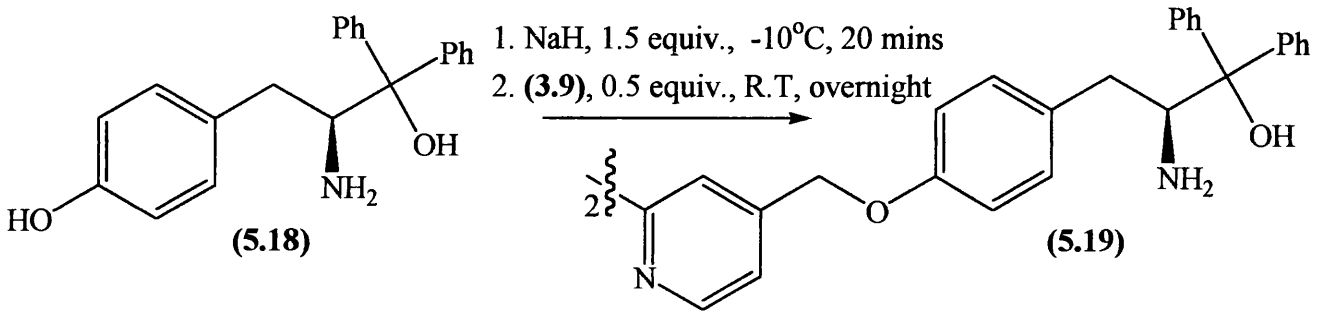
Chemical Shift [a,b]

Carbon no.	**(5.20)**	**(5.18)**
1	169.9	88.6
2	53.9	70.4
3	35.5	39.6
4	124.8	131.6
5,9	130.8	130.6
6,8	115.9	115.1
7	157.1	156.5
OMe	53.0	-
Ph	-	145.4, 148.9, 128.7, 128.2, 128.1, 127.5, 127.3

a) Spectra run in $CDCl_3$ b) δ values, ppm

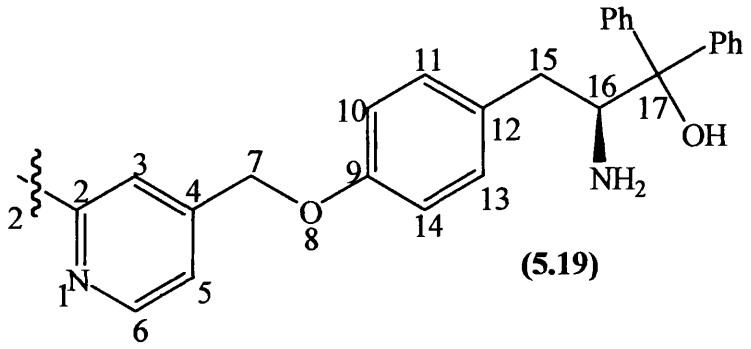
5.4 Preparation of (*S*,*S*)-4,4′-*bis*-[4-(2-amino-3-hydroxy-3,3-diphenyl-propyl)phenoxymethyl]-2,2′-bipyridine (5.19)

The tagged catalyst was generated by the reaction of **(5.18)** with **(3.9)** (Scheme 5.9). NaH was used to abstract a proton from the phenolic position of **(5.18)**, but not from the less acidic tertiary alcohol, to form an anion which subsequently attacked both CH_2 positions of **(3.9)** to generate **(5.19)** with the loss of two bromide ions. The crude mixture was purified by crystallisation to produce a 73% yield of **(5.19)**. It was characterised in ^{13}C NMR by the appearance of peaks at 157,122,147,119 and 149ppm which indicated the presence of the bipyridyl group. See Table 5.6 for ^{1}H and ^{13}C NMR data.



Scheme 5.9

Table 5.6 – ^{1}H and ^{13}C NMR data of **(5.19)**



(5.19)

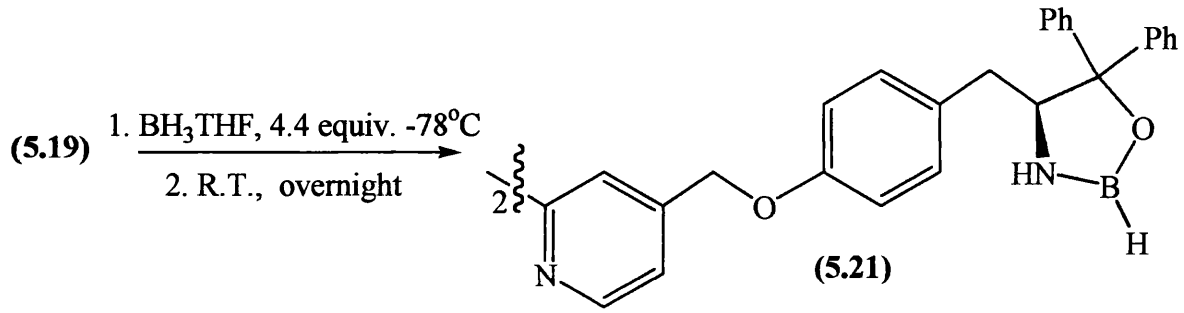
Chemical Shift [a,b]

Proton/carbon no.	**^{1}H**	**^{13}C**
2	-	156.9
3	8.38, 2H, s	121.8
4	-	147.5
5	7.35, 2H, dd (1.53, 5.02)	119.0
6	8.60, 2H, d (4.96)	149.5
7	5.08, 2H, s	68.4
9	-	156.1
10, 14	6.84, 4H, d (8.61)	115.1
11, 13	7.03, 4H, d (8.55)	130.2
12	-	132.4
15	2.32, 2H, dd (14.00, 10.79) 2.50, 2H, dd (14.04, 2.29)	35.8
16	4.05, 2H, dd (10.81, 2.53)	58.2
17	-	78.5
Ph	7.11, 4H, m 7.24, 8H, m 7.54, 8H, m	146.8, 144.3, 128.5,128.2, 126.8, 126.5, 125.8, 125.4

a) Spectra run in $CDCl_3$ b) δ values, ppm (coupling constants, Hz)

5.5 Synthesis of the boronylated catalyst (5.21)

The tagged catalyst was activated prior to the reduction by boronylation.[10] It was achieved by adding BH_3THF to a THF solution of **(5.19)** at -78°C. The mixture was stirred overnight to produce the oxazoborolidine catalyst **(5.21)** (Scheme 5.10). Due to the instability of **(5.21)** it was not purified or characterised but used directly for the enantioselective reduction of acetophenone.



Scheme 5.10

5.6 Reduction of acetophenone with activated, tagged catalyst (5.21)

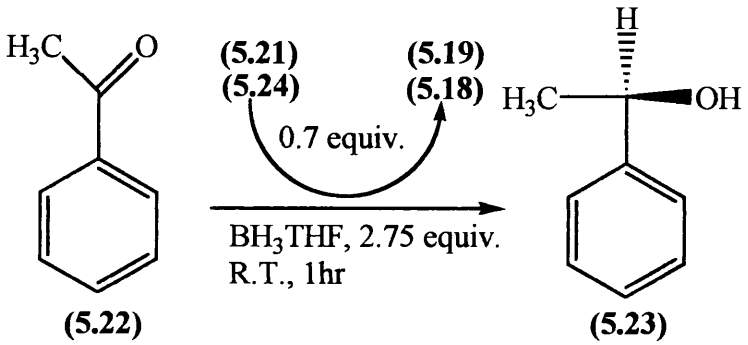
5.6.1 With literature work-up

The chiral reduction of acetophenone **(5.22)** was achieved using the active tagged catalyst **(5.21)** and BH_3THF (Scheme 5.11). The method of Itsuno *et al.*[10] was adapted to work up the reaction. After stirring at room temperature for one hour the reaction was quenched with two molar hydrochloric acid. The de-activated catalyst **(5.19)** was removed from the crude product by precipitating it as its hydrochloride salt and subsequent filtration afforded the alcohol **(5.23)**. It was identified by ^1H NMR from the appearance of a singlet at 4.8 corresponding to the OH group and a quartet at 2.8 corresponding to the CH group. Catalyst **(5.19)** was recovered as a precipitate by neutralising its hydrochloride salt with ammonia in water. The results are shown in Table 5.7.

5.6.2 With solid-phase work-up

The reaction proceeded in the same way as in Section 5.6.1 but was quenched with methanol. Excess IRC-718 Cu^{2+} chelated resin was then added and the mixture was

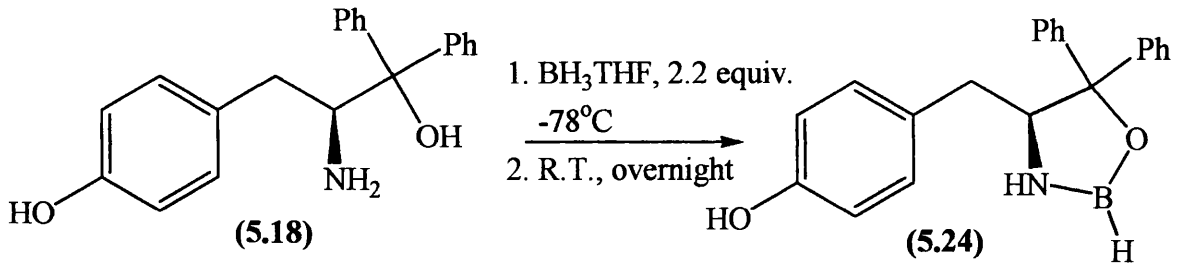
shaken overnight. The mixture was then filtered and thoroughly washed with THF. The filtrate was evaporated to afford **(5.23)**. Deactivated catalyst **(5.19)** was cleaved from the beads using excess ethylene diamine by shaking overnight. The mixture was then filtered, washed and dried to afford **(5.19)**. The results are shown in Table 5.7. It should be noted that although reproducible results were obtained for this reaction, on a number of occasions the recovered yield of tagged catalyst **(5.19)** was much lower at 30%. On these occasions, the reaction conditions had not been altered in any way and HPLC and NMR analysis showed that no **(5.19)** was present in the filtrate containing the alcohol **(5.23)**. It could therefore be speculated that **(5.19)** was not always being fully released from the resin by the addition of ethylene diamine, although no explanation could be found for why this happened on seemingly random occasions.



Scheme 5.11

5.7 Reduction of acetophenone with untagged catalyst (5.24)

As a comparison to the results gained from the tagged catalyst, ketone **(5.22)** was reduced using the activated, untagged catalyst **(5.24)** (Scheme 5.11), which was formed from the boronylation of **(5.18)** using BH_3THF (Scheme 5.12). The reaction was worked-up using the literature method to produce **(5.23)** and recover **(5.18)**. The results are shown in Table 5.7.



Scheme 5.12

5.8 Non-chiral Reduction of acetophenone

As a comparison to the results obtained using chiral catalysts, **(5.22)** was reduced without a chiral catalyst using BH_3THF. The results are shown in Table 5.7.

Table 5.7 – Comparison of results for the formation of **(5.23)**

Activated Catalyst	Work-up Procedure	Yield of **(5.23)**	e.e. of **(5.23)**	Catalyst Recovery
(5.21)	Solid Phase	80%	78%	92%
(5.21)	Literature	95%	87%	72%
(5.22)	Literature	98%	87%	68%
None	N/A	90%	3%	N/A

5.9 Molecular modelling of (5.19)

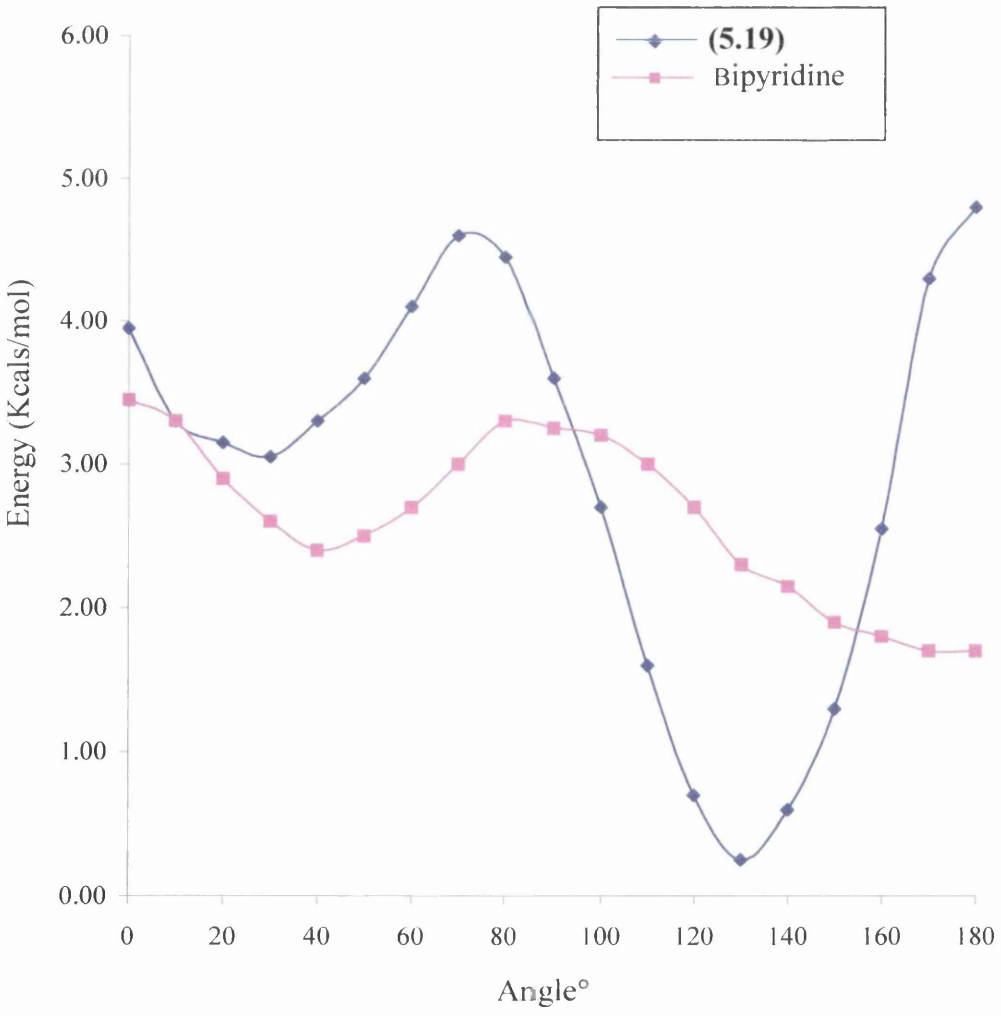
A molecular modelling investigation was carried out to determine the stability of **(5.19)** in the *cis*-conformation since it must adopt this form in order to bind to the resin (Scheme 5.7). The results were compared to those for bipyridine, which does not contain any 4-substituents and therefore is more stable in the *cis*-conformation. The compounds were drawn using Sybyl software and energetically optimised using Tripos Force Field. A systematic search procedure was applied in order to obtain the energy profile for each molecule. Rotation around the relevant bond was performed with 10° increments over a range of 0° (*cis*) to 180° (*trans*) and the energy at each step was calculated to produce an energy profile for each compound (Figure 5.2). The difference in energy between the *cis*-conformation and the global minimum

energy conformation for each compound was then determined (Table 5.8). The results of the calculations show that **(5.19)** has a large ΔE value compared to bipyridine, which means it is unstable in the *cis*-conformation and therefore a poor loading onto the resin would be expected.

Table 5.8 - The calculated energy values for **(5.19)** and bipyridine

Energy value (Kcals/mol)	**(5.19)**	**Bipyridine**
E_{min}	-0.89	1.72
E_{cis}	5.57	3.46
$\Delta E_{cis\text{-}min}$	6.46	1.74

Figure 5.2 - The energies of conformations of **(5.19)** and bipyridine



5.10 Solid Support Loading Investigation

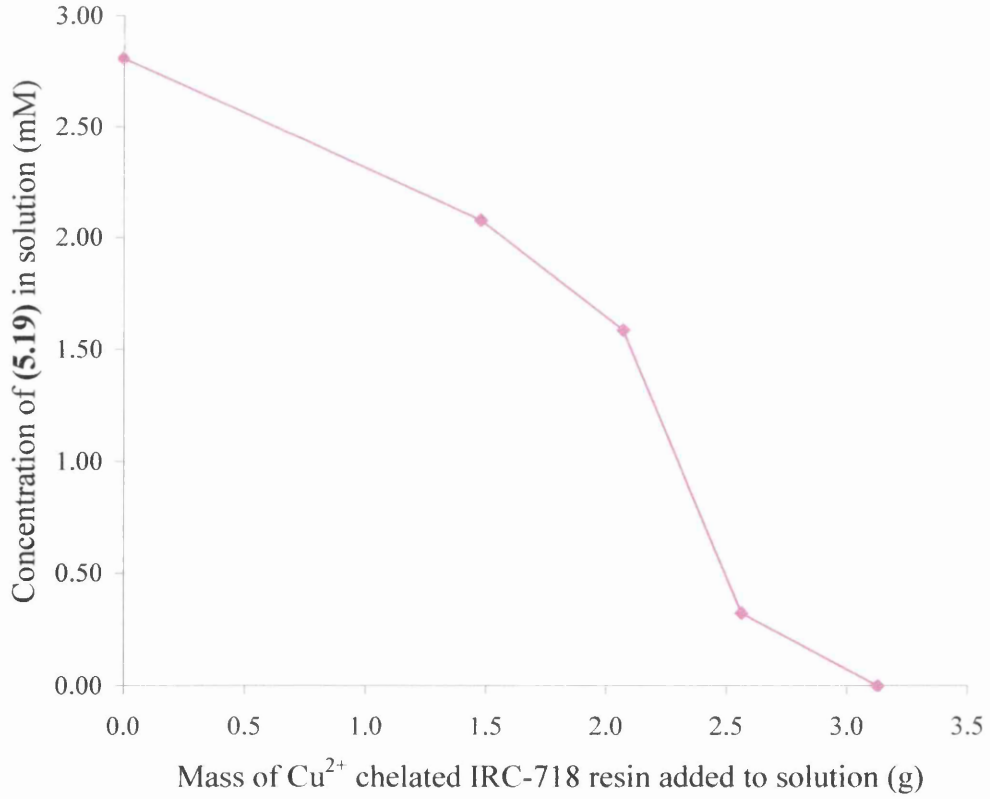
A simple investigation was performed to determine the approximate loading of **(5.19)** on to IRC-718 Cu^{2+} chelated resin. The loading was calculated by measuring, by HPLC, the peak area of **(5.19)** in a standard solution after the addition of measured amounts of resin and subsequent shaking for two hours. The peak area of an internal standard, 2-nitrotoluene, was also measured and the concentration of **(5.19)** was calculated using the following formula:

Conc. (5.19) = (Peak area (5.19) / R.F) × Conc. (standard) / Peak area (standard)

Where R.F is the response factor of **(5.19)** calculated from solutions of known concentration.

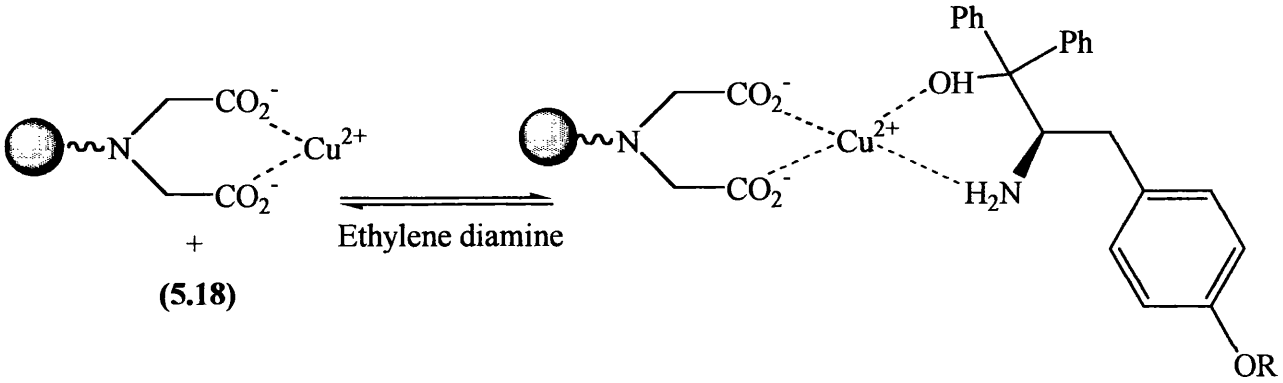
The results are shown in Figure 5.3 and correspond to a loading of 0.02mmol of **(5.19)** per gram of resin.

Figure 5.3 – A graph to show the loading of **(5.19)** on the resin.



5.11 Investigation to determine if (5.18) can co-ordinate to the resin

It was speculated that the amino and alcohol groups on **(5.18)** could have an affinity for the resin (Scheme 5.13). This was investigated by carrying out a reduction of acetophenone using **(5.18)**. At the end of the reduction the mixture was quenched with methanol and 1.4 equivalents of IRC-718 Cu^{2+} chelated resin was added. The mixture was shaken and filtered. NMR analysis showed that no catalyst was present in the filtrate. Ethylene diamine was then added to the resin and the mixture was shaken and filtered to recover 35% of the catalyst **(5.18)**. The result proved that **(5.18)** co-ordinated to the resin, probably *via* the amino and alcohol groups. It also showed that the co-ordination was only partly reversed by addition of ethylene diamine and some of **(5.18)** remained on the resin.



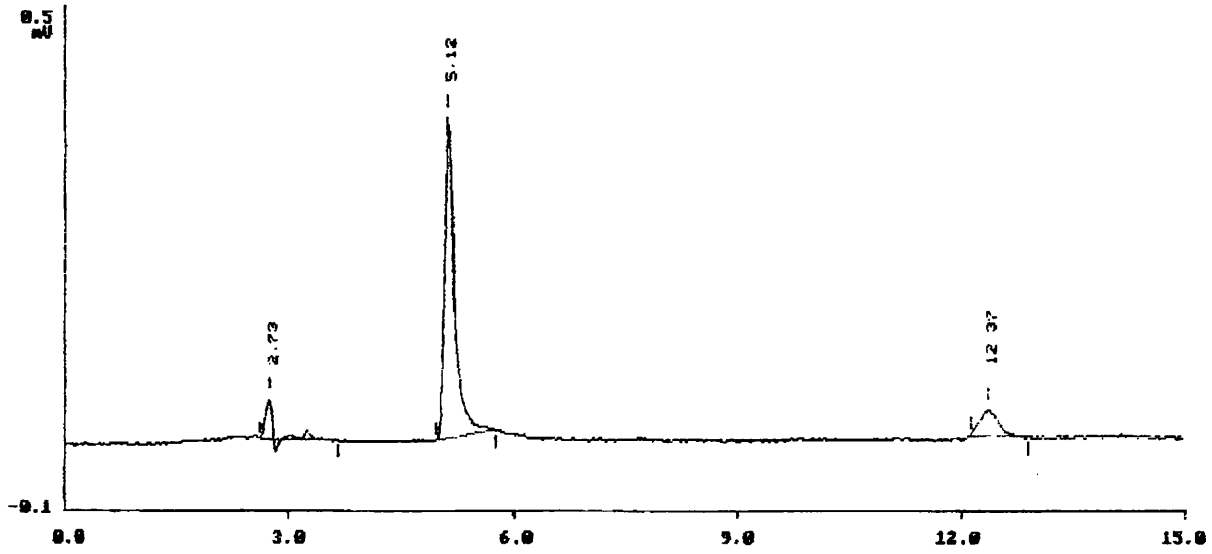
Scheme 5.13

5.12 Investigating the competition for binding sites on the resin

It was shown in Section 5.11 that the amino and alcohol groups on **(5.18)** can coordinate to the resin. It therefore follows that in compound **(5.19)** both the bipyridine and the amino and alcohol groups can co-ordinate to the Cu^{2+} ions on the resin. An investigation was carried out to discover which group has the highest affinity for the resin. A solution containing a 50/50 mixture of 2,2′-bipyridine and **(5.18)** was prepared and portions of IRC-718 Cu^{2+} chelated resin were added with shaking. Figure 5.4 is the HPLC chromatogram of the solution before addition of resin and shows bipyridine at a retention time of five minutes and **(5.18)** at a retention time of twelve minutes. After addition of enough resin to bind about 75% of the compounds, assuming a loading of 0.25g/mol, the peak corresponding to bipyridine

could no longer be observed by HLPC whereas there was still a peak corresponding to **(5.18)** (Figure 5.5). The results indicated that bipyridine had bound to the resin in preference of **(5.18)**. From the results it could be reasoned that the bipyridyl group on **(5.19)** has a higher affinity for IRC-718 Cu^{2+} chelated resin than the amino and alcohol groups.

Figure 5.4 – HPLC chromatogram of **(5.18)** and bipyridine before addition of IRC-718 Cu^{2+} chelated resin

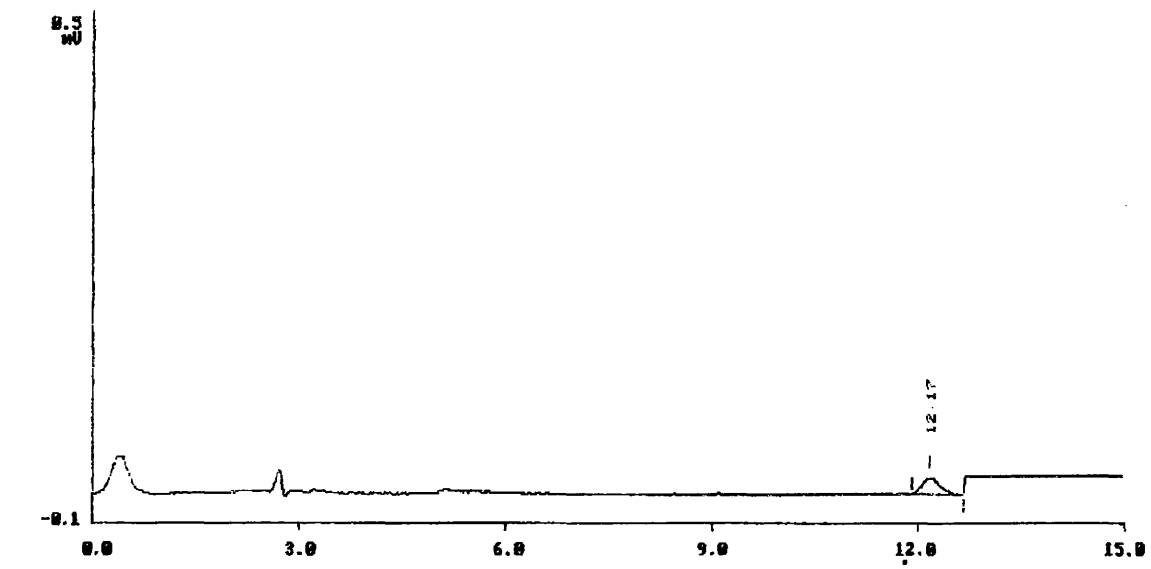


Integration Results for Channel 1

Pk #	Ret. Time	Hgt.	Height %	Area	Area %	Modified Response	Response Ratio	Solution Conc. (N/A)	Qty	Derived Result	Component Name
1	2.73	168	9.88	1226	7.42	N/A	N/A	N/A	N/A	N/A	N/A
2	5.12	1424	83.64	13412	81.12	N/A	N/A	N/A	N/A	N/A	N/A
3	12.37	110	6.48	1895	11.46	N/A	N/A	N/A	N/A	N/A	N/A
			100.00		100.00						

Total Height : 1702
Total Area : 16533

Figure 5.5 – HPLC chromatogram of **(5.18)** and bipyridine after addition of 2.1g of IRC-718 Cu^{2+} chelated resin



Integration Results for Channel 1

Pk #	Ret. Time	Hgt.	Height %	Area	Area %	Modified Response	Response Ratio	Solution Conc. (N/A)	Dfy	Derived Result	Component Name
1	12.17	70	100.00	1278	100.00	N/A	N/A	N/A	N/A	N/A	N/A
			100.00		100.00						

Total Height : 70
Total Area : 1278

5.13 Conclusion

It has been demonstrated in this chapter that the selective immobilisation approach to product purification can be successfully applied to oxazaborolidine catalysed reductions. It has also shown success in the recovery of the tagged catalyst as the method has produced a high recovered yield of catalyst. However, on occasions the recovered yield was lower, possibly due to interference in the release of the tagged auxiliary **(5.19)** from the resin, which could be attributed to the affinity of the amino and alcohol groups on the molecule with the resin.

5.14 Experimental

Instrumentation

^{1}H NMR spectra were recorded on a Bruker AC spectrometer at 400MHz. ^{13}C NMR spectra were recorded on a Bruker AC spectrometer at 100MHz. All spectra contained a tetramethylsilane internal standard. The mass spectra were recorded on a VG analytical Quattro II triple quadrupole mass spectrometer. The accurate mass measurements were obtained from a Finnigan MAT 900 XL mass spectrometer. Melting points were recorded using an electrothermal IA9100 digital melting point apparatus and are uncorrected. HPLC results were obtained from a Hewlett Packard 1100 series. All of the HPLC data were obtained from a Phenomenex Prodigy, 15cm, C18 column. The mobile phase was a gradient of 5% acetonitrile (0.1% TFA) increasing to 100% acetonitrile (0.1%TFA) over 11 minutes then held at that concentration.

Reagents

Anhydrous reactions were carried out under an inert atmosphere and used argon or nitrogen from the cylinder passed through H_2SO_4 and $CaCl_2$. THF was dried by stirring overnight over CaH_2 and then distilled from sodium wire and benzophenone. DMF was bought dry from Fluka. Solutions of *n*-BuLi in hexane were bought from Aldrich and regularly estimated. Solid starting materials were dried *in vacuo* over P_2Cl_5 prior to use. Temperatures of –78°C and –10°C were obtained from acetone/solid CO_2 and acetone/ice baths respectively.

Preparation of (*S*)-tyrosine-methylester-hydrochloride (5.20)

$[C_{10}H_{13}O_3N.HCl]$: F.W. = 231.5

To a solution of (-)-tyrosine (15.02g, 82.81mmol) in methanol (50ml) at 0°C was added thionyl chloride (6.7ml, 91.10mmol, 1.1 mol. equiv.) dropwise. The mixture was refluxed for 3 hours before allowing to cool to room temperature. The solvent was removed *in vacuo* to afford **(5.20)** as an off-white powder (19.15g, 99.8%).
M.pt. = 194-196°C (lit[11] = 190°C). See Table 5.4 for ^{1}H NMR data and Table 5.5 for ^{13}C NMR data.

Preparation of (*S*)-amino-3-(4-hydroxyphenyl)-1,1-diphenylpropan-1-ol (5.18)

$[C_{21}H_{21}NO_2]$: F.W = 319

Magnesium turnings (7.40g, 0.34mmol, 10 mol. equiv.) were added to a three necked flask fitted with a reflux condenser and a dropping funnel under nitrogen. THF (30ml) and iodine (1 crystal) were added and the mixture was stirred until the brown colouration had disappeared. Bromobenzene (1ml, 9.29mmol, 0.3 mol. equiv.) was added and the flask was heated with an air gun until the appearance of a brown colouration in the solution. A solution of bromobenzene (31ml, 0.29mol, 9.7 mol. equiv.) in THF (60ml) was added dropwise at such a rate that the mixture boiled gently without external heating. The mixture was stirred for three hours at room temperature before addition of (**5.18**) (6.95g, 0.03mol) in small portions. The mixture was stiired overnight at room temperature before quenching by pouring into a beaker of ice. HCl (6M) was added to the solution to achieve a pH of 1 and the solution was stirred for 1 hour. The solution was made alkaline with ammonia solution and the and stirring was continued for a further hour. The solution was extracted into (3 × 100ml) and the combined organic layers were washed with brine (100ml) and water (100ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was crystalized from ethanol to afford **(5.18)** as off white crystals (6.27g, 65%). M.Pt. = 213-215°C (lit.[10] = 215-217°C). See Table 5.4 for ^1H NMR data and Table 5.5 for ^{13}C NMR data.

Preparation of (*S,S*)-4,4′-*bis*-[4-(2-amino-3-hydroxy-3,3-diphenylpropyl)phenoxy-methyl]-2,2′-bipyridine (5.19)

$[C_{54}H_{50}N_4O_4]$: F.W. = 818

NaH (60% suspension in mineral oil) (0.71g, 17.70mmol, 1.5 mol. equiv.) was washed with dry petroleum spirit (3 × 1ml) and dried under a stream of nitrogen before **(5.18)** (3.74g, 11.70mmol, 1 mol.equiv.) in DMF (20ml) was added dropwise at room temperature. The evolution of hydrogen was allowed to finish before **(3.9)** (2.0g, 5.8mmol, 0.5 equiv.) was added dropwise. The resulting mixture was stirred at

room temperature under nitrogen for 3 hours before quenching with water (50ml). The solution was extracted into DCM (3 × 100ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product. Crystallization from ethanol/ethyl acetate afforded **(5.19)** as a pale brown powder (3.45g, 73%). M.pt. = 97-99°C. See Table 5.6 for ^1H and ^{13}C NMR data. *m/z* (CI): (M + H) 135 (50%), 152 (36%), 183 (20%), 391 (20%). Calculated M +H = 819.3910 Measured M + H = 819.3893.

Reduction of acetophenone with BH_3THF and (5.19) with solid phase work up

To a solution of **(5.19)** (0.23g, 0.29mmol, 0.5 mol. equiv.) in dry THF (5ml), was added BH_3THF (1.6ml, 0.79M, 1.26mmol, 1.4 mol. equiv.) slowly at -78°C under nitrogen. The mixture was then warmed to 30°C and stirred overnight at 30°C. A solution of acetophenone (0.10g, 0.83mmol, 1 mol. equiv.) in dry THF (1ml) was added dropwise simultaneously with BH_3THF (2.6ml, 0.79M, 2.05mmol, 2 mol. equiv.). The mixture was stirred for 1 hour at 30°C before it was quenched with methanol (1ml). IRC-718 Cu^{2+} chelated resin (4.6g) was added and the mixture was shaken for three days. The resin was then filtered and washed with THF (3 × 50ml). The filtrate was evaporated *in vacuo* and the residue redissolved in diethyl ether (50ml), washed with brine and dried over magnesium sulphate. The diethyl ether was evaporated off to give **(5.23)** as colourless oil (0.08g, 80%). e.e = 78%
The resin was added to a solution of ethylenediamine (2.30g) in THF (10ml) and the mixture was shaken for three days. The resin was then filtered and washed with THF (3 × 50ml). The filtrate was concentrated *in vacuo* and dried ($MgSO_4$) to afford 0.21g (92%) of **(5.19)**. Confirmed by ^1H NMR.

Reduction of acetophenone with BH_3THF and (5.18) with literature work up

To a solution of **(5.18)** (0.40g, 1.25mmol, 1.2 mol. equiv) in THF (10ml) was added BH_3THF (2.75ml, 1M, 2.75mmol, 2.7mol. equiv.) slowly at -78°C under nitrogen. The mixture was then warmed to room temperature and stirred overnight at 30°C. A solution of acetophenone (0.10g, 1.00mmol, 1 mol. equiv.) in THF (2ml) was added dropwise simultaneously with BH_3THF (1.2ml, 1M, 1.2mmol, 1.2 mol. equiv.). The

mixture was stirred for 1 hour at room temperature before it was quenched with 1N HCl (1ml). The THF was removed *in vacuo* and ether (5ml) was added to precipitate **(5.18)** as its hydrochloride salt. The solid was filtered and washed with ether (2 × 10ml). The ether fractions were washed with brine (20ml), dried ($MgS0_4$) and concentrated to afford **(5.23)** as colourless oil (0.1g, 98%). ^{1}H NMR (CD_3OD) 1.42 (d, 3H, J= 6.5, CH_3), 2.83 (q, 1H, J = 6.5, CH), 4.83 (s, 1H, OH), 7.18-7.36 (m, 6H Ph). e.e = 87%, absolute configuration = *R* by comparison to standard. The solid hydrochloride salt was dissolved in water (20ml) and made alkaline by addition of NH_3 (aq) (8ml) causing **(5.18)** to precipitate. The solid was filtered, washed with water (50ml) and dried *in vacuo* to afford **(5.18)** as white crystals (0.27g, 68%). Confirmed by ^{1}H NMR.

Reduction of acetophenone with BH_3THF and (5.19) with literaure work up

As the reduction of acetophenone with BH_3THF and **(5.18)**, only using **(5.19)**. **(5.19)** (0.51g, 0.63mmol, 0.6 mol. equiv), BH_3THF (2.75ml, 1M, 2.75mmol, 2.7mol. equiv.) acetophenone (0.12g, 1.00mmol, 1 mol. equiv.) BH_3THF (1.2ml, 1M, 1.2mmol, 1.2 mol. equiv.). Afforded **(5.23)** as colourless oil (0.1g, 95%). ^{1}H NMR (CD_3OD) as before. e.e = 87%, absolute configuration = (*R*) by comparison to standard. Afforded **(5.19)** as white crystals (0.37g, 72%). Confirmed by ^{1}H NMR.

Reduction of acetophenone with BH_3THF

To a solution of acetophenone (0.12g, 1.00 mmol) in THF (5ml) was added BH_3THF (2.5ml, 0.79M, 1.97mmol, 2 mol. equiv.) slowly at 0°C. The solution was warmed to room temperature and stirred overnight. The solution was quenched with water (2ml) and the THF was removed *in vacuo*. The mixture was extracted into ether (2 × 25ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford **(5.23)** as colourless oil (0.11g, 90%). ^{1}H NMR (CD_3OD) as before. e.e = 3%.

Reduction of acetophenone with BH_3THF and (5.18) with solid phase work up

As the reduction of acetophenone with BH_3THF and **(5.19)** with solid phase work up, only using **(5.18)**. **(5.18)** (0.40g, 1.26mmol, 0.6 mol. equiv), BH_3THF (2.75ml, 1M, 2.75mmol, 2.7mol. equiv.) acetophenone (0.12g, 1.00mmol, 1 mol. equiv.) BH_3THF (1ml, 1M, 1.0mmol, 1.2 mol. equiv.). IRC-718 Cu^{2+} chelated beads (7g). Afforded **(5.23)** as colourless oil (0.10g, 82%). ^1H NMR (CD_3OD) as before. e.e = 74%, absolute configuration = (*R*) by comparison to standard. Afforded **(5.18)** as white crystals (0.14g, 35%). Confirmed by ^1H NMR.

Preparation of Cu^{2+} chelated IRC-718 resin

IRC-718 (Amberlite) resin (50g) was placed in a large sintered funnel and washed successively with water (3 × 250ml), DMF (3 × 60ml) and DCM (3 × 100ml) to remove the brown particles present in the resin. $CuS0_4$ (aq) (0.3M, 250ml) was passed repeatedly through the clean resin until the filtrate was the same colour as the added solution. The resulting blue resin was washed successively with water (3 × 250ml), DMF (3 × 60ml) and DCM (3 × 100ml) to remove the excess $CuSO_4$. The chelated resin was stored under DCM.

Calculation of the response factor of (5.19)

A solution of **(5.19)** (0.08g, 0.10mmol) in THF (1L) was prepared in a 1L volumetric flask and was designated as Solution A. A solution of 2-nitrotoluene (0.395g, 2.88mmol) in THF was prepared in a 1L volumetric flask. A 5ml aliquot of that solution was further diluted with 45ml of THF in a 50ml volumetric flask and was designated as Solution B. The solutions were pipetted into clean, dry sample tubes in the following ratios; 1A:1B, 1A:2B, 1A:3B, 2A:1B and 3A:1B, using a different 1ml pipette for each solution. Each solution was analysed in triplicate by HPLC. The results are shown in Table 5.9.

Table 5.9 – Calculation of the response factor for **(5.19)**

Volume A (ml)	Amount A (mM)	Peak Area A	Volume B (ml)	Amount B (mM)	Peak Area B	Response Factor
		27160			5290	0.33
2	0.07	27737	1	0.04	5926	0.37
		27097			5320	0.34
		20335			8060	0.34
1	0.05	21194	1	0.06	8218	0.33
		19570			7669	0.34
		13676			11105	0.35
1	0.03	13679	2	0.08	10676	0.34
		13979			11399	0.35
3	0.07	30643 28363	1	0.03	4120 4109	0.35
		10825			12907	0.34
1	0.02	11085	3	0.086	13008	0.34
		11121			12954	0.33
					Average Response Factor	0.34

Estimation of the loading of (5.19)

To a solution of **(5.19)** (0.05g, 0.06mmol) and 2-nitrotoluene (0.13g, 0.95mmol) in THF (20ml) was added IRC-718 Cu^{2+} chelated resin (2.11g). The mixture was shaken for 2 hours before a 0.1ml sample was taken. The sample was filtered and diluted with acetonitrile (2ml) before analysis by HPLC. The sequence was repeated as shown in Table 5.10.

Table 5.10 – Estimation of the loading of **(5.19)**

Amount of Resin (g)	Peak Area (5.19)	Peak Area Nitrotoluene	Conc. of Nitrotoluene (mM)	Response Factor	Calculated Conc. of (5.19) (mM)	Average Conc. of (5.19)
	1054	8385			2.06	
2.11	2690	19749	47.40	0.34	2.23	2.11
	1005	8049			2.04	
	4047	36114			1.83	
2.07	4228	36214	47.40	0.34	1.91	1.61
	1880	28225			1.09	
2.56	194	9648	47.40	0.34	0.33	0.33
3.13	Un-detec-table	20558	47.40	0.34	-	-
3.13 +	2823	9569			4.82	
0.1ml	2598	9268	47.40	0.34	4.58	4.67
$(CH_2NH_2)_2$	2767	9808			4.61	

Investigation of the competition for binding sites between bipyridine and (5.18)

A solution of **(5.18)** (0.18g, 0.56mmol) and 2,2'bipyridine (0.09g, 0.56mmol) in THF (20ml) was prepared and a sample was taken and analysed by HPLC. IRC-718 Cu^{2+} chelated resin (3.371g) was added to the solution in three portions and the mixture was shaken for 1 hour between additions and a sample was taken and analysed by HPLC. See Figures 5.4 and 5.5 for the HPLC chromatograms of the solution before and after addition of the resin respectively.

5.15 References

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