A study into the use of ephedrine, immobilised on a silica support, and its use in asymmetric alkynylation reactions

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A study into the use of ephedrine, immobilised on a silica support, and its use in asymmetric alkynylation reactions

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Abstract

This work describes the preparation of an immobilised ephedrine silica supported catalyst and its application in asymmetric synthesis. (*1R,2S*)-(-)-Ephedrine is a controlled substance, whose use in synthesis is closely monitored by a licence regulated by the Medicines and Healthcare products Regulatory Agency (MHRA). One way of reducing the demand for controlled substances as catalysts is to tether them onto a support medium so that after use they may be recovered by filtration, washed and reactivated, if necessary, dried and then reused. In this project, *(1R,2S)*-(-)-ephedrine was tethered onto a functionalised silica support and tested for its use in asymmetric alkynylation reactions involving a range of aromatic aldehydes and a terminal alkyne, phenylacetylene.

The loading of the ephedrine on the supported catalyst was characterised by both elemental analysis and thermogravimetric analysis (TGA) due to the nature of the support material. The immobilised ephedrine catalyst was evaluated in asymmetric alkynylation reactions and was shown to provide good enantioselectivity (up to 92% for *(R)*-(+)-1,3-diphenylprop-2-yn-1-ol) and high yields for the secondary propargylic alcohols (up to 97%). The use of the immobilised ephedrine catalyst in asymmetric alkynylation reactions was assumed to be novel. The results of the newly formed secondary propargylic alcohols proved to be comparable to those achieved by homogeneous systems.

The secondary propargylic alcohols were analysed using a wide range of spectroscopic techniques such as nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass spectrometry (GC-MS), optical rotation and high performance liquid chromatography (HPLC).

Due to the restrictions placed on ephedrine, it was important to test the recyclability of the tethered catalyst to reduce the amount of the regulated drug in circulation. The catalyst demonstrated the ability to be recovered quantitatively from the reaction mixture using a simple filtration and then recycled in further asymmetric alkynylation reactions for three cycles before the yield was affected.

In addition to the study, a novel tethering of ephedrine derivatives onto a silica support was investigation and its use in asymmetric alkynylation reactions explored. This was undertaken in an effort to optimise and improve upon the results obtained from *N*-methylephedrine alone.

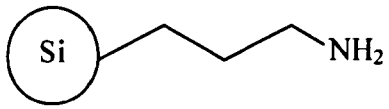
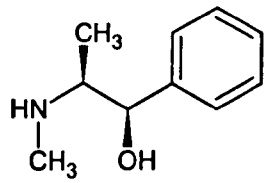
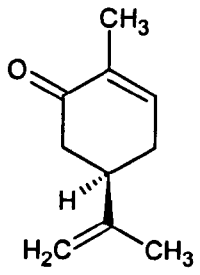
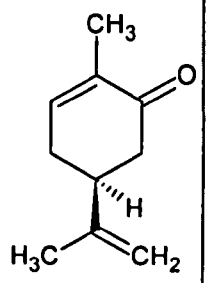
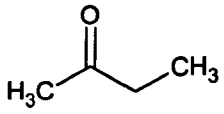
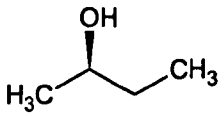
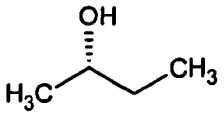
Our initial results showed that it is possible to tether ephedrine derivatives onto a silica support and then employ them in asymmetric synthesis, thus opening up the possibility to use controlled ephedrine more efficiently.

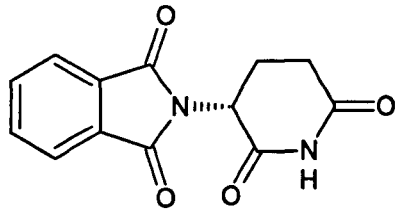
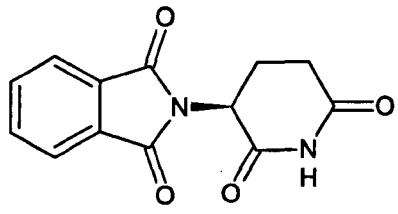
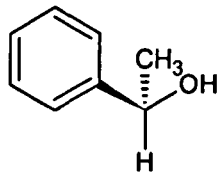
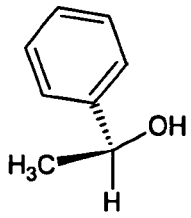
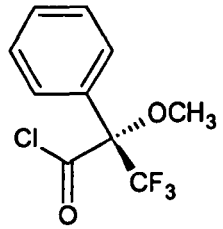
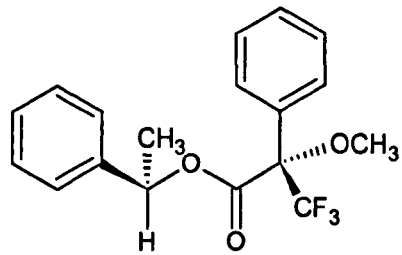
Abbreviations

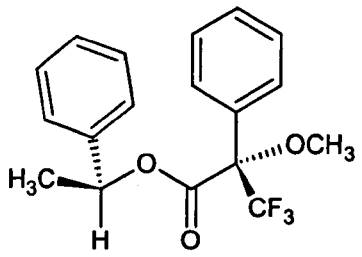
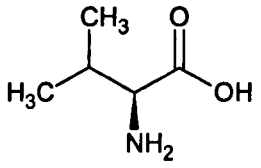
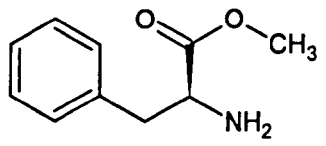
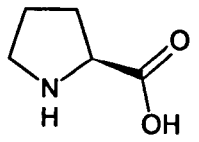
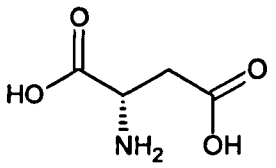
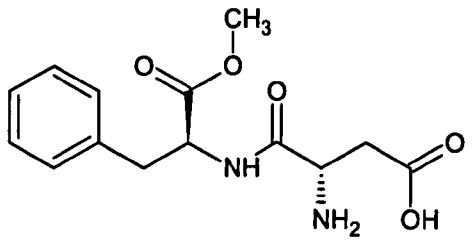
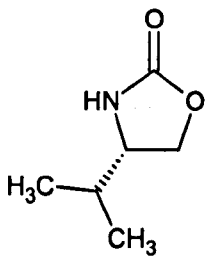
Ac	Acyl
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
b.p.	Boiling point
Cbz	Carboxybenzyl
CDA	Chiral derivatising agent
DCM	Dichloromethane
EDG	Electron donating group
ee	Enantiomeric excess
EWG	Electron withdrawing group
GC-MS	Gas chromatography-mass spectrometry
HPLC	High performance liquid chromatography
IR	Infrared spectroscopy
^{i}Pr	Isopropyl
IPA	Isopropyl alcohol
L_n	Ligands
LC-MS	Liquid chromatography mass spectrometry
LDA	Lithium diisopropylamide

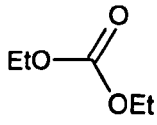
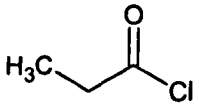
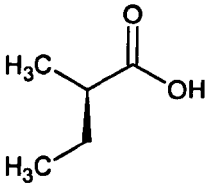
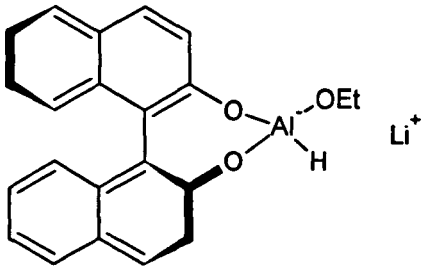
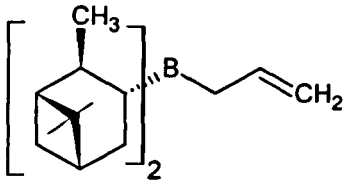
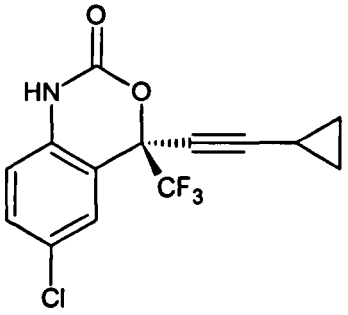
M	Metal
Me	Methyl
MHRA	The Medicines and Healthcare products Regulatory Agency
m.p.	Melting point
MCM	Mobile crystalline material
MTS	Micelle templated silica
NMR	Nuclear magnetic resonance spectroscopy
Nu	Nucleophile
OAc	Acetate
OMe	Methoxy
OTC	Over the counter
OTf	Triflate (trifluoromethanesulfonate)
Ph	Phenyl
RT	Room temperature
^{t}Bu	Tertiary butyl
THF	Tetrahydrofuran
TMS	Trimethylsilane
Ts	Tosyl (4-tolunesulfonic acid)
X	Halogen

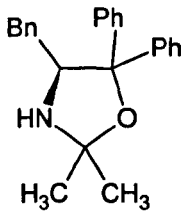
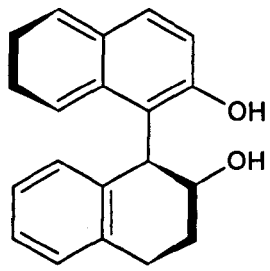
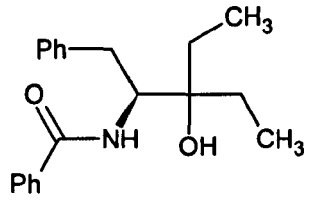
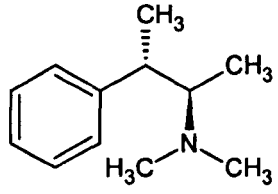
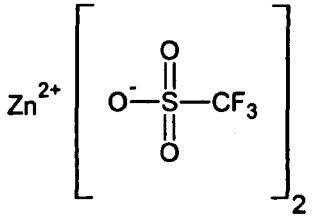
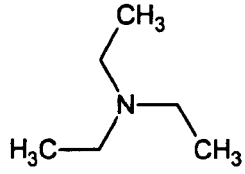
Structure Identification System

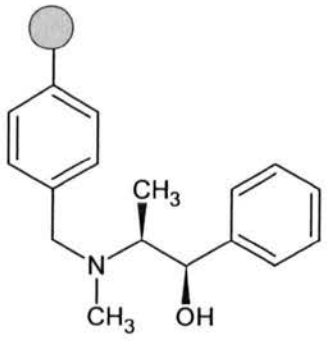
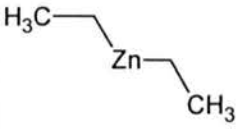
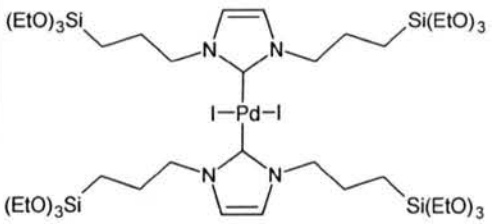
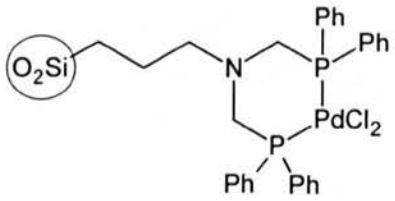
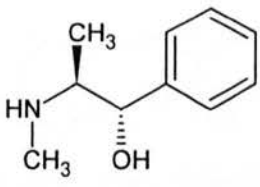
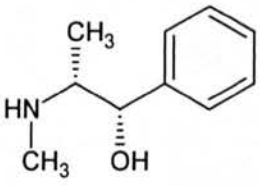
Structure number	Compound name	Structure
1	3-aminopropyl functionalised silica gel	
2	*(1R,2S)*-(-)-ephedrine	
3a 3b	*(R)*-(-)-carvone *(S)*-(+)-carvone	  (*R*)-(-)-Carvone (*S*)-(+)-Carvone
4	Butan-2-one	
5a 5b	*(R)*-butan-2-ol *(S)*-butan-2-ol	 

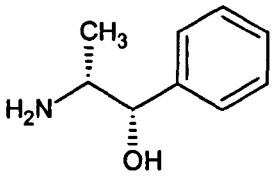
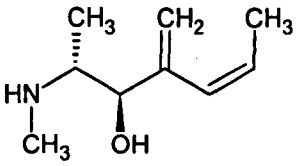
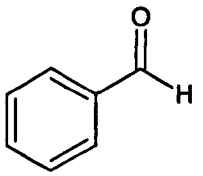
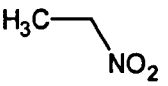
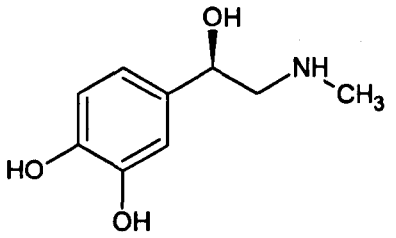
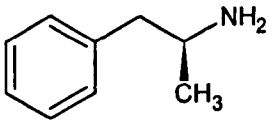
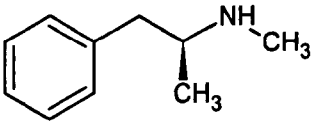
6a	*(R)*-thalidomide	
6b	*(S)*-thalidomide	
7a	*(R)*-1-phenylethanol	
7b	*(S)*-1-phenylethanol	
8	Mosher acid chloride, *(R)*-MTPA-Cl *(R)*-(-)-α-methoxy-α-(trifluoromethyl)phenylacetylene chloride	
9	*(1R)*-phenylethyl-*(2R)*-3,3,3-trifluoro-2-methoxy-2-phenylproponoate	

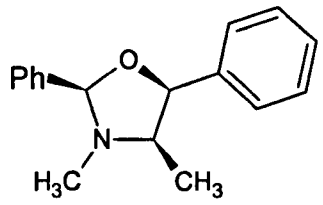
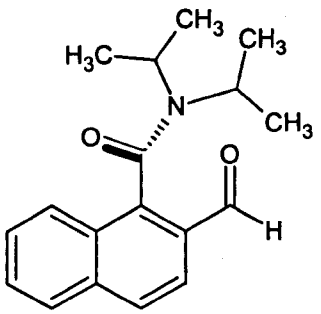
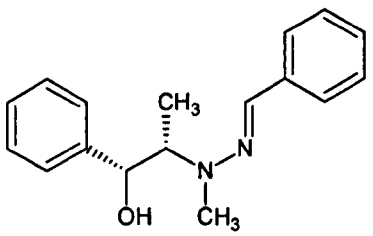
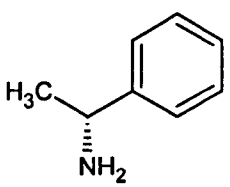
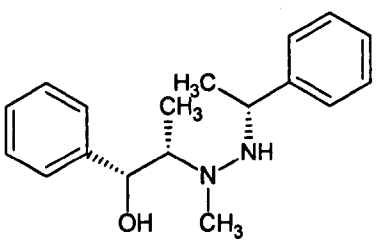
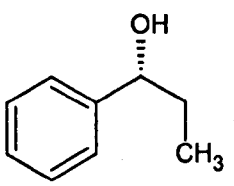
10	*(1S)*-phenylethyl-*(2R)*-3,3,3-trifluoro-2-methoxy-2-phenylproponoate	
11	*(S)*-valine	
12	*(S)*-phenylalanine	
13	*(S)*-pyrrolidine-2-carboxylic acid, *L*-proline	
14	*(S)*-aspartic acid	
15	Aspartame, *N*-(L-α-aspartyl)-L-phenylalanine methyl ester	
16	*(4S)*-4-(propan-2-yl)-1,3-oxazolidin-2-one	

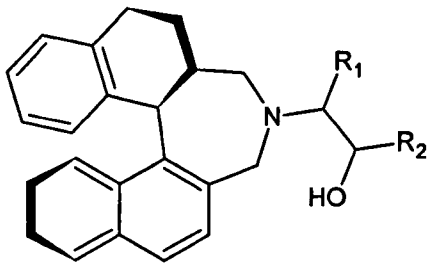
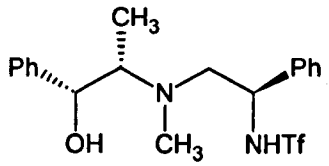
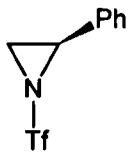
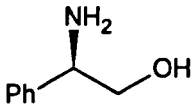
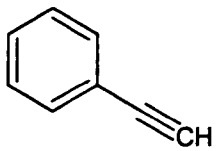
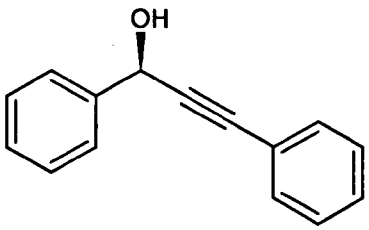
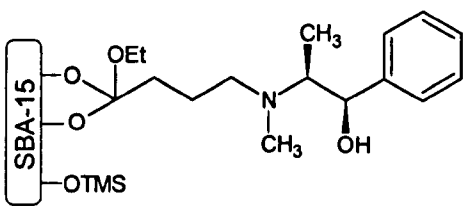
17	Diethyl ether	
18	Propanoyl chloride	
19	*(2R)*-2-methylbutanoic acid	
20	*(S)*-BINAL-H	
21	Brown's (-)-ipc$_2$ allyl borane	
22	Efavirenz, *(4R)*-6-chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-1,4-dihydro-1-benzoxazin-2-one	

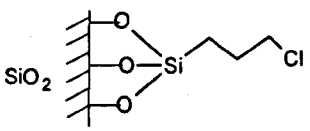
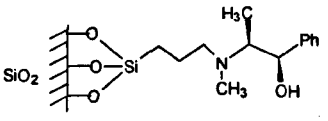
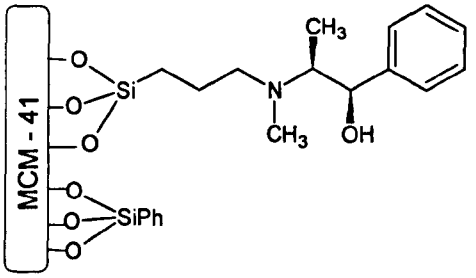
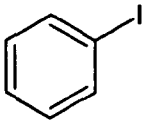
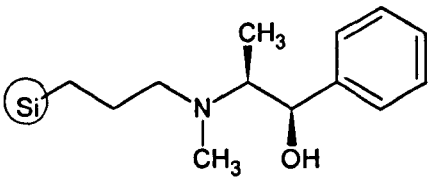
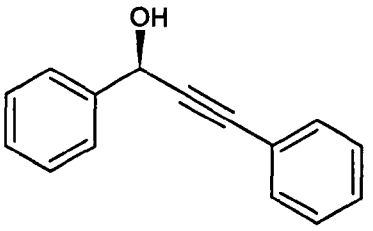
23	***(4S)***-4-benzyl-5,5-diphenyl-2,2-dimethyl-1,3-oxazolidine	
24	***(R)***-BINOL, ***(R)***-1,1'-Bi-2-naphthol	
25	*N*-[***(2S)***-3-ethyl-3-hydroxy-1-phenylpentan-2-yl]benzamide	
26	***(1S,2R)***-(+)-*N*-methylephedrine	
27	Zinc triflate	
28	Triethylamine	

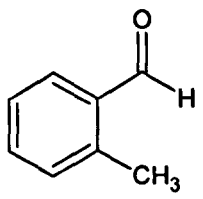
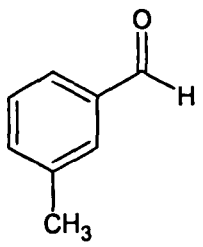
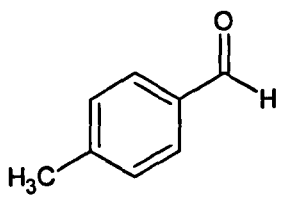
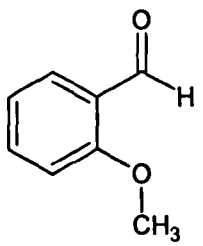
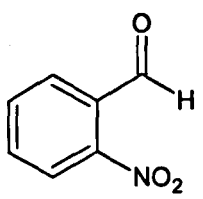
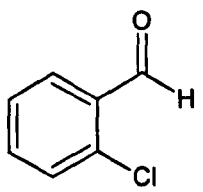
29	Polystyrene bound ephedrine catalyst	
30	Diethyl zinc	
31	Palladium-*N*-heterocyclic carbene silica complex	
32	Silica supported palladium catalyst	
33	***(1S,2S)***-(+)-pseudoephedrine	
34	***(1S,2R)***-(+)-ephedrine	

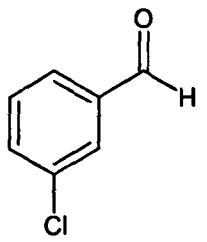
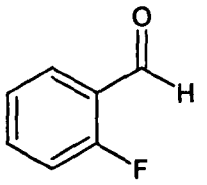
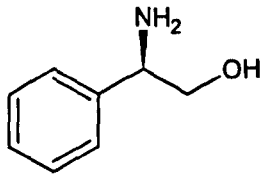
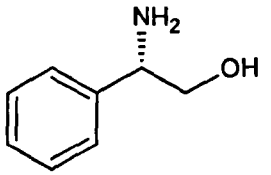
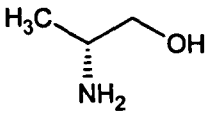
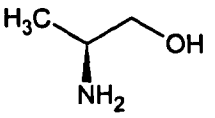
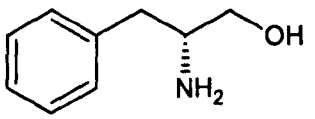
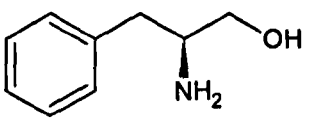
35	***(1S,2R)***-(-)-norephedrine	
36	***(1R,2R)***-(-)-pseudoephedrine	
37	Benzaldehyde	
38	Nitroethane	
39	Adrenaline, ***(1R)***-epinephrine	
40	Amphetamine, ***(2S)***-1-phenylpropan-2-amine	
41	Methylamphetamine, ***(2S)***-*N*-methyl-1-phenylpropan-2-amine	

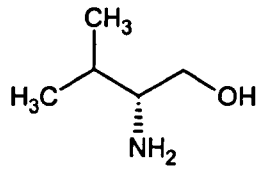
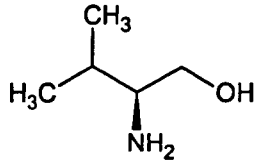
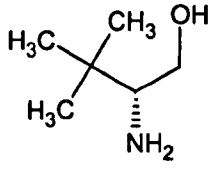
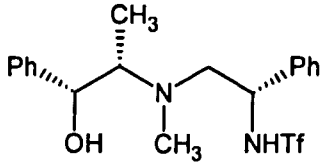
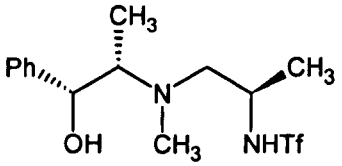
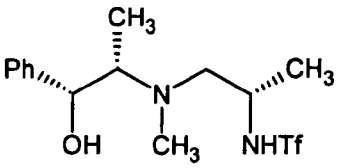
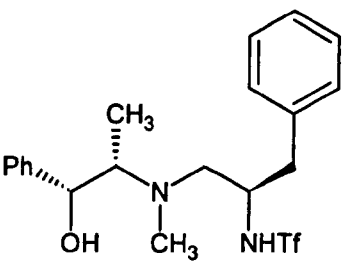
42	***(2R,4R,5S)***-3,4-dimethyl-2,5-diphenyl-1,3-oxazolidine	
43	2-formyl-*N,N*-di(propan-2-yl)naphthalene-1-carboxamide	
44	***(1R,2S)***-2-(2-benzylidene-1-methylhydrazinyl)-1-phenylpropan-1-ol	
45	***(1R)***-1-phenylethylamine	
46	***(1R,2S)***-2-(1-methyl-2-[***(1R)***-1-phenylethyl]hydrazinyl)-1-phenylpropan-1-ol	
47	***(1R)***-1-phenylpropan-1-ol	

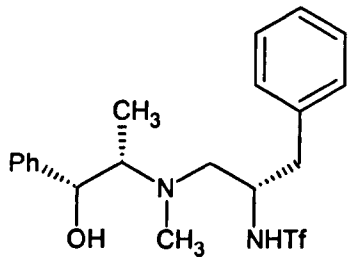
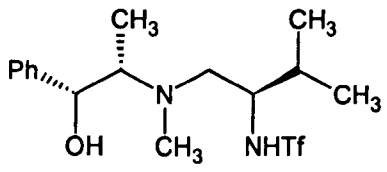
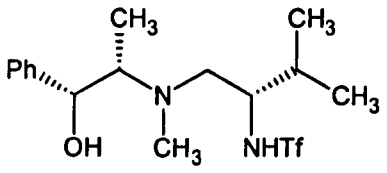
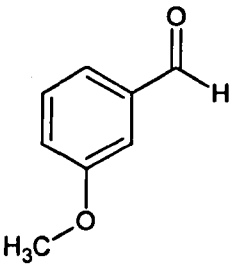
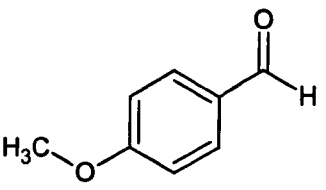
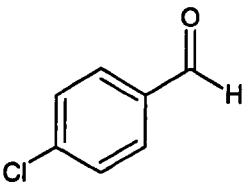
48	1,1'-bi-2-naphthol (BINOL)	
49	***(1R,2S)***-2-{*N*-methyl-[***(2R)***-2-phenyl-2-(trifluoromethylsulfonylamino)ethyl] amino}-1-phenyl-1-propanol	
50	***(2R)***-2-phenyl-1-[(trifluoromethyl)sulfonyl]aziridine	
51	***(R)***-(-)-2-phenylglycinol	
52	Phenylacetylene	
53	***(R)***-(+)-1,3-diphenylprop-2-yn-1-ol	
54	SBA-15 supported ephedrine	

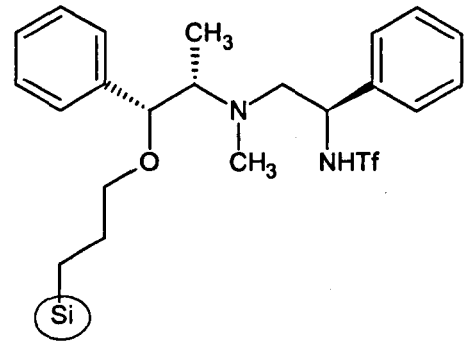
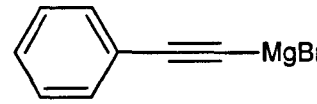
55	3-chloropropyl silyl functionalised silica gel	
56	Silica gel supported ephedrine	
57	MCM-41 supported ephedrine	
58	2-iodobenzene	
59	3-chloropropyl functionalised silica gel	
60	Ephedrine functionalised silica gel	
61	*(R)*-(+)-1,3-diphenylprop-2-yn-1-ol	

62	2-methylbenzaldehyde	
63	3-methylbenzaldehyde	
64	4-methylbenzaldehyde	
65	2-methoxybenzaldehyde	
66	2-nitrobenzaldehyde	
67	2-chlorobenzaldehyde	

68	3-chlorobenzaldehyde	
69	2-fluorobenzaldehyde	
70a	*(R)*-phenylglycinol	
70b	*(S)*-phenylglycinol	
71a	*(R)*-alaninol	
71b	*(S)*-alaninol	
72a	*(R)*-phenylalaninol	
72b	*(S)*-phenylalaninol	

73a	*(R)*-valinol	
73b	*(S)*-valinol	
74	*(R)-tert*-leucinol	
75	*(1R,2S)*-2-{*N*-methyl-[*(2S)*-2-phenyl-2-(trifluoromethylsulfonylamino)ethyl] amino}-1-phenyl-1-propanol	
76	1,1,1-trifluoro-*N*-[*(2R)*-1-{[*(1R,2S)*-1-hydroxyl-1-phenylpropan-2-yl](methyl)amino]propan-2-yl]methanesulfonamide	
77	1,1,1-trifluoro-*N*-[*(2S)*-1-{[*(1R,2S)*-1-hydroxyl-1-phenylpropan-2-yl](methyl)amino]propan-2-yl]methanesulfonamide	
78	*N*-[*(2R)*-1{[*(1R,2S)*-1-hydroxyl-1-phenylpropan-2-yl](methyl)amino}-3-phenylpropan-2-yl]-1,1,1-trifluoromethylsulfonylamide	

79	*N*-[*(2S)*-1{[*(1R,2S)*-1-hydroxyl-1-phenylpropan-2-yl](methyl)amino}-3-phenylpropan-2-yl]-1,1,1-trifluoromethylsulfonylamide	
80	1,1,1-trifluoro-*N*-[*(2R)*-1-{[*(1R,2S)*-1-hydroxy-1-phenylpropan-2-yl](methyl)amino}-3-methylbutan-2-yl]methanesulfonamide	
81	1,1,1-trifluoro-*N*-[*(2S)*-1-{[*(1R,2S)*-1-hydroxy-1-phenylpropan-2-yl](methyl)amino}-3-methylbutan-2-yl]methanesulfonamide	
82	3-methoxybenzaldehyde	
83	4-methoxybenzaldehyde	
84	4-chlorobenzaldehyde	

85	Functionalised silica supported ephedrine derived catalyst	
86	Phenylethynylmagnesiumbromide	

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1 Overview of project

1.1 Introduction

Asymmetric catalysis is an increasingly important area of interest within academia and the pharmaceutical industry. The need for novel inexpensive asymmetric catalysts is growing due to the increasing costs of existing catalysts.[1] In addition, pharmaceutical industries are looking into developing more environmentally friendly catalysts which can be reused whilst retaining the reactivity and can be used in a solvent free environment.[2] Asymmetric catalysis is a method utilised to selectively induce favoured stereochemistry into newly synthesised molecules via the formation of new stereogenic centres.[3] Asymmetric catalysis plays an important role in asymmetric synthesis and in the development of building blocks, which are used in the development of novel drugs.

Asymmetric catalysis is widely carried out under homogeneous conditions[4], comprising both catalyst and reactants present in a single phase environment[5] and this can provide an efficient way of producing products with a high degree of enantioselectivity.[6] The organic nature of the catalyst allows for it to be analysed using a wide range of spectroscopic techniques such as nuclear magnetic resonance (NMR) spectroscopy and gas chromatography (GC-MS). Despite the advantages mentioned, the ability to separate and recover a homogeneous catalyst can prove to be a difficult, time consuming and an expensive process.[7] These particular limitations are a concern as it could involve lengthy and expensive work up processes to retrieve the product and the catalyst.[8] Therefore, it has become increasingly important to research methods for recycling valuable chiral catalysts and techniques in which the environmental impact of synthesising such catalysts can be reduced.[9]

Heterogeneous catalysis, where the reactants and the catalyst are present in different phases[10], is a method of catalysis that has numerous benefits, such as the separation of the catalyst from reaction mixture and can be relatively easy and cheap. For example, a solid heterogeneous catalyst can be easy separated from its liquid reaction mixture using filtration.[11] Thus this minimises any additional work-up and the catalysts tend to be more stable than their homogeneous counterparts.[12] However, there can be a downside to heterogeneous catalysis when used in asymmetric synthesis. The catalysts generally tend to be less selective in comparison to the homogeneous equivalent catalyst, as homogeneous catalysts tend to be composed of a single molecular species with one form of active site which is present in solution, allowing the product to be more selective and fewer side products to be created. In heterogeneous catalysis the reactions may occur on the surface of the catalyst which may not be ideal as there may be many different active sites which will lead to a decrease in selectivity of the product. [13]

Since the 1990s, there has been wide interest into the research of immobilised catalysts, also known as hybrid or tethered catalysts. These new types of catalysts combine features of homogeneous and heterogeneous catalysts by tethering organic or metal complexes to inorganic support or polymer based materials.[14] A significant benefit of immobilised catalysts is that these catalysts are amenable to automated processes where the recovery of catalyst may be achieved using simple filtrations and therefore allowing reuse.[15] It is anticipated that immobilised catalysts can introduce selectivity comparable to the homogeneous counterparts and that the recovery of the catalyst would be as simple as for heterogeneous catalysts.[16] In practice, this is not always the case as there can be many complications with the tethering process, such as the difficulty in the preparation of the support materials and other issues like

the control of leaching of the organic matter or metal complex from the support material.[17] Despite these factors, it has not deterred scientists or pharmaceutical industries from developing new immobilised catalysts such as vanadium (V) oxide on silica[18] which is used in the synthesis of sulphuric acid, which helps to both reduce the overall costs of production and reducing the environmental impact. For example, silica-based catalytic supports are widely used for their stable nature and their ease of recovery from reaction mixtures, a widely used silica support is the commercially available 3-aminopropyl-functionalised silica gel, **1**[19] (Figure 1.1).

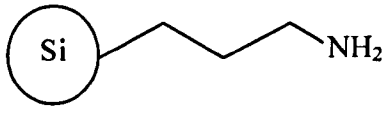
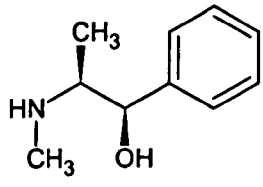


Figure 1.1 Silica-based support, 3-aminopropyl functionalised silica gel **1**



2

Figure 1.2 (*1R,2S*)-(-)-ephedrine **2**

The objectives of this research was to explore tethering (*1R,2S*)-(-)-ephedrine **2** (Figure 1.2) and its derivatives onto a silica support for testing in asymmetric alkynylation reactions which have been previously developed by Carriera[20] and optimised, using a wide range of suitable aldehyde derivatives, by Tyrrell[21]. Ephedrine **2** is a controlled substance that is regulated by a Home Office licence. By creating a tethered link between ephedrine **2** and a silica support, we aim to minimise the environmental impact and in addition, allow the

asymmetric alkynylation reaction to proceed under heterogeneous conditions. These conditions would allow for the recovery of the catalyst using a simple filtration process and then reuse the catalyst for further asymmetric reactions.

In addition this project is also focussed upon the synthesis and tethering of ephedrine-based derivatives, such as **49** (Figure 1.3), in which the carbon chain background provides an alternative site for tethering to silica. This would then allow a direct comparison with the tethered-ephedrine catalyst **60** (Figure 1.3).

The literature survey for this chapter will predominantly cover asymmetric synthesis, ephedrine and its uses. Additionally, this survey will stray into the areas of asymmetric catalysis and solid supported catalysis which are other key features that contribute to the core of the research that has been carried out throughout this project.

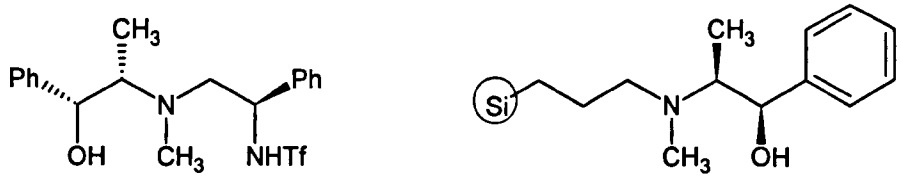


Figure 1.3 Ephedrine derived ligand **49** and Ephedrine functionalised silica gel **60**

1.2 Chiral molecules

The term chirality is used to explain a phenomenon in which molecules, due to the three dimensional array of their ligands, are non-superposable upon their mirror image[22] and in its simplest form is represented by a carbon atom where four different groups are attached to it, such as the four halogens in (Figure 1.4).[23]

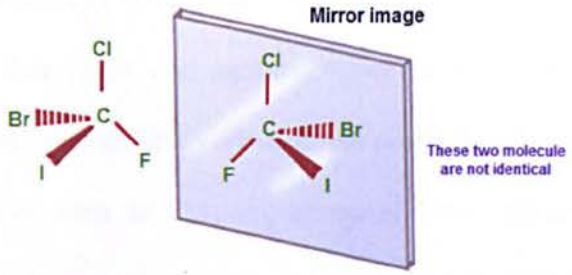


Figure 1.4 Illustration of a chiral carbon atom and the mirror-image isomer[24]

Chiral molecules are devoid of a plane of symmetry (Figure 1.5) and can exist as two optical isomers, such as those shown above (Figure 1.4) or as demonstrated with the two isomers of carvone **3a** and **3b**, such mirror images isomers are called enantiomers.[25]

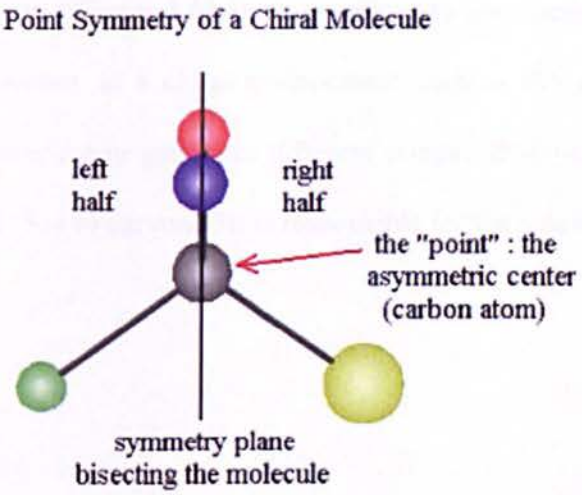


Figure 1.5 Model chiral molecule with no plane of symmetry[26]

Chirality exists largely within nature, where most chiral molecules exist as a single enantiomer.[27] Enantiomers are chemically identical, they share identical properties such as melting (m.p.) and boiling points (b.p.), however, the way in which they interact with plane-polarised light and within living systems can be very different, for instance the different interactions of chiral drug-like molecules with chiral receptors within the body, for example the enantiomers of thalidomide interact very differently within the body as explained later in Section 1.3. A common example of chirality within nature is a pair of hands, the left and the right hand are mirror images of one another, however they cannot be superimposed.[28] Enantiomers have the ability to exhibit very different properties in a chiral environment, they can affect such properties such as flavours, aroma and the efficacy of drugs due to the receptors that are within the nose, taste buds and the human body being chiral or containing amino acids or other chiral molecules which are selective to each enantiomer. Each enantiomer can interact differently with these receptors, thus creating different scents or flavours. An example of enantiomers exhibiting different properties is the pair of enantiomers for carvone **3a/3b**. This is a naturally occurring chiral molecule derived from essential oils or the seeds of caraway or dill, however it exists in the form of two enantiomers, (***R***)-(-)-carvone **3a** and (***S***)-(+)-carvone **3b**. (Figure 1.6) Both enantiomers are chemically identical in an achiral environment; however, in a chiral environment such as the smell receptors in the human nose, the enantiomeric pair generates different scents. (***R***)-(-)-carvone **3a** produces a spearmint scent, whereas (***S***)-(+)-carvone **3b** is responsible for the smell of caraway seeds.[29]

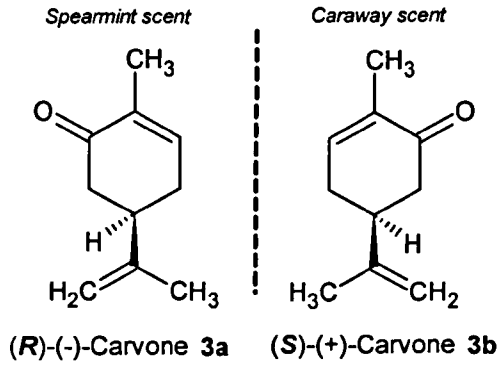


Figure 1.6 Enantiomers of carvone

1.2.1 Configuration of chiral molecules

The arrangement of functional groups around the chiral centre which is also known as its stereochemistry is a vital part of asymmetric synthesis as it defines the configuration of a molecule. The arrangement of the different functional groups around chiral carbon atom determines whether the molecule has *(R)* or *(S)* configuration, which is verified using the Cahn, Ingold and Prelog naming system (Figure 1.7).[30] Priorities are assigned after deciding which substituent atom, that is bonded to the carbon atom, has a higher relative atomic mass. Other factors which are considered are bond types and if the atom is part of a chain. The different functional groups are arranged with the highest priority rotating to the lowest prioritised functional group.

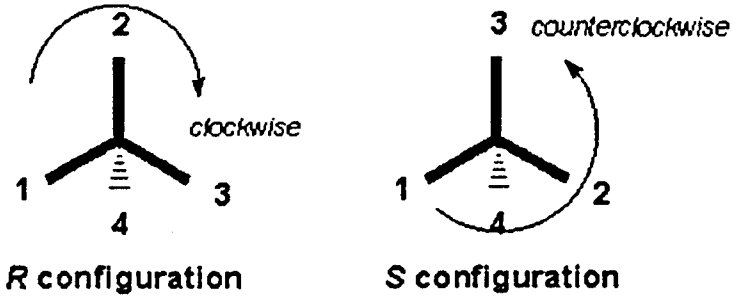


Figure 1.7 Cahn Ingold Prelog naming system[31]

1.2.2 Optical rotation

To summarise, in an achiral environment enantiomers are chemically identical, they have identical spectra and physical properties.[32] Enantiomers are often referred to as optical isomers and have the ability to rotate the plane of plane-polarised light either to the left (often referred to as (-) or levorotatory, L) or to the right (referred to as (+) or dextrorotatory, D).[33] Pairs of pure enantiomers rotate plane of plane-polarised light in opposite directions by the same number of degrees.[34] (***R***)-(-)-Carvone **3a**, for instance, rotates the plane of plane-polarised light to the left at 25°C, giving a specific rotation of -61° whereas (***S***)-(+)-carvone **3b** rotates the plane of plane-polarised light to the right at 25°C, giving a specific rotation of +61°.[33]

Polarimeters (Figure 1.8) are instruments used for detecting the angle of rotation when plane-polarised light is passed through a solution of the enantiomer.[35]

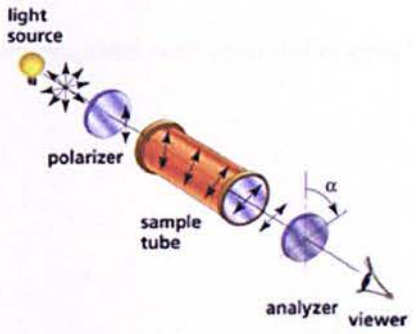


Figure 1.8 The formation of plane-polarised light by a polarimeter[36]

The amount the light that is rotated can vary depending upon the structure of the molecule, the temperature, the wavelength and the solvent.[37] The factors that are kept consistent are the concentration of the sample, which is kept at 1 g of sample per 1.00 ml of solvent; and the

path length of the cell that the solution is placed into, which is 10.0 cm.[38] In order to calculate the specific rotation, the following formula stated in the Chemical Rubber Company (CRC) handbook of chemistry and physics[39] is used:

$$[\alpha]_D^T = \frac{\alpha}{lc}$$

Where: $[\alpha]_D^T$ = Specific rotation at specific temperature, T (°C) and at specific wavelength, D, nanometres (nm)

α = Observed rotation at temperature, T (°C)

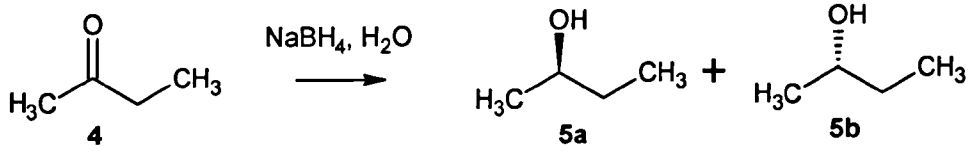
l = cell length, decimetres (dm)

c = concentration of sample solution (g/ml)

Chiral molecules can exist as pure enantiomers or as part of a racemic mixture which is the term used to describe an equimolar mixture of two enantiomers in equal proportions, such a mixture is optically inactive.[40] If plane-polarised light is passed through a racemic solution, then the light passes through unperturbed with zero deflection.[41]

1.3 Asymmetric synthesis

Asymmetric synthesis is a chemical reaction which converts an achiral molecule into stereoisomers, which are identical molecules with differing three-dimensional arrangements of atoms in space.[42] Asymmetric synthesis causes the stereoisomers to be formed in unequal amounts.[43] It is a method used to selectively introduce one or more desired elements of chirality.[44] An example of an achiral molecule being converted into stereoisomers is displayed by the reduction of butan-2-one **4**, an achiral molecule which gives two stereoisomers of butan-2-ol **5a/5b**.[45] (Scheme 1.1)



Scheme 1.1 Reduction of butan-2-one **4**

Asymmetric synthesis involves using chiral reagents or catalysts derived from natural sources to favourably form one enantiomer in excess over another.[46] Asymmetric synthesis is highly advantageous within industries such as the pharmaceutical industry as chiral drugs must be 99.9% of one isomer only. This is imperative and a strict requirement for the drug to be licenced.[47] The chiral drugs can be made more effective with the use of enantiomers as they can interact selectively within living systems.[48] Enantiomers of chiral drug molecules behave differently when interacting with receptors within living systems, this is due to the receptors themselves being chiral themselves so would interact with enantiomers differently. Pharmaceutical industries face challenges when administering chiral drugs. If the chiral drug is administered as a racemic mixture, one enantiomer would be the active component, A (Figure 1.9) and make a 3-part interaction with the receptor at **a**, **b** and **c** whilst the

enantiomer **B** makes only a one-point interaction at **b**. This may lead to a drug effect or an incompatible response. (Figure 1.8)

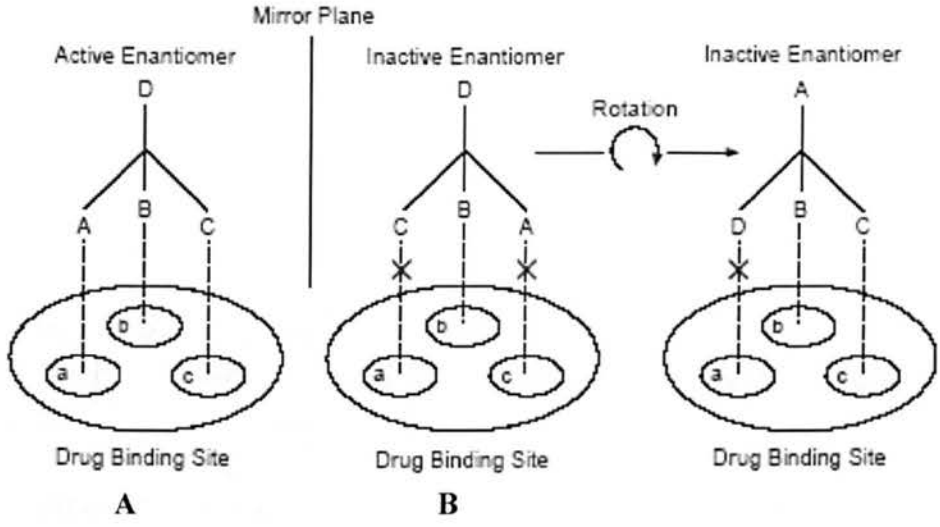
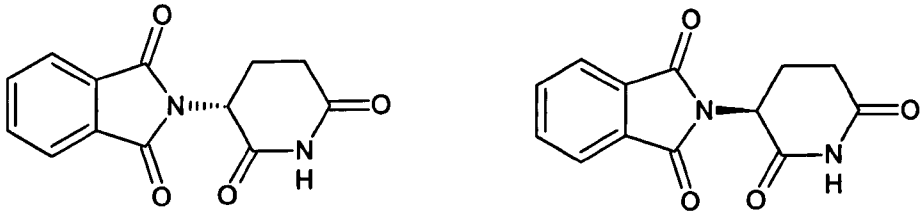


Figure 1.9 Enantiomer interactions[49]

In the 1960s, there was a crisis when an anti-nausea drug, thalidomide which is currently trademarked under Thalidomide® was administered to pregnant women as racemic drug. The ***(R)***-thalidomide **6a** enantiomer was the active ingredient; however, it was unknown at the time that the enantiomer ***(S)***-thalidomide **6b** was extremely toxic to the developing embryos. (Figure 1.10) Enantiomers are generally classified using the Cahn Ingold and Prelog naming rules as either being the ***(R)*** or ***(S)*** enantiomer; this is due to way in which functional groups are configured around the chiral carbon. The toxic effects of ***(S)***-thalidomide **6b** resulted in the babies being born with birth defects such as missing limbs.[50] Following the thalidomide incident, stronger governance was put into place to ensure better testing of chiral drugs took place and where possible, chiral drugs were to be administered as single enantiomers. In the case of thalidomide, it is now believed that the thalidomide racemised or converted to the

other enantiomer *in vivo* via the chiral carbon of thalidomide tautomerising under basic conditions into an enol, which can reverse back to the keto form resulting in a racemic mixture of both (***R***) and (***S***) enantiomers. It is presumed that the ***(R)*** enantiomer of thalidomide underwent a reversible keto-enol tautomerisation when hydrogen bonding to water *in vivo*, however when thalidomide converted back to its enantiomeric form it produces a mixture of both the ***(R)***-thalidomide **6a** and ***(S)***-thalidomide **6b**.



(R)-thalidomide, **6a** ***(S)***-thalidomide, **6b**

Figure 1.10 Enantiomers of thalidomide **6a** and **6b**

1.3.1 Asymmetric synthesis with chiral molecules

There are numerous ways to create pure enantiomers,[51] however, a key feature for this is the involvement of chiral molecules from natural sources. Chirality cannot be induced into a new molecule without the use of a chiral environment such as a solvent, reagent or catalyst or the use of naturally chiral molecule.[52] The different methods that are adopted to obtain samples of pure enantiomers are:

- the resolution of racemic mixtures (see section 1.3.2)
- the use of chiral pool molecule (see section 1.3.3)
- the use of chiral auxiliaries attached to starting materials (see section 1.3.4)
- the use of chiral reagents (see section 1.3.5)

- the use of chiral catalysts (see section 1.4)

When forming a new chiral centre on an achiral molecule using achiral reagents, a racemic mixture is formed as this creates two transition states of equal energy (Figure 1.11) and hence the enantiomers are formed in equal amounts.[53] Thus, in order to separate the individual enantiomers from the racemic mixture would require a process called resolution.

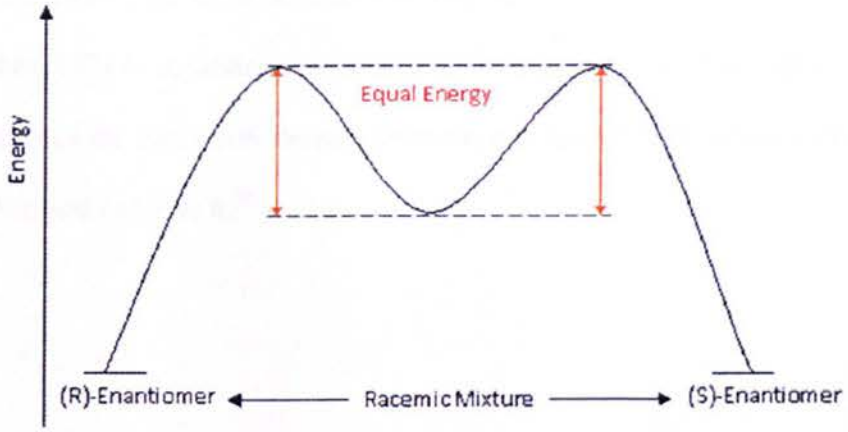
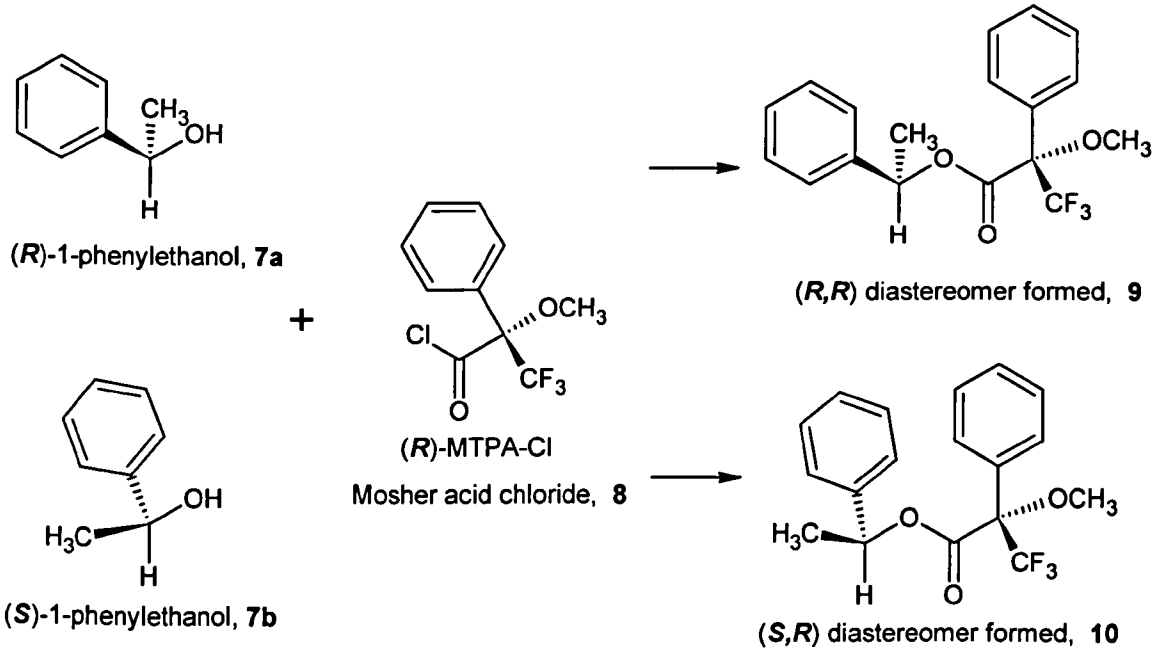


Figure 1.11 Formation of racemic mixture in an achiral environment[54]

1.3.2 Resolution of enantiomers

Resolution is a method which is used for the separation of enantiomers from a racemic mixture. One method involves attaching an enantiomerically pure resolving agent to the racemic mixture and a second technique involves the use of chiral chromatography to separate the enantiomers.[55] Chiral chromatography, which is also known as chiral column chromatography is a method of separating ***(R)*** and ***(S)*** enantiomers by using a chiral stationary phase which will cause one of the enantiomers to favourable attach whilst the other enantiomer passes through the column with the aid of a solvent.

An example of an enantiomerically pure resolving agent that is used to resolve a racemic mixture is Mosher acid chloride **8**. The chiral derivatising agent (CDA), Mosher acid chloride **8** is utilised in Scheme 1.2 to resolve a racemic carboxylic acid mixture. The chiral derivatising agent (CDA) **8** is esterified when added to the racemic acids (**7a** and **7b**) to produce two different diastereoisomeric esters **9** and **10**. These may then be readily separated or resolved (for example, selective recrystallisation, column chromatography or high performance liquid chromatography (HPLC)) as diastereoisomers have different physical characteristics. One of the most popular resolving agents, Mosher's acid **8**, was first used by Henry Mosher, 1973 to separate enantiomeric alcohols or amines.[56] Scheme 1.2 below shows the preparation of the two esters derived from the reaction of 1-phenylethanol (**7a** and **7b**) a nd the Mosher acid chloride **8**.[57]



Scheme 1.2 Resolution of 1-phenylethanol using Mosher acid chloride **8**

The esters **9** and **10** may then be readily isolated using, for instance their difference in R_f value, or by recrystallisation if one ester is solid and the other a liquid. Unlike the racemic mixture of 1-phenylethanol, the esters **9** and **10** are now diastereomers.

An alternative and increasingly popular method which is used to separate and resolve racemic mixtures of enantiomers is chiral column chromatography. This technique requires a pure enantiomer of a chiral molecule being attached to an achiral support, such as cellulose or silica gel to create a chiral stationary phase.[58] A racemic mixture is then passed through the chiral stationary phase with the aid of a solvent, causing only one of the enantiomers to attach to the stationary phase as it has a higher affinity for it, whilst the other enantiomer passes through the column and is collected. (Figure 1.12)

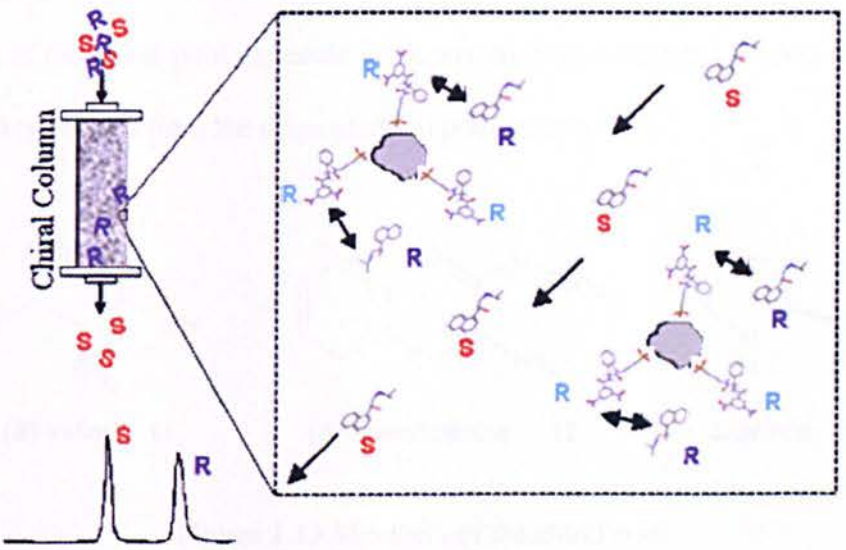


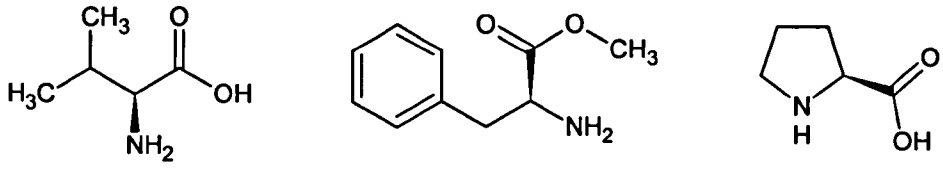
Figure 1.12 The principles of chiral chromatography[59]

The major problem for resolution of enantiomers is that only 50% of an enantiomer can be gained from a racemic mixture.[60] This is due to a racemic mixture containing equal amounts

of both the *(R)* and *(S)* enantiomer. The purpose of resolving a racemic mixture is to gain either the pure *(R)* enantiomer or the pure *(S)* enantiomer. For example, recrystallisation may cause only one of the enantiomers to crystallise out of solution, whilst the other remains in the solution. This means that the remaining 50% of the racemic mixture or the other enantiomer is effectively wasted and hence, this can become an expensive process of preparing pure enantiomers. Therefore, it would be more favourable to be able to synthesise enantiomers selectively and thus, reducing any waste.

1.3.3 Chiral pool molecules

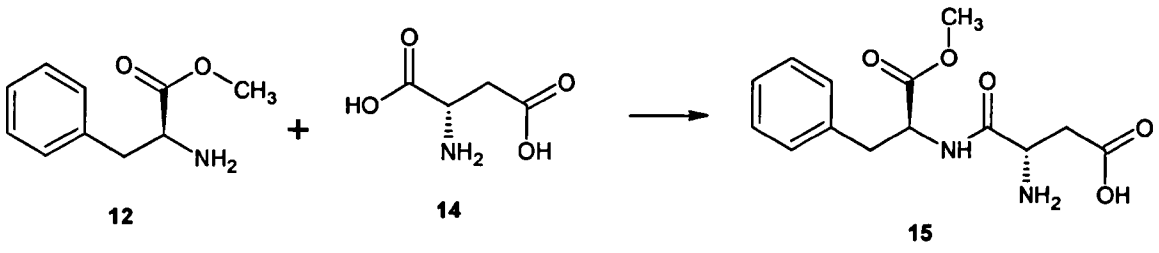
The chiral pool is a collection of relatively inexpensive and enantiomerically pure natural products such as the amino acids (*S*)-valine, **11**, (*S*)-phenylalanine **12** and *L*-proline **13**[61] (Figure 1.13) and sugars and alkaloids. During the synthesis of the desired molecule the chiral centre of the chiral pool molecule is incorporated into the final product with a known stereochemistry derived from the original chiral pool molecule.[62]



(*S*)-valine **11** (*S*)-phenylalanine **12** *L*-proline **13**

Figure 1.13 Members of the chiral pool

For example, aspartame **15**, a dipeptide sweetener used in the food industry, retains the stereochemistry of both (*S*)-phenylalanine **12** and (*S*)-aspartic acid **14**. (Scheme 1.3)



Scheme 1.3 Synthesis of aspartame **15**

The chiral pool synthetic approach offers the ability to obtain an enantiomerically pure product, however, due to the nature of the starting material there is often one enantiomer available.[62] Therefore; alternative methods of asymmetric synthesis are often explored.

1.3.4 Chiral auxiliaries

Chiral auxiliaries are molecules that are momentarily attached to a substrate during asymmetric synthesis to incorporate stereocontrol of the chiral centre. An example of a chiral auxiliary is the Evans oxazolidinone based auxiliary, **16** (Figure 1.14)[63], which forms the asymmetric centre by the formation of lithium chelated Z-enolate which is stereoselectively α-alkylated to install the new asymmetric centre, thus using a diastereoselective reaction, it only produces one enantiomer of the product.[64] Chiral auxiliaries are often formed from natural products derived from the chiral pool, for example the Evans chiral auxiliary **16** is derived from (*S*)-valine **11**.

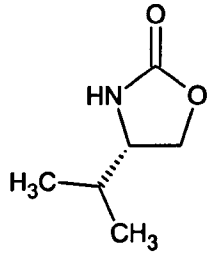
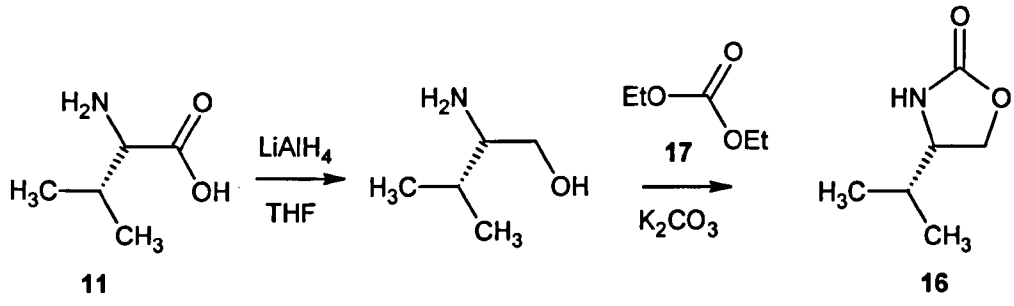


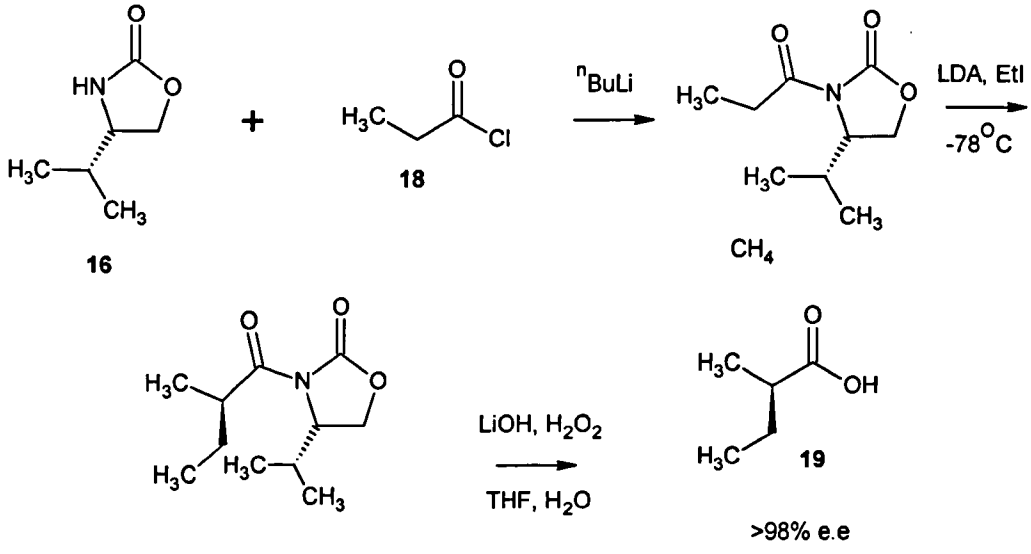
Figure 1.14 Evans chiral auxiliary, **16**

When chiral auxiliaries are utilised in asymmetric synthesis, the chiral auxiliary is attached to the starting material during the initial synthetic steps after which the asymmetric reaction proceeds creating a diastereoisomer. Once the reaction has been completed an additional hydrolysis of the chiral auxiliary is required which affords the enantioenriched product often with an ee of around 98%.[65] The synthesis of the Evan's chiral auxiliary is shown in (Scheme 1.4) and its use in the asymmetric alkylation of a carbonyl compound is displayed in (Scheme 1.5).



11 16

Scheme 1.4 Synthesis of Evan's chiral auxiliary from the chiral pool molecule, (*S*)-valine **11**



16 18 CH4 19

>98% e.e

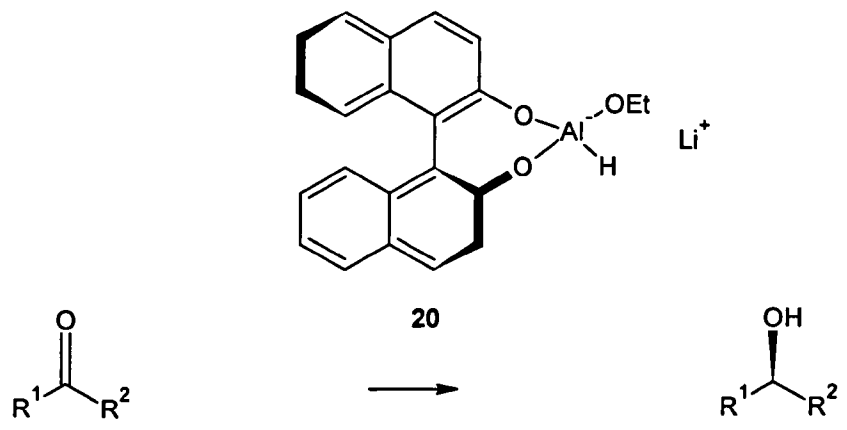
Scheme 1.5 Asymmetric alkylation using Evan's chiral auxiliary

The first step of utilising the Evan's chiral auxiliary **16** in the asymmetric alkylation involves the addition of the propanoyl chloride **18**. This is then alkylated via a diastereoselective reaction using lithium diisopropylamide (LDA). Finally, hydrolysis releases the chiral auxiliary and produces the favoured (***R***) enantiomer **19**.[66]

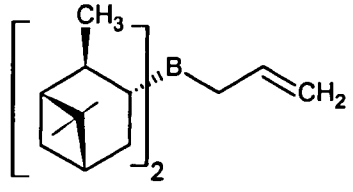
Chiral auxiliaries are effective at producing good enantiomeric excesses, which is the excess of one enantiomer over another; however, this process can become lengthy if it is difficult to remove the chiral auxiliary. The chiral auxiliary method can be more environmentally friendly if the chiral auxiliary can be recycled.[67]

1.3.5 Chiral reagents

Chiral pool and chiral auxiliary methods depend upon controlling the chirality of the substrates, however, chirality can be induced into reagents which can direct the stereochemistry of new chiral centres formed within the reaction regardless of the chirality of the substrates, and these reagents are known as chiral reagents. Chiral reagents are used in stoichiometric quantities and are not recovered upon completion of asymmetric synthesis reactions. [68] Examples of chiral reagents are (***S***)-BINAL-H **20** which was developed by Noyori (1979) for use in the asymmetric reduction of ketones (Scheme 1.6)[69] and Brown's (-)-ipc_2 allyl borane **21** (Figure 1.15) which is utilised in asymmetric allylation.[67]



Scheme 1.6 Asymmetric reduction of ketones using (*S*)-BINAL-H **20**



21

Figure 1.15 Brown's (-)-ipc_2 allyl borane **21**

The advantage of using chiral reagents is that high selectivity can be achieved and recrystallisation can improve enantiomeric purity further, however, only a small number of chiral reagents are successful.[71]

1.4 Catalysis

The definition of a catalyst is a substance that has the ability to alter the rate of a chemical reaction without appearing in the product itself.[72] The catalyst introduces an alternative reaction pathway for a reaction. If the new reaction pathway has a lower activation energy,

which is the minimum energy that the reactant requires for the reaction to take place than the reaction pathway without a catalyst, the rate of reaction increases. (Figure 1.16)[73]

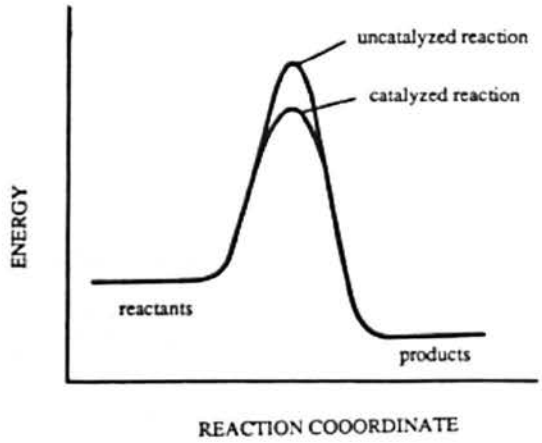


Figure 1.16 The reaction pathways with and without the use of a catalyst[74]

Catalysts are increasingly used within numerous industrial and academic processes (and have been the subject of many reviews)[75] to help make synthetic processes more efficient. Catalytic cracking, which is the process used to break down large hydrocarbon chains into smaller useful alkenes and alkanes, is widely used, where catalysts such as zeolites are used to break down large hydrocarbon chains found in petroleum oil. Zeolites are porous catalysts that allow the smaller alkanes and alkenes to filter through. Without the use of a catalyst, the cracking process would have to be carried out at an extremely high temperature and pressure to ensure the reactants have the minimum energy to react. The use of high temperatures and pressures would have a negative impact on the cost of this process.[76] Thus, there is wide interest in creating environmentally friendly catalysts which are cost effective and are recyclable, as the benefits of such catalysts are that the efficiency of reactions are increased

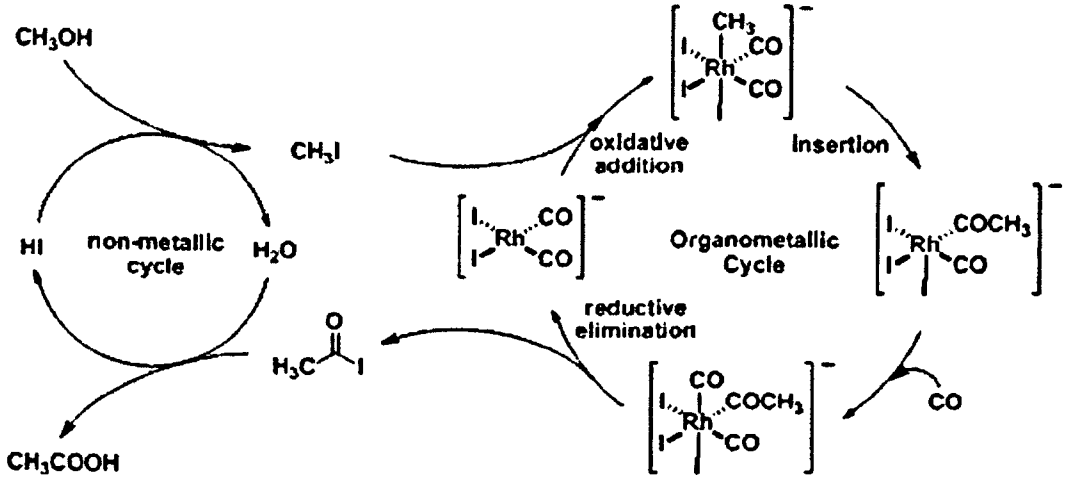
which in turn reduces the energy input required as well as the cost of the materials and the wastage produced.[77]

Catalysts tend to fall into two types of categories, homogeneous and heterogeneous catalysts. Homogeneous catalysts tend to work in the same phase as the substrates of the reactions which it catalyses.[78] Heterogeneous catalysts, on the other hand, tend to be in a different phase to the substrates of the reaction it catalyses.[79] In recent years, there has been focus on developing hybrid catalysts which combine the features of homogeneous and heterogeneous catalysts.[80]

1.4.1 Homogeneous catalysis

Homogeneous catalysts can behave in unique ways depending upon its nature and functional groups present. In general, homogeneous catalysts consist of a central atom, for example, a transition metal and one or more ligands.[81] Many industrial homogeneous catalysts involve organometallic compounds which are often composed of transition metals, such as rhodium, Rh.[82]

In the Monsanto process, the rhodium-based catalyst $[Rh(CO)_2I_2]^-$ catalyses the formation of acetic acid from methanol. (Scheme 1.7) [83] This transition metal catalyst works in a series of steps which allows the methyl iodide to attach and create acetyl iodide, which is then hydrolysed to form acetic acid. The $[Rh(CO)_2I_2]^-$ catalyst is regenerated once the acetyl iodide has been removed, thus the reaction can start again.



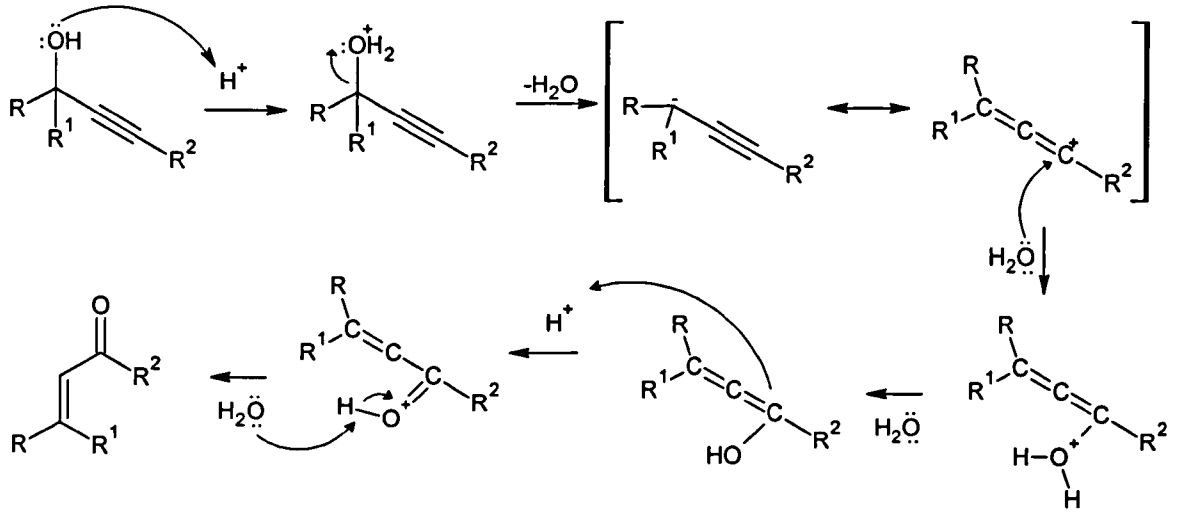
Scheme 1.7 Formation of acetic acid using the Monsanto process[84]

Homogeneous catalysts are often preferred as they are highly selective towards the formation of the desired product; however, they sometimes prove to be difficult to separate from the product as they are often miscible in the same solvents.[85] In industry, homogeneous catalysts are generally preferred for exothermic reactions as it is easier to disperse the heat from a solution than from the solid heterogeneous catalyst.[86]

1.4.1.1 Homogeneous asymmetric catalysis: the synthesis of secondary propargylic alcohols

Asymmetric catalysis is a method used to selectively yield chiral products, whereas achiral catalysis would not be able to induce stereochemistry into the product. Asymmetric catalysts can be regenerated and recovered for reuse.

The synthesis of chiral propargylic alcohols has attracted wide interest as these chiral molecules can be used as synthetic building blocks in the synthesis of natural and complex products.[83] A wide variety of complex molecules can be formed from propargylic alcohols. For example, the hydrogenation of propargylic alcohols can form substituted alkenes and acid catalysed rearrangements (such as Meyer-Schuster rearrangements) can form α,β-unsaturated aldehydes and ketones (Scheme 1.8).[87]



Scheme 1.8 Synthesis of α,β-unsaturated carbonyl compounds from propargylic alcohols

A well-known use for propargylic alcohols is for the synthesis of Merck's HIV reverse transcriptase inhibitor, Efavirenz **22** (Figure 1.17).[88]

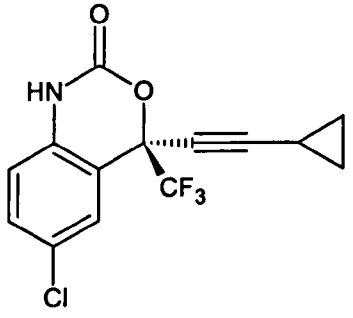
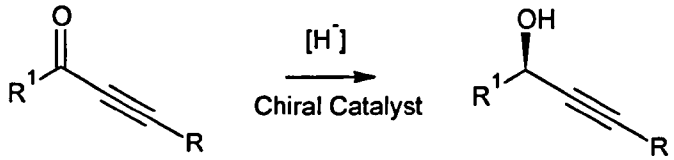


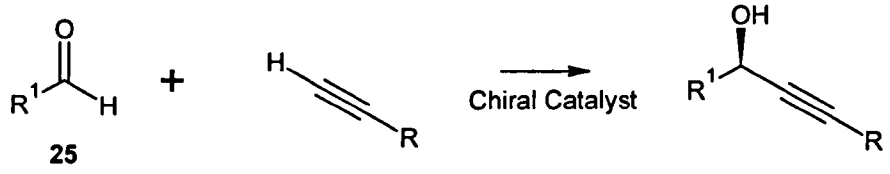
Figure 1.17 Structure of Efavirenz **22**

1.4.1.2 Asymmetric catalysis

Propargylic alcohols characteristically consist of a stable alcohol functional group and an alkyne functional group, the simplest example of a propargylic alcohol is 2-propyn-1-ol. There are two synthetic routes for the formation of secondary propargylic alcohols; the first route involves the asymmetric reduction of an α,β-ynone (Scheme 1.9) and the second involves the asymmetric alkynylation of aldehyde.[89] (Scheme 1.10) Li, Upadhyay and co-workers (1999) suggested that there is very little research undertaken into the direct method of reducing of α,β-ynones.[90] Mao and Xie (2009) suggested that the asymmetric alkynylation of aldehydes is a preferred method due to the C-C bond and the chiral centre being formed as part of one step.[91]



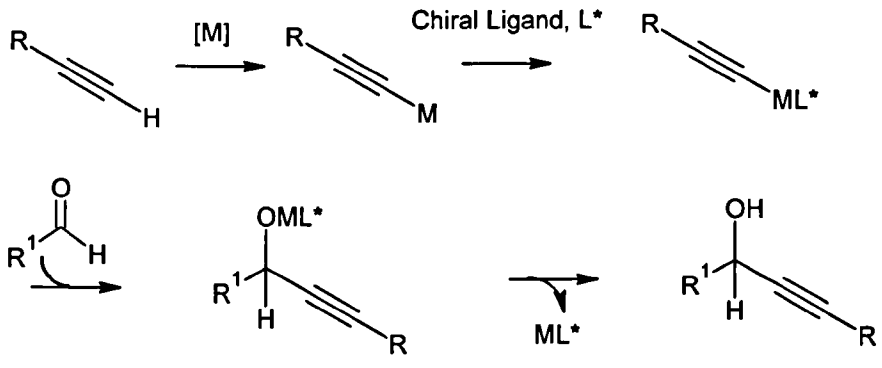
Scheme 1.9 Asymmetric reduction of α,β-ynone



Scheme 1.10 Asymmetric alkynylation of an aldehyde

Early studies into the synthesis of propargylic alcohols show Mukaiyma (1979) use *n*-butyl lithium (^{n}BuLi) to deprotonate trimethylsilylacetylene for asymmetric addition to benzaldehyde.[92] Metal complexes are often used in asymmetric alkynylation reactions to

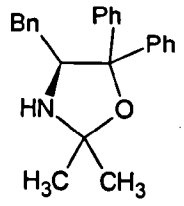
create a metal acetylide which assists the chiral catalysts involved in the reaction. (Scheme 1.11) The formation of such metalated acetylenes tends to be utilised through the use of terminal alkynes and strong bases, such as ^{n}BuLi, diethylzinc (Et_2Zn), lithium diisopropylamide (LDA) and potassium hydroxide (KOH).[93]



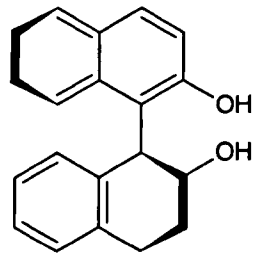
Scheme 1.11 Use of metal and chiral ligands in asymmetric alkynylation reactions

Extensive developments[94,95,96] have been made in the catalysts used for homogeneous asymmetric alkynylations. The growth of inexpensive chiral catalysts which can be used in stoichiometric quantities without lengthy reaction times has become important.[97] The synthesis of chiral catalysts tend to have a general theme of being based upon natural amino alcohols such as ephedrine, **2**.[98] Examples of chiral ligands used in asymmetric additions of phenylacetylene to aldehydes are oxazolidines **23**,[99] BINOL based catalysts **24**, [100] and modified amino alcohols ligands, **25**.[101] (Figure 1.18) These catalysts have all exhibited high yields and enantioselectivities for asymmetric alkynylations of terminal alkynes to aldehydes. They all possess planar lipophilic aromatic rings within their structure which may allow reagents to be directed to the active sites of the ligand, thus increasing the rate of reaction and ultimately the selectivity of the product formed. The need for aromatic moieties may indicate that π-stacking, the non-covalent attractive bonds between two aromatic rings; may play a

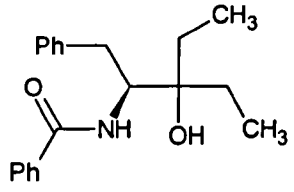
role in the catalytic process. Additionally, the use of bulky groups such as phenyl rings, ensures that the reactants do not react with other parts of the chiral ligand and therefore minimises any side products.[102]



Oxazolidine based catalyst, **23**



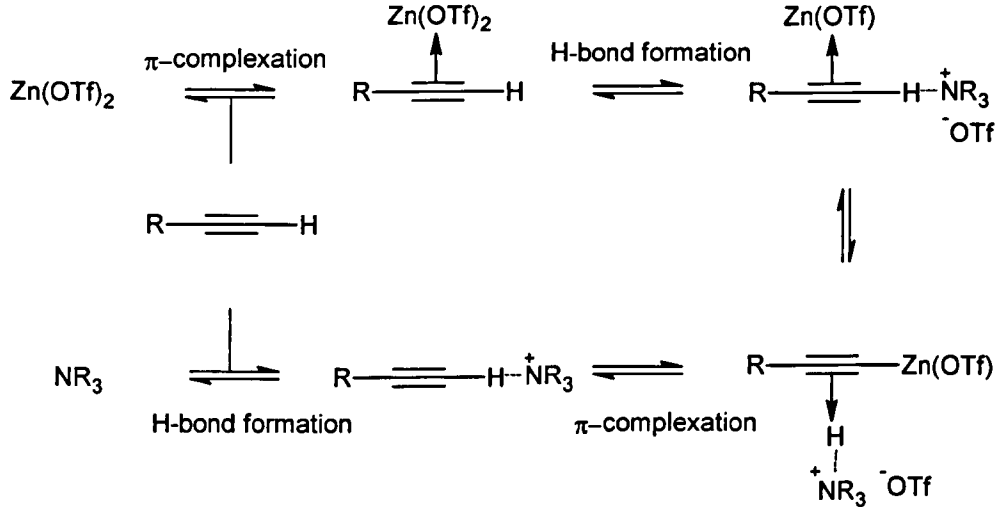
BINOL based catalyst, **24**



Amino Alcohol based Catalyst, **25**

Figure 1.18 Chiral ligands utilised in homogeneous asymmetric alkynylations

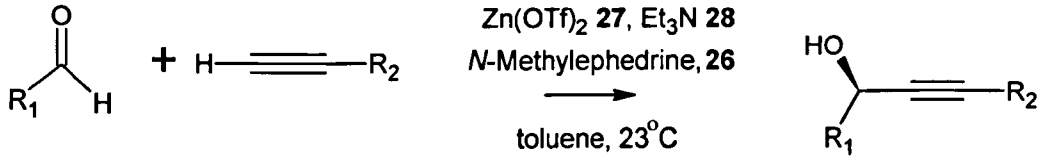
In 2000, Carreira[20] published a new method for the synthesis of propargylic alcohols that used metalated acetylene, generated *in situ*, rather than as part of a separate step. Carriera's proposed mechanism for the formation of a zinc acetylide *in situ* is shown below. (Scheme 1.12)



Scheme 1.12 Carreira's proposed zinc acetylide formation[103]

He showed that a zinc acetylide was generated *in situ* when in the presence of zinc triflate, **27** and triethylamine **28.**[103] The formation of the zinc acetylide *in situ* was confirmed through carbon NMR analysis and infrared spectroscopy. In particular, Carriera noted the disappearance of the C-H stretch (3275 cm^{-1}) on the infrared spectra as the zinc acetylide formed *in situ.*

Carriera was able to demonstrate that the asymmetric synthesis could be conducted under mild conditions which were tolerant of substrate functionality. (Scheme 1.13) The stereochemistry of the secondary alcohol is determined through the transition state, where the aldehyde coordinates to the zinc acetylide. (Figure 1.19) The *N*-methylephedrine facilitates the co-ordination of the aldehyde.



Scheme 1.13 Carreira's approach to homogeneous asymmetric alkynylation[20]

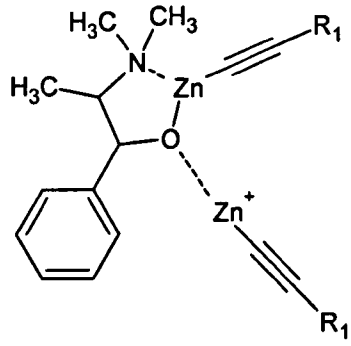
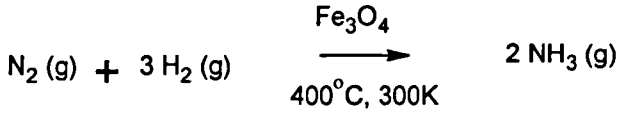


Figure 1.19 Carreira's proposed transition state

Carriera's methodology opened up the possibility of creating similar ligands; however, it became important to reduce the cost dependency on the use of drug precursors of such ligands as a large majority of these ligands were difficult to recover and reuse. Thus, an interest arose in reusable heterogeneous catalysts which had the potential to be recovered and possibly reused.

1.4.2 Heterogeneous catalysis

Heterogeneous catalysts are used widely in industry and have a much greater economic[104] impact than homogeneous catalysts due to their recyclability. It is often very expensive to synthesise such catalysts, hence it is increasingly important to be able to recover and reuse these catalysts without affecting enantiomeric purity.[105] There are numerous advantages of using heterogeneous catalysis as they are able to withstand high temperatures and pressures, and they also do not require extra steps to separate them from the product which helps it be more environmentally friendly.[106] Heterogeneous catalysis is generally divided into two categories, the first being transition metal catalysis and the latter, hybrid catalysts. An example of metal catalysis used extensively in industry is the Haber process of ammonia production which uses iron as the metal catalyst. In this process, iron catalyses the reaction of hydrogen and nitrogen to give ammonia[107] (Scheme 1.14) This process occurs heterogeneously as the iron acts a solid support which facilitates the reaction, whilst nitrogen and hydrogen are present as gases allowing for surface adsorption. The nitrogen and hydrogen gas molecules adsorb onto the iron surface, where the two molecules split into individual atoms by sharing electrons with the surface. The hydrogen atoms are able to migrate on the iron catalyst surface and react with the nitrogen atoms, to form ammonia which desorbs from the surface of the catalyst.[108]



Scheme 1.14 Haber process

There are a number of ways that reactants can interact with a heterogeneous catalyst. In general, it helps for the catalyst to have a large surface area to allow for efficient activity. If the catalyst contains large bulky ligands then these may cause sites to become unavailable for catalytic activity.[109] For example, if a catalyst that has small catalytic particles dispersed onto an alumina support; the number of available catalytic sites is increased.[110] The use of metal compounds as heterogeneous catalysts can suffer drawbacks if the metal compound is not adequately attached; weaker bonds can cause the metals to leach into reaction mixtures.[111] Ongoing research into developing better heterogeneous catalysts is still taking place and alternative hybrid catalysts are being developed in an attempt to combat the issues of such heterogeneous catalysis.

1.4.3 Hybrid catalysts

There is an increasing need to create efficient catalysts, that are cheap to synthesise and can be easily recovered for re-use.[112] Hybrid catalysts involve the tethering organic or metal complexes onto inorganic or polymer based support materials, which tend to be insoluble.[113] It is anticipated that by combining organic ligands onto a support could achieve the high selectivity of homogeneous catalysts whilst being able to recover the catalyst as in heterogeneous catalysis. It is also worth noting that hybrid catalysts are often referred to as immobilised or tethered catalysts. The formation of hybrid catalysts can cause some

limitations, as insoluble supports can cause difficulties when characterising the catalyst. In addition, the hybrid catalysts are prone to degradation and the metals used can leach from the supports.[114]

A method commonly used for synthesising a hybrid catalyst is by tethering a homogeneous catalyst to a solid support, for example, tethering an organic catalyst onto a silica surface by means of a hydrocarbon chain.[115] However, the tethering of a catalyst is not limited to covalent bonding; the catalysts can also be attached via encapsulation[116], dispersion [117] and via ionic interactions.[118] The support medium influences the way in which catalysts are tethered.

1.4.4 Types of support materials

There are a wide range of support materials utilised for the synthesis of hybrid and heterogeneous catalysts. Each support medium has its own advantages and disadvantages which can range from high surface area, availability of active sites, controlled pore sizes and recoverability and recyclability. The type of support materials used can influence the loading of the catalyst, the catalytic efficiency and stability, therefore it is crucial to choose support materials carefully.[119] The most commonly used support materials for asymmetric synthesis stated in the literature are zeolites[120], polymer-supports e.g. polystyrene[121] and silica-based supports, such as MCM-41[122,123], SBA-15[123] and functionalised silica.[124]

1.4.4.1 Zeolite supports

An example of a material used to support chiral ligands is zeolites. Zeolites are crystalline microporous support materials that exist as negatively charged three-dimensional aluminosilicate structures.[125] The zeolite structure can be modified to host a variety of cations such as K^+ and Ca^{2+}. As shown in (Figure 1.20), the three dimension structure of the zeolite can act as molecular sieves which can filter out chemical species of specific dimensions.[126]

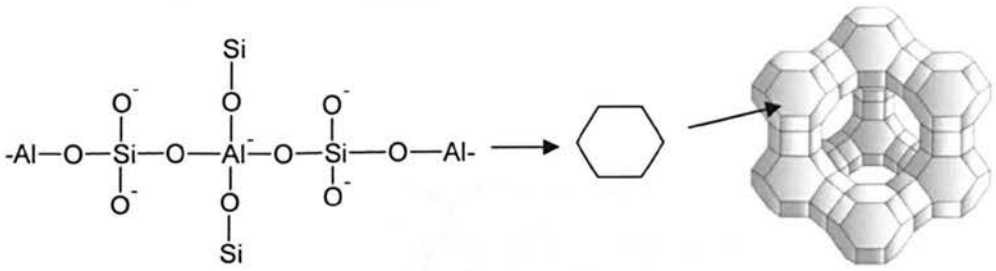


Figure 1.20 Structure of zeolite [127]

Zeolites are used as support for a wide range of asymmetric synthesis reactions, such as hydrogenation of ketones[128] and formation of aziridines from alkenes.[128] Zeolite catalysts have strong acidic sites caused by the aluminium sites; this can promote reactions such as petroleum cracking via formation of carbonium ions.[129] The porous structure of the zeolite can help to amplify stereoselectivity of chiral ligands attached by confining the reactants within its caged structure. However, the structure of zeolites limit the selectivity of more bulky ligands due to the pore size of the zeolite.[130] A further disadvantage of zeolites is that they may be moisture sensitive; therefore often have to be handled under anhydrous conditions.

1.4.4.2 Polymer supports

Polymer supports, both soluble and insoluble; are widely used in asymmetric synthesis due to varying advantages that they offer over inorganic supports. Polymer supports can be easily separated from reaction mixtures, easily functionalised and relatively stable. [131] However, unlike silica supports, polymer supports require pre-swelling in expensive, toxic organic solvents. The most commonly used polymer supports in asymmetric synthesis are cross-linked polystyrene supports. (Figure 1.21)

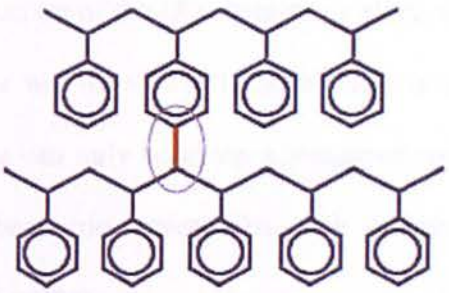
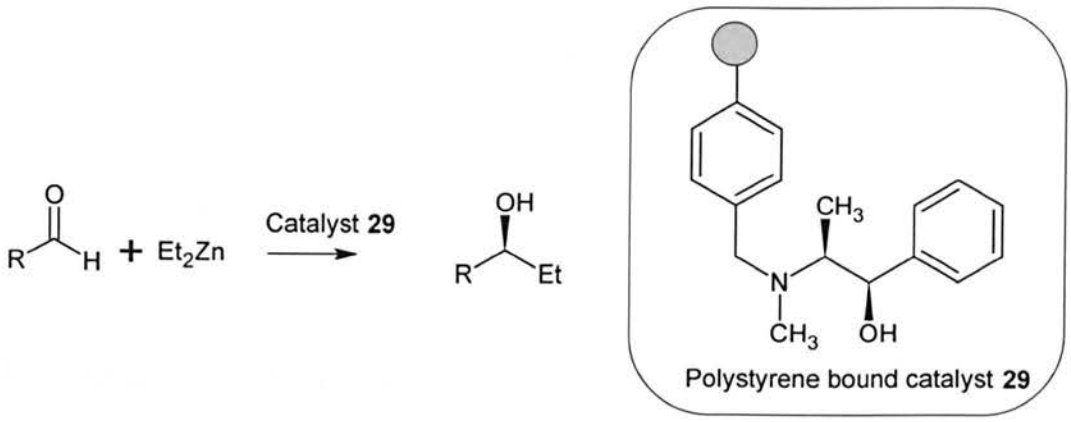


Figure 1.21 The structure of cross-linked polystyrene [132]

Polystyrene supports vary in terms of functionality, degrees of cross linking and different loading values. Soai[133] utilised a modified polystyrene supported catalyst **29** in the asymmetric alkylation of aldehydes producing good enantiomeric excesses (ee) (up to 89%) and was selective for the (***R***) enantiomers of the secondary alcohols products.[133] (Scheme 1.15) Upon completion of the reaction, Soai's catalyst **29** was recovered using a simple filtration.



Scheme 1.15 Asymmetric alkylation of aldehydes using Soai's catalyst **29**[133]

The selectivity for the production of the (***R***)-enantiomer alone was based upon the transition state of the reaction and the way in which the aldehyde interacts with the catalyst. In the transition state, the aldehyde can only bond via a staggered conformation as opposed to an eclipsed as there would be steric interactions with catalyst. Therefore, the aldehyde preferentially forms as the ***R*** isomer.

Polymer supported catalysts suffer from drawbacks which outweigh their benefits. The preparation of polymer supports can be lengthy as often the polymers require pre-swelling with solvent.[134] This can cause the polymer support to form a gelatinous phase which can result in lower catalytic loading.[135] Additionally, the viscous nature of the support can restrict access to the substrates, which would lower reaction rates and selectivity.

1.4.4.3 Silica supports

Silica has a wide range of applications, such as its use as a stationary phase for column chromatography[136] and continuous flow reactors[137] and it is commonly used as a catalytic

support.[138] Silica gel, SiO_2, is known to have very high surface area which is increased by its many pores, which can be coated covalently or via hydrogen bonds with active sites or particles, such as transition metals or organic compounds which in turn produce a large number of active sites.[139] Examples of other high surface area materials which are used vastly in this field as supports include TiO_2 and Cr_2O_3.[140] Silica supports are known to be thermally stable, chemically inert and offer easy removal of the catalyst via the use of filtration.[141]

In heterogeneous catalysis, mesoporous silica, which refers to materials that contains pores of diameters between 2nm to 50nm, is extensively used due to its availability in a wide range of forms as the pore size is variable and its functionality can be altered. Examples of mesoporous silica supports that are utilised are MCM-41 and SBA-15.[142] (Figure 1.22) The SBA-15 and MCM-41 variants of silica vary in terms of pore structures and arrangements, however they have highly ordered channels and a high surface area which allows for higher functionality within their pores. MCM-41 has even pore distribution, which is arranged in a regular hexagonal structure, with the active site located inside or outside of its pores.[143] SBA-15 tends to have larger uniform pore diameters and higher specific surface areas which can allow for materials to diffuse in and out of the pores.[144] Silica based supports, as a whole, have thermal and pressure stability, no requirement for pre-swelling making them easier for use, can be easily available and can be easily separated from their reaction mixture using filtration.[145]

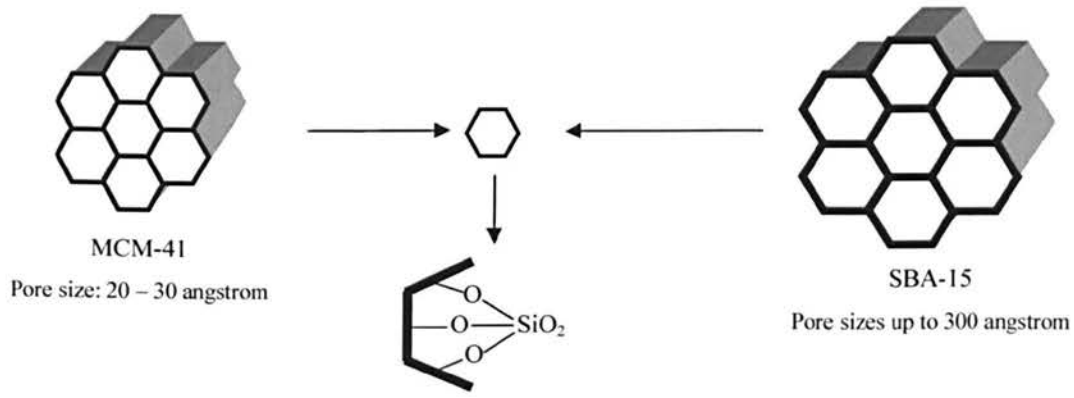


Figure 1.22 Examples of Silica based supports[146]

1.4.4.4 Silica supported catalysts in asymmetric synthesis

There are numerous examples of silica supported catalysts in scientific literature.[147,148] Iwamato and co-workers created an MCM-41 immobilised titanium catalyst for use in the asymmetric oxidation of sulphide with hydrogen peroxide. In order to attach the metal, an ion exchange was used which allowed for the titanium to be incorporated into the pores of MCM-41. [149] They found that the titanium supported MCM-41 catalyst suffered from leaching of the metal ions from the support, which suggested that the regularity of the size of the MCM-41 pores may not allow the titanium ions to sufficiently bind.

Polshettiwar[154] undertook a Mizori-Heck reaction[155], which is a reaction of a halide and an alkene in the presence of a base to form a substituted alkene; under heterogeneous conditions to synthesise substituted alkenes with the use of a palladium-*N*-heterocyclic carbene complex **31** tethered to a silica support as the catalyst. (Figure 1.23)

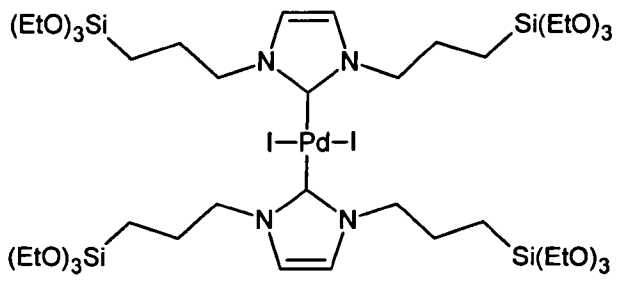


Figure 1.23 Palladium-*N*-heterocyclic carbene silica complex **31**

The silica supported palladium catalyst **31** was effective in producing substituted alkenes which were produced in yields of up to 95%. The catalyst was easily recovered and reused in up to five cycles; however, palladium leaching was detected. There is a disadvantage to using transition metals tethered to silica supports as generally the metal atoms tend to leach from the catalyst.[156] This can be problematic as catalytic activity can be reduced resulting in less selective products. Therefore, it is preferable to use silica supports that have been functionalised with organic chains.

Aminopropyl functionalised silica **1** is an example of a functionalised silica support that is used extensively as a functionalised silica support. Tyrrell[157] developed a palladium catalyst which was immobilised to aminopropyl functionalised silica. This catalyst **32** (Figure 1.24) was utilised in Sonogashira couplings[158] and was easily recovered and recycled up to four times whilst retaining catalytic activity.

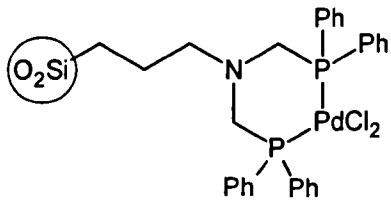


Figure 1.24 Silica supported palladium catalyst **32**

Functionalised silica supports offer many advantages to alternative support materials, such as no pre-swelling requirement, are easy to handle and have a high density of functional groups by which less silica gel is required. These supports are able to maintain catalytic activity as the silica support remains thermally stable and chemically inert. [159] The ease of removing the supported catalyst from the reaction mixture is desirable as it provides potential for recycling of catalysts.[160]

1.4.5 Analysis of hybrid catalysts used in asymmetric synthesis

The analysis of homogeneous asymmetric catalysts can be relatively simple due to the wide range of techniques available to analyse the catalyst. For example, NMR spectroscopy can help to establish the identity of a catalyst by determining the types of protons and carbons within its structure, LC-MS establishes the molecular weight of the catalyst and chiral HPLC can help to determine the enantiomer excess of any products produced via an asymmetric reaction. Unfortunately, these techniques cannot be used for the analysis of silica-based hybrid catalysts.

In order to determine the success of a hybrid catalyst, it is important to know the loading of catalytic organic material on the support material. Due to the nature of many insoluble

supports, such as silica, the loading of organic material within a hybrid catalyst can prove difficult to assess using traditional analytical techniques such as NMR and GC-MS due to interaction with the stationary phases of these techniques.

There are limited methods in the literature which provide an accurate technique of determining the loading of organic compounds tethered to silica supports. The more favoured methods are elemental analysis and thermogravimetric analysis (TGA); however, there are limitations with both approaches. Elemental analysis detects the presence and percentages of different elements within a sample, which can then be utilised to deduce a chemical formula. However, the elemental analysis results could be distorted when analysing silica supported sample which may have small percentage of surface water due to the hydroscopic nature of silica. The other technique, TGA, gently heats a sample up to 900°C to allow the various bonds of sample to break. As the sample breaks down, a chromatograph is produced which allows for the calculation of mass lost from the sample. When using elemental analysis and TGA together, it is possible to determine an approximate loading of on organic sample on a heterogeneous support.

1.5 Background of ephedrine 2

Ephedrine, **2** also known as (*1R,2S*)-(-)-2-methylamino-1-phenyl-1-propanol is a β-aminoalcohol that is extracted from the plant species *Ephedra Sinica* (Figure 1.25)[161] found predominantly in China and other parts of Asia, such as India.[162]

Figure 1.25 *Ephedra Sinica* plant species[162]

The *Ephedra Sinica* plant species is known to contain of a number of alkaloids which are naturally occurring products that consist of at least one nitrogen atom and a heterocyclic ring. The alkaloids predominantly found in *Ephedra Sinica* are (***1R,2S***)-(-)-ephedrine **2**, (***1S,2R***)-(+)-*N*-methylephedrine **26**, (***1S,2S***)-(+)-pseudoephedrine **33**, (***1S,2R***)-(+)-ephedrine **34**, (***1S,2R***)-(+)-norephedrine **35** and (***1R,2R***)-(-)-pseudoephedrine **36** (Figure 1.26).[163] Approximately, 2.5% of alkaloids are present in the stem of *Ephedra Sinica* plant with ephedrine being the major component of the alkaloid content.[159]

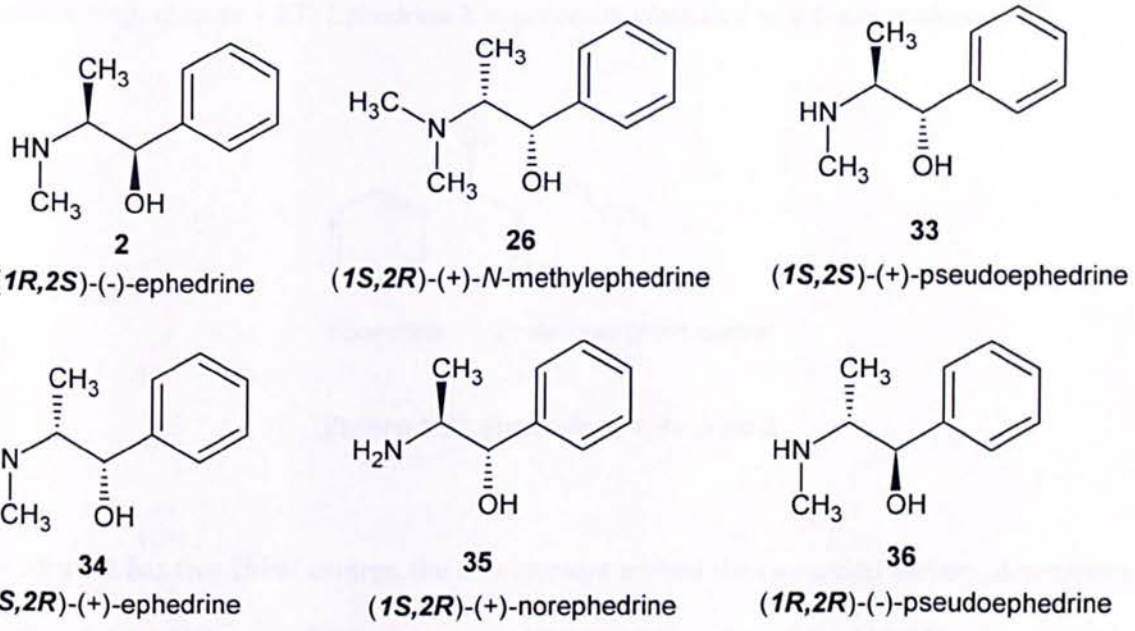
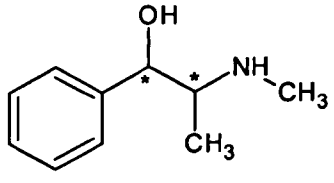


Figure 1.26 Alkaloids found in *Ephedra Sinica*

Ephedrine **2** was first isolated in 1885 by a Japanese scientist, Nagai, who used an extraction of cold benzene and dilute sodium carbonate.[164] The uses of ephedrine **2** were later explored by Chen and Schmidt (1924) who reported that it exhibited medicinal properties such as stimulating the circulatory system and acting as bronchodilator in rats.[165] The latter findings were a medical breakthrough as ephedrine **2** became a potential drug for the treatment of asthma.[166] Despite ephedrine **2** having numerous medical benefits, it is found to be important for asymmetric synthesis, which is used to introduce stereochemistry into newly synthesised molecules and ephedrine is used as a precursor to drugs.[163] Due to the structure and chiral nature of ephedrine **2**, it is able to induce stereochemistry when used either as a chiral catalyst or as a reagent within asymmetric reactions.[167]

1.5.1 Structure of ephedrine 2

The structure of ephedrine **2** is crucial to its activity and consists of a phenyl ring, a secondary benzyl alcohol group and a secondary *N*-methylamino group attached to the aromatic ring. (Figure 1.27) Ephedrine **2** is generally classified as a β-aminoalcohol.[168]



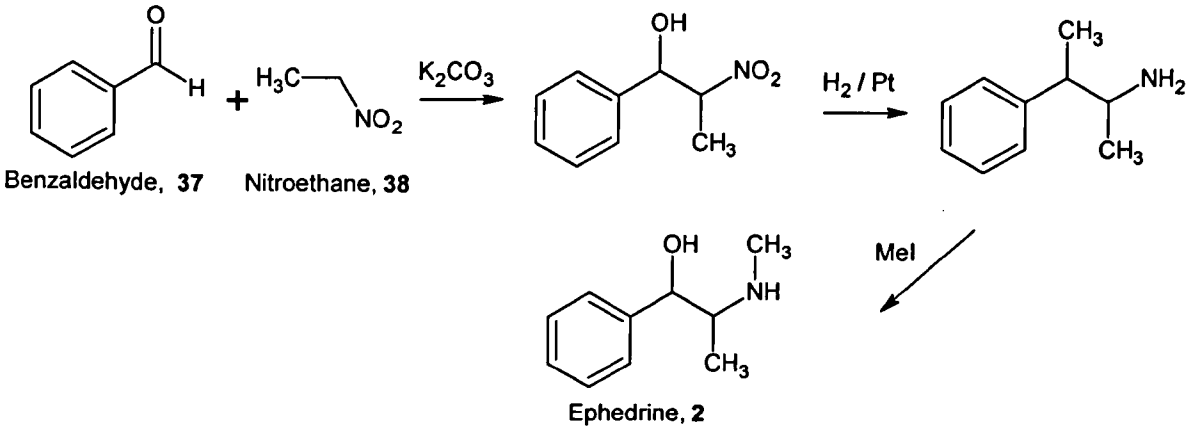
Ephedrine *(* denotes chiral centre)*

Figure 1.27 Structure of ephedrine **2**

Ephedrine **2** has two chiral centres, the arrangement around the two chiral carbons determines whether the enantiomers of ephedrine are (*1R,2S*)-(-)-ephedrine **2** or (*1S,2R*)-(+)-ephedrine

34. Alternatively if the arrangement around the chiral carbons are (*1S,2S*) or (*1R,2R*), this forms the diastereoisomers of ephedrine, which are the enantiomers of pseudoephedrine **33/36**.

Despite ephedrine **2** being extracted from the Chinese plant species, *Ephedra Sinica*, it can be synthesised in a laboratory using a common method that involves the condensation of benzaldehyde, **37** and nitroethane, **38** to produce a mixture of the ephedrine enantiomers. (Scheme 1.16)[169]

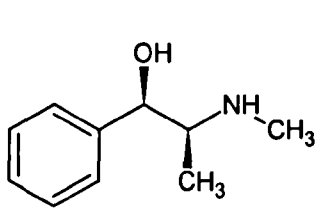


Scheme 1.16 Synthesis of ephedrine **2**

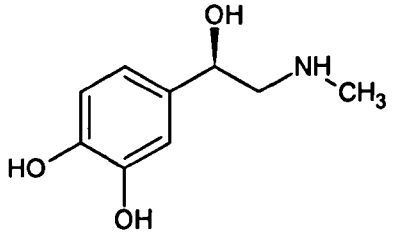
1.5.2 Medical properties of ephedrine 2

Ephedrine **2** is a sympathomimetic amine which imitates the effects of transmitter substances within the central nervous system.[170] It has a vast number of medical significances such as acting as a central nervous system stimulant, an appetite suppressant and a nasal decongestant [168] which can be beneficial to patients that suffer from asthma or narcolepsy.[171] It stimulates the activity of noradrenaline on the receptors of the central nervous system.[172] An additional

property of ephedrine is that it can assist with weight loss by inducing thermogenesis, which is the process that generates heat *in vivo* after eating.[173] Ephedrine **2** is structurally similar to the neurotransmitter epinephrine, **39** (adrenaline)[174] (Figure 1.28) and the potent Class A drugs, amphetamine **40** and methylamphetamine **41**.[175] (Figure 1.29) The similarities with the latter have led to the misuse of ephedrine **2**, forcing the UK government to put legislation in place to prevent ephedrine used as a precursor for the synthesis of these classified substances.

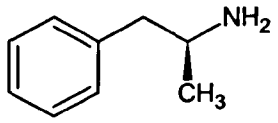


(1R,2S)-Ephedrine, **2**

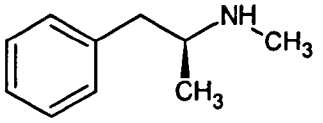


(R)-Epinephrine, **39**

Figure 1.28 Structures of ephedrine **2** and epinephrine **39** (adrenaline)



(S)-Amphetamine, **40**



(S)-Methylamphetamine, **41**

Figure 1.29 Class A drugs, amphetamine **40** and methylamphetamine **41**

1.5.3 Licence of ephedrine 2

Ephedrine **2** and its derivatives are precursors to forms of Class A drugs,[176] which are extremely potent, highly addictive and in some cases can cause fatalities as it affects the central nervous system causing damage both physically and psychologically.[177] For this reason, a licence from the Home Office is required to control the misuse of this substance and

to prevent the conversion of ephedrine **2** into these illegal drugs. In 2008, legislation was put into place by the Home Office using the Misuse of Drugs Act of 1971 to stop the misuse of ephedrine **2** and pseudoephedrine **33**. The legislation states that it is illegal to sell or supply medicinal products that contain more than 180 mg of ephedrine **2** or 720 mg of pseudoephedrine **33** without a prescription. Additionally, the sale of the products could only be carried out by a pharmacist or the licence holder.[178] Other measures that have been put into place are reducing pack sizes of medications containing either of these compounds.

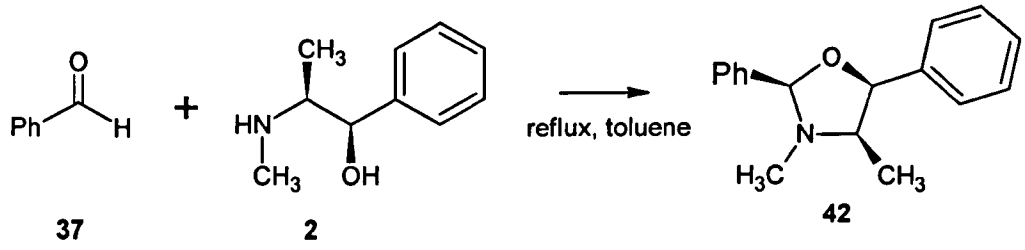
The Medicines and Healthcare products Regulatory Agency (MHRA) is a government body which encouraged the restrictions due to concern that the over the counter (OTC) medications containing ephedrine **2** could be used on small scale to synthesise these illicit class A drugs. The MHRA annually reviews the effectiveness of the licence and reports to the Home Office with their findings. If it is found that there has been misuse of either ephedrine **2** or pseudoephedrine **33**, the Serious Organised Crime Agency (SOCA), which works in combination with the MHRA, can issue penalties which can lead to imprisonment, fines and revoke of any licences held.

Ephedrine **2** has been classed as a Category 1 precursor chemical substance as it is a key component in the synthesis of amphetamines.[179] This is the highest category for drug precursor chemicals; hence a licence must be obtained by those who supply it and those who use it in manufacture. The licence requires the use of ephedrine **2** to be carefully assessed and administered by a licence holder whom needs to be present when the substance is measured out for use. The licence puts limitations on how efficiently ephedrine **2** may be used in both

industry and research environments as the use of the substance must be accurately documented.

1.6 Asymmetric synthesis with ephedrine 2

Asymmetric synthesis is an important process in which chirality can be selectively introduced into organic molecules.[180] Due to the presence of two chiral centres, ephedrine **2** is very effective in asymmetric synthesis, not only as a reagent but also as a catalyst. (*1R,2S*)-(-)-ephedrine **2** or ephedrine derived catalysts, such as *N*-methylephedrine **26**, can assist in a range of reactions such as the catalytic hydrogenation, alkylation and alkynylation of aldehydes which has been documented extensively.[181,182] Ephedrine **2** plays an essential role of a reagent in the synthesis of oxazolidine **42** which is required for the condensation of aliphatic aldehydes.[181] The oxazolidines can then be further utilised for the formation of tertiary amino alcohols. Neelakantan[182] described the use of ephedrine **2** in the synthesis of oxazolidines **42** which involved the addition of ephedrine **2** to a range of aldehydes to create a five membered ring structure **42**. (Scheme 1.17)

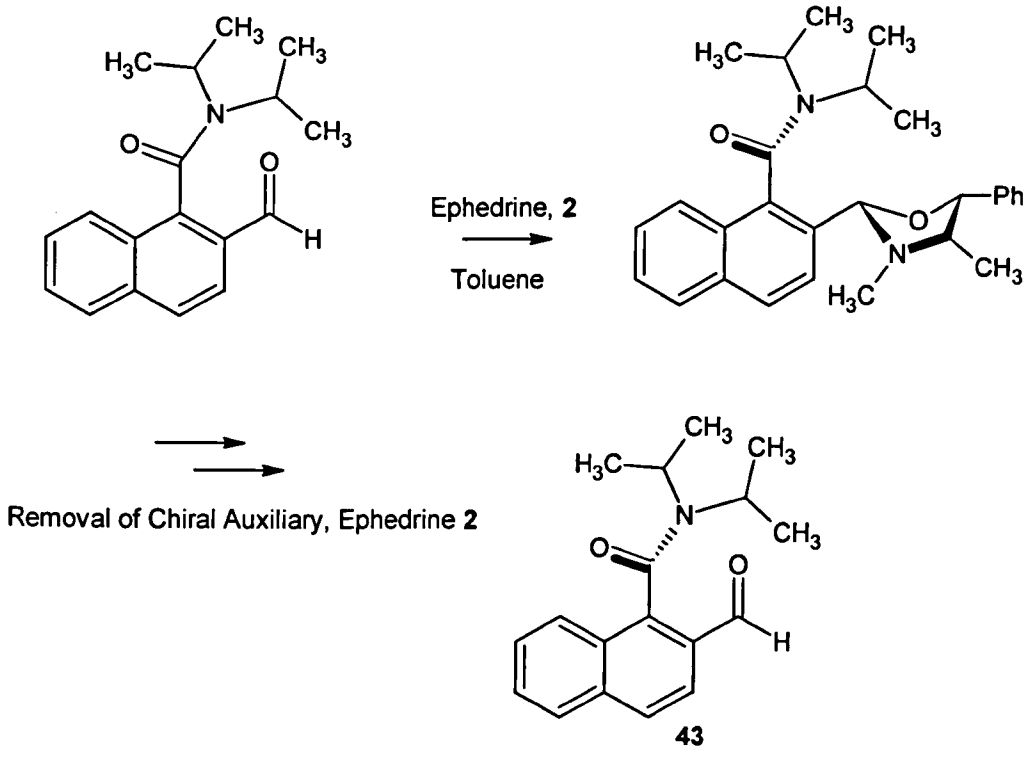


37 **2** **42**

Scheme 1.17 Synthesis of an oxazolidine **42**

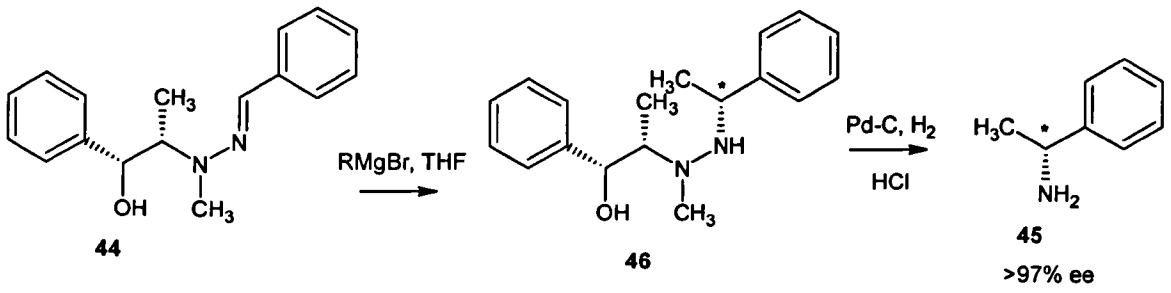
Clayden and Lai [183] utilised ephedrine **2** as an auxiliary in the asymmetric synthesis of amides to control the configuration of a neighbouring amide-carbon. (Scheme 1.18) When ephedrine

2 is removed, the product reverts back to the starting aldehyde **43**, however, retains the induced stereochemistry.



Scheme 1.18 Inducing stereochemistry into amides using ephedrine **2** as a chiral auxiliary

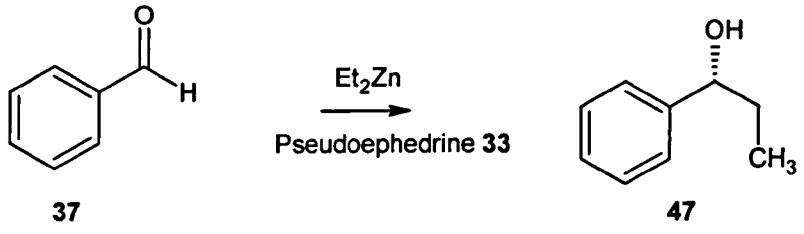
Takahashi and co-workers[184] utilised ephedrine **2** as a chiral auxiliary when reducing a chiral hydrazone **44** to form the (***R***) isomer of phenylethylamine **45**. The ephedrine moiety was attached to form the chiral hydrazone **44** which is reduced to the hydrazine **46** and allowing selectivity to be induced into the newly formed chiral centre.



Scheme 1.19 Reduction of a chiral hydrazone **44**

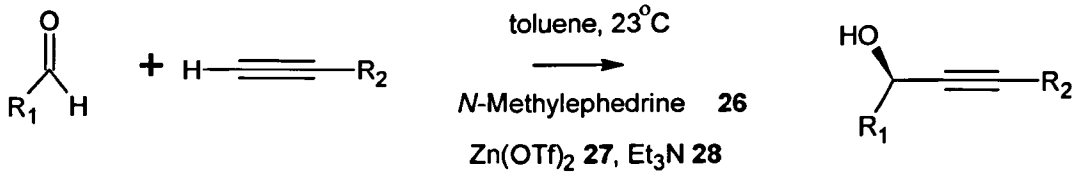
1.6.1 Asymmetric synthesis with ephedrine derivatives

There is increasing interest in developing novel catalysts for asymmetric synthesis. Ephedrine **2** is an excellent catalyst; however, due to the limitations applied by UK legislation, pharmaceutical industries are researching into alternatives based upon the structure of ephedrine, **2**. Ephedrine **2** has been utilised in many ways in asymmetric synthesis, as a reagent[185], a catalyst[186] and a chiral auxiliary.[187] Ephedrine and its derivatives such as pseudoephedrine **33** and *N*-methylephedrine **26** are commonly used as catalysts in asymmetric synthesis, for example, in the asymmetric alkylation of benzaldehyde **37** (Scheme 1.20) or in asymmetric alkynylations involving alkynes and aldehydes.[188]



Scheme 1.20 Asymmetric alkylation of benzaldehyde **37**

One of the more commonly used ephedrine derivatives is *N*-methylephedrine **26**. In the case of asymmetric alkynylation reactions, *N*-methylephedrine **26** has been found to perform better than ephedrine **2** by its interaction and effects upon the activation of the reactivity of the metal atom in the metals used to create the metal acetylide. (Scheme 1.20)[189] Carriera reported novel findings for an asymmetric alkynylation reaction with aliphatic aldehydes. It involved the generation of a zinc acetylide *in situ*, from the reaction of a terminal alkyne and an aliphatic aldehyde, in the presence of *N*-methylephedrine **26**. The product obtained high yields and enantioselectivity (up to 99%).[19] The use of (*1S,2R*)-(+)-*N*-methylephedrine **26** as a catalyst influences the stereochemistry about the newly formed chiral centre which favoured the (*R*) enantiomer of the propargylic alcohol. (Scheme 1.21)



Scheme 1.21 Asymmetric alkynylation using Carreira's method

A number of catalytic alkynylation reactions have been investigated since these novel findings. Novel catalysts based on the structure of ephedrine **2** are being developed in hope of improving enantioselectivity of the alkynylation reaction. Lu synthesised a number of 1,1'-bi-2-naphthol (BINOL) **48** (Figure 1.30) catalysts featuring a β-aminoalcohol moiety, similar in structure to that of (*1R,2S*)-(-)-ephedrine **2**.[190] However, the methyl and phenyl ring functional groups were substituted at the R_1 and R_2 positions. The catalyst was tested in a simple alkynylation reaction between an aromatic aldehyde and an alkyne and it was found that the phenyl substituted catalysts (R_1 or R_2) were more effective than the methyl groups,

this is due to the bulky nature of the phenyl rings which helps to direct attachment of the aldehyde to the alkyne. Lu's BINOL catalyst **48** was very effective and provided good enantioselectivity (up to 90%) and a high conversion rate of 95%.[191]

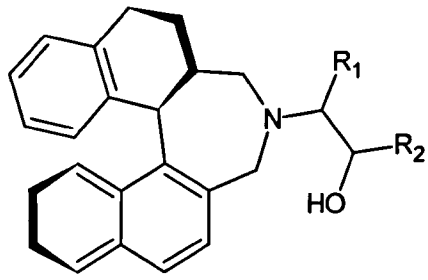
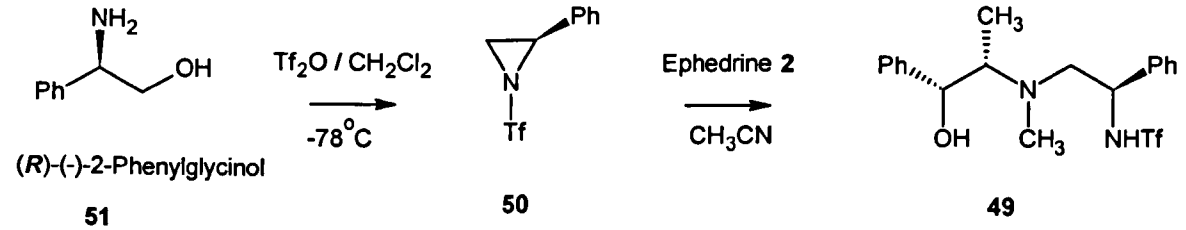
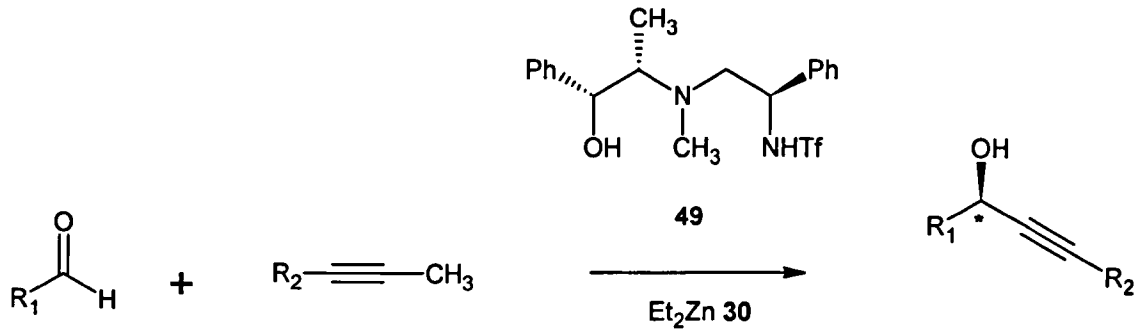


Figure 1.30 BINOL **48** based catalyst

Another group, Li *et al.*[192] later reported a novel trifluoromethanesulfonyl (Tf) based sulfamide-amine **49** catalyst (Scheme 1.22) which catalysed the asymmetric alkynylation of an alkyne with an aromatic aldehyde. (Scheme 1.23) The catalyst was formed via a synthesis using (*1R,2S*)-(-)-ephedrine **2** and an aziridine **50**, which was formed using chiral amino alcohol **51**. (Scheme 1.22)

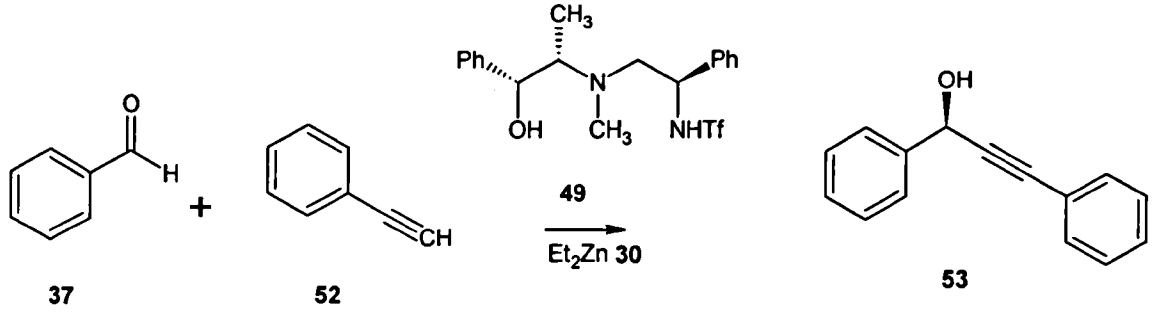


Scheme 1.22 Synthesis of triflate-based sulfamide-amine catalyst **49**



Scheme 1.23 Alkynylation of aldehydes using triflate-based sulfamide-amine catalyst **49**

The catalyst **49** was tested in the asymmetric addition of phenylacetylene **52** to benzaldehyde **37**, (Scheme 1.24) this produced high yields and enantiomeric excess values (up to 99%). The catalyst **49** was then further experimented with a range of aldehydes providing promising results.



Scheme 1.24 Asymmetric addition of phenylacetylene to benzaldehyde using **49**

1.6.2 Immobilised ephedrine catalysts

Chiral catalysts have the advantages of being economical as only a small percentage is required in asymmetric synthesis reactions. In theory, the catalyst can usually be recovered using simple techniques such as an acid wash or simple filtrations; however, this can

sometimes prove lengthy and lead to racemisation under acid or base conditions.[193] The disadvantage to using chiral catalysts is that they usually are very expensive; hence research into cheaper alternative catalysts is at its peak.[194]

Ephedrine **2** is a substance that can catalyse numerous types of asymmetric reactions, namely alkynylation reactions, alkylation of amides and conjugate additions to imidazoles.[195] It significantly decreases the time for the reaction to proceed without compromising on the product yield or enantioselectivity. Unfortunately, as a licence is required to control its misuse it limits how effectively it can be used in both research and industrial environments. By tethering a link between ephedrine **2** and an inorganic material, such as functionalised silica gel, a heterogeneous hybrid catalyst can be created. This tethered catalyst has the ability to be recovered and reused without affecting the yield or enantiomeric excess. This tethered catalyst in effect reduces the demand for ephedrine allowing for the licence to be governed more effectively.

A number of porous materials, such as polystyrene, micelle-templated silicas (MTS) and other polymers, have been tested for asymmetric immobilised catalysis over the years. Jin[196] developed a SBA-15 supported ephedrine **54** catalyst for testing in asymmetric addition of diethylzinc to aromatic aldehydes. The efficiency of SBA-15 supported ephedrine **54** was compared to results obtained by silica-supported ephedrine for the equivalent asymmetric addition reactions. It was observed that the SBA-15 supported ephedrine provided both higher yields (up to 85%) and enantiomeric excess (up to 75%) than the silica-supported

ephedrine. Jin *et al.* accounted the performance of the catalyst **54** to the regular pore structure of SBA-15 which allowed for a symmetrical arrangement of active sites.

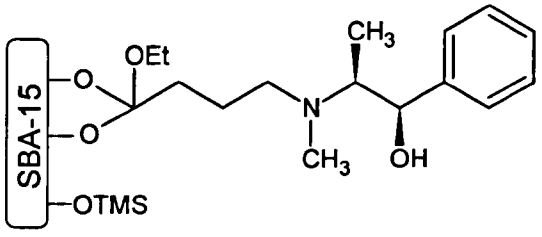
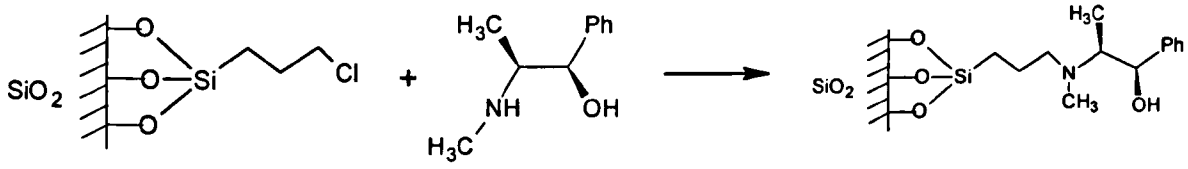


Figure 1.31 SBA-15 supported ephedrine **54**

In an early investigation conducted by Soai[197], (*1R,2S*)-(-)-ephedrine **2** was bound to the mesoporous silica surface in an effort to compare its properties as an heterogeneous catalyst compared with its use untethered in a homogeneous environment for the alkylation of benzaldehyde **37**. However, their studies found that the (*1R,2S*)-(-)-ephedrine **2** tethered to the MTS surface exhibited lower enantioselectivity than the homogeneous catalyst. It was thought that the lower enantioselectivity was as a result of the reagents being unable to reach the active site of the catalyst. Later studies showed that soluble polystyrene based catalyst support performed better in asymmetric synthesis than insoluble polystyrene catalysts due to elevated availability of the active sites.[198] This work highlighted some of the difficulties that must be overcome in order to produce effective hybrid catalysts. When developing hybrid catalysts, it is an advantage to keep costs low; however, it is more important to ensure selectivity is not compromised.

Various methods of tethering (*1R,2S*)-(-)-ephedrine **2** to a silica-based support in order to form a chiral supported catalyst have been studied. In one investigation, it was tethered to (3-chloropropyl)silyl-functionalised silica gel **55** (Scheme 1.25) and then tested in the

enantioselective addition of benzaldehyde **37** to dialkylzinc. The product of the reaction obtained both a high yield (83%) and an enantiomeric excess (89% of the (*R*) isomer).[199] This method was advantageous as the support did not have to be pre-swelled and the active sites were readily available allowing for good selectivity. Ephedrine **2** was tethered to both alumina and polystyrene supports, these supported catalysts were used in the asymmetric addition of dialkylzinc to a range of aldehydes. The silica supported catalyst **56** was recovered and reused whereupon the enantioselectivity of future reactions was not affected.[197]



55 **2** **56**

Scheme 1.25 Tethering ephedrine **2** onto functionalised silica **55**

Many studies have been carried out looking into forming supported catalysts for asymmetric synthesis, mainly for asymmetric catalysis and for chiral auxiliaries. Brunel[200] found that when excess (*1R,2S*)-(-)-ephedrine **2** was attached to the surface of micelle templated silica (MTS), it bonded via the hydroxyl group not the nitrogen atom. He accounted for this by assuming the excess ephedrine **2** was able to bind via the hydroxyl functional group because the surface area was readily approachable, which was presumably due to the fact that less surface area was covered by the organic chains.[201] The hydroxyl group displaces the halogen atom to form a linear chain with the surface of the MTS. It is thought that the surface area of the micelle templated silica is reduced once the (*1R,2S*)-(-)-ephedrine **2** is immobilised, this is most likely due to the bulky groups such as phenyl ring present on the ephedrine **2** molecule.[202] Both articles reported that the micelle-template supported silica catalysts were

not as effective as the homogeneous equivalents as the enantiomeric excess is decreased, however, the rate of reaction was found to increase. In a later paper, Brunel[203] synthesised a further two forms of supported ephedrine catalysts, one of which was (*1R,2S*)-(-)-ephedrine **2** tethered to micelle-templated silica (MTS) and the other of which was (*1R,2S*)-(-)-ephedrine **2** tethered to a polymer. Once again, the micelle-templated silica catalyst provided lower enantioselectivity; this was possibly due to the active sites being more readily available on the polymer supported catalyst.[204]

Kim[205] synthesised a MCM-41 supported ephedrine catalyst **57** (Figure 1.32) for use in the ruthenium catalysed asymmetric transfer hydrogenation of ketones. This work displayed the wide variety of asymmetric synthesis reactions that ephedrine catalyses. Kim found that the regularly arranged porous MCM-41 support performed better than the irregular silica supported ephedrine, suggesting that regular dispersion of active sites influenced enhanced the catalytic activity.

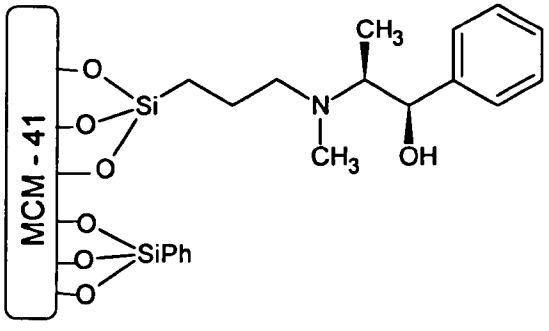


Figure 1.32 MCM-41 supported ephedrine **57**

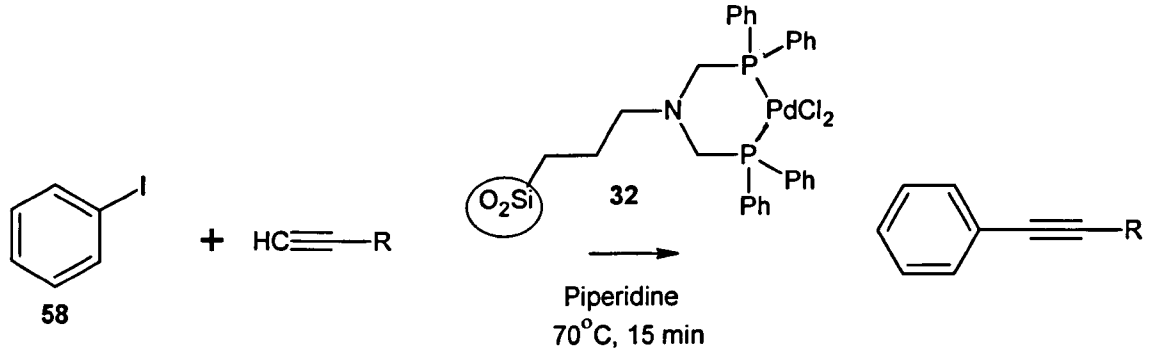
1.6.2.1 Benefits of tethering ephedrine to a support

Previous immobilisation work undertaken by Soai[197], Kim[205] and Brunel[200] has shown relative success; showing that it is possible to achieve selective results when using ephedrine **2** as part of an immobilised catalyst. The licence of ephedrine **2** limits its use, thus in order to use it to its maximum potential, it would be helpful to use it as part of an immobilised catalyst which can be recovered and reused. The choice of the support material would influence how effectively ephedrine can catalyse asymmetric reactions.

There are vast benefits for creating an immobilised ephedrine-based catalyst, such as being able to retain the homogeneous reactivity properties of ephedrine **2** and in addition, being able to recover the catalyst using simpler filtration methods as for heterogeneous catalysts.[76] Carriera[20] has shown that homogeneous alkynylations generally exhibited higher yields and enantioselectivity (up to 99%) than the tethered catalysts. This is most likely due to steric hindrance and the inability for the reagents to reach the active sites. A possible way to combat this could be to extend the chain length between the active ephedrine **2** site and its support medium.

The various advantages of tethering ephedrine **2** include making it more readily traceable, it becomes recyclable and environmentally friendly and it would be possible to provide an accurate audit for the controlled substance. The recoverability and recyclability of the catalyst would mean that only a small initial amount would be required for the first synthesis of the catalyst and then no further ephedrine **2** would be required. This would thus reduce the amount of ephedrine **2** in circulation and help the MHRA keep accurate records of the

ephedrine trail. Depending upon the type of support used, the asymmetric reaction can be made more environmentally friendly as little or no solvent would be required for work-up after completion of the reaction. The use of solvent free conditions has previously been displayed by Tyrrell[151] in Sonogashira coupling reactions in the presence of a silica supported catalyst **32**. (Scheme 1.26)



Scheme 1.26 Sonogashira coupling

Silica supports have cavities which could cause some catalytic active sites to be unavailable, however, despite the presence of these cavities, it does not hinder the diffusion of a solvent in the same way as for polymer based supports.[132] Thus, showing that silica based supports are more suited for asymmetric catalysis than polymer supports.

1.7 Aims of the research

The central objective of this research has been directed towards exploring the potential of immobilising ephedrine derivatives onto a functionalised silica support, which could then be tested in asymmetric alkynylations for both efficiency and recyclability. In order to achieve these objectives, the project is divided into two parts:

- The first part would involve the synthesis and evaluation of silica-tethered ephedrine-based catalyst
- The second would be exploring the synthesis and evaluation of silica-supported ephedrine based derivatives

The initial study would follow the work of Carreira[20] and Tyrrell[21] to understand how N-methylephedrine **26** catalyses the asymmetric alkynylations of aromatic aldehydes under mild homogeneous conditions. The subsequent step would be to tether ephedrine **2** onto a functionalised silica support for testing in asymmetric synthesis. The results derived from the functionalised silica supported ephedrine would provide comparative data for the novel testing of ephedrine derivatives that are tethered to silica supports.

2 Results and discussion

2.1 Synthesis of silica supported catalyst 60

Silica is widely used in a range of applications due to its diverse nature.[136] Silica gel is thermally stable, can withstand high pressures, it is insoluble and can be easily modified through its silanol groups (Si-OH) which are present on its surface.[143] It is used predominantly in chromatography as the stationary phase, however, it can also be adapted for heterogeneous catalysis.[134] The thermal and chemical stability of silica makes it useful for use as a solid support. The silanol groups allow for organic chains to covalently link to the surface of the silica, which subsequently can be used to tether chiral ligands.

Ephedrine **2** is a chiral catalyst that can be used for a wide variety of asymmetric synthesis reactions, such as asymmetric alkynylation of aldehydes. However, due to the limitations of its licence, it is rarely used in its full capacity. This chapter shows the work carried out to tether ephedrine **2** onto a silica support for use in asymmetric synthesis reactions. It is envisaged that the tethered catalyst will be recovered using a simple filtration and then reused in further asymmetric reactions.

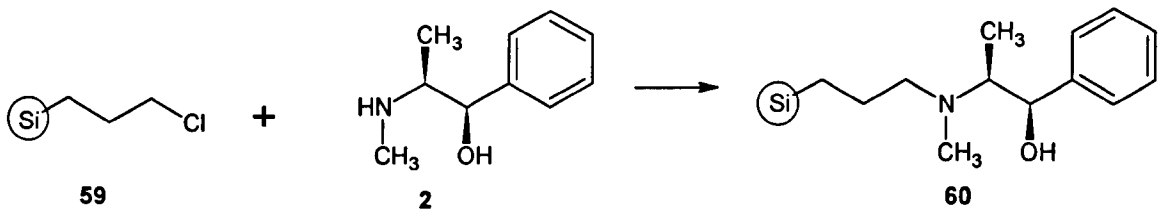
In a previous study ephedrine **2** was tethered to supports and utilised in asymmetric additions of diethylzinc to aldehydes. Kim [205] displayed the use of alternative ephedrine supported catalyst for use in the asymmetric addition of diethylzinc to aldehydes. This work showed ephedrine tethered onto an MCM-41 support, which is a silica gel variant with regular pore distribution and pore size. This immobilised catalyst provided higher yields and better selectivity, than the results obtained by Soai[197], who used an ephedrine immobilised silica gel

coated with chloromethylated polystyrene catalyst. The MCM-41 supported catalyst may have performed better due to regularity in pores of MCM-41 allowing the ephedrine active sites to be more readily available.

The work presented in this chapter models the work carried out by Soai[197] and Kim[205] to create an ephedrine functionalised silica catalyst. The work of both of these groups will help understand how to create a linker between a readily available functionalised support and ephedrine **2**.

2.2 Synthesis of ephedrine functionalised silica 60

The tethering reaction involved heating to a reflux temperature 3-chloropropylfunctionalised silica **59** (Aldrich) (Scheme 2.1) with ephedrine **2** under an atmosphere of nitrogen gas with anhydrous toluene as the solvent. The commercially available 3-chloropropyl functionalised silica **59** required pre-drying before the tethering reaction was undertaken, and this was achieved by drying it *in vacuo* at 80°C over phosphorous pentoxide for 24 hours. The tethering reaction was completed after 48 hours. Upon completion, ephedrine **2** could still be visualised using thin layer chromatography (TLC) using an alumina TLC plate as it was in excess. The solvent system for elution purposes was 2:1 petroleum ether 60: ethyl acetate and ephedrine **2** was visualised by permanganate dip with a retention factor (R_f) value of 0.78. After the tethering reaction was complete, the catalyst **60** was isolated using a simple filtration followed by washing with ether and methanol to afford the tethered catalyst, **60** as a fine white powder. This was then further dried *in vacuo* at 40°C before storage under an atmosphere of nitrogen gas at 0°C. (Scheme 2.1)



59 2 60

Scheme 2.1 Tethering *(1R,2S)*-(-)-ephedrine **2** to functionalised silica **59** to afford **60**

2.2.1 Sample analysis

The next stage of the study was to determine the loading of ephedrine **2** in the newly formed tethered catalyst **60**. Before loading analysis could commence, it was important to know the loading of 3-chloropropyl on the functionalised silica gel starting material. The numerical data provided by Sigma for the starting material, 3-chloropropylfunctionalised silica gel **59**, was stated as approximately 8% functionalised and the loading of 3-chloropropyl chains was 2.5%. These figures suggested that the maximum loading of ephedrine **2** could only be 2.5% of the total mass of the starting material used. This would only occur if all the 3-chloropropyl chains were displaced by ephedrine **2**. Due to the nature of catalyst **60**, which is silica based and therefore, insoluble, it was difficult to find an analytical technique to determine the loading of ephedrine **2**. As silica is a solid, it makes the use of techniques such as NMR and GC-MS difficult unless the silica is made soluble via digestion. The difficulty with using analytical techniques such as GC-MS is that silica would always interact with the stationary phase; therefore it was limited to methods such as thermogravimetric analysis (TGA) and elemental analysis. Alternative methods to analyse the hybrid catalyst were attempted such as Kjedahl method, which involves the digestion of the sample to release organic nitrogen, which would help to determine the presence of ephedrine **2**, however, this method did not work due to unavailability of equipment that could heat sulphuric acid to its boiling point.

2.2.1.1 Thermogravimetric analysis

Thermogravimetric analysis (TGA) was explored to determine the amount of ephedrine **2** immobilised onto the silica support. TGA is an analytical technique that measures the percentage loss of weight of a sample as a function of increasing temperature. The sample of a precise weight is slowly heated in a small oven to 900°C and the loss of organic material is measured as a percentage of the whole.[207]

In the case of the tethered catalyst it is expected that as the sample is heated to 100°C, there would be the loss of mass for due to absorbed water on the surface of the support media as well as the residual water associated with the organic tether via hydrogen bonding. As the sample is further heated, it would be expected that the organic components tethered to the silica via covalent bonds would begin to break down showing a second loss in mass. It is anticipated that these changes would be noticed over a temperature range of 100 - 650°C. If the sample presented any further losses in mass beyond 650°C, it would be assumed that the silica bonds would start to break down, thus resulting in a final loss of mass.

In order to determine the amount of ephedrine **2** tethered to the supported catalyst **60**, the loss in weight attributed to the propyl chain group of the functionalised silica **60** alone would have to be determined. This would then need to be deducted from the net loss of TGA results obtained for functionalised silica alone to help provide data for ephedrine **2** alone. The data provided from the manufacturer. [(Aldrich)] reports that the loading of the 3-chloropropyl moiety on the functionalised silica is 1 mmol/g. For the purposes of calculating the loading of ephedrine **2**, it is important to determine if the loss in mass displayed on the TGA for the starting material, 3-chloropropyl functionalised silica **59** correlates with the loading stated for the 3-chloropropyl chains. The loss in mass of ephedrine **2** displayed by TGA could help in

determining the loading of ephedrine **2** to the functionalised silica support. If the ephedrine **2** were to only bind via displacement of the chlorine atoms, it would be expected that the mass loss would equate to 1 mmol/g or less of the total mass of the catalyst sample. However, if the mass loss displayed for ephedrine would be calculated to be higher than 1 mmol/g of the catalyst sample mass, it would suggest that ephedrine could bind in more ways, for example, via covalent bonds to the hydroxyl groups present on the surface of the silica or adsorption on the surface of the silica.

The initial analysis involved using TGA to analyse the starting material, 3-chloropropyl functionalised silica gel **59** would then be used for comparative purposes to the silica bound ephedrine catalyst, **60**. A comparison of the TGA data of the silica bound ephedrine catalyst support **60** with a TGA of the starting material, 3-chloropropylfunctionalised silica **59**, would help to determine the relative increase of the organic matter, which would indicate the loading of ephedrine **2** on the support.

The TGA analysis of the starting material **59** is shown (see Figure 2.1). It shows three distinct incremental losses of sample mass where the mass of sample decreases. As expected, about 2% surface water appears to be lost from the starting material **59** as the sample is heated from 0 - 180°C. This amount would need to be subtracted from the mass of the sample **59** analysed, assuming the additional increase in mass of the solid catalyst **59** is not also accompanied by an incremental increase of water. Despite drying the sample **59** under vacuum, there would always be a minimal amount of surface moisture due to the hydroscopic nature of the silica gel. The second loss in mass of about 8% occurs between 180 - 590°C and correlates with the gradual thermal destruction of the organic backbone of the sample. The

final mass loss of about 2% between 590 - 900°C is caused by the breakdown of the Si-O bonds.

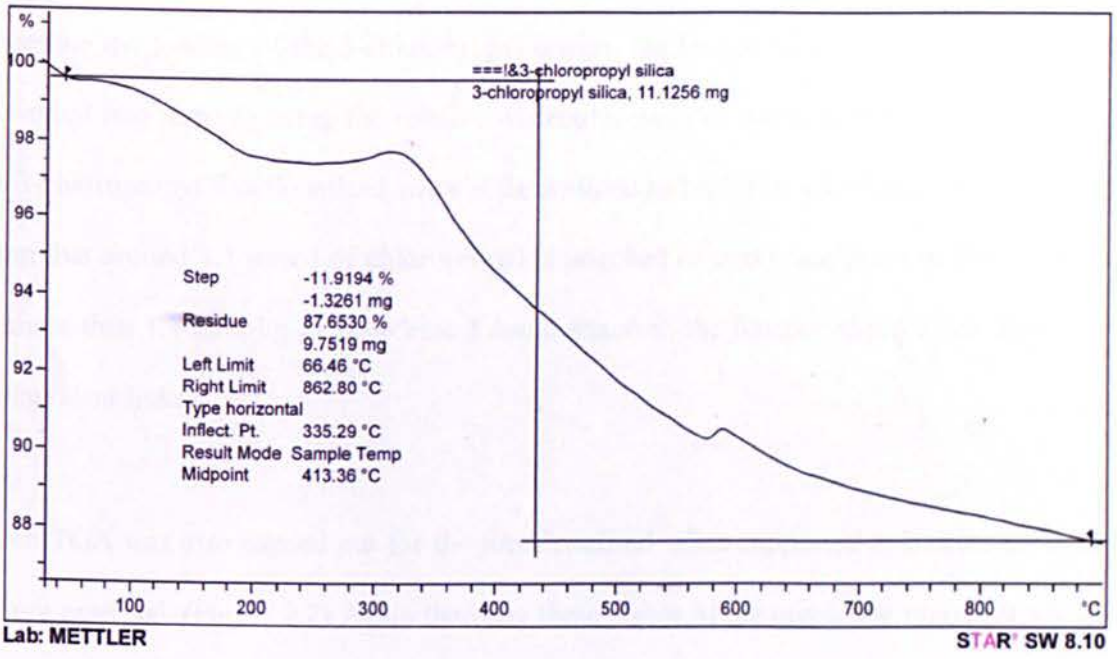


Figure 2.1 TGA analysis of 3-chloropropyl functionalised silica **59**

In order to determine the mass accounted for by the organic component of the starting material, which is the 3-chloropropyl chains, the following calculations need to take place:

1) Using the TGA chromatograph, the percentage loss of the organic material, which is the 3-chloropropyl chains, would need to be converted to a sample mass in milligrams.
2) The organic sample mass can then be converted into the loading by using the relative formula mass of the 3-chloropropyl chains.

The 8% reduction in mass of the sample would need to be converted into mmol/g to determine the accurate loading. The 8% loss of mass from the sample **59** accounts for 0.8900 mg (8% of the total sample mass) of the sample used in the TGA analysis. In order to determine the loading of the 3-chloropropyl chains, the loss in mass (mg) would need to be converted into mmol/g using the relative molecular mass of 3-chloropropyl. The loading of the 3-chloropropyl functionalised silica is determined to be 1.148×10^{-2} mmol/g. This would mean that around 1.1 mmol of chloropropyl is attached to every one gram of silica and that no more than 1.1 mmol/g of ephedrine **2** could attach to the functionalised silica support via the covalent linker.

When TGA was also carried out for the functionalised silica supported ephedrine **60** similar picture emerged. (Figure 2.2) Again there are three points of the graph that represent a loss in mass, however, the point of interest is from about 190 - 650°C, where the extended organic chain is lost which accounts for about 14% of the total organics lost. In order to calculate the loading on the functionalised silica gel **60**, it is important to ascertain the percentage of the total organic lost from the sample. This value would be a fraction of the total sample weight after the surface water mass has been subtracted. Once the loss of mass for the organic chain was established, we can then calculate the mmol of side chains per gram of the sample.

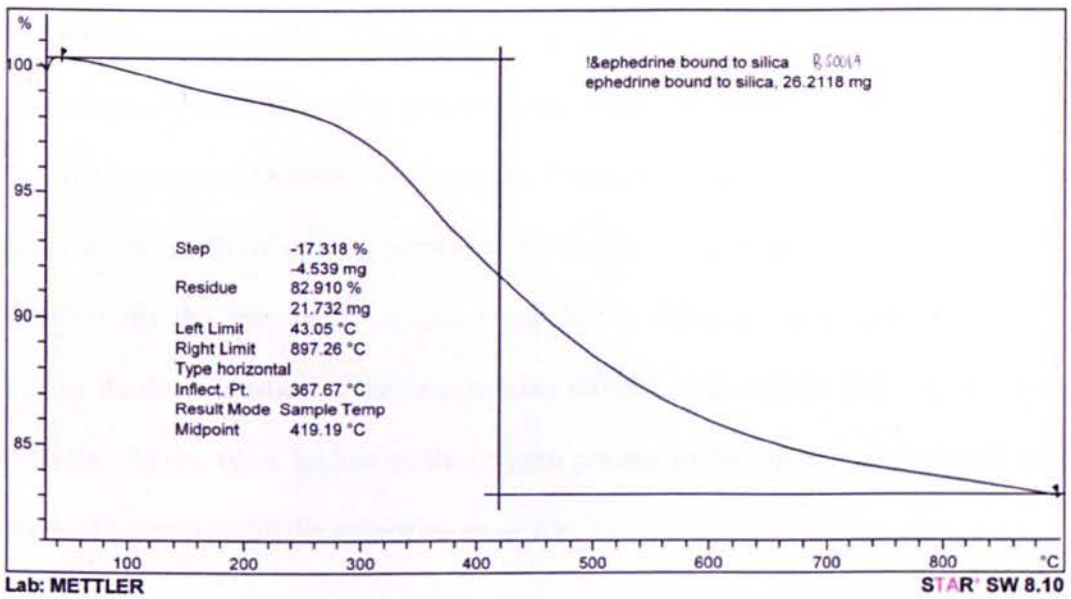


Figure 2.2 TGA analysis of ephedrine functionalised silica catalyst **60**

From Figure 2.2, it is clear that the sample mass used for analysis is 26.2118 mg. There is a 1.5% loss of surface water between 0 – 195°C. The 14% of organic side chain lost from the sample of catalyst **60** which equates to 3.5386 mg in total, this is 14% of 26.2118 mg. In order to determine how much ephedrine **2** has been tethered to the functionalised support, the loading of the ephedrine propyl chains would need to be established. A number of calculations were undertaken to determine the loading, firstly the moles of 14% sample were established using the relative formula mass of the ephedrine propyl chain. The chemical formula of the side chain is $C_{13}H_{20}NO$, which results in molecular weight of 206 g mol^{-1}.

This resulting in an ephedrine propyl loading of 2.997 x 10^{-2} mmol/g on the catalyst **60**, this is lower than the loading of the chloropropyl chains (1.1 mmol/g) suggesting that not all of the ephedrine **2** has bound to the silica support.

2.2.2 Elemental analysis

Elemental analysis is an analytical method for determining the percentage of different elements present in a sample.[208] These percentages can then be used to calculate the ratio of elements, which can then be used to determine the chemical formula. For the purpose of our analysis, it was used to determine the amount of ephedrine **2** present in the sample **60**. The focal point of this analysis was the presence of nitrogen in the molecule. Another possibility was to determine the amount of oxygen atoms in the tethered catalyst **60**; however, this would make the determination of the functionality difficult as it would detect any free oxygen atoms attached to the silica surface or the oxygen present in the silanol bonds in addition to the oxygen atom present on the ephedrine molecule.

For elemental analysis, it is typically common to use any percentages of elements found to derive a chemical formula for the product. However, as the supported catalyst **60** has a silica support, it is difficult to determine accurately its chemical formula. In this case, the analysis is used to determine the presence of ephedrine as it contains the elements carbon, nitrogen and oxygen. In addition, the analysis will display the presence of carbon in the propyl chains. However, the presence of nitrogen is vital as it establishes that ephedrine **2** has immobilised to the functionalised silica support. This is due to the only nitrogen molecule in the tethered catalyst being accounted for by the ephedrine moiety.

In order to use the data found using elemental analysis, the chemical formula of ephedrine attached to the propyl chain has to be established. (Figure 2.3) The chemical formula of the ephedrine-propyl chain is $C_{13}H_{20}NO$ and has a relative formula mass of 206 g mol^{-1}. A

summary of the elemental analysis data and the loading of ***(1R,2S)***-ephedrine **2** obtained for the tethered catalysts **60** is shown. (see Table 2.1).

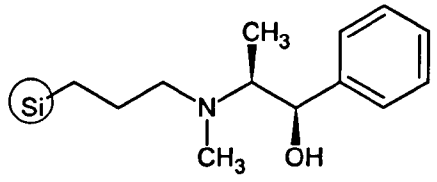


Figure 2.3 Ephedrine functionalised silica **60**

Table 2.1 Determination of loading of ***(1R,2S)***-(-)-ephedrine **2** on functionalised silica gel

Catalyst ref	% C	% H	% N	Ephedrine-propyl loading (mmol/g)
60	8.54	1.61	0.99	2.357×10^{-2}

The data (see Table 2.1) shows the breakdown of the percentage of carbon, hydrogen and . nitrogen found in the sample. This data suggests that for every one gram of the sample, 8.54% of the mass can be accounted for by the carbon atoms. In addition, 1.61% and 0.99% of the mass can be accounted for by the hydrogen and nitrogen atoms present in the sample.

The loading of propyl-ephedrine chain on the functionalised silica supported catalyst was calculated using the following steps:

1) The moles of nitrogen were calculated as it represents the moles of ephedrine in the sample using the following calculation:

Moles of nitrogen = (% nitrogen found in sample/100) / molecular weight of nitrogen

2) The moles of nitrogen would be equal to the moles of the propyl-ephedrine chain due to one nitrogen atom present in the molecule. To determine the mass of the propyl-ephedrine chain, the following calculations were used:

   Moles of nitrogen = moles of propyl-ephedrine chain

   Mass (g) = moles (propyl-ephedrine chain) x MW (propyl-ephedrine chain)

3) The mass of propyl-ephedrine chain is then subtracted from the total mass of catalyst **60** obtained to determine the mass of the support alone.

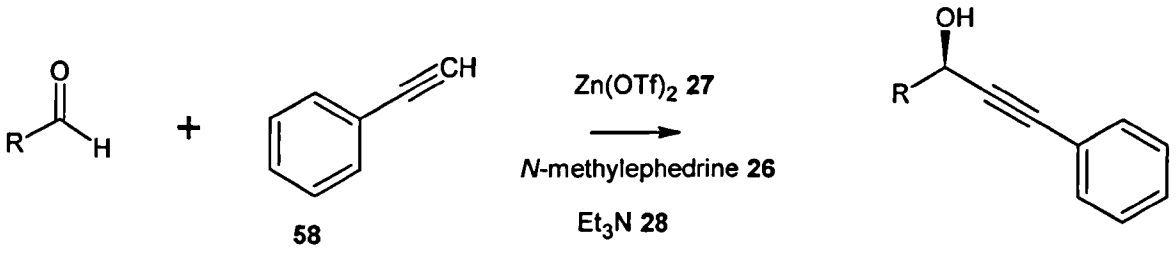
4) The moles of ephedrine are then divided by the mass of the support alone to determine the loading ($mmol/g^{-1}$) of propyl-ephedrine chains on the catalyst **60**.

The loading of ephedrine is close agreement with the loading data obtained from the TGA analysis providing reassurance that the ephedrine moiety has successfully attached to the functionalised silica support.

2.3 Synthesis of propargylic alcohols using catalysis

Propargylic alcohols are important synthetic building blocks, which have a wide range of applications such as their chemical transformation into more complex organic molecules, natural products and alkenes.[83]

The synthesis of secondary propargylic alcohols from the reaction of metal alkynylides with aldehydes has been widely studied allowing for the development of different metals complexes and chiral catalysts. A novel approach was developed by Carriera[19] that involved the *in situ* formation of a zinc acetylide species from the treatment of phenylacetylene **52** in the presence of zinc triflate **27**. (Scheme 2.2)



Scheme 2.2 Preparation of secondary propargylic alcohols using an asymmetric alkynylation

The zinc acetylide is then used in an asymmetric addition to an aldehyde. Carriera and Frantz commented that in comparison to other metal acetylides, the lower basicity of zinc acetylides allows for it to more tolerant towards the varying functional groups of the aldehyde.[100]

2.3.1 Homogeneous synthesis of secondary propargylic alcohols

The initial reactions that were carried were the homogeneous optimisation of the synthesis of secondary propargylic alcohols. This involved the use of a terminal alkyne, phenylacetylene **52** with a range of aromatic aldehydes. Previously, Tyrrell[20] used Carreira's approach for the synthesis of a range of secondary propargylic alcohols, which involved the use of stoichiometric amounts zinc triflate **27**, *N*-methylephedrine **26** and triethylamine **28** in toluene at room temperature.

In the initial study a range of asymmetric alkynylations of aromatic aldehydes replicated the reaction pioneered by Carreira[19] and extensively optimised by Tyrrell and provided comparison for the corresponding functionalised silica supported ephedrine approach. The reaction between phenylacetylene **52** and a range of aromatic aldehydes was carried out under a nitrogen atmosphere with the use of anhydrous solvents. It was important to optimise the reaction conditions for this reaction for use in comparing later findings when testing the silica-support catalyst.

In the preliminary study, a range of secondary propargylic alcohols (**61a – 61h**) were prepared by reacting phenylacetylene **52** with a range of aromatic aldehydes. The reaction was carried out under a nitrogen atmosphere with the aid of zinc triflate **27**, triethylamine **28** and *N*-methylephedrine **26** as the chiral catalyst. The reaction was stirred for 7 days at room temperature and was monitored by thin layer chromatography (TLC). In all cases, the completion of the reaction was acknowledged by the disappearance of the aldehyde via TLC. If the reaction was incomplete, the reaction mixture was left stirring. The propargylic alcohols were then analysed using NMR, GC-MS, HPLC and optical rotation. The obtained results are displayed. (see Table 2.2).

Table 2.2 Asymmetric addition of phenylacetylene **52** to a range of aromatic aldehydes

Entry	R	Aldehyde	Yield (%)	ee[a] (%)	$[\alpha]_D^{26}$
61a[1]	Ph	Benzaldehyde, **37**	98	96	+2.7
61b[1]	2-Me-Ph	2-methylbenzaldehyde, **62**	96	90	-7.1
61c[1]	3-Me-Ph	3-methylbenzaldehyde, **63**	95	89	+4.9
61d[1]	4-Me-Ph	4-methylbenzaldehyde, **64**	90	84	+3.1

61e[1]	2-MeO-Ph	2-methoxybenzaldehyde, **65**	89	90	-8.6
61f[1]	2-NO_2-Ph	2-nitrobenzaldehyde, **66**	71	85	-12.3
61g[1]	2-Cl-Ph	2-chlorobenzaldehyde, **67**	90	88	+11.6
61h[1]	3-Cl-Ph	3-chlorobenzaldehyde, **68**	86	81	-8.3
61i[1]	2-Fl-Ph	2-fluorobenzaldehyde, **69**	87	85	-6.2

[a] The enantioselectivities were determined by HPLC analysis using a Chiracel OD-H column and eluting with 90:10 hexane: iso-propanol, detection at λ_{max} = 254nm.

The synthesis of propargylic alcohols were obtained in moderate to high yields using Carreira's method of asymmetric alkynylation. The aromatic aldehydes required longer reactions than stated in the literature to achieve the optimised yields and selectivity (see Table 2.3). In addition, the literature stated that Carreira's method is suited better towards aliphatic aldehydes as opposed to aromatic aldehydes.[86] The substituent group attached to the aromatic ring and its position on the ring displayed varying results. It showed that both resonance and inductive effects of substituents could affect both the yield and selectivity. The nature of the substituents varied in terms of the electronegativity and their positioning on the aromatic ring. For example, the propargylic alcohol **61f** that contained a nitro substituent group was formed in low yield (71%), this was due to the nitro group having both electron withdrawing inductive and resonance effects, which caused the reaction rate to be reduced as the ring was deactivated towards the asymmetric addition.

Fluorine substituents and chlorine substituents were explored to determine how the synthesis of the propargylic alcohols would be affected as both halogens are electronegative by nature. These halogens are also deactivating which could cause the reaction rate to be reduced,

implying that not all of the reaction would go to completion, thus resulting in lower yields, which was observed. However, the halogen substituents provided better results when in the ortho position of the aromatic ring. The fluorine atom is more electronegative than chlorine so there were lower yields and selectivity obtained in comparison to the results obtained by the chlorine substituted aldehydes.

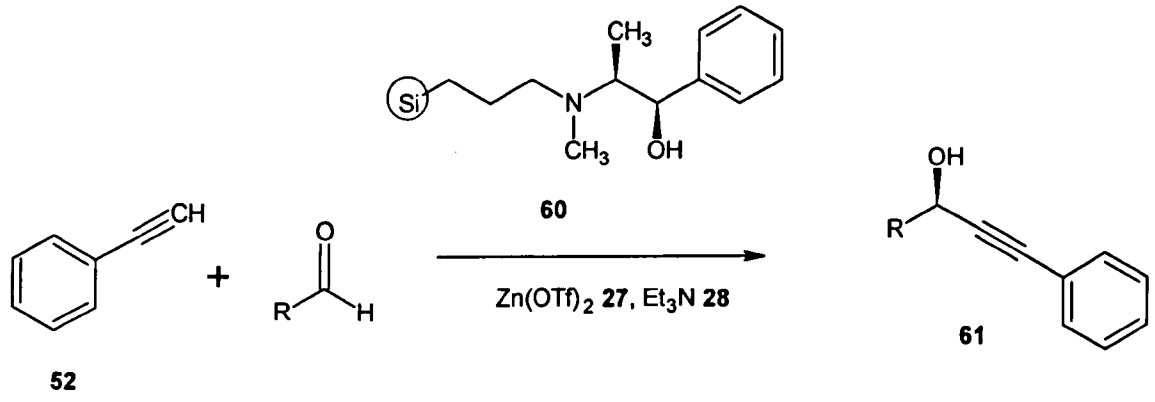
2.3.2 Mechanism of reaction

The synthesis of the propargylic alcohols occurred via a series of steps, one of which involved the generation of a zinc acetylide *in situ*. The zinc acetylide is of importance as it helps to facilitate the formation of the propargylic alcohol. The zinc triflate **27** deprotonates the phenylacetylene **52** and attaches to the alkyne to form a transition zinc acetylide complex. *N*-methylephedrine **26** is responsible for controlling the stereochemistry of the propargylic alcohol. The chiral catalyst **26** attaches to the zinc acetylide, thus maintaining control over how the aromatic aldehyde substitutes to the zinc complex. The propargylic alcohol is then formed with favoured ***(R)***-stereochemistry and released, allowing the *N*-methylephedrine-zinc catalytic complex to be regenerated. (Scheme 1.12)

The *N*-methylephedrine **26** has the ability to bring about the ***(R)*** stereochemistry in the newly formed chiral centre as it attaches to the zinc acetylide during the transition stage. The bulky phenyl group of *N*-methylephedrine **26** restricts access to the Si-face of the aldehyde. Therefore the zinc acetylide can only attack from the Re-face of the aldehyde, which allows the alkyne to attach. Once the zinc complex is removed, the resulting chiral centre is established with ***(R)*** stereochemistry.

2.4 Novel testing of tethered ephedrine catalyst 60

The newly formed ephedrine functionalised silica **60** required testing to indicate how effectively it could be used in asymmetric alkynylations reactions. It was important to determine whether the catalyst could perform as well as *N*-methylephedrine **26** and if it could be recovered and recycled for further use. The author believes that the literature contains no evidence of a functionalised silica supported ephedrine catalyst that has been used in asymmetric alkynylations, thus this initial testing made up the novel component of the research presented. The initial catalytic testing involved utilising the catalyst in the asymmetric alkynylation of benzaldehyde **37** using phenylacetylene **52**. It was important to optimise the reaction conditions before further testing with a range of aromatic aldehydes.



Scheme 2.3 Asymmetric alkynylations with ephedrine functionalised silica **60** as a catalyst

In order to prepare the catalyst for the asymmetric synthesis reaction, it was pre-dried in a vacuum pistol at 60°C for 24 hours and weighed until a constant mass was reached, it was then stored under a nitrogen environment. The asymmetric alkynylations were carried out using Carreira's method which was optimised for the homogeneous synthesis of the secondary propargylic alcohols. This synthesis also required the use of 3 equivalents of phenylacetylene **52** and was maintained for a minimum of seven days. Once the reaction was

complete, the catalyst was filtered off and washed. The propargylic alcohol was recovered after several washings. The recovered catalyst was analysed using elemental analysis and TGA, and the resulting propargylic alcohol was analysed using GC-MS, NMR, HPLC and optical rotation. The results following the synthesis of these propargylic alcohols using the ephedrine functionalised silica catalyst, **60**, have been summarised and shown in Table 2.3.

Table 2.3 Asymmetric alkynylations using ephedrine functionalised silica, **60**

Entry	R	Aldehyde	Yield (%)	ee[a] (%)	$[\alpha]_D^{26}$
61a[2]	Ph	Benzaldehyde, **37**	90	92	+2.1
61b[2]	2-Me-Ph	2-methylbenzaldehyde, **62**	97	85	-6.9
61c[2]	3-Me-Ph	3-methylbenzaldehyde, **63**	95	76	+4.0
61d[2]	4-Me-Ph	4-methylbenzaldehyde, **64**	85	80	+2.9
61e[2]	2-MeO-Ph	2-methoxybenzaldehyde, **65**	90	86	-7.9
61g[2]	2-Cl-Ph	2-chlorobenzaldehyde, **67**	86	79	+10.2
61i[2]	2-F-Ph	2-fluorobenzaldehyde, **69**	77	75	-6.4

[a] The enantioselectivities were determined by HPLC analysis using a Chiracel OD-H column and eluting with 90:10 hexane: iso-propanol, detection at λ_{max} = 254nm.

The propargylic alcohols were obtained in good yield and selectivity which were comparable to the results obtained when the reaction was carried out homogeneously with *N*-methylephedrine **26**. Due to heterogeneous nature of the catalyst, it was expected that the catalyst may not perform as well as *N*-methylephedrine **26**. However, the catalyst **60** mimicked the *N*-methylephedrine **26** structure with the propyl chain in place where the *N*-methyl group would have been positioned. The propyl linker chain helped to ensure the ephedrine **2** molecule was accessible for the formation of the metal acetylide. The structure of the catalyst **60** ensured that the reaction could go to completion. Thus, the propargylic alcohols were synthesised in relatively good yields and selectivity.

The results show that in general, the *N*-methylephedrine **26** derived secondary propargylic alcohols were obtained in higher yields and better selectivity. For the benzaldehyde derived secondary propargylic alcohol, entry **61a**[1] was comparable with **61a**[2].

2.4.1 Recycling studies

The novel success of using the ephedrine functionalised silica catalyst **60** for asymmetric alkynylations encouraged further testing of the catalyst. The catalyst was recovered after its use in the asymmetric synthesis reactions, thus an interesting study was to determine how it performed in successive reactions. In order to have created a successful hybrid catalyst, it is essential that it can both be recovered and reused in further reactions without impacting the yield obtained or the selectivity of the product. Therefore, it was vital that the ephedrine functionalised silica catalyst **60** could successfully catalyse further asymmetric alkynylations. The ephedrine functionalised catalyst **60** was recovered using a vacuum filtration; it was then washed successively with ether and methanol to remove traces of the reactants and then pre-dried at 40°C in a vacuum pistol. This ensured no moisture remained on the surface of the catalyst. The asymmetric alkynylation reactions were repeated under the previous optimised conditions. The ephedrine functionalised silica catalyst was reused up to three times as (see Table 2.4), the yield was retained with subsequent minimal changes.

Table 2.6 Reuse of the tethered catalyst **60** for asymmetric alkynylations

Entry	R	Aldehyde	Yield (%)	ee[a] (%)	$[\alpha]_D^{26}$
66a[2i]	Ph	Benzaldehyde	90	91	+4.7
66a[2ii]	Ph	Benzaldehyde	89	90	+4.6
66a[2iii]	Ph	Benzaldehyde	89	86	+4.7

[a] The enantioselectivities were determined by HPLC analysis using a Chiracel OD-H column and eluting with 90:10 hexane: iso-propanol, detection at λ_{max} = 254nm.

The completion of the reaction was determined by TLC, followed by analysis of the propargylic alcohols using NMR and GC. The ephedrine functionalised silica catalyst was recovered by filtration and then washed sequentially and dried *in vacuo* before re-use. Both the first and second entries maintained high yields and selectivity which were consistent with the previously obtained results. However, with the third entry, there was a slight reduction in enantioselectivity. This may have been caused by the ephedrine moiety leaching from functionalised silica support.

2.4.2 Discussion

The synthesis of the ephedrine functionalised silica catalyst **60** was carried out using a simple reflux reaction in toluene for a period of 30 hours . This synthesis was first carried out by Soai and co-workers in 1990, however, the purpose of the catalyst for the Soai group was for use in the asymmetric addition of benzaldehyde **37** to diethylzinc. In addition, the Soai group synthesised the starting material, 3-(chloropropyl)silyl-functionalised silica gel **55** using 3-(chloropropyl)trimethoxysilane and activated silica. For the ephedrine functionalised silica catalyst **60** synthesis carried out in this work, 3-chloropropylfunctionalised silica gel **59** was obtained from Sigma-Aldrich. In the literature, the author believes that there to be no reported work of ephedrine functionalised silica gel catalysts being utilised in asymmetric alkynylations, which therefore led into the scope of the novel research carried out for this work.

The key purpose for creating a tethered link between ephedrine **2** and functionalised silica gel was to aid a solution for the restrictions that the licence of ephedrine **2** may face researchers

and industries when using ephedrine for catalytic purposes. In the case of ephedrine **2**, the licence requires reporting of the amount of ephedrine used and how it has been utilised, recovered or disposed of. The formation of an ephedrine hybrid catalyst would result in a small known amount of ephedrine **2** being tethered to a support, utilised in asymmetric synthetic reactions and recovered once reactions are completed. Hence, this would allow the MHRA to accurately govern the licence of ephedrine as there would be more transparency in the ephedrine trail. Furthermore, this could reduce the misuse of ephedrine **2** as only small catalytic amounts could be in circulation at approved establishments.

The determination of the loading of ephedrine **2** proved to be somewhat complicated as there was no individual method to accurately quantify the loading of ephedrine on the functionalised silica support. The use of elemental analysis helped to determine the presence of ephedrine in the catalyst, due to nitrogen atoms being present in the sample. The presence of nitrogen atoms can only be accounted for by the ephedrine molecule as only one nitrogen atom exists on its structure. The elemental analysis showed low percentages of carbon atoms present in the catalyst **60**. It proved difficult to use the oxygen data obtained from elemental analysis as the percentage of oxygen detected in the sample could have been accounted for by either the alcohol group present in the ephedrine molecule, the Si-O bonds or surface water present in the sample. Therefore, the nitrogen analysis was heavily relied on for proof that ephedrine had immobilised onto the functionalised silica support. A limitation to using elemental analysis for evaluating the loading of ephedrine **2** on the catalyst is that it heavily relies on using the relative formula mass of the sample in order to calculate the number of each element present in the sample. The loading of the ephedrine-propyl chains were

determined to be 2.357 x 10^{-2} mmol/g, which is lower than the calculated 1.100 mmol/g loading of 3-chloropropyl chains on functionalised silica support **59**.

Thermogravimetric analysis was an alternative method used to quantify the loading of ephedrine. By heating the sample up to 900°C, allowed for the release of the different components of the sample. The sequence of release from the sample first involved the loss of surface moisture, followed by the breakdown of the organic chains and finally the breakdown of the silicon-oxygen bonds. For this method of analysis and its loading calculations, it was again assumed that the maximum loading of the ephedrine-propyl chain could not be higher than 2.5%. However, this assumption does not account for any ephedrine that may not have covalently bonded via the linker chain or any chlorine atoms that may not have been displaced. The TGA analysis revealed a loading of 2.997 x 10^{-2} mmol/g of the ephedrine-propyl chain on the catalyst **60**. This was in close agreement of the loading value obtained using elemental analysis, which helped to confirm ephedrine **2** had tethered to the silica support.

The initial alkynylations that were carried out were under homogeneous conditions, involving the terminal alkyne, phenylacetylene **52** and a range of aromatic aldehydes. The range of aromatic aldehydes allowed for observation of how yields obtained and the selectivity of the secondary propargylic alcohols varied with different substituent groups which were in addition, compared in the ortho, meta and para positions of the aromatic rings. The method which was used for the asymmetric alkynylations was a method developed by Carriera.[19] However, the literature did state that this method was more suited to alkynylation of aliphatic

aldehydes. The length of the reaction time was adapted for the synthetic reactions carried out in this work which helped to improve yields.

The asymmetric alkynylations with the use of *N*-methylephedrine **26** as a catalyst produced both a good range of yields (up to 98%) and selectivity (up to 97%) for the secondary propargylic alcohols. The homogeneous optimisation of asymmetric alkynylations of aromatic aldehydes opened the pathway to testing the ephedrine functionalised silica gel catalyst **60**. In order to test if ephedrine **2** had attached to the support and if the supported catalyst could be utilised in asymmetric synthesis, it was applied as a catalyst to the asymmetric alkynylations previously optimised. Due to the supported catalyst being a hybrid catalyst, it was hoped that the ephedrine **2** moiety would be able to reproduce the selectivity obtained when using *N*-methylephedrine **26**. The insoluble property of the functionalised silica gel support ensured that the catalyst underwent a heterogeneous catalysis, and thus did not dissolve in the reaction mixture. This allowed the catalyst to be recovered upon completion of the synthetic reaction using a simple filtration. The catalyst **60** then was washed using ether and methanol to ensure no reactants remained on its surface, after which the catalyst was placed to dry in the vacuum pistol.

The novel component of the supported ephedrine catalytic work was the use of the catalyst for the addition of aldehydes to phenylacetylene **52**. It was successfully shown that in the organic reaction, we could successful synthesise propargylic alcohols in good yields (up to 97%). The comparability of these results with those obtained homogeneously showed little difference, proving this tethered catalyst to be just as good as the previously used *N*-

methylephedrine **26**. The promising part of these results is that the tethered catalyst was able to exhibit good yields (up to 90%) during the recovery and recyclability process. This shows that the same ephedrine that formed the initial catalyst **60** could be reused up to three times, therefore, negating the need for noting its use every time it was used. These results prove very beneficial to industrial practices as it helps the process of being able to use the controlled substance, ephedrine more efficiently and effectively.

2.5 Conclusions and future work

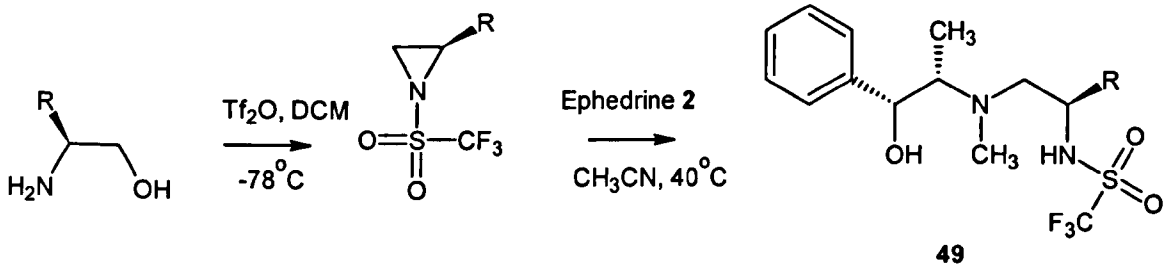
The silica supported ephedrine catalyst **60** was successful in the enantioselective addition of aldehydes to phenylacetylene **52**. The ephedrine tethered to the functionalised silica support with a relatively lower loading than the starting material, 3-chloropropyl functionalised silica **59**. The loading was determined by TGA and elemental analysis. When the catalyst **60** had completed the asymmetric alkynylation reaction, it was easy to retrieve the catalyst using a simple vacuum filtration. The supported catalyst proved that it could be recycled up to three times before it compromised on selectivity or yield. The results suggest that the ephedrine **2** can successfully be tethered to functionalised silica supports for use in enantioselective organic reactions and then recovered, thus providing a method of accurately auditing the trail of the controlled substance, ephedrine **2**.

3 Ephedrine derivatives

3.1 Introduction

Following the success of the functionalised silica supported ephedrine **60** in the use of asymmetric alkynylations reactions, the next stage of the research involved exploring the possibility of tethering ephedrine derived ligands to functionalised silica supports. This would allow the linker chain between the support and the catalyst to be increased and could potentially allow for better access to the ephedrine active site.

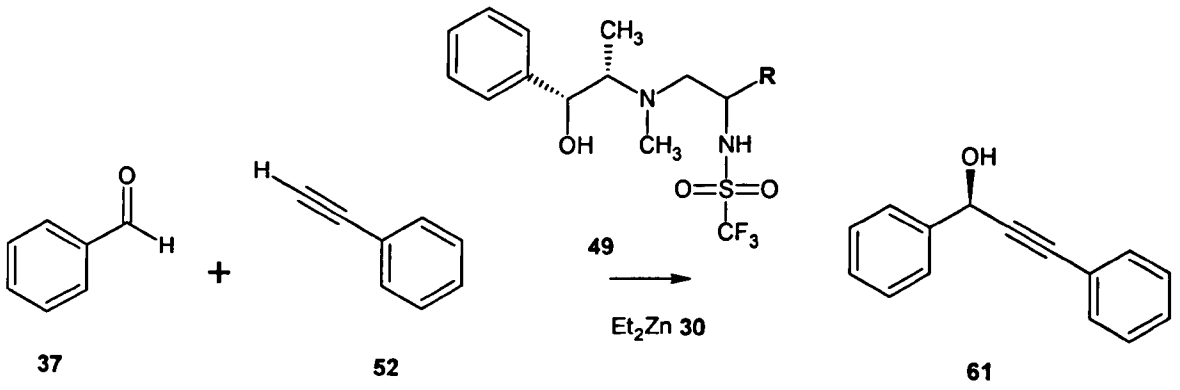
In 2008, Li introduced a triflate based sulfamide-amine alcohol **49** based upon ephedrine **2** for use in asymmetric alkynylations, up to 92% yield and up to 88% ee for the ***(R)*** enantiomer.[192] A range of ephedrine derivatives were created using a two part synthesis, the first part involved the formation of triflated aziridines derived from chiral amino alcohols; which then went on to be synthesised into ephedrine derivatives. Scheme 3.1 depicts the general route of synthesis to the ephedrine derivatives.



Scheme 3.1 Synthesis of triflate-based sulfamide-amine alcohols

Li synthesised a range of ephedrine derivatives by using the enantiomers of the chiral amino alcohols; alaninol **71**, valinol **73**, phenylglycinol **70**, phenylalaninol **72** and tert-leucinol **74** as

the starting material. The Tf-based sulfamide-amine alcohols were obtained in moderate yields (up to 65%) with the catalyst derived from *(R)*-phenylalaninol achieving the highest yield. This array of catalysts was initially tested in the asymmetric alkynylation of benzaldehyde **37** with phenylacetylene **52**, which helped to establish that the *(R)*-phenylglycinol derived catalyst **49** obtain the best yield (92%) and highest enantiomeric purity (88%) for the newly formed propargylic alcohol with the favoured *(R)* configuration. This suggests that the steric bulk of the ring of the catalyst **49** may affect the enantioselectivity. Li's research group found that *(R)* configuration of the chiral R group attached to carbon adjacent to the nitrogen of the sulfamide produced better enantioselectivity than the chiral ligands with *(S)* configuration about the same chiral centre when used in asymmetric alkynylations.



Scheme 3.2 Asymmetric addition of phenylacetylene **52** to benzaldehyde **37**

The catalyst **49** was then tested in a series of asymmetric alkynylations of aromatic aldehydes. (Scheme 3.2) It is worth noting that the asymmetric alkynylations were not undertaken using Carreira's method, instead using a method that utilises diethylzinc **30** instead of zinc triflate **27**. The propargylic alcohols were obtained in good yields (up to 99%) and selectivity (up to 92%).

3.2 Model synthesis of triflate-based sulfamide-amine alcohol

In order to get to understand how the ephedrine derived ligands worked, it was important to optimise the synthesis of the ligands and their use in asymmetric synthesis reactions. The synthesis of a series of the triflate-based sulfamide-amine alcohols was carried out using the literature stated method.[192]

The first step of the reaction involved forming the corresponding aziridine using triflic anhydride, the amino alcohol, ***(R)***-phenylglycinol **70a** and triethylamine **28**. The reaction proceeded under a nitrogen atmosphere with the use of anhydrous dichloromethane as the solvent at a temperature of -78°C. The triflic anhydride was added dropwise slowly to the mixture of the aminoalcohol and triethylamine in dichloromethane to allow the aziridine ring to form. The resulting aziridine was then converted into chiral ligand with the aid of ***(1R,2S)***-(-)-ephedrine **2** in anhydrous acetonitrile at a temperature of 40°C. The completion of the reaction was determined using TLC and visualising with a permanganate dip. The solvent system for elution purposes was 9:1 petroleum ether: ethyl acetate and the ephedrine derived ligand **49** was visualised by permanganate dip with an R_f value of 0.45. The chiral catalyst was further purified using column chromatography using a solvent system of 9:1 petroleum ether: ethyl acetate. The catalyst **49** was analysed using NMR, LC-MS, optical rotation and chiral HPLC.

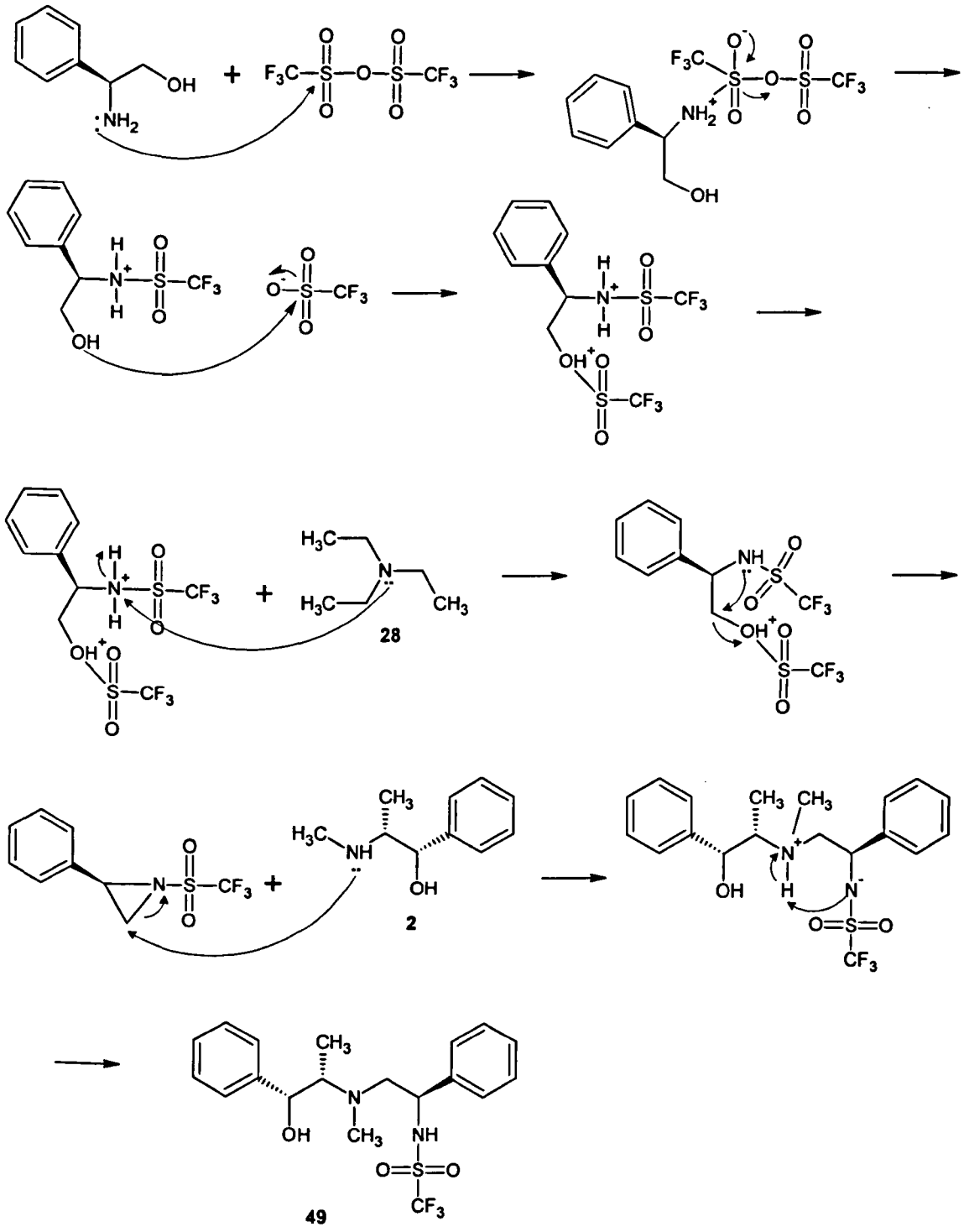
Table 3.1 Model studies: synthesis of a range of ephedrine derived ligands

Entry	Amino Alcohol	Yield (%)	$[\alpha]_D^{23}$
49	*(R)*-Phenylglycinol, **70a**	87	-36.2
75	*(S)*-Phenylglycinol, **70b**	59	+35.0
76	*(R)*-Alaninol, **71a**	68	-7.2
77	*(S)*-Alaninol, **71b**	60	+3.1
78	*(R)*-Phenylalaninol, **72a**	71	-27.1
79	*(S)*-Phenylalaninol, **72b**	66	+16.9
80	*(R)*-Valinol, **73a**	73	-15.3
81	*(S)*-Valinol, **73b**	67	-2.1

The yields of the ephedrine synthesis of the ephedrine derivatives (**49, 75-81**) were achieved in moderate yields. The ephedrine-derived catalyst **49** achieved the best yield and stereoselectivity. The yield was improved by increasing the reaction time to allow the aziridine to form slowly. This achieved better yields and selectivity than stated in the literature.

3.2.1 Mechanism of reaction

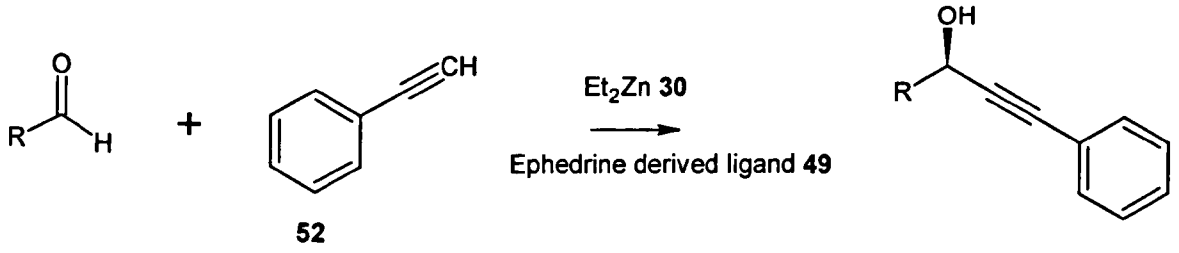
The synthesis of the ephedrine derived ligand occurs in a two-step reaction, first to form the aziridine ring and the second for the addition of ephedrine **2**. The first step is crucial as it involves the aziridine ring formation alongside the addition of the triflate group. The aziridine ring retains the stereochemistry of the amino alcohol, hence the importance of whether the starting material is *(R)* or *(S)*. The proposed mechanism for this reaction is shown. (see Scheme 3.3).



Scheme 3.3 Proposed mechanism for synthesis of **49**

3.3 Asymmetric alkynylation with ephedrine derived ligand 49

Following the synthesis of a range of ephedrine derived ligands (**49, 75-81**), the ephedrine derived ligand **49** was achieved in the highest yield and optical purity. In order to test the catalytic activity of the ligand **49**, it was utilised in the previously optimised asymmetric alkynylations for a range of aromatic aldehydes. This was process would allow for the catalyst to be tested for effectiveness and then compared to the previous collated data for the homogeneous alkynylations with the use of *N*-methylephedrine **26**. The asymmetric alkynylation reactions were initially carried out using Carreira's method; however, this resulted in low yields and selectivity. Hence, an alternative method was explored to test the catalytic activity of the ephedrine derived ligand **49**. The alternative reaction was carried out under a nitrogen atmosphere with the aid of diethylzinc **30** and ephedrine derived ligand **49** as the chiral catalyst. This reaction required a shorter reaction time than Carreira's method, as it only required stirring for 3 days at room temperature. The synthesis reaction was monitored by thin layer chromatography (TLC). The propargylic alcohols were then analysed using NMR, GC-MS, HPLC and optical rotation.



Scheme 3.4 Synthesis of secondary propargylic alcohols

A smaller range of aromatic aldehydes were tested in this asymmetric alkynylation for comparison with the data previously obtained in Section 2.3.1.

Table 3.2 Asymmetric addition of phenylacetylene **52** to aromatic aldehydes using a Tf-based sulfamide-amine alcohol chiral catalyst, **49**

Entry	R	Yield (%)	ee[a] (%)	$[\alpha]_D^{25}$
61a[3]	Ph, **37**	92	95	+3.2
61b[3]	2-MePh, **62**	94	91	-7.2
61c[3]	3-MePh, **63**	89	89	+4.8
61d[3]	4-MePh, **64**	91	90	+3.3
61e[3]	2-MeOPh, **65**	92	91	-8.9
61j[3]	3-MeOPh, **82**	86	89	+11.2
61k[3]	4-MeOPh, **83**	90	94	+6.0
61g[3]	2-ClPh, **67**	89	88	+11.3
61l[3]	3-ClPh, **68**	83	78	-6.9
61m[3]	4-ClPh, **84**	91	82	-9.0

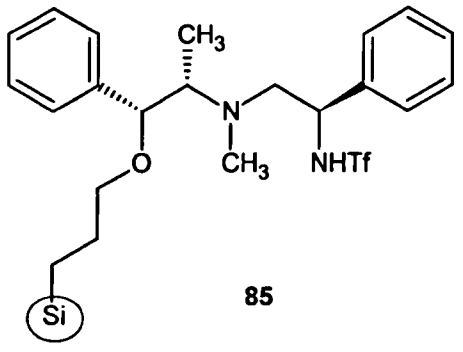
[a] The enantioselectivities were determined by HPLC analysis using a Chiracel OD-H column and eluting with 90:10 hexane: iso-propanol, detection at λ_{max} = 254nm.

The synthesis of the secondary propargylic alcohols provided good enantioselectivity and moderate to high yields. When comparing the results achieved using **49** as a catalyst with the results achieved with *N*-methylephedrine **26** (Section 2.3.1), the propargylic alcohols (61a[1]-61i[1]) produced slightly better yields (up to 94%). This is possibly due to the different asymmetric alkynylation method used which uses diethylzinc instead of zinc triflate. Additionally, it is possible that this method is more suited for the asymmetric alkynylation of aromatic aldehydes than Carreira's method.

3.4 Tethering of ephedrine derivative 49 to silica support

In order to explore the further potential of using hybrid catalysts to facilitate ephedrine recycling, the potential of tethering the ephedrine derived chiral ligand **49** was tethered to 3-

chloropropylfunctionalised silica **59** using the previously optimised method for tethering ephedrine **2** to the functionalised silica support. This involved refluxing the pre-dried 3-chloropropylfunctionalised silica with the ephedrine derived ligand **49** in anhydrous toluene. Upon completion of the reaction, the tethered catalyst **85** was isolated using a simple vacuum filtration and washing with ether and methanol. The tethered catalyst **85** was dried using a vacuum pistol and stored under nitrogen; it was collected as a fine pale yellow powder. The tethered catalyst was analysed using elemental analysis and thermogravimetric analysis. (Figure 3.1)



85

Figure 3.1 Functionalised silica supported ephedrine catalyst **85**

3.4.1 Analysis of functionalised silica supported ephedrine derived ligand 85

The analysis of the novel tethered catalyst **85** proved to be as challenging as before for functionalised silica supported ephedrine **60**. This was as due to the nature of the silica support, analytical methods were limited to thermogravimetric analysis (TGA) and elemental analysis. The TGA analysis would help to identify if the ephedrine derived ligand **49** had bound to the functionalised silica support as there would be a greater mass loss of organic material. The elemental analysis would allow us to determine the presence of the key atoms

of the ligand such as the two nitrogen atoms and sulphur atom present in the ephedrine derived ligand **49**.

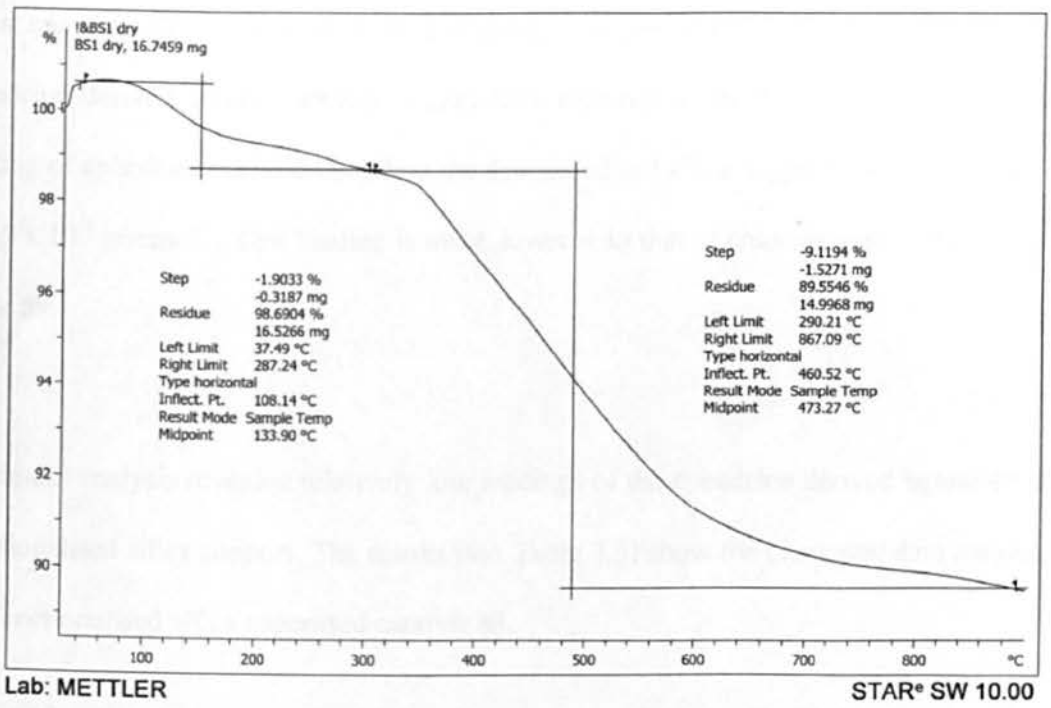


Figure 3.2 TGA of functionalised silica supported ephedrine derived catalyst **85**

The TGA analysis obtained when heating the tethered catalyst **85** is displayed (see Figure 3.2). The sample of precise weight (16.7459 mg) was heated slowly to 900°C, as expected there were three incremental points of mass loss. The initial loss of 1% appears to be loss of surface water from the material as the sample is heated from 0°C to 150°C. The second loss in mass is where we would expect the bulky organic matter of the ephedrine derived ligand to break down, this is represented by a mass loss of 9% between 290°C and 650°C. The final loss in mass of about 1% between 650°C and 900°C accounts for the breakdown of the Si-O bonds. When comparing the TGA analysis of the supported catalyst **85** to the TGA of 3-

chloropropyl functionalised silica **59** (Figure 2.1), it is clear to see that the loss of organic matter from catalyst **85** is far greater than the loss of 3-chloropropyl chains from **59**, this provides assurance that the ephedrine derived ligand **49** has tethered to the functionalised silica support. The significance of the mass loss displayed provides evidence that the ephedrine derived catalyst **49** has successfully tethered to the functionalised support. The loading of ephedrine derived ligand on the functionalised silica support was determined to be 2.159×10^{-5} g/mmol^{-1}. This loading is much lower than that of chloropropyl on functionalised silica **59**.

Elemental analysis revealed relatively low loadings of the ephedrine derived ligand **49** on the functionalised silica support. The results (see Table 3.3) show the elemental data obtained for the functionalised silica supported catalyst **85**.

Table 3.3 C,H & N Elemental analysis of catalyst **85**

Ref	% C	% H	%N	Loading (mmol/g)
85	18.34	2.87	2.98	1.419×10^{-5}

The loading of the catalyst is relatively low suggesting that it may be difficult to bind a bulky ligand to functionalised silica. However, the presence of nitrogen within the sample confirms that the ligand is present on the sample due to the two nitrogen atoms present within the ephedrine derived ligand **49**.

3.4.2 Asymmetric alkynylations with tethered catalyst 85

The newly tethered catalyst **85** was tested in the asymmetric addition of phenylacetylene to a range of aromatic aldehydes using the diethylzinc method used for the untethered ephedrine derived ligand **49**. It was important to determine how effective the novel catalyst **85** was in asymmetric alkynylation reactions. (see Table 3.4)

Table 3.4 Asymmetric addition using a supported catalyst, **85**

Entry	R	Yield (%)	ee[a] (%)	$[\alpha]_D^{26}$
61a[4]	Ph, **37**	81	85	+2.8
61b[4]	2-MePh, **62**	62	78	-6.4
61e[4]	2-MeOPh, **65**	45	60	-7.4
61g[4]	2-ClPh, **67**	57	75	+10.9
61i[4]	2-FlPh, **69**	53	66	-5.6

[a] The enantioselectivities were determined by HPLC analysis using a Chiracel OD-H column and eluting with 90:10 hexane: iso-propanol, detection at λ_{max} = 254 nm.

The propargylic alcohols listed in (see Table 3.4) were obtained in relatively low yields and low selectivity after using Li's method of asymmetric alkynylations. However, the results are promising as they show that the ephedrine derived catalysts can be tethered to functionalised silica supports for utilisation in asymmetric synthesis. There are a number of factors which could have affected the percentage yield of the products obtained such as the bulky groups of the catalyst restricting the access to active sites and the method of synthesis not being suited to the catalyst.

A comparison of the results of the asymmetric alkynylations obtained using the functionalised silica supported ephedrine derived ligand **85** and the results of the functionalised silica supported ephedrine **60** (see section 2.4) shows that the latter performs better in asymmetric synthesis. The functionalised silica supported ephedrine catalyst **60** provides good yields (up to 97%) and good selectivity (up to 92%), whereas the catalyst **85** provided moderate to low yields (up to 81%) and moderate selectivity (up to 85%). It is possible that the large bulky structure of the ephedrine derived ligand restricts the reactants from access to the active site of ephedrine, thus lowering the yield. However, it is promising that the functionalised silica supported ephedrine derived ligand **85** is able to successfully catalyse the asymmetric alkynylations of aromatic aldehydes.

3.4.3 Recycling studies

The final stage of this study involved determining whether the functionalised silica supported ephedrine derived catalyst **85** could be reused after it was recovered using a simple vacuum filtration. It was important to test the catalytic activity of the catalyst **85** after recovery; therefore it was tested with the asymmetric alkynylation of benzaldehyde **37** using phenylacetylene **52**. The results from the asymmetric alkynylations are shown. (see Table 3.5)

Table 3.5 Recycling studies of the supported ephedrine derived catalyst **85**

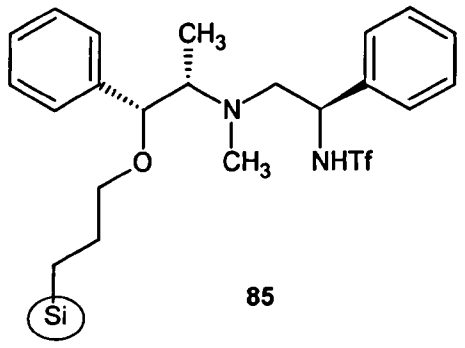
Entry	R	Yield (%)	ee[a] (%)	$[\alpha]_D^{26}$
61a[4i]	Ph, **37**	76	79	+2.7
61a[4ii]	Ph, **37**	65	21	+0.7

[a] The enantioselectivities were determined by HPLC analysis using a Chiracel OD-H column and eluting with 90:10 hexane: iso-propanol, detection at λ_{max} = 254 nm.

The functionalised silica supported ephedrine derived ligand **85** was successfully recovered and reused once in the asymmetric alkynylation of benzaldehyde. It was also tested a further time, however, the results displayed a large dip in both the yield and the selectivity, which suggested that the catalyst was no longer performing effectively. However, the results display that the novel functionalised silica supported ephedrine derived ligand can be utilised and reused in asymmetric alkynylations.

3.5 Conclusions and future work

The application of a triflate based ephedrine derived ligand tethered to a functionalised silica support **85** to an asymmetric alkynylation appears is the novel component of the work presented in this chapter. Further optimisation of tethering the ephedrine based catalyst **49** to the functionalised support could improve the loading of the organic material on the support which in turn could improve the enantioselective of the propargylic alcohols formed from the asymmetric alkynylation reaction.



85

Figure 3.3 Functionalised Silica support ephedrine derived ligand

3.6 Closing remarks

The research presented within this thesis has shown the application of an immobilised silica supported catalysts and its application within in asymmetric synthesis. Ephedrine **2**, a controlled substance, was tethered to functionalised silica support for the use in asymmetric alkynylation reactions between a terminal alkyne and a range of aromatic aldehydes.

The tethered ephedrine catalyst **60** displayed that it can be successfully applied to asymmetric alkynylation reactions, be recovered using *in vacuo* filtration and reused for a further three reactions without affecting selectivity of the products. The secondary propargylic alcohols were obtained in good yields and high enantioselectivities, proving to be comparable to the homogeneous results obtained using *N*-methylephedrine **26** as a catalyst.

The recovery of the tethered ephedrine catalyst **60** was relatively simple, and its ability to be recycled opens up the possibility whether these catalysts can be used on larger scale, for example, in continuous flow reactors. These new developments could help industries control their use of ephedrine **2** and help ease the limitations of licence placed upon ephedrine **2**.

The second part of the research led into the tethering of ephedrine derivatives onto silica supports for use in asymmetric alkynylation reactions. An ephedrine derived ligand **49** was synthesised in good yields and successfully tethered onto the functionalised silica support. The loading of the ephedrine derived catalyst on the support material was relatively low, which directly impacted the yields of the propargylic alcohols obtained. The tethered

ephedrine catalyst **85** was recovered and reused once before both enantioselectivity and yield were compromised. This was the first application of this ephedrine derived catalyst being tethered to a support and then being utilised in asymmetric synthesis.

Overall, this work has provided evidence that ephedrine **2** can be tethered onto silica supports for use in asymmetric synthesis and can also be recovered and recycled without affecting enantioselectivity. This shows that methods such as these could be applied on a larger scale, for example, in continuous phase reactors, whilst managing the amount of ephedrine in circulation and bringing more transparency to its audit trail.

4 Experimental

4.1 General experimental procedures

Starting material and general laboratory chemicals (including anhydrous solvents) were used as provided by Sigma-Aldrich limited and were used without further purification.

Spectra such as NMR were measured on a Jeol Eclipse^{+} 400 NMR spectrometer using Jeol Delta version 4.3.6 control and processing software. The NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C), with chemical shifts being reported in ppm. MS were recorded using a Varian CP-3800 gas chromatograph with Varian 1200L quadruple mass spectrometer controlled using Varian Saturn GC/MS system control version 6.41. HPLC were recorded using a Perkin Elmer 200 series with a quaternary pump and a PDA detector, running total chrom software version 6.3.1. TGA were recorded using Mettler Toledo TGA 1.

Elemental analysis was obtained from Medac Ltd.

4.1.1 Naming conventions

ν_{max} (NaCl / cm^{-1}) are data which refer to major bands in wavenumbers

δ_H (MHz : Solvent) are the data which refer to ^{1}H NMR data where s = singlet, d = doublet, t = triplet and m = multiplet

δ_C (MHz : Solvent) are the data which refer to ^{13}C NMR data.

δ_F (MHz : Solvent) are the data which refer to ^{19}F NMR data.

MS (EI) m/z: (M^{+}) refers to the mass spectroscopy data

4.2 Experimental procedures

4.2.1 The synthesis of functionalised silica supported ephedrine 60

In order to prepare the silica support, 3-chloropropyl functionalised silica **59** was pre-dried in a vacuum pistol at 40°C to constant weight.

Under a nitrogen atmosphere, chiral ligand ***(1R,2S)***-(-)-ephedrine **2** (300 mg, 1.815 mmol) and triethylamine **28** (0.14 ml, 1 mmol) were added to a round bottom flask containing 3-chloropropyl functionalised silica **59** (1.00 g) and anhydrous toluene. (50 ml) The mixture was left to reflux for 30 hours.

Upon completion of the reflux, the newly formed tethered catalyst **60** was cooled and then collected by filtration. It was washed sequentially with ether (2 x 30 ml) and methanol (2 x 30 ml). The catalyst **60** was dried *in vacuo* to constant weight at 40°C and then stored under nitrogen.

The functionalised silica supported ephedrine catalyst was analysed using thermogravimetric analysis (TGA) and elemental analysis. The catalyst was isolated as a fine white powder with a loading average of 2.357 - 2.997 x 10^{-2} mmol/g.

4.2.2 The synthesis of propargylic alcohols

This method was used to synthesise 61a[1] and 61a[2]

Under a nitrogen atmosphere, zinc triflate (1600 mg, 4.4 mmol) and chiral ligand (+)-*N*-methylephedrine **26** (430 mg, 2.4 mmol) were added to a round bottomed flask containing anhydrous toluene (52 ml). Triethylamine **28** (0.67 ml, 4.8 mmol) was added dropwise using a syringe. The reaction mixture was left to stir for 3 hours and after which phenylacetylene **52** (0.66 ml, 6.0 mmol) is added slowly. The reaction was left to stir for a further hour and then benzaldehyde **37** (212 mg, 2.0 mmol) was added to the mixture. The reaction was left to stir for 7 days at room temperature and was monitored using TLC.

Upon completion of the reaction, the mixture was quenched with saturated ammonium chloride solution (38 ml). The propargylic alcohol was then extracted using diethyl ether (3 x 40 ml). The combined organic layers were washed sequentially with saturated ammonium chloride solution (100 ml) and brine (100 ml). The combined organic layers were then dried over magnesium sulphate. The product was filtered and then concentrated *in vacuo*, resulting in the newly formed propargylic alcohol.

4.2.3 Asymmetric alkynylation using ephedrine derived ligand 49

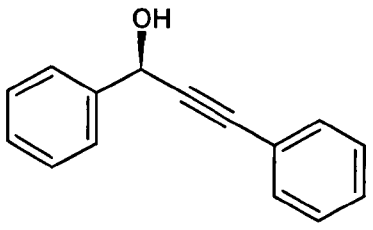
This method was used to synthesise alkynes 61[3],61[4]

Under a nitrogen atmosphere, chiral ephedrine derived ligand **49** (10 mol%, 0.025 mmol) was added to anhydrous toluene (10 ml) in a round bottomed flask at room temperature and stirred for 10 minutes. Subsequently, diethylzinc **30** (10 wt% in hexane, 9 ml) and phenylacetylene **52** (0.5 mmol , 0.549 ml) were drop wise using a syringe. The mixture was stirred at room temperature for one hour whereupon benzaldehyde **37** (0.25 mmol) was added and stirred for a further 16 hours at an ambient temperature. The reaction progress was monitored by the TLC analysis (petroleum ether 60: ethyl acetate, 2:1).

Upon completion, the reaction was quenched with aqueous hydrochloric acid (5%) and extracted with diethyl ether (3 × 6ml). The combined organic layers were then washed with a saturated solution of brine, dried over anhydrous sodium sulphate, filtered *in vacuo* and was then concentrated under vacuum to afford the compound.

The alkyne was finally purified by flash column chromatography eluted with petroleum ether 60: ethyl acetate, 2:1.

Synthesis of *(R)*-(+)-1,3-Diphenylprop-2-yn-1-ol 61a[1]



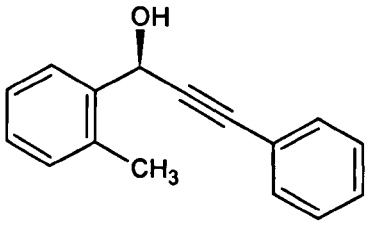
Ref	Yield (%)	e.e (%)	$[\alpha]_D^{26}$
61a[1]	98	96	+2.7
61a[2]	90	92	+2.1
61a[3i]	90	91	+4.7
61a[3ii]	89	91	+4.6
61a[3iii]	89	86	+4.7
61a4	92	95	+3.2
61a[5]	81	85	+2.8
61a[6i]	76	79	+2.7
61a[6ii]	65	21	+2.7

The reaction was carried out as outlined in section 4.2.1. Purification by column chromatography using 2:1 petroleum ether 60: ethyl acetate, yielded 98% as a pale yellow oil.

96% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), with retention times of t_{major} = 15.7 min and t_{minor} = 26.2 min. $[\alpha]_D^{25}$ = + 2.7 (*c* 0.9, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.54 (m, 2H, Ar-H), 7.49 – 7.24 (m, 8H, Ar-H), 5.68 – 5.63 (d, 1H, J = 6.1Hz, Ar-CH), 2.81-2.78 (d, 1H, J = 6.1Hz, -OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.5, 131.8, 128.7, 128.6, 128.4, 128.2, 126.8 122.5, 88.8, 86.5, 65.1; **MS (EI) m/z:** 208 (M^+)

Synthesis of *(R)*-(-)-1-(2-Methylphenyl)-3-phenylprop-2-yn-1-ol, 61b[1]



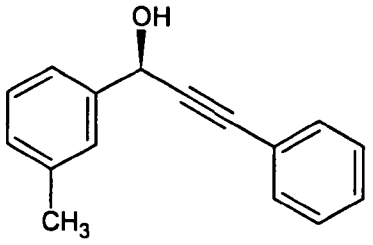
Ref	Yield (%)	e.e (%)	$[\alpha]_D^{26}$
61b[1]	96	90	-7.1
61b[2]	97	85	-6.9
61b[4]	94	91	-7.2
61b[5]	62	78	-6.4

The reaction was carried out as outlined in section 4.2.1. Purification by column chromatography yielded 96% as a pale yellow oil.

90% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), with retention times of t_{major} = 9.7 min and t_{minor} = 22.3 min. $[\alpha]_D^{25}$ = -7.1 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.71 (m, 1H, Ar-H), 7.47 – 7.43 (m, 2H, Ar-H), 7.31 – 7.24 (m, 6H, Ar-H), 5.82 (s, 1H, Ar-CH),2.60 (s, 1H, -OH), 2.44 (s, 3H, Ar-CH_3);**^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.3, 135.9, 131.6, 131.0, 128.8, 128.7, 128.4, 126.5, 126.2, 122.6, 88.7, 86.6, 63.1, 19.1; **MS (EI) m/z:** 222 (M^+)

Synthesis of *(R)*-(+)-1-(3-methylphenyl)-3-phenylprop-2-yn-1-ol, 61c[1]



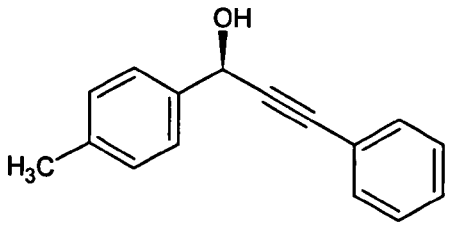
Ref	Yield (%)	e.e (%)	$[\alpha]_D^{26}$
61c[1]	95	89	+4.9
61c[2]	95	76	+4.0
61c[4]	89	89	+4.8

The reaction was carried out as outlined in section 4.2.1. Purification by column chromatography yielded 95% as a light yellow oil.

89% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), with retention times of t_{major} = 14.2 min and t_{minor} = 27.5 min. $[\alpha]_D^{25}$ = +4.9 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 - 7.46 (m, 4H, Ar-H), 7.43 - 7.40 (m, 4H, Ar-H), 7.18 - 7.15 (d, J = 6.8 Hz, 1H, Ar-H), 5.63 (s, 1H, Ar-CH), 2.65 (s, 3H, Ar-CH_3), 2.38 (s, 1H, -OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.1, 138.3, 131.6, 129.5, 128.8, 128.7, 128.4, 127.5, 123.9, 122.1, 88.7, 86.6, 66.1, 21.8 ; **MS (EI) m/z:** 222 (M^+)

Synthesis of *(R)*-(+)-1-(4-methylphenyl)-3-phenylprop-2-yn-1-ol, 61d[1]



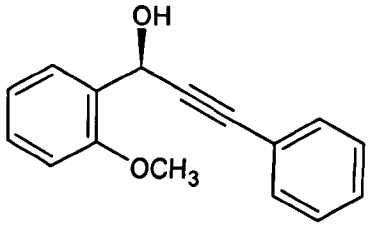
Ref	Yield (%)	e.e (%)	$[\alpha]_D^{26}$
61d[1]	90	84	+3.1
61d[2]	85	80	+2.9
61d[4]	91	90	+3.3

The reaction was carried out as outlined in section 4.2.1. Purification by column chromatography yielded 90% as a light yellow oil.

84% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), with retention times of t_{major} = 11.2 min and t_{minor} = 23.6 min. $[\alpha]_D^{25}$ = + 3.1 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 - 7.43 (m, 4H, Ar-H), 7.41 - 7.39 (m, 3H, Ar-H), 7.25 - 7.19 (m, 2H, Ar-H), 5.61 (s, 1H, Ar-CH), 2.34 (s, 3H, Ar-CH_3), 2.29 (s, 1H, -OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.4, 137.6, 131.8, 129.4, 128.7, 128.5, 128.4, 126.9, 122.7, 122.3, 88.9, 86.5, 64.8, 21.4 ; **MS (EI) m/z**: 222 (M^+)

Synthesis of *(R)*-(-)-1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-ol, 61e[1]



Ref	Yield (%)	e.e (%)	$[\alpha]_D^{26}$
66e[1]	89	90	-8.6
66e[2]	90	86	-7.9
66e[4]	92	91	-8.9
66e[5]	45	60	-7.4

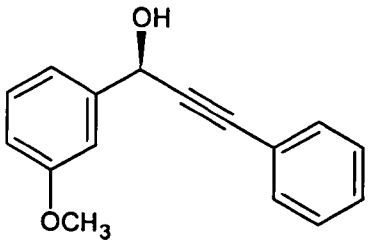
The reaction was carried out as outlined in section 4.1.2. Purification by column chromatography yielded 89% as a pale yellow oil.

90% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), with retention times of t_{major} = 12.8 min and t_{minor} = 19.3 min; $[\alpha]_D^{25}$ = -8.6 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.63 (d, J = 6.9 Hz, 1H, Ar-H), 7.56 – 7.52 (m, 2H, Ar-H), 7.41 - 7.38 (m, 4H, Ar-H), 7.09 – 7.05 (t, J = 6.9 Hz, 1H, Ar-H), 7.01 (m, 1H, Ar-H), 5.99 (s, 1H, Ar-CH), 3.89 (s, 3H, OCH_3), 3.29 (s, 1H, -OH) ; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.1, 132.0, 129.4, 128.6, 128.4, 128.3, 128.1, 123.1, 120.7, 110.6, 88.6, 86.3, 61.6, 56.1;

MS (EI) m/z: 238 (M^+)

Synthesis of *(R)*-(+)-1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-ol, 61f[4]

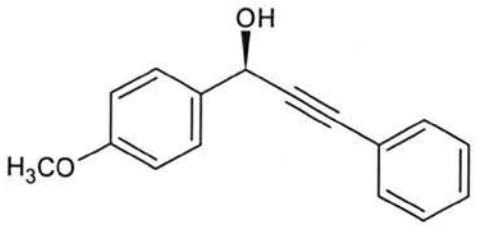


The reaction was carried out as outlined in section 4.1.2. Purification by column chromatography yielded 86% as a pale yellow oil.

89% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), with retention times of t_{major} = 15.9 min and t_{minor} = 28.6 min. $[\alpha]_D^{25}$ = +11.2 (*c* 0.9, $CHCl_3$)

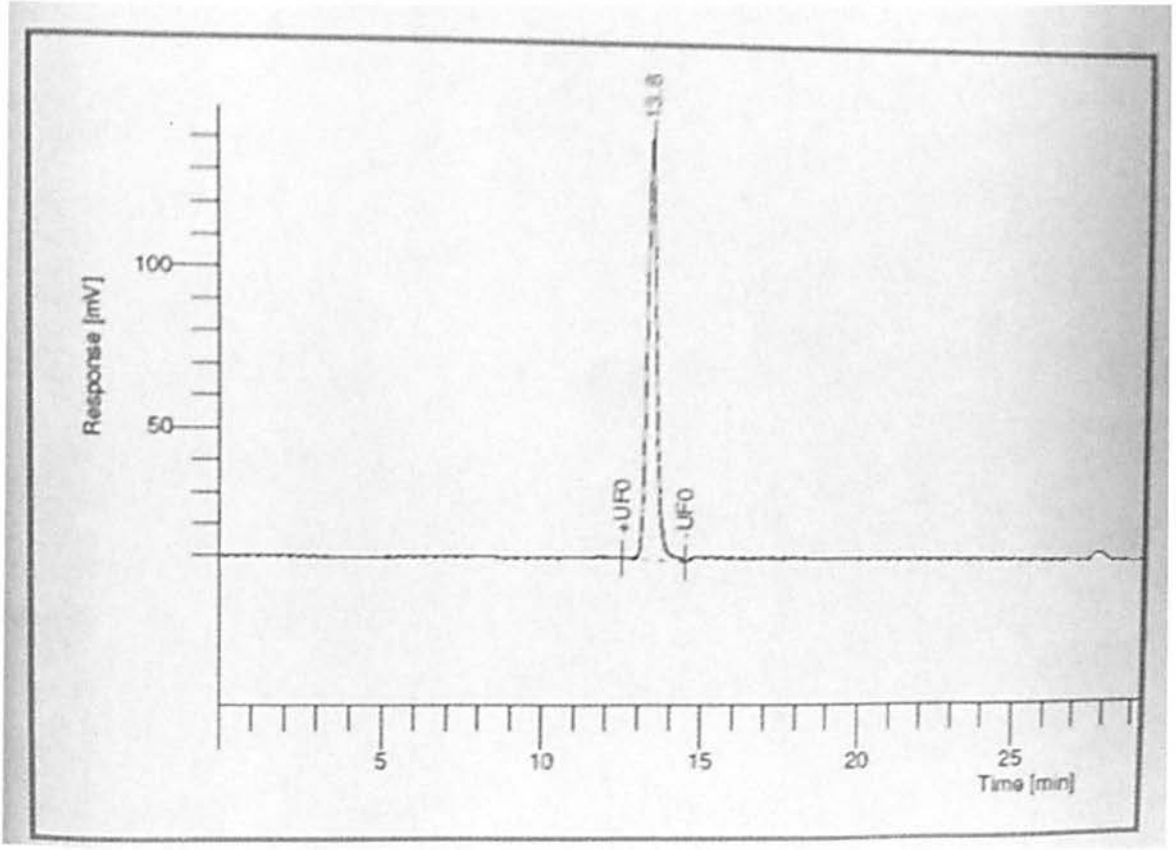
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 - 7.45 (m, 2H, Ar-H), 7.34 – 7.31 (m, 4H, Ar-H), 7.22 - 7.18 (m, 2H, Ar-H), 6.89 – 6.87 (m, 1H, Ar-H), 5.67 (s, 1H, Ar-CH), 3.81 (s, 3H, OCH_3), 2.62 (s, 1H, -OH) ; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.8, 142.0, 131.5, 129.6, 128.4, 128.3, 122.2, 120.1, 114.9, 112.3, 88.8, 86.4, 65.2, 55.8; **MS (EI) m/z:** 238 (M^+)

Synthesis of *(R)*-(+)-1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ol, 61g[4]



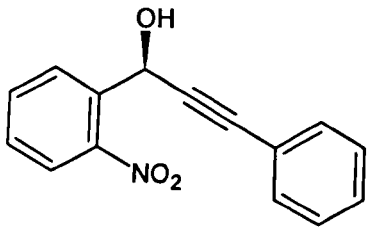
The reaction was carried out as outlined in section 4.1.2. Purification by column chromatography yielded 90% as a light brown oil.

94% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), with retention times of t_{major} = 13.8 min and t_{minor} = 30.5 min; $[\alpha]_D^{25}$ = +6.0 (*c* 0.9, $CHCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 - 7.53 (m, 4H, Ar-H), 7.32 – 7.28 (m, 3H, Ar-H), 6.99 – 6.95 (m, 2H, Ar-H), 5.69 (s, 1H, Ar-CH), 3.91 (s, 3H, $-OCH_3$), 2.19 (s, 1H, -OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.8, 133.2, 131.8, 128.8, 128.6, 128.4, 122.5, 114.3, 88.9, 86.2, 64.8, 56.1; **MS (EI) m/z:** 238 (M^+)

Synthesis of *(R)*-(-)-1-(2-Nitrophenyl)-3-phenylprop-2-yn-1-ol, 61f[4]



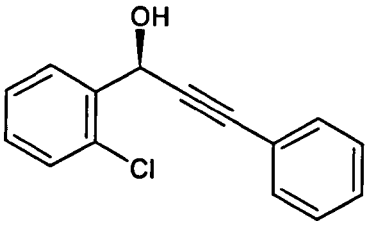
The reaction was carried out as outlined in 4.1.2. Purification by column chromatography yielded 71% as a pale orange oil.

85% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), retention time, t_{major} = 12.9 min and t_{minor} = 17.3 min. $[\alpha]_D^{25}$ = - 12.3 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.94 (m, 2H, Ar-H), 7.66 – 7.63 (m, 1H, Ar-H), 7.60 – 7.56 (m, 3H, Ar-H), 7.31 – 7.29 (m, 3H, Ar-H), 6.22 (s, 1H, Ar-CH), 3.37 (s, 1H, -OH);

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 136.4, 133.9, 132.1, 129.8, 129.7, 128.8, 128.7, 125.9, 121.7, 86.8, 86.5, 61.3, 51.4; **MS (EI) m/z:** 253 (M^+)

Synthesis of *(R)*-(+)-1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol, 61g[1]



Ref	Yield (%)	e.e (%)	$[\alpha]_D^{26}$
61g[1]	90	88	+11.6
61g[2]	86	79	+10.2
61g[4]	89	88	+11.3
61g[5]	57	75	+10.9

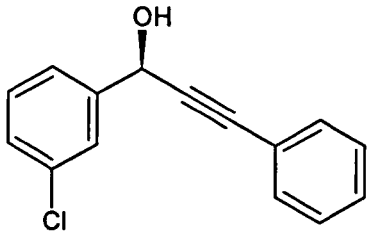
The reaction was carried out as outlined in 4.1.2. Purification by column chromatography yielded 90% as a brown oil.

88% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), retention time, t_{major} = 9.3 min and t_{minor} = 24.9 min.$[\alpha]_D^{25}$ = + 11.6 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H, Ar-H), 7.46 – 7.32 (m, 8H, Ar-H), 6.07 (s, 1H, Ar-CH), 2.81 (br, 1H, -OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.8, 132.4, 131.2, 129.9, 129.7, 128.8, 128.6, 128.2, 127.3, 122.1, 87.6, 86.6, 62.

MS (EI) m/z: 242 (M^+)

Synthesis of *(R)*-(-)-1-(3-Chlorophenyl)-3-phenylprop-2-yn-1-ol, 61h[1]



Ref	Yield (%)	e.e (%)	$[\alpha]_D^{26}$
61h[1]	86	81	-8.3
61h[4]	83	78	-6.9

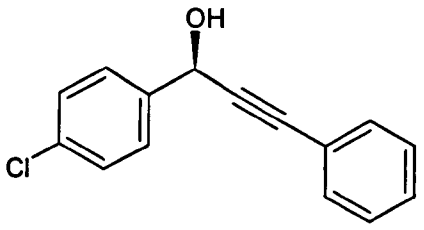
The reaction was carried out as outlined in 4.2.1. Purification by column chromatography yielded 86% as a pale brown oil.

81% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), retention time, t_{major} = 10.4 min and t_{minor} = 29.2 min. $[\alpha]_D^{25}$ = - 8.3 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H, Ar-H) 7.45– 7.38 (m, 3H, Ar-H), 7.32 – 7.29 (m, 5H, Ar-H), 5.62 (s,1H,Ar-CH), 2.53 (br, 1H, -OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 143.4, 135.4, 131.9, 130.1, 129.8, 129.4, 128.7, 127.5, 122.5, 122.3, 88.4, 87.0, 65.4

MS (EI) m/z: 242 (M^+)

Synthesis of *(R)*-(-)-1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol, 66i[4]

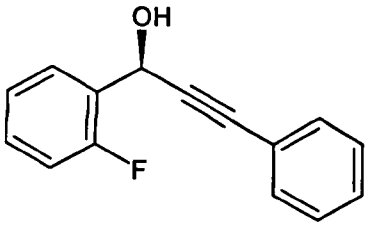


The reaction was carried out as outlined in 4.1.2. Purification by column chromatography yielded 91% as a pale brown oil.

82% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), retention time, t_{major} = 10.6 min and t_{minor} = 27.3 min. $[\alpha]_D^{25}$ = - 9.0 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.49 (m, 2H, Ar-H), 7.47 – 7.44 (m, 2H, Ar-H), 7.30 – 7.26 9(m, 5H, Ar-H), 5.70 (s, 1H, Ar-CH), 2.37 (br, 1H, -OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.1, 139.4, 134.0, 131.5, 128.8, 128.6, 128.2, 127.9, 122.9, 121.7, 88.8, 87.8, 64.3; **MS (EI) m/z:** 242 (M^+)

Synthesis of *(R)*-(-)-1-(2-Fluorophenyl)-3-phenylprop-2-yn-1-ol, 61j[1]



Ref	Yield (%)	e.e (%)	$[\alpha]_D^{26}$
61j[1]	87	85	-6.2
61j[5]	53	66	-5.6

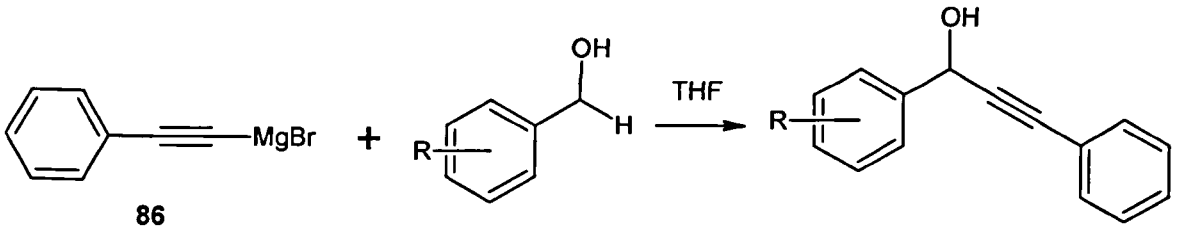
The reaction was carried out as outlined in 4.1.2. Purification by column chromatography yielded 87% as a pale yellow oil.

85% *ee* was determined by HPLC analysis (Chiracel OD-H column, 10% IPA in hexane), retention time, t_{major} = 9.9 min and t_{minor} = 19.3 min. $[\alpha]_D^{25}$ = - 6.2 (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.71 (m, 1H, Ar-H), 7.44 – 7.41 (m, 2H, Ar-H), 7.31 – 7.27 (m, 4H, Ar-H), 7.20 – 7.16 (m, 1H, Ar-H), 7.14 – 7.10 (m, 1H, Ar-H), 5.98 (s, 1H, Ar-CH), 2.56 (s, 1H, -OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.1, 130.9, 130.2, 130.0, 128.7, 128.3, 128.1, 124.6, 122.7, 115.8, 87.9, 86.8, 60.1

MS (EI) m/z: 226 (M^+)

4.1.3 Synthesis of racemic alkynes for use in HPLC

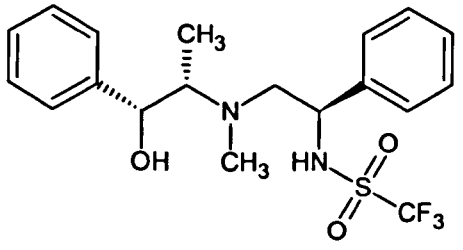


Scheme 4.1 Formation of racemic propargylic alcohols

Under a nitrogen atmosphere, phenylethynylmagnesiumbromide **86** (102 mg, 0.50 mmol) and benzaldehyde (0.25 mmol) were added to a round bottomed flask containing anhydrous Tetrahydrofuran (THF). The reaction mixture was left to stir for 7 days and was monitored using thin layer chromatography (TLC) using a solvent system of 1:1 ethyl acetate and hexane. The aldehyde spot (R_f: 0.46) was visualised under a UV lamp, once the spot disappeared the reaction was determined to have reached completion.

The racemic propargylic alcohols were stored under nitrogen for use in the HPLC analysis of the previously obtained propargylic alcohols.

Synthesis of *(1R,2S)*-2-{N-methyl-[*(2R)*-2-phenyl-2-(trifluoromethylsulfonylamino)ethyl]amino}-1-phenyl-1-propanol 49

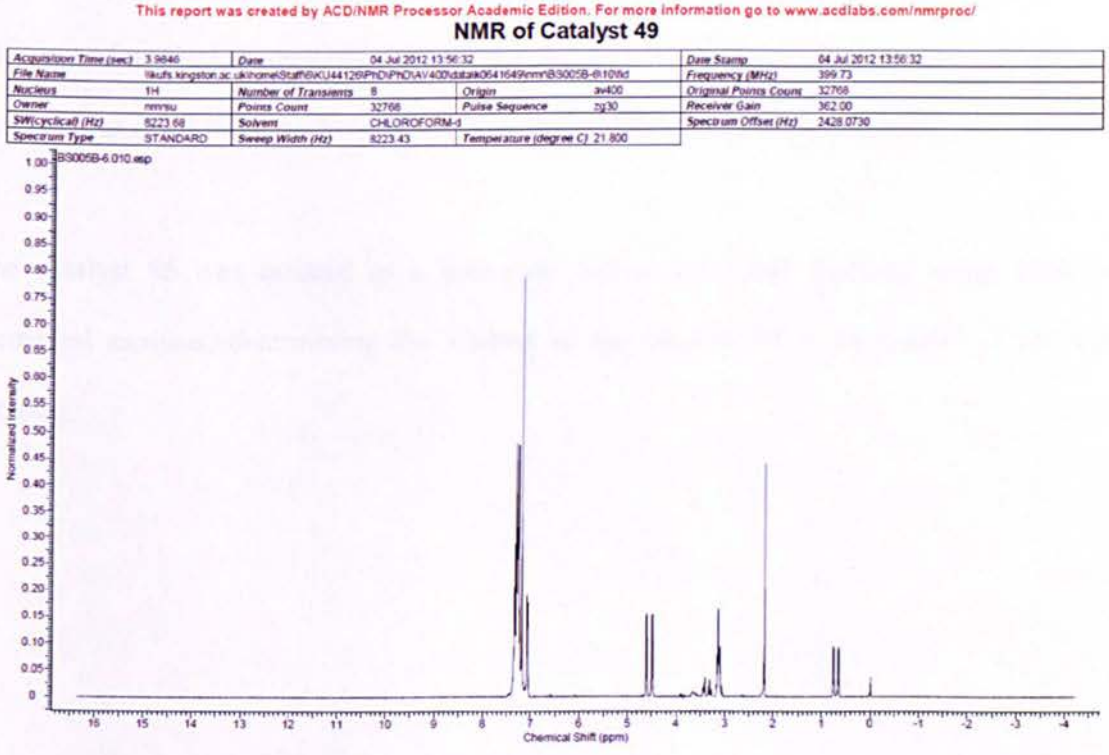


Under a nitrogen atmosphere, triflic anhydride (1.8 ml, 11 mmol) was added dropwise to a solution of *(R)*-phenylglycinol **70a** (685 mg, 5 mmol) and triethylamine **28** (1.4 ml, 10 mmol) in anhydrous dichloromethane (DCM) (20 ml) over a period of two hours whilst the reaction was cooled to -78°C. The reaction mixture was left to stir for a further two hours and was monitored using TLC. Upon completion, the TLC plate visualised a new spot for the newly formed aziridine (R_f: 0.32) and the spot for the phenylglycinol (R_f: 0.45) disappeared.

The reaction mixture was washed sequentially with chilled 0.1M hydrochloric acid (HCl) (2 x 10 ml) and chilled saturated aqueous sodium carbonate (2 x 10 ml). The organic phase was then extracted and dried with magnesium sulphate.

The newly formed aziridine which was a dark yellow oil added immediately dropwise to a solution of *(1R,2S)*-(-)-ephedrine **2** (825 mg, 5 mmol) in anhydrous acetonitrile (40 ml) at 0°C. The mixture was stirred at room temperature for 12 hours and then at 40°C for a further three days. The acetonitrile was evaporated isolating the newly formed ligand. The ligand **49** was purified using column chromatography yielding 87% as a pale yellow crystalline solid. 90% *de* was determined by HPLC analysis (Chiracel OD-H column, 10% iso-propyl alcohol in hexane, detection at λ_{max} = 254 nm of t_{major} = 8.9 min. $[\alpha]_D^{26}$ -36.2 (*c* 1.0, $CHCl_3$); R_f: 0.45 (9:1 hexane: ethyl acetate)

IR (neat) ν = 2928 cm^{-1}, 1602 cm^{-1}, *1451 cm^{-1}*, *1389 cm^{-1}*, *1264 cm^{-1}*, 1186 cm^{-1}, 1148 cm^{-1}, 1079 cm^{-1}, 990 cm^{-1}, 920 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.41 – 7.31 (m, 8H, Ar-H), 7.13 – 7.09 (d, 2H, Ar-H), 4.57 (d, J = 6.04 Hz, 1H, Ar-CH), 3.70 (dd, J = 4.76 and 5.40 Hz, 1H), 3.51 – 3.45 (m, 1H), 3.34 (dd, J = 4.76 and 8.70 Hz), 3.07 (m, 1H), 2.21 (s, 3H, N-CH_3), 0.62 (d, J = 6.8 Hz, 3H, C-CH_3) ; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.8, 137.0, 128.9, 128.5, 128.0, 126.6, 118.3, 76.5, 77.7, 57.6, 44.9, 36.0, 11.3; **^{19}F NMR ($CDCl_3$):** δ -77.3, -76.4, -76.3; **LC-MS (EI) m/z:** 417 (M^+)



4.2.2 Synthesis of functionalised silica supported ephedrine derived catalyst 85

3-chloropropyl functionalised silica **59** was pre-dried to constant weight *in vacuo* via pistol at 40°C using phosphorus pentoxide. Under a nitrogen atmosphere, the ephedrine derived ligand **49** (832 mg, 2 mmol) and triethylamine **28** (0.14 ml, 1 mmol) was added to a round bottomed flask contained the pre-dried 3-chloropropyl functionalised silica **59** (1.00 g) and anhydrous toluene (50 ml). The reaction was left to reflux for 48 hours.

Upon completion, the reaction mixture was left to cool and the newly formed catalyst **85** was filtered and washed sequentially with diethyl ether (3 x 30 ml) and methanol (1 x 30 ml). The catalyst was dried *in vacuo* for 5 hours at 40°C and then stored under nitrogen.

The catalyst **85** was isolated as a fine pale yellow solid and analysed using TGA and elemental analysis, determining the loading of the catalyst **85** to be 1.419 – 2.159 $x10^{-5}$ mmol/g.

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