Heterogeneous asymmetric aziridination of styrene using Cu^{2+}-exchanged zeolite Y

Thesis submitted in accordance with the requirements of the University of Cardiff for the degree of Doctor of Philosophy

by

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February 2006

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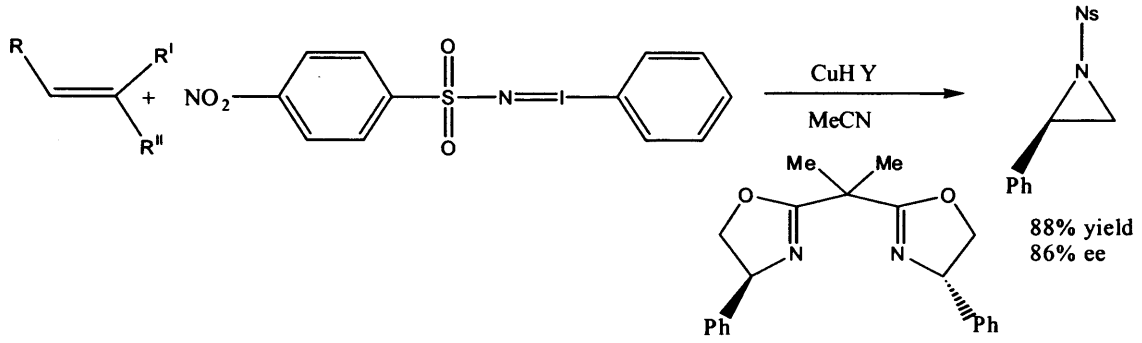
Abstract

The synthesis of pure enantiomers using catalytic processes continues to receive considerable research attention. The aziridination of olefins is an important reaction in organic synthesis as the aziridines formed are precursors to pharmaceuticals and agrochemicals. Aziridines can be synthesised by many synthetic routes, the most relevant being the homogeneous catalytic formation of aziridine demonstrated by Evans. A heterogeneous system was further developed, catalysed by copper-exchanged zeolite Y and using bis(oxazoline) as chiral modifier.



Scheme A: Aziridination of styrene using PhI=NNs

The copper-catalysed aziridination of styrene and styrene derivatives using either $Cu(OTf)_2$ as a homogeneous catalyst or copper exchanged zeolite Y modified as a heterogeneous catalyst with bis(oxazoline) using [N-(*p*-nitrophenylsulfonyl)imino]phenyliodinane (PhI=NNs) as nitrene donor was carried out. Detailed time on line profiles (TOL) for the progression of the reaction was monitored revealing high chemical yields and enantioselectivities (Scheme A).

In this study, C_2-symmetric Cu-bis(oxazoline) complexes were used to catalyse styrene-using [N-(p-tosylsulfonyl)imino]phenyliodinane (PhI=NTs) as nitrene donor. The course of the reaction was investigated by EPR and UV-Vis spectroscopy and was supported by catalytic studies carried out studies in order to reveal how the chirality of the formed Cu-bis(oxazoline) complex was crucial for the overall enantioselectivity and yield of the aziridination reaction.

During the aziridination of styrene using copper bis (oxazoline) complexes the ee increases with conversion due to further reactions of the product. Kinetic resolution experiments were carried out to investigate the mechanism involved, the effect of adding reaction breakdown products and the major product, aziridine to the reaction and also to investigate the shape of the reaction profile and its rate of reaction.

Acknowledgements

I would like to thank my supervisor, Prof. Graham J. Hutchings for his help and support throughout this project. Also thanks goes to Paul McMorn for his guidance in my early days and for his help in writing the thesis. A special mention to Prof. Don Bethell whose advice and input into the project was always much appreciated.

Thanks to the technical staff especially Rob Jenkins for always helping with my Hplc and NMR problems, Gaz for providing entertainment and general supplies at stores! Thanks to Pat for all the chats before meetings and help over the last 3 years.

A big thanks to Damien, for been a sound bloke and for bringing about my start in Cardiff. On the technical side 'Go raibh mile maith agat' for all the help with the EPR studies. Thanks also to Eilish in D.I.T, Dublin for giving me the push to study for my PhD.

Thanks to the many friends I have made in Cardiff. Thanks to John for all the help at the start, to Nicola, Owain, Phil, Aoife, Sarah, Chen and Nick D thanks for all the laughs in and out of the lab and the pints at lunchtime! To Graham and Chris thanks for keeping me sane in the final 2 years and for the many nights out (e.g. 'Dentist Chair night'!) with Neville and co. and the many arguments over the best (rugby) nation, i.e. Ireland!
Thanks to the EPR crew, especially 'Heir' Schmidt for his help with the EPR study, James, Emma and Greenslug for the chats and coffee breaks in a clean lab! To the present crew, Jenny, Jo, Ferg, Kieran, Pete and all the rest I have left out, cheers for the slaggings, stirring, gossiping and generally good times! Thanks to the guys I have lived with, especially 'scouser' Chris for putting up with me and my Man U/ Ireland devotion, and for the many nights of distraction away from chemistry!
Lastly, thanks to my girlfriend Neha, for her love, support and encouragement to complete this thesis in the face of many difficulties over the last year. Thank you pebbles!

Finally and most importantly I would like to thank my family. Mum, Dad, Sean, Niamh, Aileen and especially Gearoid who will not see me complete this thesis, I am eternally grateful for your love and support (both financial and spiritual), without which I would not be writing this here today.

For Mum and Dad, who helped

Fulfil one of my dreams

And my brave brother Gearoid,

Who continues to live in my dreams.

Contents

Glossary/ Abbreviations

A.A.S.	Atomic Absorption Spectroscopy
Ar	Aryl group
BET	Brunauer, Emmet and Tellar
(Bis)oxazoline	(S,S)-2,2'isopropylidene-*bis*(4-phenyl-2-oxazoline)
CuHY	copper exchanged zeolite Y
$Cu(OTf)_2$	copper(II) trimethylsulphonate (copper(II) triflate)
DMSO	dimethylsulfoxide
$CDCl_3$	*d*-chloroform
ee	enantiomeric excess
EPR	Electron Paramagnetic Resonance
ESR	Electron Spin Resonance
h	hour
HF	hydrofluoric acid
HPLC	High Performance Liquid Chromatography
MAS-NMR	Magnetic Angle Spinning Nuclear Magnetic Resonance
MeCN	acetonitrile
MeOH	methanol
ml	millilitre
N donor	nitrogen donor
NMR	Nuclear Magnetic Resonance
$NsNH_2$	nitrobenzene sulphonamide
Ph	Phenyl
PhI	iodobenzene
PhI=NNs	[*N*-(*p*-nitrophenylsulfonyl)imino]phenyliodinane

PhI=NTs	[*N*-(*p*-tosylsulfonyl)imino]phenyliodinane
ppm	parts per million
RT	Room Temperature
TGA	Thermal Gravimetric Analysis
TLC	Thin Layer Chromatography
$TsNH_2$	toluene sulphonamide
XRD	X-ray diffraction

Chapter 1

Introduction

1.0 Introduction

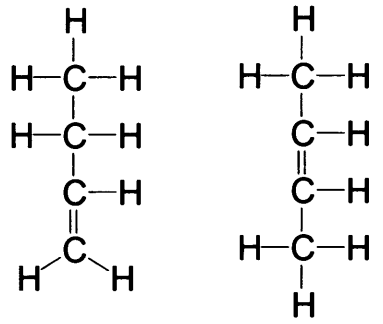
1.1 Aims of project

The aim of this project was to develop further the heterogeneous asymmetric aziridination reaction. From previous work carried out by Langham, Taylor and Gullick, high yields of aziridine and high enantioselectivities were observed for the reaction of styrene with nitrene donors. An investigation was carried out to study parameters such as reactant ratios and a range of substrates with different electronic properties in order to optimise yield of aziridine and enantiomeric excess (ee). The course of the reaction was investigated by EPR spectroscopy and supported by catalytic studies in order to reveal how the chirality of the formed Cu-bis(oxazoline) complex was crucial for the overall enantioselectivity and yield of the aziridination reaction. Kinetic resolution experiments were carried out to investigate the mechanism involved in the reaction and to test ideas arising from the simulations in both homogeneous and heterogeneous systems.

1.2 Principles of stereochemistry

The study of stereoisomers and the chemical effects of stereoisomerism is called stereochemistry[1]. Stereochemistry is the branch of chemistry concerned with the three-dimensional aspects of molecules[2]. Compounds with the same chemical formulae but different arrangement of atoms are called isomers, from Greek *isos* +

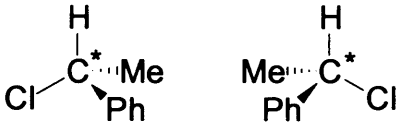
meros meaning "made of the same parts". Isomers are compounds that have the same numbers and kind of atoms but differ in the way the atoms are arranged (Figure 1).



Structural Isomers

Figure 1

A molecule that is not identical to its mirror image is a special kind of stereoisomer called an enantiomer, Greek *enantio,* "opposite". If an isomer possesses a stereogenic centre it will have two enantiomers, (Figure 2) which are defined as a pair of non-super imposable mirror images.



Enantiomers

* = stereogenic centre

Figure 2

Molecules that are not identical to their mirror images and thus exist in two enantiomeric forms are said to be chiral. A molecule that has a plane of symmetry in any of its possible conformations must be identical to its mirror image and hence must

be nonchiral, or achiral, e.g. ethanol. The most common cause of chirality in organic molecules is the presence of a carbon atom bonded to four different groups (Figure 2). Such carbons are referred to as asymmetric centres, or stereogenic centres.

A pair of enantiomers[3] also have identical densities, indices of refraction, heats of formation, standard free energies and many other properties. However with chiral molecules when a plane-polarised light (light with an electric field that oscillates in only one plane) is passed through a sample of one of the enantiomers, the plane of polarisation of the incident light rotates by a certain degree in an anti-clockwise or clockwise direction. Polarised light is obtained by passing ordinary light through a polariser, such as a Nicol prism. The orientation of the polariser's axis of polarisation determines the plane of the resulting polarised light. An enantiomer that rotates the plane of polarised light in the clockwise direction, the optical rotation is given a (+) sign. Such a sample is said to be dextrorotatory (Latin *dexter*, meaning "right"). If the enantiomer rotates the plane of polarised light in the counter clockwise direction, the optical rotation is given a (-) sign, and the sample is said to be levorotatory (Latin *laevus,* meaning "left"). A sample of a pure chiral compound uncontaminated by its enantiometer is said to be enantiomerically pure. The enantiomeric purity of an unequal mixture of enantiomers can be obtained by firstly calculating optical purity (Equation 1), which relies on the measurement of plane-polarised light, [α].

$$\text{Optical purity (\%)} = \frac{[a]_{\text{mixture of enantiomers}}}{[a]_{\text{pure enantiomer}}} \times 100$$

(Equation 1)

If a sample is enantiomerically pure, it means that it has only one enantiomer of the chiral compound. The term enantiomeric excess (ee) is the measure of the enantiomeric makeup of a sample and is as follows (Equation 2):

$$\text{e.e. (\%)} = \frac{[\text{major enantiomer A}] - [\text{minor enantiomer B}]}{[\text{major enantiomer A}] + [\text{minor enantiomer B}]} \times 100$$

(Equation 2)

Throughout this thesis, enantiomers are labelled either *R* or *S* in accordance with the Cahn-Ingold-Prelog rules and the enantiomeric purity is quoted in enantiomeric excess (e.e.) of the major enantiomer. Enantiomeric excess relies on the determination of the relative concentrations of both enantiomers by analytical methods such as HPLC and GC. In this work the ee is measured by chiral HPLC.

A mixture containing equal amounts of two enantiomers is called a racemate or racemic mixture. The ee of a racemate is zero, because a racemate contains equal amounts of two enantiomers whose optical rotations of equal magnitude and opposite sign cancel each other. The process of forming a racemate from a pure enantiomer is called racemisation. The simplest method of racemisation is to mix equal amounts of enantiomers. The separation of a pair of enantiomers is called enantiomeric resolution.

1.3 Zeolites

1.3.1 Introduction

Zeolites are hydrated aluminosilicate minerals discovered in 1756 by Cronstedt[4]. He noticed the intumescent properties of stilbite- the manner in which crystals of the mineral visibly lost water when heated and this observation led to the name zeolite. This was derived from classical Greek, meaning 'boiling stones'. Today, there are thirty-six known zeolites (naturally occurring) and there are more than one hundred aluminosilicates that are synthetic (no natural analogues).

Zeolites have been of intense interest as catalysts for more than three decades because of their advantages over homogeneous catalysts due to the high activity and unusual selectivity they provide, mostly in a variety of acid-catalyzed reactions[5]. Zeolites also have the ability to withstand harsh reaction conditions (*i.e.* high temperature gas phase reactions) and can be easily separated from the reaction mixture. The added value of using zeolite supported catalysts is that they are much cleaner and environmentally safer than the homogeneously catalysed equivalent reactions. Structural studies[6] showed that zeolites are crystalline solids with 'framework' structures based upon an infinitely extending three dimensional network of SiO_4 and AlO_4 units joined by sharing every corner oxygen of their tetrahedral oxygen arrangements. Cations can be present within the pores as they act as an absorbant. Zeolites[7] can be represented by the general formulae $M_v[(AlO_2)_x(SiO_2)_y].{}_zH_2O$ where n is the cation valency, x is greater than or equal to two and y is a function of the porosity of the framework. The porosity of the minerals[6] is such as to reach roughly 50 per cent of the total crystal volume in some zeolites and is achieved by the presence of regular cavities and

channels in which cations and water molecules reside. Usually these entities are mobile and give rise to the characteristic ion exchange and water loss properties.

Zeolites are of practical interest for various applications beyond catalysis. Zeolites have long been used for water softening, utilizing their ion-exchange capabilities and more recently used as drying agents for both liquids and gases[8] and are also used in purification (waste water treatment) and separation processes. The fine pore structure permits adsorption separations to be carried out on the basis of molecular size and shape, termed molecular sieving. Synthetic zeolites have a broad range of applications; they are used in commercial detergents (used to take potassium out of sea water), used for soil benefication (controlling pH). In industry zeolites are used for things such as petrochemical cracking, ion exchange, the separation of reactants, and removal of solvents and other volatile organic chemicals from feedstocks.

1.3.2 Properties of zeolites

Zeolites can be grouped on the basis of their Si/Al ratio. They consist of tetrahedrally co-ordinated silicon and aluminium atoms, which are connected by single oxygen bridges. The aluminium is therefore carrying a negative charge so in order to counter balance this charge; cations are present within the intracrystalline space of the zeolite. Zeolites with high concentrations of H^+ are hydrophilic and therefore have a strong affinity with polar molecules that are small enough to fit in the pores, whereas zeolites with low concentrations of H^+ are hydrophobic. The zeolite Y used in this project has a low ratio (Si/Al), so is highly hydrophilic.

Brönsted and Lewis acidity can be present in the zeolite framework. Hydroxyls within the zeolite channels provide the active Brönsted sites. These are usually prepared via ammonium ion exchange:

$$NaZ + NH_4^+ (aq) \rightleftharpoons NH_4Z + Na^+ (aq)$$

$$NH_4Z \rightleftharpoons NH_3 (g) + HZ$$

This generates protonic sites within the zeolite. In silica-rich zeolites, where the structure is not destroyed by acids, the hydrogen forms (HZ) can be prepared by direct exchange of Na^+ by H^+ ions using mineral acids. In the hydrogen form, these hydroxyls may be regarded as protons bonded to negatively charged framework oxygens associated with AlO_4^- tetrahedral. At higher temperatures (greater than 200^0C) these can be mobile, moving between sites[9], and at even higher temperatures (greater than 550^0C) they may be lost to form Lewis sites (Figure 3). The exchange of these cations for ammonium ions, and thermal treatment leads to the acidic properties of zeolites. Suitable treatment with water vapour can interconvert Lewis and Brönsted acid sites in zeolites. Without aluminium in the structure these materials are non-acidic.

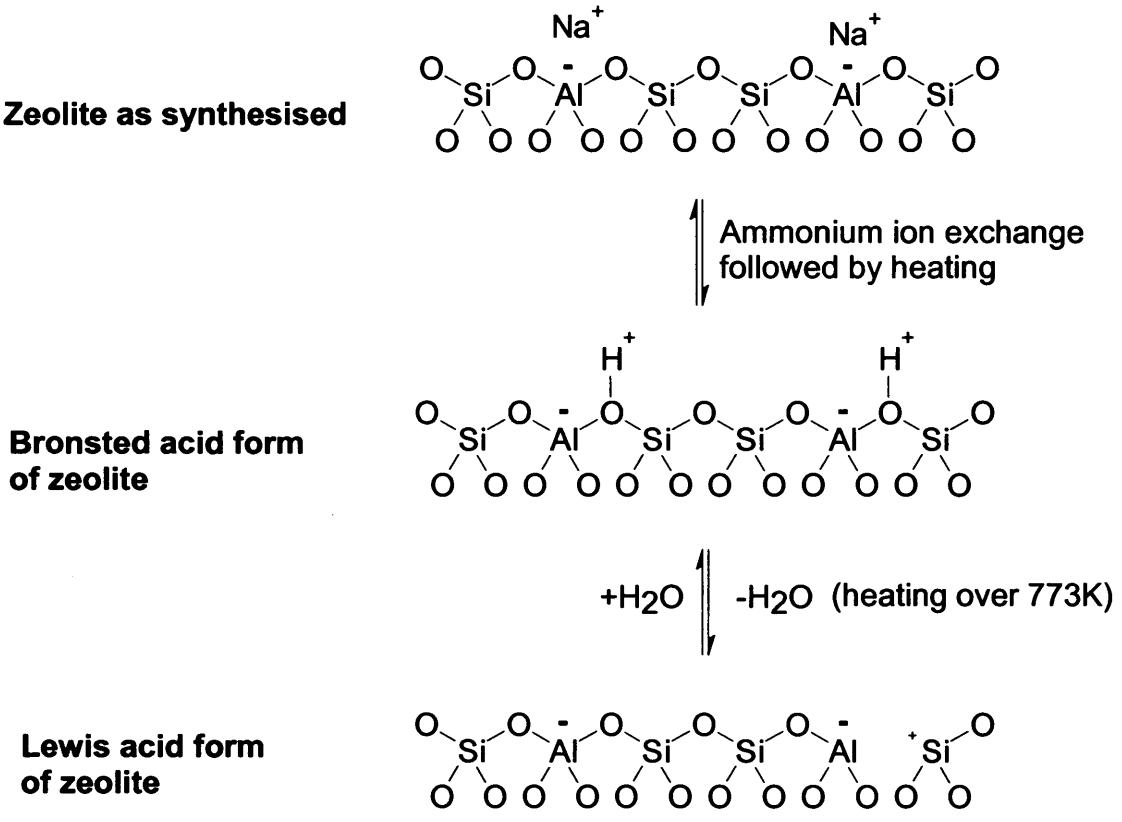


Figure 3

From the catalytic point of view, zeolites are of special interest in that they exhibit unusually high activity for various acid-catalysed reactions such as cracking and their unusual selectivity behaviour. Their fine pore structure permits adsorption separations to be carried out on the basis of molecular size and shape, termed molecular sieving, as in the physical separation of *n*-paraffins from isoparaffins. Structures[10] may be described in terms of the kind of pore channels present, which can exist in considerable variety. An array of parallel channels is termed a one-dimensional structure. If this array is interconnected with a second array at right angles, the structure is two-dimensional. A third array at right angles produces a three-dimensional pore structure. In each array the pores may be of the same size and shape or, more commonly, different. With any zeolite the effective pore diameter can vary

moderately with the type of cations present, the degree of hydration and also the temperature. As a result of the well-defined pore dimensions, zeolites have the ability to be shape selective. There are three types of selectivity that can occur: reactant, product and transition state selectivity. In transition state selectivity, first proposed by Csicsery[11] there is more than one pathway in the reaction. He explained the absence of symmetrical triakyl benzenes in the product from the disproportionation of a diakyl benzene in H-mordenite. From this and other studies Csicsery concluded that insufficient space was available in the pores for two molecules of the diakyl benzene to come together. The reaction is therefore more selective to one product over another; this is due to certain pathways being restricted. Unlike reactant or product selectivity, transition state selectivity should not be affected by crystal size.

Depending on the arrangement of the tetrahedra within the framework, there are areas of localised charge that can act as adsorption centres or catalytically active sites. These active sites can be utilised to exchange cations from an external solution and therefore replace the original stabilising cations. They are termed exchangeable cations. These non-framework cations play a major role in determining the catalytic nature of zeolites. However, the position of the cations within the zeolite is important for several reasons. The dimensions of the rings and channels in the structures can be altered by changing the size or charge of the cations (the higher the charge, the fewer the number of cations), and this significantly affects the size of the molecules that can be adsorbed. A change in cationic occupation can also affect the charge distribution within the cavities, therefore affecting the adsorptive behaviour and catalytic activity. For these reasons it has become important to determine the exchangeable cation positions within the framework[12]. The exchangeable cations can be any alkaline and/or alkaline earth metals but are most commonly Na^+, K^+, Ca^{2+} or H^+. They can be

replaced through a number of processes, such as solid state exchange, sol-gel methods or aqueous ion exchange. The replacement of these cations by transition metal ions (e.g. Cu^{2+}, Ti^{4+}) enhances the natural catalytic properties of the zeolites. It is only possible to achieve partial ion exchange, as the volume of the hydrated ions is such that the intracrystalline space in the channels is completely filled before 100 percent exchange can be attained[13].

All the properties mentioned previously, show zeolites are very important in catalysis, especially on an industrial basis. They are used as catalysts in a variety of organic reactions ranging from hydrogenation[14] to oxidation[15] reactions. Tatsumi *et al*[15] showed how the reactivity of the hydrogen peroxide-TS-1 system towards a range of unsaturated alcohols is determined by oxidation at the alcohol group to yield the corresponding ketone or aldehyde. Selective oxidation reactions are known to be important in the chemical industry. Hutchings[16] showed that they are particularly useful in activating alkenes and alkanes.

Tsuruya *et al.*[17] used Copper-exchanged zeolite Y to catalyse the vapour-phase oxidation of benzyl alcohol. The main oxidation products were benzaldehyde, carbon dioxide and carbon monoxide. The main active site for this oxidation was found to be Cu(II) ion in the zeolite. The catalytic activity for the oxidation of benzyl alcohol was found to be affected by the addition of amine. Piperidine addition increased the oxidation activity, while pyridine addition was found to decrease the oxidation activity.

The potential of zeolites in the selective synthesis of optically pure enantiomers is a current challenge in the area of heterogeneous catalysis. Recent approaches to obtain enantiomeric molecular sieve catalysts rely on the modification of zeolites. This is achieved by the immobilisation of a chiral metal complex or by treatment with a chiral

auxiliary or co-catalyst[18,19]. The preparation of zeolites with chiral frameworks requires further work and investigation, as the conversions on such zeolites have not yet resulted in appreciably high enantiomeric excess.

1.3.3 Zeolite Y

Zeolite Y belongs to the class of faujasites. These are the most widely used zeolites in catalysis. The basic unit of a faujasite is the regular cubo-octahedron or sodalite unit consisting of 24 tetrahedra of either SiO_4^{4-} or AlO_4^{5-}. When the sodalite units are joined through their hexagonal faces, the Y-zeolite is obtained. Throughout this work Zeolite Y was used (Figure 4) which is available in many forms including NH_4Y, NaY and HY. These can all be converted to the ultrastabilised form, USY by the process of dealumination.

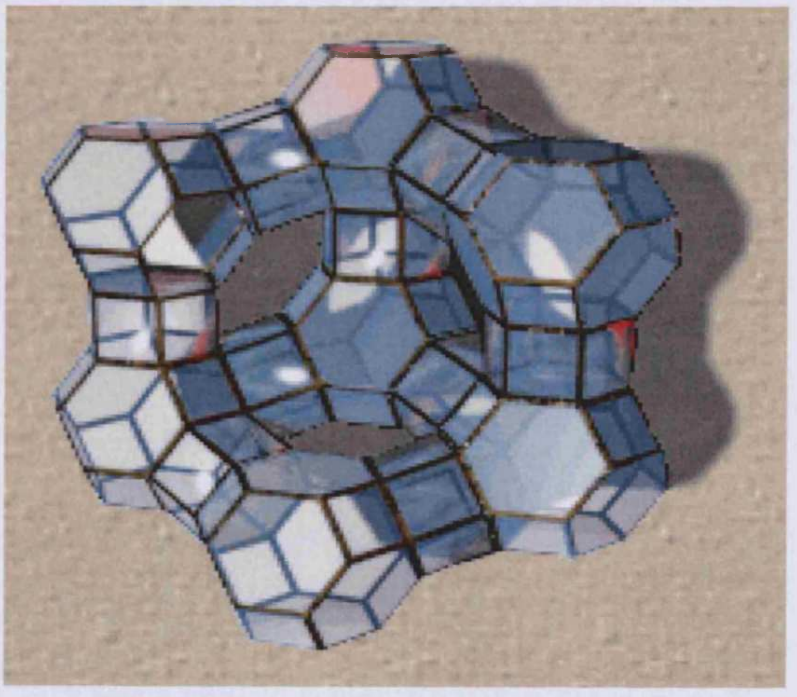


Figure 4: Zeolite Y viewed along [111] axis

The unit cell for zeolite Y[20] contains 192 $(Al/Si)O_4$ tetrahedra. Zeolite Y has an SiO_2/Al_2O_3 ratio of 3:6. This zeolite is isostructural with naturally occurring faujasite. Zeolite Y consists of spherical cages (supercages) with a diameter of 1.3 nm connected tetrahedrally through windows with a diameter of 0.74 nm formed by a ring comprising of 12 oxygen atoms (Figure 5). Zeolite Y has among the largest minimum aperture restrictions of any zeolite and the highest void fraction. Zeolite Y has quite large cages joined by smaller openings, therefore they have a high internal surface area in the form of pores of fixed geometry. The size of the opening between the cages determines the size of adsorbing molecule that can gain access, e.g. hydrocarbons larger than naphthalene can diffuse into their cavities. This enhances their potential for reaction selectivity. Their main role in industry is to catalyse the cracking of crude oil to shorter chained alkanes and alkenes.

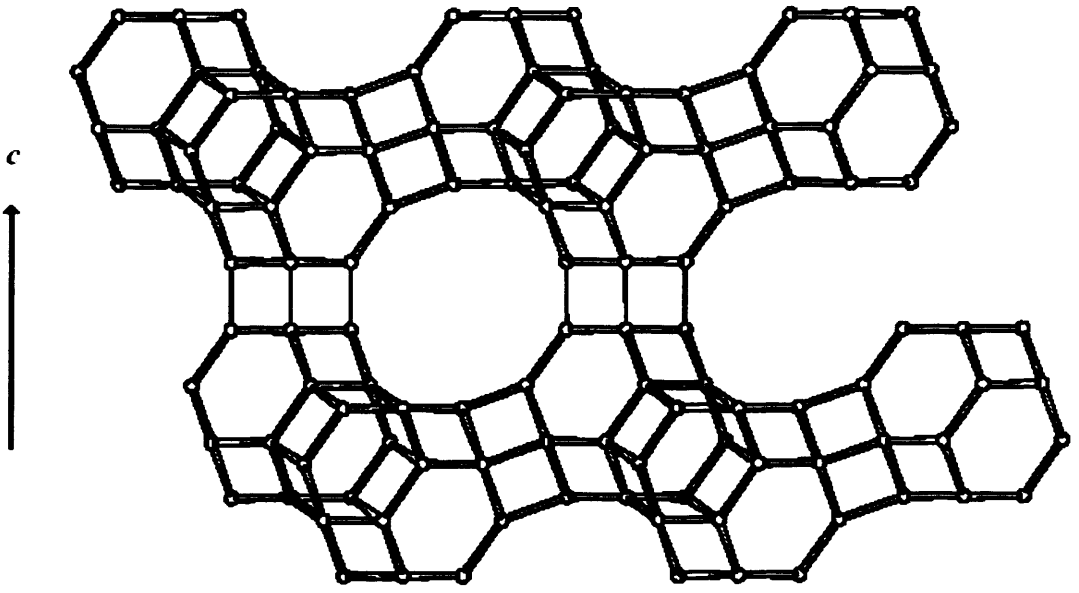


Figure 5: FAU along the [110] axis

1.4 Aziridines

1.4.1 Introduction

Aziridines (Figure 6) are saturated three membered heterocycles. They are the nitrogen analogues of epoxides and exhibit similar reactivity patterns as electrophilic reagents[21]. They undergo highly regio- and stereoselective transformations and therefore are useful building blocks for organic synthesis[22]. In addition, aziridines may exhibit antitumour or antibiotic activity or still other biological properties, which makes them attractive synthetic targets in their own right[22].

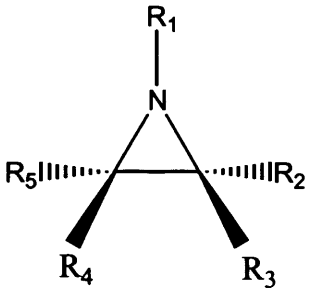


Figure 6: Structure of aziridine

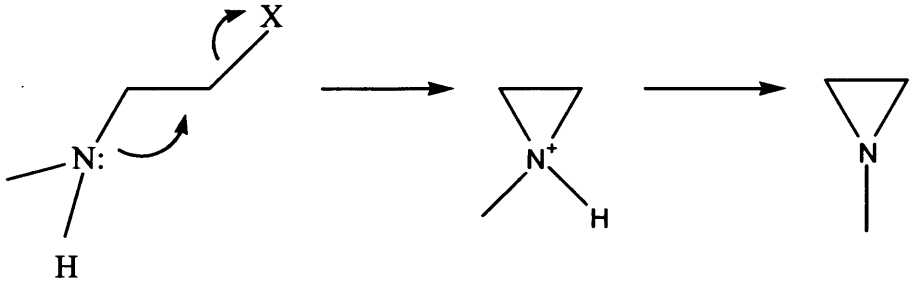
Considerable attention has been devoted to the development of reactions that effect catalytic atom transfer to olefins. Due to the utility of these processes in organic synthesis, such reactions have been extensively refined for both epoxidation[23] and cyclopropanation[24]. However, the analogous nitrogen atom-transfer processes, particularly metal-catalysed variants, have been less developed in spite of the fact that the broad utility of aziridines as electrophiles has been amply demonstrated[25]. Chiral aziridines have been shown to act as efficient chiral auxiliaries, ligands for transition metals as well as in applications for enantioselective catalysis[26].

1.5 Synthesis of Aziridines

Aziridines can be synthesised by many different routes. As a result only a few examples will be discussed in this thesis. Deyrup[25] has discussed in detail the various routes and methods to synthesise aziridines in a comprehensive review.

1.5.1 Intramolecular Cyclisation

The oldest and perhaps most obvious approach to aziridine synthesis involves the internal cyclisation of an amino group situated beta to a leaving group. The best known of these procedures are the Gabriel and Wenker synthesis (Scheme 1).



X = Br, Cl, I (Gabriel)

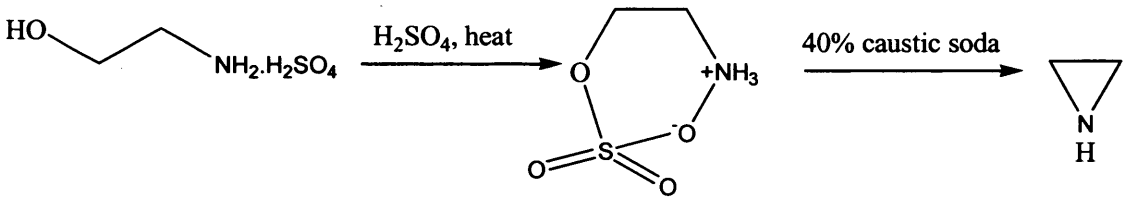
X = OSO_3^- (Wenker)

Scheme 1

These reactions show the expected stereospecificity[27,28] and side reactions include dimerisation, polymerisation and elimination. Recent developments in this synthetic approach have been in the routes to the cyclisation precursor (new reagents, higher yields, greater stereospecificity) and in the cyclisation step (ease of isolation, milder conditions).

1.5.2 Aziridines from amino alcohols

The amino alcohols necessary for the aziridine synthesis are readily available from epoxides and occasionally from the reduction of α-amino ketones. One of the earliest procedures for converting amino alcohols to aziridines has been reported by Wenker[29] (Scheme 2).



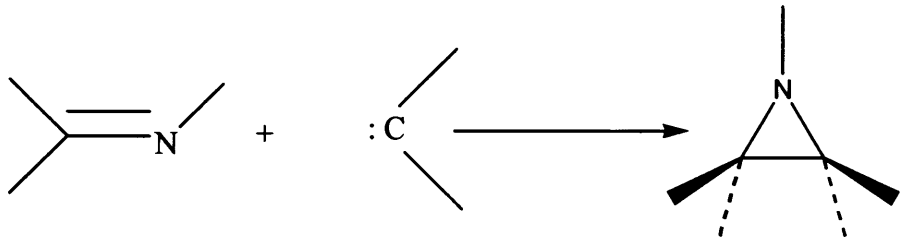
71 % yield

Scheme 2

The aziridine, ethylene amine was prepared from monoethanolamine. β-aminoethyl sulphuric acid is formed by the thermal dehydration of monoethylamine. The prepared β-aminoethyl sulphuric acid is then reacted with 40% caustic soda solution to form aziridine in 71% yield.

1.5.3 Aziridines from imines

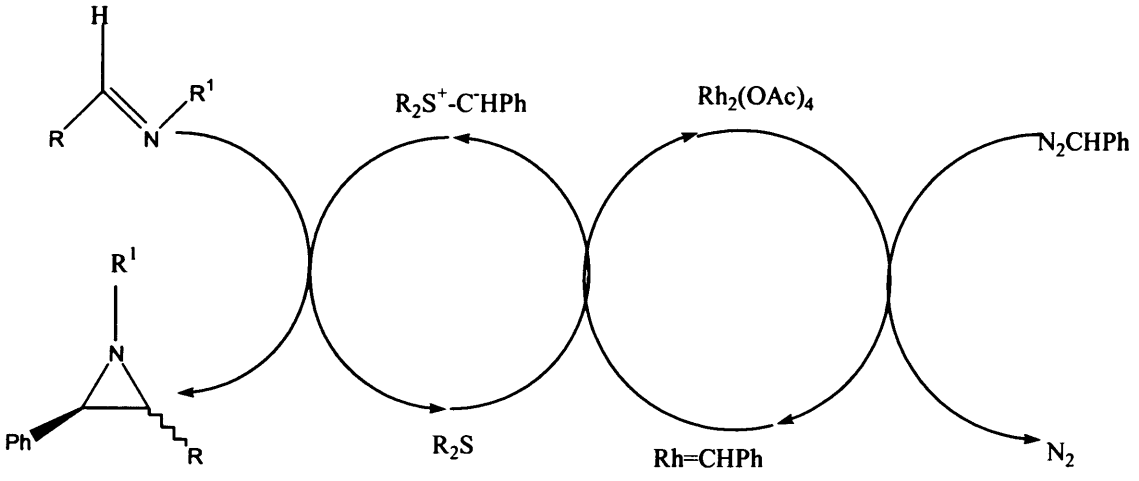
The simplest catalytic formation of aziridines is, in principle, the addition of a carbine fragment to an imine (Scheme 3). The catalytic preparation of aziridines as outlined in scheme 3 has been achieved.



Scheme 3

Jørgensen *et al.*[30,31] investigated the metal-catalysed aziridination of imines with ethyl diazoacetate as the carbene fragment donor using various Lewis acids as the catalyst. The catalytic properties of different Lewis acid complexes ($Yb(OTf)_3$ and $Zn(OTf)_2$) were tested. Both $Zn(OTf)_2$ and $Yb(OTf)_3$ in combination with various chiral ligands were tested as catalysts for the formation of optically active aziridines, but only low ees were obtained. It was also found that the selectivity was dependant on the substrate, catalyst and solvent used (80% yield using $Cu(OTf)_2$, 5-95% yield using various imines, R-groups and solvents).

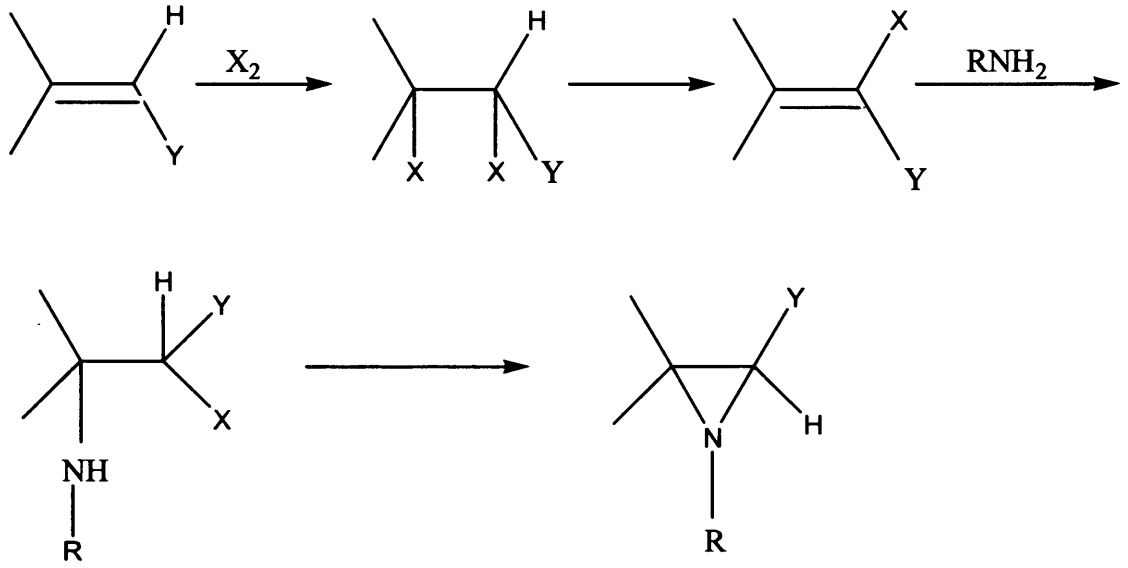
Aggarwal[32,33] *et al.* have investigated the development of metal catalysed imine aziridination using diazo-compounds (Scheme 4). High yields were obtained with all imines but diastereoselectivity varied considerably.



Scheme 4

1.5.4 Aziridines from nucleophilic addition

Most of the approaches used for the synthesis of aziridines are lacking electron-withdrawing substituents since most of the precursors are prepared via electrophilic attack on alkenes. However an alternative method involves the nucleophilic attack on vinyl halides[34-36] (Scheme 5). The reaction is facilitated by electron-attracting substituents. The reaction of the vinyl group with amine and halogen (I_2) allows direct formation of the desired aziridine.



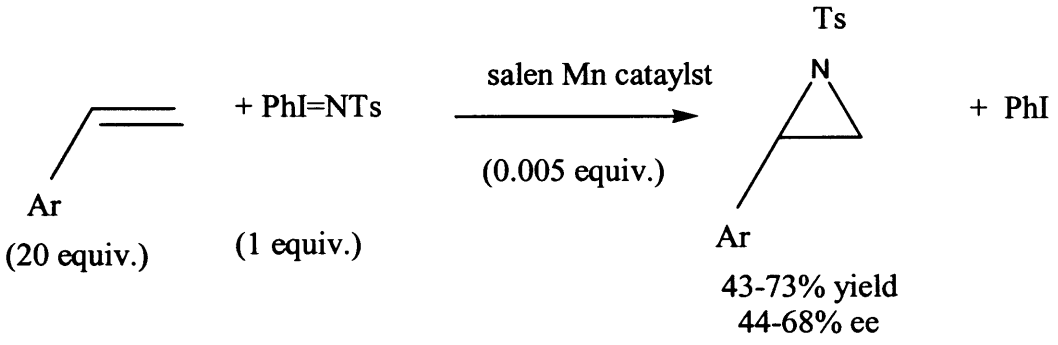
Y = electron withdrawing group

X = I

Scheme 5

1.5.5 Aziridines from epoxides

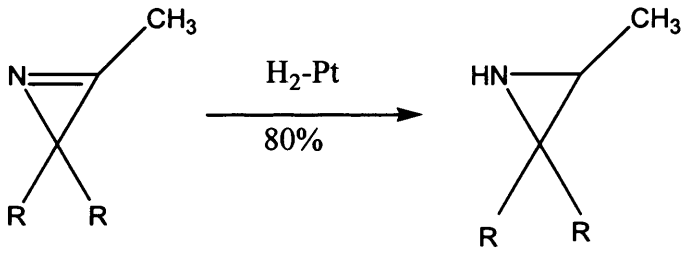
The formation of aziridine is possible via the ring opening of epoxides. A large number of chiral porphyrin catalysts have been developed for study in asymmetric epoxidation chemistry[37]. Tanner *et al* carried out an example of aziridine synthesis from epoxides[38] using the epoxides 2,3-dicarboxylic acid as the starting material. High yields of aziridine were achieved. Lai and co-workers[39] reported the use of Halterman porphyrin catalyst in the aziridination of styrene derivatives with moderate enantioselectivity (Scheme 6).



Scheme 6

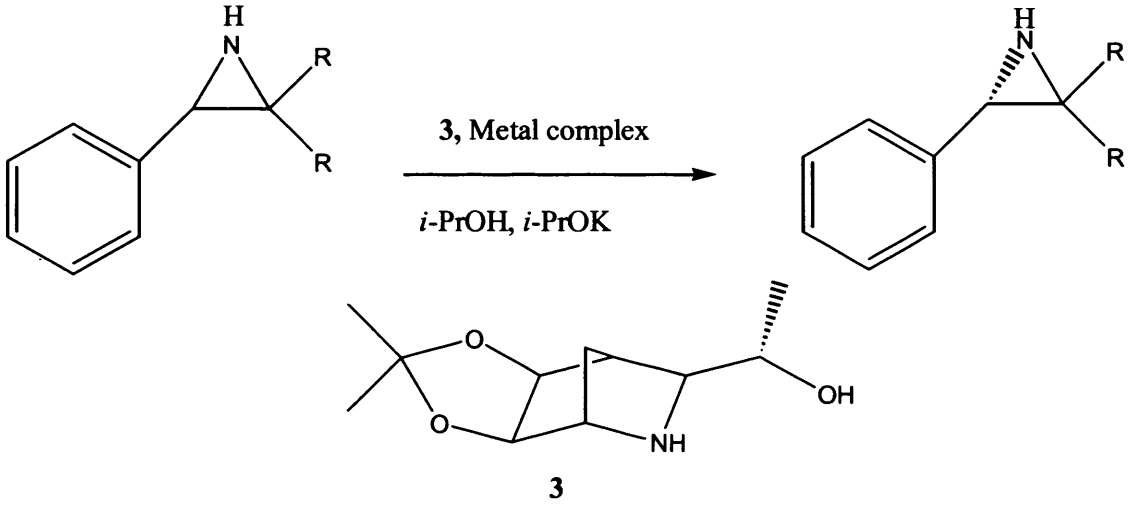
1.5.6 Aziridines from azirines

Azirines have become useful precursors of aziridines. There are numerous examples of azirine reduction by $LiAlH_4$ to give the corresponding aziridines in good yield. The reduction proceeds with good stereospecificity[40]. Other reducing agents such as $NaBH_4$ and $NaAlH(OCH_2CH_2OCH_3)_2$ have been used[41] (Scheme 7).



Scheme 7

Andersson *et al.*[42] reported that chiral aromatic aziridines could be obtained from the symmetric transfer hydrogenation of azirines (Scheme 8). The azirines is reduced with 70% enantiomeric excess

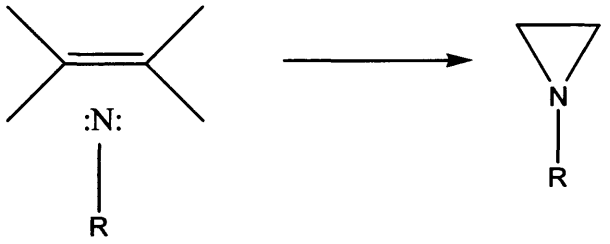


3

Scheme 8

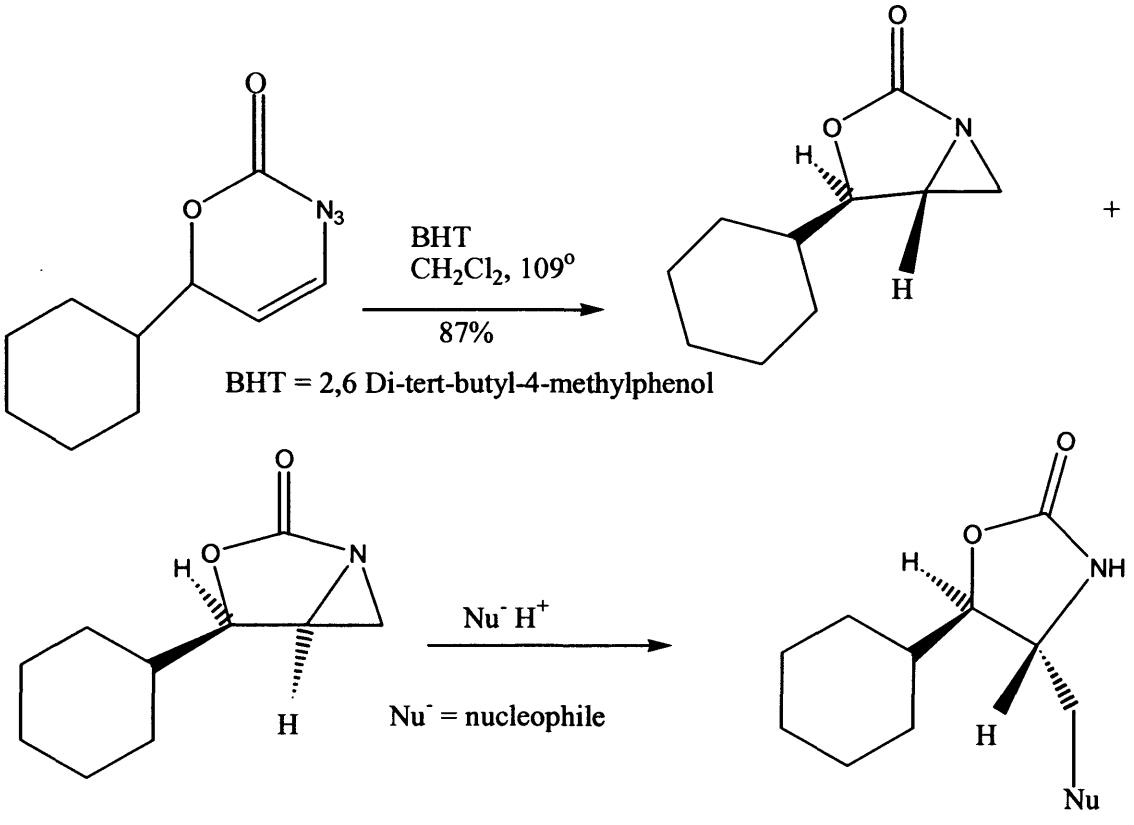
1.5.7 Aziridines from alkenes

The most direct approach to aziridine synthesis via cycloaddition to alkenes is the addition of nitrenes to alkenes[25] (Scheme 9). The reactions in this project follow this synthesis. A nitrene source is added directly across the double bond, which is an example of a 2 + 1 cycloaddition.



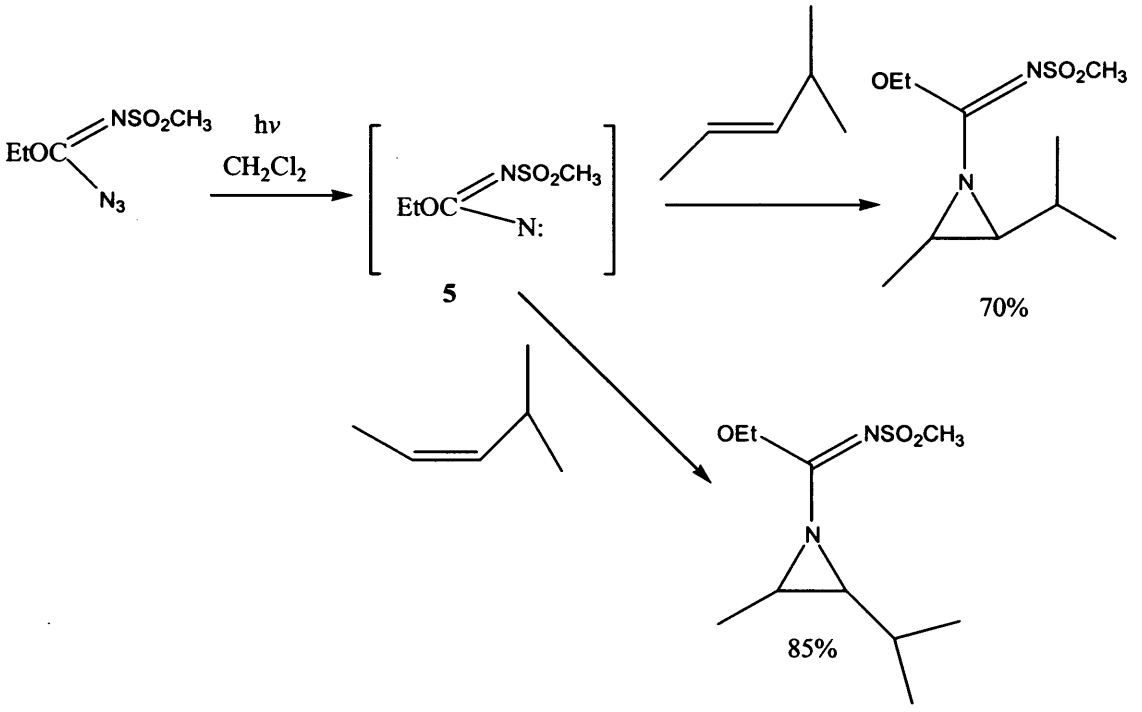
Scheme 9

Aziridination of cyclic *cis*-alkenes[43] and intramolecular aziridination using alkoxycarbonylnitrenes (scheme 10)[44] are other examples of aziridination via nitrene addition to alkenes.



Scheme 10

Atkinson *et al*[45] proposed that other substituents on the nitrene may reduce the reactivity, stabilise the singlet state and increase the selectivity for aziridination:[45,46] the *N*-(methanesulfonyl)ethoxycarbimidoyl nitrene **5** reacts stereospecifically with *cis*- and with *trans*-4-methylpent-2-ene[46] (Scheme 11).



Scheme 11

Closs *et al.*[47] reported one of the earliest methods of aziridines formed from alkenes. A three-step synthesis was devised involving the chloronitrosation of a tetraalkylethylene (II), followed by the reduction of the nitroso chloride to the chloramines derivative (III) using hydrochloric acid-tin dichloride complex as the reducing agent and finally ring closure with an alkali to form the desired 2,2,3,3-tetraalkylaziridine (IV) in good yield (79%).

1.5.8 Metal catalysed aziridination

The most common approach for the aziridination of alkenes involves using a range of nitrogen precursors. Metal catalysed aziridination using (N-(*p*-tosylsulfonyl)imino)phenyliodinane, PhI=NTs (Figure 7) is the most investigated approach. A hypervalent iodine-leaving group is attached to the nitrogen, this weak N=I bond results in a reactive intermediate susceptible to attack by an alkene.

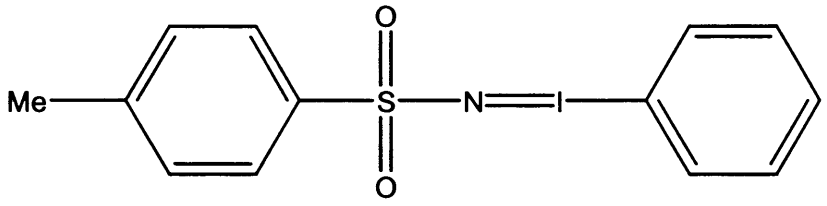
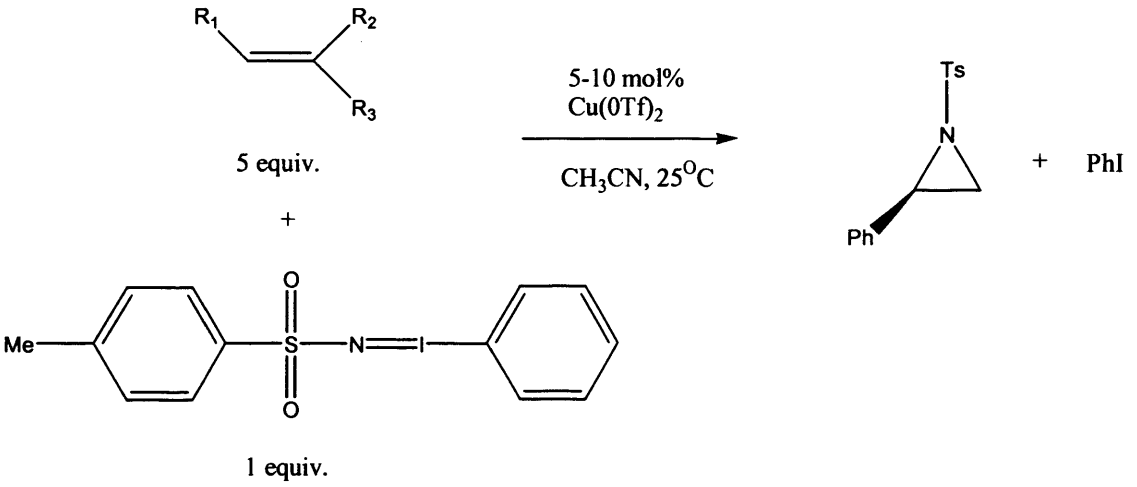


Figure 7: Structure of PhI=NTs

The possibility of transferring nitrenes to olefins by means of transition metal catalysts was recognised well before asymmetric catalysis was established[22]. The aziridination of alkenes by PhI=NTs under catalysis by Fe- or Mn- porphyrins was developed by Mansuy *et al*[48], while Groves and Takahashi described the stoichiometric aziridination of alkenes with an in situ generated (porphyrine)manganese-imido complex[49]. The group of Evans[50] developed the formal nitrene transfer to alkenes with PhI=NTs into a synthetically useful method. Cu(I) and Cu(II) salts in MeCN were found to be the most efficient catalyst/solvent combination for nitrene transfer. The substrate was used in a five fold excess compared to PhI=NTs and in the presence of 5-10 mol % of catalyst which afforded yields of aziridine in the range of 23-95% (Scheme 12).



Scheme 12

The solvent used in the reaction was also investigated; acetonitrile (MeCN) and nitromethane ($MeNO_2$), which are polar aprotic solvents, enhanced the reaction rates and yields. Toluene and dichloromethane, less polar solvents slowed the reaction rates. Evans[50] found that soluble Cu(I) and Cu(II) triflate salts were efficient catalysts for the aziridination of olefins employing PhI=NTs as nitrene precursor. Electron rich (styrene) and electron deficient (cyclohexene) olefins were investigated, with the aziridines from styrene giving yields 55-95% and the aziridines from cyclohexene giving yields in the range of 30-60%. Other metal complexes were found to be less effective at catalysing the reaction (Mn- and Fe- giving yields in the range 30-70% with styrene). PhI=NTs was also the superior nitrene precursor tested, in comparison to other imido group donors. Reaction stereospecificity in the aziridination of *cis* and *trans* disubstituted olefins was evaluated and found to be catalyst and substrate dependent. The aziridination of *cis*-β-methylstyrene resulted in varying amounts of *cis* and *trans* aziridines depending on the nature of the copper catalyst employed. At –20°C, the $CuClO_4$ gave an 89% yield of a 93:7 *cis/trans* ratio of aziridines. However, reactions catalysed by $CuBr_2$ and $Cu(acac)_2$ afforded predominantly the *trans* adduct.

1.5.9 Aziridination using nitrogen sources

PhI=NTs was the dominant choice of nitrene donor used in the development of the aziridination reaction. Several groups attempted improvement of the aziridination system. This included changing the nitrene donor, this was carried out by replacing the methyl substituent on the phenyl group of PhI=NTs with a different substituent. One example of this is replacing the methyl substituent with a nitro substituent (NO_2) to form (N-(*p*-nitrophenylsulfonyl)imino)phenyliodinane, PhI=NNs (Figure 8).

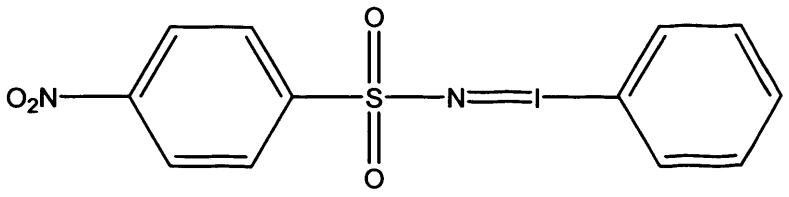
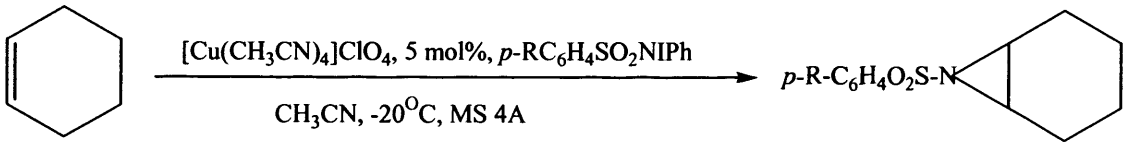


Figure 8: Structure of PhI=NNs

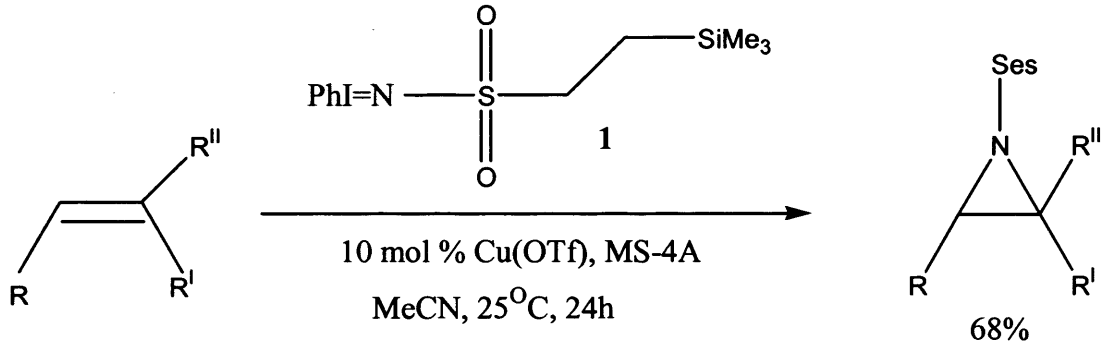
Andersson *et al*[51,52] proposed the replacement of PhI=NTs by PhI=NNs in order to improve yields of aziridines. Initially cyclohexene was investigated as choice of substrate, styrene was also examined as the substrate. The reactions were carried out in analogy with the method described by Evans[50] The best results were obtained using *p*-MeO-$C_6H_4SO_2N$=IPh and *p*-$NO_2C_6H_4SO_2N$=IPh with yields of 98% and 92% of aziridine respectively (Scheme 13)



R = CH_3 74% R = CF_3 88%
R = I 76% R = NO_2 92%
R = F 69% R = OMe 98%

Scheme 13

Dauban *et al*[53] improved the synthetic potential of the aziridination by the discovery that phenyl imino iodinanes derived from aliphatic sulphonamides are isolable. They made [N-((trimethylsilyl)imino]phenyliodinane, PhI=NSes (**1**) and with it obtained aziridination yields in the range 40-68% with Cu(OTf) as catalyst (Scheme 14). PhI=NSes was used for aziridination of 11-pregnen-3,20-dione which resulted in 53% yield[54].



Scheme 14

Another successful nitrene donor used in the aziridination of alkenes is (N-chloro-N-sodio-*p*-toluenesulfonamide) [TsNClNa.$(H_2O)_3$] referred to as Chloramine-T hydrate (Figure 9).

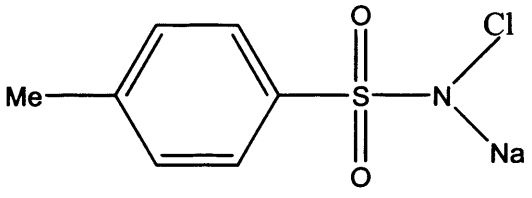
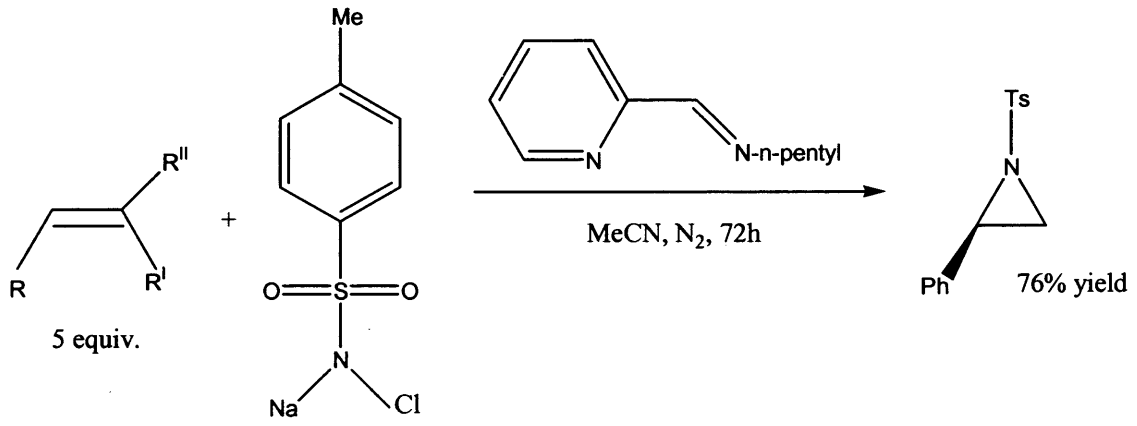


Figure 9: Structure of Chloramine-T

Chloramine-T requires dehydration before use, which is a hazardous process. Taylor *et al*[55] used Chloramine-T trihydrate as the nitrogen source as it did not require

dehydration. Aziridine yields of 76% were recorded using styrene as the substrate and a Cu-*N*-(2-pyridinylmethylene)-1-pentanamine catalyst (Scheme 15).



Scheme 15

Bromamine-T (Figure 10) has also been used as nitrene precursor in Cu-catalysed aziridinations and good results have been reported. Vyas *et al*[56] examined Bromamine-T as a nitrene source and compared the results to Chloramine-T. The aziridines obtained from the various olefins gave higher yields with Bromamine-T than Chloramine-T, when using styrene as substrate and CuCl as catalyst 48% and 31% yield were recorded respectively.

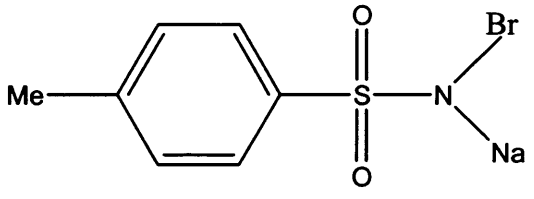


Figure 10: Structure of Bromamine-T

Bromamine-T has also been used as nitrene precursor in Cu-catalysed aziridination reactions, which were carried out under ultra-sound irradiation[57]. This work showed

that copper halides were most suitable for this reaction, giving yields of aziridine, 70% using $CuCl_2$ as the catalyst.

The potential of both Chloramine-T and Bromamine-T as nitrene source in the asymmetric aziridination with copper-exchanged zeolite Y as catalyst has been examined, however, PhI=NTs was found to be the preferred nitrene donor[58]. Chloramine-T and Bromamine-T were found not to be effective nitrene donors with the CuHY catalyst for the aziridination of alkenes. In contrast to PhI=NTs, it was observed that Chloramine-T and Bromamine-T solubilised the Cu^{2+} present within CuHY and thereby destroying the integrity of the heterogeneous catalyst.

1.6 Enantioselective Catalysis

Enantioselective catalysis entails the catalytic, selective and reproducible generation of a given enantiomer of a chiral product from achiral reactants[59]. Enantioselective catalysts are without exception chiral and non-racemic. Effective catalysts are either synthetic (chemocatalysis) or can be of natural origin (biocatalysis)[60]. Horner *et al*[61] was first to discover enantioselectivity during the hydrogenation of a prochiral olefin using a Wilkinson-type rhodium catalyst and a chiral phosphorus monodentate ligand.

To date, three types of enantioselective chemocatalysts have proven to be synthetically useful. The most versatile ones are homogeneous metal complexes containing bidentate ligands with a chiral backbone carrying two heteroatoms. For noble atoms, especially Rh, Pd, Ru, Ir and Os these are tertiary P or N atoms, for metals such as Ti, B, Zn, Co, Mn or Cu ligands with coordinating O or N atoms are usually preferred. This methodology culminated in the award in 2001 of the Nobel Prize to Knowles and Noyori for enantioselective hydrogenation and Sharpless for

enantioselective oxidation catalysis[62]. Homogeneous catalysts have been developed for numerous C-H, C-C, C-O and C-N bond formation reactions, which give high enantioselection. The design has been predicated on the synthesis of chiral ligands for active catalyst centres that ensure that the desired chiral transition state is readily accessed. However, these ligands are often difficult to recover and re-use and, for this reason, chiral homogeneous catalysts have not had the significant commercial input that researchers had initially hoped for[63].

Therefore, attention has been focused on the design of immobilised homogeneous chiral catalysts or heterogeneous chiral catalysts, since these can be readily recovered by filtration for a slurry reactor, or can be used in the numerous fixed bed reactor options available. This introduces a different aspect of catalyst usability, namely the stability of the heterogeneous catalyst, since leaching of active components can represent a real problem concerning commercialisation[64].

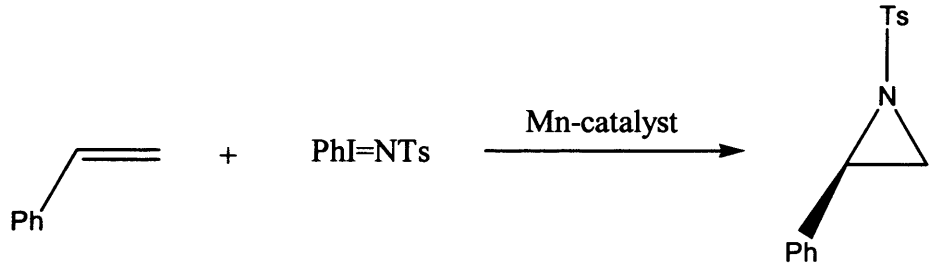
Blaser and Benoit[65] have also reviewed the scope and limitations of heterogeneous enantioselective catalysts using three strategies, modification of metal and metal oxides by chiral ligands, chiral organic polymers and tethering chiral catalysts by covalent bonding. They concluded that only a few catalysts offered a way forward in the design of enantioselective heterogeneous catalysts.

Up to now, relatively few enantioselective catalysts are used on an industrial scale. However, the field of research in enantioselective catalysts is a relatively young discipline but is rapidly expanding and it is contemplated that stable heterogeneous asymmetric catalysts will soon find commercial applications.

1.7 Asymmetric Aziridination

1.7.1 Chiral ligand

Enantioselective synthesis promoted by chiral catalysts is a topic of known importance in chemical research[66]. Within the field of enantioselective catalysis, the development of heterogeneous catalysts able to promote enantioselective organic reactions is an area of growing interest due to the inherent advantages of heterogeneous-to-homogeneous catalysts[67]. The chiral ligand plays an important role in achieving high enantioselectivities in asymmetric catalytic reactions. The combination of chiral bis(oxazoline) ligands and Lewis acids has been used extensively as enantioselective catalysts for many different reactions, such as aziridination[68], cyclopropanation[69], cycloaddition[70], allylic substitution[71], Diels-Alder[72] and Friedel-Crafts[73] reactions. Chiral Mn salen complexes have been used successfully in the asymmetric aziridination reactions. Catalytic and asymmetric Mn-catalysed aziridinations using an optimised salen complex (Scheme 16) have been developed by Nishikori and Katsuki, who reached up to 94% ee for aziridination of styrene with PhI=NTs[74].



Mn : 76 % yield, 94 % ee
Mn : 73 % yield, 55 % ee
Mn : 34 % yield, 57 % ee

Scheme 16

The presence of catalytic quantities of 4-phenyl-pyridine-N-oxide was required to obtain high enantioselectivities. A chiral Mn(III)-porphyrin complex in conjunction with PhI=NTs (Scheme 16) provided aziridination products in moderate yield and enantioselectivity, 73% and 55% respectively[39,75]. Marchon *et al*[76] examined a chiral Mn(III)-porphyrin catalyst (Scheme 16) and reported an ee of 57% for styrene aziridination with PhI=NTs.

More recently, new achiral ligands have been introduced for Cu-catalysed aziridinations with PhI=NTs with potential for development of asymmetric reactions. Halfen *et al*[77] described the synthesis of a Cu-1-(2-pyridylmethyl)-5-methyl-1,5-diazacyclooctane tri-fluoroacetate complex (Figure 11), which exhibited remarkable efficiency in the aziridination of styrene, giving 86% yield and 59% ee.

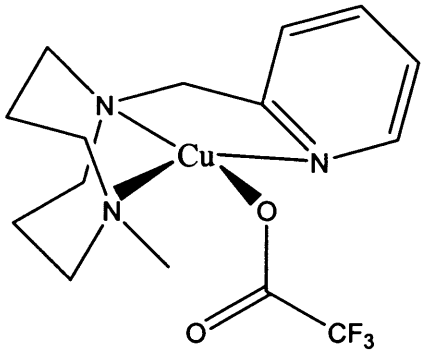


Figure 11

Recent developments by the Hutchings group showed that a copper exchanged zeolite (CuHY) was highly efficient as heterogeneous catalyst for the aziridination of olefins using PhI=NTs[78]. Modification of this zeolite with bis(oxazoline) ligands lead to an enantioselective aziridination catalyst.

1.7.2 Bis(oxazoline)

The bis(oxazoline) ligand (Figure 12) was first introduced in 1990 by the group of Masamune *et al*[79]. This was followed shortly after by Evans *et al*[69], Corey *et al*[72] and the group of Pfaltz[80].

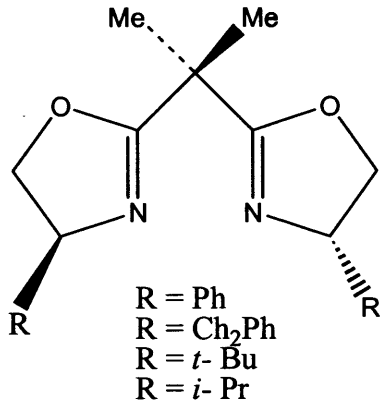


Figure 12: Structure of bis(oxazoline) ligand

Bis(oxazoline)s are a well-known family of chiral ligands that have been used in a large number of enantioselective reactions[81]. This fact has led to increased interest in the immobilisation of such systems and they have been covalently bonded to insoluble inorganic[82] and organic[83] supports. Bis(oxazoline)-copper complexes, which are useful catalysts for several reactions are cationic in nature and, therefore, they can be immobilised by formation of ion pairs with anionic supports[84].

(Bis)oxazolines have been the ligand used in the asymmetric aziridination of alkenes ever since the early work carried out by Evans *et al*[68]. They examined the variation of the R- and Me-groups on the ligand and worked with a variety of substrates, which resulted in ees of 19-97% (Figure 12).

Throughout the work completed on this thesis the modifier with R = Ph has been used ((S,S)-2,2'isopropylidene-*bis*(4-phenyl-2-oxazoline)) (Figure 13).

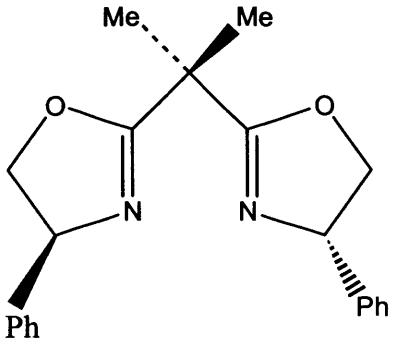


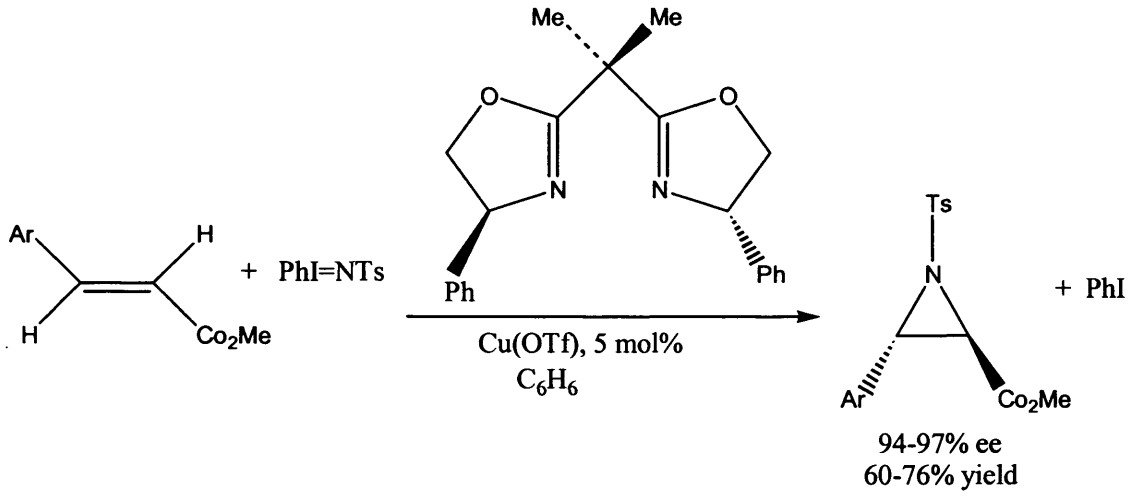
Figure 13

1.7.3 Homogeneous asymmetric aziridination

A crucial discovery in aziridination catalysts was made by Evans in the early 1990s, when he demonstrated that low-valent metal ions typically used for cyclopropanation were competent catalysts for the aziridination of alkenes with PhI=NTs[50,69]. Simple copper(I) and copper(II) salts were found to be effective catalysts for the preparation of a wide range of racemic aziridines. Along with Sharpless's recently-disclosed bromonium ion-catalysed reaction[85], the copper catalysed aziridination of olefins with PhI=NTs is probably the most general catalytic method devised thus far for the direct synthesis of racemic aziridines from alkenes[86]. The discovery that metal ions useful for catalysis of carbene transfer to alkenes were also effective for nitrene transfer to the same substrates opened a clear new direction for research in asymmetric aziridination. Subsequently new methods on bis(oxazoline) copper catalysed

asymmetric aziridination were revealed in two independent studies published by Jacobsen[87] and Evans[68].

The Evans group used chiral bis(oxazoline) ligands with copper(I) triflate. Exceptionally high levels of enantioselection were observed in the aziridination of cinnamate ester derivatives (Scheme 17). Different solvents, ranging from polar and nonpolar, were also examined, in the case of cinnamate esters; the enantioselectivity was enhanced when the reaction was performed in nonpolar solvents, benzene rather than polar solvents such as MeCN.

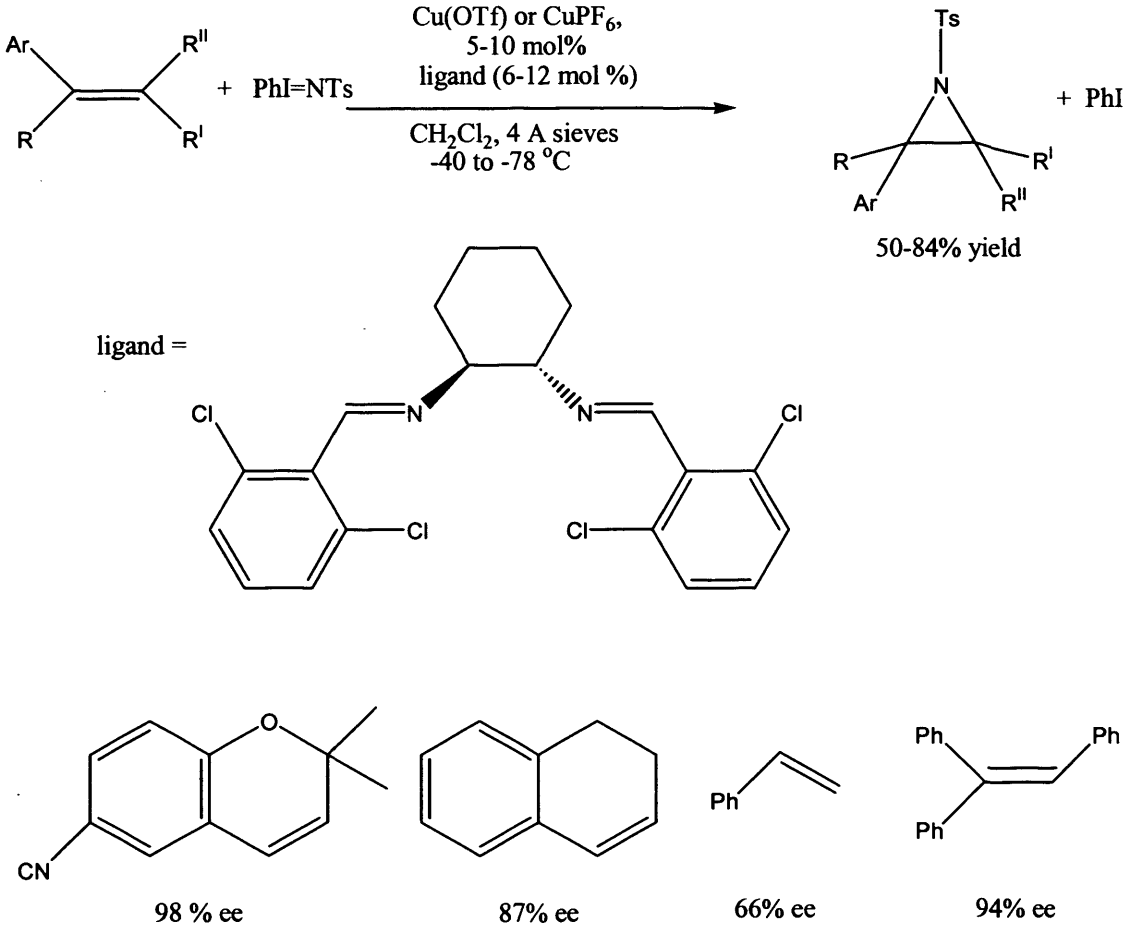


Scheme 17

However, simple olefins such as *trans*-β-methylstyrene and styrene were significantly less suited and gave only 70% and 63% ee, respectively.

The Jacobsen system used 1,2-diimine derivatives as chiral ligands with copper(I) salts. The optimal diamine precursor was found to be 1,2-diaminocyclohexane, and among the large number of benzaldehyde derivatives examined[88], ligands prepared from 2,6-dichlorobenzaldehyde proved most enantioselective in promoting catalysis of

the aziridination reaction by Cu(I) salts. High levels of enantioselection 66-98% were observed for alkenes with a variety of substitution patterns[87] (Scheme 18).



Scheme 18

Jacobsen proposed a mechanism[88] for copper catalysed aziridination using PhI=NTs (Figure 14). Copper is a redox catalyst and aziridination proceeds through a discrete, high-valent copper-imido intermediate. This mechanism was favoured over the idea that, the copper catalyst may serve only as a Lewis acid for activation of the hypervalent iodine reagent. Mechanistic analysis of the (diimine) Cu-catalysed aziridination reaction provided support for the redox mechanism.

Redox Mechanism

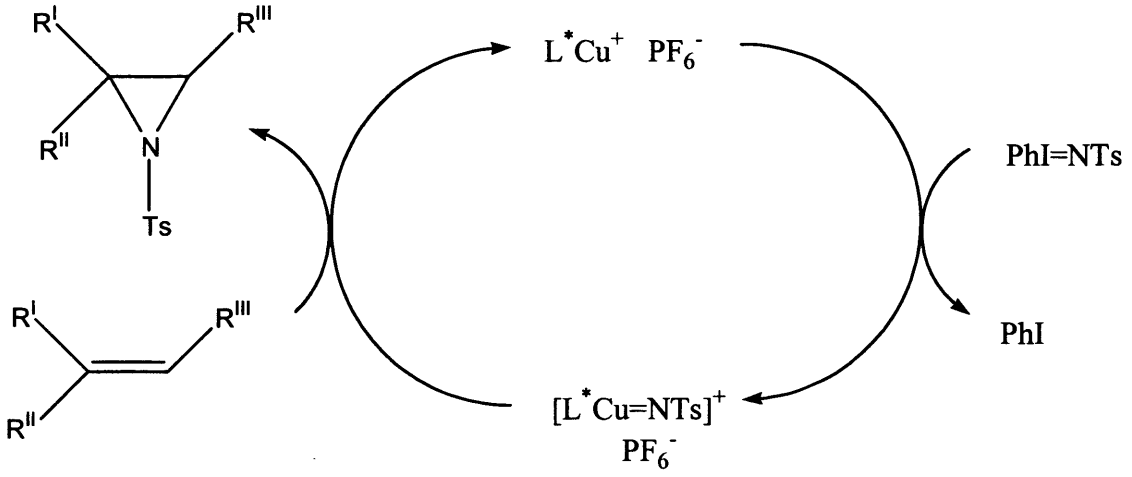


Figure 14

Several groups attempted improvement of the aziridination system. Thus, Andersson *et al.*[89] proposed the replacement of PhI=NTs by PhI=NNs in order to improve yields of aziridines. Enantioselectivities comparable to those achieved by Evans with the same bis(oxazoline) ligands were obtained[51,52]. In addition, Andersson investigated anionic di-imine ligands (Figure 15) and reported enantioselectivities of up to 34% for the same reaction[89] and an ee of 33% with the chiral bis(aziridine) ligand[90] (Figure 16).

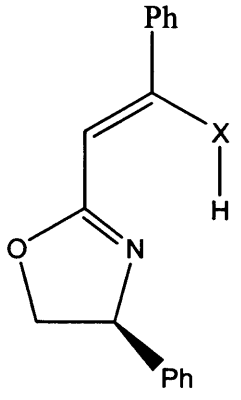


Figure 15

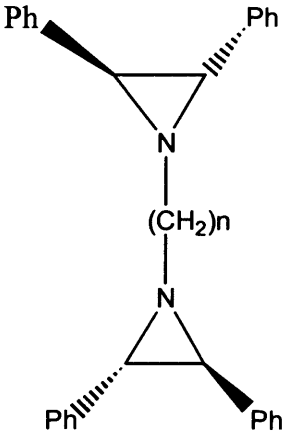
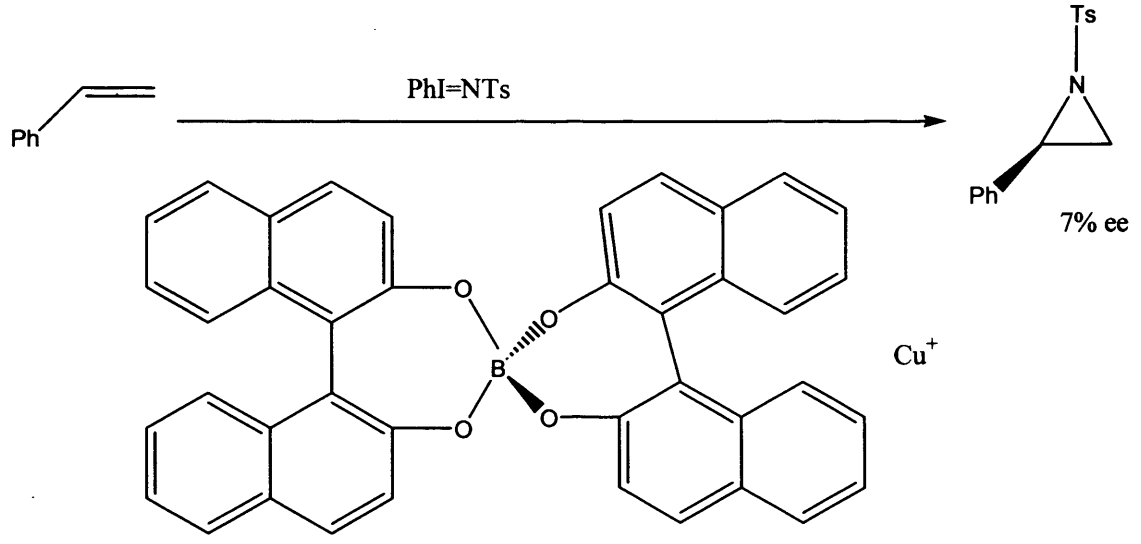


Figure 16

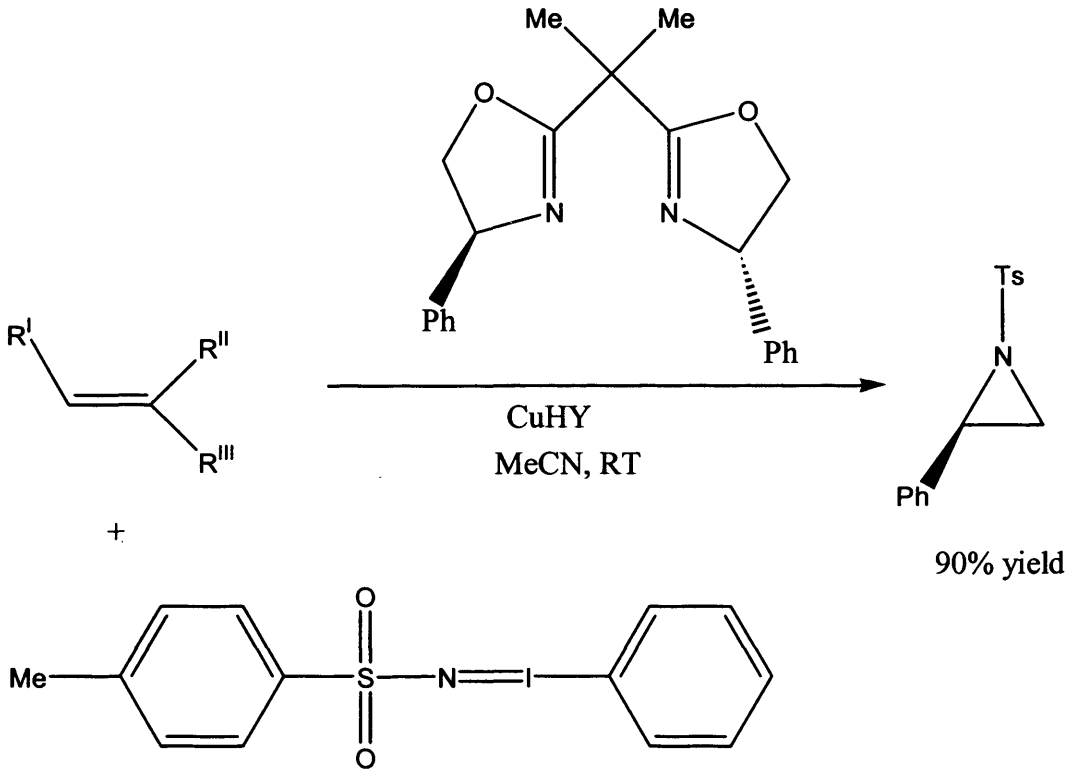
Llewellyn *et al*[91] observed that the enantioselectivity of the aziridination of styrene with bis(oxazoline) copper catalysts was dependent upon the counter ion. This idea investigated the possibility of asymmetric aziridination by means of association of the copper ion with a chiral anion via ion pairing. This work was completed by the use of a chiral boronate having binaphthol ligands, however, the enantioselectivity observed was only 7% (Scheme 19).



Scheme 19

1.7.4 Heterogeneous asymmetric aziridination

The first example of heterogeneous asymmetric aziridination of olefins using PhI=NTs as the nitrogen donor was developed by Langham *et al*[92,93] (Scheme 20). They prepared a copper exchanged zeolite (CuHY), which was found highly efficient as a heterogeneous catalyst for the aziridination of olefins. High yields of the aziridine (90%) were obtained using this system. Modification of this zeolite with bis(oxazoline) as the ligand lead to an enantioselective aziridination catalyst.



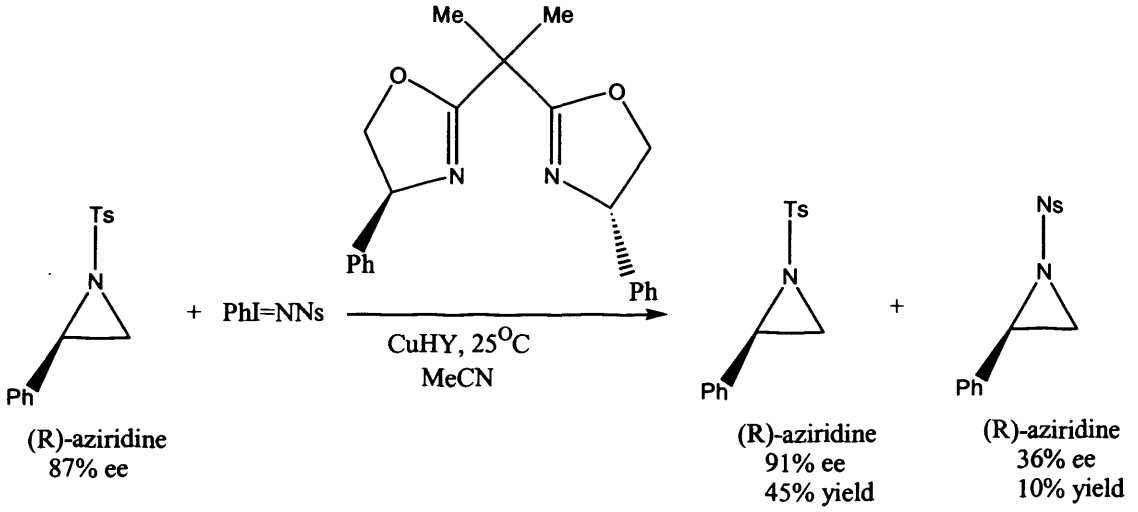
Scheme 20

Styrene was used as choice of substrate and acetonitrile as solvent in the reaction as it gave high yields, 87%, and comparable ee of 36% with the Evans[50] system.

Other metal exchanged zeolites were tested, but none were as effective catalysts as CuHY for the aziridination of styrene. A set of bis(oxazoline) chiral modifiers were also investigated in the reaction and the phenyl substituted bis(oxazoline) (S)-2,2'isopropylidenebis(4-phenyl-2-oxazoline) was found to perform best, giving ees of over 80%. The use of lower temperatures gave the highest enantioselectivities, aziridination of styrene using (S)-2,2'isopropylidenebis(4-phenyl-2-oxazoline) as the chiral modifier in MeCN at $-10^{o}C$ gave aziridine yield of 80% and an ee of 42%.

The highest yields of aziridine were obtained when the nitrene donor was added in slight excess over styrene, and PhI=NNs was found to be the most efficient nitrene

source. The heterogeneous catalyst gave higher enantioselectivity than the homogeneous catalyst under controlled conditions. CuHY afforded 77% yield of aziridine and 95% ee at 25°C while the homogeneous catalyst gave 99% yield and an ee of 80%[94]. During the aziridination of styrene using copper bis(oxazoline) complexes the ee increased with conversion due to further reactions of the product[95]. This was due to interaction of the aziridine with sulphonamide, which is a breakdown product of the nitrene donor. When (R)-N-(*p*-tosylsulfonyl)-2-phenyl aziridine, 87% ee was reacted with PhI=NNs and bis(oxazoline) CuHY, a small amount (10%) of (R)-N-(*p*-nosylsufonyl)-2-phenyl aziridine was recovered in a lower ee, 36% (Scheme 21).



Scheme 21

The copper catalysed aziridination of styrene derivatives[96] using either CuHY or $Cu(OTf)_2$ as a homogeneous catalyst with bis(oxazoline) using PhI=NNs as nitrene donor was investigated. For the heterogeneous catalysed reaction the styrene derivatives often gave enhanced yield, particularly when the substituent was in the 4-position. Particularly high ee was observed for 2-chlorostyrene, 95% and 4-chlorostyrene, 94% and in general the ee observed for the heterogeneously catalysed

reaction with the 2- and 4-substituted derivatives was significantly higher than that for the equivalent homogeneously catalysed reaction.

The catalyst was recovered and reused; leaching of Cu from the zeolite was shown to be limited, and this leached copper did not interfere with the aziridination process[97].

An EPR study[98] has shown that in the catalyst CuNaY, there are two copper(II) sites inside the zeolite pores with pseudo-octahedral and square planar geometries. Upon addition of the chiral modifier, two new copper(II)-bis(oxazoline) complexes were identified with square pyramidal and square planar geometries. This provided direct experimental evidence for a copper(II)-bis(oxazoline) complex inside the zeolite pores.

1.8 References

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Chapter 2

Experimental

2.0 Experimental

2.1 Preparation and purification of reagents and solvents

All experiments were performed at atmospheric pressure and 25^0C unless otherwise stated. All reactions were carried out in fresh sample vials. All solvents were used as received. The chemicals used are as follows with information of their source and purity.

Acetone, 99% Fischer

Acetonitrile (HPLC grade), 99.99% Fischer

Allyl alcohol, 99+% Aldrich

Allyl ether, 99% Aldrich

Anthracene, 99% Aldrich

Atomic absorption standard, 1028μg/ml of Cu in 1% wt% HNO_3 Aldrich

Benzaldehyde, 99% Aldrich

Biphenyl, 99% Aldrich

2-Bromo styrene, 97% Aldrich

3-Bromo styrene, 97% Aldrich

4-Bromo styrene, 98% Aldrich

Chloroform-*d* ($CDCl_3$), 99.98% atom% D Aldrich

2-Chloro styrene, 97% Aldrich

3-Chloro styrene, 98% Aldrich

4-Chloro styrene, 97% Aldrich

Copper (II) acetate, 98% Aldrich

Copper (II) sulphate, 98% Fischer

Copper (II) trifluoromethanesulfonate (copper(II) triflate), 98% Strem

Dimethylsulphoxide-*d* (DMSO), 99.9% atom % D Aldrich

Ethyl acetate, >99% Fischer

2-Fluoro styrene, 98% Aldrich

3-Fluoro styrene, 97% Aldrich

4-Fluoro styrene, 99% Aldrich

Glacial acetic acid, Aldrich

Hexane (HPLC grade), 95% *n*-hexane Fischer

HF, 5 wt% prepared from 48% ACS reagent, Aldrich

Iodobenzene, 98% Aldrich

Iodobenzene diacetate, 98+% Lancaster

Iodobenzene, 98% Aldrich

Isopropanol (HPLC grade), 99.99% Fischer

(R,R)-2,2'isopropylidene-bis(4-phenyl-2-oxazoline), 98% Fischer

(S,S)-2,2'isopropylidene-bis(4-phenyl-2-oxazoline), 98% Fischer

Matrix silica 60, Fischer

Methanol (HPLC grade), 99.5% Fischer

4-Methoxy styrene, 96% Acros

2-Methyl styrene, 96% Aldrich

3-Methyl styrene, 96% Aldrich

4-Methyl styrene, 96% Aldrich

α-Methyl styrene, 99% Aldrich

Trans-β-Methyl styrene, 99% Aldrich

3-Nitroaniline, 99+% Aldrich

4-Nitrobenzene sulphonamide, 97% Aldrich

Petroleum ether (40:60), 2% *n*-hexane, Fischer

Potassium hydroxide, >85%, Fischer

Sand, low iron, Fischer

Sodium hydroxide, >97%, Fischer

Styrene, 99+%, Aldrich

Styrene oxide, 97% Aldrich

4-tert-Butylstyrene, 93% Aldrich

P-toluene sulphonamide, 98%, Aldrich

Ultra stabilised zeolite Y (LZY84), UOP

4-Vinylaniline, 97% Aldrich

4-Vinylanisole, 97% Aldrich

2.2 Instrumentation and experimental techniques

2.2.1 ^{1}H NMR

The ^{1}H NMR spectra were obtained using a Bruker 'Avance' 400MHz DPX spectrometer, equipped with Silicon Graphics workstation running 'X win 1.3' with results reported in ppm with number of protons, multiplicity and assignment. All chemical shifts for ^{1}H NMR were recorded in deuterated chloroform (*d*-$CDCl_3$) and deuterated dimethylsulfoxide (d_6-DMSO) unless otherwise stated.

2.2.2 ^{27}Al MAS-NMR

The ^{27}Al MAS-NMR spectra were recorded on Chemagnetics CMX-Infinity 400MHz. The frequency of the ^{27}Al MAS-NMR was 104.25 MHz, pulse delay 1.00s, pulse width 2.00u and spinning speed 5kHz. Aluminium nitrate was used as reference. The technique was used to detect the presence of any extra framework Al species.

2.2.3 Flash column chromatography

Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) and analytical TLC on silica gel 60 F-254 plates eluted by Pet Ether: EtOAc =10:1.5 mixture.

2.2.4 High-pressure liquid chromatography

High-pressure liquid chromatography analysis was performed using a Varian pro-star HPLC system (PDA detector set to λ=235nm, a 230 Solvent delivery system and a 410 autosampler). For the product analysis the solvent used was acetonitrile: water (85:15), with an APEX ODS 5μ column (size 0.6cm I.D. x 25cm) with the solvent pumped at a rate of 0.5ml/min. For analysis of the reaction mixture, (40μl) was flushed through a plug silica with 10ml of Biphenyl/Anthracene standard (0.564g/0.0667g in 1L MeCN). A Chiralcel OJ column (size 0.46cm I.D. x 25cm) was used to separate the chiral compounds (solvent mixture hexane (90%): isopropanol (10%)).

2.2.5 Atomic Absorption Spectroscopy (AAS)

Atomic Absorption Spectroscopy was performed using a Perkin-Elmer 2100 Atomic Absorption spectrometer using an air-acetylene flame and copper samples were analysed at wavelength (λ) 324.7nm. Samples for analysis were prepared by dissolving 0.1g of the dried catalyst in 5% wt. HF solution (30ml HF in 100ml deionised water) and then 250ml of deionised water was added to dilute the sample. Samples were prepared for leaching tests by filtering off the catalyst and diluting the reaction mixture by the addition of MeCN. The filtrate was then diluted in acetonitrile (100g) before being analysed by AAS to determine the Cu content. AAS was used to determine the weight % of the metal incorporated into the zeolite after ion exchange and also the concentration (ppm) of copper that had leached out into solution during reactions.

2.2.6 X-ray Diffractometer (XRD)

Powder XRD was performed on ENRAF Nonius FRS90 Generator with PSD 120 and CuK_α source 30mA, 40KeV. Samples were prepared by grounding into a fine powder and then loaded flat into the sample holder. Diffraction patterns were obtained from between 5^0 and 50^0 2θ. The technique was used to identify the materials and the crystal structure of the zeolite prepared and also examines the changes to the framework after the reaction and also any extra framework species that may be present.

2.2.7 Electron Paramagnetic Resonance (EPR)

A sample (80μl) was then taken during the reaction and placed in an EPR/ENDOR tube, mixed with toluene (30μl) and frozen in liquid nitrogen. The EPR spectra were recorded in Cardiff by the Murphy group on a Varian E109 and a Bruker ESP 300-E Series X-band spectrometer at *ca* 120K. The *g* values were determined using a Bruker NMR gaussmeter calibrated using the perylene radical cation in concentrated H_2SO_4 with g = 2.00256. Sim32 was used for the simulation of the EPR spectra. Samples were taken from standard homogeneous reactions (2.10.1).

2.3 Preparation of catalysts

2.3.1 Synthesis of catalysts

All of the heterogeneous catalysts were made using zeolite Y that was supplied as NH_4^+Y. These were converted to HY by calcination at 550°C for 4h before use.

2.3.2 CuHY

For the standard heterogeneous catalyst, NH_4^+Y zeolite (4.0g) was stirred in copper (II) sulphate (0.1M, 100ml) for 24h at room temperature. The solution was then filtered and washed with distilled water. The sample was then dried in an oven at 100°C for 24 hours. The copper-zeolite was recalcined (550°C) for 2 hours prior to use. Cu content 3% by weight determined by atomic absorption.

2.3.3 Co-cation exchanged CuHY

NH_4^+Y zeolite (4.0g) was refluxed with Group I metal (Li, Na, K, Rb, Cs) nitrates (0.1M, 100ml, 100°C) for 24h, then filtered, washed with water and the process repeated a further two times (each with a fresh solution of metal nitrate). After the third reflux and filtration, the metal exchanged zeolite was partially dried before addition to the copper sulphate solution (0.1M, 100ml) and stirred at room temperature overnight. The reaction mixture was then filtered, washed and dried as with the CuHY above, giving CuMY.

2.3.4 Characterisation of catalysts (Atomic Absorption Spectroscopy)

Calibration of the Atomic Absorption Spectrometer:

For copper analysis, standard copper solutions ranging from 2ppm to 30ppm were prepared from a standard 1000ppm copper solution to calibrate the atomic absorption spectrometer (Figure 1). The absorbance of the standard copper solutions was analysed prior to each use of the machine.

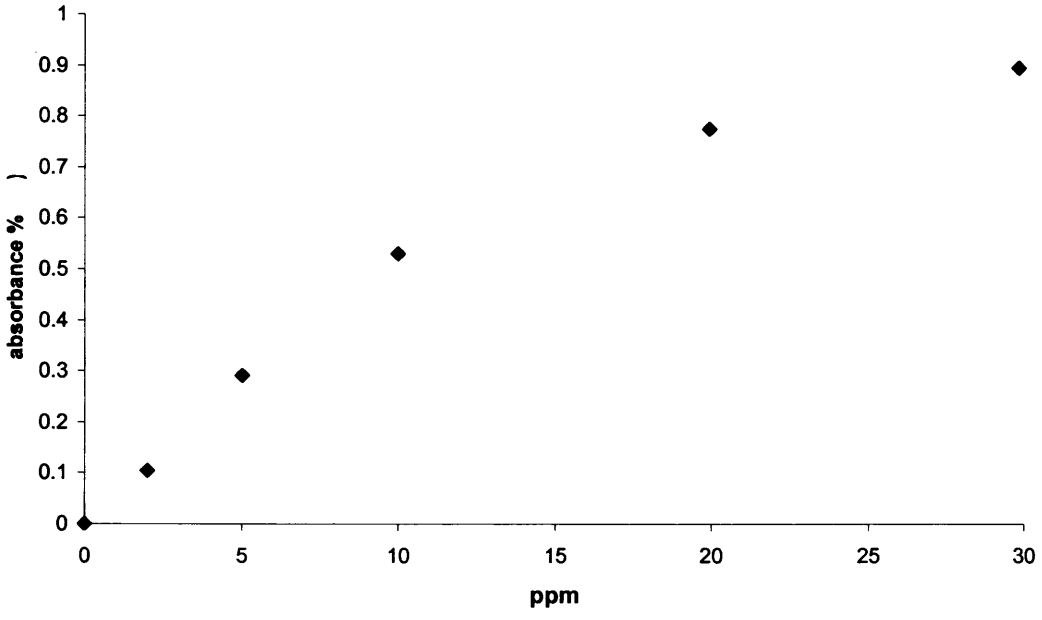

Figure 1: The calibration curve obtained for standard copper solutions.

Flame atomic absorption spectroscopy is a technique used to determine the amount of trace metals present in solution. Atomic absorption spectrometry[1] uses a flame to atomise a sample. A solution containing metal ions is aspirated into the flame through a nebuliser, where it is converted into atomic vapour. Some of the metal atoms in the flame are thermally excited, whilst others remain in the ground state. The atoms that remain in the ground state can absorb radiation that is given off by a lamp, which is specific to the metal being investigated. The lamp emits radiation at the same

wavelength that the atoms in the flame will absorb. Absorption[2] is governed by two laws; Lambert's Law and Beer's Law. Lambert's Law states that the amount of light absorbed is independent of the incident light intensity and Beer's Law states that the amount of absorption light is exponentially proportional to the number of absorbing species in the path of the beam. Therefore a calibration can be made of concentration in solution *versus* absorbance.

The absorbance (A) is defined by:

$$A=\log_{10}(I_O/I)$$

where I is the intensity of the transmitted light and I_O is the intensity of the incident light beam.

The light source for absorption measurements should emit intense, narrow lines and the hollow cathode lamp gives the best results for all elements[3]. This emits wavelengths specific to the element under investigation, so for different elemental analysis different lamps will be required. A burner (premix burner chamber used in this project) is used so that large droplets of the sample can condense, leaving only the fine droplets to enter the flame (*ca.* 10% of the sample). The most commonly used flame is the air/acetylene flame. Nitrous oxide/ acetylene flames are used when there are risks of interference at particular wavelengths. The intensity of the flame (absorbance) relates to the concentration (ppm) of the trace metal present in solution. The absorbance is then measured by a detector on the opposite side of the flame to the radiation source. The sensitivity observed on an AAS is defined as the concentration required to give 1% absorption, and the detection limit is generally defined as the concentration required to give three times the standard deviation of the baseline

2.4 Copper: chiral modifier complex

Both CuHY (0.3g, 3%wt.) and $Cu(OTf)_2$ (0.015g, $4.1x10^{-5}$ mmol, 5%wt.) were stirred with the chiral modifier (*S,S*)-2,2'-Isopropylidenebis(4-phenyl-2-oxazoline) (0.039g, $1.2x10^{-4}$ mmol) (Figure 2) in acetonitrile (5ml) for 15 minutes at room temperature. This was found to be the preferred *bis*(oxazoline), as with the heterogeneous catalyst it gave consistently higher yields and ees with the nitrene donors in use (PhI=NTs and PhI=NNs).

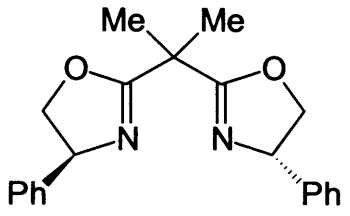

Figure 2

2.5 Synthesis of nitrene donors

2.5.1 Synthesis of (*N*-(*p*-tosylsulfonyl)imino)phenyliodinane (PhI=NTs)

Potassium hydroxide (11.2g, 0.2 mmol) was mixed with *p*-toluene sulphonamide (13.68g, 0.08 mmol) in a round bottom flask (500ml) with HPLC grade methanol (320ml) and stirred until complete dissolution had occurred. This solution was then cooled to below 10°C and iodobenzene diacetate (25.70g, 0.08 mmol) added slowly and stirred on ice until a yellow solution was formed[4]. The solution was then

removed from the ice and stirred at room temperature for a further 3h. The solution was then poured into distilled water (~800ml), covered and left in a fridge overnight where over a period of 12 hours a yellow precipitate formed and this product was then filtered and washed with distilled water, and then dried and stored in a desiccator in the dark until used. The spectroscopic data was consistent with the literature and was as follows: ^{1}H NMR (d_6-DMSO, 400MHz) δ7-7.8 (multiplet, 9H), δ2.32 (singlet, 3H).

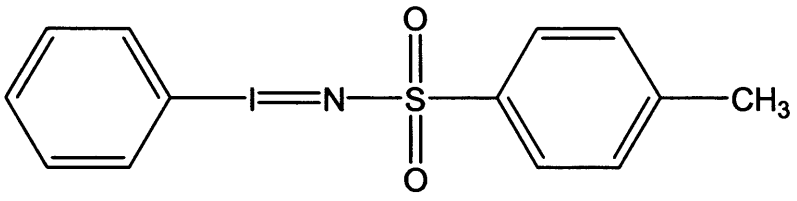

Figure 3: Structure of PhI=NTs

2.5.2 Synthesis of (*N*-(*p*-nosylsulfonyl)imino)phenyliodinane (PhI=NNs)

Potassium hydroxide (11.2g, 0.2 mmol) was mixed with 4-nitrobenzene sulphonamide (16.16g, 0.08 mmol) in a round bottom flask (500ml) with HPLC grade methanol (320ml) and stirred until complete dissolution had occurred[5]. This solution was then cooled to below 10°C and iodobenzene diacetate (25.70g, 0.08 mmol) was added slowly, keeping the temperature below 10°C at all times. This was then stirred on ice until a cream precipitate was formed, at which point the ice was removed and the solution stirred for a further 3h at room temperature. The solution was then poured into distilled water (~800ml), covered and left in a fridge overnight. The product was then filtered and washed with distilled water, and then dried/stored in a desiccator in

the dark, until used. The spectroscopic data was consistent with the literature and was as follows: ^{1}H NMR (d_6-DMSO, 400MHz) δ8.2 (doublet, 2H), δ7.95 (multiplet, 4H), δ7.56 (multiplet, 1H), δ7.4 (multiplet, 2H).

2.6 Aziridination catalysed by $Cu(OTf)_2$ and CuHY

2.6.1 Standard homogeneous reactions

Copper triflate (0.015g, $4.1x10^{-5}$ mmol) was pre-stirred with *bis*(oxazoline) chiral modifier (0.039g, $1.2x10^{-4}$ mmol) in acetonitrile (5ml) for 15min. Styrene (111μl, $9.7x10^{-4}$ mmol) was then added followed by nitrene donor (PhI=NTs 0.5430g or PhI=NNs 0.5881g, $1.5x10^{-3}$ mmol) and stirred continuously until the reaction had gone to completion. Reactions were sampled and analysed by HPLC to determine reaction completion (disappearance of the nitrogen source). A sample (40μl) was then taken and passed through a silica plug with acetonitrile/biphenyl (10ml, 1l/0.543g) or acetonitrile/anthracene (10ml, 1l/0.0667g) for product analysis. The product was then isolated using flash column chromatography (1.5x20 cm silica, 10:1.5 petroleum ether 40:60/ ethyl acetate) and analysed by chiral HPLC. The aziridine was formed as a white crystalline solid. For the racemic reaction, the same procedure was followed, but without the addition of the chiral modifier.

The spectroscopic data for *N*-(*p*-tosylsufonyl)-2-phenyl-aziridine ($CDCl_3$, 400MHz) δ7.86 (doublet, 2H, ArH), δ7.27 (multiplet, 7H, ArH), δ3.77 (doublet, 1H, CHPh), δ2.98 (doublet, 1H, *cis*-CH aziridine), δ2.43 (singlet, 3H, Ar-Me), δ2.38 (doublet, 1H, *trans*-CH aziridine), which compares to the literature values[6]. The spectroscopic data for *N*-(*p*-nosylsufonyl)-2-phenylaziridine ($CDCl_3$, 400MHz) δ8.38 and δ8.18 (double

doublet, 4H, ArH), δ7.33 (multiplet, 3H), δ7.21 (multiplet, 2H), δ3.90 (double doublet, 1H), δ3.12 (doublet, 1H), δ2.51 (doublet, 1H), which compares to the literature values[6].

2.6.2 Standard heterogeneous reaction

CuHY (0.3g) was pre-stirred with *bis*(oxazoline) chiral modifier (0.039g, $1.2x10^{-4}$ mmol) in acetonitrile (5ml) for 15min. Styrene (111μl, $9.7x10^{-4}$ mmol) was then added followed by nitrene donor (PhI=NTs 0.5430g or PhI=NNs 0.5881g, $1.5x10^{-3}$ mmol) and stirred continuously until the reaction had gone to completion. Reactions were sampled and analysed by HPLC to determine reaction completion (disappearance of the nitrogen source) A sample (40μl) was then taken and passed through a silica plug with acetonitrile/biphenyl (10ml, 1l/0.543g) or acetonitrile/anthracene (10ml, 1l/0.0667g) for product analysis. The catalyst was then filtered off and the product isolated using flash column chromatography (1.5x20 cm silica, 10:1.5 petroleum ether 40:60/ ethyl acetate) and analysed by chiral HPLC. Again, for the racemic reaction, the same procedure was followed but without the addition of the chiral modifier.

2.6.3 Chromatography

Chromatography operates on the same principle as extraction, but one phase is held in place while the other moves past it[7]. Chromatography is divided into categories based on the mechanism of interaction of the solute with the stationary phase. A stationary phase and a mobile phase are required and due to adsorption, partition, ion exchange or molecular exclusion properties, the components can be separated.

Liquid chromatography uses adsorption, where each solute has its own equilibrium between adsorption onto the surface of the stationary phase, and the solubility in the mobile phase. The least soluble (the most readily adsorbed compounds) travel through the column the slowest.

Partition chromatography are utilised in techniques such as paper chromatography, where a liquid stationary phase forms a thin film on the surface of a solid support. Solute equilibrates between the stationary liquid and the mobile phase.

Ion exchange chromatography also has a coated solid as the stationary phase, and in this case ions are covalently bonded to this surface. Ions of opposite charge are electrostatically bound to this surface, so that when the mobile phase passes over it, other ions can preferentially replace those already bonded to the column.

Molecular exclusion chromatography also called gel filtration chromatography; this technique separates molecules by size, with the larger solutes passing through most quickly. It is the molecular size that decides the velocity of the components that pass through a porous gel.

2.6.4 Thin Layer chromatography

This is a chromatography technique, and is used to select conditions for a chromatographic separation. It is very similar to paper chromatography except that instead of having paper as the stationary phase, a thin layer of either alumina or silica on an inert base such as aluminium foil or glass is used. In this method, a tiny spot of sample is applied near the bottom of a sheet of glass or plastic coated with a thin layer of stationary phase. When the plate is placed in a shallow pool of solvent in a closed chamber, solvent ascends into the stationary phase by capillary action and performs a

chromatographic separation. When solvent nears the top, the plate is withdrawn and dried. The retention ratio (R_f = distance moved by solute / distance moved by solvent) can then be calculated by measuring the distances moved by the solvent front and the solute spots. The spots are usually observed by looking at the developed plate under a UV lamp (solute spots may mask fluorescence on the plate, hence giving dark spots), or by staining the plate with iodine, the iodine vapour is reversibly adsorbed on most substances and creates a dark spot whenever a compound is located which are useful for aromatic compounds and especially those with electron donating groups.

2.6.5. Flash column chromatography (liquid)

The stationary phase for liquid chromatography is an inert solid such as silica gel or alumina supported in a glass column (Figure 4). The stationary phase must be equilibrated with solvent before pouring the column.

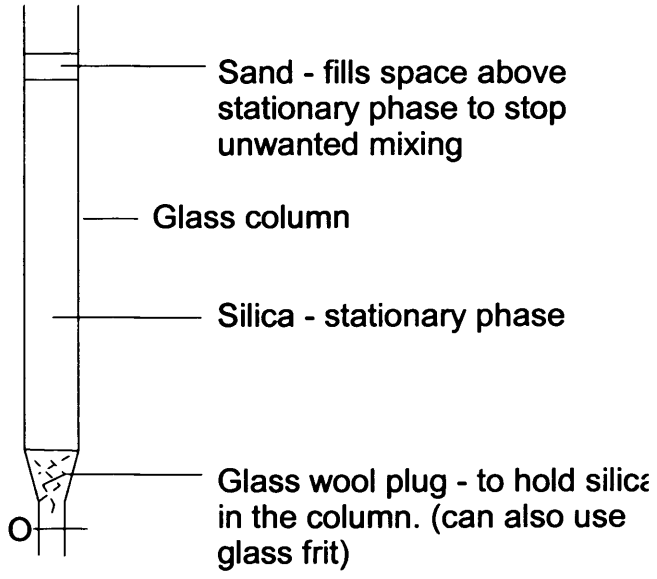

Figure 4

A column is prepared by carefully packing the solid material (small particles) in a column[8]. The solid used in the column will be dependant on the components that require separation. Silica readily adsorbs basic solutes due to its slightly acidic nature. In contrast there are three types of alumina: acidic, basic and neutral. By varying the type of alumina different solutes can be adsorbed. When using alumina with a slightly acidic nature, basic solutes can be readily adsorbed, where as using alumina with a slightly basic nature, acidic solutes can be readily adsorbed. Neutral alumina is used for the adsorption of neutral solutes. The mobile phase is generally chosen by first separating a sample by TLC to see which solvent or mixture of solvents will separate the solutes. This may be one or more different solvents mixed together in different ratios, until the optimum has been found. Before the column can be run, the stationary phase must be saturated with the solvent, as any air bubbles will form in the column, rendering it less effective. The sample is placed in a small volume on top of the column. A solvent should be used in which the sample is readily soluble, so that the volume can be kept small. But there should be a compromise for desirable eluting characteristics. The solvent is allowed to flow slowly from the column until all the of the sample just reaches the top of the solid. Then, solvent is added at the top of the column at the same rate that it flows out, or else a given volume is added at once. The solvent level must not drop to below the top of the solid phase or air channels in the column will result. Force is then applied to the top of the column, either by applying pressurised inert gas to the headspace above the solvent or by using a set of bellows attached to the top of the column (pressure up to ~ 2 atmospheres). The solvent (eluent) is collected as it emerges from the column. Usually, equal volume aliquots of eluent are collected in individual sample vials. If the flow rate is constant, then samples may be collected at equal time intervals. The eluent from the column can then

be run on TLC plates again to identify where the solute is, which can then be isolated by evaporating off the solvent from the relevant vials.

2.6.6. High Performance Liquid Chromatography (HPLC) Theory

HPLC uses high pressure to force eluent through a closed column packed with micron-size particles that provide equisite separations of picograms of analyte in a matter of minutes. The porous silica particles are typically 10^{-6}m in diameter, with a surface pore diameter of 10^{-8} – 10^{-9} m giving a very high total surface area. The particles then have a non-volatile liquid bonded to them by means of covalent bonds, which reacts with the solute by different amounts based on their polarity. The rate of distribution of solutes between the stationary and mobile phase is largely diffusion-controlled. Separation by this method is very efficient, so only a short column is required (*ca.* 10-30cm). When the particles are very small, the capillary action is such that the solvent must be pumped at a high pressure through the column for it to work. A pump is used which can provide a uniform pressure, giving a typical flow rate of 0.5-5 cm^3 min^{-1}. A small (*ca.* 5-20 mm^3) sample is injected onto the column so that it can be quickly and precisely injected without disrupting the flow of solvent through the column. Where the column has a small bore (5μm) it has a limited adsorption capacity which also makes it a necessity to inject small samples, as if too much is used there can be a loss of resolution (*i.e.* separation is reduced). Once separated the solute passes through a detector, which can be one of several different types (infrared, ultra violet, fluorescence, conductivity measurement or refractive index). Most common is the UV detector that is now available as a diode array. This allows the detection of a whole range of wavelengths simultaneously, rather than just a single wavelength. The peaks

produced can be identified by the retention time of particular solutes and the area integrated to give a quantitive amount of the solute after calibration.

2.6.7. HPLC Analysis

A Varian pro-star HPLC system was used for the analysis (PDA detector set to λ=235nm, a 230 Solvent delivery system and a 410 autosampler). For the product analysis the solvent used was acetonitrile: water (85:15), with an APEX ODS 5μ column (size 0.6cmI.D. x 25cm) with the solvent pumped at a rate of 0.5ml/min, while for the aziridine enantiomer separation hexane: isopropyl alcohol (90:10) was used with a Chiracel OJ column (size 0.46cm I.D. x 25cm) with the solvent pumped at a rate of 1.5ml/min.

The standardised reaction samples were put into 2ml vials and loaded onto the auto sampler, with 10μl samples taken for analysis. The amount of the different components was then recorded by comparing the area of the desired peak to that of the internal standard (biphenyl/anthracene) and applying a response factor, calculated for each reaction component. The response factors were recalculated on a regular basis, using a set of five dilutions to obtain a straight-line calibration plot.

2.7 Catalytic methods

2.7.1 Aziridination catalysed by $Cu(OTf)_2$ and CuHY using PhI=NNs and PhI=NTs

The standard heterogeneous reaction (2.6.2) was used with CuHY as catalyst and PhI=NTs or PhI=NNs as nitrene donor. Homogeneous equivalents (2.6.1) were also run where the $Cu(OTf)_2$ catalyst was used. The reactions were also repeated without the presence of the chiral modifier, to replicate earlier work carried out by Gullick[9].

2.7.2 Effect of reaction conditions

2.7.2.1 Addition of reaction breakdown products to reactions using PhI=NNs and PhI=NTs as nitrene donor

2.7.2.2 Standard homogeneous reaction: addition of *p*-toluene sulphonamide/ 4-nitrobenzene sulphonamide and iodobenzene to start of the reaction at 25°C

Copper triflate (0.015g) was pre-stirred with *bis*(oxazoline) chiral modifier (0.039g) in acetonitrile (5ml) for 15min. Styrene (111μl, 1 equivalent) was then added followed by the nitrene donor (PhI=NNs, 0.5881g, PhI=NTs 0.5430g, 1.5 equivalents) and 10 mol% equivalent of PhI=NTs/ PhI=NNs breakdown product ($pTsNH_2$ 0.0166g, $NsNH_2$ 0.0196g and/or PhI 0.0313g) and stirred continuously over 24h. Samples (40μl) were taken at regular intervals and passed through a silica plug with

acetonitrile/biphenyl (10ml, 1l/0.543g) for product analysis. The catalyst was then filtered off and the product isolated using flash column chromatography (pet ether: ethyl acetate 10:1.5), and analysed by chiral HPLC.

A complete set of reactions included the addition of *p*-toluene sulphonamide and iodobenzene, both separately and together, as well as a blank reaction with no breakdown materials added at all. This was then repeated with 5 mol% equivalents of PhI=NTs breakdown products added in various combinations, and compared to data for 0.1 equivalents added[10].

2.7.2.3 Standard heterogeneous reaction: addition of *p*-toluene sulphonamide/ 4-nitrobenzene sulphonamide and iodobenzene to start of the reaction at 25°C

The standard heterogeneous method (2.6.2) was followed using PhI=NNs/ PhI=NTs as nitrene donor, but with 10 mol% equivalent of PhI=NTs/ PhI=NNs breakdown product ($pTsNH_2$ 0.0166g, $NsNH_2$ 0.0196g and/or PhI 0.0313g) added to the start of the reaction. The sampling and analysis protocols were also followed. A complete set of reactions included the addition of *p*-toluene sulphonamide and iodobenzene, both separately and together, as well as a blank reaction with no breakdown materials added at all. This was then repeated with 5 mol% equivalents of PhI=NTs breakdown products added in various combinations, and compared to data for 0.1 equivalents added[10].

2.7.2.4 Addition of sulphonamide to the standard reactions using both PhI=NTs and PhI=NNs

Standard homogeneous and heterogeneous reactions were carried out as detailed before, (with or without the chiral modifier) but with 10 mol% equivalents of sulphonamide added to the reaction. In the case of the PhI=NTs reaction, *p*-toluene sulphonamide was added (0.0166g) whilst with the PhI=NNs reactions 4-nitrobenzene sulphonamide was added (0.0196g) Analysis was also performed as detailed above.

2.7.3 Leaching studies

The general procedure was followed for each reaction and when the desired end point was reached (analysed by HPLC) the mixture was filtered through a celite plug and washed with a small amount of acetonitrile. The filtrate was then diluted in acetonitrile (100g) before being analysed by AAS to determine the Cu content The AAS was calibrated by means of running a set of standard copper solutions over a range of dilutions (1ppm to 30ppm) to obtain a straight-line calibration graph. All copper readings were recorded as mg/l (ppm), and compared to the theoretical maximum to give a percentage of copper leached from the catalyst. The amount of copper in the heterogeneous catalyst was analysed similarly, but with the addition of 5wt% HF to allow the zeolite to be dissolved. The result was expressed as copper weight percent of the overall catalyst.

2.8 Effect of the counter cation on enantioselection and the reaction profile

2.8.1 Co-cation exchanged CuHY

The standard heterogeneous reaction (2.6.2) was used with MHY (where M = transition metal) used in place of the CuHY catalyst, and PhI=NTs used as nitrene donor. The sampling protocol was also used. Homogeneous equivalents (2.6.1) were also run where the MHY catalyst was replaced by the analogous metal acetate (0.3g). Characterisation studies and leaching tests were carried out on each metal catalyst after the reaction had reached completion[11]. Kinetic simulations were carried out using the program "Kinetics" (Chemistry Courseware Consortium, University of Liverpool).

2.9 Alternative substrates

2.9.1 Aziridination of styrene and styrene derivatives catalysed by $Cu(OTf)_2$ and CuHY using PhI=NNs

The standard heterogeneous reaction (2.6.2) was used with CuHY as catalyst and PhI=NNs as nitrene donor. Homogeneous equivalents (2.6.1) were also run where the $Cu(OTf)_2$ catalyst was used and in each case modified by ((*S,S*)-2,2'-Isopropylidenebis(4-phenyl-2-oxazoline). In these reactions a 50% molar excess of the nitrene donor relative to styrene or styrene derivative (1.0 mmol) was used (i.e. substrate: nitrene donor = 1: 1.5). For each substrate ^{1}H and ^{13}C NMR data were

collected of the starting material and isolated products. Before the products could be isolated, a relevant separating solvent mix had to be developed using TLC. Samples (40μl) were taken at regular intervals and passed through a silica plug with anthracene/biphenyl (10ml, 1l/0.0667g) for product analysis. The yield of products was recorded at the end of the reaction only. Following reaction, as described above, the reaction mixture was filtered through a celite plug to remove the zeolite catalyst. The filtrate was then analysed for Cu^{2+} using atomic absorption spectroscopy and the product isolated using flash column chromatography (pet ether: ethyl acetate 10:1.5), and analysed by chiral HPLC.

2.9.2 Competitive reaction of styrene and chlorostyrene derivatives

The standard reaction parameters outlined above were used for both the homogeneous and heterogeneous reactions, but with equimolar starting concentrations of the two substrates (styrene (55μl)/chlorostyrene (58μl)) were used, but each being one half of that used in 2.9.1. For each reaction, time on line (TOL) data was recorded for the conversion of styrene or chlorostyrene and for the formation of aziridine.

2.10 Mechanistic and spectroscopic studies

2.10.1 Homogeneous reactions

Copper (I) triflate (0.0088g, $2.43x10^{-5}$ mmol) or Copper (II) triflate (0.015g, $4.5x10^{-5}$ mmol) was pre-stirred with bis(oxazoline) chiral modifier (0.039g, $1.2x10^{-4}$ mmol) in methanol (2.5/5/10ml) or acetronile (2.5/5/10 ml) for 15 min. Styrene (111μl, $9.7x10^{-4}$

mmol) was then added followed by nitrene donor PhI=NTs (0.543g, $1.5x10^{-3}$ mmol) or PhI=NNs (0.5881g, $1.5x10^{-3}$ mmol) and stirred continuously until the reaction had gone to completion. A sample (40μl) was then taken and passed through a silica plug with acetonitrile/biphenyl (10ml, 1l/0.154g) for product analysis. This was then run on a HPLC system, with the biphenyl acting as the internal standard (solvent mix MeCN: Water, 85:15). The catalyst was then filtered off and the product isolated using flash column chromatography (pet ether:ethyl acetate 10:1.5) and analysed by chiral HPLC. In the case of the racemic reaction, the same procedure was followed, but without the addition of the chiral modifier.

2.10.2 Homogeneous reactions variation of copper triflate: chiral modifier ratio

The standard reaction parameters outlined above (2.10.1) were used for the homogeneous reactions, but with the ratio of copper triflate to chiral modifier altered. Initially a large range was investigated, from 2:1 to 1:5 and compared to an even larger range (2:1 – 1:0.09). More in depth analysis was carried out in the range of most interest (1.1-1.5). Below in Table 1 showing the ratios used and the amount of reactants required for each reaction.

Table 1

Ratio	Cu(OTf) (g)	Bis(oxazoline) (g)	$Cu(OTf)_2$ (g)	Bis(oxazoline) (g)
1:0.09	0.0088	0.0013	0.015	0.0012
1:0.24	0.0088	0.0033	0.015	0.0031
1:0.46	0.0088	0.0064	0.015	0.0060
1:0.87	0.0088	0.0121	0.015	0.011
1:1	0.0088	0.0139	0.015	0.013
1:2	0.0088	0.0278	0.015	0.026
1:3	0.0088	0.0417	0.015	0.039
1:4	0.0888	0.0556	0.015	0.052
1:5	0.0088	0.0695	0.015	0.065
2:1	0.0176	0.0139	0.030	0.013

For each reaction, time on line (TOL) data was recorded for the conversion of styrene, formation of aziridine, and in the case of the asymmetric reactions, the ee of the isolated aziridine.

2.10.3 Homogeneous reactions variation of copper triflate: styrene ratio

The standard reaction parameters outlined above (2.10.1) were used for the homogeneous reactions, but with the ratio of copper triflate to substrate (styrene) altered. Initially a large range was investigated, from 1:1 to 1:30 and compared to an even larger range (1:1 – 1:100). More in depth analysis was carried out in the range of most interest (1:8-1:50). Below in Table 2 showing the ratios used and the amount of

substrate required for each reaction. The above experiment was repeated using CuHY as catalyst and acetonitrile the solvent used.

Table 2

Ratio	$Cu(OTf)_2$ (g)	Styrene (μl)	CuHY (g)	Styrene (μl)
1:1.1	0.015	5.3	0.3	3.3
1:8.0	0.015	38.6	0.3	24.0
1:15.1	0.015	72.8	0.3	45.3
1:29.4	0.015	141.9	0.3	88.2
1:37.5	0.015	180.9	0.3	111
1:50	0.015	241.3	0.3	150
1:100	0.015	482.6	0.3	300

2.10.4 EPR spectrometers

Samples were placed in an EPR tube, mixed with toluene (30μl) and frozen in liquid nitrogen. The Murphy group carried out the experiments in Cardiff. EPR spectra were run at 120 K. All EPR spectra were recorded on a varian E109 and a Bruker ESP 300-E Series X-band spectrometer. The *g* values were determined using a Bruker NMR gaussmeter and the spin Hamilitonian parameters were determined by simulation of the spectra using the Sim 32 software.

2.11 Kinetic resolution experiments

2.11.1 Reactions adding preformed racemic aziridine to the start of the reaction

$Cu(OTf)_2$ (0.015g, $4.15x10^{-5}$), CuHY (0.3g, $2.6x10^{-5}$) was prestirred with racemic PhI=NNs/PhI=NTs aziridine (0.0114g, 0.0072g) (N-(*p*-nosylsulfonyl)-2-phenylaziridine/ N-(*p*-tosylsulfonyl)-2-phenylaziridine) with and without bis(oxazoline) (*S,S*)-2,2'-Isopropylidenebis(4-phenyl-2-oxazoline) (0.039g, $1.2x10^{-4}$ mmol) in acetonitrile (5ml) for 15 mins at 25^0C. (Copper : Aziridine = 1:1) Styrene (111 µl) was then added followed by the nitrene donor PhI=NNs (0.5881g, $1.5x10^{-3}$ mmol) and stirred for 24h. Samples (40ul) were taken at regular intervals and passed through a silica plug with acetonitrile/biphenyl (10ml, 1l/0.543g) for product analysis. For each reaction, time on line (TOL) data was recorded for the conversion of styrene, formation of aziridine. The catalyst was then filtered off (heterogeneous case only) and the product isolated using flash column chromatography (pet ether:ethyl acetate 10:1.5), and analysed by chiral HPLC.

2.11.2 Reactions adding preformed chiral aziridine to the start of the reaction

The above procedure (2.11.1) was followed for the heterogeneous and homogeneous reactions, but preformed chiral aziridine was added to the start of the reaction. For each reaction, time on line (TOL) data was recorded for the conversion of styrene, formation of aziridine. The catalyst was then filtered off (heterogeneous case only) and the product isolated using flash column chromatography (pet ether: ethyl acetate 10:1.5), and analysed by chiral HPLC.

2.11.3 Reactions adding preformed chiral aziridine at the start of the reaction, variation in Copper: Aziridine ratio

$Cu(OTf)_2$ (0.015g, $4.15x10^{-5}$ mmol), CuHY (0.3g, $2.6x10^{-5}$ mmol) was prestirred with chiral PhI=NNs/PhI=NTs aziridine (but with the ratio of copper to aziridine altered) and with/ without bis(oxazoline) (0.039g, $1.2x10^{-4}$ mmol) in acetonitrile (5ml) for 15 mins at 25^0C. Styrene (111 μl) was then added followed by the nitrene donor PhI=NNs (0.5881g, $1.5x10^{-3}$ mmol) and stirred for 24h. Samples (40ul) were taken at regular intervals and passed through a silica plug with acetonitrile/biphenyl (10ml, 1l/0.543g) for product analysis. For each reaction, time on line (TOL) data was recorded for the conversion of styrene, formation of aziridine. The catalyst was then filtered off (heterogeneous case only) and the product isolated using flash column chromatography (pet ether:ethyl acetate 10:1.5), and analysed by chiral HPLC. Below in Table 3 showing the ratios used for the amount of copper and aziridine required for each reaction.

Table 3

Ratio	CuHY (g)	Aziridine (g)	$Cu(OTf)_2$ (g)	Aziridine (g)
1:0.25	0.3	0.0018	0.015	0.0029
1:0.5	0.3	0.0036	0.015	0.0057
1:1	0.3	0.0072	0.015	0.0114
1:2	0.3	0.0144	0.015	0.029
1:5	0.3	0.036	0.015	0.057

2.11.4 Homogeneous reactions variation of copper: chiral modifier ratio

The standard reaction parameters outlined in (2.6.1) were used for the homogeneous reactions, but with the ratio of copper triflate to chiral modifier (bis(oxazoline)) altered. This is a similar reaction outlined in (2.10.2) however these reactions were carried out using CH_3CN as solvent. For each reaction, time on line (TOL) data was recorded for the conversion of styrene, formation of aziridine, and in the case of the asymmetric reactions, the ee of the isolated aziridine. Below in Table 4 showing the ratios used and the amount of reactants required for each reaction. The above experiment was repeated using CuHY as catalyst and acetonitrile the solvent used.

Table 4

Ratio	$Cu(OTf)_2$ (g)	Bis(oxazoline) (g)	CuHY (g)	Bis(oxazoline) (g)
1:1	0.015	0.013	------	------
1:2	0.015	0.026	0.3	0.019
1:3	0.015	0.039	0.3	0.029
1:4	0.015	0.052	0.3	0.039
1:5	0.015	0.065	0.3	0.048
1:6	------	------	0.3	0.057

2.11.5 Heterogeneous reactions with styrene reacted with mixtures of nitrene donors and differently *N*-substituted sulfonamides

Heterogeneous experiments were run where styrene (111μl) and CuHY (0.3g, $2.6x10^{-5}$) was reacted with mixtures of PhI=NTs (0.543g, $1.5x10^{-3}$ mmol) and PhI=NNs (0.5881g, $1.5x10^{-3}$ mmol) and differently *N*-substituted sulfonamides (1 equivalent) $TsNH_2$ (0.3354g) and $NsNH_2$ (0.2840g) and both *N*-substituted aziridine products were formed.

2.12 Catalyst characterisation

2.12.1 Nuclear magnetic spectroscopy (^{27}Al MAS-NMR)

2.12.1.1 Nuclear Magnetic Resonance Theory

NMR is a technique used to study molecules at an atomic level. NMR is essentially the study of molecules containing magnetic nuclei, *i.e.,* the number of unpaired protons and neutrons in the nuclei, e.g., ^{1}H, ^{13}C, ^{27}Al, by applying a magnetic field and observing the frequency at which they come into resonance with an electromagnetic field[12]. All magnetic nuclei possess angular momentum, P, referred to as spin. When a nucleus possesses a spin, this can line up with an external field, either with (+) or against (-) it. If the spin is aligned it is said to be + ½ where as if it is against the external field it is –½. Many nuclei spin about an axis, which gives rise to a magnetic field, which means that the spinning nucleus has a magnetic moment that will line up in a preferred orientation when put in an external magnetic field. Quantum laws are

obeyed where in the simplest case one of two orientations can be adopted (+ or – ½). These are said to be the most and least favoured orientations that give rise to a splitting pattern (Figure 5).

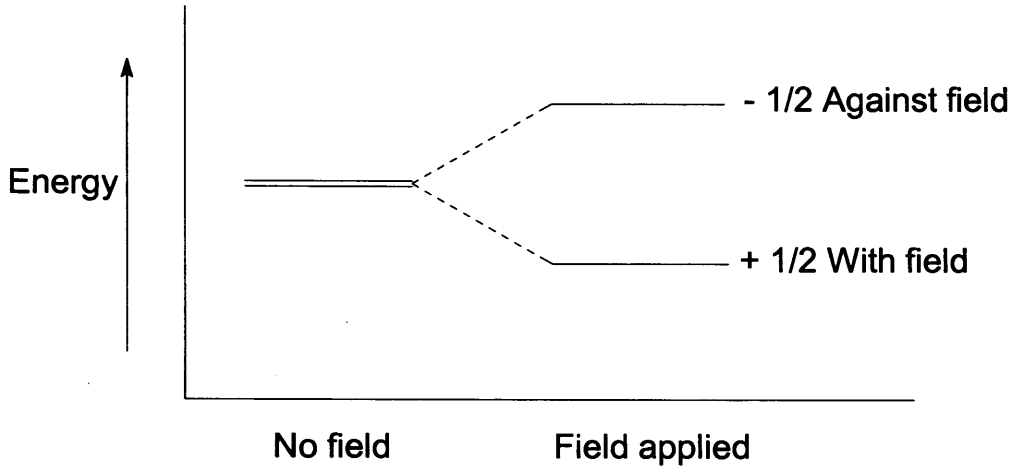

Figure 5

Energy is distributed between the two energy levels by means of nuclear spin and the thermal motion of the molecules. Transitions between the two spin states can occur if absorption of radiation at the right frequency occurs. Once the radiation energy has been absorbed, spin-lattice relaxation processes reach equilibrium again, where the energy is distributed amongst surrounding nuclei (spin-spin relaxation) or to the surroundings (spin-lattice relaxation).

The chemical shift of a nucleus is the difference between its resonance frequency and that of a reference standard. The chemical shift is dependant on the electronegativity of the atoms in the molecules, as well as delocalised electrons (aromatic ring / double bond) that can cause extra shielding or deshielding. The splitting of resonances into individual lines is called the fine structure of the spectrum. It arises because each magnetic nucleus contributes to the local field experienced by the other nuclei and modifies their resonance frequencies. The strength of the interaction is expressed in

terms of the spin-spin coupling constant J measured in hertz (Hz). Spin-spin coupling constants are independent of the strength of the applied field since they do not depend on the latter's ability to generate local fields. The coupling patterns observed will give information both from the number of peaks observed and the intensity of the peaks. In general, if there are n protons three bonds away from the resonating group, the absorption will be split into a multiplet of n+1 lines, with their intensities predicted by Pascal's triangle.

2.12.1.2 Magnetic Angle Spinning Nuclear Magnetic Resonance

There are differences between solid and liquid state NMR. Solutions give rise to high resolution NMR, whereas solids give broader, unstructured resonance patterns. In recent times there has been the development of high resolution NMR for solids[13]. In solid state NMR there is line broadening caused by dipole-dipole interactions. The NMR signal of the nucleus is dependant on the magnetic field, which brings about the chemical shift. Each nuclei has its own dipole moment, which will interact with other dipole moments. This gives rise to changes in the resonance frequency due to the different local fields at the nucleus, resulting in broad resonance lines. In liquid state NMR the chemical shifts are averaged over the different orientations of the molecule when placed in a magnetic field. Chemical shift anisotropy affects the NMR spectrum by giving rather broad, complex patterns. When the sample is powdered, groups of molecules will have fixed orientations with respect to the magnetic field. In this case the shift anisotropy cannot be averaged, resulting in a range of contributions to each different chemical shift and therefore the presence of broad spectral lines. Nuclei in solids possess long relaxation times. After each pulse, the nuclei must relax back to

equilibrium. An FID (free induction decay) is then obtained and Fourier transformation will then produce a spectrum with reasonable signal-noise ratio.

2.12.2 Powder X-ray diffraction (XRD)

Diffraction is the interference caused by an object in the path of waves. The diffraction pattern results from the varying intensities caused by the waves interfering with each other, either constructively (increased intensity) or destructively (decreased intensity). Diffraction occurs when the dimensions of the diffracting object are comparable to the wavelength of the radiation. Powder X-ray diffraction is a useful technique as X-rays are of a suitable wavelength to determine the bond length of molecules and atom spacing in crystal structures. X-rays, which are electromagnetic radiation with wavelengths of about 100ppm, are produced by bombarding a metal with high-energy electrons[12]. The electrons decelerate as they plunge into the metal and generate radiation with a continuous range of wavelengths called Bremsstrahlung. Superimposed on the continuum are a few high-intensity, sharp peaks. These peaks arise from the interaction of incoming electrons with the electrons in the inner shells of the atoms. A collision expels an electron, and an electron of higher energy drops into the vacancy, emitting the excess energy as an X-ray photon. From the diffraction pattern it is possible to determine the locations of atoms in the sample. For powder XRD X-rays are directed at the sample over a range of angles and the reflections resulting from the fulfilment of Bragg's equation are measured. For a given angle, some of the crystallites in the sample will be orientated in such a way that the reflected waves are in phase and will interfere constructively, giving rise to a peak of increased intensity. However in some cases the crystallites are arranged that certain planes are

preferentially exposed to X-rays. The intensity of the reflection associated with that crystal plane is therefore much greater than expected and the intensities of reflections due to the non preferred crystal planes are much lower than expected.

Bragg's Law (Figure 6): $n\lambda = 2d\sin\theta$, where θ is the angle of incidence, d is the spacing between the planes of the crystal, λ is the wavelength of radiation and n is the order of reflection.

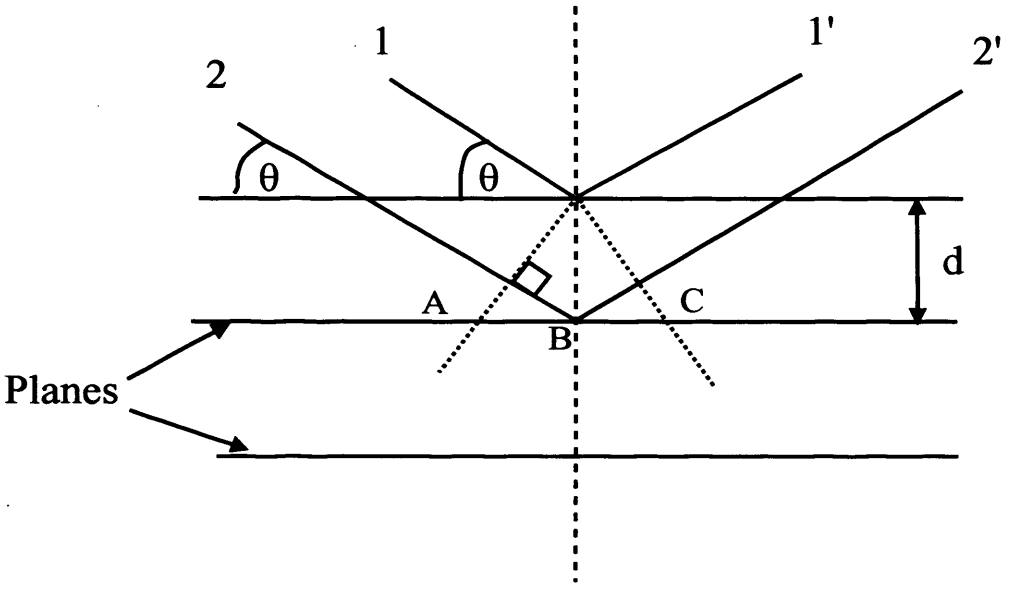

Figure 6

2.12.3 Electron Paramagnetic Resonance (EPR)

Electron Paramagnetic Resonance (EPR) is the study of molecules containing unpaired electrons by observing the magnetic fields at which they come into resonance with monochromatic radiation[12]. EPR is a direct and sensitive technique for the investigation of paramagnetic species. EPR allows you to study the paramagnetism in

solids, liquids and gases. Paramagnetism arises as a result of unpaired electrons present within a molecule or atom.

Electron magnetic resonance occurs when an electromagnetic wave of suitable frequency interacts with the sample immersed in a magnetic field. EPR is based on the difference between the energies of the two spin states of the unpaired electron when the electron is placed in a magnetic field. A resonance occurs when the value of the magnetic field satisfies the following equation:

$$\Delta E = g\mu_B B$$

where g is the g-value of the electron, μ_B is the Bohr magneton and B is the applied magnetic field.

An electron has a property known as Spin. The most transparent manifestation of electron spin is that the electron has a magnetic moment. A free electron is a negatively charged particle and moves in orbitals around the nucleus. As a consequence it has orbital angular momentum and because it also spins about its own axis it has spin angular momentum within the orbit S that in a given direction can only assume two values ($+^1/_2$, $-^1/_2$). The energy splitting between the two allowed spin states is referred to as the Zeeman effect and in such conditions, an electron in the lower state is promoted to the higher state by absorption of a photon of specific energy. Further interaction between the unpaired electron and the nucleus containing the nuclear magnetic moment gives rise to further splitting of the Zeeman energy levels resulting in the EPR hyperfine structure. Additional information can be obtained from the hyperfine structure, in the case of transition metal ions, oxidation state, ground state, crystal field and interaction with complex ligands can be determined.

2.13 References

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Chapter 3

Aziridination of styrene derivatives

3.0 Aziridination of styrene derivatives

3.1 Introduction

Evans *et al.*[1,2] had developed a catalytic homogeneous system for the aziridination of alkenes. Copper salts were used in conjunction with (N-(*p*-toluenesulfonyl)imino)phenyliodinane, PhI=NTs, as nitrogen source in the reaction which resulted in high aziridine yields. Langham *et al.*[3,4] followed on from this work by developing a heterogeneous aziridination system using copper exchanged zeolite Y (CuHY) as catalyst. This system was then modified with a chiral bis(oxazoline) ligand to induce enantioselectivity. Gullick *et al*[5] showed that the highest yields of aziridine were attained when using (N-(*p*-(nosylsulfonyl)imino)phenyliodinane, PhI=NNs as nitrogen source. This study is therefore an extension of the work carried out previously in the Cardiff group. All of the reactions carried out in this chapter have been carried out both homogeneously, using $Cu(OTf)_2$ as catalyst and heterogeneously using copper-exchanged zeolite Y in order to have a direct comparison between the two systems.

3.2 Heterogeneous aziridination of styrene derivatives

To date, work carried out in the Cardiff group, concentrated on styrene as a model reactant; earlier work did explore some alternative substrates[4], but in general these were less reactive than styrene. In this work the range of substrates was extended and the reactivity of the substituted styrene derivatives investigated for both the homogeneously and heterogeneously catalysed reactions using [N-(*p*-

nitrophenylsufonyl)imino]phenyliodinane (PhI=NNs) as nitrene donor. Previous studies by Nishikori and Katsuki[6], using homogeneous manganese salen catalysts with PhI=NTs as nitrene donor, showed that 4-methylstyrene and 4-chlorostyrene gave lower yields compared with styrene. Diaz Requejo *et al.*[7] studied a range of styrene derivatives using a homogeneous bis(oxazoline) modified copper catalyst and showed that the reaction intermediate is a paramagnetic copper nitrene species. More recently Jain and Sain[8] have shown that a new nitrene donor, N-iodo-N-potassio-*p*-toluenesulfonamide, is effective with CuCl as homogeneous catalyst in the absence of bis(oxazoline) for the aziridination of styrene derivatives. Gullick *et al.*[9] have shown recently that the ee increases with conversion for the aziridination reaction for both the homogeneously and heterogeneously catalysed reaction using copper bis(oxazoline) catalysts, and this work extends the investigation to the reactivity and reaction profiles of the aziridination of substituted styrenes.

3.3 Reaction of styrene derivatives

The aziridination of styrene and styrene derivatives was investigated using PhI=NNs as nitrene donor with Cu-exchanged zeolite Y or copper (II) triflate modified by (S,S)-2,2-isopropylidenebis(4-phenyl-2-oxazoline) and the results are shown in Tables 1 and 2 following reaction for 12 hours. In these reactions a 50% molar excess of the nitrene donor relative to the styrene derivative was used.

Table 1: Homogeneous aziridination of styrene derivatives[a]

	$Cu(OTf)_2$		
Substituent[b]	**Yield (%)**	**ee (%)**	**Substituted benzaldehydes (%)**
None	96	81	18
2-Cl	90	83	24
3-Cl	89	72	24
4-Cl	90	93	22
2-F	85	71	17
3-F	80	81	17
4-F	85	41	21
2-Br	90	68	15
3-Br	79	83	16
4-Br	90	59	17
2-CH_3	80	68	9
3-CH_3	78	80	3
4-CH_3	85	66	3
α-CH_3	61	15	13
Trans-β-CH_3	63	23	25
4-OCH_3	76	76	19
3-NO_2	48	68	20

[a] Reaction conditions: bis(oxazoline) (7 mol %), CH_3CN, 25 °C, PhI=NNs:styrene = 1.5 mol ratio, 12 h reaction time, catalyst: $Cu(OTf)_2$ (15 mol %)

[b] Styrene substituent

For the homogeneously catalysed reaction all the styrene derivatives gave lower yields of the aziridine products than that of styrene and substituted benzaldehydes were observed as the by-product. The by-products are considered to result from the formation of PhIO, enhanced at these nitrene: substrate mol ratios; this subsequently reacts with the substrates to form the substituted benzaldehyde and other oxygenated products, thereby decreasing the aziridine yield[10]. The ee for reaction of 4-chlorostyrene (93%) was significantly higher than that observed with styrene (81%). This and 2-Cl were the only enhancement in ee observed with the homogeneously catalysed reactions investigated. However, the yield of aziridine was reduced to (90%) for 2- and 4-Cl which was at the expense of the enhancement in ee observed. Diffusion limitations are not expected in the homogeneously catalysed reaction thereby allowing the substrate access to the active site. However, compared with CuHY catalysis, the ee is lower in the homogeneously catalysed reaction. All the Cl- derivatives gave higher ee in the heterogeneous reaction, than that of the homogeneous reaction (Table 1).

The 3- substituted F-, Br-, CH_3- derivatives gave higher ee all above (80%) than the corresponding 2- and 4- derivatives, and these values were similar to the ee observed with styrene. In fact the 4- substituted F-, Br-, CH_3 derivative gave the lowest ee for each substituent. However the aziridine yield was lower for the 3-substituted styrenes. This effect appears to be similar for substituents of quite different electronic character; and therefore the decreased yield can probably be attributed to steric factors. In general the properties of the elements and their compounds change progressively with increasing size. The F- substituted derivatives gave lower ee values than its corresponding group VII elements. The small size and high electronegativity[11] of the F atom account for many of the other differences between fluorine and the other halogens.

Table 2: Heterogeneous aziridination of styrene derivatives[a]

	CuHY		
Substituent[b]	**Yield (%)**	**ee (%)**	**Substituted benzaldehydes (%)**
None	78	85	16
2-Cl	83	88	22
3-Cl	82	95	19
4-Cl	85	94	19
2-F	82	72	13
3-F	75	58	16
4-F	83	53	18
2-Br	60	85	15
3-Br	59	64	13
4-Br	90	74	17
2-CH_3	60	79	3
3-CH_3	75	48	3
4-CH_3	83	67	15
α-CH_3	57	34	12
Trans-β-CH_3	42	24	10
4-OCH_3	71	64	20
3-NO_2	63	65	18

[a] Reaction conditions: bis(oxazoline) (7 mol %), CH_3CN, 25 °C, PhI=NNs:styrene = 1.5 mol ratio, 12 h reaction time, catalyst: CuHY (300mg/mmol, 3.7 wt % Cu)

[b] Styrene substituent

The heterogeneously catalysed reactions (Table 2) show significant differences for the same substrate when compared to the homogeneously catalysed reactions, the most significant being the yield of aziridine, which is markedly enhanced, compared with styrene. This effect is most noted with the 4- substituted F-, Cl-, Br-, and CH_3-derivatives where the aziridine yield is (83%, 85%, 90%) and (83%) respectively compared to (78%) using styrene as substrate. This effect is probably due to the reaction proceeding in a more controlled environment within the pores of the zeolite. The zeolite may also capture water from the solvent and this leads to a decrease in the formation of PhIO, and an enhancement in aziridine yield. However, this effect would be expected to be present to a similar extent for all the substrates, the 2- and 3-substituted CH_3 form small amounts of PhIO, 3%, but this does not result in a significant increase in the corresponding aziridine yield, rather, only forming (60%) and (75%) respectively. Since it is variable, this effect is therefore not considered significant.

A substituent-dependent enhancement in yield is possible if the rate of PhI=NNs hydrolysis is comparable to the rate of aziridination; the enhancement could be greatest then for the more reactive styrenes, but this does not seem to be the case in this study. However, since the 4-substituted styrenes and the derived aziridines have smaller cross-sections than the corresponding 2- and 3- substituted analogues and consequently will diffuse more rapidly through the zeolite pore system, the reduced steric effects that can be expected for the 4-substituted styrenes over the 2- and 3-derivatives are considered to be crucial. This is seen in the final aziridine yields (Table 2) for each derivative where the 4-substituted styrene has enhanced yield over its 2- and 3- substituted counterparts.

The ee observed with the heterogeneously catalysed reactions is in general higher than that observed with the homogeneously catalysed reaction (Tables 1 & 2), except for the 3-substituted derivatives discussed previously. 3-Chlorostyrene reacts with very high ee in the heterogeneous system[12] (95%); this is one of the highest ee's reported to date for a heterogeneously catalysed asymmetric reaction, and is to be compared with the homogeneous system for which a poor ee is recorded (72%). This high ee is a result of a confinement effect within the pores of the zeolite catalyst. Previous work by Taylor *et al.*[13] has shown that with the immobilised CuHY catalyst, the chiral modifier need not be as bulky as that required by the non-immobilised Cu^{2+} homogeneous catalyst. This is thought to be due to the zeolite framework occupying part of the coordination sphere of Cu^{2+} in the CuHY catalyst and this confinement affects the conformation of the bis(oxazoline) which in turn modifies the requirements of the chiral modifier for the immobilised catalyst. The heterogeneously catalysed reaction therefore affords higher enantioselection than the corresponding homogeneous reaction, and is also consistent with the observations with Raynor *et al.*[14] for an asymmetric amination reaction. The additional steric bulk of the substrate significantly affects its interaction with the catalytically active site, which is more constrained within the zeolite, and leads to improved enantioselection.

However, steric factors alone cannot explain this effect since high enantioselection would be expected for all 2- and 3- substituted substrates and this is not observed, 2-F and 3-Br have an ee of (72%) and (64%) respectively. As a result, it must be a combination of electronic and steric factors that combine to induce high enantioselection for 3-chlorostyrene in the heterogeneously catalysed reaction. This theory can also be applied to 4-chlorostyrene in the heterogeneous system where the corresponding aziridine is afforded in particularly high ee (94%) and yield (85%).

For the heterogeneously catalysed reactions the introduction of a methyl group on the alkene group suppresses the ee (Table 2) but the effect is less marked with α-methylstyrene (34%) than with *trans*-β-methylstyrene (24%). The homogeneously catalysed reactions with α-methylstyrene and *trans*-β-methylstyrene afford the corresponding aziridine in low yields (Table 1), (61%) and (63%) respectively and very low ees of (15%) and (23%). Hence, as with the heterogeneously catalysed reactions, α-methylstyrene and *trans*-β-methylstyrene are aziridinated but the process is predominantly racemic.

4-Methoxy styrene affords the corresponding yield and ee lower than that for styrene for both catalysts. However, the aziridine yield (76%) in the homogeneously catalysed reaction is higher than the corresponding heterogeneously reaction (71%). 3-Nitro styrene also gave lower yields and ees for both catalysts, compared to styrene. The ee for the homogeneously catalysed reaction (68%) was higher than that of the heterogeneous system (65%), although the yield was suppressed for the homogeneous reaction (48%) with the notable formation of (20%) PhIO.

For both catalysts investigated, 4-amino and 4-^{t}butyl-styrene do not form aziridines; instead a very broad range of products is observed mainly the result of amination rather than aziridination. For the heterogeneously catalysed reaction of 4-^{t}butyl-styrene, steric hindrance causes the reaction to most likely take part on the exterior surface of the zeolite. However, with 4-amino-styrene it is probable that this substrate interacts with the Brönsted acid sites of the zeolite. As the Brönsted acid sites are not modified by the bis(oxazoline), only achiral, non-aziridination reactions will be catalysed there.

3.4 Copper-exchanged zeolite catalyst stability

The effect of the different substrates on the stability of the copper-exchanged zeolite catalyst during the reaction was also investigated and the Cu^{2+} leaching was determined (Table 3). Taylor *et al.*[15] carried out a detailed study investigating Cu^{2+} leaching in the catalytic heterogeneous system using styrene as substrate. From this study it was concluded that *ca.* 10.3% of the Cu^{2+} initially present in the Cu-H/Y catalyst leaches under standard reaction conditions (PhI=NNs:styrene = 1.5:1 molar ratio, bis(oxazoline), 25°C, CH_3CN). It was also noted that, the leached Cu^{2+} was ineffective as a catalyst since the homogeneously catalysed aziridination reaction was poisoned preferentially by the presence of PhI, a by-product of the decomposition of the nitrene donor.

The most significant aspect of Table 3 is that the leaching of Cu^{2+} was decreased for the reaction of the substituted styrenes. All the substrates tested had lower levels of Cu leaching (Table 3) during the reaction than that of styrene (10.3%). In the cases of 3- and 4- methyl styrene the Cu leached during the reaction is very small, 0.4% and 0.8% respectively. This is also the case with 3-bromostyrene (0.8%). One plausible explanation is that the increased steric effects due to these relatively larger substrates contribute to improving the stability of the catalyst. Cu^{2+} leaching during the reaction is a result of either the bis(oxazoline), the solvent, the nitrene donor and the aziridine all competing as nitrogen ligands for the Cu^{2+}. Another possible explanation is that the substrate competes for the liganded Cu^{2+}. The result of which, been that the relative solubility of the complexes could also play a role in the eventual leaching of Cu^{2+}.

Table 3: Effect of substrate on catalyst stability[a]

Substituent[b]	Cu leached during reaction (%)
None	10.3
2-Cl	6.9
3-Cl	5.2
4-Cl	3.6
2-F	3.6
3-F	4.2
4-F	1.8
2-Br	1.6
3-Br	0.8
4-Br	2.3
2-CH_3	2.5
3-CH_3	0.4
4-CH_3	0.8
α-CH_3	3.9
***Trans*-β-CH_3**	2.3
4-OCH_3	3.0
3-NO_2	4.6

[a] Reaction conditions: bis(oxazoline), CH_3CN, 25 °C, PhI=NNs:styrene = 1.5 mol ratio using Cu-exchanged zeolite Y containing 3.7 wt% Cu, 12 h reaction time.

[b] Styrene substituent

The low levels of Cu^{2+} leaching cannot be attributed to steric factors only. The reason been that the least sterically hindered substrate, the 4-substituted styrene, would be expected to give higher Cu^{2+} leaching and this is generally not the case. In fact apart from 4-bromostyrene (2.3%) the substituents in the 4- position have lower levels of Cu^{2+} leaching than their 2- and 3- substrate counterparts. However, confinement effects have been observed to play a significant role with microporous and mesoporous heterogeneous asymmetric catalysis. A comparison between the yield of aziridine and the amount of Cu^{2+} leached during the reaction (Figure 1) makes it clear that there is no relationship between these factors and this confirms that the leached Cu^{2+} does not play an important role in these asymmetric reactions.

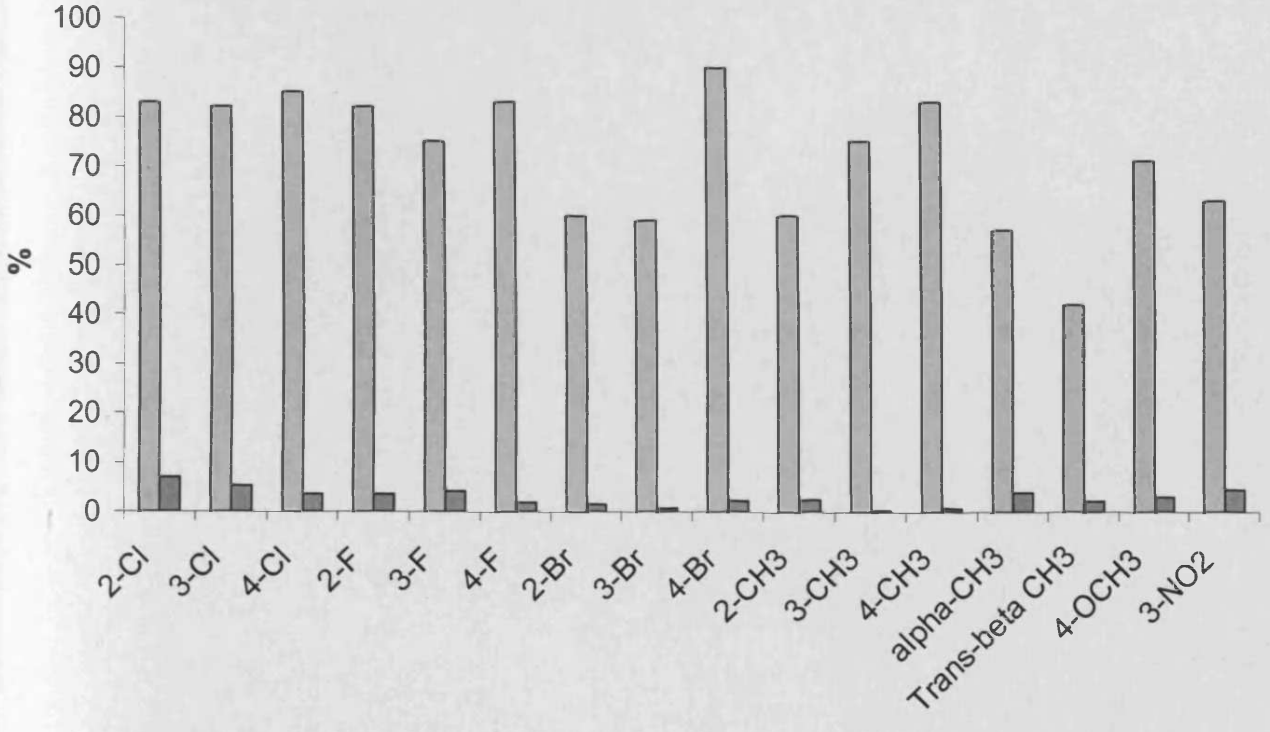

Figure 1: Comparison of aziridine yield (light grey) and amount of Cu leached (dark grey) for different substrates reacted under standard reaction conditions with bis(oxazoline), CH_3CN, 25°C, PhI=NNs:styrene = 1.5 mol ratio. Key: ■ aziridine yield; ■ Cu^{2+} leached.

3.5 Effect of reaction time on aziridine yield

The effect of reaction time on the conversion of styrene and yield of aziridine was investigated for all the substrates for both the homogeneously and heterogeneously catalysed reaction (Figures 2-6).

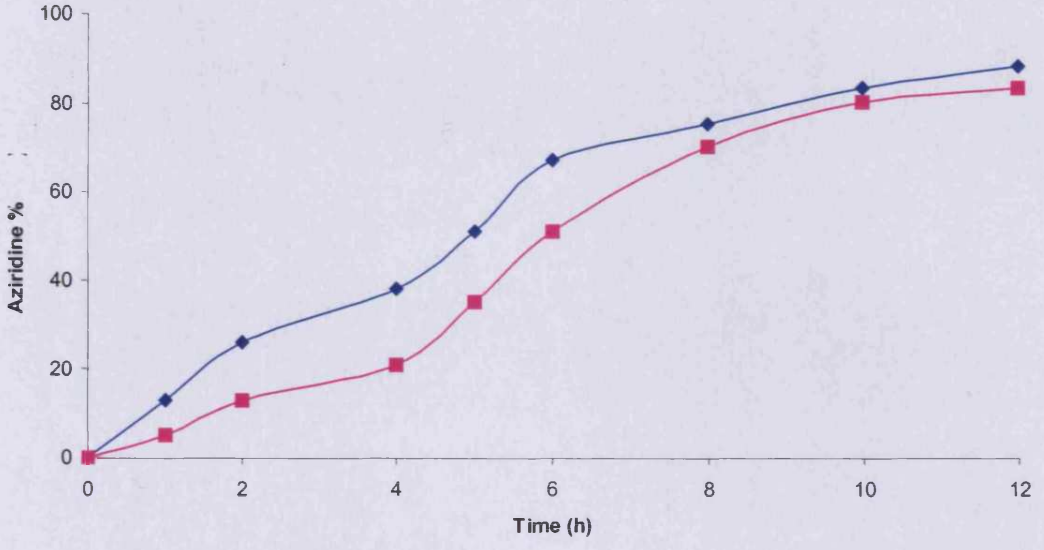

Figure 2: Effect of reaction time on the aziridination of styrene with bis(oxazoline), CH_3CN, 25°C, PhI=NNs:styrene = 1.5 mol ratio using (a) Cu-exchanged zeolite Y, and (b) $Cu(OTf)_2$.

Key: ◆ aziridine yield $Cu(OTf)_2$; ■ aziridine yield CuHY

It is clear that the different substrates exhibit different reaction rates, but more important is the observation that the reaction profile for aziridine yield that is observed for styrene (Figure 2) using Cu-exchanged zeolite Y and $Cu(OTf)_2$ is also present for the 2- and 3- substituted styrene derivatives (Figures 3-6). The effect of reaction time on aziridine yield reveals a reaction profile in which the reaction initially proceeds rapidly then slows prior to accelerating in the latter part of the reaction.

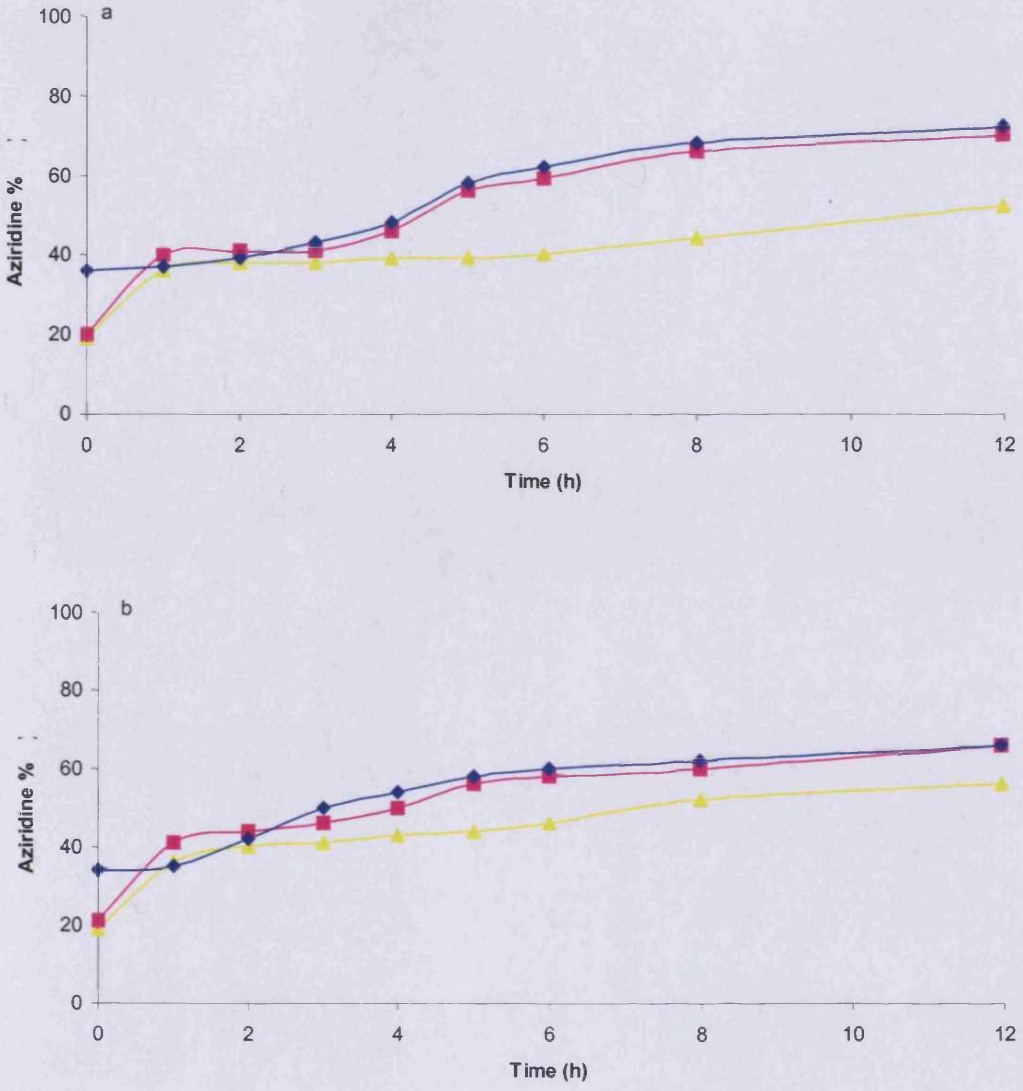

Figure 3: Effect of reaction time on the aziridination of fluorostyrene

(a) Cu-exchanged zeolite Y and (b) $Cu(OTf)_2$
Key: Aziridine yield ◆ 4-fluorostyrene; ■ 3-fluorostyrene; ▲ 2-fluorostyrene

Although, the final yield of aziridine is lower for both the homogeneously and heterogeneously catalysed reaction of substrates for fluorostyrene compared to styrene, the decreased yield can probably be attributed to steric factors, as mentioned previously. However, the reaction profile for aziridine yield that is observed for styrene is also evident for 3-fluorostyrene using both catalysts.

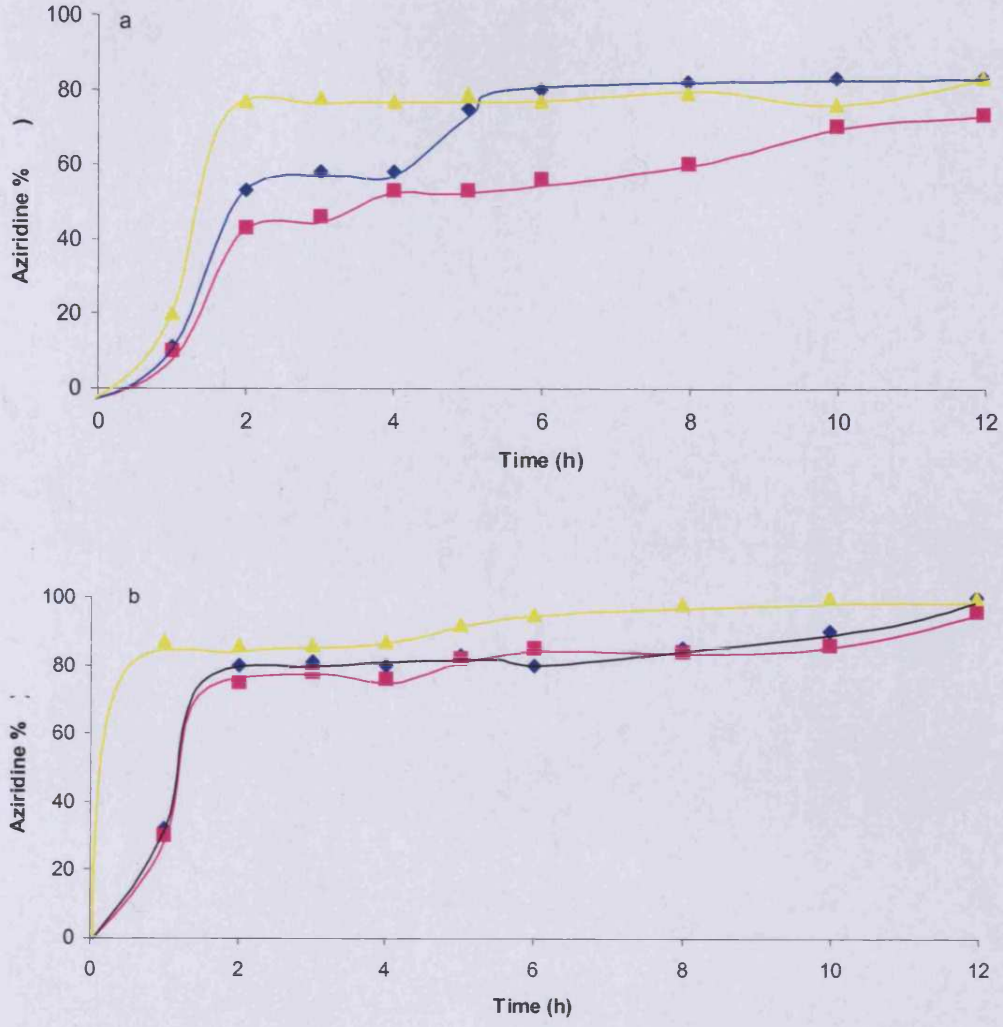

Figure 4: Effect of time on the aziridination of chlorostyrene
(a) Cu-exchanged zeolite Y and (b) $Cu(OTf)_2$
Key: Aziridine yield ◆ 2-chlorostyrene; ■ 3-chlorostyrene; ▲ 4-chlorostyrene

In particular, the reaction of 4-chlorostyrene for both catalysts is very rapid, when compared with the 2- and 3-chlorostyrenes. The reaction is almost complete after 1h for the homogeneously catalysed reaction and after 2h for the heterogeneous reaction of 4-chlorostyrene. This may be the underlying effect that leads to this substrate giving such a high ee (≥93%). The heterogeneous reaction of 2- and even 3-chlorostyrene gives a reaction profile very similar to that of styrene (Figure 2) for aziridine yield.

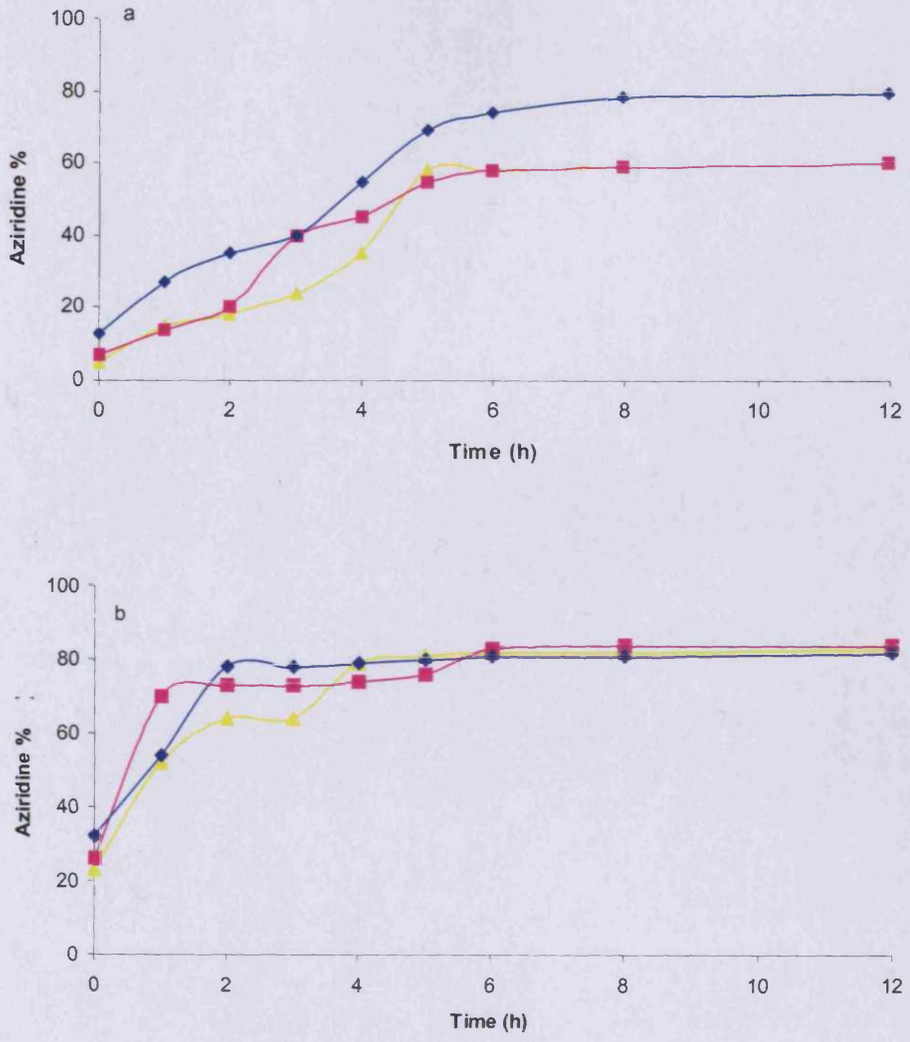

Figure 5: Effect of reaction time on the aziridination of bromostyrene

(a) Cu-exchanged zeolite Y and (b) $Cu(OTf)_2$
Key: Aziridine yield ◆ 4-bromostyrene; ■ 3-bromostyrene; ▲ 2-bromostyrene

The reaction rate and profile for the heterogeneously catalysed reaction of bromostyrene is observed in the reaction profile for the aziridine yield of styrene. The 3-step profile is evident where the reaction proceeds rapidly over the first hour then slows over the next two hours and finally accelerates in the latter part of the reaction. The homogeneous reaction proceeds rapidly and reaches completion after four hours; therefore the profile that is observed for styrene is evident here.

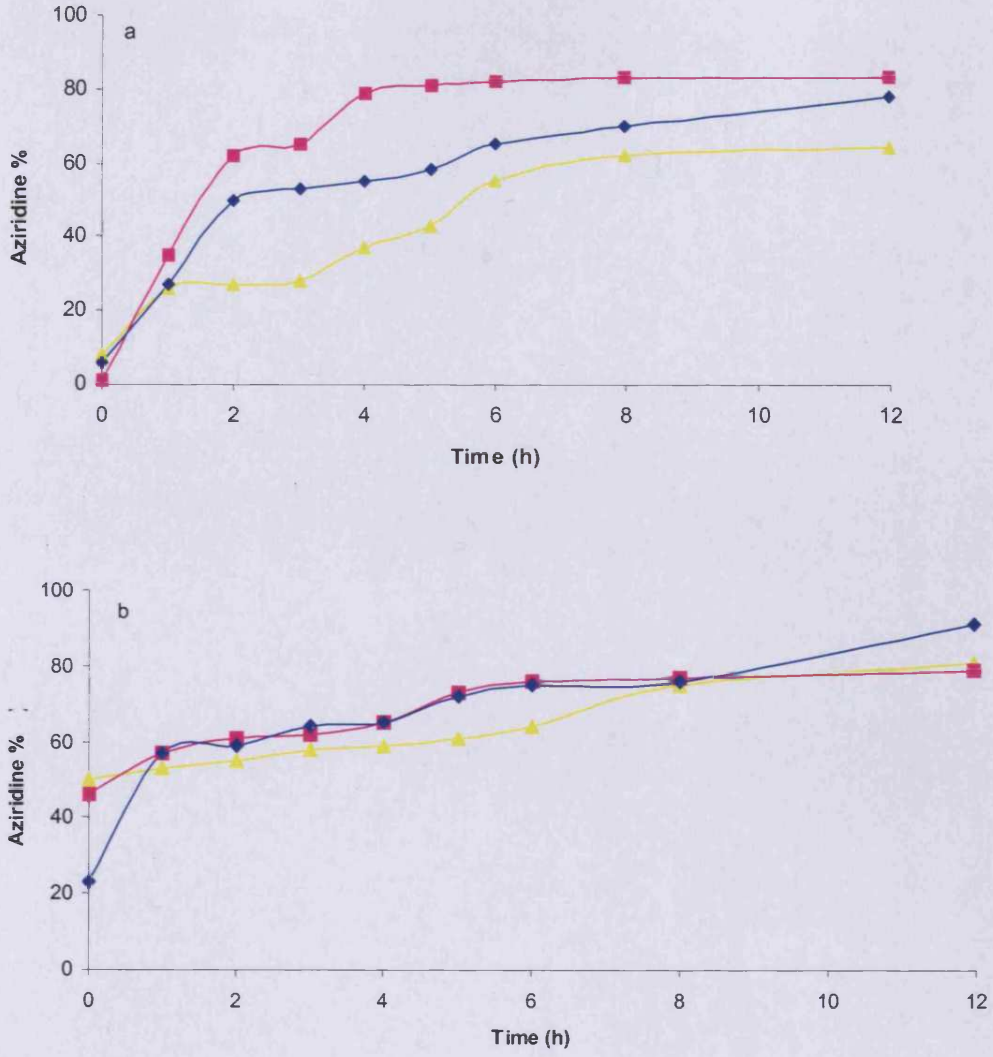

Figure 6: Effect of reaction time on the aziridination of methylstyrene

(a) Cu-exchanged zeolite Y and (b) $Cu(OTf)_2$

Key: Aziridine yield ◆ 4-methylstyrene; ■ 3-methylstyrene; ▲ 2-methylstyrene

Different reaction rates can be seen between the homogeneously and heterogeneously catalysed reactions of methylstyrene. For the 2-, 3- and 4- methylstyrene using CuHY, the reaction profile and rate observed for aziridine yield in styrene is clearly evident. The homogeneous reaction has a rapid reaction rate and the reaction profile observed confirms this. However this rapid reaction rate for the homogeneous catalyst does

result in higher aziridine yields, for the 2- and 3- derivatives rather than the corresponding heterogeneously catalysed reaction.

In the heterogeneously catalysed reaction, the active site within the supercage of the zeolite is highly confined. As mentioned previously[13], this leads to an enhancement in the ee observed with these catalysts. It is also known that the active site can also interact with reaction by-products, e.g. PhI, $NsNH_2$, as well as the aziridine product and the nitrene donor. Previously within the Cardiff group[9] it has been shown that the aziridine could interact with $NsNH_2$ and the nitrene donor and these interactions played a role in the observed enhancement in ee with styrene conversion.

This observation shows that the coordination sphere of the Cu^{2+}, although highly confined within the zeolite, changes its nature during the reaction. Therefore, the size of the substrate could play a significant role by enhancing steric confinement of the active centre. Although this is not considered to influence the nature of the reaction profile curves observed in this study, since the effect is observed in the homogeneously catalysed reactions when confinement effects cannot occur. The reaction of 2-bromostyrene for both catalysts (Figure 5) reveals a profile in which the reaction initially proceeds rapidly then slows prior to accelerating in the latter part of the reaction and this is also evident with 3-methylstyrene (Figure 6) in both the homogeneously and heterogeneously catalysed reactions.

3.6 Competitive reaction of styrene and chlorostyrene derivatives

Experiments were designed and investigated in order to evaluate the reaction of styrene in competition with a styrene derivative. In these set of experiments equimolar starting concentrations of the two substrates were used, but each being one half of that used in the previous experiments. Therefore, all the reaction parameters could remain unchanged. These experiments would show the effect of reaction time on the yields of aziridine products (Figures 7-9) for the competition reaction of styrene with 2-, 3- and 4-chlorostyrene respectively. These reactions were carried out with the same conditions used for the reaction of the individual substrates (i.e. total substrate: nitrene donor = 1: 1.5 mol ratio) except that half of the styrene was replaced by the 2-, 3- and 4- chlorostyrene. However, for the data reported in figures 7-9 the concentration of the substrate reacted was doubled to permit a direct comparison with the individual substrate.

In competitive experiments of this type to assess relative reactivities, it is normally the case that the competing molecules (styrenes) are allowed to react with a deficiency of the reagent (PhI=NNs) and the amount of reaction of each of the two styrenes is measured after all the reagent has been consumed. However, in this series of experiments the nitrene donor was only partially soluble in the reaction mixture and attempts to use molar ratios substantially lower (i.e. styrenes: nitrene donor = 1: 0.5 mol ratio) resulted in low yields of aziridine (~ 15%) in all cases. Hence, the experiments were carried out with higher amounts of the PhI=NNs reagent.

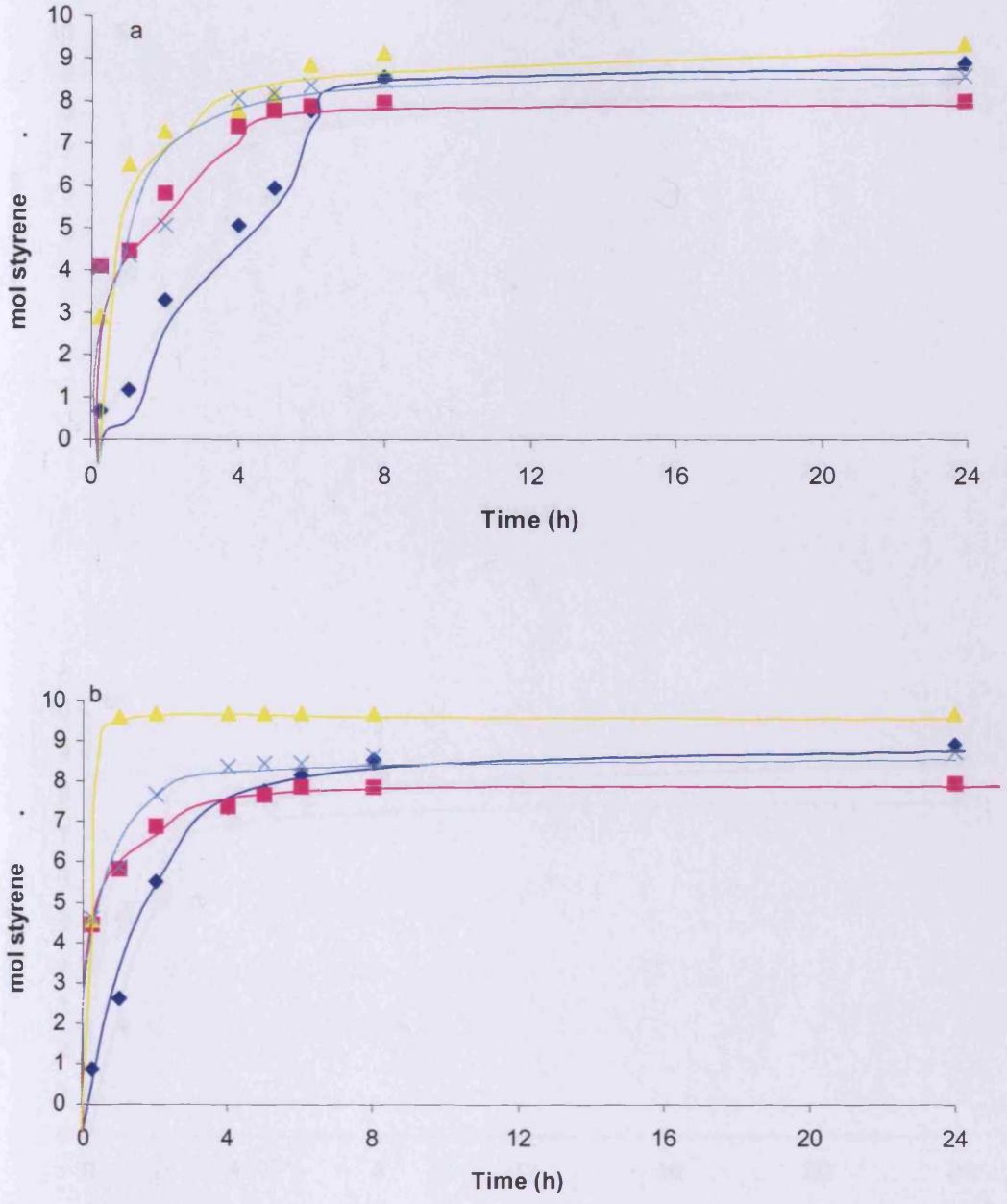

Figure 7: Effect of reaction time on the competitive aziridination of styrene and 2-chlorostyrene with bis(oxazoline), CH_3CN, 25^{0}C, PhI=NNS: total substrate = 1.5 mol ratio using (a) Cu-exchanged Zeolite Y, and (b) $Cu(OTf)_2$

Key aziridine yield: ◆ styrene only, ■ styrene reacted with 2-chlorostyrene; ▲ 2-chlorostyrene only; × 2-chlorostyrene reacted with styrene.

(Data for competitive reactions are doubled observed concentrations to permit direct comparison with single substrate reactions)

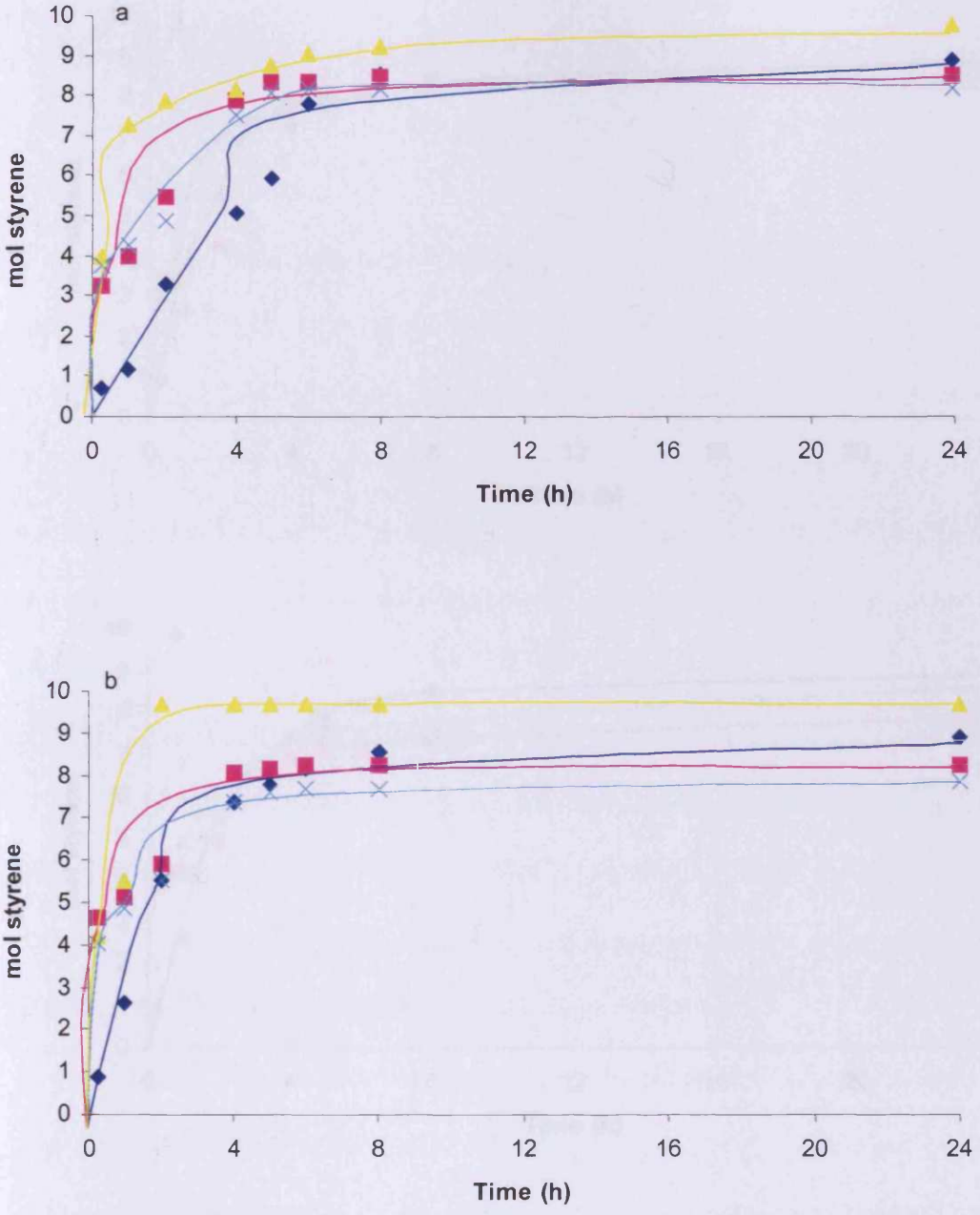

Figure 8: Effect of reaction time on the competitive aziridination of styrene and 3-chlorostyrene with bis(oxazoline), CH_3CN, 25^0C, PhI=NNS: total substrate = 1.5 mol ratio using (a) Cu-exchanged Zeolite Y, and (b) $Cu(OTf)_2$

Key aziridine yield: ◆ styrene only, ■ styrene reacted with 3-chlorostyrene; ▲ 3-chlorostyrene only; × 3-chlorostyrene reacted with styrene.

(Data for competitive reactions are doubled observed concentrations to permit direct comparison with single substrate reactions)

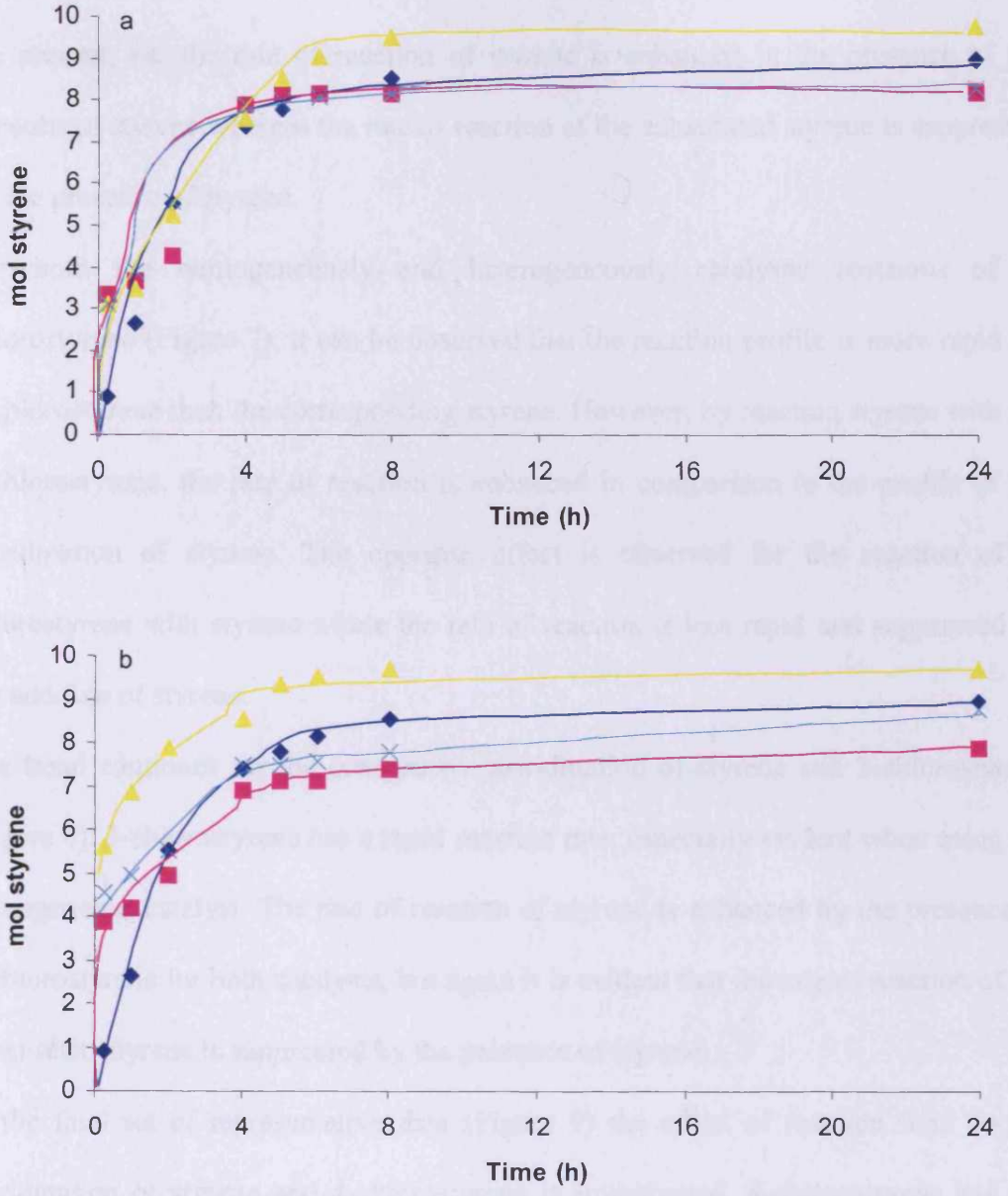

Figure 9: Effect of reaction time on the competitive aziridination of styrene and 4-chlorostyrene with bis(oxazoline), CH_3CN, 25^0C, PhI=NNS: total substrate = 1.5 mol ratio using (a) Cu-exchanged Zeolite Y, and (b) $Cu(OTf)_2$

Key aziridine yield: ◆ styrene only, ■ styrene reacted with 4-chlorostyrene; ▲ 4-chlorostyrene only; × 4-chlorostyrene reacted with styrene.

(Data for competitive reactions are doubled observed concentrations to permit direct comparison with single substrate reactions)

The results (Figures 7-9) show that the two substrates react at similar rates when both are present, i.e. the rate of reaction of styrene is enhanced in the presence of the substituted styrene whereas the rate of reaction of the substituted styrene is suppressed by the presence of styrene.

For both the homogeneously and heterogeneously catalysed reactions of 2-chlorostyrene (Figure 7), it can be observed that the reaction profile is more rapid for 2-chlorostyrene than the corresponding styrene. However, by reacting styrene with the 2-chlorostyrene, the rate of reaction is enhanced in comparison to the profile of the aziridination of styrene. The opposite effect is observed for the reaction of 2-chlorostyrene with styrene where the rate of reaction is less rapid and suppressed by the addition of styrene.

The trend continues for the competitive aziridination of styrene and 3-chlorostyrene (Figure 8). 3-chlorostyrene has a rapid reaction rate, especially evident when using the homogeneous catalyst. The rate of reaction of styrene is enhanced by the presence of 3-chlorostyrene for both catalysts, but again it is evident that the rate of reaction of the substituted styrene is suppressed by the presence of styrene.

In the final set of representative data (Figure 9) the effect of reaction time on the aziridination of styrene and 4-chlorostyrene is investigated. 4-chlorostyrene has the most rapid reaction profile corresponding to the previous figures. For both catalysts, however, the reaction rate of styrene is similar to that of the two substrates reacted together. The reaction rate of 4-chlorostyrene is suppressed by the presence of styrene, but in this case, the rate of reaction of styrene is not significantly enhanced in the presence of the substituted styrene.

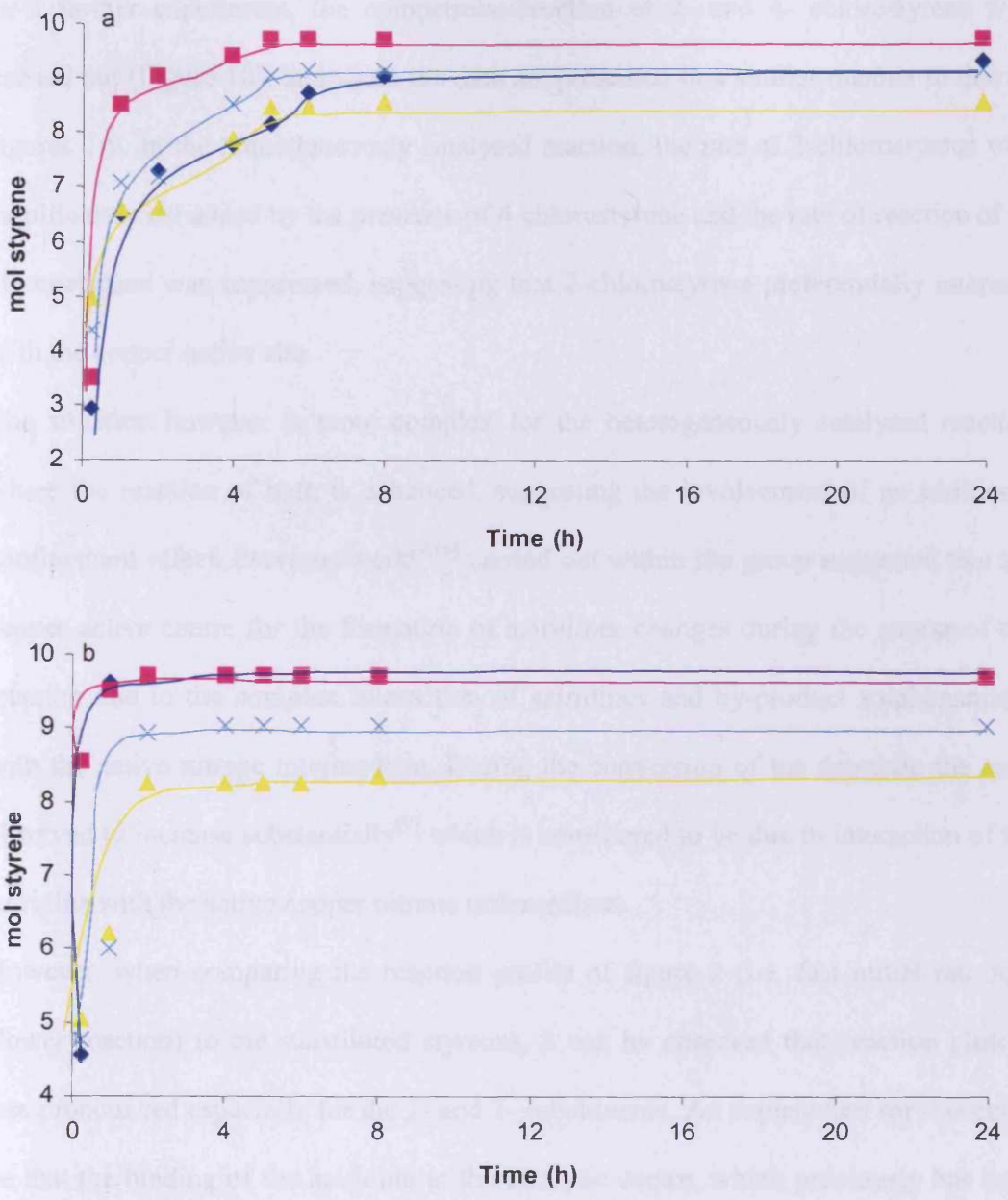

Figure 10: Effect of reaction time on the competitive aziridination of styrene and 4-chlorostyrene with bis(oxazoline), CH_3CN, 25^{0}C, PhI=NNS: total substrate = 1.5 mol ratio using (a) Cu-exchanged Zeolite Y, and (b) $Cu(OTf)_2$

Key aziridine yield: ◆ 2-chlorostyrene only; ▲ 4-chlorostyrene only; ■ 2-chlorostyrene reacted with 4-chlorostyrene; × 4-chlorostyrene reacted with 2-chlorostyrene.

(Data for competitive reactions are doubled observed concentrations to permit direct comparison with single substrate reactions)

In a further experiment, the competitive reaction of 2- and 4- chlorostyrene was carried out (Figure 10), and again the data are presented in a similar manner to that in figures 7-9. In the homogeneously catalysed reaction, the rate of 2-chlorostyrene was significantly enhanced by the presence of 4-chlorostyrene and the rate of reaction of 4-chlorostyrene was suppressed, suggesting that 2-chlorostyrene preferentially interacts with the copper active site.

The situation however is more complex for the heterogeneously catalysed reaction where the reaction of both is enhanced, suggesting the involvement of an additional confinement effect. Previous work[9,16] carried out within the group suggested that the copper active centre for the formation of aziridines changes during the course of the reaction due to the complex interaction of aziridines and by-product sulphonamides with the active nitrene intermediate. During the conversion of the substrate the ee is observed to increase substantially[9] which is considered to be due to interaction of the aziridine with the active copper nitrene intermediate.

However, when comparing the reaction profile of figure 2 (i.e. fast initial rate to a slower reaction) to the substituted styrenes, it can be observed that reaction plots is less pronounced especially for the 2- and 3- substituents. An explanation for this could be that the binding of the aziridine to the catalytic centre, which previously has been investigated in the group gives rise to the initial levelling off of the conversion/time curves[16] and is therefore weaker so that the catalyst is able to turn over more times on average before inhibition occurs. This does not seem an unreasonable explanation in terms of steric effects; as the substituent in the phenyl group is fairly well insulated from the nitrogen and should exert little polar effect on the Lewis basicity.

Therefore it must be considered that the data from the competitive experiments show that the interaction of the substrates with the active centre, as well as the products, have an important role to play in any model for the mechanism of this reaction.

3.7 Conclusions

In the catalysed aziridination of styrene derivatives using copper-bis(oxazoline) complexes with PhI=NNs, higher enantioselection can be achieved with the heterogeneously catalysed reaction when compared with the homogeneously catalysed reaction. This is evident with 2-, 3- and 4-chlorostyrene which all gave higher ee (ranging from 88-95%) using the heterogeneous catalyst when compared to the ee of homogeneous catalyst (83-93%). The effect is considered to be due mainly to the enhanced confinement of the substrate within the pores of the zeolite. This confinement effect also contributes to the increased stability of the heterogeneous catalyst for the reaction of styrene derivatives when compared with the reaction of styrene. The leaching of Cu^{2+} was decreased for the reaction of styrene derivatives; in some cases the leaching was almost eliminated, as observed for the reaction of 3- and 4-methyl and 3-bromostyrenes ($\geq 0.8\%$).

The structure of the styrene derivative has a marked effect on the rate of aziridination and by-product formation. This is evident especially with 4-chlorostyrene where particularly high yields (85-90%) and ee ($\geq 93\%$) are observed with both catalyst systems.

Competitive reactions in which styrene and a styrene derivative are reacted together reveal that the rate of styrene aziridination is enhanced by the presence of substituted

styrenes; this is evident for 2-, 3- and 4-chlorostyrene, whereas the rate of aziridination of the substituted styrene is suppressed by the presence of styrene. Further competitive experiments showed that the rate of aziridination is enhanced by reactions involving 2- and 4-chlorostyrene for both homogeneously and heterogeneously catalysed reactions where confinement effects play a role in enhancing the rate in the heterogeneous reaction.

3.8 References

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Chapter 4

Spectroscopic study of the catalytic asymmetric aziridination of styrene

4.0 Spectroscopic study of the catalytic asymmetric aziridination of styrene using Cu-bis(oxazoline) complexes

4.1 Introduction

The synthesis of pure enantiomers using catalytic processes continues to receive considerable research attention. The significant success achieved with homogeneous catalysts has been recognised with the recent award of the Nobel Prize for Chemistry to Sharpless, Noyori and Knowles[1]. The design and reactivity of asymmetric catalysts continues to provide a fruitful field of research given the importance of the availability of homochiral molecules for the production of pharmaceuticals and agrochemicals. Recently, attention has started to focus on the immobilisation of homogeneous catalysts[2] particularly using bis(oxazoline) ligands[3], which are known to be versatile chiral ligands[4], as this will improve the potential for the application of asymmetric catalysts in commercial processes.

Particularly high enantioselection of these saturated three membered heterocycles is crucial and can be achieved using homogeneous catalysts. Despite the importance of this reaction, details on the precise mechanism of the aziridination in the homogeneous reaction are not fully understood.

Recently, Gullick *et al.*[5] have shown that the ee increases with conversion for the aziridination reaction and that the reaction profile is sigmoid with an initial rapid formation of the aziridine that then slows prior to a subsequent rapid formation phase for both the homogeneously and heterogeneously catalysed reaction using copper-bis(oxazoline) catalysts.

In this study, C_2-symmetric Cu-bis(oxazoline) complexes were used to catalyse the aziridination of styrene using [N-(p-tosylsulfonyl)imino]phenyliodinane (PhI=NTs) as nitrene donor. The course of the reaction has been investigated by EPR and UV-Vis spectroscopy and has been supported by catalytic studies.

Electron Paramagnetic Resonance (EPR) spectroscopy is a technique used to detect and quantify paramagnetism (i.e. the presence of unpaired electrons) primarily in solids and liquids[6]. This technique has been applied to studies in heterogeneous catalysis for many years[7] to explore the nature of the active sites, identify reaction intermediates, follow the co-ordination and oxidation states of supported transition metal ions and understand electron transfer reactions important in catalysis.

In the specific case of metal-doped zeolites, EPR spectroscopy has been widely used for many years to study the bonding, co-ordination and location of copper ions[8] and copper complexes[9] inside the pores of the zeolites.

Together with EPR spectroscopy these experimental techniques reveal how the chirality around the formed Cu-bis(oxazoline) complex is crucial for the overall enantioselectivity and yield of the aziridination reaction and aids in providing an understanding of the reaction profiles and reaction mechanism of the aziridination of styrene.

4.2 Reaction of styrene

A study was carried out where, the aziridination of styrene was investigated using PhI=NTs as nitrene donor with copper (I) and (II) triflate modified by (*S,S*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) **1** with MeOH as solvent. The ratio of copper triflate: chiral modifier was investigated over a range and the results are shown in Table 1 and Table 2 following reaction for 12h.

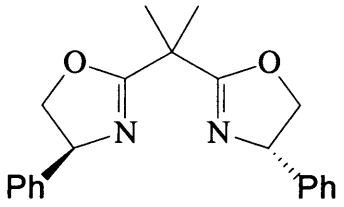

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Table 1: Homogeneous aziridination of styrene[a]

	Cu(OTf)			$Cu(OTf)_2$		
Ratio[b]	Yield (%)	ee. (%)	Solvent	Yield (%)	ee. (%)	Solvent
1:1	34	28	MeOH	57	30	MeOH
1:2	38	31	MeOH	61	33	MeOH
1:3	37	29	MeOH	51	31	MeOH
1:4	36	30	MeOH	54	32	MeOH
1:5	34	27	MeOH	57	28	MeOH

[a] Reaction conditions: bis(oxazoline) **1** (7 mol %), MeOH (5 ml), 25°C, PhI=NTs: styrene (111 µl) = 1.5 mol ratio, 12 h reaction time, catalyst: Cu(OTf) (15 mol %); $Cu(OTf)_2$ (15 mol %).

[b]Cu: bis(oxazoline) ratio

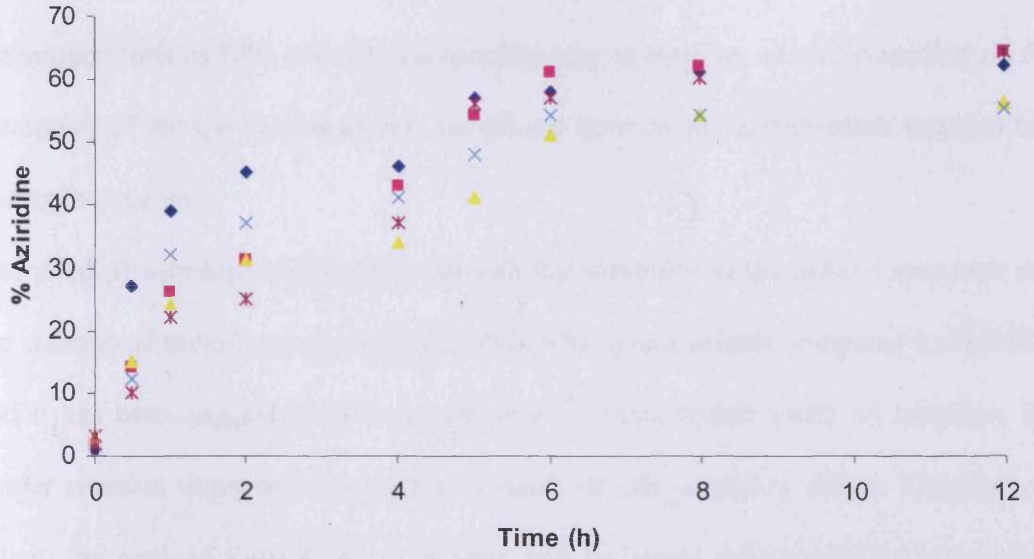


Figure 1: Effect of reaction time on the aziridination of styrene with bis(oxazoline) **1**, $Cu(OTf)_2$, MeOH, 25 ^{0}C, PhI=NTs: styrene = 1.5 mol ratio using (a) 1Cu: 1bis(ox), (b) 1Cu: 2bis(ox), (c) 1Cu: 3bis (ox), (d) 1Cu: 4bis(ox) and (e) 1Cu: 5bis(ox)

Key ◆ aziridine yield; 1Cu: 1bis(ox); ■ aziridine yield; 1Cu: 2bis(ox); ▲ aziridine yield; 1Cu: 3bis(ox), × aziridine yield; 1Cu: 4bis(ox) and ✱ aziridine yield; 1Cu: 5bis(ox).

For these homogeneously catalysed reactions the conversion is often followed by the dissolution of the nitrene donor[10]. PhI=NTs, like its oxygen analogue PhI=O, is insoluble in a variety of solvents, including MeCN, and the course of the reaction may be followed by the dissolution of this reagent. However, when methanol is used as solvent the PhI=NTs nitrene donor is soluble and consequently there are no complications caused by the dissolution of the nitrene donor during the initial reaction phase. Both Cu(I) and Cu(II) complexes have been investigated and their results reported above (Table 1). In methanol, although the yield of aziridine is maintained the enantioselection is lower than that observed with solvents in which the nitrene donor dissolves slowly over a period of hours. The ee obtained with methanol is still significant and therefore this wholly homogeneous reaction system has been used as a

model to base a detailed mechanistic study in conjunction with experimental techniques such as EPR and UV-vis spectroscopy to develop an understanding on the formation of the Cu-bis(oxazoline) complexes prior to the aziridination reaction and during the course.

The yield of aziridine is dependent on both the solubility of the nitrene precursor and the stability of the nitrene intermediate. PhI=NNs is less soluble compared to PhI=NTs and it has been suggested by Sodergen *et al.*[11], that higher yields of aziridine, but longer reaction times are observed as a result of this solubility effect. Therefore, in effect, the ratio of Cu(nitrene) to styrene will be lower, which will lead to a more selective use of the nitrene intermediate to form the aziridine rather than breakdown to form the corresponding sulphonamide. This solubility effect is increased in the heterogeneously catalysed reaction by diffusion limitations. For PhI=NNs the formation of the Cu(nitrene) intermediate will be slower than that of PhI=NTs as a result of both the solubility effect and additional diffusion through the zeolite framework.

Increasing the Cu: bis(oxazoline) ratio (Table 1) for the homogeneously catalysed reaction using Cu(I) and Cu(II) did not significantly effect the yield or ee in the reaction. Using both Cu(I) and Cu(II) the final yield of aziridine (34%) and (57%) respectively did not change over a range of ratios varying from 1: 1 to 1: 5. The ee was also similar in both cases, reaching a maximum at a Cu: bis(oxazoline) ratio of 1: 2, (31%) for Cu(I) and (33%) for Cu(II).

Samples (80μl) were taken during the course of all the homogeneously catalysed reactions and EPR spectra were recorded. These experiments were carried out by Murphy *et al.* in Cardiff, therefore corresponding with the catalytic analysis and data recorded. The results of which will be discussed in a later section (4.4).

Table 2: Homogeneous aziridination of styrene[a]

	Cu(OTf)			$Cu(OTf)_2$		
Ratio[b]	Yield (%)	ee. (%)	Solvent	Yield (%)	ee. (%)	Solvent
1:0.09	12	---	MeOH	17	---	MeOH
1:0.24	18	---	MeOH	22	---	MeOH
1:0.46	19	---	MeOH	24	---	MeOH
1:0.87	22	19	MeOH	25	17	MeOH
1:1	34	28	MeOH	32	30	MeOH
2:1	32	26	MeOH	33	24	MeOH

[a] Reaction conditions: bis(oxazoline) **1** (7 mol %), MeOH (5 ml), 25°C, PhI=NTs: styrene (111µl) = 1.5 mol ratio, 12 h reaction time, catalyst: Cu(OTf) (15 mol %); $Cu(OTf)_2$ (15 mol %).

[b]Cu: bis(oxazoline) ratio

From Tables 1 and 2 it can be observed that Cu(I) and Cu(II) complexes produce similar results. Enantioselectivity values were not obtained for Cu: bis(oxazoline) ratios ≥1: 0.46 (Table 2) as not enough aziridine was isolated for analysis. By increasing the molar ratio the ee is no longer suppressed and results are recorded at 1: 0.87, where Cu(I) and Cu(II) have ee values of (19%) and (17%) respectively. However, compared with yields of ≥ 80% aziridine in MeCN, the yields were 34% and 32% using both catalysts respectively. An initial rapid formation of aziridine was observed (Figure 1), followed by a period of relatively slow reaction, before once again observing a relative reaction profile. This can also be seen at a Cu: bis(oxazoline) ratio of 2: 1 (Figure 2). This indicates that there may be a two-stage process. First, there is a rapid, initial reaction leading to the formation of aziridine and by-products. The product and by-products subsequently interact with the copper active centre and modify the course of the reaction. During this second period the ee is enhanced[12] due to the complex interactions occurring at the active centre. Although,

in the case of methanol the enhancement in ee is quite small, the effect can still be observed (Figures 1 and 2). This is a central feature for both homogeneous and heterogeneous catalysed reactions.

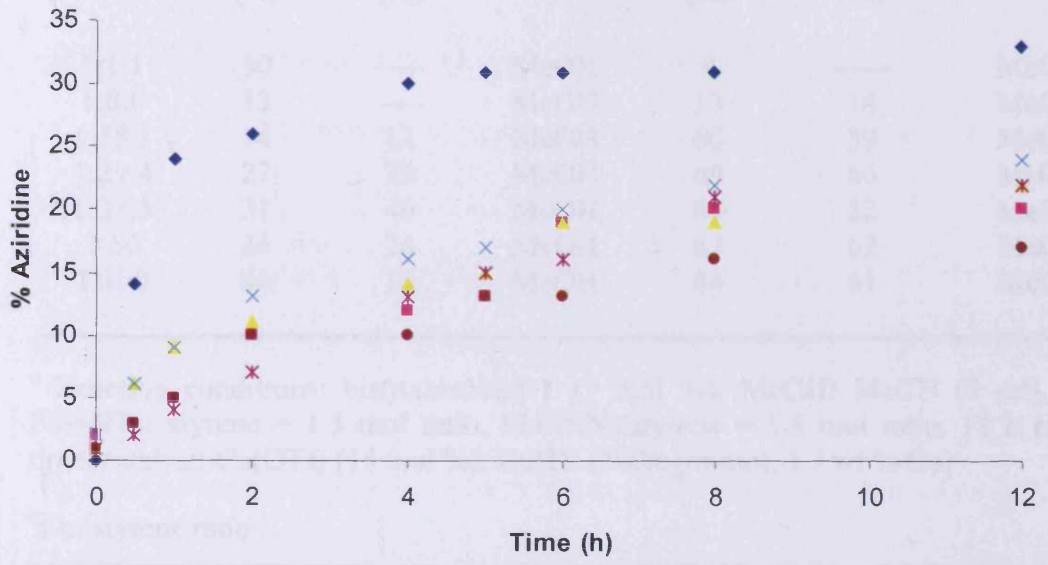


Figure 2: Effect of reaction time on the aziridination of styrene with bis(oxazoline) **1**, $Cu(OTf)_2$ MeOH, 25 ^{0}C, PhI=NTS: styrene = 1.5 mol ratio using (a) 2Cu: 1bis(ox), (b) 1Cu: 1bis(ox), (c) 1Cu: 0.87 bis (ox), (d) 1Cu: 0.46 bis(ox), (e) 1Cu: 0.24bis(ox) and (f) 1Cu:0.09bis(ox).

Key ◆ aziridine yield 2Cu: 1bis(ox); ■ aziridine yield 1Cu: 1bis(ox); ▲ aziridine yield 1Cu: 0.87 bis (ox), × aziridine yield 1Cu: 0.46 bis(ox), ✱ aziridine yield 1Cu: 0.24bis(ox), ● aziridine yield; 1Cu:0.09bis(ox).

Both Cu(I) and Cu(II) complexes produce very similar results. Varying the Cu: bis(oxazoline) ratio in the homogeneously catalysed reaction does not significantly affect the ee or final yield of the corresponding aziridine. Cu(II) affords higher yields than Cu(I) as the molar ratio is increased reaching a maximum at 1: 2 (61%). However the ee results are almost identical. This is also observed as the molar ratio is decreased (Table 2) suggesting that changing the Cu: bis(oxazoline) ratio does not enhance the yield of aziridine or ee for both catalysts tested.

Table 3: Homogeneous and heterogeneous aziridination of styrene[a]

	$Cu(OTf)_2$			CuHY		
Ratio[b]	Yield (%)	ee. (%)	Solvent	Yield (%)	ee. (%)	Solvent
1:1.1	10	-----	MeOH	9	------	MeCN
1:8.0	13	-----	MeOH	13	14	MeCN
1:15.1	14	12	MeOH	60	39	MeCN
1:29.4	27	29	MeOH	69	66	MeCN
1:37.5	31	46	MeOH	84	82	MeCN
1:50	34	24	MeOH	83	62	MeCN
1:100	44	16	MeOH	84	51	MeCN

[a] Reaction conditions: bis(oxazoline) **1** (7 mol %), MeOH/ MeCN (5 ml), 25°C, PhI=NTs: styrene = 1.5 mol ratio, PhI=NNs:styrene = 1.5 mol ratio, 12 h reaction time, catalyst: Cu(OTf) (15 mol %); CuHY (300mg/mmol, 3.7 wt % Cu)

[b]Cu: styrene ratio

Homogeneously and heterogeneously catalysed reactions were carried out using $Cu(OTf)_2$ and CuHY as catalysts with MeOH and MeCN as solvent and the representative data recorded (Table 3). The ratio of Cu: styrene was examined with both larger and smaller aliquots of styrene used compared to the standard reaction (1: 37.5). Evans *et al*[10] have shown that, with Cu(I) and Cu(II) complexes, acetonitrile is the optimal solvent for the aziridination of styrene. Further evidence of this point can be seen (Table 3) where the highest yield of aziridine formed (84%) was obtained using CuHY as catalyst and MeCN as solvent at the standard Cu: styrene ratio (1: 37.5). EPR spectra were recorded for all reactions carried out for comparison with the catalytic data achieved. However, by increasing the Cu: styrene ratio only, the yield of the corresponding aziridine was increased for the homogeneously catalysed reaction. At low levels of Cu: styrene (1: 1.1) aziridine afforded was only (10%).

However as the ratio of styrene was increased the aziridine formed was seen to increase also, (44%) at 1: 100. Although, this was seen to have a marked effect on the ee, as the Cu: styrene ratio was enhanced the ee levels were lowered, (16%) at 1: 100. The highest ee value obtained (46%) was at the standard reaction ratio of 1: 37.5 and afforded aziridine (31%) yield. At the lower Cu: styrene ratios (i.e. 1: 1.1 and 1: 8.0) ee values were unobtainable as the amount of aziridine formed was too small to be isolated.

Heterogeneous reactions were carried out using CuHY as catalyst and MeCN as solvent to compare with the homogeneous system. A similar pattern of results for the homogeneous system was also seen in the heterogeneous system (Table 3). The highest yield of aziridine (84%) was obtained at the highest Cu: styrene ratio (1: 100), this value of aziridine was also recorded at the standard Cu: styrene molar ratio (1: 37.5) for this reaction. Low levels of aziridine ($\leq$13%) were afforded at molar ratios ($\leq$1: 8.0). As in the homogeneous system the highest ee value recorded (82%) was at the standard molar ratio (1: 37.5) for this heterogeneous reaction. By increasing the molar ratio of styrene a decrease in ee values was noticed. At the highest molar ratio tested (1: 100) the ee had decreased to (51%). However, this ee value (51%) was still higher than any ee value recorded in the homogeneously catalysed reaction and including all the Cu: styrene ratios tested.

The above results (Table 3) have shown that soluble Cu(I) and Cu(II) complexes are efficient catalysts for styrene aziridination using PhI=NTs and MeOH or MeCN as solvent. However, solvent optimisation is a crucial factor and contributes significantly to both yield improvement and rate acceleration, and the polar aprotic solvent MeCN appears to be optimal choice for these reactions.

4.3 Effect of reaction time on aziridine yield

The effect of the reaction time on the conversion of styrene and the yield of aziridine was investigated for the homogeneously catalysed reaction using methanol as solvent and representative data are given in Figure 3. A sigmoid reaction profile for aziridine yield is clearly observed with this solvent and can also be seen when MeCN was used as solvent (Figure 4). We have previously observed this in the heterogeneously catalysed reaction[12] where the active site within the supercage of the zeolite is highly confined.

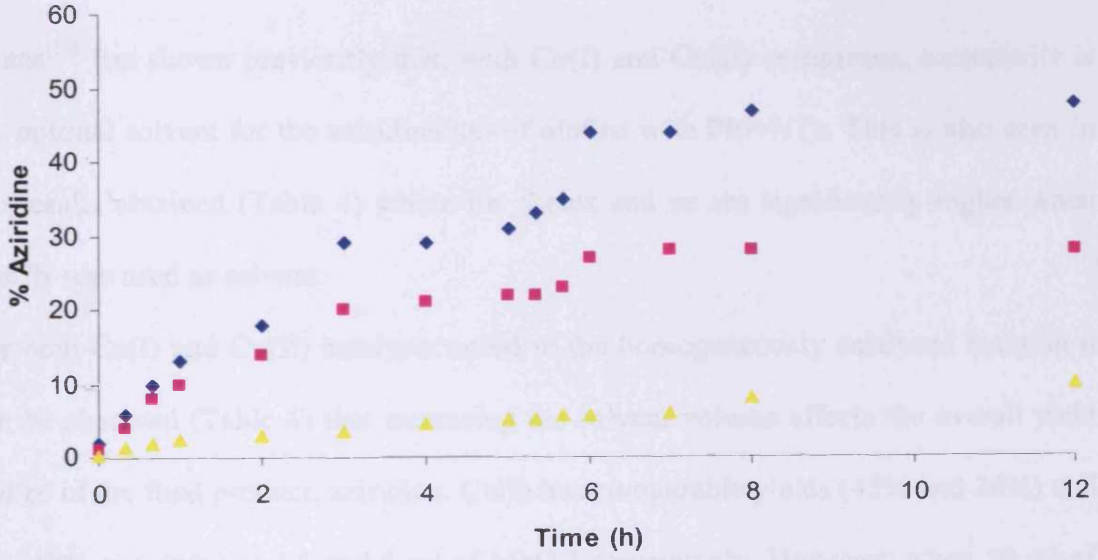


Figure 3: Effect of reaction time on the aziridination of styrene with bis(oxazoline) **1**, $Cu(OTf)_2$, MeOH, 25 ^{0}C, PhI=NTS:styrene = 1.5 mol ratio using (a) 2.5 ml MeOH, (b) 5 ml MeOH and (c) 10 ml MeOH

Key ◆ aziridine yield 2.5 ml; ■ aziridine yield 5 ml; ▲ aziridine yield 10 ml

Table 4: Homogeneous aziridination of styrene[a]

	Cu(OTf)			$Cu(OTf)_2$		
Volume (ml)	Yield (%)	ee. (%)	Solvent	Yield (%)	ee. (%)	Solvent
2.5	43	42	MeOH	44	48	MeOH
5	36	46	MeOH	28	55	MeOH
10	12	36	MeOH	11	33	MeOH
2.5	78	85	MeCN	90	79	MeCN
5	86	87	MeCN	96	81	MeCN
10	76	75	MeCN	78	74	MeCN

[a] Reaction conditions: bis(oxazoline) **1** (7 mol %), MeOH, MeCN, 25°C, PhI=NTs: styrene = 1.5 mol ratio, 12 h reaction time, catalyst: Cu(OTf) (15 mol % Cu); $Cu(OTf)_2$ (15 mol %).

Evans[10] has shown previously that, with Cu(I) and Cu(II) complexes, acetonitrile is the optimal solvent for the aziridination of olefins with PhI=NTs. This is also seen in the results obtained (Table 4) where the yields and ee are significantly higher when MeCN was used as solvent.

For both Cu(I) and Cu(II) catalysts tested in the homogeneously catalysed reaction it can be observed (Table 4) that increasing the solvent volume affects the overall yield and ee of the final product, aziridine. Cu(I) has comparable yields (43% and 36%) and ees (42% and 46%) at 2.5 and 5 ml of MeOH respectively. However, when 10 ml of MeOH was used in the reaction the system was saturated with solvent and only afforded low yield (12%) but a consistent ee (36%). Similar results were noted for Cu(II) using MeOH as solvent. Higher levels of aziridine were recorded (44% and 28%) using 2.5 and 5 ml of MeOH respectively than 10 ml, which afforded (11%) aziridine. The ee value decreased at higher volumes of solvent. An ee (33%) was

recorded at 10 ml of solvent, however when using 5 and 2.5 ml of MeOH the ee was significantly enhanced (55% and 48%) respectively.

This maybe explained in terms of a distribution equilibrium for solutes between a bulk solution phase and a pore phase; as the volume of MeOH increases, less reactants will be in the pores where catalysis occurs. This will therefore affect the overall yield and ee of the aziridine product (Table 4) resulting in lower yields and ees as the volume of MeOH increases.

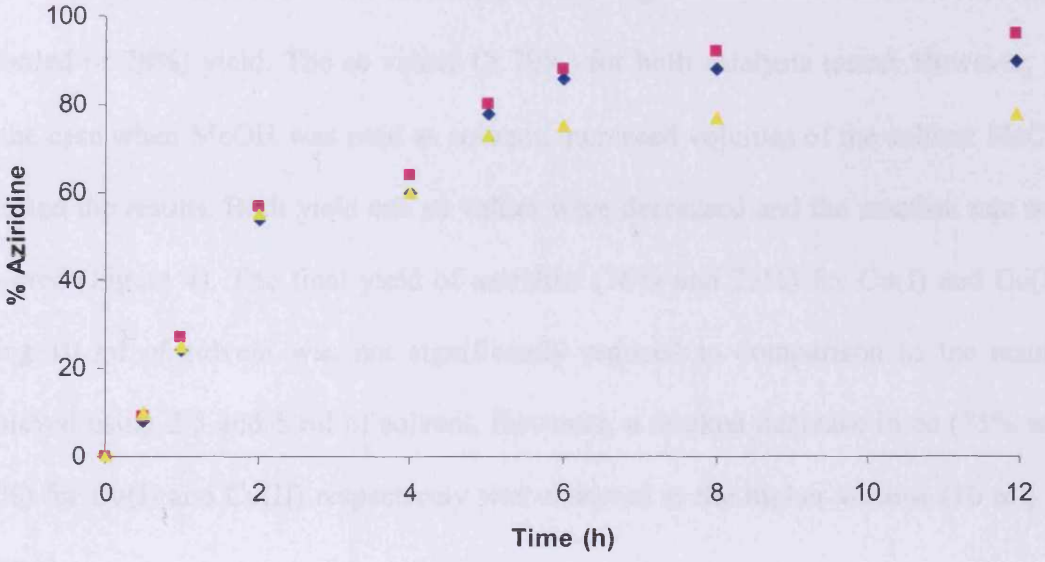


Figure 4: Effect of reaction time on the aziridination of styrene with bis(oxazoline) **1**, $Cu(OTf)_2$, MeCN, 25 ^{0}C, PhI=NTs: styrene = 1.5 mol ratio using (a) 2.5 ml CH_3CN, (b) 5 ml CH_3CN and (c) 10 ml CH_3CN

Key ◆ aziridine yield 2.5 ml; ■ aziridine yield 5 ml; ▲ aziridine yield 10 ml

The reaction rates and yields were enhanced in a polar aprotic solvent, MeCN. Representative data (Figure 4) illustrate this enhanced reaction rate. An interesting observation with these reaction time studies concerns the nature of the reaction profile for the aziridine yield. This profile is also apparent for CuHY reaction and will be discussed in detail in a later section. From the results (Table 4) it can be observed that the reaction is optimised at 5 ml of solvent for both yield and ee of aziridine. This applies to both catalysts investigated. Aziridine yields (86% and 96%) were recorded for Cu(I) and Cu(II) respectively using 5 ml of MeCN. High ee values (≥ 81%) were also noted. Similar results were recorded when using 2.5 ml of solvent, aziridine was afforded (≥ 78%) yield. The ee values (≥ 79%) for both catalysts tested. However, as in the case when MeOH was used as solvent, increased volumes of the solvent MeCN affected the results. Both yield and ee values were decreased and the reaction rate was lowered (Figure 4). The final yield of aziridine (76% and 78%) for Cu(I) and Cu(II) using 10 ml of solvent was not significantly reduced in comparison to the results achieved using 2.5 and 5 ml of solvent. However, a marked decrease in ee (75% and 74%) for Cu(I) and Cu(II) respectively was observed at the higher volume (10 ml) of solvent.

In the presence of bis(oxazoline), variation in both yields of aziridine and enantioselectivity was observed in the different solvents tested. The homogeneous catalyst $Cu(OTf)_2$ was observed to give higher yields of aziridine for PhI=NTs as nitrene donor compared to Cu(I). Methanol and acetonitrile, both of which are coordinating solvents, afforded enantioselectivities (≥ 46%) when using 5 ml of solvent. The results clearly demonstrate that the product yields and enantioselectivity for both the homogeneous and heterogeneous systems are strongly dependent on the choice of solvent and catalyst in the presence of the different solvents.

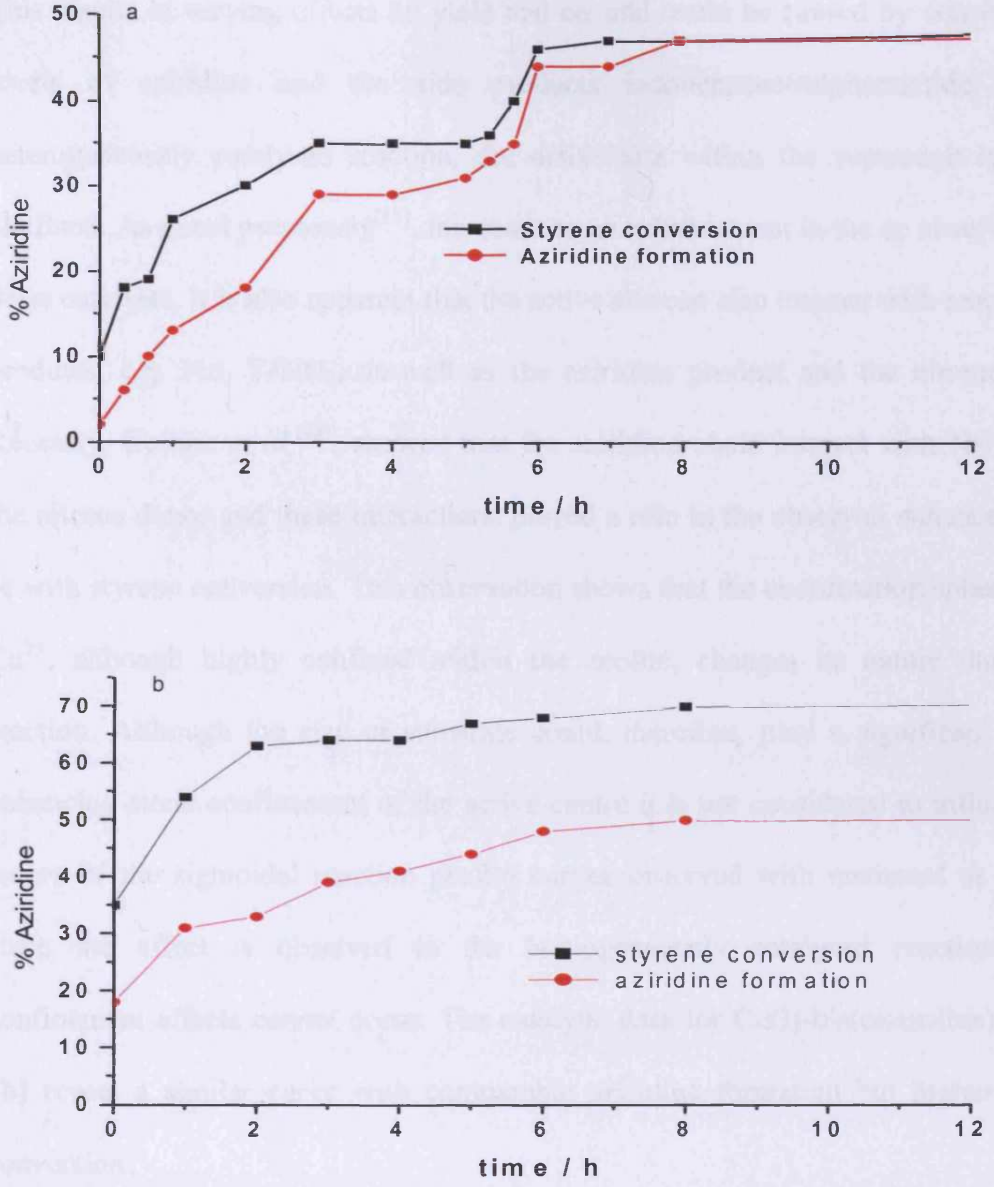


Figure 5: Homogeneous aziridination reaction of styrene in Methanol using Cu(II)-(a) and Cu(I)-(bis(oxazoline) catalyst (b), showing aziridine yields and styrene conversion

The catalytic data for Cu(II)-bis(oxazoline) (Figure 5a) show an evident "*S*" shaped curve. The form of the conversion/time curve indicates a two-stage process for the consumption of the alkene: (i) a primary phase related by the initial ratio of catalyst to alkene and which is completed after one hour and (ii) a secondary phase, which starts slowly but then accelerates before slowing down as the reaction reaches completion.

This results in varying effects on yield and ee, and could be caused by concentration levels of aziridine and the side products iodobenzene/sulphonamide. In the heterogeneously catalysed reaction, the active site within the supercage is highly confined. As noted previously[13], this leads to an enhancement in the ee observed with these catalysts. It is also apparent that the active site can also interact with reaction by-products, e.g. PhI, $TsNH_2$, as well as the aziridine product and the nitrene donor. Recently, Gullick *et al.*[12], showed that the aziridine could interact with $NsNH_2$ and the nitrene donor and these interactions played a role in the observed enhancement in ee with styrene conversion. This observation shows that the coordination sphere of the Cu^{2+}, although highly confined within the zeolite, changes its nature during the reaction. Although the size of substrate could, therefore, play a significant role by enhancing steric confinement of the active centre it is not considered to influence the nature of the sigmoidal reaction profile curves observed with methanol as solvent, since the effect is observed in the homogeneously catalysed reactions when confinement effects cannot occur. The catalytic data for Cu(I)-bis(oxazoline) (Figure 5b) reveal a similar curve with comparable aziridine formation but higher styrene conversion.

The mechanism of aziridination catalysed by copper cations is a very complex process and has yet to be fully elucidated. Previous studies[15,16] have suggested the possible co-existence of two mechanisms, involving singlet and triplet nitrene intermediates. However, free nitrenes and carbenes, unless stabilised by conjugation with lone pair electrons, are exceedingly reactive, with a lifetime of microseconds. Their formation would be expected to be rate limiting, so therefore no dependence on rate of alkene concentration. However, in terms of the oxidation state of the active metal species, there is still some doubt. The work carried out by Evans *et al*[10] would suggest that a

common oxidation state is reached in both cases. The introduction of a bis(oxazoline) as the chiral ligand affords the same level of asymmetric induction with Cu(OTf) and $Cu(OTf)_2$. Evans concluded that the active catalyst is in a +2 oxidation state and that the nitrogen source, PhI=NTs, can act as an oxidant for Cu(I). Li *et al.*[14] have suggested that a Cu(III)-nitrene species to be the reactive intermediate in the Cu(I)/ Cu(III) cycle. This idea is further investigated in a later section.

4.4 EPR Results

The formation of the copper-bis(oxazoline) complex was followed by EPR spectroscopy during the reaction. An initial pseudo-octahedral Cu species (**Species A**, Table 5) is found in neat Cu(II)-triflate/methanol solution. When the chiral modifier (i.e., the bis-oxazoline ligand) was systematically added to the solution, the EPR spectrum changed to a signal characteristic of a tetragonal pyramid [17,18] (**Species B**, Table 5). At a Cu – bis(oxazoline) ratio of around 1:1 all Cu^{2+} ions have been coordinated with one ligand (Figure 6). Further increase of the ratio resulted in an extra set of EPR peaks (**Species C**, Table 5) assigned to two coordinated bis(oxazoline) molecules.

Table 5: EPR values of detected species

Species	g_z	g_x	g_y	A_z/G	$A_{x,y}$/G
A	2.435	2.105	2.075	105	6
B	2.32	2.065	2.065	152	6
C	2.258	2.065	2.080	150	6

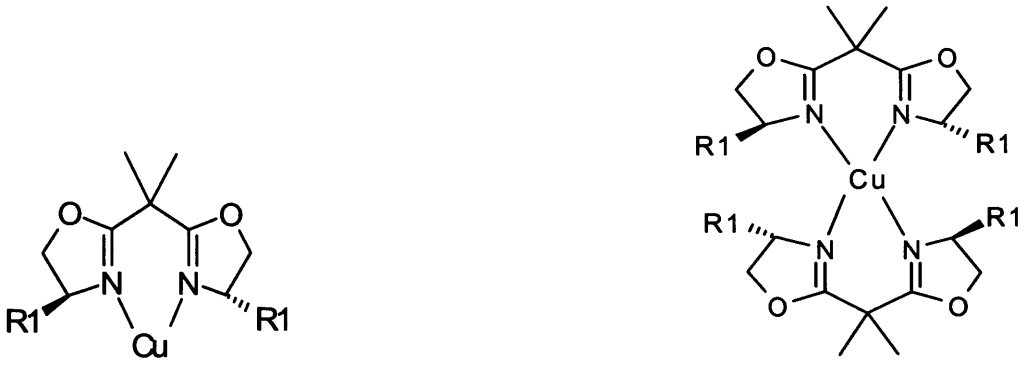
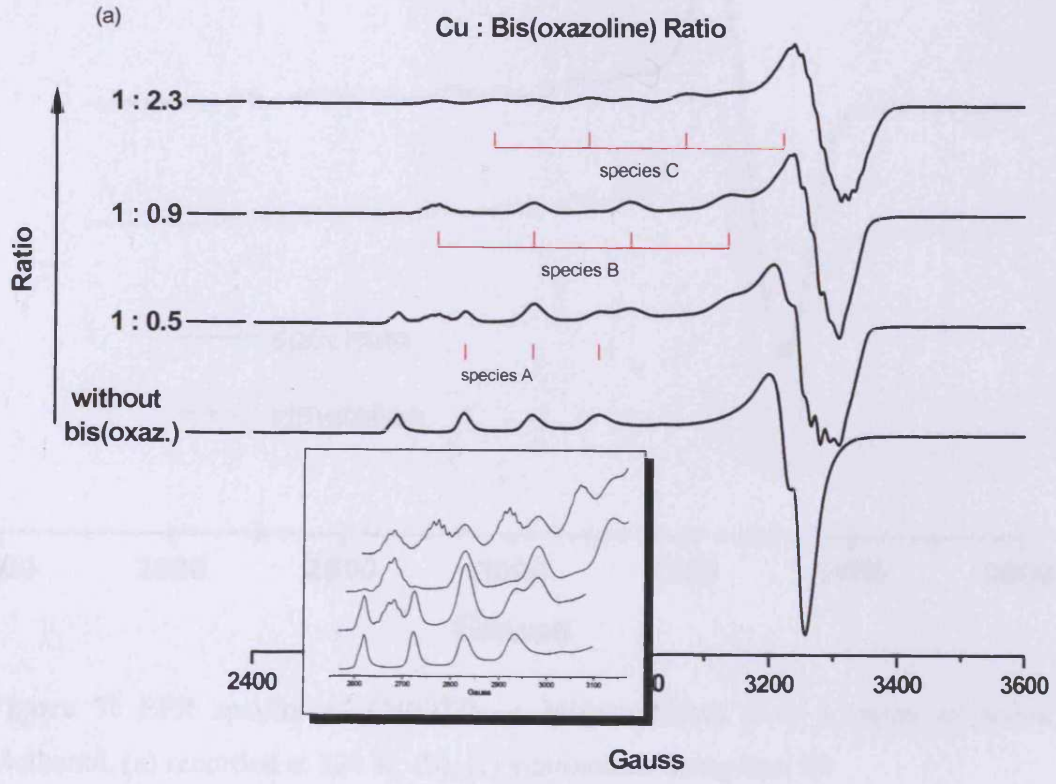
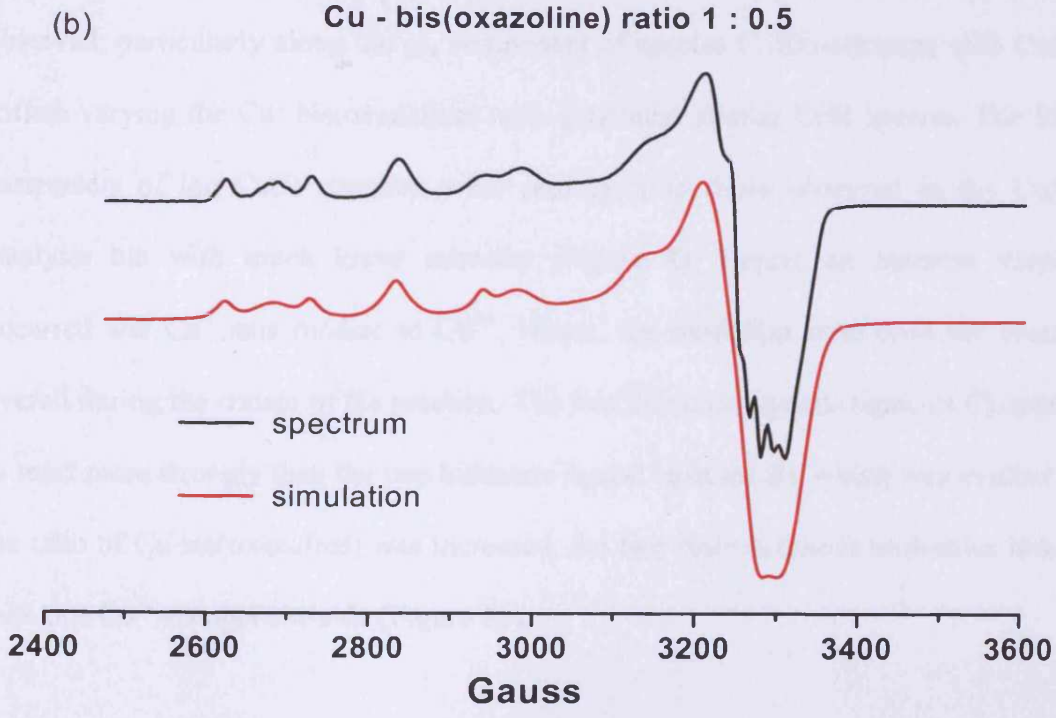


Figure 6: Sketch of Cu catalyst; (a) one bidentate bis(oxazoline) molecule is attached metal centre (Species B), (b) two bidentate ligands are attached (Species C)

Starting from the copper salt in methanol with pseudo-octahedral coordination (species A, Table 5), adding the chiral modifier leads to formation of the copper bis(oxazoline) complex. The formation of the copper-bis(oxazoline) complex was followed by EPR spectroscopy before and after the catalytic reaction. The EPR spectra showed two different sets of peaks, one related to pseudo-octahedral coordinated Cu and one pseudo-square planar due to the bidentate chiral modifier (species B, Table 5). As the ratio of bis(oxazoline)-Cu increased up to 1:1, only the pseudo-square planar copper bis(oxazoline) complexes were visible, hence, all Cu^{2+} ions have been coordinated with one ligand (Figure 6a). Further increase of the ratio resulted in an extra set of EPR peaks (species C, Table 5). These are related to two bis(oxazoline) molecules linked with one Cu^{2+} on opposite side (Figure 6b).


(a)
Cu : Bis(oxazoline) Ratio
1 : 2.3
species C
1 : 0.9
species B
1 : 0.5
species A
without bis(oxaz.)
Ratio
2400
3200
3400
3600
Gauss


(b)
Cu - bis(oxazoline) ratio 1 : 0.5
spectrum
simulation
2400
2600
2800
3000
3200
3400
3600
Gauss

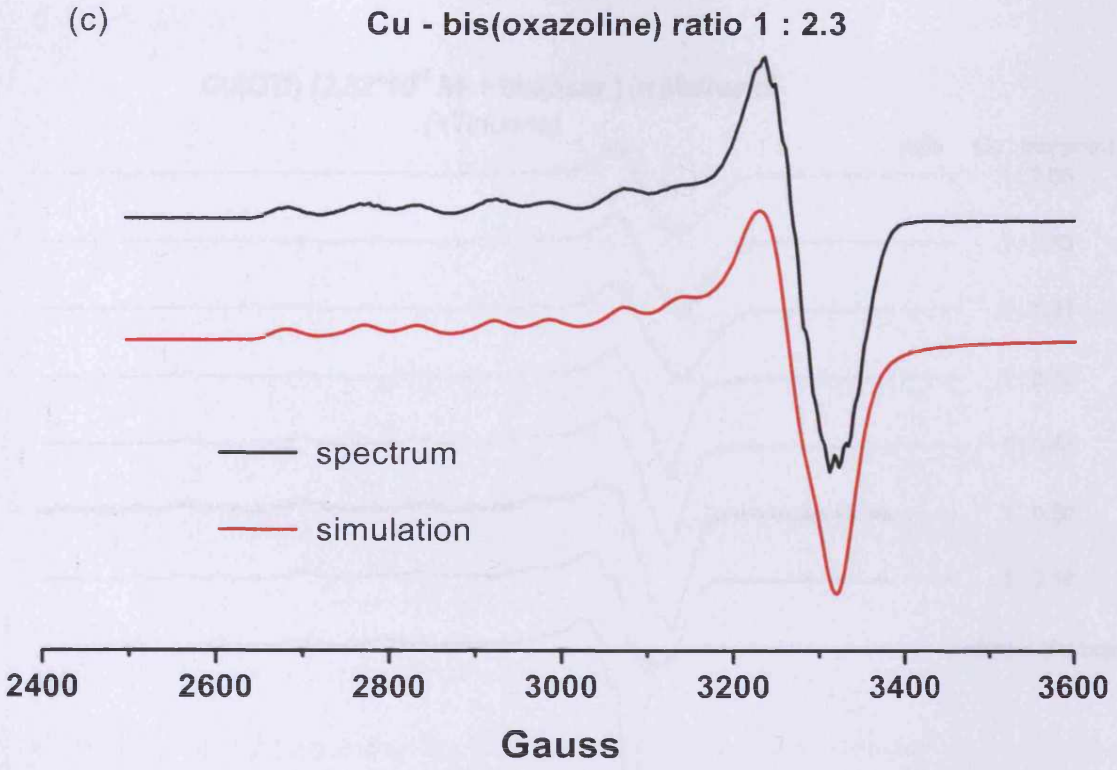


Figure 7: EPR spectra of $Cu(OTf)_2$ + bis(oxazoline) over a range of ratios in Methanol, (a) recorded at 120 K; (b), (c) simulations using Sim 32.

A well-resolved hyperfine structure, due to the interaction with the N – atoms, is observed; particularly along the g_{zz} component of species C. Experiments with Cu(I)-triflate varying the Cu: bis(oxazoline) ratio generated similar EPR spectra. The EPR parameters of the Cu(I) complex were analogous to those observed in the Cu(II) catalysts but with much lower intensity (Figure 8). Hence, an electron transfer occurred and Cu^{+} ions oxidise to Cu^{2+}. Hence, the oxidation state does not change overall during the course of the reaction. The two bidentate ligands (species C) appear to react more strongly than the one bidentate ligand (species B), which was evident as the ratio of Cu-bis(oxazoline) was increased, the two bis(oxazoline) molecules linked with one Cu^{2+} on opposite side (Figure 6b).

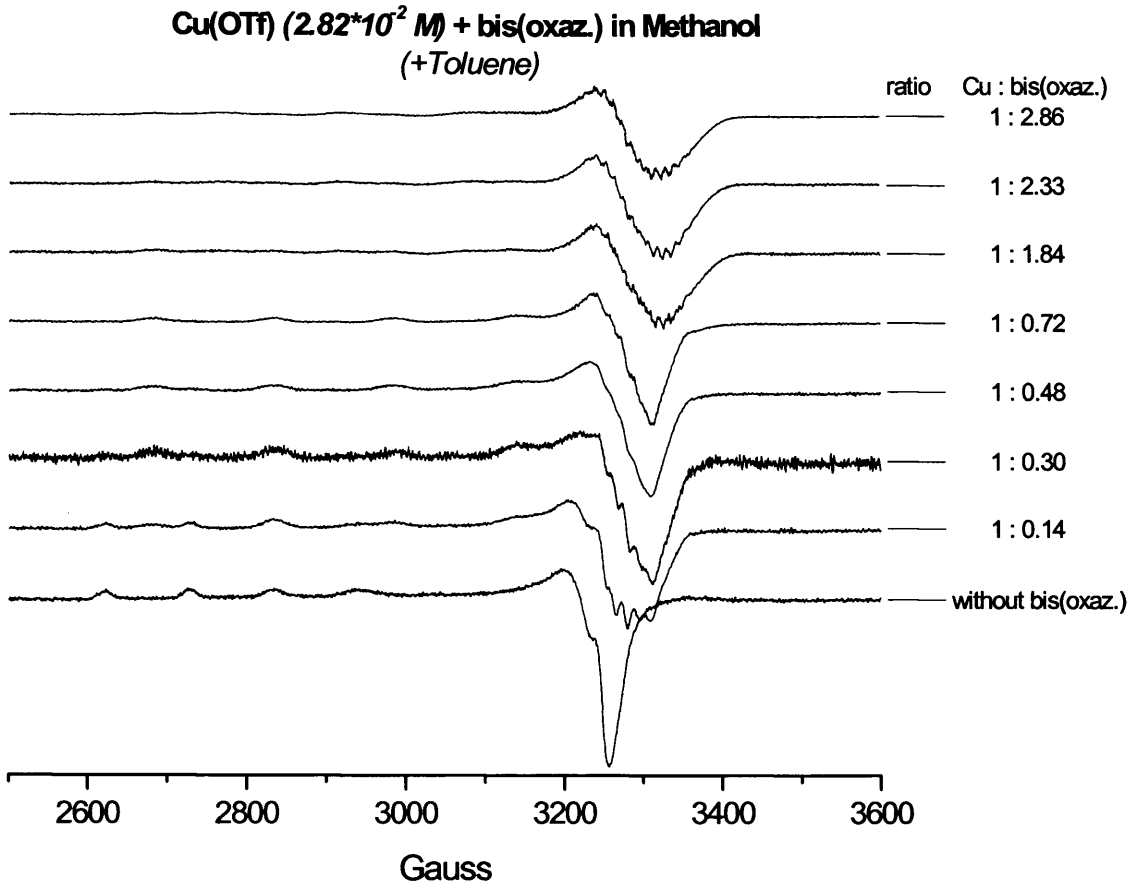


Figure 8: EPR spectra of Cu(OTf) + bis(oxazoline) over a range of ratios in Methanol

In the heterogeneous reaction, attempts have been previously made to eludicate the oxidation of the active copper catalyst by using EPR spectroscopy. Traa *et al.*[18] observed the depletion of the Cu(II) signal on addition of PhI=NTs with the bis(oxazoline). However, EPR spectroscopy is insensitive to either copper (I) or copper (III) species and therefore they were unable to comment on the mechanism further.

In order to explore the changes to the co-ordination and oxidation state of the Cu(II) ions, the EPR spectra were measured after various substrates, including PhI=NTs and styrene, had been added to the $Cu(OTf)_2$ catalyst in methanol containing the bis(oxazoline) ligand (Section 4.6).

4.5 UV Results

In the case of Cu(I)-triflate the metal centred d-d band in the UV-Vis spectrum shifts during the formation of the copper-bis(oxazoline) complex from 722.9 to 635.8 nm (Figure 9a). The different peaks are due to different coordination sites of the copper complex, e.g. the maximum of 722.9 nm is related to neat Cu salt and of 636 nm is related to a pure Cu-bis(oxazoline) complex. Here, a Cu(I) – bis(oxazoline) ratio of 1: 2.9 was used. Varying again the Cu – bis(oxazoline) ratio did not generate a two-peak signal, one for the remaining Cu salt and one for the Cu complex (Figure 9a). Although it is known that alkene can bind to copper centred catalysts[19], addition of styrene did not change either the UV-Vis or the EPR spectra. Therefore, the structure of the complex remained the same. After initiating the aziridination reaction using PhI=NTs the peak underwent a further smaller shift to 667.5 nm and remained there during the course of the reaction, likely due to the coordinated side products.

Cu(II)-triflate, on the other hand, showed no change at all in the Uv-Vis spectrum after forming the Cu-bis(oxazoline) complex (Figure 9b). The peak maximum of 668.4 nm indicates, that the coordination of the active catalyst must be similar, whether using Cu(I) or Cu(II) -triflate as parent metal salt.

After the copper-bis(oxazoline) had been formed the metal centred d-d band appeared in the UV-Vis spectrum at 668 nm.

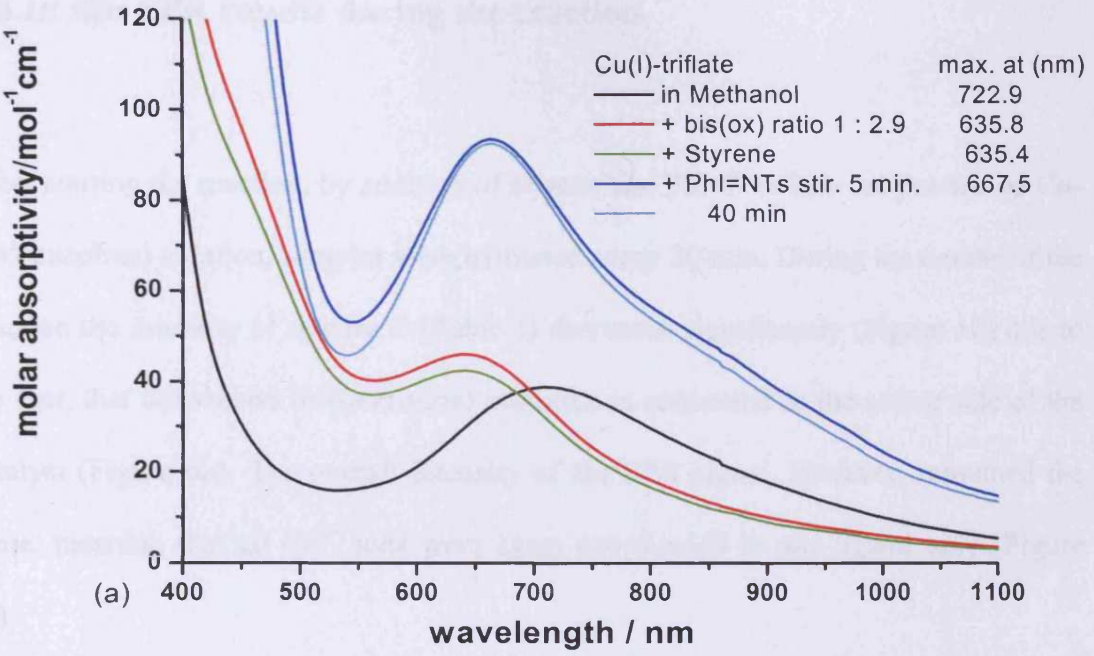


Figure 9a: UV-Vis spectra of Cu(I)-triflate (a) during the formation of the catalyst and in the course of the aziridination reaction

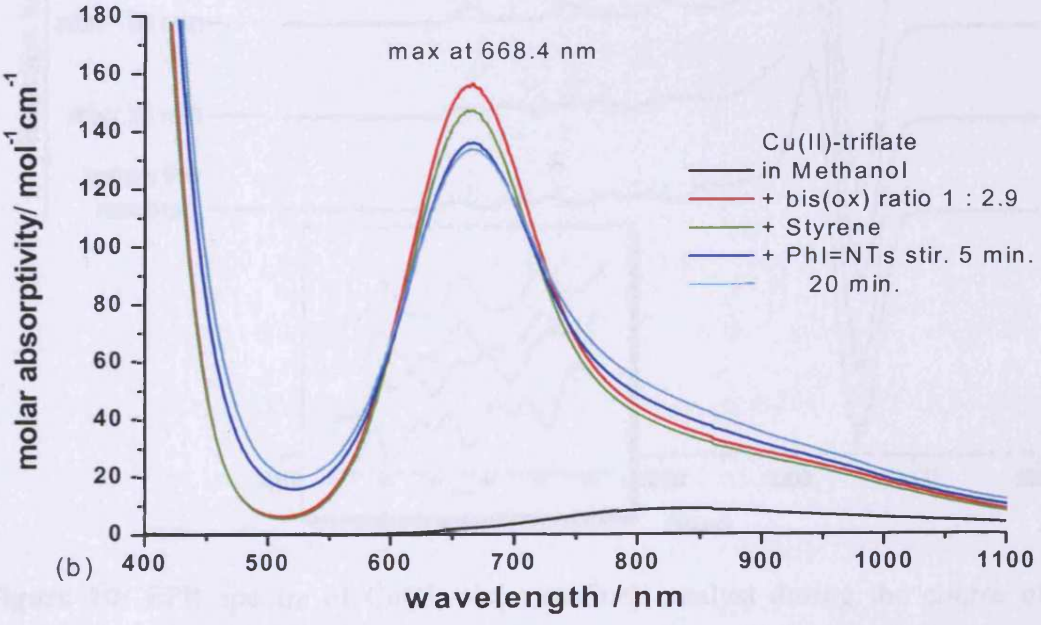


Figure 9b: UV-Vis spectra of Cu(II)-triflate (b) during the formation of the catalyst and in the course of the aziridination reaction

4.6 *In situ* EPR results during the reaction

After starting the reaction, by addition of styrene and PhI=NTs into the pre-stirred Cu-bis(oxazoline) solution, samples were extracted every 20 min. During the course of the reaction the intensity of species C (Table 5) decreased significantly (Figure 10) due to the fact, that the second bis(oxazoline) molecule is connected to the active side of the catalyst (Figure 6b). The overall intensity of the EPR signal, however, remained the same, meaning that all Cu^{2+} ions were again coordinated to one ligand only (Figure 6a).

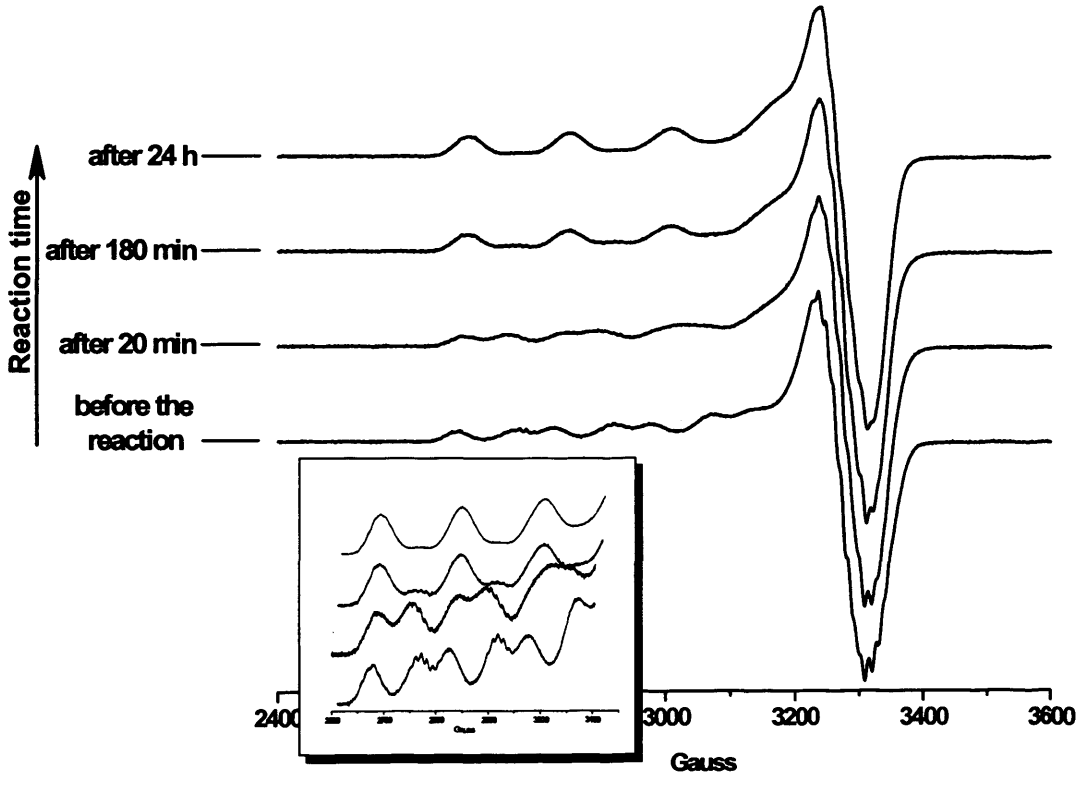


Figure 10: EPR spectra of Cu(II)-bis(oxazoline) catalyst during the course of the aziridine reaction. In the extra box expanded parallel region.

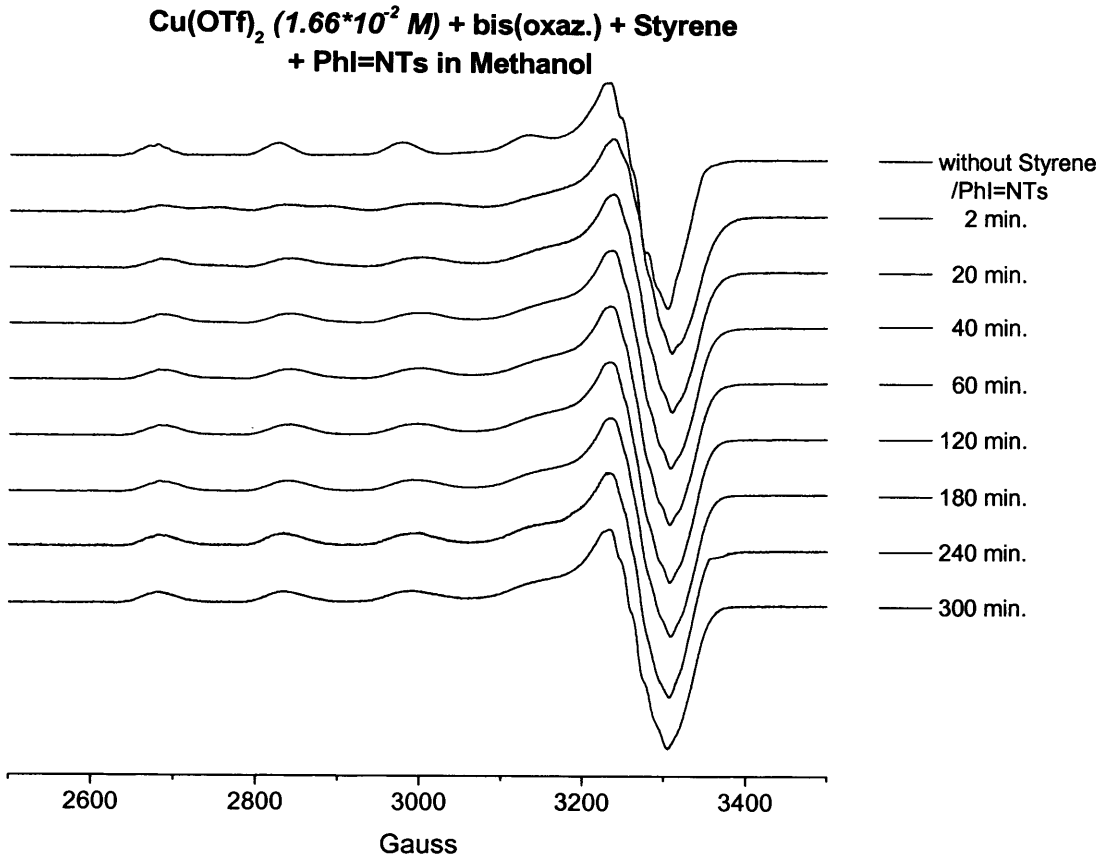


Figure 11: EPR spectra of Cu(II)-bis(oxazoline) catalyst during the course of the aziridine reaction.

In order to explore the changes to the co-ordination and oxidation state of the Cu(II) ions, the EPR spectra were measured after various substrates, including PhI=NTs and styrene, had been added to the $Cu(OTf)_2$ catalyst in methanol containing the bis(oxazoline) ligand (Figure 11). As previously seen (Figure 10), during the course of the reaction the intensity of species C (Table 5) decreased significantly (Figure 11). This was a result of the second bis(oxazoline) molecule connected to the active side of the catalyst (Figure 6b). However, the intensity of the EPR signal was seen to remain the same, confirming that all the Cu^{2+} ions were coordinated to one ligand only (Figure 6a).

Both Cu(I) and Cu(II) salts have been shown to be efficient catalysts for the homogeneous aziridination of styrene[10,14]. However, the oxidation state of the active metal species is still not eludicated. Evans[10] has shown that there is strong experimental evidence to suggest that a common oxidation state is reached in both cases. The introduction of a bis(oxazoline) as the chiral ligand affords the same level of asymmetric induction with Cu(OTf) and $Cu(OTf)_2$. Evans concluded that the active catalyst is in a +2 oxidation state and the nitrogen source, PhI=NTs, can act as an oxidant for Cu(I). It has been proposed [14], that copper-bis(oxazoline) catalyst breaks down the nitrogen donor and forms a copper nitrene (Cu^{3+}=NTs) intermediate to generate aziridine and iodobenzene as a side product. This intermediate possesses the ability to produce a paramagnetic Cu^{2+}-nitrene radical intermediate[20]. Recently Brandt *et al.*[21] have investigated the mechanism of the homogeneous copper catalysed aziridination of alkenes by computational studies. The results strongly indicated that the active catalyst is a Cu(I) species. Computational studies have also shown how Cu(II) can enter the Cu(I)/ Cu(III) cycle through reaction with the nitrogen source, PhI=NTs. Gullick *et al*[12] have proposed that the nitrene donor and catalyst react with aziridine in a pseudo-equilibrium process, forming a 5-centred intermediate. Nevertheless, apart from the loss of species C, the EPR spectra remained the same over the period of 24 hours.

4.7 Conclusions

In the presence of bis(oxazoline), variation in both yield and aziridine was observed in the different solvents tested. The homogeneous catalyst $Cu(OTf)_2$ was observed to give higher yields and ee of aziridine using PhI=NTs as nitrene donor compared to Cu(OTf). Methanol and acetonitrile, both of which are coordinating solvents, afforded enantioselectivities (≥ 46%). However reaction rates and yields were enhanced for both the homogeneously and heterogeneously catalysed reactions when using MeCN as solvent. This demonstrates that the product yields and enantioselectivity for both the homogeneous and heterogeneous systems are strongly dependent on the choice of solvent and the catalyst in the presence of the different solvents.

The formation of aziridine with reaction time demonstrates a complex profile, which, although more pronounced in the heterogeneously catalysed reaction, is still observed in the homogeneously catalysed reaction using Cu(I) and Cu(II) as catalyst. This effect is caused in part by the interaction of the product, aziridine, and the by-products, $TsNH_2$ and PhI, with the active copper site during the course of the reaction. Work carried out within the group[13] previously suggested that there was a complex relationship between reactants, products, chiral modifier and solvent at the active site in the heterogeneous aziridination reaction. Other contributing factors may arise from product inhibition, i.e. aziridine, of the catalytic centres as the reaction proceeds. Previous studies[15,16] have suggested the possible coexistence of two mechanisms, involving singlet and triplet nitrene intermediates. These two processes could play an important role in the observed reaction profile, particularly as it is still apparent in the homogeneously catalysed process.

As expected, EPR and UV-vis spectroscopy confirmed the formation of the Cu-bis(oxazoline) complex as central to the catalytic reaction in homogeneous solution (the enantioselectivity being related to the chirality of this complex). Both the Cu-complex containing a single bis(oxazoline) group, and two bis(oxazoline) groups appear to be active in the reaction. In addition, both oxidation states of copper (II and I) are effective in the catalytic reaction. No evidence has been found for the formation of any copper nitrene type intermediate, as proposed in the literature (although the lifetime of these intermediates may be outside the scope of EPR and UV-vis data). The failure to detect Cu=NTs may suggest that it is a transient species that is so reactive that its concentration is too low to be detected.

4.8 References

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Chapter 5

Effect of reaction parameters on enantioselectivity and on the reaction profile

5.0 Effect of reaction parameters on enantioselectivity and on the reaction profile

5.1 Introduction

The synthesis of pure enantiomers using catalytic processes is continuously been investigated. Recently, attention has started to be focused on the immobilisation of homogeneous catalysts[1], particularly using chiral bis(oxazoline) ligands[2]. This is particularly important as many homogeneous catalysts utilise relatively expensive chiral ligand and their recovery and re-use are of immense importance. Immobilisation can avoid the necessity of ligand recovery and hence will improve asymmetric catalysts potential in commercial processes applications.

Previous work in the group has shown that Cu^{2+} immobilised within microporous and mesoporous materials prepared by ion-exchange and modified by chiral bis(oxazoline) is effective in the asymmetric aziridination of alkenes[3-6]. In particular, high enantioselection can be observed with these immobilised catalysts investigated under identical conditions[6].

Work carried out within the group[5] previously also suggested that there was a complex relationship between reactants, products, chiral modifier and solvent at the active site in the heterogeneous aziridination reaction. Therefore a study of the possible variations in enantioselectivity during the course of the reaction was investigated. In these experiments the effect of the addition of iodobenzene and sulphonamide, the potential breakdown products of the nitrene donor, on the aziridination of styrene was examined.

These products were either added separately or together at the start of the homogeneously and heterogeneously catalysed reactions and aziridine formation was then monitored with time over the course of the reaction.

The enantioselectivity of the aziridination of styrene was monitored over time to examine the possible increase in ee due to further reactions of the product[7].

An investigation into the role of various reaction components was undertaken in order to optimise the aziridination of styrene. The reaction profile that is common for the aziridination of styrene was examined in detail. The reaction profile was observed for the homogeneously catalysed pathway[8] as well as the heterogeneously catalysed pathway and consequently, it cannot be due solely to confinement effect with the zeolite pores. Addition of reaction by-products ($NsNH_2$, PhI) and the final product (tosyl/nosyl aziridine) were examined to determine whether the effects accentuated the shape of the reaction profile in terms of the interactions of such molecules at the active site. These experiments were also examined for aziridine formation over time and enantioselectivity of the final product.

5.2 Addition of iodobenzene/ corresponding sulphonamide

Experiments were carried out in order to investigate the role of the breakdown products in the role of the aziridination of styrene. The addition of the corresponding breakdown products from the nitrogen source could have either an inhibiting or promoting effect on the enantioselectivity of the reaction. Asymmetric heterogeneous and homogeneous reactions, with the addition of both 5 mol% and 10 mol% PhI or 5 mol% and 10 mol% of the corresponding sulphonamide along with either PhI=NNs or PhI=NTs were carried out. This is in contrast to work done before in the group, which was carried out at room temperature[6] and with 1.0 and 0.1 equivalents of breakdown product added.

5.2.1 Reactions with PhI=NTs

Table 1: Effect on the formation of aziridine and enantioselectivity by the addition of iodobenzene and $TsNH_2$ to heterogeneous and homogeneous aziridination of styrene using PhI=NTs with bis(oxazoline)

PhI=NTs +	**CuHY/ $Cu(OTf)_2$**	**Time (h)**	**Aziridine (%)**	**ee (%)**
	CuHY	24	82	75
	$Cu(OTf)_2$	24	89	72
5 mol% PhI	CuHY	24	80	70
5 mol% PhI	$Cu(OTf)_2$	24	72	73
5 mol% $TsNH_2$	CuHY	24	78	59
5 mol% $TsNH_2$	$Cu(OTf)_2$	24	75	79
5 mol% PhI + $TsNH_2$	CuHY	24	80	64
5 mol% PhI + $TsNH_2$	$Cu(OTf)_2$	24	70	76
10 mol% PhI	CuHY	24	82	68
10 mol% PhI	$Cu(OTf)_2$	24	65	70
10 mol% $TsNH_2$	CuHY	24	86	52
10 mol% $TsNH_2$	$Cu(OTf)_2$	24	77	77
10 mol% PhI + $TsNH_2$	CuHY	24	83	58
10 mol% PhI + $TsNH_2$	$Cu(OTf)_2$	24	67	74

Reaction conditions: bis(oxazoline) (7 mol %), MeCN (5 ml), 25°C, PhI=NTs: styrene = 1.5 mol ratio, 24 h reaction time, catalyst: CuHY (300mg/mmol, 3.7 wt % Cu); $Cu(OTf)_2$ (15 mol %)

In the heterogeneously catalysed reaction using PhI=NTs after 24h, an aziridine yield (82%) and enantiomeric excess (75%) was observed. From the results obtained with the reactions with PhI=NTs (Table 1) it can be observed that the addition of iodobenzene resulted in the yield of aziridine remaining the same but a decrease in the in enantioselectivity was observed (68% and 70%) for 10 and 5 mol% additions respectively. However with the addition of the corresponding sulphonamide, there was an increase in the aziridine formation (86%) for 10 mol% additions; also the enantioselectivity had dropped (52% and 59%) for 10 and 5-mol% respectively. When both the breakdown products were added to the reaction, there was a decrease in the enantiomeric excess (58% and 64%), however similar yields were obtained compared to the yield of aziridine formed in the reaction with only PhI=NTs present.

In the standard homogeneously catalysed reaction using PhI=NTs after 24h, a high yield (89%) and ee (72%) were observed. By the addition of 5 and 10-mol% PhI to the reaction, there was a decrease in the formation of aziridine (72% and 65%) respectively, the enantioselectivities (73% and 70%) were comparable to the typical homogeneous reactions. With the addition of the corresponding sulphonamide, the aziridine formation (75% and 77%) for 5 and 10 mol% additions respectively, compared similarly to the standard reaction. There was an increase in enantioselectivity (79% and 77%) observed for both 5 and 10 mol% additions. However, with the presence of both the breakdown products, a decrease in formation of aziridine was observed (70% and 67%) for both additions. The enantioselectivity, however was observed to increase (76% and 74%) over 24h compared to the ee (72%) observed in the reaction with PhI=NTs only.

5.2.2 Reactions with PhI=NNs

Table 2: Effect on the formation of aziridine and enantioselectivity by the addition of iodobenzene and $NsNH_2$ to heterogeneous and homogeneous aziridination of styrene using PhI=NNs with bis(oxazoline)

PhI=NNs +	**CuHY/ $Cu(OTf)_2$**	**Time (h)**	**Aziridine (%)**	**ee (%)**
	CuHY	24	82	86
	$Cu(OTf)_2$	24	95	82
5 mol% PhI	CuHY	24	88	59
5 mol% PhI	$Cu(OTf)_2$	24	70	57
5 mol% $NsNH_2$	CuHY	24	91	56
5 mol% $NsNH_2$	$Cu(OTf)_2$	24	70	63
5 mol% PhI + $NsNH_2$	CuHY	24	89	58
5 mol% PhI + $NsNH_2$	$Cu(OTf)_2$	24	59	60
10 mol% PhI	CuHY	24	90	54
10 mol% PhI	$Cu(OTf)_2$	24	62	52
10 mol% $NsNH_2$	CuHY	24	92	51
10 mol% $NsNH_2$	$Cu(OTf)_2$	24	67	56
10 mol% PhI + $NsNH_2$	CuHY	24	93	54
10 mol% PhI + $NsNH_2$	$Cu(OTf)_2$	24	53	55

Reaction conditions: bis(oxazoline) (7 mol %), MeCN (5 ml), 25°C, PhI=NNs:styrene = 1.5 mol ratio, 24 h reaction time, catalyst: CuHY (300mg/mmol, 3.7 wt % Cu); $Cu(OTf)_2$ (15 mol %)

In the heterogeneously catalysed reaction using PhI=NNs after 24h, 82% yield and 86% ee of the aziridine was observed (Table 2). All reactions were allowed 24h to reach completion. With the addition of 5 and 10 mol% iodobenzene there was a slight increase in the yield of aziridine obtained, (88% and 90%) respectively. However, in both cases there was a significant decrease in the enantiomeric excess (59% and 54%) respectively. The addition of 4-nitrobenzenesulphonamide resulted in comparable results to that of the additions of PhI. A slight increase in aziridine yield (91% and 92%) was observed for 5 and 10 mol% additions, however a marked decrease in ee was observed (56% and 51%) for both cases. When the reaction was carried out in the presence of both the breakdown products, the results in terms of yield (89% and 93%) and enantiomeric excess (58% and 54%) for 5 and 10 mol% additions were similar to the previous reactions carried out.

For the homogeneously catalysed reactions using PhI=NNs after 24h, a high yield (95%) and ee (82%) of aziridine was observed. However, in the presence of the breakdown products, either added separately or together, the results changed significantly. The addition of 5 and 10-mol% PhI resulted in a decrease in both yield (70% and 62%) and ee (57% and 52%). This followed a similar pattern from the addition of the corresponding sulphonamide; 70% and 67% observed yield of aziridine for 5 and 10 mol% additions respectively. A decrease in ee was observed (63% and 56%) for both cases. With the addition of both the breakdown products, a marked decrease in yield (59% and 53%) of aziridine was observed for 5 and 10-mol% which was similar to previous reactions. A similar result was observed for enantiomeric excess (60% and 55%) for both cases respectively, which again was a decrease compared to the standard homogeneous reaction.

5.2.3 Effect of the addition of iodobenzene/sulphonamide on the aziridination of styrene

It is apparent that complex relationships exist between the components of the reaction mixture, *i.e.* reactants and products and the addition of the products can cause a decrease in both the rate of reaction and the final yield of aziridine. In the homogeneously catalysed reaction, in the absence of bis (oxazoline), the addition of the breakdown products leads to a marked decrease in the rate of reaction and the final yield of aziridine (Figures 1 and 2). The effect is more marked for PhI=NNs than PhI=NTs.

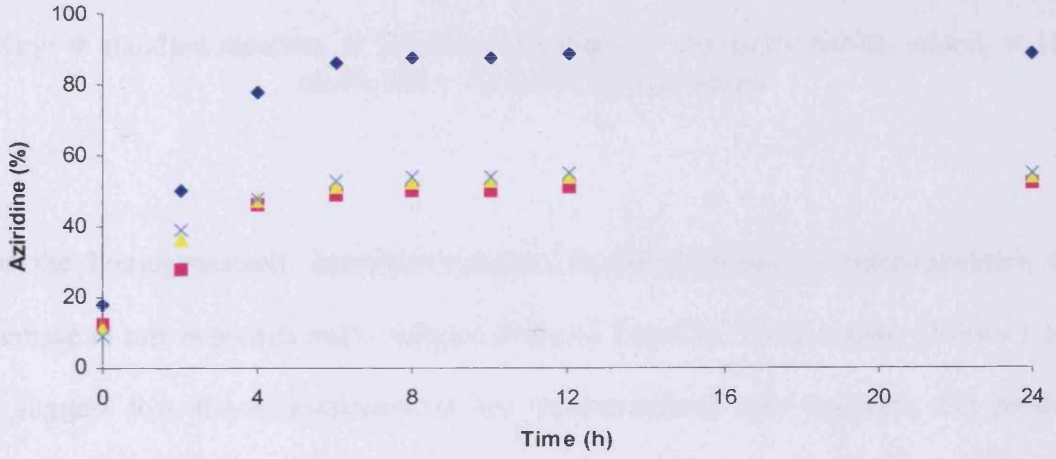


Figure 1: Effect of addition of iodobenzene and toluenesulphonamide on the formation of aziridine in the absence of the chiral modifier, 25^{0}C, CH_3CN, PhI=NTs: styrene mol ratio = 1.5: 1, $Cu(OTf)_2$ (0.015g).

Key: ◆ standard reaction, ■ 10 mol% PhI added, ▲ 10 mol% $TsNH_2$ added, × 10 mol% PhI + 10 mol% $TsNH_2$ added

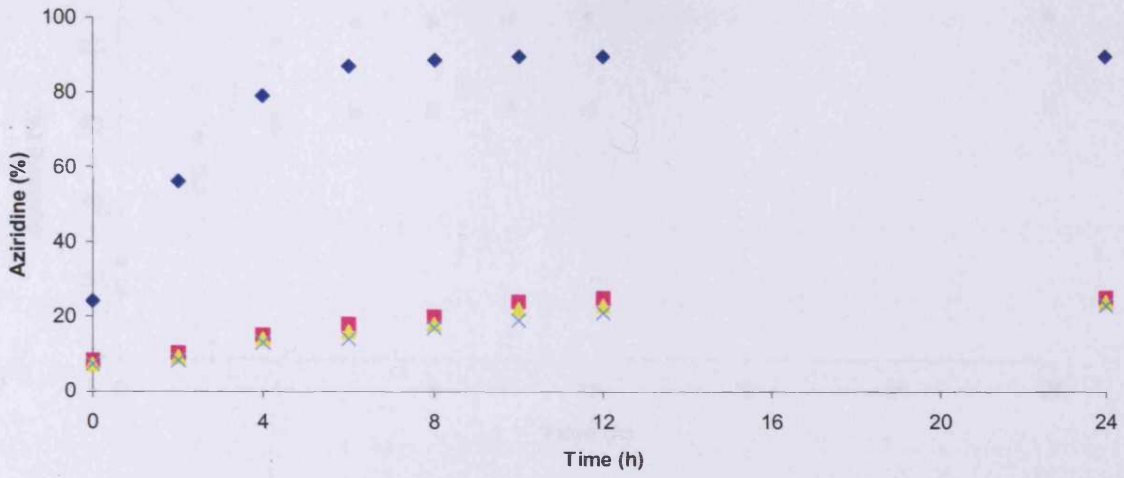


Figure 2: Effect of addition of iodobenzene and 4-nitrobenzenesulphonamide on the formation of aziridine in the absence of the chiral modifier, 25^0C, CH_3CN, PhI=NNs: styrene mol ratio = 1.5: 1, $Cu(OTf)_2$ (0.015g).

Key: ◆ standard reaction, ■ 10 mol% PhI added, ▲ 10 mol% $NsNH_2$ added, × 10 mol% PhI + 10 mol% $NsNH_2$ added

For the homogeneously catalysed reaction in the presence of bis(oxazoline), the decrease in rate is significantly reduced (Figures 3 and 4). These results (Tables 1 and 2) suggest that the coordination of the bis(oxazoline) may suppress the product inhibition effects, and this may be an alternative explanation for the ligand accelerating effect with this catalysed reaction.

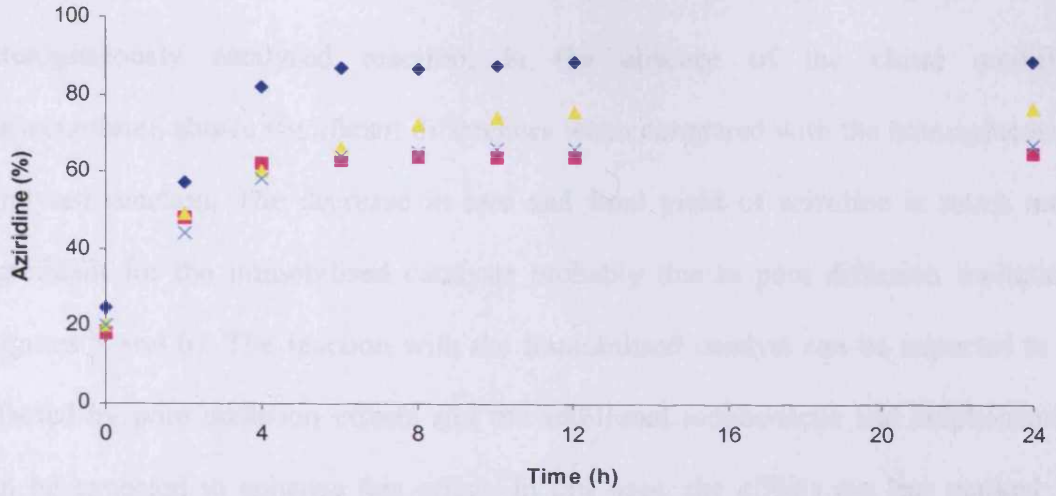


Figure 3: Effect of addition of iodobenzene and toluenesulphonamide on the formation of aziridine with the chiral modifier, bis(oxazoline) (0.039g), 25^{0}C, CH_3CN, PhI=NTs: styrene mol ratio = 1.5: 1, $Cu(OTf)_2$ (0.015g).

Key: ◆ standard reaction, ■ 10 mol% PhI added, ▲ 10 mol% $TsNH_2$ added, × 10 mol% PhI + 10 mol% $TsNH_2$ added

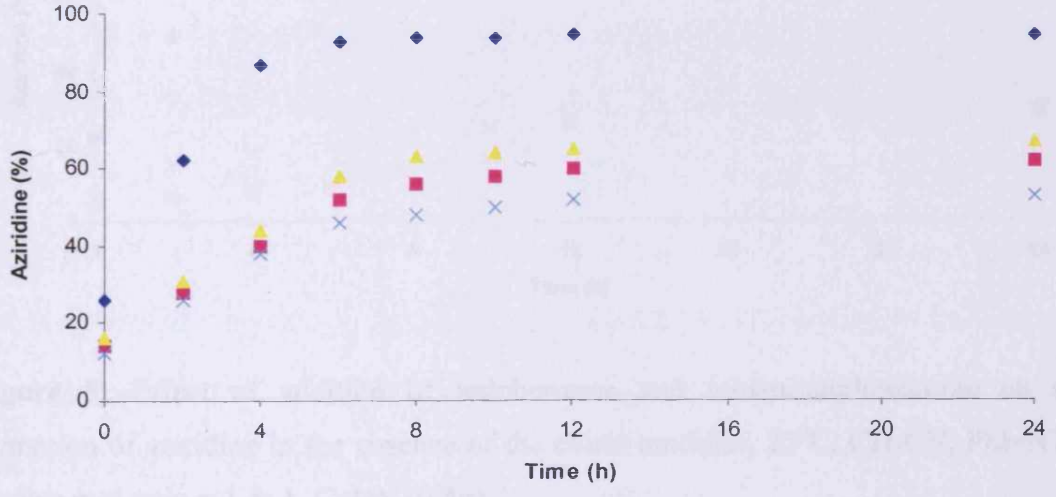


Figure 4: Effect of addition of iodobenzene and 4-nitrobenzenesulphonamide on the formation of aziridine with the chiral modifier, bis(oxazoline) (0.039g), 25^{0}C, CH_3CN, PhI=NNs: styrene mol ratio = 1.5: 1, $Cu(OTf)_2$ (0.015g).

Key: ◆ standard reaction, ■ 10 mol% PhI added, ▲ 10 mol% $NsNH_2$ added, × 10 mol% PhI + 10 mol% $NsNH_2$ added

The addition of the breakdown products either separately or together to the heterogeneously catalysed reaction, in the absence of the chiral modifier, bis(oxazoline), shows significant differences when compared with the homogeneously catalysed reaction. The decrease in rate and final yield of aziridine is much more significant for the immobilised catalysts probably due to pore diffusion limitations (Figures 5 and 6). The reaction with the immobilised catalyst can be expected to be affected by pore diffusion effects and the additional iodobenzene and sulphonamide can be expected to enhance this effect. In this case, the effects are less marked for PhI=NNs (Figure 6) when contrasted with PhI=NTs (Figure 5).

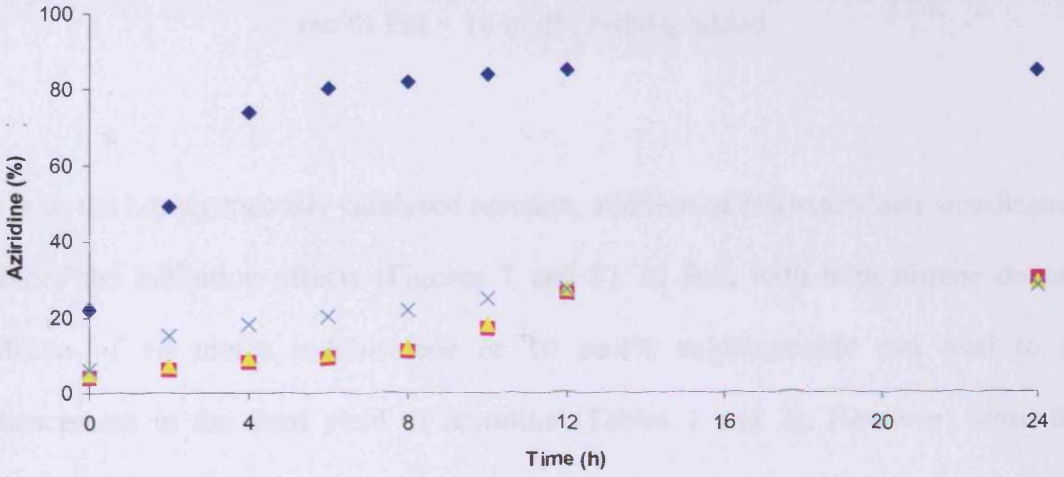


Figure 5: Effect of addition of iodobenzene and toluenesulphonamide on the formation of aziridine in the absence of the chiral modifier, 25^0C, CH_3CN, PhI=NTs: styrene mol ratio = 1.5: 1, CuHY (0.3g).

Key: ◆ standard reaction, ■ 10 mol% PhI added, ▲ 10 mol% $TsNH_2$ added, × 10 mol% PhI + 10 mol% $TsNH_2$ added

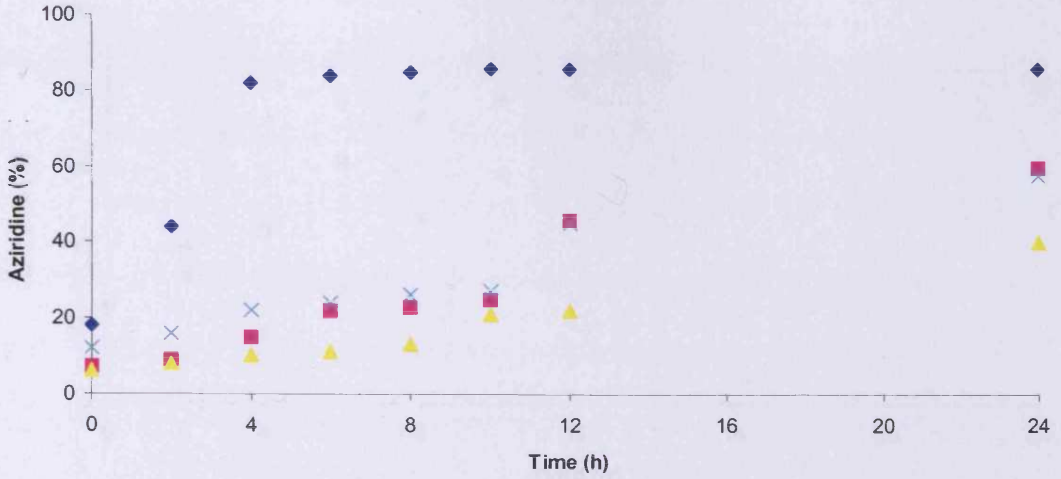


Figure 6: Effect of addition of iodobenzene and 4-nitrobenzenesulphonamide on the formation of aziridine in the absence of the chiral modifier, 25^{0}C, CH_3CN, PhI=NNs: styrene mol ratio = 1.5: 1, CuHY (0.3g).

Key: ◆ standard reaction, ■ 10 mol% PhI added, ▲ 10 mol% $NsNH_2$ added, × 10 mol% PhI + 10 mol% $NsNH_2$ added

As with the homogeneously catalysed reaction, addition of bis(oxazoline) significantly reduces the inhibition effects (Figures 7 and 8). In fact, with both nitrene donors, addition of 10 mol% iodobenzene or 10 mol% sulphonamide can lead to an enhancement in the final yield of aziridine (Tables 1 and 2). However, when the iodobenzene and the corresponding sulphonamide are added together, the reduction in rate of reaction and final yield of aziridine is still observed for PhI=NTs, but the effect is less significant for PhI=NNs.

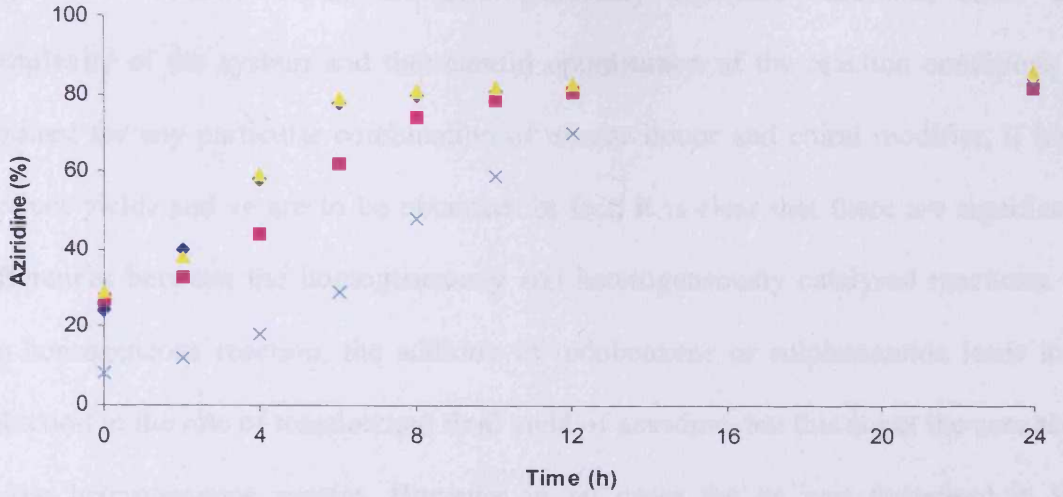


Figure 7: Effect of addition of iodobenzene and toluenesulphonamide on the formation of aziridine with the chiral modifier, bis(oxazoline) (0.039g), 25^{0}C, CH_3CN, PhI=NTs: styrene mol ratio = 1.5: 1, CuHY (0.3g).

Key: ◆ standard reaction, ■ 10 mol% PhI added, ▲ 10 mol% $TsNH_2$ added, × 10 mol% PhI + 10 mol% $TsNH_2$ added

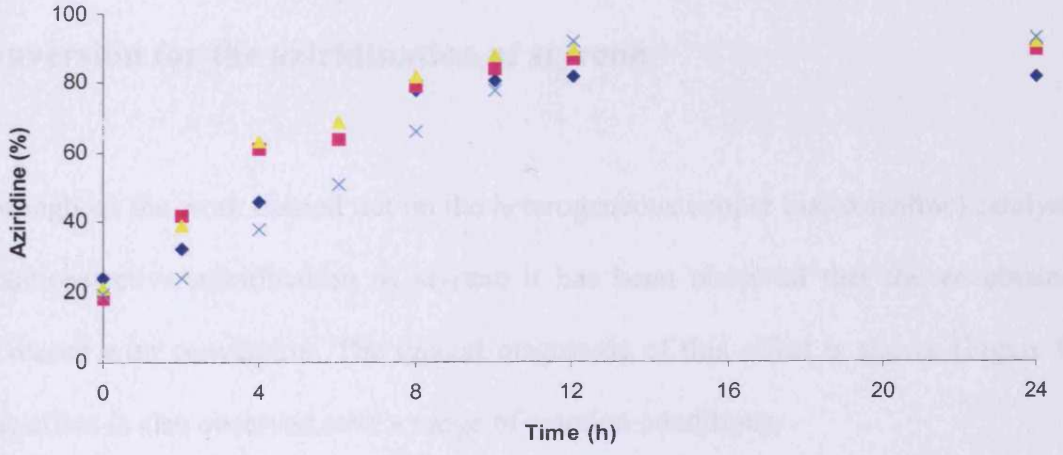


Figure 8: Effect of addition of iodobenzene and 4-nitrobenzenesulphonamide on the formation of aziridine with the chiral modifier, bis(oxazoline) (0.039g), 25^{0}C, CH_3CN, PhI=NNs: styrene mol ratio = 1.5: 1, CuHY (0.3g).

Key: ◆ standard reaction, ■ 10 mol% PhI added, ▲ 10 mol% $NsNH_2$ added, × 10 mol% PhI + 10 mol% $NsNH_2$ added

The results obtained from the heterogeneously catalysed reactions, show the complexity of the system and that careful optimisation of the reaction conditions is required for any particular combination of nitrene donor and chiral modifier, if high product yields and ee are to be obtained. In fact, it is clear that there are significant differences between the homogeneously and heterogeneously catalysed reactions. In the homogeneous reaction, the addition of iodobenzene or sulphonamide leads to a reduction in the rate of reaction and final yield of aziridine, but this is not the case seen in the heterogeneous system. However in all cases the ee was decreased in the presence of the breakdown products. These results indicate that it is possible for PhI, $NsNH_2$ and $TsNH_2$ to influence both the rate of aziridine formation and ee during the course of the reaction.

5.3 Observation of the enhancement in enantioselectivity with conversion for the aziridination of styrene

Throughout the work carried out on the heterogeneous copper bis(oxazoline) catalysed enantioselective aziridination of styrene it has been observed that the ee obtained increased with conversion. The typical magnitude of this effect is shown (Figure 9). The effect is also observed over a range of reaction conditions.

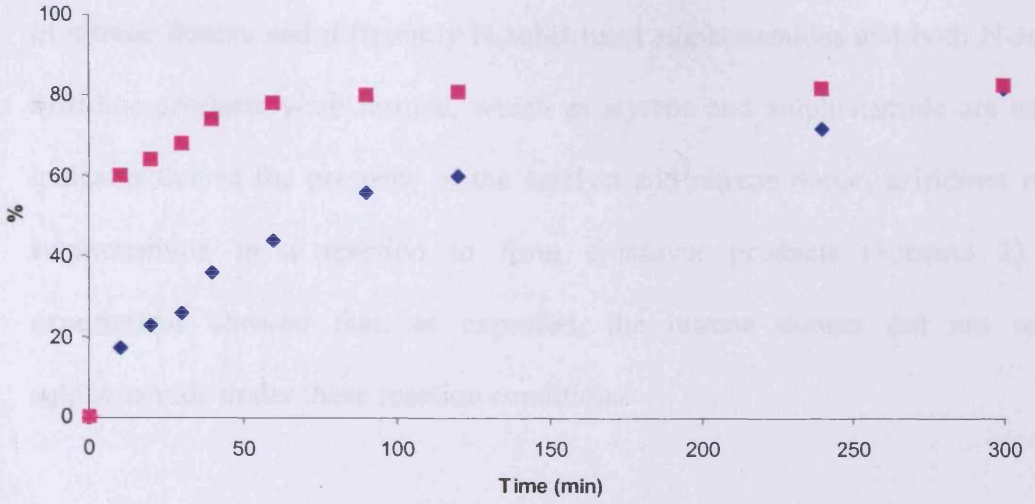
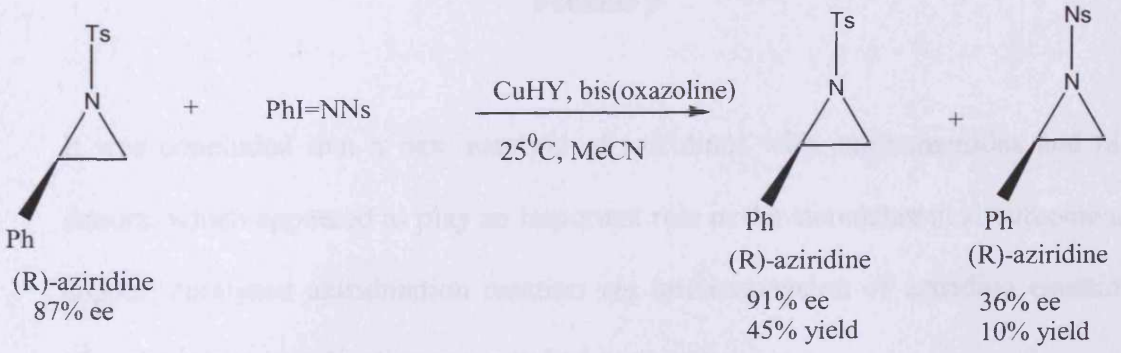


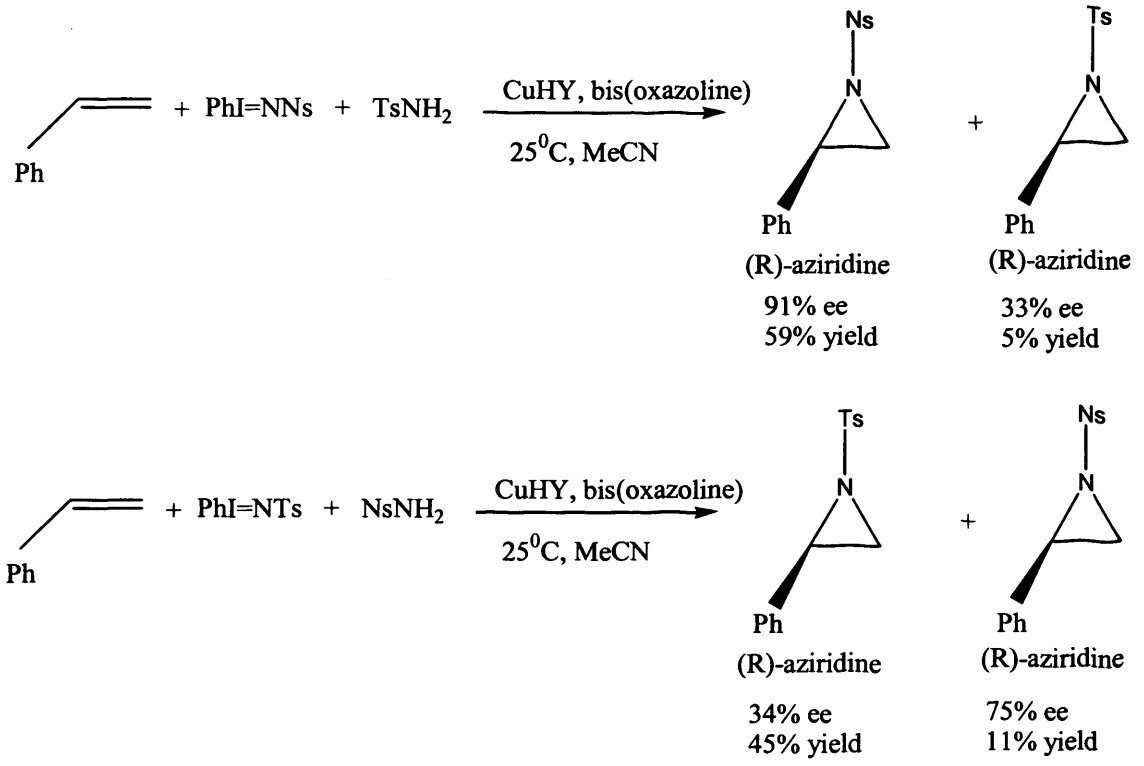
Figure 9: Effect of reaction time on yield and ee of (R)-aziridine [styrene (1mmol) reacted with CuHY (0.3g), PhI=NNs (1.5 mmol) with (R,R) bis(oxazoline) in CH_3CN at 25^0C]. Key: ◆aziridine yield, ■ ee

Previous work carried out in the group[7] showed that when (R)-N-(p-tosylsulfonyl)-2-phenyl aziridine (87 % ee) was reacted with PhI=NNs and bis(oxazoline) and CuHY in addition to any decomposition of N-tosyl aziridine, a small amount (*ca.* 10%) of (R)-N-(p-nosylsulfonyl)-2-phenyl aziridine was recovered in a lower ee (36%) (Scheme 1). Therefore, this demonstrated that, under the reaction conditions, product aziridine is continually reacting with nitrene donor.



Scheme 1

Additionally, experiments were carried out in which styrene was reacted with mixtures of nitrene donors and differently N-substituted sulphonamides and both N-substituted aziridine products were formed, which as styrene and sulphonamide are unreactive, indicates that in the presence of the catalyst and nitrene donor, aziridines react with sulphonamide in a reaction to form crossover products (Scheme 2). Control experiments showed that, as expected, the nitrene donors did not react with sulphonamide under these reaction conditions.



Scheme 2

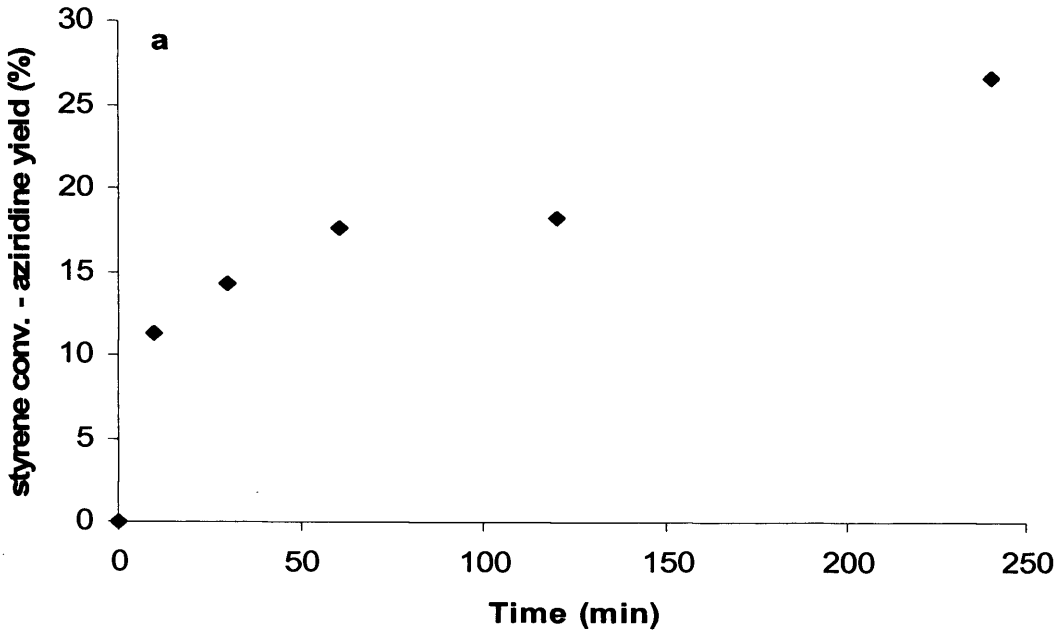
It was concluded that a new reaction of aziridines with sulphonamides and nitrene donors, which appeared to play an important role in the stereochemical outcome of the copper, catalysed aziridination reaction *via* interconversion of aziridine enantiomers after the initial aziridination reaction had occurred.

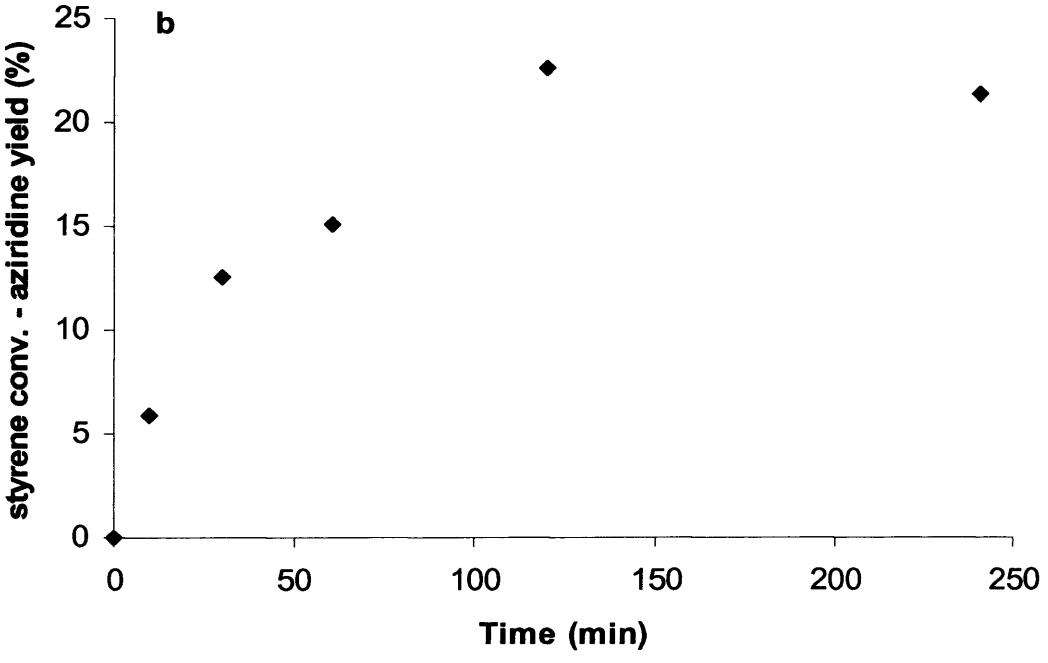
5.4 Effect of the counter cation on the reaction profile

In this study the effect of introducing alternative counter cations from group I (Li^+, Na^+, K^+, Rb^+, Cs^+) to replace protons was investigated, in particular their effect on the formation of aziridine in the early stages of the reaction. As mentioned in an earlier section (5.3) it has been shown that the ee increases with conversion[7] in the aziridination reaction and this study was an extension on the investigation on the reaction profile of the aziridination of styrene.

5.4.1 Effect of reaction profile on aziridine yield, group I ion-exchanged zeolite Y

From the reaction time studies carried out it was observed that the nature of the reaction profile for both styrene conversion and aziridine followed a similar pattern. This effect is also apparent for CuHY catalyst[6] data reported. The aziridination reaction is characterised by an initial rapid conversion of styrene and formation of aziridine; however, after the initial period, the rates of styrene conversion and aziridine formation slow down before subsequently accelerating as the reaction proceeds. It is apparent that there is a marked difference in the yield of aziridine and styrene conversion, and plots of styrene conversion minus aziridine yield are useful in quantifying this effect since it varies with reaction time and clearly shows the key characteristic of the reaction profile (Figure 10).


a
styrene conv. - aziridine yield (%)
30
25
20
15
10
5
0
0
50
100
150
200
250
Time (min)


b
styrene conv. - aziridine yield (%)
25
20
15
10
5
0
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200
250
Time (min)

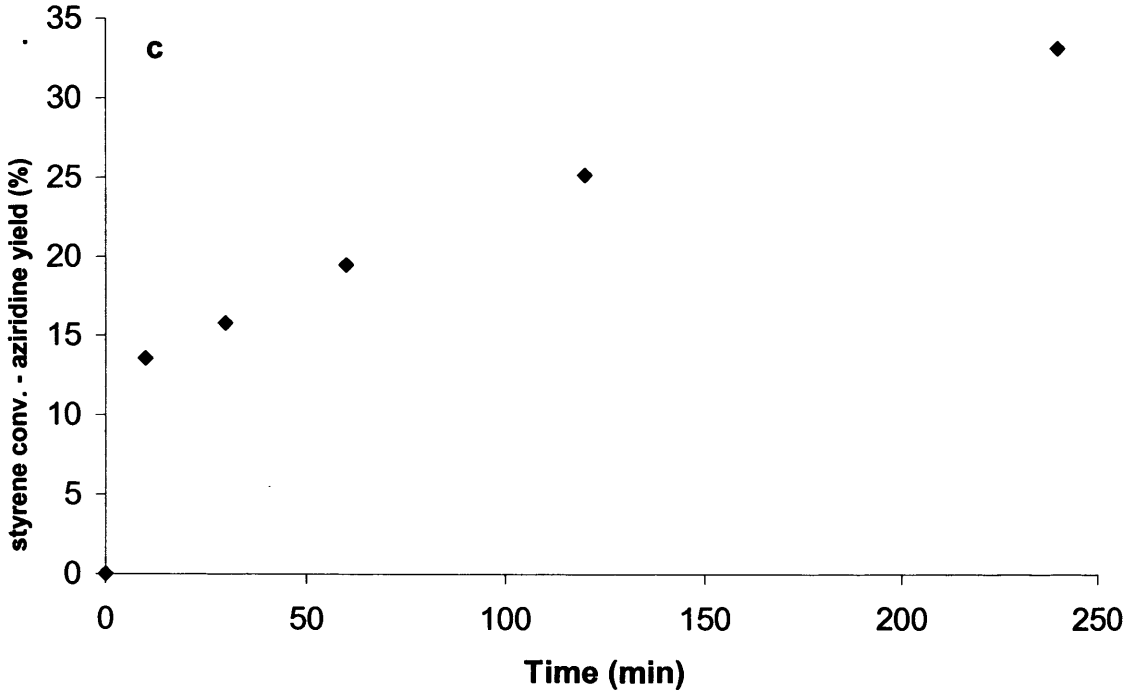


Figure 10: Plots of styrene conversion minus aziridine yield to demonstrate the nature of the reaction profile (a) Cu-LiY, (b) Cu-NaY, (c) Cu-CsY.

It is observed that, the larger the size of the counter-cation, the more apparent the effect. In the heterogeneously catalysed reaction, the active site within the supercage of the zeolite is highly confined. This leads to an enhancement in ee observed with these catalysts[6]. It is also apparent that the active site can also interact with reaction breakdown products (e.g. PhI, $NsNH_2$) as well as the resulting aziridine and the starting nitrene donor. Previously it has been shown that aziridine could interact with $NsNH_2$ and the nitrene donor and these interactions played a role in the observed enhancement in ee with styrene conversion. This observation shows that the coordination sphere of Cu^{2+}, although highly confined within the zeolite, changes its nature during the reaction. This idea is linked in closely to the observation of the S-shaped reaction profile and the size of the cation would, therefore, play a significant role by enhancing steric confinement of the active centre.

5.4.2 Comments on the reaction profile

The shape of the conversion *versus* time curve indicates a two-stage process for the consumption of the alkene: (i) an initial phase, the extent of which appears to be determined roughly by the initial ratio of catalyst to alkene and which is complete after about one hour under the conditions used in the previous experiments; and (ii) a second phase, which starts slowly but then accelerates before slowing down as the reaction reaches completion, resulting in the characteristic reaction profiles observed for both heterogeneous and homogeneous catalysts.

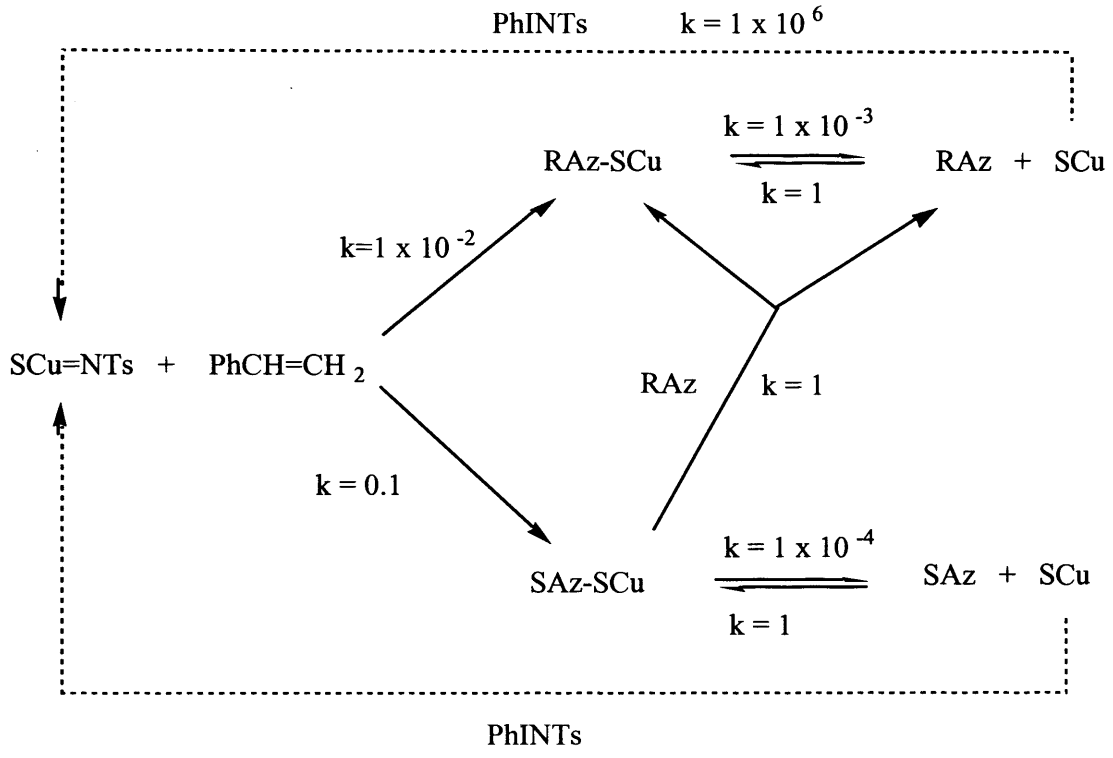
The mechanism of aziridination catalysed by copper cations is known to be a very complex process. Previous studies[9,10] have suggested the possible coexistence of two mechanisms, involving singlet and triplet nitrene intermediates. However, free nitrenes and carbenes, unless stabilised by conjugation with lone pair electrons, are exceedingly reactive, with a lifetime of microseconds. Their formation would be expected to be rate limiting, so therefore no dependence on the rate of alkene concentration. These two processes would need to be further investigated to see whether they could play an important role in the observed reaction profile, particularly as it is still apparent in the homogeneously catalysed process.

However, it is clear that many factors affect the rate of the aziridination reaction and the extent of enantioselectivity. In particular, the presence of the breakdown products together with aziridine can influence the process as shown earlier when the reaction profile is shown to be very sensitive to the introduction of the sulphonamide by-product.

Therefore, given this complexity, it was considered that the nature of the reaction pathway would lead to the generation of a reaction profile in which an initial rapid

reaction is followed by a period of relatively slow reaction, before once again observing a relative reaction profile. This type of behaviour is not immediately apparent for the operation of two pathways involving different nitrene intermediate, but is more likely to result from competitive interaction at the active centre of the many competing reaction components. Leaving aside the complicating role exerted by the sulphonamide by-product and of the iodobenzene produced in the reaction, a possible interpretation of the initial phase is that it arises from a simple competitive formation of enantiomeric aziridines by reaction of the alkene with the bis(oxazoline) complexed copper(II)-nitrene, the product aziridines then acting as competitive inhibitors of the catalytic copper centres. The rate of conversion of alkene then approaches zero when all the copper is complexed with aziridine. At this stage a second route, slow up to this point begins to become apparent and its form suggests the occurrence of a co-operative effect, which could be autocatalysis. This interpretation is speculative at this point as not all of the simulation of the kinetics is complete at this stage but some preliminary remarks can be made.

As mentioned earlier work carried out in the group[7] observed the enhancement of enantioselectivity with conversion in the aziridination of styrene using copper bis(oxazoline) complexes. This was interpreted in terms of interconversion of (R) and (S) aziridines by reaction with the copper nitrene species perhaps by way of an intermediate ring-opened diamine.



Scheme 3

Scheme 3 [in which S represents the S-enantiomer of the bis(oxazoline) used] incorporates this process. A two-phase conversion *versus* time curve (Figure 11) resulted from attempts to simulate the scheme. However, the plateau and subsequent sigmoid appeared in the styrene conversion curve, but not in the aziridine appearance. However, further studies in this area are required to eludicate the mechanism.

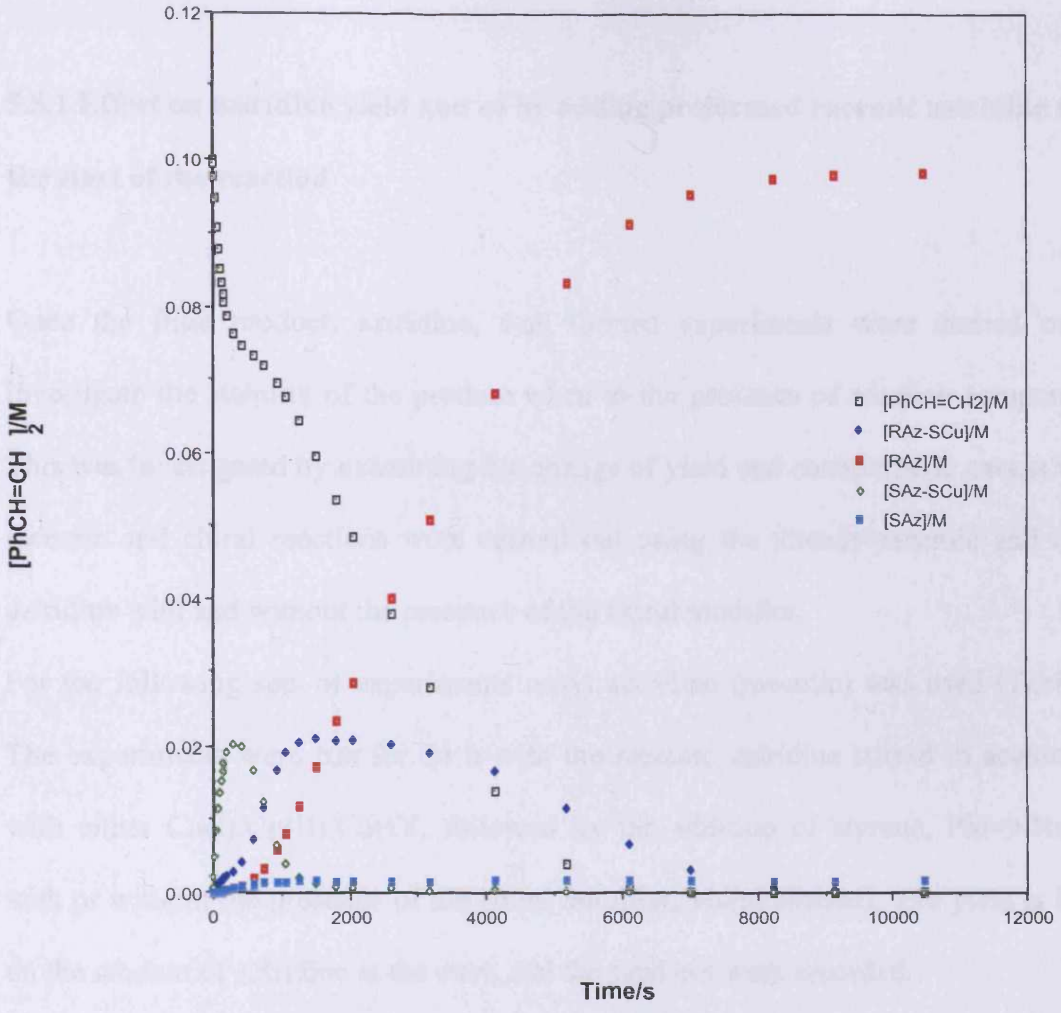


Figure 11: Graphical representation of Scheme 3

Simulations were carried out using the program "Kinetics"

(Chemistry Courseware Consortium, University of Liverpool).

A two-phase conversion *versus* time curve is illustrated (Figure 11). A sigmoidal curve is evident for the styrene conversion but not in the aziridine appearance.

The formation of aziridine with reaction time demonstrates a complex profile, which although more pronounced in the heterogeneously catalysed reaction, is still observed in the homogeneously catalysed reaction using $Cu(OTf)_2$ as catalyst. Further studies are required to understand the mechanism and complex profile involved.

5.5 Kinetic Resolution experiments

5.5.1 Effect on aziridine yield and ee by adding preformed racemic aziridine to the start of the reaction

Once the final product, aziridine, was formed experiments were carried out to investigate the stability of the product when in the presence of reaction components. This was investigated by examining the change of yield and enantiomeric excess when racemic and chiral reactions were carried out using the already racemic and chiral aziridine with and without the presence of the chiral modifier.

For the following sets of experiments nosyl aziridine (racemic) was used (Table 3). The experiments were run for 24 h with the racemic aziridine stirred in acetonitrile with either Cu(I)/Cu(II)/CuHY, followed by the addition of styrene, PhI=NNs and with or without the presence of the chiral modifier, bis(oxazoline). The yield is based on the amount of aziridine at the start, and the final ees were recorded.

Table 3: Change in % ee and yield of aziridine when heterogeneous/homogeneous reactions using PhI=NNs with the corresponding racemic nosyl aziridine with/without the presence of the modifier were performed to produce chiral aziridine.

	Temp ^{0}C	% Yield (0h)	% Yield (24h)	Δ Yield	% ee	Modifier added
Cu(I)	25^{0}C	100	34	66		
Cu(I)	25^{0}C	100	77	23	14	YES
Cu(II)	25^{0}C	100	62	38		
Cu(II)	25^{0}C	100	92	8	14	YES
CuHY	25^{0}C	100	90	10		
CuHY	25^{0}C	100	93	7	12	YES

Reaction conditions: bis(oxazoline) (7 mol %), MeCN (5 ml), 25°C, PhI=NNs: styrene = 1.5 mol ratio, 24 h reaction time, catalyst: CuHY (300mg/mmol, 3.7 wt % Cu); $Cu(OTf)_2$ (15 mol %); Cu(OTf) (15 mol %)

On the mechanistic side experiments were carried out to test ideas coming from the simulations in both homogeneous and heterogeneous systems. The effect of the reaction time on the conversion of styrene and the yield of aziridine was investigated. An interesting observation with these reaction time studies concern the nature of the reaction profile for both styrene conversion and aziridine yield. This is also apparent for the CuHY catalyst in data previously published[6]. Recently, it has been shown that the ee increases with conversion[7] for the aziridination reaction and that the reaction profile is sigmoid with an initial rapid formation of the aziridine that then slows prior

to a subsequent rapid formation phase for both the homogeneously and heterogeneously catalysed reaction using copper-bis(oxazoline) catalysts.

Experiments were carried out to study the changes in % ee and yield of aziridine when heterogeneously and homogeneously reactions using PhI=NNs with the corresponding racemic nosyl aziridine with/without the presence of the modifier were performed to produce chiral aziridine. When aziridine is stirred with the catalyst, in the absence of the modifier, the amount of aziridine remaining at the end of 24 h is greatly reduced for both homogeneously and heterogeneously modified catalysts. However, a small ee can be induced (~14%) [(pre-dominant *S*) and is in the same sense as the formation of aziridine from PhI=NNs and styrene in the presence of the same bis(oxazoline)] when the modifier is present in the heterogeneous and homogeneous reactions. A significant change in yield (66%) is observed for Cu(I) with no modifier added, this is also the case for Cu(II), a change in yield (38%) was observed without the presence of the modifier. CuHY gave the lowest change in yield after 24h in all cases (>10%). During reactions with racemic aziridine, in the heterogeneous and homogeneous case, enhancements in enantioselectivity were observed. There are two pathways in which enantiomeric excess from a racemic mixture of the enantiomers can be obtained. The first pathway is interconversion, which preferentially enhances the pathway of one enantiomer over the other. The second pathway is hydrolysis, which is the selective destruction of one enantiomer over the other. In the latter case, depending upon the preferred enantiomer, either a decrease or increase in enantioselectivity can occur.

There is the possibility that the observed increase in ee with conversion is a result of kinetic resolution. Chen *et al.*[11] introduced an elegant format for the organisation of chemical resolution data. They showed that the use of equations and graphs that were verified experimentally possessed predictive values in relating the parameters of the

extent of conversion of racemic substrate (c), the optical purity expressed as enantiomeric excess (ee), and the enantiomeric ratio (E). Although, it should be known that the biochemical constant E has a vastly different connotation than the corresponding chemical constant K. In chemical kinetic resolutions, the chiral reagent (bis(oxazoline)) is always in excess and is not recycled. Further work needs to be applied to develop the equations and useful graphs for the quantitative treatment of chemical kinetic resolution data for the above experiment (Table 3).

The results achieved are interesting since the reaction profiles are similar whether the modifier is present (Figure 13) or not (Figure 12). This effect is more pronounced in the heterogeneously catalysed reactions. The sigmoid curve can be seen in all cases when the modifier is present. There is an initial rapid formation of the aziridine in the first hour followed by a slow stage prior to a rapid formation phase of aziridine. These trends in profile are comparable with previous experiments carried out.

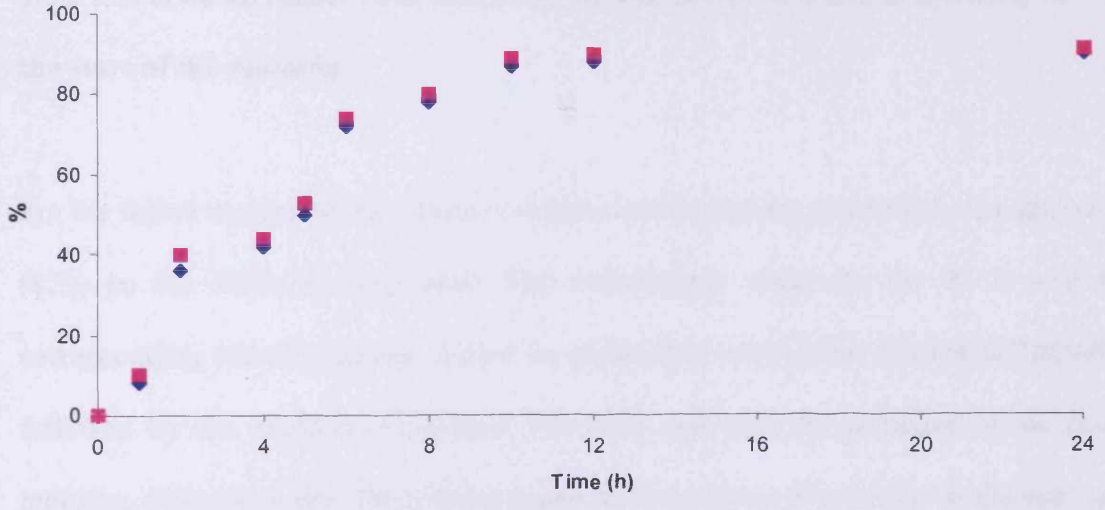


Figure 12: Effect of reaction time on yield of aziridine by addition of the corresponding racemic aziridine [styrene (1mmol) reacted with CuHY (0.3g), PhI=NNs (1.5 mmol) in CH_3CN at 25^0C].

Key: ◆aziridine yield, ■ styrene conversion

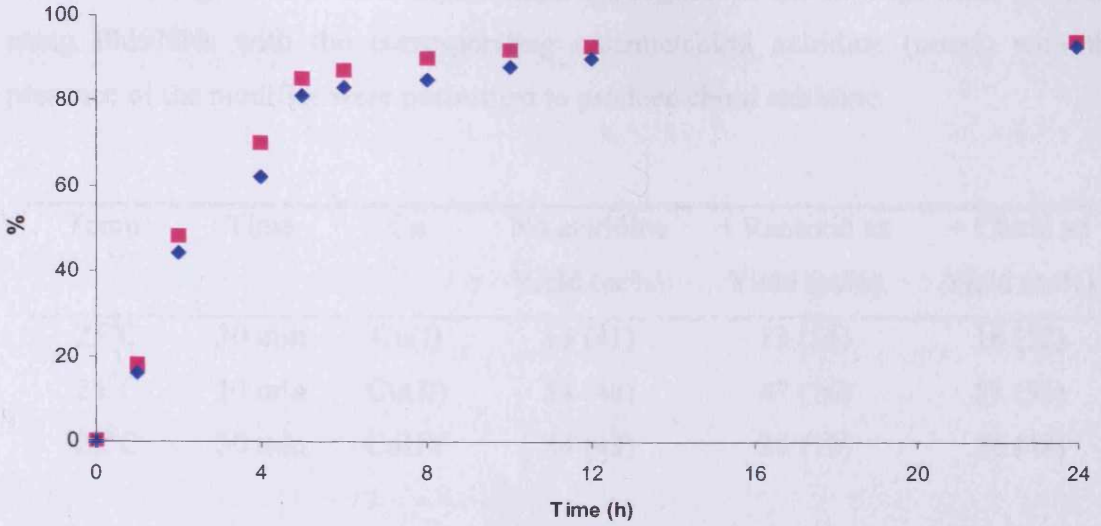


Figure 13: Effect of reaction time on yield of aziridine by addition of the corresponding racemic aziridine [styrene (1mmol) reacted with CuHY (0.3g), PhI=NNs (1.5 mmol) with bis(oxazoline (0.039g) in CH_3CN at 25^0C].

Key: ◆aziridine yield, ■ styrene conversion

5.5.2 Effect on aziridine yield and ee by adding preformed chiral aziridine to the start of the reaction

For the following sets of experiments racemic and chiral nosyl aziridine of a known ee (82% ee for Table 4) was used. The experiments were run for 24 h with the corresponding chiral aziridine stirred in acetonitrile with either Cu(I)/Cu(II)/CuHY, followed by the addition of styrene, PhI=NNs and with the presence of the chiral modifier, bis(oxazoline). The yield is based on the amount of aziridine at the start, and the final ees were recorded.

Table 4: Change in % ee of aziridine when heterogeneous and homogeneous reactions using PhI=NNs with the corresponding racemic/chiral aziridine (nosyl) with the presence of the modifier were performed to produce chiral aziridine.

Temp.	Time	Cu	No aziridine Yield (ee%)	+ Racemic az Yield (ee%)	+ Chiral az Yield (ee%)
25^{0}C	30 min	Cu(I)	15 (41)	13 (15)	18 (52)
25^{0}C	30 min	Cu(II)	54 (48)	47 (16)	51 (55)
25^{0}C	30 min	CuHY	34 (43)	25 (12)	26 (48)
25^{0}C	90 min	Cu(I)	39 (64)	37 (16)	33 (71)
25^{0}C	90 min	Cu(II)	73 (71)	84 (24)	85 (80)
25^{0}C	90 min	CuHY	62 (67)	88 (18)	87 (84)
25^{0}C	300 min	Cu(I)	63 (70)	83 (17)	84 (76)
25^{0}C	300 min	Cu(II)	88 (76)	87 (26)	87 (81)
25^{0}C	300 min	CuHY	81 (79)	91 (22)	92 (84)
25^{0}C	24 h	Cu(I)	79 (73)	90 (18)	91 (77)
25^{0}C	24 h	Cu(II)	90 (81)	89 (27)	89 (82)
25^{0}C	24 h	CuHY	88 (83)	91 (24)	92 (88)

A comparative study was carried out where a standard homogeneously and heterogeneously catalysed reaction was examined in relation to two further reactions where preformed racemic and chiral aziridine were added to the start of the reaction with the nitrene donor and chiral modifier. These set of reactions were carried out to investigate the stability of the chiral aziridine product in the presence of the various reaction components. From the above results (Table 4), it can be seen that the addition of the corresponding chiral nosyl aziridine (ee 82%) increases the overall ee (≥ 5%) of each catalyst tested after 30 minutes in comparison to the results achieved using the

standard reaction, however the yield of aziridine was only increased in the case of Cu(OTf). The addition of the corresponding racemic aziridine produced lower levels of aziridine yield for each catalyst tested compared to the results obtained for the standard reaction after 30 minutes. A notable decrease in ee (~ 30%) for each catalyst was observed after 30 minutes by the addition of racemic aziridine to the start of the reaction. The overall ee was been depressed by the addition of the racemic aziridine to the start of the reaction and this trend continued throughout the lifetime of the reaction. Further investigation of the reactions after 90 minutes revealed similar trends to that of 30 minutes. The enantiomeric excess was again higher when the chiral aziridine was added, than that recorded for the standard reaction. A large difference in ee (17%) was seen for CuHY, with the addition of the chiral aziridine in comparison to standard reaction conditions. For both homogeneously catalysts tested an increase in ee (≥ 7%) was observed. However, notably, the yield of aziridine was now greater with the addition of the chiral aziridine for Cu(II) and CuHY than previously noted after 30 minutes. A slight increase in ee (≥ 6%) was observed for Cu(II) and CuHY after 90 minutes by the addition of racemic aziridine than that of 30 mins. However this was a marked decrease on the ee values (71% and 67%) for the corresponding catalysts tested in a standard reaction at the noted time. However, an increase in aziridine yield was noted for each catalyst tested in comparison to the values recorded for the standard reactions.

After 300 minutes it was observed that there was no significant enhancement in enantiomeric excess or yield of aziridine for any of the catalysts tested by the addition of either the corresponding racemic or chiral aziridine. Only Cu(OTf) showed relevant changes, a marked increase in aziridine yield (~ 50%) was noted in comparison to the yield after 90 minutes. The ee values and aziridine yields were similar to that after 90

minutes for the addition of chiral aziridine for both $Cu(OTf)_2$ and CuHY. The most significant point been that the rate of reaction increased markedly for the two catalysts tested by the addition of the preformed chiral aziridine. The reaction had almost reached completion after 90 minutes. This effect could be seen by representative data (Figures 14 and 15).

After 24h there was no significant change in the observed results, as was the case after 300 minutes. Therefore, it could be concluded that the reaction had reached completion after ~3h, as ee values or aziridine yields did not increase significantly. The final yield of aziridine corresponded to the standard reaction except for Cu(I) where an increase (12%) was observed. An increase in ee (5%) was also observed for the heterogeneous reaction by the addition of the preformed chiral aziridine over the corresponding standard reaction.

During reactions with racemic aziridine, in both the heterogeneous and homogeneous cases, there were observed enhancements in enantioselectivity. As mentioned earlier, in hydrolysis, (which is the selective destruction of one enantiomer over the other) depending upon the preferred enantiomer, either a decrease or increase in enantioselectivity will occur. When the chiral aziridine was present together with all components (*i.e.* catalyst, nitrene donor, and modifier), there was an observed increase in enantioselectivity, which could be simply a result of the addition of further chiral product. A similar amplification of enantiomeric excess has recently been reported by Soai *et al.*[12], which describes the successful enantioselective automultiplication of *sec*-alkanols.

Enantioselectivity exhibited a gradual increase during the reaction with PhI=NNs, this can be seen with all 3 catalysts tested. This effect is termed the initial transient period, has been attributed to the establishment of the chirally active site during the reaction.

In this investigation the gradual increase in enantioselectivity was observed in both the homogeneous and heterogeneous reactions and therefore is not considered to be due to the zeolite framework. Therefore it is apparent that the formation of the chirally active site reaches a steady state during the reaction, presumably as a direct consequence of conversion. Further work is required to study the effect of the addition of chiral product during the aziridination of styrene.

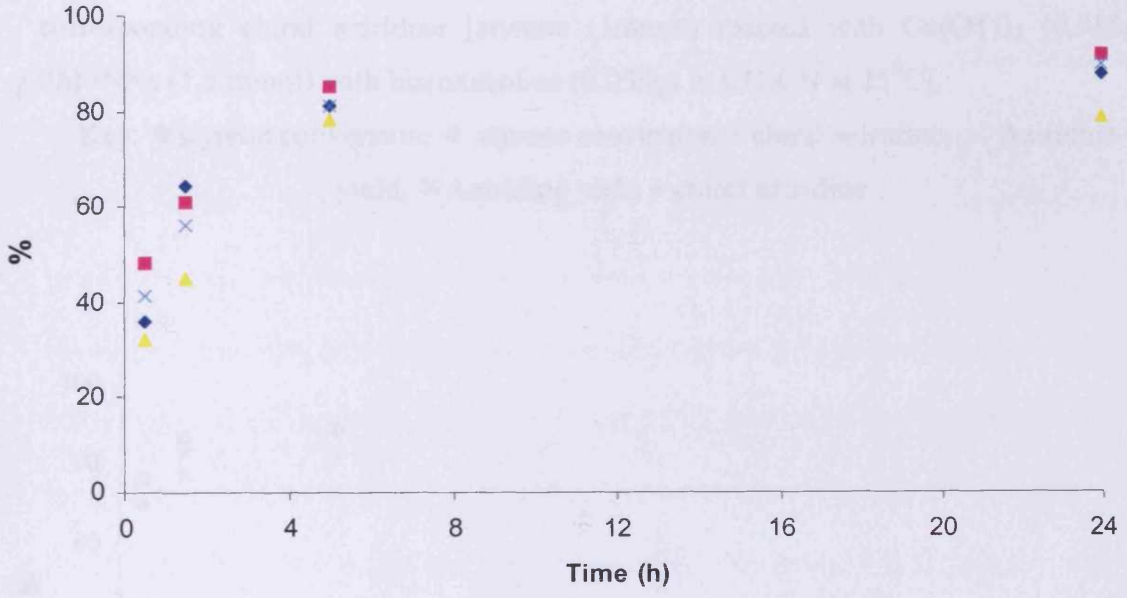


Figure 14: Effect of reaction time on yield of aziridine by addition of the corresponding chiral aziridine [styrene (1mmol) reacted with Cu(OTf) (0.0088g), PhI=NNs (1.5 mmol) with bis(oxazoline (0.039g) in CH_3CN at 25^0C].

Key: ◆styrene conversion, ■ styrene conversion + chiral aziridine, ▲ Aziridine yield, × Aziridine yield + chiral aziridine

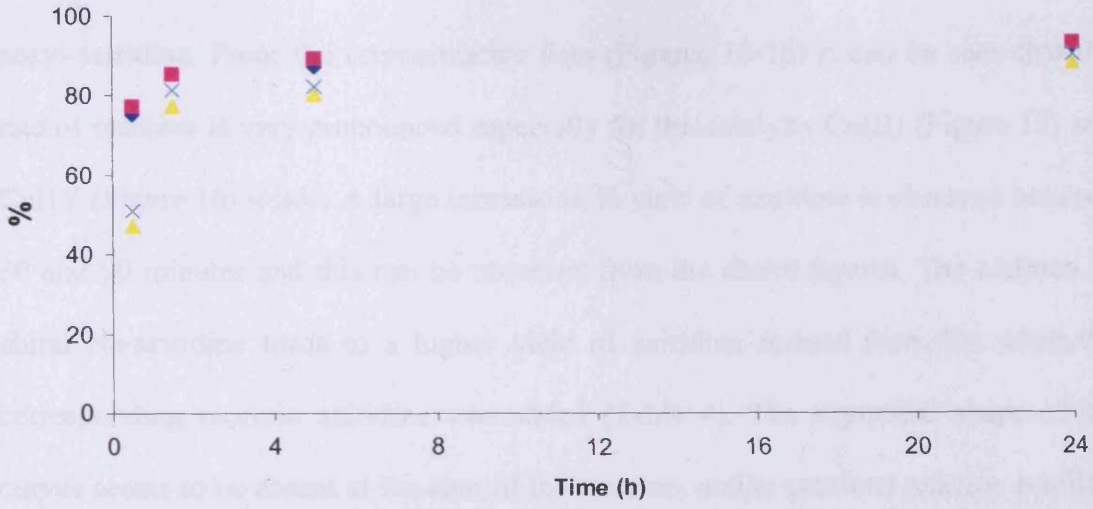


Figure 15: Effect of reaction time on yield of aziridine by addition of the corresponding chiral aziridine [styrene (1mmol) reacted with $Cu(OTf)_2$ (0.015g), PhI=NNs (1.5 mmol) with bis(oxazoline (0.039g) in CH_3CN at 25^0C].

Key: ◆styrene conversion, ■ styrene conversion + chiral aziridine, ▲ Aziridine yield, × Aziridine yield + chiral aziridine

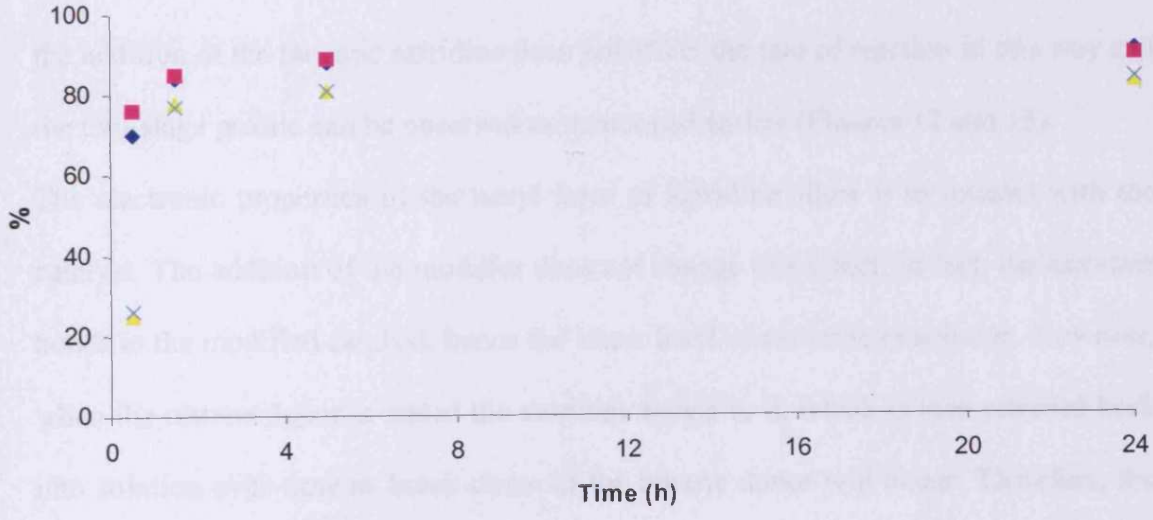


Figure 16: Effect of reaction time on yield of aziridine by addition of the corresponding chiral aziridine [styrene (1mmol) reacted with CuHY (0.3g), PhI=NNs (1.5 mmol) with bis(oxazoline (0.039g) in CH_3CN at 25^0C].

Key: ◆styrene conversion, ■ styrene conversion + chiral aziridine, ▲ Aziridine yield, × Aziridine yield + chiral aziridine

The aziridine added in the experiments was either racemic nosyl-aziridine or chiral nosyl-aziridine. From the representative data (Figures 14-16) it can be seen that the rate of reaction is very pronounced especially for the catalysts Cu(II) (Figure 15) and CuHY (Figure 16) tested. A large increase in % yield of aziridine is observed between 30 and 90 minutes and this can be observed from the above figures. The addition of chiral Ns-aziridine leads to a higher yield of aziridine formed than that when the corresponding racemic aziridine was added (Table 4). The sigmoidal shape of the curves seems to be absent at the start of the reaction, unlike previous reaction profiles, there is not an initial rapid formation of aziridine in the first hour followed by a slow stage, rather the reaction has an initial rapid formation for 90 minutes where it has almost reached completion followed by a constant slow stream to completion after ~3h. Therefore, it would seem that the addition of the preformed chiral aziridine to the heterogeneously and homogeneously reactions removes the first stage in the two-stage reaction profiles that have previously been observed in the standard system. However, the addition of the racemic aziridine does not affect the rate of reaction in this way and the two-stage profile can be observed as mentioned earlier (Figures 12 and 13).

The electronic properties of the nosyl form of aziridine allow it to interact with the catalyst. The addition of the modifier does not change this effect; in fact, the aziridine bonds to the modified catalyst, hence the lower level of aziridine in solution. However, when the nitrene donor is added the aziridine bonds to it, which is then released back into solution over-time as break down of the nitrene donor will occur. Therefore, the catalyst is less effective at bonding with the aziridine when only the PhI=NNs is present, as it appears that the nitrene donor competes for the sites around the catalyst in place of the aziridine. When all three components are added, as in the case of the above reactions, there is a combination of these effects taking place, with the modifier

making the catalyst more accessible to the aziridine than the nitrene donor, but also some aziridine going onto the nitrene donor that is then released back into solution with time as it breaks down.

The same trend is observed for the homogeneous catalyst as the heterogeneous catalyst with the nosyl aziridine. Consequently, these experiments show that there are many complex processes taking place, involving not only concentrations of various reaction components, but also with the mechanisms involved with how the aziridine, once formed, interacts with the catalyst, modifier and nitrene donor.

5.5.3 Effect on aziridine yield and ee by adding preformed chiral aziridine at the start of the reaction, variation in Copper: Aziridine ratio

On the mechanistic side experiments were carried out to test ideas coming from the simulations in both homogeneous and heterogeneous systems. Therefore if Cu(II)/ CuHY were allowed to stand with preformed aziridine (Cu:Az = 1:1, and other various ratios) so as to mimic the situation at the end of the first stage in the standard reaction, *i.e.* the point when the rate of conversion drops almost to zero, would addition of PhI=NNs and styrene reproduce the second stage, especially its autocatalytic form. To examine this idea the following sets of experiments were carried out where nosyl aziridine of a known ee (78% ee for Table 5 and 82% ee for Table 6) was used. The experiments were run for 24 h with the corresponding chiral aziridine stirred in acetonitrile with either $Cu(OTf)_2$ or CuHY, followed by the addition of styrene, PhI=NNs and with/without the presence of the chiral modifier, bis(oxazoline). The yield is based on the amount of aziridine at the start, and the final ees were recorded.

Table 5: Change in % ee of aziridine when heterogeneous and homogeneous reactions using PhI=NNs with the corresponding chiral aziridine (known ee, 78%) without the presence of the modifier were performed to produce chiral aziridine. (Cu: Aziridine ratio varied).

Cu:Az	Cu	S_{start} (g)	R_{start} (g)	See_{start} (%)	S_1 ee_{end} (%)	S_{end} (g)	R_{end} (g)	ΔS (g)	ΔR (g)	Δee (%)
1:0.25	Cu(II)	0.0026	0.0003	78	11	0.0429	0.0337	0.0404	0.0334	S 1(
1:0.5	Cu(II)	0.0051	0.0006	78	13	0.0604	0.0465	0.0553	0.0459	S 9
1:1	Cu(II)	0.0102	0.0013	78	13	0.0605	0.0570	0.0503	0.0557	R 5
1:2	Cu(II)	0.0203	0.0025	78	12	0.0460	0.0586	0.0257	0.0561	R 4
1:5	Cu(II)	0.0507	0.0063	78	14	0.0326	0.0246	0.0181	0.0183	-----
1:0.25	CuHY	0.0016	0.0002	78	61	0.0583	0.0139	0.0569	0.0137	S 61
1:0.5	CuHY	0.0032	0.0004	78	38	0.0755	0.0234	0.0723	0.0230	S 5(
1:1	CuHY	0.0064	0.0008	78	27	0.0547	0.0315	0.0483	0.0307	S 2(
1:2	CuHY	0.0128	0.0016	78	59	0.0677	0.0175	0.0549	0.0307	S 2(
1:5	CuHY	0.0320	0.0040	78	40	0.0519	0.0223	0.0199	0.0183	S 4.

For the above set of experiments, homogeneous and heterogeneous reactions were carried out, with the addition of preformed chiral (*S* been the predominant enantiomer) nosyl aziridine. Prior to the reaction, the chiral aziridine was analysed by HPLC, observing an enantiomeric excess of 78%. However, there was no chiral modifier added to the reaction. The experiments investigated also examined the Cu: aziridine ratio, to examine if there was competitive inhibition of the catalyst by aziridines and bis(oxazoline). Therefore, to see the effects, a range of ratios was used (Table 5). These set of reactions were carried out to further investigate the stability of the chiral aziridine product (5.5.2) in the presence of the various reaction components.

From the above results (Table 5), it can be seen that the addition of the corresponding chiral nosyl aziridine (ee 78%) to the start of the racemic reaction, resulted in a favourable ee of each catalyst tested after completion of the reaction (24h). For the homogeneously catalysed reaction the ee at the end of the reaction was similar (11%-14%) for each Cu: aziridine ratio tested. The ee varied (3%) over the range of Cu: aziridine ratio. However, significant enantiomeric excess was recorded at the end of the reaction for the heterogeneously catalysed reactions. At a low Cu: aziridine ratio (1:0.25) an ee (61%) was recorded. The lowest ee (27%) was recorded at 1:1 ratio, however the ee increased once more as the Cu: aziridine ratio was increased, an ee (59%) was noted for 1 Cu: 2 aziridine.

The change in ee (Δ ee) was measured at the end of the reaction (Table 5). From these results, it was noted that the predominant enantiomer (*S*) of the chiral aziridine added in the absence of bis(oxazoline) did not give the opposite stereochemistry in the aziridine subsequently produced for the heterogeneously catalysed reactions. The Δ ee values recorded would suggest that there is no significant effect from adding chiral aziridine to the start of the reaction. However, for the heterogeneously catalysed reaction at lower Cu: aziridine ratios (1: 0.25) the Δ ee value (61%) was significantly higher. Although there was no promotion in ee from the addition of chiral aziridine, in fact at Cu: aziridine ratio (1:5) there was a distinct decrease in Δ ee (4%) observed. Further reactions (Table 7) were carried out at lower Cu: aziridine concentrations to examine whether the addition of chiral aziridine could promote or even inhibit the ee for the final aziridine product in the reaction system.

However, in the homogeneously catalysed reactions, at high ranges (1:1 and 1:2) of Cu: aziridine, there was a change in the stereochemistry from *S* to *R* in the aziridine subsequently produced. This was the only example of a change in stereochemistry

occurring. The low ee values obtained at the end of the reaction and the Δ ee values obtained would suggest that the preformed chiral aziridine is not having an effect in promoting ee in the homogeneous system. Over a period of time, racemisation of the enantiomers will inevitably occur. Also, as mentioned earlier (5.2.3) the breakdown products of the nitrogen source (PhI and corresponding sulphonamide) are having an inhibiting effect on the enantioselectivity. However, it is important to note that these results are only preliminary results. It would be necessary to carry out multiple repeat reactions in order to obtain more reliable data sets.

Table 6: Change in % ee of aziridine when heterogeneous and homogeneous reactions using PhI=NNs with the corresponding chiral aziridine (known ee, 82%) with the presence of the modifier (*S,S*) were performed to produce chiral aziridine. (Cu: Aziridine ratio varied).

Cu:Az	Cu	S_{start} (g)	R_{start} (g)	See $_{start}$ (%)	S_1 ee_{end} (%)	S_{end} (g)	R_{end} (g)	ΔS (g)	ΔR (g)	Δee (%)
1:0.25	Cu(II)	0.0026	0.0003	82	95	0.1143	0.0029	0.1117	0.0027	S 95
1:0.5	Cu(II)	0.0052	0.0006	82	97	0.0739	0.0011	0.0687	0.0006	S 97
1:1	Cu(II)	0.0104	0.0010	82	94	0.0818	0.0025	0.0714	0.0015	S 96
1:2	Cu(II)	0.0207	0.0021	82	97	0.0862	0.0013	0.0653	0.0007	------
1:5	Cu(II)	0.0519	0.0051	82	72	0.0926	0.0073	0.0407	0.0020	S 91
1:0.25	CuHY	0.0016	0.0002	82	53	0.0564	0.0173	0.0547	0.0172	S 7
1:0.5	CuHY	0.0033	0.0003	82	78	0.0837	0.0103	0.0805	0.0101	S 78
1:1	CuHY	0.0066	0.0007	82	73	0.0356	0.0056	0.0290	0.0049	S 71
1:2	CuHY	0.0125	0.0013	82	76	0.0501	0.0068	0.0376	0.0055	S 74
1:5	CuHY	0.0328	0.0032	82	86	0.0639	0.0048	0.0311	0.0016	S 90

For the above set of experiments (Table 6), homogeneously and heterogeneously reactions were carried out, with the addition of preformed chiral nosyl aziridine. Prior to the reaction, the chiral aziridine was analysed by HPLC, observing an enantiomeric excess of 82%. However, in comparison to earlier experiments (Table 5) carried out, the chiral modifier, bis(oxazoline) was added to the start of the reaction.

The most significant effect observed from the above results (Table 6) is the marked change in the results obtained for the homogeneous system compared to the results obtained for the homogeneously catalysed system observed (Table 5). The effect caused by the addition of the chiral modifier is significant. The addition of the chiral aziridine together with all components (*i.e.* catalyst, nitrene donor, modifier) leads to an increase in enantioselectivity observed. This was observed for Cu: aziridine ratios tested, except at high levels (1:5) where there was a decrease in ee (72%) observed at the end of the reaction. The Δ ee values recorded are comparable with the ee values obtained at the end of the reaction, in fact, in some cases (1:1 and 1:5) there is an enhancement in enantiomeric excess. For the heterogeneously catalysed reaction, it seems that the extra aziridine is competing with the bis(oxazoline) for the available sites in the zeolite. Therefore, the preformed aziridine is promoting the ee, as mentioned earlier; the ee obtained is increasing with conversion over time[7]. It is known that ligands can influence the rate of metal-catalysed reactions and often-significant promotion on the rate of reaction and enhancement in ee is observed. It has been shown that this approach can be extended to heterogeneous catalysts[13]. However the addition of the preformed aziridine has an effect on the rate of reaction; the first phase of the two-stage sigmoidal curve is removed and the reaction proceeds straight to the second phase of the curve (Figures 17 and 18).

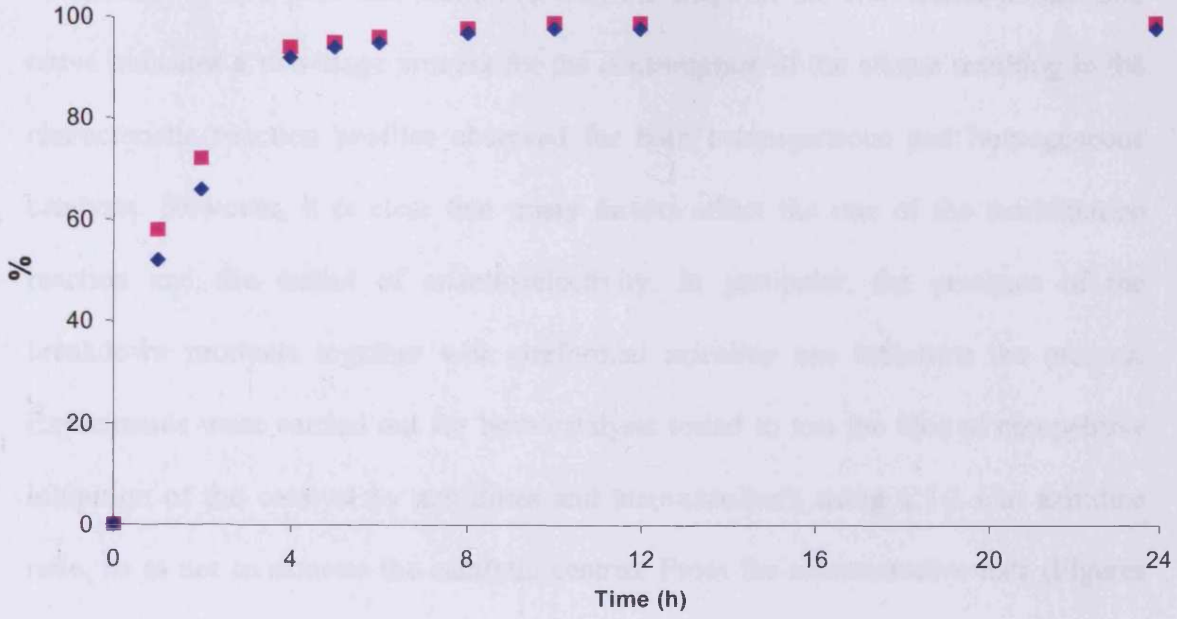


Figure 17: Effect of reaction time on yield of aziridine by addition of the corresponding chiral aziridine [styrene (1mmol) reacted with $Cu(OTf)_2$ (0.015g), PhI=NNs (1.5 mmol) with bis(oxazoline (0.039g) in CH_3CN at 25^0C, (Cu: aziridine = 1:1)]. Key: ◆aziridine yield, ■ styrene conversion

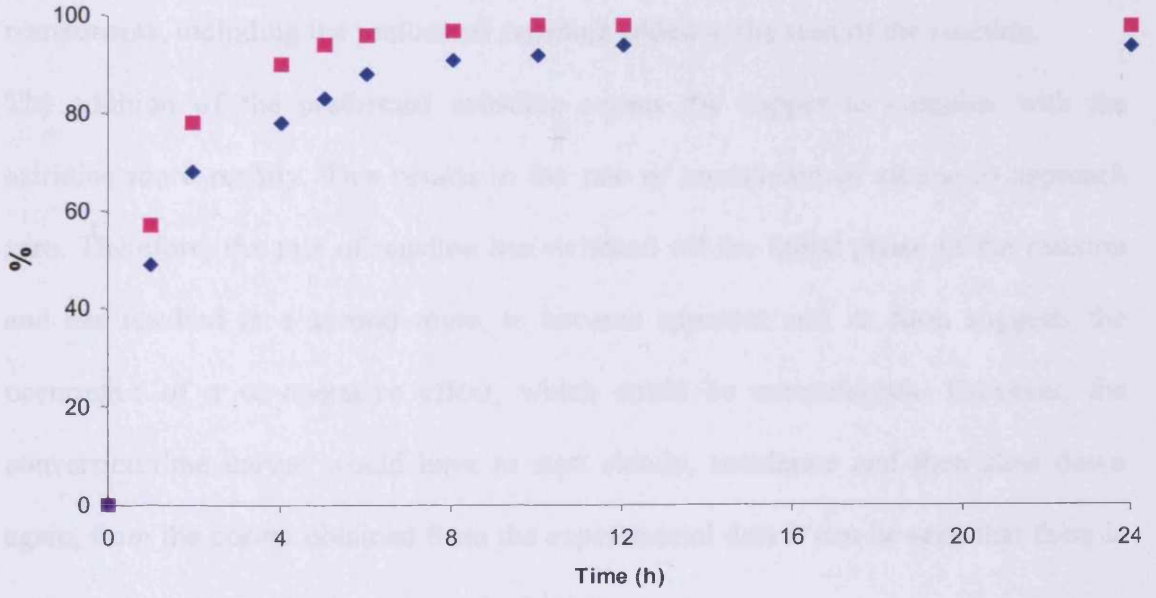


Figure 18: Effect of reaction time on yield of aziridine by addition of the corresponding chiral aziridine [styrene (1mmol) reacted with CuHY (0.3g), PhI=NNs (1.5 mmol) with bis(oxazoline (0.039g) in CH_3CN at 25^0C, (Cu: aziridine = 1:1)].

Key: ◆aziridine yield, ■ styrene conversion

As mentioned in a previous section (5.4.2), the shape of the conversion *versus* time curve indicates a two-stage process for the consumption of the alkene resulting in the characteristic reaction profiles observed for both heterogeneous and homogeneous catalysts. However, it is clear that many factors affect the rate of the aziridination reaction and the extent of enantioselectivity. In particular, the presence of the breakdown products together with preformed aziridine can influence the process. Experiments were carried out for both catalysts tested to test the idea of competitive inhibition of the catalyst by aziridines and bis(oxazoline), using a 1:1 Cu: aziridine ratio, so as not to saturate the catalytic centres. From the representative data (Figures 17 and 18), it can be seen that the addition of the preformed aziridine switches "off" the initial rapid reaction and rather starts at the second phase where a relative reaction profile is observed. This effect is observed for both the homogeneously and heterogeneously catalysed systems. This type of behaviour is likely to result from competitive interaction at the active centre of the many competing reaction components, including the preformed aziridine added to the start of the reaction.

The addition of the preformed aziridine causes the copper to complex with the aziridine more readily. This results in the rate of conversion of alkene to approach zero. Therefore, the rate of reaction has switched off the initial phase of the reaction and has resulted in a second route, to become apparent and its form suggests the occurrence of a co-operative effect, which could be autocatalysis. However, the conversion/time curves would have to start slowly, accelerate and then slow down again, from the curves obtained from the experimental data it can be seen that there is not a gradual start in the formation of aziridine.

Table 7: Change in % ee of aziridine when heterogeneous (CuHY) reactions using PhI=NNs with the corresponding chiral aziridine (known ee, 78%, 82%, 95% and 97%) without the presence of the modifier were performed to produce chiral aziridine. (Cu: Aziridine ratio varied).

Cu:Az	S_{start} (g)	R_{start} (g)	See $_{start}$ (%)	S_1 ee_{end} (%)	S_{end} (g)	R_{end} (g)	ΔS (g)	ΔR (g)	Δee (%)
1:1	0.0064	0.0008	78	30	0.0560	0.0302	0.0496	0.0294	S 26
1:2	0.0128	0.0016	78	32	0.0562	0.0290	0.0434	0.0274	S 21
1:0.25	0.0016	0.0002	82	49	0.0529	0.0186	0.0513	0.0184	S 47
1:0.5	0.0032	0.0004	82	36	0.0513	0.0242	0.0481	0.0238	S 34
1:0.25	0.0018	.00003	97	63	0.0580	0.0136	0.0562	0.0136	S 61
1:0.5	0.0036	.00005	97	52	0.0574	0.0181	0.0538	0.0181	S 50
1:0.05	0.0003	.00004	95	58	0.0686	0.0183	0.0683	0.0183	S 58

Further experiments were carried out for the heterogeneously catalysed system to investigate the effect of adding high ee values (≥ 95%) of the chiral aziridine product to the start of the reaction. Lower levels of Cu: aziridine (1:0.05) were examined to study the possible promotion of ee by the preformed aziridine.

The above reactions (Table 7) were a repeat of the reactions carried out previously (Table 5), except that the ee value of the preformed chiral (*S*) aziridine added was higher than that of previously. Prior to the reaction, the chiral aziridine was analysed by HPLC, observing an enantiomeric excess of 78%, 82%, 95% and 97% respectively. However, there was no chiral modifier added to the reaction. From the above results (Table 7), it can be seen that the addition of the corresponding chiral nosyl aziridine (ee 78%) to the start of the racemic reaction, resulted in similar results to the identical reaction carried out earlier (Table 5). The Δ ee values (26% and 21%) correspond to

the earlier ee values (22% and 28%) for Cu: aziridine ratios tested. This was followed by experiments where the addition of chiral aziridine (82%) ee was a direct comparison to previous experiments using preformed aziridine (78% ee). The resulting reaction afforded ee values (49% and 36%) at the end of the reaction, these results were lower than that recorded for similar Cu: aziridine ratios (1:0.25 and 1:0.5) using chiral aziridine (78% ee). This was also reflected in the Δ ee results obtained. The Δ ee values obtained (Table 7) (47% and 34%) were lower than that recorded at the end of the reaction and therefore followed a similar trend to the Δ ee values recorded in Table 5. The next set of experiments investigated was to use the same Cu: aziridine ratio (i.e. 1:0.25 and 1:0.5) respectively, but adding chiral aziridine (97% ee) to the start of the reaction. These experiments afforded high levels of ee (63% and 52%) at the completion of the reaction (24 h). The Δ ee values (61% and 50%) were similar to that recorded at the end of the reaction. However, a point to note was, that by adding aziridine with a high ee (97%) at the start of the reaction, resulted in a higher value of ee at the end of the reaction in comparison to similar reactions using preformed aziridine with a lower value of ee (78% and 82%). This trend was also seen in the Δ ee values recorded. Following on from this it was also noted that the highest levels of ee and Δ ee were recorded at a low Cu: aziridine ratio (i.e. 1:0.25). This was reflected over the range of values of ee of chiral aziridine added at the start of the reaction. Therefore, a further experiment was carried out to test the assumptions that at lower levels of Cu: aziridine the preformed chiral aziridine enhanced the final enantiomeric excess of the product. A heterogeneous experiment was conducted with Cu: aziridine (1:0.05) and with the addition of preformed chiral nosyl aziridine (95% ee). However, the ee value (58%) achieved at the end of the reaction and the Δ ee value (58%) did not follow the trend expected and in fact gave lower values than that achieved using a

Cu: aziridine (1: 0.25). The Δ ee values recorded would suggest that there is no significant effect from adding chiral aziridine to the start of the reaction. Although from the experiments carried out the most favourable results were obtained at Cu: aziridine levels of 1: <1, because of the possibility of saturation of the catalytic centres at higher Cu: aziridine levels. However, another possibility is that the aziridine is a poorer ligand for Cu than the oxazoline, so that in the above experiments (Table 7) there is significantly more catalysis by non-modified Cu, which would then yield racemic aziridine.

Nonlinear behaviour in asymmetric catalysis[14] is typically reported as product enantioselectivity (ee_{prod}) vs. catalyst enantiomeric excess (ee_{cat}), where a positive deviation from the linear relationship is termed an "asymmetric amplification" of ee_{prod}. Less emphasis has been placed on the consequences for reaction rate, although even the earliest discussions of such nonlinear effects noted influences on both product ratio and reaction rate[15]. The possibility of asymmetric amplification has been well established recently[16] and seems a consequence of the intervention of positive nonlinear effects. There are quite a few identified asymmetric autocatalytic reactions[17]. Addition of dialkylzinc compound to aromatic aminoaldehydes was the reaction pioneered by Soai *et al.*[18] in the search of autocatalytic systems. Subsequent investigations by Soai *et al.*[18] on various types of aromatic aldehydes allowed the ee value of the product to be increased, which was also obtained with the same absolute configuration as the initiator.

A catalytic enantioselective autoinductive reaction is a process that may be used to propagate high ee's. This process is based on stereoselective reactions in which the products initially formed may influence the steroselectivity of the proceeding reaction. Soai *et al.*[19] recently reported a catalytic enantioselective reaction with autoinduction

in the particular case of addition of diisoproplyzinc on an aromatic dialdehyde. The absolute configuration of the product was found to be the same as for the initiator engaged in the catalyst. However the product was obtained in lower ee value (30%) than the initial ee value (> 99%).

From the experiments carried out above it was observed that the addition of the chiral aziridine together with all components resulted in an increase in enantioselectivity. In the experiments carried out the observed increase in enantiomeric excess by the addition of chiral aziridine was observed after complete conversion of the styrene.

Similar amplifications have been mentioned above. However, as mentioned earlier, at this stage the possibility of autocatalysis and autoinduction cannot be ruled out and further work is required to study the effect of the chiral product to the start and during the aziridination of styrene.

5.6 Effect on % ee of aziridine by variation of copper: chiral modifier ratio

For the set of experiments below (Table 8), homogeneously and heterogeneously reactions were carried out to investigate the effect of altering the Cu: chiral modifier ratio. Therefore, the following results represent the variation of the amount of bis(oxazoline) and its effect on ee in the aziridination reaction with styrene. For the standard homogeneous and heterogeneous reaction the mol ratio for Cu: bis(oxazoline) was calculated to be 1:3, therefore a list of experiments were conducted in which the amount of bis(oxazoline) was increased and decreased in relation to the Cu to study its effect on ee in the reaction system.

Table 8: Change in % ee of aziridine when heterogeneous and homogeneous reactions using PhI=NNs with the presence of the modifier were performed to produce chiral aziridine. (Cu: bis(oxazoline) ratio varied).

Mol ratio bis (ox): $Cu(OTf)_2$	**(ee) after 24h**	**Mol ratio bis (ox): CuHY**	**(ee) after 24h**
1:1	79	1:1	79
2:1	81	2:1	79
*3:1	87	3:1	80
4:1	81	*4:1	81
5:1	79	5:1	79
		6:1	79

*Represents standard mol ratio of bis(ox)/Cu for this reaction

From the results recorded (Table 8) it was observed that by varying the amount of bis(oxazoline) in the reaction resulted in an adverse effect on the ee of the final product, aziridine. Similar trends in results were observed for both catalysts tested and this can be observed by the representative data (Figures 19 and 20). For the homogeneously catalysed reaction increasing the amount of bis(oxazoline) from the standard ratio (3:1), which gave, an ee (87%) leads to a decrease in enantiomeric excess (79%) at a ratio (5:1). This effect was also observed by lowering the amount of bis(oxazoline) added, i.e. an ee (79%) was observed at the lowest Cu: bis(oxazoline) ratio tested (1:1). These effects were also observed for the heterogeneously catalysed reaction, where the highest ee (81%) observed was at the standard Cu: bis(oxazoline) ratio (1:4). By enhancing the amount of bis(oxazoline) or even decreasing the amount, similar effects were observed where the ee values (79%) respectively, decreased on the values obtained using the standard mol Cu: bis(oxazoline).

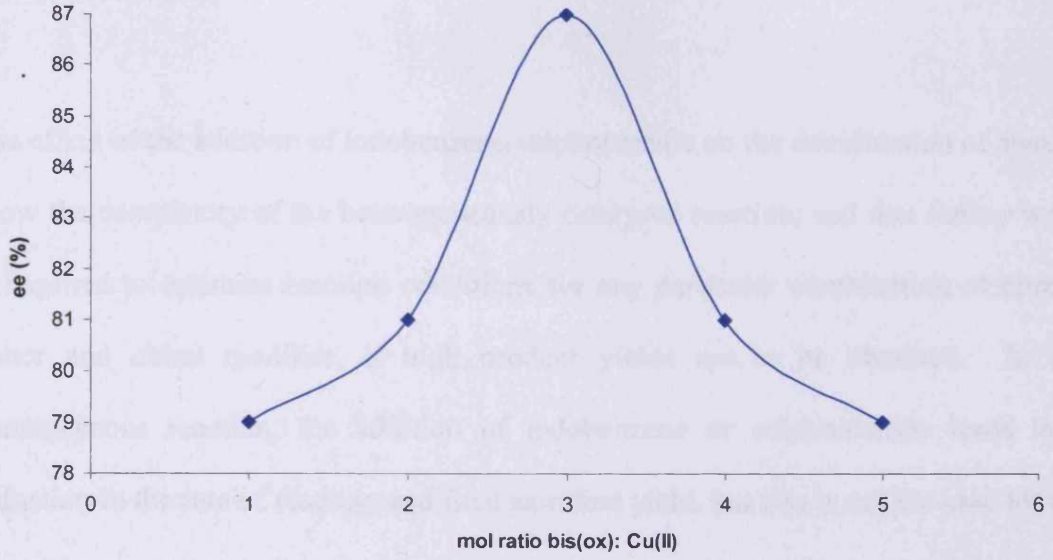


Figure 19: Effect of bis(oxazoline): Cu ratio on ee of aziridine [styrene (1mmol) reacted with $Cu(OTf)_2$ (0.015g), PhI=NNs (1.5 mmol) with bis(oxazoline) in CH_3CN at 25^0C]. Key: ◆aziridine (ee %)

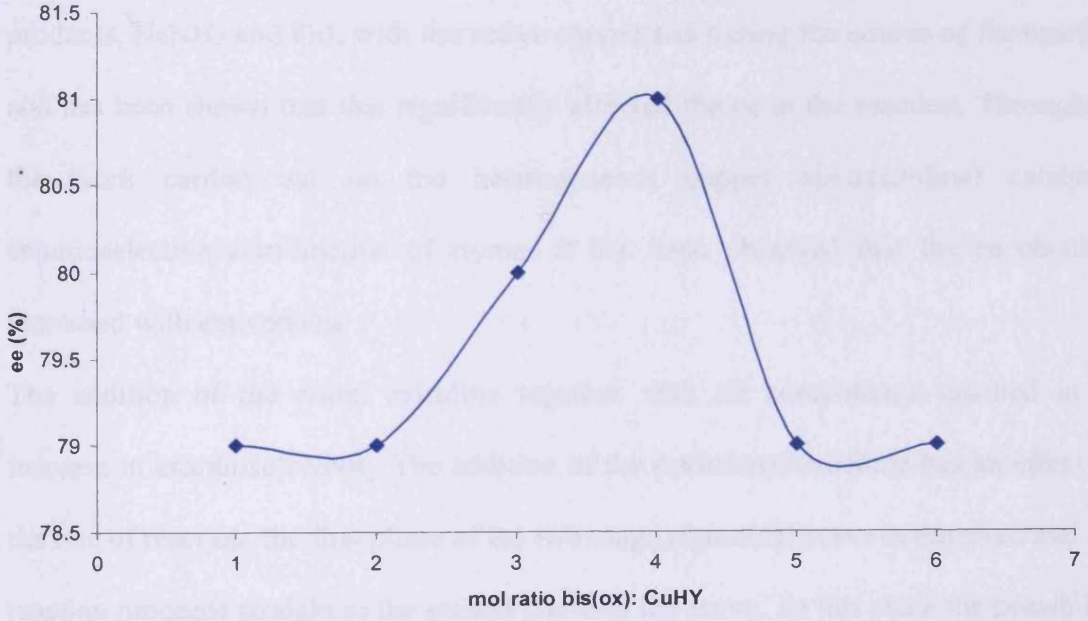


Figure 20: Effect of bis(oxazoline): Cu ratio on ee of aziridine [styrene (1mmol) reacted with CuHY (0.3g), PhI=NNs (1.5 mmol) with bis(oxazoline) in CH_3CN at 25^0C]. Key: ◆aziridine (ee %)

5.7 Conclusions

The effect of the addition of iodobenzene/sulphonamide on the aziridination of styrene show the complexity of the heterogeneously catalysed reaction, and that further work is required to optimise reaction conditions for any particular combination of nitrene donor and chiral modifier, if high product yields are to be obtained. In the homogeneous reaction, the addition of iodobenzene or sulphonamide leads to a reduction in the rate of reaction and final aziridine yield, but this is not the case for the heterogeneously catalysed reaction.

The formation of aziridine with reaction time demonstrates a complex profile, which, although more pronounced in the heterogeneously catalysed reaction, is still observed in the homogeneously catalysed reaction using $Cu(OTf)_2$ as catalyst. This effect is considered to be caused in part by the interaction of the product, aziridine, and the by-products, $NsNH_2$ and PhI, with the active copper site during the course of the reaction and has been shown that this significantly affected the ee in the reaction. Throughout the work carried out on the heterogeneous copper bis(oxazoline) catalysed enantioselective aziridination of styrene it has been observed that the ee obtained increased with conversion.

The addition of the chiral aziridine together with all components resulted in an increase in enantioselectivity The addition of the preformed aziridine has an effect on the rate of reaction, the first phase of the two-stage sigmoidal curve is removed and the reaction proceeds straight to the second phase of the curve. At this stage the possibility of autocatalysis and autoinduction cannot be ruled out and further work is required to study the effect of the chiral product to the start and during the aziridination of styrene.

5.8 References

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Chapter 6

Conclusions & Future work

6.0 Conclusions

6.1 Aziridination of styrene derivatives

In conclusion, it has been demonstrated that copper-exchanged zeolite Y, when modified by chiral bis(oxazoline) ligands, can be an effective enantioselective heterogeneous aziridination catalyst.

In the catalysed aziridination of styrene derivatives using copper-bis(oxazoline) complexes with PhI=NNs, higher enantioselection can be achieved with the heterogeneously catalysed reaction when compared with the homogeneously catalysed reaction. This is evident with 2-, 3- and 4-chlorostyrene which all gave higher ee (ranging from 88-95%) using the heterogeneous catalyst when compared to the ee of homogeneous catalyst (83-93%). The effect is considered to be due mainly to the enhanced confinement of the substrate within the pores of the zeolite. This confinement effect also contributes to the increased stability of the heterogeneous catalyst for the reaction of styrene derivatives when compared with the reaction of styrene.

The structure of the styrene derivative has a marked effect on the rate of aziridination and by-product formation. This is evident especially with 4-chlorostyrene where particularly high yields (85-90%) and ee ($\geq$ 93%) are observed with both catalyst systems.

Competitive reactions in which styrene and a styrene derivative are reacted together reveal that the rate of styrene aziridination is enhanced by the presence of substituted styrenes; this is evident for 2-, 3- and 4-chlorostyrene, whereas the rate of aziridination of the substituted styrene is suppressed by the presence of styrene. Further competitive

experiments showed that the rate of aziridination is enhanced by reactions involving 2- and 4-chlorostyrene for both homogeneously and heterogeneously catalysed reactions where confinement effects play a role in enhancing the rate in the heterogeneous reaction.

6.2 Spectroscopic study of the catalytic asymmetric aziridination of styrene

In the presence of bis(oxazoline), variation in both aziridine yield and ee was observed in the different solvents tested. The homogeneous catalyst $Cu(OTf)_2$ was observed to give higher yields and ee of aziridine using PhI=NTs as nitrene donor compared to Cu(OTf). Methanol and acetonitrile, both of which are coordinating solvents, afforded enantioselectivities ($\geq$ 46%). However, reaction rates and yields were enhanced for both the homogeneously and heterogeneously catalysed reactions when using MeCN as solvent. This demonstrates that the product yields and enantioselectivity for both the homogeneous and heterogeneous systems are strongly dependent on the choice of solvent and catalyst used in the aziridination reaction.

The formation of aziridine with reaction time demonstrates a complex profile, which, although more pronounced in the heterogeneously catalysed reaction, is still observed in the homogeneously catalysed reaction using Cu(I) and Cu(II) as catalyst. This effect is caused in part by the interaction of the product, aziridine, and the by-products, $TsNH_2$ and PhI, with the active copper site during the course of the reaction.

As expected, EPR and UV-vis spectroscopy confirmed the formation of the Cu-bis(oxazoline) complex as central to the catalytic reaction in homogeneous solution (the enantioselectivity being related to the chirality of this complex). Both the Cu-

complex containing a single bis(oxazoline) group, and two bis(oxazoline) groups appear to be active in the reaction. In addition, both oxidation states of copper (II and I) are effective in the catalytic reaction. No evidence has been found for the formation of any copper nitrene type intermediate, proposed in the literature (although the lifetime of these intermediates may be outside the scope of EPR and UV-vis data).

6.3 Effect of reaction parameters on enantioselectivity and the reaction profile

The effect of the addition of iodobenzene/sulphonamide on the aziridination of styrene show the complexity of the heterogeneously catalysed reaction, and that further work is required to optimise reaction conditions for any particular combination of nitrene donor and chiral modifier, if high product yields are to be obtained. In the homogeneous reaction, the addition of iodobenzene or sulphonamide leads to a reduction in the rate of reaction and final aziridine yield, but this is not the case for the heterogeneously catalysed reaction.

On the mechanistic side experiments were carried out to test ideas coming from the simulations in both homogeneous and heterogeneous systems. A change in % ee and yield of aziridine was observed when racemic nosyl aziridine was added to both homogeneously and heterogeneously reactions with/without the chiral modifier added. When aziridine was stirred with the catalyst, in the absence of the modifier, the amount of aziridine remaining at the end of 24 h was greatly reduced for both homogeneously and heterogeneously modified catalysts, but a small ee was induced (~14%) when the modifier was present in the heterogeneous and homogeneous

reactions. During reactions with racemic aziridine, in the heterogeneous and homogeneous case, enantioselectivity was observed.

An interesting observation with these reaction time studies concern the nature of the reaction profile for both styrene conversion and aziridine yield. The results showed that the reaction profiles were similar whether the modifier was present or not. This effect was more pronounced in the heterogeneously catalysed reactions. The sigmoid curve was seen in all cases when the modifier was present. These trends in profile are comparable with previous experiments carried out.

The stability of the chiral aziridine product in the presence of the various reaction components was investigated. The addition of chiral nosyl aziridine (ee 82%) increased the overall ee (≥ 5%) of each catalyst (Cu(I)/Cu(II)/CuHY) tested after 30 minutes in comparison to the results achieved using the standard reaction. The addition of the corresponding racemic aziridine produced lower levels of aziridine yield for each catalyst tested compared to the results obtained for the standard reaction after 30 minutes. The overall ee was being depressed by the addition of the racemic aziridine to the start of the reaction and this trend continued throughout the lifetime of the reaction. Further investigation of the reactions after 90 minutes revealed similar trends to that of 30 minutes. After 300 minutes it was observed that there was no significant enhancement in enantiomeric excess or yield of aziridine for any of the catalysts tested by the addition of either the corresponding racemic or chiral aziridine. During reactions with racemic aziridine, in both the heterogeneous and homogeneous cases, there were observed enhancements in enantioselectivity. When the chiral aziridine was present together with all components (*i.e.* catalyst, nitrene donor, and modifier), there

was an observed increase in enantioselectivity. The same trend was observed for the homogeneous catalyst as the heterogeneous catalyst with the nosyl aziridine. Consequently, these experiments showed that there are many complex processes taking place, involving not only concentrations of various reaction components, but also with the mechanisms involved with how the aziridine, once formed, interacts with the catalyst, modifier and nitrene donor.

The stability of the chiral aziridine product in the presence of the various reaction components was studied. The addition of the corresponding chiral nosyl aziridine (ee 78%) to the start of the racemic reaction, resulted in a favourable ee of each catalyst tested after completion of the reaction. The Δ ee values recorded would suggest that there was no significant effect from adding chiral aziridine to the start of the reaction. The low ee values obtained at the end of the reaction and the Δ ee values obtained would suggest that the preformed chiral aziridine is not having an effect in promoting ee in the homogeneous system. The breakdown products of the nitrogen source (PhI and corresponding sulphonamide) are having an inhibiting effect on the enantioselectivity.

The effect caused by the addition of the chiral modifier was significant. The addition of the chiral aziridine together with all components (*i.e.* catalyst, nitrene donor, modifier) leads to an increase in enantioselectivity observed. This was observed for Cu: aziridine ratios tested, except at high levels (1:5) where there was a decrease in ee (72%) observed. The Δ ee values recorded were comparable with the ee values obtained at the end of the reaction, in fact, in some cases (1:1 and 1:5) there was an enhancement in enantiomeric excess. Addition of the preformed chiral aziridine had an

effect on the rate of reaction; the reaction starts sooner and the first phase of the two-stage sigmoidal curve is removed.

A further experiment was carried out to test the assumptions that at lower levels of Cu: aziridine the preformed chiral aziridine enhanced the final enantiomeric excess of the product. The results achieved in the heterogeneous reaction showed that the ee value (58%) achieved at the end of the reaction and the Δ ee value (58%) did not follow the trend expected and in fact gave lower values than that achieved using a higher Cu: aziridine ratio. The Δ ee values recorded would suggest that there is no significant effect from adding chiral aziridine to the start of the reaction. Although from the experiments carried out the most favourable results were obtained at Cu: aziridine levels of 1: <1, because of the possibility of saturation of the catalytic centres at higher Cu: aziridine levels.

The shape of the conversion *versus* time curve indicated a two-stage process for the consumption of the alkene resulting in the characteristic reaction profiles observed for both heterogeneous and homogeneous catalysts. However, it is clear that many factors affect the rate of the aziridination reaction and the extent of enantioselectivity. In particular, the presence of the breakdown products together with preformed chiral aziridine can influence the process. It can be seen that the addition of the preformed chiral aziridine switches "off" the initial rapid reaction and rather starts at the second phase where a reaction profile is observed. This effect was observed for both the homogeneously and heterogeneously catalysed systems. This type of behaviour is likely to result from competitive interaction at the active centre of the many competing reaction components, including the preformed aziridine added to the start of the

reaction. However, the addition of the racemic aziridine did not affect the rate of reaction in this way and the two-stage profile was observed.

The addition of the preformed aziridine would seem to help the copper to complex with the aziridine more readily. This resulted in the rate of conversion of alkene to approach zero. Therefore, the rate of reaction has switched off the initial phase of the reaction and has resulted in a second route, to become apparent and its form suggests the occurrence of a co-operative effect, which could be autocatalysis. Further work is required to study the effect of the addition of chiral product at the start and during the aziridination of styrene.

6.4 Future work

The development of the heterogeneous catalytic system using zeolites is achieving considerable success in recent times. This has opened up a vast area of research. Although various substrates were examined in the course of this project and proved successful in achieving higher enantioselection than with styrene, further substrates could be examined. It is thought that attempted asymmetric aziridination of more bulky substrates would lead to improved enantioselectivity. This work could then involve other larger-pore zeolites, such as MCM-41 in order to work with the more bulky substrates. Previously in the group[1] it has been shown that that CuMCM-41 is effective in catalysing the aziridination reaction. This material reduces diffusion and confinement effects and could be further examined in the heterogeneous aziridination reaction.

Further competitive aziridination reactions could be examined in order to achieve high enantioselection. Reactions could be carried out using styrene and the appropriate Cl substituted ethylbenzene, this could then be compared to the results achieved using styrene and the appropriate chlorostyrene. Therefore, further improvements in the reaction system maybe achieved by altering the solvent polarity in the reaction or changing the composition of the solvent sphere around the active site. This may cause changes in the conformation of the transition state or alter the balance of inhibition/ racemic reaction with the enantioselective reaction.

Bis(oxazoline) has been used as a chiral modifier in the aziridination reaction throughout the course of this project. Therefore, bis(oxazolines) with larger substituents could also be used as ligands to improve enantioselectivity. The

computer-modelling group[2] within Cardiff have shown that altering the size of the oxazoline ring which coordinates to the metal can have a significant effect as activation barriers are changed. Therefore, making these oxazoline structures and then using them in the aziridination reaction could be used for further study of the system.

The effect of the addition of iodobenzene/sulphonamide on the aziridination of styrene[3] show the complexity of the heterogeneously catalysed reaction, and that further work is required to optimise reaction conditions for any particular combination of nitrene donor and chiral modifier, if high product yields are to be obtained.
However, addition of the chiral aziridine to the start of the reaction leads to an increase in enantioselectivity. Further investigation is required to fully determine the role of the chiral aziridine, (i.e. whether the chiral product autocatalyses the formation of the aziridine) and in the improved enantioselectivity observed. Further work could also include the deracemisation reactions of either the chiral or racemic aziridine in the presence of a variety of metal-exchanged zeolites, e.g. Mn, Co etc.

The formation of aziridine with reaction time demonstrates a complex profile[4], which, although more pronounced in the heterogeneously catalysed reaction, is still observed in the homogeneously catalysed reaction using $Cu(OTf)_2$ as catalyst. This effect is considered to be caused in part by the interaction of the product, aziridine, and the by-products, $NsNH_2$ and PhI, with the active copper site during the course of the reaction and has been shown that this significantly affected the ee in the reaction. Further work is required to interpret the two-phase conversion *versus* time curve that results and to fully eludicate the mechanism involved in the reaction. Therefore, further simulations of the kinetics involved in the reaction are required to interpret the

two-phase conversion *versus* time curve fully. Further experiments involving the addition of preformed aziridine to both the homogeneously and heterogeneously catalysed reactions are required to investigate the switching "off" of the first phase of the reaction profile. This would involve the addition of both chiral and racemic preformed aziridine to the start of the reaction. Investigation into the Cu: aziridine ratio, where the aziridine is added at the start of the reaction without modifier present could be further examined. An enhancement in ee was observed. Therefore, lower Cu: aziridine ratios could be examined to achieve high enantioselectivity at the end of the reaction without any modifier present. A clearer understanding of the complexing of Cu(II) by aziridine alone and in conjunction with bis(oxazoline) is required in order to understand fully the two-stage behaviour of the reaction profile.

Another possible area worth investigating is that the aziridine is a poorer ligand for Cu than the oxazoline, so that in the above experiments there is significantly more catalysis by non-modified Cu, which would then yield racemic aziridine.

EPR and UV-vis spectroscopy confirmed the formation of the Cu-bis(oxazoline) complex as central to the catalytic reaction in homogeneous solution. Therefore, EPR and UV-vis spectroscopy could be studied together with ENDOR in order to further examine the formation of any copper nitrene type intermediate in the reaction system. The timescale for the disappearance of species C is comparable to the first phase of styrene conversion. This could be further developed with EPR spectroscopy in providing an understanding to the reaction profiles and reaction mechanism of the aziridination of styrene. Further study of the heterogeneous reaction could include attempts to eludicate the oxidation of the active copper catalyst by using EPR spectroscopy.

6.5 References

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