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

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

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Abstract

By synthesising *S*-2-phenyl-*N*-(4-nitrophenyl)aziridine from *S*-phenylglycinol, it has been demonstrated that the aziridination of styrene by [*N*-(4-nitrobenzenesulfonyl)imino]phenyliodinane, (nosyliminophenyliodinane, PhINNs) in the presence of *S*,*S*-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline), catalysed by copper(II) triflate in CH_3CN solution or heterogeneously by CuHY, has predominantly an *R*-configuration. The enantioselectivity of the aziridination of styrene by [*N*-arenesulfonylimino]-phenyliodinanes catalysed by copper-exchanged zeolite Y (CuHY), in conjunction with a chiral bis-oxazoline ligand, has been re-examined. In the case of PhINNs, it is shown that the product mixture of enantiomeric aziridines, on treatment with hexane, gives rise to a solid phase of low enantiomeric excess (ee) and a solution phase of high ee. Separation of the solid phase and recrystallisation afforded a true racemate (racemic compound), which has been confirmed by X-ray crystallography. The aziridine obtained from the solution phase could be recrystallised to produce the pure enantiomer originally in excess. A consequence of the new findings is that previous reports on the enantioselectivity of copper-catalysed aziridination, both in heterogeneous and homogeneous conditions, should be regarded with caution if the analytical procedure involved HPLC with injection of the enantiomeric mixture in a hexane-rich solvent. Such a method has been used in previous work from this laboratory, but has also been used elsewhere, following the procedure developed by Evans and co-workers when the (homogeneous) copper-catalysed aziridination by PhINTs was first discovered. Evidently, the change of substituent in the benzenesulfonyl group reduces the solubility in hexane, affording a solution phase of enhanced ee.

Acknowledgements

I would like to thank my supervisor Graham Hutchings, and Don Bethell for all their input, help, and support.

Thanks to Dave Willock, Phil Page, Ben Buckley, Damien Arquier, and Rob Jenkins. Also, to my fellow students and post docs past and present.

A special thank you must go to Kieran, for always being there for me, I could not have done it without you!

Thank you Mom, Dad, and Michael, this thesis is dedicated to you.

Contents

Chapter 1

Introduction

1.1 Principles of stereochemistry

Compounds with the same chemical formulae but different arrangement of atoms are called isomers (Figure 1).

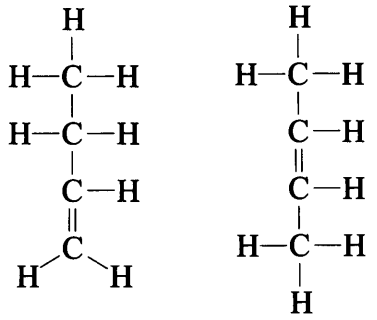


Figure 1: Structural isomers

Compounds which share the same chemical formulae and bond structure but a different spatial arrangement of their atoms are called stereoisomers. If a stereoisomer possesses a stereogenic centre it will have two enantiomers, which are defined as a pair of non-super imposable mirror images. A stereogenic centre is a carbon atom bonded to four different groups (Figure 2).

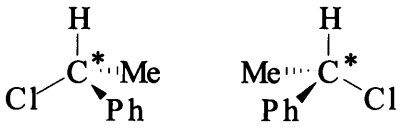


Figure 2: Enantiomers

Structures that are not identical to their mirror images and therefore exist in two enantiomeric forms are chiral. A structure that has a plane of symmetry in any of its possible conformations are said to be achiral.

Distinguishing between a pair of enantiomers proves difficult as they are very similar. However, when plane polarised light is passed through a sample of one of the enantiomers, the plane of polarisation of the incident light rotates by a certain degree in a clockwise or anti-clockwise direction. Polarised light is obtained by passing ordinary light through a Nicol prism (polariser). An enantiomer that rotates the plane of polarised light in the clockwise direction is dextrorotatory and the optical rotation is given a (+) sign. If the enantiomer rotates the plane of polarised light by the same amount but in the opposite direction the sample is levorotatory and the optical rotation is given a (-) sign. If a sample is enantiomerically pure it means that it has only one enantiomer of the chiral compound. The enantiomeric purity of an unequal mixture of enantiomers can be obtained by calculating optical purity (Figure 3), which relies on the measurement of plane polarised light, [α].

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

Figure 3

Enantiomeric excess (ee) is the measure of the enantiomeric makeup of a sample (Figure 4). In this work the ee relies on the determination of the relative concentrations of both enantiomers by chiral HPLC.

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

Figure 4

In 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 (ee) of the major enantiomer.

A mixture containing an equal amount of two enantiomers is called a racemic mixture and has an ee of 0%. Racemisation is the process of forming a racemate from a pure enantiomer. The separation of a pair of enantiomers is called enantiomeric resolution.

1.2 Zeolites

1.2.1 Introduction

In 1756, the Swedish mineralogist Cronstedt discovered that a natural mineral, stilbite, visibly lost water when heated, leading him to name the class of materials zeolites from the classical Greek words meaning 'boiling stones'. Zeolites are three-dimensional, microporous, crystalline solids, that have aluminosilicate frameworks with cavities and channels that can allow cations, water, or other molecules inside. A defining feature of zeolites is that their frameworks are made up of SiO_4 and AlO_4 tetrahedra linked to each other by sharing corner oxygen atoms. Depending on the framework type and geometry dimensions, zeolites can (i) selectively allow other molecular species to move into the porous network, (ii) permit a particular

intermediate to form within their channels, and (iii) allow the product species formed to move out. Zeolites can be manufactured by synthetic routes, in addition to occurring naturally. They have the ability to withstand harsh reaction conditions and can be easily separated from reaction mixtures. The added value of using zeolite supported catalysts is that they are much cleaner and environmentally safer than the homogeneously catalysed equivalent reactions. Synthetic zeolites are particularly important for petroleum refining catalysts. Zeolites are used as adsorbents, which includes drying, purification, and separation. They are also used for water softening, due to their ion-exchange capabilities.

1.2.2 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.

The ion-exchange capacity is dependent on the Si/ Al ratio and so structures with low Si/ Al ratio have a higher ion-exchange capability and therefore a higher concentration of catalytic sites. If the cation is a proton then Brönsted acid sites are present.

Zeolites with high concentrations of H^+ are hydrophilic and consequently 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^- tetrahedra. At higher temperatures (greater than 200°C) these can be mobile, moving between sites[1], and at even higher temperatures (greater than 550°C) they may be lost to form Lewis sites (Figure 5). 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.

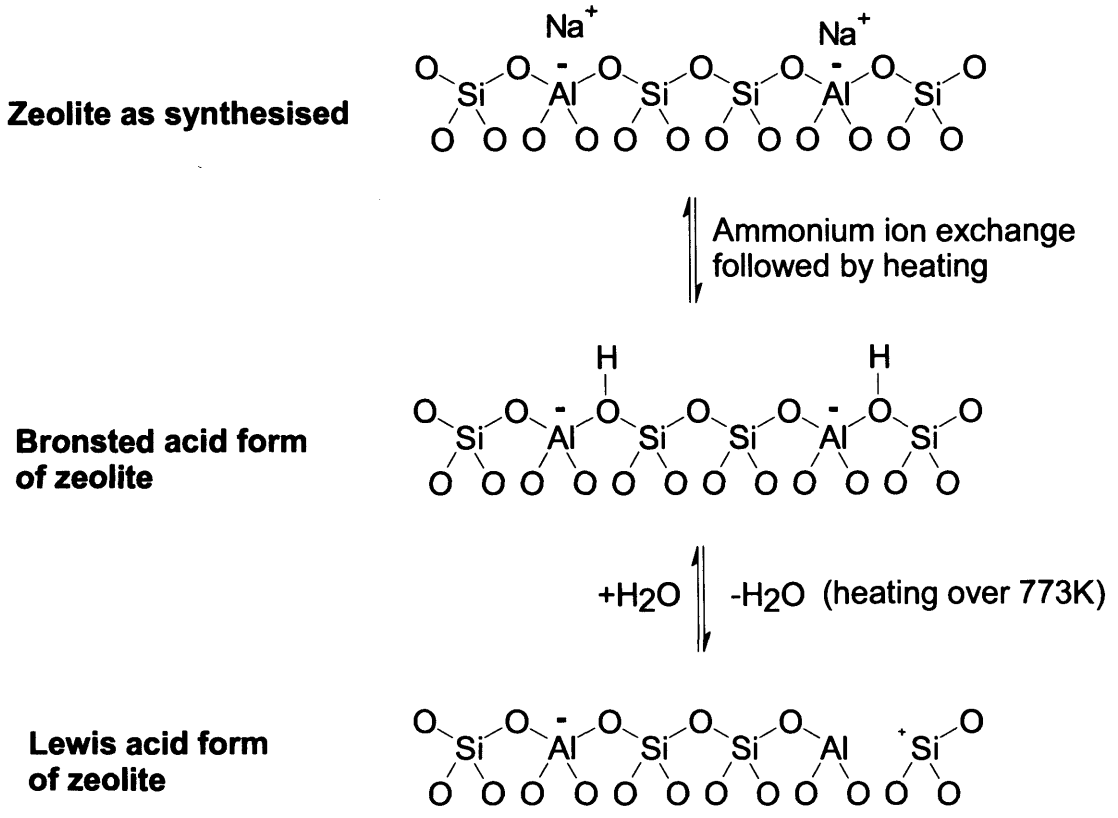


Figure 5

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[2] 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[3] there is more than one pathway in the reaction. He explained the absence of symmetrical trialkyl benzenes in the product from the disproportionation of dialkyl benzene in H-mordenite. From this and other studies Csicsery concluded that insufficient space was available in the pores for two molecules of the dialkyl 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[4]. 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[5].

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[6] to oxidation[7] reactions. Tatsumi et al[7] 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[8] showed that they are particularly useful in activating alkenes and alkanes.

Tsuruya et al[9] 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[10,11]. 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.

1.2.3 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 6), 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.

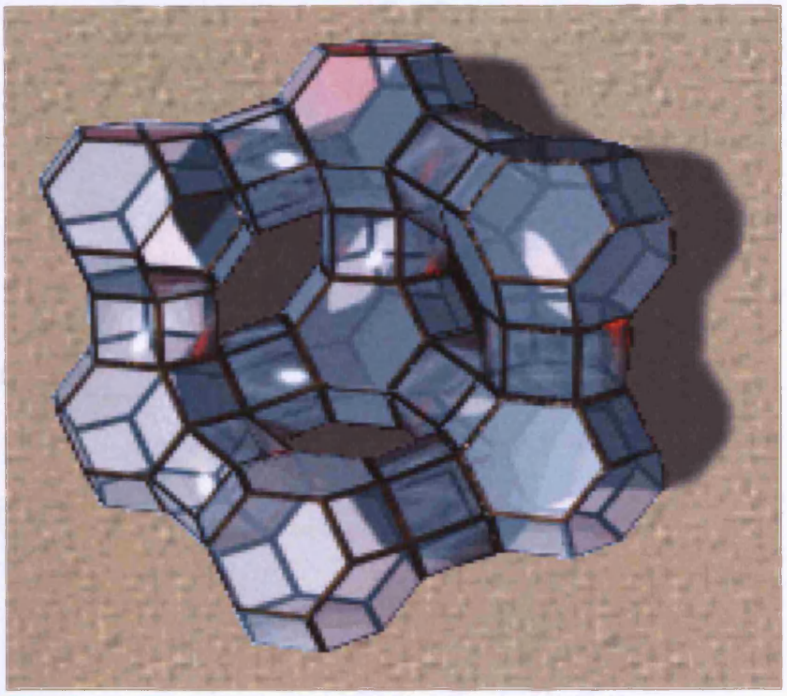


Figure 6: Zeolite Y viewed along [111] axis[12]

The unit cell for zeolite Y[13] contains 192 $(Al/ Si)O_4$ tetrahedra. Zeolite Y has a 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 7). 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.

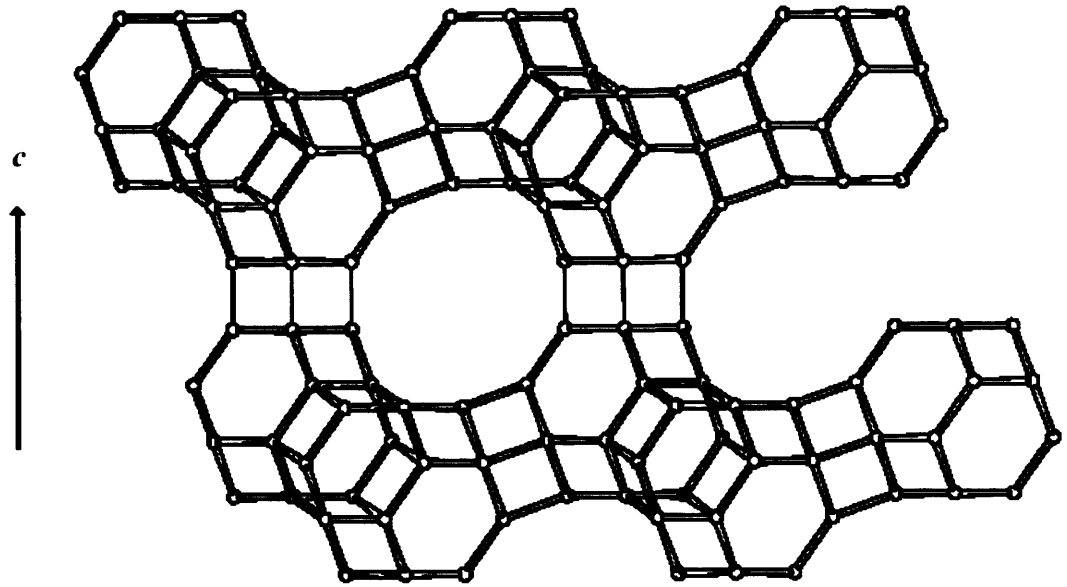


Figure 7: FAU along the [110] axis

1.3 Aziridines

1.3.1 Introduction

Aziridines (Figure 8) are the nitrogen analogues of epoxides and exhibit similar reactivity patterns as electrophilic reagents. They undergo highly regio- and stereoselective transformations and, therefore, are useful building blocks for organic synthesis. In addition, aziridines may exhibit antitumor or antibiotic activity or still other biological properties, which makes them attractive synthetic targets in their own right.[14]

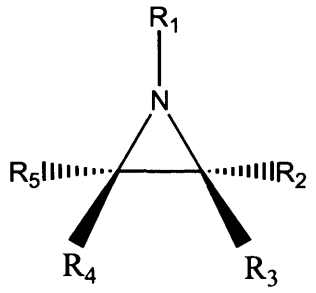


Figure 8: Structure of aziridine

A lot of research has been done in the development of reactions that effect catalytic transfer of atoms to alkenes. The value of these reactions in organic chemistry has led to the epoxidation[15] and cyclopropanation[16] of alkenes to be extensively studied. Progress in the analogous reaction of an alkene with a nitrene donor to give aziridine has been slow despite its significant utility as important intermediates for pharmaceuticals and agrochemicals.

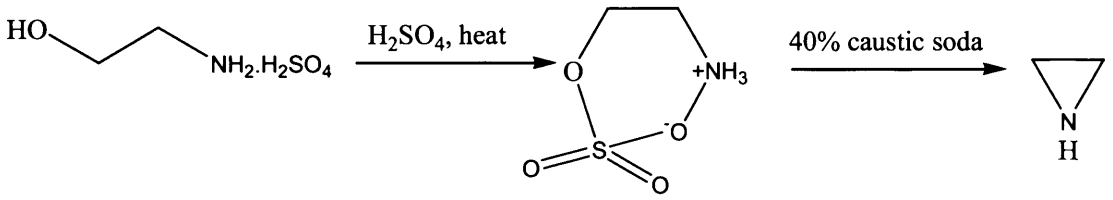
1.4 Synthesis of aziridines

There are many ways to synthesise aziridines, as a result only a few examples will be discussed in this chapter. A comprehensive review of the various methods has been reported by Deyrup[17].

1.4.1 Aziridines from amino alcohols

One of the oldest and perhaps most obvious approach to aziridine synthesis is the use of an amino alcohol as a precursor. The hydroxyl functional group is converted to a good leaving group, which is then displaced by the amine group in an intramolecular cyclisation reaction to give aziridine. In 1888, Gabriel showed that aziridines could be

prepared in a two-step process, by chlorination of ethanolamines with thionyl chloride, followed by alkali-mediated cyclisation. Subsequently, Wenker reported that heating ethanolamine in the presence of sulphuric acid at high temperature produced 'β-aminoethyl sulphuric acid', which was distilled from aqueous base to yield aziridine (Figure 9). However, the intermediate in the reaction might be considered to be the cyclic sulfamidate of ethanolamine.



71% yield 27% yield

Figure 9

By using enantiopure amino alcohols, asymmetric synthesis of enantiomerically pure aziridines is possible.

1.4.2 Aziridines from imines

The addition of a carbene fragment or equivalent (ylid or metal carbenoid) to an imine is a useful aziridination method (Figure 10).

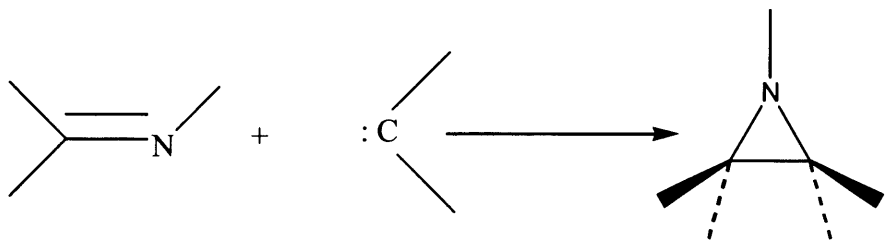


Figure 10

Jørgensen et al[18,19] investigated the metal catalysed aziridination of imines with ethyl diazoacetate as the carbene fragment donor. Different Lewis acid complexes (e.g. $Cu(OTf)_2$, $Zn(OTf)_2$, and $Yb(OTf)_3$) were found to catalyse the formation of aziridines. These catalysts in combination with various chiral ligands gave optically active aziridines, albeit in low ee. The aziridination gave mainly the cis-aziridines as the major diastereoisomer, but the selectivity was dependent on the substrate, catalyst, and solvent used.

Imine aziridination using diazo-compounds and catalytic quantities of metal salts and sulfides was reported by Aggarwal et al[20] (Figure 11). High yields of aziridines were obtained with all imines but diastereoselectivity varied considerably.

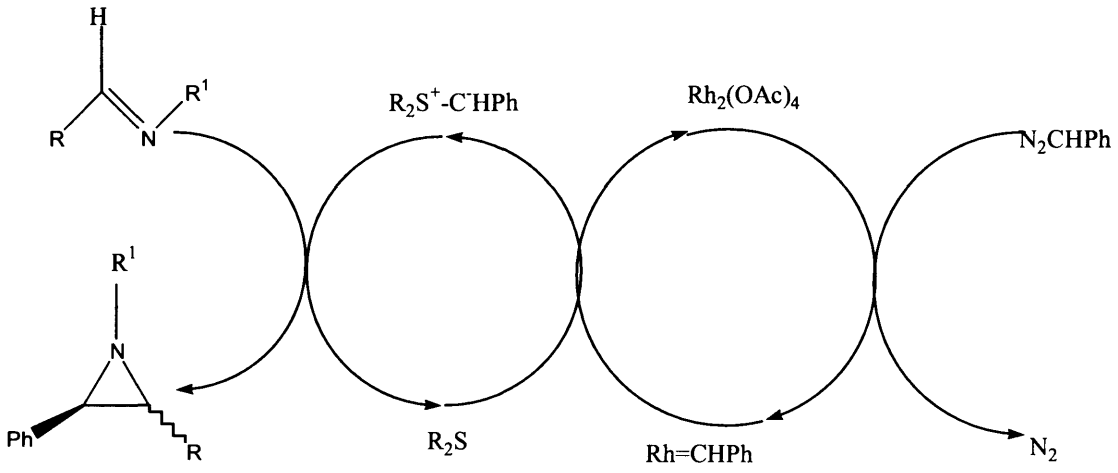
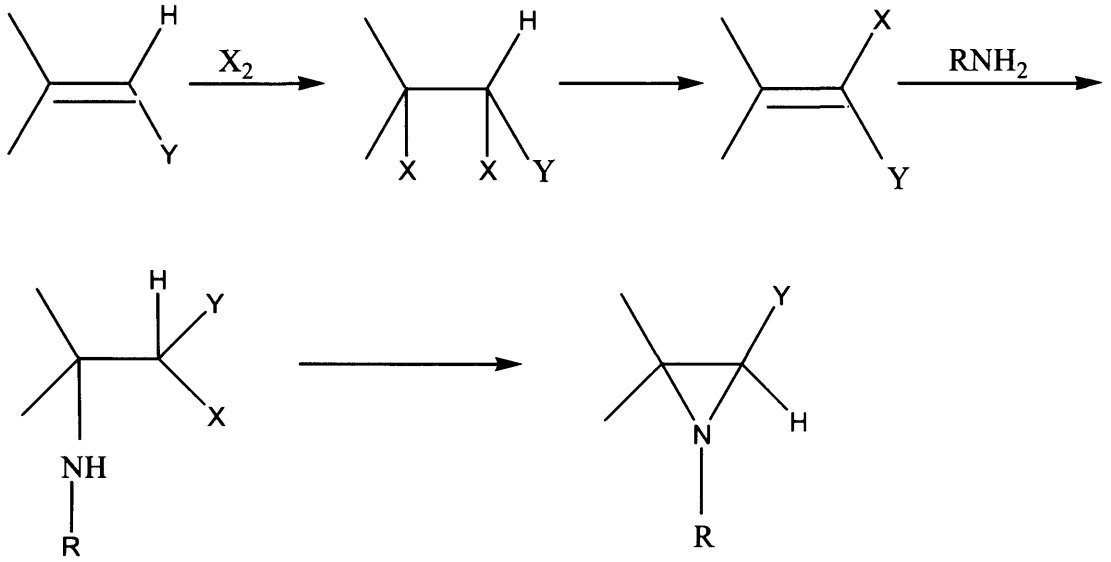


Figure 11

They also reported a novel procedure for the synthesis of aziridines using Simmons-Smith reagent (diethyl zinc), where high yields of aziridine were observed.[21]

1.4.3 Aziridines from nucleophilic addition

If there are electron-deficient substituents present, this gives an alternative method for synthesising the aziridines. An example of this would be nucleophilic attack of vinyl halides. Firstly, I_2 adds across the double bond, which is followed by the elimination of HI, reforming the double bond. The amine then attacks the double bond via nucleophilic addition, before the final cyclisation forming the aziridine with the loss of HI (Figure 12).



Y = electron withdrawing group

X = I

Figure 12

1.4.4 Aziridines from epoxides

Formation of the corresponding aziridine is possible via the ring opening of epoxides. An example of aziridine synthesis from epoxides was carried out by Tanner et al[22], using the epoxide-2,3-dicarboxylic acid as the starting material. Firstly the epoxide is reacted with an azide ion to form the azido alcohol, which is then reduced with triphenylphosphine in benzene to give the oxaazaphospholine intermediate. For the tosyl analogue of the aziridine, it is subsequently reacted with p-TsCl in pyridine to produce the aziridine in high yield (73%).

1.4.5 Aziridines from azirines

Azirine reduction by $LiAlH_4$ gave the equivalent aziridine with good stereospecificity (Figure 13).[23] Other reducing agents, such as $NaBH_4$ and $NaAlH(OCH_2CH_2OCH_3)_2$ have been used.[24]

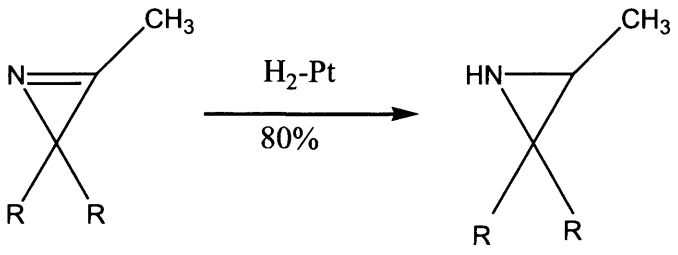


Figure 13

Andersson et al[25] reported that the first enantioselective reduction of aromatic 2*H*-azirines, which afforded aziridines in up to 70% ee, using the aminoalcohol-$[RuCl_2(p\text{-cymene})]_2$ catalysed asymmetric transfer hydrogenation reaction (Figure 14).

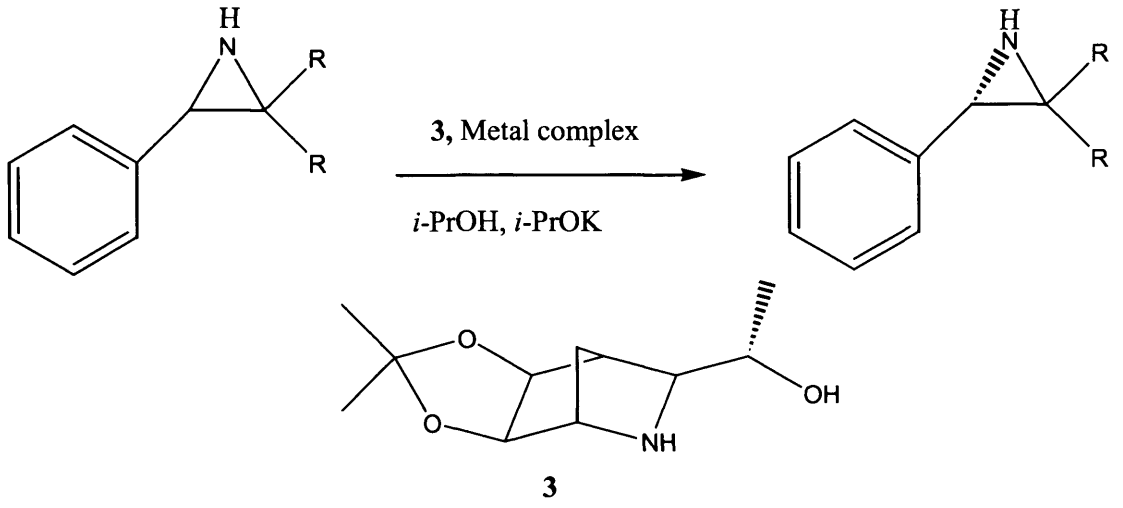


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Figure 14

1.4.6 Aziridines from alkenes

The reactions in this project follow this method of aziridine synthesis. A nitrene source is added directly across the double bond, which is an example of a 2 + 1 cycloaddition (Figure 15).

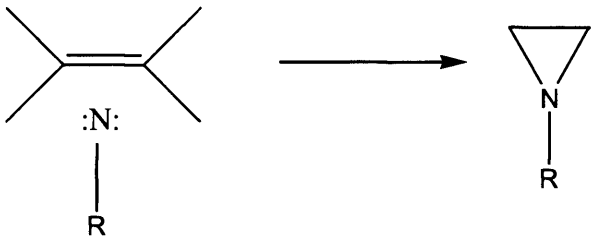


Figure 15

Closs et al[26] reported one of the earliest methods of aziridines formed from alkenes. A three-step reaction sequence involved the chloronitrosation of a tetraalkylethylene, reduction of the nitroso chloride to the chloroamine hydrochloride, and finally ring closure with alkali to form the desired 2,2,3,3-tetraalkylaziridine in 79% yield.

1.4.7 Aziridination using nitrogen sources

The nitrene donor of choice throughout the development of the aziridination reaction has been PhI=NTs. Several groups attempted improvement of the aziridination system. This included altering the nitrene donor, this was generally carried out by replacing the methyl substituent on the phenyl group of PhI=NTs with a different substituent. One example of this is the replacement of the methyl substituent with a nitro substituent (NO_2) to form (N-(*p*-nitrophenylsulfonyl)imino)phenyliodinane, PhI=NNs (Figure 16).

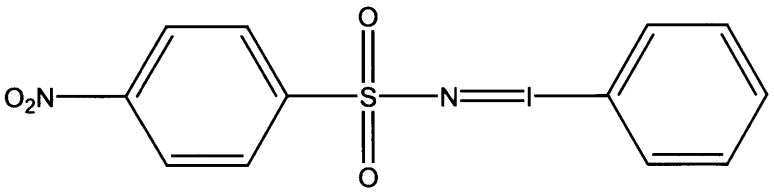
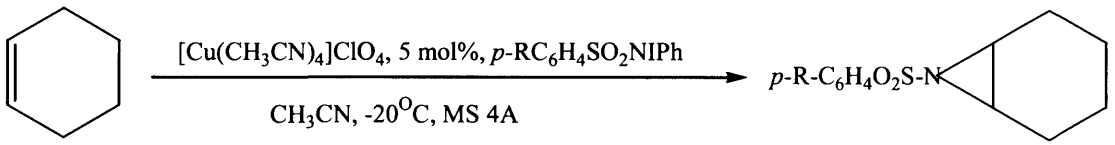


Figure 16: Structure of PhI=NNs

Sodergren et al[27,28] proposed the replacement of PhI=NTs by PhI=NNs in order to improve yields of aziridines. Initially cyclohexene was investigated as choice of substrate, but styrene was also examined. The reactions were carried out in analogy with the method described by Evans[29]. The best results were obtained using *p*-MeO-$C_6H_4SO_2N$=IPh and *p*-NO_2-$C_6H_4SO_2N$=IPh with yields of 98% and 92% of aziridine respectively (Figure 17).



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

Figure 17

Dauban et al[30] improved the synthetic potential of aziridination by the discovery that phenyl imino iodinanes derived from aliphatic sulfonamides can be isolated. They made [*N*-((trimethylsilyl)ethanesulfonyl)imino]phenyliodinane, PhI=NSes **(1)**, which although exhibited comparable reactivity to PhI=NTs, was easier to make and the aziridines formed could be opened by nucleophiles under mild conditions. Using PhI=NSes, aziridination yields in the range 40-68% were obtained for simple olefins with Cu(OTf) as catalyst (Figure 18). Also, the copper catalysed reaction of PhI=NSes with 11-pregnene-3,20-dione gave the corresponding aziridine in 53% yield[31].

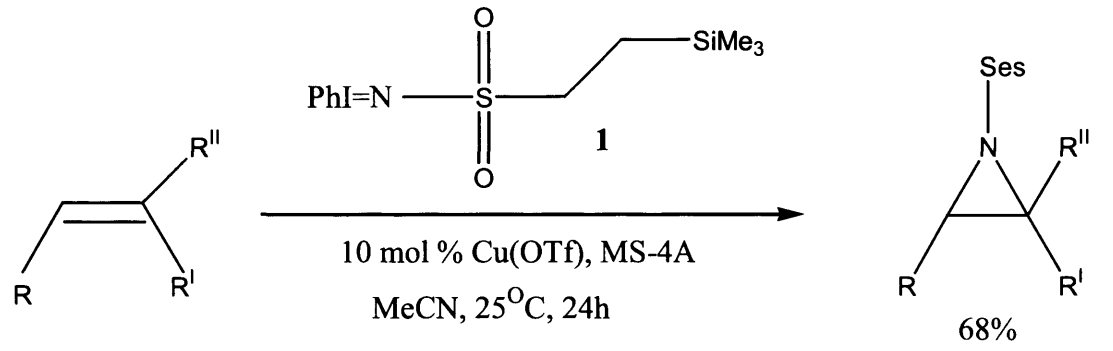


Figure 18

Another successful nitrene donor used in the aziridination of alkenes was (N-chloro-N-sodio-*p*-toluenesulfonamide) [TsNClNa.$(H_2O)_3$] referred to as chloramine-T hydrate (Figure 19).

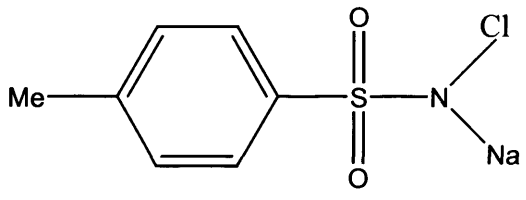


Figure 19: Structure of Chloramine-T

Chloroamine-T requires dehydration before use, which is a hazardous process. Taylor et al[32] used the commercially available chloramine-T trihydrate as the nitrene source, as it did not need dehydration. Using styrene as the substrate, the Cu(OTf). *N*-(2-pyridinylmethylene)-1-pentanamine catalyst, gave aziridine yields of 76% (Figure 20).

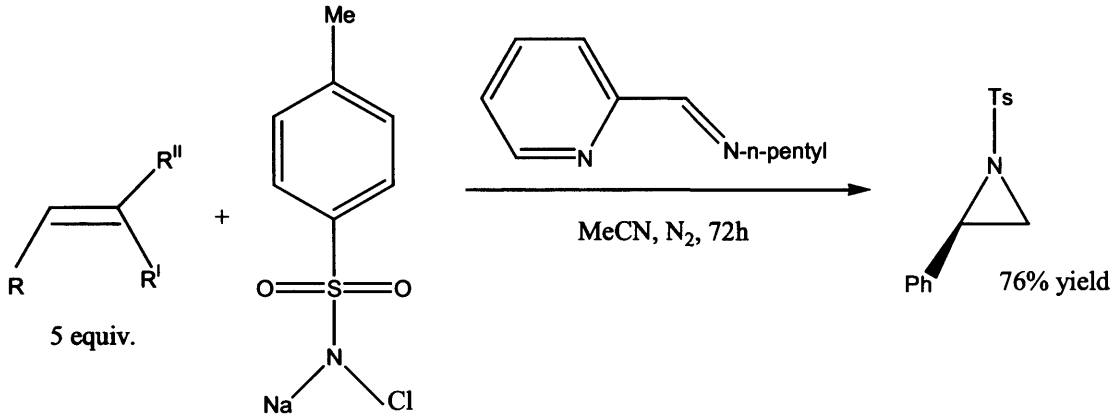


Figure 20

Bromamine-T (Figure 21) has also been used as nitrene precursor in copper catalysed aziridinations and good results have been reported.

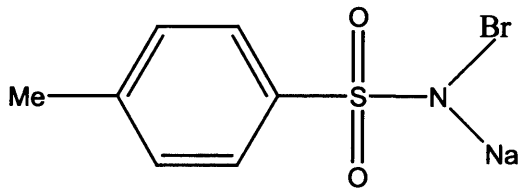


Figure 21: Structure of Bromamine-T

Encouraged by the results reported by Komatsu[33] for the copper catalysed aziridination of alkenes using chloramine-T as the nitrene donor, Vyas et al[34] investigated and compared the use of bromamine-T as the nitrogen precursor. The

aziridines obtained from the various olefins gave higher yields with bromamine-T compared with chloroamine-T, for example when styrene was used with CuCl as catalyst, 48% and 31% yields were obtained respectively.

Bromamine-T has also been used as the nitrene donor in copper catalysed aziridination reactions, which were carried out under microwave and ultrasound irradiation.[35] The copper halides were found to be the most suitable catalysts for this reaction, using $CuBr_2$ as catalyst aziridine yields of 88% were obtained.

Chloramine-T, bromamine-T, and PhI=NTs were contrasted as nitrene donors for the aziridination of styrene using copper (II) triflate, and copper exchanged zeolite Y (CuHY) as catalysts. For both catalysts, PhI=NTs was found to give significantly higher yields of the aziridine both in the presence and absence of a chiral bis(oxazoline) modifier. In contrast to PhI=NTs, it was observed that chloramine-T and bromamine-T induced leaching of most of the copper from CuHY, meaning that with these nitrene donors CuHY does not function as a heterogeneous catalyst[36].

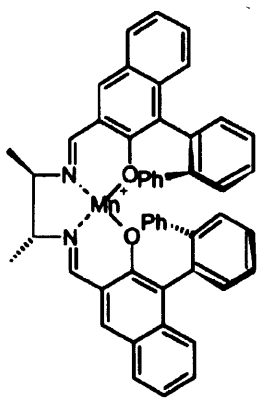
1.5 Asymmetric aziridination

1.5.1 Chiral ligand

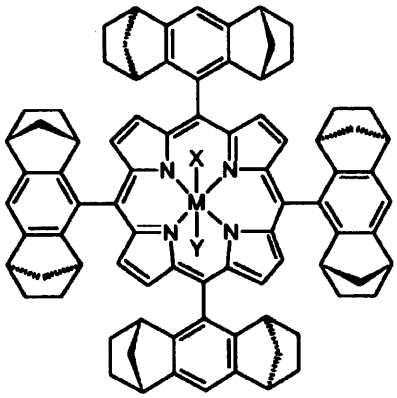
The chiral ligand plays an important role in achieving high enantioselectivities in asymmetric catalytic reactions. The combination of chiral bis(oxazoline) ligands and Lewis acids have been used extensively as enantioselective catalysts for many different reactions, such as aziridination[37], cyclopropanation[38], cycloaddition[39], allylic substitution[40], Diels-Alder[41], and Friedel-Crafts[42] 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 (Mn-1), have been developed by Nishikori and Katsuki, who reached up to 94% ee for aziridination of styrene with PhI=NTs (Figure 22).[43] The presence of catalytic quantities of 4-phenyl-pyridine-*N*-oxide was required to obtain high enantioselectivities.

Lai et al[44] used D_4-manganese(III) porphyrin (Mn-2) in conjunction with PhI=NTs to provide aziridination products in moderate yield and enantioselectivity (Figure 22). Marchon et al[45] examined a chiral Mn(III)-porphyrin catalyst (Mn-3) and reported an ee of 57% for styrene aziridination with PhI=NTs (Figure 22).

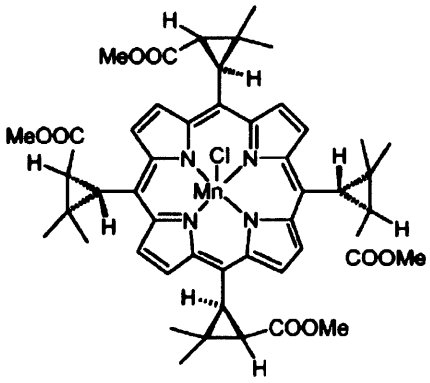


Mn-1

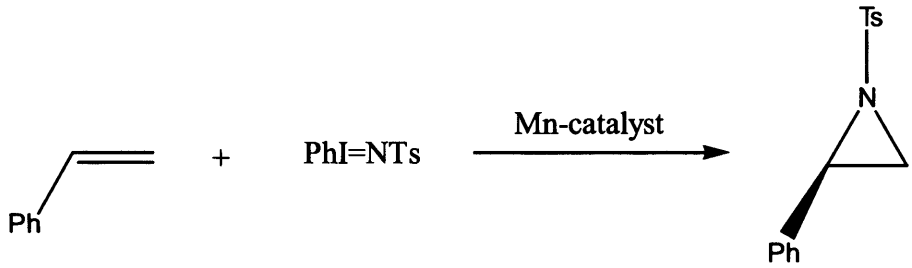


X = H, Y = MeOH

Mn-2



Mn-3



Katsuki[43], **Mn-1**: 76% yield, 94% ee

Lai[44], **Mn-2**: 73% yield, 55% ee

Marchon[45], **Mn-3**: 34% yield, 57% ee

Figure 22

Several new achiral ligands have been introduced for copper catalysed aziridinations with PhI=NTs with potential for development of asymmetric reactions. Halfen et al[46] described the synthesis of a Cu-1-(2-pyridylmethyl)-5-methyl-1,5-diazacyclooctane tri-fluoroacetate complex (Figure 23), which exhibited remarkable efficiency in the aziridination of styrene, giving 86% yield and 59% ee.

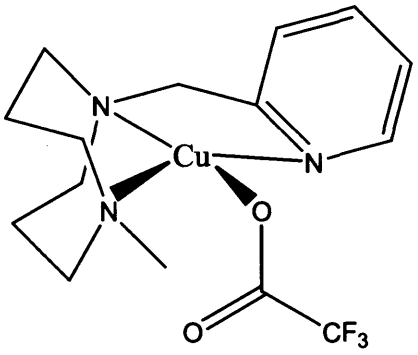


Figure 23

The use of bis(oxazoline) ligands (Figure 24) in the asymmetric catalytic cyclopropanation of olefins was reported by Masamune et al[47] in 1990, shortly followed by Evans et al[38].

Evans et al[37] used bis(oxazoline) ligands to successfully induce enantioselectivity in the aziridination of olefins. They evaluated the variation of the R- groups on the ligand with a range of substrates, which resulted in aziridine ees of 19 – 97%.

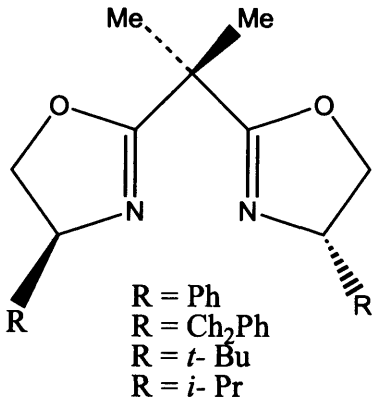


Figure 24: Structure of bis(oxazoline) ligand

The Hutchings group have shown that copper exchanged zeolite (CuHY) was highly efficient as heterogeneous catalyst for the aziridination of olefins using PhI=NTs.[48] Modification of this zeolite with bis(oxazoline) ligands lead to an enantioselective aziridination catalyst.

In this research, the ((S,S)-2,2'isopropylidene-bis(4-phenyl-2-oxazoline)) chiral modifier was used (Figure 24, R = Ph).

1.5.2 Homogeneous asymmetric aziridination

Kwart and Khan[49] reported the first metal-catalysed nitrogen atom transfer process. The reaction of benzenesulfonyl azide with cyclohexene gave products, which were consistent with the involvement of a nitrene intermediate. Mansuy et al[50-52] demonstrated that Mn(III)-derived porphyrin catalysts catalysed the reaction of styrene with [*N*-(*p*-tolylsulfonyl)imimo]phenyliodinane, PhI=NTs, giving aziridine in 80% yield.

Based on the proven ability of Cu(I) based catalysts to promote olefin cyclopropanation, Evans et al[53] explored the scope of soluble copper catalysts in the analogous aziridination reactions. The copper (I)- or copper (II)- salt catalysed aziridination of both electron rich and electron deficient olefins using PhI=NTs, afforded aziridines in 55-95% yields. The olefin was used in excess to PhI=NTs (5: 1 molar ratio), and the reaction rates and yields were enhanced using MeCN. The copper catalysts were found to be superior to the other metal complexes investigated, and PhI=NTs to be the best out of a list of compounds that undergo imido group

transfer compiled by Holm[54].

The Evans group[37] achieved high levels of enantioselection in the aziridination of cinnamate ester derivatives using copper (I) triflate with chiral bis(oxazoline) ligands (Figure 25). For the cinnamate esters, reactions carried out in benzene were significantly more enantioselective that those performed in polar solvents, such as MeCN.

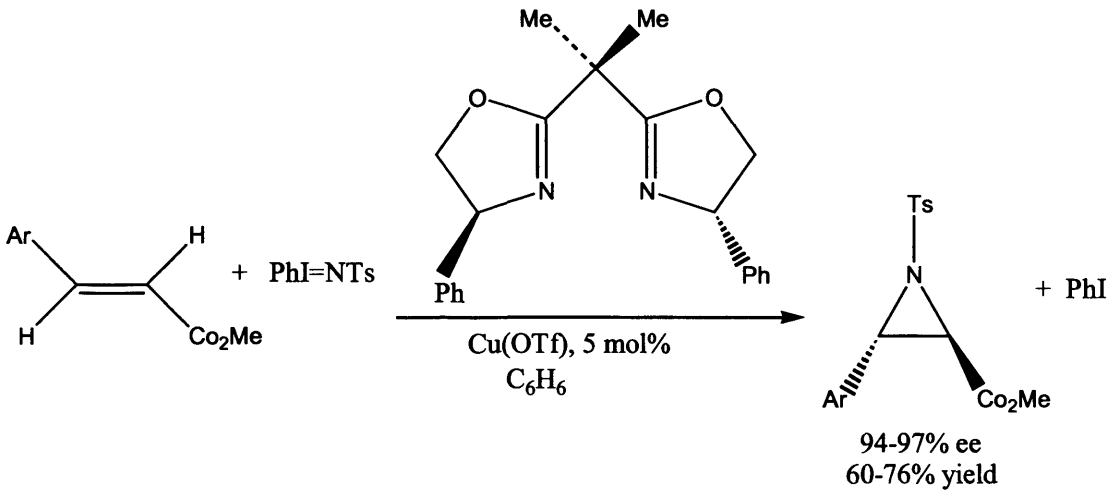


Figure 25

The optimal conditions identified for the aziridination of the cinnamate esters could not be reliably extrapolated to other olefins. For trans-β-methylstyrene, the highest aziridine ee of 70%, was obtained in MeCN, at -20°C, using the tert-butyl analogue of bis(oxazoline). For styrene, 63% ee aziridine was observed, when the reaction was completed in neat styrene, at 0°C, also with the tert-butyl bis(oxazoline).

The Jacobsen group employed 1,2-diimine derivatives as chiral ligands for copper(I) salts in the aziridination reaction. The most important catalyst design feature was the recognition that multiple coordination sites, in this case two sites on copper was crucial for the success. The optimal ligand was the bis(imine) derived from 1,2-diaminocyclohexane and 2,6-dichlorobenzaldehyde. This system affords high enantioselectivities with cis-olefins, which is complementary to the process developed by Evans, which is more suited for the trans isomers. High levels of enantioselection (66-98%) were observed for alkenes with a variety of substitution patterns[55] (Figure 26).

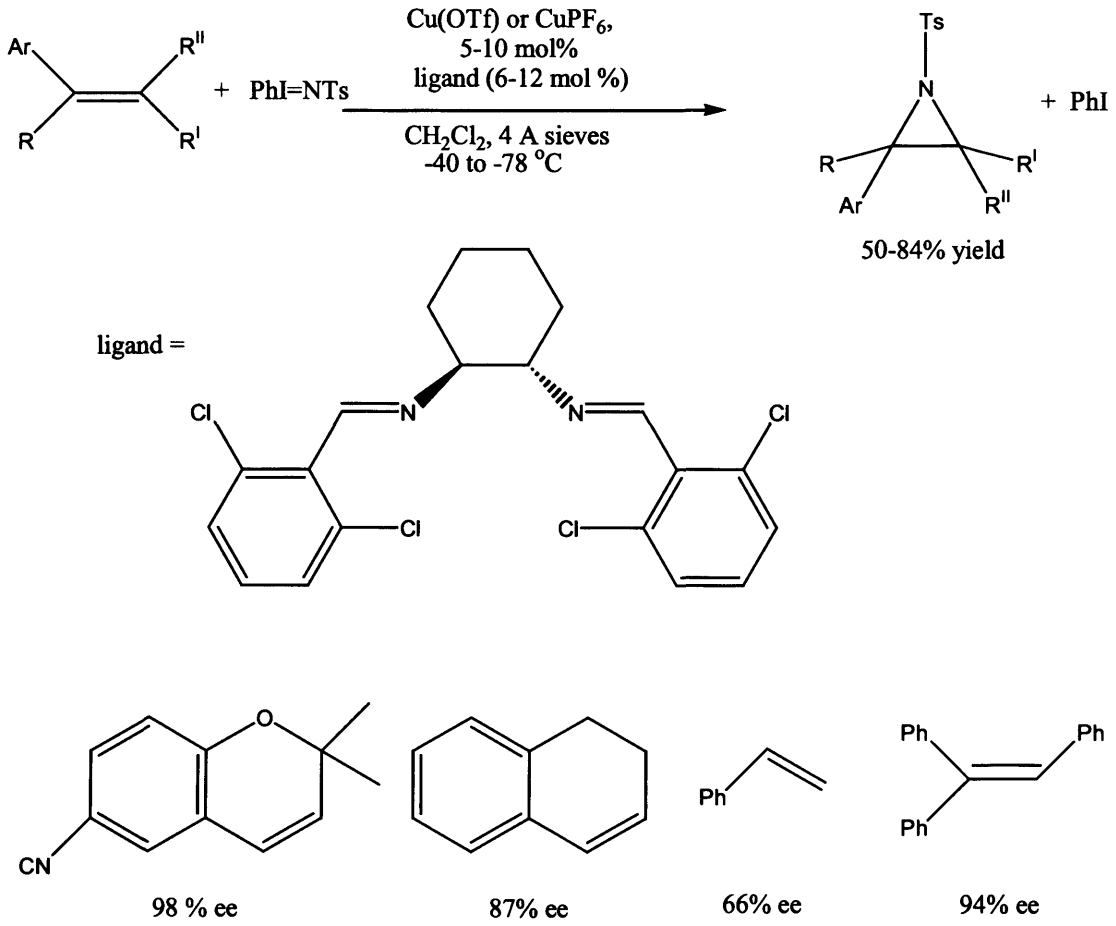


Figure 26

Jacobsen proposed a mechanism[56] for copper catalysed aziridination using PhI=NTs (Figure 27). 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

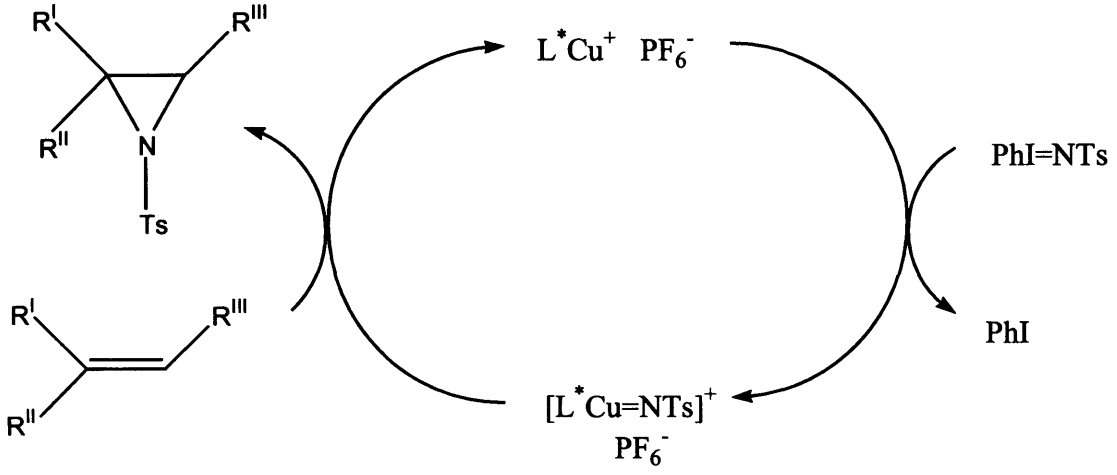


Figure 27

Several groups attempted improvement of the aziridination system. Thus, Sodergren et al proposed the replacement of PhI=NTs by PhI=NNs in order to improve yields of aziridines. Enantioselectivities comparable, and in many cases higher than those achieved by Evans with the same bis(oxazoline) ligands were obtained[27,28]. In addition, Sodergren investigated anionic di-imine ligands (Figure 28) and reported enantioselectivities of up to 34% for the same reaction,[57] and an ee of 33% with the chiral bis(aziridine) ligand[58] (Figure 29).

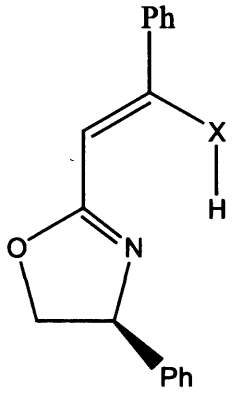


Figure 28

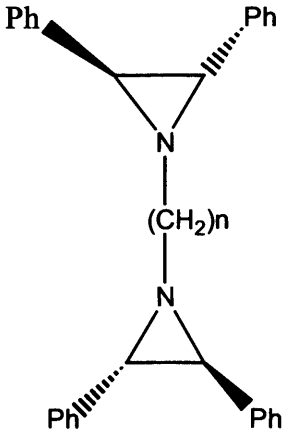


Figure 29

Llewellyn et al[59] observed that the enantioselectivity of the aziridination of styrene with bis(oxazoline) copper catalysts was dependent upon the counter ion. This suggested the possibility of asymmetric aziridinations 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 observed enantioselectivity was only 7% (Figure 30).

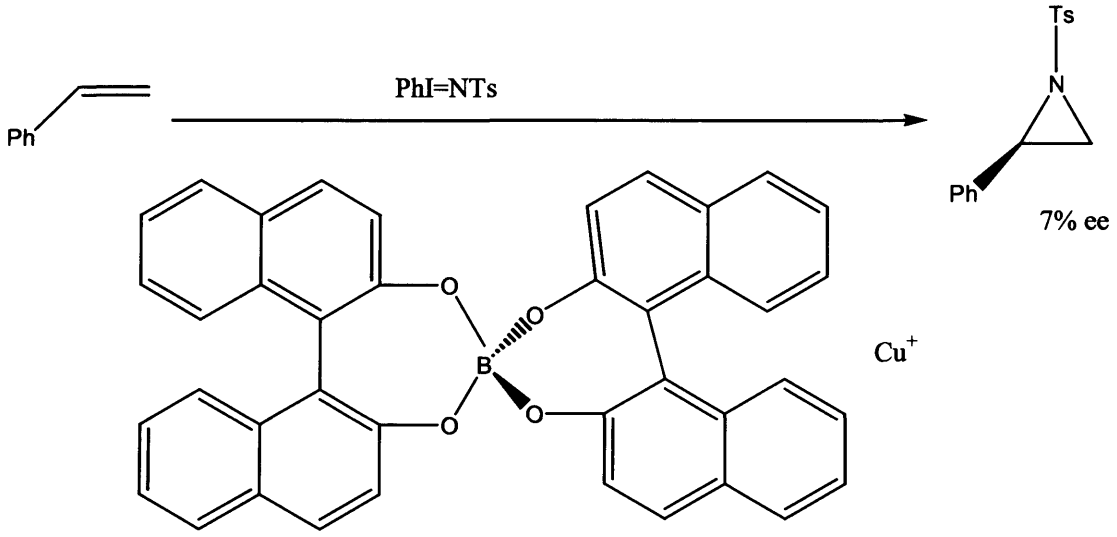


Figure 30

Jacobsen[55] found a method for enantioselective alkene aziridination using benzylidene derivatives of 1,2-diaminocyclohexane which are excellent ligands for Cu(I) catalysed aziridination of olefins by PhI=NTs.

1.5.3 Heterogeneous asymmetric aziridination

Bis(oxazoline) ligands are relatively expensive and must be recovered and re-used if the catalytic process is to be viable, however this often proves difficult and expensive. A method for overcoming this difficulty is to immobilise the asymmetric catalyst on a non-soluble support, in so doing creating a chiral heterogeneous catalyst that can be readily recovered from reaction mixtures[60].

Langham et al[61-63] found copper-exchanged zeolite Y, CuHY to be a highly active catalyst for the aziridination of alkenes, using PhI=NTs as the nitrene donor. CuHY was initially screened in the aziridination of styrene, since this alkene affords good yields of aziridine when $Cu(OTf)_2$ was used as a homogeneous catalyst.

Using a five-fold molar excess of styrene to PhI=NTs, high yields of the corresponding aziridine (90%) was obtained. When equimolar quantities of styrene and PhI=NTs were used, 87% aziridine yield was observed; in contrast to the homogeneous reaction using $Cu(OTf)_2$ which gave aziridine in low yield (35%).

Modification of the CuHY catalyst with bis(oxazolines) lead to the preparation of the first heterogeneous enantioselective aziridination catalyst. Higher enantioselection was achieved with the immobilised catalyst, CuHY, than with the homogeneous

catalyst, $Cu(OTf)_2$. This is thought to be due to the confinement of the catalyst within the micropores of the zeolite.

The optimum conditions for racemic heterogeneous aziridination of alkene, in the absence of bis(oxazoline), was observed to be at 25°C using MeCN as solvent. For the enantioselective reaction, the use of lower reaction temperatures was found to give the highest enantioselectivities. At a styrene to PhI=NTs molar ratio of 5 : 1 respectively, modification of CuHY with (S)-2,2'isopropylidene-bis(4-phenyl-2-oxazoline) in MeCN at -10°C afforded the aziridine in 82% yield and an ee of 44%. Under the same conditions but with a pyridine-bridged bis(oxazoline), 61% ee aziridine was attained albeit in low yield (4%)[63].

The ratio of nitrene donor to styrene was shown to be an important factor controlling both the yield and ee of aziridine formed. Aziridination using a slight excess of PhI=NTs to styrene (1.5 : 1 molar ratio), was catalysed with CuHY modified with (S)-2,2'isopropylidene-bis(4-phenyl-2-oxazoline) in MeCN at 25°C. Aziridine with an ee of 76% at a 78% yield resulted[64].

Sodergren et al[27,28] reported that alteration of the 4-substituent in PhI=NTs (e.g. to NO_2 or OMe) afforded an aziridinating agent that gave higher yields of aziridine in homogeneous reactions without an excess of alkene, and gave greater enantioselectivities in reactions in the presence of S,S-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline).

For CuHY bis(oxazoline), the use of the nitro-substituted aziridinating agent PhI=NNs in the reaction with styrene gave *N*-nosyl-2-phenylaziridine with higher ee (85%). The PhI=NNs was in slight excess to styrene (1.5 : 1), and the reaction time 5 hours. Under the same conditions, but with a longer reaction time of 16 hours, the ee increased to 88%. Using bis(oxazoline)-modified CuHY with styrene to PhI=NNs ratios of 1 : 1.3 and 1 : 1.4, it was possible to achieve an ee greater than 90%[65].

With CuHY as catalyst, with both PhI=NTs and PhI=NNs the (S)-aziridine was formed when the (S,S)-bis(oxazoline) was used. When the (R,R)-bis(oxazoline) was used the (R)-aziridine was formed.

Ryan et al[66] investigated the copper catalysed aziridination of styrene derivatives using CuHY and $Cu(OTf)_2$ with bis(oxazoline) using PhI=NNs. For the homogeneously catalysed reaction nearly all the styrene derivatives gave lower yields and ee of aziridine compared to styrene, although 4-chlorostyrene gave a higher ee (93%) compared to styrene (81% ee). For the heterogeneously catalysed reaction the styrene derivatives often gave better yield, particularly when the substituent was in position 4. Particularly high ee was observed for 2-chlorostyrene (95%) and 4-chlorostyrene (94%). In general the ee observed with CuHY with 2- and 4-substituted derivatives was higher than that for $Cu(OTf)_2$.

During the aziridination of styrene using copper bis(oxazoline) complexes the ee of the aziridine obtained was observed to increase with conversion due to further reactions of the product[67]. This was coupled with the effect of reaction time on aziridine yield, which revealed an S-shaped profile. The reaction initially proceeded

rapidly, and then slowed down prior to accelerating again in the latter part of the reaction.

A number of hypotheses were presented to account for the observed increase in aziridine ee with conversion. A possible explanation was during the initial phase as aziridine was produced it competes with the bis(oxazoline) for complexation of the catalytic copper sites. The rate of conversion of the 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[68].

When (R)-*N*-tosyl-2-phenylaziridine (76% ee) was treated with CuHY bis(oxazoline) and a nitrene donor, a decrease in the amount of aziridine together with an increase in ee was observed (82%). This indicated that the preferential consumption of the minor enantiomer: (S)-aziridine, could play a part in the enhancement observed. Crucially, this would appear to be a very minor role as these effects were small and the timescale long compared to the reaction time of <5 hours[67].

In the presence of the catalyst and the nitrene donor, aziridine reacts with sulfonamide, which is a breakdown product of the nitrene donor, in a reaction where parts of each are interchanged to form cross over products. This means aziridine of a different ee and / or N-substituent to the original can be formed. When (R)-*N*-tosyl-2-phenylaziridine, 87% ee was reacted with PhI=NNs and CuHY bis(oxazoline), a small amount (10%) of (R)-*N*-nosyl-2-phenylaziridine was recovered in a lower ee, 36% (Figure 31)[67].

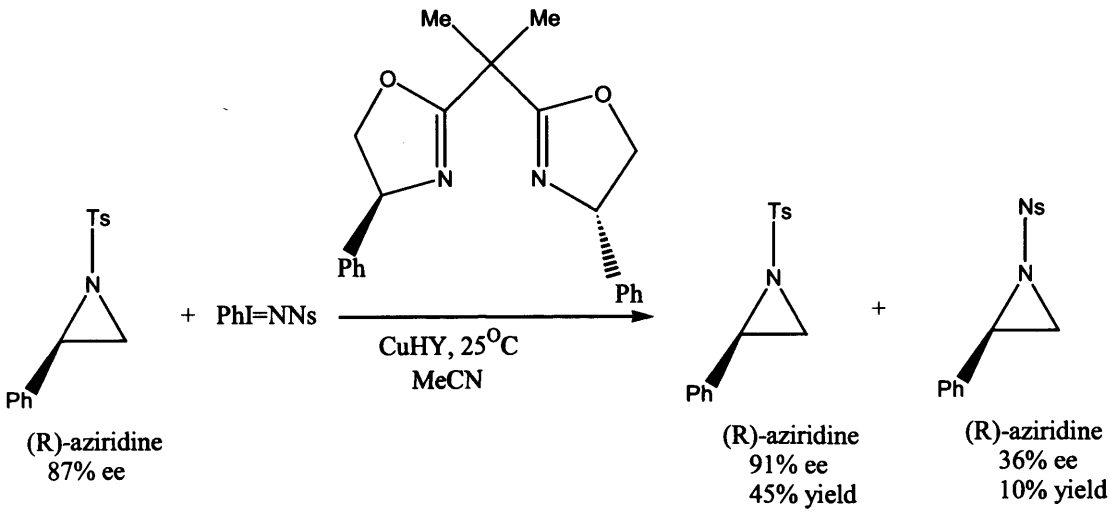


Figure 31

Racemic aziridine reacted with nitrene donor and CuHY bis(oxazoline) to give a slight ee, which at lower temperatures increased to 38%. It was proposed that aziridine reacted with a nitrogen nucleophile, derived from either the nitrogen donor or sulfonamide (break down product of nitrogen donor), to form a ring opened aziridine intermediate. Rotation about the C-C bond then allowed inversion of the stereogenic centre, which may have been catalysed by Cu^{2+} acting as a Lewis acid. When the aziridine interacts with the $Cu^{\delta+}$ / bis(oxazoline) / nitrene donor, the increased steric bulk of the system may favour the conversion of the (S)-aziridine to (R)-aziridine. The diamine intermediate may exist as a chelate ring around the copper ion. The formation of the five-membered intermediate in the presence of the bis(oxazoline) may give improved control in the micropores of the zeolite catalyst, explaining why higher enantioselectivity can be observed with the heterogeneous system[67,69]. Attempts to simulate this, led to a two phase conversion versus time curve, but did not reproduce the plateau that is observed, as well as the sigmoidal shape thereafter. This was attributed to the absence of an autocatalytic process[68].

Preliminary work by the Cardiff group[70] found that the addition of chiral aziridine to a racemic aziridination of styrene reaction resulted in an increase in enantioselectivity. The addition of preformed aziridine was thought to have an effect on the rate of reaction, the first phase of the two stage sigmoid curve being removed and the reaction proceeding straight to the second phase of the curve. The possibility of autocatalysis could not be ruled out as an explanation for this effect. The following work studies further the effect of the chiral product (Figure 32) on the aziridination of styrene.

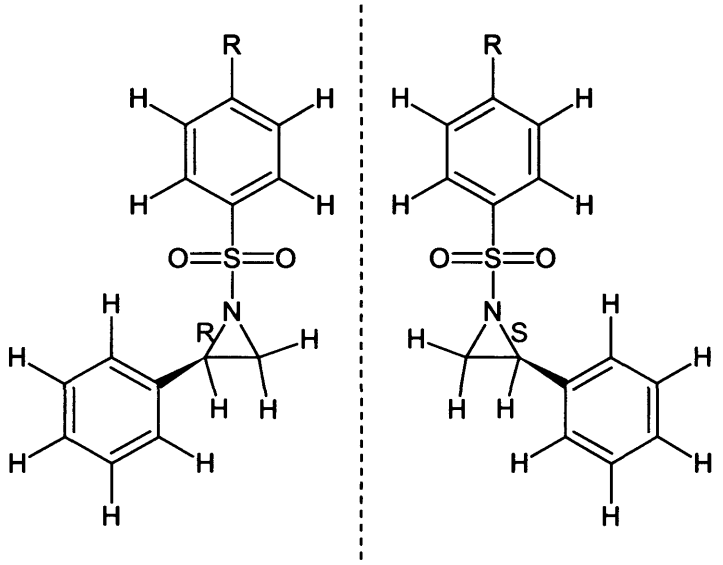


Figure 32: Aziridine

N-nosyl-2-phenylaziridine, R = NO_2

N-tosyl-2-phenylaziridine, R = CH_3

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Chapter 2

Aziridination of styrene

2.1 Introduction

The group of Evans[1,2] developed a catalytic homogeneous system for the aziridination of alkenes. Copper salts were used to catalyse the reaction using (N-(p-toluenesulfonyl)imino)phenyliodinane, PhI=NTs, as the nitrogen donor to obtain aziridine in high yields. The formation of a complex between copper and chiral bis(oxazoline) ligands was found to induce enantioselectivity[3].

Subsequently Langham et al[4-6] found copper exchanged zeolite Y, CuHY, to be a highly active catalyst for the aziridination of alkenes. Modification using bis(oxazoline) led to the preparation of the first heterogeneous enantioselective aziridination catalyst. Gullick et al[7] showed that the use of (N-(p-(nosylsulfonyl)imino)phenyliodinane, PhI=NNs, as a nitrogen source enabled the highest yields of aziridine to be attained. Higher enantioselection was achieved with the immobilised catalyst, CuHY, than with the homogeneous catalyst, $Cu(OTf)_2$. This was thought to be due to the confinement of the catalyst within the micropores of the zeolite. The Cardiff group concentrated on the substrate styrene for this research. This was because it has been previously used for the homogeneous aziridination reaction process by several groups[2,8,9]. It was also commercially available and inexpensive, and was easily detected by UV absorption allowing the reactions to be monitored by both TLC and HPLC analysis. Ryan et al[10] extended the range of substrates and investigated the reactivity of substituted styrene derivatives for both the homogeneously and heterogeneously catalysed aziridination reactions. The Cardiff group observed high yields of aziridine and high enantioselectivities for the reaction of styrene or its derivatives with the nitrene donors PhI=NTs or PhI=NNs.

During the aziridination of styrene using copper bis(oxazoline) complexes the ee of the aziridine obtained was observed to increase with conversion[11]. The effect of reaction time on aziridine yield revealed an S-shaped profile[10,12]. The reaction initially proceeded rapidly, and then slowed down prior to accelerating again in the latter part of the reaction. Preliminary work by the Cardiff group found that the addition of chiral aziridine to an aziridination of styrene reaction, without bis(oxazoline), resulted in an increase in enantioselectivity[13].

The addition of preformed aziridine was thought to have an effect on the rate of reaction, the first phase of the two stage sigmoid curve being removed and the reaction proceeding straight to the second phase of the curve. The possibility of autocatalysis could not be ruled out as an explanation for this effect. The following work studies further the effect of the chiral product (Figure 1) on the aziridination of styrene.

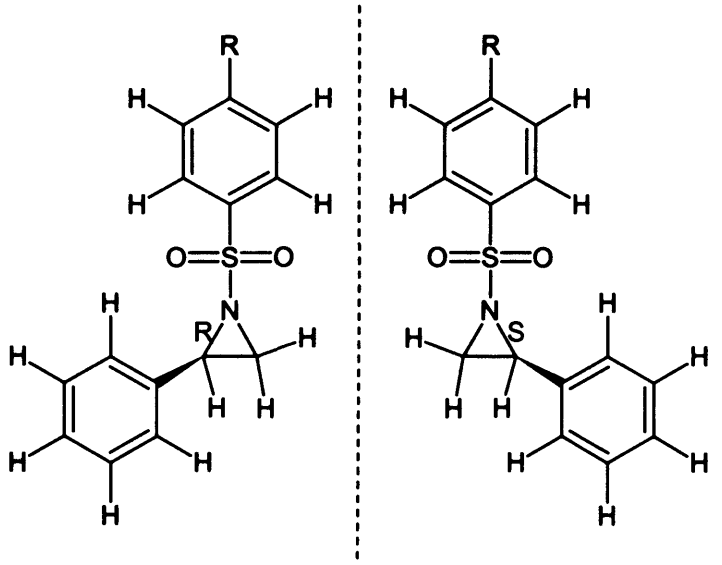

Figure 1: Aziridine

N-nosyl-2-phenylaziridine, R = NO_2

N-tosyl-2-phenylaziridine, R = CH_3

2.2 Aziridination of styrene

The aziridines were made according to the standard homogeneous and heterogeneous aziridination reaction conditions which were established in the previous work.[4,5,7,13-17] An overview of the method used is given below.

CuHY or $Cu(OTf)_2$ (4.15×10^{-5} mol of Cu) was pre-stirred with bis(oxazoline) chiral modifier (1.17×10^{-4} mol) in acetonitrile (5mL) for 15 minutes. Styrene (9.69×10^{-4} mol) was then added followed by the nitrene donor PhI=NNs or PhI=NTs (1.46×10^{-3} mol) and stirred continuously until the reaction had gone to completion. The product was then isolated using flash column chromatography (1.5 x 20 cm silica, 10: 1.5 petroleum ether 40: 60/ ethyl acetate). The aziridine was formed as a white crystalline solid.

The ee of the aziridine produced was determined using a new and more flexible analytical procedure. Chiral HPLC analysis using a Chiralpak IA column allowed free choice of any miscible solvents to make up the mobile phase. This permitted THF to be used to fully dissolve the sample of aziridine thus ensuring both enantiomers were in solution. The solution was then diluted with four times its volume of hexane. This was to prevent the aziridine crashing out of solution when it was injected into the column. Separation of aziridine enantiomers was achieved using a mobile phase consisting of 85% hexane and 15% IPA. The result showed that aziridine with an ee of 35% was made, which was much lower than the ca. 80% previously reported.

2.3 Use of anhydrous acetonitrile, and a nitrogen atmosphere for the aziridination reaction

The aziridination reactions were carried out using PhI=NNs, but with anhydrous MeCN, in air or a nitrogen atmosphere. This had no effect on the ee of the aziridine produced.

2.4 Variation in solvent for the aziridination reaction

The heterogeneous racemic aziridination reaction using PhI=NNs in either MeCN or MeOH gave complete conversion of styrene into the corresponding aziridine. When the reaction was carried out in hexane or THF no aziridine was formed.

2.5 Aziridine made using (S,S)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline)

The pure (S) enantiomer of *N*-nosyl-2-phenylaziridine was made by nosylation of (S)-(+)-2-phenylglycinol and cyclisation effected by potassium hydroxide [18,19]. This was then injected into the Chiralpak IA column to confirm the retention time of the (S) enantiomer from the catalytic reactions. This evaluation showed that the major enantiomer produced from the (S,S)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline) modified aziridination reaction was the (R)-aziridine. This was substantiated by polarimeter measurements. It was thought that a misassignment had been made in the previous work that has now been corrected.

Table 1: Polarimeter measurements of the *N*-nosyl-2-phenylaziridine made using (S,S)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline)

Sample	Weight (g)	A	[α]D	% ee of aziridine by chiral HPLC	Calculated % ee of aziridine by Polarimetry
1	0.1018g	-0.57	-22.40	(R) 35	(R) 29
2	0.0138g	-0.079	- 23.00	(R) 30	(R) 30
3	0.0109g	-0.061	-22.39	(R) 37	(R) 29

[α]D from reference for (S) 100% *N*-nosyl-2-phenylaziridine = + 77.8 (c= 1.0 in $CHCl_3$)

[α]D = α / (concentration x cell length)

Concentration- grams per millilitre (sample in 1mL $CHCl_3$)

Cell length= 0.25 dm

2.6 Enhancement in ee with conversion

Gullick et al[11] observed that during the heterogeneous copper bis(oxazoline) catalysed aziridination reaction of styrene the ee of aziridine increased with conversion. Figure 2 shows the typical magnitude of this effect which was also observed over a range of reaction conditions.

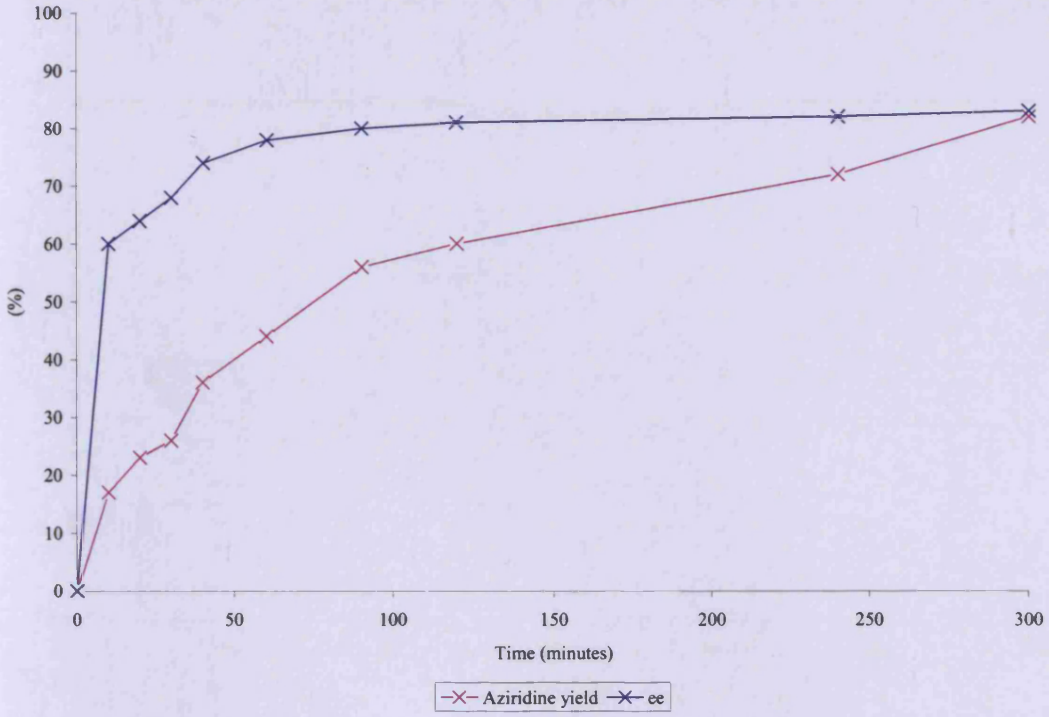

Figure 2: Effect of reaction time on yield and ee of (R) aziridine[11]

Reaction conditions: CuHY (0.3g), bis(oxazoline), PhI=NNs (1.5mmol), Styrene (1mmol), MeCN

In the present investigation, attempts were made to replicate the enhancement in ee with conversion; the aziridine made was analysed by chiral HPLC using the Chiralpak IA column. It was found that the ee of the aziridine produced did not increase with conversion. The ee of aziridine isolated at a reaction time of 1 minute was (R) 34%. The aziridine remained at this ee throughout the aziridination reaction (Figure 3).

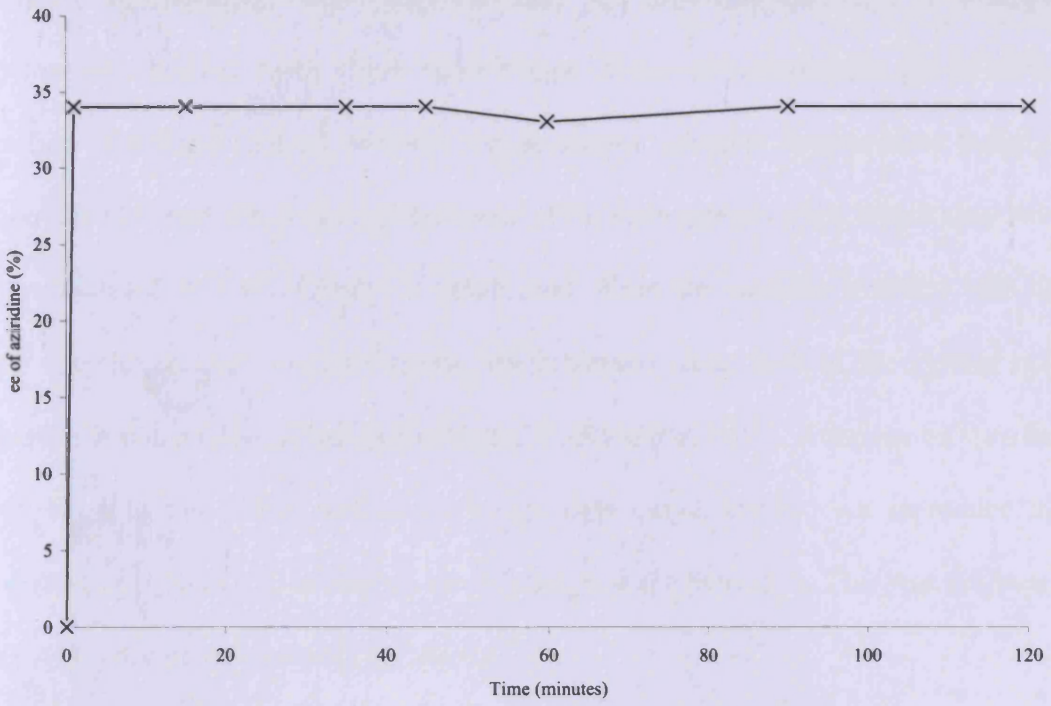

Figure 3: Enhancement in ee with conversion

Reaction conditions: CuHY (0.3062g), bis(oxazoline) (0.0458g), PhI=NNs (0.4872g), Styrene (92μL), MeCN (5mL)

2.7 Formation of a CuHY- aziridine complex

A number of hypotheses were presented to account for the observed increase in aziridine ee with conversion. A possible explanation was during the initial phase as aziridine was produced it competes with the bis(oxazoline) for complexation of the catalytic copper sites. The rate of conversion of the 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[12].

Another interpretation was proposed that aziridine reacted with a nitrogen nucleophile, derived from either the nitrogen donor or sulfonamide (break down product of nitrogen donor), to form a ring opened aziridine intermediate. Rotation about the C-C bond then allowed inversion of the stereogenic centre, which may have been catalysed by Cu^{2+} acting as a Lewis acid. When the aziridine interacts with the $Cu^{\delta+}$ / bis(oxazoline) / nitrene donor, the increased steric bulk of the system may favour the conversion of the (S)-aziridine to (R)-aziridine[11,16]. Attempts to simulate this, led to a two phase conversion versus time curve, but did not reproduce the plateau that is observed, as well as the sigmoidal shape thereafter. This was attributed to the absence of an autocatalytic process[12].

The failure to replicate the increase in ee with conversion experiment suggests that all the reaction components play a key role in the enantioselection.

Experiments were carried out to see if aziridine coordinates strongly enough to CuHY that it is not displaced by solvent. CuHY and aziridine were stirred in MeCN. The mixture was filtered and the solid washed with MeCN to remove uncoordinated aziridine. The filtrate and washings were combined and rotary evaporated to solid. The solid was weighed to see how much aziridine was uncoordinated. If full complexation of aziridine occurred, 0.0398g of aziridine would have been bound to copper. Table 2 shows that no aziridine was coordinated, suggesting either MeCN displaces aziridine or a complex is not formed. This was repeated with THF as solvent with the same result.

Table 2: Formation of a CuHY- aziridine complex

Cu: Aziridine ratio	Solvent	Aziridine- start (g)	Aziridine- filtrate (g)	Aziridine- coordinated (g)
1: 2.2	MeCN	0.0398	0.0355	0.0043
1: 2.2	THF	0.0396	0.0400	-0.0004

Line 1: CuHY (0.222g) and aziridine (0.0398g) stirred for 1 hour 5 minutes in MeCN (10mL)

Line 2: CuHY (0.2110g) and aziridine (0.0396g) stirred for 1 hour 25 minutes in THF (10mL)

2.8 Aziridination of styrene using PhI=NNs, with both bis(oxazoline) and *N*-nosyl-2-phenylaziridine as chiral modifiers (aziridine yield by flash column chromatography)

As shown in Table 3, the copper bis(oxazoline) catalysed aziridination reaction produces aziridine with an ee of 35%. When this was repeated with the addition of (R) 70% ee aziridine to the start of the reaction, this had no significant effect on the enantioselectivity of the aziridine made.

Table 3: Aziridination reaction using both bis(oxazoline) and aziridine as ligands

Aziridine- start		Aziridine- end		Aziridine- produced		
(g)	(% ee)	(g)	(% ee)	(g)	(% yield)	(% ee)
-	-	0.122	R 35	0.122	100	R 35
0.0208	R 70	0.1428	R 43	0.122	100	R 38

Line 1: CuHY (0.15g), bis(oxazoline) (0.02283g), PhI=NNs (0.2435g), Styrene (46μL), MeCN (5mL), Reaction time: 17 hours 55 minutes

Line 2: CuHY (0.15g), bis(oxazoline) (0.02283g), PhI=NNs (0.2435g), Styrene (46μL), Aziridine (0.0207756g), MeCN (5mL), Reaction time: 17 hours 55 minutes

2.9 Aziridination of styrene using PhI=NNs, with (R)–*N*-nosyl-2-phenylaziridine as chiral modifier (aziridine yield by flash column chromatography)

The addition of aziridine with an ee of (R) 72% and (R) 69% to an aziridination reaction did not result in chiral aziridine being produced (Table 4). This suggests that aziridine may not be a good chiral ligand.

Table 4: Addition of nosyl phenyl aziridine with an ee of (R) 72% and (R) 69% to a racemic styrene reaction using PhI=NNs

Cu: Aziridine Ratio	Aziridine- start		Aziridine- end		Aziridine- produced		
	(g)	(% ee)	(g)	(% ee)	(g)	(% yield)	(% ee)
1: 1.2	0.0157	R 72	0.1377	R 6	0.122	100	0
1: 2.2	0.0270	R 69	0.149	R 13	0.122	100	0

Line 1: CuHY (0.1513g), PhI=NNs (0.2435g), Styrene (46μL), Aziridine (0.0157g), MeCN (5mL), Reaction time: 18 hours 25 minutes

Line 2: CuHY (0.1511g), PhI=NNs (0.2435g), Styrene (46μL), Aziridine (0.0270g), MeCN (5mL), Reaction time: 20 hours and 9 minutes

2.10 Experiment to check if the aziridine put in at the start of the reaction is racemising

Synthesised (S)-*N*-nosyl-2-phenylaziridine was stirred together with CuHY and PhI=NNs in MeCN. Styrene was not included, so no new aziridine was made. There was no change in the ee of the aziridine. Therefore, these results suggest that the aziridine put in at the start of each reaction is not being racemised.

Table 5: Experiment to check if the aziridine put in at the start of the reaction is racemising

Aziridine- start (% ee)	**Aziridine- end (% ee)**
S 100	S 100

Reaction conditions: CuHY (0.3273g), PhI=NNs (0.5292g), Aziridine (0.1117g), MeCN (5mL), Reaction time: 5 hours

2.11 Aziridination of styrene using PhI=NNs, with pure (S)-*N*-nosyl-2-phenylaziridine as chiral modifier (aziridine yield by HPLC)

These experiments used shorter reaction times of =< six hours. This resulted in much lower aziridine yields being obtained (< 30mg). It was thought that for these quantities, obtaining the yield by HPLC rather than flash column chromatography would be more accurate.

A racemic aziridination reaction stirred for five hours gave an aziridine yield of 10%. This was repeated with the addition of (S)-*N*-nosyl-2-phenylaziridine to the start of the reaction. An aziridine yield of 10% was also achieved, with an ee of (S) 34%. This result is similar to the ee of aziridine obtained from a copper bis(oxazoline) catalysed reaction (35%). (S)-*N*-nosyl-2-phenylaziridine was also added to an aziridination reaction, which used a reactant concentration of less than half of the amount used in the aforementioned experiments. An aziridine yield of 8% was made, with an ee of (S) 4%. The lower concentration could have affected the rate of reaction which resulted in nearly racemic aziridine being made. It may have been interesting to repeat this experiment without the addition of aziridine to see if a yield of 8% is also obtained.

These results seem to propose that the addition of (S)-*N*-nosyl-2-phenylaziridine to an aziridination of styrene reaction can give rise to enantioselection albeit with low ee. However, just a 2% increase in the measured ee of the total amount of aziridine at the end of the reaction, would make a disproportionately large increase in the ee of the produced aziridine. If the aziridine at the end of the reaction, shown in Line 2 of Table

6, gave an ee of (S) 88.7% instead of (S) 87%, the ee of the produced aziridine would increase from (S) 34% to (S) 43%. Therefore, the accuracy of the ee determination could have had a significant bearing on the results.

Table 6: Addition of pure (S)-*N*-nosyl-2-phenylaziridine to a racemic styrene reaction using PhI=NNs

Aziridine- start		Aziridine- end		Aziridine- produced		
(g)	(% ee)	(g)	(% ee)	(g)	(% yield)	(% ee)
-	-	0.027	0	0.027	10	0
0.1043	S 100	0.130	S 87	0.02566	10	S 34
0.0484	S 100	0.058	S 84	0.00967	8	S 4

Line 1: CuHY (0.3277g), PhI=NNs (0.5317g), Styrene (100μL), MeCN (5mL) Reaction time: 5 hours

Line 2: CuHY (0.3272g), PhI=NNs (0.5304g), Styrene (100μL), Aziridine (0.1043g), MeCN (5mL), Reaction time: 5 hours 16 minutes

Line 3: CuHY (0.1516g), PhI=NNs (0.2492g), Styrene (46μL), Aziridine (0.0484g), MeCN (5mL), Reaction time: 5 hours 9 minutes

2.12 Cross over reactions

The problem with the experiments so far is that distinguishing between aziridine added to the reaction and aziridine made has not been possible. Although the results suggest that the aziridine put in at the start is not being racemised, it may be destroyed or changed during the reaction. Cross over experiments permit the differentiation to be made.

2.12.1 General procedure

An outline of the method used for the following experiments is given below.

CuHY with/ without aziridine was stirred in MeCN for 15 minutes. Styrene/ 4-methylstyrene and PhI=NNs/ PhI=NTs were then added and the reaction stirred for the required time. The reaction mixture (5mL) was filtered and the solid washed with MeCN (45mL). The filtrate and washings were combined, 5mL of the solution taken and evaporated to solid. A sample for HPLC analysis was prepared by first fully dissolving the solid in THF (2.5mL), followed by the addition of hexane (2.5mL). Some of the solution was transferred to a HPLC vial and analysed using the Chiralpak IA HPLC column to obtain the ee of the aziridine without purification.

2.12.2 Aziridination of 4-methylstyrene using PhI=NNs, with (R) 81% *N*-nosyl-2-phenylaziridine as chiral modifier

In an aziridination of 4-methylstyrene reaction using PhI=NNs, the addition of nosyl phenyl aziridine with an ee of (R) 81% did not induce enantioselectivity. The nosyl methyl phenyl aziridine produced was racemic.

Table 7: Aziridination of 4-methylstyrene using PhI=NNs, with (R) 81% *N*-nosyl-2-phenylaziridine as chiral modifier

N-nosyl-2-phenylaziridine- start (% ee)	*N*-nosyl-2-(4-methylphenyl)aziridine- produced (% ee)
R 81	0

Reaction conditions: CuHY (0.3260g), PhI=NNs (0.5291g), 4-methylstyrene (115μL), Aziridine (0.1486g), MeCN (5mL), Reaction time: 6 hours

2.12.3 Addition of (S)-*N*-tosyl-2-benzylaziridine to a racemic styrene reaction using PhI=NNs

The addition of the commercially available (S)-*N*-tosyl-2-benzylaziridine to a racemic styrene reaction with PhI=NNs had no effect on the enantioselectivity of the aziridine produced. The *N*-nosyl-2-phenylaziridine made was racemic. The ee of the *N*-tosyl-2-benzylaziridine remained unchanged at the end of the reaction.

Table 8: Addition of (S)-*N*-tosyl-2-benzylaziridine to a racemic styrene reaction using PhI=NNs

Cu: Tosyl aziridine ratio	Tosyl aziridine-start (% ee)	Tosyl aziridine-end (% ee)	Nosyl aziridine-produced (% ee)
1: 4.2	S 100	S 100	0
1: 10.2	S 100	S 100	0

Line 1: CuHY (0.327g), PhI=NNs (0.5294g), Styrene (100μL), Aziridine (0.1052g), MeCN (5mL), Reaction time: 5 hours 48 minutes

Line 2: CuHY (0.3277g), PhI=NNs (0.5298g), Styrene (100μL), Aziridine (0.2565g), MeCN (5mL), Reaction time: 5 hours

2.12.4 Addition of (S)-*N*-tosyl-2-phenylaziridine to a racemic styrene reaction using PhI=NNs

The pure (S) enantiomer of tosyl phenyl aziridine was made by tosylation of (S)-(+)-2-phenylglycinol and cyclisation by potassium carbonate[20]. The addition of tosyl phenyl aziridine with an ee of (S) 100% to a racemic styrene reaction using PhI=NNs did not result in chiral aziridine being formed. As in the last experiment the nosyl aziridine made was racemic. The ee of the tosyl phenyl aziridine also remained unchanged at the end of the reaction.

Table 9: Addition of (S) tosyl phenyl aziridine to a racemic styrene reaction using PhI=NNs

Tosyl aziridine- start (% ee)	Tosyl aziridine- end (% ee)	Nosyl aziridine- produced (% ee)
S 100	S 100	0

Reaction conditions: CuHY (0.3273g), PhI=NNs (0.5293g), Styrene (100μL), Aziridine (0.1035g), MeCN (5mL), Reaction time: 3 hours 20 minutes

2.12.5 Addition of (S)-*N*-nosyl-2-phenylaziridine to a racemic styrene reaction using PhI=NTs

In a racemic styrene reaction using PhI=NTs the addition of (S) nosyl phenyl aziridine did not bring about enantioselectivity in the tosyl aziridine produced. The ee of the nosyl phenyl aziridine was unaltered at the end of the reaction.

Table 10: Addition of (S) nosyl phenyl aziridine to a racemic styrene reaction using PhI=NTs

Nosyl aziridine- start (% ee)	Nosyl aziridine- end (% ee)	Tosyl aziridine- produced (% ee)
S 100	S 100	0

Reaction conditions: CuHY (0.3265g), PhI=NTs (0.4914g), Styrene (100μL), Aziridine (0.1116g), MeCN (5mL), Reaction time: 5 hours 24 minutes

Therefore, the addition of chiral aziridine does not lead to an increase in enantioselection in the aziridination of styrene.

2.13 Effect of the analytical procedure on the ee of the aziridine

Aziridine with an ee of 35% was made reproducibly in the homogeneous and heterogeneous aziridination reactions. This was in sharp contrast to the high enantioselectivities reported previously. The following examines the analytical procedure used, which was the major difference between this investigation and the preceding work.

Aziridine was made using the method shown in 2.2. The ee was determined by the HPLC analysis method used in the previous work. The aziridine was prepared for this by dissolving in hexane. A Chiralcel OJ column, which to date has been the column of choice in the Cardiff group was used with a mobile phase of 70% hexane and 30% IPA to separate the enantiomers. The results showed that the ee of the aziridine was ~90% (Figure 4).

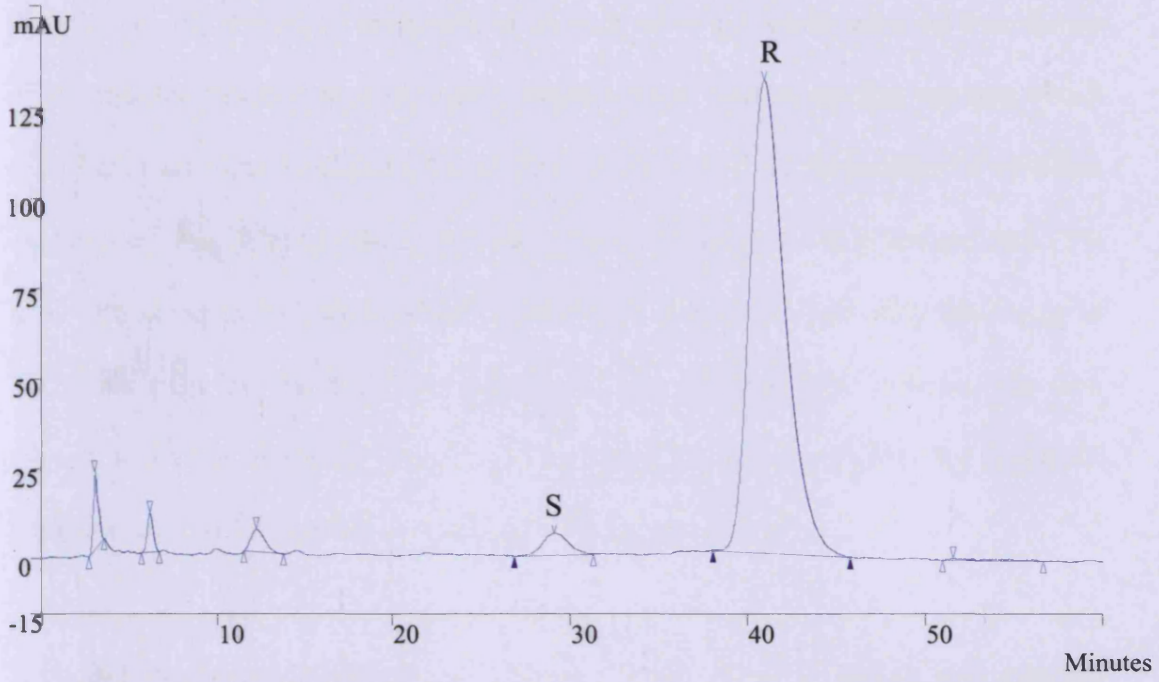

Figure 4: Chromatogram of the aziridine analysed using the Chiralcel OJ column with hexane as the sample injection solvent

The Chiralcel OJ column is packed with cellulose tris (4-methylbenzoate) coated on 10μm silica-gel. Only alkane and alcohol solvents could be used with this type of column. This is because solvents commonly used in HPLC eluents such as THF and DCM may destroy the chiral stationary phase if they are present even in residual quantities. The separate aziridine enantiomers should be equally soluble in an achiral solvent such as hexane or IPA. The aziridine had low solubility in the aforementioned solvents and the reasonable assumption had been made that the two enantiomers were equal even if incompletely soluble in such solvent combinations.

The Chiralpak IA column came to our attention as a possible replacement to the Chiralcel OJ column. It has a packing composition of amylose tris (3,5-dimethylphenylcarbamate) immobilized on 5μm silica gel which allowed free choice of any miscible solvents to make up the mobile phase. This meant that solvents which offer better aziridine solubility such as THF could be utilised. Separation of aziridine enantiomers was achieved using a mobile phase consisting of 85% hexane and 15% IPA. The aziridine was prepared for chiral HPLC analysis by first fully dissolving in THF thus ensuring that both enantiomers were in solution. The solution was then diluted with four times its volume of hexane. This was to prevent the aziridine crashing out of solution when it was injected into the column.

Aziridine ascertained to have a high ee using the Chiralcel OJ column was prepared for HPLC analysis as above and re-analysed using the Chiralpak IA column. As mentioned earlier, the ee was found to be only 35% (Figure 5). Polarimeter measurements showed that the sample had an ee of ~30% thus corroborating the results of the new column. When hexane alone was used as the sample injection solvent the ee of the aziridine was found to be ~90% (Figure 6). This suggests that when aziridine is in hexane the enantiomers apparently do not dissolve equally.

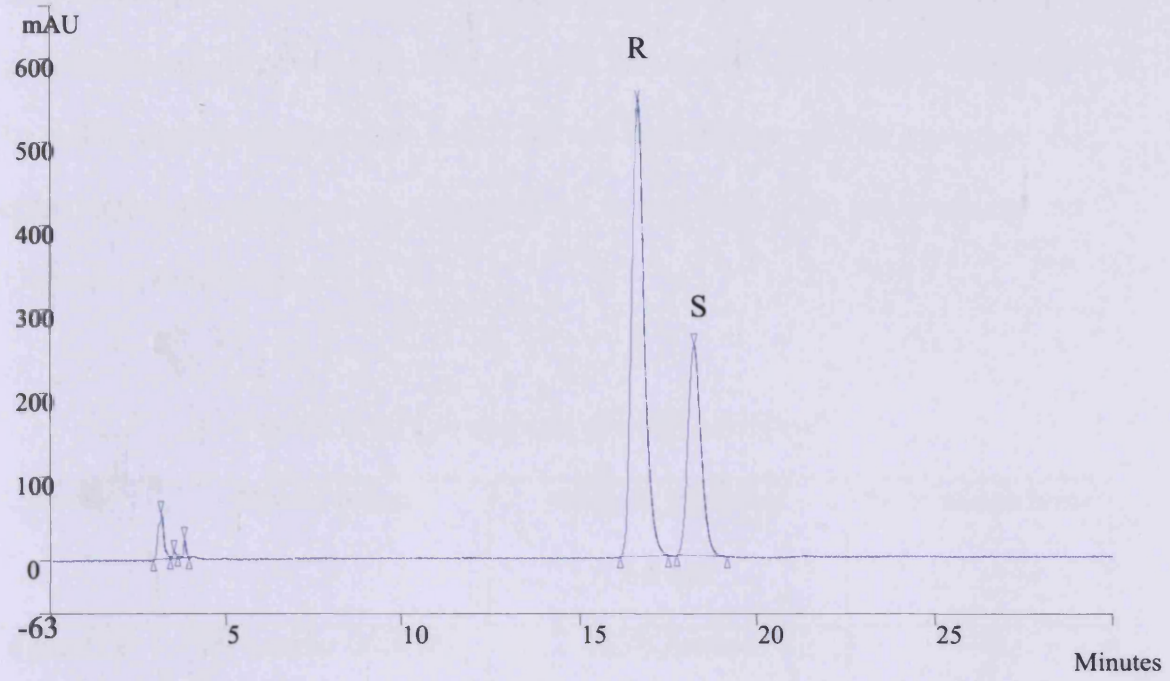

Figure 5: Chromatogram of the aziridine analysed using the Chiralpak IA column with THF and hexane as the sample injection solvent

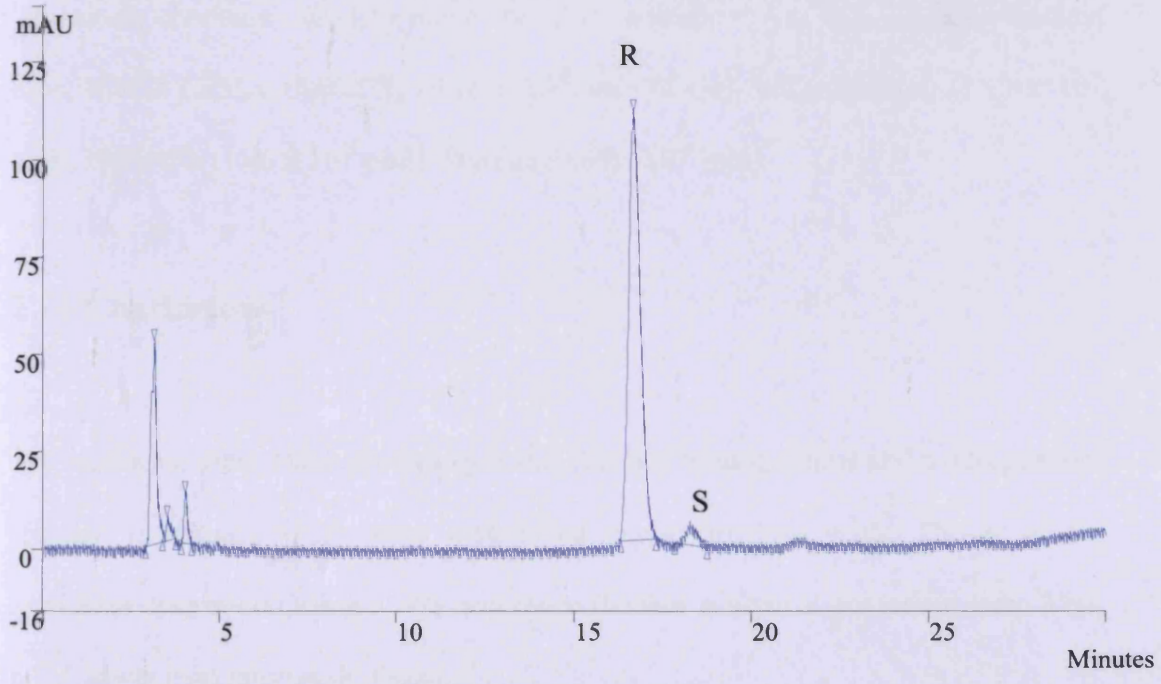

Figure 6: Chromatogram of the aziridine analysed using the Chiralpak IA column with hexane as the sample injection solvent

As the mobile phase selected for the Chiralpak IA column was different to the sample injection solvent, a test was completed to check that this had no effect on the results. The mobile phase was changed to 20% THF and 80% hexane; so that it matched the sample injection solvent. Full separation of enantiomers was achieved and no difference in ee was found.

Table 11: HPLC analysis of nosyl aziridine[a]

Column	Mobile phase	Sample injection solvent	% ee of aziridine
Chiralcel OJ	70% hexane: 30% IPA	100% hexane	~90
Chiralpak IA	85% hexane: 15% IPA	100% hexane	~90
Chiralpak IA	85% hexane: 15% IPA	20% THF: 80% hexane	35
Chiralpak IA	20% THF: 80% hexane	20% THF: 80% hexane	36

[a] Reaction conditions used to make the nosyl aziridine: Air, RT, 12 hour reaction time, MeCN (5mL), $Cu(OTf)_2$ (4.15×10^{-5} mol of Cu), bis(oxazoline) (1.17×10^{-4} mol), PhI=NNs (1.46×10^{-3} mol), Styrene (9.69×10^{-4} mol).

2.14 Conclusions

The aziridines were made according to the standard homogeneous and heterogeneous reaction conditions which were established in the previous work. The ee of the aziridines determined using a new and more flexible analytical procedure were 35%, much lower than previously found.

The major enantiomer produced from the (S,S)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline) modified aziridination reaction was the (R)-aziridine. This was substantiated by injecting the pure (S) enantiomer into the Chiralpak IA column and by polarimeter measurements. A misassignment had been made in the previous work that has now been corrected.

When CuHY and aziridine were stirred in MeCN or THF no aziridine was coordinated. This suggests that aziridine does not coordinate strongly enough to CuHY that it is not displaced by solvent, a complex is not formed or the other reaction components may be important in forming a strong complex between aziridine and CuHY.

The ee of aziridine was thought to increase with conversion due to further reactions of the product for the aziridination of styrene using copper bis(oxazoline) complexes[1]. This reaction was repeated and the aziridine made analysed using the Chiralpak IA column. It was found that the ee of the azirdine produced did not increase with conversion. The ee of aziridine made at a reaction time of 1 minute was (R) 34%. The aziridine remained at this ee throughout the aziridination reaction.

The addition of (S)-*N*-nosyl-2-phenylaziridine to an aziridination of styrene reaction stirred for five hours apparently gave rise to enantioselection, albeit with low ee. However, experimental uncertainty may be responsible, in view of the results of the more reliable cross-over experiments.

Crossover reactions allowed a distinction to be made between the aziridine put in at the start and aziridine made during the aziridination reaction. In a racemic 4-methylstyrene reaction using PhI=NNs, where nosyl phenyl aziridine with an ee of (R) 81% ee was added, the nosyl phenyl methyl aziridine made was racemic. Similarly the addition of (S) tosyl phenyl aziridine or (S) tosyl benzyl aziridine to a racemic styrene reaction using PhI=NNs had no effect on the enantioselectivity of the aziridine produced. The nosyl aziridine made was racemic. Also, racemic tosyl aziridine was produced in a reaction where (S) nosyl phenyl aziridine was added to a racemic styrene reaction using PhI=NTs. The addition of chiral aziridines did not lead to additional enantioselection. It appears that the product aziridine is not a good ligand for copper in the racemic aziridination reaction of styrene.

This led to the discovery that the old analytical procedure used to determine the ee of aziridines was flawed. Hexane was used as the HPLC injection solvent. The aziridine had low solubility in hexane and the enantiomers were found not to dissolve equally. There was an issue when hexane used, which will be looked at in more detail in the next chapter.

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Chapter 3

Phase behaviour of *N*-nosyl-2-phenylaziridine

3.1 Introduction

Aziridines were made from the reaction of styrene with PhI=NNs catalysed by copper triflate or CuHY in the presence of bis(oxazoline) in MeCN. An improved analytical procedure found the ee of the aziridines to be much lower than previously found (35%). The discrepancy was attributed to the earlier use of hexane as a HPLC injection solvent. Separate pure enantiomers of aziridine should have the same solubility in an achiral solvent, such as hexane. The observed anomaly must arise because of the interaction of the two enantiomers when both are present in the same product mixture. A potential explanation is that the low ee aziridine made in the aziridination reaction could be made up of a less soluble racemic compound and the enantiomer which is present in excess. The following work investigates the effect of solvent on aziridine in more detail.

3.2 Effect of solvent on *N*-nosyl-2-phenylaziridine

3.2.1 *N*-Nosyl–2-phenylaziridine with an ee of (R) 26 - 35% in hexane

The observation that the two enantiomers of the aziridine apparently do not dissolve equally in hexane was further investigated. (R) 28% ee aziridine was stirred in hexane at a ratio of 1mg aziridine to 3.4mL hexane. The solution was filtered to remove undissolved aziridine. A sample of the filtrate was taken and injected into the HPLC. The ee was (R) 81%. The rest of the filtrate was evaporated to solid and re-dissolved in 20% THF, followed by the addition of 80% hexane. This conforms to the new preparation procedure for HPLC samples. The ee obtained was also (R) 81% as

anticipated. The filtered off aziridine was treated in the same way and the ee was (R) 10.5%.

The aziridine to hexane ratio is an important factor in achieving the best possible ee and high yield of aziridine in solution. As shown in Table 1, when too much hexane was used the ee of aziridine dissolved in solvent was lower than the optimum. Many other factors such as temperature, ee of the starting aziridine and the length of time that the aziridine is stirred in hexane can also affect the result.

These results show that low ee aziridine in hexane gives high ee in solution and lower ee solid. Hence, provides a means of easily isolating the major enantiomer.

Table 1: Nosyl aziridine with an ee of (R) 35% in hexane

Aziridine: hexane ratio	**Aziridine-start**		**Aziridine-dissolved in solvent**			**Aziridine-residual solid**	
mg : mL	**g**	**% ee**	**g**	**% yield**	**% ee**	**g**	**% ee**
1 : 3.4	0.149	(R) 28	0.037	25	(R) 81	0.112	R 10.5
1 : 4	0.209	(R) 35	0.062	30	(R) 73	0.147	R 19
1 : 5	0.152	(R) 26	0.059	39	(R) 72	0.087	R 3

A potential explanation for this phenomenon is that the low ee aziridine made in the aziridination reaction could be made up of a racemic compound, comprising a 1:1 crystalline arrangement of enantiomers and the enantiomer which is present in excess.

The racemic aziridine is less soluble in hexane than the individual enantiomer leading to solution that has an enhanced ee.

Undissolved solid which was filtered off from the solution of (R) 28% aziridine in hexane was recrystallised from DCM. Racemic crystals were identified using a polarising microscope. There are four ways that a racemate can crystallise. Two of these are as a racemic compound or as a conglomerate. A racemic compound is sometimes called a true racemate. Molecules have a greater affinity for the opposite enantiomer than the same enantiomer. The substance forms a single crystalline phase in which the two enantiomers are present in an ordered 1:1 ratio in the elementary cell. A conglomerate, by contrast, is a mechanical mixture of enantiomerically pure crystals of one enantiomer and its opposite. Molecules in the crystal structure have a greater affinity for the same enantiomer than the opposite enantiomer.

Wallach's rule states that racemic crystals tend to be denser than their chiral counterparts[1]. However, Brock found the rule to be only valid for resolvable enantiomers[2]. These are enantiomers that are chemically stable and that are not in rapid exchange between one another. Statistically, 90 - 95% of racemic species exist as racemic compounds while only 5 - 10% of racemic species are conglomerates. The greater occurrence of racemic compounds may be attributed to the greater compactness of their crystal structures than those of the corresponding conglomerates.

Most racemic compounds crystallise in three space groups: $P2_1/c$, $C2/c$, and $P\text{-}1$, which possess elements of inverse symmetry. In contrast, enantiomers can crystallise only into dissymmetric space groups, which are devoid of inverse symmetry elements.

The inverse symmetry in the racemic compound may lead to close packing and ultimately contributes to the greater stability of the racemic compound.

X-ray crystallography confirmed that the racemic crystals were true racemates, as can be seen in Figure 1 adjacent pairs of molecules are enantiomeric and pack centro symmetrically. An (S)-enantiomer crystal was obtained from recrystallisation of synthesised pure (S)-*N*-nosyl-2-phenylaziridine from DCM. Its identity was confirmed by X-ray crystallography. The energy difference between the racemic crystal and pure (S) enantiomer crystal was calculated using periodic DFT by Willock, D[3]. The result was 11kJ mol^{-1} in favour of the racemic crystal. This supports the theory that the racemic crystal is more strongly bound than the pure enantiomer crystal leading to the racemic crystal being less soluble than the homochiral crystal.

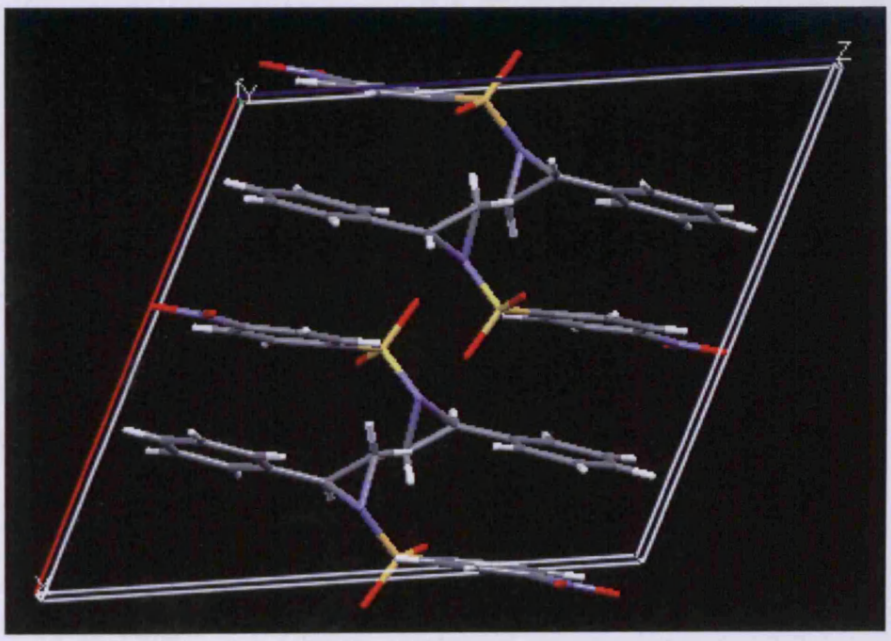

Figure 1: Racemic crystal

Table 2: Racemic crystal data and structure refinement

Identifier	gjh0804
Empirical formula	$C_{14}H_{12}N_2O_4S$
Formula weight	304.32
***T*/K**	150(2)
Crystal size/mm^3	0.35 x 0.30 x 0.05
Crystal system	Monoclinic
Space group	$P2_1/a$
***a*/Å**	13.4830(5)
***b*/Å**	7.5430(3)
***c*/Å**	14.7650(5)
***β*(°)**	114.997(2)
Volume/Å^3	1360.98(9)
Z	4
ρ_{cal}/Mg m^{-3}	1.485
R_1 [$I > 2\sigma(I)$]	0.0450
wR_2	0.0997

Table 3: (S) enantiomer crystal data and structure refinement

Identifier	gjh0807dt
Empirical formula	$C_{14}H_{12}N_2O_4S$
Formula weight	304.32
***T*/K**	100(2)
Crystal size/mm^3	0.25 x 0.05 x 0.03
Crystal system	Monoclinic
Space group	$P2_1$
***a*/Å**	6.7710(3)
***b*/Å**	26.8040(15)
***c*/Å**	7.4480(3)
β(°)	89.867(3)
Volume/Å^3	1351.73(11)
Z	4
ρ_{cal}/Mg m^{-3}	1.495
R_1 [$I > 2\sigma(I)$]	0.0964
wR_2	0.2224

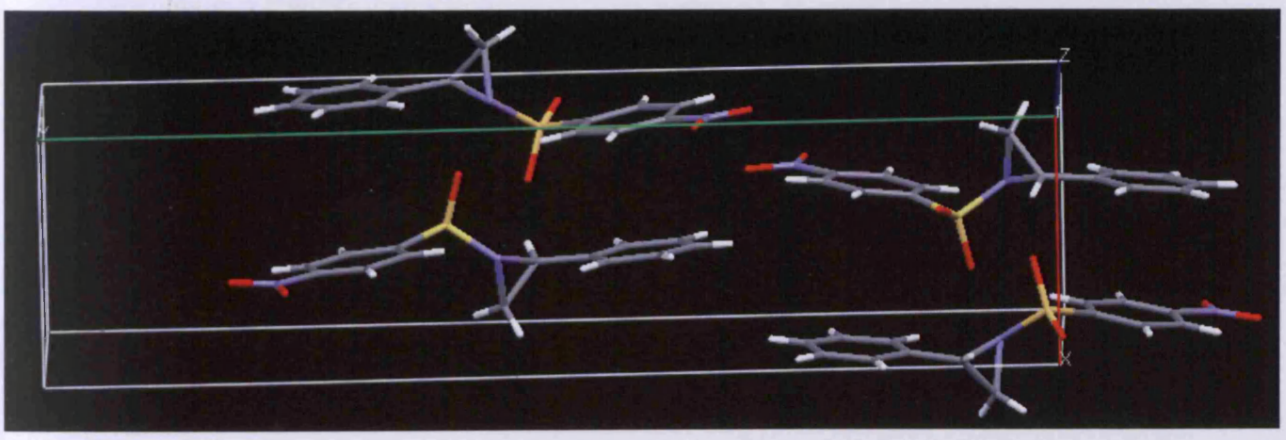

Figure 2: (S) enantiomer crystal

Jacques, Collet and Wilen[4] describe that the solid phases observed in saturated solutions of partially resolved racemic compounds are the crystals of racemic compounds (pure or solvated) in addition to those of the enantiomer present in excess (also either pure or solvated). Phase diagrams can be constructed from solubility data at constant temperature. Figure 3 shows a theoretical phase diagram. Due to the poor solubility of aziridine, solvent dominates the total phase diagram, therefore only the small area at the apex is shown in detail. The phase rule dictates that under equilibrium conditions, provided sufficient material is available, the solution composition will be that of the eutectic (E or E') as long as three phases (the solid racemic compound, the solid enantiomer present in excess, and the saturated solution) are present.

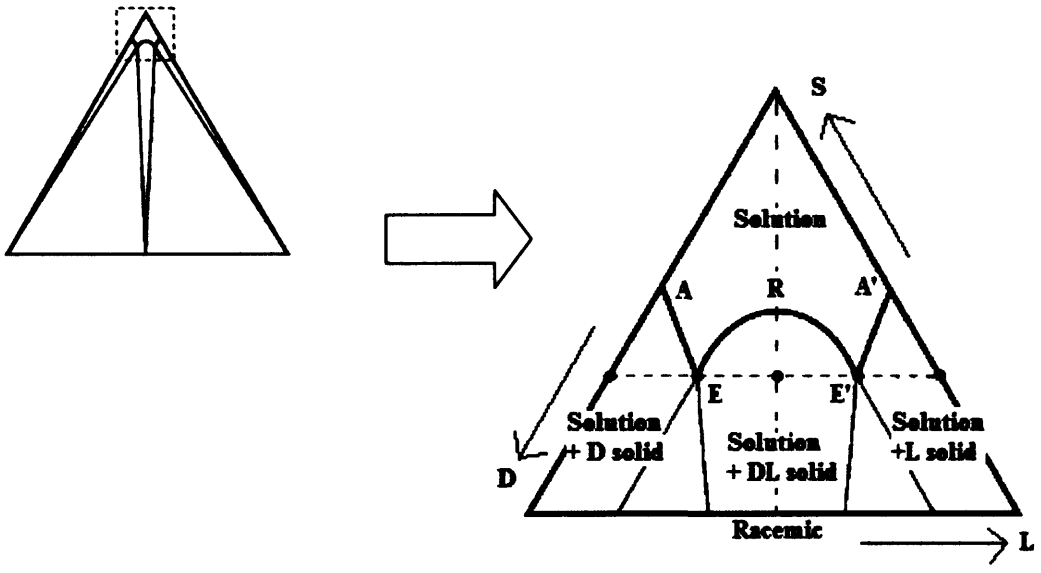

Figure 3: Theoretical phase diagram[4]

This seemed very similar to the situation described by Blackmond et al in connection with amino-acids[5]. They found that when the enantiomers of proline are present in

unequal proportions above their solubility limit in dimethyl sulphoxide (DMSO), two separate solid phases are formed at equilibrium. These were confirmed to be a racemic compound and an enantiopure solid of the excess enantiomer. The phase rule dictates that at constant temperature the composition of a solution of proline in equilibrium with the two solid phases is fixed, and this composition is given by the eutectic.

Studies by Soloshonok et al were found to be highly relevant to our research. They found that a sample of (S)-α-(trifluoromethyl)lactic acid with an ee of 80% sublimes by evaporation in open air at room temperature. The enantiomeric purity of the sample increased to >99.9% ee.[6] The racemic crystals sublimed considerably faster than the corresponding enantiomerically pure crystals.

3.2.2 *N*-Nosyl-2-phenylaziridine with different enantiomeric excesses in hexane

N-Nosyl-2-phenylaziridines with a range of different enantiomeric excesses were stirred in hexane (5mg in 5mL). The solution was filtered to remove undissolved aziridine and injected into the HPLC. At a ratio of 1mg aziridine to 1mL hexane it was thought that there was sufficient material available for the solution composition to be that of the eutectic. As shown in Figure 4 the ee of the aziridine in solution was fixed at (R) 82% regardless of the ee of the aziridine utilised. It appears that (R) 82% was the ee of the aziridine in solution at the eutectic. Only when the ee of the aziridine used was too low or too high was there deviation. When the initial aziridine had an ee of (R) 6% or less there was an insufficient amount of the excess enantiomer to establish the enantiopure solid phase. Similarly, when the aziridine had an ee of (R)

100% there was no minor enantiomer available for the creation of the solid racemic compound phase. High ee in solution was obtainable when aziridine with an ee as low as (R) 13% was stirred in hexane.

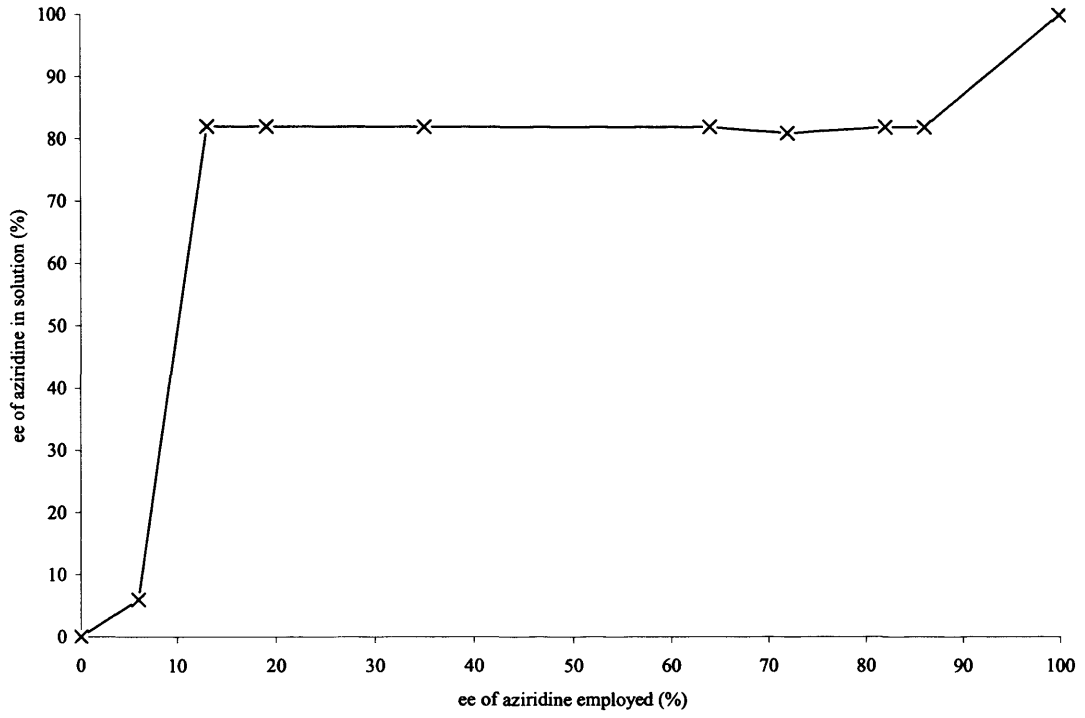

Figure 4: Nosyl aziridine with different enantiomeric excesses in hexane[a]

[a] 1mg azirdine: 1mL hexane

3.2.3 *N*-Nosyl-2-phenylaziridine from styrene derivatives in hexane

Nishikori and Katsuki used (salen)manganese(III) complexes for the catalytic aziridination of styrene derivatives using PhI=NTs as the nitrene donor. They showed that 4-chlorostyrene and 4-methylstyrene gave high enantioselectivity and yield of aziridine. However, these were lower compared with styrene.[8] Andersson et al reported the comparison of nitrene precursors for the copper catalysed asymmetric

aziridination of olefins. They obtained aziridine derivatives of several olefins in moderate to excellent yields and with enantioselectivity up to 95% ee.[9]

The Cardiff group have concentrated on styrene as a model reactant. Ryan et al[10] extended the range of substrates and investigated the reactivity of substituted styrene derivatives for both the homogeneously and heterogeneously catalysed aziridination reactions using (N-(*p*-(nosylsulfonyl)imino)phenyliodinane, PhI=NNs as the nitrene donor. They reported a particularly high ee of 95% for the reaction of 3-chlorostyrene in the heterogeneous system.

The following work corrects the enantiomeric excesses of aziridines formed by the reaction of PhI=NNs with ring-substituted styrenes catalysed by $Cu(OTf)_2$ and by CuHY. Reactions were conducted in an identical manner to those described by Ryan et al, but enantiomeric analyses were carried out using a Chirapak IA HPLC column with injection of the aziridines in THF diluted with hexane. The aziridines were also stirred in hexane (5mg in 5mL), the solution filtered to remove residual solid, and the filtrate injected into the HPLC column. These results along with the earlier reported ee values are shown in Table 4. The corrected ee for each of the substituents is much less than previously reported, being about 30%. The aziridine dissolved in hexane exhibited high ee values, and showed that the formation of a solid racemate that is less soluble in hexane than the pure enantiomers is not limited to nosyl unsubstituted phenyl aziridines.

Table 4: Nosyl aziridine from styrene derivatives in hexane[a]

Styrene substituent	Reported % ee of aziridine[10]		Corrected % ee of aziridine	% ee of aziridine dissolved in hexane
	CuHY	$Cu(OTf)_2$		
3-F	(S) 58	(S) 83	(R) 25	(R) 94
4-CH_3	(S) 67	(S) 66	(S) 25	(S) 89
3-Cl	(S) 95	(S) 72	(R) 30	(R) 87

[a] 1mg azirdine: 1mL hexane

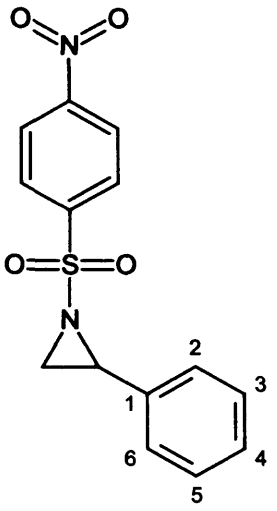

Figure 5: Nosyl aziridine

3.2.4 *N*-Nosyl-2-phenylaziridine in different solvents

Aziridine with a known ee of (R) 33% was stirred in various solvents (10mg in 10mL). The solution was filtered to remove residual aziridine. The filtrate was evaporated to solid and 20% THF and 80% hexane added to make a sample for chiral HPLC analysis. This gave the ee of the dissolved aziridine. The polarity of the solvent

may be a key factor which affects the solubility of the aziridine. Aziridine was fully soluble in THF, DCM and MeCN, which are polar aprotic solvents. The aziridine was partially soluble in the polar protic solvents ethanol and IPA. However, the ee of the aziridine in solution was not the same for these two solvents. When aziridine was stirred in ethanol the ee of the aziridine utilised was the same as the dissolved aziridine. But, this was not the case when IPA was used; the ee of the dissolved aziridine was higher, (R) 49%. This is thought to be attributable to the higher polarity of ethanol compared to IPA. Ethanol's properties stem from the dominant effect of the presence of the hydroxyl group and the shortness of the carbon chain, whereas in IPA the opposing effects are about equally balanced. The aziridine has low solubility in hexane, cyclohexane, heptane and petroleum ether which are all non-polar solvents. High ee aziridine, (R) 81% to (R) 94% was obtained from solutions made using these solvents.

Table 5: Nosyl aziridine with an ee of (R) 33% injected using different solvents[a]

Solvent	Dielectric constant, ε[11]	Dipole moment, μ/D[11]	Full or partial solubility	% ee of aziridine dissolved in solvent
THF	7.52 (22°C)	1.75	Full	(R) 33
DCM	8.93 (25°C)	1.60	Full	(R) 33
MeCN	36.64 (20°C)	3.92	Full	(R) 33
ethanol	25.30 (20°C)	1.69	Partial	(R) 33
IPA	20.18 (20°C)	1.56	Partial	(R) 49
hexane	1.89 (20°C)	≈0	Partial	(R) 81
cyclohexane	2.02 (20°C)	≈0	Partial	(R) 88

heptane	1.92 (20°C)	≈0	Partial	(R) 91
pet ether	-	-	Partial	(R) 94

[a] 1mg azirdine: 1mL solvent

3.2.5 *N*-Nosyl-2-phenylaziridine in petroleum ether and ethanol mixtures

N-Nosyl-2-phenylaziridine with an ee of (R) 33% was stirred in petroleum ether and ethanol mixtures (5mg in 5mL). The solution was filtered and the filtrate injected into the HPLC. The amount of aziridine dissolved is considered to depend on the mixture of solvents used. Aziridine has been found to be more soluble in ethanol than petroleum ether. The effect of high ee aziridine in solution is not exhibited in ethanol, but in contrast it is in petroleum ether. As 100% ethanol is replaced by petroleum ether the ee of aziridine in solution increases and it is deemed that the quantity of aziridine that dissolves decreases. The relationship between the mixture used and the ee of the aziridine in solution appears to be non-linear. However, it is thought that if the quantity of aziridine dissolved in solution was plotted against the solution ee, a linear relationship may result.

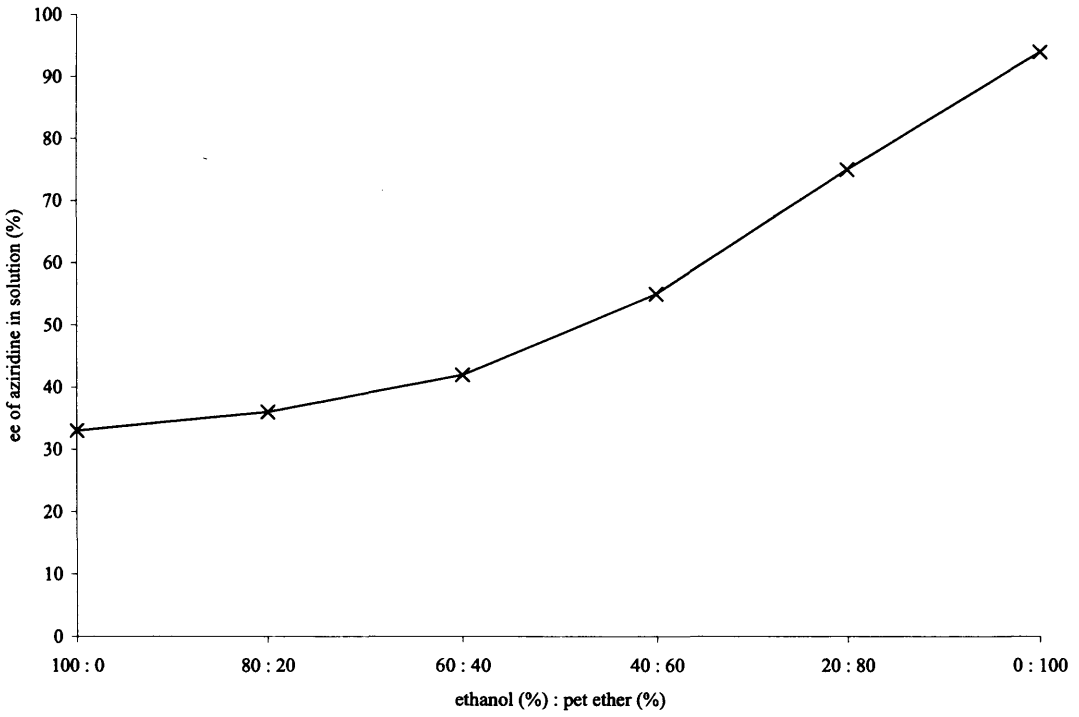

Figure 6: Nosyl aziridine with an ee of (R) 33% in pet ether and ethanol mixtures

3.3 Effect of solvent on *N*-tosyl-2-phenylaziridine

3.3.1 *N*-Tosyl-2-phenylaziridine with an ee of (R) 28% in hexane

There was no separation of the enantiomers of tosyl aziridine with the Chiralpak IA column. Attempted separation using the Chiralpak OD column was also unsuccessful. However, separation was achieved with the Chiralpak IC column. It has a packing composition of cellulose tris (3,5-dichlorophenylcarbamate) immobilised on a 5μm silica-gel. There are no restrictions on the solvents that can be used with this column.

Tosyl aziridine was stirred in hexane according to the ratios in Table 6. The solution was filtered to remove undissolved aziridine and injected into the HPLC. A more

concentrated solution of tosyl aziridine in hexane was found to be required compared to the nosylaziridine in order to exhibit high ee in solution. This was due to the greater solubility of tosyl aziridine in hexane.

Table 6: Tosyl aziridine with an ee of (R) 28% in hexane

Amount of aziridine (mg) in 1mL hexane	% ee in solution
1	(R) 28
2	(R) 32
3.64	(R) 41
26.8	(R) 70

3.4 Conclusions

Prior to recent experiments it had been thought that high ee aziridines (~90%) had been made in both the homogeneous and heterogeneous aziridination reactions. An improved analytical procedure found the actual ee to be 35%.

X-ray crystallography confirmed that the low ee aziridine made in the aziridination reaction was made up of a racemic compound, comprising of a 1:1 arrangement of enantiomers and the enantiomer which is present in excess.

Racemic crystals tend to be denser than their chiral counterparts. The energy difference between the racemic crystal and the pure (S) enantiomer crystal was calculated using periodic DFT and the result was 11 kJ mol^{-1} in favour of the racemic

crystal. This supported the theory that the racemic crystal is more strongly bound than the pure enantiomer which can lead to a difference in solubility.

Aziridine has low solubility in hexane. Aziridine with a known ee of (R) 33% was stirred in hexane at a ratio of 1mg aziridine to 1mL hexane. This led to the separation of a solid phase, which consists largely of the solid racemic compound, and a solution phase that contains mostly the enantiomer originally present in excess. High ee aziridine, (R) 82% was obtained from the solution, hence providing a means of achieving asymmetric amplification in solution.

The ee of the aziridine in solution is fixed at (R) 82% regardless of the ee of the aziridine utilised. Only when the ee of the aziridine originally used is too low or too high is there deviation. High ee in solution is obtainable when aziridine as low as (R) 13% is stirred in hexane.

The effect of high ee in hexane was found to be applicable to nosyl aziridines made from styrene derivatives.

Aziridine was fully soluble in THF, DCM and MeCN, which are polar aprotic solvents. The aziridine was partially soluble in the polar protic solvents ethanol and IPA. Aziridine has low solubility in hexane, cyclohexane, heptane and pet ether which are all non-polar solvents. High ee aziridine, (R) 81% to (R) 94% was obtained from solution using the latter.

A more concentrated solution of tosyl aziridine in hexane is required compared to nosyl aziridine in order to exhibit high ee in solution. This may be due to the greater solubility of tosyl aziridine in hexane.

These results show that a reappraisal of our understanding of the copper catalysed aziridination reaction and of what is in the literature is required. It also demonstrates that extra care should be taken in the purification and analysis of non-racemic compounds.

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Chapter 4

Conclusions

4.1 Enantiomeric excess of *N*-nosyl-2-phenylaziridine

The reactions of styrene with PhI=NNs catalysed by copper(II) triflate or CuHY in the presence of bis(oxazoline) in MeCN, were carried out following the conditions established prior to this work. The resultant aziridines were isolated and the ee ascertained by chiral HPLC.

In earlier work, a Chiralcel OJ column was used with a mixture of hexane and IPA as the mobile phase, comparable to the analytical methods used by Evans and co-workers[1] and by Sodergren et al[2,3]. This column is packed with cellulose tris(4-methylbenzoate) coated on 10μm silica-gel. Only alkane and alcohol solvents could be used with this type of column. This is because solvents commonly used in HPLC eluents such as THF and DCM may destroy the chiral stationary phase if they are present even in residual quantities. Therefore, hexane was used as the sample injection solvent. Analysis of the aziridines using this procedure, with a mobile phase of 70% hexane and 30% IPA showed that the ee was (R) 90%.

In this work, the ee of the aziridines produced were determined using a new and more flexible analytical procedure. Chiral HPLC analysis using a Chiralpak IA column with a packing composition of amylose tris(3,5-dimethylphenylcarbamate) immobilized on 5μm silica gel, allowed free choice of any miscible solvents for the sample injection and to make up the mobile phase. This permitted THF to be used to fully dissolve the sample of aziridine thus ensuring both enantiomers were in solution. The solution was then diluted with four times its volume of hexane. Separation of aziridine enantiomers was achieved using a mobile phase consisting of 85% hexane and 15% IPA. The

result showed that aziridine with an ee of 35% was made, which was much lower than previously found. Polarimeter measurement gave $[\alpha]_D$= -22.4, corresponding to an ee of 29%, thus corroborating the results of the new column.

When hexane alone was used as the sample injection solvent for the Chiralpak IA column, the ee of the aziridine was found to be ~90%. This led to the discovery that the analytical procedure previously used to determine the ee of aziridines was flawed. The discrepancy was attributed to the use of hexane as the sample injection solvent.

Sodergren et al[2,3] used an analytical procedure similar to our use of the Chiralcel OJ column, and reported the preparation of nosyl aziridine with an ee of 66%. Other studies have been published in which nosyl aziridines have been made and their ee values determined using similar suspect procedures[4,5]. In all three instances, the reliability of the ee values cannot be assessed without knowledge of the composition of the solvent used for injection onto the chiral HPLC column.

The major enantiomer produced from the (S,S)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline) modified aziridination reaction was the (R)-(–)-aziridine. This was substantiated by injecting the pure (S) enantiomer into the Chiralpak IA column and by polarimeter measurements. A misassignment had been made in the previous work that has now been corrected. This observation in conjunction with the findings of Evans et al, using PhI=NTs, shows that the sense of stereochemical induction during the aziridination is independent of the 4-substituent in the arenesulfonyl group.

4.2 *N*-Nosyl-2-phenylaziridine as a chiral ligand

Preliminary work by the Cardiff group found that the addition of chiral aziridine to a racemic aziridination of styrene reaction resulted in an increase in enantioselectivity[6]. The effect of the chiral product on the aziridination of styrene was studied further because it offered a possible explanation of the apparent increase in ee with conversion.

When CuHY and aziridine were stirred in MeCN or THF no aziridine was coordinated. This suggests that aziridine does not coordinate strongly enough to CuHY that it is not displaced by solvent, a complex is not formed or the other reaction components may be important in forming a strong complex between aziridine and CuHY.

Crossover reactions allowed a distinction to be made between the aziridine put in at the start and aziridine made during the aziridination reaction. In an aziridination of 4-methylstyrene reaction using PhI=NNs, where nosyl phenyl aziridine with an ee of (R) 81% was added, the nosyl phenyl methyl aziridine made was racemic. Similarly the addition of (S) tosyl phenyl aziridine or (S) tosyl benzyl aziridine to a racemic styrene reaction using PhI=NNs had no effect on the enantioselectivity of the aziridine produced. The nosyl aziridine made was racemic. Also, racemic tosyl aziridine was produced in a reaction where (S) nosyl phenyl aziridine was added to a racemic styrene reaction using PhI=NTs. The addition of chiral aziridines did not lead to additional enantioselection. It appears that the product aziridine is not a good ligand for copper in the aziridination reaction of styrene.

4.3 Enhancement in ee with conversion

The ee of aziridine was thought to increase with conversion due to further reactions of the product for the aziridination of styrene using copper bis(oxazoline) complexes. This experiment was repeated and the aziridine made analysed using the Chiralpak IA column. It was found that the ee of the aziridine produced did not increase with conversion. The ee of aziridine made at a reaction time of 1 minute was (R) 34%. The aziridine remained at this ee throughout the aziridination reaction.

4.4 The ternary system

N-Nosyl-2-phenylaziridine has low solubility in hexane. Nosyl aziridine with a known ee of (R) 33% was stirred in hexane at a ratio of 1mg aziridine to 1mL hexane. This led to the separation of a solid phase, which consists largely of the solid racemic compound, and a solution phase that contains mostly the enantiomer originally present in excess. High ee aziridine, (R) 82% was obtained from the solution, hence providing a means of easily isolating the major enantiomer.

The ee of the aziridine in solution is fixed at (R) 82% regardless of the ee of the aziridine utilised. This is the solution composition at the eutectic point when the saturated solution in hexane is in equilibrium with the solid racemate and the pure solid enantiomer in excess. Only when the ee of the aziridine originally used is too low or too high is there deviation. High ee in solution is obtainable when aziridine as low as (R) 13% is stirred in hexane.

N-Nosyl-2-phenylziridine was fully soluble in THF, DCM and MeCN, which are polar aprotic solvents. The aziridine was partially soluble in the polar protic solvents ethanol and IPA. Aziridine has low solubility in hexane, cyclohexane, heptane and pet ether which are all non-polar solvents. High ee aziridine, (R) 81% to (R) 94% was obtained from solution using the latter.

N-Tosyl-2-phenylaziridine with a concentration as high as 1 mg mL^{-1} of hexane afforded the true ee in the solution phase. At much higher ratios of tosyl aziridines to hexane, which far exceed the solubility, the observed ee of the solution phase did increase but we consider that published ee values for tosyl aziridines are correct.

4.5 X-Ray crystallography

X-ray crystallography confirmed that the low ee aziridine made in the aziridination reaction was made up of a racemic compound, comprising of a crystalline 1:1 arrangement of enantiomers and the enantiomer which is present in excess.

Racemic crystals tend to be denser than their chiral counterparts. The energy difference between the racemic crystal and the pure (S) enantiomer crystal was calculated using periodic DFT and the result was 11 kJ mol^{-1} in favour of the racemic crystal[7]. This supported the theory that the racemic crystal is more strongly bound than the pure enantiomer which can lead to a difference in solubility.

4.6 Enantioselectivity in the aziridination of substituted styrenes

The effect of high ee in hexane was found to be applicable to nosyl aziridines made from styrene derivatives.

4.7 Future work

This thesis has shown that previous reports of high enantioselectivity in the aziridination of styrene reactions with PhI=NNs are in error. Therefore, the factors controlling the enantioselectivity, such as the catalyst, chiral ligand, solvent, nitrene donor, substrate, and their relative ratios should be re-investigated.

4.8 References

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Chapter 5

Experimental

5.1 Preparation and purification of reagents and solvents

All experiments were performed at atmospheric pressure and at room temperature unless otherwise stated. The chemicals used are as follows with information on their source and purity.

Acetone, 99%, Fisher

Acetonitrile, HPLC grade, 99.99%, Fisher

Acetonitrile, 99.9%, water ≤0.005 %, over molecular sieve, Acros Organics

Acetonitrile-d_3, 99.8 atom % D, Aldrich

Benzene, 99.8%, Aldrich

2,2'Biphenyldimethanol, 98%, Aldrich

Chloroform-*d*, H_2O < 0.01%, euriso-top

3-Chlorostyrene, 98%, Aldrich

Copper (II) sulphate, 98%, Fischer

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

Copper solution 1000ppm in ca. 1M nitric acid, Calibrated standard solution

Cyclohexane, HPLC grade, 99.8+%, Fisher

Dichloromethane anhydrous, ≥99.8%, Aldrich

Dichloromethane, HPLC grade, 99.8+%, Fisher

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

Ethanol, HPLC grade, 99.8+%, Fisher

Ethyl acetate, >99%, Fisher

3-Fluorostyrene, 97% Aldrich

Hydrochloric acid solution, 2M, Fisher

Heptane, HPLC grade, 99% *n*-heptane, Fisher

Hexane, HPLC grade, 95% *n*-hexane, Fisher

HF, 48% ACS reagent, Aldrich

Iodobenzene diacetate, 98+%, Lancaster

Isopropanol (HPLC grade), 99.99%, Fisher

(S,S)-2,2'isopropylidene-bis(4-phenyl-2-oxazoline), ≥96%, Fluka

Methanol (HPLC grade), 99.5%, Fisher

4-Methyl styrene, 96% Aldrich

4-Nitrobenzene sulfonamide, 97%, Aldrich

4-Nitrobenzenesulfonyl chloride, 97%, Aldrich

Petroleum ether, 40-60°C, Fisher

(S)-(+)-2-phenylglycinol, 98%, Aldrich

Potassium carbonate anhydrous, 99+%, Fisher

Potassium hydroxide, >85%, Fisher

Pyridine, anhydrous, 99.8%, Aldrich

Sand, low iron, Fisher

Silicagel rubin, cobalt free, Fluka

Silica, 60A Particle size 35-70 micron, Chromatography grade, Fisher

Sodium sulphate, anhydrous, 99+%, Fisher

Styrene, 99.9%, Aldrich

Tetrahydrofuran, HPLC grade, 99.8+%, Fisher

Tetramethylsilane (TMS), ≥99.9%, Aldrich

Toluene, Fisher

p-Toluene sulfonamide, 99+%, Aldrich

p-Toluenesulfonyl chloride, ≥99%, Fluka

(S)-(N-p-tosyl)-2-benzylaziridine, 98%, Aldrich

Ultra stabilised zeolite Y, LZY84, UOP

5.2 Preparation of catalyst

5.2.1 CuHY

NH_4Y zeolite was calcined in air at 550°C overnight to obtain HY zeolite. HY zeolite (4.0g) was stirred in aqueous copper (II) sulphate (0.1M, 100mL) overnight at room temperature. The mixture was then filtered and the solid catalyst washed with distilled water. The catalyst was dried in an oven at 100°C. The copper-zeolite was recalcined at 550°C for four hours prior to use. The Cu content was 1.7% by weight, which was determined by atomic absorption spectroscopy.

5.2.2 Characterisation by Atomic Absorption Spectroscopy (AAS)

Atomic absorption spectroscopy was employed to determine the weight percent of copper incorporated into the zeolite after ion exchange. The instrument used was a Varian SpectrAA 220Z Flame AA Spectrometer with an air-acetylene flame and copper samples were run at wavelength (λ) 324.7nm. Samples for analysis were prepared by dissolution of the dried catalyst (30mg) in 48 wt. % HF solution (1mL), followed by dilution with deionised water (200mL).

5.2.3 AAS Calibration

For copper analysis, standard copper solutions ranging from 1ppm to 8ppm were prepared from a standard 1000ppm copper solution to calibrate the atomic absorption spectrometer (Figure 1). The standard copper solutions were analysed prior to each use of the machine.

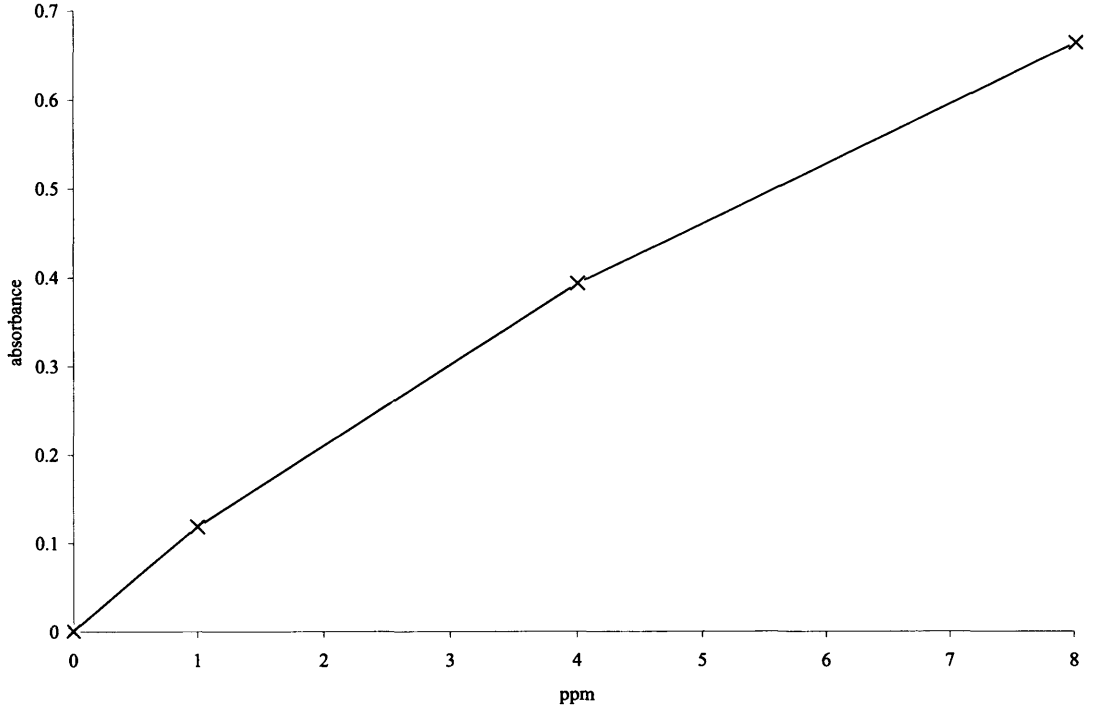

Figure 1: The calibration curve obtained for standard copper solutions

5.3 Copper-chiral modifier complex

Both CuHY (0.326g, 1.7% weight Cu, 8.73×10^{-5} mol of Cu) and $Cu(OTf)_2$ (0.0316g, 17.6% weight Cu, 8.73×10^{-5} mol) were stirred with the chiral modifier (*S,S*)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline) (0.0584g, 1.75×10^{-4} mol) (Figure 2) in

MeCN (5mL) for 15 minutes at room temperature. This was found to be the preferred bis(oxazoline) by Taylor et al[1], as with the heterogeneous catalyst it gave consistently higher yields and ees with the nitrene donors in use (PhI=NTs and PhI=NNs).

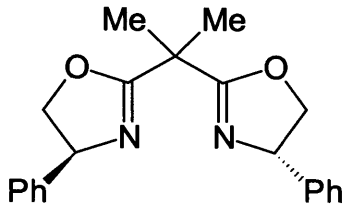

Figure 2: (S,S)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline)

5.4 Synthesis of nitrene donors

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

The synthesis was carried out following the method described by Yamada et al.[2] Potassium hydroxide (11.2g, 0.2 mol) was mixed with *p*-toluene sulphonamide (13.68g, 0.08 mol) in a 500mL round-bottomed flask containing HPLC grade methanol (320mL), and stirred until complete dissolution had occurred. This solution was cooled to below 10°C, iodobenzene diacetate (25.70g, 0.08 mol) added slowly, and the mixture stirred over ice until a yellow solution was formed. The ice was removed, and the mixture stirred at room temperature for a further three hours. The mixture was then poured into distilled water (~800mL), covered and refrigerated overnight. Over a period of 12 hours a yellow precipitate formed, and this was filtered, washed with distilled water and dried/stored in a desiccator in the dark until used. The spectroscopic data were consistent with the literature[2] and were as follows: ^{1}H NMR (d_6-DMSO, 400MHz) δ7-7.8 (multiplet, 9H), δ2.32 (singlet, 3H).

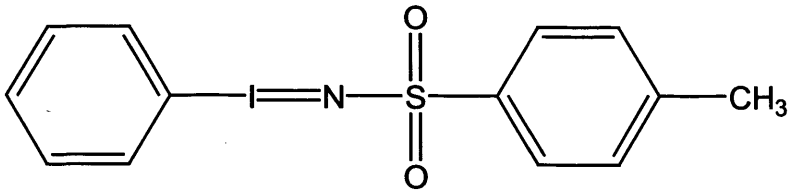

Figure 3: Structure of PhI=NTs

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

Potassium hydroxide (11.2g, 0.2 mol) was mixed with 4-nitrobenzene sulphonamide (16.16g, 0.08 mol) in a 500mL round-bottomed flask containing HPLC grade methanol (320mL), and the mixture stirred until complete dissolution had occurred. This solution was cooled to below 10°C and iodobenzene diacetate (25.70g, 0.08 mol) added slowly, keeping the temperature below 10°C at all times. The mixture was stirred over ice until a cream precipitate was formed, at which point the ice was removed and the mixture stirred for a further three hours at room temperature. The mixture was then poured into distilled water (~800mL), covered and refrigerated overnight. The product was filtered, washed with distilled water and dried/stored in a desiccator in the dark until used. The spectroscopic data were in agreement with the literature[3] and were 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).

5.4.3 Characterisation by ^{1}H Nuclear Magnetic Resonance (NMR)

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

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

5.5.1 Standard homogeneous reaction

Copper triflate (0.0316g, $8.73x10^{-5}$ mol) was stirred with the *bis*(oxazoline) chiral modifier (0.0584g, $1.75x10^{-4}$ mol) in acetonitrile (5mL) for 15 minutes. Styrene (100μL, $8.73x10^{-4}$ mol) was added followed by the nitrene donor (PhI=NTs 0.4886g or PhI=NNs 0.5292g, $1.31x10^{-3}$ mol), and the mixture stirred continuously until all the nitrene donor had been consumed. The product was 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 colourless 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*-tosylsulfonyl)-2-phenylaziridine ($CDCl_3$, 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), are in agreement with the literature values[4]. The spectroscopic

data for *N*-(*p*-nosylsulfonyl)-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), agree with the literature values[4].

5.5.2 Standard heterogeneous reaction

CuHY (0.326g, 1.7% weight Cu, $8.73x10^{-5}$ mol of Cu) was stirred with the *bis*(oxazoline) chiral modifier (0.0584g, $1.75x10^{-4}$ mol) in acetonitrile (5mL) for 15 minutes. Styrene (100μL, $8.73x10^{-4}$ mol) was added followed by the nitrene donor (PhI=NTs 0.4886g or PhI=NNs 0.5292g, $1.31x10^{-3}$ mol), and the mixture stirred continuously until the reaction had gone to completion. The catalyst was removed by filtratation and the product isolated using flash column chromatography (1.5 x 20cm 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.

5.6 Analysis of pure aziridine

5.6.1 High Performance Liquid Chromatography (HPLC)

High pressure liquid chromatography analysis was performed using a Varian Pro-star HPLC system (PDA detector set to λ = 254nm, a 230 Solvent delivery system and a 410 Autosampler).

A Chiralcel OJ column of size 250mm x 4.6mm ID and a packing composition of cellulose tris(4-methylbenzoate) coated on 10μm silica gel was first used to separate the chiral compounds. A solvent mixture of hexane 70%: isopropanol 30% was used, pumped at a rate of 1mL min^{-1}. The *N*-nosyl-2-phenylaziridines were prepared for chiral HPLC analysis by the addition of hexane.

A Chiralpak IA column of size 250mm x 4.6mm ID and a packing composition of amylose tris(3,5-dimethylphenylcarbamate) immobilized on 5μm silica gel was used to replace the Chiralcel OJ column for separating the chiral compounds. A solvent mixture of hexane 85%: isopropanol 15% was used, pumped at a rate of 1mL min^{-1}. The *N*-nosyl-2-phenylaziridines were prepared for chiral HPLC analysis by dissolving 5mg in 1mL THF and adding 4mL hexane.

The efficiency of the Chiralpak IA column was examined by injecting racemic *N*-nosyl-2-phenylaziridine into the column. Varian Star was used to integrate the two resultant peaks and obtain the areas. A 50: 50% separation of the (S) and (R) enantiomers was observed, as shown in Figure 4. The retention time of the (S) enantiomer was confirmed by injecting the synthesised (S) enantiomer of *N*-nosyl-2-phenylaziridine (5.8.2) into the Chiralpak IA column.

In this work the Chiralpak IA column was used for HPLC analysis, unless otherwise stated.

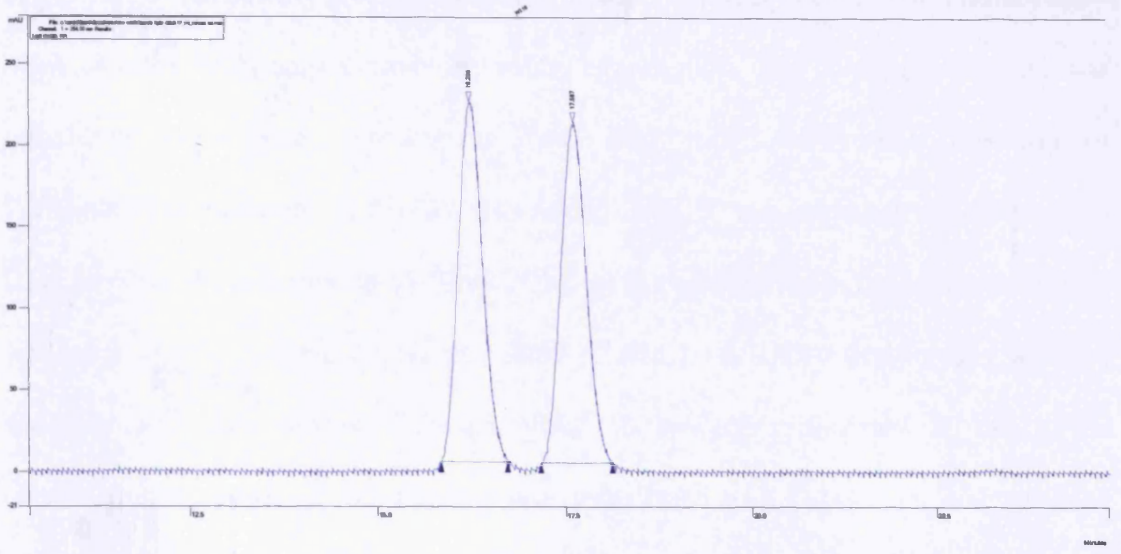

Figure 4: Chromatogram of the separation of racemic *N*-nosyl-2-phenylaziridine

5.7 Analysis of aziridine without purification

5.7.1 HPLC analysis of reaction mixture to obtain the ee

The reaction mixture (5mL) was filtered and the solid washed with MeCN (45mL). The filtrate and washings were combined, 5mL of the solution taken and evaporated to solid. A sample for HPLC analysis was prepared by first fully dissolving the solid in THF (2.5mL), followed by the addition of hexane (2.5mL). Some of the solution was transferred to a HPLC vial and analysed using the Chiralpak IA HPLC column.

5.7.2 HPLC analysis of reaction mixture to obtain the ee and yield

The reaction mixture (5mL) was filtered and washed with MeCN (45mL). The filtrate and washings were combined. A maximum volume of 45mL is required for the next

stage. There was usually some evaporation of MeCN during filtration, but if necessary some of the solvent was removed by rotary evaporation. The combined solution was transferred to a 50mL volumetric flask. 5mL of a 0.01 mol/L solution of 2,2'Biphenyldimethanol in MeCN was added. MeCN was added to the volumetric flask to make the solution up to 50mL. 5mL of the solution from the volumetric flask was taken and the solvent evaporated. THF (2.5mL) was added first to fully dissolve the solid and then hexane (2.5mL) added to prevent split peaks in the HPLC chromatogram. Some of the solution was transferred to a HPLC vial and analysed using the Chiralpak IA HPLC column.

The areas of the (S) and (R) aziridine enantiomer peaks were added together and then divided by the area of the 2,2'Biphenyldimethanol peak, which was used as the internal standard.

5.7.3 ^{1}H NMR without the removal of the solvent

The reaction mixture was filtered and the solid washed with MeCN (45mL). The filtrate and washings were combined and poured into a 50mL volumetric flask. During filtration some of the MeCN would evaporate under the vacuum, so MeCN was added to make the volume up to 50mL. The volumetric flask was shaken and 0.5mL of solution was taken from the flask and transferred to an NMR tube. 0.1mL of d-MeCN was added by micropipette to the NMR tube and then the TMS insert (1% TMS in $CDCl_3$) added. NMR analysis with suppression of the MeCN signal was carried out.

The TMS insert was used as the internal standard and was calibrated against solutions of aziridine with a known concentration.

5.8 Preparation of *N*-arene-sulfonyl-2-phenylaziridine for use as a chiral ligand

5.8.1 Preparation of (R) 69 - 81% *N*-nosyl-2-phenylaziridine

The *N*-nosyl-2-phenylaziridine ~(R) 35% was stirred in hexane. The solution was filtered to remove undissolved aziridine. The filtrate was evaporated to solid to give *N*-nosyl-2-phenylaziridine with an ee of (R) 69 – 81%.

5.8.2 Synthesis of (S)-*N*-nosyl-2-phenylaziridine

A method similar to that first described by Farras et al was used[5]. 4-Nitrobenzenesulfonyl chloride (13.3g, 60mmol) was added in one portion to a suspension of (S)-(+)-2-phenylglycinol (2.744g, 20mmol) in dry DCM-pyridine (2: 1 v/v, 20mL) at 0°C. The resulting mixture was stirred at room temperature for four hours. It was diluted with DCM (300mL) and washed with aqueous HCl (2M, 3 x 100mL); the aqueous washings were extracted with DCM (50mL). The combined organic layers were carefully shaken with aqueous KOH (2M, 6 x 200mL), and the aqueous portions subsequently extracted with DCM (150mL). The organic portions were combined, washed with water (300 mL), dried (Na_2SO_4) and the solvent removed to yield (S)-(N-p-nosyl)-2-phenylaziridine, which was purified by flash column chromatography twice using DCM. Recrystallisation was from DCM-hexane.

5.8.3 Synthesis of (S)-*N*-tosyl-2-phenylaziridine

A procedure reported by Bieber et al was followed[6]. 4-Toluenesulfonyl chloride (2.0972g, 11 mmol) was added portion wise at room temperature to a stirred mixture of (S)-(+)-2-phenylglycinol (0.6859g, 5 mmol), anhydrous K_2CO_3 (2.764g, 20 mmol), and MeCN (10mL). After five hours, toluene (25mL) was added, the solid was filtered off, and the solvents evaporated, to give (S)-(N-p-tosyl)-2-phenylaziridine, which was purified by flash column chromatography.

5.9 Aziridination of styrene

5.9.1 Use of anhydrous acetonitrile, and a nitrogen atmosphere for the aziridination reaction

The standard aziridination reactions (5.5.1 & 5.5.2) were carried out using PhI=NNs, but with anhydrous MeCN, in air or a nitrogen atmosphere, as shown in Table 1.

Table 1

RXN	Atmosphere	MeCN
1	Air	99.9%, water ≤0.005 %, over molecular sieve, Acros Organics
2	Nitrogen	99.9%, water ≤0.005 %, over molecular sieve, Acros Organics
3	Nitrogen	Dried over calcium hydride

5.9.2 Variation in solvent for the aziridination reaction

The standard heterogeneous racemic reaction (5.5.2) was completed using PhI=NNs, with MeCN, MeOH, THF, or hexane as solvent.

5.9.3 Aziridine made using (S,S)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline)

The pure (S) enantiomer of nosyl phenyl aziridine was made by nosylation of (S)-(+)-2-phenylglycinol and cyclisation affected by potassium hydroxide (5.8.2)[5]. This was then injected into the Chiralpak IA column to confirm the retention time of the (S) enantiomer from the catalytic reactions.

5.9.4 Polarimeter measurements

Aziridines were made following the standard homogeneous reaction (5.5.1) using PhI=NNs. They were analysed by chiral HPLC with the Chiralpak IA column to obtain the ee. Samples of each aziridine in chloroform were prepared for polarimeter measurement.

The optical rotation α, of each sample was recorded. This is affected by the concentration and cell length. Therefore, the specific rotation, $[\alpha]_D$ was calculated, (Figure 5).

$[\alpha]_D = \alpha$ / (concentration x cell length)

Concentration = sample (g) in 1mL $CHCl_3$, cell length= 0.25 dm

Figure 5

The % ee of the aziridines were calculated by polarimetry as follows, (Figure 6).

ee = (observed $[\alpha]_D$ / $[\alpha]_D$ of pure enantiomer) * 100%.

$[\alpha]_D$ from reference for (S) 100% *N*-nosyl-2-phenylaziridine = + 77.8 (c= 1.0 in $CHCl_3$)

Figure 6

The % ee calculated by polarimetry was compared to the % ee obtained by chiral HPLC.

5.9.5 Enhancement in ee with conversion

CuHY (0.3062g) was stirred with the *bis*(oxazoline) chiral modifier (0.0458g) in acetonitrile (5mL) for 15 minutes. Styrene (92μL) was added followed by the nitrene donor PhI=NNs (0.4872g) and stirred. The reaction mixture was analysed by chiral HPLC, using the Chiralpak IA column, following procedure 5.7.1.

5.9.6 Formation of a CuHY- aziridine complex

CuHY (0.2g) was stirred with *N*-nosyl-2-phenylaziridine (0.04g) in MeCN (10mL) for one hour. A ratio of 1 Cu to 2.2 aziridine was used. The mixture was filtered and the

solid washed with MeCN to remove uncoordinated aziridine. The filtrate was rotary evaporated to solid and weighed to see how much aziridine was uncoordinated. This was repeated using THF as the solvent.

5.9.7 Aziridination of styrene using PhI=NNs, with both bis(oxazoline) and *N*-nosyl-2-phenylaziridine as chiral modifiers

CuHY (0.15g) was stirred with bis(oxazoline) (0.02283g) in MeCN (5mL) for 15 minutes. Styrene (46μL) was added, followed by PhI=NNs (0.2435g), and the reaction stirred for 17 hours and 55 minutes. The product was isolated using flash column chromatography and analysed by chiral HPLC, with the Chiralpak IA column.

This was repeated with the addition of (R) 70% ee aziridine (0.0208g) to the start of the reaction. The weight of aziridine added to the beginning of the reaction was subtracted from the weight of aziridine isolated at the end to give the yield of aziridine made during the reaction.

5.9.8 Aziridination of styrene using PhI=NNs, with (R)-*N*-nosyl-2-phenylaziridine as chiral modifier

CuHY (0.15g) was stirred with aziridine in MeCN (5mL) for 15 minutes. Styrene (46μL) was added, followed by PhI=NNs (0.2435g), and the reaction stirred. The product was isolated using flash column chromatography and analysed by chiral HPLC, with the Chiralpak IA column.

5.9.9 Experiment to check if the aziridine put in at the start of the reaction is racemising

Aziridine (0.1117g) was stirred together with CuHY (0.3273g) and PhI=NNs (0.5292g) in MeCN (5mL) for five hours. Styrene was not included, so no new aziridine was made. The reaction mixture was analysed by chiral HPLC, using the Chiralpak IA column, following procedure 5.7.2.

5.9.10 Aziridination of styrene using PhI=NNs, with pure (S)-*N*-nosyl-2-phenylaziridine as chiral modifier

The standard heterogeneous reaction (2.5.2) was carried out using PhI=NNs, and the reaction stirred for five hours. The reaction mixture was analysed by chiral HPLC, using the Chiralpak IA column, following procedure 5.7.2.

This was repeated with the addition of (S) *N*-nosyl-2-phenylaziridine (0.1043g) to the start of the reaction.

5.9.11 Cross over reactions

Cross over reactions were carried out, where a different type of *N*-arene-sulfonyl-2-phenylaziridine was made to the one added at the start of the reaction. The following procedure was used.

CuHY (0.326g) was stirred with aziridine in MeCN (5mL) for 15 minutes. Styrene (100μL) / 4-methylstyrene (115μL) was added, followed by PhI=NNs (0.5292g)/

PhI=NTs (0.4886g), and the reaction stirred. The reaction mixture was analysed by chiral HPLC, using the Chiralpak IA column, following procedure 5.7.1.

Table 2 shows the reactants used for each cross over reaction.

Table 2

RXN	Aziridine	Substrate	Nitrene donor	Reaction time
1	(R) 81% nosyl phenyl 0.1486g	4-methylstyrene	PhI=NNs	6 hours
2	(S) tosyl benzyl 0.1052g	styrene	PhI=NNs	5 hours 48 mins
3	(S) tosyl benzyl 0.2565g	styrene	PhI=NNs	5 hours
4	(S) tosyl phenyl 0.1035g	styrene	PhI=NNs	3 hours 20 mins
5	(S) nosyl phenyl 0.1116g	styrene	PhI=NTs	5 hours 24 mins

5.9.12 Effect of the analytical procedure on the ee of the *N*-nosyl-2-phenylaziridine

$Cu(OTf)_2$ (4.15×10^{-5} mol of Cu) was pre-stirred with bis(oxazoline) chiral modifier (1.17×10^{-4} mol) in acetonitrile (5mL) for 15 minutes. Styrene (9.69×10^{-4} mol) was then added followed by the nitrene donor PhI=NNs (1.46×10^{-3} mol) and stirred for 12 hours. The product was then isolated using flash column chromatography (1.5 x 20

cm silica, 10: 1.5 petroleum ether 40: 60/ ethyl acetate). The aziridine was formed as a white crystalline solid, and the ee was determined by each of the HPLC methods shown in Table 3.

Table 3: HPLC analysis of *N*-nosyl-2-phenylaziridine

METHOD	Column	Mobile phase	Sample injection solvent
1	Chiralcel OJ	70% hexane: 30% IPA	100% hexane
2	Chiralpak IA	85% hexane: 15% IPA	100% hexane
3	Chiralpak IA	85% hexane: 15% IPA	20% THF: 80% hexane
4	Chiralpak IA	20% THF: 80% hexane	20% THF: 80% hexane

5.10 Phase behaviour of *N*-arene-sulfonyl-2-phenylaziridine

5.10.1 *N*-Nosyl-2-phenylaziridine with an ee of (R) 26 – 35% in hexane

The *N*-nosyl-2-phenylaziridine was stirred in hexane. The solution was filtered to remove undissolved aziridine. A sample of the filtrate was taken and injected into the HPLC. The rest of the filtrate was evaporated to solid and re-dissolved in 20% THF, followed by the addition of 80% hexane, and analysed by HPLC. The filtered off aziridine was treated in the same way.

5.10.2 X-ray Crystallography of *N*-nosyl-2-phenylaziridine

(R) 28% *N*-nosyl-2-phenylaziridine was stirred in hexane. The undissolved solid was separated by filtration, and recrystallised from DCM. Racemic crystals were identified using a polarising microscope.

An (S) enantiomer crystal was obtained from recrystallisation of pure (S)-*N*-nosyl-2-phenylaziridine from DCM.

Data were recorded for crystalline racemic *N*-nosyl-2-phenylaziridine, and authentic *S*-enantiomer on a Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystem cryostat and a molybdenum source (λ = 0.71073 Å). The structures were solved by direct methods with additional light atoms found by Fourier methods using SHELX-97.[7] Hydrogen atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 or 1.5 times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached.

5.10.3 *N*-Nosyl-2-phenylaziridine with different enantiomeric excesses in hexane

N-Nosyl-2-phenylaziridine with a range of enantiomeric excesses (0%, 6%, 13%, 19%, 35%, 64%, 72%, 82%, 86% and 100%) were stirred in hexane (5mg in 5mL). The solution was pushed through a plugged pipette to remove undissolved aziridine and injected into the HPLC.

5.10.4 *N*-Nosyl-2-phenylaziridine made from different styrene derivatives

N-Nosyl-2-phenylaziridine made from styrene derivatives (3-fluorostyrene, 4-methylstyrene and 3-chlorostyrene) were stirred in hexane (5mg in 5mL). The liquid was pushed through a plugged pipette to remove undissolved aziridine and injected into the HPLC.

5.10.5 *N*-Nosyl-2-phenylaziridine in different solvents

N-Nosyl-2-phenylaziridine with an ee of (S) 33% was stirred in solvent (10mg in 10mL). The solvents employed were THF, DCM, MeCN, benzene, ethanol, IPA, hexane, cyclohexane, heptane and pet ether. The liquid was pushed through a plugged pipette to remove undissolved aziridine, and then evaporated to solid. THF (1mL) and hexane (4mL) was added to make a sample for chiral HPLC analysis.

5.10.6 *N*-Nosyl-2-phenylaziridine in petroleum ether and ethanol mixtures

N-Nosyl-2-phenylaziridine with an ee of (S) 33% was stirred in a pet ether and ethanol mixture (5mg in 5mL) for five minutes. Six mixtures were made, with varying ratios of pet ether to ethanol. The liquid was pushed through a plugged pipette and analysed by HPLC.

5.10.7 *N*-Tosyl-2-phenylaziridine with an ee of (R) 28% in hexane

N-Tosyl-2-phenylaziridine with an ee of (R) 28% was stirred in hexane (1mg in 1mL, 2mg in 1mL, 3.64mg in 1mL and 26.8mg in 1mL). The solution was pushed through a plugged pipette to remove undissolved aziridine and injected into the HPLC.

5.11 References

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