Studies Towards the Development of New Organocatalysts for the
Synthesis of Chiral Aziridines

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Abstract

It is of the utmost importance to have control over the stereochemistry of the molecules that we synthesise, be they for use as drugs, materials or substrates for further chemical transformation, etc. In recent years, organocatalysis has been presented as a previously unexploited route for this purpose that is both highly tuneable to specific requirements and avoids totally the use of transition metals, which can be costly or can contaminate.

The use of organocatalysts to catalyse asymmetric aziridination reactions is a relatively new concept. In recent years several examples of organocatalytic enantioselective aziridination reactions have now been successfully developed. Among these examples are reactions that are catalysed by quaternary salts of cinchona alkaloids, which are able in many cases to transfer chirality to the aziridine heterocycle.

Recent work within the Bew group has demonstrated that racemic aziridination reactions can be catalysed using fluoronium sources. Herein we investigate the potential of N-fluoro cinchona salts as a new method of enantioselectively catalysing aziridinations using the fluoronium ion. The synthesis of catalysts by etherification/esterification and fluorination and their application in catalysing aziridinations will be discussed.

During the course of the fluoronium investigation, we also became interested in the use of ionic liquids as organocatalysts for the same class of reactions. Symmetrical imidazolium-based ionic liquids have been shown to simultaneously solvate and catalyse racemic aziridine formation and are also recyclable and remove the need for solvent. There are now several reported chiral ionic liquids built around this key imidazolium functionality. Therefore we will also discuss our strategy to control the absolute stereochemistry of this method by using chiral ionic liquids containing the imidazolium motif.
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1 - Introduction

1.1 - A Brief History of Asymmetric Catalysis and Organocatalysis

Methods of inducing enantiopurity in chiral reaction products have been the focus of research for many years. It is of the utmost importance to have control over the stereochemistry of the molecules that we synthesise, be they for use as drugs, materials or substrates for further chemical transformation, etc. An increasingly large proportion of these methods now also take carefully into consideration the “atom economy” of such reactions. Asymmetric catalysts cater well to this desire for economy by efficiently passing chirality onto the reaction product. This allows for the production of many more molecules of valuable, asymmetric product than the loading of the catalyst itself and reduces or removes entirely the need to use stoichiometric quantities of chiral auxiliaries.

Until very recently asymmetric catalysis has been dominated by transition metal complex and enzyme catalysts. Transition metal catalysts offer a high degree of customisability, meaning that they can be tailored and refined to produce high enantioselectivity and catalytic activity. The 2001 Nobel Prize in Chemistry to Knowles and Noyori “for their work on chirally catalysed hydrogenation reactions”, and to Sharpless “for his work on chirally catalysed oxidation reactions” (See Scheme 1.), demonstrating just how important this class of reactions is considered to be in modern times.

Scheme 1. Transition metal catalysis related to the 2001 Nobel Prize in Chemistry: a) Sharpless Asymmetric Epoxidation. b) Noyori Asymmetric Hydrogenation. c) Knowles’s asymmetric hydrogenation for the synthesis of L-DOPA, 2.
However, transition metal catalysts are not without their disadvantages. Transition metal catalysts can often be highly prone to degradation upon exposure to moisture or oxygen or ambient temperatures, making them difficult and expensive to handle, in addition to transition metals themselves often being expensive. The use of transition metals is seen as undesirable in processes such as drug manufacture, which do not tolerate metal contamination.

Enzyme catalysis or "biocatalysis" is the use of enzymes to facilitate chemical transformations in synthetic chemistry. Biocatalysts are highly efficient, always require mild reaction conditions and also have the advantage of being extremely regiospecific as the active sites of these molecules are tailored in size and shape to recognise specific region of the substrate. An example of the synthetic application of biocatalysts would be Smallridge et al.'s use of yeast to reduce ethyl acetoacetate, 3 to the acetoalcohol, 4 (See Scheme 2).

Scheme 2. The yeast mediated reduction of ethyl acetoacetate, 3.

However, despite the discovery of preparatively useful enzymes from novel organisms, and the optimization of enzyme performance by selective mutation or by evolutionary methods, biocatalysts do not offer the same degree of customisable flexibility as small synthetic molecules.

Organocatalysts can be defined as small organic catalytic molecules that are composed mainly of carbon, nitrogen and oxygen and represent a third route to asymmetric catalysis. Generally speaking, organocatalysts are resilient molecules and not sensitive to moisture or oxygen and contain no metals and therefore pose no risk of contaminating the final product. It is for these reasons that organocatalysts are attracting so much attention in recent years.

The first reported example of an asymmetric organocatalytic by Bredig and Fiske et al. almost 100 years ago (See Scheme 3). The authors observed that using catalytic quantities the enantiopure cinchona alkaloids, quinine or quinidine facilitated the
addition of hydrogen cyanide to benzaldehyde and produced an enantio-enriched reaction product. Although the enantiomeric excesses generated in these reactions were no higher than 10%, at that time the use of small organic catalytic molecules to induce any asymmetry in a reaction product was unprecedented.

**Figure 1.** The asymmetric alkaloid catalysts 5 & 6 employed by Bredig and Fiske in 1912.

**Scheme 3.** The catalytic cycle in which quinine or quinidine catalyse the addition of hydrogen cyanide to benzaldehyde.

Similar work by Pracejus *et al.* carried out in 1960 demonstrated the potential potency of this group of alkaloids as asymmetric organocatalysts by using O-acetyl protected quinine to mediate the addition of methanol to phenylmethylketene, 9 to afford methyl-2-(R)-phenylpropanoate, 11 in 74% enantiomeric excess (*See Scheme 4*).^6^
Scheme 4. Pracejus et al.’s use of 10 to mediate the reaction between ketene, 9 and methanol.

Despite the discovery of asymmetric organocatalysis occurring in the early 20th century, further advances in enantioselectivity of organocatalysis were not made until 1971 when Hajos and Parish reported the (S)-(-)-proline catalysed asymmetric intramolecular aldol cyclisation of the Wieland-Miescher ketone to form a key intermediate in steroid synthesis in 93% enantiomeric excess.\(^7\)

Scheme 5. The original (S)-(-)-proline catalysed reaction carried out by Hajos and Parish

Further investigations into the potential of (S)-proline as an asymmetric catalyst were not conducted until much later by List et al. in 2000.\(^8\) The resultant findings ultimately gave rise to a general reaction protocol for the synthesis of asymmetric aldols using (S)-Proline known as the Hajos-Parrish-Eder-Sauer-Wiecher Reaction (See Scheme 6).
In order to investigate new organocatalysts, one first needs to understand the principles that underpin organocatalysis as a whole. It is true that despite the enormous growth and interest in the field over recent years, that organocatalysts can generally be placed in one of two simply defined groups: “covalent” and “non-covalent”.

Covalent organocatalysts form covalent adducts with the substrates and the resultant adducts are activated towards a desired reaction. In general, the formation of covalent substrate–catalyst adducts proceed by single-step Lewis-acid–Lewis-base addition or by multi-step reactions such as the formation of enamines from aldehydes and secondary amines as discussed in the Hajos-Parrish-Eder-Sauer-Wiecher example. (Schemes 5 and 6). A prominent example of modern iminium catalysis being Macmillan’s enantioselective Diels–Alder reaction of \(\alpha,\beta\)-unsaturated aldehydes and ketones with dienes using the chiral imidazolidinone catalyst 17, this catalyst is directly derived from earlier proline-based catalysts and employs steric hindrance around the enamine functionality of the adduct to induce enantioselectivity without the need for the formation of hydrogen bonds (See Scheme 7).
Scheme 7. Macmillan et al.’s strategy for the asymmetric imidazolidinone catalysed Diels-Alder reaction mediated by 17.

An example of a more simple Lewis-acid–Lewis-base addition mechanism would be the phosphine-catalysed acyl transfer reactions. Vedejs et al. reported an enantioselective acylations catalysed by the chiral phosphine, 21 (See Scheme 8).10 21 reacts nucleophilically to form a chiral cationic adduct with one acyl unit of an appropriate anhydride. (20 in the case of the optimal example). The adduct recognises enantiomers of secondary alcohols, in this case 2,2,6-trimethyl-1-phenylpropan-1-ol, 19 and is able to acylate the R-enantiomer selectively, generating an 81% enantiomeric excess in this example.


There are many diverse examples of covalent organocatalysis reported in literature to date and a large proportion of them proceed via one of these two general pathways.11
1.1.2 - Non-covalent Organocatalysis

In many cases, non-covalent organocatalysts rely on the formation of hydrogen bonds and/or protonation/deprotonation between the catalyst and the substrate molecules. One such example would be Jacobsen’s thiourea catalyst for the asymmetric Strecker reaction. The extensively functionalised chiral thiourea forms hydrogen bonds with the lone pair of the imine, N-allylbenzaldimine in this case, and activates it towards nucleophilic addition of cyanide, giving the (S) enantiomer of the addition product in an impressive 95 % enantiomeric excess. (See Scheme 9).

Scheme 9. Jacobsen et al.’s strategy for the enantioselective Strecker reaction between cyanide and imines catalysed by the chiral thiourea 24.

An important class of organic catalysts that can be considered as non-covalent organocatalysts are phase transfer catalysts. Asymmetric phase transfer catalysts are quite remarkable because, as their name suggests, phase transfer catalysts allow for ionic reactants generated in an aqueous phase to cross the phase boundary and have access to reagents in the organic phase, in addition to influencing the absolute stereochemistry of the reaction. It was Dolling et al. developed the first efficient chiral phase-transfer catalyst, 27, an N-substituted cinchoninium salt. In this study, the acidic β-keto proton of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone, 26, was removed with aqueous sodium hydroxide and the catalyst functions by forming a chiral ion-pair with deprotonated 26 in the aqueous phase. The chiral ion pair is then soluble enough
to cross the phase boundary into a toluene/chloroform mixture, where the deprotonated indanone, 26 reacts readily with chloroform to give the β-methylated ketone, 28 in an excellent 95% yield and 92% enantiomeric excess (See Scheme 10).

Scheme 10. Dolling et al.’s pioneering work demonstrating the first asymmetric reaction catalysed by a chiral phase-transfer catalyst, 21.

Terada et al. have reported highly enantioselective Mannich reactions of aldimes catalysed by the chiral BINOL-derived phosphoric acid, 23.14 This particularly strong organic acid is likely to protonate the aldime to form a chiral phosphate-iminium ion pair, leading to the enantioselective nucleophilic addition of deprotonated acetyl acetonate to the α-carbon of the aldime (See Scheme 11).
Scheme 11. Terada et al.’s use of chiral phosphoric acid, 30, as a highly efficient enantioselective organocatalyst for Mannich type reactions.

1.2 - Aziridines

Aziridines are a family of molecules defined by a three membered, saturated heterocyclic motif containing a single nitrogen atom, and are widely considered to be analogues or “cousins” of the oxygen-containing epoxides due to their similar structure, reactivity and stereochemistry.\(^\text{15}\) The internal bond angles within an aziridine molecule can be considered to be approximately 60°, which differs considerably to the minimum energy bond angle of 109.5° for $\text{Sp}^3$ hybridised centres. Therefore, the aziridine motif incorporates high strain energies (typically -1) and the result can be considered to be a “spring-loaded” structure.

Figure 2. The core structure of aziridine molecules.

It is this structural feature that makes aziridines highly amenable to ring-opening reactions via nucleophilic attack or cycloaddition reactions, both of which result in the cleavage of the C-N bond and are driven by the relieving the molecule of its high ring-
strain. In addition to this ease of ring-opening, aziridine molecules incorporate two adjacent stereocentres, which directly affect the stereochemistry of ring-opened products, making aziridines tremendously appealing reactive intermediates in synthetic chemistry (See Scheme 12). Aziridines allow for the selective 1,2-functionalisation with respect to the nitrogen atom and therefore represent to synthetic chemists a convenient method of accessing many nitrogen-containing molecules of interest.¹⁶

Scheme 12. An illustration of an aziridine undergoing nucleophilic ring-opening

It is of little surprise then that aziridines have been attracting much attention from chemists for many years because of they provide an easy route to pharmacologically and biologically active compounds. Aziridines have many applications as chiral building blocks for the construction of various chiral nitrogen compounds such as chiral amines, amino acids, β-aminosulfonic acids, amino alcohols, alkaloids and β-lactam antibiotics. By ring opening the chiral aziridine, 32, and the subsesquently reducing and deprotecting the resultant product, Wulff’s synthesis of (-)-Chloramphenicol is a prime example of how biologically active nitrogen-containing molecules can be easily and access from chiral aziridine starting materials (See Scheme 13).¹⁷

Scheme 13 Wulff’s synthesis of (-)-Chloramphenicol, 34 from chiral aziridine 32.

In addition to aziridines being of importance as reactive intermediates, they are also incorporated into many biologically active compounds. The anti-tumour and antibiotic properties of a great number of aziridine-containing compounds are of particular interest among other biological properties, which make them not only useful intermediates but desirable synthetic targets.¹⁸
Fig 3. Examples of biologically active aziridines-containing molecules.

Many aziridines have the ability to act as DNA cross-linking agents via nucleophilic ring opening of the aziridine moiety. Structure–activity relationships have identified the aziridine ring as being essential for the anti-tumour activity and various anti-tumour agents related to mitosanes and mitomycins have been synthesised and demonstrated to possess activity against a variety of cancers. A number of other synthetic chiral aziridines are shown to exhibit other useful biological properties such as enzyme-inhibitory activities.

Fig 4. A molecule of 37 cross-linking DNA strands by binding to two guanine residues via nucleophilic ring opening of the aziridine and epoxide moieties.\textsuperscript{19a-b}

Thus, obtaining aziridines and especially enantiopure chiral aziridines is considered highly important in synthetic organic chemistry.\textsuperscript{20}
1.2.1 - Syntheses of Asymmetric Aziridines

The first synthesis of an aziridine molecule was reported by Gabriel in 1888 and since then a multitude of different methods for the synthesis of this class of compound have been reported and continue to increase in number to the present day.\textsuperscript{21} Chiral aziridines can be accessed using asymmetric catalysis or from chiral auxiliaries, in the interest of relevance to the current study the later will not be discussed any further here. Catalytic methods for the formation of chiral aziridines fall generally within, but are not restricted to, two sub-types: Addition of nitrogen to alkenes and the addition of carbon to imines.

Evans \textit{et al.} reported one of the first asymmetrically catalysed syntheses of an aziridine molecule in 1991 using chiral \textit{bis}(oxazoline) copper catalysts, producing a mixture of the two possible diastereomers, both in moderate enantiomeric excess.\textsuperscript{22} In 1993 Using a chiral ligand, \textbf{40} in combination with copper(I)trifluoromethanesulfonate the same authors added nitrogen across achiral olefin substrates using \textit{[N-(p-toluenesulfonyl)iminophenyliodonium]} as a nitrene source.\textsuperscript{23} This revised method produce the desired aziridines exclusively in the \textit{trans}-orientation and in exceptional optimal 97\% enatiomeric excess (\textit{See Scheme 14}).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Scheme14}
\caption{An example of Evans's pioneering asymmetrically copper-catalysed aziridinations.}
\end{figure}

It is true that the majority of reported metal-catalysed asymmetric aziridinations are concerning the transfer of nitrogen across alkenes. However, there are examples of formation of chiral aziridines upon transition metal-catalysed reaction of diazo compounds with imines and is well established. In particular, the reaction of ethyl diazoacetate with imines mediated by a Lewis acid is normally selective for the formation of the \textit{cis}-aziridine. A good example of this class of asymmetric metal catalysed reactions would be a study carried out by Hossain \textit{et al.}, who employed an
Iron(II)-pybox catalyst, 44, in combination with silverhexafluoroantimonate(V) as an initiator to mediate an asymmetric aza-Darzens reaction between substituted aldimines and ethyl diazoacetate, affording mainly cis-aziridines in up to a 49% enantiomeric excess (See Scheme 15).

**Scheme 15.** Hossain *et al.*’s use of an Iron(II)-pybox catalyst, 44 for in combination with silverhexafluoroantimonate(V) for the asymmetric aza-Darzens reaction.

### 1.2.2 - Asymmetrically Organocatalysed Aziridination

The use of organocatalysts to generate chiral aziridines is a concept that has not been realised until recently. However, several methods for organocatalytic enantioselective aziridination of olefins have now been successfully established and have become a topic of interest in asymmetric organocatalysis. As is the case with chiral metal catalysis of aziridines, organocatalytic protocols can be broadly grouped into the addition of nitrogen to alkenes and the addition of carbon to imines. Work carried out by Fioravanti, Pellacani, Tardella *et al.* demonstrates well the asymmetric addition of nitrogen to alkenes. The authors used the quaternary cinchona alkaloid salt, 47, as a catalyst to mediate a Michael-initiated ring-closure reaction and induce chirality in the aziridination product of 2-(phenyl-sulfanyl)-2-cycloalkenones, producing a 75% enantiomeric excess (See Scheme 16).
**Scheme 16.** Fioravanti, Pellacani and Tardella’s use of quaternary cinchona alkaloid salt, 38, as a catalyst to mediate a Michael initiated asymmetric aziridination.

In 2007, Wulff *et al.* reported the most successful and versatile procedure to date for the asymmetric organocatalysed aza-Darzens reaction of *N*-dianisylmethyl aldimines with ethyl diazoacetate mediated by (S)-VANOL and (S)-VAPOL based boric acid catalysts, achieving high yields and up to a 97% enantiomeric excess.\(^{26}\) Two subsequent studies were carried out by the same author using *N*-biphenylmethyl aldimine and *N*-3,5-di-tert-butyldianisylmethyl aldimine substrates with diazoacetate respectively.\(^{27,28}\) This brought the total number of reported examples for these (S)-VANOL/(S)-VAPOL based organocatalytic reactions to 60, all of which exhibited high yields and between the range of 75-97% enantiomeric excess [See Scheme 17], demonstrating the excellent versatility of this catalyst system.

**Scheme 17.** An optimum example taken from Wulff’s work towards asymmetric aziridination mediated by (S)-VANOL-derived, 50, or (S)-VAPOL-derived, 51.

1.3 - Aims of Research

1.3.1 - Fluoronium Organocatalysts for the Asymmetric aza-Darzens Aziridination.

In 2009 the Bew research group reported a protocol for the organocatalysed aza-Darzens aziridination of aldimines with diazoacetates using pyridinium...
trifluoromethanesulfonate as a Brønsted type acid catalyst (See Scheme 18).²⁹

Noteworthy features of this reaction are that it is extremely mild in comparison with the majority of acid catalysts and that it is exceptionally selective towards the formation of cis-aziridines, producing no observable trans-isomer in many cases. Much work has been carried out within the Bew group since this publication to develop other acid catalysts that exhibit control over the absolute stereochemistry of the aziridine product, with very encouraging results that will no doubt find their way into the public domain in the near future.

Scheme 18. (above) Examples of the Bew group’s use of pyridinium trifluoromethanesulfonate to catalyse the stereoselective aza-Darzens aziridination
(below) The proposed mechanism for the pyridinium trifluoromethanesulfonate-mediated aziridination.

However, during the same period, it was also reported by the Bew group that the very same aza-Darzens aziridinations could be mediated by a catalytic amount of a N-fluoropyridinium trifluoromethanesulfonate, which incorporated fluoronium as opposed to an acidic proton (See Scheme 19).³⁰ This unprecedented organocatalytic use for a fluoronium containing species was incredibly interesting not only due to its novelty but also because for the potential for the aziridination of substrates that are intolerant of
Brønsted acids, a hypothesis that was confirmed in the same publication by the asymmetric aziridination of acetal-containing aldimine, 63, with ethyl diazoacetate, mediated by N-fluoropyridinium trifluoromethanesulfonate, after which the preservation of the acetal moiety was observed (See Scheme 19).

**Scheme 19.** Above Examples of the Bew group's use of 60 to catalyse the stereoselective aza-Darzens aziridination. Below: An example illustrating the aziridination of 60 with ethyl diazoacetate, mediated by 60 with the preservation of the acetyl moiety in all reaction products.

To date, there has not been any development of an asymmetric fluoronium-based catalytic pathway for the aza-Darzens aziridination. It was therefore proposed to use N-fluorinated, O-protected versions of the cinchona alkaloid, dihydroquinidine. These chiral fluoronium-containing species had previously been developed by Cahard *et al.* as an asymmetric electrophilic fluorinating species and had been successfully utilised in the synthesis of the 3-Fluorooxindole, BMS-Maxipost™, 69 which is a potent potassium channel opener and has potential uses as a protector of neural cells. Importantly, these asymmetric fluorinated agents do not require the handling of elemental fluorine for their synthesis and can be generated easily from commercially available fluorine-transfer agents.
Scheme 20. Cahard et al.’s synthesis of BMS-Maxipost™, 69, using and fluorinated dihydroquinidine derivative, 68, as an electrophilic fluorinating agent.

An aim of this study is to test the hypothesis that the aza-Darzens reaction can be mediated by the same class of [N-F]+ alkaloids as used in aforementioned electrophilic fluorination reactions. Reactions mediated by fluorinated alkaloid salts will be similar to reactions carried out using 60, with the key exception of the presence of the stereocentres of the alkaloid. A chiral intermediate may be formed through “Halogen Bonding” between the catalyst and substrate.32 The formation of such an intermediate might hinder the approach of ethyl diazoacetate in an aza-Darzens aziridination and produce an enantiomeric excess of aziridine product (See Scheme 21). Variation of the O-protecting group may be used to alter both steric and electronic properties of catalyst, affecting any observed yields and/or enantiomeric excesses (See Fig 5).

Scheme 21. The proposed method for the asymmetric organocatalysed aza-Darzens aziridination, using O-protected, N-fluorinated dihydroquinidine derivatives
Fig 5. Some proposed Dihydroquinidine-derived alkaloids for use in this study.

1.3.2 - Imidazolium-Based Ionic liquids as Organocatalysts for the Asymmetric aza-Darzens Aziridination.

During the study of the asymmetric fluoronium-catalysed pathway for the aza-Darzens aziridination, an interest arose in the use of imidazolium based ionic liquids to solvate said reactions. It was proposed that carrying out the reactions in a liquid salt might increase the mobility of the catalyst salts and a similar logic had already been used for asymmetric fluorination with the fluoronium-alkaloid salts. However, it became quickly apparent that the ionic liquid that was used, was itself catalysing the aza-Darzens aziridination. A study carried out in 2003 by Xia et al. did indeed confirm that a number of symmetric imidazolium ionic liquids, including 1-butyl-3-methylimidazolium hexafluorophosphate, 80, had been successfully used to mediate the same class of reactions between aldimines and diazoacetates, producing high cis-selectivity (See Scheme 22).
Scheme 22. Xia et al’s use of 80 to solvate and catalyse the aza-Darzens aziridination between aldmines and diazoacetate.

Although the ionic liquid mediated reaction had previously established, Xia et al. offered no discussion regarding the mechanism of the reaction or as to the possibility of tuning this strategy to control the absolute stereochemistry of the product and so we became interested in answering some of these questions. It was therefore proposed two separate strategies to develop an asymmetric method, the first strategy was to install chirality into the counter-anion of the ionic liquid, using a method previously reported by Tran et al., in which imidazolium halide salts underwent an ion metathesis with chiral sodium salts possessing an chiral borate anion.\(^{35}\)

Fig 6. Imidazolium ionic liquids, 81 and 82, bearing chiral borate anions.

The second strategy focuses on installing chirality directly onto the cation by substituting a chiral moiety onto the imidazolium ring itself. For this purpose we chose an ionic liquid that had already been reported by Vo-Thanh et al. and has been successfully been employed by the authors to mediate the asymmetric aza-Diels alder reaction between Danishefsky's diene, 84, and aldmine, 83 (See Scheme 23).\(^{36}\)
Scheme 23. Above: The asymmetric aza-Diels-Alder reaction carried out by Vo-Thanh et al. mediated by asymmetric ionic liquids, 85 or 86. Below: The proposed analogous asymmetric aza-Darzens aziridination mediated by, 85 or 86.

1.4 - Methodology
1.4.1 - Synthesis of O-Protected Alkaloid Derivatives

For this study it was necessary to have access to a wide range of Cinchona Alkaloid derivatives. Dihydroquinidine (S enantiomer) was chosen for the initial work for availability reasons. Derivatives were synthesised in accordance with procedures set out by Zhang et al.\textsuperscript{37} Alkaloid ester derivatives were prepared simply by deprotonation of the secondary alcohol moiety of the alkaloid, which was reacted with the appropriate acyl chloride, leading to displacement of the chloride and the formation of the ester. Alkaloid ether derivatives were deprotonated similarly potassium carbonate and then with potassium hydroxide, in addition to adding appropriate chloride and refluxing in toluene with the aziotropic removal of water.
1.4.2 - $N$-Fluorination of $O$-Protected Alkaloids

Catalytically active fluorinated quinidine alkaloids were obtained according to a procedure reported by Cahard et al. Alkaloids were stirred in the presence of Selectfluor™, leading to the transfer of the fluoronium ion to the nitrogen of the basic quinuclidine moiety along with a tetrafluoroborate counter-anion. Addition of sulfuric acid solution is used to precipitate the 1-chloromethyl-4-hydro-1,4-diazeniabicyclo[2.2.2]octane hydrogen sulphate tetrafluoroborate by-product, making the subsequent re-crystallisation of the $N$-fluorinated alkaloids possible. The fluorinated alkaloid salts can then be used as chiral fluoronium catalysts for the asymmetric aza-Darzens aziridination.

1.4.3 - Preparation of a Symmetrical 1-butyl-3-methylimidazolium Ionic Liquids

To repeat and observe findings reported in literature, we need access to ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate. For this aim, we employed procedures set out by Dupont et al. and targeted the hexafluorophosphate salt. The first step of the synthesis involves the heating of 1-chlorobutane in the presence of 1-methylimidazolium, resulting in the formation of the 1-butyl-3-methylimidazolium chloride salt, $87$. The second step involves an ion metathesis between $87$ and hexafluorophosphate at room temperature. This ionic liquid could then be used as an “all-in-one” solvent/catalyst for the aza-Darzens aziridination.
1.4.4 - Preparation of Chiral 1-Butyl-3-methylimidazolium Ionic Liquids: Formation of the Chiral Borate Anions

An asymmetric strategy employed was the use of asymmetric ionic liquids bearing a chiral anion. Based on the assumption that the imidazolium acts as a hydrogen bond donor to activate imine substrates, a chiral anion may provide a suitably chiral environment in order to generate an enantiomeric excess from the aza-Darzens aziridination. We chose chiral borate anions for this aim, which is easily synthesised from very accessible starting materials. Formation of the chiral borate was carried out in accordance with a procedure reported by Leitner et al. by heating boric acid with two equivalents of either (S)-malic or (S)-mandelic acid in the presence of one equivalent of aqueous sodium hydroxide, allowing for evaporation of all water to give the chiral sodium borate salts.40

1.4.5 - Preparation of Chiral 1-Butyl-3-methylimidazolium Ionic Liquids: Generation of Chiral 1-Butyl-3-methylimidazolium Salts

1-butyl-3-methylimidazolium borate salts were generated by following procedures set out by Tran et al., involving an ion metathesis between 88 or 89 and 1-butyl-3-methylimidazolium chloride, 87, at room temperature. This ionic liquid could then be used as an “all-in-one” solvent/catalyst for the asymmetric aza-Darzens aziridination
1.4.6 - Isosorbide-Derived Imidazolium Chiral Ionic Liquid: Selective - 
*O*-protection of the Isosorbide scaffold

The alternative asymmetric ionic liquid strategy involved the synthesis of an 
imidazolium ionic liquid bearing chirality on the cation. We chose to target a species 
reported recently by Vo-Thanh *et al.*, a chiral isomannide molecule singly substituted 
with an imidazolium moiety and trifluoromethansulfonate anion. The synthesis 
actually begins with isosorbide (*a* diastereomer of isomannide) and involves the 
selective mono-acetylation of the *endo*-hydroxy group using a procedure reported by 
Stoss *et al.*, stirring isosorbide in the presence of a little over one equivalent of acetic 
anhydride and a catalytic amount of lead(II)oxide. Having protected the *endo*-hydroxy 
group, the next step of this synthesis replaces the *exo*-hydroxy group with the 
trifluoromethanesulfonate leaving group. This is achieved first by deprotonation of the 
isosorbide with pyridine and followed by the low-temperature slow addition of a 
stoichiometric amount of trifluoromethanesulfonic anhydride.

1.4.7 - Isosorbide-Derived Imidazolium Chiral Ionic Liquid: 
Nucleophilic Substation of the Trifluoromethansulfonate 
Leaving Group

Having functionalised the isosorbide scaffold with a trifluoromethansulfonate leaving 
group, the next task was to install the imidazolium functionality onto the molecule. By 
following procedures set out by Vo-Thanh *et al.*, 1-methylimidazolium is heated with the
trifluoromethansulfonate in solvent-free conditions for 2 days.\textsuperscript{41} An S\textsubscript{N}2 type substitution occurs during this time, resulting in the displacement of the trifluoromethansulfonate with the imidazolium moiety. This step also leads to the inversion of stereochemistry of the concerned carbon centre, converting the isosorbide scaffold into that of an isomannide one and giving quite a restricted chiral environment around the imidazolium moiety. It is hypothesised that this gives a high likelihood of producing enantiomeric excess when employed as a catalyst for the aza-Darzens aziridination. It is noteworthy that the reaction time of the S\textsubscript{N}2 step is long and therefore makes the synthesis less attractive. Many new protocols for the formation of ionic liquids employing the use of microwave radiation have been reported, often greatly reducing reaction times.\textsuperscript{43} It was also therefore proposed to investigate the use of microwaves in this step with the aim of increasing the reaction rate.
2 - Results and Discussion

2.1 - Synthesis of O-Protected Alkaloid Derivatives

All O-protected alkaloids were formed by the same general procedure of deprotonation at the alcohol group of the alkaloid molecule using a base to deprotonate and subsequent substitution with an appropriate acyl chloride or chloride. All acyl chloride examples required only triethylamine as the base for the deprotonation step, the resultant deprotonated alkaloid reacts with acyl chlorides vigorously and exothermically. It was necessary for acyl chlorides to be added slowly and at reduced temperature. The resultant O-protected alkaloids were washed with aqueous saturated sodium hydrogen carbonate solution and the free alkaloid bases were found to re-crystallise from methanol.

The reaction of 1,4-dichlorophthalazine with two equivalents of dihydroquinidine required relatively harsh conditions. In this case, a combination of potassium hydroxide and potassium carbonate bases were implemented for the deprotonation step. Inorganic bases are considerably stronger than pyridine and bring about a more absolute deprotonation of the alkaloid. The mixture of the deprotonated alkaloid and 1,4-dichlorophthalazine required refluxing with the aziotropic removal of water overnight for complete conversion. The ammonium hydrogen sulfate salt of the alkaloid was first precipitated using sulfuric acid and the free base was then re-generated by washing with aqueous with aqueous saturated sodium hydrogen carbonate solution and the free alkaloid base was then re-crystallised from warm methanol.

![Ortep representation of the crystals structure of 72](image)

**Fig.7** An Ortep representation of the crystals structure of **72**. The hydrogen atoms are omitted for sake of clarity. Thermal ellipsoids are drawn at 50% probability level.
Figure 8. An Ortep representation of two independent molecules of 75. All Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability level.

All alkaloids generated for the purposes of this study were found to be highly hygroscopic, however degrees of hygroscopicity varied depending on O-functionalisation. Some alkaloid derivatives synthesised were found to be so hygroscopic that removal of water and re-crystalisation without a very dry atmosphere was not possible and thus these were impractical to purify (See Fig 9).

Fig 9. Alkaloid species that were synthesised but not isolated or used further for this study.

2.2 - N-Fluorination of O-Protected Alkaloids

N-Fluorination of O-protected alkaloids was carried out according to reported literature procedures, in which importantly use of elemental fluorine was not required. Instead one equivalent of a fluorinating agent, Selectfluor (1-Chloromethyl-4-fluoro-1,4-diazaoniabicyclo[2.2.2]octane bis(tetrafluoroborate)), 97, was stirred with alkaloids in acetonitrile, resulting in a transfer of fluorine to the nitrogen of the quinuclidine moiety of the alkaloid. As with the free alkaloid bases, fluorinated examples were highly hygroscopic and thus their purification was difficult and time-consuming. For this reason, attention was turned to work carried out by Shibata et al., whereby the same class of chiral [N-F]+ reagents were generated in situ by combining Selectfluor™, 97 and
the appropriate alkaloid derivative in acetonitrile for use in asymmetric electrophilic fluorination.45 Using this technique removed the need to purify chiral [N-F]+ reagents and avoided the storage of the highly hygroscopic salts. It was important before proceeding in this manner to confirm the presence of the correct F+ species was present in the reaction mixture and determine the time it took before Selectfluor™ was no longer observed in the fluorinated form. In order to obtain this information, a 0.05 M reaction solution of 97 and alkaloid 78 in acetonitrile-d3 was added to an NMR tube and observed using 19F-NMR (Scheme 24, Fig 11) this was referenced against a solution of 97 in acetonitrile-d3 (Scheme 24, Fig 10).

Fig 10. The 19F-NMR of Selectfluor™, 97 in acetonitrile-d3.

Scheme 24. The reaction of 78 with 97 in CD3CN in an NMR tube, under 19F-NMR observation.
In the time that elapsed between loading the NMR tube and performing the first $^{19}$F-NMR scan, the reaction could already be observed to be complete, as the fluoronium signal had shifted up-field from 48.00 ppm in the reference sample to 37.42 ppm. This difference of -10.58 ppm indicates that the fluorine atom situated at the quinuclidine moiety of 98 is significantly more shielded by electron density than the equivalent fluorine atom in 97. This observation is in agreement with logic, as the fluorine atom has transferred from a di-cationic environment to a mono-cationic one, which is likely to be more susceptible to polarisation by the electronegative fluorine atom. This may also indicate that 98 has a reduced capacity to act as a Lewis acid with respect to 97, this would not have any significant adverse consequences in the case of electrophilic fluorination (as reaction with a carbanion is thermodynamically very favourable) but may be responsible for observed adverse effects on the catalytic rate, which will be discussed in the next section.

2.3 - Aziridination with F+ Catalysts

Seven of the most readily purified and thus, most accessible alkaloid derivatives 69, 72-76 and 78 were used for the preliminary studies into the use of chiral [N-F]+ catalysts.
Figure 12. Chiral [N-F]+ catalysts generated for preliminary screening.

Once chiral [N-F]+ species were formed \textit{in situ} by following the procedure set out by Shibata \textit{et al.}, aziridinations were carried out by adding an aldimine substrate to the solution and 1 equivalent of ethyl diazoacetate. Reactions were monitored by extraction of a small sample of crude reaction mixture and subsequent \textsuperscript{1}H-NMR analysis of the sample.

Scheme 25. The aziridination of aldimine 107 and EDA, using fluorinated alkaloid catalysts.
<table>
<thead>
<tr>
<th>[N-F]$^+$ catalyst$^a$</th>
<th>yield (%)</th>
<th>% e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>23</td>
<td>Racemic$^b$</td>
</tr>
<tr>
<td>101</td>
<td>33</td>
<td>Racemic$^c$</td>
</tr>
<tr>
<td>102</td>
<td>8</td>
<td>Racemic$^c$</td>
</tr>
<tr>
<td>103</td>
<td>0$^d$</td>
<td>N/A</td>
</tr>
<tr>
<td>104</td>
<td>18</td>
<td>Racemic$^c$</td>
</tr>
<tr>
<td>105</td>
<td>13</td>
<td>Racemic$^c$</td>
</tr>
<tr>
<td>106</td>
<td>20</td>
<td>Racemic$^c$</td>
</tr>
</tbody>
</table>

Table 1. Yields and e.e.s for the formation of 108 using fluorinated alkaloid catalysts and EDA. a) Catalysts were generated in situ from 10 mol% of either 69,72-76 or 78 in combination with 10 mol% of Selectfluor, 98 in acetonitrile at ambient temperature. b) Racemate identified using a Chiralpak HPLC column and optical polarimetry. c) Racemate identified using optical polarimetry only. d) Minimal aziridine product observed by $^1$H-NMR observation of crude mixture, but not isolated.

The first screening of the chiral [N-F]$^+$ catalysts involved the transformation of (E)-2-Butoxy-N-(4-nitrobenzylidene)phenylamine, 107 into aziridine 108 (See Scheme 25). 107 was selected due to a bulky, electron-donating tert-butoxy group situated ortho on the aniline ring, which could possibly enhance enantioselectivity through steric interactions and also donates electron density to activate the aldimine towards the forming an adduct with catalysts. This particular aldimine also bears an electron withdrawing para-nitrobenzene moiety, which activates the $\alpha$-carbon of the imine towards nucleophilic attack by ethyl diazoacetate. Rates of reaction for this substrate/catalyst combination were slow, reactions were permitted to proceed for 48 h and then purified via column chromatography. Yields are notably poor and range from 8% - 33%. Catalyst 103 failed to produce any recoverable yield at all, however minimal aziridine product was observed in the crude $^1$H-NMR of the reaction mixture. All reaction products gave $[\alpha]^{20}_D = 0$ (c = 1.0, CHCl$_3$), indicating that no excess of chiral species was present (See Table 1.). When observing the separation of the two aziridine enantiomers when run through a chiralpak HPLC column and eluted with 2% MeOH in $^3$PrOH, the mixture could be seen to be racemic.
Scheme 26. The aziridination of aldime 109 and EDA, using fluorinated alkaloid catalysts.

<table>
<thead>
<tr>
<th>[N-F]⁺ catalyst</th>
<th>yield (%)</th>
<th>% e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>5</td>
<td>Racemicᵇ</td>
</tr>
<tr>
<td>101</td>
<td>8</td>
<td>Racemicᶜ</td>
</tr>
<tr>
<td>102</td>
<td>0ᵈ</td>
<td>N/A</td>
</tr>
<tr>
<td>103</td>
<td>0ᵈ</td>
<td>N/A</td>
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<tr>
<td>104</td>
<td>5</td>
<td>Racemicᶜ</td>
</tr>
<tr>
<td>105</td>
<td>8</td>
<td>Racemicᶜ</td>
</tr>
<tr>
<td>106</td>
<td>13</td>
<td>Racemicᶜ</td>
</tr>
</tbody>
</table>

Table 2. Yields and e.e.s for the aziridination of 109 using fluorinated alkaloid catalysts and EDA. a) Catalysts were generated *in situ* from 10 mol% of either 69, 72-76 or 78 in combination with 10 mol% of Selectfluor, 97 in acetonitrile at ambient temperature. b) Racemate identified using a Chiralpak HPLC column and optical polarimetry. c) Racemate identified using optical polarimetry only. d) Minimal aziridine product observed by ¹H-NMR observation of crude mixture, but not isolated.

Scheme 27. The aziridination of aldime 111 and EDA, using fluorinated alkaloid catalysts.
Table 3. Yields and e.e.s for the aziridination of 109 using fluorinated alkaloid catalysts and EDA. a) Catalysts were generated in situ from 10 mol% of either 69, 72-76 or 78 in combination with 10 mol% of Selectfluor, 97 in acetonitrile at ambient temperature. b) Racemate identified using a Chiralpak HPLC column and optical polarimetry. c) Racemate identified using optical polarimetry only.

Further attempts were made to asymmetrically catalyse the aza-Darzens reaction with the chiral [N-F]$^+$ catalysts. The aldimine substrate, (E)-4-methoxy-N-(benzylidene)phenylamine, 109, (See Scheme 26) was used as this much less functionalised molecule and was used primarily to minimise and observe any affects on yield or enantioselectivity that substituents may have and thus can be considered as a reference aldimine substrate. The replacement of an electron-withdrawing group with benzylidene results in significantly reduced yields. As with the aziridination of 108, all samples of aziridine product, 110, give $[\alpha]^{20}_{D} = 0$ (c = 1.0, CHCl$_3$), indicating that no excess of chiral species is present (See Table 2). When observing the separation of the two aziridine enantiomers when run through a chiralpak HPLC column and eluted with 5% MeOH in $^1$PrOH, the mixture can be seen to be racemic.

The (E)-4-methoxy-N-(2-pyridinylidene)phenylamine, 111, was also observed under identical aziridination conditions as the previous two runs (See Scheme 27). The presence of the electron withdrawing 2-pyridinylidene group has a positive effect on the yield of the reaction, producing yields within the range of 15-52%. However, all samples of aziridine product, 112, $[\alpha]^{20}_{D} = 0$ (c = 1.0, CHCl$_3$), indicating that no excess of chiral species is present (See Table 3). Observation of the separation of the two aziridine enantiomers when run through a chiralpak HPLC column and eluted with 10% MeOH in $^1$PrOH, the mixture could be seen to be racemic.
Aziridination of substrates 107, 109 and 111 were also mediated by non-chiral 60 and later also, for the first time using 97, producing very similar catalytic activity (See Scheme 28). These reactions were carried out to provide racemic samples of aziridines 108, 110 and 112.

Scheme 28. Aziridination reactions mediated by achiral 60 or 97.

2.4- Aziridination with F+ Catalysts - Conclusions and Future Work

The results presented in this study shows that the chiral [N-F]+ reagents 101-107 can indeed mediate the aza-Darzens aziridination between aldimines and ethyl diazoacetate. The rates of reaction are slow compared to similar such reactions using N-fluoropyridinium trifluoromethanesulphonate, 60 or even Selectfluor, 97 as the fluoronium source, which both typically require ca. 12 h before no more starting material can be observed. It is likely that the dihydroquinidine derivatives used here may indeed be too basic, reducing the Lewis acidity of the conjugate acid formed in the reaction with Selectfluor. There is also no evidence to suggest that the [N-F]+ alkaloid salts used here have the capacity to produce an enantiomeric excess.
Upon further consideration of the mechanism of these reactions it is possible to hypothesise a probable cause for the formation of racemic aziridine products. As aforementioned, this study assumes the formation of a complex between catalyst and substrate, forming a chiral adduct and biasing ethyl diazoacetate to approach one face of the activated imine more frequently than from the other. However, it is entirely possible that the activation of the aldime substrate goes *via* a slightly different pathway, whereby the fluorine ion dissociates completely from the alkaloid, giving a cationic fluoro-iminium species with an achiral tetrafluoroborate anion and a neutral alkaloid base (*See Scheme 29*). Importantly, this proposed mechanism give a symmetrical activated substrate and therefore accounts for the formation of racemic product.

*Scheme 29.* A proposed mechanism for the formation of racemic aziridines, using chiral [N-F]⁺ alkaloid reagents.

In light of this problem, it is possible to envisage two possible strategies that would overcome this hurdle: 1) Use a neutral fluoronium source, leading to the formation of a chiral ion-pair between catalyst and substrate. 2) Use an F⁺ salt bearing a chiral anion.

In order to address the neutral catalyst strategy, attempts where made to fluorinate (S)-BINOL based phosphoramide, 113, an N-H Brønsted acid catalyst, which has been utilised within the Bew group. The attempt involved the use of potassium hydride as a base, producing hydrogen and the potassium salt of 113, followed by the addition of 98 to generate the N-fluorophosphoramide, 114. However, ¹H-NMR analysis of the crude mixture showed no observable product or starting material, leading to the conclusion that the reaction conditions had decomposed phosphoramide, 113 (*See Scheme 30*).
Attempts were also made to generate an [N-F]+ salt containing a chiral anion. Chiral sodium borate salts 90 and 91 had already been synthesised for use in synthesising chiral ionic liquids and an ion metathesis between Selectfluor, 60 and 89 in acetone was attempted (See Scheme 31). However the expectation was that, if the metathesis was favourable, it would result in the precipitation of solid sodium trifluoromethanesulfonate, 116 from the solution and this was not observed and thus unlikely that a metathesis had occurred between the two. Separation of the mixture was achieved by concentrating the mixture in vacuo and the addition of dichloromethane to produce a precipitate, which was identified as being the starting material, 89.

In order to successfully synthesise an [N-F]+ salt bearing a chiral anion, one might consider the industrial synthesis of N-fluoropyridinium salts, which is carried out in accordance with a procedure reported by Umemoto et al. in 1991.46 The method
involves the reaction of pyridine with elemental fluorine at low temperatures to yield $N$-fluoropyridinium fluoride, which is not stable above $-40 \, ^\circ C$. The fluoride salt then reacts with a sodium salt of the desired anion, which is either added or present in the initial mixture in the case of a one-pot reaction. Umemoto et al. reportedly generated in excess of 60 different $N$-fluoropyridinium salts incorporating 11 various anions including sulphonates, phosphates and perchloroate, highlighting the versatility of this reaction with regards to the type of anion used. It is therefore proposed that an analogous reaction of pyridine, 117 with $F_2$ in the presence of 89 would produce chiral anion-bearing $[N$-$F]^+$ salt, 115. There is a tremendous scope for the number of chiral anions that could be utilised for this aim, for example the chiral $\Delta$-tris(tetrachlorobenzene diolato)phosphate(V) ($\Delta$-TRISPHAT), the sodium salt of which is easily obtainable from commercially available [cinchonidinium][$\Delta$-TRISPHAT] (See Scheme 32).47,48,49

Scheme 32. (above) The synthesis of 60 detailed by Umemoto et al. (middle and below) The hypothetical synthesis of chiral anion-bearing $N$-fluoropyridinium salts, 115 and 119, using the same methodology.
The arrival at this particular conclusion not only provides a viable solution to the problem but also places that solution outside the capabilities of the Bew research group. The use and storage of elemental fluorine is extremely hazardous and requires highly specialised equipment and safety protocols that are not realistically obtainable within the group due to cost and safety considerations.

2.5 - Synthesis of a Symmetrical 1-butyl-3-methylimidazolium Ionic Liquid

Symmetrical 1-butyl-3-methyl ionic liquids were produced using a procedure reported by Dupont et al. (See Scheme 33), whereby a mixture of 1-methylimidazole, 120, and 1-chlorobutane were refluxed in acetone for 48 hr, followed by the addition of ethyl acetate and recrystallisation at -40 °C, to yield 87. Potassium hexafluorophosphate could then be added to an aqueous solution of 87 to form 80 which is immiscible with water and can be easily extracted and dried and was pure enough to be used without further purification.

2.6 - Preparation of Chiral 1-Butyl-3-methylimidazolium Ionic Liquids: Synthesis of the Chiral Borate Anions

Formation of chiral sodium borate salts were formed in accordance with a procedure reported by Leitner et al., in which either maleic acid, 121, or mandelic acid, 122 were heated to 100 °C in the presence of boric acid and aqueous sodium hydroxide (See Scheme 34). The resultant, highly crystallisation condensation product was allowed to boil dry in air and was recovered in a quantitative yield and was pure enough to use without further purification.
Scheme 34. The mechanism by which the chiral sodium borate salts 88 and 89 are generated from 121 and 122 respectively.

2.7 - Preparation of Chiral 1-Butyl-3-methylimidazolium Ionic Liquids: Synthesis of Chiral 1-Butyl-3-methylimidazolium Salts.

Scheme 35. The synthesis of 90 or 91 via an ion metathesis between 87 and 88 or 89 respectively.
Fig. 13 Energy-minimised 3D representations of chiral ionic liquids 90 (left) and 91 (right) rendered using Cambridgesoft Chem3D software (hydrogen atoms and lone electron-pairs have been omitted for simplicity).

Chiral ionic liquids 90 and 91 were synthesised by mixing 1-butyl-3-methyl imidazolium chloride, 87, in a solution of acetone with the appropriate sodium borate salt. Immediately solid sodium chloride salt started to precipitate, and after an hour, the solution was filtered and concentrated *in vacuo* to give the desired chiral ionic liquid in a quantitative yields, which was pure enough to use without further purification (*See Scheme 35*).

### 2.8 - Isosorbide-Derived Imidazolium Chiral Ionic Liquid: Selective O-Protection of the Isosorbide Scaffold

Scheme 36. The selective catalytic acetylation of 123 to 92, followed by the triflation of the remaining alcohol group to give 93.

As reported by Stoss *et al.*, selective protection of isosorbide, 123, was carried out by a lead(II)oxide mediated reaction of acetic anhydride (*See Scheme 36*). It is likely that
the relatively large lead centre coordinates to the exo alcoholic oxygen, effectively blocking it from acetylation (See Scheme 37).

**Scheme 37.** An illustration of how a lead cation blocks the exo oxygen of 123 from acetylation, leading to the selective formation of 93.

The large quantity of acetic acid by-product produced by this step was removed in vacuo, which was a time-consuming process. Alternatively, washing the crude product with aqueous sodium hydrogen carbonate to remove the organic acid was attempted, but 92 was found to be highly soluble in aqueous media and re-extraction using a variety of organic solvents to be highly inefficient. Removing acetic acid using a reduced pressure distillation at 10 mbar was attempted, however at this pressure heating was required to evaporate acetic acid. After distillation a crystalline solid was recovered and it was found that heating had been sufficient to initiate an intramolecular trans-esterification, resulting in the thermodynamically favoured isomer, 124 (See Scheme 38).

**Scheme 38.** The unintended intramolecular trans-esterification of 92 to 124 as a result of heating.

92 was purified on a chromatography column using 5% methanol in dichloromethane to remove minor traces of the bis-acetylated by-product, 125 (See Fig 14) and was ready for further steps.
Fig 14. The minor *bis*-acetylated byproduct produced during the synthesis of 92.

Triflation of the remaining alcohol group of 92 was then achieved according to a procedure set out by Vo-Thanh *et al.*, involving the deprotonation of 92 using pyridine, 117, in dichloromethane and the subsequent reaction with trifluoromethanesulfonic anhydride, 125 (See Scheme 39). Washing the crude organic solution with water followed by an aqueous 5 M aqueous hydrochloric acid solution purified the product, 93. It is noteworthy that 93 tolerates 5 M hydrochloric acid and does not undergo elimination of the trifluoromethanesulfonate group, this is indicative of high stability for a trifluoromethanesulfonate-protected molecule. Subsequently, 93 was recovered by drying and removal of solvent *in vacuo* in a good yield and was pure enough for further steps.

Scheme 39. The mechanism by which the remaining alcohol group of 92 is replaced with trifluoromethanesulfonate.

2.9 - Isosorbide-Derived Imidazolium Chiral Ionic Liquid:

Nucleophilic Substitution of the Trifluoromethanesulfonate Leaving Group

Installation of the imidazolium functionality onto the imidazolium scaffold was also carried out according to a procedure set out by Vo-Thanh *et al.*, involving the mild heating (40 °C) of 93 in 1-methylimidazolium, 120 for 48 h.41 Compound 93 undergoes
an $S_N2$ nucleophilic substitution with 120, which displaces the trifluoromethanesulfonate group and installs it as the cation of the ionic liquid while simultaneously inverting the stereochemistry of the concerned carbon centre. This results in the restricted, concave, chiral and imidazolium-bearing structure of 94. The organocatalytic properties of 94 make themselves apparent immediately in this procedure; it seems that 94 mediates the elimination of the relatively stable trifluoromethanesulfonate functionality of 93, resulting in approximately one equivalent of the elimination product, 127 (See Scheme 40).

**Scheme 40.** The mechanisms by which 94 and by-product, 127 are formed.

A similar reaction was carried out using microwave radiation *in lieu* of conventional heating methods. In this instance, dichloromethane (1 ml per 1 ml of 120) was added to the mixture, in order to reduce the absorbance of microwave energy but the mixture remained the same in all other respects. The mixture was heated to 110 °C and after 90 min, all starting materials could be observed to be consumed by means of crude $^1$H-NMR analysis and the aforementioned mixture of 94, 120 and 127 was again present (See Scheme 41). Despite the same purification problems, the 90 min reaction time for the microwave-assisted synthesis is a marked improvement over the 48 h reaction time required for conventional heating methods.
**Scheme 41.** The microwave-assisted synthesis of 94.

Separation of residual 120 and 94 has proven extremely difficult to date and has not yet been achieved in this study. Vo-Thanh et al. describe a chromatography column using alumina as the stationary phase and dichloromethane and methanol (methanol starting at 0% with gradual increase to 15%). However attempts to duplicate only served to remove most of elimination product, 127 and was not adequate to separate 94 and 120.

**Fig. 15** Energy-minimised 3D representation of chiral ionic liquid 94 rendered using Cambridgesoft Chem3D software (hydrogen atoms and lone electron-pairs have been omitted for simplicity).
The crude $^1$H-NMR of this mixture shows strong evidence of the presence of 94 (See Fig. 16). Three singlets at 9.20, 7.83 and 7.73 ppm signify the three protons of an imidazolium ring, which are clearly separate from the analogous protons of the residual 120. A singlet at 4.07 ppm indicates the presence of the $N$-methyl group, again clearly separate from the analogous $N$-methyl signal of 120.

### 2.10 - Aziridination Mediated by Imidazolium Ionic Liquid Catalysts - Results

Aziridinations using ionic liquids were carried out between aldimine substrate 111 and ethyl diazoacetate having already established that 111 gives good yields under aziridination conditions. In order to duplicate results observed by Xia et al., initially, the ionic liquid, 80 was used. Compound 80, 111 and ethyl diazoacetate were combined and stirred for 16 h. As anticipated, the ionic liquid produced cis-aziridines, 112 in a good yield (82%) (See Scheme 42).
Scheme 42. The aziridination of aldimine 111 mediated by 80.

Chiral ionic liquids 90 and 91 were also used to mediate the aziridination of 111 and . Due to the very high viscosity of these ionic liquids in comparison with 80, it was necessary to add small amount of dichloromethane (a few drops per 1 mL) in order to make stirring possible. Solutions of 111 and ethyl diazoacetate were prepared in 90 and 91 respectively and were stirred for 16 h (See Scheme 43). Both ionic liquid solutions generated aziridine 112, however both samples of aziridine product gave, [α]$_{20}^{20}$ = 0 (c = 1.0, CHCl$_3$), indicating that no excess of chiral species is present. Separation of the two aziridine enantiomers when run through a Chiralpak HPLC column and eluted with 10% MeOH in iPrOH, in mixture could be observed to be racemic.

Scheme 43. The aziridination of aldimine 111 mediated by 91 or 92.

2.11 - Aziridination Mediated by Imidazolium Ionic Liquid Catalysts - Conclusions and Future Work

It was hypothesised that 90 and 91 would behave as Brønsted acids when activating aldimine substrates (See Scheme 44), either hydrogen bonding to or protonating the lone pair of the imine, the closely coordinated chiral anions were then intended to induce chirality upon addition of the nucleophilic attack of the diazoacetate. However,
the failure of 90 or 91 to produce any enantiomeric excess at all prompted a re-evaluation of the mechanism by which these catalysts mediate the aza-Darzens reaction.

Scheme 44. The hypothesised mechanism for the aziridination of 111 with ethyl diazoacetate mediated by 90 or 91.

In order to obtain insight into the mechanism of the imidazolium ionic liquid-catalysed aza-Darzens reaction, it was proposed to carry out a test-reaction using 1,2-dimethylimidazolium chloride, 128 (See Scheme 45). As 128 is missing the acidic proton found on 80 and given our original hypothesis, should not mediate the aza-Darzens aziridination. However, 128 successfully catalysed the reaction between 111 and ethyl diazoacetate, meaning that the mechanism of activation of aldimines by ionic liquids is not a Brønsted acidic one.

Scheme 45. The aziridination of 111 with ethyl diazoacetate mediated by 128.

We now propose that imidazolium ionic liquids must activate aldimine substrates to nucleophilic attack by electrostatic interactions alone. It is conceivable that in such a highly polar medium, a great enough dipole may be induced along the length of the N=C bond that nucleophilic attack at the α-carbon of the imine can occur. In the event that this is the case, the cation of the ionic liquid is likely to be in very close proximity to the
activated aldime substrate at the moment of nucleophilic attack. This therefore leads to the re-emphasis that the chiral ionic liquid 94 is in fact a highly likely candidate for the asymmetric catalysis of the aza-Darzens aziridination between aldimes and diazoacetate, future studies should therefore concern the purification of this liquid catalyst and its application to that end.
3 Experimental

General

All reactions were carried out under nitrogen / argon in flame dried apparatus which were allowed to cool under an inert nitrogen atmosphere. Reactions at 0 °C were carried out in a water / ice bath. Reactions carried out at -78 °C were carried out in a dry acetone / dry ice bath. Solvents removed in vacuo were removed using either a rotary evaporator or a Genevac. Column chromatography was carried out on silica gel (Fluka silica gel 60 70 – 230 mesh) at ambient temperature unless otherwise stated. TLC was carried out on Merck plates (aluminium coated 0.2 mm silica gel 60 F_{254}) and visualised under UV light (254 nm) or after exposure to an aqueous potassium permanganate solution, containing 3 g of KMnO₄, 10 g K₂CO₃, 2.5 mL of aqueous 2 M NaOH and 150 mL of de-ionised water.

Characterisation

Infrared spectra were recorded using a Perkin Elmer 1720 FTIR spectrometer. ¹H NMR, ¹³C NMR and ¹⁹F NMR spectra were recorded on Bruker 270 or 300 MHz, Oxford 300 or 400 MHz machines and samples are prepared as solutions of CDCl₃ unless otherwise stated. Chemical shifts (δ) are reported in parts per million relative to TMS as internal standard. J values are given in hertz. Mass spectrometry was attained using a Shimadzu LCMS with an electro-spray probe and samples were prepared as solutions of methanol unless otherwise stated. Melting points were obtained using Stuart Scientific Melting Point SMP 1 apparatus.
3.1 - Synthesis of Benzoyl-\textit{O}-dihydroquinidine (76).\textsuperscript{37}

In a dry 100 mL round-bottomed flask was added \textbf{129} (2.37 g, 7.26 mmol) and triethylamine (8.16 ml, 58.1 mmol) in dichloromethane (36.3 ml) at 0 °C to give a colourless solution. Benzoyl chloride (0.670 ml, 7.41 mmol) was added slowly via a dropping funnel over a period of ten min. The solution was left to stir for 1 h. Water (20 ml) was added to the solution and the organic layer was separated. The organic layer was then washed with 5\% sodium hydrogen carbonate solution (20 ml) and then water (20 ml). The solvent was removed \textit{in vacuo} to yield an off-white solid foam. This was recrystallised from the minimum amount of warm methanol to yield \textbf{76} (2.94 g, 6.83 mmol, 94 \% yield) as thick colourless crystals. \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \textit{δ} 8.69 (d, 1H, Ar\textit{H}, \textit{J} = 4.51 Hz), 8.08 (d, 2H, Ar\textit{H}, 2\textit{J} = 8.10 Hz), 7.99 (d, 1H, Ar\textit{H}, \textit{J} = 9.22 Hz), 7.53 (d, 2H, Ar\textit{H}, \textit{J} = 3.54 Hz), 7.45-7.40 (m, 3H, Ar\textit{H}), 7.34 (dd, 1H, Ar\textit{H}, \textit{J} = 9.15 Hz, \textit{J} = 2.08 Hz), 6.82 (d, 1H, COO\textit{CH}, \textit{J} = 6.67 Hz), 3.95 (s, 3H, OCH\textsubscript{3}), 3.40 (q, 1H, COOCH\textit{CHN(CH\textsubscript{2})\textsubscript{2}}, \textit{J} = 8.00 Hz), 2.98-2.71 (m, 4H, CHN(CH\textsubscript{2})\textsubscript{2}), 1.93 (t, 1H, alkyl, \textit{J} = 11.16 Hz), 1.72 (s, 1H, alkyl), 1.61-1.38 (m, 6H, alkyl), 0.86 (t, 3H, CH\textsubscript{3}, \textit{J} = 6.32 Hz)

3.2 - Synthesis of \textit{para}-Chlorobenzoyl-\textit{O}-dihydroquinidine (78).\textsuperscript{37}

In a dry 100 mL round-bottomed flask was added \textbf{129} (2.37 g, 7.26 mmol) and triethylamine (8.16 ml, 58.1 mmol) in dichloromethane (36.3 ml) at 0 °C to give a
colourless solution. \textit{para}-chlorobenzoyl chloride (0.670 ml, 7.41 mmol) was added slowly \textit{via} a dropping funnel over a period of ten min. The solution was left to stir for 1h. Water (20 ml) was added to the solution and the organic layer was separated. The organic layer was then washed with 5% sodium hydrogencarbonate solution (20 ml) and then water (20 ml). The solvent was removed \textit{in vacuo} to yield an off-white solid foam. This was recrystallised from the minimum amount of warm methanol to yield 78 (2.94 g, 6.83 mmol, 94 %) as thick colourless crystals. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.65 (d, 1H, ArH, $J = 4.54$ Hz), 7.95 (dq, 3H, ArH, $J = 8.78$ Hz, $J = 2.11$ Hz), 7.41-7.29 (m, 5H, ArH), 6.65 (d, 1H, COOCH, $J = 7.36$ Hz), 3.90 (s, 3H, OCH$_3$), 3.34 (q, 1H, COOCHCHN(CH$_2$)$_2$, $J = 8.00$ Hz), 2.88-2.61 (m, 4H, CHN(CH$_2$)$_2$), 1.80 (t, 1H, alkyl, $J = 11.20$ Hz), 1.69-1.65 (m, 2, alkyl), 1.55-1.40 (m, 6H, alkyl), 0.83 (t, 3H, CH$_2$CH$_3$, $J = 7.15$ Hz). $^{13}$C NMR (400MHz, CDCl$_3$): $\delta$ 165.03, 158.12, 147.65, 143.93, 132.05, 131.20, 129.13, 128.40, 122.09, 118.81, 101.57, 77.22 (t, CDCl$_3$), 59.66, 55.780, 51.02, 50.14, 37.55, 27.38, 26.32, 25.65, 23.85, 12.12. LC-MS (El$^+$) $m/z$ 487.1 (M+Na$^+$)

3.3 - Synthesis of 1,2-(\textit{bis-O-dihydroquinidinyl}) Phthalate (72).$^{37}$

In a dry 100 mL round-bottomed flask was added 129 (2.37 g, 7.26 mmol) and Triethylamine (8.16 ml, 58.1 mmol) in Dichloromethane (36.3 ml) at 0 $^\circ$C to give a colourless solution. Benzoyl chloride (0.670 ml, 7.41 mmol) was added slowly \textit{via} a dropping funnel over a period of ten min. The solution was left to stir for 1h. Water (20 ml) was added to the solution and the organic layer was separated. The organic layer was then washed with 5% sodium hydrogencarbonate solution (20 ml) and then water (20 ml). The solvent was removed \textit{in vacuo} to yield an off-white solid foam. This was recrystallised from the minimum amount of warm methanol to yield 72 (2.94 g, 6.83 mmol, 94 %) as thick colourless crystals. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.73 (d, 2H, ArH, $J = 4.55$ Hz), 7.99 (d, 2H, ArH, $J = 9.21$ Hz), 7.72 (dd, 2H, ArH, $J = 5.67$ Hz, $J = 3.32$ Hz), 7.58
(dd, 2H, ArH, J = 5.71 Hz, J = 3.33 Hz), 7.46-7.44 (m, 2H, ArH), 7.34 (td, 4H, ArH, J = 7.21 Hz, J = 2.59 Hz), 6.65-6.58 (m, 2H, COOCH), 3.92 (s, 6H, OCH₃), 2.61 (q, 2H, COOCHCH(CH₂)₂, J = 8.00 Hz), 2.73-2.54 (m, 8H, CHN(CH₂)₂), 3.21-3.18 (m, 2H, alkyl), 1.48-1.20 (m, 14H, alkyl), 0.75 (t, 3H, CH₂C₃H₅, J = 6.90 Hz). ¹³C NMR (300MHz, CDCl₃): δ 195.07, 185.66, 185.12, 166.30, 157.98, 147.59, 144.90, 131.93, 131.61, 128.92, 127.40, 122.135, 115.98, 59.94, 55.70, 50.80, 49.97, 37.44, 27.34, 26.23, 25.51, 12.05, 5.39; MS (EI)+ m/z 779.9 (M+H⁺)

3.4 - Synthesis of bis-O-Dihydroquinidinylphthalazine (68)

In a 250 mL round-bottomed flask was 1,4-dichlorophthalazine (1.54 g, 7.74 mmol), potassium carbonate (3.21 g, 23.21 mmol), and 129 (5.04 g, 15.47 mmol) in Toluene (60ml) to give a yellow suspension. The reaction vessel was fitted with a Dean-Stark condenser and refluxed at 110 °C for 2 h. Potassium hydroxide (1.302 g, 23.21 mmol) was added and the mixture was refluxed for a further 16 h. The resultant orange solution was allowed to cool to room temperature, was added to water (20 ml) and extracted with ethyl acetate (3x 20 ml). All organic fractions were combined and washed first with water (30 ml) and then saturated sodium chloride solution (30 ml) and dried over anhydrous magnesium sulphate. The resultant yellow solid was re-dissolved in ethanol (30 ml) and 1M sulphuric acid in ethanol was added slowly over a period of 10 min with rapid stirring, the resulting colourless solution was cooled to -5 °C and left to stand for 16 h. The resultant white precipitate was collected and washed with cold ethanol and diethyl ether. The white solid was dissolved in water (20 ml) and sodium hydrogen carbonate was carefully added until the solution reached pH 9. The free base was then extracted with ethyl acetate (3 x 20 ml), dried over anhydrous magnesium sulphate and concentrated in vacuo to give a white solid foam. This solid
was then recrystallised from the minimum amount of warm methanol to yield pure 68 (3.67 g, 4.72 mmol, 61 % yield) as white crystals. $^1$H NMR (400MHz, CDCl$_3$): δ 8.63 (d, 2H, ArH, $J$ = 4.53 Hz), 8.31 (dd, 2H, ArH, $J$ = 6.15 Hz, $J$ = 3.26 Hz), 7.98 (d, 2H, ArH, $J$ = 9.21 Hz), 7.92 (dd, 2H, ArH, $J$ = 6.11 Hz, $J$ = 3.29 Hz), 7.55 (dd, 2H, ArH, $J$ = 9.21 Hz, $J$ = 2.66), 7.43 (d, 2H, ArH, $J$ = 4.57 Hz), 7.35 (dd, 2H, ArH, $J$ = 9.21, $J$ = 2.68), 6.97 (d, 2H, COOC$_3$H$_7$), 3.89 (s, 6H, OCH$_3$), 2.76-2.67 (m, 8H, CHN(CH$_2$)$_2$), 0.79 (t, 6H, CH$_2$CH$_3$), 0.79 (t, 6H, CH$_2$CH$_3$), 0.79 (t, 6H, CH$_2$CH$_3$), 0.79 (t, 6H, CH$_2$CH$_3$).

$^{13}$C NMR (400MHz, CDCl$_3$): δ 186.09, 157.80, 147.55, 145.21, 144.86, 132.34, 131.71, 127.57, 123.01, 122.65, 122.05, 118.74, 102.29, 60.44, 55.85, 51.06, 37.64, 27.50, 26.50, 25.53, 23.69, 12.09. MS (EI) $^+$ m/z 779.6 (M+H$^+$).

### 3.5 - Synthesis of para-Chlorobenzoyl-O-(N-fluorodihydroquinidine tetrafluoroborate) (98).$^{38}$

![Chemical diagram]

In a 100 mL round-bottomed flask was 78 (400 mg, 0.860 mmol) in acetonitrile (2ml) to give a yellow solution. Selectfluor (305 mg, 0.860 mmol) in acetonitrile (8 ml) was slowly added over 10 min. The reaction was left to stir for 30 min. Sulfuric acid 0.1M in acetone (7.74 ml, 0.774 mmol) was slowly added to the solution over a period of 10 min to precipitate 1-chloromethyl-4-hydro-1,4-diazoniabicyclo[2.2.2]octane hydrogen sulphate tetrafluoroborate as a white solid. All solvent was removed in vacuo and dry acetone (10 ml) was added. The white solid was then removed via filtration. 30 ml dry diethyl ether was added to the acetone solution to precipitate a white solid. All solvents were removed in vacuo and the solid was re-dissolved in the minimum amount of acetone. The resultant solution was stored under nitrogen at -10 °C for a period of 24 h to yield 98 (83 mg, 0.146 mmol, 17 % yield) as yellow crystals $^1$H NMR (300MHz, acetone-d6): δ 8.77 (d, 1H, ArH, $J$ = 4.5 Hz), 7.70 (d, 2H, ArH, $J$ = 8.59 Hz), 8.07 (d, 1H,
ArH, J = 9.24 Hz), 7.88 (d, 1H, ArH, J = 4.53 Hz), 7.70 (d, 1H, ArH, J = 8.62 Hz), 7.62 (s, 1H, ArH), 7.53 (dd, 1H, ArH, J = 9.25 Hz, J = 2.60 Hz), 7.41 (d, 1H, COOCH, J = 2.53 Hz), 5.25 (t, 1H, J = 0.39 Hz), 4.77-4.68 (m, 3H), 4.50 (t, 1H, J = 0.37 Hz), 4.06 (s, 3H, OCH3), 3.40 (t, 1H, J = 7.20 Hz), 2.90-2.87 (m, 3H), 2.53 (t, 1H, J = 8.40 Hz), 1.95 (quin, 2H, CH2CH3, J = 7.53 Hz), 0.98 (t, 3H, CH2CH3, J = 7.41 Hz). 19F NMR (270 MHz, CD3CN): δ 37.41 (1F, [N-F]+), -151.27 (4F, BF4) MS (EI) + m/z 483.1 (M - BF4).

3.6 - Synthesis of 1-Butyl-3-methylimidazolium chloride (87).

\[
\begin{align*}
1.0 \text{ eq.} & \\
\text{Cl} & \\
\text{CH}_3\text{CN, } \Delta, 48 \text{ h} & \\
\text{121} & \\
\rightarrow & \\
\text{Cl} & \\
\text{nBu}^+ & \\
\text{N} & \\
\text{N-Me} & \\
\text{87}
\end{align*}
\]

In a 500 mL round-bottomed flask fitted with a reflux condenser was 121 (22.82 ml, 286 mmol) and 87 (27.0 ml, 372 mmol) in acetonitrile (15.5 ml) to give a yellow solution. The solution was brought to a gentle reflux and left to reflux for 48 h. The reaction solution was allowed to cool to room temperature and the solvent was removed in vacuo. The resultant pale yellow oil was re-dissolved in dry acetonitrile (40 ml) and added drop wise via a cannula to 200 ml dried ethyl acetate with stirring. The resultant solution was cooled to -40°C for 2 h to yield 87 (49.7 g, 285 mmol, 99 %) as very pale yellow crystals. 1H NMR (300MHz, CDCl3): δ 10.58 (s, 1H, NCHN), 7.87 (t, 1H, N\text{CHCHN, } J = 1.70 Hz), 7.81 (t, 1H, N\text{CHCHN, } J = 1.66 Hz), 4.03 (t, 2H, NCH2, J = 7.24 Hz) 4.01 (s, 3H, NCH3), 1.82 (quin, 2H, NCH2CH2, J = 7.20 Hz), 1.25 (hex, 2H, NCH2CH2CH2, J = 7.59 Hz), 0.84 (t, 3H, NCH2CH2CH2CH2, J = 7.36 Hz)

3.7 - Synthesis of 1-Butyl-3-methylimidazolium hexafluorophosphate (80).

\[
\begin{align*}
1.0 \text{ eq. KPF}_6 & \\
\text{H}_2\text{O, 2 h} & \\
\text{87} & \\
\rightarrow & \\
\text{88}
\end{align*}
\]

Into a 250 ml round-bottomed flask was added 87 (40.7 g, 233 mmol), and potassium hexafluorophosphate (42.8 g, 233 mmol) in distilled water (50 ml). The reaction
mixture was stirred at room temperature for 2 h affording a two-phase system. The organic phase is washed with water (3 x 20 ml), dichloromethane (40 ml) and anhydrous magnesium sulfate (20 g) were added. After an hour, the suspension was filtered and the volatile material was removed in vacuo to yield 80 (44.3 g, 156 mmol, 67 %) as a light yellow viscous liquid, mp 10 °C, ¹H NMR (300MHz, CD₃OD): δ 8.73 (s, 1H, NCHN), 7.53 (t, 1H, MeNCHCHNBu, J = 1.74 Hz) 7.47 (t, 1H, MeNCHCHNBu, J = 1.68 Hz), 4.15 (t, 2H, NCH₂, J = 7.34 Hz), 3.87 (s, 3H, NCH₃), 1.82 (quintet, 2H, NCH₂CH₂, J = 7.61 Hz), 1.33 (sextet, 2H, NCH₂CH₂CH₂, J = 7.54 Hz), 0.94 (t, 3H, NCH₂CH₂CH₂CH₃, J = 7.37 Hz), ¹³C NMR (400MHz, CD₃OD): δ 136.30, 123.40, 122.10, 48.96, 44.7 (dt, CD₃OD) 34.78, 31.38, 18.78, 12.04.

3.8 - Synthesis of Sodium Dimalatoborate (88).⁴⁰

In a 100 mL round-bottomed flask was L-(−)-Malic acid (5.36 g, 40.0 mmol) in water (10.00 ml) to give a colourless solution. Boric acid (1.237 g, 20 mmol) was added and sodium hydroxide (0.800 g, 20.00 mmol) in water (10.00 ml) was added. The mixture was stirred and heated to 100 °C for 3 h until all water had evaporated to give 88 (5.84 g, 19.60 mmol, 98 %) as a white crystalline solid. ¹H NMR (300MHz, acetone-d₆): δ 4.34-4.25 (m, 2H, CHCOOH), 2.55-2.51 (m, 2H, CHCOOH), 2.26-2.21 (m, 2H, BOOCCH₃)

3.9 - Synthesis of 1-Butyl-3-methylimidazolium Dimalatoborate (90).³⁵
87 1.737 g, 9.94 mmol) was dissolved in acetone (22.60 ml) and treated with 89 (2.963 g, 9.94 mmol) in acetone (22.60 ml). The reaction mixture was stirred at room temperature overnight. During this period sodium chloride precipitated as a white solid. The reaction mixture was filtered and the solvent was removed in vacuo to give 90 (4.04 g, 9.75 mmol, 98 %) as a very pale yellow, highly viscous oil. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 9.11 (s, 1H, NCHN), 7.65 (t, 1H, MeNCHCHNBu, $J = 1.72$ Hz), 7.61 (t, 1H, MeNCHCHNBu, $J = 1.68$ Hz), 4.40-4.34 (m, 2H, CHCOOH), 4.26 (t, 2H, NCH$_2$, $J = 7.28$ Hz) 3.94 (s, 3H, NCH$_3$), 2.59-2.55 (m, 2H, CHCOOH), 2.41-2.34 (m, 2H, BOOCCH), 1.80 (quintet, 2H, NCH$_2$CH$_2$, $J = 7.27$ Hz), 1.27 (sextet, 2H, NCH$_2$CH$_2$CH$_3$, $J = 7.75$ Hz), 0.83 (t, 3H, NCH$_2$CH$_2$CH$_3$, $J = 8.17$ Hz).

3.10 - Synthesis of Sodium Dimandelatoborate (89).^{40}

In a 100 mL round-bottomed flask was 122 (9.433 g, 62.0 mmol) in water (15.50 ml) to give a colourless solution. Boric acid (1.917 g, 31.0 mmol) was added. Sodium hydroxide (1.240 g, 31.0 mmol) in water (15.50 ml) was added. The solution was then heated to 100 for 2 h and the water allowed to evaporate to yield 89 (10.25 g, 30.7 mmol, 99 %) as a white crystalline solid $^1$H NMR (300MHz, acetone-d$_6$): $\delta$ 7.56-7.47 (m, 2H, ArH), 7.24-7.14 (m, 3H, ArH), 5.13-5.04 (m, 1H, PhCH).

3.11 - Synthesis of 1-Butyl-3-methylimidazolium Dimandelatoborate (91).^{35}
In a 100 mL round-bottomed flask was 87 (2.327 g, 13.32 mmol) in with stirring to give a white suspension. The suspension was filtered to remove all solids concentrated using a rotary evaporator to give 91 (5.87 g, 13.04 mmol, 98 %) as a very pale yellow, highly viscous oil. \([\alpha]^{20}_D = 123.8 \pm 0.2\) (c=0.39, CH3CN); \(^1\)H NMR (300MHz, acetone-d6): \(\delta\) 8.97 (s, 1H, NC\(\text{H}N\)), 7.68-7.60 (m, 4H, ArH), 7.59 (t, 1H, N•CH\(\text{CHN}, J = 1.57\) Hz), 7.51 (t, 1H, N•CH\(\text{CHN}, J = 1.75\) Hz), 7.37-7.23 (m, 6H, ArH), 5.21 (d, 2H, PhCH, \(J = 5.21\) Hz), 4.15 (t, 2H, NCH\(\text{CHN}\), \(J = 7.34\) Hz), 3.83 (s, 3H, NC\(\text{H}3\)), 1.76 (quin, 2H, NCH\(\text{CHN}\), \(J = 7.50\) Hz), 1.25 (hex, 2H, NCH\(\text{CHCH2}\), \(J = 7.49\) Hz), 0.87 (t, 3H, NCH\(\text{CHCH2CH3}\), \(J = 7.35\) ); \(^{13}\)C NMR (300MHz, CDCl3) \(\delta\) 178.28, 178.16, 139.80, 139.76, 135.26, 128.25, 128.13, 127.65, 127.47, 126.17, 126.04, 123.26, 121.83, 78.00, 77.88, 49.56, 35.94, 31.72, 19.16, 13.30.

3.12 - Synthesis of (3\(R\), 3a\(R\), 6\(S\), 6a\(S\))-3-(Acetoxy)hexahydrofuro[3,2-b]furan-6-ol (93).\(^{42}\)

![123](image1.png) 1.1 eq Ac\(\text{O}2\) 2 mol% PbO DCM, 12 h ![93](image2.png)

100 mL round-bottomed flask was added Isosorbide (7 g, 47.9 mmol), acetic anhydride (5.88 ml, 62.3 mmol), and lead (II) oxide (0.267 g, 1.197 mmol) in DCM (10 ml) to give a colorless solution. The solution was stirred for 24 h. TLC (5% MeOH : 95% CH\(2\text{Cl2}\)) showed only trace starting materials remained. Solvent was removed in vacuo and residual acetic anhydride and acetic acid by-product was removed under high vacuum (8 mbar) with mild heating to afford a yellow oil. The crude material was purified on a chromatography column (5% MeOH : 95% DCM) to afford 93 (2.2 g, 11.69 mmol, 27.5 % yield) as a viscous, colourless oil. \(^1\)H NMR (300MHz, CDCl3): \(\delta\) 5.13 (quin, 1H, \(J = 5.66\) Hz, 4.83 (q, 1H, \(J = 4.50\) Hz), 4.30 (t, 1H, \(J = 4.62\) Hz), 3.95-3.87 (m, 3H), 3.78-3.72 (m, 1H), 2.17 (q, 1H, \(J = 1.36\) Hz), 2.13-2.11 (m, 3H, COOCH\(3\)). \(^{13}\)C NMR (CDCl3, 300 MHz): \(\delta\) 185.55, 88.37, 80.52, 77.22 (t, CD\(3\)Cl), 76.44, 75.77, 74.29, 70.36, 20.90 LC-MS (EI)* \(m/z\) 189.00 [M+H].
3.13 - Synthesis of (3R, 3aR, 6S, 6aS)-3-(Acetoxy)hexahydrofuro[3,2-b]furan-6-yl trifluoromethanesulfonate. (94).\textsuperscript{41}

In a 50 mL round-bottomed flask was 93 (827 mg, 4.39 mmol) and pyridine (391 µl, 4.83 mmol) in dichloromethane (1.03E+04 µl) to give a yellow solution. The solution was cooled to 0 °C and stirred rapidly for 30 min. Trifluoromethanesulfonic anhydride (780 µl, 4.61 mmol) was added carefully. After half an hour, the solution was allowed to warm to room temperature and stirred for a further 2 h. The solution was washed with water (30 ml), 5 M HCl solution (30 ml) and saturated sodium chloride solution (30 ml). The organic phase was collected, dried with MgSO\textsubscript{4} and solvent was removed in vacuo to give 94 (1.2 g, 3.75 mmol, 85 % yield) as an orange oil. 1H NMR (300MHz, CDCl\textsubscript{3}): δ 5.25 (t, 1H, J = 2.85 Hz), 5.12 (q, 1H, J = 5.45 Hz), 4.89 (t, 1H, J = 5.09 Hz), 4.60 (d, 1H, J = 4.70 Hz), 4.14 (d, 1H, J = 11.94 Hz), 3.98-3.90 (m, 2H), 3.73 (dd, 1H, J = 10.03 Hz, J = 5.01 Hz), 2.04 (s, 3H, COOC\textsubscript{3}H\textsubscript{3}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 300 MHz): δ 170.17, 89.31, 85.36, 80.80, 77.01 (t, CD\textsubscript{3}Cl), 73.35, 72.71, 70.65, 20.35. MS (EI)\textsuperscript{+} m/z 321.00 [M+H]\textsuperscript{+}.

3.14 - Synthesis of 2-tert-Butoxynitrobenzene (131)

In a 100 mL round-bottomed flask was added a potassium hydride (1.52 g, 38.1 mmol) in dry tetrahydrofuran (25 ml). The resulting white suspension was stirred rapidly and hexamethyldisilazane (7.58 ml, 36.3 mmol) was added drop-wise over a period of ten min. After the addition was completed the suspension stirred for 16 h to give a pale yellow solution. In a 250 mL round-bottomed flask was then added 130 (3.2 ml, 33.5 mmol) in Tetrahydrofuran to give a colourless solution. The solution was stirred with a
magnetic stir bar. tert-Butanol (3.2 ml, 33.5 mmol) was added and the solution cooled to 0°C and the reaction was stirred. The hexamethyldisilazane solution was slowly added via a cannula, allowed to warm to RT and stirred for 16 h. The resulting Dark yellow oil was diluted with 30 ml ethyl acetate and washed with ammonium chloride (50 ml), water (2x50 ml) and brine (50 ml). All aqueous washings were then back-extracted with ethyl acetate (50 ml). All organic fractions were then combined and dried over magnesium sulfate and all solvent removed under reduced pressure to yield 130 (5.88 g, 30.1 mmol, 90 %) as a dark brown oil. ¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, 1H, ArH, J = 8.07 Hz), 7.44 (dd, 1H, ArH, J = 8.37 Hz, J = 7.41 Hz), 7.20 (d, 1H, ArH, J = 8.37 Hz), 1.39 (s, 9H, OC(CH₃)₃)

3.15 - Synthesis of 2-tert-Butoxyaniline (132)

A mixture of 131 (5 g, 25.6 mmol) and 10% palladium on charcoal (2.73 g, 2.56 mmol) in ethanol (16 ml) to give a black suspension, which was evenly divided between four 5 mL hydrogenation vials. Hydrogen gas was then bubbled through suspension until it ceased to be consumed (6 h). The reaction mixture was filtered through celite and eluted with diethyl ether. The solution was concentrated using a rotary evaporator to yield 132 (4.19 g, 25.4 mmol, 99 %) as a red oil. ¹H NMR (400 MHz, CDCl₃): δ 6.95 (d, 1H, ArH, J = 7.95 Hz), 6.88 (d, 1H, ArH, J = 8.07 Hz), 6.74 (dd, 1H, ArH, J = 8.37 Hz, J = 7.41 Hz), 6.65 (t, 1H, ArH, J = 8.37 Hz), 1.39 (s, 9H, OC(CH₃)₃).
3.16 - Synthesis of (E)-2-Butoxy-N-(4-nitrobenzylidene)phenylamine (107)

![Chemical Structure]

In a 100 ml round-bottomed flask was 132 (915 mg, 6.05 mmol) and 2-butoxyaniline (1 g, 6.05 mmol) in dichloromethane (20 ml) to give a brown solution. The reaction was stirred with a magnetic stir bar for 10 min. Anhydrous magnesium sulphate (1 g) was added and the solution was briefly stirred to mix and then the solution was left to stand for 16 h under nitrogen. The resultant orange solution was filtered and concentrated in vacuo to yield 107 (1.408 g, 4.72 mmol, 78 % yield) as a crystalline pale brown solid. $^1$H NMR (400MHz, CDCl₃): δ 8.55 (s, 1H, N=CH), 8.30 (d, 2H, o-NO₂-ArH, $J = 8.32$ Hz), 8.05 (d, 2H, m-NO₂-ArH, $J = 8.11$ Hz), 7.13-7.07 (m, 4H, ArH), 1.30 (s, 9H, OC(CH₃)).

3.17 - Synthesis of (E)-4-Methoxy-N-benzylidenephenylamine (109)

![Chemical Structure]

In a 100 ml round-bottomed flask was 134 (0.641 g, 6.05 mmol) and 2-butoxyaniline (744 mg, 6.05 mmol) in Dichloromethane (20 ml) to give a brown solution. The reaction was stirred with a magnetic stir bar for 10 min. Anhydrous magnesium sulphate (1 g) was added and the solution was left to stand for 16 h under nitrogen. The resultant orange solution was filtered and concentrated in vacuo to yield 109 (1.15 g, 5.44 mmol,
90 % yield) as a crystalline pale brown solid. $^1$H NMR (400MHz, CDCl$_3$): δ 8.48 (s, 1H, N=CH), 7.91-7.88 (m, 2H, ArH), 7.46 (t, 3H, ArH, $J = 3.22$ Hz), 7.24 (d, 2H, m-MeO-ArH, $J = 9.01$ Hz), 6.94 (d, 2H, m-MeO-ArH, $J = 8.98$ Hz), 3.83 (s, 3H, OCH$_3$).

### 3.18 Synthesis of (E)-4-Methoxy-N-(2-pyridinylidene)phenylamine (111)

![Reaction Scheme](reaction_scheme.png)

In a 100 mL round-bottomed flask was added 136 (8.43 ml, 83 mmol) and 135 (10.24 g, 83 mmol) in dichloromethane (40 ml) to give a brown solution. 10 g dried magnesium sulphate was added and the solution was briefly stirred to mix and then left to stand for 16 h. The solution was filtered to remove magnesium sulphate and the solvent removed in vacuo to yield 111 (13.11 g, 62.1 mmol, 74.6 % yield) as a brown solid. $^1$H NMR (400MHz, CDCl$_3$): δ 8.68 (dd, 1H, $o$-pyridinyl-H, $J = 4.86$ Hz, $J = 1.60$ Hz), 8.62 (s, 1H, N=CH), 8.17 (d, 1H, $m$-pyridinyl-H, $J = 7.95$ Hz), 7.78 (t, 1H, $m$-pyridinyl-H, $J = 7.50$ Hz), 7.33 (dt, 3H, $m$-pyridinyl-H, $m$-OMe-ArH, $J = 6.58$ Hz, $J = 2.75$ Hz), 6.94 (d, 2H, $o$-OMe-ArH, $J = 8.90$ Hz), 3.82 (s, 3H, OCH$_3$).

### 3.19 - F⁺ Mediated Aziridinations$^{29}$

![Reaction Scheme](reaction_scheme2.png)

Cis-Rac 108
In a dry 10 mL round-bottomed flask was added 107 (80 mg, 0.268 mmol) and N-fluoropyridinium Trifluoromethanesulfonate (6.63 mg, 0.027 mmol) in dry dichloromethane (3 ml) under an atmosphere of nitrogen to give a dark yellow solution, which was stirred for 5 min. Ethyl diazoacetate (32.7 µl, 0.268 mmol) was added and the reaction was stirred for 12 h, during which time nitrogen bubbles could be observed evolving from the solution. The solution was filtered through a plug of celite and the solvent was removed in vacuo. Purification via flash chromatography with diethyl ether/petroleum ether (20:80) yielded 108 (46 mg, 0.120 mmol, 44.6%).

\[ \text{In H NMR (300 MHz, CDCl}_3\text{):} \delta 8.20 (d, 2H, o-NO}_2\text{ArH, }J = 8.86 \text{ Hz}), 7.73 (d, 2H, m-NO}_2\text{ArH, }J = 8.81 \text{ Hz}), 7.03-6.95 (m, 4H, MeOArH), 4.03 (dd, 2H, COOCH}_2\text{, }J = 9.47, J = 7.17), 3.58 (d, 1H, CHCOOEt, }J = 6.64 \text{ Hz), 3.19 (d, 1H, CPhNO}_2\text{, }J = 6.65 \text{ Hz), 1.32 (s, 9H, O(CH}_3\text{)), 1.08, (t, 3H, COOCH}_2\text{CH}_3, J = 7.14 \text{ Hz);} \]

\[ \text{13C NMR (CDCl}_3\text{, 300 MHz):} \delta 166.8, 155.9, 147.8, 144.1, 140.9, 127.6, 123.7, 120.6, 114.4, 61.5, 55.3, 46.6, 45.1, 13.9 \]

In a dry 25 mL round-bottomed flask was 109 (124 mg, 0.585 mmol) and Selectfluor (20 mg, 0.056 mmol) in acetonitrile (2.17 ml) under an atmosphere of nitrogen to give a brown solution, which was stirred for 5 min. Ethyl diazoacetate (69.8 µl, 0.565 mmol) was added and the reaction was stirred for 12 h, during which time nitrogen bubbles could be observed evolving from the solution. The solution was filtered through a plug of celite and the solvent was removed in vacuo. Purification via flash chromatography with diethyl ether/petroleum ether (40:60) yielded 110 (99 mg, 0.333 mmol, 59 % yield).

\[ \text{In H NMR (300MHz, CDCl}_3\text{):} \delta 7.49 (dd, 2H, o-CHArH, }J = 6.60 \text{ Hz), }J = 1.50 \text{ Hz), 7.34-7.31 (m, 3H, ArH), 6.99 (d, 2H, m-MeOArH, }J = 9.09 \text{ Hz), 6.81 (d, 2H, m-MeOArH, }J = 9.04 \text{ Hz), 4.01 (dd, 2H, COOCH}_2\text{, }J = 15.83 \text{ Hz, }J = 7.13 \text{ Hz), 3.77 (s, 3, OCH}_3\text{), 3.52 (d, 1H, CHCOOEt, }J = 6.84 \text{ Hz), 3.13 (d, 1H, CPh, }J = 6.83 \text{ Hz), 0.98 (t, 3H, COOCH}_2\text{CH}_3\text{).} \]
In a dry 25 mL round-bottomed flask was 111 (145 mg, 0.565 mmol) and Selectfluor (20 mg, 0.056 mmol) in acetonitrile (2.17 ml) under an atmosphere of nitrogen to give a yellow solution, which was stirred for 5 min. Ethyl diazoacetate (69.8 µl, 0.565 mmol) was added and the reaction was stirred for 12 h, during which time nitrogen bubbles could be observed evolving from the solution. The solution was filtered through a plug of celite and the solvent was removed in vacuo. Purification via flash chromatography with diethyl ether/petroleum ether (40:60) yielded 112 (141 mg, 0.412 mmol, 73 %); 1H NMR (300MHz, CDCl3): δ 8.21 (d, 2H, o-NO2ArH, J = 8.87 Hz), 7.69 (d, 2H, m-NO2ArH, J = 8.53 Hz), 6.97 (d, 2H, m-MeOArH, J = 8.98 Hz), 6.83 (d, 2H, o-MeOArH, J = 8.99 Hz), 4.02 (dd, 2H, COOCH2, J = 9.00 Hz, J = 7.14 Hz), 3.77 (s, 3H, OCH3), 3.57 (d, 1H, CHOOEt, J = 6.78 Hz), 3.21 (d, 1H, CHPH, J = 6.76 Hz), 1.04 (t, 3H, COOCH2CH3, J = 7.13 Hz). 13C NMR (CDCl3, 300 MHz): δ 167.4, 156.2, 149.5, 149.2, 145.2, 135.5, 122.9, 120.7, 114.5, 61.1, 55.4, 45.5, 45.0, 13.8; MS (El)+: m/z 597 (100%).

Into a 12 Reaction carrousel were placed seven carousel tubes and each was charged with an O-protected alkaloid (tube 1: 69, 21.8 mg; tube 2: 72, 22.0 mg, 0.027 mmol; tube 3: 73, 20.5 mg, 0.027 mmol; 74, 22.1 mg, 0.027 mmol; 75, 14.7 mg, 0.027 mmol; 76, 12.1 mg,
0.027 mmol; 78, 13.1 mg, 0.027 mmol) and 97, 19 mg, 0.054 mmol in acetonitrile (1 ml) to give a colourless solution and was stirred for 30 min. 107 (80 mg, 0.268 mmol) was added to each solution, the solution was stirred for a further 15 min. Ethyl diazoacetate (32.7 µl, 0.268 mmol) was added to each tube and the solution was stirred for 48 h. Each solution was filtered through a plug of celite and the solvent was removed in vacuo. Purification via flash chromatography with diethyl ether/ petroleum ether (40:60) yielded 108 (Yields: Tube 1 = 24 mg, 23 %; Tube 2 = 34 mg, 33 %; Tube 3 = 8 mg, 8 %; Tube 4: no yield; Tube 5 = 19 mg, 18 %; Tube 6 = 13 mg, 13 %; Tube 7 = 21 mg, 20 %). All tubes: α$^20_D$ = 0 (c=1.0, CH₃Cl)

![Diagram](image)

Into a 12 Reaction carrousel were placed seven carousel tubes and each was charged with an O-protected alkaloid (tube 1: 69, 21.8 mg; tube 2: 72, 22.0 mg, 0.027 mmol; tube 3: 73, 20.5 mg, 0.027 mmol; 74, 22.1 mg, 0.027 mmol; 75, 14.7 mg, 0.027 mmol; 76, 12.1 mg, 0.027 mmol; 78, 13.1 mg, 0.027 mmol) and 97, 19 mg, 0.054 mmol in acetonitrile (1 ml) to give a colourless solution and was stirred for 30 min. 109 (80 mg, 0.268 mmol) was added to each solution, the solution was stirred for a further 15 min. Ethyl diazoacetate (32.7 µl, 0.268 mmol) was added to each tube and the solution was stirred for 48 h. Each solution was filtered through a plug of celite and the solvent was removed in vacuo. Purification via flash chromatography with diethyl ether/ petroleum ether (40:60) yielded 110 (Yields: Tube 1 = 4 mg, 5 %; Tube 2: 6 mg, 8 %; Tube 3 = no yield; Tube 4: no yield; Tube 5 = 4 mg, 5 %; Tube 6 = 6 mg, 8 %; Tube 7 = 10 mg, 13 %). All tubes: α$^20_D$ = 0 (c=1.0, CH₃Cl)
Into a 12 Reaction carrousel were placed seven carousel tubes and each was charged with an O-protected alkaloid (tube 1: 69, 21.8 mg; tube 2: 72, 22.0 mg, 0.027 mmol; tube 3: 73, 20.5 mg, 0.027 mmol; tube 4: 74, 22.1 mg, 0.027 mmol; tube 5: 75, 14.7 mg, 0.027 mmol; tube 6: 76, 12.1 mg, 0.027 mmol; tube 7: 78, 13.1 mg, 0.027 mmol) and 97, 19 mg, 0.054 mmol in acetonitrile (1 ml) to give a colourless solution and was stirred for 30 min. 111 (80 mg, 0.268 mmol) was added to each solution, the solution was stirred for a further 15 min. Ethyl diazoacetate (32.7 µl, 0.268 mmol) was added to each tube and the solution was stirred for 48 h. Each solution was filtered through a plug of celite and the solvent was removed in vacuo. Purification via flash chromatography with diethyl ether/ petroleum ether (40:60) yielded 112 (Yields: Tube 1 = 38 mg, 47 %; Tube 2: 42 mg, 52 %; Tube 3 = 30 mg, 38 %; Tube 4: 12 mg, 15 %; Tube 5 = 38 mg, 47 %; Tube 6 = 39 mg, 49 %; Tube 7 = 43 mg, 54 %). All tubes: $\alpha^{20}_{D} = 0$ (c=1.0, CH$_3$Cl)

### 3.20 Ionic Liquid Mediated Aziridinations

Into a 12 reaction carrousel was placed two carousel tubes and each was charged with an ionic liquid (tube 1: 80, 1 ml; tube 2: 128, 1 ml) and 111 (200 mg, 0.94 mmol) to give yellow solutions, which were stirred for 15 min. Ethyl diazoacetate (117 µL, 0.94 mmol)
was added to each tube and the solutions were stirred for 16 h. Each solution was filtered through a plug of celite and the solvent was removed in vacuo. Purification via flash chromatography with diethyl ether/ petroleum ether (40:60) yielded 112 (yields: Tube 1 = 231 mg, 82 %; Tube 2 = 236 mg, 84 %).

Into a 12 reaction carrousel was placed two carousel tubes and each was charged with a chiral ionic liquid (tube 1: 80, 1 ml; tube 2: 92, 1 ml) and 111 (200 mg, 0.94 mmol) to give yellow solutions, which were stirred for 15 min. Ethyl diazoacetate (117 μL, 0.94 mmol) was added to each tube and the solutions were stirred for 16 h. Each solution was filtered through a plug of celite and the solvent was removed in vacuo. Purification via flash chromatography with diethyl ether/ petroleum ether (40:60) yielded 112 (yields: tube 1 = 196 mg, 70 %; tube 2 = 206 mg 73 %). All tubes: $\alpha^{20}_{20} = 0$ (c=1.0, CH$_3$Cl).
Definitions:

**BINAP:** Binaphthalene

**CIL:** Chiral ionic liquid

**$^{13}$CNMR:** Carbon-13 nuclear magnetic resonance (spectroscopy)

**COD:** Cyclooctadiene

**DCM:** Dichloromethane

**DET:** Diethyl Tartrate

**DHQD:** Dihydroquinidine

**DIPAMP:** Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]

**D.R.** Diastereoisomeric ratio

**EDA:** Ethyl diazoacetate

**e.e.** Enantiomeric excess

**$^{19}$FNMR:** Fluorine-19 nuclear magnetic resonance (spectroscopy)

**FTIR:** Fourier transform infrared (spectroscopy)

**$^1$H-NMR:** Proton nuclear magnetic resonance (spectroscopy)

**HPLC:** High performance liquid chromatography

**IL:** Ionic liquid

**L-DOPA:** (S)-2-amino-3-(3,4-dihydroxyphenyl)proanoic acid

**MS:** Mass spectrometry

**ppm:** Parts per million

**S$_e$Ar:** Electrophilic aromatic substitution

**S$_n$:** Nucleophilic substitution

**VAPOL:** Vaulted biphenanthrol
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