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

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Research Thesis

Submitted in partial fulfilment of the award of:

Master of Science by Research

University of East Anglia

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.

Acknowledgement

I would like to thank all my family and friends and my partner Emily for supporting me throughout my degree, I could not have managed it without them. I would like to thank to all members of the Bew research group past and present, with special thanks to Paolo Pesce, Sean Thurston, Glyn Hiatt-Gipson, Polly-Anna Ashford, Luis Martinez Lozano and Dominika Bachera for all of their support and advice. I would also like to thank my co-workers Vincent Bizet and Nathalie Fresneau, Alicia Foucort, Anaïs Largesse and Baptiste Feasard at IRCOF, Rouen, who all made my feel so welcome and were always available to lend a hand or discuss with. Outside of my research groups, I would also like to thank Ketan "Mudz" Panchal, Ian Strutt, James Wolfe, Dr. Yohan Chan, Doyle Cassar, Rebbeca Turner, Gareth Couperthwaite, Chris Pierce and David Day for their valued support and friendship this year.

Finally I would like to say thank you to Dr. Sean Bew and Dr. Dominique Cahard for allowing me use of their laboratories and for the invaluable guidance that they have both given me throughout the duration of this project.

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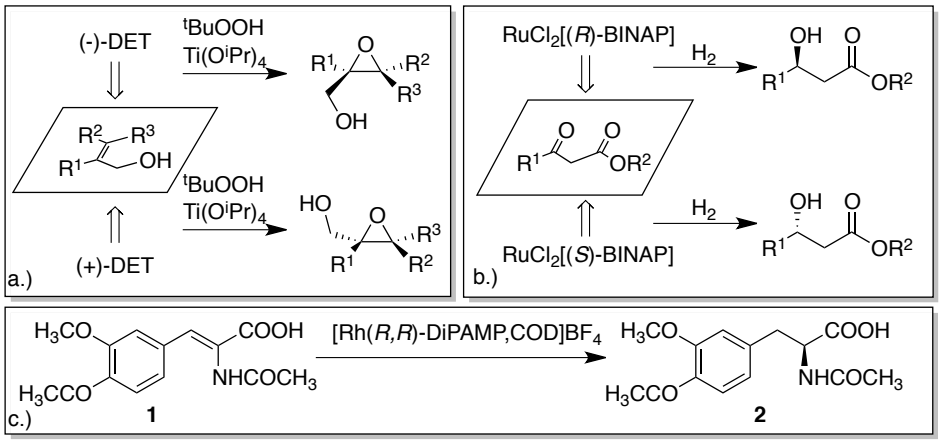
1 - Introduction

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.[1] 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.[2]

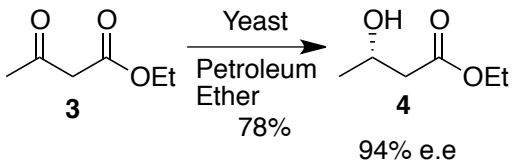
Until very recently asymmetric catalysis has been dominated by transition metal complex and enzyme catalysts. Transition metal catalysts offer a high degree of customisability, meaning that they can be tailored and refined to produce high enantioselectivity and catalytic activity. The 2001 Nobel Prize 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.[3a-c]



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 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*)**.** [4]



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*).[5] 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.

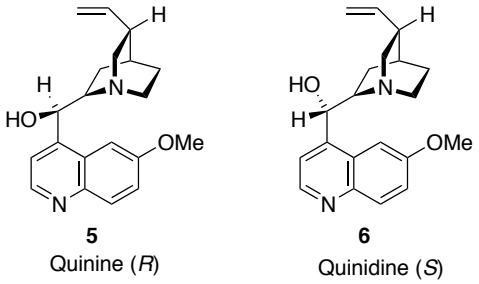
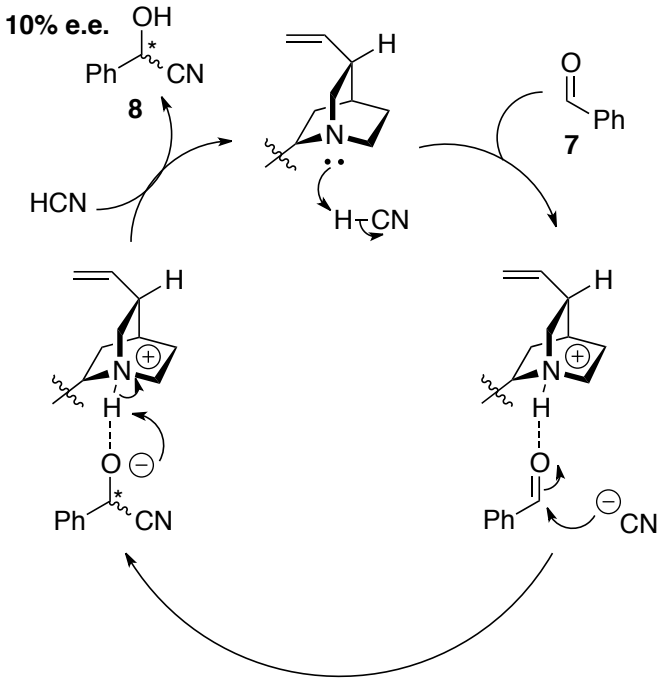
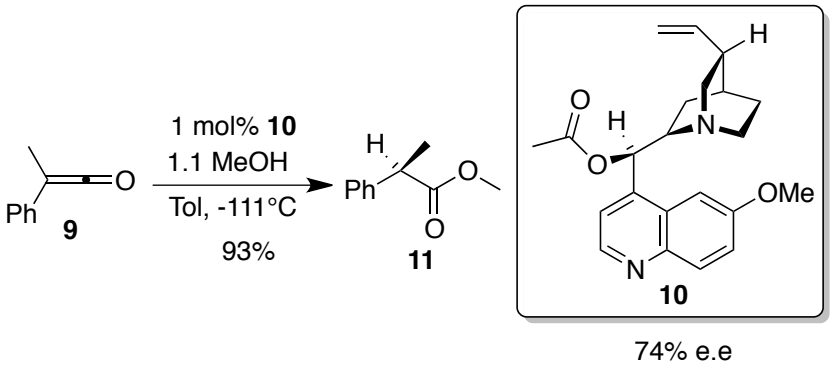


Figure 1. The asymmetric alkaloid catalysts **5** & 6 employed by Bredig and Fiske in 1912.



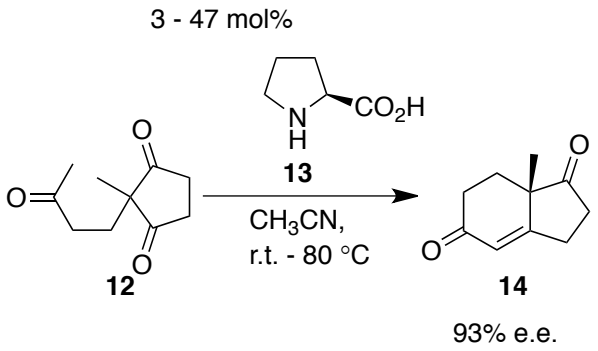
Scheme 3. The catalytic cycle in which quinine or quinidine catalyse the addition of hydrogen cyanide to benzaldehyde.

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 phenylmethyketene, **9** to afford methyl-2-(*R*)-phenylpropanoate, **11** in 74% enantiomeric excess (*See Scheme 4*).[6]



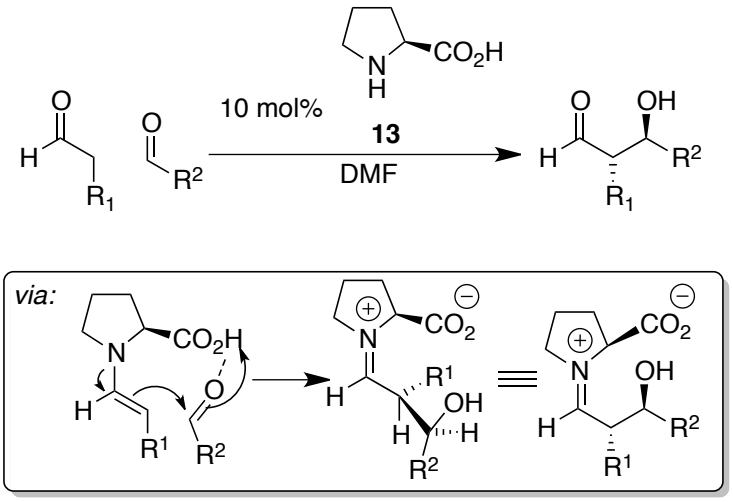
Scheme 4. Pracejus *et al.*'s use of **10** to mediate the reaction between ketene, **9** and methanol.

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*).

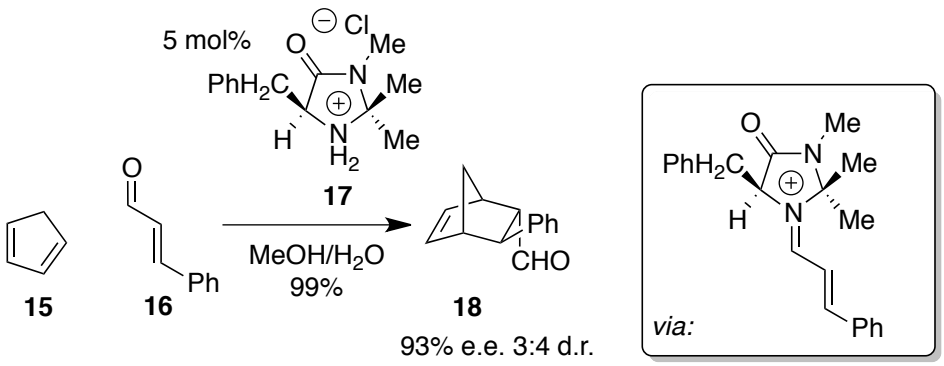


Scheme 6. General Hajos-Parrish-Eder-Sauer-Wiecher Reaction scheme

1.1.1 - Covalent Organocatalysis

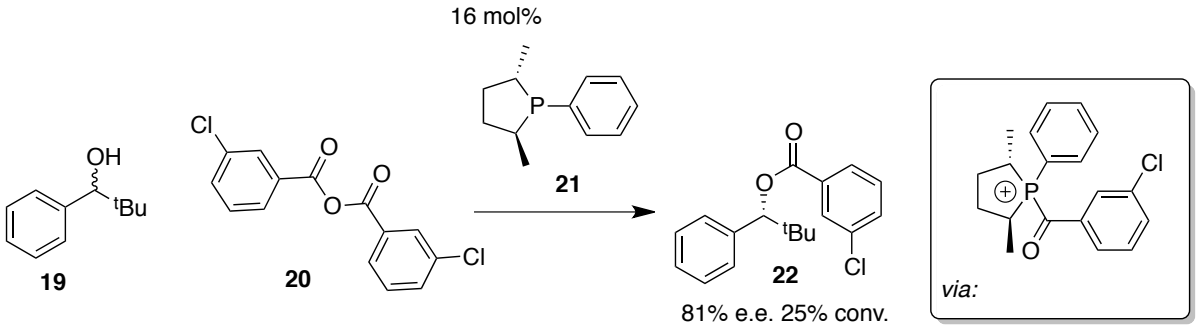
In order to investigate new organocatalysts, one first needs to understand the principles that underpin organocatalysis as a whole. It is true that despite the enormous growth and interest in the field over recent years, that organocatalysts can generally be placed in one of two simply defined groups: "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 *α,β*-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*).[9]



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,-dimethyl-1-phenylpropan-1-ol, **19** and is able to acylate the *R*-enantiomer selectively, generating an 81% enantiomeric excess in this example.

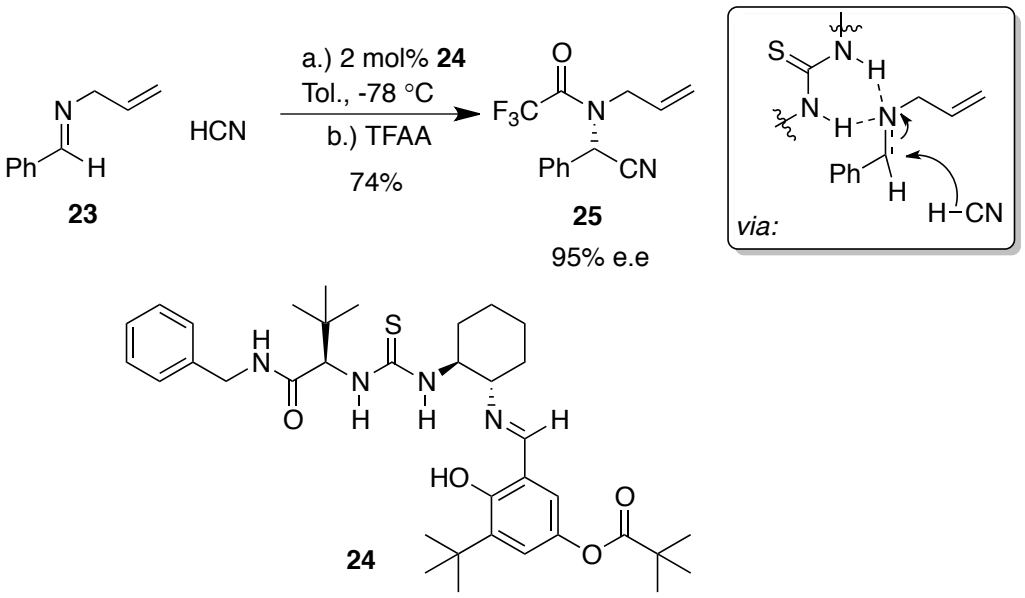


Scheme 8. Vedejs *et al.*'s strategy for the enantioselective acylation of secondary alcohols using chiral phosphine, **21**.

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

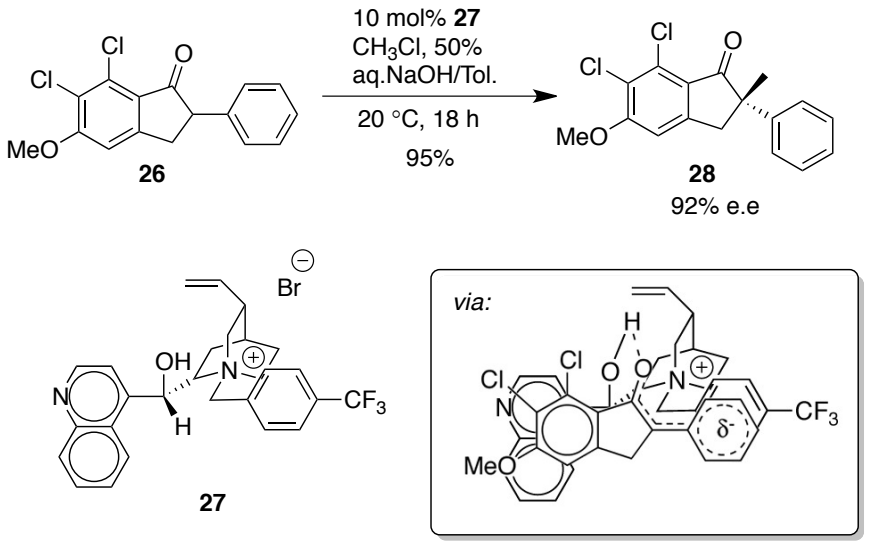
In many cases, non-covalent organocatalysts rely on the formation of hydrogen bonds and/or protonation/deprotonation between the catalyst and the substrate molecules. One such example would be Jacobsen's thiourea catalyst for the asymmetric Strecker reaction.[12] The extensively functionalised chiral thiourea **24** 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**.

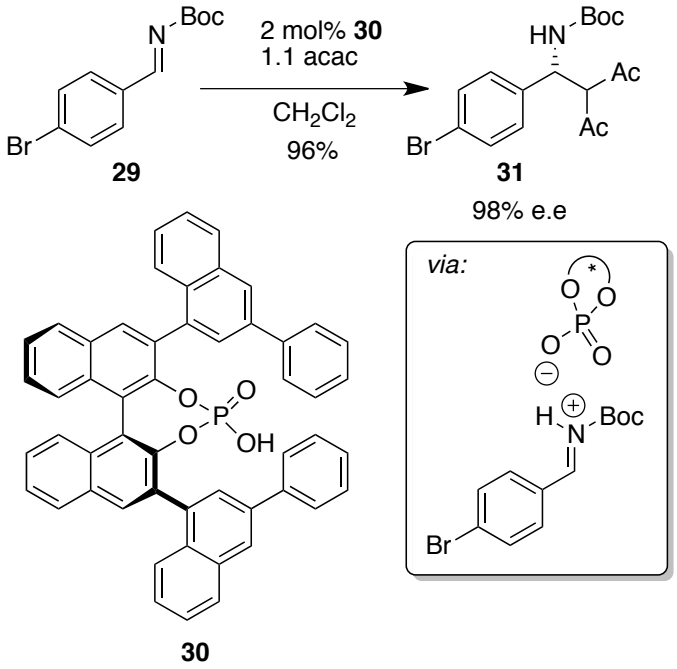
An important class of organic catalysts that can be considered as non-covalent organocatalysts are phase transfer catalysts. Asymmetric phase transfer catalysts are quite remarkable because, as their name suggests, phase transfer catalysts allow for ionic reactants generated in an aqueous phase to cross 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.[13] 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% enatiomeric 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 aldimines catalysed by the chiral BINOL-derived phosphoric acid, **23**.[14] This particularly strong organic acid is likely to protonate the aldimine to form a chiral phosphate-iminium ion pair, leading to the enantioselective nucleophilic addition of deprotonated acetyl acetonate to the *α*-carbon of the aldimine (*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.[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 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.

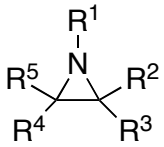
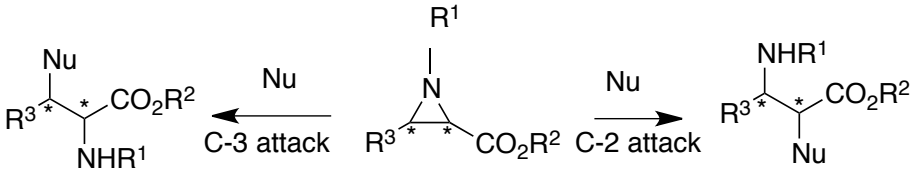


Figure 2. The core structure of aziridine molecules.

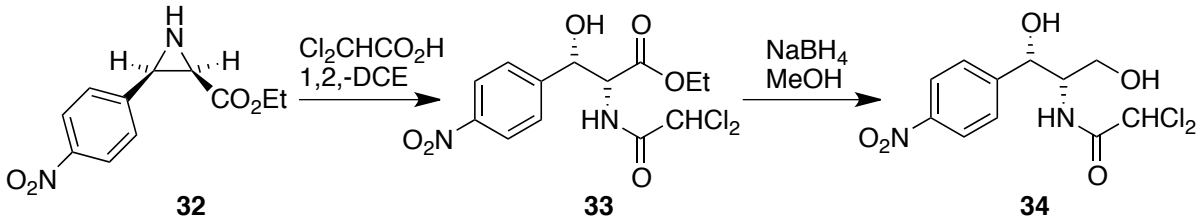
It is this structural feature that makes aziridines highly amenable to ring-opening reactions *via* nucleophilic attack or cycloaddition reactions, both of which result in the cleavage of the C-N bond and are driven by the relieving the molecule of its high ring-

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-functionalistion 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-openning

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 subsesequently 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]

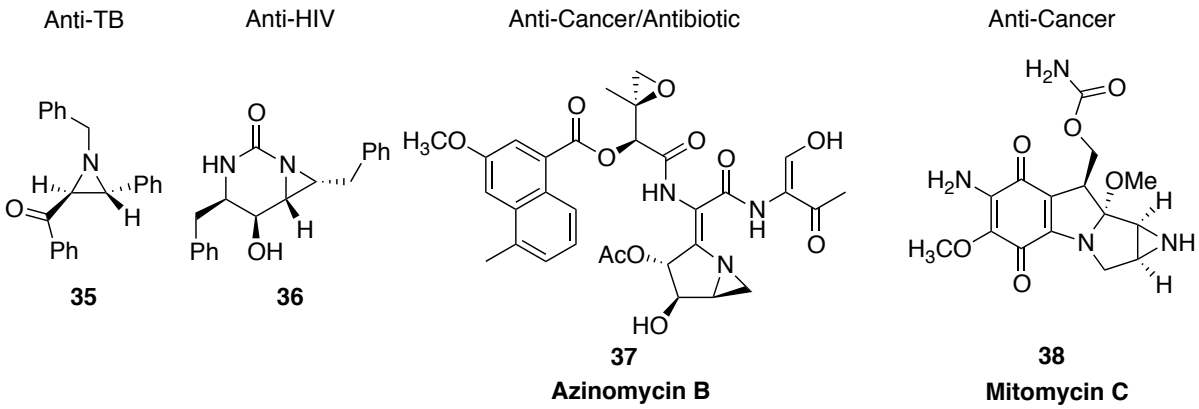


Fig 3. Examples of biologically active aziridines-containing molecules.

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.

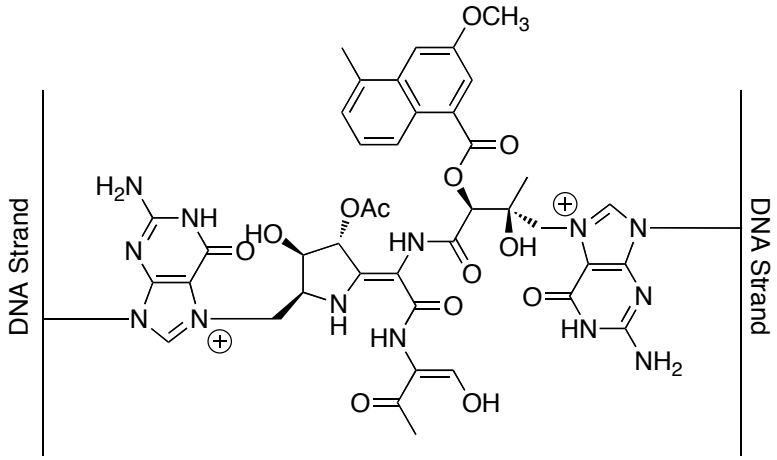


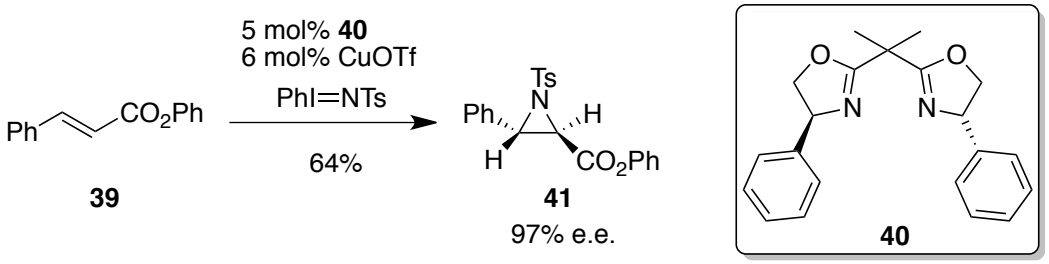
Fig 4. A molecule of **37** cross-linking DNA strands by binding to two guanine residues *via* nucleophilic ring opening of the aziridine and epoxide moieties.[19a-b]

Thus, obtaining aziridines and especially enantiopure chiral aziridines is considered highly important in synthetic organic chemistry.[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.[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.

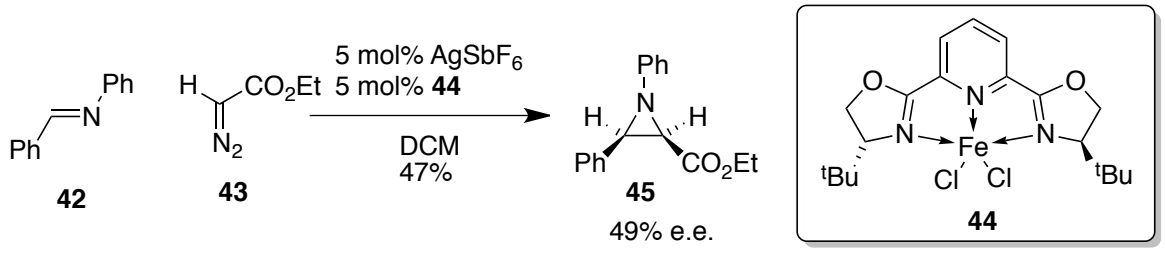
Evans *et al.* reported one of the first asymmetrically catalysed syntheses of an aziridine molecule in 1991 using chiral *bis*(oxazoline) copper catalysts, producing a mixture of the two possible diastereomers, both in moderate enantiomeric excess.[22] In 1993 Using a chiral ligand, **40** in combination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



Scheme 14. An example of Evans's pioneering asymmetrically copper-catalysed aziridinations.

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 *cis*-aziridine. A good example of this class of asymmetric metal catalysed reactions would be a study carried out by Hossain *et al.*, who employed an

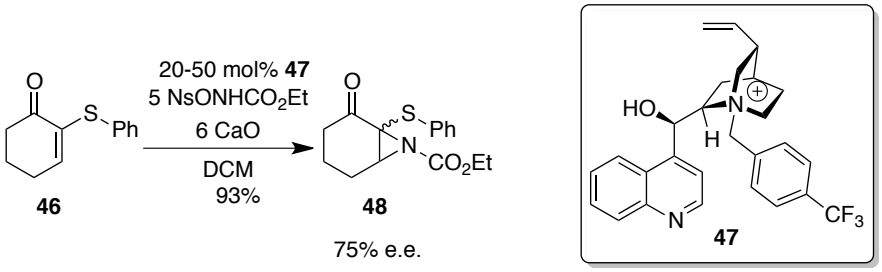
Iron(II)-pybox catalyst, **44**, in combination with silverhexafluoroantimonate(V) as an initiator to mediate an asymmetric aza-Darzens reaction between substituted aldimines and ethyl diazoacetate, affording mainly *cis*-aziridines in up to a 49% enantiomeric excess (*See Scheme 15*).



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.

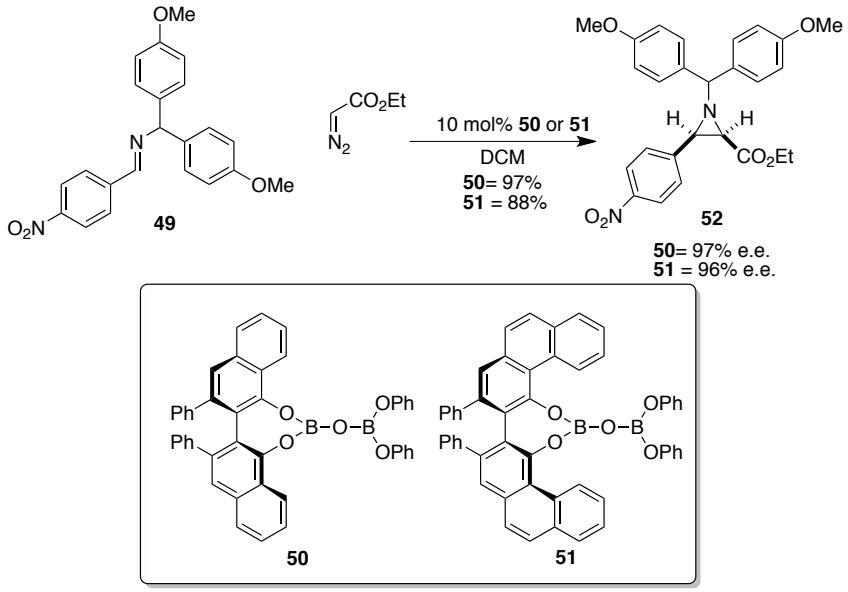
1.2.2 - Asymmetrically Organocatalysed Aziridination

The use of organocatalysts to generate chiral aziridines is a concept that has not been realised until recently.[24] 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.[25] 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% enatiomeric 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 broughtthe 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% enatiomeric excess (*See Scheme 17*), demonstrating the excellent versatility of this catalyst system.



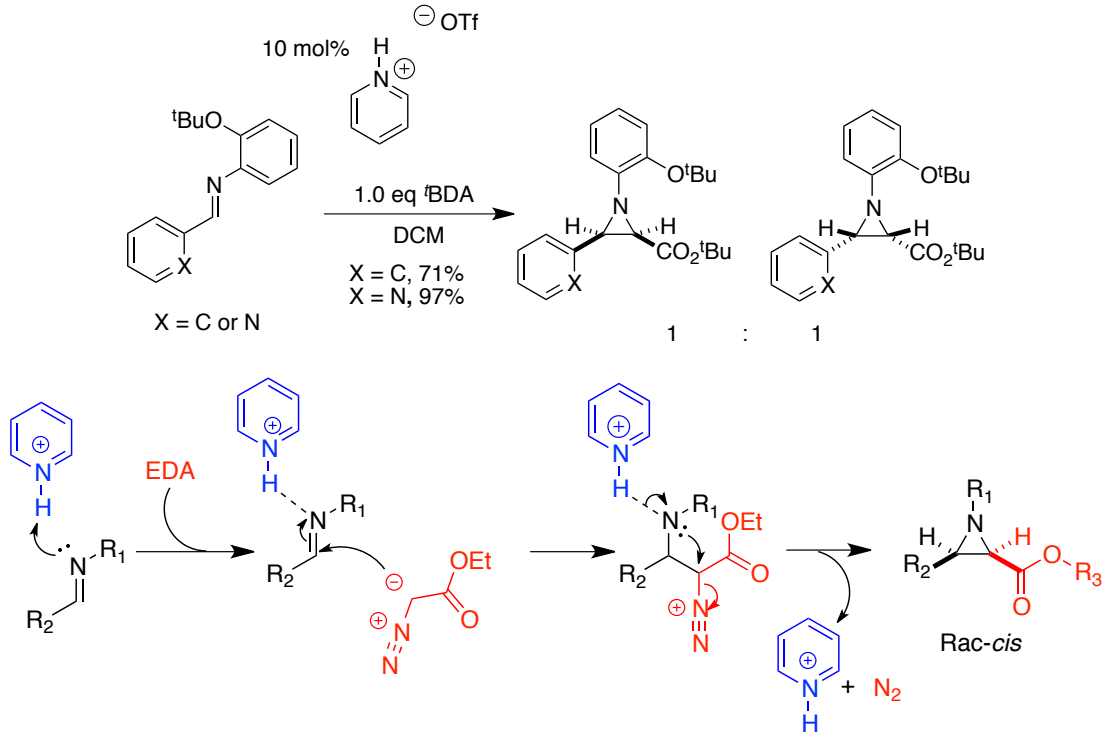
Scheme 17. An optimum example taken from Wulff's work towards asymmetric aziridination mediated by (*S*)-VANOL-derived, **50**, or (*S*)-VAPOL-derived, **51**.

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

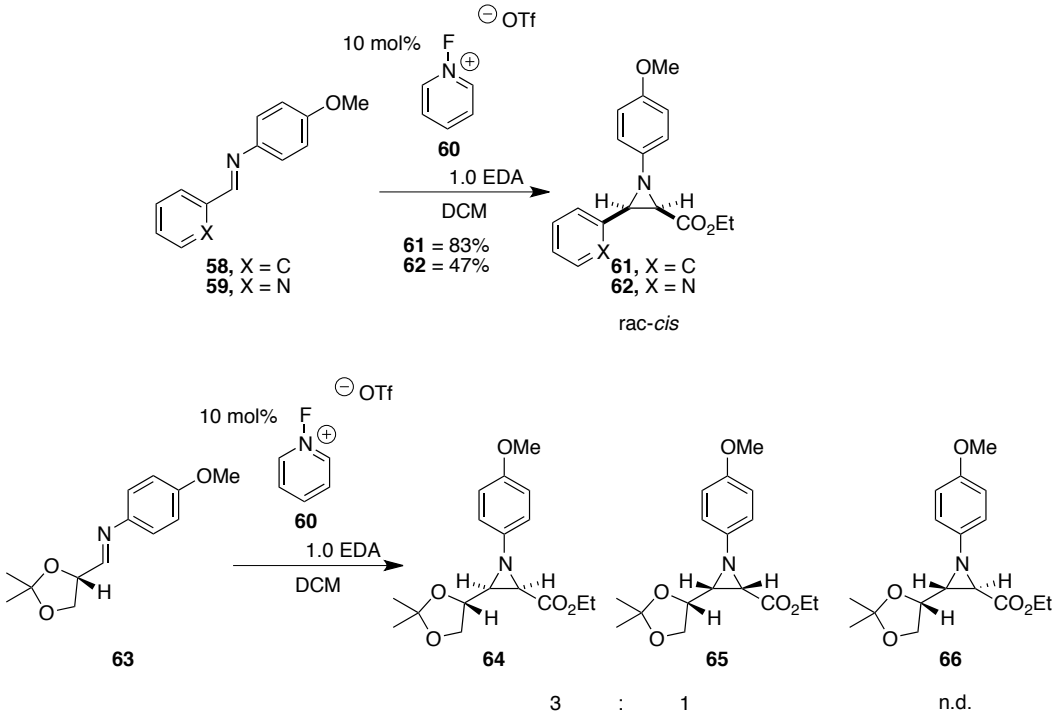
trifluoromethanesulfonate as a Brønsted type acid catalyst (*See Scheme 18*).[29] Noteworthy features of this reaction are that it is extremely mild in comparison with the majority of acid catalysts and that it is exceptionally selective towards the formation of *cis*-aziridines, producing no observable *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.

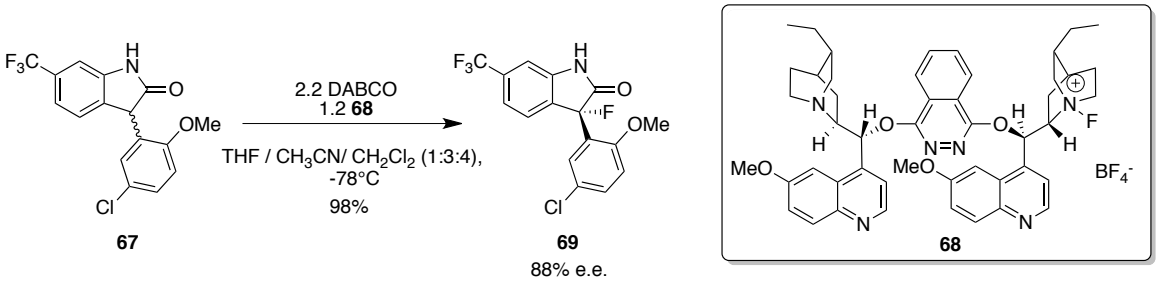
However, during the same period, it was also reported by the Bew group that the very same aza-Darzens aziridinations could be mediated by a catalytic amount of a *N*-fluoropyridinium trifluoromethansulfonate, which incorporated fluoronium as opposed to an acidic proton (*See Scheme 19*).[30] This unprecedented 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*).



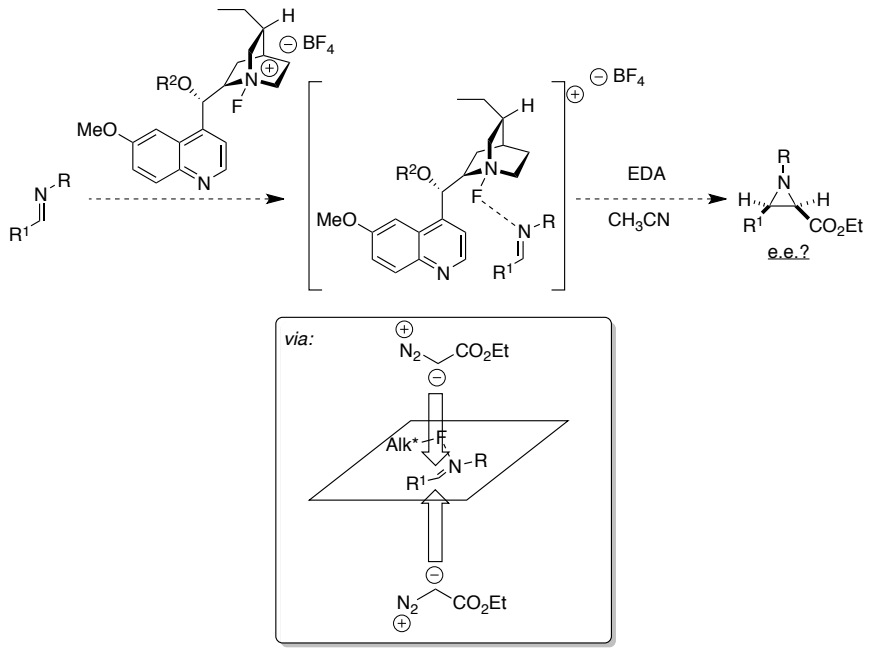
Scheme 19. Above Examples of the Bew group's use of **60** to catalyse the stereoselective aza-Darzens aziridination. Below: An example illustrating the aziridination of **60** with ethyl diazoacetate, mediated by **60** with the preservation of the acetyl moiety in all reaction products.

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.[31] 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-Darens 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

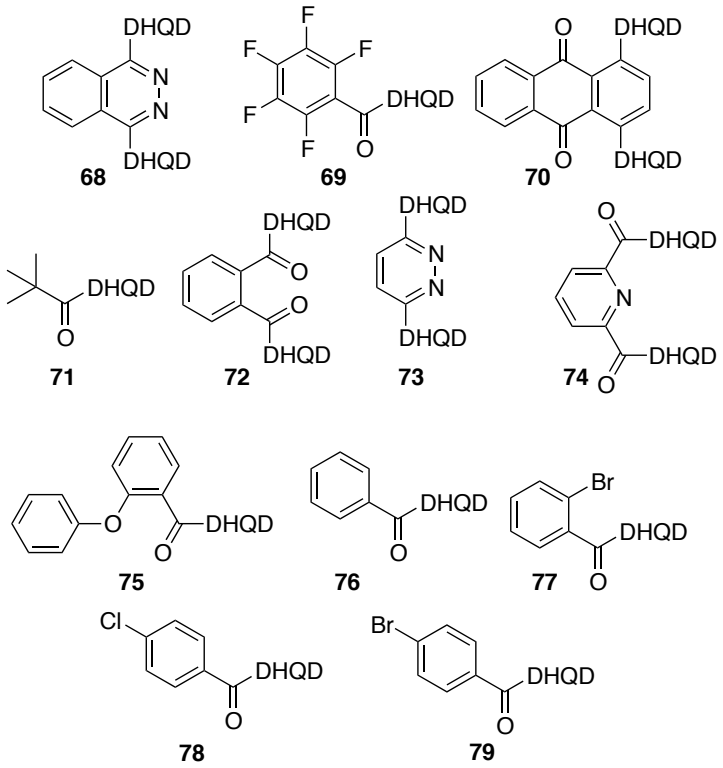
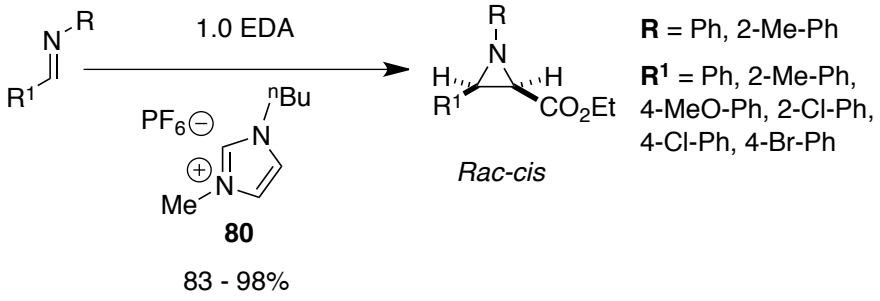


Fig 5. Some proposed Dihydroquinidine-derived alkaloids for use in this study.

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.[33] 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*).[34]



Scheme 22. Xia *et al.*'s use of **80** to solvate and catalyse the aza-Darzens aziridination between aldimines 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]

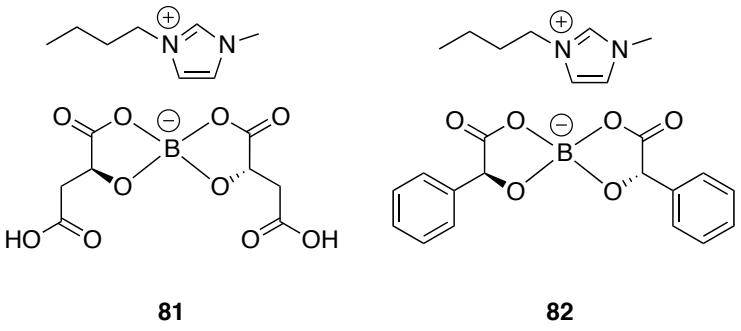
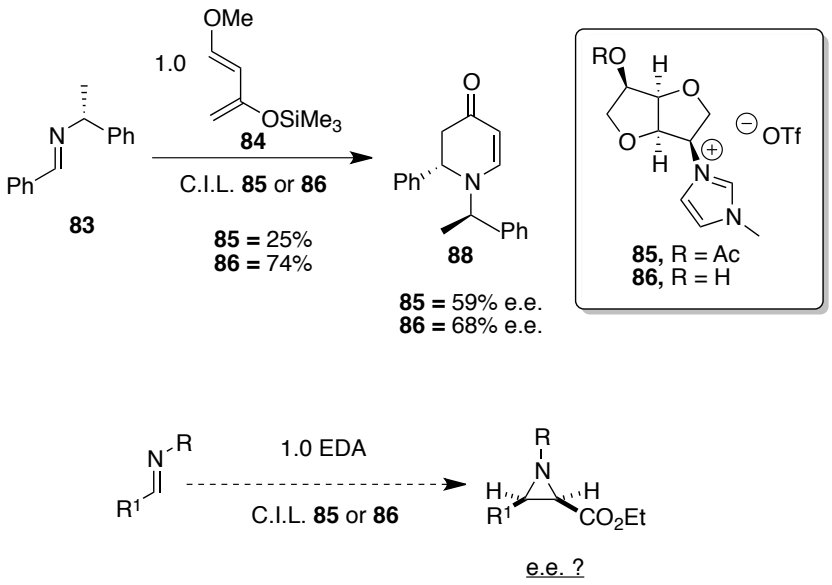


Fig 6. Imidazolium ionic liquids, **81** and **82**, bearing chiral borate anions.

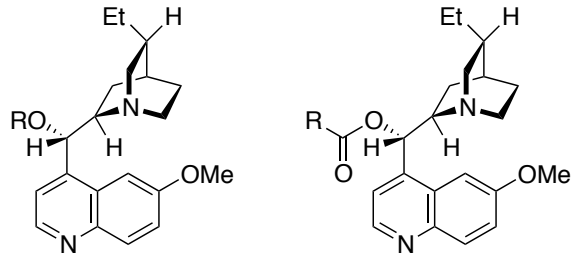
The second strategy focuses on installing chirality directly onto the cation by substituting a chiral moiety onto the imidazolium ring itself. For this purpose we chose an ionic liquid that had already been reported by Vo-Thanh *et al.* and has been successfully been employed by the authors to mediate the asymmetric aza-Diels alder reaction between Danishefsky's diene, **84**, and aldimine, **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**.

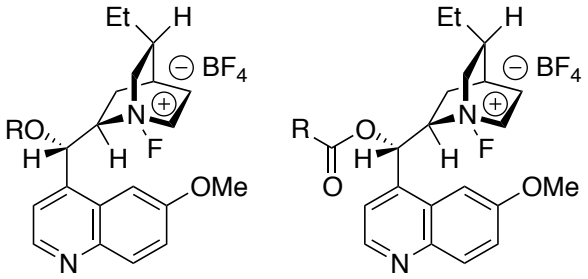
1.4 - Methodology

1.4.1 - Synthesis of *O*-Protected Alkaloid Derivatives



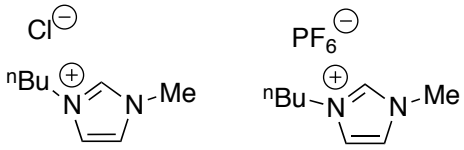
For this study it was necessary to have access to a wide range of Cinchona Alkaloid derivatives. Dihydroquinidine (S enantiomer) was chosen for the initial work for availability reasons. Derivatives were synthesised in accordance with procedures set out by Zhang et al.[37] Alkaloid ester derivatives 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.[38] Addition of sulfuric acid solution is used to precipitate the 1-chloromethyl-4-hydro-1,4-diazoniabicyclo[2.2.2]octane hydrogen sulphate tetrafluoroborate by-product, making the subsequential 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.

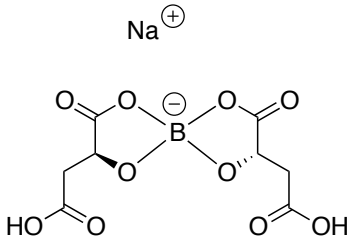
1.4.3 - Preparation of a Symmetrical 1-butyl-3-methylimidazolium Ionic Liquids



87 **80**

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.[39] 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



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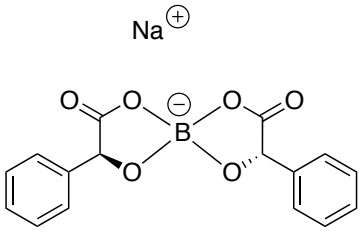

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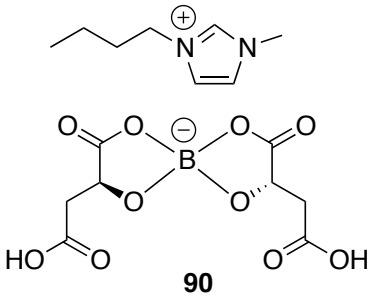
An asymmetric strategy employed was the use of asymmetric ionic liquids bearing a chiral anion. Based on the assumption that the imidazolium acts as a hydrogen bond donor to activate imine substrates, a chiral anion may provide a suitably chiral environment in order to generate an enantiomeric excess from the aza-Darzens aziridination. We chose chiral borate anions for this aim, which is easily of 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



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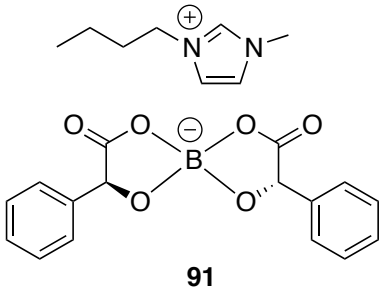
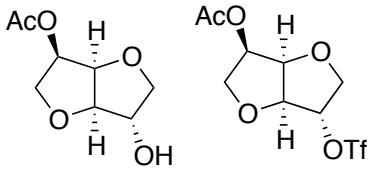


91

1-butyl-3-methylimidazolium borate salts were generated by following procedures set out by Tran *et al.,* invloving 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

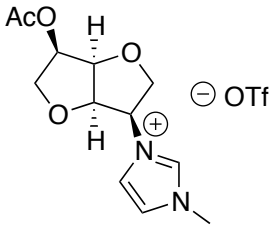
1.4.6 - Isosorbide-Derived Imidazolium Chiral Ionic Liquid: Selective - *O*-protection of the Isosorbide scaffold



92 **93**

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.[41] 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.[42] 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



94

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.[41] An S_N2 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_N2 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.[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-crystalise 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.

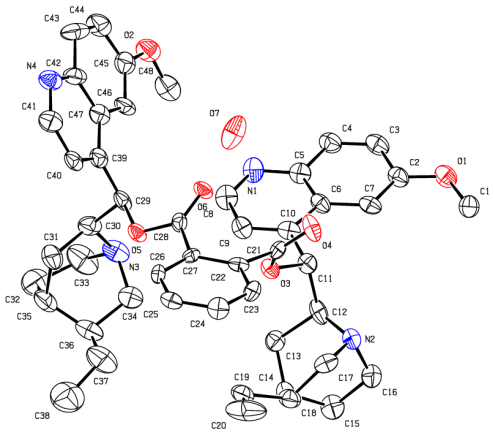


Fig.7 An Ortep representation of the crystals structure of **72**. The hydrogen atoms are omitted for sake of clarity. Thermal ellipsoids are drawn at 50% probability level.

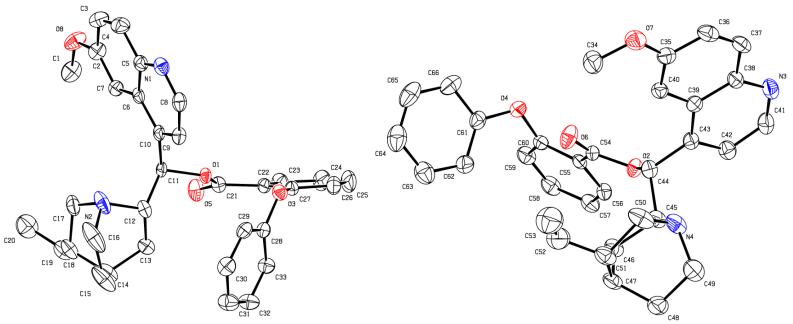


Figure 8. An Ortep representation of two independent molecules of **75**. All Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability level.

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.*).

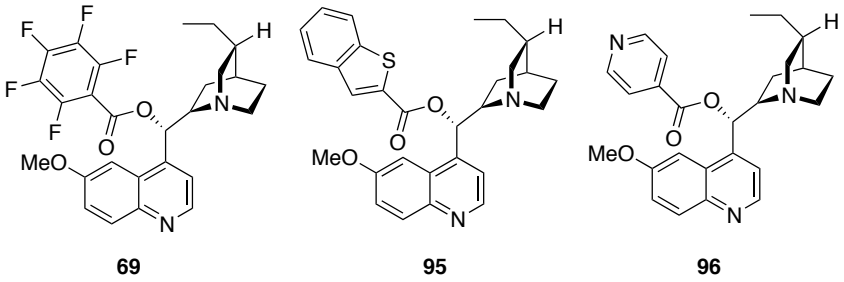


Fig 9. Alkaloid species that were synthesised but not isolated or used further for this study.

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.[44] Instead one equivalent of a fluorinating agent, Selectfluor (1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[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 $[N\text{-}F]^+$ 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 ^{19}F-NMR (*Scheme 24*, *Fig 11)* this was referenced against a solution of **97** in acetonitrile-d^3 (*Scheme 24*, *Fig 10)*.

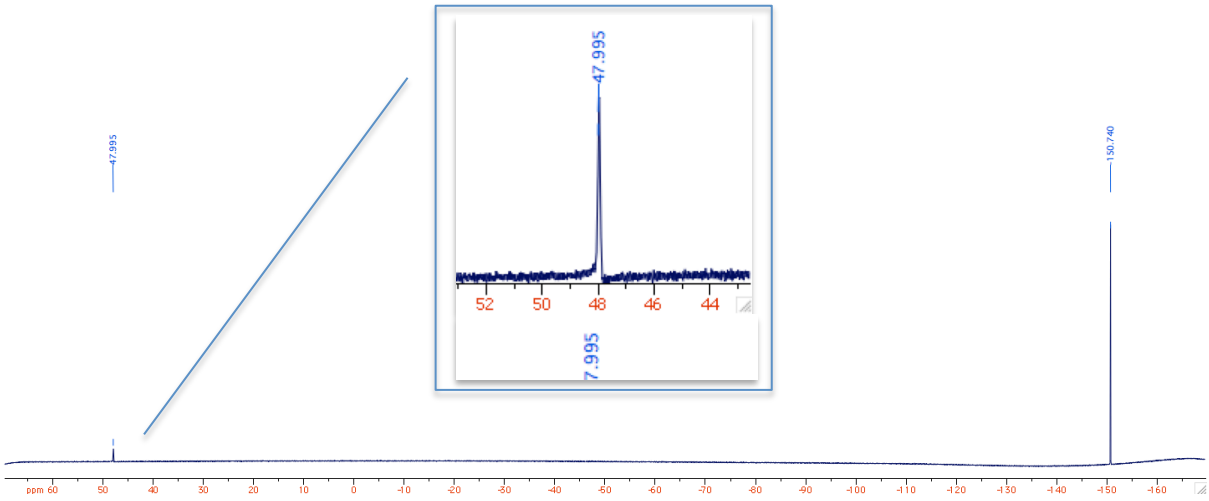
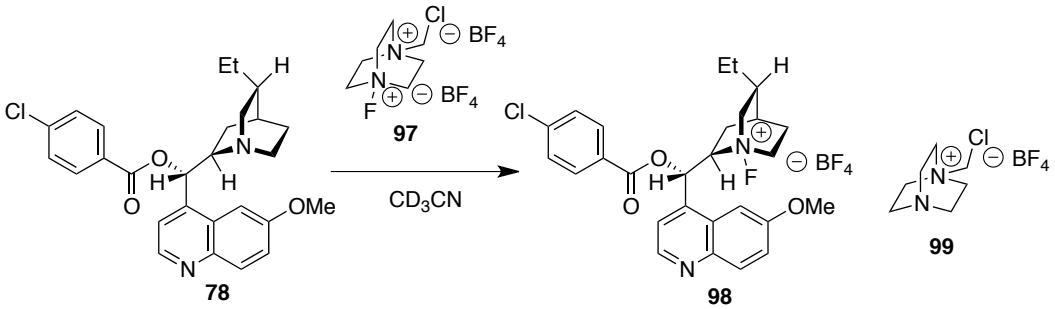


Fig 10. The ^{19}F-NMR of Selectfluor™, **97** in acetonitrile-d^3.



Scheme 24. The reaction of **78** with **97** in CD_3CN in an NMR tube, under ^{19}F-NMR observation.

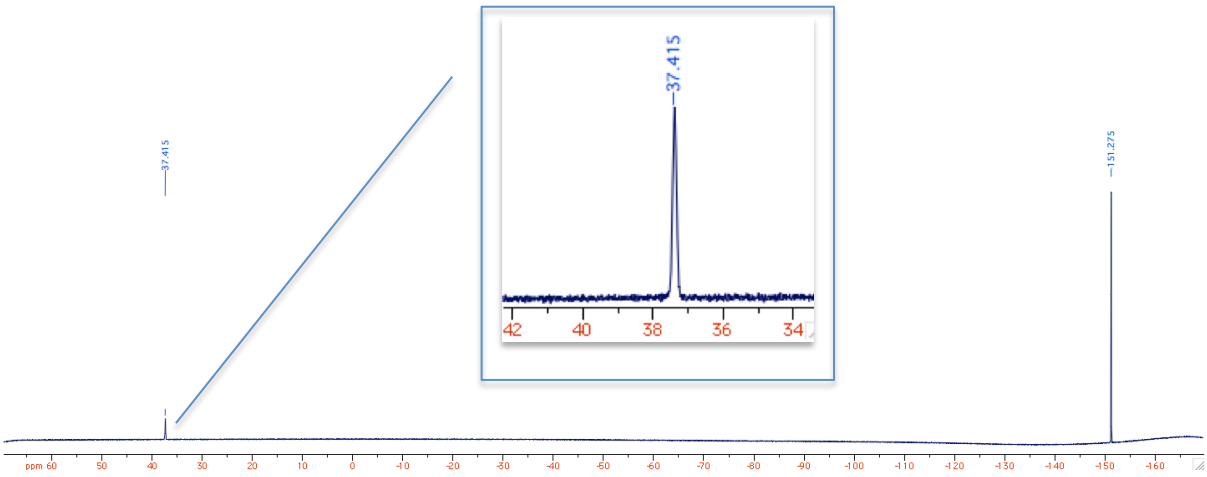


Fig 11. The ^{19}F-NMR of **97** in combination with **78** in acetonitrile-d3.

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.

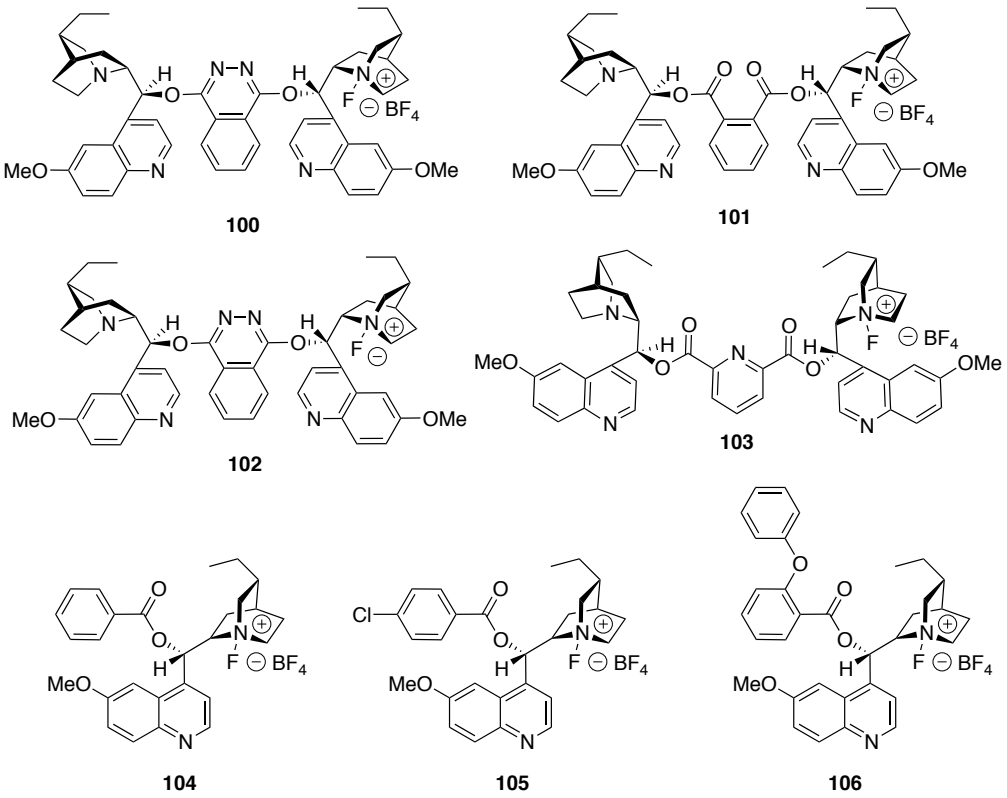
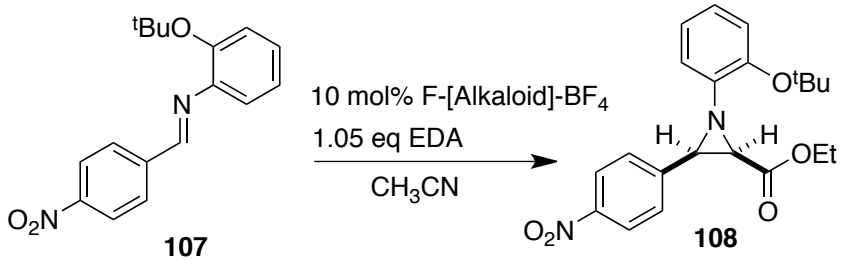


Figure 12. Chiral [N-F]$^+$ catalysts generated for preliminary screening.

Once chiral [N-F]$^+$ species were formed *in situ* by following the procedure set out by Shibata *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 ^{1}H-NMR analysis of the sample.

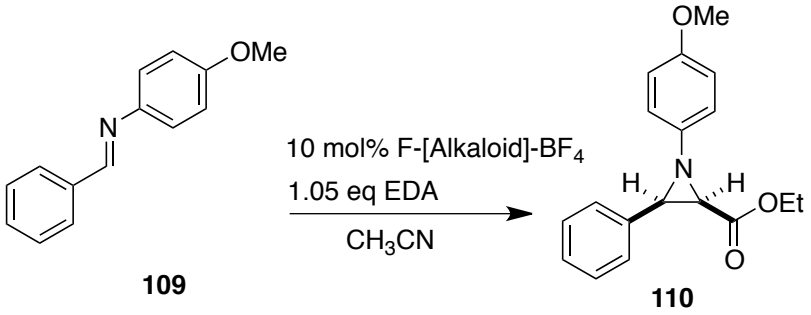


Scheme 25. The aziridination of aldimine **107** and EDA, using fluorinated alkaloid catalysts.

[N-F]$^+$ catalyst[a]	yield (%)	% e.e.
100	23	Racemic[b]
101	33	Racemic[c]
102	8	Racemic[c]
103	0[d]	N/A
104	18	Racemic[c]
105	13	Racemic[c]
106	20	Racemic[c]

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.

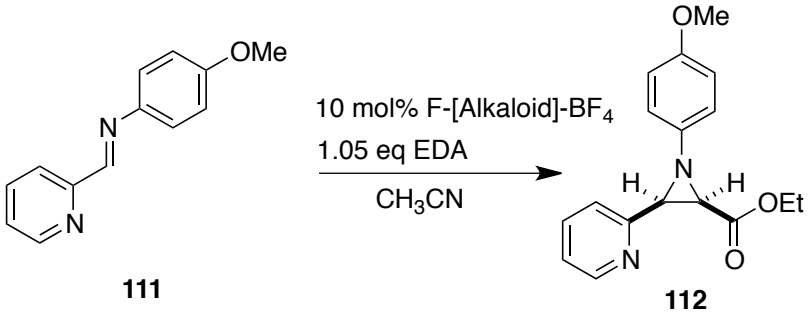
The first screening of the chiral [N-F]$^+$ catalysts involved the transformation of (*E*)-2-Butoxy-*N*-(4-nitrobenzylidene)phenylamine, **107** into aziridine **108** (*See Scheme 25*). **107** was selected due to a bulky, electron-donating *tert*-butoxy group situated *ortho* on the aniline ring, which 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 α-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 ^{i}PrOH, the mixture could be seen to be racemic.



Scheme 26. The aziridination of aldimine **109** and EDA, using fluorinated alkaloid catalysts.

[N-F]$^+$ catalyst[a]	yield (%)	% e.e.
100	5	Racemic[b]
101	8	Racemic[c]
102	0[d]	N/A
103	0[d]	N/A
104	5	Racemic[c]
105	8	Racemic[c]
106	13	Racemic[c]

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 ^{1}H-NMR observation of crude mixture, but not isolated.



Scheme 27. The aziridination of aldimine **111** and EDA, using fluorinated alkaloid catalysts.

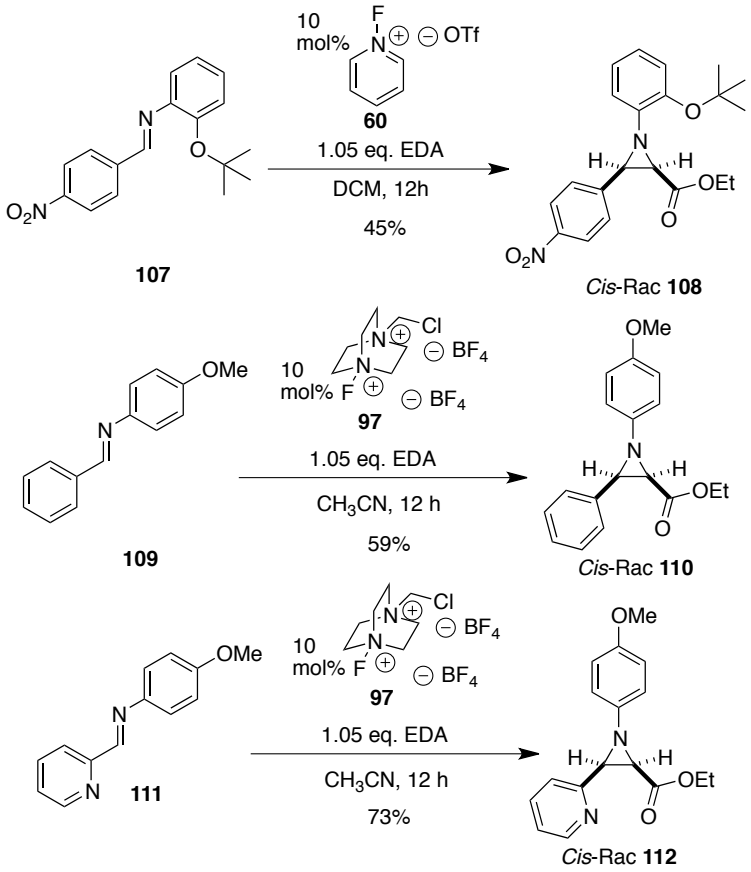
[N-F]$^+$ catalyst[a]	yield (%)	% e.e.
100	47	Racemic[b]
101	52	Racemic[c]
102	38	Racemic[c]
103	15	Racemic[c]
104	47	Racemic[c]
105	49	Racemic[c]
106	54	Racemic[c]

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 ^{i}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 ^{i}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**.

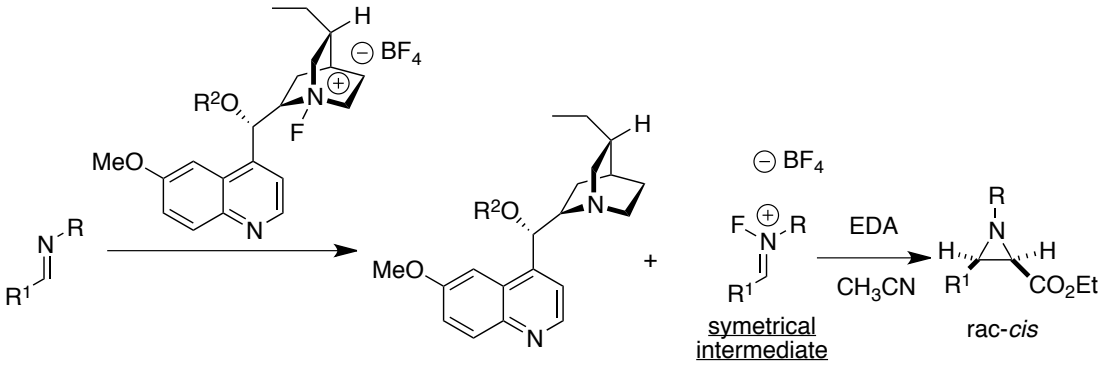


Scheme 28. Aziridination reactions mediated by achiral **60** or **97**.

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 trifluoromethanesulfonate, **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.

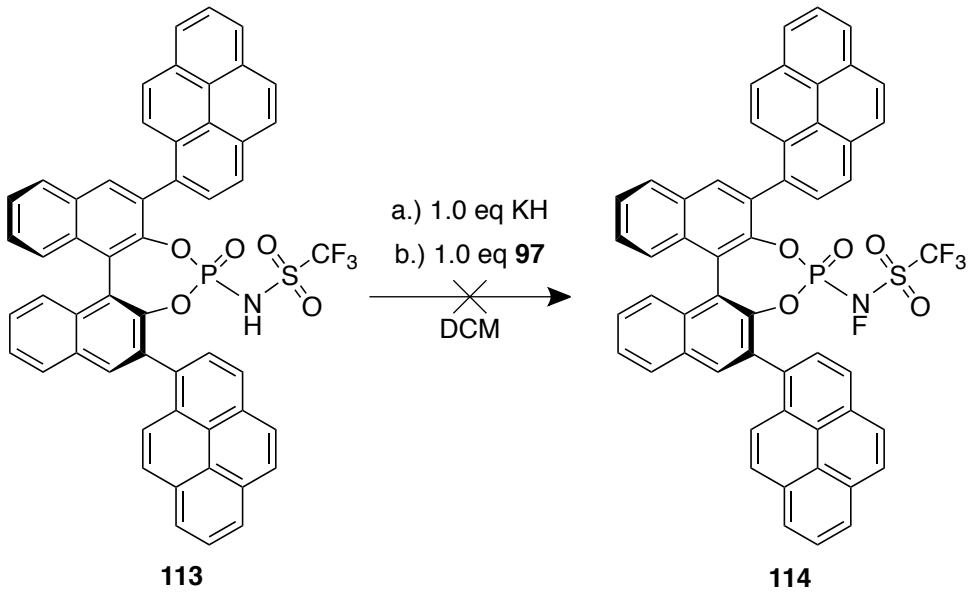
Upon further consideration of the mechanism of these reactions it is possible to hypothesise a probable cause for the formation of racemic aziridine products. As aforementioned, this study assumes the formation of a complex between catalyst and substrate, forming a chiral adduct and biasing ethyl diazoacetate to approach one face of the activated imine more frequently than from the other. However, it is entirely possible that the activation of the aldimine 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 $[N\text{-}F]^+$ alkaloid reagents.

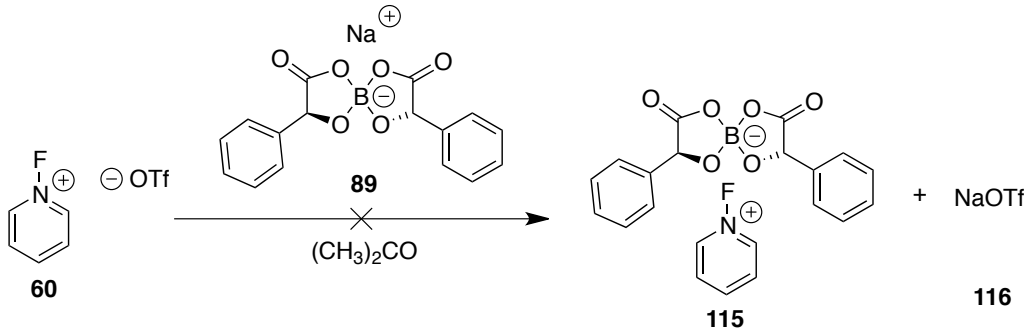
In light of this problem, it is possible to envisage two possible strategies that would overcome this hurdle: 1) Use a neutral fluoronium source, leading to the formation of a chiral ion-pair between catalyst and substrate. 2) Use an F^+ salt bearing a chiral anion.

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, ^{1}H-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*).



Scheme 30. The attempted *N*-fluorination of phosphoramide, **113**.

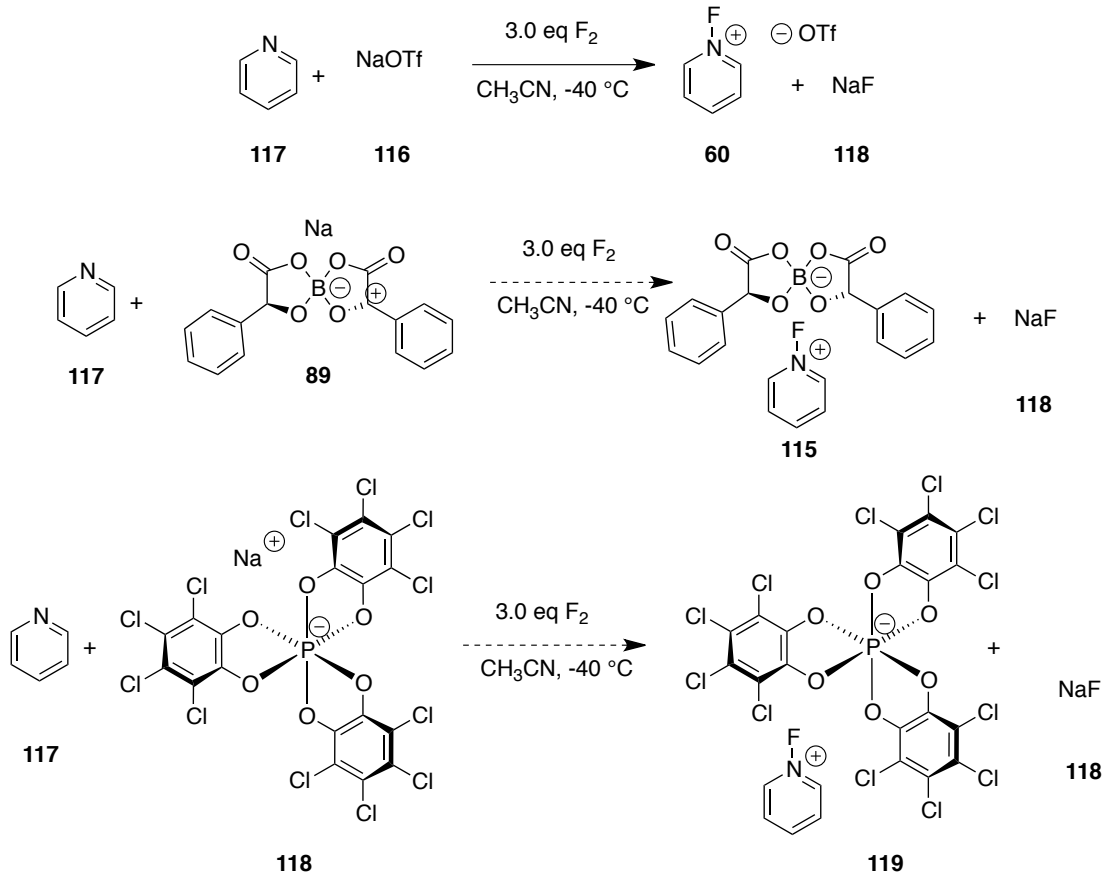
Attempts were also made to generate an [N-F]$^+$ salt containing a chiral anion. Chiral sodium borate salts **90** and **91** had already been synthesised for use in synthesising chiral ionic liquids and an ion metathesis between Selectfluor, **60** and **89** in acetone was attempted (*See Scheme 31*). 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**.



Scheme 31. The attempted ion metathesis between **60** and **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

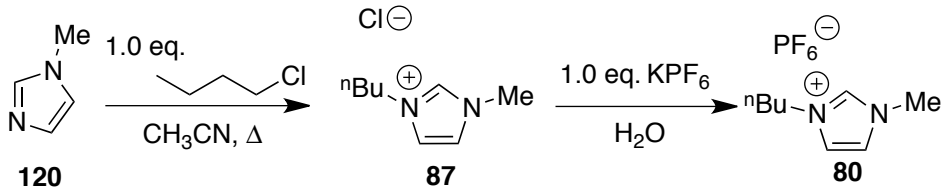
involves the reaction of pyridine with elemental fluorine at low temperatures to yield *N*-fluoropyridinium fluoride, which is not stable above -40 °C. The fluoride salt then reacts with a sodium salt of the desired anion, which is either added or present in the initial mixture in the case of a one-pot reaction. Umemoto *et al.* reportedly generated in excess of 60 different *N*-fluoropyridinium salts incorporating 11 various anions including sulphonates, phosphates and perchoroate, 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 $[N\text{-}F]^+$ salt, **115**. There is a tremendous scope for the number of chiral anions that could be utilised for this aim, for example the chiral Δ-tris(tetrachlorobenzene diolato)phosphate(V) (Δ-TRISPHAT), the sodium salt of which is easily obtainable from commercially available [cinchonidinium][Δ-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

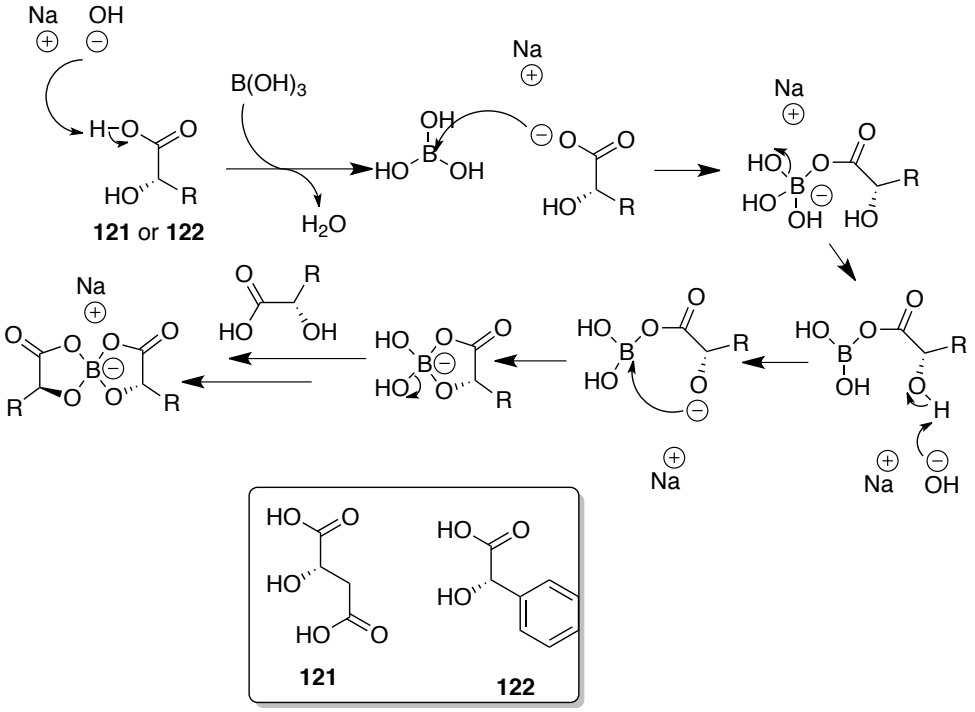


Scheme 33. The synthesis of **87** and **88**

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**.[39] 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.

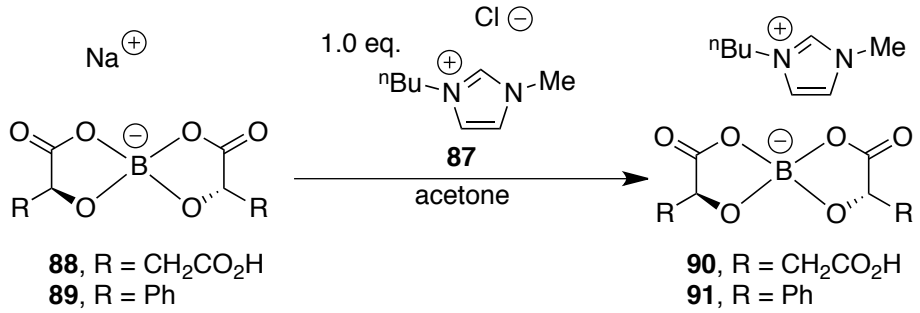
2.6 - Preparation of Chiral 1-Butyl-3-methylimidazolium Ionic Liquids: Synthesis of the Chiral Borate Anions

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*).[40] 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.

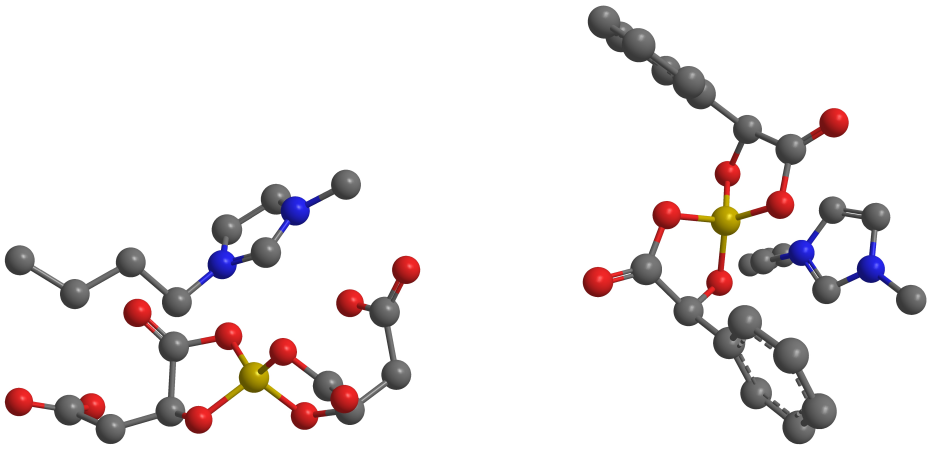
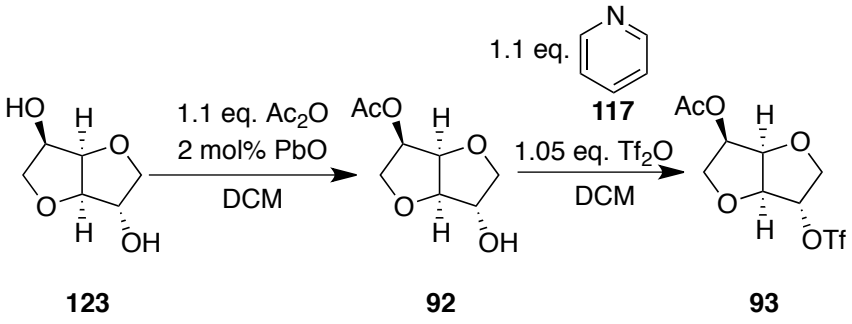


Fig. 13 Energy-minimised 3D representations of chiral ionic liquids **90** (left) and **91** (right) rendered using Cambridgesoft Chem3D software (hydrogen atoms and lone electron-pairs have been omitted for simplicity).

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*).

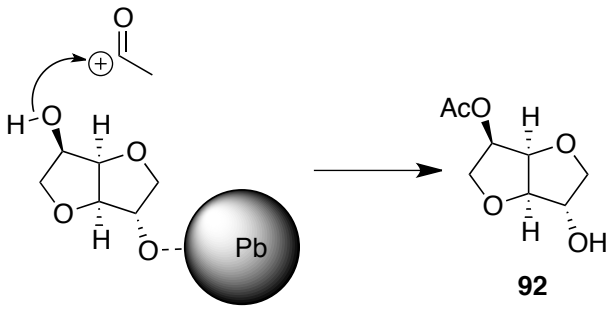
2.8 - Isosorbide-Derived Imidazolium Chiral Ionic Liquid: Selective *O*-Protection of the Isosorbide Scaffold



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

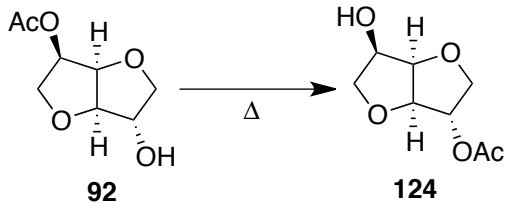
As reported by Stoss *et al.,* selective protection of isosorbide, **123**, was carried out by a lead(II)oxide mediated reaction of acetic anhydride (*See Scheme 36*).[42] It is likely that

the relatively large lead centre coordinates to the *exo* alcoholic oxygen, effectively blocking it from acetylation (*See Scheme 37*).



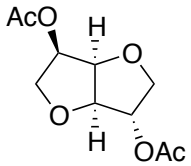
Scheme 37. An illustration of how a lead cation blocks the *exo* oxygen of **123** from acetylation, leading to the selective formation of **93**.

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.

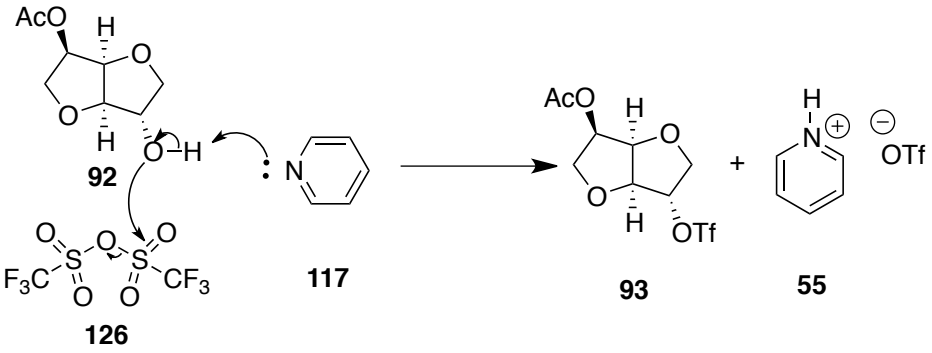
92 was purified on a chromatography column using 5% methanol in dichloromethane to remove minor traces of the *bis*-acetylated by-product, **125** (*See Fig* 14) and was ready for further steps.



125

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.

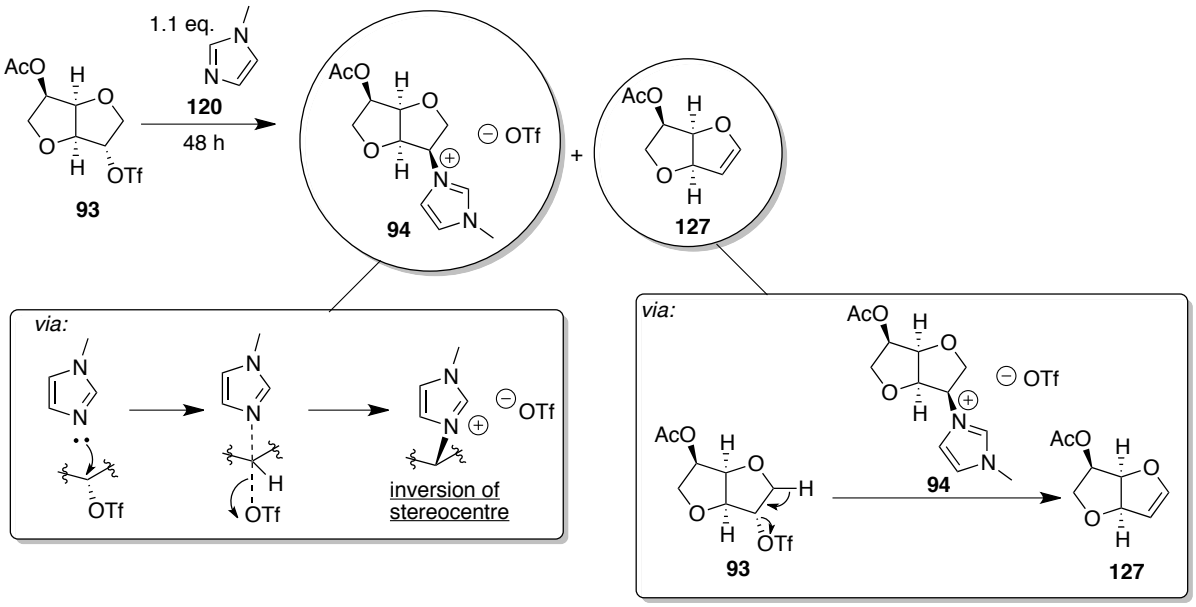


Scheme 39. The mechanism by which the remaining alcohol group of **92** is replaced with trifluoromethanesulfonate.

2.9 - Isosorbide-Derived Imidazolium Chiral Ionic Liquid: Nucleophilic Substitution of the Trifluoromethanesulfonate Leaving Group

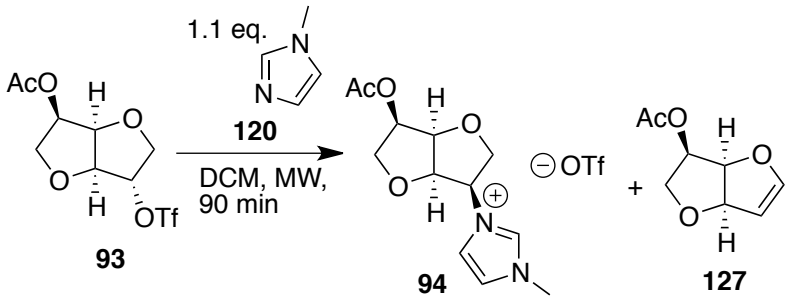
Installation of the imidazolium functionality onto the imidazolium scaffold was also carried out according to a procedure set out by Vo-Thanh *et al.,* involving the mild heating (40 °C) of **93** in 1-methylimidazolium, **120** for 48 h.[41] Compound **93** undergoes

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 leu* 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**.

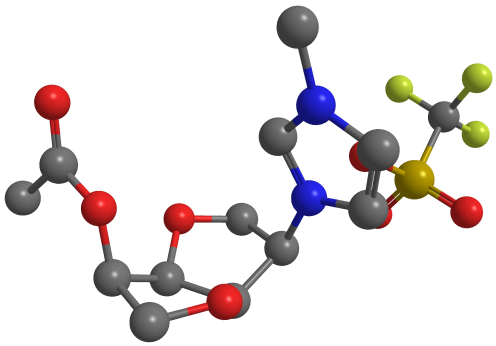


Fig. 15 Energy-minimised 3D representation of chiral ionic liquid **94** rendered using Cambridgesoft Chem3D software (hydrogen atoms and lone electron-pairs have been omitted for simplicity).

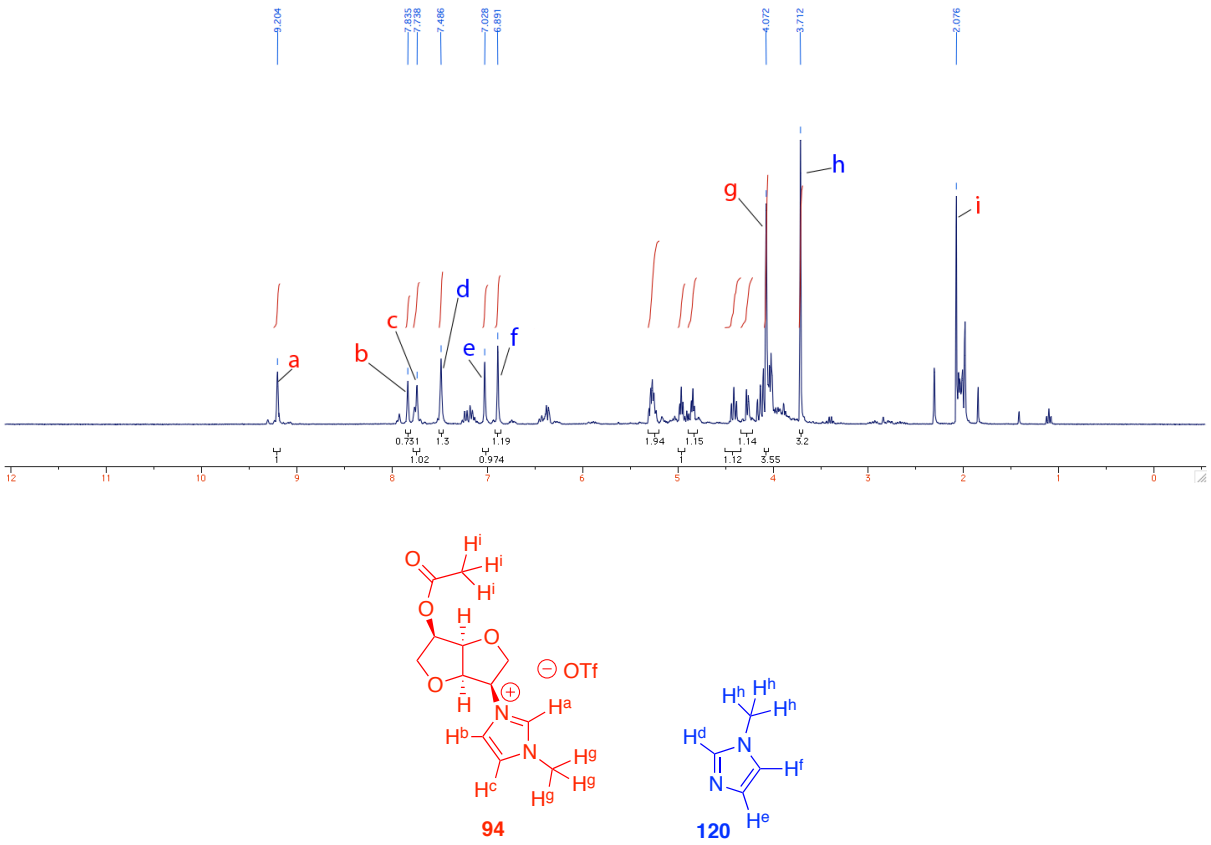
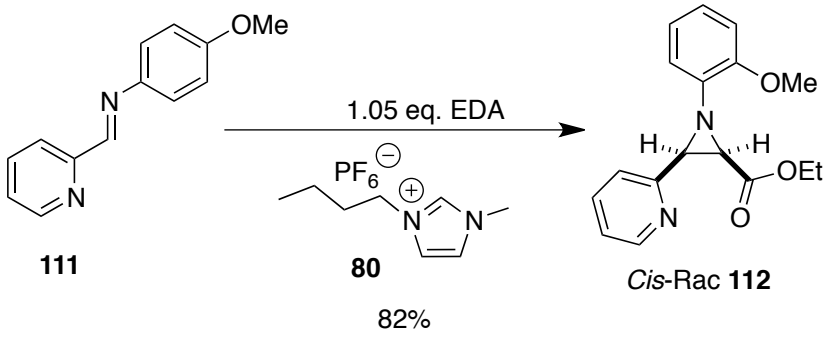


Fig 16. The ^{1}H-NMR of the crude reaction mixture containing **94** and **120** in acetone-d^{6} (anotated and colour-coded)

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 thre 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**.

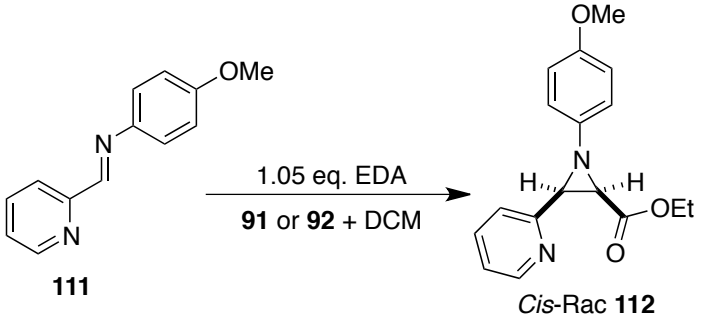
2.10 - Aziridination Mediated by Imidazolium Ionic Liquid Catalysts - Results

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.[34] 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, $[\alpha]^{20}_{D} = 0$ (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 ^{i}PrOH, in mixture could be observed to be racemic.

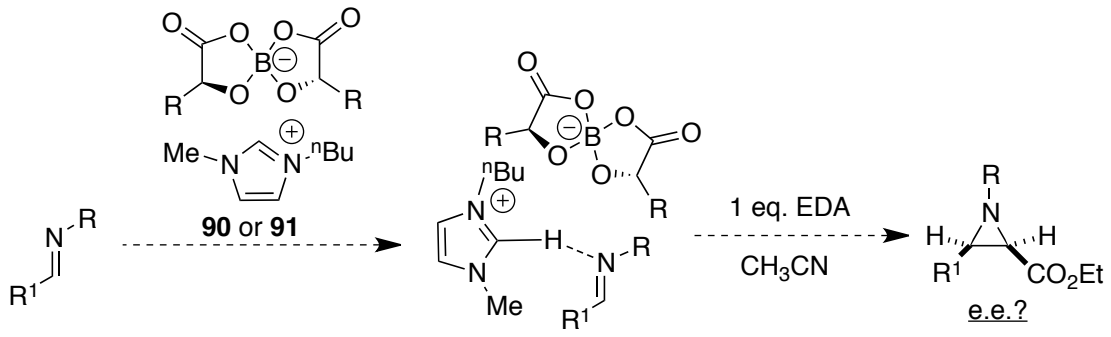


Scheme 43. The aziridination of aldimine **111** mediated by **91** or **92**.

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

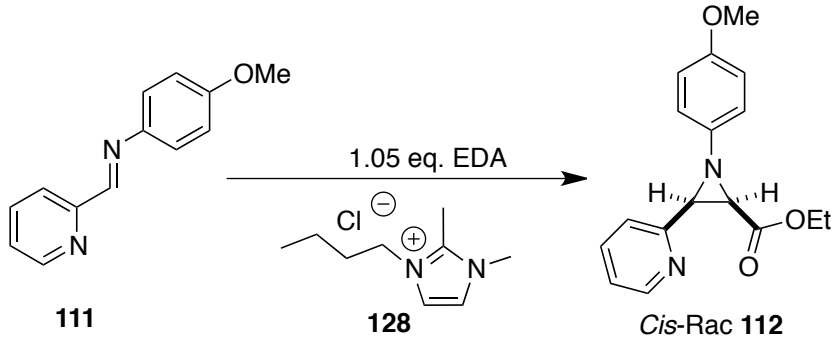
It was hypothesised that **90** and **91** would behave as Brønsted acids when activating aldimine substrates (*See Scheme 44*), either hydrogen bonding to or protonating the lone pair of the imine, the closely coordinated chiral anions were then intended to induce chirality upon addition of the nucleophilic 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 aldimine 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 aldimines and diazoacetate, future studies should therefore concern the purification of this liquid catalyst and its application to that end.

3 Experimental

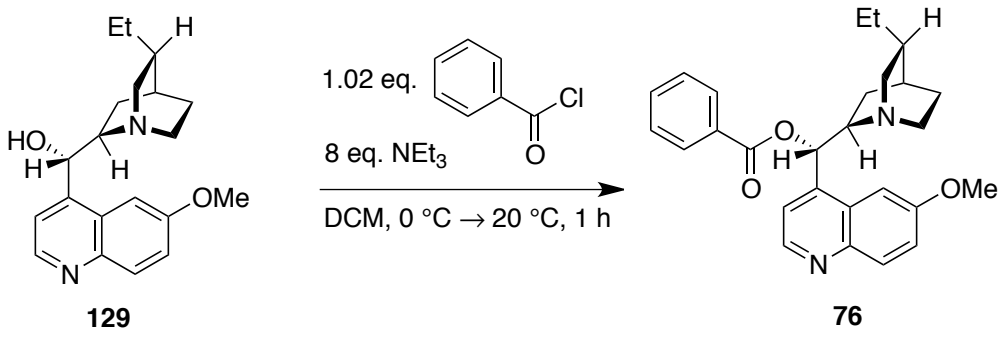
General

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 $KMnO_4$, 10 g K_2CO_3, 2.5 mL of aqueous 2 M NaOH and 150 mL of de-ionised water.

Characterisation

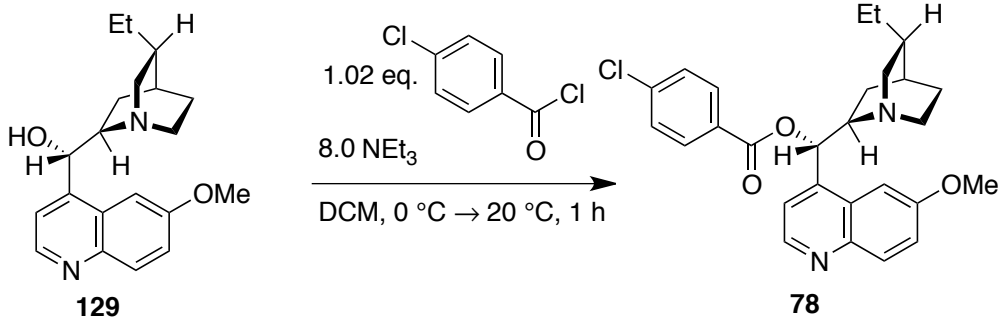
Infrared spectra were recorded using a Perkin Elmer 1720 FTIR spectrometer. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Bruker 270 or 300 MHz, Oxford 300 or 400 MHz machines and samples are prepared as solutions of $CDCl_3$ unless otherwise stated. Chemical shifts (δ) are reported in 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-*O*-dihydroquinidine (76).[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 °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 hydrogencarbonate solution (20 ml) and then water (20 ml). The solvent was removed *in vacuo* to yield an off-white solid foam. This was recrystalised from the minimum amount of warm methanol to yield **76** (2.94 g, 6.83 mmol, 94 % yield) as thick colourless crystals. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.69 (d, 1H, Ar*H*, *J* = 4.51 Hz), 8.08 (d, 2H, Ar*H*, *2J* = 8.10 Hz), 7.99 (d, 1H, Ar*H*, *J* = 9.22 Hz), 7.53 (d, 2H, Ar*H*, *J* = 3.54 Hz), 7.45-7.40 (m, 3H, Ar*H*), 7.34 (dd, 1H, ArH, *J* = 9.15 Hz, *J* = 2.08 Hz), 6.82 (d, 1H, COOC*H*, *J* = 6.67 Hz), 3.95 (s, 3H, OCH_3), 3.40 (q, 1H, COOCHC*H*N$(CH_2)_2$, *J* = 8.00 Hz), 2.98-2.71 (m, 4H, CHN$(CH_2)_2$), 1.93 (t, 1H, alkyl, *J* = 11.16 Hz), 1.72 (s, 1H, alkyl), 1.61-1.38 (m, 6H, alkyl), 0.86 (t, 3H, CH_2CH_3, *J* = 6.32 Hz)

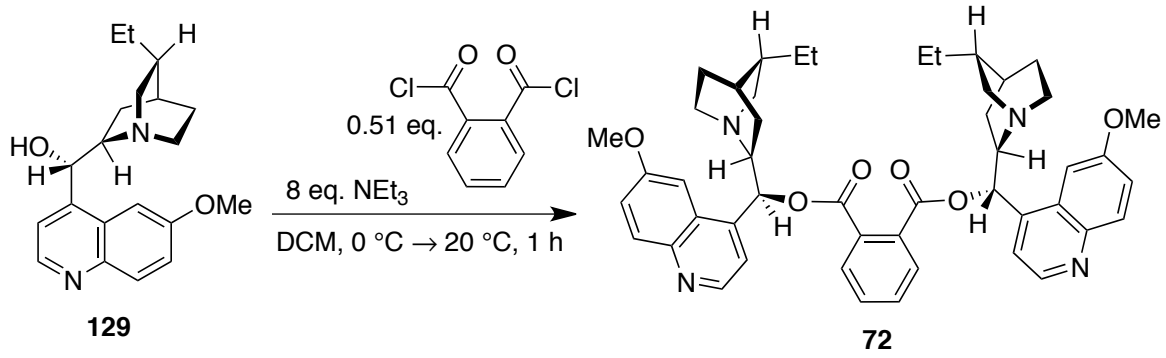
3.2 - Synthesis of *para*-Chlorobenzoyl-*O*-dihydroquinidine (78).[37]



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 °C to give a

colourless solution. *para*-chlorobenzoyl 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 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 *in vacuo* to yield an off-white solid foam. This was recrystalised 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, $CDCl_3$): δ 8.65 (d, 1H, Ar*H*, *J* = 4.54 Hz), 7.95 (dq, 3H, Ar*H*, *J* = 8.78 Hz, *J* = 2.11 Hz), 7.41-7.29 (m, 5H, Ar*H*), 6.65 (d, 1H, COOC*H*, *J* = 7.36 Hz), 3.90 (s, 3H, OCH_3), 3.34 (q, 1H, COOCHC*H*N$(CH_2)_2$, *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_2CH_3, *J* = 7.15 Hz). ^{13}C NMR (400MHz, $CDCl_3$): δ 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 $(EI)^+$ *m/z* 487.1 $(M+Na^+)$

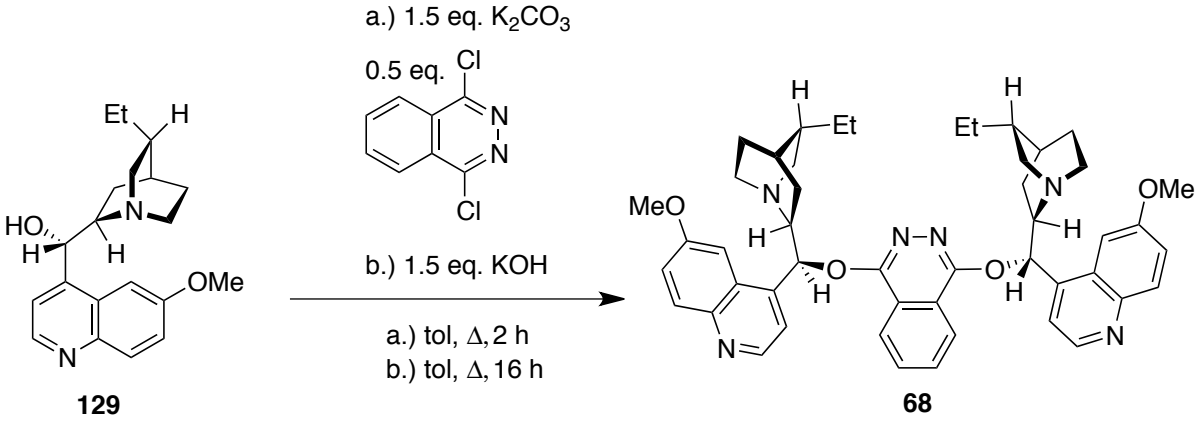
3.3 - Synthesis of 1,2-(*bis-O*-dihydroquinidinyl) Phthalate (72).[37]



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 °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 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 *in vacuo* to yield an off-white solid foam. This was recrystalised 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, $CDCl_3$): δ 8.73 (d, 2H, Ar*H*, *J* = 4.55 Hz), 7.99 (d, 2H, Ar*H*, *J* = 9.21 Hz), 7.72 (dd, 2H, Ar*H*, *J* = 5.67 Hz, *J* = 3.32 Hz), 7.58

(dd, 2H, Ar*H*, *J* = 5.71 Hz, *J* = 3.33 Hz), 7.46-7.44 (m, 2H, Ar*H*), 7.34 (td, 4H, Ar*H*, *J* = 7.21 Hz, *J* = 2.59 Hz), 6.65-6.58 (m, 2H, COOC*H*), 3.92 (s, 6H, OCH_3), 2.61 (q, 2H, COOCHC*H*N$(CH_2)_2$, *J* = 8.00 Hz), 2.73-2.54 (m, 8H, CHN(C$H_2)_2$), 3.21-3.18 (m, 2H, alkyl), 1.48-1.20 (m, 14H, alkyl), 0.75 (t, 3H, CH_2CH_3, *J* = 6.90Hz). ^{13}C NMR (300MHz, $CDCl_3$): 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 ($M+H^+$)

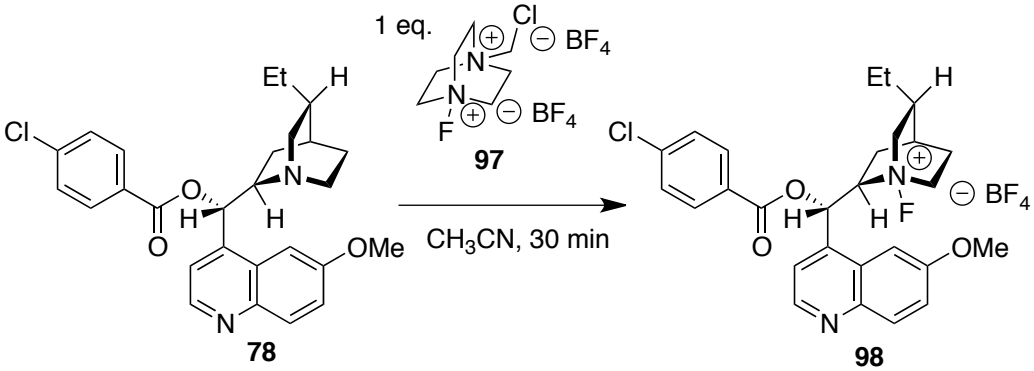
3.4 - Synthesis of *bis-O*-Dihydroquinidinylphthalazine (68).[37]



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 recrystalised 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, Ar*H*, *J* = 4.53 Hz), 8.31 (dd, 2H, Ar*H*, *J* = 6.15 Hz, *J* = 3.26 Hz), 7.98 (d, 2H, Ar*H*, *J* = 9.21 Hz), 7.92 (dd, 2H, Ar*H*, *J* = 6.11 Hz, *J* = 3.29 Hz), 7.55 (d, 2H, Ar*H*, *J* = 2.66), 7.43 (d, 2H, Ar*H*, *J* = 4.57 Hz), 7.35 (dd, 2H, Ar*H*, *J* = 9.21, *J* = 2.68), 6.97 (d, 2H, COOC*H*, *J* = 6.35 Hz), 3.89 (s, 6H, OCH_3), 2.76-2.67 (m, 8H, CHN(CH_2)$_2$, 2.00-1.92 (m, 2H, alkyl) 1.69 (m, 2H, alkyl), 156-1.37 (m, 12H, alkyl), 0.79 (t, 6H, CH_2CH_3, *J* = 7.20Hz). ^{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, 50.17, 37.64, 27.50, 26.50, 25.53, 23.69, 12.09. MS $(EI)^+$ *m/z* 779.6 $(M+H^+)$

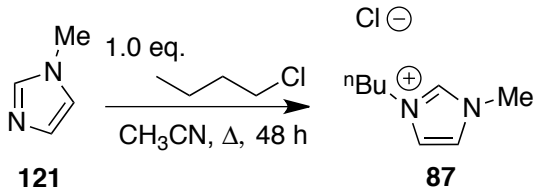
3.5 - Synthesis of *para*-Chlorobenzoyl-*O*-(*N*-fluorodihydroquinidine tetrafluoroborate) (98).[38]



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, Ar*H*, *J* = 4.5 Hz), 7.70 (d, 2H, Ar*H*, *J* = 8.59 Hz), 8.07 (d, 1H,

Ar*H*, *J* = 9.24 Hz), 7.88 (d, 1H, Ar*H*, *J* = 4.53 Hz), 7.70 (d, 1H, Ar*H*, *J* = 8.62 Hz), 7.62 (s, 1H, Ar*H*), 7.53 (dd, 1H, Ar*H*, *J* = 9.25 Hz, *J* = 2.60 Hz), 7.41 (d, 1H, COOC*H*, *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, OCH_3), 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, CH_2CH$_3$, *J* = 7.53 Hz), 0.98 (t, 3H, CH$_2$CH_3, *J* = 7.41 Hz. ^{19}F NMR (270 MHz, CD$_3$CN): δ 37.41 (1F, [N-*F*]$^+$), -151.27 (4F, BF_4^-) MS (EI)$^+$ *m/z* 483.1 (M - BF$_4^-$).

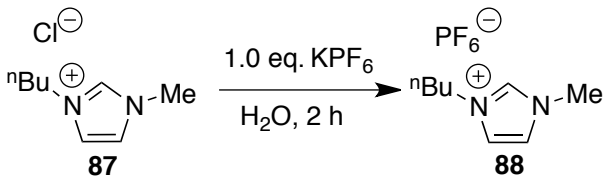
3.6 - Synthesis of 1-Butyl-3-methylimidazolium chloride (87).[39]



121 **87**

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. ^{1}H NMR (300MHz, CDCl$_3$): δ 10.58 (s, 1H, NC*H*N), 7.87 (t, 1H, N$^+$C*H*CHN, *J* = 1.70 Hz), 7.81 (t, 1H, N$^+$CHC*H*N, *J* = 1.66 Hz), 4.03 (t, 2H, NCH_2, *J* = 7.24 Hz) 4.01 (s, 3H, NCH_3), 1.82 (quin, 2H, NCH$_2$CH_2, *J* = 7.20 Hz), 1.25 (hex, 2H, NCH$_2$CH$_2$CH_2, *J* = 7.59 Hz), 0.84 (t, 3H, NCH$_2$CH$_2$CH$_2$CH_3, *J* = 7.36 Hz)

3.7 - Synthesis of 1-Butyl-3-methylimidazolium hexafluorophosphate (80).[39]

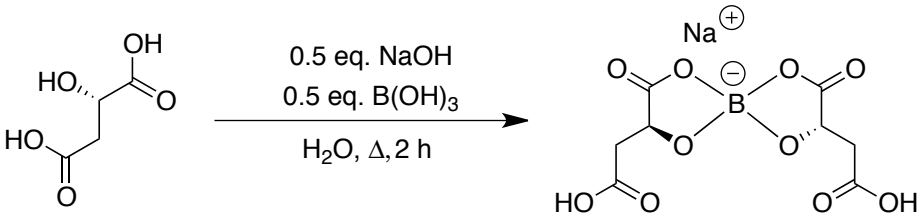


87 **88**

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, ^{1}H NMR (300MHz, CD_3OD): δ 8.73 (s, 1H, NC*H*N), 7.53 (t, 1H, MeNC*H*CHNBu, *J* = 1.74 Hz) 7.47 (t, 1H, MeNCHC*H*NBu, *J* = 1.68 Hz), 4.15 (t, 2H, NCH_2, *J* = 7.34 Hz), 3.87 (s, 3H, NCH_3), 1.82 (quintet, 2H, NCH_2CH_2, *J* = 7.61 Hz), 1.33 (sextet, 2H, $NCH_2CH_2CH_2$, *J* = 7.54 Hz), 0.94 (t, 3H, $NCH_2CH_2CH_2CH_3$, *J* = 7.37 Hz), ^{13}C NMR (400MHz, CD_3OD): δ 136.30, 123.40, 122.10, 48.96, 44.7 (dt, CD_3OD) 34.78, 31.38, 18.78, 12.04.

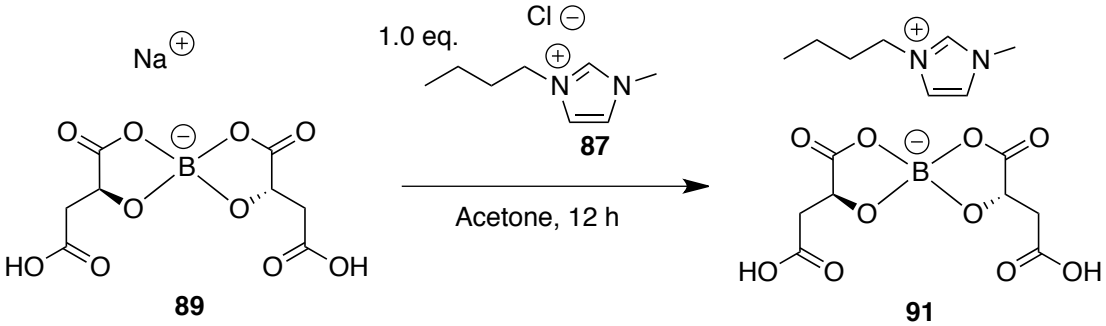
3.8 - Synthesis of Sodium Dimalatoborate (88).[40]



121 **89**

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. ^{1}H NMR (300MHz, acetone-d_6): δ 4.34-4.25 (m, 2H, C*H*COOH), 2.55-2.51 (m, 2H, C*H*COOH), 2.26-2.21 (m, 2H, BOOCC*H*)

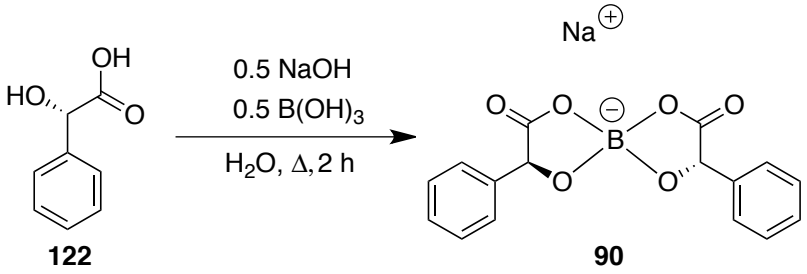
3.9 - Synthesis of 1-Butyl-3-methylimidazolium Dimalatoborate (90).[35]



89 **91**

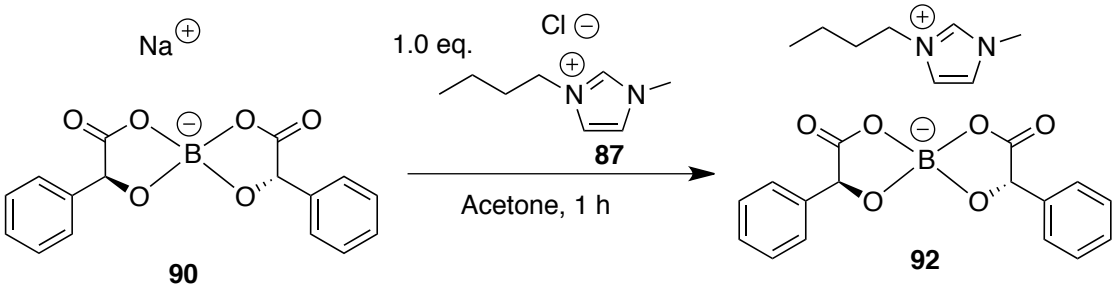
87 1.737 g, 9.94 mmol) was dissolved in acetone (22.60 ml) and treated with **89** (2.963 g, 9.94 mmol) in acetone (22.60 ml). The reaction mixture was stirred at room temperature overnight. During this period sodium chloride precipitated as a white solid. The reaction mixture was filtered and the solvent 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, $CDCl_3$): δ 9.11 (s, 1H, NC*H*N), 7.65 (t, 1H, MeNC*H*CHNBu, *J* = 1.72 Hz), 7.61 (t, 1H, MeNCHC*H*NBu, *J* = 1.68 Hz), 4.40-4.34 (m, 2H, C*H*COOH), 4.26 (t, 2H, NCH_2, *J* = 7.28 Hz) 3.94 (s, 3H, NCH_3), 2.59-2.55 (m, 2H, C*H*COOH), 2.41-2.34 (m, 2H, BOOCC*H*), 1.80 (quintet, 2H, NCH_2CH_2, *J* = 7.27 Hz), 1.27 (sextet, 2H, $NCH_2CH_2CH_2$, *J* = 7.75 Hz), 0.83 (t, 3H, $NCH_2CH_2CH_2CH_3$, *J* = 8.17 Hz).

3.10 - Synthesis of Sodium Dimandelatoborate (89).[40]



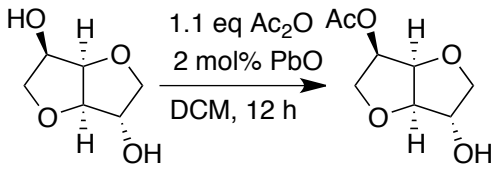
In a 100 mL round-bottomed flask was **122** (9.433 g, 62.0 mmol) in water (15.50 ml) to give a colourless solution. Boric acid (1.917 g, 31.0 mmol) was added. Sodium hydroxide (1.240 g, 31.0 mmol) in water (15.50 ml) was added. The solution was then heated to 100 for 2 h and the water allowed to evaporate to yield **89** (10.25 g, 30.7 mmol, 99 %) as a white crystalline solid ^{1}H NMR (300MHz, acetone-d_6): δ 7.56-7.47 (m, 2H, Ar*H*), 7.24-7.14 (m, 3H, Ar*H*), 5.13-5.04 (m, 1H, PhC*H*).

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±0.2 (c=0.39, CH_3CN); ^{1}H NMR (300MHz, acetone-d_6): δ 8.97 (s, 1H, NC*H*N), 7.68-7.60 (m, 4H, Ar*H*), 7.59 (t, 1H, N^+C*H*CHN, *J* = 1.57 Hz), 7.51 (t, 1H, N^+CHC*H*N, *J* = 1.75 Hz), 7.37-7.23 (m, 6H, Ar*H*), 5.21 (d, 2H, PhC*H*, *J* = 5.21 Hz), 4.15 (t, 2H, NCH_2, *J* = 7.34 Hz), 3.83 (s, 3H, NCH_3), 1.76 (quin, 2H, NCH_2CH_2, *J* = 7.50 Hz), 1.25 (hex, 2H, $NCH_2CH_2CH_2$, *J* = 7.49 Hz), 0.87 (t, 3H, $NCH_2CH_2CH_2CH_3$, *J* = 7.35); ^{13}C NMR (300MHz, $CDCl_3$) δ 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.

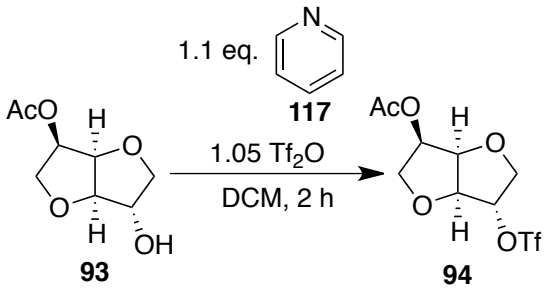
3.12 - Synthesis of (3*R*, 3a*R*, 6*S*, 6a*S*)-3-(Acetoxy)hexahydrofuro[3,2-b]furan-6-ol (93).[42]



123 **93**

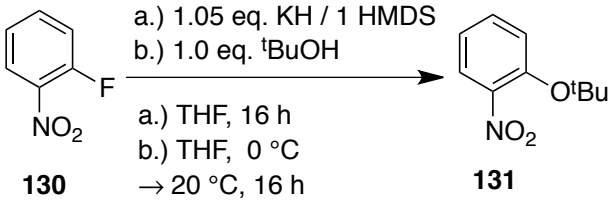
100 mL round-bottomed flask was added Isosorbide (7 g, 47.9 mmol), acetic anhydride (5.88 ml, 62.3 mmol), and lead (II) oxide (0.267 g, 1.197 mmol) in DCM (10 ml) to give a colorless solution. The solution was stirred for 24 h. TLC (5% MeOH : 95% CH_2Cl_2) showed only trace starting materials remained. 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, $CDCl_3$): δ 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 ($CDCl_3$, 300 MHz): δ 185.55, 88.37, 80.52, 77,22 (t, CD_3Cl), 76.44, 75.77, 74.29, 70.36, 20.90 LC-MS $(EI)^+$ *m/z* 189.00 $[M+H]^+$.

3.13 - Synthesis of (3*R*, 3a*R*, 6*S*, 6a*S*)-3-(Acetoxy)hexahydrofuro[3,2-b]furan-6-yl trifluoromethanesulfonate. (94).[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 $MgSO_4$ and solvent was removed in vacuo to give **94** (1.2 g, 3.75 mmol, 85 % yield) as an orange oil. 1H NMR (300MHz, $CDCl_3$): 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, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 170.17, 89.31, 85.36, 80.80, 77.01 (t, CD_3Cl), 73.35, 72.71, 70.65, 20.35. MS $(EI)^+$ *m/z* 321.00 $[M+H]^+$.

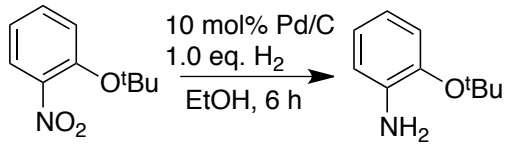
3.14 - Synthesis of 2-*tert*-Butoxynitrobenzene (131)



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 30ml ethyl acetate and washed with ammonium chloride (50ml), water (2x50ml) and brine (50ml). All aqueous washings were then back-extracted with ethyl acetate (50ml). 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. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.69 (d, 1H, Ar*H*, *J* = 8.07 Hz), 7.44 (dd, 1H, ArH, *J* = 8.37 Hz, *J* = 7.41 Hz), 7.20 (d, 1H, Ar*H*, *J* = 8.37 Hz), 1.39 (s, 9H, OC(CH_3)$_3$)

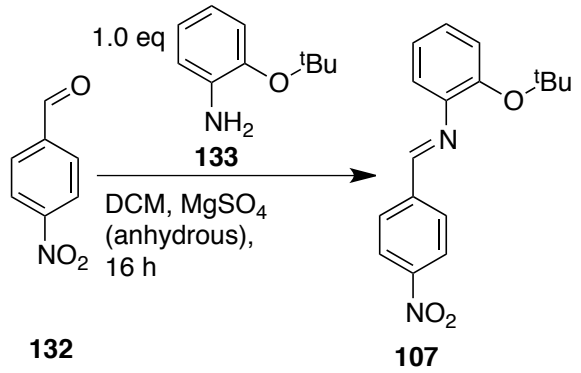
3.15 - Synthesis of 2-*tert*-Butoxyaniline (132)



131 **132**

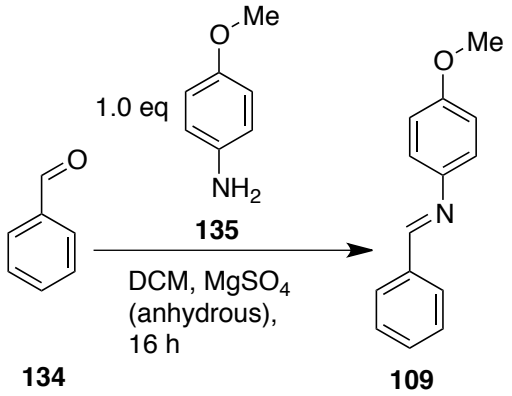
A mixture of **131** (5 g, 25.6 mmol) and 10% palladium on charcoal (2.73 g, 2.56 mmol) in ethanol (16 ml) to give a black suspension, which was evenly divided between four 5 mL hydrogenation vials. Hydrogen gas was then bubbled through suspension until it ceased to be consumed (6 h). The reaction mixture 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. ^{1}H NMR (400MHz, $CDCl_3$): δ 6.95 (d, 1H, Ar*H*, *J* = 7.95 Hz), 6.88 (d, 1H, Ar*H*, *J* = 8.07 Hz), 6.74 (dd, 1H, ArH, *J* = 8.37 Hz, *J* = 7.41 Hz), 6.65 (t, 1H, Ar*H*, *J* = 8.37 Hz), 1.39 (s, 9H, OC(CH_3)$_3$).

3.16 - Synthesis of (*E*)-2-Butoxy-*N*-(4-nitrobenzylidene)phenylamine (107)



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, $CDCl_3$): δ 8.55 (s, 1H, N=C*H*), 8.30 (d, 2H, *o*-NO_2-Ar*H*, *J* = 8.32 Hz), 8.05 (d, 2H, *m*-NO_2-Ar*H*, *J* = 8.11 Hz), 7.13-7.07 (m, 4H, Ar*H*), 1.30 (s, 9H, OC(CH_3)).

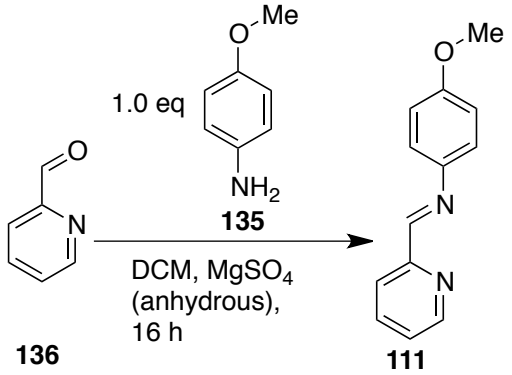
3.17 - Synthesis of (*E*)-4-Methoxy-*N*-benzylidenephenylamine (109)



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,

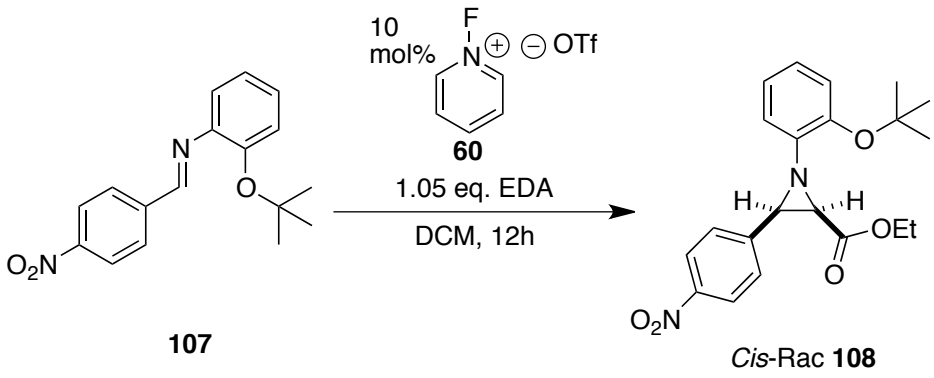
90 % yield) as a crystalline pale brown solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.48 (s, 1H, N=C*H*), 7.91-7.88 (m, 2H, Ar*H*,) 7.46 (t, 3H, Ar*H*, *J* = 3.22 Hz), 7.24 (d, 2H, *m*-MeO-Ar*H*, *J* = 9.01 Hz), 6.94 (d, 2H, *m*-MeO-Ar*H*, *J* = 8.98 Hz), 3.83 (s, 3H, OCH_3).

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

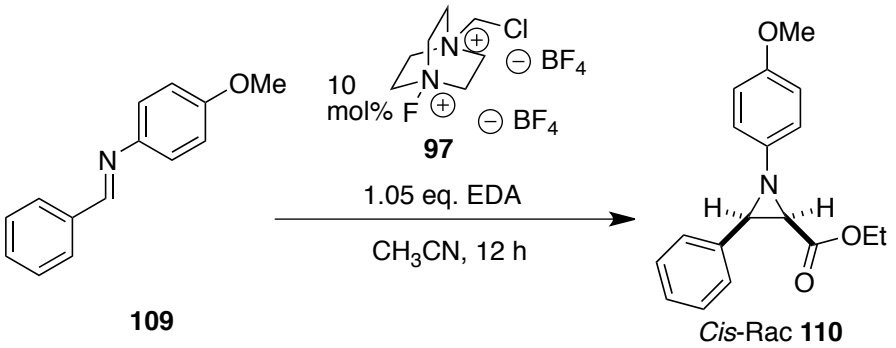


In a 100 mL round-bottomed flask was added **136** (8.43 ml, 83 mmol) and **135** (10.24 g, 83 mmol) in dichloromethane (40 ml) to give a brown solution. 10 g dried magnesium sulphate was added and the solution was briefly stirred to mix and then left to stand for 16 h. The solution was filtered to remove 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=C*H*), 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-Ar*H*, *J* = 6.58 Hz, *J* = 2.75 Hz), 6.94 (d, 2H, *o*-OMe-Ar*H*, *J* = 8.90 Hz), 3.82 (s, 3H, OCH_3).

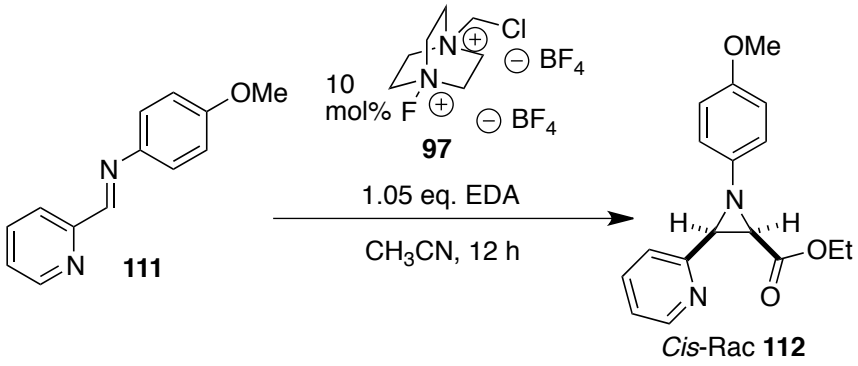
3.19 - F^+ Mediated Aziridinations.[29]



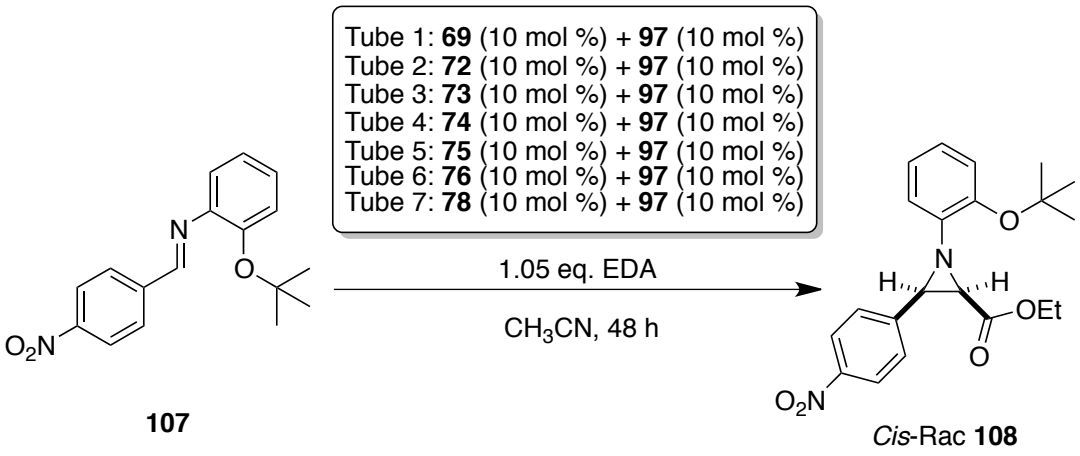
In a dry 10 mL round-bottomed flask was added **107** (80 mg, 0.268 mmol) and *N*-fluoropyridinium Trifluoromethanesulfonate (6.63 mg, 0.027 mmol) in dry dichloromethane (3 ml) under an atmosphere of nitrogen to give a dark yellow solution, which was stirred for 5 min. Ethyl diazoacetate (32.7 µl, 0.268 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%),[1]H NMR (300MHz, $CDCl_3$): δ 8.20 (d, 2H, *o*-NO_2Ar*H*, *J* = 8.86 Hz), 7.73 (d, 2H, *m*-NO_2Ar*H*, *J* = 8.81 Hz), 7.03-6.95 (m, 4H, MeOAr*H*), 4.03 (dd, 2H, COOCH_2, *J* = 9.47, *J* = 7.17), 3.58 (d, 1H, C*H*COOEt, *J* = 6.64 Hz), 3.19 (d, 1H, C*H*PhNO_2, *J* = 6.65 Hz), 1.32 (s, 9H, O(CH_3)), 1.08, (t, 3H, $COOCH_2CH_3$, *J* = 7.14 Hz); [13]C NMR ($CDCl_3$, 300 MHz): δ 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). [50] [1]H NMR (300MHz, $CDCl_3$): δ 7.49 (dd, 2H, *o*-CHAr*H*, *J* = 6.60 Hz, *J* = 1.50 Hz), 7.34-7.31 (m, 3H, Ar*H*), 6.99 (d, 2H, *m*-MeOAr*H*, *J* = 9.09 Hz), 6.81 (d, 2H, *m*-MeOAr*H*, *J* = 9.04 Hz), 4.01 (dd, 2H, COOCH_2, *J* = 15.83 Hz, *J* = 7.13 Hz), 3.77 (s, 3, OCH_3), 3.52 (d, 1H, C*H*COOEt, *J* = 6.84 Hz), 3.13 (d, 1H, C*H*Ph, *J* = 6.83 Hz), 0.98 (t, 3H, $COOCH_2CH_3$).

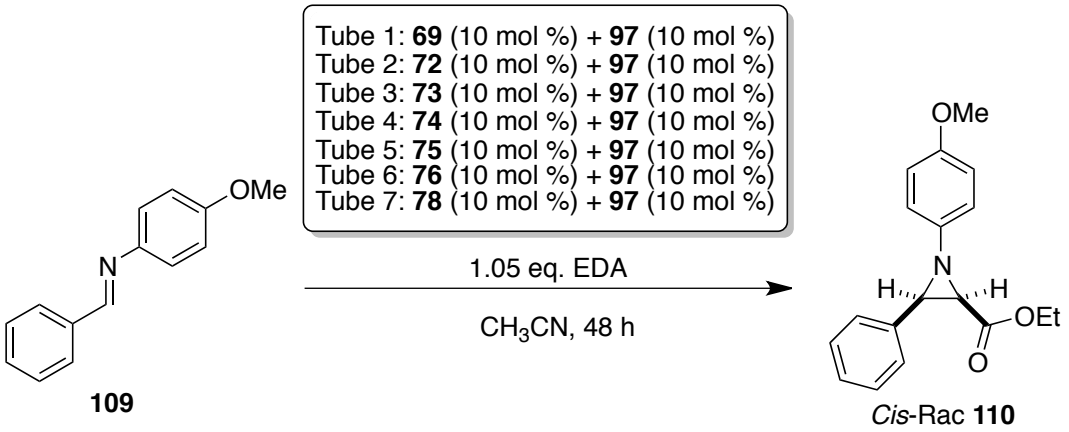


In a dry 25 mL round-bottomed flask was **111** (145 mg, 0.565 mmol) and Selectfluor (20 mg, 0.056 mmol) in acetonitrile (2.17 ml) under an atmosphere of nitrogen to give a yellow solution, which was stirred for 5 min. Ethyl diazoacetate (69.8 µl, 0.565 mmol) was added and the reaction was stirred for 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 %).; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.21 (d, 2H, *o*-O_2NAr*H*, *J* = 8.87 Hz), 7.69 (d, 2H, *m*-O_2NAr*H*, *J* = 8.53 Hz), 6.97 (d, 2H, *m*-MeOAr*H, J* = 8.98 Hz), 6.83 (d, 2H, *o*-MeOAr*H, J* = 8.99 Hz), 4.02 (dd, 2H, COOCH_2, *J* = 9.00 Hz, *J* = 7.14 Hz), 3.77 (s, 3H, OCH_3), 3.57 (d, 1H, C*H*COOEt, *J* = 6.78 Hz), 3.21 (d, 1H, C*H*Ph, *J* = 6.76 Hz), 1.04 (t, 3H, $COOCH_2CH_3$, *J* = 7.13 Hz). ^{13}C NMR ($CDCl_3$, 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 (EI)$^+$: *m/z* 597 (100%)

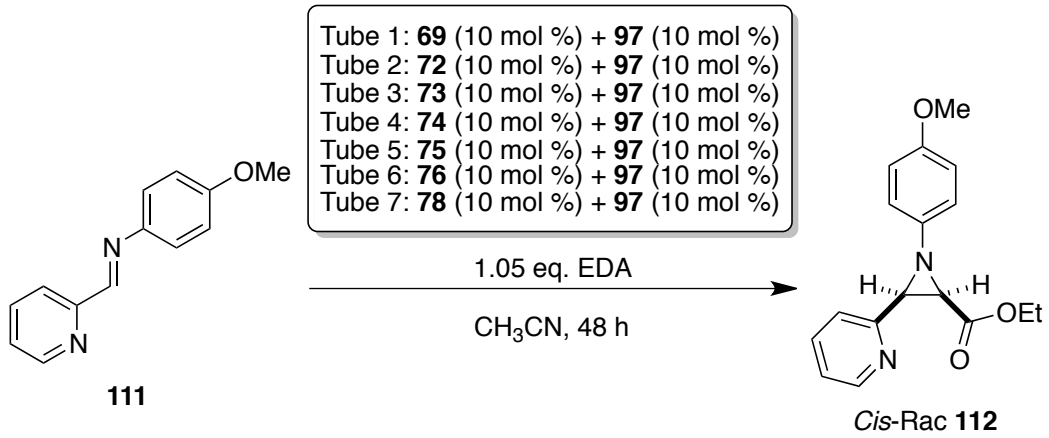


Into a 12 Reaction carrousel were placed seven carousel tubes and each was charged with an *O*-protected alkaloid (tube 1: **69,** 21.8 mg; tube 2: **72**, 22.0 mg, 0.027 mmol; tube 3: **73**, 20.5 mg, 0.027 mmol; **74**, 22.1 mg, 0.027 mmol; **75**, 14.7 mg, 0.027 mmol; **76**, 12.1 mg,

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: $\alpha]^{20}_{D} = 0$ (c=1.0, CH_3Cl)

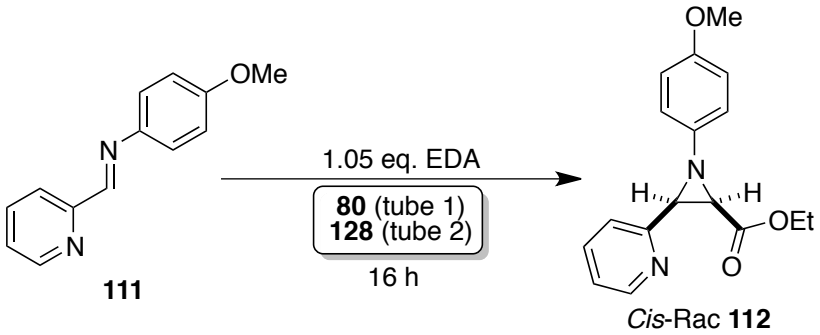


Into a 12 Reaction carrousel were placed seven carousel tubes and each was charged with an *O*-protected alkaloid (tube 1: **69,** 21.8 mg; tube 2: **72**, 22.0 mg, 0.027 mmol; tube 3: **73**, 20.5 mg, 0.027 mmol; **74**, 22.1 mg, 0.027 mmol; **75**, 14.7 mg, 0.027 mmol; **76**, 12.1 mg, 0.027 mmol; **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: $\alpha]^{20}_{D} = 0$ (c=1.0, CH_3Cl)



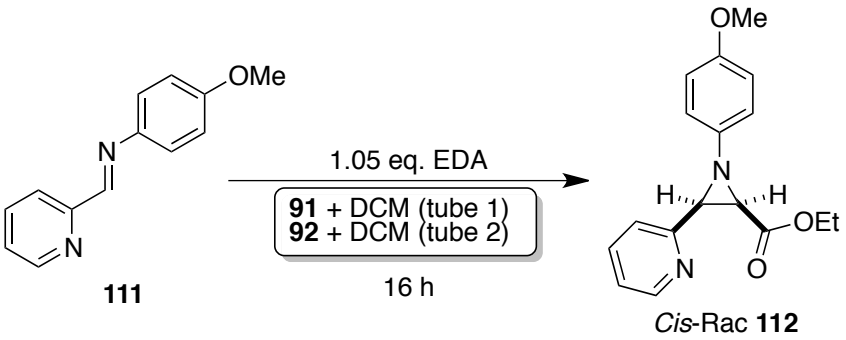
Into a 12 Reaction carrousel were placed seven carousel tubes and each was charged with an *O*-protected alkaloid (tube 1: **69,** 21.8 mg; tube 2: **72**, 22.0 mg, 0.027 mmol; tube 3: **73**, 20.5 mg, 0.027 mmol; **74**, 22.1 mg, 0.027 mmol; **75**, 14.7 mg, 0.027 mmol; **76**, 12.1 mg, 0.027 mmol; **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. **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_3Cl)

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 1: **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: $\alpha]^{20}_{D}$ = 0 (c=1.0, CH_3Cl).

Definitions:

BINAP: Binapthalene

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)propanoic acid

MS: Mass spectrometry

ppm: Parts per million

S_EAr: Electrophilic aromatic substitution

S_N: Nucleophilic substitution

VAPOL: Vaulted biphenanthrol

References

1 Trost, B.M, *Science* **1991**, 254, 1471-1477

2 Trost, B.M, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 259-281

3 (a) Katsuki, T., & Sharpless, K. B. *J. Am. Chem. Soc.,* **1980**, *102*(18), 5974–5976. (b) Vineyard, B. D., Knowles, W. S., Sabacky, M. J., Bachman, G., & Weinkauff, D., *J. Am. Chem. Soc.*, **1977**, *99*(18), 5946–5952. (c) Noyori, R., Ohkuma, T., Kitamura, M., Takaya, H., Sayo, N., Kumobayashi, H., & Akutagawa, S.. *J. Am. Chem. Soc.*, **1987**, *109*(19), 5856–5858.

4 Ayasinghe L. Y., Smallridge A. J., and Trewhella M. A. *Tetrahedron Lett.* **1993**, 34 (24): 3949.

5 Bredig G., Fiske W. S., *Biochem. Z.* **1912**, 7

6 Pracejus H., *Justus Liebigs Ann. Chem.* **1960**, 634, 9–22

7 Hajos, Z. G., & Parrish, D. R. **1974**, *39* (12), 1615-1621.

8 (a)B. List, R. A. Lerner, C. F. Barbas III, J. Am. Chem. Soc. **2000**, 122, 2395–2396.

9 K. A. Ahrendt, Borths C. J., MacMillan D.W. C., *J. Am. Chem. Soc.,* **2000**, 122, 4243–4244

10 E. Vedejs, O. Daugulis,, S. T. Diver, *J. Org. Chem.* **1996**, 61, 430-431

11 Jacobsen, E. N., & MacMillan, D. W. C., *PNAS,* **2010**, *107*(48), 20618-9.

12 (a)M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc*., **1998**, 120, 4901–4902; (b)M. S. Sigman, P. Vachal and E. N. Jacobsen, *Angew. Chem*., **2000**, 112, 1336–1338.

13 Dolling, U. H., Davis, P., & Grabowski, E. J. J., *J. Am. Chem. Soc.*, **1984**, *106*(2), 446-447.

14 Uraguchi, D., & Terada, M.. *J. Am. Chem. Soc.*, **2004**, *126*(17), 5356-7.

15 Sweeney, J. B. *Chem. Soc. Rev.*, **2002**, *31*(5), 247-258.

16 (a) D. Tanner, *Angew. Chem., Int. Ed. Engl.* **33 1994**, pp. 599–619. (b) W. McCoull and F.A. Davis, *Synthesis* (**2000**), pp. 1347–1365 (c) J.B. Sweeney, *Chem. Soc. Rev.* 31 (**2002**), pp. 247–258 (d) X.E. Hu, *Tetrahedron* 60 (**2004**), pp. 2701–2743. (e) B. Zwanenburg and P. ten Holte In: P. Metz, Editor, *Stereoselective Heterocyclic Synth. III*, *Topics in Current Chemistry* Vol. 216, Springer, Berlin (2001), pp. 93–124. (f) M. Pineschi, *Eur. J. Org. Chem.* (**2006**), pp. 4979–4988. (g) J. Aires-de-Sousa, S. Prabhakar, A.M. Lobo, A.M. Rosa, M.J.S. Gomes, M.C. Corvo, D.J. Williams and A.J.P. White, *Tetrahedron: Asymmetry* 12 (**2002**), pp. 3349–3365. (h) R.S. Atkinson, *Tetrahedron* 55 (**1999**), pp. 1519–1559. (l) A. Yudin, Aziridines and Epoxides in Organic Synthesis, Wiley-VCH, Weinheim (**2006**).

17 Loncaric, C., & Wulff, W. D. *Org. Lett.*, **2001,** *3*(23), 3675-3678.

18 Zalialov, I. A.; Dahanubar, V. H. *Curr. Opin*. *Drug Discovery Devel.* **2002**, 5,918– 927.

19 (a) Alcaro, S.; Ortuso, F.; Coleman, R. S. *J. Med. Chem*. **2002**, 45, 861. (b) Coleman, R. S.; Perez, R. J.; Burk, C. H.; Navarro, A. *J. Am. Chem. Soc.* **2002**, 124, 13008.

20 Pellissier, H.. *Tetrahedron*, **2010**, *66*(8), 1509-1555.

21 Gabriel, S. *Chem. Ber.*, **1888,** *21*(1), 1049-1057.

22 Evans, D. A., Woerpel, K. A., Hinman, M. M., & Faul, M. M., J. *Am. Chem. Soc.*, **1991**, *113*(2), 726-728. doi:10.1021/ja00002a080

23 Evans, D. A., Faul, M. M., Bilodeau, M. T., Anderson, B. A., & Barnes, D. M *J. Am. Chem. Soc.*, **1993**, *115*(12), 5328-5329

24 Pellissier, H. *Tetrahedron*, **2007**, *63*(38), 9267-9331.

25 Fioravanti, S., Mascia, M. G., Pellacani, L., & Tardella, P., *Tetrahedron*, **2004**, *60*(37), 8073-8077.

26 Lu, Z., Zhang, Y., & Wulff, W. D., *J. Am. Chem. Soc.*, **2007**, *129*(22), 7185-94.

27 A.P. Patwardhan, V.R. Pulgam, Y. Zhang and W.D. Wulff, *Angew Chem., Int. Ed.* **2005**, 44, 6169–6172.

28 Zhang, Y., Lu, Z., Desai, A., Wulff, W.D., *Org. Lett.* **2008**, 10, 5429–5432.

29 Bew, S., Carrington, R., Hughes, D., Liddle, J., & Pesce, P., *Adv. Synth. Cat.* **2009**, *351*(16), 2579-2588.

30 Bew, S. P., Ashford, P.-A., Fairhurst, S. A., Hughes, D. L., Legentil, L., Liddle, J., Pesce, P., **2009**, *Org. let.*, *11*(20), 4552-5.

31 Zoute, L., Audouard, C., Plaquevent, J.-C., & Cahard, D. *Org. & biomol. Chem.*, **2003**, *1*(11), 1833-4.

32 Corradi, E., Meille, S., Messina, M., Metrangolo, P., & Resnati, G., *Angew. Chem. Int. ed.*, **2000**, *39*(10), 1782-1786.

33 Baudequin, C., Plaquevent, J.-C., Audouard, C., & Cahard, D. *Green Chem.,* **2002**, *4*(6), 584-586.

34 Sun, W., Xia, C., & Wang, H., *Tetrahedron Lett.*, **2003**, *44*(11), 2409-2411.

35 Yu, S., Lindeman, S., & Tran, C. D., *J. Org. Chem.* **2008**, *73*(7), 2576-91.

36 Danishefsky, S., Kitahara, T., *J. Am. Chem. Soc.*, **1974**, *96* (25), pp 7807–7808

37 (a) Chen, H., Jin, Y., Jiang, R., Sun, X.-L., Li, X.-Y., Zhang, S.-Y. *Catal. Commun*, **2008**. *9*(9), 1858-1862 (b) Jin, Y., Liu, X.Y, Jing, L.L., He, W., Sun, X.L., Zhang, S.Y., *Chirality* **2007**, 19, 386. (c) Y. Jin, Z.J. Yao, P. Liu, Jiang, R., Zhang, S.Y., Chin. *J. Org. Chem*. **2008**, 28, 94.

38 Cahard, D., Audouard, C., Plaquevent, J. C., & Roques, N. *Org. lett.*, **2000**, *2*(23), 3699-3701

39 Dupont, J., Consorti, C., Suarez, P., de Souza, R., *Org. Synth.* **2002**, 79, 236–243

40 Gausepohl, R., Buskens, P., Kleinen, J., Bruckmann, A., Lehmann, C. W., Klankermayer, J., Leitner, W., *Angew. Chem. Int. ed.*, **2006**, *45*(22), 3689-92.

41 Van Buu, O., Aupoix, A., & Vo-Thanh, G. *Tetrahedron,* **2009**, *65*(11), 2260-2265.

42 Stoss, P., Merrath, P., & Schlueter, G. *Synthesis*, **1987**, (2), 174–176.

43 Deetlefs, M., Seddon, K.R., *Green Chem.* (**2003**), 5, 181–186.

44 Abdul-Ghani, M., Banks, R. E., Besheesh, M. K., Sharif, I., Syvret, R. G. J. *Fluorine Chem*. 1995, 73, 255–257.

45 Shibata, N., Suzuki, E., Asahi, T., & Shiro, M.. *J. Am. Chem. Soc.*, **2001**, *123*(29), 7001-9.

46 Umemoto, T., Harasawa, K., Tomizawa, G., Kawada, K., & Tomita, K. *Bull. Chem. Soc. Jpn.*, **1991** *64*(4), 1081-1092.

47 Lacour, J., & Hebbe-Viton, V., *Chem. Soc. Rev.*, **2003**, *32*(6), 373.

48 Lacour, J., Ginglinger, C., Grivet, C., & Bernardinelli, G., *Angew. Chem. Int. Ed.*, **1997**, *36*(6), 608-610.

49 Snelders, D. J. M., Kunna, K., Müller, C., Vogt, D., Koten, G. V., & Klein Gebbink, R. J. M., **2010** *Tetrahedron: Asymmetry*, *21*(11-12), 1411-1420.

50 L. Casarrubios, J. A. Perez, M. Brookhart, J. L. Templeton*, J. Org. Chem*., **1996**, 61, 8358