“Asymmetric Organocatalytic Synthesis of Aziridines”

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Abstract

The herein illustrated Master project presents novel and unprecedented approaches towards the synthesis of chiral racemic and chiral non-racemic C2,3-disubstituted cis-aziridines through organocatalytic aza-Darzens reaction.

A first section includes introduction part for all the subsections listed below where as second section will give more insight on the result and discussion. The First introductory subsection is dedicated to the properties, synthesis and importance of aziridines. These three-membered nitrogen-containing heterocycles are considered valuable building blocks, as much as their parent epoxides, and pharmacologically active compounds on there own.

A second subsection dedicated to the Synthesis of optically pure C2,3-disubstituted N-aryl and N-H cis-aziridines was achieved by means of a chiral BINOL-derived N-triflylphosphoramide Brønsted acid catalyst. The observed excellent yields, regioselectivities and enantioselectivities find no rivals in other organocatalytic aziridine synthesis. Successful cleavage of various N-substitutions gave access to valuable N-H aziridines and pharmacologically active compounds.

A third subsection dedicated to investigate and develop the ability of series of bespoke, unique and optically active organocatalysts derived from the readily available cinchona alkaloid are able to mediate the asymmetric synthesis of enantiopure aziridines. A one step transfer-fluorination of the quinidine moiety with N-fluoropyridinium triflate gave the $[N\text{-}F]^+$reagent, this $[N\text{-}F]^+$ species is highly reactive and unstable. Starting from N-aryl imine and N-alkyl diazoacetate using 10 mol% of chiral non-racemic organocatalyst N-fluoro quaternary ammonium salt gives a highly pure N-alkyl and N-aryl aziridine. The whole process is environmentally friendly, giving only water and nitrogen as a byproduct at the end.

A fourth subsection described the synthesis of stable enantiomerically pure chiral NH-oxaziridine and also described attempts towards the synthesis of five membered heterocycle by cyclization of NH-oxaziridines with alkenes are considered as novel and interesting aspects. Furthermore NH – Oxaziridines is potentially of great value today as relatively 'green' sources of electrophilic nitrogen.

Acknowledgements

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List of Abbreviation

$(DHQD)_2$-PHAL	Hydroquinidine 1,4-phthalazinediyl diether
$(DHQD)_2$-PYR	Hydroquinidine 2,5-diphenyl-4,6-pyrimidine-diyl diether
BINOL	1,1'-Bi-2-naphthol
CAN	Ammonium cerium (IV) nitrate
CDI	Carbonylbis[1*H*-imidazole]
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyno-1,4-benzoquinone
DHQ	Dihydroquinidine
DHQB	Dihydroquinidine-benzoate
DIBAL-H	Diiso-butyl aluminium hydride
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Boc	*Tert*-butyloxycarbonyl
e.e.	Enantiomeric excess
AD	Asymmetric dihydroxylation
EDA	Ethyl diazoacetate
EtMgBr	Ethylmagnesium bromide
HPLC	High Pressure Liquid Chromatography
IFB	"Interrupted" Feist−Bénary Reaction
IR spectroscopy	Infrared spectroscopy
LC	Liquid Chromatography
LDA	Lithium diisopropylamide
LG	Leaving Group
LUMO	Lowest Unoccupied Molecular orbital
m–CPBA	3-Chloroperoxybenzoic acid
MM	Molecular mechanics
MS	Mass Spectrometry

NMR	Nuclear magnetic resonance
NOE effect	Nuclear Overhauser Effect
p.p.m	Parts-per-million
PMP	*Para*-methoxyphenyl
PyTf	Pyridinium triflate
Rt	Room temperature
SET	Single electron transfer
S_N	Nucleophilic substitution
TBACN	Tetrabutylammonium cyanide
^{t}BuDA	*Tert*-butyl diazoacetate
TCCA	Trichloroisocyanuric acid
TLC	Thin Layer Chromatography
TMG	1,1,3,3-Tetramethylguanidine
TMS	Tetramethylsilyl
VAPOL	Vaulted biphenanthrol

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SECTION - I

INTRODUCTION

1 Aziridines: A Comprehensive Overview

Aziridines, which are three-membered nitrogen containing heterocycles, have created considerable research interest because of their fundamental and practical importance, they have been known as a class of versatile intermediates in the synthesis of different kinds of amino acids, natural products and biologically active compounds.

A recent review by Pellissier based on developments of asymmetric aziridination, testifies that the synthesis of chiral non-racemic aziridines is still a hot issue in synthetic chemistry.[1] Reports on the generic subject of aziridines have always covered an extensive part of literature. Interest in the three-member nitrogen-containing heterocycles can be dated back to Gabriel's studies in 1888.[2] For their analogies with epoxides and cyclopropanes and their unique chemical and physical properties, aziridines are valuable compounds in terms of chemical, biological and pharmacological activities. The high strain energy (27 Kcal/mol) associated with the three-membered aziridine cyclic structure is at the origin of several features characteristic of this class of compounds, including physical and chemical properties, as well as synthesis and reactivity.

1.1 Physical and chemical properties of aziridines

The chemical bonding system of the aziridine ring resides in the category of bent bonds (or banana bonds, Figure 1). Thus, for the atoms involved in ring formation, it is not possible to assume a 60° angle required by the cycle with a standard sp^3-hybridization. The σ-bonds that comprise the cycle result in an increase in p-character. At the same time, the C-H and N-H molecular orbitals gain more s-character and, as a result, they are shorter. The increased s-character of the nitrogen lone pair causes the weaker basicity of aziridines (the aziridinium ion has $pK_a = 7.98$) compared to acyclic aliphatic amines.[3]

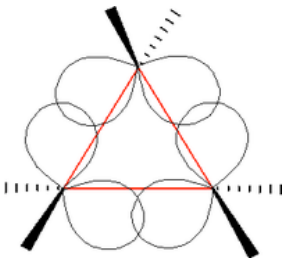


Figure 1. *Chemical bonding system of cyclopropane made of bent bonds.*

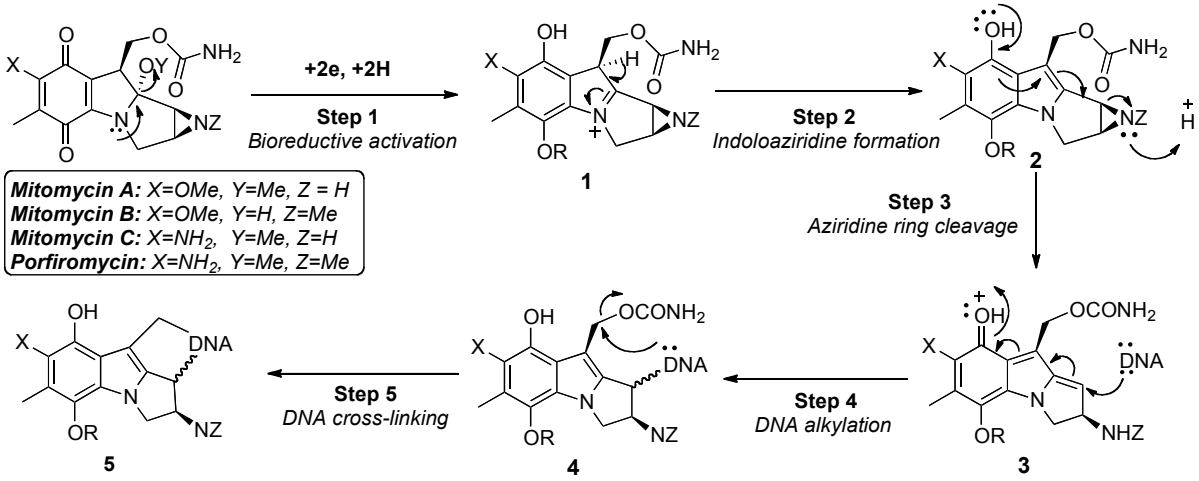
The additional bond strain caused by the geometric constraints of the trigonal ring system also has a significant effect on the barrier to inversion at nitrogen, which results considerably higher than in acyclic analogues.[4]

The chemical reactivity of an aziridine originates from the high strain energy associated with their three-membered cyclic nature. This property facilitates cleavage of the C–N bonds of the ring under either acidic or basic conditions. Aziridines can either undergo ring-opening reactions with a range of nucleophiles or cycloaddition reactions with dipolarophiles, constituting precious building blocks towards the synthesis of a plethora of chemical compounds.

1.2 Cleavage of the aziridine ring

1.2.1 Importance of aziridines in pharmacology

Aziridines are powerful alkylating agents, whose toxicity is at the origin of their intrinsic *in vivo* potency.[5] The three-membered ring does not show selectivity or specific activity in the alkylation process. However, if the aziridine ring is incorporated in a larger organic framework, such selectivity could be achieved, as it is the case of several aziridine-containing natural products, *i.e.* mitosanes A-C.



Scheme 1. *Mode of action of mitosanes.*

The mitosanes are a class of compounds isolated from soil extracts of the bacteria *Streptomyces verticillatus*. The observed anti-tumour and antibiotic activity of these natural products is attributed to the presence of the aziridine ring. The anti-tumour activity of these natural products relies on DNA alkylation, in which the aziridine ring-opening is the key feature. Scheme 1 illustrates the postulated mechanism of action of mitosanes.

Another important class of natural products displaying cytotoxic activity is the Azinomycin

family (Figure 2), isolated from *Streptomyces grieseofuscus S42227* by Nagaoka and coworkers. Similarly to Mitosanes, Azinomycins incorporate in their structure the three-membered aziridine ring, which is the active site for the cross-linkage of DNA. Again, the ring confers a potent anti-tumour activity against a wide range of cancers, including solid tumours. To better understand the role of the aziridine ring in biological systems, Figure 2 offers a selection of aziridine-containing compounds, which, regardless of their structure complexity, show pharmacological activity.

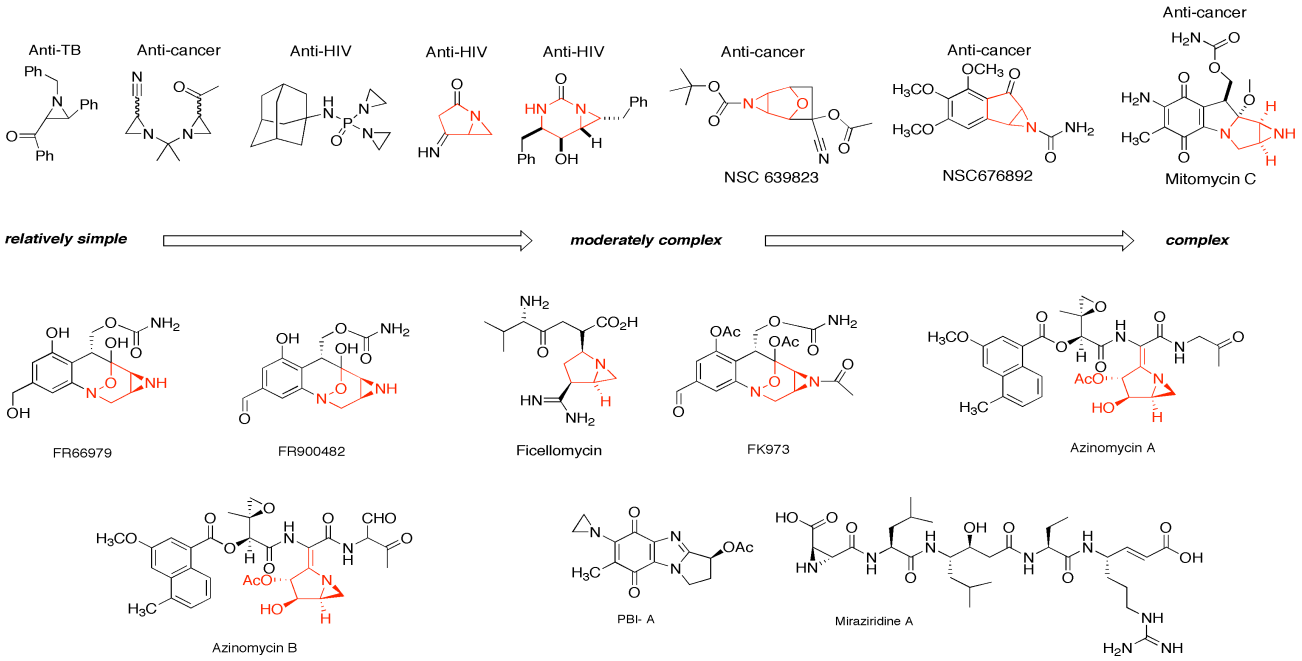


Figure 2. *Examples of pharmacologically active products that contain the aziridine moiety.*

1.2.2 General features of ring-opening reactions

At the origin of tendency to ring-open, one could identify the Bæyer strain inherent in the three-membered heterocycle and the electronegativity of the heteroatom that polarizes the bonds of the ring. Intuitively, due to the diminished electronegativity of nitrogen compared to oxygen, ring-opening reactions of aziridines are less facile than the corresponding reactions of epoxides. Still, a wealth of examples of such chemistry is possible, as outlined in Figure 3.

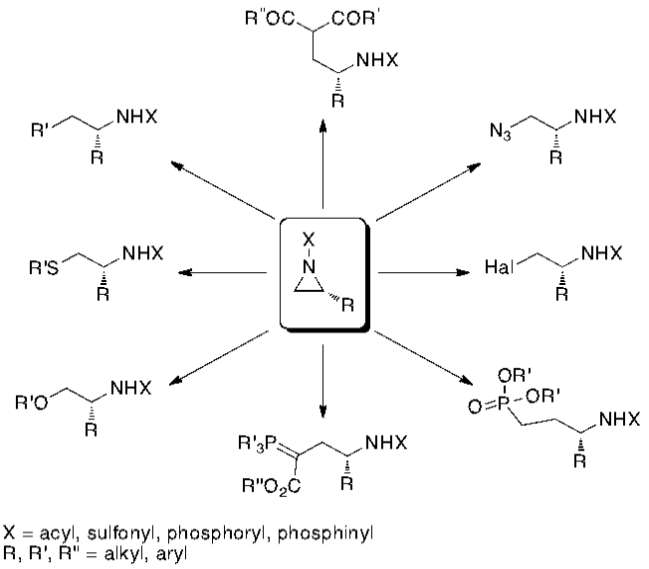


Figure 3. *Overview diagram for ring-opening reactions of aziridines.*

Analogously to epoxide, a ring-cleavage reaction of aziridines takes place *via* nucleophilic attack at carbon, in both acidic and basic conditions. When aziridines are unsymmetrically substituted, the nucleophilic cleavage can lead to the formation of two products of ring opening (Figure 4).

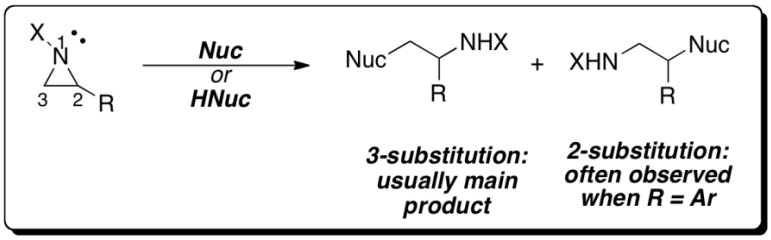


Figure 4. *Nucleophilic ring opening of an aziridine.*

The regiospecificity of the attack obeys the classic rules for nucleophilic substitution reactions, *i.e.* the combination of steric and electronic factors will drive the nucleophile towards one carbon or the other, dictating the final distribution of products. Generally, high regiospecificity could be achieved.

1.3 Effect of Lewis acids and N-substituents on the ring-opening of aziridines

Having a basic non-bonded electron pair, the aziridine nitrogen is susceptible to interaction with Lewis acids, similarly to their analogous epoxides. Co-ordination to a Lewis acid enhances the rate of ring-opening processes. Indeed, the Lewis acid-coordinated aziridine nitrogen would greatly suffer from the strain of the cycle. Nonetheless, Lewis acid-mediated ring-opening of aziridines are not as common as for epoxides. The reason behind this lies on the requirement for polar activating *N*-substituents to facilitate the ring-opening process of

aziridines. In the majority of the cases, these *N*-substituents contain at least an oxygen atom, *i.e.* carbonyl, sulfonyl, phosphoryl groups, etc. The presence of the oxygen atom impedes the direct interaction of the aziridine nitrogen with the Lewis acid. As a matter of fact, the acid will coordinate preferentially to the oxygen of the *N*-substituent rather than to the nitrogen itself (Figure 5). Nonetheless, the desirability of a polar, oxygenated *N*-substituent for ring-opening still allows for some use of this type of activation, *via* coordination of oxygen lone-pairs to Lewis acid (*vide infra*).

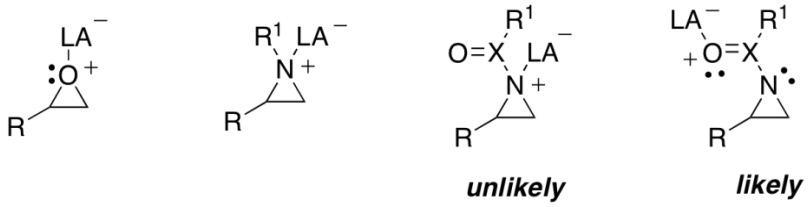
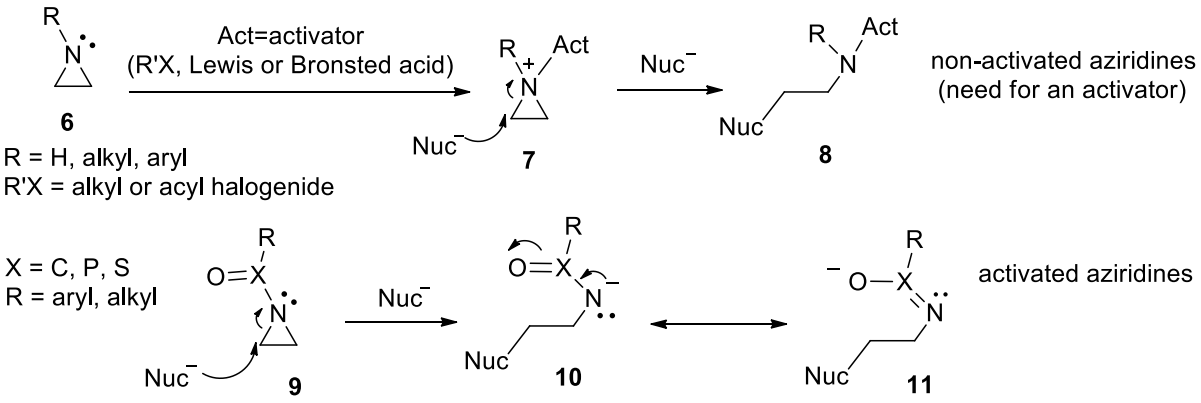


Figure 5. *General features of Lewis acid coordination to epoxide and aziridines*

Since the 1960s, aziridines have been classified as 'activated' or 'non-activated' according to whether or not nucleophilic ring-opening reactions proceed in the absence of positive charge at nitrogen[6] and this classification is intimately related to the nature of the substituent at the nitrogen atom of the heterocycle. Typically, non-activated aziridines contain a basic nitrogen atom. *N*-aryl, *N*-alkyl and free N-H aziridines **6** are considered as non-activated towards the ring-opening reaction (Scheme 2). Ring-opening of non-activated aziridines usually occurs only after protonation, quaternization or formation of a Lewis acid adduct, as shown for **7**. Instead, activated aziridines contain *N*-substituents capable of conjugatively and/or inductively stabilizing the negative charge that develops on the aziridine nitrogen atom as a consequence of the nucleophilic attack, *cf* **10** and **11**. Thus, the role of activating group is often neatly filled by oxygenated substituents such as sulfonyl, sulfinyl, phosphoryl, phosphinyl or carbonyl functional groups (Figure 6).



Scheme 2. *Nucleophilic ring-opening of non-activated and activated aziridines.*

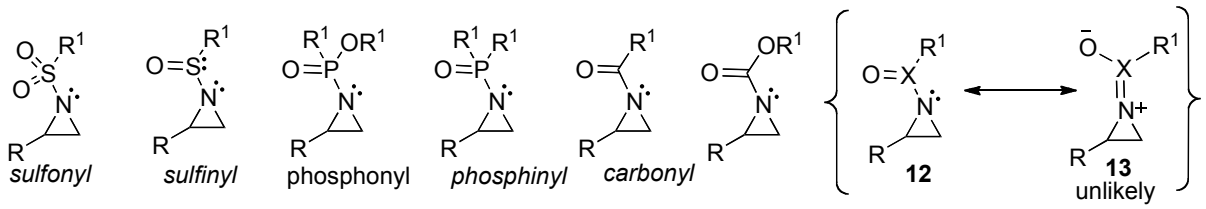
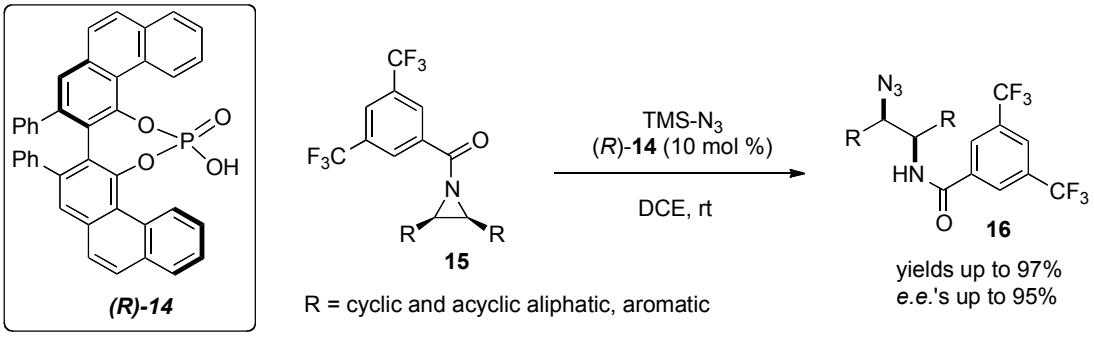


Figure 6. *Activating N-functionalised groups for the ring-opening of aziridines.*

The aziridines shown in Figure 6 are all functionalised with activating groups. The activation is primarily due to inductive effects, exerted by the electron-withdrawing groups that further polarize the C-N bonds of the ring. Resonance effects play a very limited role in the overall *kinetic* activation. Indeed, the nitrogen lone pair of **12** would not be easily involved in the X=O π-bond system as for **13** (Figure 6), as this would lead to an increase of the ring-strain. The electron-withdrawing *N*-substituent also offers a *thermodynamic* contribution to the activation, as it would stabilize the anion produced after the nucleophilic attack. The stabilization of sulfonamide, phosphonamide and phosphinamide anions is again primarily based on inductive effect.

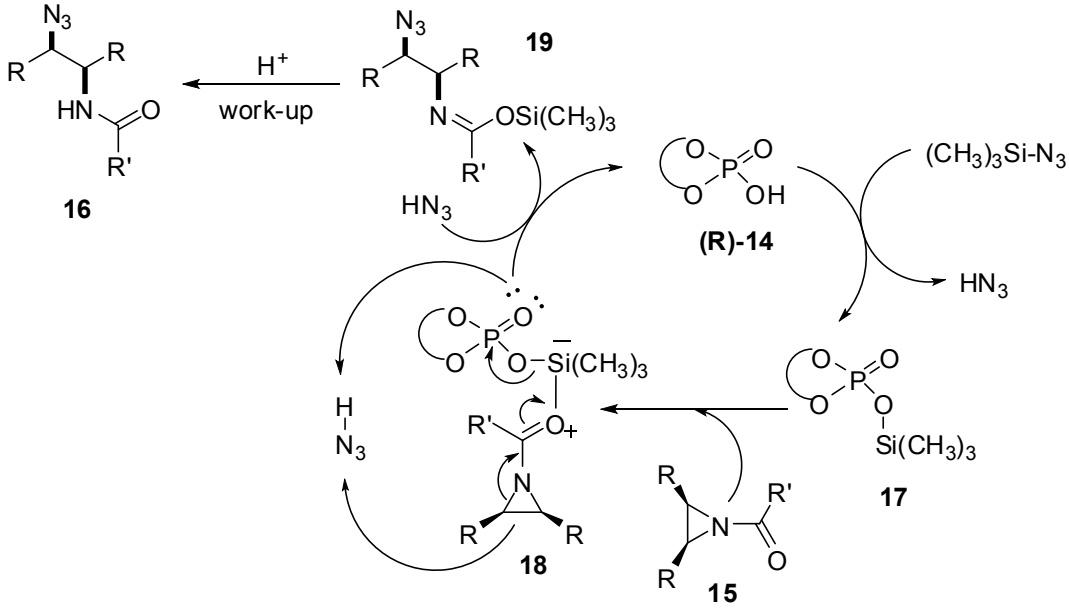
Recently, Antilla et al.[7] reported the enantioselective ring-opening of *N*-activated *meso*-aziridines **15** with trimethylsilylazide using 10 mol% of chiral (*R*)-VAPOL-derived phosphoric acid (*R*)-**14** (Scheme 3). The reaction provides a good example for this chemistry, being also closely related to the content of this dissertation.



Scheme 3. *Antilla's (R)-**14**-catalysed desymmetrization of meso-aziridine.*

Antilla's preliminary studies into the mechanism of the organocatalytic desymmetrization of *meso*-aziridines suggested that the presence of the trimethylsilyl group is required for the formation of the ring-opened product. Preliminary ^{1}H-NMR studies indicated formation of the TMS-containing compound **19** (Scheme 4). The proposed mechanism involves generation of the active catalyst **17** by displacement of the azide. The resulting silylated **15** coordinates to the carbonyl functionality of the *N*-substituent of the aziridine **15**, resulting in the formation of **18**. The species **18** then undergoes nucleophilic attack by the hydrazoic acid,

affording **19** and regenerating the catalyst (*R*)-**14**. The desired product **16** was finally obtained by decomposition of **19** on silica gel during the workup procedure.



Scheme 4. *Antilla's proposed mechanism for the (R)-**14**-catalysed desymmetrization reaction of meso-aziridines.*

However, if on the one hand, electron-withdrawing *N*-substitutions proved to be highly effective for the activation of aziridines towards ring opening, their reluctance to undergo *N*-deprotection reaction is a significant drawback of the system. The possibility to afford unprotected N-H products, either aziridines or their ring-opened derivatives, becomes a crucial point whenever embarking on the synthesis of these three-membered heterocycles. The choice of the *N*-substitution is therefore critical not only for the synthesis of aziridines but also for their subsequent transformation. The requirement for easily cleavable *N*-substitutions on aziridines strongly influenced the development of the synthetic methodologies introduced by this dissertation.

1.4 Aziridine synthesis overview

Preparation of aziridines can now count on a number of methodologies, as in Figure 7. The majority of synthetic protocols developed for the synthesis of aziridines can be grouped into three main reaction categories: carbon transfer to imines, nitrogen transfer to alkenes and cyclization reactions.

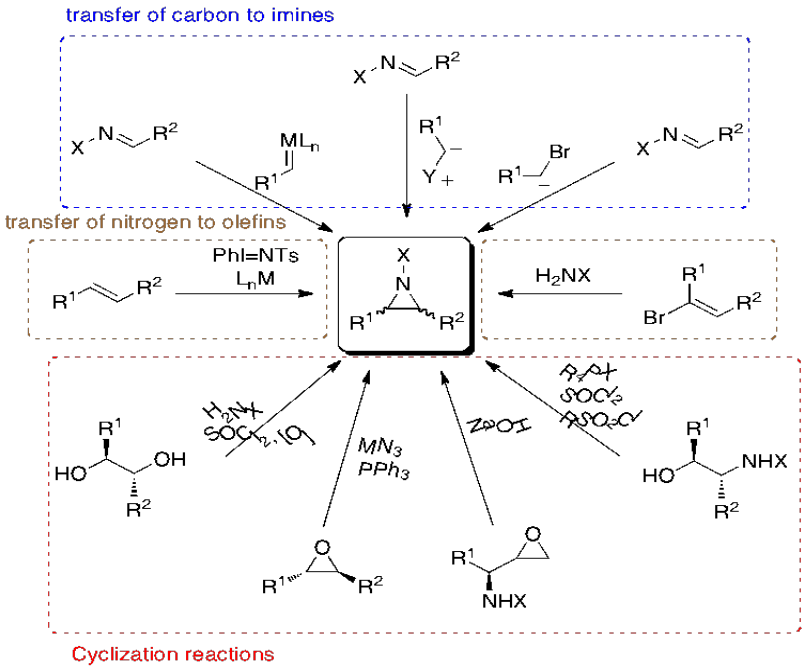


Figure 7. *Synthetic methods affording aziridines grouped in three categories of reaction.*

A more versatile and perhaps efficient approach to the synthesis of aziridines consists in the ring-closure of amines bearing a leaving group. The amine and the leaving group functionalities must be in a 1,2-relationship with each other. The process may be considered as the reverse of the ring opening of aziridines, as both the processes occur *via* S_N2-type mechanism. The only difference is that, for the ring-closure, the position next to the amine must be occupied by, or must be converted into, a nucleofuge. The cyclisation process may involve materials such 1,2-amino alcohols, 1,2-amino halides, 1,2-azido alcohols, 1,2-amino sulfides, 1,2-amino selenides or epoxides. This synthetic route becomes particularly useful for the preparation of enantiopure aziridines. In this case, however, the method requires the use of already established stereocenters on the starting material in order to afford the corresponding chiral non-racemic aziridine product. Moreover, stoichiometric amount of auxiliaries and/or reagents are often employed, which are discarded as by-products once the reaction takes place. This generates poor atom economy and chemical waste issues.

A third convincing approach to obtain aziridines groups a class of transformations that goes under the name of aza-Darzens reactions. The strategy involves the reaction of imines with carbenes/carbenoids, α-haloenolates or ylides (Figure 9 and 10), or in general, with stabilised anions bearing α-leaving groups, *i.e.* α-halogeno, α-diazo and α-sulfonio anions. These anions could be stabilised *via* a broad range of substitutions, often being carbonyl or sulfur functionalities. The great choice of anions confers a high degree of flexibility to the aza-Darzens reaction, which has become one of the most suitable techniques to afford aziridines, especially in an enantiopure fashion. Enantiocontrol can be achieved by using either chiral

imines, chiral nucleophiles or, more conveniently, chiral catalysts. The mechanism of the aza-Darzens reaction has two distinct steps: initial nucleophilic attack upon the C=N bond, followed by favoured (and normally irreversible) *3-exo-tet* cyclization of the intermediate amide anions (Figure 9).

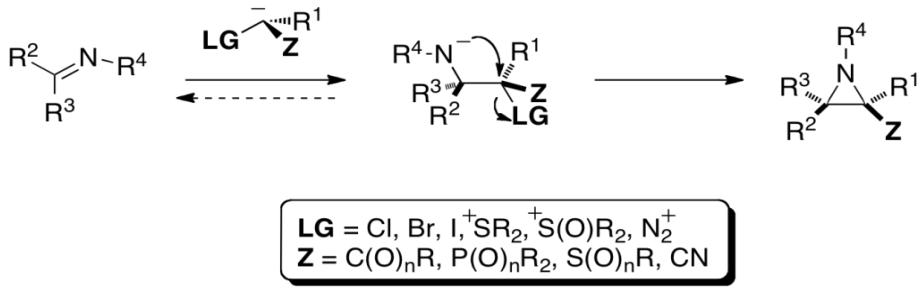


Figure 9. *Two-steps mechanism for the aza-Darzens reaction.*

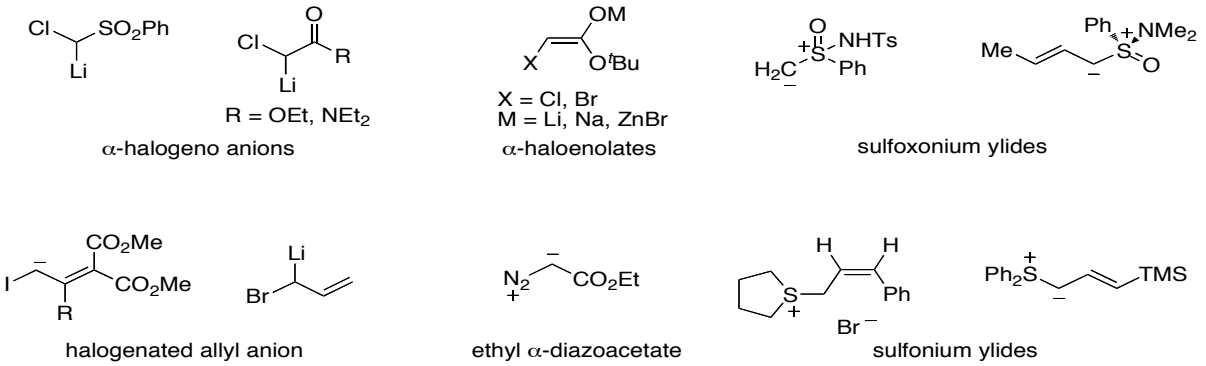


Figure 10. *Examples of nucleophiles employed in the aza-Darzens reaction.*

Moreover, the reaction offers the possibility for either nucleophile or electrophile activation. Nucleophiles such as carbenoids, for example, can be successfully activated to more reactive carbenes by transition-metal based catalysts (especially rhodium, cobalt and copper-based complexes), thermolysis or photolysis. Formation of carbine-coupling products, *e.g.* fumarates or maleates, could however represent a problem. Alternatively, electrophile activation by Lewis or Brønsted acid catalysis occurs by lowering the LUMO energy of the electrophile. Coordination of an acid to the lone pair of the nitrogen atom of an imine would induce a positive charge on the already polarized imine substrate.

As the project discussed in this thesis involved acid-catalysed aza-Darzens reactions between imines and diazoacetate, the following introductory sections will be confined to this synthetic methodology and to currently reported organocatalytic methods affording chiral non-racemic aziridines

1.5 Acid-catalysed addition of alkyl diazoacetates to N-substituted imines

As mentioned before, the aza-Darzens reaction between imines and diazoacetates requires the activation of at least one of the components. Although imines are fairly tuneable electrophiles due to functionalization of the *N*-substituent, no reaction occurs simply by mixing the two species together. This observation is consistent with the poor nucleophilicity resulting from the diazoacetate structure (Figure 11). The negative charge is highly delocalised by both diazo and carbonyl electronic π-system. In addition, the inductive effect exerted by these two electron-withdrawing substituents contributes to further stabilisation of compound. These features confer enhanced stability to carbenoid species, opposite to that of carbenes, known for their explosive nature. Ethyl diazoacetate however was found to be thermally stable against detonations and other safety concerns.

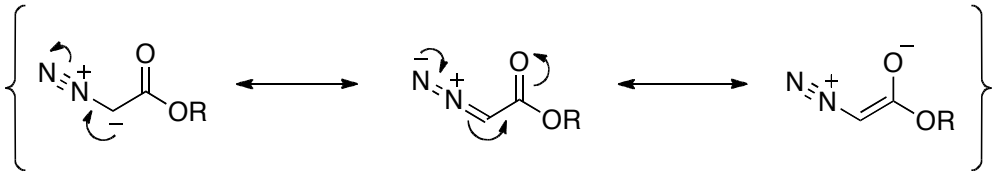
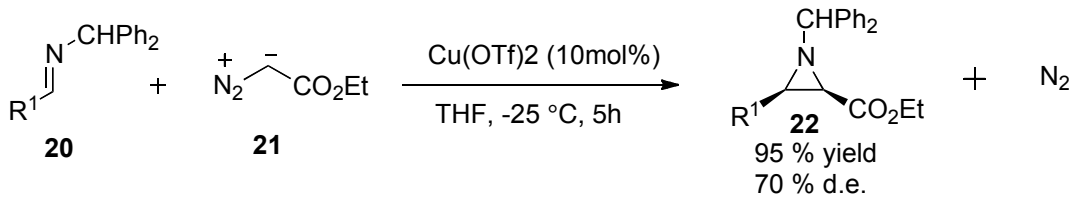


Figure 11. *Diazoacetate resonance structures.*

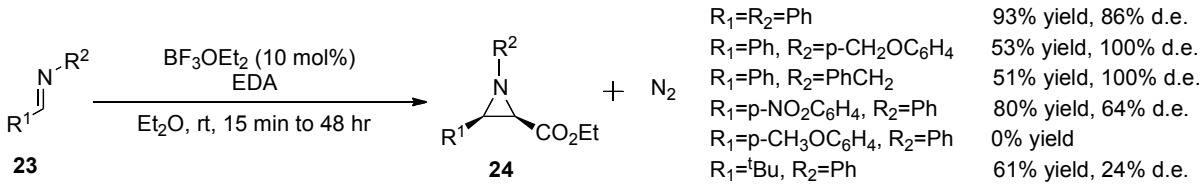
1.6 Lewis acid-catalysed aza-Darzens reaction

Following the pioneering work of Jørgensen and Rasmussen on the copper(II) triflate-catalysed addition of ethyl diazoacetate to *N*-substituted benzylideneimines[8] for the synthesis of aziridine, the Lewis acid-catalysed aza-Darzens reaction became a valid strategy towards the synthesis of $C_{2,3}$-disubstituted aziridines.[9] The technique has made use of the metal-centred catalysts, *i.e.* aluminium(III) chloride, boron trifluoride / diethyl ether complex, titanium(IV) chloride, zinc(II) triflate, ytterbium(III) triflate, just to mention a few. Under certain reaction conditions *cis*-aziridines could be returned in a highly diastereoselective fashion and in good to excellent yields. Moreover, the system matches atom-economy criteria as the waste material resulting from the reaction only consists of nitrogen gas. The possibility to establish a catalytic process, with all the benefits and potentialities associated to it, also contributed to develop an interest in both industrial and academic contexts.



Scheme 5. *Jørgensen's copper(II) triflate-catalysed reactions between* ***20*** *and* ***21****.*

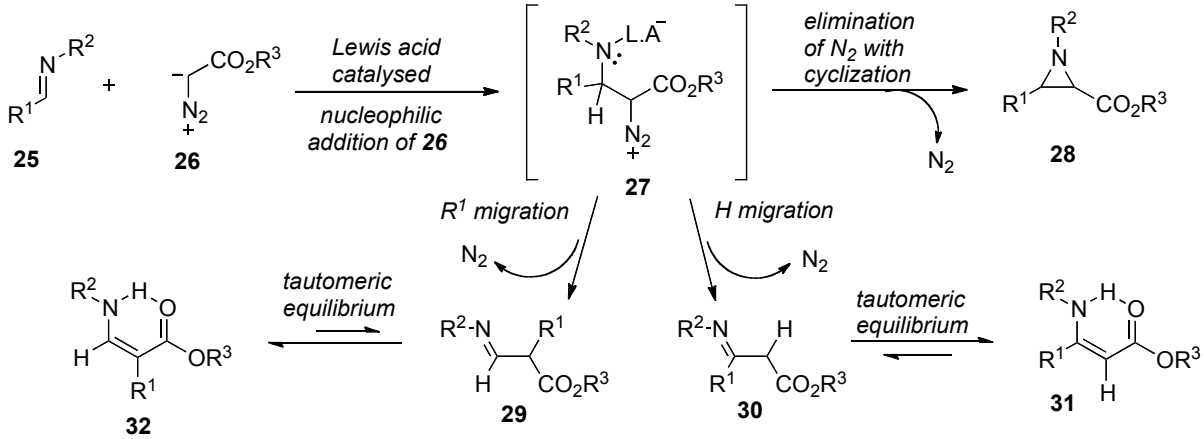
The major contributions to the development of Lewis acid-catalysed aza-Darzens reactions came from the study of Templeton et al.[10] The results obtained by Templeton, combined with the simplicity of the method, were very promising indeed and encouraged further exploration of the methodology. $C_{2,3}$-disubstituted aziridines **24** were produced catalytically, in good to excellent yields (up to 93%) and diastereoselectivities (up to 100%), and employing readily available starting materials (Scheme 6). The Templeton group observed a tendency of the system to afford *cis*-aziridines preferentially.



23 **24**

Scheme 6. *Templeton's boron trifluoride-catalysed aza-Darzens reaction.*

Templeton's proposed mechanism for formation of $C_{2,3}$-disubstituted *cis*-aziridines (Scheme 7) involves coordination to Lewis acid, including the simplest proton, allowing the nucleophilic addition of diazoacetate **26**, resulting in formation of the zwitterionic intermediate **27**. Subsequent ring closure and loss of nitrogen gas provides aziridines **28**. By-products **31** and **32** result at the zwitterionic intermediate from 1,2-migration of either the R^1 substituent or H to the incipient carbocation to yield initially **29** and **30**. The tautomeric equilibrium favours formation of enamides **31** and **32**, which have a conjugated π-system and a six-membered hydrogen-bonded ring conformation.

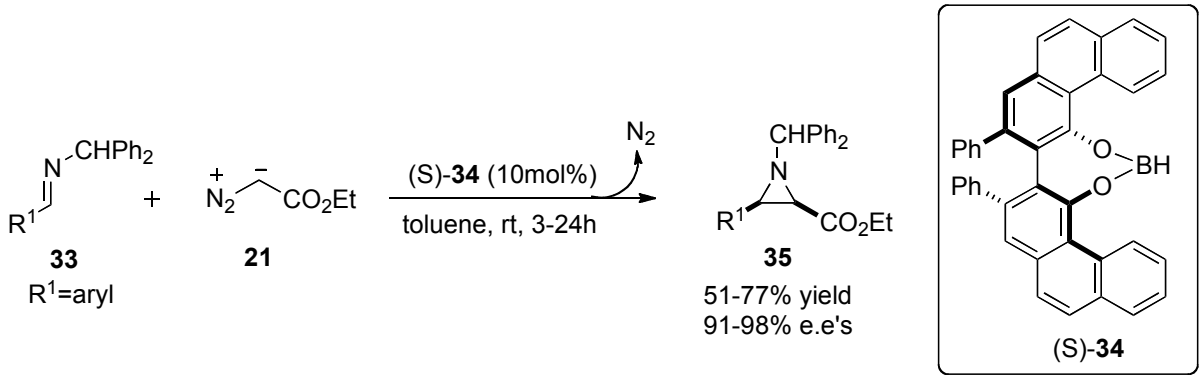


25 **26** **27** **28** **29** **30** **31** **32**

Scheme 7. *Templeton's mechanism accounting for the formation of aziridine **28** and enamide byproducts **31** and **32**.*

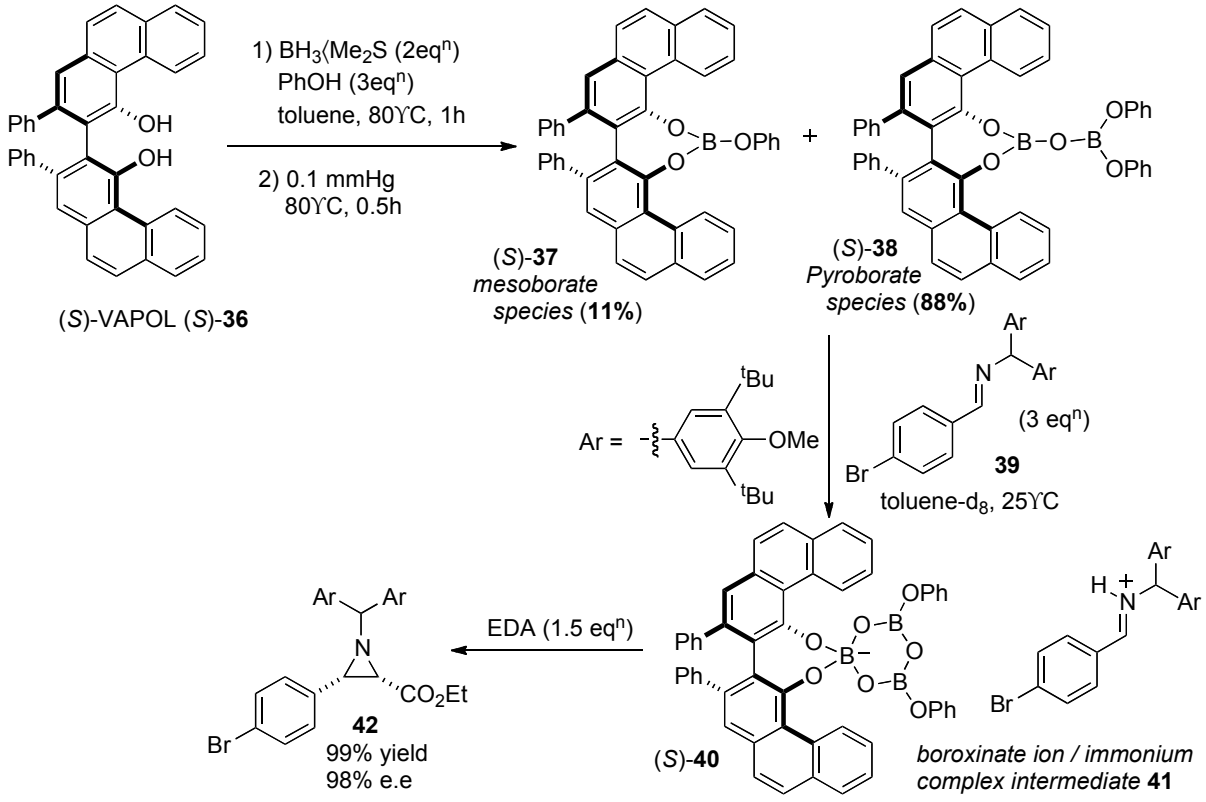
These achiral catalytic systems foreshadowed the work of Wulff *et al.* To date, Wulff's studies are among the most successful contributions to the Lewis acid-catalyzed enantioselective aziridination of *N*-substituted imines with alkyl diazoacetates.[11] The first catalytic system developed in 1999 by Wulff and Antilla was based on the use of the chiral

vaulted biphenanthrol ligand (*S*)-VAPOL-derivative (*S*)-**34** (Scheme 8). The chiral Lewis acid was prepared from the reaction of the (*S*)-VAPOL ligand with borane-tetrahydrofuran complex. The achievement of a high level of both diastereoselectivity and enantioselectivity was restricted to the use *N*-benzhydryl substituted imines **33**.



Scheme 8. *Wulff's (S)-**34**-catalysed enantioselective synthesis of $C_{2,3}$-disubstituted cis-aziridines*

Further optimization studies led to a refinement of the catalyst structure as well as to the identification of an active (*S*)-VAPOL-derived boroxinate catalytic species (*S*)-**40**, generated from the reaction between (*S*)-VAPOL (*S*)-**36** and triphenyl borate $B(OPh)_3$ (Scheme 9).[11h]

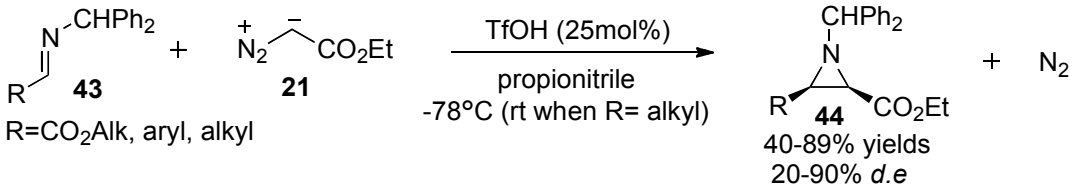


Scheme 9. *(S)-VAPOL-derived boroxinate species (S)-**40** formation and potential catalytic aziridine formation.*

Mechanistic investigations carried out by the Wulff research group have found evidences for Brønsted acid catalysis, which would be exerted by the boroxinate anion / immonium cation complex intermediate **41**, depicted in the reaction Scheme 9. According to Wulff, reaction of (*S*)-VAPOL (*S*)-**36** with a solution of borane and phenol affords two species, characterized by the mesoborate (*S*)-**37** and the pyroborate (*S*)-**38** functionality (Scheme 9). However, treatment of this mixture with three equivalents of imine **39** generated the boroxinate intermediate **41**, which was scrutinized and identified by ^{1}H- and ^{11}B-NMR spectroscopy. The boroxinate catalyst (*S*)-**40** was found to induce high levels of asymmetry for the addition of ethyl diazoacetate to *N*-benzhydrylimine. If the activation mode proposed by Wulff and his group is correct, then the developed catalytic system would no longer be a Lewis acid but a Brønsted acid.

1.7 Brønsted acid-catalysed aza-Darzens reaction

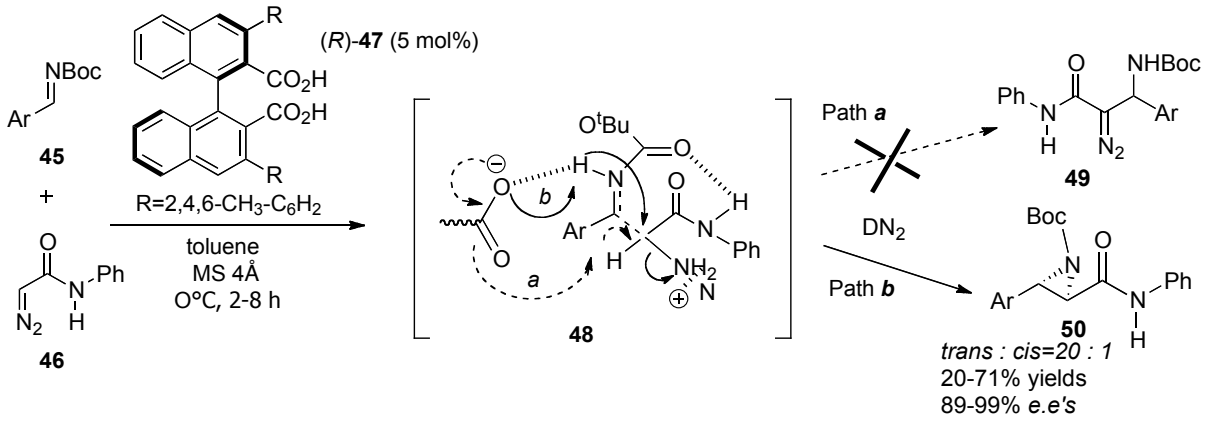
Johnston's observation that Brønsted acids could catalyse addition of ethyl diazoacetate to *N*-substituted imines[12] holds the same importance of Templeton's and Jorgensen's studies in the regard of the corresponding Lewis acid-catalysed reaction. Johnston's discovery allowed organocatalysis to access the aza-Darzens synthetic system, offering the chance to develop organocatalytic enantioselective methodologies. Johnston's group, after investigating the effect of the strength of Brønsted acids on the aza-Darzens reaction, developed a triflic acid-catalysed protocol for the synthesis of *cis*-aziridines **44** from *N*-benzhydryl imines **43** and ethyl diazoacetate **21** (Scheme 10). The Johnston group found that formation of the resulting *cis*-aziridines **44** heavily depended on the strength of the acid employed as catalyst. They observed no reaction when acetic acid (pK_a = 4.76) was used as catalyst. However, catalysis by stronger acids (pK_a < 0) resulted in a high yielding and faster (2.5-5h) process (58-74%). The triflic acid catalysis afforded an excellent level of yield and diastereoselectivity for aziridines **44** when the *N*-benzhydryl imines **43** were functionalized with electron-deficient *C*-substituents, affording racemic *cis*-aziridines **44** as the major isomers.



Scheme 10. *Johnston's synthesis of cis-aziridines **44** catalysed by triflic acid.*

In apparent contradiction to the effect of pK_a on the aza-Darzens reaction found by Johnston, Maruoka *et al.* described the *trans*-selective asymmetric aziridination of diazoacetamide **46**

and *N*-Boc-imines **45** catalysed by axially chiral dicarboxylic acid (*R*)-**47** (Scheme 11).[13]



Scheme 11. *Maruoka's asymmetric aziridination of diazoacetamide* ***46*** *and N-Boc-imines* ***46*** *catalysed by (R)-****47****. The transition states leading to the alkylation products* ***49*** *(Path* ***a****, dashed arrows) and to the formation of aziridines* ***50*** *(path* ***b****, continuous arrows) are shown, as well as for the H-bonding system (bold dashed lines).*

Maruoka *et al.* envisaged that lowering the acidity of the α-proton of the diazocarbonyl group by using diazoamides, the formation of the aziridine motif **50** would become the favoured synthetic path over the Friedel-Crafts type adduct **49** observed. The BINOL-derived dicarboxylic acid catalytic system (*R*)-**47** returned $C_{2,3}$-disubstituted *trans*-aziridines **50** in high diastereo- and enantioselectivities, although yields were relatively low for many examples. The *trans*-selectivity was explained in terms of steric and H-bonding interactions of the diazoamide functionality **46** respectively with the aryl group and the Boc-protecting groups of imines **45** (Figure 12).

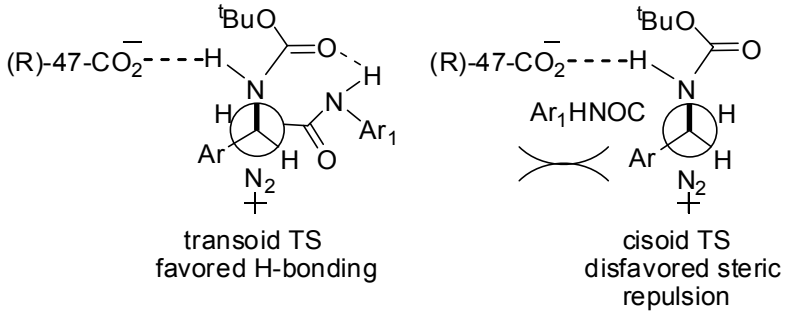
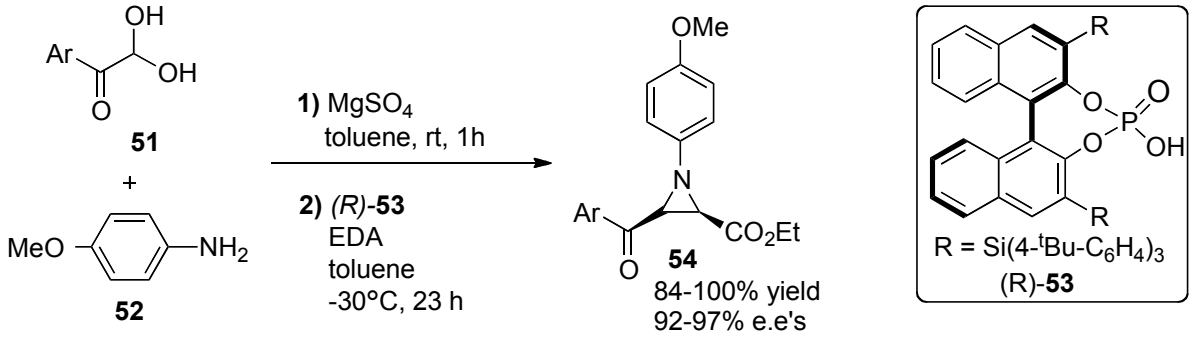


Figure 12. *Maruoka's possible explanation for the observed diastereoselectivity.*

Formation of alkylation products can also be inhibited in favour of the aziridine synthesis increasing the nucleophilicity of the nitrogen, *i.e.* replacing the electron-withdrawing *N*-Boc-group with an appropriate *N*-substituent. The Akiyama[14] research group reported a very high yielding and highly selective asymmetric addition of ethyl diazoacetate to *N*-(*p*-methoxyphenyl)-substituted imines **52** catalyzed by (*R*)-BINOL-derived phosphoric acid (*R*)-

53 (Scheme 12). However, the method is restricted to the use of electron-deficient aryl-substituted glyoxals **51**, which are among the most reactive starting materials for the aza-Darzens reaction. It is interesting to note that Maruoka's and Akiyama's (and perhaps Wulff's) methods are the only organocatalytic asymmetric aza-Darzens reactions affording chiral non-racemic aziridines reported to date, although their methods are shadowed by strong limitations.

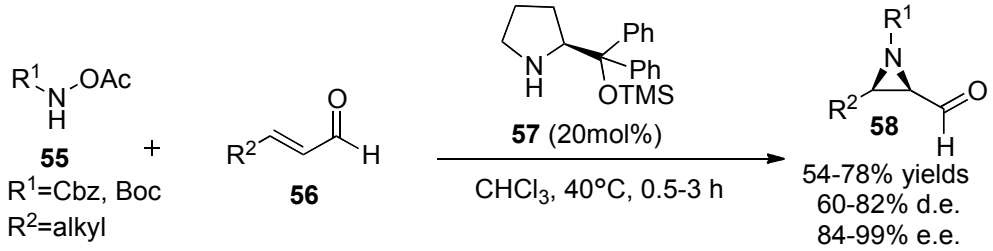


Scheme 12. *Akiyama's enantioselective aza-Darzens reaction of glyoxals* ***51*** *catalysed by (R)-****53****.*

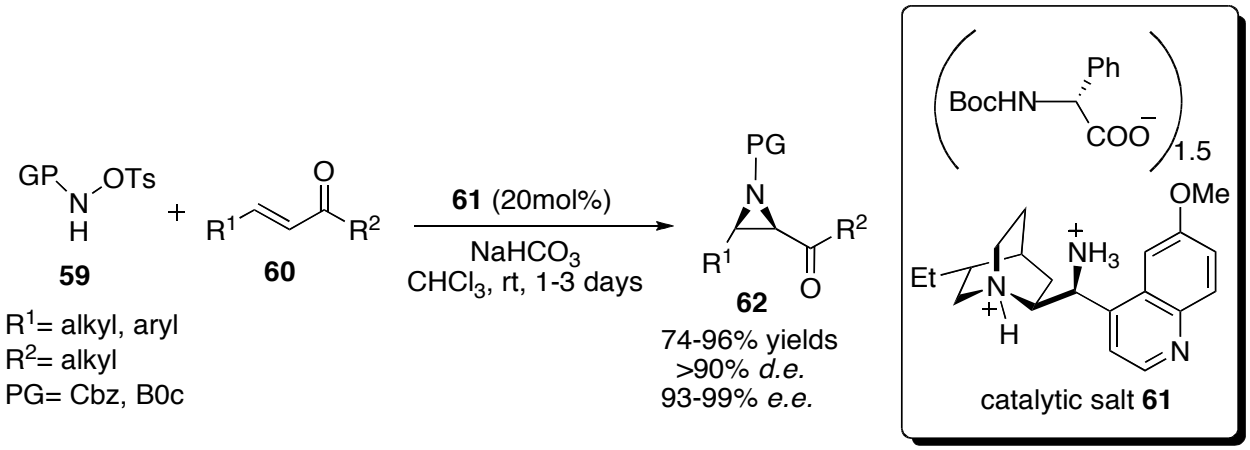
1.8 Other organocatalytic methods for the synthesis of chiral non-racemic aziridines

The use of quaternary salts of chiral cinchona alkaloids as phase-transfer catalysts[15] represented the main catalytic approach, although chiral Troger's base[16] and quinine[17] were also found to promote the asymmetric reaction. Nevertheless, the induced level of enantioselectivity for these examples was promising but still unsatisfactory, as for yields in many cases too.

Excellent progress on the organocatalytic enantioselective aziridination of electron-deficient olefins were reported by Cordova *et al.* in 2007.[18] The Cordova research group reported a highly chemo- and enantioselective organocatalytic aziridination of α,β-unsaturated aldehydes **56** with acylated hydroxycarbamates **55** (Scheme 13). The organocatalyst employed to promote the reaction consisted in the simple chiral pyrrolidine derivative **57**, which afforded *trans*-2-formylaziridines **58** in moderate-to-good yields with diastereoselectivities of up to 82% and enantioselectivities of up to 99%.



Scheme 13. *Cordova's enantioselective aziridination of α,β-unsaturated aldehydes* ***56****.*



Scheme 14. *Melchiorre's asymmetric aziridination of enones* ***60*** *catalysed by salt* ***61***.

A closely related strategy was applied by Melchiorre *et al.* in 2008 to the asymmetric aziridination of α,β-unsaturated ketones. The catalytic system introduced was a chiral primary amine salt **61** (Scheme 14), derived from reaction between the easily available 9-amino(9-deoxy)*epi*-hydroquinine with D-*N*-Boc-phenylglycine.[19] Catalyst **61** mediated the reaction of both linear and cyclic α,β-unsaturated ketones **60** with tosylated hydroxycarbamates **59**. *Trans*-aziridines **62** were afforded in high selectivities.

2 Organocatalysis

The use of small organic molecules to catalyse organic transformations, called organocatalysis, has been documented periodically over the past century; the field had to wait the 1990s to be born.[20] There are essentially four types of organocatalysis, Lewis bases, Lewis acids, Brønsted bases and Brønsted acids. These catalysts initiate their catalytic cycles by providing or removing electrons or protons from the transition state. The state-of-the-art in asymmetric catalysis is dominated by metal based chiral catalysts almost exclusively. The kingdom of metal-centred catalysis covered a wealth of asymmetric oxidation, reduction, σ-bond insertions, π-bond activations and Lewis-acid-catalysed reactions.

Metal-centred Lewis acid catalysis is certainly a highly versatile and powerful technique and it may seem to have several key advantages for Brønsted acid catalysis. Lewis acids are highly tuneable, which is a fundamental aspect of catalyst design.[21] The steric and electronic environment of the catalyst could be adjusted through a number of parameters, *e.g.* the identity of the Lewis acidic element, the counterion, and the chiral organic ligand framework. Moreover, a Lewis acid/base interaction consists of dative bonds, which are considerably stronger and more directional than H-bonds.

The great success of the field lies indeed upon the identification of generic modes of catalyst activation, induction and reactivity.[22] These properties are crucial for determining the efficiency of a catalytic system. Privileged catalysts are those that, because of their generic mode of action, can participate in many reaction types with consistently high enantioselectivity (as opposed to one or two unique transformations). The catalytic species interacts with one or more functional groups (such as a ketone, aldehyde, alkene or imine) in a highly organised and predictable manner. The value of generic activation modes is that, after they have been established, it is relatively straightforward to use them as a platform for designing new enantioselective reactions. Indeed, most of the 130 organocatalytic reactions that have been reported since 1998 are based on only five or six activation modes.

2.1 Activation modes in organocatalysis

Catalysis by means of proton donors has been widely understood in the course of the past decades.[23] There are two fundamental mechanisms according to which Brønsted acids can accelerate organic reactions: reversible protonation of the electrophile prior to nucleophilic attack (specific acid catalysis), or proton transfer to the transition state in the rate-determining step (general acid catalysis). The discussion of the activation modes that follows herein is also meant to group and classify the various classes of organocatalysts, as reported by

Jacobsen in his excellent review.[21] Thus, organocatalysts could be classified as: bifunctional hydrogen-bond donor catalysts, double hydrogen-bond donor catalysts and single hydrogen-bond donor catalysts. Particular emphasis is given to BINOL-derived Brønsted acid catalysts, which are the main subject of this dissertation. More detailed informations about enantioselective organocatalysed chemical transformation are available in several excellent reviews.[24]

2.2 Bifunctional hydrogen-bond donor catalysts

The development of dual activation strategies represents one of the most innovative advantages that organocatalysis offers over metal-centered catalytic systems. A bifunctional catalyst is a molecule bearing both Lewis basic and acidic sites, thus capable of simultaneous activation of nucleophile and electrophile. Proline and its analogues, cinchona alkaloids and their derivatives, bifunctional thiourea derivatives, oligopeptides, catalytic antibodies, RNA and H-bonding phase transfer catalysts belong to this class of organocatalysts (Figure 13).

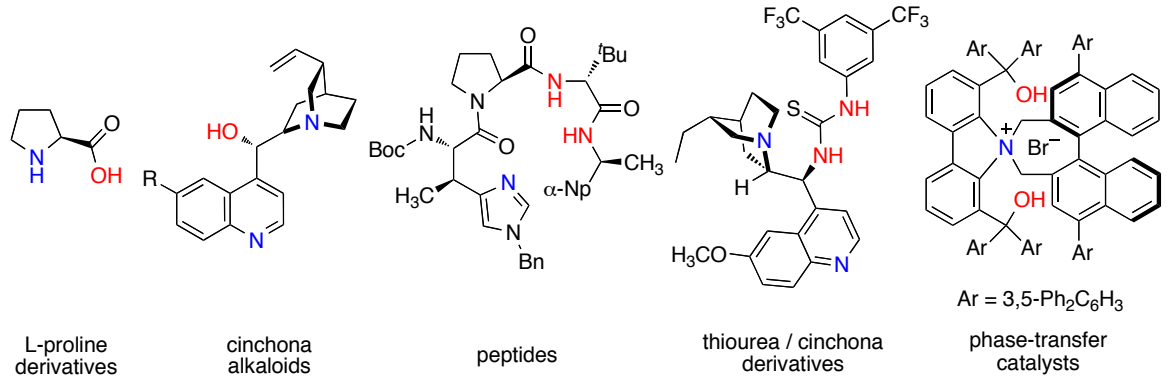
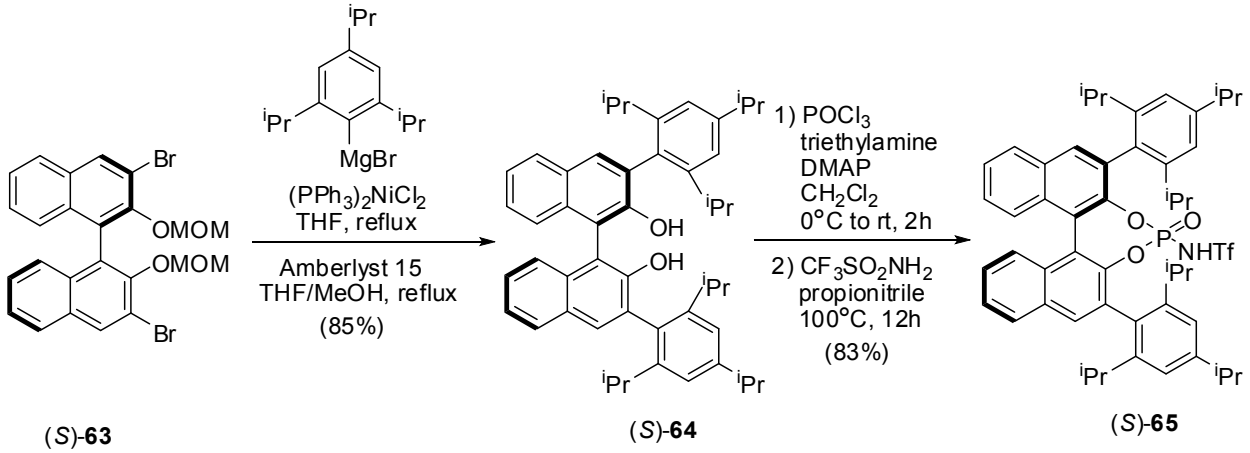


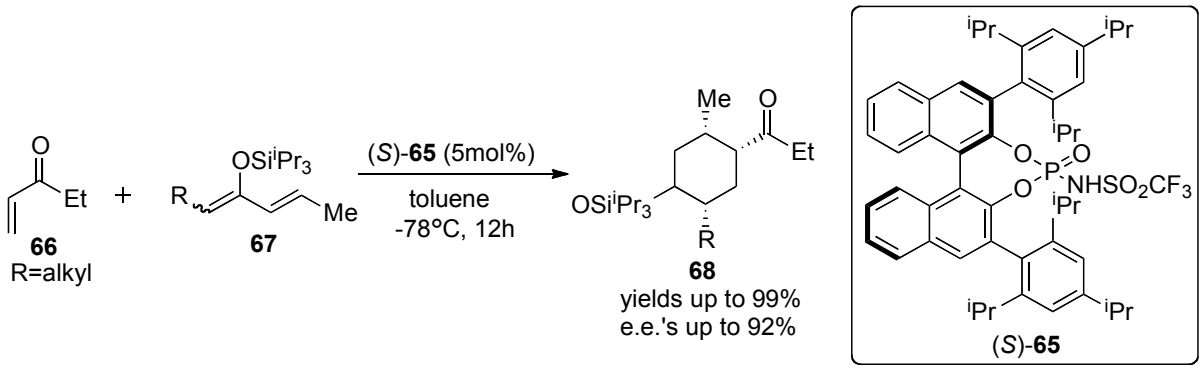
Figure 13. *Examples of generic bifunctional catalysts. Activation sites for nucleophiles (in blue) and electrophiles (in red) are shown.*

This chapter describes the synthesis of chiral non-racemic enantiopure aziridines using N-triflylphosphoramide catalysts, while highlighting the synthesis of (+)-chloramphenicol, which is the main goal of this project. (S)-BINOL-derived N-triflylphosphoramides were used as catalysts, which had already been prepared in the Bew group, inspired from Yamamoto's work using his methodology and results. Since Yamamoto's report was published at the end of 2006, the novel *N*-triflyl phosphoramide catalytic system has experienced an impressively growing number of successful applications in asymmetric synthesis.[25]



Scheme 15. *Synthesis of Yamamoto's catalyst.*

In an effort to expand the substrate scope of chiral Brønsted-acid-catalysed reactions, Yamamoto and co-workers developed a stronger chiral Brønsted acid catalytic system. The Yamamoto group synthesised the *N*-triflyl phosphoramide (*S*)-**65**, bearing an axially chiral BINOL backbone, and demonstrated its ability to catalyse the Diels-Alder reaction of the α,β-unsaturated ketone **66** with electron-rich dienes **67** affording cyclohexene derivatives **68** with high enantioselectivities (Scheme 16)

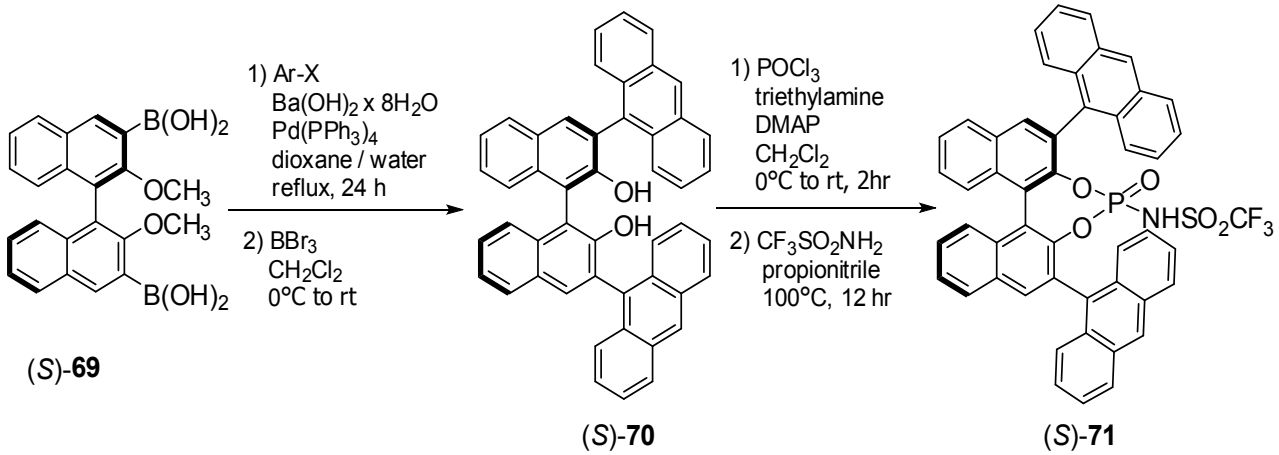


Scheme 16. *Yamamoto's asymmetric Diels-Alder reaction catalysed by the chiral N-triflylphosphoramide (S)-**65**.*

2.3 Synthesis of the (S)-BINOL-derived N-triflylphosphoramides

By using Yamamoto's concept mentioned above, the Bew group came up with a new strategy and developed a stronger chiral Brønsted acid catalytic system. The synthesis of the *N*-triflylphosphoramides was accomplished following Yamamoto's synthetic protocol (Scheme 17). Suzuki couplings were carried out with the BINOL diboronic acid **69**. The phosphoramidation reactions consisted of straightforward one-pot two-step transformations involving the 3,3'-substituted BINOL (*S*)-**69** as starting material. Similar to the phosphorylation reaction protocol, (*S*)-**70** was reacted with phosphorus oxychloride (1.2 eq) in the presence of organic bases, such as triethylamine (7 eq) and 4-dimethylaminopyridine (2

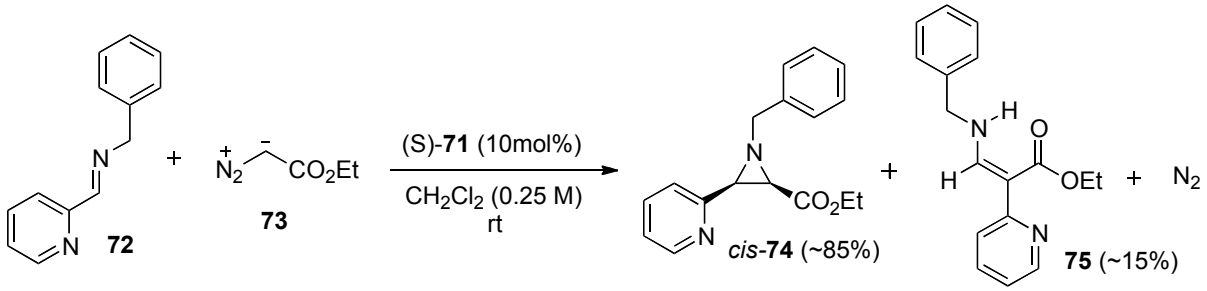
eq), at room temperature. Subsequent *in situ* addition of trifluoromethanesulfonylamide generated catalyst (*S*)-**71** (57% yield).



Scheme 17. *Synthesis of Bew group's catalyst (S)-**71***

2.4 Aza-Darzens reactions catalyzed by the N-triflylphosphoramides (S)-71

The catalytic activity of the chiral Brønsted acids (*S*)-**71** was investigated by performing the experiment depicted in Scheme 18. This catalyst was used to promote the reaction between the *N*-benzylimine **72** and ethyl diazoacetate **73** at room temperature. The Bew group observed in all the experiments not only the exclusive formation of the aziridine *cis*-**74** (~85% yield), but also the completion of the reaction overnight. Moreover, careful scrutinization of the ^{1}H-NMR crude spectra proved that 1) consumption of the starting *N*-benzylimine **72** was achieved; 2) the only by-product consisted in the formation of enamide **75** (~15% yield); 3) no traces of *trans*-aziridine were found in the crude mixtures.



Scheme 18. *Bew group's template reaction for the screening of catalyst (S)-**71**.*

In terms of yields, the experiment fully demonstrated the importance of the strength of the Brønsted acid employed to catalyse the aza-Darzens reaction under these conditions. By simply replacing BINOL-derived phosphoric acids with the analogue *N*-triflylphosphoramides, the yields and reaction rates for the formation of the aziridine *cis*-**74** changed drastically from less than 5% to up to 85%. After reaching this point The Bew group studied different parameters such as observations about the spatial geometry of the catalyst structures, screening of the N-protecting group on the starting imine, screening of the

temperature, concentration, solvent, catalyst loading, C-substituent on the starting *N*-(2-tert-butoxyphenyl) imine etc. and finally they established a optimized method and catalyst for the synthesis of aziridines which gave excellent yields (99%) and high enantioselectivities (99% e.e)

2.5 Synthesis of (+)-Chloramphenicol

The last stage when developing a synthetic methodology is to ensure that its efficiency could find practical applications. For their tendency to ring-open, chiral non-racemic aziridines are extremely valuable intermediates, representing the precursors for the synthesis of a great number of pharmacologically and biologically active compounds. Here we propose the synthesis of (+)-chloramphenicol, which seemed to be suitable to our task to provide a simple example of the efficiency of the method.

3 Asymmetric Organocatalytic Synthesis of Aziridine Using F+ Salt

As discussed in Chapter 1, aziridines are relatively reactive, synthetically useful, three-membered ring heterocycles that are commonly employed in the synthesis of other heterocyclic entities.[26] Although there are numerous protocols for the synthesis of *N*-activated aziridines,[11b, 27] there are in comparison fewer protocols that detail generally applicable methods for *N*-trimethylsilyl or *N*-arylaziridine synthesis from imines.[28] Furthermore, few innovative organocatalytic methods that generate NH[16, 29] and *N*-arylaziridines[30] have been reported, despite the acknowledged potent biological activity of *N*-arylaziridines.[31] Methodology for *N*-arylaziridine synthesis has focused, in the main, on employing strong Lewis acid or transition-metal complexes. Thus, Templeton *et al.* reacted ethyl diazoacetate with a Lewis acid, *i.e.* BF_3•Et_2O, $AlCl_3$, or $TiCl_4$ (10 mol %) activated *N*-arylimine and generated racemic mixtures of *cis*- and *trans*-$C_{2,3}$-disubstituted *N*-arylaziridines in variable yields (2-76%).

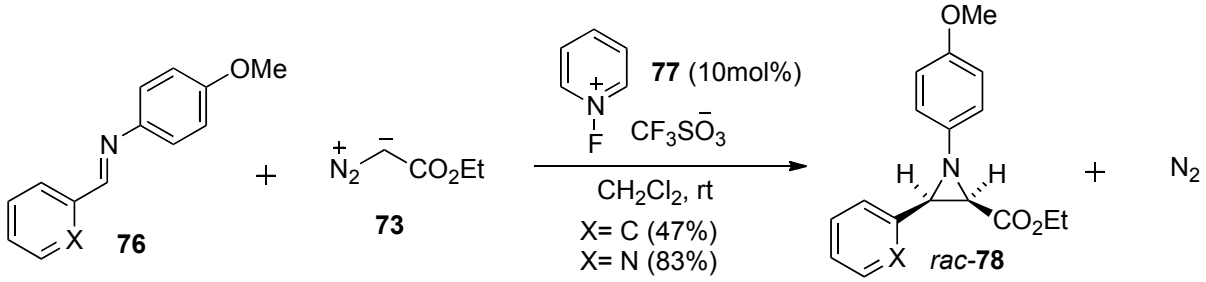
The Bew group has reported the first application of the fluoronium cation i.e., F^+ derived from an *N*-fluoroheterocyclic salt. They have demonstrated in this work that *N*-fluoroheterocyclic salts are powerful, versatile organocatalysts. One organocatalytic entity is capable of generating both *N*-aryl- and NH-$C_{2,3}$-disubstituted aziridines. The successful application of the pyridinium triflate catalysis to the aza-Darzens reaction, led us to explore the catalytic properties of a structurally similar salt, the *N*-fluoropyridinium triflate. To date, there is no application of the fluoronium cation, F^+, derived from N-fluoroheterocyclic salts,[32] as a convenient, highly effective organocatalyst in organic synthesis. The use of this class of compounds has been so far restricted to fluorination reactions. The results reported in this project demonstrate that easily available *N*-fluoroheterocyclic salts are powerful, versatile organocatalysts that mediate, possibly through halogen bonding substrate activation, the reaction between ethyl diazoacetate and *N*-arylimines or *N*-trimethysilylimines such that a diverse range of *N*-aryl-$C_{2,3}$-disubstituted aziridines or NH-$C_{2,3}$-disubstituted aziridines are generated in good yields and often with good stereoselectivities.[33]

The Bew group discounted the use of triflic acid (*cfr*. Johnston work)[34] and the application of protic salts and acids because of their incompatibility[35] with our desire to utilize *N*-TMS imines as precursors to $C_{2,3}$-disubstituted *N*-TMS-aziridines. The *N*-TMS protecting group offers several advantages to this particular study: 1) the lower stability of the N-F bond, compared to the N-H bond, should prevent any eventual cleavage of the TMS group exerted

by the triflate; 2) considering the high electrophilic nature of the F^+ ion, eventuality of redox processes taking place in the system must be taken in account; if this happened, the resulting fluoride F^- would probably be subtracted from the equilibrium by the TMS and the catalytic cycle would stop; 3) The *N*-TMS group is so labile that was found to be easily removed from aziridines during the chromatographic purification on silica gel, therefore allowing a direct one-pot synthesis of valuable N-H aziridines from the corresponding imines. The Bew group also considered the fluoronium salts to have properties and benefits that many currently employed Lewis and Brønsted acids do not always have, *i.e.*, easily handled, stable, crystalline, non-hygroscopic, organic soluble salts which produce a relatively benign and easily removed by-product.[36]

3.1 Optimization studies of the catalytic system

The Bew group's preliminary studies focused on the reaction between *N*-arylimine **76** (X = N), ethyl diazoacetate **73**, and *N*-fluoropyridinium triflate **77** (10 mol %, Scheme 19). Gratifyingly, after 5 hours at ambient temperature, TLC analysis indicated complete consumption of **76**.



Scheme 19. *Synthesis of N-arylaziridines rac-**78***

Workup (filtration through a plug of alumina) and ^{1}H-NMR analysis indicated that *rac*-**78** was afforded cleanly (83% yield), and, from the $J_{2,3}$ coupling constant of 6.8 Hz, with $C_{2,3}$-*cis*-stereochemistry. There was no indication that any of the *trans*- isomer of *rac*-**78** was present.

As part of our on-going investigation towards new synthetic routes to aziridines, we wanted to develop a chiral non-racemic organocatalyst using an F^+ salt. Cinchona alkaloids have a venerable history in the field of asymmetric synthesis owing to their established ability to induce asymmetry, and we decided to take advantage of this naturally occurring cheap source of chirality. In this chapter we demonstrate that a unique and optically active chinchona alkaloid organocatalyst can mediate the asymmetric synthesis of enantiopure aziridine.

3.2 Introduction of cinchona alkaloid

The role of cinchona alkaloids in organic chemistry was firmly established with the discovery

of their potential as resolving agents by Pasteur in 1853, which ushered in an era of racemate resolutions by the crystallisation of diastereomeric salts.[37] Today, there are countless examples in which cinchona alkaloids are used as chiral resolving agents[38] Besides the classical resolution process, significant progress has also been made in the past two decades in the field of cinchona-based enantioseparation, as well as in their use as enantioselective analytical tools.

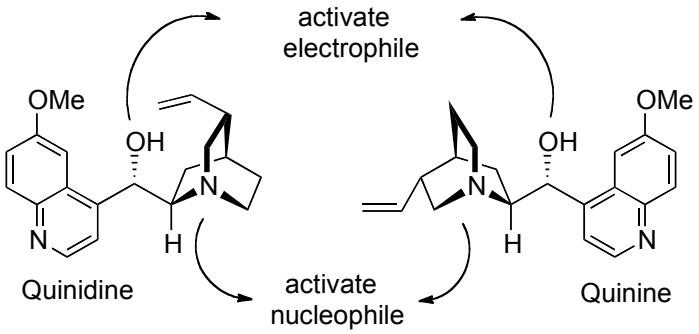


Figure 14. *Activated electrophile and nucleophile in Quinine and Quinidine*

However, possibly the most interesting application of cinchona alkaloids in chemistry resides in their ability to promote enantioselective transformations in both homogeneous and heterogeneous catalysis. Pracejus was first to obtain useful levels of enantioselectivity (74% e.e) by using O-acetylquinine as a catalyst (1 mol%), in the addition of methanol to phenylmethylketene, affording (-)-phenylmethylpropionate.[39] Two decades (in the late 1970s and early 1980s) after Pracejus, Wynberg and coworkers began a new era in asymmetric catalysis driven by cinchona alkaloids.[40] Their extensive studies on the use of cinchona alkaloids as chiral Lewis base/nucleophilic catalysts demonstrated that this class of alkaloid could serve as highly versatile catalysts for a broad spectrum of enantioselective transformations (e.g., conjugate additions and the addition of ketenes to carbonyl compounds, resulting in β-lactones). During the late 1980s and early 1990s, quite successful examples in terms of the catalytic activity and enantioselectivity were reported, where the asymmetry was induced by cinchona alkaloids. Furthermore, since 2000, the dramatically expanding interest in chiral organocatalysis as a new stream of catalysis[41] has sparked a second renaissance in the use of cinchona alkaloids. Thus, nowadays, cinchona alkaloids and their derivatives are classified as one of the most privileged of organic chirality inducers efficiently catalysing nearly all classes of organic reactions in a highly stereoselective fashion.

3.3 Active Sites in Cinchona Alkaloids

The key feature responsible for their successful utility in catalysis is that they possess diverse chiral skeletons and are easily tuneable for diverse types of reactions (Figure 15). The presence of the 1,2-aminoalcohol subunit containing the highly basic and bulky quinuclidine,

which complements the proximal Lewis acidic hydroxyl function, is primarily responsible for their catalytic activity. The presence of the quinuclidine base functionality makes them effective ligands for a variety of metal-catalysed processes. The most representative example is the osmium-catalysed asymmetric dihydroxylation of olefins.[42] The metal binding properties of the quinuclidine nitrogen also allows the use of cinchona alkaloids as metal surface modifiers.

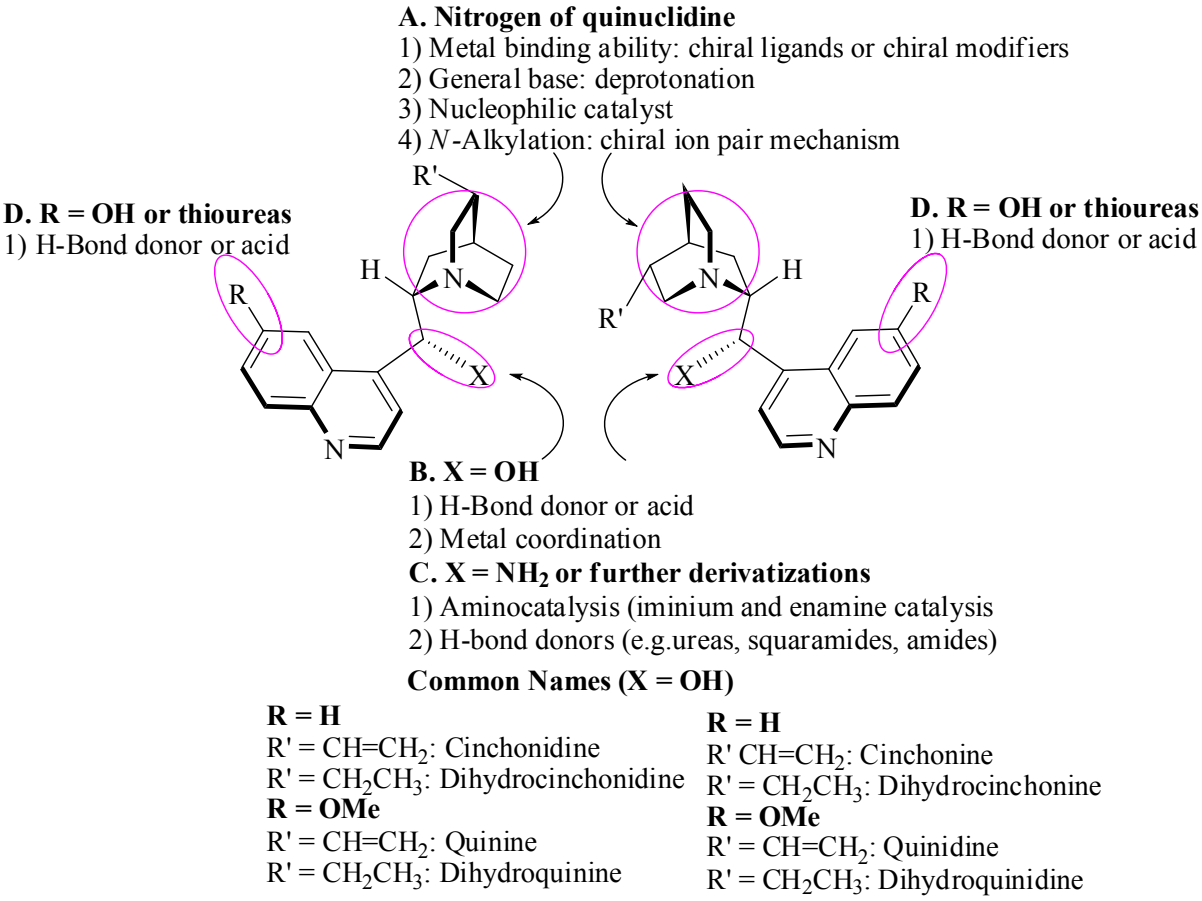


Figure: 15 *Active sites in cinchona alkaloids and their derivatives.*

In addition to its utility for metal binding, the quinuclidine nitrogen can be used as a chiral base or a chiral nucleophilic catalyst promoting many of organocatalytic reactions. Finally, the related quaternized ammonium salts of cinchona alkaloids have proved to catalyse numerous reactions under phase-transfer conditions, where asymmetric inductions occur through a chiral ion pairing mechanism between the cationic ammonium species and an anionic nucleophile.[43] The secondary 9-hydroxy group can serve as an acid site or hydrogen bond donor. The derivatization of the OH group into ureas, amides, and so on, with either retention or inversion of configuration, provides a more powerful acidic site or hydrogen bond donor. The 6'-methoxy group of quinine and quinidine can also be readily derivatized for example to the free OH group or thiourea moiety, which can serve as an effective H-bond donor. Moreover, the substitution of 9-OH by a free amino group with the inversion of the

configuration enables enantioselective aminocatalysis, which includes reactions of the so-called generalized enamine cycle[44] and charge-accelerated reactions through the formation of iminium intermediates.[45] However, in general, these active sites in cinchona alkaloids and their derivatives act in catalysis not independently but cooperatively; that is, they interact with reacting molecules simultaneously. Furthermore, in many cases, the catalysis is also supported by a π–π interaction with the aromatic quinoline ring or by its steric hindrance.

3.4 Structural information of cinchona alkaloids

Cinchona alkaloids have characteristic structural features that separate their conformations and self-association phenomena. Therefore, knowledge of their real structure in solution can provide original information on the chiral inducing and discriminating ability of these alkaloids.

Conformational investigations of this class of alkaloids, based on computational and spectroscopic methods, have been undertaken with the aim of providing information that would help to understand these chiral induction and discrimination processes. Dijkstra et al. were the first to investigate in 1989 the conformational behaviour by means of NMR spectroscopic and molecular mechanics (MM) calculations, and to identify that the C8-C9 and C4'-C9 bonds are the most important in determining the overall conformation, resulting in four low-energy conformers (*syn*-closed, *syn*-open, *anti*-closed, and *anti*-open conformers) (Figure 16).[46] MM calculations showed that the parent alkaloids preferentially adopt an *anti*-open conformation in nonpolar solvents. More sophisticated *ab initio* calculations conducted later also revealed that anti-open is the most stable conformer in apolar solvents.[47,48] In polar solvents, two other conformers, *syn*-closed and *anti*-closed, are strongly stabilized compared to the *anti*-open conformer, due to the greater support provided by their large dipole moments[48].

However, upon protonation, the *anti*-open conformation is observed exclusively.[48] The protonation of cinchona alkaloids appears to hinder rotation around the C4'-C9 and C9-C8 bonds and favour only a narrow range of the conformational space of the molecule.[49] The pivotal role of the conformational behaviour of a cinchona alkaloid (e.g., cinchonidine) on its enantioselectivity was nicely illustrated in the platinum-catalysed enantioselective hydrogenation of keto-pantolactone in different solvents.[48] The achieved enantiomeric excess shows the same solvent dependence as the fraction of *anti*-open conformer in solution, suggesting that this conformer plays a crucial role in the enantiodifferentiation. In addition to

the solvent polarity, many other factors such as intermolecular interactions are also responsible for the complex conformational behaviour of cinchona alkaloids in solution.

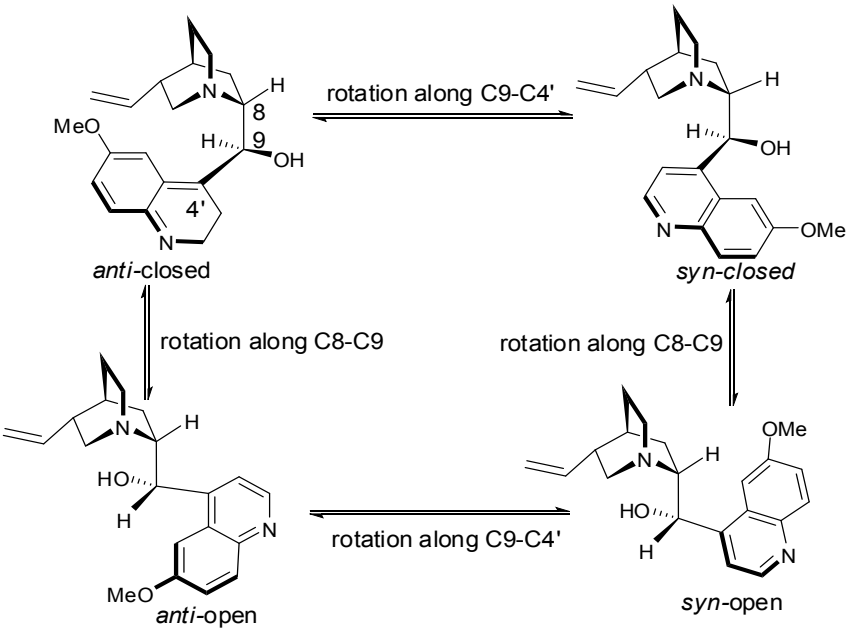
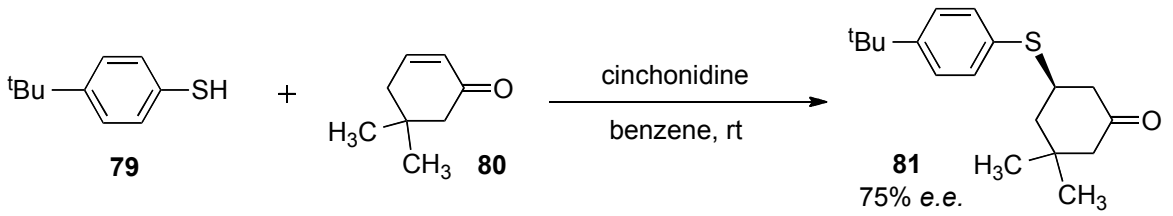


Figure 16. *The four conformers of quinidine showing the lowest energy.*

As discussed, the solvent dipole moments, concentration, and temperature play a significant role in determining the structure of cinchona alkaloids and their derivatives in solution. In order to delineate the intimate details of the mechanism of action of cinchona alkaloids and their derivatives, a thorough understanding of their real structure in solution is needed. Furthermore, such detailed information on the real structure in solution would make it possible to develop new and more powerful chiral catalysts and discriminators.

3.5 Cincona alkaloids and their derivatives in organocatalysis

The bifunctional mode of activation of these compounds arises from the acidic hydroxy group that is present on their structure. Wynberg and Hiemstra in 1981 observed that the enantioselective conjugate addition of aromatic thiols, *i.e.* **79**, to cycloalkenones, *i.e.* **80**, (Scheme 20) proceeds with highest reaction rates and enantioselectivies when alkaloids that possess a free hydroxy group, such as cinchonidine **83**, cinchonine **85**, quinine **82**, and quinidine **84** (Figure 17), are used as catalysts.[50] This led Wynberg and Hiemstra to consider the bifunctional nature of these compounds, by which the nucleophile is activated by general base catalysis, and the electrophile by H-bonding.



Scheme 20. *Wynberg's enantioselective conjugate addition of thiol **79** to cycloalkenone **80**.*

In contrast, Deng and co-workers[51] reported a highly enantioselective variant of this transformation employing a cinchona-derived catalyst that lacked the free hydroxy group. The catalyst employed was the dimeric ligand $(DHQD)_2$-PYR **86** (Figure 17), previously developed by *Sharpless et al.* for asymmetric osmium-catalysed dihydroxylation of alkenes. However, it is likely that such a ligand operates by a different mechanism from that proposed by Wynberg, possibly discriminating between the prochiral faces of the substrate by steric factors rather than by hydrogen-bonding coordination.

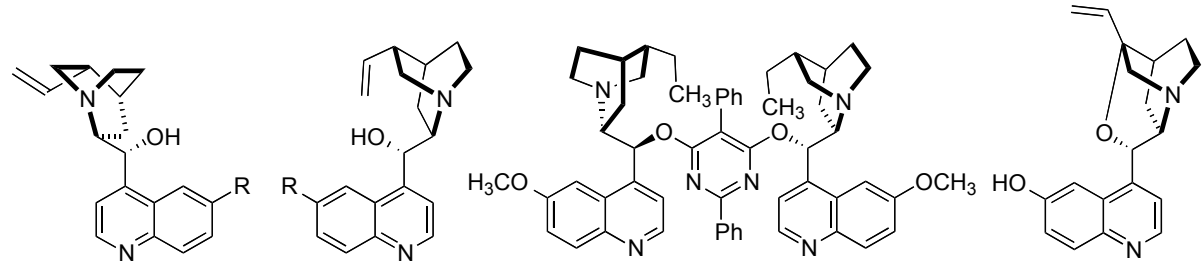
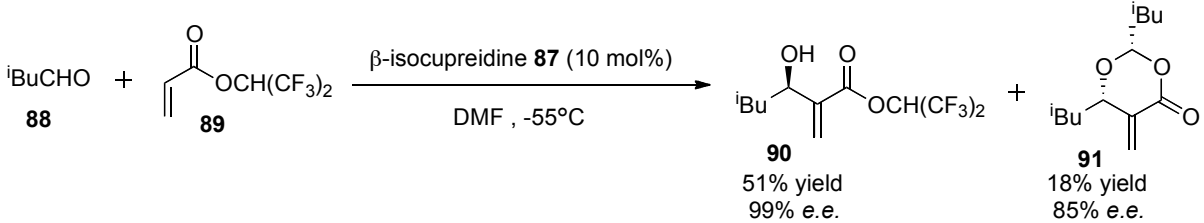


Figure 17. *Examples of natural and semi-synthetic alkaloids.*

In support of the bifunctional activation mode of these alkaloids, Hatakeyama *et al.* reported the organocatalysed enantioselective Baylis–Hillman reactions of hexafluoroisopropyl acrylate **89** with aromatic and aliphatic aldehydes, *i.e.* **88** (Scheme 21).[52] The catalyst employed was β-isocupreidine **87** (Figure 17), which bears an acidic phenolic hydroxy group. When the hydroxy group was methylated, the catalyst dramatically lost its enantioselectivity. Hatakeyama suggested that the occurrence of a hydrogen bond between catalyst and intermediate was the key for the high level of enantioinduction.



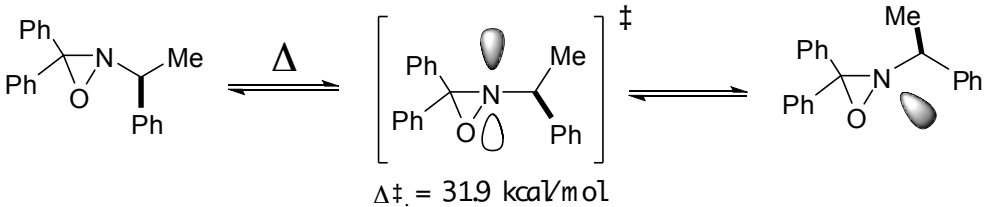
Scheme 21. *Hatakeyama's Baylis–Hillman-type reactions catalysed by β-isocupreidine **87**.*

4 Attempted Synthesis of Five-Membered Ring Heterocycles by Cyclization of NH-Oxaziridines with Alkenes

Oxaziridines, three-membered rings containing nitrogen, oxygen and carbon, have been of mechanistic and structural interest since their first report in a classic paper by Emmons in 1957.[53] This paper not only describes the preparation and structural proof of a new heterocycle, it also contains the basis for most oxaziridine chemistry known to the present day, including rich rearrangement chemistry and the decomposition of oxaziridines by low-valent metal salts.[54] In the years that followed, oxaziridines were mostly a curiosity that found little synthetic utility. This was despite significant efforts to devise nice methods for the synthesis of oxaziridines-ultimately settling on the oxidation of imines with peracids as the best method-and the attention of chemists interested in the configurational stabilization of a potential nitrogen stereocentre. It turns out that the combination of placing a nitrogen in a three-membered ring (which destabilizes the 120" angle of the sp2-like transition state involved in pyramidal inversion) with attaching the electron-withdrawing oxygen atom (which opposes the increased *S*-orbital character of nitrogen during inversion) makes simple oxaziridines the most easily prepared and synthetically useful class of compounds containing a *bonafide* nitrogen stereogenic centre. More recently, N-sulfonyl oxaziridines have become popular oxygen-transfer agents for the oxidation of olefins, sulfides and especially enolates. Asymmetric induction is often possible. This area has considerable promise in the use of oxaziridines as nitrogen-transfer reagents, for example for the synthesis of aziridines and hydrazine derivatives.

4.1 Stereochemistry of oxaziridine

The stereochemistry of the oxaziridine ring has received considerable attention mainly due to the chirality of the nitrogen atom and the appreciable barrier to its inversion. This barrier to inversion was determined to be 25-32 kcal/mol in N-alkyl oxaziridines.[55] The transition state for thermal epimerization was shown to have increased ring strain, thus providing the large barrier to nitrogen inversion.[56]



Oxaziridines have also been shown to epimerize photochemically through a nitrone intermediate.[57] While the inversion barrier is considerable in N-alkyl oxaziridines, when the N- substituent is capable of p- conjugation or hyperconjugation the inversion barriers are smaller. N-aryl as well as N-acyl oxaziridines both have inversion barriers near 20 kcal/mol[58] due to their p-conjugation. N-sulfonyl oxaziridines also exhibit lower barriers to inversion due to the hyperconjugation present in the system.

4.2 Synthesis and reactivity of oxaziridines

Chemical reactions involving electrophilic sources of nitrogen commonly require toxic or otherwise undesirable reagents, including tosyl azide, nitroso compounds, diimides, or azodicarboxylates, and new reagents are therefore desirable; indeed, the use of green sources of electrophilic nitrogen has been identified as an "aspirational reaction" by the pharmaceutical manufacturers.[59] Oxaziridines, characterized by a reactive strained C,N,O three-membered ring, have shown interesting reactivities as nitrogen and oxygen atom transfer reagents, and the synthesis and chemistry of oxaziridines have been widely studied.[60] It has been established that the attack of a nucleophile occurs at either the oxygen or the nitrogen atoms of the ring, depending upon the nature of the nucleophile and the substituents on the oxaziridine, especially at the nitrogen atom. For example, oxaziridines bearing electron-withdrawing substituents on the nitrogen atom or on both the nitrogen and the carbon atoms of the three-membered ring have been developed for their ability to transfer oxygen atoms to nucleophiles. In particular, *N*-(fluoroalkyl)oxaziridines,[61] N-phosphanyloxaziridines[62] and *N*-sulfonyloxaziridines [63] have proved to be efficient reagents for the oxidation of sulfides to sulfoxides, the asymmetric hydroxylation of enolates, and the stereoselective epoxidation of olefins. Davis in particular has shown that N-substituted camphoryl oxaziridines transfer oxygen to various nucleophiles with very good stereoselectivity, perhaps due to the steric hindrance close to the oxaziridine ring.[64] Oxygen transfer may also be performed with hindered oxaziridines and hindered nucleophiles,[65] and may be promoted by acid, forming an N-protonated oxaziridinium ion which is believed to be the active oxidizing species.[66]

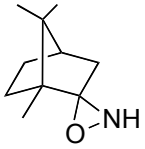
Nitrogen transfer has also been performed, mainly using N-H, N-alkyl-, N-aryl-, N-acyl-, N-carboxamido- or N-(alkoxycarbonyl) oxaziridines, with sulfur, nitrogen, phosphorus and carbon nucleophiles.[67] However, few electrophilic aminations have been carried out with enantiomerically pure chiral N-substituted oxaziridines.[68] To date, only a handful of reports of enantiomerically pure chiral N-acyloxaziridines have been published.[68-69] N-H oxaziridines, first reported in the early 1960s,[70] can be effective for the amination of nitrogen,

oxygen, sulphur and carbon nucleophiles,[71] and are potentially of great value today as relatively "green" sources of electrophilic nitrogen. Due to their general instability, however, very few N-H oxaziridines have been prepared, and fewer used for their ability to transfer nitrogen.[72] N-H oxaziridines also offer the attractive additional potential as enantioselective nitrogen transfer agents by incorporation of chiral elements into their structure.

4.3 Synthesis and Reactivity of NH-oxaziridine

N-H oxaziridines, first reported in the early 1960s, induce amination of nitrogen, oxygen, sulfur and carbon nucleophiles,[73] including aziridination of alkenes and amination of enolates. Page group reported the preparation of the first stable enantiomerically pure chiral N-H oxaziridines **92** and **93** together with a brief survey of their derivatization and chemical reactivity. Due to their instability, N-H oxaziridines must generally be prepared and used in dilute solution. The only one that has been isolated as a stable compound in pure form is compound **94**,[72] and the chemical reactivity of only one has been thoroughly investigated (compound **95**).

Their instability no doubt accounts for the dearth of knowledge and awareness of N-H oxaziridines. Nevertheless, this functional group appears to offer an intriguing alternative potential solution to the problem of asymmetric electrophilic nitrogen transfer, usually accomplished by use of chiral auxiliary chemistry.[74] For this reason Page group turned their attention to the synthesis and chemistry of chiral, non-racemic N-H oxaziridines **92** and **93**, derived from camphor and fenchone, respectively.



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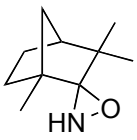

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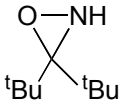

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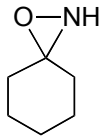

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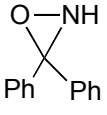

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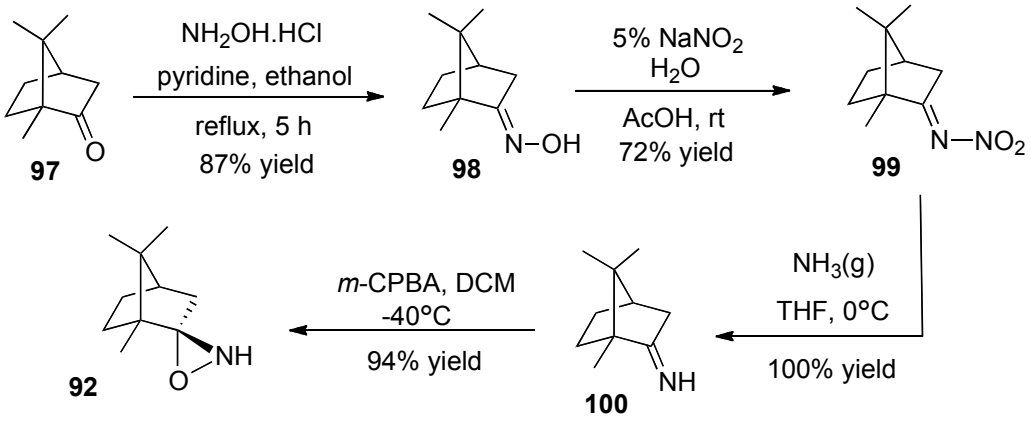
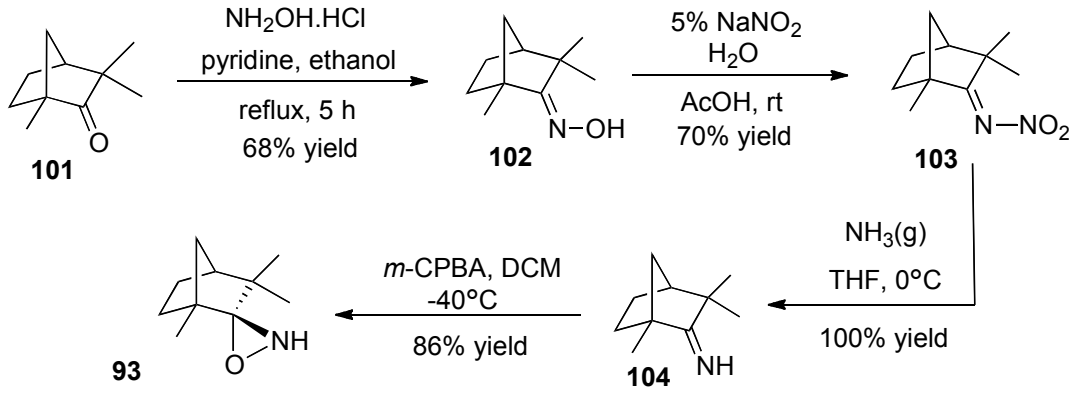
N-Acyl- and N-alkoxycarbonyloxaziridines have been shown to transfer their nitrogen moiety to a number of sulfur, nitrogen, phosphorus, and carbon nucleophiles and tend to be more stable. There has, however, been only one report of a chiral enantiomerically pure N-acyloxaziridine.[69] Most of N-acyl- and N alkoxycarbonyloxaziridines have been prepared by oxidation of N-protected imines of benzaldehydes.[75] N-Sulfonyl-[76] and *N*-phosphinoyloxaziridines,[77] useful oxygen transfer agents, are prepared in the same way. This method is efficient for the oxidation of *N*-sulfonylimines, which are commonly easily prepared and stable, but is less satisfactory for the oxidation of N-phosphinoylimines, which are more prone to hydrolysis. N-Acylimines are even less stable and are commonly only

available when prepared from a ketone that is non-enolizable and contains R-electron-withdrawing groups.[78] Derivatization at the nitrogen atom of an oxaziridine, as opposed to oxidation of the derivatized imine, could therefore provide a useful alternative method of preparation of N-functionalized oxaziridines, if the corresponding N-H oxaziridines can themselves be readily prepared. Indeed, some examples of acyl derivatives have been prepared *in situ* by use of solutions of unstable N-H oxaziridines.[79] N-H oxaziridines have been prepared from ketones by treatment with hydroxylamine-O-sulfonic acid or precursors of chloramine.[73] Neither of these two techniques proved successful for camphor or fenchone, possibly due to the steric hindrance about the ketone moiety.



Scheme 22. *Synthesis of N-camphor oxaziridine*

The Page group therefore sought an alternative route and selected oxidation of the primary (N-H) imine with peracid, a method used in the preparation of N-H oxaziridines **94** and **96**, derived respectively from di-tert-butyl ketone and benzophenone. Preparation of primary imines by simple condensation of ammonia with ketones is problematic, as primary imines are commonly unstable above room temperature. Sealed tube methods have been used,[80] but they are unreliable. The primary imines **100** and **104**, derived from camphor and fenchone, respectively, are, however, both stable up to ca. 30 °C and were prepared via the nitrimines **99** and **103**.[81] Nitrosation/rearrangement of the corresponding oximes **98** and **102** followed by ammonolysis of the resulting nitrimines in THF[82] gave the primary imines in quantitative yields. Oxidation of each imine with 1 equiv of *m*-CPBA at -30 to -40 °C in dichloromethane took place to give the N-H oxaziridines **92** and **93** in 98% and 86% yields respectively.



Scheme 23. *Synthesis of N-fenchone oxaziridine*

These N-H oxaziridines are remarkably stable in their pure form in comparison to their simpler analogues and can be kept at 5 °C for at least 6 months without decomposition. They are stable to silica gel chromatography. The camphor-derived oxaziridine **92** is crystalline and can be heated under reflux in THF solution for at least 6 h without decomposition, although it is unstable under reflux in toluene. In this context, it is interesting to note that **92** has been implicated as a reactive intermediate in the thermal rearrangement of camphor oxime.[83] The fenchone-derived oxaziridine **93**, an oily liquid, is stable under reflux overnight in THF and toluene solutions.

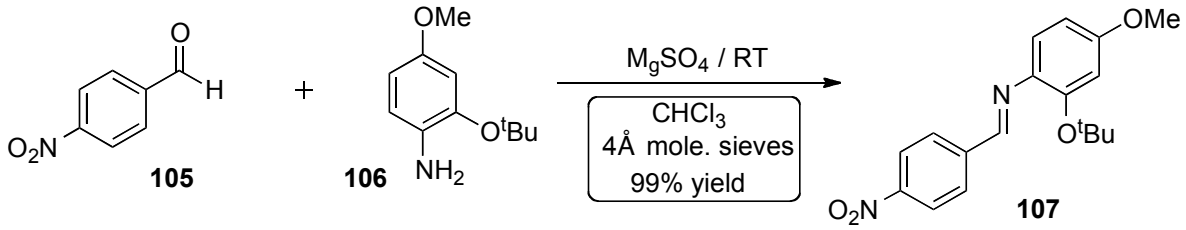
The aim of this part of research work was to discover a friendly protocol for the synthesis of five membered ring heterocycles using NH-oxaziridine and alkene as reactant, through cleavage of the N-O bond.

SECTION - II

RESULTS AND DISCUSSION

1 Organocatalysis

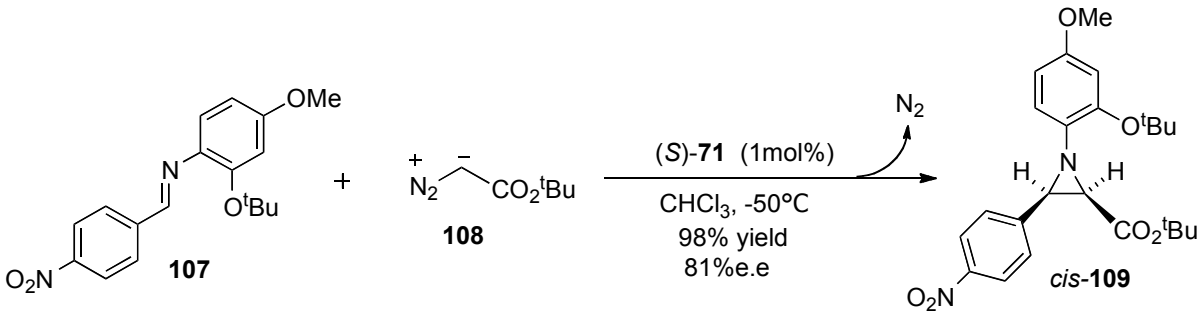
1.1 Synthesis of the starting material N-(2-tert-butoxy 4-methoxy phenyl)imine 107



Scheme 24. *Synthesis of (E)-2-tert-butoxy-4-methoxy-N-(4-nitrobenzylidene)aniline*

In these reactions, the imine is the most important starting material for the synthesis of aziridines. To obtain the desired imine product, the by-product water must be removed from the reaction mixture in order to drive the equilibrium in favour of the imine. This result can be achieved by using dry molecular sieve or magnesium sulfate powder. 2-tert-Butoxy-4-methoxy phenyl amine **106** (1eqⁿ) reacted with 4-nitro benzaldehyde **105** (1.02 eqⁿ) in anhydrous chloroform in the presence of 4Å molecular sieve and the reaction mixture was left overnight at room temperature. The reaction mixture was filtered and solvent removed under reduced pressure. ^{1}H NMR analysis of the crude mixture showed this to be the desired product **107** (99% yield).

1.2 Screening of the catalyst loading for the synthesis of cis-109



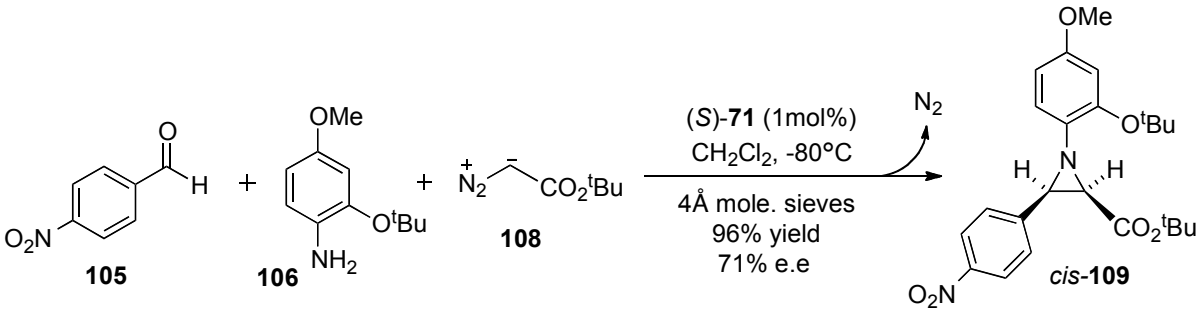
Scheme 25. *Catalyst loading experiment for the synthesis of cis-**109**.*

It is stated that by controlling different parameter such as solvent, temperature, loading of catalyst, substituent on starting material imine, etc., a better yield as well as enantioselectivity can be obtained. This experiment was designed to complete the studies for the optimisation of the reaction conditions, therefore providing a fully optimised protocol. *(E)*-2-*tert*-Butoxy-4methoxy-*N-(*4-*nitrobenzylidene*) imine **107** was reacted with *tert*-butyl diazoacetate **108** in chloroform at -50 °C. To promote the reaction, a catalyst loading of only 1 mol% of (*S*)-**71**

was employed. The experiment went to completion in 16 hrs as observed by TLC. The resulting reaction mixture was dried, affording crude brownish oil. Purification via column chromatography using solvent petroleum ether and diethyl ether (80:20), eluent mixture gave pure product *cis*-**109** with excellent yield 98% and 81% enantioselectivity. Having established that substitution of the *ortho*-position of the *N*-aryl group has a strong effect on the enantiomeric enrichment, the eventuality of steric hindrance was taken in consideration. More specifically, the functionalisation of the aryl with bulky *o*-alkoxy substituents was thought to force the catalyst to approach the imine from the unsubstituted side. On the other hand, the introduction of the alkoxy functionality on the aromatic *N*-substitution should also facilitate the subsequent removal of the *N*-protecting group to afford cleaved N-H aziridines.

1.3 One pot reaction for synthesis of cis-109 by decreasing temperature

To increase the enantioselectivity, the method now known to work on this system, it should be possible to use this knowledge for changing other parameters. Temperature control is one of the most powerful tools that organic chemists can use to optimise and influence the performance of a reaction. Every change in a molecule (from simple bond rotations to any structural modifications) implies an energetic barrier to be overcome. To act directly on the energy content of the system by means of the temperature may allow a strong degree of control over the specificity and/or selectivity of a process.



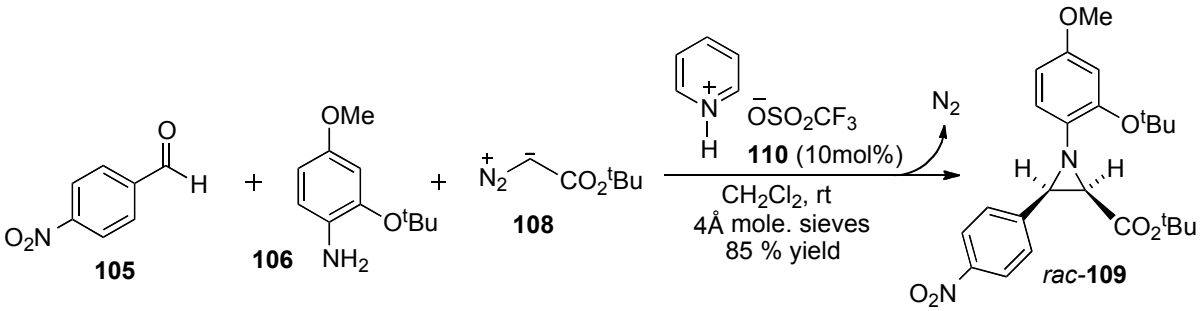
Scheme 26. *Temperature screening experiment for the synthesis of cis-**109**.*

We decided to bring the temperature down from -50°C to -80°C, but by decreasing the temperature, the solvent chloroform froze. We decided to use dichloromethane instead of chloroform. Although decreasing the temperature substantially slowed down the reaction rates, it conferred great benefit to both yields and enantiomeric enrichments. Synthesising aziridines directly from aldehydes and amines has significant experimental advantages over multi-step procedures that require imine isolation. Investigating the possibility of simplifying the aziridination procedure, one equivalent each of 4-nitrobenzaldehyde **105** and 2-*tert*-butoxy-4-methoxyaniline **106** was reacted with *tert*-butyl 2-diazoacetate **108** in dichloromethane at -80°C in the presence of 4Å molecular sieve and a loading of the catalyst

of only 1 mol% of (*S*)-**71** was employed. The reaction was vigorously stirred for two days and found complete by TLC analysis. The resulting reaction mixture was filtered and solvent removed under reduced pressure affording a crude brownish oil. Purification by column chromatography using solvent petroleum ether and diethyl ether (80:20), eluent mixture gave pure product *cis*-**109** in an excellent yield of 96%. The reaction carried out at –80 °C was found to be very slow. Nonetheless, almost quantitative conversion of aldehyde **105** and amine **106** into aziridine *cis*-**109** was observed at –80 °C (96% yield), but we found surprisingly low enantioselectivity (75%e.e).

1.4 Synthesis of rac-109 for parallel study

Basically all the aziridines previously shown were part of a systematic program of investigation regarding the synthesis of chiral non-racemic aziridines. The Bew group has already developed a methodology to use pyridinium triflate **110** as catalyst allowed an easy, fast, robust and high yielding preparation of racemic aziridines, which confers additional merits to a protocol already valuable on its own.

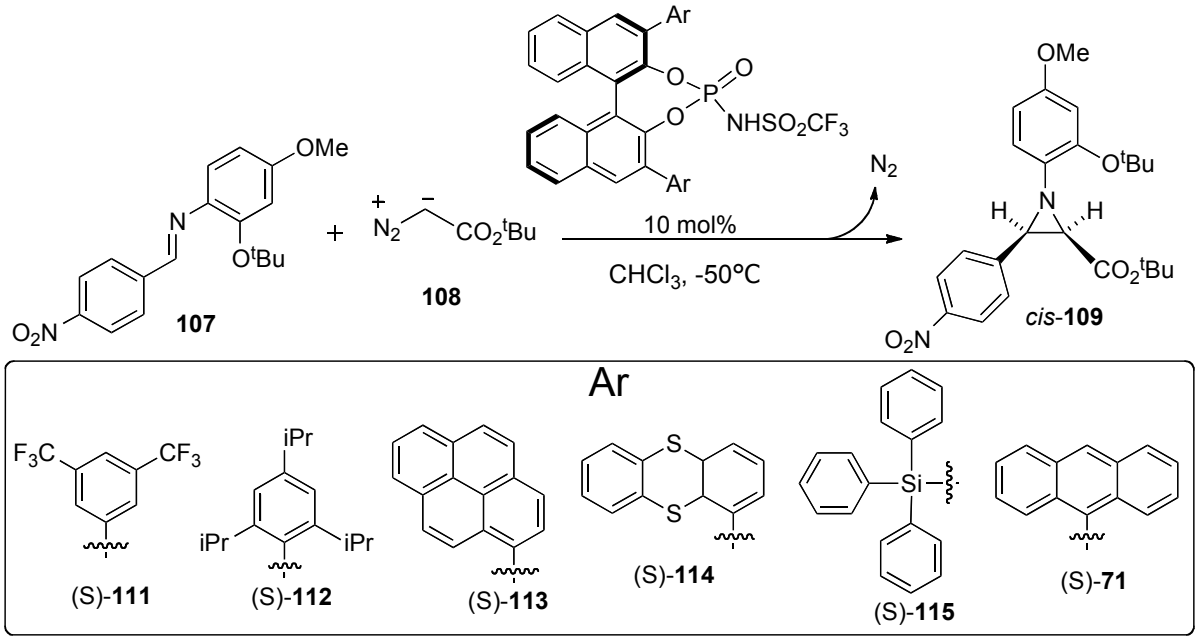


Scheme 27. *Synthesis of rac-**109**.*

One equivalent each of 4-nitrobenzaldehyde **105**, 2-tert-butoxy-4-methoxyaniline **106**, and tert-butyl diazoacetate **108** were reacted in dichloromethane in the presence of 4Å molecular sieve, and a catalytic amount of triflate salt **110** (10 mol%). The pyridinium triflate **110** catalyses the imine formation as well as the aziridine synthesis, and shows excellent substrate selectivity. The combination between high nucleophilicity of **106**, catalysis of **110**, and the presence of molecular sieve makes the imine formation step kinetically very fast, moving the overall equilibrium towards aziridine formation. After 5 hr at ambient temperature, TLC analysis indicated complete consumption of starting material. Purification using flash chromatography afforded the desired product as light yellowish oil; NMR analysis indicated product to be *rac*-**109** (85% yield).

1.5 Screening of catalysts (S)-111, (S)-112, (S)-113, (S)-114, (S)-115, (S)-71

Having found so far that the 9-anthracenyl substitution of the 3,3'-positions on the (*S*)-BINOL scaffold, i.e. (*S*)-**71**, had afforded the best enantiomeric enrichments, at this point we decided to spend more time investigating different selective catalysts and increasing the loading of catalysts from 1 mol% to 10 mol%. With this intent, catalysts (*S*)-**111** – (*S*)-**113** were tested on the aza-Darzens reaction of the *N*-arylimine **107** with *tert*-butyl diazoacetate **108**. Catalyst (*S*)-**111**, bearing the 3,5-bis(trifluoromethyl)phenyl substitution, is a good example of aliphatic transversal shielding. Unfortunately the enantiofacial discrimination exerted on imine **107** was to be inconsistent, returning poorly enantiomerically enriched aziridine *cis*-**109** (54% *e.e.*). The enantioselectivity substantially improved when the reaction was promoted by catalyst (*S*)-**113**. The four condensed aromatic rings of the 1-pyrenyl groups, expected to behave like large flat shields, raised the enantiomeric excess to 74%. This is not surprising, considering that the 1-pyrenyl group extends its aromatic system both transversally and longitudinally, more or less as the 9-phenanthryl does (Scheme 28).



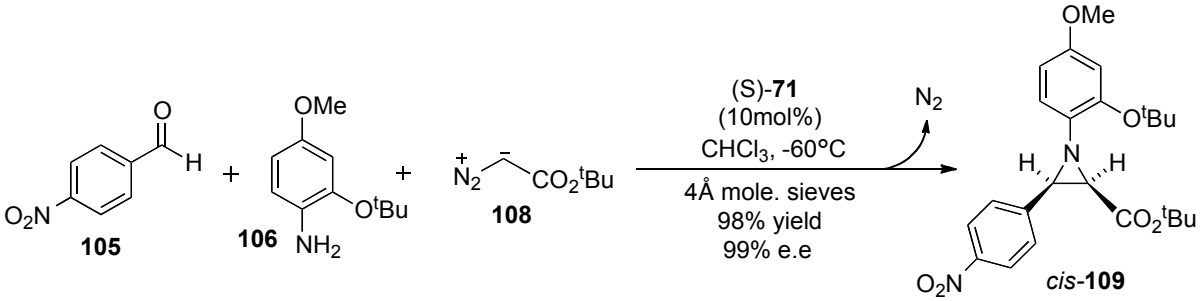
Scheme 28. *Screening of catalysts for the synthesis of aziridine cis-**109**.*

It was anticipated that the efficiency of catalyst (*S*)-**114** would be higher, as the structure of the 1-thiantryl elongates transversally even more than the 9-anthracenyl. The tetrahedral character of the sulfur atoms confers a peculiar bending to the shape of the substituent. Disappointingly, the observed enantiomeric excess (71% *e.e.*) was inferior to the one afforded by catalyst (*S*)-**71** (75% *e.e.*) and similar to as (74% *e.e.*) obtained with catalyst (*S*)-**127**. Optimization of the catalyst (*S*)-**129** with aza-Darzens reactions; imine **107** was prepared and reacted with *tert*-butyl diazoacetate **108** at -50°C (Scheme 28), disappointingly, the enantiomeric enrichment achieved by the experiment was poor (15% *e.e.*). The efficiency of

catalyst (*S*)-**112** was affected by the bulkiness of the diazoacetate negatively; when imine **107** was used as substrate with *tert*-butyl diazoacetate **108** low enantioselectivity was observed (S)-**115** (10% *e.e.*). Finally with great pleasure, bringing up the catalyst loading from 1 mol% to 10 mol%, affected the reaction efficiency. Formation of aziridine *cis*-**109** was found in the case of catalyst (S)-**71** to be fast, TLC analysis indicated complete consumption of starting material. Purification using flash chromatography afforded clean, high yielding (98% yield) and highly enantioenriched (96% *e.e.*) product.

1.6 Fully optimised protocol for the synthesis of cis-109

In order to extend the scope of the optimised catalytic system and encouraged by the excellent results obtained for the asymmetric synthesis of aziridine *cis*-**109** (98% yield, 96% *e.e.*), in order to obtained excellent enantioselectivity, we decided to decrease the temperature from -50°C to -60°C.



Scheme 29. *(S)-71-catalysed synthesis of aziridine cis-109.*

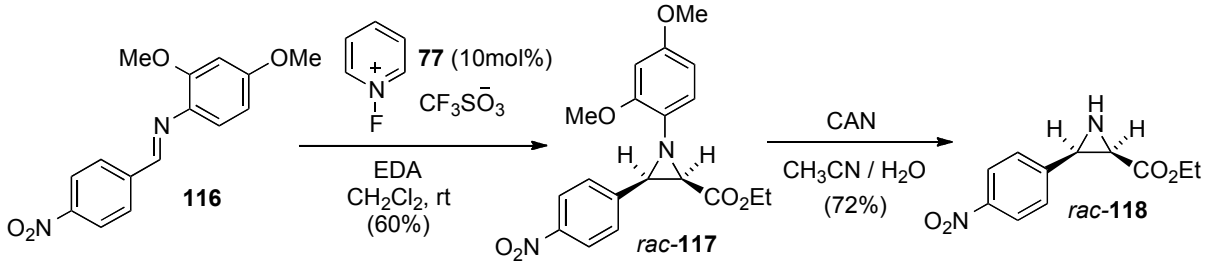
4-Nitrobenzaldehyde **105** and 2-*ter*t-butoxy-4-methoxyaniline **106** reacted with *tert*-butyl 2-diazoacetate **108** in chloroform at –60 °C. To promote the reaction, a catalyst loading of 10 mol% of (S)-**71** was employed. The reactions were vigorously stirred overnight and found to be complete the following morning. The ^{1}H-NMR spectra of the crude mixtures were so clean that purification by simple filtration on a pad of silica to remove the catalyst was sufficient. An excellent level of enantioselectivity (99%) and high yield (98%) was achieved for the synthesis of aziridine *cis*-**109**. The method afforded overall satisfactory results, providing the basis for useful practical applications.

1.7 Synthesis of Chloramphenicol

1.7.1 Synthesis of racemic-chloramphenicol

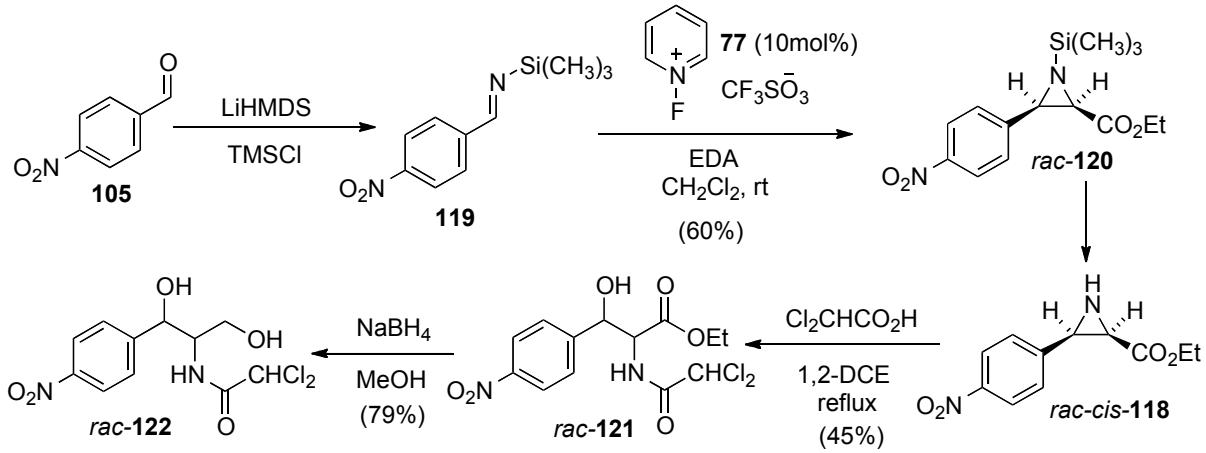
A key step in our design strategy was the ability to generate NH-aziridines either using a one-pot organocatalytic protocol (*vide infra*) or by the expeditious removal of a suitable electron-rich group off an aziridine. Synthesising rac-*cis*-**117** (*via* addition of ethyl diazoacetate to **116** mediated by 10 mol % of **77**) on a multigram scale allowed the efficient oxidative cleavage of

the *N*-substituent from rac-*cis*-**117** using ammonium cerium (IV) nitrate (CAN). The NH-aziridine rac-*cis*-**118** was afforded in a 72% yield (Scheme 30).



Scheme 30. *Cleavage of electron-rich N-aryl group off rac-cis-***117**.

Reacting EDA, catalyst **77** and **119** (Scheme 31) afforded, presumably, (based on ^{1}H-NMR of the crude reaction) rac-**120**. Gratifyingly, when rac-**120** was purified by column chromatography using silica gel, the TMS group cleaved affording rac-**118** ($J_{2,3}$ = 6.4 Hz, 60% yield from **119**), in agreement with Jørgensen's observation. Exemplifying our methodology, we synthesised racemic chloramphenicol rac-**122**, applying Wulff's protocol. Rac-*cis*-**118** was ring-opened with dichloroacetic acid affording rac-**121**. Subsequent reduction of the ethyl ester of rac-**121** afforded the corresponding primary alcohol and completed the synthesis of rac-**122** in four steps from the *p*-nitrobenzaldehyde **105**. However, although the aziridination carried on the *N*-TMS-imine **119** was successful, a weakness of the method is represented by the synthesis of **119** itself. The reaction is not very clean; purification of **119** is required and generally consists in a bulb-to-bulb distillation carried out under very harsh conditions (180 °C, 0.3 Torr), which requires the use of good equipment and elaborate procedures.



Scheme 31. Synthesis of racemic chloramphenicol rac-**122** from **105**.

1.7.2 Synthesis of chiral enantiopure(–)-chloramphenicol

(–)-Chloramphenicol is one of the oldest antibacterial agents, first isolated from *Streptomyces venezuelae* in 1947. This antibiotic is obtained commercially by chemical synthesis and is biologically active only as its (2*R*,3*R*)-enantiomer. It is used clinically as a broad-spectrum antibiotic and is particularly useful for the treatment of salmonella, rickettsia, and meningeal infections. A number of chemical syntheses of racemic chloramphenicol have been reported, as well as a few in the past decade that are selective for the formation of (–)-chloramphenicol. Wulff *et al.* reported an asymmetric synthesis of optically pure (–)-chloramphenicol that is the shortest of all syntheses reported to date. Their synthetic strategy is outlined in (Figure 18, 19) and featured an asymmetric catalytic aza-Darzens reaction as key step promoted by the (*R*)-VAPOL-derived borate Lewis acid (*R*)-**124**, protocol. The synthetic strategy for the synthesis of optically pure (-)chloramphenicol is, however, undoubtedly valid. The alternative approach proposed towards the synthesis of chiral non-racemic chloramphenicol is an adaptation of the Wulff protocol to the *N*-triflylphosphoramide catalytic method. The two methods are illustrated in Figure 18, 19 to facilitate comparison.

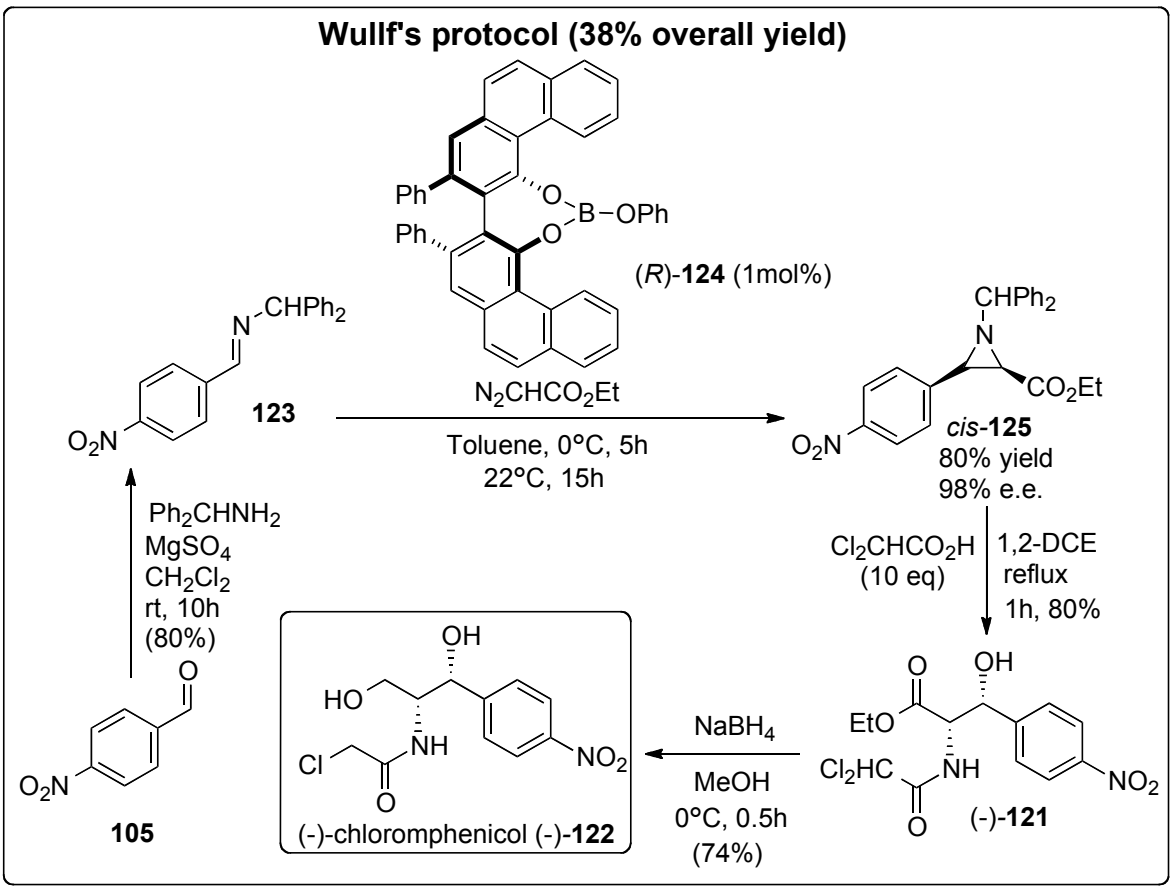


Figure 18. *Wulff's protocol for the synthesis of optically active chloramphenicol.*

Both the methods involve the aza-Darzens reaction as key step. The Wulff protocol afforded chiral non-racemic aziridine *cis*-**125** in two steps from the *p*-nitrobenzaldehyde **105**. The *N*-

benzahydrylimine **123** was first formed by reaction of **105** with benzahydrylamine and then reacted with ethyl diazoacetate in the presence of 10 mol% of catalyst (*R*)-**124** to afford the corresponding aziridine *cis*-**125** in 87% yield and 96% enantiomeric excess. In an effort to minimize the number of steps required, we demonstrated that a one-step one-pot reaction could be successfully performed using our organocatalytic approach, involving a tandem imine formation / aziridination reaction. *p*-Nitrobenzaldehyde **105**, 2-*tert*-butoxy-4-methoxyamine **106** and *tert*-butyl diazoacetate **108** were dissolved in chloroform and the reaction promoted by (*S*)-**71** at –60 °C. A catalyst loading of 10 mol% was required to afford aziridine *cis*-**109** in 99% yield and 96% enantiomeric excess. A lower loading of (*S*)-**71** (1 mol%) returned *cis*-**109** in 77% *e.e.*, although in quantitative yields from the aldehyde **105**. The introduction of the *p*-methoxy substituent on the *N*-aryl group of amine **106** was made necessary in order to perform the following cleavage reaction. Indeed, any attempt to perform the cleavage of the 2-*tert*-butoxyphenyl *N*-group systematically returned starting material.

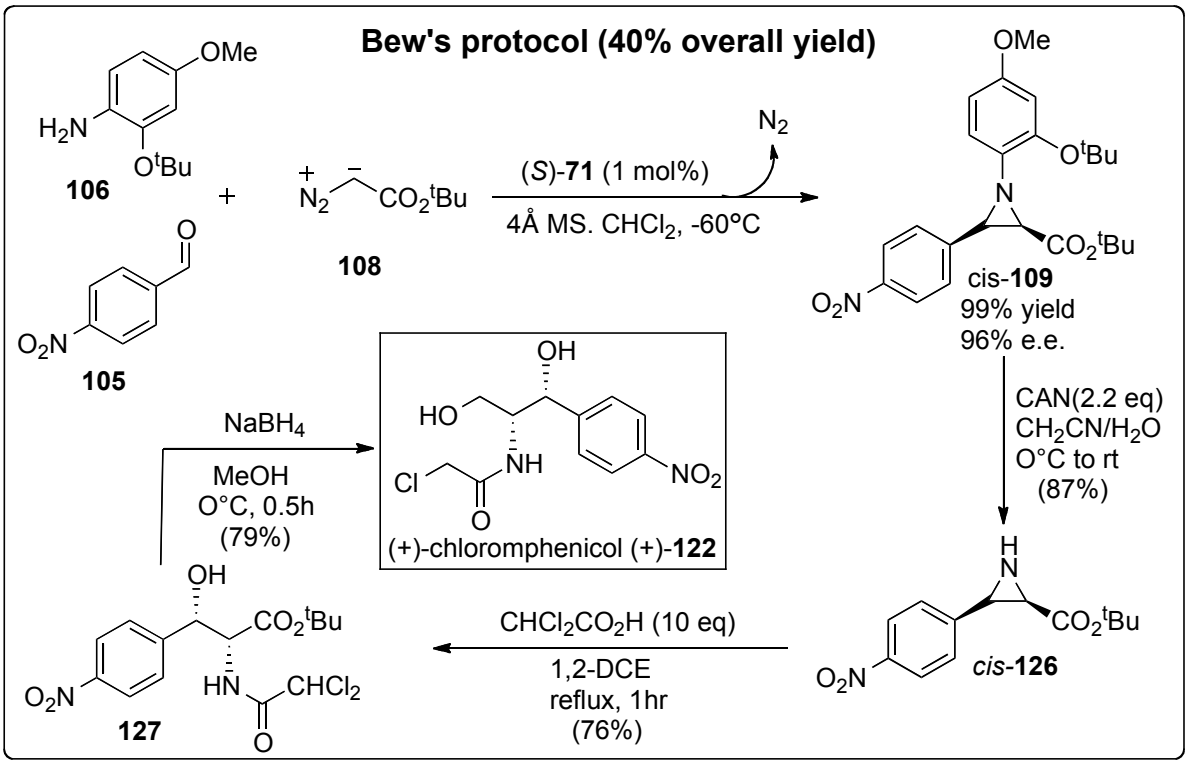


Figure 19. *Bew's N-triflylphosphoramide catalytic protocol for the synthesis of optically active chloramphenicol.*

However, the one-pot reaction is a remarkable achievement that highlights the excellent substrate-selectivity of catalyst (*S*)-**71**. Performance of the same reaction by use of the (*R*)-VAPOL-boron (*R*)-**124** is arguable, as it is likely that the boron atom would show a higher affinity towards the oxygen of the aldehyde **105** rather than the nitrogen of the *N*-benzhydrylimine **123**, thus inhibiting the catalytic activity. Summarising this point, we observed quantitative formation of aziridine *cis*-**109** (99% yield) by a one-pot reaction from

the aldehyde **105**, whereas Wulff's method required a two-step reaction for the formation of *cis*-**125** from **123**, affording *cis*-**125** in 64% overall yield, although the same level of enantioinduction (96% *e.e.*) was achieved by the two methods. On the other hand, Wulff's synthetic approach benefits from the one-pot *N*-group cleavage / ring-opening reaction performed in a single step using dichloroacetic acid. The reaction afforded intermediate (–)-**121** in 80% yield. In our case, the removal of the alkoxyaryl *N*-protecting group required the use of an oxidant. Therefore, the synthesis of the unprotected N-H aziridine *cis*-**126** was accomplished in 67% yield by reaction of *cis*-**109** with ammonium cerium (IV) nitrate (CAN) in water / acetonitrile solvent system. Although the reaction conditions have not been optimised, the oxidation is fast and formation of cerium (III), resulting from the one-electron transfer, is clearly detected by colour change. The ring-opening reaction was then performed on aziridine *cis*-**126** using dichloroacetic acid, as described by Wulff *et al*, affording intermediate **127** in 76% yield. It is note worthy that, although the cleavage and ring-opening are two different steps and do not represent an advantage for this particular example, having the two steps separated could be desirable, if not even necessary, in other circumstances. The synthesis of N-H aziridines, *i.e. cis*-**126**, represents both the goal of our method and the starting point towards a plethora of applications. The *N*-cleaved ring could be incorporated as it is in larger molecular frameworks or subject to ring-opening reactions, regardless if promoted by acids, bases, nucleophiles or electrophiles.

Finally, reduction of the ester moiety of (–)-**121** and **127** with sodium borohydride afforded respectively the natural (–)-chloramphenicol in 74% yield for Wulff and coworkers and the unnatural (+)-chloramphenicol in 79% yield in our case. In order to confirm the possibility to generate the active (–)-configuration of the antibiotic, we embarked in the synthesis of the opposite (+)-enantiomer of aziridine *cis*-**109**, promoted by catalyst (*R*)-**71**, that is the corresponding *N*-triflylphosphoramide catalyst derived from (*R*)-BINOL rather than from (*S*)-BINOL. The one-pot imine formation / aziridination reaction quantitatively returned aziridine (**–**)-*cis*-**109** in 95% enantiomeric excess.

Future work

In this Chapter the development of an efficient methodology for the organocatalytic synthesis of enantiomerically enriched *N*-aryl-$C_{2,3}$-disubstituted aziridines and NH-$C_{2,3}$-disubstituted aziridines is described. The development of a catalytic protocol capable of achieving yields up to 99% and enantioselectivities up to 98% is a remarkable. However, although the protocol is an efficient asymmetric organocatalytic aza-Darzens synthetic strategy, it is still to be considered as a pioneering study that would surely benefit from several improvements. The scope of the reaction needs to be extended, as well as the structural diversity of the chiral non-racemic aziridines created; the enantiomeric enrichments have to be possibly brought to a level; the reaction has to be carried out preferably at room temperature; the synthesis of the catalyst made as simple as possible; finally, the possibility to set up efficient *in-situ* acid-catalysed "domino" or "cascade" transformations of the formed aziridines has to be taken in account.

2 Asymmetric Organocatalytic Synthesis of Aziridine Using F^+ Salt

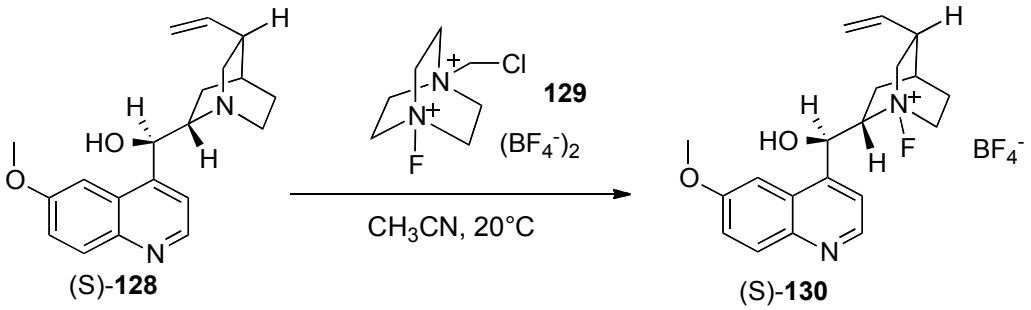
Whenever examining a reaction system, several parameters must be taken in account: nature of the reagents, structure of the catalyst, temperature, solvent, concentration, catalyst loading, etc. In order to maximize the efficiency of a reaction system in terms of yield and stereoselectivity, the systematic variation of one parameter time needs to be undertaken. Thus, the first fundamental component to be preliminary screened in this study was the asymmetric organocatalyst. The choice of the candidate catalysts was mainly influenced by previous investigations carried out in our research group. As discussed in the Introduction, the aza-Darzens synthesis of broadly functionalized chiral but racemic *cis*-aziridines was efficiently achieved by means of pyridinium triflate catalysis. Mimicking the mode of action of the pyridinium triflate salt, our current research on the asymmetric aza-Darzens reaction focused on the use of triflate salts of chiral cinchona alkaloids or camphor sulphonic acid derived heterocyclic salts. In the time mean, a new class of chiral Brønsted acid started to rapidly flourish in the field of organocatalysis. Chiral BINOL-derived phosphoric acids have being found capable of highly effective catalysis as discussed in chapter 2.

2.1 Electrophilic Fluorination

The synthesis of cyclic and acyclic chiral fluoro-organic compounds is an important topic in modern pharmaceutical chemistry. The replacement of hydrogen atoms with fluorine substituents in organic substrates is of great interest in synthetic chemistry because of the strong electronegativity of fluorine and relatively small steric footprint of fluorine atoms. Many sources of nucleophilic fluorine are available for the derivatization of organic molecules under acidic, basic, and neutral conditions. However, electrophilic fluorination has historically required molecular fluorine, whose notorious toxicity and explosive tendencies limit its application in research. There are several advantages of fluorine substitution, including an increase in stability, changes in lipophilicity, introduction of a centre of high electronegativity, and altered patterns of reactivity of the C-F vs the C-H bond. The necessity for an electrophilic fluorination reagent that is safe, stable, highly reactive, and amenable to industrial production as an alternative to very hazardous molecular fluorine was the inspiration for the discovery of selectfluor **129**. This reagent is not only one of the most reactive electrophilic fluorinating reagents available, but it is also safe, nontoxic, and easy to handle. Now days there are many procedures reporting enantioselective fluorination.

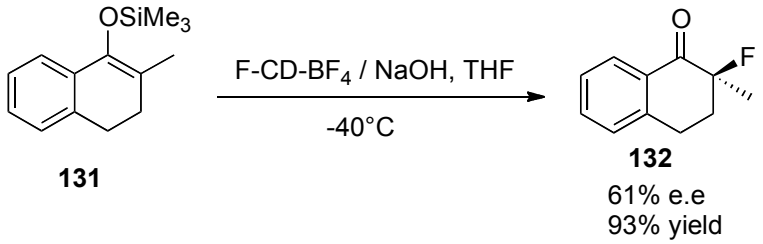
2.2 Synthesis of N-fluoro quaternary ammonium salt (F-CD-BF₄)

The synthesis of the *N*-fluoro ammonium salt of chinchona alkaloids was accomplished by as following Dominique Cahard's synthetic protocol. Cahard reported the first ever enantiopure *N*-fluoro quaternary ammonium salt of cinchonidine (*F-CD-BF₄*), prepared as an enantioselective fluorinating agent. A one step transfer-fluorination of the quinuclidine moiety with selectfluor gave the [N-F] $^{+}$reagent. At first the fluorine-transfer procedure was applied to an equimolar mixture of chinchonidine and selectfluor in acetonitrile. Complete transfer was achieved within 20 min according to the ^{19}F NMR analysis of the reaction mixture. A double precipitation procedure yielded the *N*-fluoro cinchonidinium salt, which was recrystallised in acetone to yield pure *F-CD-BF₄* (Scheme 32). It is virtually non-hygroscopic, free flowing, crystalline and high melting (189°C) colourless solid.



Scheme 32. *Synthesis of F-CD-BF₄*

To evaluate the ability of this reagent to promote enantioselective fluorination, Cahard report the first enantioselective electrophilic fluorination on the trimethylsilyl enol ether **131** of 2-methyl-1-tetralone in presence of sodium hydroxide at -40°C afforded quaternary α-fluoro carbonyl compounds in excellent yield (93%) and good enantioselectivity (61%).

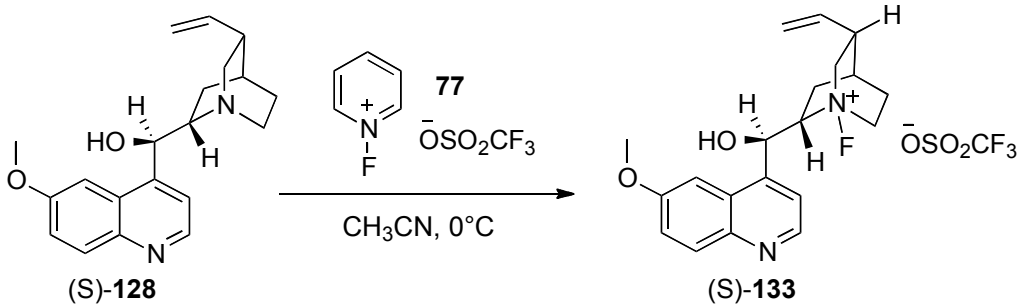


Scheme 33. *Cahard's Fluorination of the Trimethyl Silyl Enol Ether of 2-Methyl-1-tetralone.*

2.3 Synthesis of N-fluoro quaternary ammonium salt (F-CD-OTf¯)

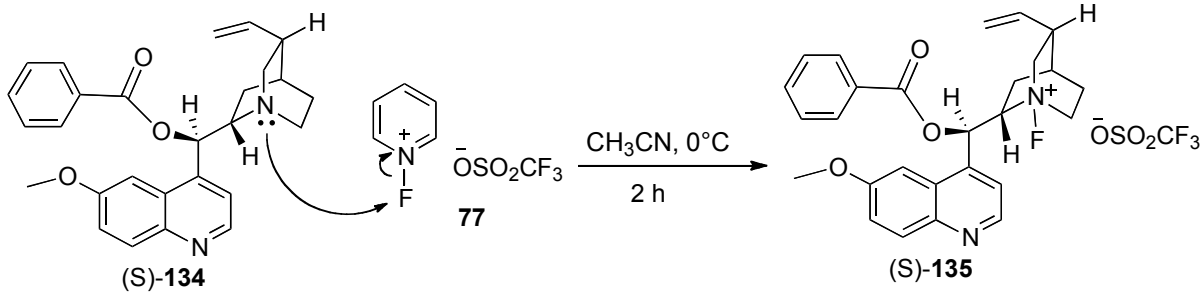
Inspired by Cahard's work and using his methodology, we prepared the enantioselective quaternary ammonium salt (+) using *N*-fluoropyridinium triflate, knowing the advantages and mimicking the mode of action of the triflate salt. A one step transfer-fluorination of the

quinuclidine moiety with an equimolar mixture of chinchonidine and *N*-fluoropyridinium triflate in acetonitrile at 0°C for 20 min, change in the colour of the reaction mixture immediately occoured after addition of triflate salt **77** indicating the formation of *N*-fluoroquaternary ammonium salt (S)-**133**. This enantiopure quaternary ammonium salt of chinchonidine (*F-CD-OTf* ¯) (S)-**133** is highly unstable and reactive. Complete transfer was achieved within 20 min according to ^{19}F NMR analysis of the reaction mixture.



Scheme 34. *Synthesis of enantioselective N-fluoroquaternary ammonium salt*

At this point we decided to spend some more time on experiment to discover a simple protocol for the formation of the reactive intermediate called *N*-fluoroquaternary ammonium salt (F-CD-OTf¯) (S)-**133**. We based our development of the alkaloid / *N*-fluoropyridinium triflate combination as enantioselective fluorinating reagent on the fundamental idea that transfers fluorination would generate the *N*-fluorocinchona alkaloid (Scheme 34). Our hope was that the *N*-fluoropyridinium species **77** would be capable of transferring fluorine to a cinchona alkaloid (DHQ) enantioselectively. The successful realisation of enantioselective fluorination is suggestive of this mechanism (Scheme 35) but, in itself, does not prove that *N*-fluorocinchona alkaloids are intermediates. Therefore, we have examined this question in greater depth. We report here the results of experiments that confirm that this novel enantioselective fluorination reaction is mediated by *N*-fluoropyridinium triflate **77**.

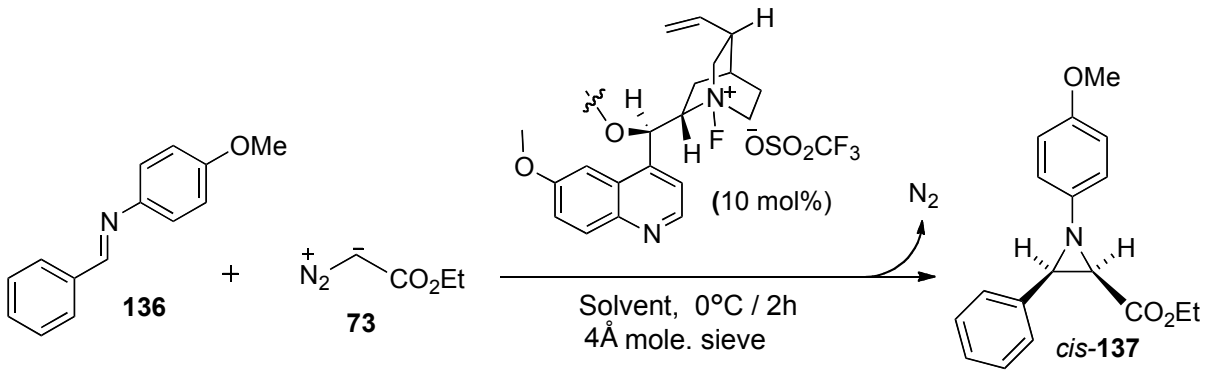


Scheme 35. *Transfer-fluorination of (S)-**134** with Pyridinium triflate.*

The ^{19}F NMR spectrum of *N*-fluoropyridinium triflate in CD_3CN at room temperature showed a peak at -79.3 ppm (singlet, triflate N-F), whereas the spectrum of the species

produced by the (S)-**134** and **77** combination, (S)-**135**, with ^{19}F NMR spectroscopy at O°C in CD_3CN displayed singlets at different intensity -73.2 ppm and -73.9 ppm. The peak at -73.2 ppm was larger than the peak at -73.9 ppm. As we expected, the singlet at -79.3 ppm disappeared completely with addition of (S)-**134** (1 eq), while the singlets at -73.2 ppm and -73.9 ppm remained. Unfortunately the **77** singlet (at -73.3 ppm) wasn't disappeared; it was larger than the (S)-**135** (-73.2 ppm and -73.9 ppm) singlets. Different temperatures and different solvents were used to find a useful protocol. The results obtained from increasing the temperature of the reaction from 0 °C to 20 °C affected the reaction efficiency. Formation of (S)-**135** was found to be faster at 20 °C (completion reached in 20 min) than at 0°C, clean and high yielding (98%), but the enantioselectivity of (S)-**135** was affected when the reaction was screened to obtain *cis*-**137**. Further increase of the temperature resulted, in the decomposition of the product.

2.4 Screening of the solvent for the synthesis of cis-137 to check the reactivity of N-fluoroquaternary ammonium salt



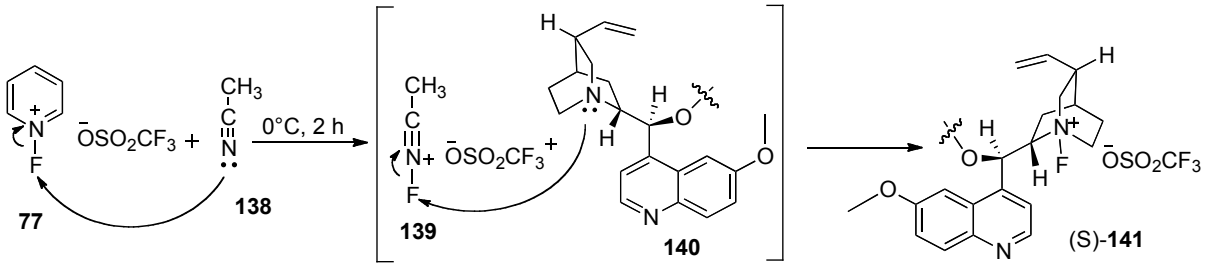
Scheme 36. *Solvent screening for the synthesis of cis-**137***

The quinine/*N*-fluoropyridinium triflate combination was prepared as follows; DHQB (1 eq^n) and *N*-fluoropyridinium triflate **77** were stirred in dry CH_3CN at 0 °C for 2 h. The resulting *N*-fluoroquaternary ammonium salt was used without any further treatment. Imine **136** and ethyl diazoacetate **73** were the standard substrates used to examine this system under different reaction conditions. In our initial experiment we were encouraged to find that *cis*-aziridine **137** was formed 30% yield with 20% e.e (Scheme 36). Optimisation of the reaction conditions by altering the solvent did not improve the yield (Table 3)

Entry	Solvent	Yield (%)
1	Acetonitrile	27
2	Propionitrile	30
3	Dichloromethane	24
4	Chloroform	50
5	Dimethylformamide	15

Table 3. Solvent screening for the synthesis of *cis*-**137**

The expected outcome of the reaction (Scheme 36) was to show an increase of the *N*-fluoroquaternary ammonium salt (S)-**135** singlet and disappearance of the **77** singlets. As discussed above unfortunately the *N*-fluoropyridinium triflate **77** peak was larger than the resulting (S)-**135** combination singlets. Acetonitrile is the best solvent for fluorination reaction. DHQB (S)-**134** (1 eq) and *N*-fluoropyridinium triflate **77** (1 eq) were stirred in dry CH_3CN at 0 °C for 2 h. The reaction solvent was removed under reduced pressure and free residue dissolved in $CDCl_3$. The 300 MHz ^{19}F NMR showed an outstanding result, with increased singlet integral of DHQB/*N*-fluoropyridinium triflate (S)-**135** and decreased singlet integral of *N*-fluoropyridinium triflate **77**. In order to understand the reasons behind this, we study the mechanism of the reaction, which state that acetonitrile is the best solvent and carries the fluoronium cation.

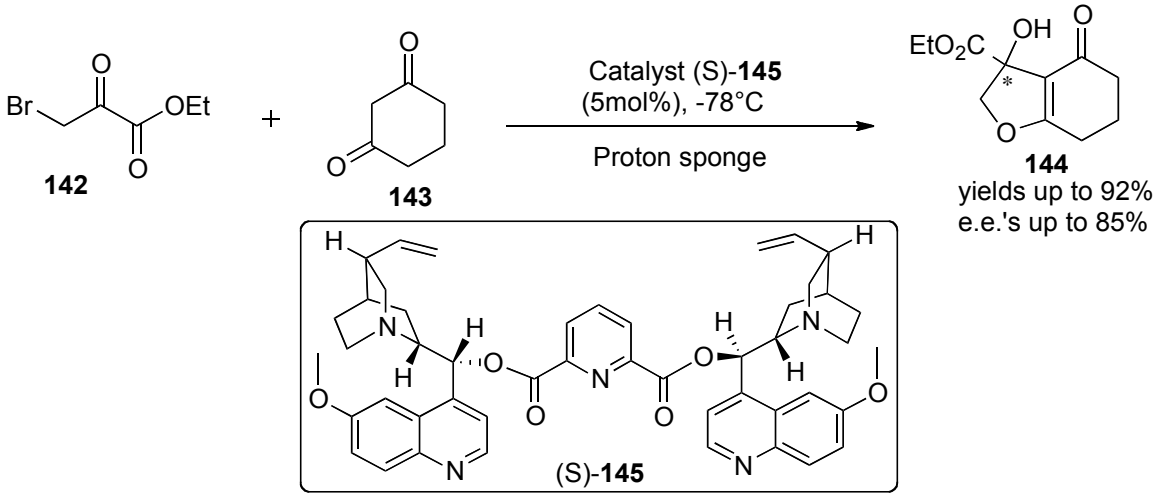


Scheme 37. *Hypothetical mechanism of synthesis of reactive intermediate.*

The mechanism of fluorination with N-F reagents has been a subject of debate since their introduction. There are two possible mechanistic pathways: single-electron transfer (SET) or nucleophilic S_N2 substitution. The hypothetical mechanism shown in (Scheme 37) indicates that the electrophilic transformation of fluorine is carried out *via* acetonitrile. The pair of electron on nitrogen of acetonitrile **138** attacks the fluorine of the triflate salt **77** and forms an intermediate **133**. Further nucleophilic attack of the nitrogen of cinchona alkaloid on **140** forms a reactive *N*-fluoroquaternary ammonium salt species (S)-**141**. It perhaps happens because of low concentration of corresponding starting material **77** and **140** as compare to solvent, resulted give chance to acetonitrile to attack first on triflate salt **77**.

2.5 Asymmetric IFB reaction of ethyl bromopyruvate using catalyst (S)-145

To prove the validity of the role of the *N*-fluoroquaternary ammonium salt in the aza-Darzens reaction, it was necessary to prepare a more reactions *cinchona alkaloid* derivative. The task was achieved thanks to an article published by Sheng-Yong Zhang *et al.* in 2008, reported the asymmetric Feist-Benary reaction catalysed by the chiral 3,6-dichloropyridazine **145** cinchona alkaloid derivatives (Scheme 38).



Scheme 38. *Asymmetric IFB reaction of ethyl bromopyruvate with 1,3 cyclohexadione.*

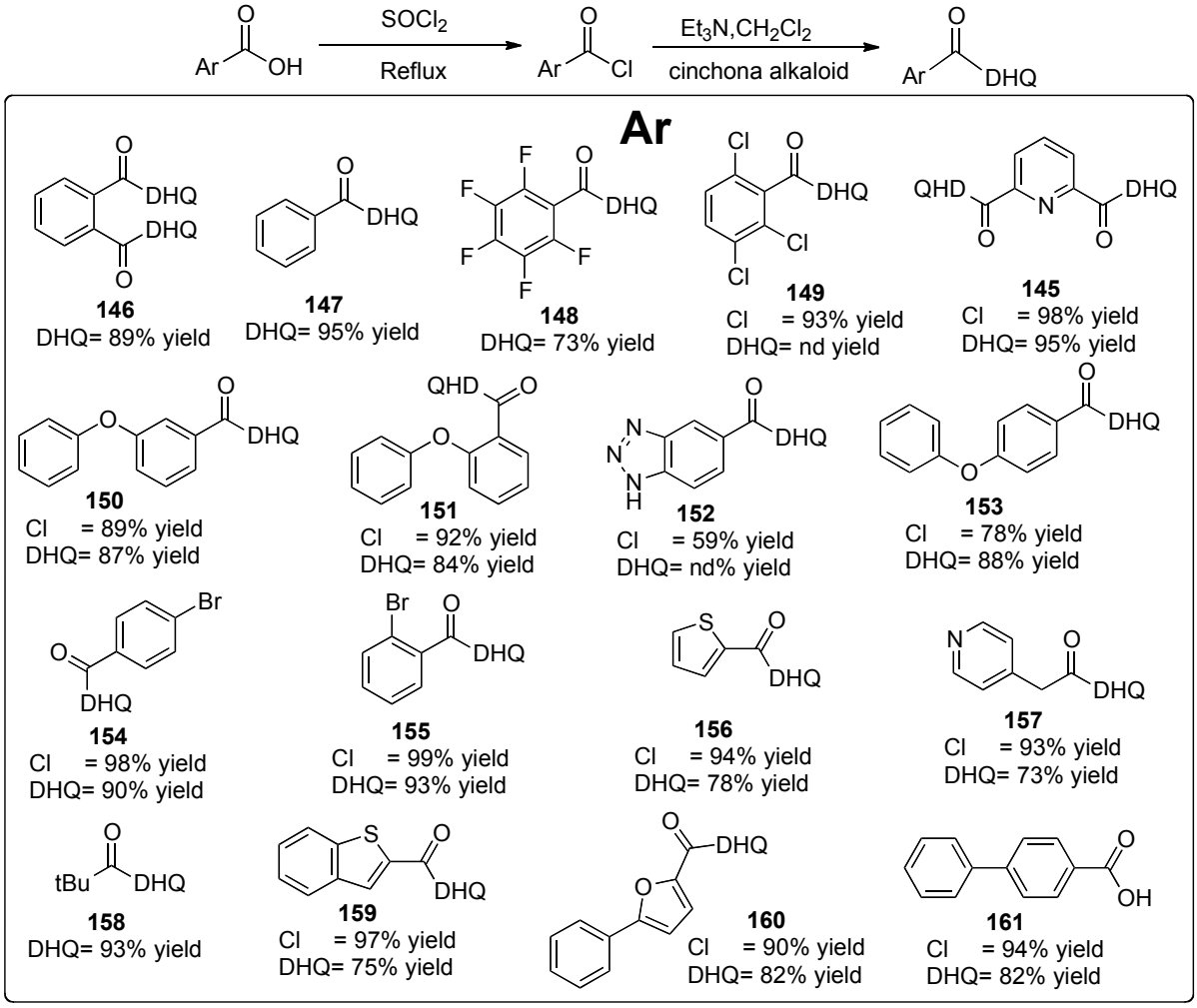
The idea is based on the concept that changes in the substituents of the catalyst or in the nature of the cinchona alkaloid used significantly affected the enantiometric purity of the products. Encouraged by these results, Sheng-Yong Zhang further investigated the reaction with various organocatalysts to search for more active and enantioselective catalysts. He reported the preparation of cinchona alkaloid ester derivatives and the evaluation of their potential as asymmetric catalysts in the IFB reaction.

2.6 Synthesis of cinchona alkaloid ester derivatives

The synthesis of the cinchona alkaloid ester derivatives was accomplished by us using Sheng-Yong Zhang's synthetic protocol (Scheme 39). The ester derivatives were prepared from the corresponding carboxylic acids and cinchona alkaloid with excellent yield. A mixture of corresponding carboxylic acid and thionyl chloride was heated under reflux and turned clear after 5 h. The excess of thionyl chloride was subsequently removed by distillation. After purification by recrystallisation from CCl_4 or toluene, the product (shown in scheme 39) was obtained as a colourless solid.

Into a solution of cinchona alkaloid in anhydrous dichloromethane, 0.5M anhydrous triethyl amine at 0°C was added. A solution of the corresponding chloride in anhydrous

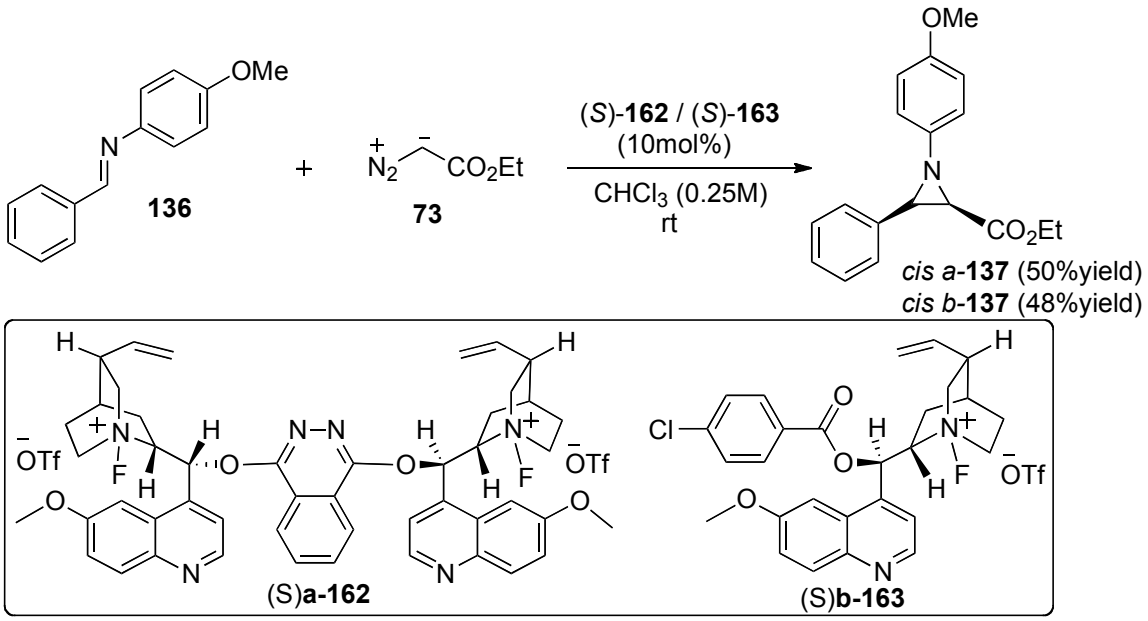
dichloromethane was slowly added. After 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 2 h. Upon completion of reaction as indicated by TLC, after work up followed by purification by flash chromatography on silica gel, excellent yield were obtained.



Scheme 39. *Synthesis of catalysts*

2.7 Aza-Darzens reactions catalyzed by the N-fluorocinchona alkaloid (S)-162 - (S)-163

The catalytic activity of the chiral the *N*-fluorocinchona alkaloid (*S*)-**162** - (*S*)-**163** was investigated by performing the experiment depicted in Scheme 40. These catalysts were used to promote the reaction between the *p*-methoxy benzylimine **136** and ethyl diazoacetate **73** at 0 °C temperature. ^{1}H-NMR crude spectra proved that consumption of the starting *N*-benzylimine **136** was achieved and no traces of *trans*-aziridine were found in the crude mixtures.



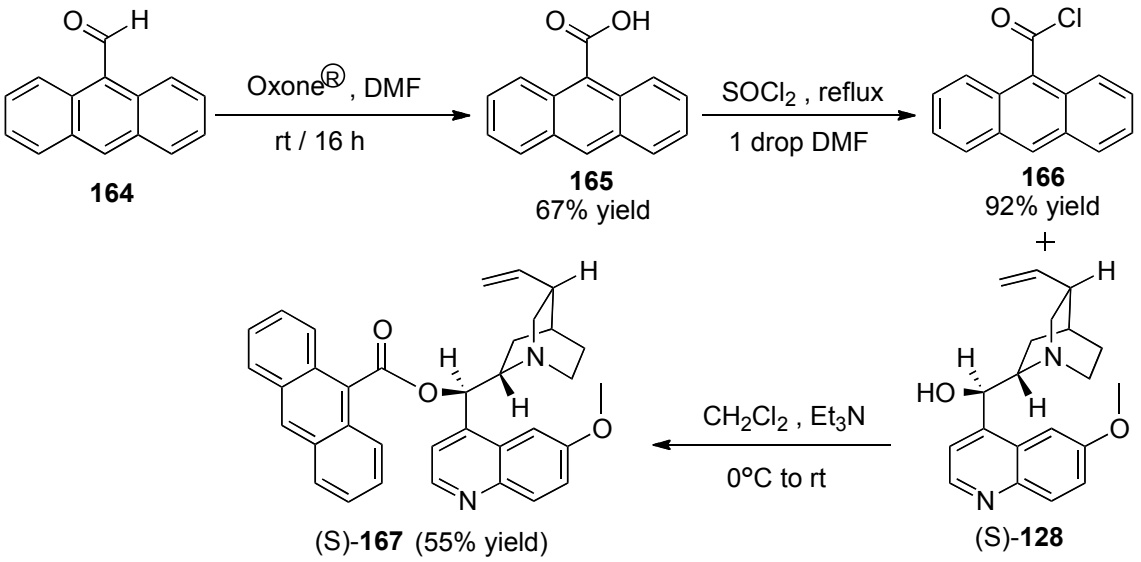
Scheme 40. *Template reaction for the screening of catalysts (S)-**162** and (S)-**163**.*

In terms of yields, the described experiment fully demonstrated the importance and the reactivity of the *N*-fluorocinchona alkaloid employed to catalyse the aza-Darzens reaction under these conditions. By simply replacing the cinchona alkaloid derivative with analogues, the yields and reaction rates for the formation of the aziridine *cis*-**137a** changed drastically from less than 5% to up to 50% overnight. Although this was only the starting point of a long study towards the development of an optimised asymmetric methodology. The crude mixtures were filtered on a pad of silica gel to remove the catalyst, and after evaporation of the solvent; the residues were eluted through a Chiralpak-AD analytical HPLC column. The measured enantiomeric excesses were found to be 8% when the reaction was catalysed by (*S*)-**162** and non-existent for the (*S*)-**162** catalysed synthesis of *cis*-**137**. Formation of racemic product from the (*S*)-**163** catalysed process was assumed to be caused by temperature. In order to achieve better result we tried the same reaction at different temperatures. In the case of catalyst (*S*)-**162**, at -30 °C, -50 °C and -80 °C the resulting formation of *cis*-**137a** was observed 26%, 21%, 18% yields and enantioselectivity 9%, 12% and 13% respectively.

2.8 Alternative protocols for the synthesis of chiral (S)-cinchona alkaloid derivatives

The synthesis of differently disubstituted *N*- fluorocinchona alkaloid derivatives was undertaken, as per the observation of change in the substituent of the catalyst affecting the enantiometric purity. An alternative approach for the synthesis of *N*-fluorocinchona alkaloid derivatives was sought.

2.8.1 9-anthracene substituted (S)-cinchona alkaloid derivatives



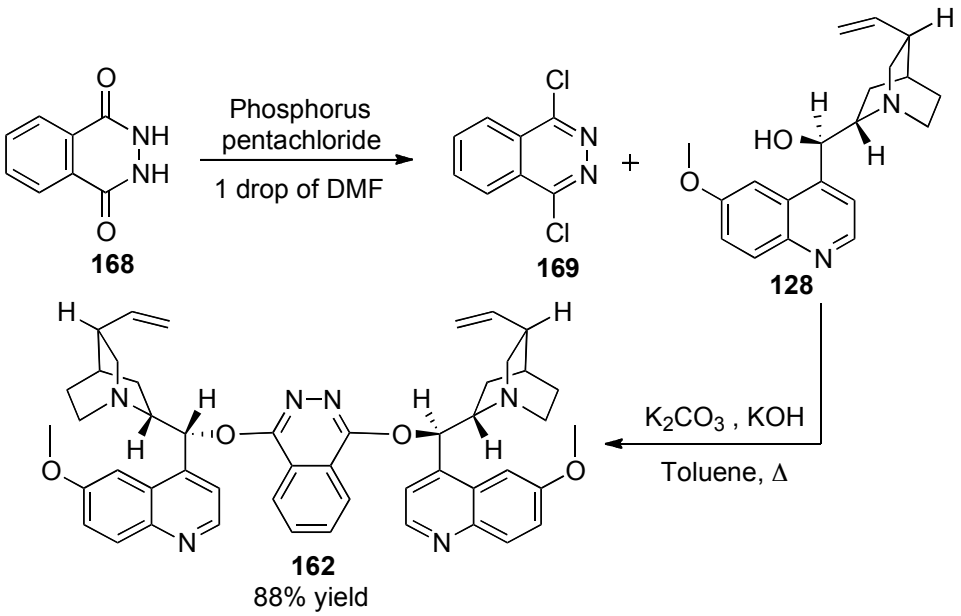
Scheme 41. *Synthesis of catalyst (S)-**167***

Oxone, a potassium triple salt containing potassium peroxymonosulfate, is an effective oxidant for numerous transformations. 9-anthracenaldehyde **164** (1eq) was reacted with Oxone (1.1equiv) in DMF at room temperature. The reaction went to completion overnight, with complete consumption of the aromatic aldehyde to the corresponding carboxylic acid **165** in (67%yield). As per the well known procedure, carboxylic acid **165** was converted into chloride **166** using thionyl chloride at reflux and 1 drop of DMF to activate the reaction. Complete consumption of starting material **165** into chloride **166** occurred in overnight gave 92% yield. Further Aryl chloride **166** reacted with cinchona alkaloid (DHQ) (S)-**128** (1eq) in anhydrous dichloromethane in presence of triethyl amine at 0 °C for 2 hr to give (S)-**167** in (55% yield).

2.8.2 Synthesis of the cinchona alkaloid derivative1,4-Bis(9-0-dihydroquinidinyl) phthalazine

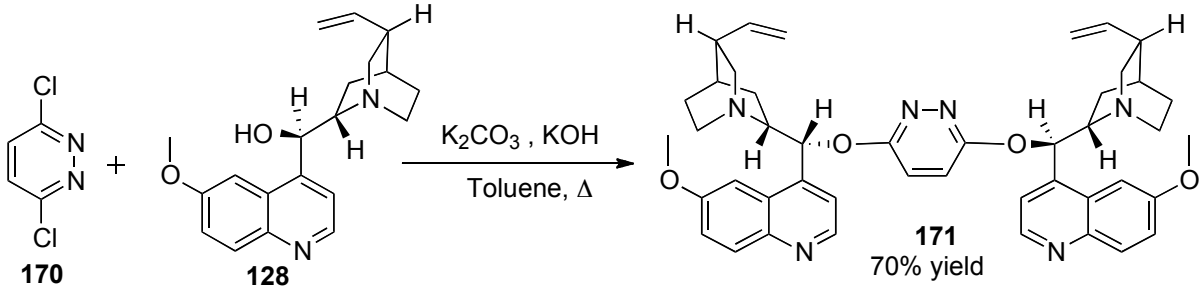
A big jump in effectiveness came with the discovery of the phthalazine class of ligands $(DHQ)_2PHAL$ (S)-**162** which have two dihydroquinine entities attached at the 1,4-position of a phthalazine ring. This class of ligands has proven to be excellent for the Asymmetric dihydroxylation (AD) of olefins with high levels of enantioselectivity. Phthalhydrazide (1eq) **168** was reacted with phosphorous pentachloride (2.1eq) in presence of DMF (1drop) to activate the reaction. The condenser was fitted with a calcium chloride drying tube and directly connected to the condenser to prevent moisture contamination and allow HCl evolution, the solid mixture was gently heated from room temperature to 145 °C over 60 min, upon which a steady (over~3h) evolution of HCl occurred. The resulting white solid was dissolved in methylene chloride and eluted through the neutral alumina Column. After further

work up, the colourless solid isolated, was recrystallised from THF to give a pure colourless needle-like crystals of **169** (78% yield).



Scheme 42. *Synthesis of catalyst (S)-**162***

The crystal of 1,4-dichlorophthalazine (1eq) **169** was reacted with (S)-**128** (2eq) in the presence of K_2CO_3 (3eq) and KOH (3eq) in toluene, equipped with a Dean-Stark-condenser under nitrogen, the mixture was heated under reflux at 135°c for 14 hours with azeotropic removal of water. The reaction was followed by TLC, after further work up procedure gave a solid which was dried in *vacuo* to give pure ligand (S)-**162** (88% yield). The same protocol was applied to the synthesis of catalyst (*S*)-**171**. 3,6-Dichloropyridazine **170** was reacted with DHQ **128** (2eq) in the presence of K_2CO_3 (3eq) and KOH (3eq) in toluene to give (S)-**171** 70% yield.

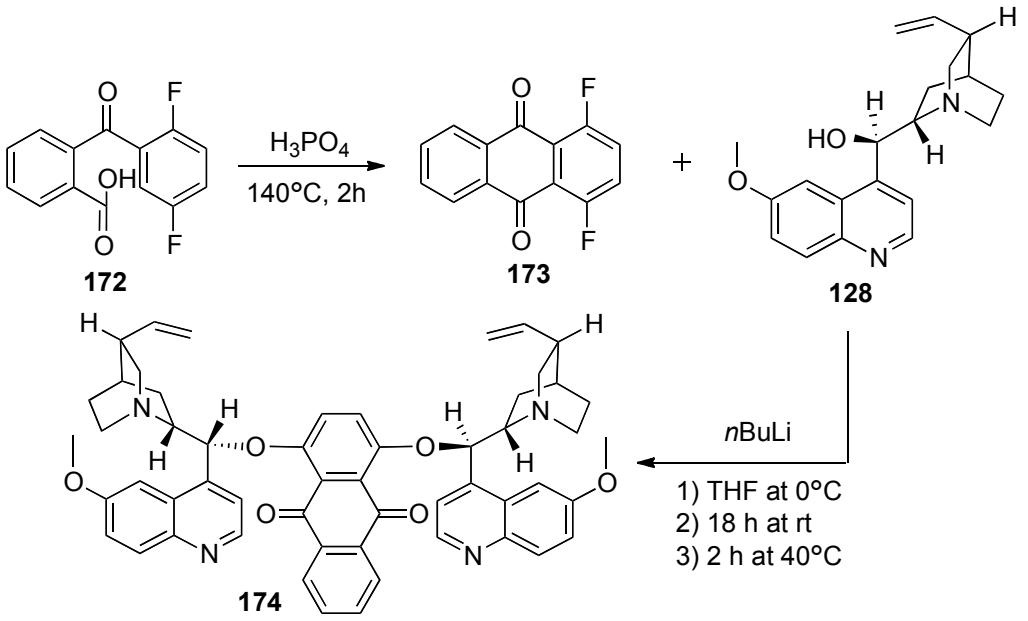


Scheme 43. *Synthesis of catalyst (S)-**171***

2.8.3 Synthesis of the cinchona alkaloid derivative (S)-174 Anthraquinone core

Anthraquinone core (*S*)-**174** was synthesised by the following method 2-(2,5)-difluorobenzoic acid (1eq) **172** was reacted with excess polyphosphoric acid and the mixture was refluxed at 140 °C for 2 hours. Subsequent ring closure by reaction with polyphosphoric acid afforded anthraquinone core **173** in 25% overall yield. The two fluorine atoms of **173** are

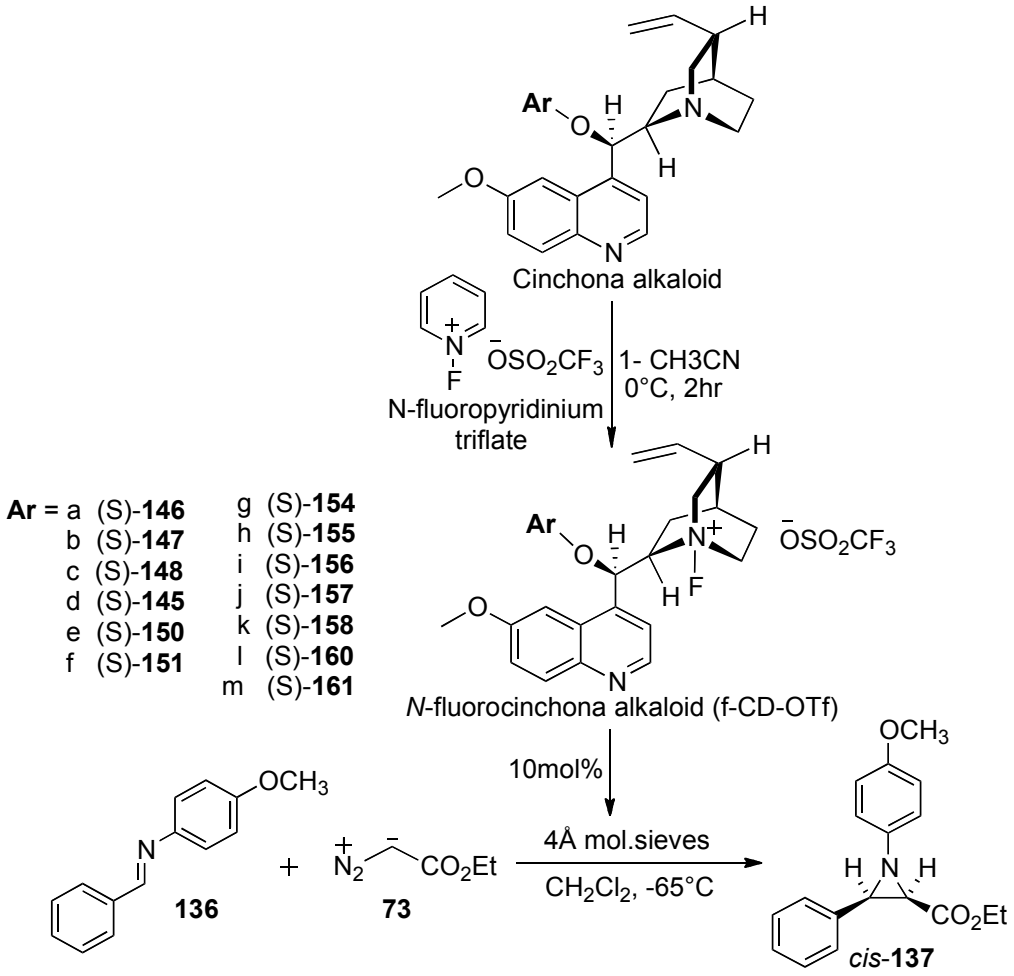
easily displaced by dihydroquinidine (S)-**128** to give a anthraquinone (S)-**174**. Addition of **173** to a mixture of dihydroquinidine (2.5eq) and *n*BuLi (2.5eq) in THF at 0 °C, then stirring for 18 hour at room temperature and 2 hours at 40 °C, provided 35% overall yield.



Scheme 44. *Synthesis of catalyst (S)-**174***

2.9 Screening of (S)-Cinchona alkaloid-derived N-fluoroquaternary salt catalysts

The initial screening involved chinchona alkaloids (*S*)-**146**, (*S*)-**147**, (*S*)-**148**, (*S*)-**150** (*S*)-**151**, (*S*)-**155** and (*S*)-**156**. Some of the catalysts were not used, and therefore the efficiency of catalyst (S)-**152**, (S)-**153,** (S)-**159,** (S)-**149** remained undetermined, due to the large number of reactions resulting from the set of experiment**.** *N*-Benzyl imine **136** was reacted with ethyl diazoacetate **73** in the presence of chiral *N*-fluoroquaternary ammonium salt catalysts at -65°C to afford aziridine *cis*-**137** in poor yields, *i.e.* ~30% (Scheme 45). Products were isolated through chromatographic purification on a silica column. The pure samples obtained were directly submitted to chiral HPLC analysis. The observed enantiomeric excess is shown in Table 4. When *bulky* substituted aryl groups were attached to the (*S*)-*N* fluoro-chinchona alkaloid scaffold (catalysts (*S*)-**150, 151, 161** and (*S*)-**158**), the induced enantioselectivity was revealed to be very poor (5-8%), if not nonexistent, independently of the starting materials employed. A slight improvement in the *e.e.'s* was observed when formation of aziridines *cis*-**137** was promoted by catalysts (*S*)-**146, 145, 155** (18%, 11% and 9% respectively). The efficiency of catalysts (*S*)-**158, 150, 151,** and **161** was affected by the bulkiness of the attached group, positively for the transformation of imine (8% to 21% *e.e.*).



Scheme 45. *Reaction scheme for the screening of catalysts.*

Aryl groups (Ar)	Yield	*e.e.* (*cis*-137)
$(DHQ)_2$-PHL-(*S*)-**146-a**	26%	21%
(DHQ)-benzoate-(*S*)-**147-b**	30%	6%
(DHQ)-pentafluorobenzoate-(*S*)-**148-c**	17%	(R)
$(DHQ)_2$-pyridine-dicarboxylate-(*S*)-**145-d**	21%	11%
(DHQ)-3-phenoxybenzoate-(*S*)-**150-e**	18%	4%
(DHQ)-2-phenoxybenzoate-(S)-**151-f**	25%	7%
(DHQ)-4-bromobenzoyl ester-(*S*)-**154-g**	19%	8%
(DHQ)-2-bromobenzoyl ester-(S)-**155-h**	35%	8%
(DHQ)-thiophene-2-carboxylate-(*S*)-**156-i**	38%	4%
(DHQ)-2-(pyridin-4-yl)-acetate-(S)-**157-j**	18%	7%
(DHQ)-pivalate-(*S*)-**158-k**	31%	5%
(DHQ)-5-phenylfuran-2-carboxylate-(S)-**160-l**	21%	5%
(DHQ)-biphenyl-4-carboxylate-(S)-**161-m**	23%	6%

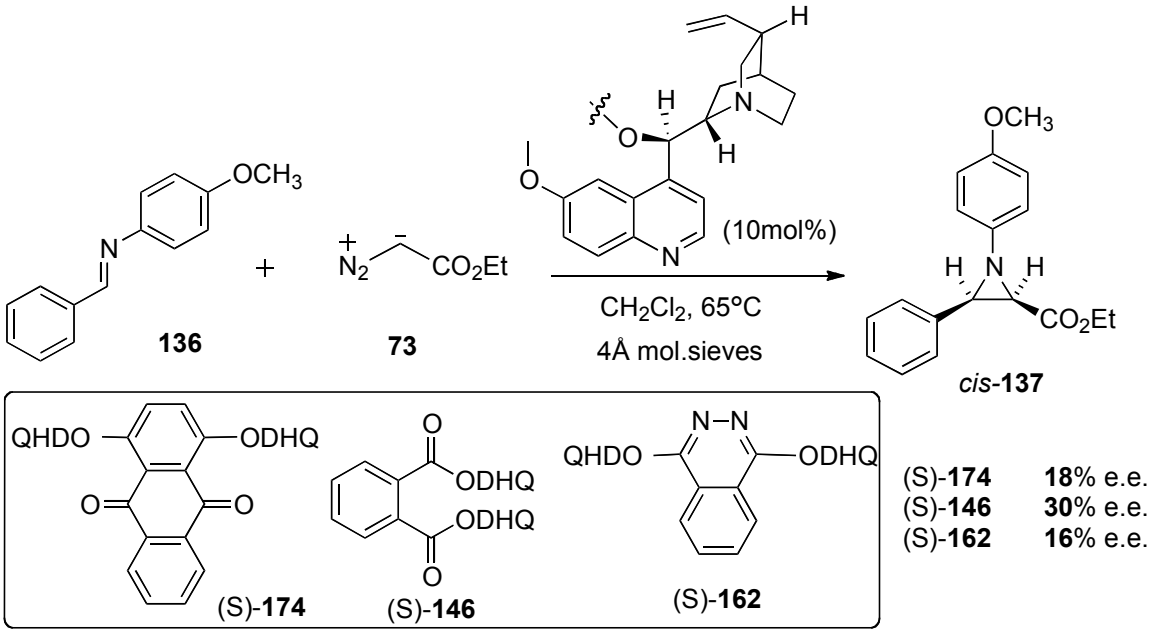
Table 4. *Enantiomeric enrichments for the reactions in Scheme 45.*

The disubstituted *N*-fluorocinchona alkaloid catalyst (*S*)-**145** was able to induce a higher, but still unsatisfactory, level of enantioselectivity (17%) with the *N*-benzyl imine **136**. The spatial

environment shaped by the "homologue" catalyst (*S*)-**174** anthraquinone core ligand showed a enantioselectivity (18%). The -substituted cinchona alkaloid catalyst (*S*)-**171** afforded very poor enantiomerically enriched products (7-12% *e.e.*). Extremely useful information was collected from the (*S*)-cinchona alkaloid-derived catalytic systems functionalized with disubstitutions of *N*-fluorochinchona alkaloid. Aziridinations promoted by catalysts (*S*)-**146** - (*S*)-**174** and (*S*)-**167** on the *N*-benzylimine **136** worked better in terms of *e.e.* Although the **174** and (*S*)-**156**, (*S*)-**157,** (*S*)-**154,** (*S*)-**160** substituted systems displayed a low selectivity (13%,4%, 7% ,8%, 5%, and 8% *e.e.*'s of *cis*-**137**), higher *e.e.* values were obtained with catalysts (*S*)-**146** (21%), **145** (17%), **174** (18%) and (*S*)-**171** (11%). These experimental findings could contribute to shed light on the mechanism of co-ordination or complex formation at the transition states of the reaction.

2.10 Screening of catalysts (S)-174, (S)-146, (S)-162

Having found so far that the disubstitution of the cinchona alkaloid on benzyl ring of the 3,3'-positions, i.e. (*S*)-**146**, had afforded at least some enantiomeric enrichments (Table 4 above), it seemed appropriate to carry forward the experiment for further investigating. With this intent, catalysts (*S*)-**146, 174** and (*S*)-**162** were tested in the aza-Darzens reaction of the *N*-benzyllimine **136** with ethyl diazoacetate **73** (Scheme 46). Catalyst (*S*)-**146**, carrying the di substitution of cinchona alkaloid on 1,2 position of phthalate ring, is a good ligand for enantiometric enrichment. The enantioselectivity substantially improved when the reaction was promoted at -80°C, raising the enantiomeric excess to 30%. This value is closer to the one afforded for the same reaction by the disubstitution of anthraquinone core of (*S*)-**174** (18% *e.e.*) than by the disubstitution of cinchona alkaloid on the 1,4-position of the phthalazine ring of (*S*)-**162** (16% *e.e.*).

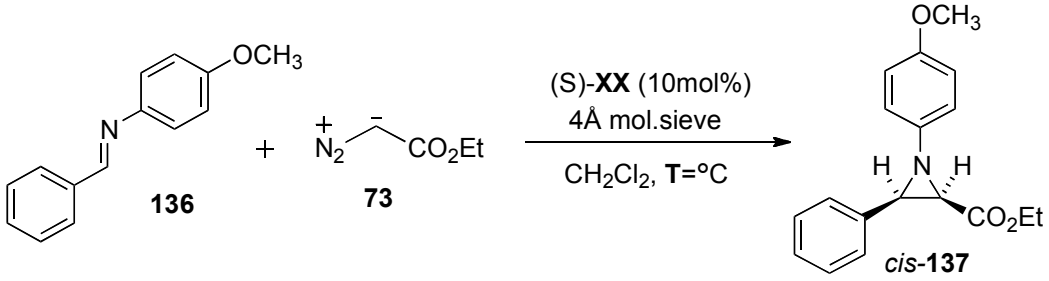


Scheme 46. *Screening of catalysts (S)-**174**, (S)-**146**, (S)-**162** for the synthesis of aziridine cis-**137**.*

Catalyst (*S*)-**174**, gave an enantioselectivity of 21%. Disappointingly, the observed enantiomeric excess for use of catalyst (S)-**162** (23%) was inferior to the one afforded by catalyst (*S*)-**146** (31% *e.e.*) at -80°C.

2.11 Screening of the temperature for the synthesis of cis-137

Temperature control is one of the most powerful tools that organic chemists can use to optimise and influence the performance of the reaction. A transformation carried out under kinetic control may end up with a different distribution of products than the same reaction carried on under thermodynamic control. To act directly on the energy content of the system by means of the temperature may allow a strong degree of control over the specificity and/or selectivity of a process. Hydrogen bonds are temperature sensitive. Increase of temperature increases the vibrational motion of the A-H bonds in an A-H···B hydrogen-bonding equilibrium system, thus weakening the hydrogen bonding itself.



Scheme 47. *Temperature screening experiment for the synthesis of cis-**137**.*

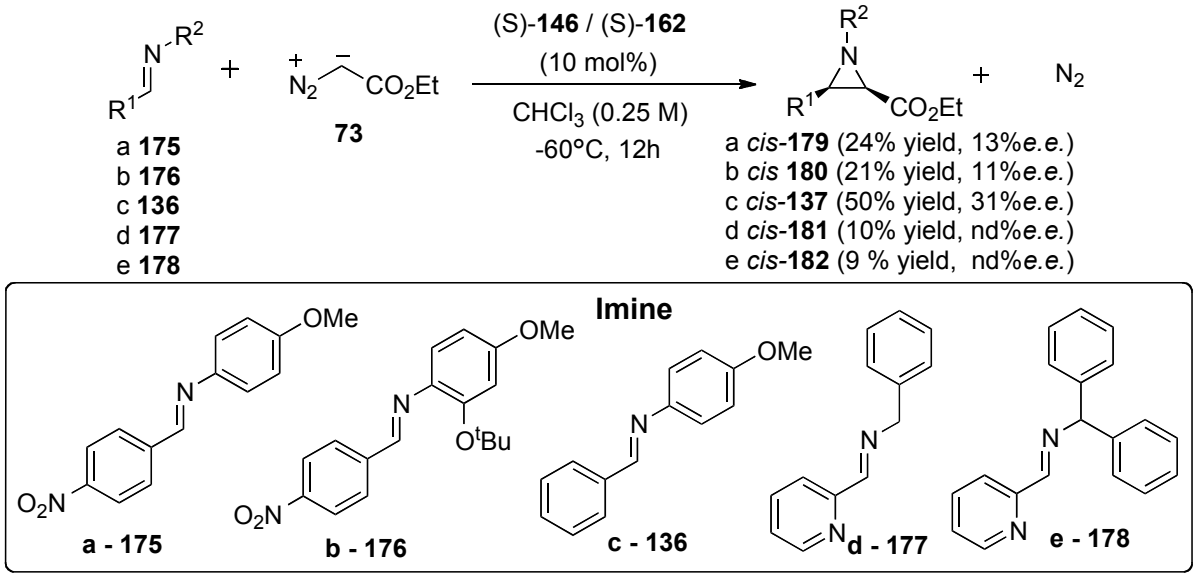
Entry	Catalyst	T(^{0}C)	*e.e.* (%)	Yield (%)	Reaction time (h)
1	$(DHQ)_2PHAL$	RT	(R)	51	6
2	(DHQB)-Cl	0	(R)	37	8
3	(DHQB)-Cl	–40	11	21	~14
4	$(DHQ)_2PHAL$	–80	13	24	~24
5	$(DHQ)_2PHAL$	–50	14	30	~16
6	$(DHQ)_2PHL$	–65	21	20	~20
7	DHQB	–35	19	22	~12
8	$(DHQ)_2PHAL$	–65	18	19	~20
9	$(DHQ)_2PHL$	–80	30	20	~24

Table 5. *Temperature effect for the synthesis of aziridine cis-**137** illustrated in Scheme 47.*

Although decreasing the temperature substantially slowed down the reaction rates, it conferred great benefit to both yields and enantiomeric enrichments. Complete consumption of the starting materials was quickly achieved above room temparature in 4 to 8 hours (entries 1). The reactions were performed in the range from –50 °C to –20 °C (entries 2-4) were checked the following day and found complete. The reaction carried out at –80 °C (entry 4-9) was found to be exceptionally slow. Nonetheless, some conversion of imine **136** into aziridine *cis*-**137** was observed at –50 °C and –80 °C (20% yield). Performing the reaction at -40 °C or -35°C is not advisable, as the reaction shows no real improvement in either yield or enantiomeric excess (11% and 19%, respectively).

2.12 Screening of the N-substituted imine for the synthesis of cis-aziridine

In order to extend the scope of the optimized catalytic system and encouraged by the results obtained for the asymmetric synthesis of aziridine *cis*-**182** (50% yield, 31% *e.e.*), the method was applied to a range of electron-withdrawing and electron-donating *C*-substituted *N*-(O-methoxyphenyl)imines (Scheme 48).



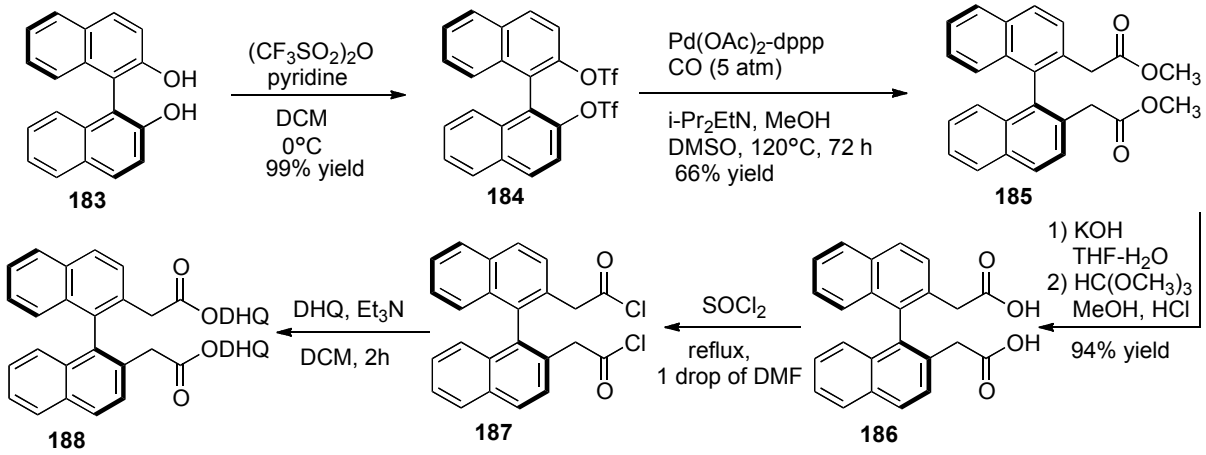
Scheme 48. *Screening of the N-substituted imine*

N-O-methoxyphenyl) imines **175, 176, 136, 177** and **178** were reacted with ethyl diazoacetate **73** in chloroform at –60 °C. To promote the reaction, a catalyst loading of 10 mol% of (*S*)-**146, 162** was employed. The reactions were vigorously stirred overnight. The ^{1}H-NMR spectra of the crude mixtures were clean; purification by flash chromatography on silica gel resulted, in many cases, the pure product. As already observed for the O-methoxy-substituted aziridine *cis*-**179**, the reaction works generally very well only when the starting imine **136**, was functionalized with electron-rich aromatic groups on the carbon, i.e. **c- 136** (50% yield and 31% e.e); reaction with an electron deficient aromatic substituted imine i.e. **175** and **176** resulted in an unsatisfactory yield and enantioselectivity (24%, 21% yield and 13%, 11% e.e. respectively). Reaction with **177** and **178** did not improve the yields (10% and 9% yield); because of the low yields enantioselectivity of these compound were not calculated.

Future work

As we have already discussed in the introduction section that the nature of the reagents, structure of the catalyst, temperature, solvent, concentration, catalyst loading, etc are very important. In order to maximize the efficiency of a reaction system in terms of yield and stereoselectivity, the systematic variation of one parameter per time needs to be undertaken. Thus, the first fundamental component to be preliminary screened in this study was the asymmetric organocatalyst. As we have made known in the study the catalyst (S)-**146** gave 50% yield and 30% enantioselectivity. The disubstitution of the cinchona alkaloid scaffold shows moderate enantiometric enrichment. Therefore the future work is to modify the disubstituted cinchona alkaloid scaffold catalyst and to study all the parameters such as nature of the reagents, structure of the catalyst, temperature, solvent, concentration, catalyst

loading, etc. In order to develop the catalyst or the system to more efficient we attempted some of the experiments using (S)-BINOL as a Bronsted acid. Continuous efforts are dedicated not only to optimising already existing catalytic systems, but also to extending the scope and the limits of organocatalysis itself, and, for this particular case, of Brønsted acid catalysis. Due to the interest in chiral Brønsted acids and their contributions to organocatalysis, the search for novel and universal "super-acids" is still open and constitutes a big challenge for organocatalysis.



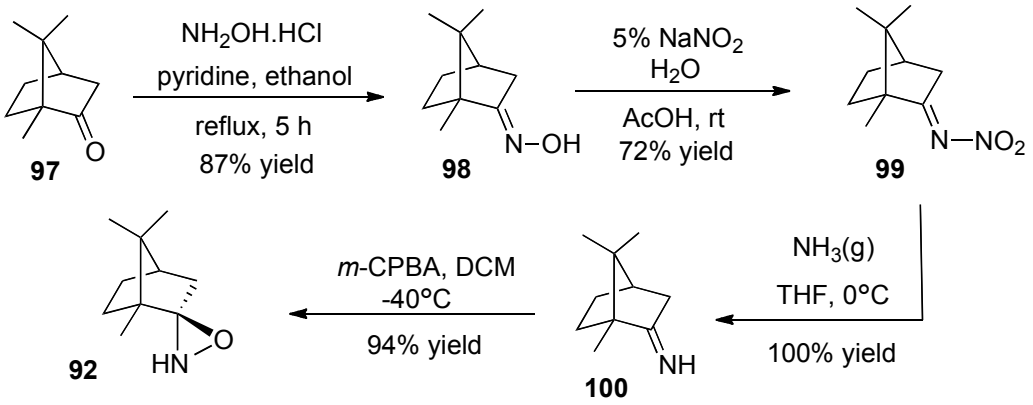
Scheme 49. *Attempted synthesis of (S)-**188**.*

Thus, after treatment of **183** with triflic anhydride, the resulting triflate **184** was subjected to palladium-catalysed carbonylation in the presence of $Pd(OAc)_2$/dppp catalyst and diisopropylethylamine in DMSO–MeOH at 120°C for 72 h under 5 atm of carbon monoxide to afford (S)-2,2'-bis(methoxycarbonyl)- 6-(2-methoxycarbonyl)ethyl-1,'1-binaphthyl ((S)-**185**) in 66% yield. The triester **185** was hydrolysed under aqueous alkaline conditions, and the resulting 6-aliphatic acid was selectively protected to give 2,2'-bis(hydroxycarbonyl)-1, 10-binaphthyl (S)- **186**. A mixture of (S)-**186** and thionyl chloride was heated at reflux and turned clear after 5 h. The excess of thionyl chloride was subsequently removed by distillation. The product **187** was obtained as a white solid. Into a solution of cinchona alkaloid in anhydrous dichloromethane, 0.5M anhydrous triethyl amine at 0°C was added. A solution of the corresponding chloride **187** in anhydrous dichloromethane was slowly added. After 1 h the reaction mixture was warmed to room temperature and stirred for additional 2 h. Upon completion of reaction indicated by TLC, after work up followed by purification by flash chromatography on silica gel, an excellent yield of **188** was isolated. Unfortunately, because of the lack of time we didn't test the resulting catalyst (S)-**188** in Aza-darzen reaction.

3 Attempted Synthesis of Five-Membered Ring Heterocycles by Cyclization of NH-Oxaziridines with Alkenes

3.1 Synthesis of NH-oxaziridine

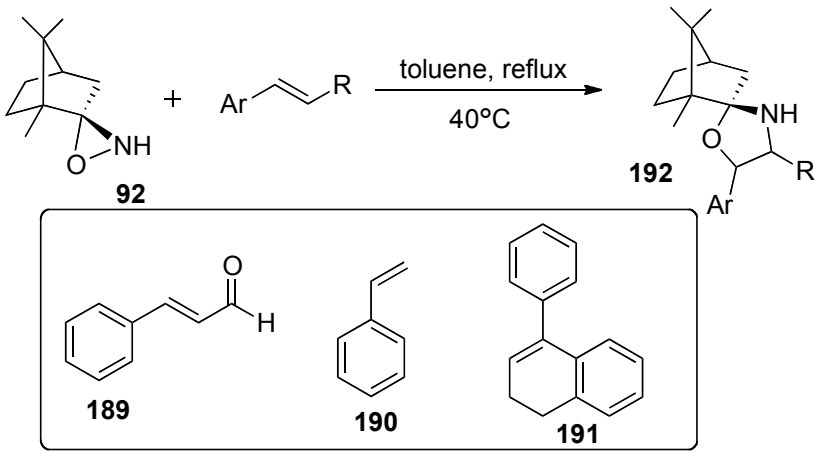
As already discussed in the introduction, novel and interesting NH-oxaziridine syntheses **92**, were carried out by oxidation of the corresponding imines with m-chloroperbenzoic acid (m-CPBA) in presence of anhydrous dichloromethane at -40° C. The crude mixture was isolated by chromatographic purification providing NH-oxaziridine **92** in 94% yield (Scheme 50).



Scheme 50. *Synthesis of N-camphor oxaziridine* ***92***

3.2 Attempt to synthesise 4,5-diarylisoaxazolidines using alkenes

The first step towards the synthesis of five membered-heterocycle using alkenes and NH-oxaziridine was to use a simple alkene and to investigate temperature control and suitable solvent etc. Here we have tried to discover simple protocol, which gives the efficient [3+2] cycloaddition of a variety of aryl alkenes with our NH-oxaziridine, leading to 4,5-diarylisoxazolidines.

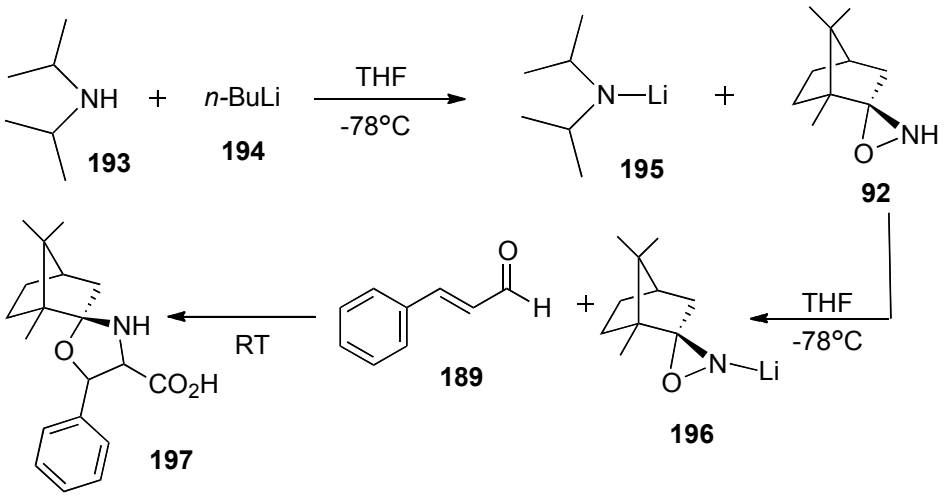


Scheme 51. *Synthesis of* ***192***

NH-oxaziridine **92** was treated with each of alkene **189, 190, 191** (1.5eq) in the presence of toluene at 40 °C, unfortunately the resulting reaction mixture did not contain any of the desired products. The first reaction was carried out with styrene at different temperatures such as 20°C, 40°C, 60°C, but the result obtained at different temperatures disappointingly did not show the desired product. No reaction occurred at 20°C and 40°C, and the oxaziridine was found to decompose at 60°C.

3.3 Deprotonation of NH-oxaziridine using diisopropylamine and nBuLi

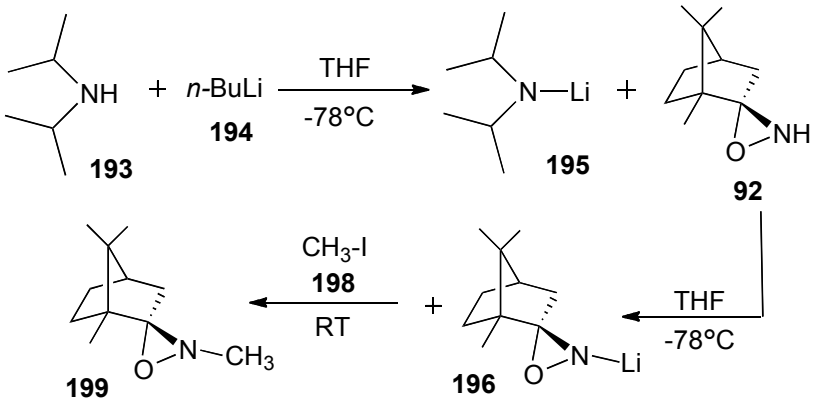
We next attempted to deprotonate the NH-oxaziridine **92**, using *LDA* to determine if addition conjugate to alkene **189** would result in cleavage of the N-O bond and formation of a cyclic product. NH-camphore oxaziridine was reacted with (1.5 eq) of LDA at -78°C in THF as solvent. After 2 hours cinnamaldehyde (1eq) was added at room temperature.



Scheme 52. *Synthesis of* ***197***

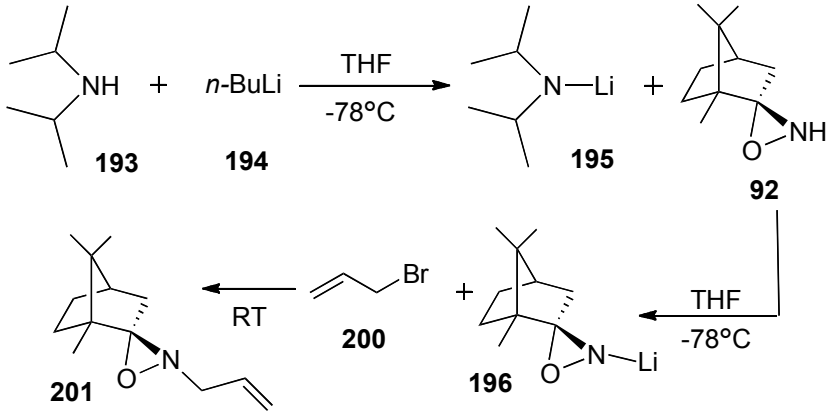
3.4 Synthesis of 199 from NH-oxaziridine using diisopropylamine and nBuLi

Unfortunately this reaction did not show any of the desired products. We therefore decided to check if the deprotonation of the NH-oxaziridine was effectively working or not.



Scheme 53. *Synthesis of* **199**

As before isopropyamine (1.5 eq) and *n*-BuLi (1.5eq) were reacted at -78 °C in anhydrous THF under nitrogen. Reaction of diisopropylamine with *n*BuLi in THF is significantly fast and rapid, the deprotonation of di-isopropylamine easily obtained. The resulting LDA is a strong base suitable for the deprotonation of weakly acidic compound. After 1 hour NH-oxaziridine **92** (1eq) was added, and after 2 hours methyl iodide was added to the reaction mixture. Methyl iodide is an excellent substrate for substitutions reactions. It is sterically open for attack by nucleophiles, and iodide is a good leaving group. Successful deprotonation of the NH-oxaziridine occurred, and the resulting reaction mixture was worked up and purified using column chromatography. ^{1}H NMR spectroscopy confirmed the resulting compound **199** which wasisolated in (79% yield). After obtaining this successful result, allyl bromide was used. The same procedure was applied as discussed above.

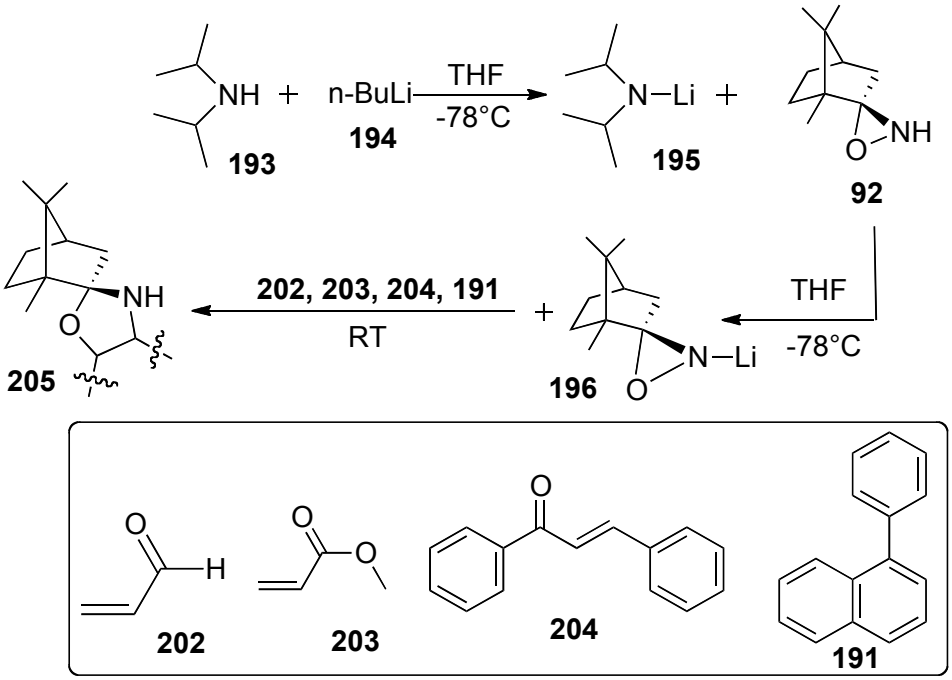


Scheme 54. *Synthesis of **201***

The reaction was monitored by TLC and showed an additional spot after 2 hours. The crude reaction mixture was worked up and purified by column chromatography. ^{1}H NMR spectroscopy confirmed the resulting compound to be **201**, which was isolated in 57% yield.

3.5 Attempt to synthesize five-membered heterocycle using LDA

The above experiments demonstrated the success of the LDA, deprotonation of the NH-oxaziridine **92** by LDA **195** followed by alkylation with methyl iodide **198** and allyl bromide **200.** The successful deprotonation of NH-oxaziridine **92** led us to test a number of electron-deficient alkenes in the hope that a cyclization would occur.

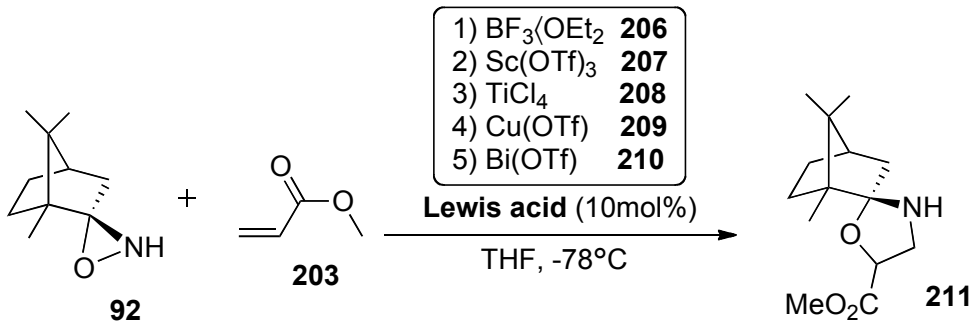


Scheme 55. *Synthesis of* **205**

Di-isopropylamine (1.5 eq) and *n*-BuLi (1.5eq) was reacted at -78°C in anhydrous THF under nitrogen. After 1 hour NH-oxaziridine (1eq) was added to the reaction mixture. After 2 hours, methyl acrylate **203**, acrolein **202**, chalcone **204**, 1,2-dihydro-4-phenylnaphthalene **191** were added in separate reaction to the reaction mixture. The reactions were monitored by TLC. Acrolein is the simplest unsaturated aldehyde, and unfortunately did not work. Reaction with methyl acrylate **203** showed an additional spot by TLC but the resulting compound decomposed upon chromatographic purification. Chalcone **204** and 1,2-dihydro-4-phenylnaphthalene **191** were unsuccessful for the protocol.

3.6 Attempt to synthesize five-membered heterocycle using Lewis acid

Disappointingly, it was necessary to seek a new method for the synthesis of five membered-heterocycles. There is some literature that reports the use of Lewis acids for related cyclization reactions. Yoon reported the cycloaddition of *N*-sulfonyl nitrones generated by a Lewis acid catalysed rearrangement of oxaziridines. He reported a novel method for Lewis acid-catalysed formation and cycloaddition of inaccessible N-nosyl nitrones, which produce isoxazolidines that can be deprotected under mild conditions without accompanying ring cleavage. Inspired from Yoon's result we decided to investigate Lewis acid catalysed protocols.



Scheme 56. *Attempted synthesis of* **211** *using Lewis acid*

We hypothesized that Lewis acid activation of oxaziridines **92** would increase their electrophilicity and, consequently, their reactivity towards alkenes. The reaction was carried out between oxaziridine **92** and methyl acrylate **203** (1 eq) catalysed by Lewis acid $BF_3 \cdot OEt_2$ **206** (10 mol %) in anhydrous THF at -78°C. As expected from earlier reports of oxaziridine reactivity, the reaction was unsuccessful. The new reaction was attempted in the presence of a variety of Lewis acid. Sc(III)OTf was used with catalyst loadings as low as 10 mol % under optimized reaction conditions. An additional spot was detected by TLC plate but unfortunately that proved not to be the desired product. $TiCl_4$ **208** (10 mol %) was employed with methyl acrylate **203** (1eq) and oxaziridine **92** (1eq), giving an immediate colour change was occure immediately. The reaction was followed by TLC, shown that all starting material oxaziridine **92** was reacted within 5 hours. The reaction mixture was worked up and purified by column chromatography, but the resulting compound decomposed on the column. Cu(II)OTf **209** and Bi(III)OTf **210** was employed for further investigation. Both catalysts gave fast colour immediately after addition of methyl acrylate **203**. The reactions were left stirring overnight for in order to obtain the product. The resulting reaction mixtures were worked up and purified but only the starting material camphor **98** was observed by ^{1}H NMR spectroscopy.

4 EXPERIMENTAL SECTION

1. General experimental methods

The chiller employed in experiments was a Cole-Parmer Immersion Cooler equipped with a flexible hose connected to an immersible probe. The probe was placed in a dewar of the appropriate size filled with *iso*-propanol. Analytical Thin Layer Chromatography (TLC) was performed on Silica Gel 60 F254 pre-coated aluminum sheets and visualized under UV light by dipping in an appropriate TLC stain anisaldehyde followed by heating with heat gun. Flash chromatography was carried out using Silica gel 60 (40-63 mesh). Optical rotation $[\alpha]_D$ were measured using Perkin-Elmer Model 241 Polarimeter. FTIR spectra were recorded on a Perkin Elmer Spectrum BX. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian 300 MHz Gemini 2000 or a 400 MHz Unity Plus 400 NMR.

2. General procedure for the preparation of the asymmetric samples

A 5 mL microwave-type vial was charged with a magnetic stirrer bar and flame dried. The vial was capped with a rubber seal. The rubber seal was pierced with a syringe needle connected to an Schlenk line. An inert gas was allowed to flow from the Schlenk line into the vial and the vial was cooled to room temperature. The vial was subsequently loaded with the starting material imine (0.26 mmol) and catalyst (*S*)-**71** / (S)-**XX** (2.1 mg, 2.6 mmol, 1mol%). Three cycles of vacuum / nitrogen were applied to the vial using the Schlenk line before any liquid was introduced. The cycles ensure the removal of moisture from the vial volume, replacing air with an inert gas (argon or nitrogen). Anhydrous chloroform (1 mL, 0.26 M) was then injected *via* syringe through the seal and the vial was placed in the cooling bath of *iso*-propanol at –60 °C as close as possible to the external thermometer. Vigorous stirring is required to ensure the best performance for the reaction in terms of reaction time. After a pre-stirring time of one minute, generally enough to take all the reactants into solution, *tert*-butyl diazoacetate (0.28 mmol, 38 μL, 1.1 eq^n) was added by syringe. The reaction mixture was stirred vigorously for 12 hours or until completion. The presence of the rubber seal allows a facile monitoring of the reaction by TLC, without compromising the overall setting of the system.

3. General procedure for the preparation of N-fluoroquaternary ammonium salt

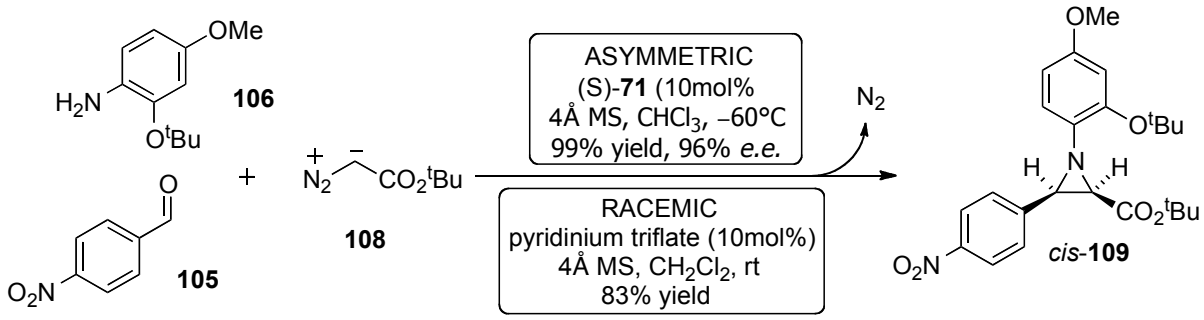
A 5 mL microwave-type vial was charged with a magnetic stirrer bar and flame dried. The vial was capped with a rubber seal. The rubber seal was pierced with a syringe needle

connected to a Schlenk line. An inert atmosphere was allowed to flow from the Schlenk line into the vial and the vial was cooled to room temperature. Application of this procedure is intended to remove moisture from the glass surface of the vial. The vial was subsequently loaded with the starting material *N*-fluoropyridinium triflate **77** (64.2 mg, 0.26mmol), and dihydroquinidine **128** (84 mg, 0.26mmol, 1eq^{n} / 2 eq^{n}). Three vacuum / nitrogen cycles were applied to the vial. The mixture was dissolved in anhydrous acetonitrile (1 mL) and stirred for two hours at 0 °C solvents were removed under reduced pressure.

SYNTHESIS AND CHARACTERISATION

Organocatalysis

Synthesis of cis-109 via a three component one-pot imine condensation / aza-Darzens reaction



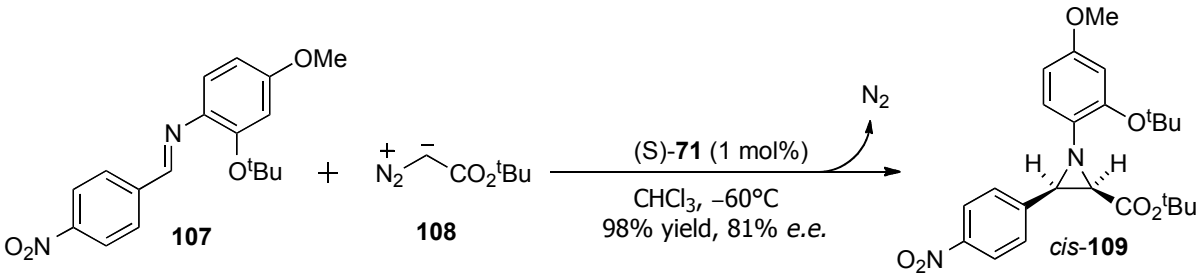
<u>*Asymmetric synthesis*</u>. A 5 mL microwave vial was charged with a magnetic stirrer bar. The vial was flame dried and then cooled to room temperature under an inert atmosphere. 2-*tert*-butoxy-4-methoxyaniline **106** (51 mg, 0.26 mmol), 4-nitrobenzaldehyde **105** (39.3 mg, 0.26 mmol), (*S*)-**71** (21 mg, 0.026 mmol, 10 mol %) and 4Å molecular sieve (~100 mg) were loaded into the reaction vial. Three vacuum / nitrogen cycles were applied to the vial. Anhydrous chloroform (1 mL) was injected into the microwave vial *via* the rubber seals on the tube. The reaction vial was then transferred to a Dewar containing *iso*-propanol as coolant at -60 °C, The solution was cooled to -60 °C and stirred for one minute. Liquid *tert*-butyl diazoacetate (0.038 mL, 0.28 mmol, 1.1 eq^{n}) was added *via* syringe and the solution was stirred at -60 °C for a further 12 hours. A subsequent TLC (hexane / diethyl ether: 80 / 20) indicated complete consumption of the starting material. Chloroform was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (elution with hexane / diethyl ether : 8 / 2). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. A sample of *cis*-**109** was submitted to chiral analytical HPLC analysis [Chiralpak AD, *iso*-hexane / *iso*-propanol : 95 / 5, 1 mL / min, 13.6 min (1st peak), 16.9 min (2nd peak)]. The reaction afforded *cis*-**109** as a thick orange oil in 99% yield and 96% *e.e.*

<u>*Racemic synthesis.*</u> A 5 mL reaction vial was charged with a magnetic stirrer bar. The vial was loaded with 2-*tert*-butoxy-4-methoxyaniline **106** (51 mg, 0.26 mmol), 4-nitrobenzaldehyde **105** (39.3 mg, 0.26 mmol), (*S*)-**71** (21 mg, 0.026 mmol, 10 mol%) and 4Å molecular sieve (~100 mg). The mixture was dissolved in dichloromethane (1 mL) and stirred for one minute. Liquid *tert*-butyl diazoacetate (0.038 mL, 0.28 mmol, 1.1 eq^{n}) was added by

syringe at room temperature while stirring the solution. The reaction was stirred for 15 hours. A subsequent TLC (hexane / diethyl ether : 80 / 20) indicated complete consumption of the starting material. Dichloromethane was removed *in vacuo* and the reaction residue was purified by flash chromatography on silica gel (elution with hexane / diethyl ether : 8 / 1). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound *rac*-**109** was afforded in 83% yield.

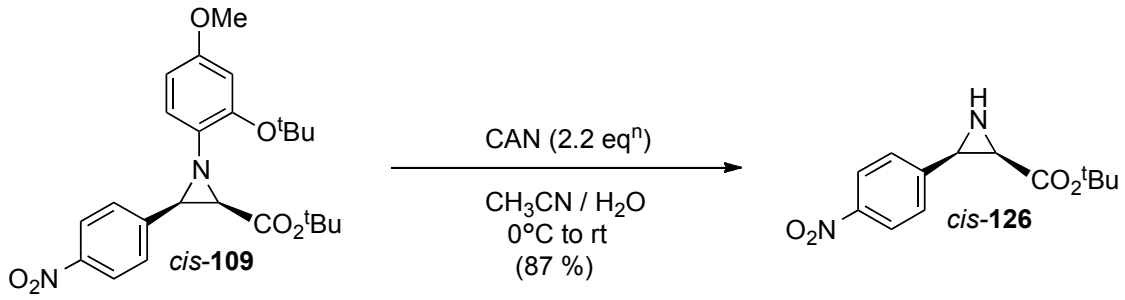
^{1}H NMR ($CDCl_3$, 400 MHz) 8.19 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 1H), 6.61 (d, J = 2.6 Hz, 1H), 6.50 (dd, J = 8.6, 2.7 Hz, 1H), 3.74 (s, 3H), 3.46 (d, J = 6.7 Hz, 1H), 3.06 (d, J = 6.8 Hz, 1H), 1.34 (s, 9H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 165.4, 154.8, 147.7, 146.3, 142.2, 137.9, 128.0, 121.9, 119.7, 108.5, 106.1, 80.8, 79.5, 54.5, 46.8, 45.9, 27.7, 26.8; $[\alpha]_D^{26}$ = -84.6 (c = 4.3, $CHCl_3$), FT-IR (thin film, cm^{-1}): 2979, 2934, 1742 (CO), 1715, 1606, 1585, 1517, 1498, 1346, 1226, 1151, 1046, 972, 912, 854, 810, 736; MS $(EI)^+$: *m/z* 443.1 (40%) $[M+H]^+$, *m/z* 465.2 (100%) $[M+Na]^+$, *m/z* 907.4 (30%) $[2M+Na]^+$; HRMS $(EI)^+$: exact mass calculated for $[C_{24}H_{30}N_2O_6 + H]^+$ requires *m/z* 443.2177, found *m/z* 443.2176.

Synthesis of cis-109



Procedure is same as asymmetric synthesis of *cis*-**109** stated above, except the catalyst (S)-**71** loading was employed 1 mol %. Reaction mixture was purified by flash chromatography on silica gel (elution with hexane / diethyl ether : 8 / 2). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. A sample of *cis*-**109** was submitted to chiral analytical HPLC analysis [Chiralpak AD, *iso*-hexane / *iso*-propanol : 95 / 5, 1 mL / min, 13.6 min (1st peak), 16.9 min (2nd peak)]. The reaction afforded *cis*-**109** as thick orange oil in 98% yield and 81% *e.e.* Spectroscopical data is also same as *cis* -**109**.

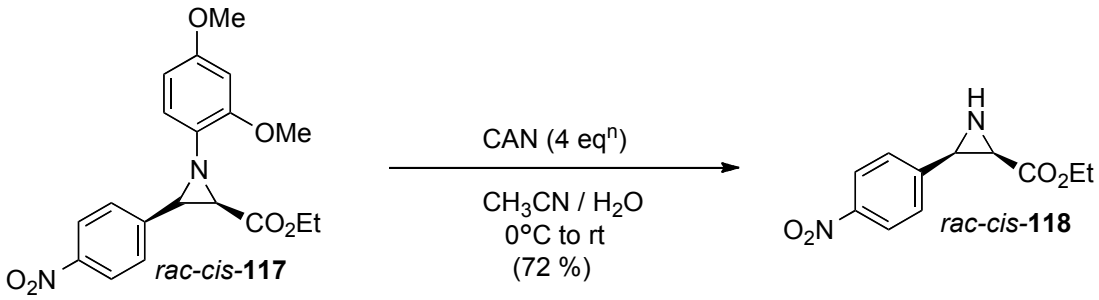
Synthesis of cis-126



A solution of a ammonium cerium(IV) nitrate (1.56 g, 2.85 mmol, 2.2 eq^n) in water (7 mL) was slowly added to an ice-cold solution of (–)-*cis*-**109** (573 mg, 1.2 mmol) in acetonitrile (26 mL). The reaction mixture was stirred at room temperature and monitored by TLC until complete consumption of the starting material aziridine (–)-*cis*-**109** was observed. The pH of the solution was then adjusted to neutral by addition of a few drops of 5% aqueous sodium hydrogen carbonate solution. Solid sodium sulfite was added in small portions until formation of brown slurry. After extraction with ethyl acetate (3x10 mL), the combined organic phases were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification *via* flash chromatography on silica gel (eluent diethyl ether / hexane: 1 / 1 → 2 / 1→ diethyl ether) afforded 200 mg of a white solid in 87% yield. Subsequent physicochemical analysis of the purified product confirmed formation of the title compound *cis*-**126**.

M.p. = 133.5 – 135.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 8.18 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 3.50 (s, 1H), 3.06 (d, J = 6.5 Hz, 1H), 1.9 (s, 1H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.5 (*C*O), 147.4, 142.8, 128.8, 123.2, 82.2, 38.6, 38.1, 27.7; $[\alpha]_D^{26}$ = -8.0 (c = 1.0, $CHCl_3$), FT-IR (thin film, cm^{-1}): 3208, 2976, 2933, 1725 (CO), 1600, 1515, 1369, 1347, 1218, 1154, 908, 883, 859, 854, 733; MS (EI)$^+$: *m/z* 663.2 (100%), 465 (20%). HRMS (EI)$^+$: exact mass calculated for $[C_{13}H_{16}N_2O_4 + H]^+$ requires *m/z* 265.1188, found *m/z* 265.1190.

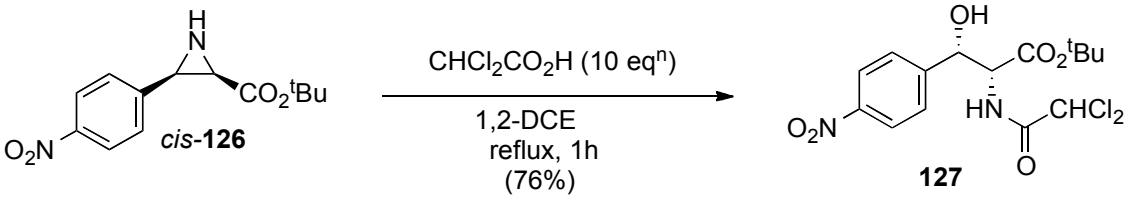
Synthesis of rac-cis-118



A solution of Ammonium cerium(IV) nitrate (1.2 g, 2.19 mmol, 4 eq^{n}) in water (4 mL) was slowly added to an an ice-cold solution of rac-*cis*-**117** (204 mg, 0.55 mmol) in acetonitrile (8 mL). Purification *via* flash chromatography on silica gel (eluent diethyl ether / hexane : 1 / 1 → 2 / 1→ diethyl ether) afforded a yellow solid in 72% yield. Subsequent physicochemical analysis of the purified product confirmed formation of the title compound rac-*cis*-**118**. (Procedure same as *cis*-**126**).

^{1}H NMR (300 MHz, CD_3CN) 8.13 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 3.88 (q, *J* = 7.0 Hz, 2H), 3.60 (d, *J* = 6.4 Hz, 1H), 3.10 (d, *J* = 6.4 Hz, 1H), 1.3 (d, *J* = 6.3 Hz, 1H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ 168.5 (*C*O), 147.5, 144.6, 129.1, 123.0, 60.7, 37.9, 29.6, 13.7; FT-IR (thin film, cm^{-1}): 2983, 1732 (CO), 1602, 1519, 1344, 1201, 1108, 1026, 852, 741. MS (EI)$^{+}$: *m/z* 237.2 (100%) $[M+H]^{+}$, *m/z* 607.3 (100%).

Synthesis of (–)-127

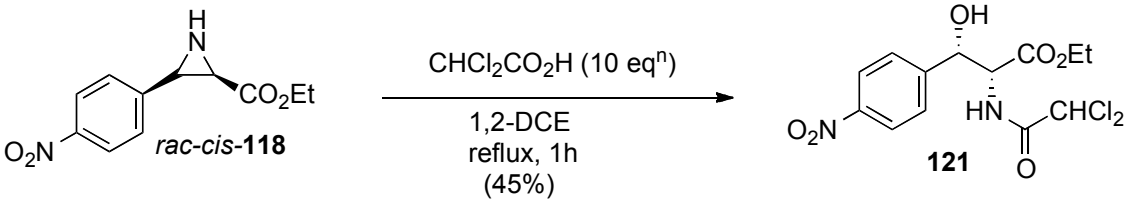


A 10 mL two-necked round-bottom flask was equipped with a condenser and a magnetic stirrer bar. The flask was loaded with a solution of *cis*-**126** (160 mg, 0.6 mmol) in 2.5 mL of 1,2-dichloroethane. Dichloroacetic acid (0.5 mL, 6 mmol, 10 eq^{n}) was added to the solution and the mixture was heated at reflux for one hour. The excess of dichloroacetic acid was removed by evaporation. The resulting residue was dissolved in dichloromethane and treated with a saturated aqueous solution of sodium carbonate. The aqueous layer was extracted with dichloromethane and the combined organic extracts were dried over anhydrous magnesium sulfate. Purification *via* flash chromatography on silica gel (hexane / diethyl ether: 1 / 2)

afforded 180 mg of a red oil in 76% yield. Subsequent physicochemical analysis of the purified product confirmed formation of the title compound **127**.

^{1}H NMR (300 MHz, $CDCl_3$) 8.20 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 9.3 Hz, 1H), 5.77 (s, 1H), 5.49 (s, 1H), 4.77 (dd, *J* = 9.1, 2.6 Hz, 1H), 2.98 (s, 1H), 1.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 167.8, 164.1, 147.8, 146.4, 126.9, 123.7, 84.1, 72.7, 65.9, 58.1, 27.8; $[\alpha]_D^{26}$ = + 13.3 (c = 1.0, $CHCl_3$), IR (thin film, cm^{-1}): 3406, 2958, 2926, 2854, 1732 (CO), 1683, 1608, 1520, 1348, 1259, 1157, 1074, 811, 735; MS $(EI)^+$: *m/z* 441 (20%), 365 (5%), 337 (20%), 268 (100%), 264 (50%), 247 (35%); HRMS $(EI)^+$: exact mass calculated for $[C_{15}H_{18}Cl_2N_2O_6 + H]^+$ requires *m/z* 421.0569, found *m/z* 421.0570.

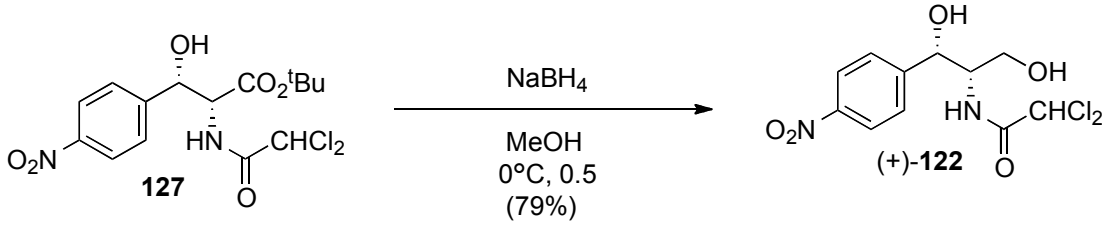
Synthesis of rac-121



Purification *via* flash chromatography on silica gel (hexane / diethyl ether : 1 / 2) afforded a light yellow solid in 45% yield. Subsequent physicochemical analysis of the purified product confirmed formation of the title compound *rac*-**121**. (Procedure same as **143**127

^{1}H NMR (300 MHz, CD_3CN) 8.21 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 2.7 Hz, 1H), 6.05 (s, 1H), 5.50 (d, *J* = 2.4 Hz, 1H), 4.79 (dd, *J* = 8.9, 2.8 Hz, 1H), 4.30 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN): 168.9 (*C*O), 164.2 (*C*O), 148.3, 147.9, 127.6, 123.4, 71.7, 66.2, 61.9, 58.5, 13.4; FT-IR (thin film, cm^{-1}): 2926, 1742 (CO), 1683, 1608, 1517, 1348, 1206, 1110, 1074, 1015, 812.

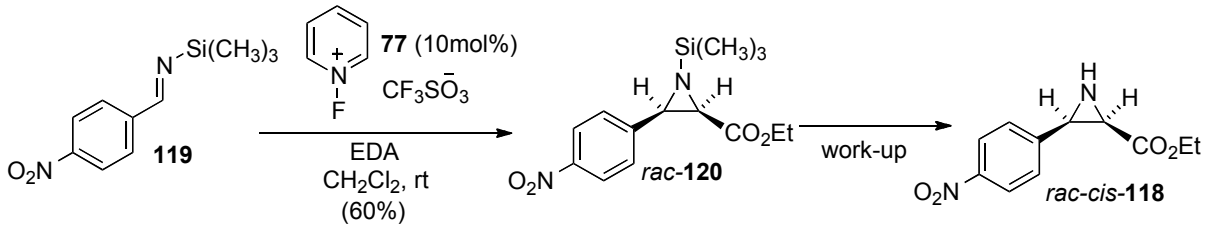
Synthesis of (+)-chloramphenicol (+)-122



A 2 mL vial was flame dried and charged with a magnetic stirrer bar. The vial was cooled to room temperature under inert atmosphere. Compound (–)-**127** (29 mg, 0.07 mmol) was loaded into the vial and three vacuums / nitrogen cycles were applied. **127** was then dissolved in 0.2 mL of methanol and cooled to 0 °C. Sodium borohydride (14 mg, 0.4 mmol, 5 eq^{n}) was added to the solution all at once and the reaction mixture was stirred for 30 minutes. The product was quenched with water (2.5 mL) and extracted with ethyl acetate three times. The combined organic phases were dried over anhydrous magnesium sulfate. Purification *via* flash chromatography on silica gel (hexane / ethyl acetate : 3 / 7) afforded 19 mg of a white solid in 79% yield. Subsequent physicochemical analysis of the purified product confirmed formation of the title compound (+)-**122**.

^{1}H NMR (300 MHz, DMSO): 8.32 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz), 6.46 (s, 1H), 6.06 (s, 1H), 5.04 (s, 1H), 4.97 (s, 1H), 3.92 (q, J_1 = 8.1 Hz, 1H), 3.57 (t, J = 8.1 Hz, 1H), 3.34 (m, 1H). ^{13}C NMR (75 MHz, DMSO): 163.6, 151.5, 146.6, 127.5, 123.1, 69.1, 66.5, 60.3, 56.9; $[\alpha]_D^{26}$ = + 23.9 (c = 1.0, EtOAc); FT-IR (thin film, cm^{-1}): 3298, 2924, 1682, 1514, 1348, 1070, 812.

Synthesis of rac-118 via imine 119

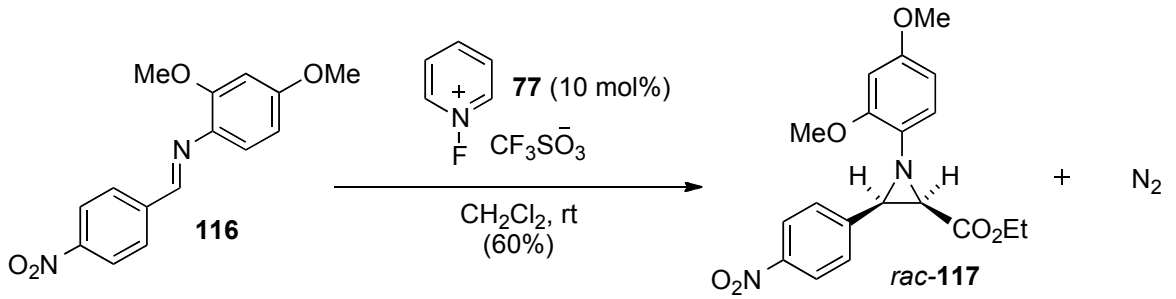


A 25 mL two-necked round-bottom flask was equipped with a dropping funnel and a magnetic stirrer bar. The flask was charged with a solution of 4-nitrobenzaldehyde (1.0 g, 6.66 mmol) in tetrahydrofuran (5 mL) and cooled to 0 °C. A 1.06 M solution of lithium *bis*(trimethylsilyl)amide in tetrahydrofuran (6.28 mL, 6.28 mmol, 0.95 eq^{n}) was added dropwise to the flask at 0°C. The reaction mixture was allowed to warm at room temperature, stirred for 2 hours and then treated with chlorotrimethylsilane (6.66 mmol, 0.85 mL). After 1 hour, anhydrous hexane was added resulting in a white precipitate. The solution was filtered under argon through anhydrous sodium sulfate and washed with a small amount of anhydrous hexane. The solvents were removed *in vacuo* and the impure *N*-TMS-imine **119** (1.0 g, ~ 4.5 mmol) placed in a 10 mL two-necked round-bottom flask under an inert atmosphere. The same flask was charged with *N*-fluoropyridinum triflate (111 mg, 0.45 mmol, 0.1 eq^{n}).

Anhydrous dichloromethane (6.5 mL) was injected into the flask and the resulting solution stirred for one minute. Liquid ethyl diazoacetate (0.52 mL, 5.0 mmol, 1.1 eq^{n}) was added *via* syringe to the solution. The reaction mixture was stirred at room temperature for 12 hours, the solvent was removed *in vacuo* and the crude product purified *via* flash chromatography on silica (gradient elution: petroleum ether / ethyl acetate, 9 /1 → 4 /1). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Compound rac-*cis*-**118** was afforded as a yellow solid in 20% overall yield from 4-nitrobenzaldehyde.

^{1}H NMR (300 MHz, CD_3CN) 8.13 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 3.88 (q, *J* = 7.0 Hz, 2H), 3.60 (d, *J* = 6.4 Hz, 1H), 3.10 (d, *J* = 6.4 Hz, 1H), 1.3 (d, *J* = 6.3 Hz, 1H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN): 168.5 (*C*O), 147.5, 144.6, 129.1, 123.0, 60.7, 37.9, 29.6, 13.7; FT-IR (thin film, cm^{-1}): 2983, 1732 (CO), 1602, 1519, 1344, 1201, 1108, 1026, 852, 741. MS (EI)$^{+}$: *m/z* 237.2 (100%) [M+H]$^{+}$, *m/z* 607.3 (100%).

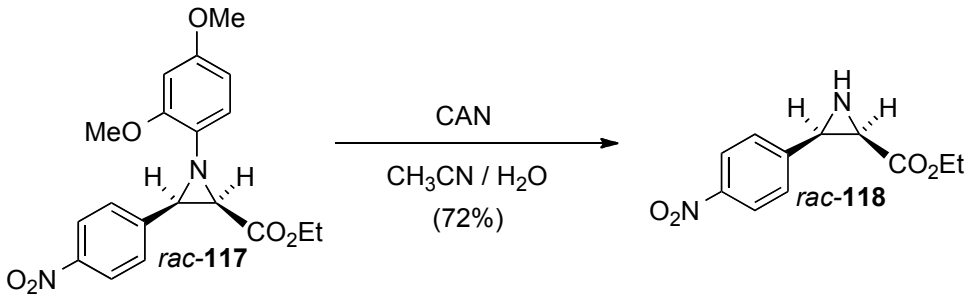
Synthesis of rac-cis-131



A 5 mL microwave vial was charged with a magnetic stirrer bar. The vial was flame dried and then cooled to room temperature under an inert atmosphere. The vial was loaded with (*E*)-2,4-dimethoxy-*N*-(4-nitrobenzylidene)phenylamine **116** (1.68 g, 5.86 mmol) and *N*-fluoropyridinium triflate (145 mg, 0.58 mmol, 10 mol%). The mixture was dissolved in dichloromethane (1 mL) and stirred for one minute. Liquid ethyl diazoacetate (0.7 mL, 6.45 mmol, 1.1 eq^{n}) was added *via* syringe at room temperature while stirring the solution. The reaction was stirred for 15 hours. A subsequent TLC (hexane / diethyl ether: 80 / 20) indicated complete consumption of the starting imine **116**. Dichloromethane was removed *in vaccuo* and the reaction residue was purified *via* flash chromatography on silica gel (elution with hexane / diethyl ether : 80 / 20). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample rac-*cis*-**117** was afforded in 60% yield.

^{1}H NMR (300 MHz, $CDCl_3$) 8.09 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.38 (s, 1H), 6.29 (d, *J* = 8.4 Hz, 1H), 3.98 (q, *J* = 7.0 Hz, 1H), 3.89 (q, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.45 (d, *J* = 6.6 Hz, 1H), 3.05 (d, *J* = 6.6 Hz, 1H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 166.4 (*C*O), 155.9, 151.8, 146.3, 141.8, 132.6, 127.9, 126.4, 122.0, 118.6, 102.6, 98.5, 60.1, 54.6, 54.5, 46.0, 45.2, 13.0. FT-IR (thin film, cm^{-1}): 2963, 1746 (CO), 1592, 1506, 1437, 1341, 1185, 1120, 1031. MS $(EI)^+$: *m/z* 373.1 (60%) $[M+H]^+$, *m/z* 395.2 (100%) $[M+Na]^+$, *m/z* 767.4 (20%) $[2M+Na]^+$; HRMS $(EI)^+$: exact mass calculated for $[C_{19}H_{21}N_2O_6 + H]^+$ requires *m/z* 373.1394, found *m/z* 373.1395.

Synthesis of rac-cis-118

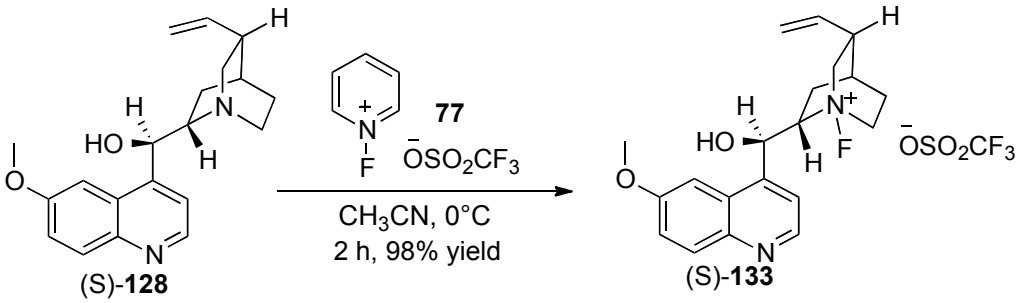


Purification *via* flash chromatography on silica gel (eluent diethyl ether / hexane: 1 / 1 → 2 / 1→ diethyl ether) afforded a yellow solid in 72% yield. Subsequent physicochemical analysis of the purified product confirmed formation of the title compound rac-*cis*-**118**. (Procedure same as ***cis*-126**)

^{1}H NMR (300 MHz, CD_3CN) 8.13 (d, 2H, *J* = 8.8 Hz), 7.60 (d, 2H, *J* = 8.7 Hz), 3.88 (q, 2H, *J* = 7.0 Hz), 3.60 (d, 1H, *J* = 6.4 Hz, C_2-*H*), 3.10 (d, 1H, *J* = 6.4 Hz), 1.3 (d, 1H, *J* = 6.3 Hz), 0.90 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, CD_3CN): δ ppm 168.5, 147.5, 144.6, 129.1, 123.0, 60.7, 37.9, 29.6, 13.7; FT-IR (thin film, cm^{-1}): 2983, 1732 (CO), 1602, 1519, 1344, 1201, 1108, 1026, 852, 741. MS $(EI)^+$: *m/z* 237.2 (100%) $[M+H]^+$, *m/z* 607.3 (100%).

Asymmetric Organocatalytic Synthesis of Aziridine Using F^+ Salt

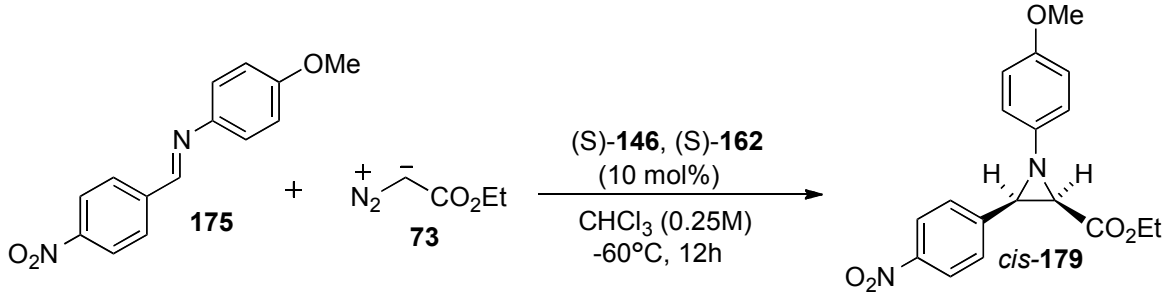
Synthesis of cis-133



A 5 mL microwave vial was charged with a magnetic stirrer bar. The vial was flame dried and then cooled to room temperature under an inert atmosphere. The vial was loaded with *N*-fluoropyridinium triflate **77** (64.2 mg, 0.26mmol), dihydroquinidine **128** (84 mg, 0.26mmol, 1eq^n). The mixture was dissolved in anhydrous acetonitrile (1 mL) and stirred for two hour at 0°C. Solvent was removed under reduced pressure. **133** afforded in 98% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) 8.44 (d, *J* = 6.1 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.52 (m, 1H), 7.29 (m, 2H), 6.48 (s, OH), 5.17 (m, 3H), 4.88-4.69 (s, 1H), 3.98 (s, 3H), 3.49(d, *J* = 5.2 Hz, 1H), 2.91-2.82 (m, 1H), 2.78-2.74 (m, 2H), 1.55-1.90 (m, 3H), 1.29-1.37 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 150.3, 148.9, 144.5, 136.9, 132.7, 129.8, 128.2, 127.6, 125.7, 123.9, 120.8, 118.4, 68.6 (d, *J* = 8.7 Hz), 63.8 (d, *J* = 5.8 Hz), 59.5 (d, *J* = 9.4 Hz), 43.8 (d, *J* = 3.6 Hz), 28.9 (d, *J* = 5.1 Hz), 27.8 (d, *J* = 5.1 Hz), 24.1 (d, *J* = 1.5 Hz); ^{19}F NMR($CDCl_3$ 400M Hz) δ -73.2 (1F), -73.9 (3F) ppm.

Synthesis of cis-179

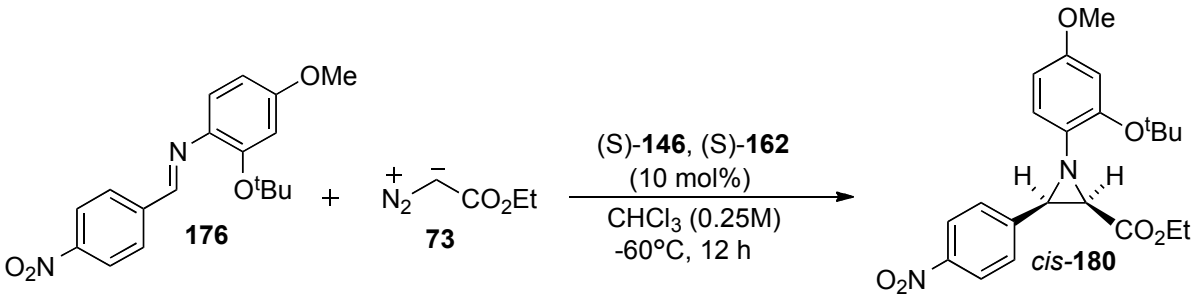


A 5 mL microwave vial was charged with a magnetic stirrer bar. The vial was flame dried and then cooled to room temperature under an inert atmosphere. The vial was loaded with *N*-fluoroquternary ammonium salt (S)-**146, 162** (0.026 mmol, 10 mol%). (*E*)-4-methoxy-*N*-(4-nitrobenzylidene) phenylamine **175** (127 mg, 0.50 mmol), and 4Å molecular sieves (~100

mg) were added into the reaction vial. Anhydrous chloroform (1 mL) was injected into the microwave vial *via* the rubber seals on the tube. The solution was cooled to -60 °C and stirred for one minute. Liquid *tert*-butyl diazoacetate (0.038 mL, 0.28 mmol, 1.1 eq^{n}) was added *via* syringe and the solution was stirred at -60 °C for a further 15 hours. A subsequent TLC (hexane / diethyl ether : 80 / 20) indicated complete consumption of the starting material **175**. Chloroform was removed *in vacuo* and the reaction residue was purified *via* flash chromatography on silica gel (hexane / diethyl ether : 80 / 20 → 70 / 30). Subsequent physicochemical analysis of the purified products confirmed formation of the title compounds *cis*- **179** afforded in 24% yield and 13% e.e.

^{1}H NMR ($CDCl_3$, 400 MHz) 8.21 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 4.09-3.95 (m, 2H), 3.78 (s, 3H), 3.57 (d, *J* = 6.7 Hz, 1H), 3.22 (d, *J* = 6.7 Hz, 1H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 167.1 (*C*O), 156.3, 147.7, 144.9, 142.2, 128.7, 123.3, 120.7, 114.6, 61.2, 55.4, 46.4, 46.0, 13.8; FT-IR (thin film, cm^{-1}): 2979, 1747 (CO), 1506, 1343, 1242, 1185, 1040; MS (EI)$^{+}$: *m/z* 343.1 (100%) $[M+H]^{+}$; HRMS (EI)$^{+}$: exact mass calculated for $[C_{18}H_{18}N_2O_5 + H]^{+}$ requires *m/z* 343.1288, found *m/z* 343.1292.

Synthesis of cis-180

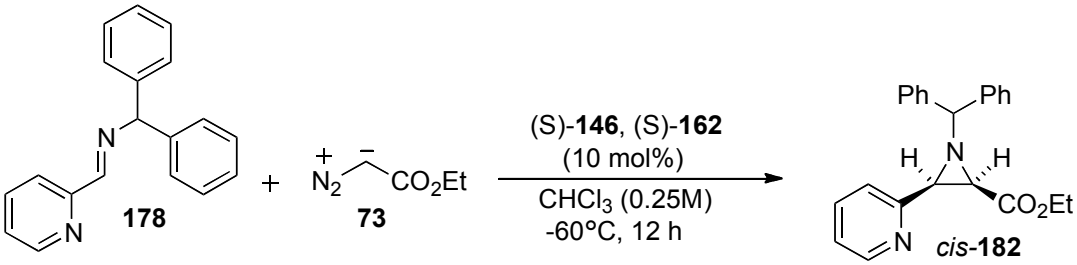


Subsequent physicochemical analysis of the purified product confirmed formation of the title compound *cis*-**180** was submitted to chiral analytical HPLC analysis [Chiralpak AD, *iso*-hexane / *iso*-propanol: 95 / 5, 1 mL / min, 13.6 min (1st peak), 16.9 min (2nd peak)]. The reaction afforded *cis*-**180** as a thick orange oil in 21% yield and 11% *e.e.* (Procedure same as **179**)

^{1}H NMR ($CDCl_3$, 400 MHz) 8.19 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 2.6 Hz, 1H), 6.50 (dd, *J* = 8.6 Hz, J_1 = 2.7 Hz, 1H), 3.74 (s, 3H), 3.46 (d, *J* = 6.7 Hz, 1H), 3.06 (d, *J* = 6.8 Hz, 1H), 1.34 (s, 9H), 1.21 (s, 9H); ^{13}C NMR

($CDCl_3$, 75 MHz) 165.4 (*C*O), 154.8, 147.7, 146.3, 142.2, 137.9, 128.0, 121.9, 119.7, 108.5, 106.1, 80.8, 79.5, 54.5, 46.8, 45.9, 27.7, 26.8; FT-IR (thin film, cm^{-1}): 2979, 2934, 1742 (CO), 1715, 1606, 1585, 1517, 1498, 1346, 1226, 1151, 1046, 972, 912, 854, 810, 736; MS $(EI)^+$: *m/z* 443.1 (40%) $[M+H]^+$, *m/z* 465.2 (100%) $[M+Na]^+$, *m/z* 907.4 (30%) $[2M+Na]^+$; HRMS $(EI)^+$: exact mass calculated for $[C_{24}H_{30}N_2O_6 + H]^+$ requires *m/z* 443.2177, found *m/z* 443.2176.

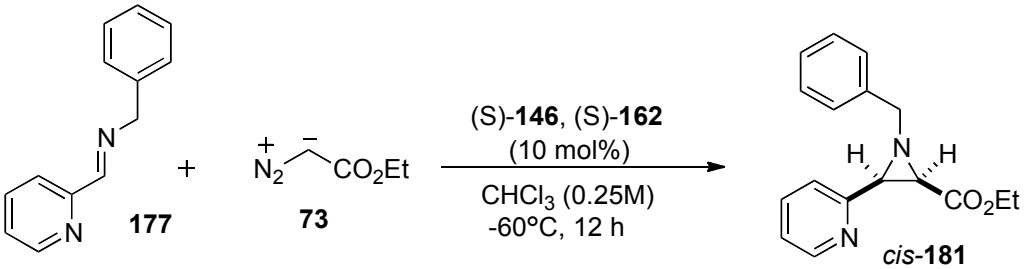
Synthesis of cis-182



Reaction residue was purified *via* flash chromatography on silica gel (hexane / ethyl acetate : 5 / 1). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. (Procedure same as **179**)

M.p. 116.1 – 117.8 °C, ^1H NMR ($CDCl_3$, 400 MHz) 8.43-8.41 (m, 1H), 7.61-7.56 (m, 4H), 7.47-7.44 (m, 2H), 7.34-7.29 (m, 2H), 7.26-7.22 (m, 2H), 7.18-7.13 (m, 1H), 7.12-7.08 (m, 1H), 3.99-3.91 (m, 3H), 3.38 (d, *J* = 6.8 Hz, 1H), 2.76 (d, *J* = 6.8 Hz, 1H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 167.7 (*C*O), 155.4, 148.8, 142.6, 142.4, 136.4, 128.8, 127.8, 127.7, 127.5, 127.3, 122.95, 122.6, 77.7, 60.9, 49.5, 46.3, 14.2; FT-IR (thin film, cm^{-1}): 3062, 3027, 2981, 1742 (CO), 1590, 1569, 1493, 1477, 1454, 1436, 1373, 1354, 1304, 1208, 1186, 1094, 1068, 1038, 1005, 854, 747, 703; MS $(EI)^+$: *m/z* 359.1 (100%) $[M+H]^+$; HRMS $(EI)^+$: exact mass calculated for $[C_{23}H_{22}N_2O_2 + H]^+$ requires *m/z* 359.1754, found *m/z* 359.1753.

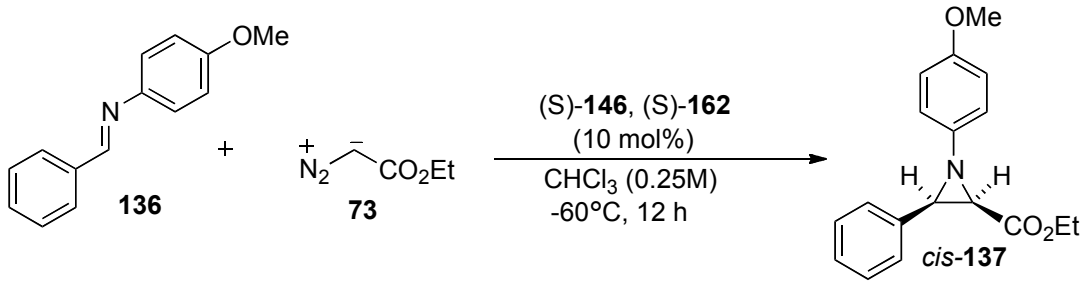
Synthesis of cis-181



Reaction residue was purified *via* flash chromatography on silica gel (hexane / ethyl acetate: 5 / 1). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound *cis*-**181** was afforded as a white solid in 10% yield. (Procedure same as **179**)

^{1}H NMR ($CDCl_3$, 400 MHz) 8.48-8.46 (m, 1H), 7.65-7.59 (m, 1H), 7.58-7.56 (m, 1H), 7.44-7.41 (m, 2H), 7.35-7.25 (m, 3H), 7.16-7.11 (m, 1H), 4.05-3.88 (m, 3H), 3.67 (d, J = 13.6 Hz, 2H), 3.25 (d, J = 6.9 Hz, 1H), 2.72 (d, J = 6.9 Hz, 1H), 1.02 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 167.9 (*C*O), 155.4, 148.8, 137.6, 136.0, 128.5, 128.1, 127.4, 122.8, 122.4, 63.3, 60.7, 48.8, 45.4, 13.8; IR (thin film, cm^{-1}): 3430, 2983, 2092, 1738 (CO), 1638, 1591, 1472, 1455, 1435, 1372, 1264, 1195, 1095, 748, 700; MS (EI)$^+$: *m/z* 283.1 (85%) $[M+H]^+$ *m/z* 305.1 (95%) $[M+Na]^+$ *m/z* 587.3 (100%) $[2M+Na]^+$; HRMS (EI)$^+$: exact mass calculated for $[C_{17}H_{18}N_2O_2 + H]^+$ requires *m/z* 283.1441, found *m/z* 283.1441.

Synthesis of 137

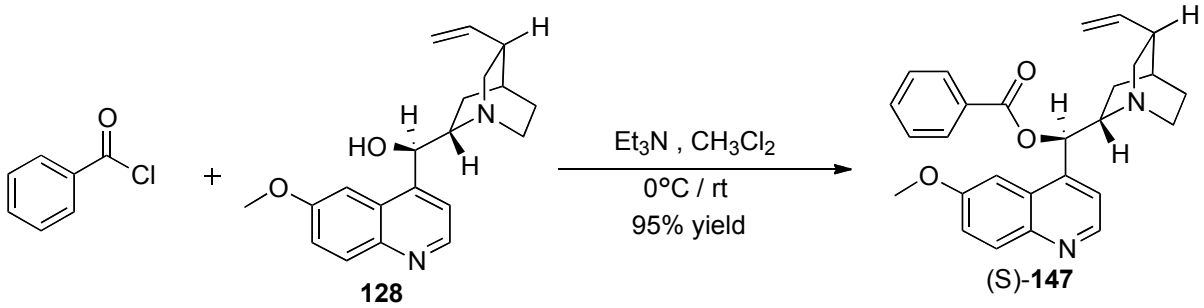


Reaction residue was purified *via* flash chromatography on silica gel (hexane / diethyl ether : 80 / 20). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound *cis*-**137** was submitted to chiral analytical HPLC analysis [Chiralpak AD, *iso*-hexane / *iso*-propanol : 95 / 5, 1 mL / min]. Sample *cis*-**137** was afforded in 50% yield and 31% *e.e*. (Procedure same as **179**)

^{1}H NMR (300 MHz, $CDCl_3$) 7.50 (d, J = 7.4 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.00 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 4.09-3.95 (m, 3H), 3.77 (s, 3H), 3.53 (d, J = 6.8 Hz, 2H), 3.14 (d, J = 7.2 Hz, 1H), 0.98 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 167.1 (*C*O), 156.3, 147.7, 144.9, 142.2, 128.7, 128.5, 127.9, 123.3, 120.7, 114.6, 61.2, 55.4, 46.4, 46.0 (C_3-H), 13.8; FT-IR (thin film, cm^{-1}): 2979, 1747 (CO), 1506, 1343, 1242, 1185, 1040; MS (EI)$^+$: *m/z* 298.1 (100%) $[M+H]^+$; HRMS (EI)$^+$: exact mass calculated for $[C_{18}H_{18}O_3 + H]^+$ requires *m/z* 298.1488, found *m/z* 298.1492.

SYNTHESIS OF CINCHONA ALKALOID DERIVATIVES

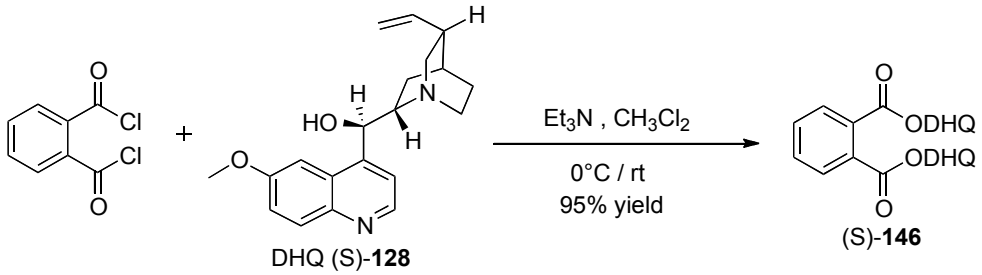
9-O-dihydroquinyl benzoyl ester - 147



Into a solution of cinchona alkaloid (S)-**128** (389 mg, 2.75 mmol, 1 eq^{n}) in anhydrous dichloromethane (5 ml), 0.5M anhydrous triethyl amine (2 ml) at 0°C was added. A solution of benzoyl chloride (1gm, 2.75 mmol, 1 eq^{n}) in anhydrous dichloromethane (5ml) was slowly added. After 1 h the reaction mixture was warmed to room temperature and stirred for additional 2 h. Upon completion of reaction indicated by TLC, resulting mixture was poured into (10 ml) of distilled water; the organic layer was separated and washed with saturated $NaHCO_3$ solution, and then with water. The organic solution was dried by anhydrous $MgSO_4$ and evaporated in *vaccuo* after work up followed by purification by flash chromatography on silica gel (ethyl acetate / ethanol / triethyl amine : 7 / 0.15 / 0.15). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound (S)-**147** was afforded in 95% yield.

White solid, mp; 104- 107°C; $[\alpha]^{20}_{D}$ = + 113.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 8.64 (d, *J* = 4.5 Hz, 1H), 8.13-8.00 (m, 3H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.40 (dd, *J* = 27.0 Hz, 2H), 7.21 (s, 2H), 6.69 (d, *J* = 6.8 Hz, 1H), 4.05 (d, *J* = 7.1 Hz, 2H), 3.94-3.80 (m, 1H), 3.62 (q, *J* = 6.9 Hz, 1H), 3.33 (d, *J* = 7.3 Hz, 3H), 2.75 (m, 4H), 2.47 (d, *J* = 7.1 Hz, 1H), 2.28 (s, 1H), 1.98 (s, 1H), 1.85 (d, *J* = 9.1 Hz, 1H), 1.74-1.63 (m, 1H), 1.43 (s, 1H), 1.16 (dd, *J* = 14.1 Hz, 1H), 0.96 (t, *J* = 7.1 Hz, 1H), 0.83 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 164.2, 157.1, 146.2, 143.5, 142.3, 132.4, 130.7, 129.4, 127.5, 126.7, 120.9, 117.2, 100.3, 73.0, 57.9, 57.0, 54.7, 41.5, 36.1, 27.1, 26.5, 24.2, 22.2, 10.9; IR (KBr, cm^{-1}): 2932, 2864,1788, 1620, 1593, 1508, 1473, 1315, 1267, 1108, 1068, 1026, 918, 854, 768, 711; HRMS for $C_{27}H_{30}N_2O_3$: *m/z* 431.2 ($M+H^+$).

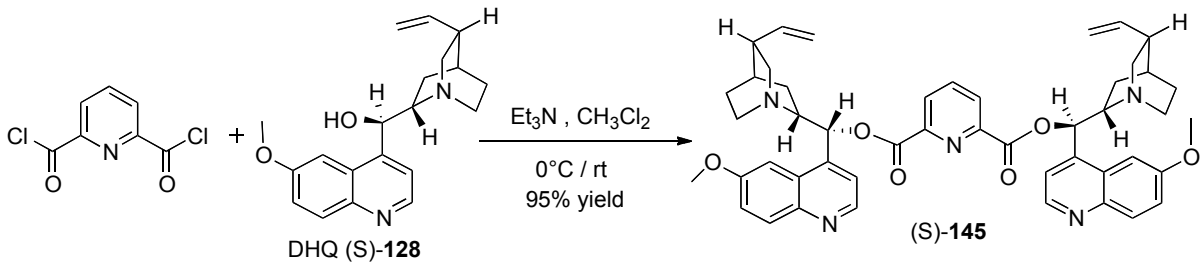
1,2-Bis (9-O-dihydroquinyl) phthalate 146



Into a solution of cinchona alkaloid (S)-**128** (9 gm, 1.23 mmol, 2 eq[n]) in anhydrous dichloromethane (20 ml), 0.5M anhydrous triethyl amine (8 ml) at 0°C was added. A solution of phthaloyl dichloride (1gm, 2.75 mmol, 1 eq[n]) in anhydrous dichloromethane (20 ml) was slowly added. After 1 h the reaction mixture was warmed to room temperature and stirred for additional 2 h. Upon completion of reaction indicated by TLC, resulting mixture was poured into (30 ml) of distilled water; the organic layer was separated and washed with saturated $NaHCO_3$ solution, and then with water. The organic solution was dried by anhydrous $MgSO_4$ and evaporated in *vacuo* after work up followed by purification by flash chromatography on silica gel (ethyl acetate / ethanol / triethyl amine: 7 / 0.15 / 0.15). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound (S)-**146** was afforded in 89% yield.

White solid, mp; 108- 110°C; $[\alpha]^{20}_{D}$ = + 13.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 8.70 (d, *J* = 4.5 Hz, 2H), 7.96 (d, *J* = 9.1 Hz, 2H), 7.67 (dd, *J* = 5.7 Hz, 2H), 7.53 (dd, *J* = 5.7 Hz, 2H), 7.33 (m, 4H), 6.54 (d, *J* = 8.1 Hz, 2H), 3.86 (s, 6H), 3.15 (m, 2H), 2.73 (m, 2H), 2.54 (m, 2H), 2.00 (s, 2H), 1.64 (dd, *J* = 13.3 Hz, 8H), 1.30 (m, 10H), 0.75 (t, *J* = 7.1 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) 12.1, 24.4, 25.0, 26.3, 27.7, 37.4, 42.4, 50.7, 55.7, 58.1, 59.6, 101.6, 108.5, 121.9, 128.6, 129.5, 129.7, 131.8, 144.0, 144.8, 147.4, 157.8, 157.9, 163.1 ; HRMS for $C_{48}H_{54}N_4O_6$: *m/z* 783.2 ($M+H^+$)

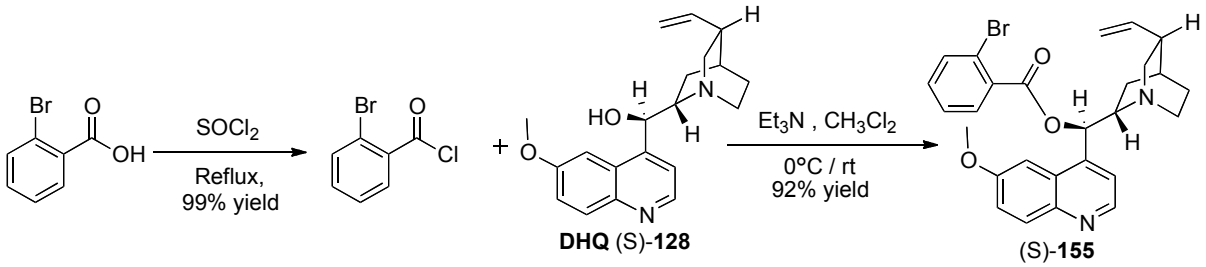
2,6-Bis (9-O-dihydroquinyl)- pyridine-dicarboxylate 145



Purification by flash chromatography on silica gel (ethyl acetate / ethanol / triethyl amine : 7 / 0.15 / 0.15). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**145** was afforded in 95% yield. (Procedure same as **146**)

White solid, mp; 110- 113°C; $[\alpha]^{20}_{D}$ = + 124.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 0.82, (m, 10H), 1.83-1.21 (m, 10H), 3.15-2.06 (m, 10H), 3.87 (s, 2H), 3.99 (s, 6H), 7.26 (m, 2H), 7.41 (d, *J* = 9.3 Hz, 2H), 7.48 (m, 4H), 8.03 (m, 3H), 8.32 (d, *J* = 7.8 Hz, 2H), 8.68 (d, *J* = 4.5 Hz, 2H); HRMS for $C_{47}H_{55}N_5O_6$: *m/z* 785.0 ($M+H^+$); ^{13}C NMR (75 MHz, $CDCl_3$) 168.1, 157.3, 148.2, 147.6, 147.1, 143.9, 141.3, 139.8, 130.9, 127.9, 126.8, 122.0, 121.2, 114.4, 101.3, 73.6, 56.7, 55.8, 42.9, 39.9, 27.4, 21.5.

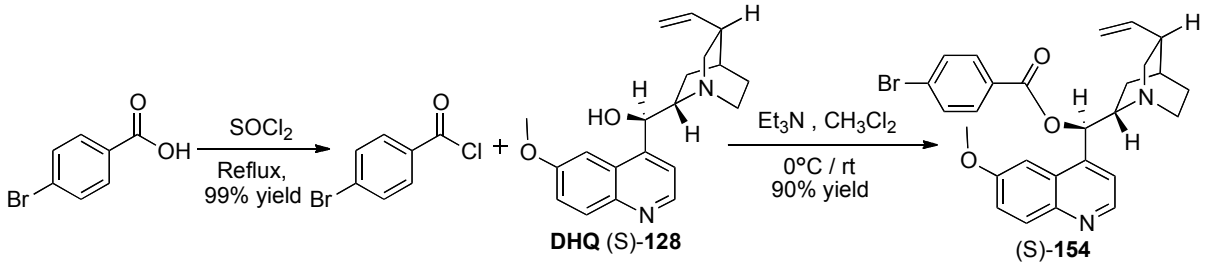
9-O-dihydroquinyl-2-bromobenzoyl ester 155



Subsequent physicochemical analysis of the purified product confirmed formation of the title compound (S)-**155** was afforded in 92% yield. (Procedure same as **147**)

White solid; 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 8.64 (d, *J* = 4.5 Hz, 1H), 8.13-8.00 (m, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.40 (dd, *J* = 27 Hz, 1H), 6.69 (d, *J* = 6.8 Hz, 1H), 4.05 (d, *J* = 7.1 Hz, 1H), 3.94-3.80 (m, 3H), 3.62 (q, *J* = 6.9 Hz, 1H), 3.33 (d, *J* = 7.3 Hz, 1H), 2.75 (m, 3H), 2.47 (d, *J* = 7.1 Hz, 1H), 2.28 (s, 1H), 1.98 (s, 1H), 1.85 (d, *J* = 9.1 Hz, 2H), 1.74-1.63 (m, 3H), 1.43 (s, 1H), 1.16 (dd, *J* = 14.1 Hz, 3H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 158.16, 147.65, 147.31, 144.98, 134.79, 133.15, 132.44-130.93, 127.46, 122.10, 119.23, 101.59, 78.93, 75.86, 59.63, 55.92, 50.50, 37.51, 25.97, 12.13.

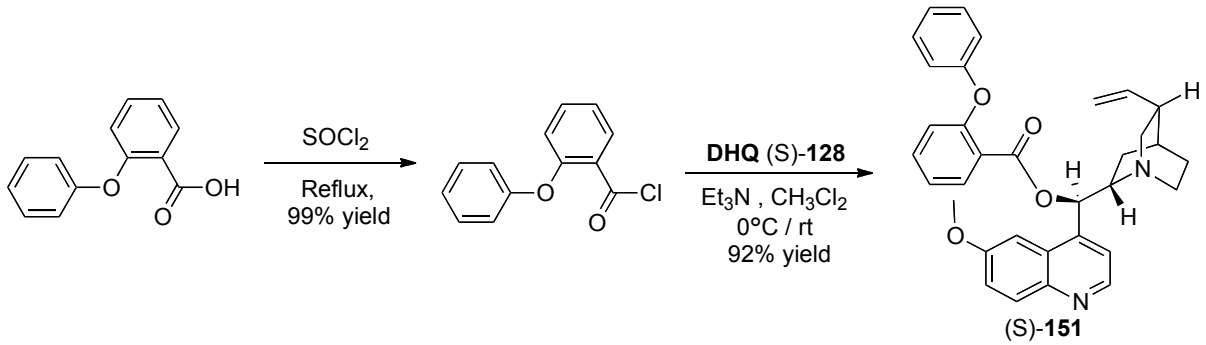
9-O-dihydroquinyl-4-bromobenzoyl ester 154



Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**154** was afforded in 90% yield. (Procedure same as **147**)

White solid; 90% yield ;^{1}H NMR (400 MHz, $CDCl_3$) 8.65 (d, *J* = 4.5 Hz, 1H), 7.91 (dd, *J* = 25.7 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.43 (s, 1H), 7.31 (dd, *J* = 11.3 Hz, 2H), 7.19 (s, 1H), 3.92 (s, 3H), 3.35 (q, *J* = 8.6 Hz, 2H), 3.03-2.49 (m, 3H), 1.98 (s, 2H), 1.83 (s, 2H), 1.71 (s, 1H), 1.63-1.32 (m, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 158.16, 147.55, 147.21, 144.98, 134.79, 133.17, 132.24, 131.5, 130.93, 127.46, 122.10, 119.23, 101.59, 78.93, 75.86, 59.63, 55.92, 50.50, 37.51, 25.97, 12.13.

9-O-dihydroquinyl-2-phenoxybenzoate 151

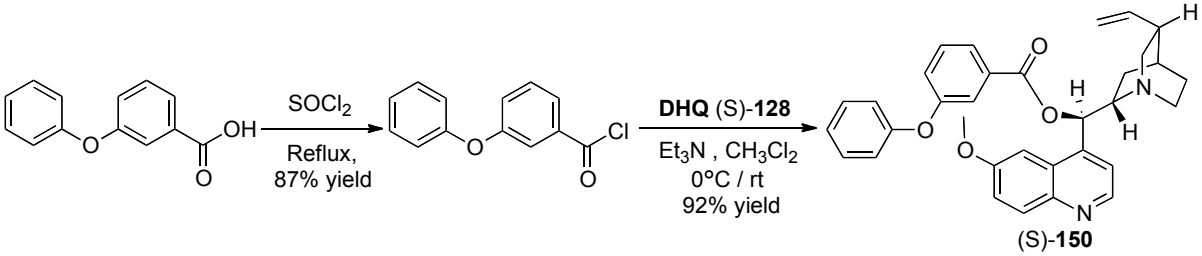


Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**151** was afforded in 84% yield. (Procedure same as **147**)

Brownish solid ; ^{1}H NMR (400 MHz, $CDCl_3$) 8.58 (d, *J* = 4.5 Hz, 2H), 7.92 (m, 2H), 7.45 (m, *J* = 1H), 7.30 (dd, *J* = 13.9 Hz, 1H), 7.24-7.19 (m, 1H), 7.15 (m, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.93 (dd, *J* = 22.1 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.26 (s, 1H), 4.08 (q, *J* = 7.14 Hz, 1H), 3.90 (s, 3H), 3.20 (d, *J* = 8.4 Hz, 1H), 2.83 (dd, *J* = 13.6 Hz, 1H), 2.63 (d, *J* = 8.1 Hz, 1H), 2.01 (s, 1H), 1.70 (dd, *J* = 27.8 Hz, 3H), 1.41 (dd, *J* = 17.8 Hz, 3H), 1.22 (t, *J* = 7.15 Hz, 3H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 165.32, 157.91, 155.21,

148.32, 147.14, 146.29, 144.82, 135.63, 134.29, 131.88, 130.07, 123.83, 121.68, 118.35, 117.55, 105.57, 102.48, 100.34, 59.84, 49.63, 38.35, 28.32, 25.81, 17.98, 12.08.

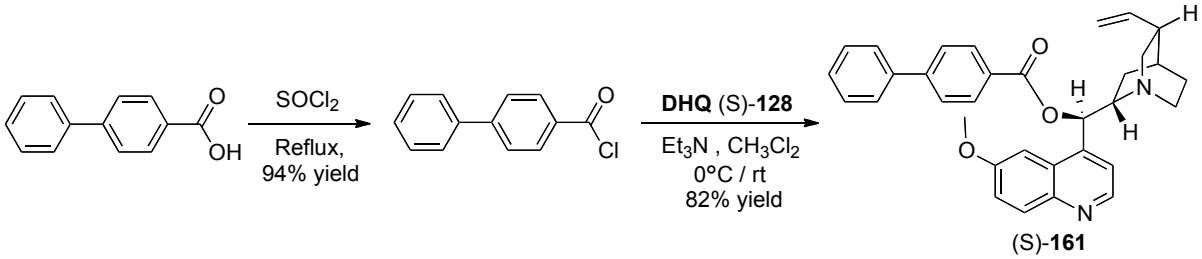
9-O-dihydroquinyl-2-phenoxybenzoate 150



Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**150** was afforded in 87% yield. (Procedure same as **147**)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) 8.64 (d, *J* = 4.5 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.68-7.60 (m, 1H), 7.40 (d, *J* = 2.6 Hz, 1H), 7.33 (m, 1H), 7.27 (dd, *J* = 13.9 Hz, 1H), 7.19 (s, 1H), 7.13 (dd, *J* = 8.2 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.93 (dd, *J* = 8.66 Hz, 1H), 6.63 (d, *J* = 7.3 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 3.33 (m, 3H), 2.83 (dd, *J* = 13.6 Hz, 1H), 2.64 (t, *J* = 8.3 Hz, 1H), 1.96 (s, 1H), 1.76 (d, *J* = 8.9 Hz, 3H), 1.48 (dd, *J* = 75.4 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.1 Hz, 3H);

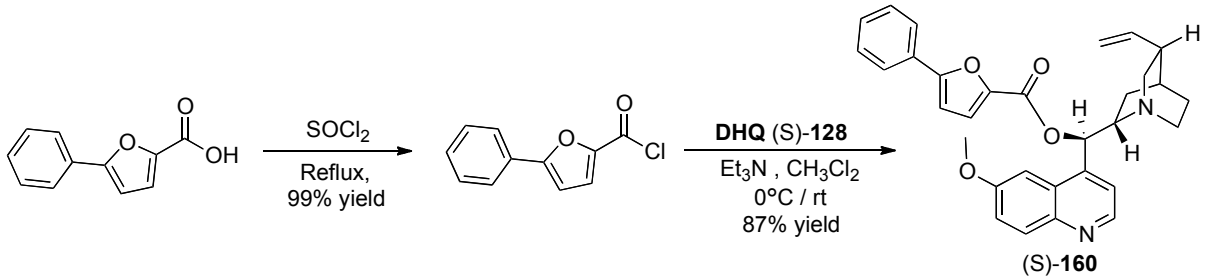
9-O-dihydroquinyl-biphenyl-4-carboxylate 161



Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**161** was afforded in 82% yield. (Procedure same as **147**)

^{1}H NMR (300 MHz, $CDCl_3$) 8.76 (d, *J* = 4.6 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.39 (dd, *J* = 13.7 Hz, 2H), 7.26 (d, *J* = 0.8 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 3.97 (s, 3H), 3.41 (q, *J* = 8.3 Hz, 3H), 2.91 (dd, *J* = 13.9 Hz, 3H), 2.83-2.50 (m, 2H), 2.17 (s, 1H), 2.04 (s, 3H), 1.92-1.71 (m, 3H), 1.56 (m, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H).

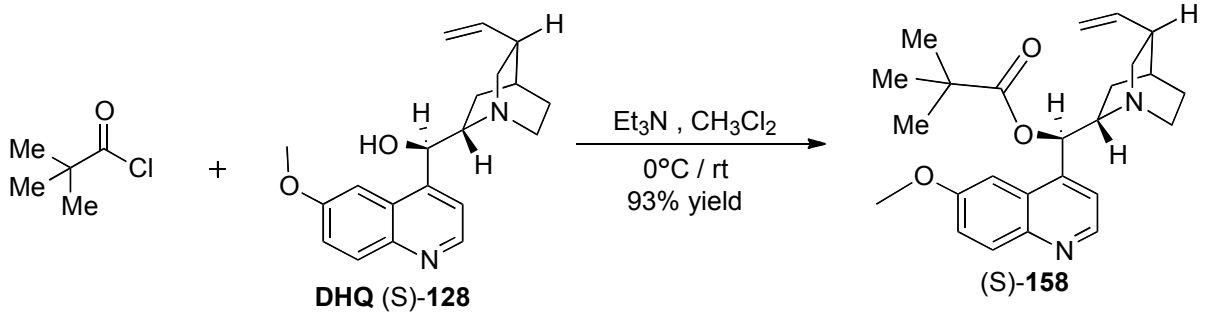
9-O-dihydroquinyl-5-phenylfuran-2-carboxylate 160



Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**160** was afforded in 82% yield. (Procedure same as **147**)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) 8.66 (d, *J* = 4.5 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 2H), 7.72 (dd, *J* = 8.3 Hz, 2H), 7.32 (m, 2H), 6.72 (d, *J* = 3.6 Hz, 2H), 3.93 (s, 3H), 3.34 (dd, *J* = 15.0 Hz, 3H), 2.82 (d, *J* = 68.7 Hz, 3H), 1.98 (s, 3H), 1.75 (s, 2H), 1.47 (m, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H).

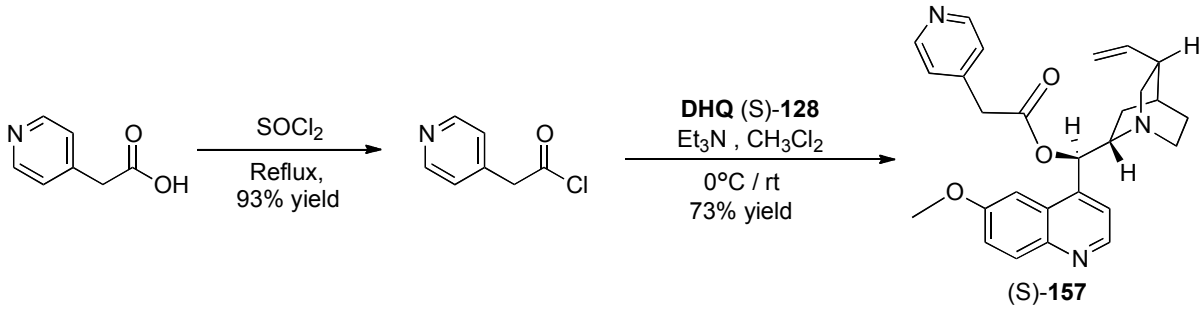
9-O-dihydroquinyl pivalate 158



Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**158** was afforded in 93% yield. (Procedure same as **147**)

^{1}H NMR (400 MHz, $CDCl_3$) 8.66 (d, *J* = 4.5 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.38 (s, 1H), 7.30 (dd, *J* = 9.1 Hz, 1H), 7.24 (d, *J* = 4.2 Hz, 1H), 7.20 (d, *J* = 0.9 Hz, 1H), 3.91 (s, 3H), 3.34-3.14 (m, 9H), 2.87 (s, 3H), 2.67 (s, 1H), 1.70 (s, 3H), 1.59-1.34 (m, 3H), 1.17 (s, 3H), 0.86 (t, *J* = 7.02 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 178.68, 165.38, 148.9, 147.1, 143.9, 141.3, 138.34, 131.96, 121.3, 122.6, 126.09, 109.99, 56.48, 52.50, 49.96, 39.05, 27.3, 23.56, 12.15,

9-O-dihydroquinyl-2-(pyridin-4-yl)-acetate 157

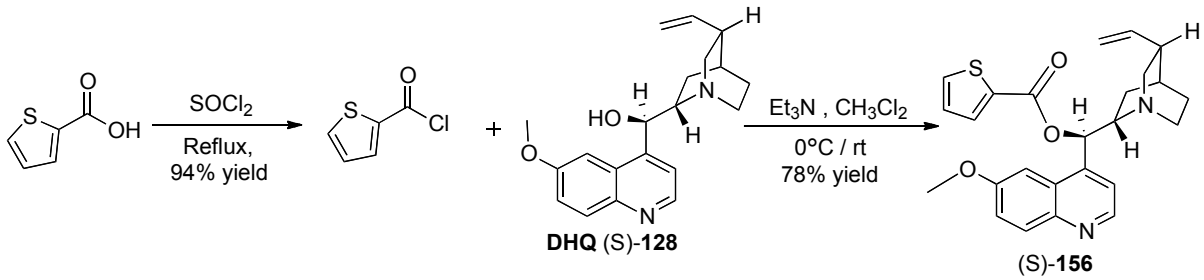


(S)-**157**

Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**157** was afforded in 73% yield. (Procedure same as **147**)

^{1}H NMR (400 MHz, $CDCl_3$) 8.63 (d, *J* = 4.4 Hz, 1H), 7.81 (d, *J* = 9.5 Hz, 1H), 7.55 (d, *J* = 4.5 Hz, 1H), 7.37 (dd, *J* = 21.9 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 3.69 (s, 3H), 3.10 (m, 3H), 2.86 (m, 1H), 2.66 (d, *J* = 8.6 Hz, 1H), 2.52 (s, 1H), 2.11 (s, 1H), 1.77 (m, 3H), 1.66-1.30 (m, 3H), 1.21 (s, 3H), 0.96 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H)

9-O-dihydroquinyl-thiophene-2-carboxylate 156



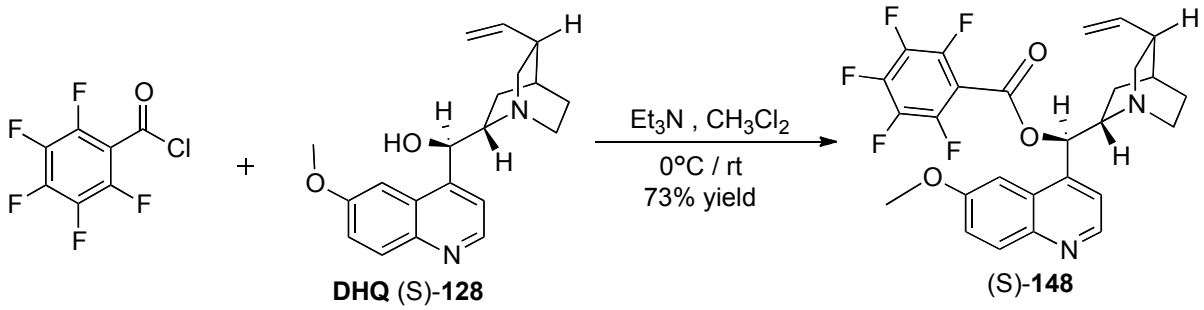
DHQ (S)-**128**

(S)-**156**

Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**156** was afforded in 78% yield. (Procedure same as **147**)

^{1}H NMR (400 MHz, $CDCl_3$) 8.65 (d, *J* = 4.5 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.80 (dd, *J* = 3.7 Hz, 1H), 7.56 (dd, *J* = 4.9 Hz, 1H), 7.47 (s, 1H), 7.32 (dd, *J* = 9.1 Hz, 1H), 7.20 (s, 1H), 7.08 (dd, *J* = 4.9 Hz, 1H), 3.96 (s, 3H), 3.43-3.23 (m, 3H), 3.03-2.61 (m, 1H), 1.98 (s, 1H), 1.75 (s, 3H), 1.48 (m, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H).

9-O-dihydroquinyl-2,3,4,5,6-pentalfluorobenzoate 148



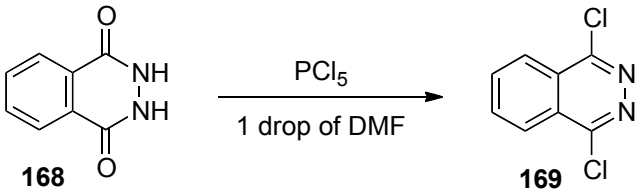
DHQ (S)-**128** (S)-**148**

Subsequent physicochemical analysis of the purified product confirmed formation of the title compound. Sample (S)-**148** was afforded in 73% yield. (Procedure same as **147**)

^{1}H NMR (300 MHz, $CDCl_3$) 8.76 (d, *J* = 4.6 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.40 (m, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 3.97 (s, 3H), 3.41 (q, *J* = 8.5 Hz, 3H), 2.91 (dd, *J* = 13.6 Hz, 1H), 2.68 (m, 3H), 2.04 (s, 1H), 1.75 (s, 1H), 1.52 (dd, *J* = 45.0 Hz, 3H), 1.25 (t, *J* = 7.14 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H)

1,4-Bis (9-O-dihydroquinyl) phthalazine 162

Preparation of 1,4-Dichlorophthalazine 169

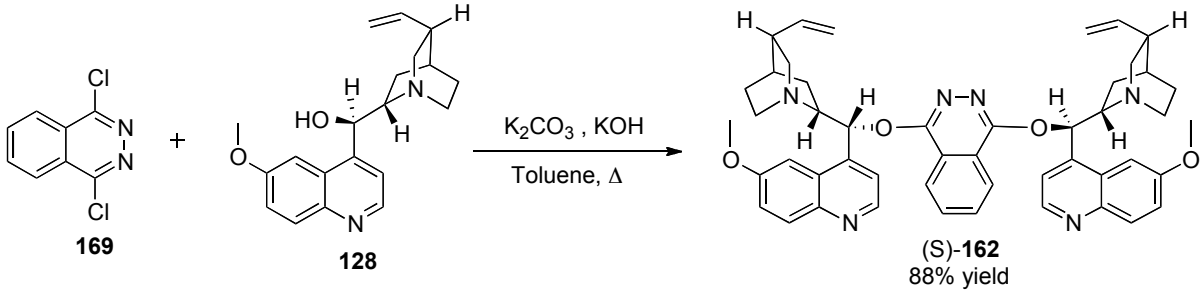


168 **169**

A 250 mL round-bottomed flask was equipped with a condenser and a mechanical stirrer. The system was flame-dried under a strong flow of nitrogen and cooled to room temperature. The flask was charged with (8.0 g, 0.049 mol, 1 eq^n) of phthalhydrazide **168** (Aldrich), and (22.0 g, 1.05 mol, 2.1 eq^n) of phosphorus pentachloride, and 2 drops of DMF. The condenser was fitted with a calcium chloride drying tube (4 × 1 in. of $CaCl_2$ having a cotton plug on each side and directly connected to the condenser to prevent moisture contamination and allow HCl evolution), and the solid mixture was gently heated from room temperature to 145 °C (oil bath temperature) over 60-min period. The mixture slowly liquefied, and the orange solution was heated for an additional 4 hours. The condenser was then replaced with a distillation apparatus, and the phosphorus oxychloride was distilled off. The residual off-white solid was cooled to room temperature, crushed to a fine powder, and then dissolved in

100 mL of dichloromethane with stirring. After 1 h the solution was filtered and the filtrate was added to 25 g of neutral alumina. After being stirred for an additional 1 hour, the solution was filtered through a 3 in. deep pad of alumina, and the pad was washed with more DCM. The organic layers were combined, dried over MgSO, and then evaporated in *vacuo* to give a white solid. Recrystallization from 75 mL of THF gave 5.2g of product **169**; concentration of the mother liquor and crystalisation gave an additional 2.0 g of pure white needles (78% yield) *(R_f 0.35*, CH_2Cl_2), mp 162-163.5°C (lit.[10] mp 164°C). ^{1}H NMR (300 MHz, $CDCl_3$) 8.33 (dd, *J* = 5.6 Hz, 2H), 8.08 (dd, *J* = 6.3 Hz, 2H).

Preparation of1,4-Bis (9-O-dihydroquinyl) phthalazine 162

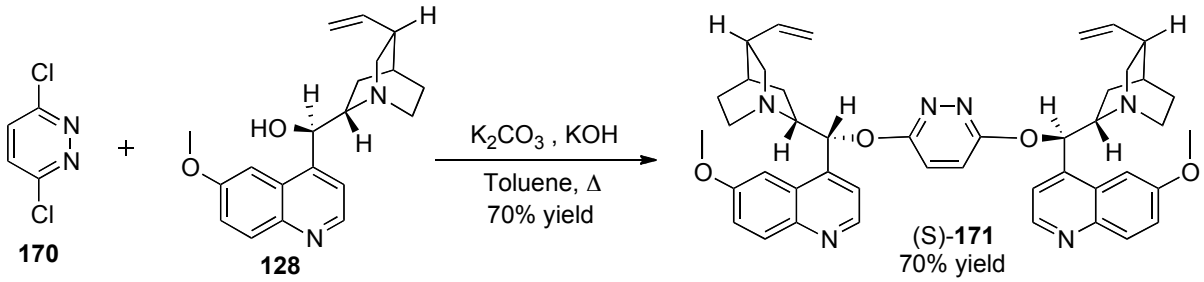


A 250 mL flame-dried one-neck round-bottom flask was charged with dihydroquinidine (S)-**128** (8.49 g, 2.6 mmol, 2 eq^n), 1,4-dichlorophthalazine **169** (2.70 g, 1.35 mmol, 1eq^n)**,** K_2CO_3 (5.61 g, 4.05 mmol, 3eq^n), and 100 mL of anhydrous toluene. The flask was equipped with a Dean-Stark-condenser. Under nitrogen atmosphere, the mixture was refluxed for 2 hour. Then, KOH pellets (87%) (2.27 g, 4.05 mmol, 3eq^n) were added and the mixture was refluxed (with azeotropic removal of water) under nitrogen atmosphere for an additional 12 h. [The reaction can be followed by TLC using 20:1, CH_2Cl_2 / MeOH. The *Rf* of the ligand is 0.22]. The light orange solution was cooled to room temperature, mixed with (20 mL) of water, and then extracted with EtOAc (3 × 30 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried over $MgS0_4$, and evaporated to dryness. The crude slightly yellow solid was dissolved in absolute EtOH (50 mL), and a solution of 4.6 ml of concentrated H_2SO_4 in 100 mL of absolute EtOH was added over a 10-min period with vigorous stirring. The clear solution was refrigerated (-5 °C) for 2 hour, the resulting white precipitate of the tetrasulfate salt was collected by filtration through a 10-20-µcm sintered glass funnel and washed first with cold EtOH (20 mL) and then with diethyl ether (50 mL). If difficulty occurs during the filtration, the ethanolic precipitate solution should be heated until clear and cooled at -5 °C to provide a salt easier to filter. The free base was easily prepared by dissolving the

off-white tetrasulfate salt in water (20 mL) and adding saturated sodium bicarbonate ($NaHCO_3$) until the solution became basic (pH 9-10), This solution was then extracted with EtOAc (3 X 20 mL), dried over $MgS0_4$, and concentrated to yield a solid which was dried in vacuo to give (88% yield) pure ligand.

mp 133-135°C; $[\alpha]^{20}_D$ = -262.5 (c = 1.15, MeOH); ^{1}H NMR (400 MHz, $CDC1_3$) 8.63 (d, *J* = 4.5 Hz, 2H), 8.31 (m, 2 H), 7.97 (d, *J* = 9.2 Hz, 2 H), 7.91 (m, 2 H), 7.55 (d, *J* = 2.6 Hz, 2 H), 7.43 (d, *J* = 4.6 Hz, 2 H), 7.35 (d, *J* = 9.2 Hz, 1 H), 7.34 (d, *J* = 9.2 Hz, 1H), 6.96 (d, *J* = 6.6 Hz, 2H), 3.9 (s, 6H), 3.39 (q, *J* = 15.7 Hz, 2H), 2.81-2.60 (m, 8H), 2.34 (s, 1H), 2.20 (s, 1 H), 1.94 (t, *J* = 11.1 Hz, 2H), 1.68 (s, 2H), 1.58-1.50 (m, 4H), 1.46-1.38 (m, 6H), 0.79 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 156.40, 147.36, 145.03, 144.70, 132.09, 131.55, 127.38, 122.79, 122.42, 121.77, 118.54, 102.09, 76.30, 60.26, 55.56, 50.87, 49.96, 37.45, 27.32, 26.28, 25.29, 23.56, 11.88; IR (KBr, cm^{-1})ν : 2933, 2871, 1623, 1509, 1474, 1455, 1393, 1354, 1262; HRMS for $C_{48}H_{54}N_6O_4$: *m/z* 911.3270 ($M+H^+$).

Preparation of 1,4-Bis (9-O-dihydroquinyl) pyridazine 171

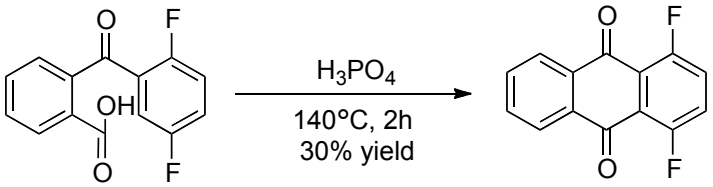


A 250 mL flame-dried one-neck round-bottom flask was charged with dihydroquinidine (S)-**128** (13 g, 4.01 mmol, 2 eq^n), 3,6-dichloropyridazine **170** (3 g, 2.01 mmol, 1eq^n)**,** K_2CO_3 (8.33 g, 6.03 mmol, 3eq^n), and 125 mL of anhydrous toluene. The flask was equipped with a Dean-Stark-condenser. Under nitrogen atmosphere, the mixture was refluxed for 2 hour. Then, KOH pellets (87%) (3.38 g, 6.03 mmol, 3eq^n) were added and the mixture was refluxed (with azeotropic removal of water) under nitrogen atmosphere for an additional 12 h. [The reaction can be followed by TLC using 20:1, CH_2Cl_2 / MeOH. The *Rf* of the ligand is 0.22]. The light orange solution was cooled to room temperature, mixed with (25 mL) of water, and then extracted with EtOAc (3 × 35 mL). The organic layer was washed with water (25 mL) and brine (25 mL), dried over $MgS0_4$, and evaporated to dryness. The crude slightly yellow solid was dissolved in absolute EtOH (75 mL), and a solution of 7.5 ml of concentrated

H_2SO_4 in 163 mL of absolute EtOH was added over a 10-min period with vigorous stirring. The clear solution was refrigerated (-5 °C) for 2 hour, the resulting white precipitate of the tetrasulfate salt was collected by filtration through a 10-20-μcm sintered glass funnel and washed first with cold EtOH (25 mL) and then with diethyl ether (75 mL). The free base was easily prepared by dissolving the off-white tetrasulfate salt in water (25 mL) and adding saturated sodium bicarbonate ($NaHCO_3$) until the solution became basic (pH 9-10), This solution was then extracted with EtOAc (3 × 25 mL), dried over $MgS0_4$, and concentrated to yield a solid which was dried in vacuo to give (70% yield) pure ligand.

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) 8.60 (d, *J* = 4.64 Hz, 2H), 7.89 (dd, *J* = 22.0 Hz, 2H), 7.32 (m, 1H), 7.28 (d, *J* = 0.7 Hz, 4H), 6.88 (d, *J* = 28.6 Hz, 2H), 3.81 (s, 6H), 3.21 (d, *J* = 6.7 Hz, 2H), 2.79 (m, 4H), 1.98 (s, 2H), 1.64 (m, *J* = 15.3 Hz, 2H), 1.39 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 6H), 0.78 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.3, 152.5, 148.2, 144.7, 139.3, 131.2, 127.6, 123.8, 122.4, 121.8, 114.8, 101.5, 81.2, 57.5, 56.9, 55.8, 43.9, 40.2, 37.5, 27.4, 26.9, 25.5, 24.1, 12.9;

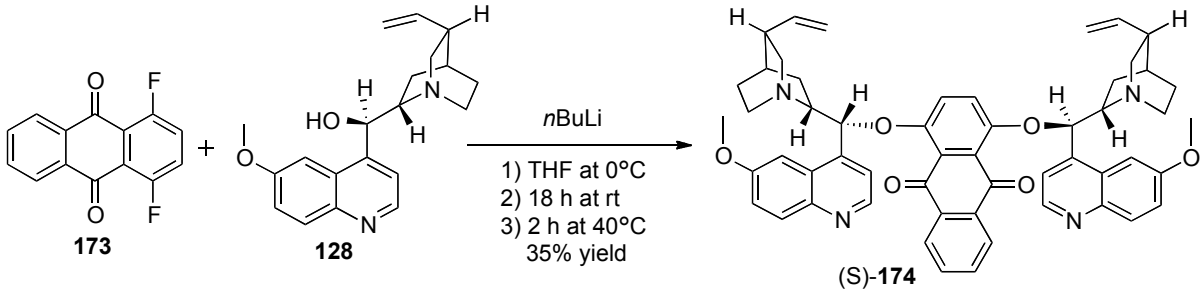
Preparation of 1,4-Difluoroanthracene-9,10-dione 173



172 **173**

A mixture of 2-(2,5-Difluorobenzoyl) benzoic acid (3gm, 0.011 mol, 1 eq) and polyphosphoric acid (0.2 M) was heated under reflux at 140°C and turned clear after 2 hour. Upon cooling the reaction mixture was poured into ice water and extracted with DCM. The organic layer was washed with water and brine (25 mL), dried over $MgS0_4$, and evaporated to dryness. The crude brownish black sticky reaction residue was purified *via* flash chromatography on silica gel (elution with chloroform only). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound **173** 30% yield

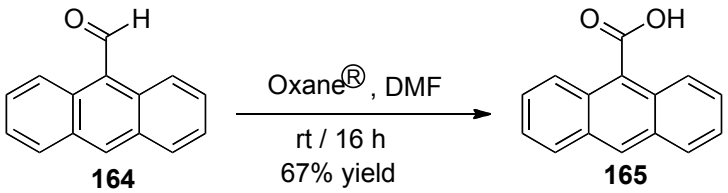
Preparation of 1,4-Bis (9-O-dihydroquinyl) anthracene-9,10-dione 174



The flask was charged with dihydroquinidine (S)-**128** (2.36 g, 0.72 mol, 2.5 eq^{n}) and 50 mL anhydrous THF. *n*BuLi (2.5 M, 2 mL) at -78°C was slowly added in the reaction mixture, then 1,4-Difluoroanthracene-9, 10-dione (0.70 g, 0.29 mol, 1 eq^{n}) was added and the reaction mixture was stirred for 2 hour at -78°C, additional 18 hour at room temperature and 2 hour at 40°C. Reaction can be followed by TLC using (EtOAc / EtOH / Et_3N; 96%: 2%: 2%). The reaction mixture allows cooling down at room temperature, quenched with saturated NH_4Cl at 0°C and then extracted with EtOAc (3 X 10 ml). The organic layer was washed with water (25 mL), dried over $MgS0_4$, and evaporated to dryness. The crude yellowish solid was purified *via* flash chromatography on silica gel (elution with EtOAc / EtOH / Et_3N; 96%: 2% : 2%). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound **174** 35% yield.

^{1}H NMR (300 MHz, $CDCl_3$) 8.60 (dd, *J* = 12.5 Hz, 2H), 8.26-8.10 (m, 2H), 7.97 (dd, *J* = 14.5 Hz, 2H), 7.75 (dd, *J* = 9.3 Hz, 2H), 7.58 (m, 2H), 6.86 (d, *J* = 1.9 Hz, 2H), 6.41 (s, 2H), 3.98 (d, *J* = 28.0 Hz, 4H), 3.41 (m, *J* = 7.0 Hz, 2H), 3.30-3.10 (m, 4H), 3.05-2.83 (m, 1H), 2.39-2.11 (m, 1H), 1.98 (s, 2H), 1.84 (s, 2H), 1.59 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 4H), 0.87 (t, *J* = 5.8 Hz, 6H)

Synthesis of anthracene -9-carboxylic acid 165

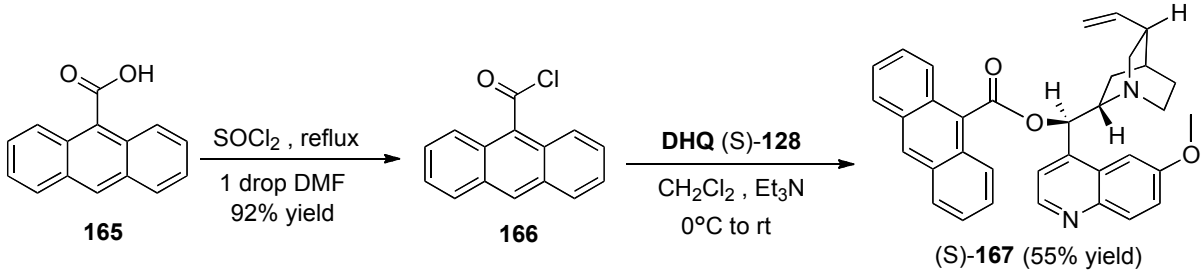


A 50 mL flame-dried round-bottom flask was charged with 9-anthracenaldehyde (1 g, 0.48 mmol, 1 eq^{n}), Oxone (3.19 g, 0.52 mmol, 1.1 eq^{n}) and then added anhydrous DMF (5 ml).

The reaction mixture was stirred at room temperature. After 16 hour TLC analysis (75: 25; petroleum ether / diethyl ether) indicate the absence of starting material. The resulting solid residue was dissolved by the addition of aqueous HCl (1 M) and the mixture was transferred into separating funnel, and then extracted with EtOAc (3 X 20 ml). The combined organic layer was washed with (1 M) HCl (3 X 20 ml) and once with brine (20 ml). The organic layer was dried over $MgS0_4$, and evaporated to dryness. The residue was dissolve in DCM (10 ml), solution was transferred into separating funnel and then extracted with (0.4 M) of NaOH (4 X 20 ml). The basic aqueous extract was acidified with (1 M) HCl and then extracted with EtOAc (4 X 10 ml). The organic layer was dried over $MgS0_4$, and evaporated to dryness. Recrystalisation from toluene gave orange needle like crystals. Subsequent physicochemical analysis of the purified product confirmed formation of the title compound **165** 67% yield.

^{1}H NMR (300 MHz, $CDCl_3$) 8.68 (d, J = 1.1 Hz, 1H), 8.40 (s, 2H), 8.02 (t, J = 7.7 Hz, 2H), 7.53 (m, 4H);

Synthesis of (9-O-dihydroquinyl) anthracene -9-carboxylate 167



165 **166** (S)-**167** (55% yield)

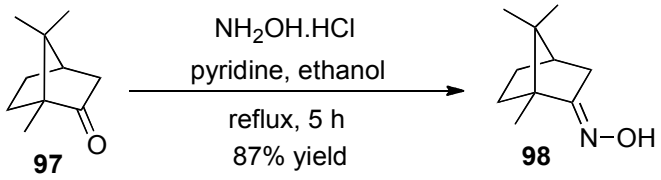
A mixture of anthracene-9-carboxylic acid (0.72 g, 0.32 mmol, 1 eq^n) and thionyl chloride (1.5 ml) was heated in reflux and turned clear after 5 h. The excess of thionyl chloride was subsequently removed by distillation or evaporated in *vacuo*. The product was obtained as a solid (99% yield). Into a solution of cinchona alkaloid (S)-**128** (1.74 g, 0.42 mmol, 1eq^n) in anhydrous dichloromethane (5 ml), 0.5M anhydrous triethyl amine (2 ml) at 0°C was added. A solution of anthracene-9-carbonyl chloride (1 g, 0.42 mmol, 1 eq^n) in anhydrous dichloromethane (5 ml) was slowly added. After 1 h the reaction mixture was warmed to room temperature and stirred for additional 2 h. Upon completion of reaction indicated by TLC, resulting mixture was poured into (10 ml) of distilled water; the organic layer was separated and washed with saturated $NaHCO_3$ solution, and then with water. The organic solution was dried by anhydrous $MgSO_4$ and evaporated in *vacuo* after work up followed by purification by flash chromatography on silica gel (ethyl acetate / ethanol / triethyl amine : 7 /

0.15 / 0.15). Subsequent physicochemical analysis of the purified product confirmed formation of the title compound afforded in 55% yield.

^{1}H NMR (300 MHz, $CDCl_3$) 8.56 (m, 3H), 8.44 (d, *J*=1.5Hz, 1H), 7.92 (m, 2H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.48 (m, 5H), 7.29 (m, 2H), 6.63 (s, 1H), 6.33 (d, *J*=3.8 Hz, 2H), 3.98 (s, 3H), 3.38 (m, 1H), 3.30-3.10 (m, 1H), 2.97 (m, 2H), 2.78 (m, 1H), 2.25 (m, 1H), 2.39 (1H) 1.98 (s, 1H), 1.84 (s, 2H), 1.19 (t, *J* = 7.1 Hz, 4H), 0.87 (t, *J* = 5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 158.2, 156.9, 148.2, 144.7, 143.7, 132.3, 130.9, 129.7, 128.4, 127.6, 127.2, 126.5, 126.8, 125.8, 122.2, 121.8, 117.1, 104.8, 101.5, 78.8, 60.3, 55.8, 51.0, 43.9, 37.5, 27.4, 26.9, 25.5, 24.1, 12.9;

Attempted Synthesis of Five-Membered Ring Heterocycles by Cyclization of NH-Oxaziridines with Alkenes

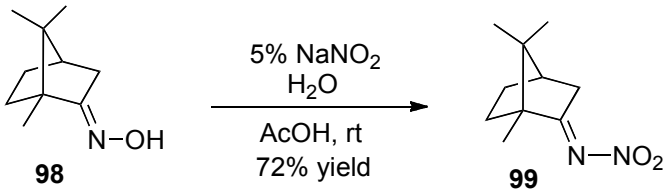
Synthesis of (E)-1, 7, 7-trimethylbicyco[2.2.1]heptan-2-one oxime 98



A 100 mL round bottom flask was loaded with hydroxylamine hydrochloride (1.98 g, 2.8 mmol, 2.2 eq^n), (1*R*)-(+)-camphor (2 g, 1.3 mmol, 1 eq^n) and picoline (2 ml, 1.95 mmol, 1.5 eq^n) were heated under reflux in presence of ethanol (20 ml) for 5 hours. After cooling, the reaction mixture was concentrated. Water was then added, causing the crude oxime to precipitate from the solution as colourless crystals, which were isolated by filtration and washed with distilled water. The crystalline material was dissolve in DCM and dried over $MgSO_4$ and evaporated in *vacuo* to afford camphor oxime (87 % yield).

White solid mp 119-121°C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.19 (s, 1H), 2.66-2.40 (m, 1H), 2.02 (d, *J* = 17.8 Hz, 1H), 1.89 (t, *J* = 4.3 Hz, 3H), 1.79 (m, 1H), 1.65 (m, *J* = 11.9 Hz, 1H), 1.50-1.34 (m, 1H), 1.28-1.13 (m, 1H), 0.97 (s, 3H), 0.88 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.7, 51.8, 48.2, 43.6, 33.1, 32.6, 27.7, 19.4, 18.5, 11.1; IRν_{max} /cm^{-1} 3293, 1684; HRMS calcd. For $C_{10}H_{17}NO$ (M^+) 167.13101, found 167.13095.

Synthesis of (E)-N-(1, 7, 7-trimethylbicyco[2.2.1]heptan-2-ylidene)nitramide 99

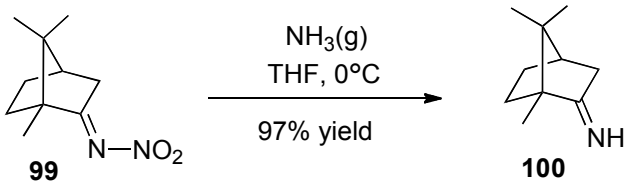


98 **99**

A 150 ml round bottom flask was loaded with (1*R*, 4*S*)-(−)-Camphor oxime **98** (2 g, 1.2 mmol) in glacial acetic acid (60 ml) was treated with 5T aqueous sodium nitrite (30 ml). A bright yellow colour developed and dispersed over 30 minutes. After a further 1.5 hours, water was added and the product was extracted with diethyl ether (2 X 20 ml), dried over $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by column chromatography on silica gel (dichloromethane / light petroleum) to afford the title compound 72% yield as a colourless crystalline solid.

Mp 41-42°C; ^{1}H NMR (300 MHz, $CDCl_3$) 2.70 (m, 1H), 2.13 (d, J = 18.6 Hz, 1H), 2.00-1.74 (m, 3H), 1.61-1.43 (m, 1H), 1.34-1.21 (m, 1H), 1.00 (s, 3H), 0.94 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 189.8, 54.5, 49.2, 43.8, 35.5, 31.9, 27.1, 19.8, 19.0, 10.7; IRν_{max} /cm^{-1} 1645, 1569.

Synthesis of 1, 7, 7-trimethylbicyco[2.2.1]heptan-2-imine 100

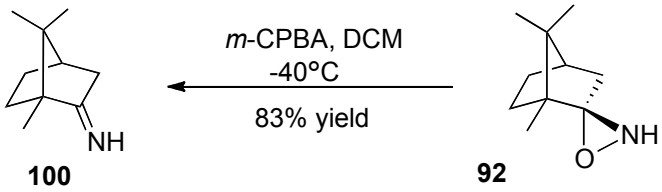


99 **100**

A 50 ml round bottom flask was loaded with (1*R*, 4*S*)-(–)-Camphor nitrimine **99** (1.87g, 1.0 mmol, 1 eq^n) and anhydrous THF (14 ml) was treated at 0°C with slow stream of ammonia gas for 15 minute. The mixture was allowed to reach at room temperature and solvent was removed under reduced pressure (keeping water bath below 30°C) to give the imine **100** as pale yellow solid (97% yield).

^{1}H NMR (300 MHz, $CDCl_3$) 8.13 (s, 1H), 2.5 (m, 1H), 2.03 (d, J = 17.6, 1H), 1.95 (t, J = 4.4, 1H), 1.93-1.84 (m, 1H), 1.69 (dt, J = 12.8, 1H), 1.41-1.22 (m, 2H), 0.97 (s, 3H), 0.94 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 194.0, 54.8, 47.3, 43.8, 40.4, 32.1, 27.1, 19.6, 19.2, 10.4; IRν_{Max} (CH_2Cl_2) /cm^{-1} 3446, 1667.

Synthesis of (1R, 4S)-(–)-Camphoryl oxaziridine 92

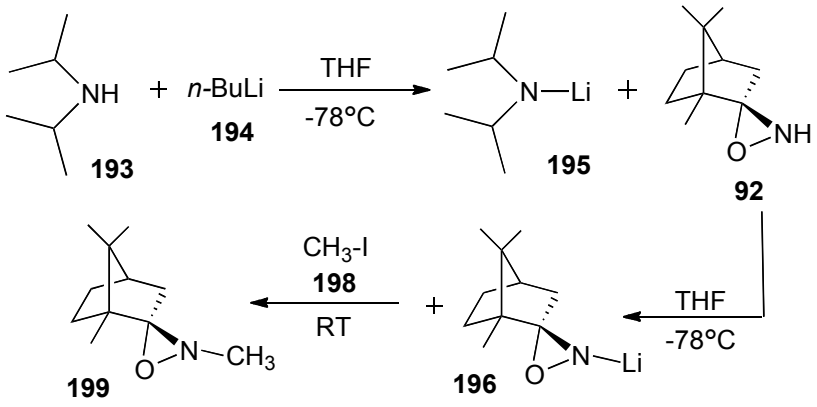


100 **92**

A solution of purified *m*-CPBA (10.35 g, 0.06 mol, 1eq^{n}) in dry DCM (150 ml) was cooled to -40°C, causing some of the peracid to crystallize from the solution. A solution of the imine (6.44 g, 0.04 mol, 1.5eq^{n}) in dry DCM (90 ml) was added in the reaction mixture over period of 4-5 minute. The reaction mixture was stirred overnight at -40°C, and allowed to reach at room temperature. The reaction mixture was stirred at room temperature for further 2 hour until all the peracid had reacted (TLC), by which time much of the *m*-chlorobenzoic acid by-product had crystallized from the solution. The solution was concentrated under reduced pressure until approximately 25% of the original volume remained. Petroleum ether was added and the process was repeated three times, and finally petroleum ether (90 ml) was added in the mixture. The precipitated *m*-chlorobenzoic acid was removed by filtration, and the rest of this by-product washed from the resulting solution with aqueous NaOH. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (light petroleum / ethyl acetate) to afford the desired oxaziridine **92** (83% yield).

Colourless solid mp 153-155°C; $[\alpha]\nu_{max}$ + 6° (C=1.0,$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 4.19 (s, 1H), 3.71 (s, 1H), 2.35-2.14 (m, 1H), 1.92-1.29 (m, 1H), 1.25-1.10 (m, 1H), 1.00 (m, 3H), 0.83 (s, 3H), 0.63 (s, 3H), 0.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 89.7, 89.4, 48.1, 47.8, 47.7, 47.5, 44.5, 44.3, 37.7, 36.5, 30.3, 29.5, 27.3, 27.0, 19.6, 19.5, 19.34, 19.31, 8.6, 8.4; HRMS Calcd. for $C_{10}H_{17}NO$ (M+) 167.13101, found 167.13120; IRν_{max} (CH_2Cl_2) /cm^{-1} 3202

1,2',7,7-tetramethylspiro[bicycle[2.2.1]heptanes-2.3'-[1,2]oxaziridine 199



A 25 ml flame dried round bottom flask was loaded with a solution of Diisopropylamine (0.32 ml, 0.0023 mmol, 1.5 eq^{n}) and anhydrous THF (5 ml), while cooling the ice bath to -78°C. *n*BuLi (0.22 ml, 0.0023 mmol, 1.5 eq^{n}) at -78°C was slowly added in the reaction mixture while stirring. After 1 hour the oxaziridine (0.25 g, 0.0015 mmol, and 1eq^{n}) was added in the reaction mixture. The reaction mixture was stirred for additional 2 hours and then methyl iodide (0.21 g, 0.0015 mmol, 1eq^{n}) was added at room temperature. Completion of the reaction after 4 hour by TLC. Solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (petroleum ether / ethyl acetate; 8:1) to afford the desired product **199**. Subsequent physicochemical analysis of the purified product confirmed formation of the title compound **199** afforded 52% yield.

^{1}H NMR (400 MHz, $CDCl_3$) 5.95-5.42 (m, 1H), 5.20 (s, 1H), 2.87 (s, 1H) 2.40-2.30 (m, 1H), 2.21-2.13 (m, 1H), 2.09 (s, 1H) 2.08 (s, 1H) 1.95-1.82 (m, 1H), 1.80-1.70 (m, 1H), 1.60-1.58 (m, 1H), 1.22-1.20 (m, 1H), 1.00 (m, 1H), 0.83 (s, 1H), 0.80 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) 170.6, 140.8, 120.2, 40.7, 30.7, 30.6, 20.6, 20.0, 10.25.

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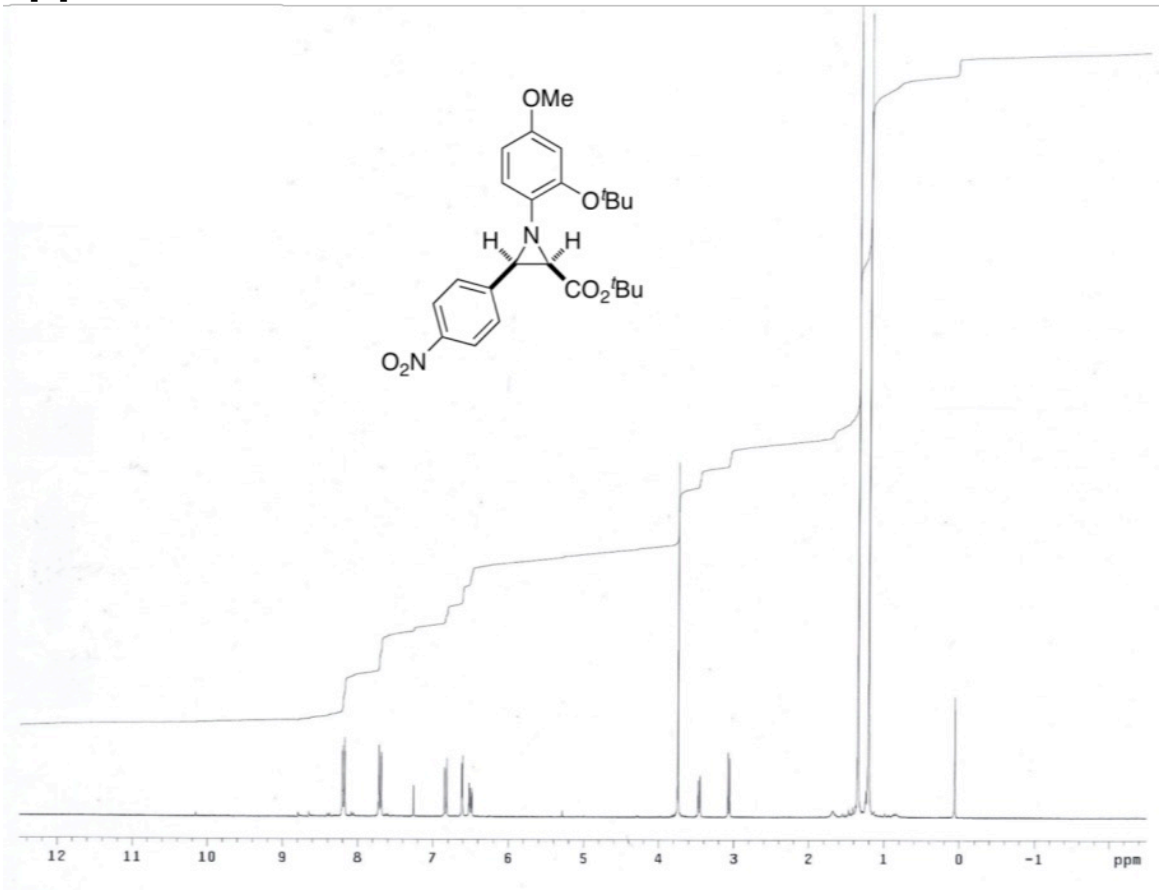
Appendix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N
H
CO$_2$^{t}Bu
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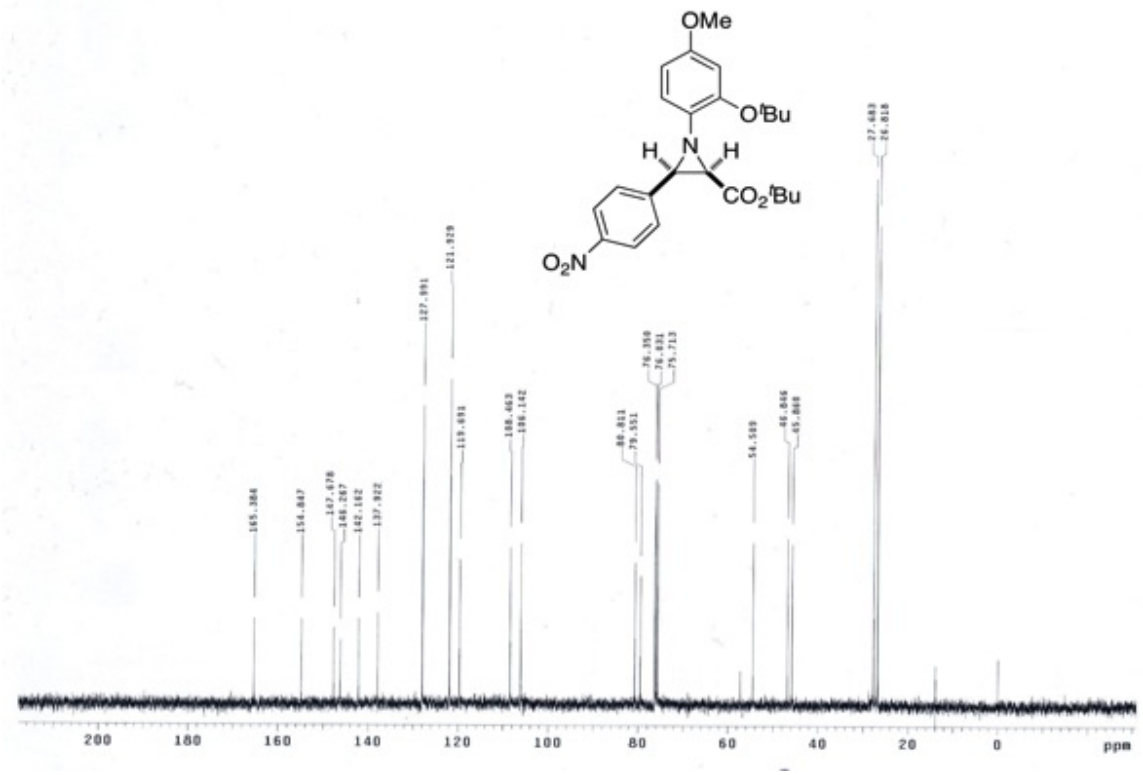
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm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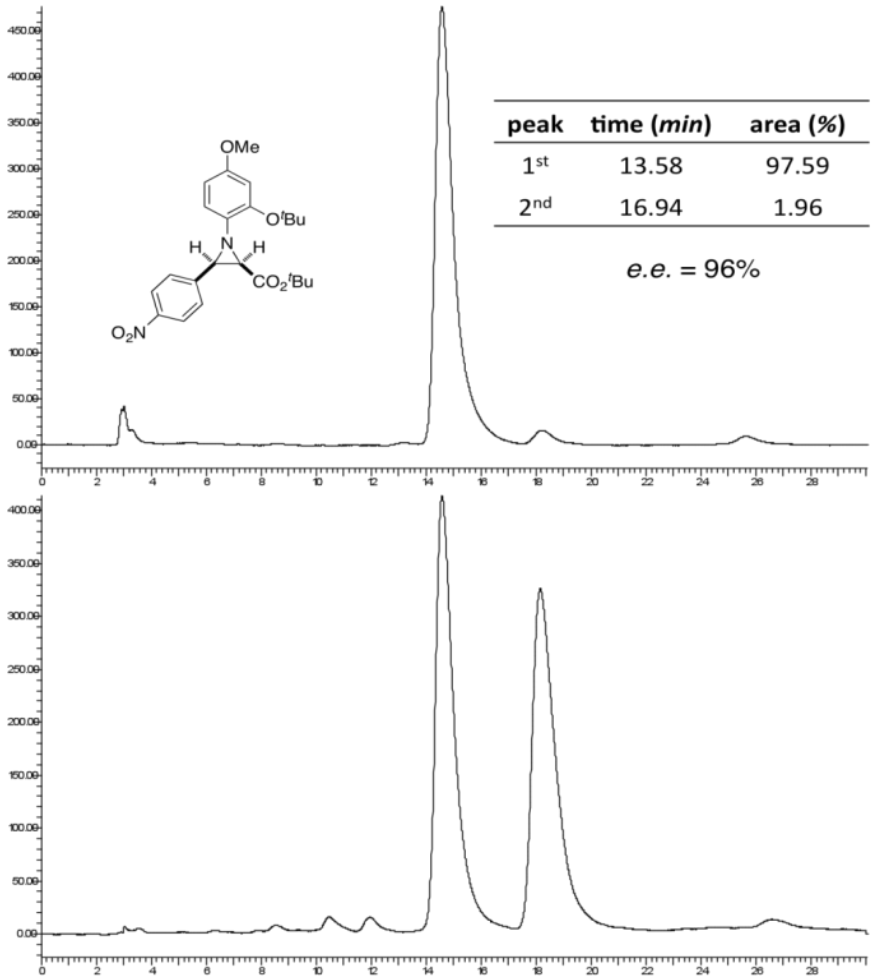
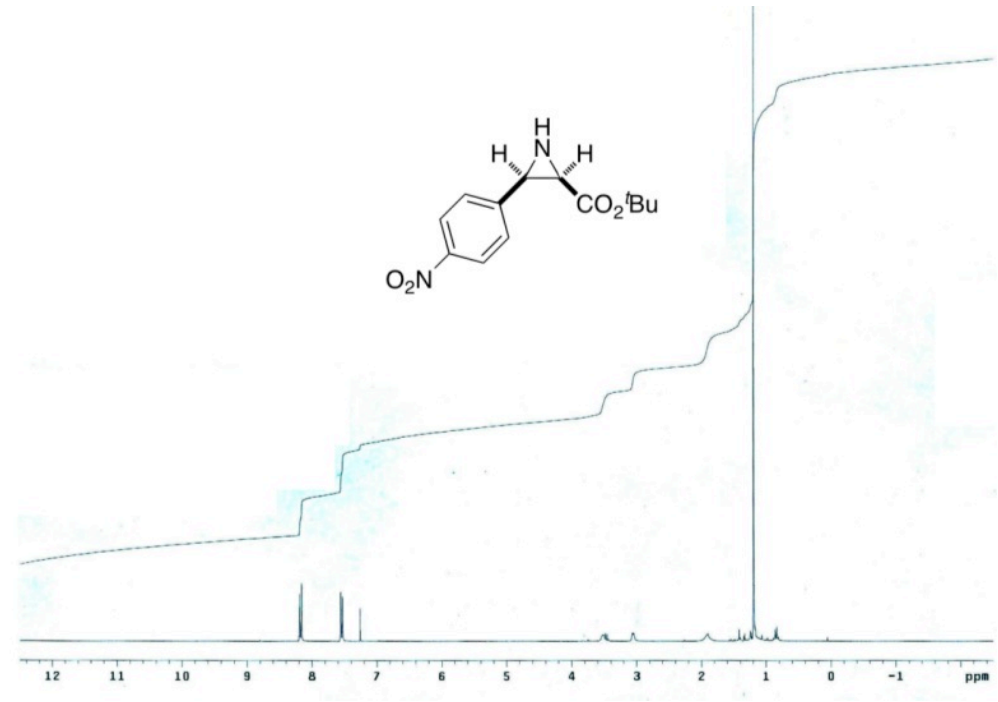
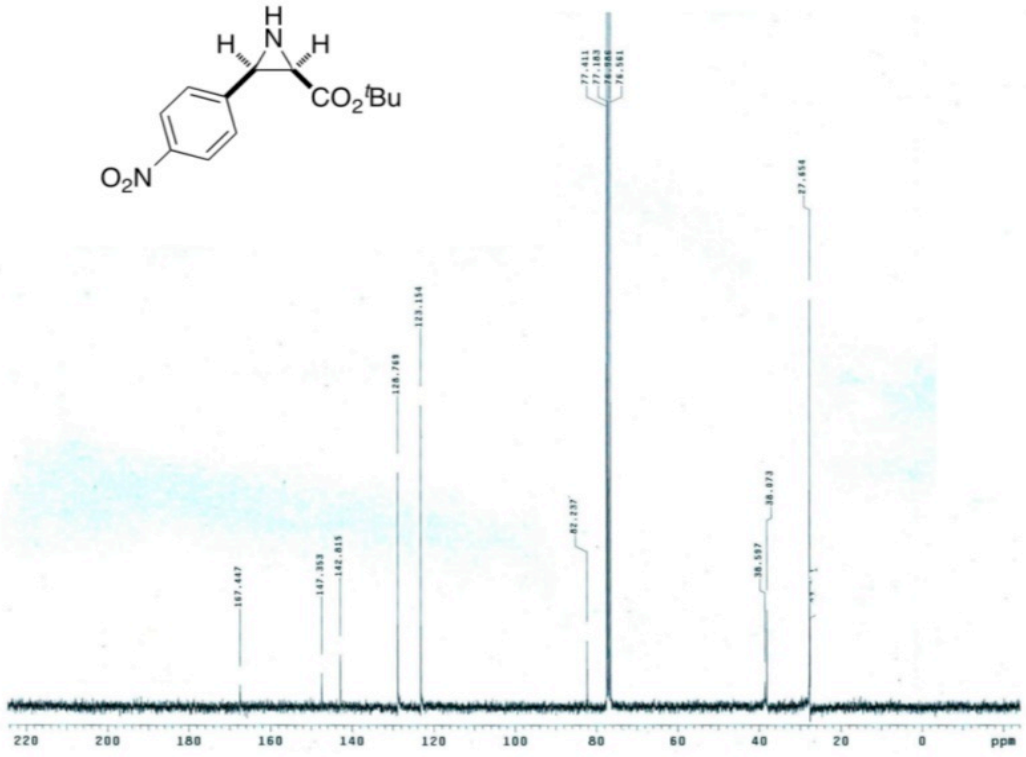
40
20
0
ppm



peak	time (*min*)	area (%)
1st	13.58	97.59
2nd	16.94	1.96

e.e. = 96%

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H
CO2tBu
O2N
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142.815
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123.154
82.237
77.411
77.183
76.956
76.561
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38.073
27.454
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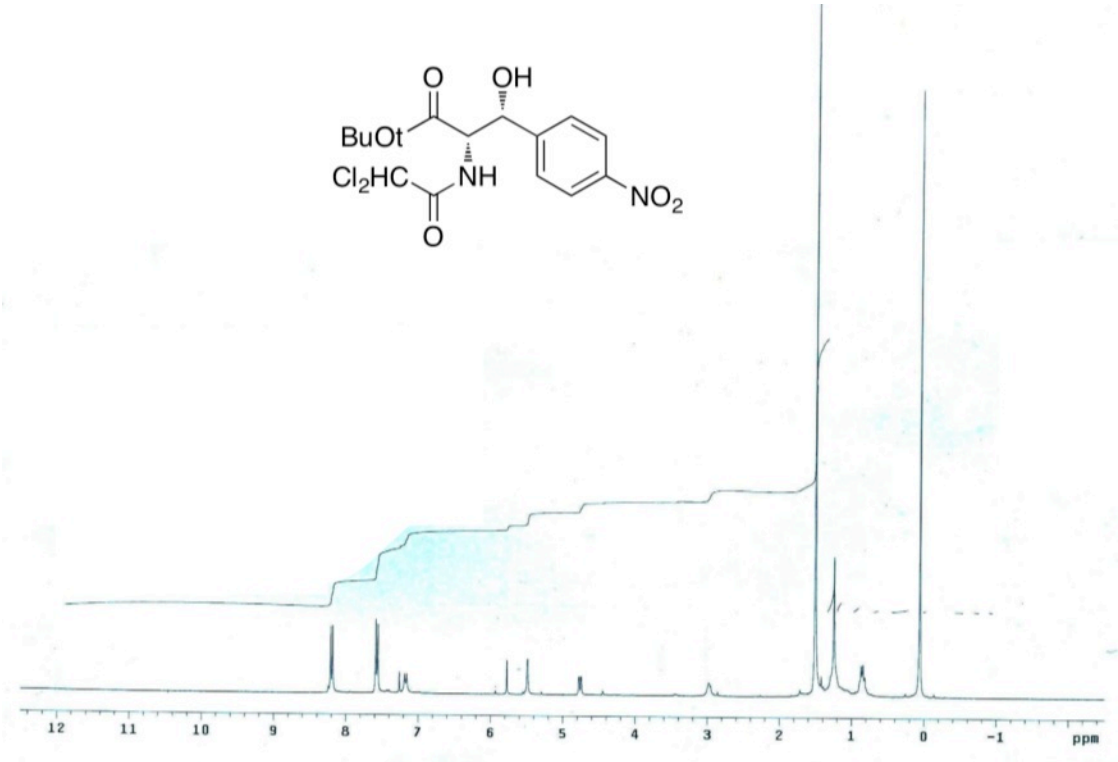
200
180
160
140
120
100
80
60
40
20
0
ppm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1
0
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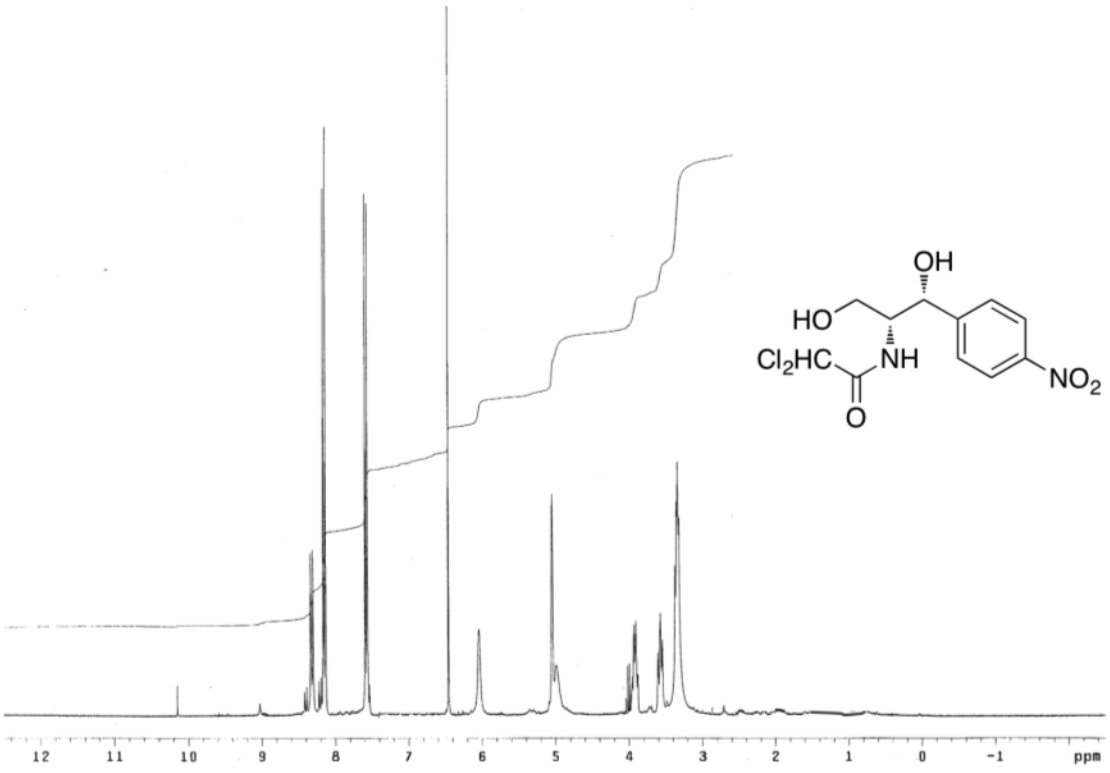
ppm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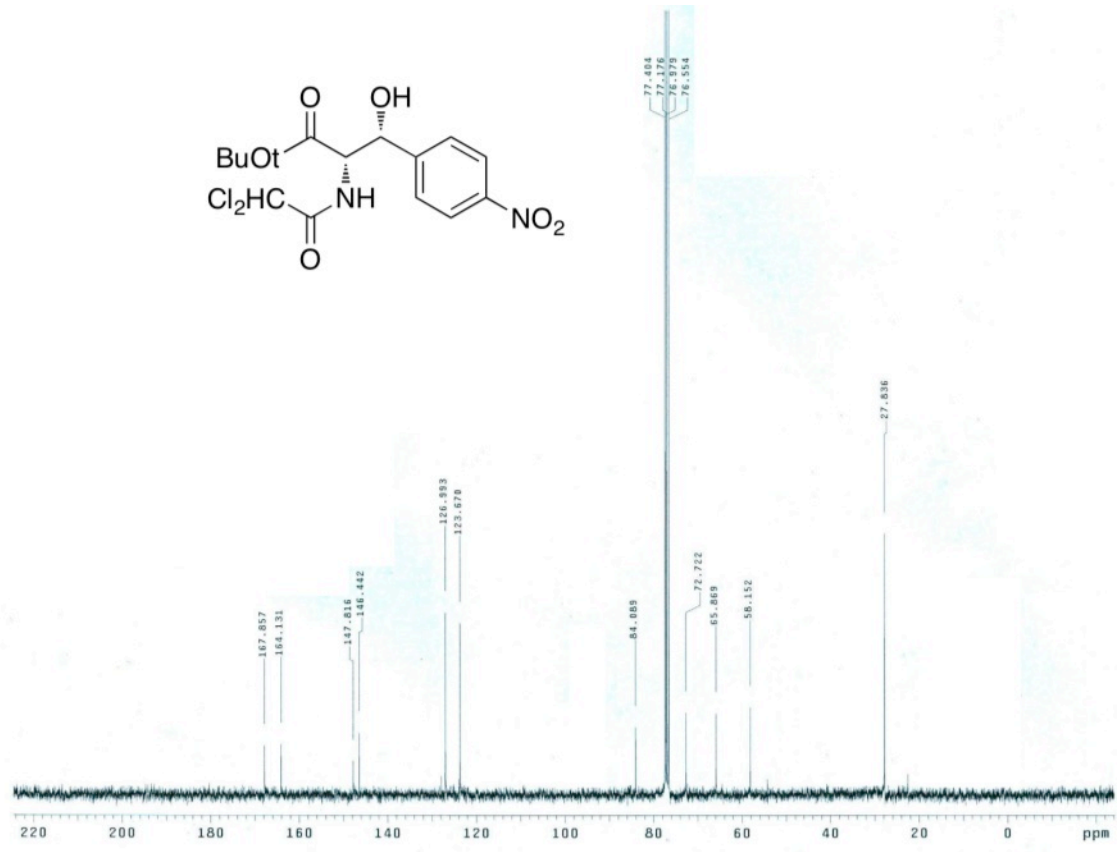
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NO2
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167.857
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147.816
146.442
126.993
123.670
84.089
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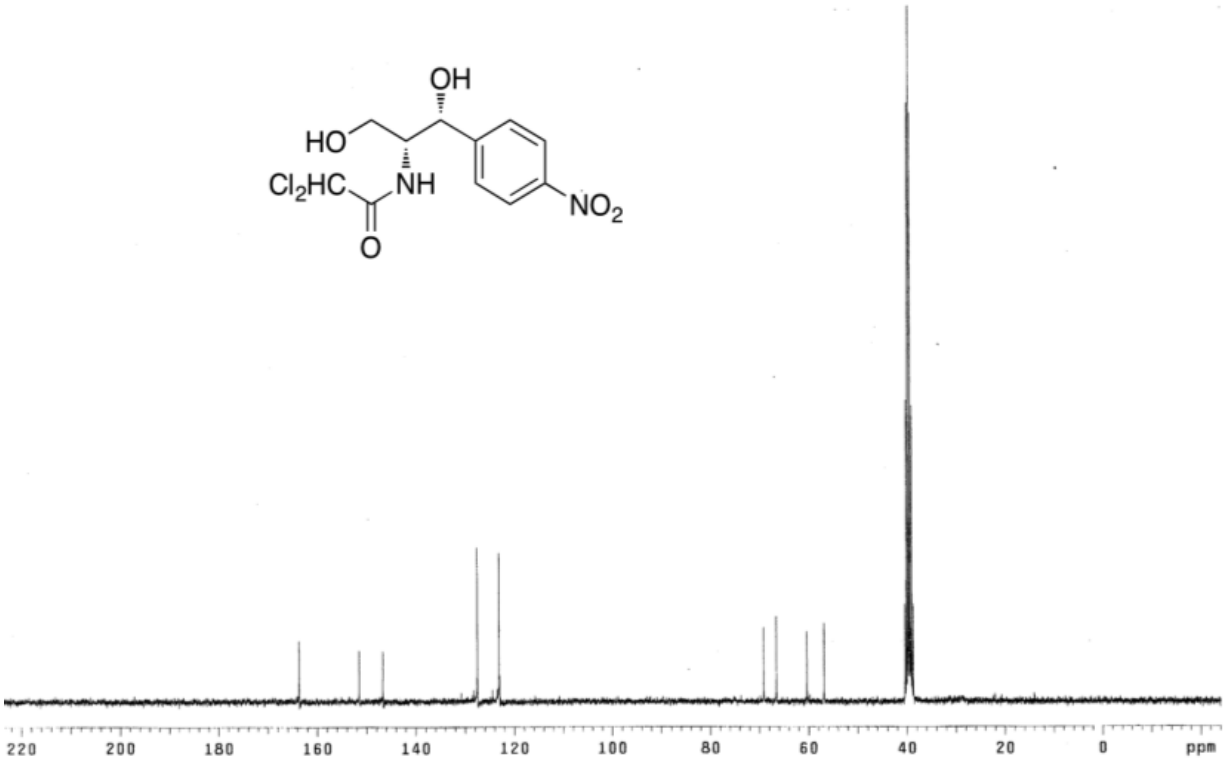
40
20
0
ppm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HO
Cl2HC
NH
NO2
O
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200
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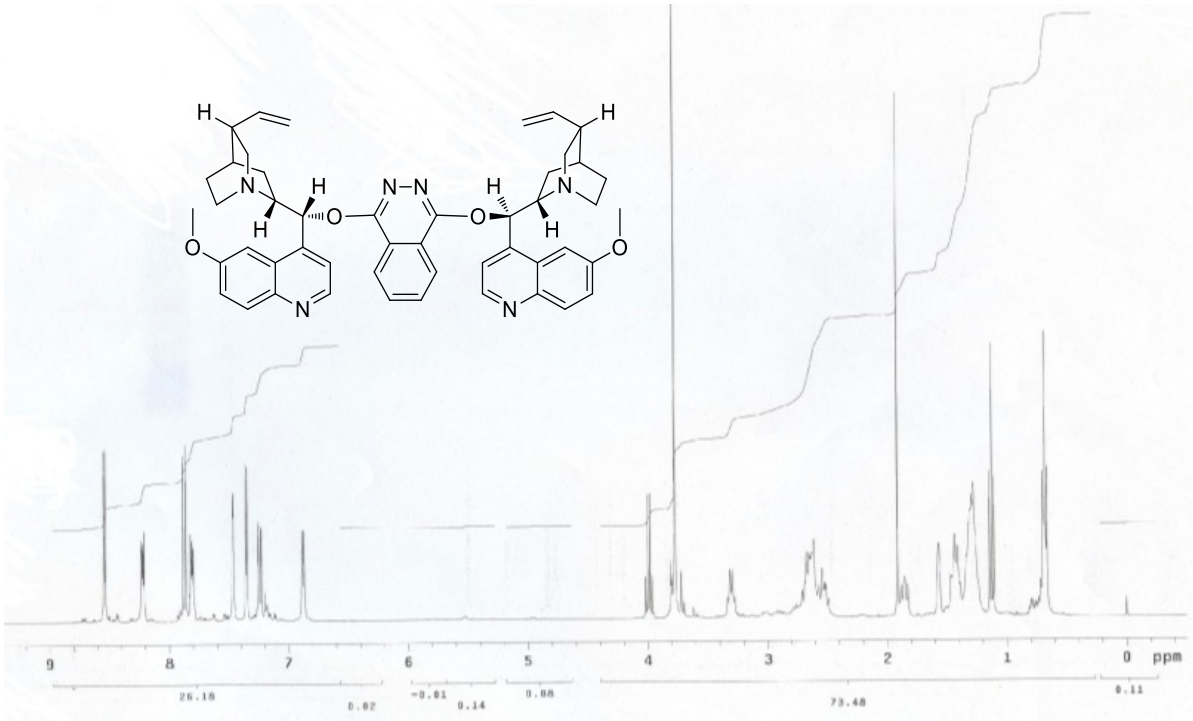
160
140
120
100
80
60
40
20
0
ppm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N
H
O
N–N
O
H
N
H
H
O
O
N
N
9
8
7
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3
2
1
0
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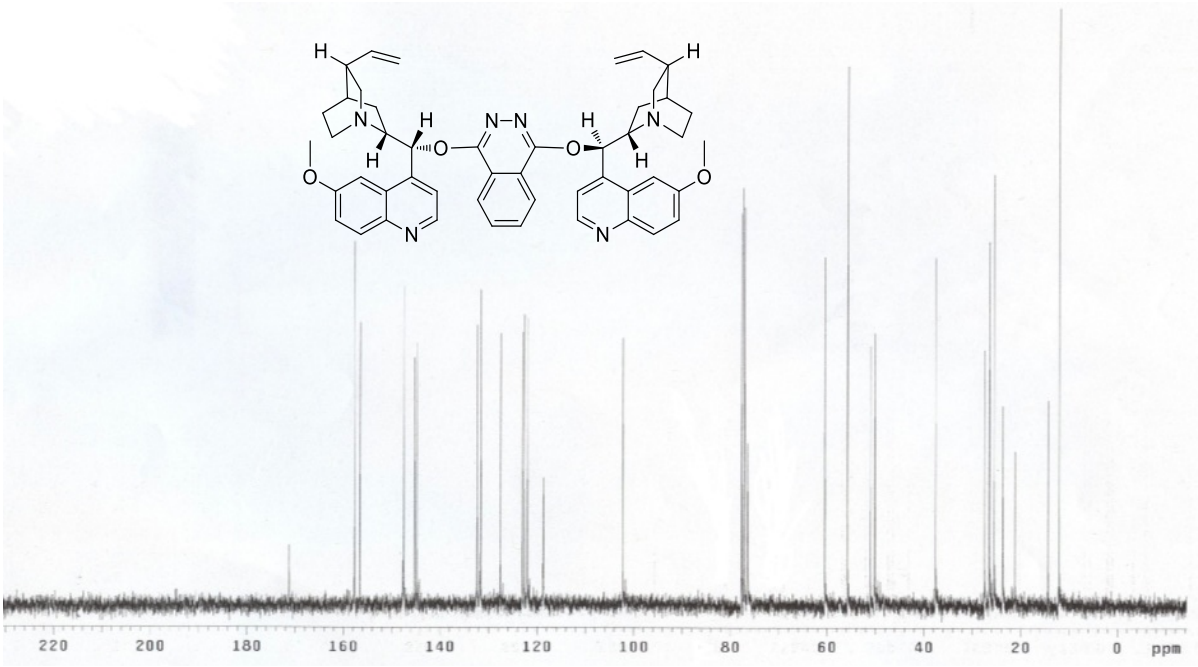
0.02
-0.01
0.14
0.88
73.48
0.11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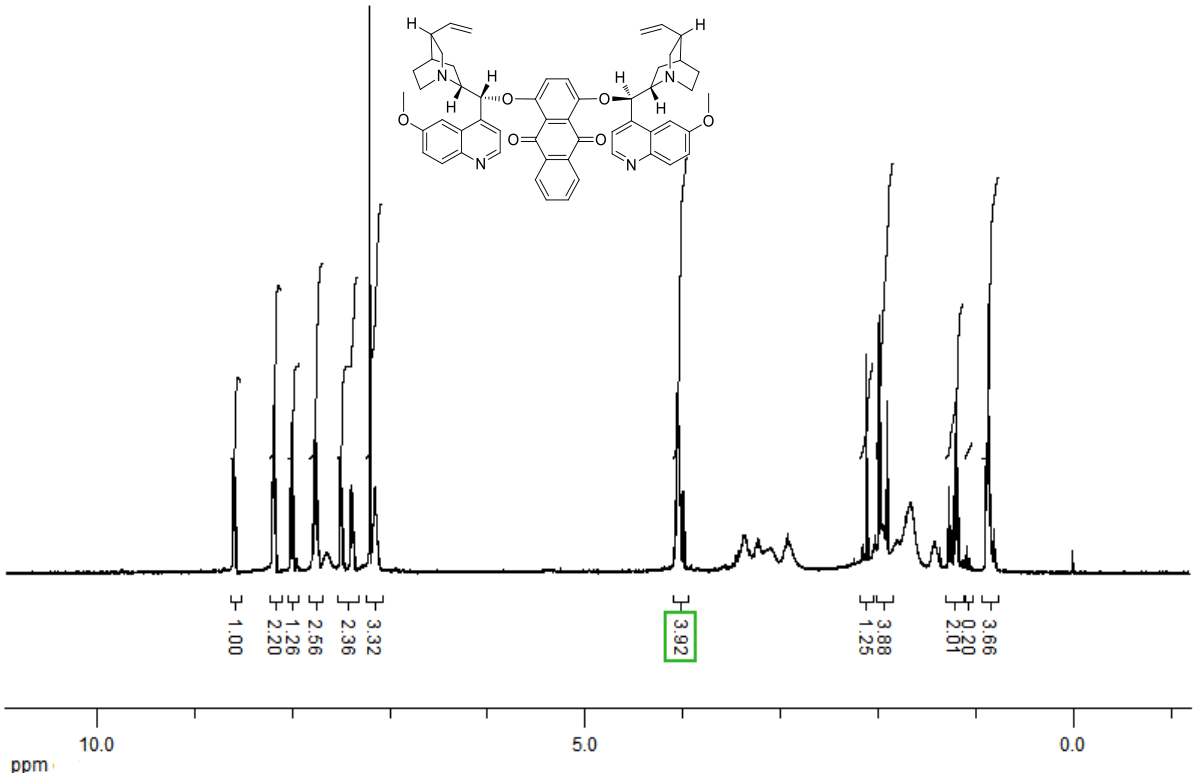
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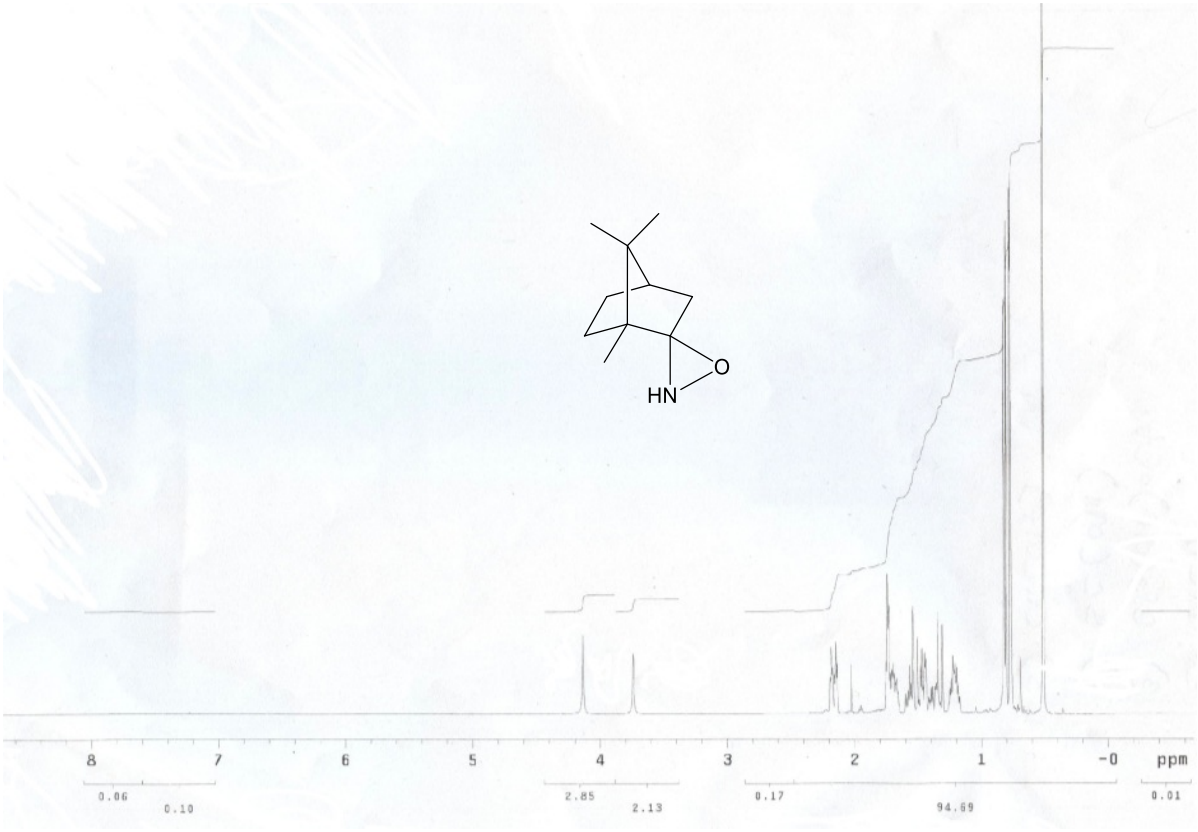
5.0
0.0
ppm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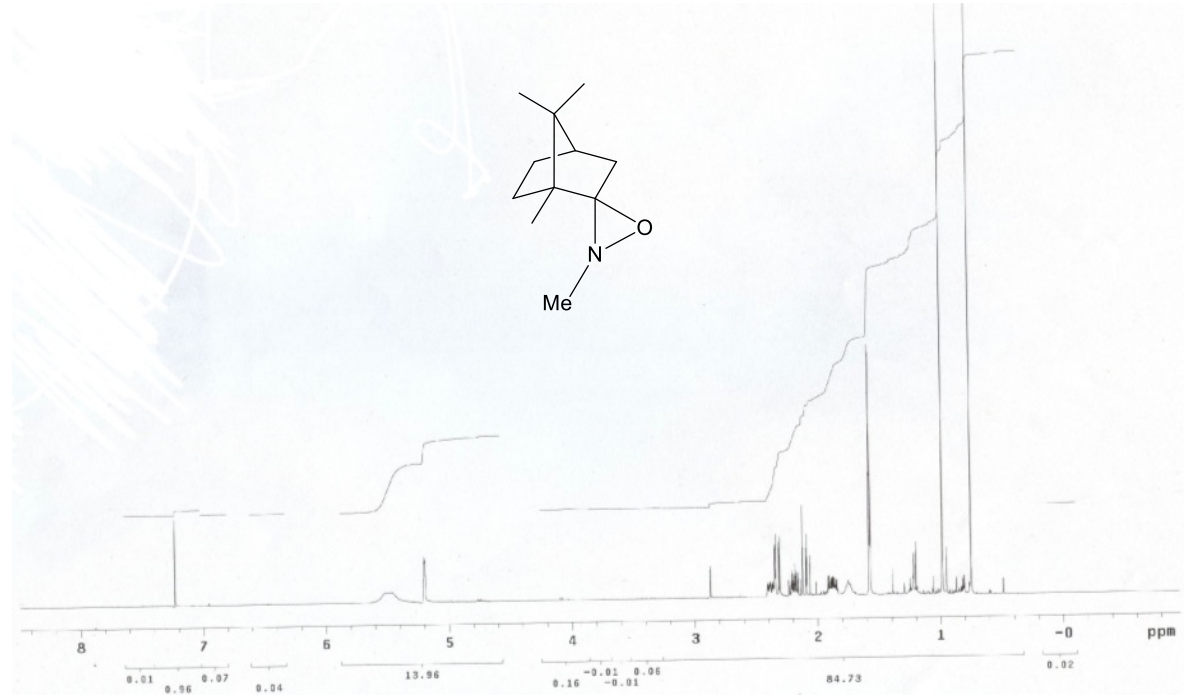
94.69
0.01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