Asymmetric synthesis of heterocycles via cation-directed cyclizations and rearrangements

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Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between October 2009 and June 2013. The dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

Alan Lamb

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hadn't been cocooned in the writing up bubble then you too would now be blessed with a phrase in quote marks!

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An extra debt of gratitude is owed to those in the group who proof read this thesis; Craig, Emily, Jamie and Roly. What it now lacks in ostentatious turns of phrase and flamboyant metaphors it has surely gained in accuracy.

Finally I'd like to thank my friends and family, most importantly of all my parents; without whose support and encouragement I would undoubtedly not be typing this now. Which means they've got a lot to answer for, now that I think of it.

Abbreviations

1D	one-dimensional
2D	two-dimensional
A value	representation of relative steric effect of a substituent
Å	Ångströms
AIBN	2,2′-azobis(2-methylpropionitrile)
Ac	acetyl
aq.	aqueous
Ar	*denotes a generic aromatic system*
BARF	$[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bis(oxazoline)
Bu	*n*-butyl
°C	degrees Celsius
c	centi-
c	concentration
cal	calories
CAN	ammonium cerium(IV) nitrate
COSY	correlation spectroscopy
d	deci-
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalents

ESI	electrospray ionization
Et	ethyl
EWG	*electron-withdrawing group*
FI	field ionization
fod	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate
FT	Fourier transform
g	grams
h	hours
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	hertz
i	*iso*
IPA	isopropanol
IR	infra-red
IUPAC	International Union of Pure and Applied Chemistry
k	kilo-
λ	wavelength
L	ligand
L	litres
LDA	lithium diisopropylamide
LRMS	low-resolution mass spectrometry
μ	micro-
m	milli-
M	moles per litre
m	*meta*-
m	metres
MALDI	matrix-assisted laser desorption/ionization
Me	methyl
min	minutes
mol	moles

MOM	methoxymethyl
MP	melting point
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
n	normal
n	*denotes a generic integer*
n	nano-
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NCS	norcoclaurine synthase
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
o	*ortho*-
ONSH	oxidative nucleophilic substitution of hydrogen
p	*para*-
PEG	polyethylene glycol
petrol	petroleum ether
Ph	phenyl
ppm	parts per million
Pr	propyl
PTC	phase-transfer catalysis
quant.	quantitative
R	*denotes a generic substituent*
RT	room temperature
s	solid
s	suprafacial
SET	single electron transfer
SM	starting material
S_NAr	nucleophilic aromatic substitution
t	*tertiary*
TBAHS	tetrabutylammonium bisulfate
TBDMS	*tert*-butyldimethylsilyl
Temp	temperature

tert	*tertiary*
TDA-1	tris[2-(2-methoxyethoxy)ethyl]amine
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin-layer chromatography
TMEDA	*N*, *N*, *N'*, *N'*-tetramethylethylenediamine
TMS	trimethylsilyl
UV	ultraviolet
wt%	weight percent

Epigraph

The wizards of the Unseen University on attempting to cure the God of Hangovers;

"Then the Dean repeated the mantra that has had such a marked effect on the progress of knowledge throughout the ages.

'Why don't we just mix up absolutely everything and see what happens?' he said.

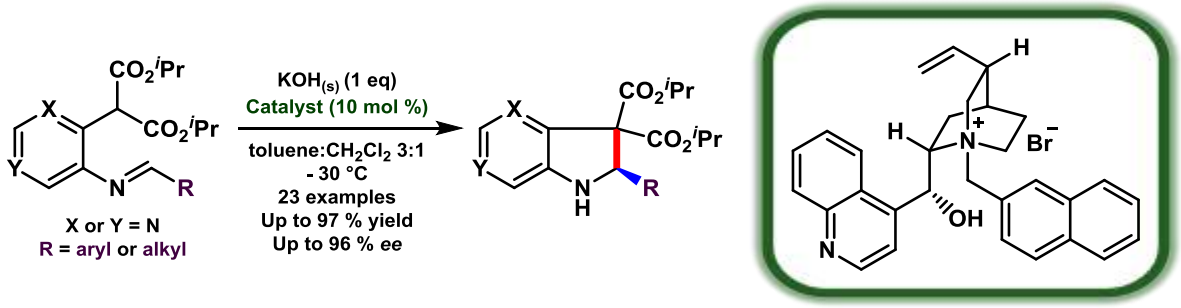
And Ridcully responded with the traditional response.

'It's got to be worth a try,' he said."

From "The Hogfather" by Sir Terry Pratchett.

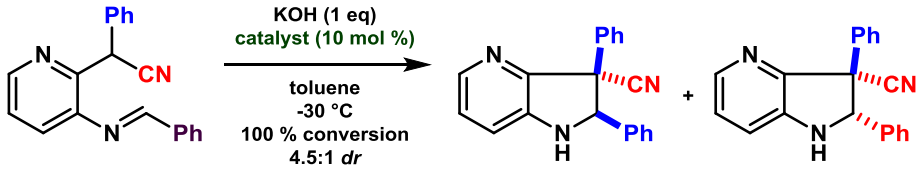
Abstract

The aim of this project was to utilize chiral cation-directed catalysis in the asymmetric synthesis of novel heterocycles. This goal was initially realized by the synthesis of azaindolines in high yields and enantioselectivities (Chapter 2 and Scheme 1).



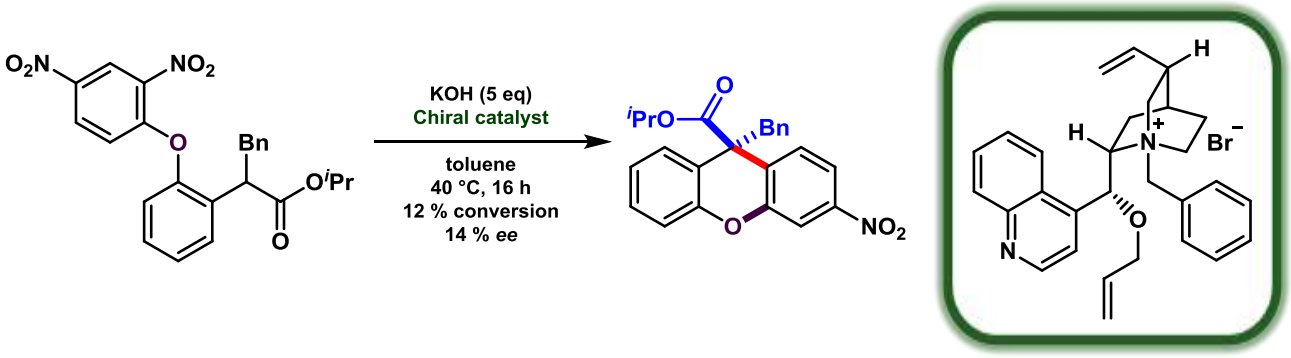
Scheme 1 – Chiral cation-directed cyclizations to form 4- and 6-azaindolines

Extension of this methodology to substrates bearing two stereogenic centres was successful, although control over both diasteroselectivity and enantiselectivity in this process was modest (Chapter 2 and Scheme 2).



Scheme 2 – Diastereoselective cyclization

Finally the synthesis of heterocycles utilizing cation-directed rearrangement processes was examined, with proof of concept obtained for a novel asymmetric cyclization to form xanthenes (Chapter 3 and Scheme 3).



Scheme 3 – Chiral cation-directed rearrangement to form xanthenes

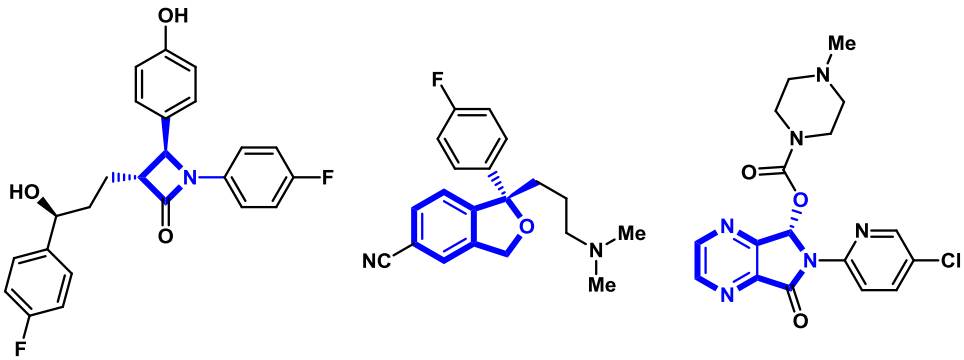
Asymmetric synthesis of heterocycles via cation-directed cyclizations and rearrangements

1. Introduction

1.1. Asymmetric synthesis of heterocycles

Heterocyclic compounds are defined by the IUPAC Gold Book as "cyclic compounds having as ring-members atoms of at least two different elements."[1] Heterocycles are an integral part of many biologically active molecules[2] and natural products, with the journal Heterocycles having collated from the literature a database of almost 60,000 natural products with heterocyclic units.[3] Heterocyclic compounds also find use as dyes[4] and as monomeric units in the synthesis of polymers.[5]

The asymmetric synthesis of heterocyclic compounds is of great importance, particularly in the pharmaceutical industry, as opposing enantiomers of a drug can have markedly different biological effects. Given the prevalence of chiral drugs containing heterocyclic units (Scheme 1.1), methods of synthesizing a single enantiomer of a given heterocyclic compound are an active area of research.

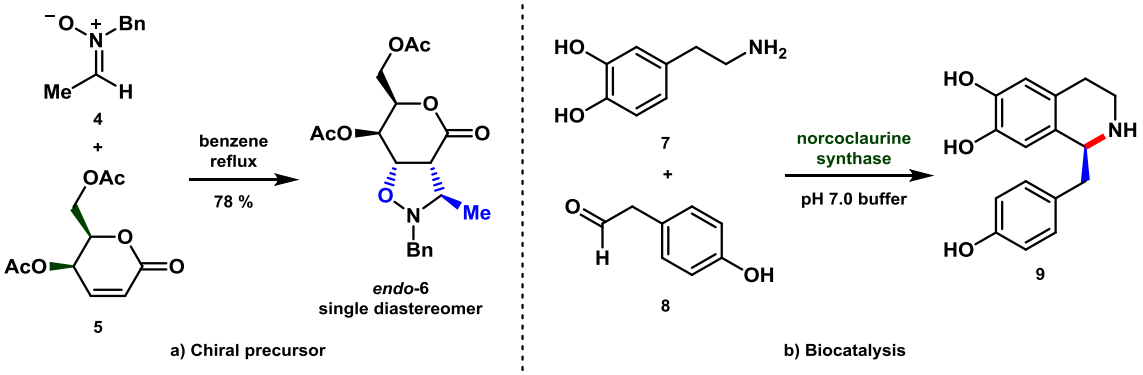


Scheme 1.1 – Drug molecules containing chiral heterocyclic units

Approaches towards the asymmetric synthesis of heterocycles include stereospecific reactions from chiral precursors, biocatalysis,[6,7] the use of chiral auxiliaries,[8] transition metal

catalysis,[9] and chiral Lewis acid catalysis.[10] Representative examples of each of these processes will now be discussed.

One method of obtaining enantiomerically enriched heterocycles is to synthesize the desired heterocycle from a substrate which already has the required stereogenic centre installed, either by established asymmetric methods or by utilizing naturally occurring chiral molecules as starting materials. An example of this approach is Chmielewski's diastereoselective 1,3-dipolar cycloaddition of nitrone **4** onto sugar enlactone **5** (Scheme 1.2 a).[11]

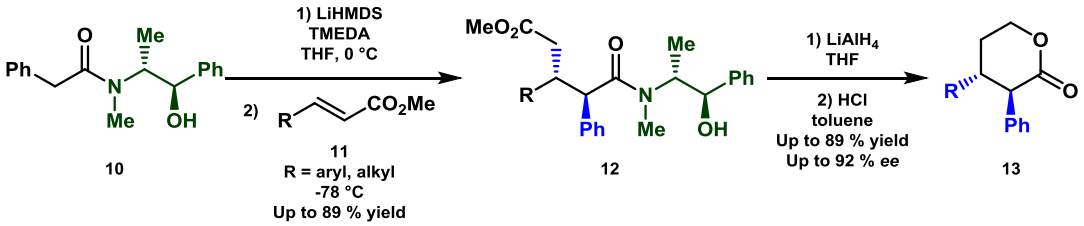


Scheme 1.2 – Methods for the asymmetric synthesis of heterocycles

Due to the ubiquity of heterocyclic systems in Nature, particularly in alkaloids, Nature has evolved enzymes for asymmetric processes which can direct the synthesis of enantiomerically pure heterocyclic building blocks.[7] For example, "Pictet-Spenglerases," such as norcoclaurine synthase, can catalyze the formation of dopamine derivative **9** in a process analogous to the Pictet-Spengler reaction. (Scheme 1.2 b).[12]

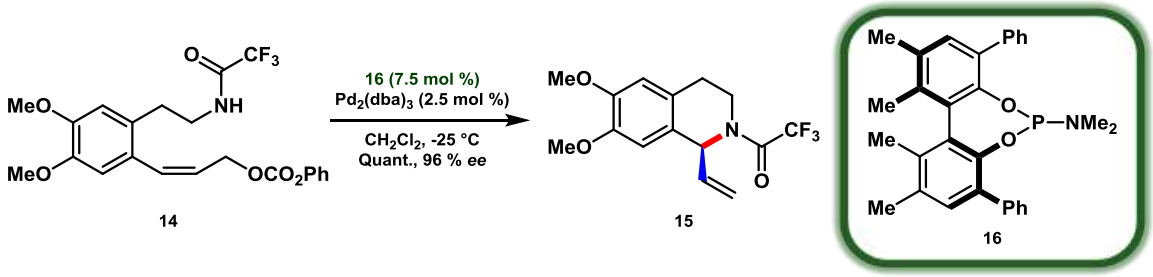
A further method developed for controlling the stereochemical outcome of reactions is the use of chiral auxiliaries. By introducing a chiral group onto an achiral precursor a reaction can be carried out diastereoselectively, affording enantiomerically enriched products on cleavage of the auxiliary. One common auxiliary is pseudoephedrine, which is particularly

effective in controlling the stereochemical outcome of Michael additions. Chemists from Merck developed a reaction where **10**, derived from pseudoephedrine and an acid chloride, undergoes 1,4-addition to form products such as **12**. Subsequent ester reduction followed by auixlliary cleavage with HCl provides access to lactones (Scheme 1.3).[13] Disadvantages of the auxiliary approach are that stoichiometric quantities of the auxiliary have to be used and that addition and cleavage of the auxiliary increase the step count of the synthesis.



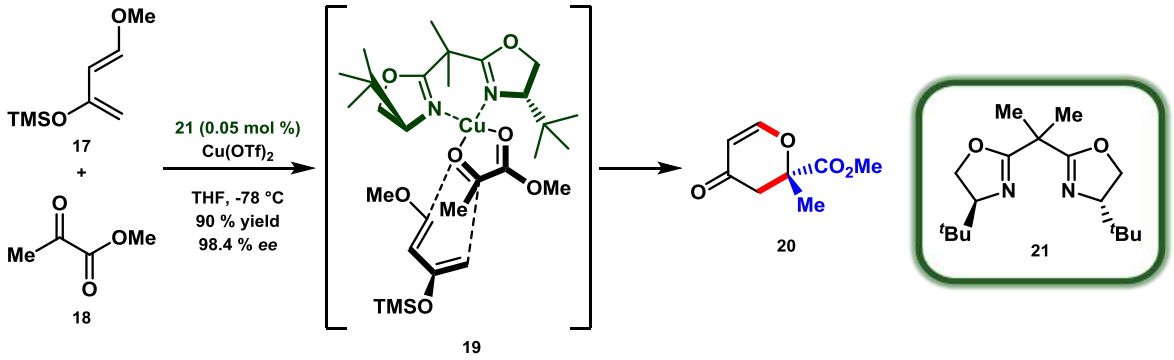
Scheme 1.3 – Auxiliary controlled asymmetric synthesis of heterocycles

Another approach is to employ a chiral non-racemic catalyst to impart stereocontrol on a reaction. This has the advantage of using only a sub-stoichiometric quantity of a chiral molecule to control the stereochemical outcome of the reaction. Two common variants of asymmetric catalysis are transition metal catalysis, and chiral Lewis acid catalysis, both of which employ a chiral ligand bound to the metal centre responsible for catalysis. A typical example of the transition metal-mediated approach is Ojima's palladium-catalyzed intramolecular allylic amination of allyl carbonate **14**, with the asymmetry originating from axially chiral phosphoramidite ligand **16** (Scheme 1.4).[14]



Scheme 1.4 – Transition metal-catalyzed asymmetric synthesis of heterocycles controlled by a chiral ligand

A representative class of chiral ligands employed in chiral Lewis acid catalysis are the C_2-symmetric bis(oxazoline) (BOX) ligands, which in conjunction with a suitable metal such as copper or zinc, are wide-ranging and highly stereoselective asymmetric catalysts. Indeed the hetero-Diels-Alder reaction of activated ketones such as **18** with Danishefsky's diene **17** has been shown by Jørgensen to proceed with levels of enantioselectivity and catalyst loadings comparable to chemoenzymatic reactions.[15] After Lewis acid activation of the dienophile **18** the facial selectivity of the approach of the diene is controlled by the bulky *tert*-butyl group of BOX-ligand **21**, which blocks approach from the *Re* face resulting in the formation of the *S* isomer of Diels-Alder product **20** in excellent *ee* (Scheme 1.5).



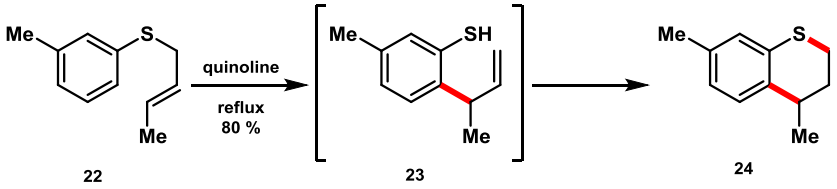
Scheme 1.5 – Lewis acid-catalyzed asymmetric synthesis of heterocycles controlled by a chiral ligand

1.2. Asymmetric rearrangements

Rearrangement reactions are a powerful tool in organic chemistry as they have the potential to allow the formation of complex products, which could be challenging to synthesize directly, from simple and readily accessible precursors.[16]

Rearrangements which directly form heterocyclic compounds are somewhat rare and typically arise when the product of the rearrangement is sufficiently reactive to partake in an intramolecular cyclization process. An example of this, disclosed by Kwart and Evans, is

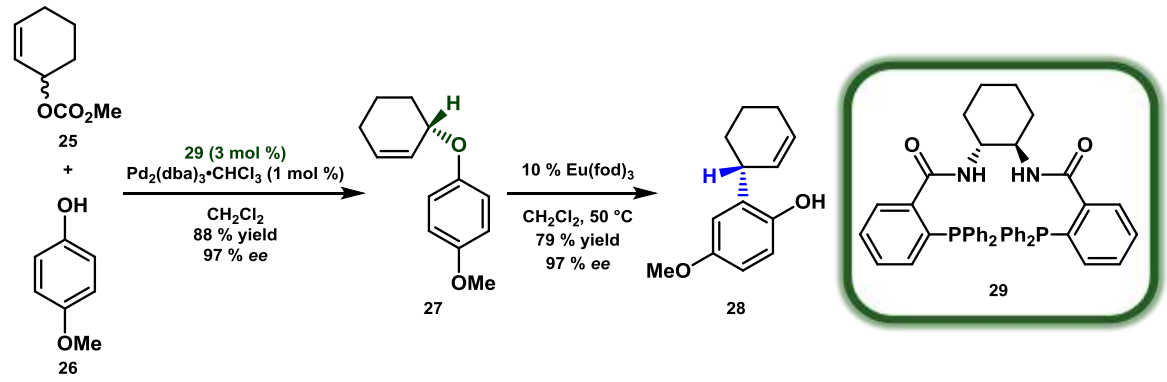
the formation of thiachroman **24** *via* a thio-Claisen rearrangement of **22** and subsequent 6-*endo*-*trig* cyclization of reactive intermediate **23** (Scheme 1.6).[17]



Scheme 1.6 – Synthesis of thiachroman 24 *via* a thio-Claisen rearrangement

Asymmetric rearrangements have been well studied,[18,19] particularly [3,3]-sigmatropic rearrangements such as the Claisen and Cope rearrangements.[20] As in the case of the synthesis of heterocyles, methods of carrying out rearrangements asymmetrically have developed in chronological order from stereospecific reactions utilizing chiral precursors, to chiral auxiliaries, and then to transition metal and Lewis acid catalysis. Due to the scarcity of heterocycle formations *via* rearrangements, the representative examples in the section will not focus on the synthesis of heterocyclic compounds.

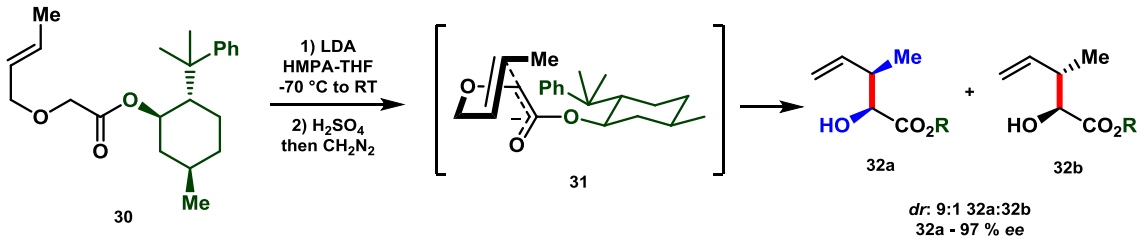
An example of the use of a chiral precursor is Trost and Toste's Lewis acid catalyzed Claisen rearrangement of enantiomerically pure aryl ether **27**, which was generated *via* palladium catalyzed asymmetric installation of phenol **26** using ligand **29** (Scheme 1.7).[21]



Scheme 1.7 – Claisen rearrangement from a chiral precursor

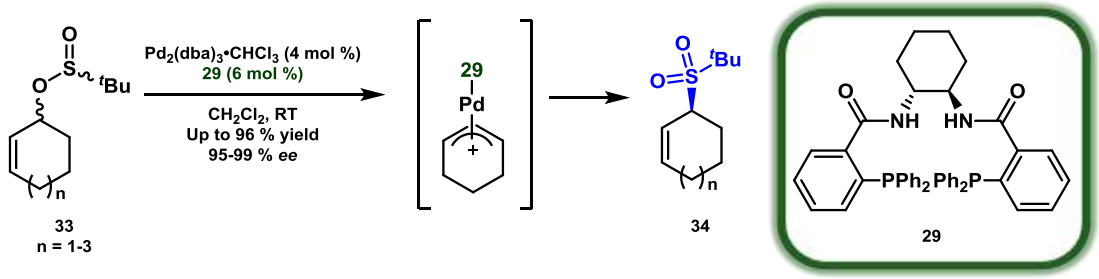
Chirality transfer to the rearranged product **28** is very efficient, with several examples showing little or no racemization.

The use of chiral auxiliaries is exemplified by substrate **30**, which bears a menthyl ester as an auxiliary. Nakai has demonstrated that upon deprotonation with LDA, the ester undergoes a diastereoselective [2,3]-Wittig rearrangement which favours the *syn* diastereomer (Scheme 1.8).[22] The authors explain the stereochemical outcome by reaction through transition state **31**, which minimises steric clashes between the menthol aromatic group and the allylic ether. The auxiliary can be cleaved with acid followed by addition of diazomethane to yield methyl esters.[23]



Scheme 1.8 – Auxiliary-controlled [2-3]-Wittig rearrangement

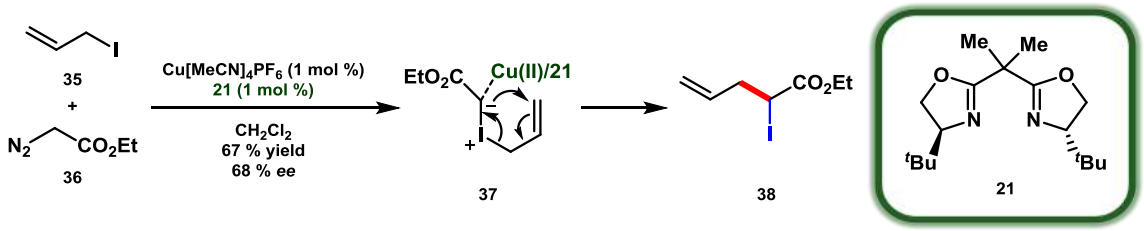
Gais took advantage of transition metal catalysis in the development of a formal [1,3]-rearrangement of allylic sulfinates **33** to form optically pure sulfones **34** (Scheme 1.9).[24]



Scheme 1.9 – Transition metal-catalyzed asymmetric [1,3] rearrangement controlled by a chiral ligand

The reaction proceeds *via* formation of a π-allyl complex, with the sulfinate group leaving. This sulfinate then acts as a nucleophile, attacking the π-allyl complex through sulfur. In the presence of chiral phosphine ligand **29** this process yields sulfones in excellent *ee*.

Lewis acid/chiral BOX-ligand complexes are also effective asymmetric catalysts of rearrangement processes.[10a,b] Doyle has shown that iodonium ylide **37** generated from allyl iodide (**35**) and ethyl diazoacetate (**36**) undergoes a [2,3]-sigmatropic rearrangement to form α-iodo esters **38** (Scheme 1.10). When chiral BOX-ligand **21** is utilized to effect this transformation, enantioselectivity of 68 % *ee* is observed.[25]



Scheme 1.10 – Lewis acid-catalyzed asymmetric [2,3]-sigmatropic rearrangement controlled by a chiral ligand

1.3. Asymmetric organocatalytic methods

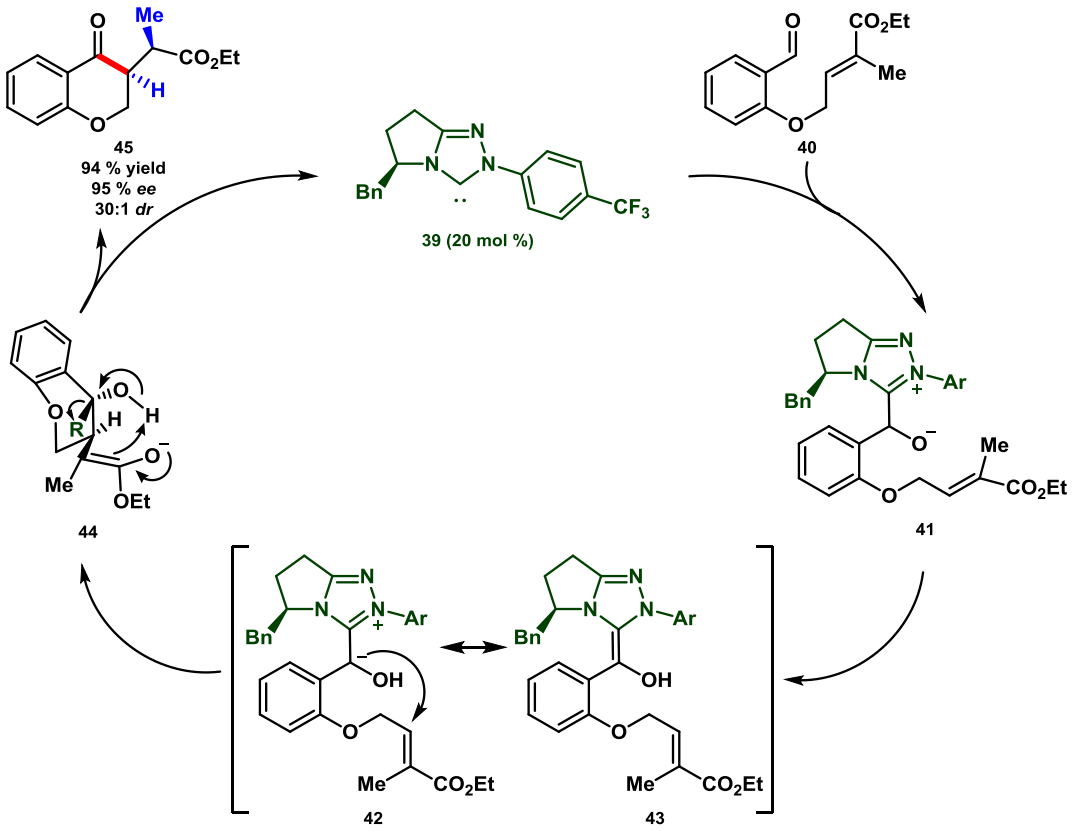
One method of introducing asymmetry in reactions which has not yet been introduced is asymmetric organocatalysis. This field emerged subsequently to biocatalysis and transition metal catalysis, but has seen a massive expansion over the last two decades with a plethora of asymmetric organocatalytic methods being published.[18,26,27] Organocatalysis complements biocatalysis and transition metal catalysis, and has resulted in the development of procedurally simple reactions with environmentally benign catalysts, which can produce chiral compounds in high degrees of enantiopurity. This has led to the increasing utilization of organocatalysis by industry.[28] Organocatalytic methods can be split broadly into two areas; covalent catalysis and non-covalent catalysis. Covalent catalysis utilizes Lewis bases (such as carbenes[29] and chiral amines[30]), while non-covalent catalysis

includes Brønsted acids (either through hydrogen-bonding[31] or anion-recognition[32]), Brønsted bases[33] and chiral ion-pairing catalysis.[34] Some bifunctional catalysts incorporate both covalent and non-covalent modes of activation.[35] Examples of each of these modes of activation will be discussed, with a focus on the synthesis of heterocyclic compounds[27] and rearrangement processes.[18]

1.3.1. Covalent asymmetric organocatalysis

Covalent organocatalysis is an effective method of introducing asymmetry because the formation of a covalent bond between the catalyst and substrate is a reliable method of creating a chiral environment close to the reactive centre of the substrate.

Lewis bases have seen extensive use as covalent organocatalysts. One important class of Lewis basic organocatalysts are the *N*-heterocyclic carbenes (NHCs).[29] NHCs contain a highly nucleophilic lone pair which can participate in the nucleophilic attack of carbonyl groups. The resultant Breslow intermediate is highly amenable to 1,4-addition and if the NHC is chiral, it can influence the stereochemical outcome of the addition. An example of this approach applied to the synthesis of heterocycles is the catalytic asymmetric intramolecular Stetter reaction developed by Rovis (Scheme 1.11).[36] Initial highly enantioselective intramolecular 1,4-addition of Breslow intermediate **42**, generated from aldehyde **40** and chiral NHC **39** results in the formation of enolate intermediate **44**. The authors propose that this intermediate then undergoes an intramolecular proton-transfer which must occur from the more hindered face of the enolate. This results in the observed diastereomer of oxochroman product **45** and regenerates the chiral NHC.

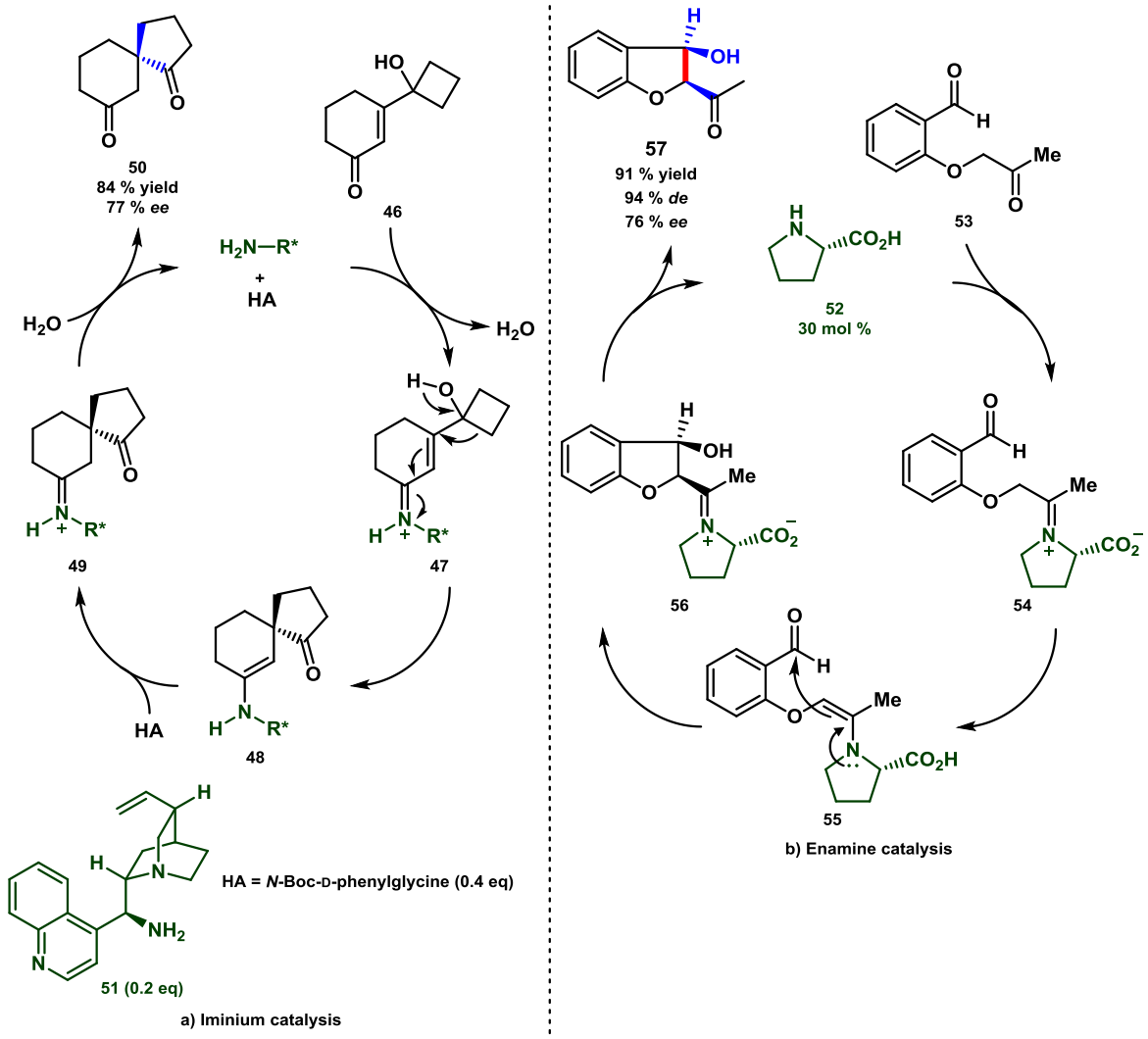


Scheme 1.11 – Carbene catalysis – asymmetric intramolecular Stetter reaction

Two closely related forms of Lewis base asymmetric organocatalysis are iminium and enamine catalysis.[30,37,38] Both of these approaches involve nucleophilic addition of a Lewis basic chiral amine to a carbonyl compound. In iminium catalysis the resultant iminium ion is attacked by a nucleophile (**47**, Scheme 1.12 a); whereas in enamine catalysis the iminium ion tautomerizes to an enamine which can then itself perform a nucleophilic attack, assisted by the nitrogen lone pair (**55**, Scheme 1.12 b).

Iminium catalysis has been applied by Tu to perform the first catalytic enantioselective vinylogous α-ketol rearrangement using *cinchona*-derived primary amine **51** as the organocatalyst. (Scheme 1.12 a).[39] The process involves a 1,2-carbon migration to construct the all-carbon quaternary stereocentre of spiroketone **50** in good *ee* and high yield.

One particularly prevalent example of enamine catalysis is the proline-catalyzed aldol reaction known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction. Enders utilized an intramolecular variant of this process in the synthesis of heterocycles, with aldol reaction of **53** yielding dihydrobenzafuranols **57** with good enantioselectivity and as essentially a single diastereomer (Scheme 1.12 b).[40] The relatively high catalyst loading of 30 % is fairly typical for this type of reaction and indeed is one issue with covalent organocatalysis as a whole, with catalysts loadings of 10-30 % often required. This is in contrast to transition metal catalysis where catalyst loadings are often significantly lower.

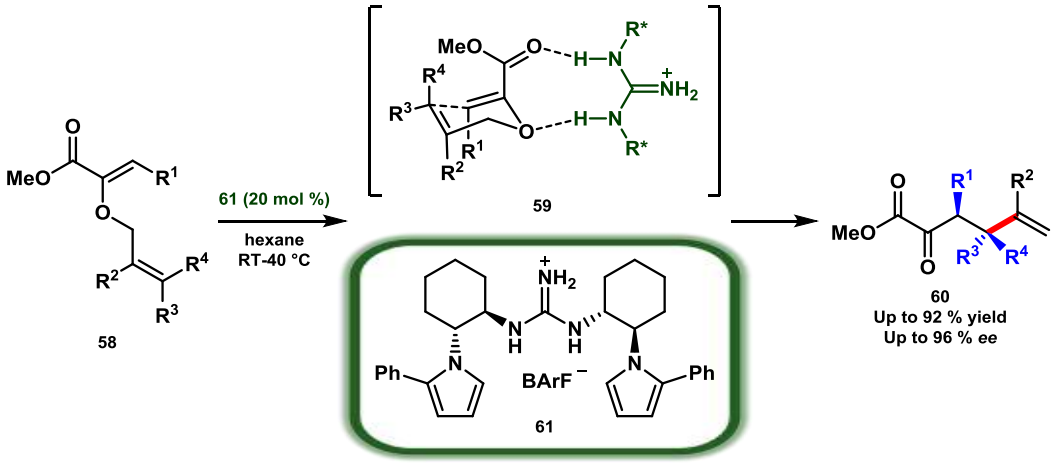


Scheme 1.12 – Iminium and enamine catalysis

1.3.2. Non-covalent asymmetric organocatalysis

As implied in its name, non-covalent catalysis does not rely on the creation of a chiral environment through formation of a covalent bond. Instead enantioselective reactions are achieved through non-covalent interactions between the catalyst and the substrate, such as ion-pairing, hydrogen-bonding, anion-binding, and π-stacking interactions. Such interactions also often have a crucial role in processes which involve covalent organocatalysis.

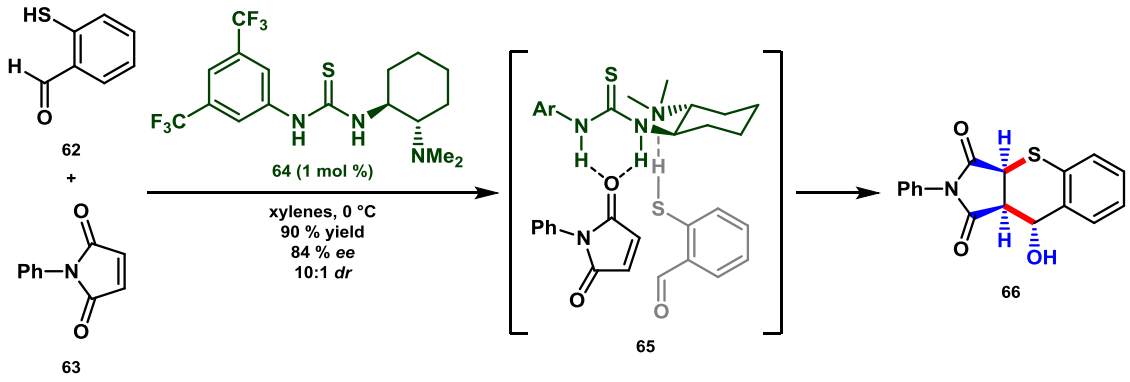
Brønsted acids are commonly used in organocatalytic reactions as either hydrogen-bond donors[31] or anion-binders (this will be discussed in the subsequent section). Typical hydrogen-bond donors include ureas, thioureas and guanadinium salts. Jacobsen developed the first organocatalytic asymmetric Claisen rearrangement by employing a chiral guanadinium catalyst **61** as a hydrogen-bond donor, with the catalyst undergoing two-point binding to the carbonyl and ether groups of substrate **58** and creating a chiral environment through which high levels of enantioinduction were obtained (Scheme 1.13).[41]



Scheme 1.13 – H-bonding organocatalysis in an asymmetric Claisen rearrangement

Brønsted bases alone are not particularly effective catalysts due to the non-directionality of their interactions, however when coupled with a Brønsted acid to form a bifunctional catalyst they become useful organocatalysts.[33] Bifunctional catalysts are becoming increasingly prevalent in organocatalysis due to their ability to activate both nucleophilic

and electrophilic components of a reaction, often enabling them to bring the reacting partners into close proximity to each other.[35] One frequently exploited type of bifunctional catalyst scaffold is a Brønsted basic chiral amine bearing a thiourea moiety which can act as a H-bond donor. Takemoto's catalyst (**64**) exemplifies this type of structure and has been implemented by Wang in domino Michael-Aldol reactions to afford benzothiopyran **66**.[42] It is proposed that the Brønsted base binds to thiol **62** and the thiourea to the carbonyl of maleimide **63**, ensuring nucleophilic attack occurs from one face, resulting in the formation of **66** in high *ee* and excellent *dr* (Scheme 1.14).



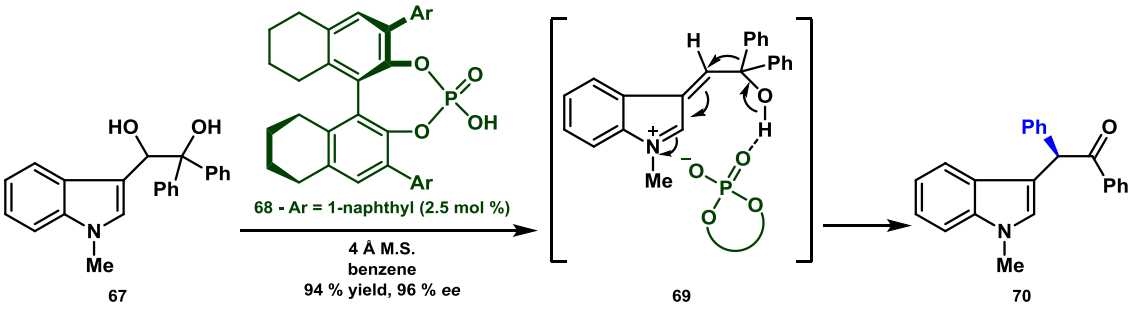
Scheme 1.14 – Brønsted base/H-bonding bifunctional organocatalyst

1.4. Chiral ion-pairing catalysis

One asymmetric organocatalytic method not yet introduced is the use of chiral ion pairs to impart enantioselectivity.[34] This type of catalysis can utilize both chiral anions and chiral cations. In both cases a further division can be made between counterion-directed catalysis, which employs catalysts which are charged and themselves act as the chiral counterion, and counterion-binding catalysis, where the asymmetric catalyst is uncharged but becomes intimately associated with an existing ion-pair by binding non-covalently to one of the ions. These concepts can also be united in various combinations by bifunctional catalysts.[43] These

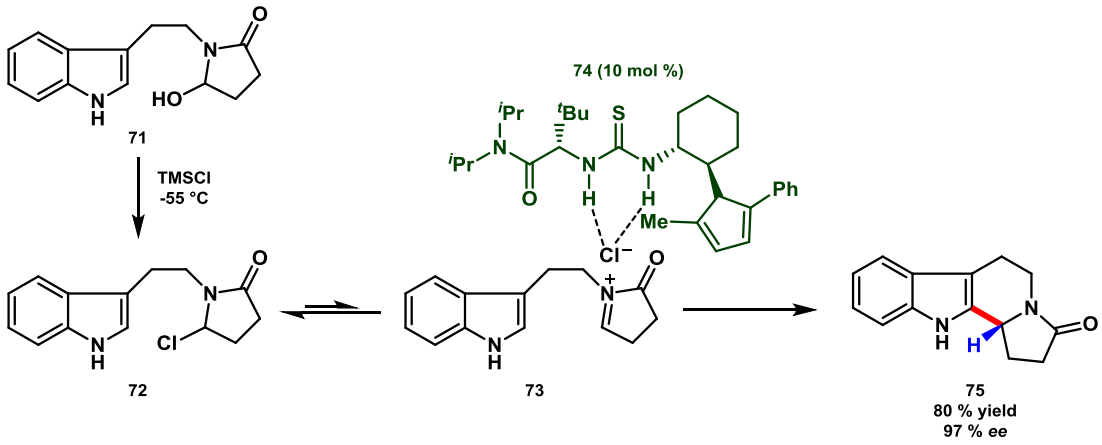
methods of catalysis will now be described, again with a focus on the synthesis of heterocyclic compounds and on rearrangement processes.

Chiral counteranion asymmetric organocatalysis in both counterion -directed and -binding forms is a relatively recent development but has been the focus of much interest in recent years.[34,43,44] An example of anion-directed catalysis is Antilla's use of axially chiral phosphoric acid catalyst **68** to realize the first enantioselective pinacol rearrangement.[45] After dehydration of **67** to form iminium cation **69** it is proposed that the phosphoric acid anion forms a tight ion-pair with the cation and also interacts through hydrogen bonding with the remaining hydroxyl group. The chiral environment this creates allows the rearrangement to proceed in a stereoselective fashion to form indole **70** in excellent yield and *ee* (Scheme 1.15).



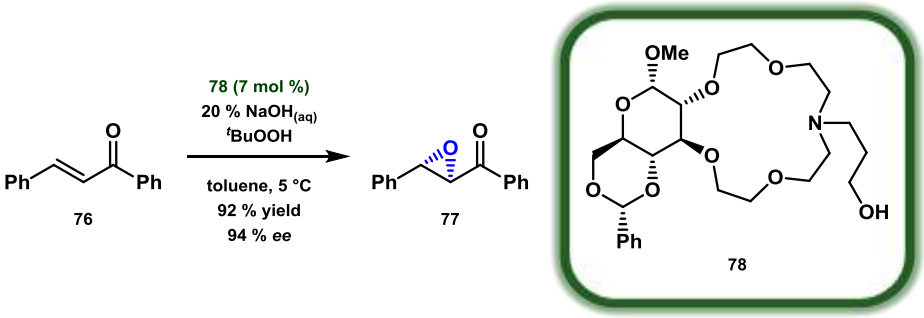
Scheme 1.15 – Chiral anion-directed catalysis

Examples of anion-binding catalysis are rarer. One elegant demonstration is an asymmetric Pictet-Spengler-like cyclization of hydroxylactam **71** disclosed by Jacobsen (Scheme 1.16).[46] The reaction proceeds *via* an S_N1-type process accelerated by thiourea catalyst **74**, which acts as a receptor for the departing chloride anion. Thus, the chloride counterion now exists in a chiral environment and can impart asymmetry onto the cyclization process, with indole **75** formed in 97 % *ee*. This mechanistic proposal is supported by the observation that enantioselectivities diminished as the size of halide anion utilized was increased.



Scheme 1.16 – Chiral anion-binding catalysis

Chiral countercation asymmetric organocatalysis is well established, particularly the field of asymmetric phase-transfer catalysis (PTC).[47] PTC can occur *via* either cation-directed catalysis, in the case of ammonium or phosphonium salts, or cation-binding catalysis, in the case of crown ethers and lipophilic phosphates. Cation-directed catalysis will be examined in more detail in the following section. Cation-binding catalysis is less commonly utilized, perhaps due to the challenges of creating a chiral environment around the reactive substrate anion by binding its associated cation. While this is also a problem with anion-binding catalysis, it has perhaps benefited from more attention as the required Brønsted acid catalysts are somewhat more facile to synthesize. Nevertheless, highly enantioselective examples of asymmetric processes catalyzed by chiral crown ethers do exist, for example chalcone (**76**) can be epoxidised in high yield and enantiomeric excess by *tert*-butyl hydroperoxide using an α-methylglucopyranoside derived crown ether **78**, developed by Bakó, as a phase-transfer catalyst (Scheme 1.17).[48]

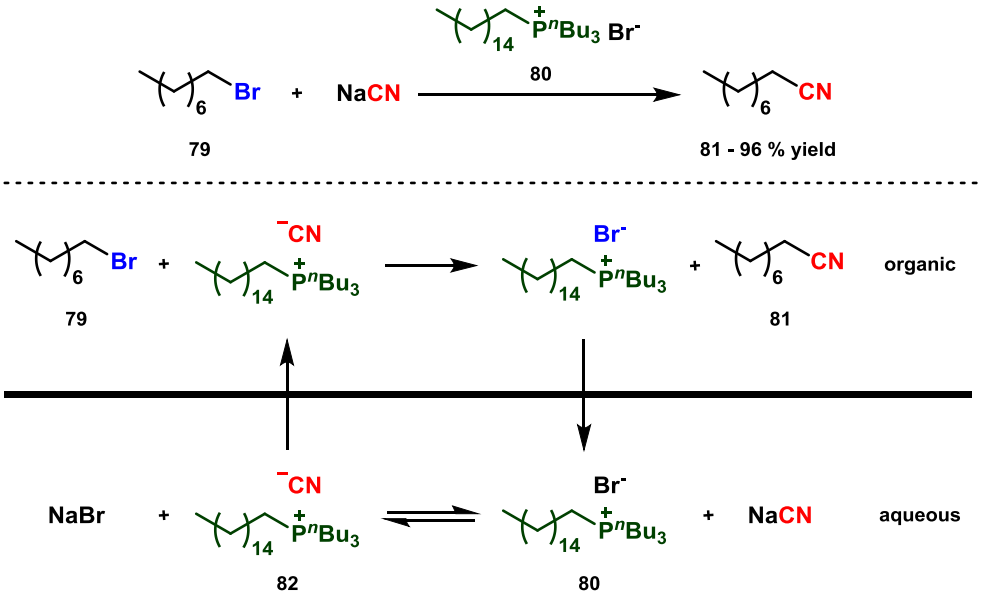


Scheme 1.17 – Chiral cation-binding catalysis by a crown ether

1.5. Chiral cation-directed catalysis utilizing phase-transfer catalysts

1.5.1. Early developments

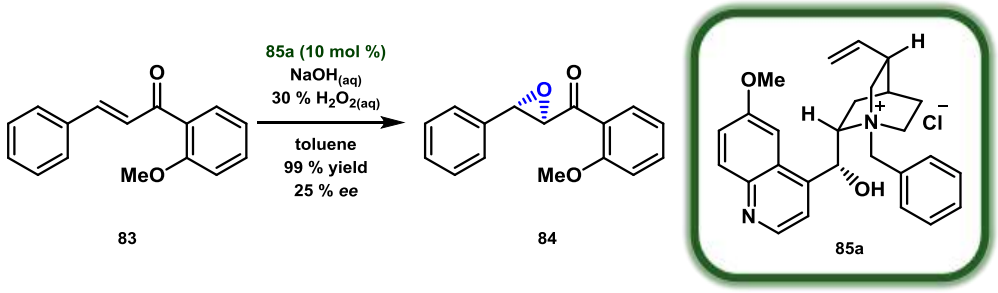
Phase-transfer catalysis (PTC) was first brought to the attention of the synthetic community in 1971 by Starks, who employed quaternary ammonium and phosphonium salts for the alkylation of ^{n}octyl halides (Scheme 1.18).[49]



Scheme 1.18 – First report of PTC and proposed extractive mechanism

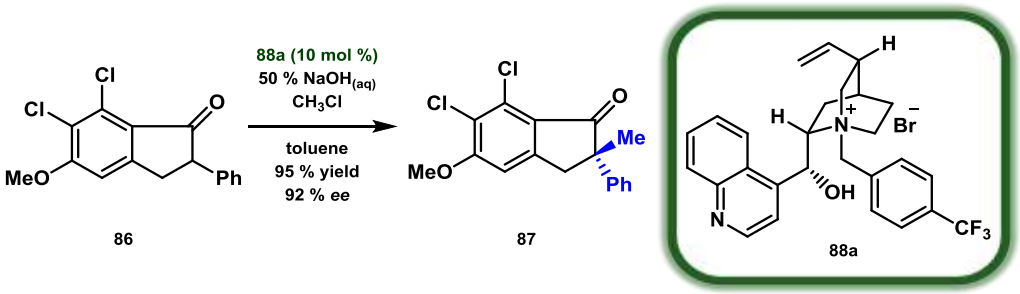
Since this initial discovery and important developments by Mąkozsa,[50] PTC has become a well-established process due to the use of benign catalysts and amenability to large-scale processes. However, it was some time before a process in which PTC could be utilized to

control the stereochemical outcome of a reaction was developed.[47] Advances in this area were initiated by Wynberg, who was the first to recognize the potential of quaternary ammonium salts derived from the naturally occurring, optically pure *cinchona* alkaloids in imparting asymmetry. In 1976 he reported the use of *N*-benzylquininium chloride (**85a**) as a phase-transfer catalyst in the asymmetric epoxidation of chalcones, resulting in the formation of epoxides in high chemical yields but modest enantioselectivities (Scheme 1.19).[51]



Scheme 1.19 – Wynberg's asymmetric phase-transfer-catalyzed epoxidation

The first highly enantioselective phase-transfer-catalyzed reaction was pioneered by a Merck research group in 1984, who performed an alkylation of indanone **86**, catalyzed by chiral *cinchona*-derived catalyst **88a**, in excellent yield and 92 % *ee* (Scheme 1.20).[52]

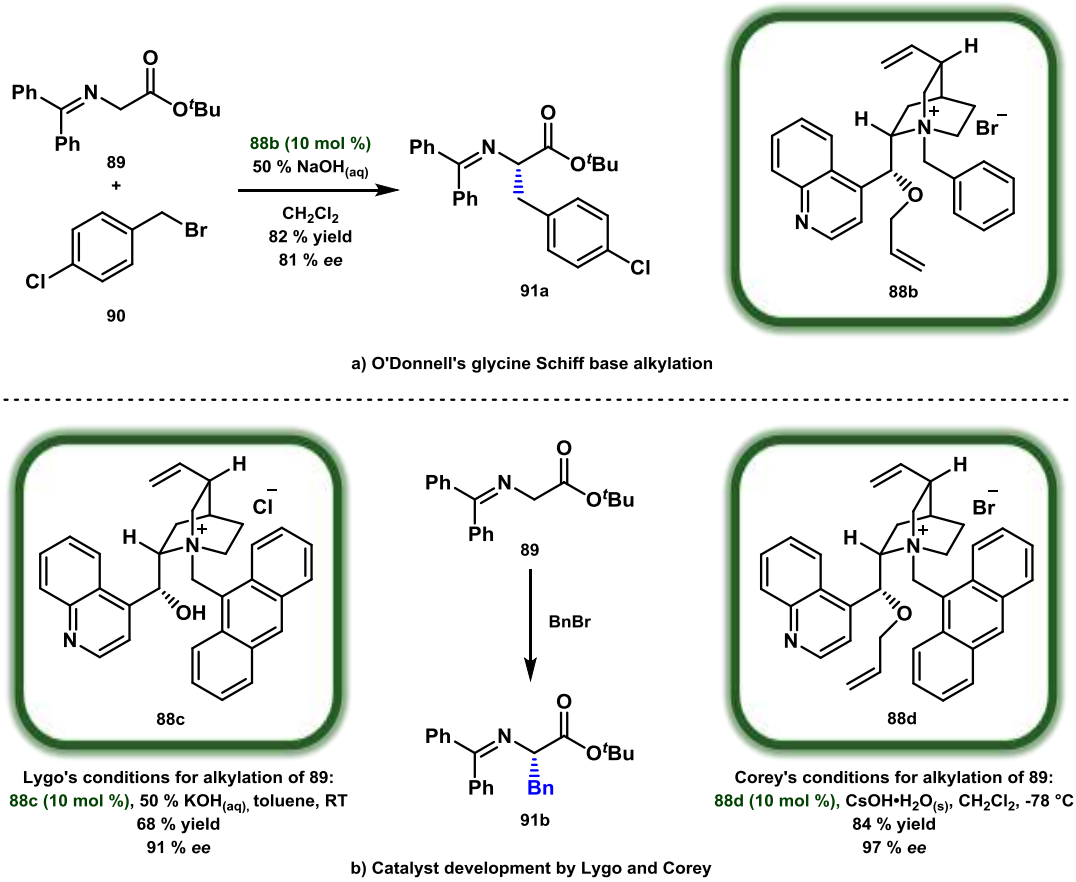


Scheme 1.20 – Merck's asymmetric phase-transfer catalyzed alkylation

The authors proposed an ion-pairing model to account for the stereochemical outcome in which π-stacking interactions also played an important role, which was supported by the

fact that altering the substituents on the quaternizing group of the catalyst had a profound effect on the enantiomeric excess.[53]

Another important development was the introduction of phase-transfer catalyzed glycine-derived Schiff base alkylations by O'Donnell in 1989. While his initial report of 62 % *ee* utilizing *N*-benzylcinchonidinium chloride was promising, the most important advance was the introduction of *O*-allylated catalyst **88b**, which improved selectivity to 81 % *ee* (Scheme 1.21 a).[54] This was further improved independently in 1997 by Lygo[55] and Corey,[56] who introduced catalysts with bulky *N*-anthracenyl groups featuring either a free OH (**88c)** or *O*-allyl group (**88d)**. Both of these catalysts enhanced the enantioselectivity of the reaction (Scheme 1.21 b).

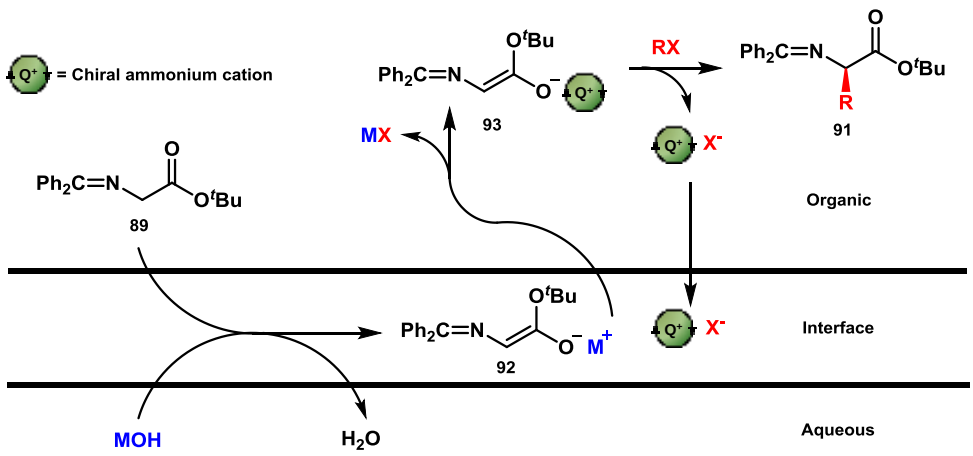


Scheme 1.21 – Development of phase-transfer catalyzed asymmetric alkylations of glycine Schiff base 89

To this day this transformation remains an important benchmark for the development of new phase-transfer catalysts.[47c,d,e]

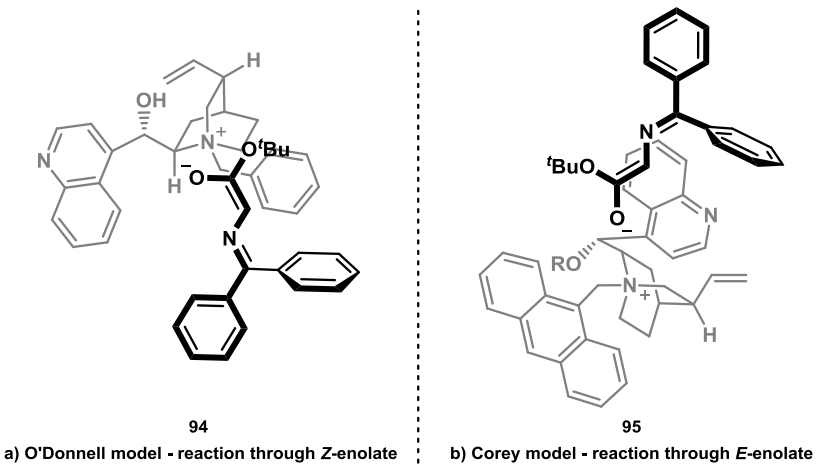
1.5.2. Mechanism

To understand why PTC can affect the stereochemical outcome of a reaction the mechanism of phase-transfer catalyzed processes must be considered. Two mechanisms for PTC have been proposed; the Starks extractive mechanism,[49] where the catalyst escorts either the reactant anion or the hydroxide required to generate it into the organic phase (analogous to Scheme 1.18), and the Mąkozsa interfacial mechanism.[50] The majority of hydroxide-initiated asymmetric phase-transfer processes proceed *via* the interfacial mechanism,[47b,57] which can be illustrated using the O'Donnell alkylation as an example (Scheme 1.22). Deprotonation of Schiff base **89** occurs at the interface between the aqueous and organic layers to form metal-anion pair **92**. This undergoes cation-exchange with the chiral phase-transfer catalyst $\mathbf{Q^+}$ at the interface and the resultant anion/chiral cation pair **93** is transferred into the organic layer. This tight ion-pair then undergoes alkylation with the required electrophile, with the chiral environment created by chiral cation $\mathbf{Q^+}$ controlling the stereochemical outcome of the reaction.



Scheme 1.22 – Asymmetric phase-transfer catalysis *via* the interfacial mechanism

The stereochemical course of the O'Donnell alkylation using *cinchona* alkaloids has been well studied. The exact nature of the binding is dependent on the catalyst stereochemistry and substitution as can be seen by contrasting models proposed by O'Donnell[58] and Corey[56] for cinchonine- (Scheme 1.23 a) and cinchonidine-derived catalysts (Scheme 1.23 b), with the former proceeding through the *Z*-enolate and the latter through the *E*-enolate. However, in both cases the most important factor is the tight ion pair formed between the reactive enolate anion and the ammonium catalyst; which binds to one face and leads to alkylation occurring from the other face of the enolate. Other interactions, such as π-stacking,[53] van der Waals' forces,[56] and [N^+-C-H···O] hydrogen bonding,[59] can also contribute to the formation of the preferred transition state.



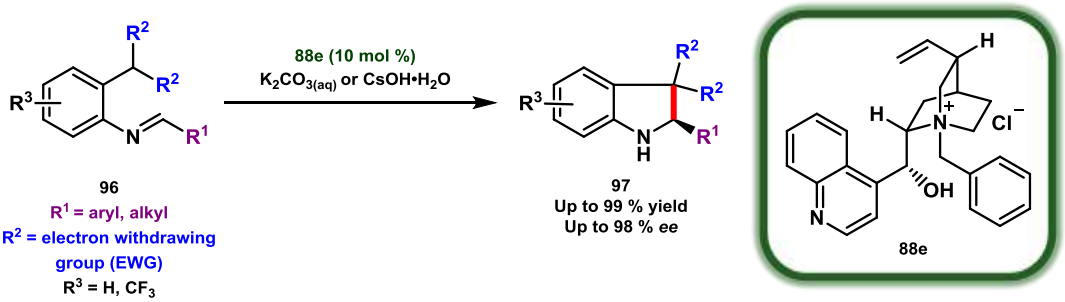
Scheme 1.23 – Stereochemical models for the glycine-Schiff base alkylation

Since these initial advances the same principles have been applied to a vast array of synthetic transformations, which have been well reviewed in the literature.[47]

1.6. Aims of the project

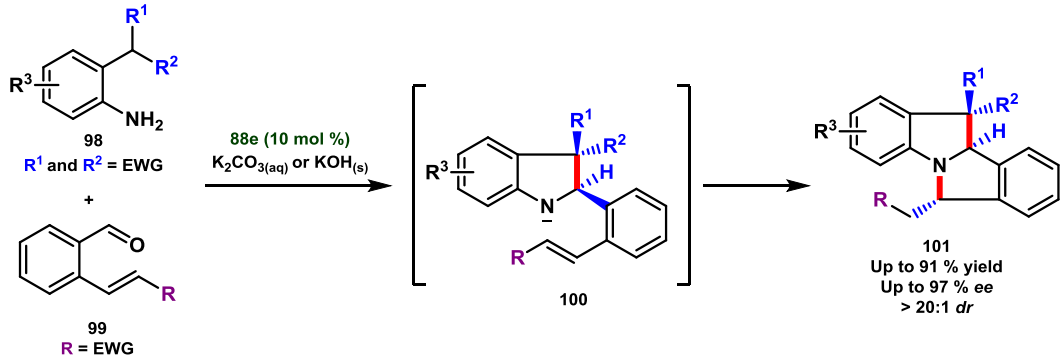
1.6.1. Previous work in the Smith group

One area of research in the Smith group is the application of cation-directed asymmetric catalysis to new reaction manifolds. Reactions developed by our group include a phase-transfer catalyzed 6π-electrocyclization process to form indolines **97** in high yields and enantioselectivities (Scheme 1.24).[60] This process, including mechanistic considerations and stereochemical outcome, will be discussed in more detail later in this thesis (Chapter 2.2).



Scheme 1.24 – Chiral-cation directed electrocyclization to form indolines

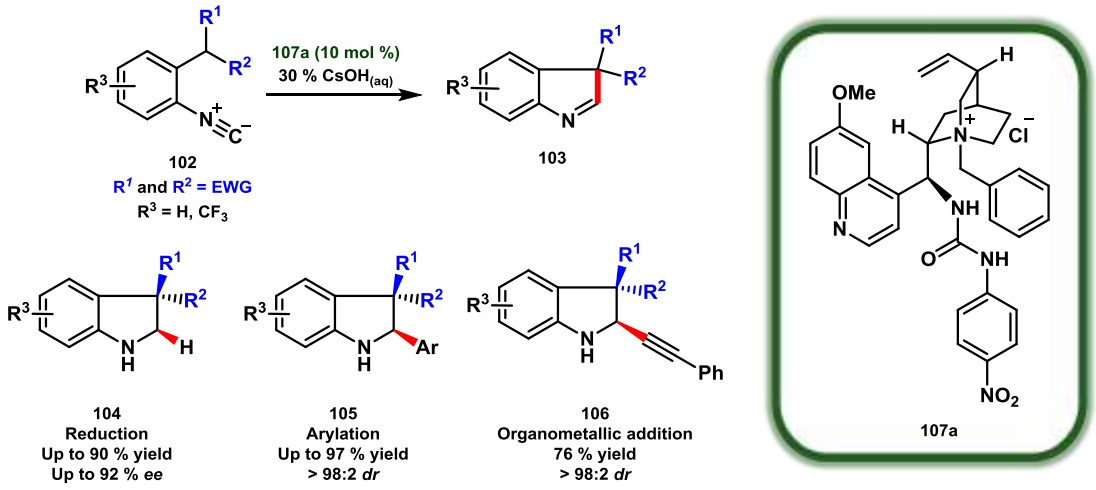
This methodology has been extended to encompass a cascade process by carrying out the reaction with an imine bearing a pendant 1,4-acceptor (Scheme 1.25).[61]



Scheme 1.25 – Cation-directed electrocyclization/1,4-addition cascade

After formation of the initial indoline product the resultant nitrogen anion **100** acts as a nucleophile in a conjugate addition process to form indoline **101**, which contains two new rings and three new stereocentres. This process proceeds with excellent diasteo- and enantio-control.

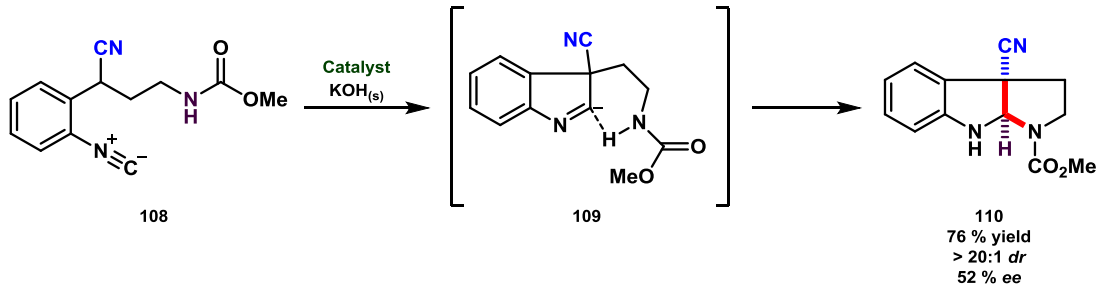
Chiral cations are also effective in the asymmetric catalysis of intramolecular nucleophilic additions to isocyanides.[62] Bifunctional phase-transfer catalysts, which also contain Brønsted acid functionality to activate the isocyanide, can catalyze an asymmetric 5-*endo*-dig cyclization of carbanions onto isocyanides such as **102** to form enantiomerically enriched indolenines **103** (Scheme 1.26).[62] The internal imine can then be reduced to form indolines **104** or further elaborated to substituted indolines **105** and **106** as single diastereomers, with no erosion of *ee*.



Scheme 1.26 – Isocyanide cyclization catalyzed by a bifunctional phase-transfer catalyst

As with the indoline synthesis this methodology can be extended to cascade processes. For example, after cyclization of isocyanide **108** the resultant indoline **109** can be trapped by a pendant carbamate to yield pyrolloindoline **110** as a single diastereomer, with modest

degrees of enantiocontrol (Scheme 1.27).[63] Work on improving the enantioselectivity of this reaction is currently ongoing in our group.



108 109 110
76 % yield
> 20:1 *dr*
52 % *ee*

Scheme 1.27 – Cascade reaction to form pyrolloindoline 110

1.6.2. Project blueprint

We envisaged that the cation-directed electocyclization process could be utilized to synthesize potentially biologically interesting fragments by introducing nitrogen atoms into the aromatic backbone of the substrate. This may provide access to densely functionalized and enantioenriched analogues of the isomeric family of azaindolines, which show promise as bioisosteres of indoline.

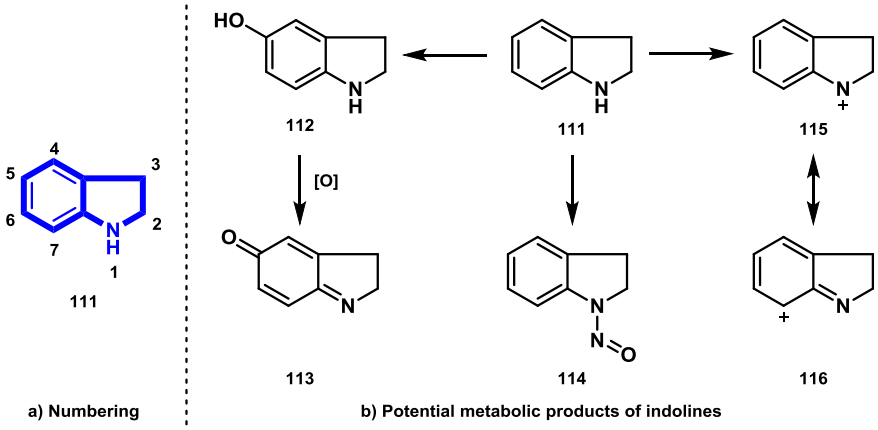
Furthermore, we postulated that chiral cation-directed catalysis could also be applied in rearrangement reactions where the reaction proceeds *via* an anionic intermediate. In particular the development of the first asymmetric Truce-Smiles rearrangement may be achievable utilizing this approach.

2. Asymmetric synthesis of azaindolines *via* cation-directed cyclization

2.1. Azaindoline background

2.1.1. Structure and properties

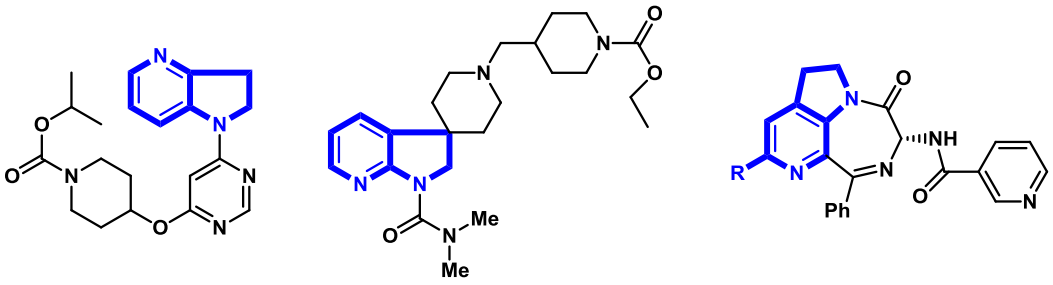
Azaindolines are analogues of indolines which contain a nitrogen atom within the aromatic ring. It has been proposed by medicinal chemists from Pfizer that azaindolines may find use as bioisosteres of indoline.[64] Indoline (**111**) is a derivative of aniline, a structural motif known to be responsible for adverse reactions to drugs due to metabolic formation of reactive intermediates. For example, hydroxylation of **111** can form highly reactive iminoquinone **113**. Oxidation can form reactive nitrenium ion **115**. Nitrosation of anilines to produce potentially carcinogenic nitrosoamines is also known.[65]



Scheme 2.1 – Numbering of indoline scaffold and potential metabolites of indoline

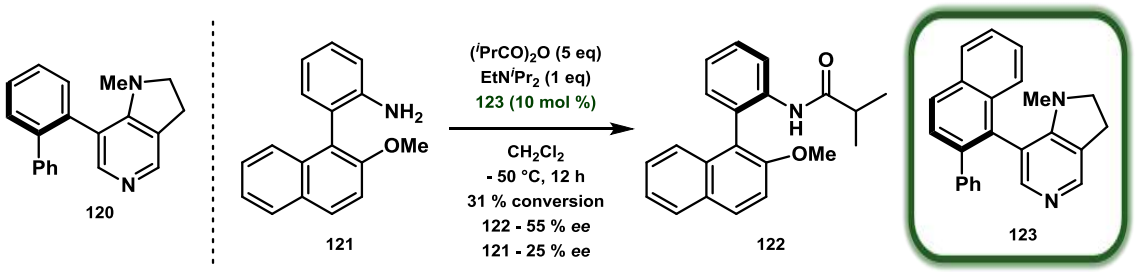
Azaindolines can be found in several bioactive molecules in the literature (Scheme 2.2),[66] though direct comparisons between indoline and azaindoline derivatives in terms of both activity and metabolic fate are rare.[66b] Despite this caveat, the development of routes

towards highly functionalized azaindolines, which may serve as building blocks in the synthesis of safer drug molecules, is a worthwhile endeavour.



Scheme 2.2 – Selected bioactive azaindolines

Azaindolines have also been shown to act as chiral equivalents of DMAP. 5-Azaindoline derivative **120**, developed by Spivey, exists as a mixture of atropisomers due to restricted rotation around the aryl-aryl bond.[67] This compound was an important stepping stone on the path to develop atropisomeric chiral DMAP equivalents for the acylative resolution of hindered chiral secondary alcohols.[68] Catalyst **123**, a modified version of **120** bearing a naphthalene substituent, has been employed in the first organocatalytic acylative kinetic resolution of an atropisomeric substrate.[69] Treatment of racemic **121** with isobutyric anhydride and catalyst **123** resulted in 31 % conversion to the desired product **122**, with 55 % *ee* (Scheme 2.3).

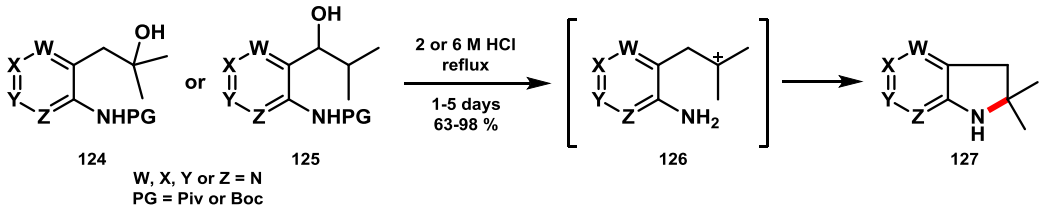


Scheme 2.3 – Acylative kinetic resolution using azaindoline catalyst 123

2.1.2. *Synthesis of azaindolines*

Relatively few general routes to azaindolines can be found in the literature and methods which can be used to access all four azaindoline isomers are particularly uncommon.[70-72] Routes to the 5- and 7-isomers can be found more frequently than those for the 4- and 6-isomers, with reports of syntheses of the 4-azaindoline isomer proving particularly scarce.[71]

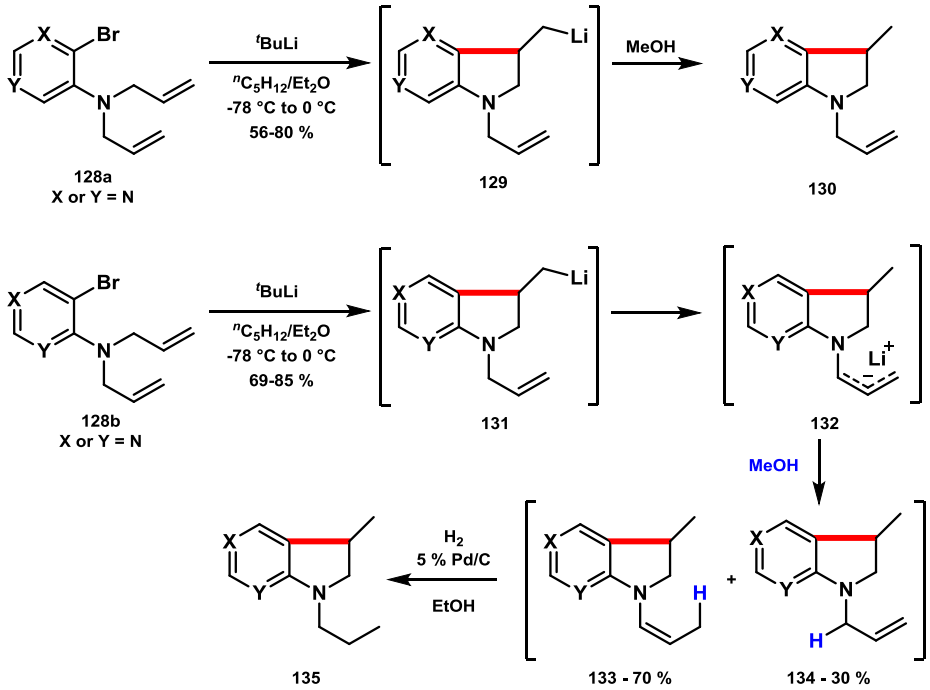
One approach to obtaining each of the isomeric azaindolines is nucleophilic attack onto a carbocationic intermediate (Scheme 2.4).[70] Generation of tertiary carbocation **126**, either directly from acidic treatment of **124** or through rearrangement of the less stable secondary carbocation generated from **125**, occurs in tandem with deprotection of the amine group. The liberated amine is then free to cyclize onto the carbocation to form geminal-dimethyl substituted azaindolines **127**. While the process has wide scope and affords good yields, some examples require harsh conditions, employing boiling 6 M HCl and reaction times of several days.



Scheme 2.4 – Synthesis of azaindolines by cyclization onto a carbocationic intermediate

Another method which can successfully generate the entire series of isomeric azaindolines is intramolecular carbolithiation (Scheme 2.5).[71] Lithium-halogen exchange of **128a** using ^{t}BuLi is followed by an intramolecular carbolithiation onto one of the pendant allyl units to form **129**, which affords 4- and 6-azaindolines **130** when quenched with methanol. Complications arose during the synthesis of 5- and 7-azaindolines, with a mixture of allyl

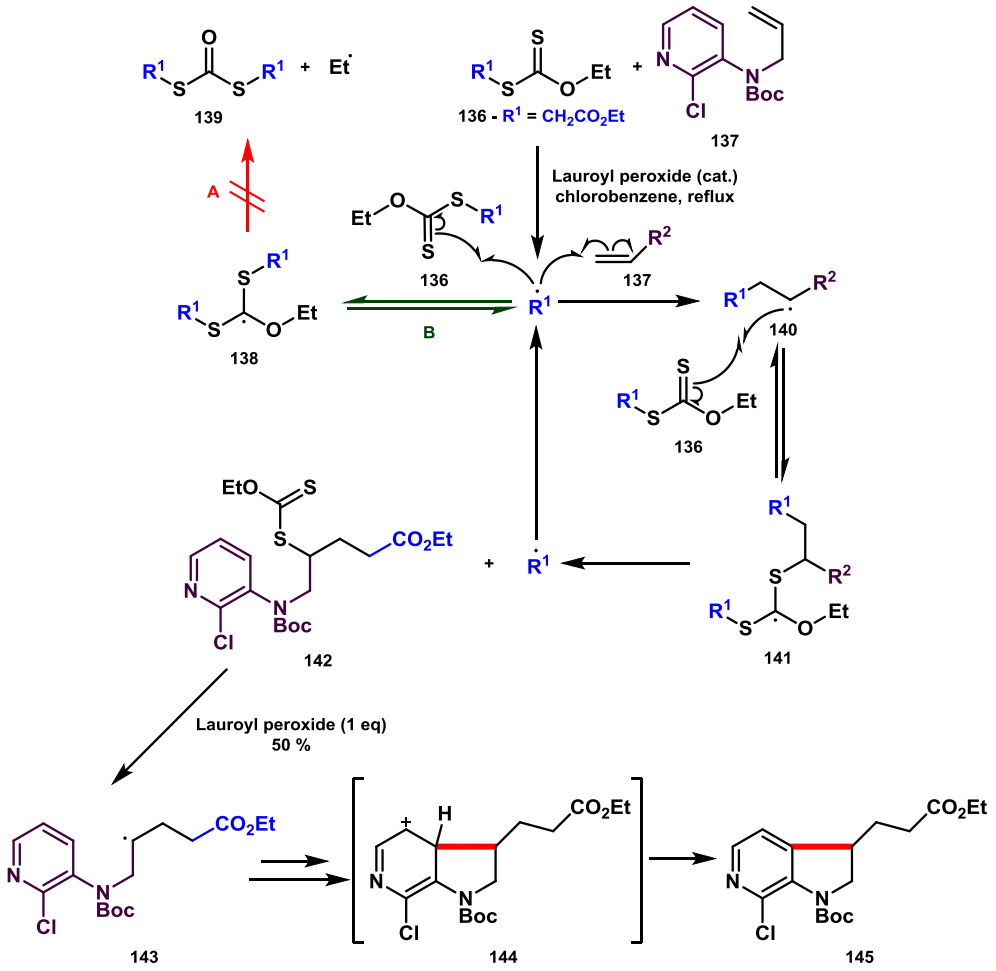
isomers **133** and **134** observed. Subsequent hydrogenation furnished *N*-propyl azaindolines **135**. Deuterium labelling studies indicated that deuterium was incorporated at the hydrogen positions highlighted in **133** and **134**, with no deuterium incorporation observed on the methyl group. This suggests the methyl group is protonated *via* intramolecular proton transfer resulting in the formation of allyl anion **132**, which is subsequently quenched by methanol. The authors propose that this process is favoured because of the electron-withdrawing effect of the pyridine nitrogen in an *ortho*- or *para*- relationship to the indoline nitrogen. This enhances the acidity of the indoline nitrogen and hence aids the proton transfer process.



Scheme 2.5 – Synthesis of azaindolines by intramolecular carbolithiation

Synthesis of the isomeric family of azaindolines has also been achieved by radical-mediated processes.[72] Zard has developed stabilized xanthene radicals which are particularly effective in additions to unactivated alkenes. This powerful carbon-carbon bond-forming methodology has been applied to the synthesis of a wide range of compounds[73] including

azaindolines. The reaction begins with peroxide-initiated decomposition of xanthate **136** to form alkyl radical $\mathbf{R^1}$ (Scheme 2.6). The most favourable reaction pathway for this radical is to combine with a further molecule of xanthate **136** to form a new radical **138**. **138** is too bulky to dimerize or does so in a reversible fashion so the only remaining options are radical scission of the O-Et (pathway **A**) or S-R^1 bonds (pathway **B**). As the C-O bond is stronger and its rupture would also result in the formation of a high energy ethyl radical this process is disfavoured in comparison to breaking the C-S bond. Thus, radical $\mathbf{R^1}$ is regenerated as it is more thermodynamically stable than the products of pathway **A** and the only remaining irreversible reaction pathway is that of the desired reaction.



Scheme 2.6 – Synthesis of azaindolines *via* radical cyclization

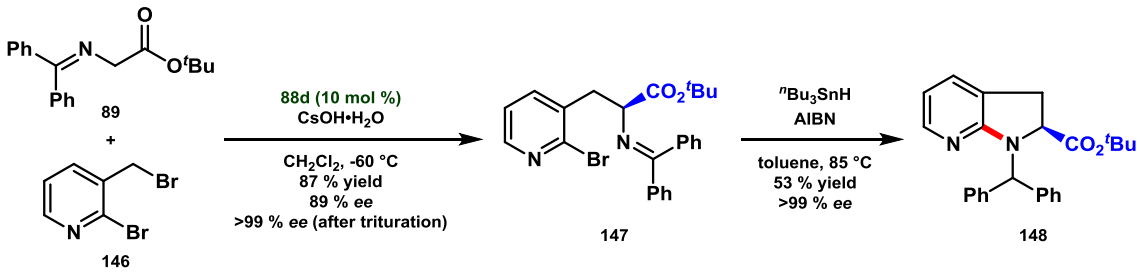
Therefore, the route followed is addition to alkene **137**, which generates the new carbon-carbon bond of intermediate **140**. **140** subsequently combines with another molecule of xanthate **136** to form radical **141**, which again breaks at the C-S bond in a reversible process to regenerate $\mathbf{R^1}$ and stable xanthate **142**. This xanthate can be isolated or treated with stoichiometric peroxide to form alkyl radical **143**, which cyclizes onto the aromatic ring, with stoichiometric peroxide required to oxidise the resulting aromatic radical to cation **144**, which rapidly loses a proton to regenerate aromaticity and form azaindoline **145**. Careful control of the substituents on the aromatic ring is required to avoid forming mixtures of isomers, with use of blocking groups such as the chlorine in **137**, providing control over the product generated. Analogous procedures with similar substrates can be used to synthesize the remaining azaindoline isomers.

Other general methods which have been employed to access one or two specific azaindoline isomers include high-temperature nucleophilic substitution with ammonia,[74] palladium-mediated cyclization,[75] [1,5]-electrocyclization,[76] multicomponent reactions,[77] reduction of the corresponding azaindole,[64] and nucleophilic attack of nitrogen onto mesylates,[64] tosylates[66c] or triflates.[78] There are also several isolated examples of azaindoline synthesis *via* various methods in the literature.[79]

2.1.3. Asymmetric synthesis of azaindolines

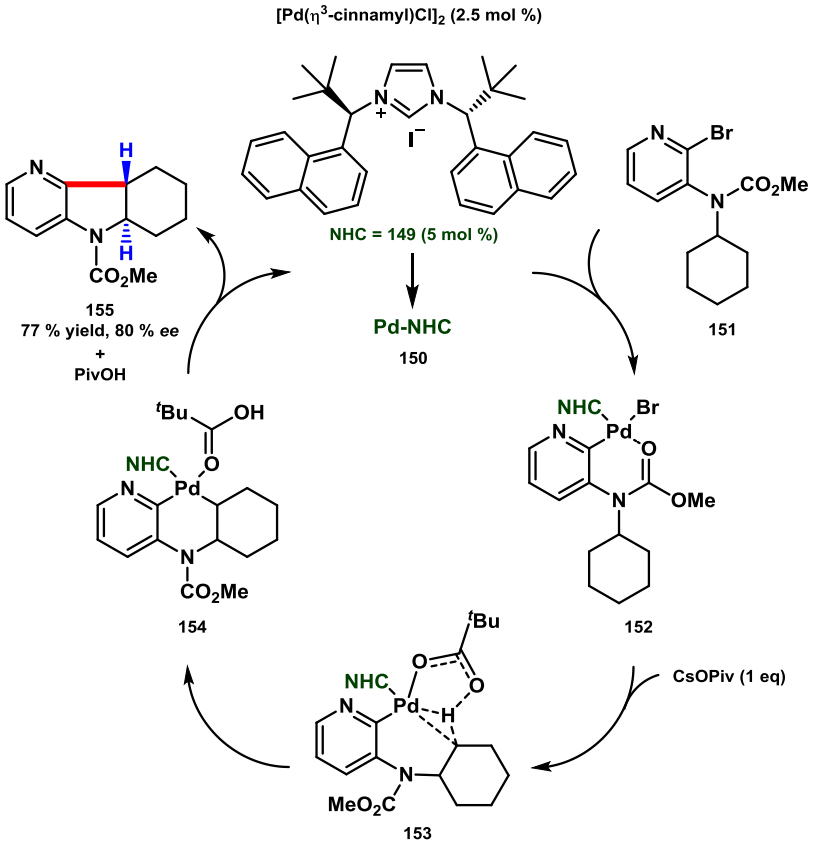
There are only two examples of asymmetric synthesis of azaindolines in the literature (the optically pure atropisomers **120** and **123** discussed in Chapter 2.1.1 was obtained *via* purification by semipreparative chiral HPLC). The first is an example of asymmetric synthesis starting from a chiral precursor, as the stereocentre is set in the previous step by the well-established O'Donnell alkylation of glycine-Schiff base **89** using Corey's

O-allyl-*N*-anthracenylcinchonidinium bromide catalyst **88d**. This reaction proceeds in 89 % *ee* with recrystallization affording alkylated product **147** in >99 % *ee*. Use of the pseudoenantiomeric cinchoninium catalyst forms the opposite enantiomer, also in excellent *ee*. Subsequent free radical-mediated amine arylation formed the enantiomerically pure 7-azaindoline **148** (Scheme 2.7).[80]



Scheme 2.7 – First synthesis of an enatiomerically pure azaindoline

The only catalytic asymmetric synthesis of azaindolines in which the stereogenic centre is introduced during the bond-forming step was recently published by Kündig in an investigation of the scope of a previously developed sp^3-C-H activation approach to the synthesis of indolines.[75a,81] This is the only example of a palladium-mediated synthesis of azaindolines in which enantioenriched products are formed. The reaction is catalyzed by chiral NHC/palladium complex **150**, which undergoes oxidative addition to aryl bromide **151** (Scheme 2.8). The bromide ligand exchanges with a pivalate ligand to form intermediate **153**. Deprotonation at the desired sp^3 centre and metallation to form palladacycle **154** is proposed to occur in a concerted fashion. Subsequent reductive elimination furnishes the desired azaindoline **155** and regenerates the NHC/palladium complex. The authors propose that the observed enantioselectivity is set in the concerted-metallation-deprotonation step. A steric clash between the substrate and the aryl groups of the NHC ligand occurs in the transition state which leads to the (*S*) enantiomer, disfavouring formation of this product.[75a]



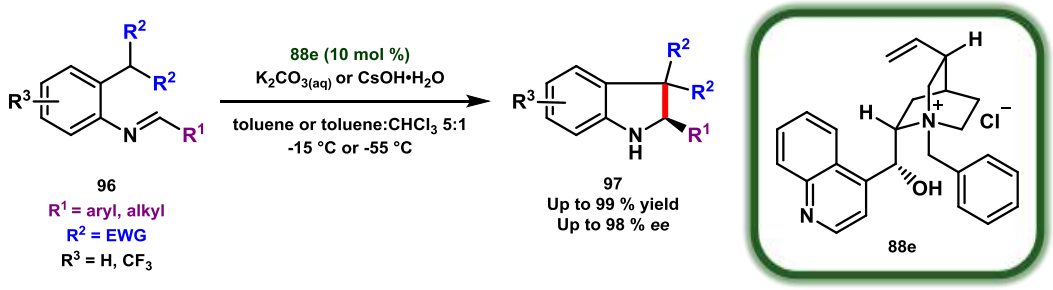
Scheme 2.8 – Kündig's asymmetric synthesis of azaindolines *via* C-H activation

In contrast to this strategy we intended to approach the asymmetric synthesis of azaindolines using an organocatalytic methodology developed in our group.

2.2. Previous work in the Smith group

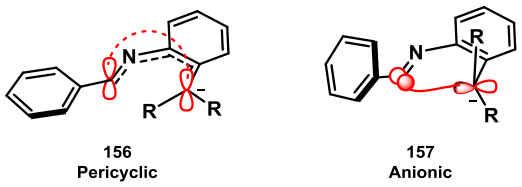
Work on chiral cation-directed synthesis in the Smith group was instigated during our efforts to develop a catalytic asymmetric 6π-electrocyclization.[60] Electrocyclic ring closures often require harsh conditions, such as high temperatures, which are not particularly amenable to asymmetric synthesis. However, introduction of a heteroatom into the electrocyclic manifold greatly reduces the activation energy of the cyclization process and also stabilizes the anionic products of the reaction.[82] This principle was exploited by Speckamp to develop an asymmetric 6π-electrocyclization, however this process required the use of stoichiometric quantities of chiral catalyst and was particularly substrate-dependent.[83]

Inspired by this work and employing the principles of cation-directed catalysis, as described in the Introduction, we were able to exploit tight ion pairing to obtain excellent levels of control over the absolute stereochemistry in the catalytic asymmetric electrocyclization of imines **96** to indolines **97**, utilizing chiral *cinchona* alkaloid-derived phase-transfer catalyst **88e** (Scheme 2.9).[60]



Scheme 2.9 – Cation-directed asymmetric electrocyclization

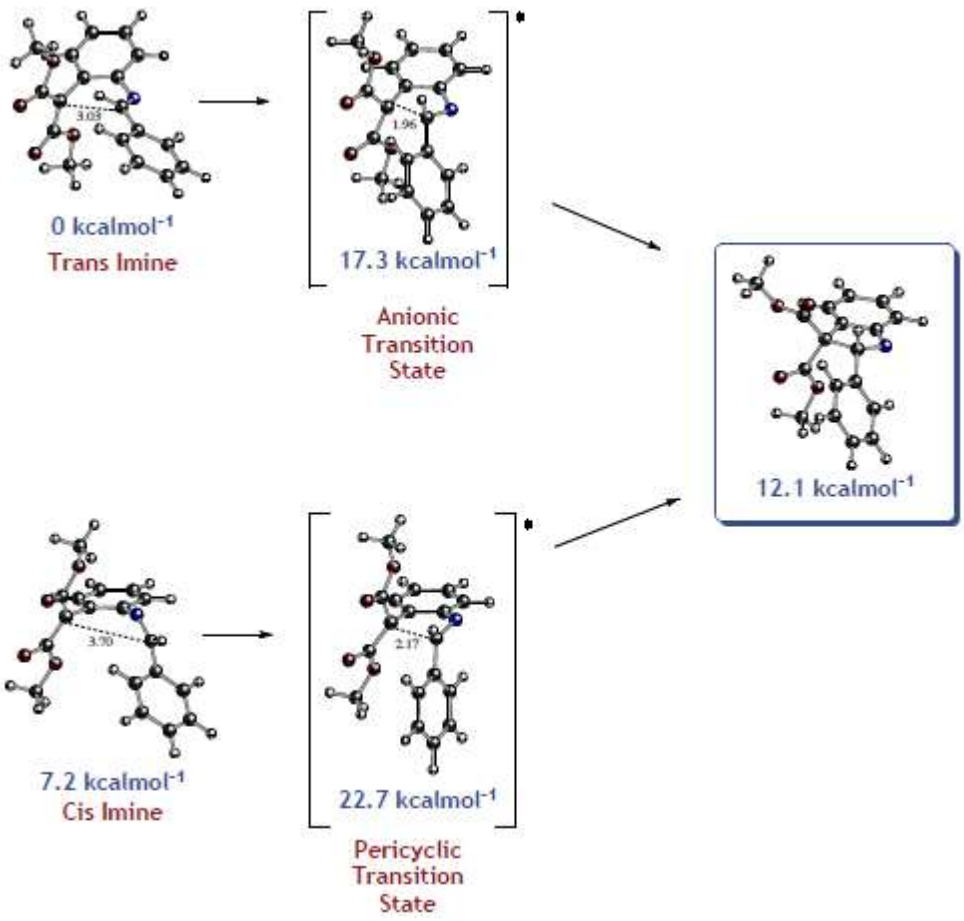
An alternative mechanism to the electrocyclization exists where the reaction could be seen to proceed *via* an anionic Mannich-like reaction (Scheme 2.10). However, this reaction pathway involves a 5-(*enolexo*)-*endo*-trig cyclization, which is disfavoured by the Baldwin rules for ring closure.[84]



Scheme 2.10 – Potential mechanisms for indoline formation

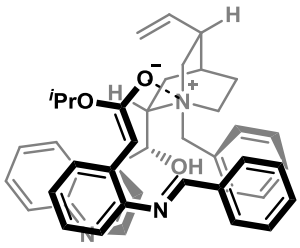
The pathway of the reaction is challenging to determine experimentally, thus computational modelling of potential transition states has been carried out in collaboration with Professor Dean Tantillo at UC Davis.[85] Probing of the possible reactive intermediates by nucleus independent chemical shifts investigated whether any ring current builds up as the reaction proceeds, which would be indicative of a pericyclic pathway rather than an anionic one. This

study has shown that the transition state associated with the imine reacting in the *cis* configuration is likely to be pericyclic, whereas the *trans*-imine is likely to follow the anionic pathway. The *cis* imine is calculated to be approximately 7 kcal mol^{-1} higher in energy than the *trans* imine and the pericyclic transition state is higher in energy by a margin of approximately 5 kcal mol^{-1} (Scheme 2.11). These results would appear to favour the Mannich-like reaction mechanism, however they do not account for interactions with the bulky chiral cation, which is exceptionally challenging to model, therefore the pericyclic process cannot be ruled out. Further work on elucidating the precise mechanism of this and related reactions is ongoing.



Scheme 2.11 – Transition state energies of the pericyclic and anionic transition states of the cyclization

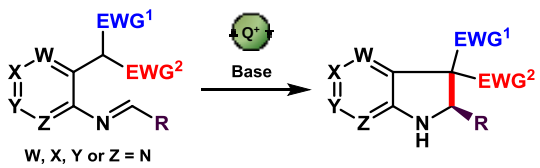
The stereochemical outcome of the reaction was rationalized for the pericyclic pathway by a catalyst-substrate tight ion-pair analogous to that of the Corey model.[56] Tight ion-pairing of the ammonium cation with the oxygen of one of the enolate groups, supplemented by π-stacking interactions results in a conformation which, upon disrotatory electrocyclization away from the catalyst bulk, results in the observed absolute configuration of indoline **97** (Scheme 2.12).[60] An alternative stereochemical model for the anionic pathway will be discussed in Chapter 2.5.1.



159

Scheme 2.12 – Corey tight ion-pairing model for electrocyclization of 97 (2nd ester omitted for clarity)

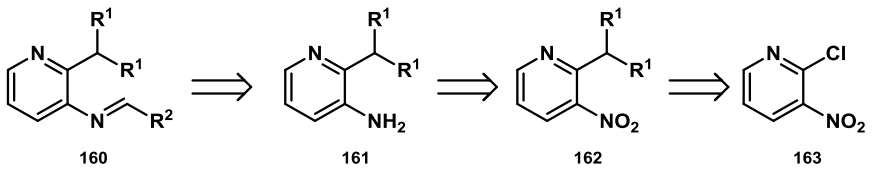
The aim of this project was to investigate whether the methodology developed for the synthesis of indolines could be applied to the asymmetric synthesis of densely functionalized azaindolines, hence providing a route to enantiomerically enriched analogues of these interesting scaffolds. Furthermore, we also planned to extend the methodology to substrates bearing two different electron-withdrawing groups, to investigate the diastereoselctivity of the resulting cyclized products (Scheme 2.13).



Scheme 2.13 – Blueprint for synthesis of enantiomerically enriched azaindolines

2.3. Synthesis of 4-azaindolines – substrate synthesis

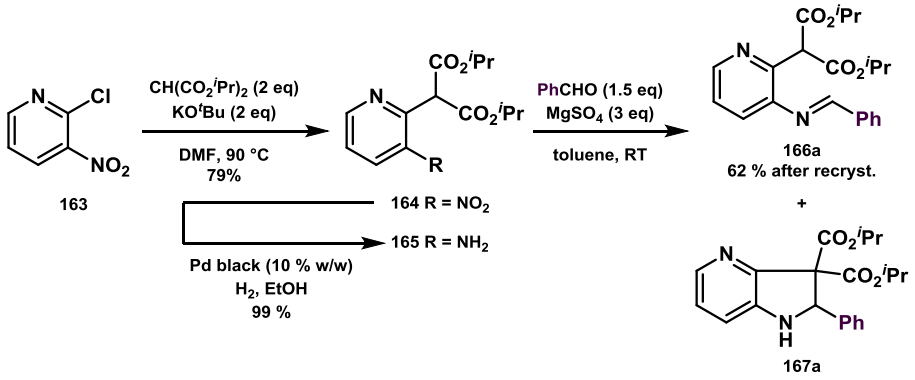
The synthetic route towards the required pyridine-derived imine **160** mirrors the one developed for the synthesis of indolines.[60] Initial efforts focused on the synthesis of 4-azaindolines. The required imine derivatives can be formed by reacting aldehydes with aminopyridine **161**, which is accessed from reduction of nitropyridine **162**. This nitropyridine should be easily obtained from a S_NAr reaction with commercially available 2-chloro-3-nitropyridine (**163**) (Scheme 2.14).



Scheme 2.14 – Retrosynthesis of 4-azaindoline precursor 160

Previous work within our group led to the development of scalable conditions for this route (Scheme 2.15), with isopropyl esters chosen as the electron-withdrawing groups to provide a direct comparison with the indoline system.[86] S_NAr of **163** with diisopropyl malonate proceeded in 79 % yield when K_2CO_3 was employed as the base. Palladium black catalyzed reduction of the resultant nitropyridine **164** with hydrogen proceeded in quantitative yield, to form aminopyridine **165**. This product was found to decompose under aerobic conditions which rendered it less effective in the subsequent imine formation step and hence was used immediately or stored under argon. Imine formation with benzaldehyde proceeded smoothly, with the small caveat that a trace quantity of 4-azaindoline **167a** was observed. This side product may arise from the slight Lewis acidity of $MgSO_4$ which catalyzes the cyclization through a Mannich-type process. Indeed acid catalysis of the cyclization appeared general, with cyclization observed during attempts to chromatograph the imine on silica and also when running NMR spectra in chloroform which had not been treated with

basic alumina. This unwanted side product was removed by recrystallization, affording imine **166a** in 62 % yield.



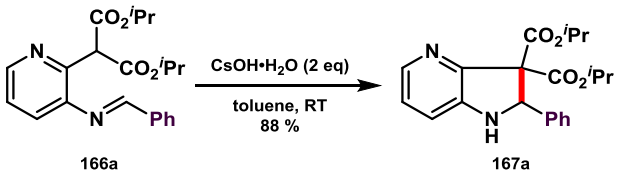
Scheme 2.15 – Synthesis of imine 166a

With the required test substrate in hand the conditions for the desired asymmetric cyclization reaction could now be developed.

2.4. Synthesis of 4-azaindolines – reaction optimization

2.4.1. Racemic cyclization

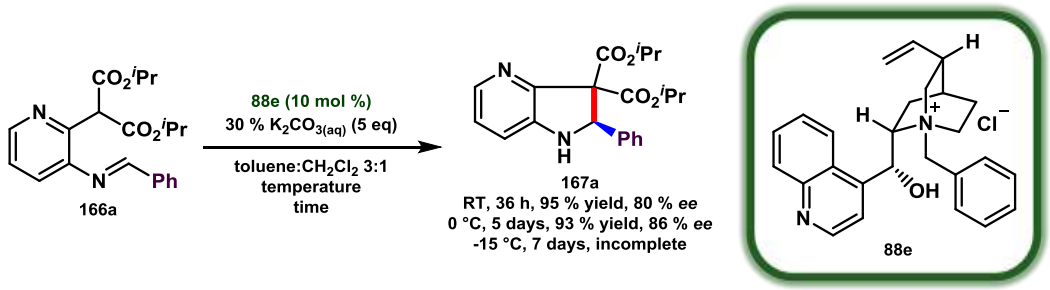
Prior to carrying out the cyclization in an asymmetric fashion an analytically pure sample of the desired azaindoline was synthesized by treatment of imine **166a** with cesium hydroxide monohydrate. This resulted in formation of the desired azaindoline in 88 % yield (Scheme 2.16). The same conditions were applied for the racemic synthesis of the azaindoline derivatives described throughout this thesis.



Scheme 2.16 – Racemic cyclization to form 4-azaindolines

2.4.2. *Asymmetric cyclization*

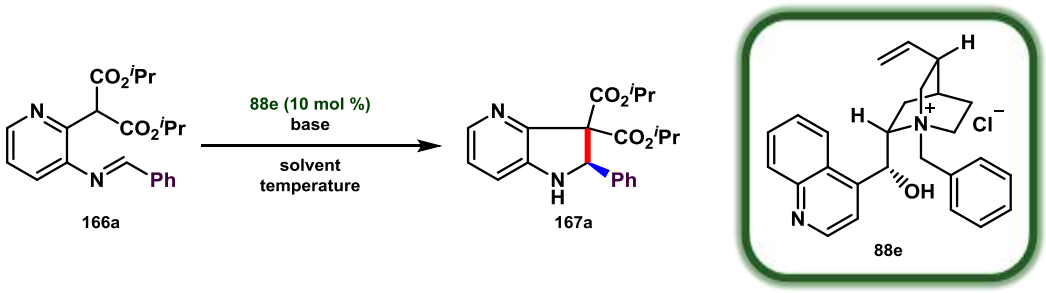
Initial optimization[86] began from the starting point of the conditions successfully employed for the synthesis of indolines.[60] These conditions utilized aqueous potassium carbonate as the base and *N*-benzyl cinchonidinium chloride (**88e**) as the catalyst. As with several examples in the indoline system, a polar solvent was required as an additive to solubilize the imine. Given the previously observed tendency of imine **166a** to cyclize in the presence of chloroform this was deemed unsuitable as a solvent and it was replaced by dichloromethane. Initial results showed a highly promising *ee* of 80 % when the reaction was carried out at room temperature (Scheme 2.17). Enantioselectivity was improved on lowering of the reaction temperature to 0 °C, but the reaction time was extended significantly. Further lowering of the temperature resulted in the reaction failing to go to completion after one week.



Scheme 2.17 – Initial screening – liquid-liquid PTC

In an effort to circumvent the long reaction times suffered by this process at low temperatures, while still retaining good levels of enantioselectivity, solid-liquid PTC systems were investigated (Table 1).[86] Pleasingly, the reaction proceeded smoothly with one equivalent of solid KOH at -15 °C and was complete within 24 h, albeit with a slightly decreased *ee* of 78 % (entry **1**). The presence of the phase-transfer catalyst was essential for the reaction to occur, with no cyclization observed in its absence (entry **2**). Encouraged by

these results, efforts were made to improve the enantioselectivity by adjusting the solvent ratio, however the reaction proved sensitive to these changes with removal or increasing the quantity of CH_2Cl_2 both resulting in diminished selectivity (entries **3** and **4**). The *ee* was also dependent on the metal counterion of the base. While little difference was observed between potassium and sodium hydroxide (entries **1** and **5**), switching to cesium hydroxide resulted in a lower *ee* (entry **6**). This may be attributed to the greater solubility of organic anions bearing a cesium cation, which could result in cyclization occurring in the organic phase without the intervention of the phase-transfer catalyst.



Entry	Conditions	Yield (%)	ee (%)[a]
1	$KOH_{(s)}$ (1 eq), toluene:CH_2Cl_2 3:1, -15 °C	90	78
2	$KOH_{(s)}$ (1 eq), toluene:CH_2Cl_2 3:1, -15 °C, no **88e**	No reaction	-
3	$KOH_{(s)}$ (1 eq), toluene, -15 °C	ND[b]	61
4	$KOH_{(s)}$ (1 eq), toluene:CH_2Cl_2 1:1, -15 °C	ND	60
5	$NaOH_{(s)}$ (1 eq), toluene:CH_2Cl_2 3:1, -15 °C	ND	77
6	$CsOH{\cdot}H_2O_{(s)}$ (1 eq), toluene:CH_2Cl_2 3:1, -15 °C	97	46
7	$LiOH{\cdot}H_2O_{(s)}$ (1 eq), toluene:CH_2Cl_2 3:1, -15 °C	Incomplete after 3 days	-
8	$KOH_{(s)}$ (3 eq), toluene:CH_2Cl_2 3:1, -15 °C	ND	0
9	$KOH_{(s)}$ (1 eq), toluene:CH_2Cl_2 3:1, -30 °C	97	86

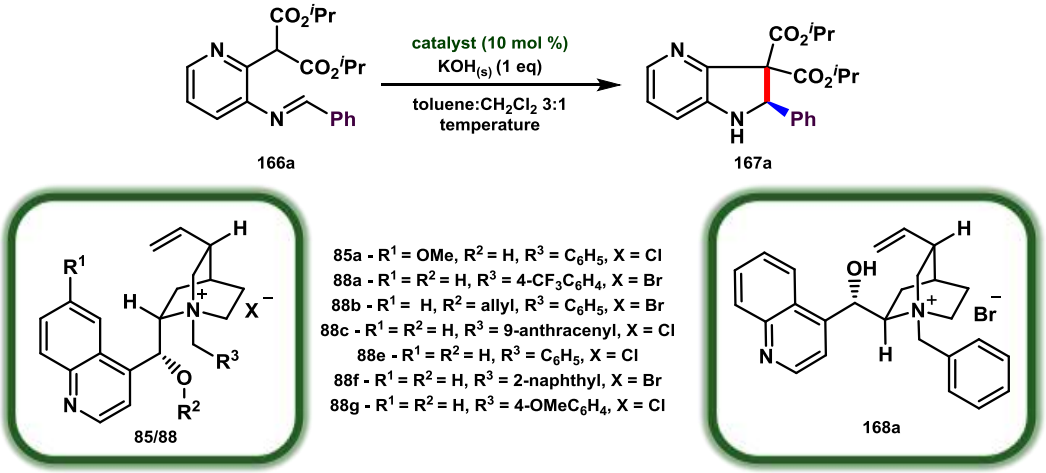
a) Determined by chiral HPLC, b) ND = not determined

Table 1 – Reaction optimization – solid-liquid PTC

The use of lithium hydroxide led to incomplete conversion after three days, presumably due to the greater stability of the lithium enolate intermediate (entry **7**). The stoichiometry of base was also important, with superstoichiometric quantities of base yielding a racemic mixture (entry **8**). With the already established conditions appearing optimal the temperature of the reaction was further lowered to -30 °C (entry **9**). This led to an improved *ee* of 86%, which is comparable to the best enantioselectivity observed with K_2CO_3 but with the reaction reaching completion within 24 hours instead of 5 days.

One parameter that had not yet been investigated was the choice of catalyst, so a screen of catalysts was carried out (Table 2). It was found that a catalyst derived from quinine **85a** gave comparable levels of selectivity to cinchonidine-derived catalyst **88e** (entries **1** and **2**). Use of the pseudoenantiomeric catalyst **168a** derived from cinchonine did furnish the opposite enantiomer, but only in modest *ee* (entry **3**). Using the *O*-allylated catalyst **88b** originally developed by O'Donnell[54] resulted in the formation of a racemic mixture, suggesting the hydroxyl group of the catalyst may have an important role to play in the stereochemical outcome of the reaction (entry **4**). Bearing this in mind, the commercially available anthracenylmethyl-substituted catalyst **88c** with a free hydroxyl group was trialled and we were gratified to see that this led to an improved *ee* of 90 % (entry **5**). Further decreases in the temperature of the reaction using this catalyst either had no effect on *ee* or prevented the reaction from going to completion (entries **6** and **7**). Further adjusting the steric bulk of the quaternizing group by employing a 2-naphthyl-substituted catalyst **88f** led to an improvement in enantioselectivity (entry **8**). The effect of altering the electronic nature of the quaternizing group was also investigated, with both electron-poor **88a** and electron-rich **88g** aromatic groups giving similar results to benzyl-substituted catalyst **88e**

(entries **1**, **9** and **10**). This suggests that the effect of the quaternizing group on enantioselectivity is predominantly steric, rather than electronic, in nature.



Entry	Catalyst	Temperature	Yield (%)	ee (%)[a]
1	**88e**	-30 °C	97	86
2	**85a**	-30 °C	ND[b]	85
3	**168a**	-30 °C	89	-26[c]
4	**88b**	-30 °C	90	0
5	**88c**	-30 °C	98	90
6	**88c**	-45 °C	80	90
7	**88c**	-78 °C	Incomplete after 3 days	-
8	**88f**	-30 °C	96	94
9	**88a**	-30 °C	ND	85
10	**88g**	-30 °C	ND	84

a) Determined by chiral HPLC, b) ND = not determined, c) Opposite enantiomer isolated

Table 2 – Catalyst screen for asymmetric cyclization of 166a

As the catalyst architecture had been modified; a small selection of alternative solvents for the reaction was evaluated using the optimized conditions (Table 3). Both a hexane-CH_2Cl_2 mixture and THF resulted in decreasing enantioselectivity (entries **2** and **3**). Furthermore, reducing the concentration of the reaction had little effect on the observed enantioinduction (entry **4**).

Entry	Solvent[a]	ee (%)[b]
1	toluene:CH_2Cl_2, 3:1 (0.07 M)	94
2	hexane:CH_2Cl_2, 3:1	46
3	THF	66
4	toluene:CH_2Cl_2, 3:1 (0.03 M)	92

a) Conditions: 10 mol % catalyst **88f**, $KOH_{(s)}$ (1 eq), -30 °C, b) determinded by chiral HPLC

Table 3 – Solvent and concentration screen

Thus, after optimization, the model imine substrate **166a** was found to undergo cyclization with a yield of 96 % and *ee* of 94 %. The use of solid base allows the reaction to proceed within an acceptable timeframe compared to aqueous base. With these conditions developed the scope of the cyclization reaction to form 4-azaindolines could now be evaluated.

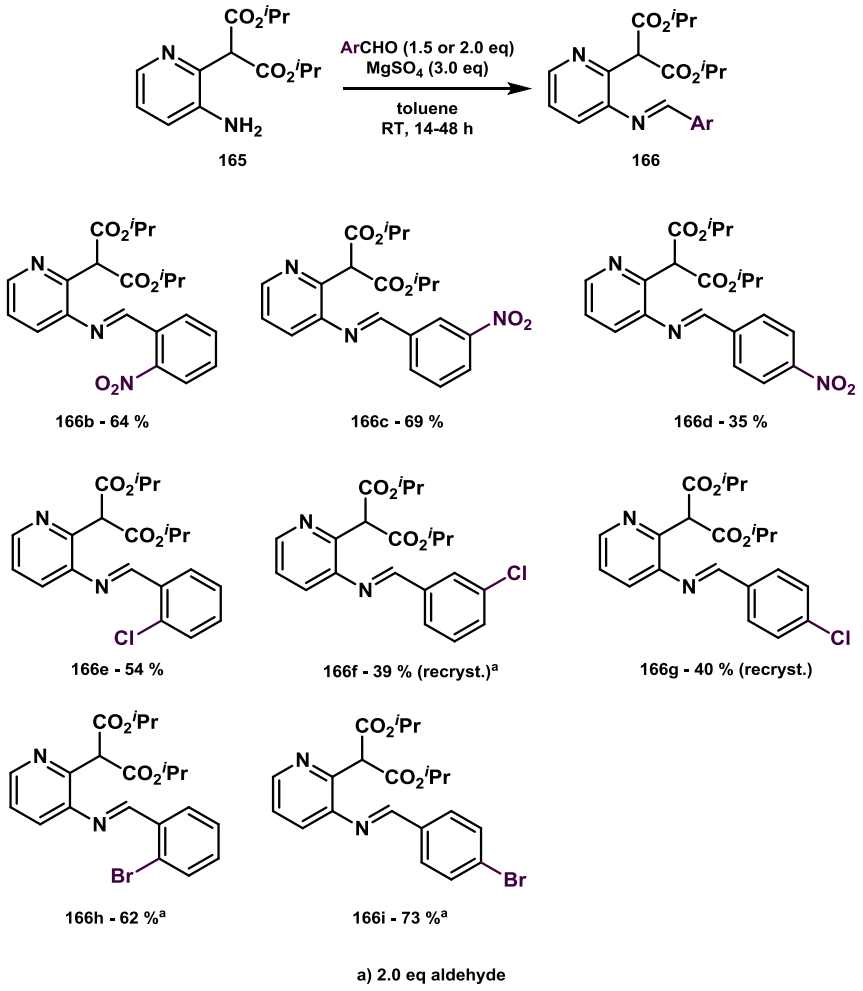
2.5. Scope of chiral cation-directed synthesis of 4-azaindolines

During the course of optimization it had been observed that a "one-pot" cyclization from the crude imine **166a** resulted in marginally lower *ee* values, with a drop of approximately 3 % observed. This was also observed in the indoline system[60] and in that case the "one-pot" method was used during the evaluation of scope due to its practical ease and the difficulty of isolating the imine products, which can be unstable. However, early on during our evaluation of substrate scope we observed that the decrease in enantioselectivity could be

far more pronounced than in the indoline case with reductions of >10 % observed for some substrates, even when no prior underired cyclization had occurred. Hence, wherever possible the imines were purified by recrystallization or chromatography to achieve maximum selectivity in the cyclization.

2.5.1. Aromatic imine substituents

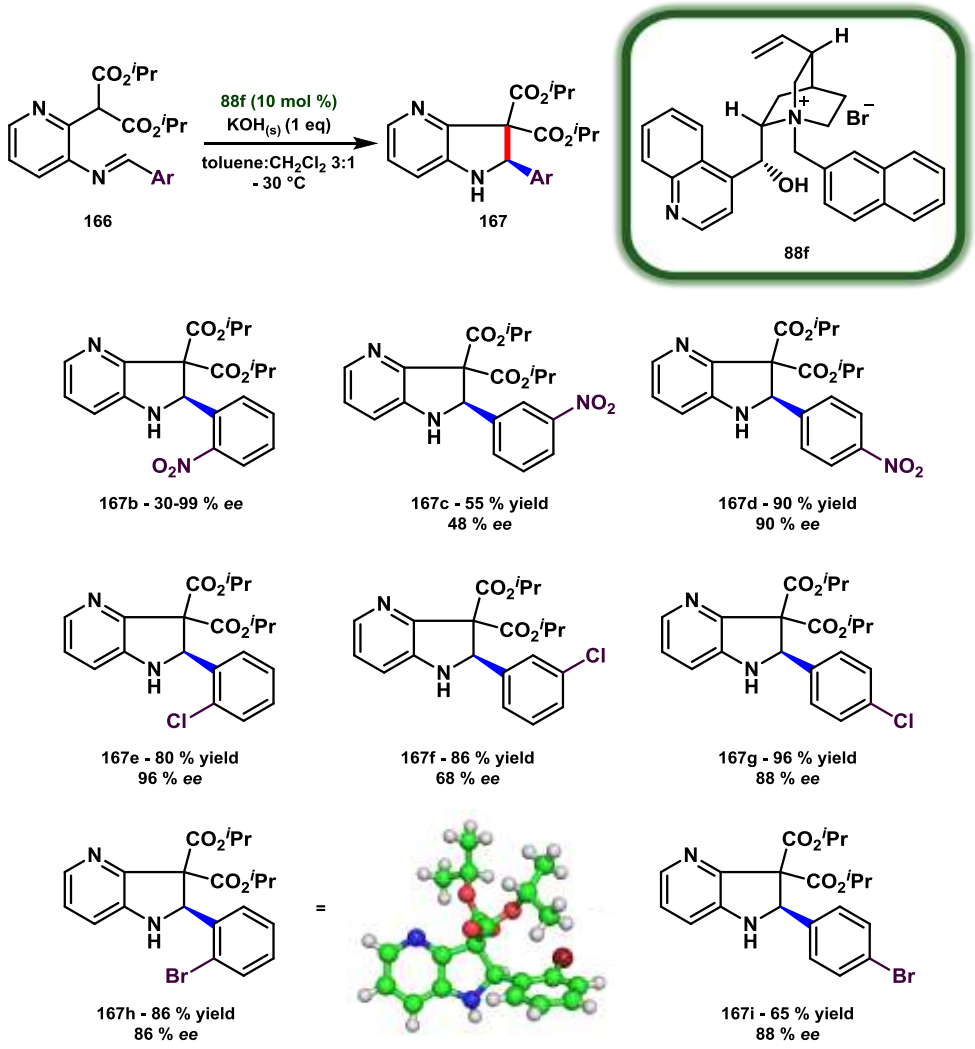
The first area of reaction scope that was examined was the use of alternative aryl substituents on the imine. This required the use of a range of aromatic aldehydes in the imine formation. Due to the tendency of these aldehydes to oxidize to benzoic acids on prolonged storage they were purified by distillation or recrystallization prior to use to prevent undesired acid catalysis of the cyclization process during the imine formation stage. In certain cases a larger excess of aldehyde was required to drive the imine formation to completion. When electron-poor aldehydes were used, synthesis of the desired imines was straightforward, with no undesired cyclization occurring during the reaction. This meant that some imines could be purified by silica gel chromatography, which generally resulted in higher yields of imine for small-scale reactions when compared to recrystallization. For example, the yield of imine **166b** improved from 27 % to 64 % when switching from recrystallization to chromatography. The extent of this improvement was limited by partial hydrolysis of the imine during chromatography. The isolated yields of pure imines ranged from 35-73 % (Scheme 2.18).



Scheme 2.18 – Synthesis of imines bearing electron-poor aryl groups

The imines were then subjected to the optimized cyclization conditions (Scheme 2.19). Imine **166b**, bearing an aromatic ring with an *ortho*-substituted nitro group, had extremely inconsistent results in the cyclization reaction, with results ranging from a spectacular >99 % *ee* to a somewhat more sobering 30 %. This is most likely due to the particularly low solubility of the product, which can be seen precipitating during the course of the reaction. As phase-transfer catalyzed reactions rely on efficient mixing it is possible that the presence of this precipitate leads to irreproducible results. For the best results observed it is also possible that the low solubility of the product resulted in enantioenrichment *via* crystallization during chromatography. Substrates **166e** and **166h**, with halide substituents in the same position, cyclize with excellent *ee*, with *ortho*-chloro derivative **167e** having the

highest *ee* of any substrate at 96 %. This lends further credence to the explanation that the unreliable selectivity of **167b** is due to solubility issues because if it was due to the steric demands of cyclizing *ortho*-substituted substrates then these halogenated imines might be expected to suffer from the same problem. Additionally, nitro-substituted imine **166b** was the only case where precipitation of the cyclized product was observed during the course of the reaction.

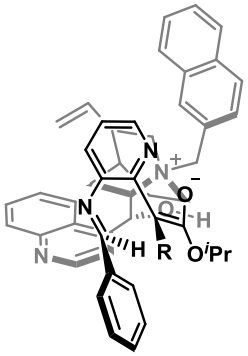


Scheme 2.19 – Asymmetric cyclization of imines bearing electron-poor aryl groups

The presence of a bromine atom in **167h** allowed the absolute stereochemistry of the azaindoline to be determined, and other analogues are assumed to possess the same

configuration.[87] This absolute stereochemistry is identical to that observed in the indoline system.[60]

A proposed stereochemical model for the reaction involving a Mannich-like reaction pathway would also be applicable to the indoline system (Scheme 2.20). The substrate interacts with the catalyst in the quadrant of the *cinchona* alkaloid which has been shown by nOe studies to be the most likely anion receptor.[88] The enolate is in close proximity to the positively charged catalyst and may also be stabilised by hydrogen bonding interactions with the hydroxyl group of the catalyst. The Lewis basic pyridine nitrogen may also participate in ion-pairing interactions with the catalyst. The observed stereochemistry arises from the aryl substituent on the imine orientating itself away from the quinoline group of the catalyst, with the opposite orientation resulting in unfavourable steric interactions between the two aromatic groups.



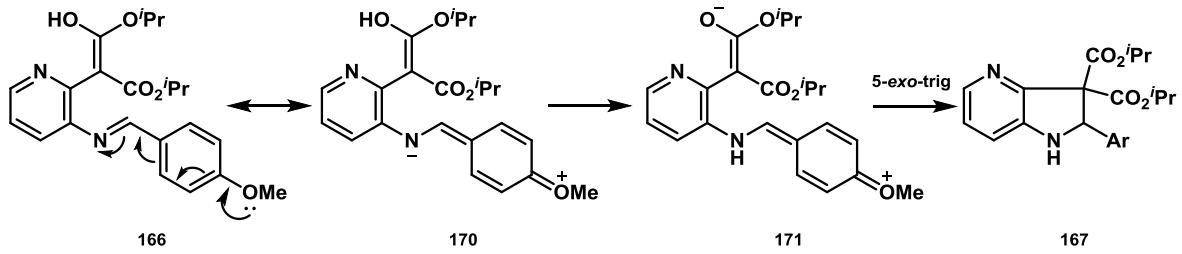
169 - R = $CO_2{}^i$Pr

Scheme 2.20 – Stereochemical model for cyclization proceeding *via* an anionic mechanism

Azaindolines with electron-withdrawing groups in the *para* position are also reliably formed in high *ee* with nitro, chlorine and bromine substituents all cyclizing in approximately 90 % *ee*. Substrates **166c** and **166f**, which bear *meta* electron-withdrawing groups both suffer from more moderate enantioselectivities, with the drop more pronounced for the more strongly withdrawing *meta*-nitro substrate **166c**, which cyclizes in only 48 % *ee*. This

suggests that a steric or electronic interaction between the substrate and catalyst is affecting the geometry of binding.

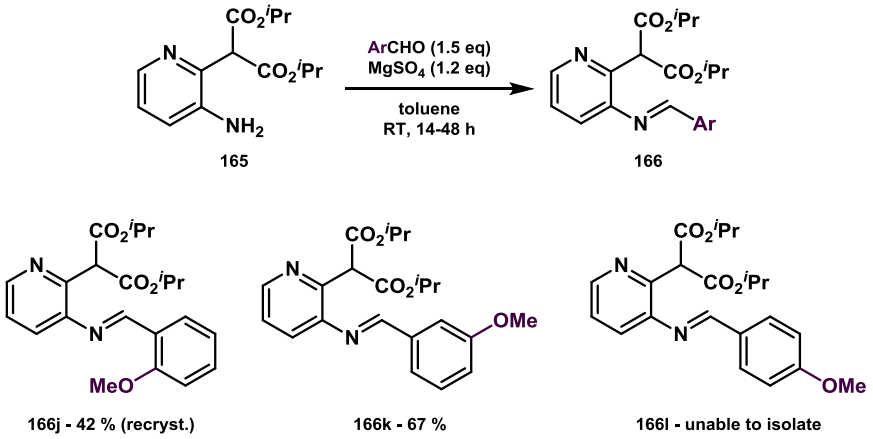
The synthesis of imines bearing electron-rich aromatic groups proved slightly less straightforward with the formation of up to 38 % cyclized material observed under the reaction conditions previously employed. This effect was most marked with *ortho*- and *para*-anisaldehyde, and may be a result of the importance of resonance form **170** which, after proton transfer to isomer **171**, facilitates a Mannich-type reaction. This Mannich process is made more favourable by the availability of a 5-(*enolexo*)-*exo*-trig pathway, which is allowed by the Baldwin rules (Scheme 2.21). Similar reasoning to this has been postulated for acid-catalyzed intramolecular Michael additions.[89] This preponderance of cyclized material prevented efficient purification of the imine by recrystallization.



Scheme 2.21 – Acceleration of racemic cyclization process of imine 166

As this was assumed to be an acid-catalyzed process promoted by $MgSO_4$, an alternative drying agent for the reaction was sought. Unfortunately due to the requirement to avoid acidic species, choices were somewhat limited. Na_2SO_4 had previously been shown to prevent cyclization, while increasing reaction times, in the case of benzaldehyde.[86] However, when this was attempted during imine formation with *para*-anisaldehyde, the worst affected example, the reaction failed to go to completion. $CaSO_4$ also failed to facilitate the reaction. The problem of cyclization was finally circumvented by simply lowering the

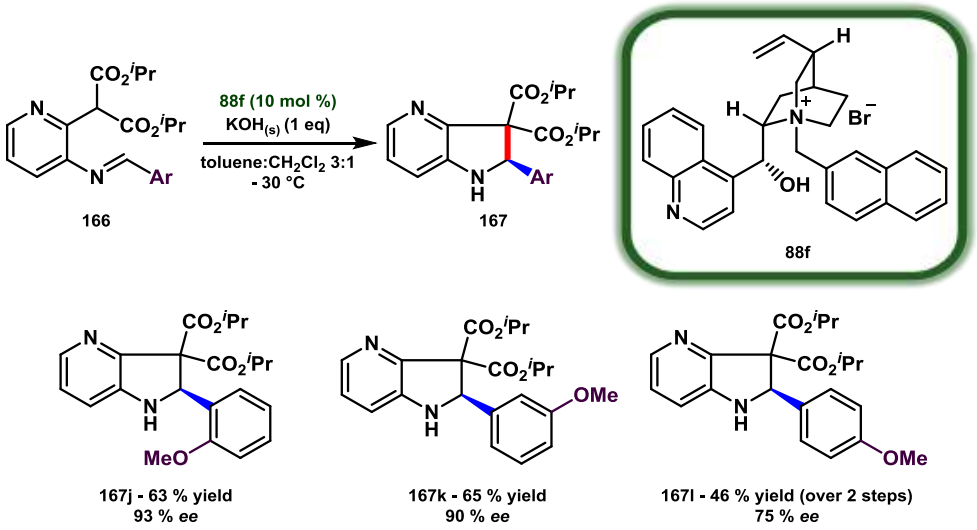
number of equivalents of $MgSO_4$ used during the reaction from 3.0 to 1.2 (Scheme 2.22). This reduced the formation of the undesired azaindoline to 9 % in the case of *para*-anisaldehyde and to trace quantities for the remaining aldehydes. After this advance, purification of imine **166j** was now possible by recrystallization and a good yield of imine **166k** was obtained by chromatography. Imine **166l** could not be purified and had to be taken forward crude to the cyclization reaction.



Scheme 2.22 – Synthesis of imines bearing electron-rich aryl groups

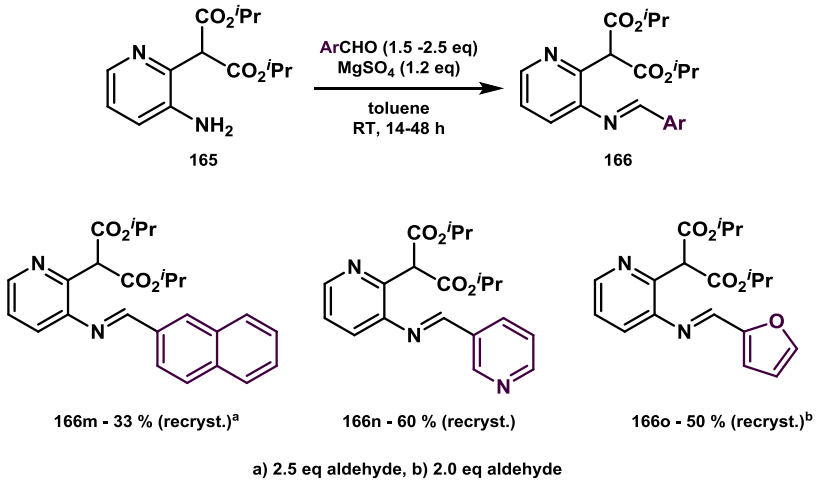
Cyclization of the sterically demanding *ortho*-substituted imine **166j** again proceeded with excellent enantioselectivity, with azaindoline **167j** isolated in 93 % *ee*, consistent with halide substituents in the same position (Scheme 2.23). Basic conditions preclude the cyclization mechanism in Scheme 2.21, ensuring that cyclization occurs in the presence of the cationic catalyst. In contrast to the examples with electron-poor aryl groups, *meta*-substitution was now well tolerated with a vastly improved *ee* of 90 %. Given that the steric bulk of a methoxy group (A value 0.7) is marginally greater than that of chlorine (A value 0.4),[90] this suggests that the interaction responsible for the diminished selectivity in the case of electron-withdrawing substituents in the *meta* position is electronic, rather than steric in nature. *Para*-methoxy-substituted azaindoline **167l**, was obtained from the crude imine in

46 % yield over two steps and in a moderate 75 % *ee*. While this result may seem poor compared to the 90 % *ee* obtained previously for *para*-substituted aromatics, it is easily explained by the presence of 9 % of racemic azaindoline formed by the acid-catalyzed background reaction during the imine formation step. When this is taken into account, along with the tendency for crude imines to lead to lower enantioselectivities, it is likely that the inherent selectivity of the reaction is on a par with the previous examples.



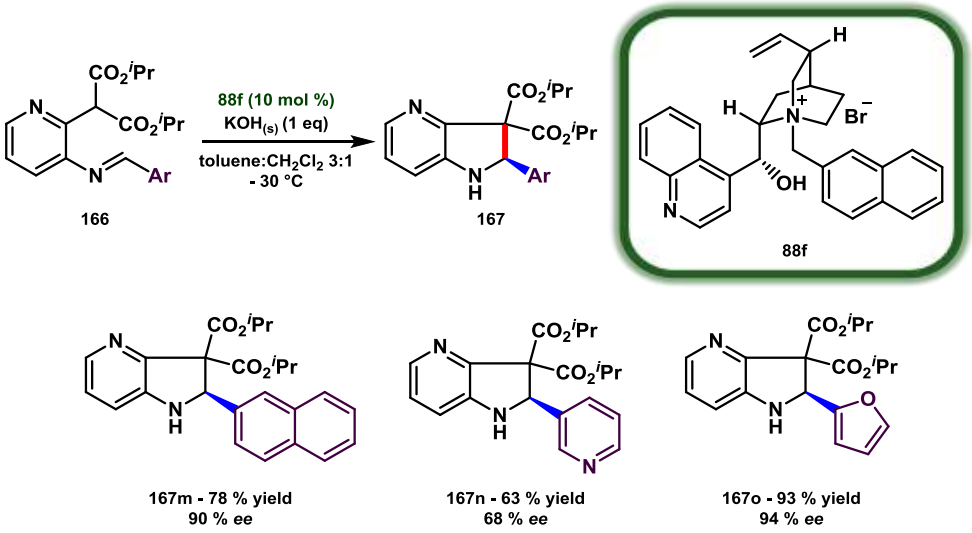
Scheme 2.23 – Asymmetric cyclization of imines bearing electron-rich aryl groups

The next area examined was the application of bulkier or heterocyclic aromatic groups in the reaction. As with the electron-rich aryl rings these reactions required that only a small excess of $MgSO_4$ was added to the imine formation reaction to prevent the formation of cyclized material (Scheme 2.24). Imine formation with 2-naphthaldehyde to yield imine **167m** was particularly sluggish and required the addition of a further equivalent of aldehyde to drive the reaction to completion. Recrystallization furnished a collection of pure imines in acceptable yields.



Scheme 2.24 – Synthesis of imines bearing bulky or heterocyclic aromatic groups

These imines were subjected to the optimized cyclization conditions, with all cyclizations proceeding smoothly (Scheme 2.25). The bulky 2-naphthyl-substituted imine **166m** cyclized in good yield and with an *ee* only marginally lower than when the substituent is a simple phenyl group. Pyridine-substituted azaindoline **167n** is formed with a moderate *ee* of just under 70 %. On the other hand, 2-furanyl-substituted imine **166o** cyclizes with both excellent yield and stereocontrol.

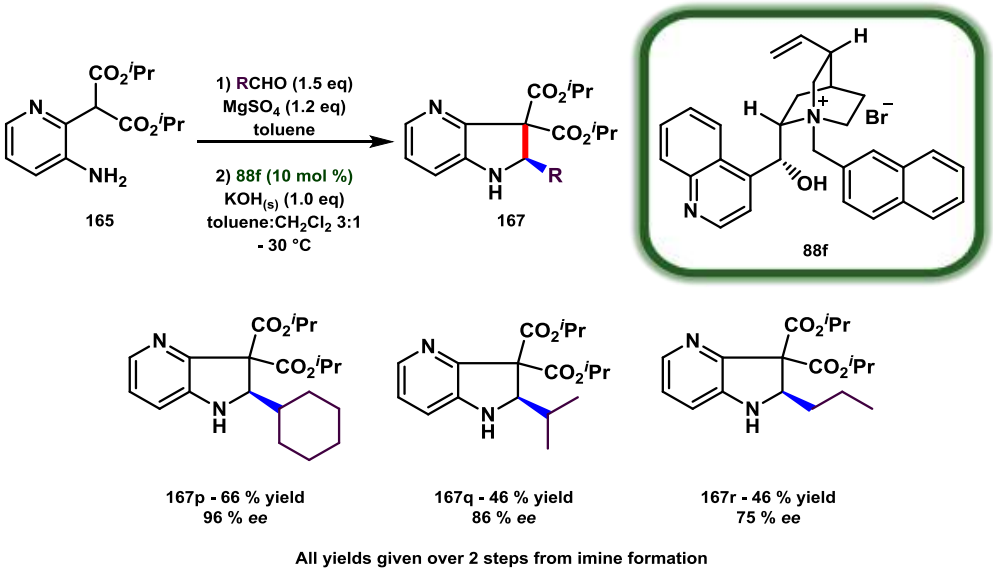


Scheme 2.25 – Asymmetric cyclization of imines bearing bulky or heterocyclic groups

Having thoroughly examined the scope of aromatic imine substituents, it was then decided to investigate whether this approach would be successful for imines bearing aliphatic groups.

2.5.2. *Aliphatic substituents*

The synthesis of alkyl imines was carried out in a "one-pot" process as both recrystallization and chromatography proved not to be viable purification options. Volatile alkyl aldehydes were utilized in the imine formation reaction to ensure that the majority of the aldehyde could be removed by drying the crude product under high vacuum. Cyclization of the crude imines was successful in all cases, in 46-66 % yield over the two steps (Scheme 2.26).



Scheme 2.26 – "One-pot" asymmetric cyclization of imines bearing alkyl substituents

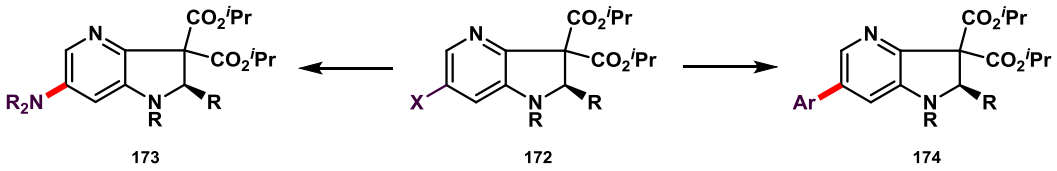
Cyclohexane-substituted azaindoline **167p** was formed with a particularly high *ee* of 96 %, matching the highest *ee* achieved with aryl substituents. Azaindoline **167q**, bearing a branched alkyl chain, also cyclized in high *ee* and compares favourably with the 73 % *ee* obtained in the indoline system.[60] Straight-chain alkyl groups, which were not tolerated in

the indoline system, proved effective in the azaindoline system, with a moderate *ee* of 75 % observed for *n*-propyl-substituted azaindoline **167r**.

With few other major alterations available to the imine substituent attention now turned to altering the pyridine segment of the substrates.

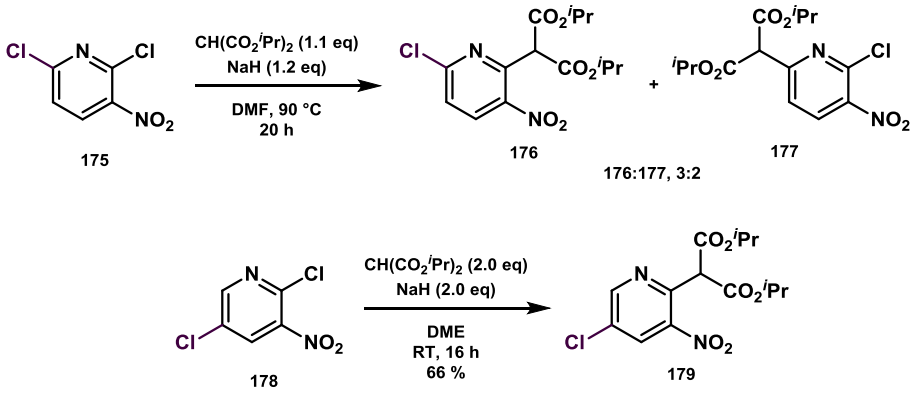
2.5.3. Substituted pyridines

The first area to be investigated was the introduction of substituents onto the pyridine ring. The installation of halide units would be particularly beneficial as they provide synthetic handles on which further transformations can be performed. For example cross-coupling reactions, such as Suzuki couplings or Buchwald-Hartwig aminations, would be effective ways to elaborate the azaindoline core (Scheme 2.27).



Scheme 2.27 – Functionalization of azaindolines by cross-coupling reactions

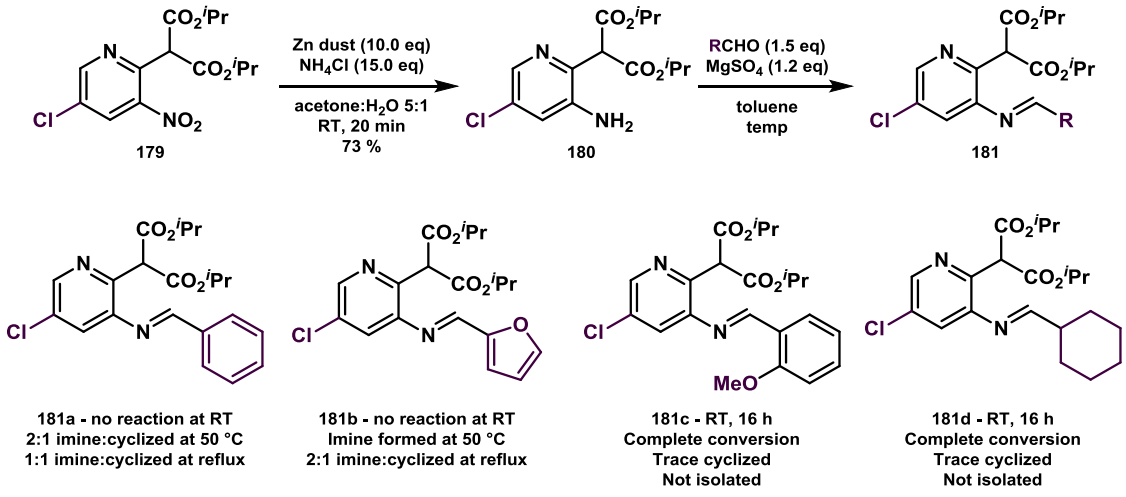
The planned synthesis followed an analogous route to the previous construction of 4-azaindolines. Initial attempts at S_NAr of 2,6-dichloro-3-nitropyridine (**175**) with diisopropyl malonate used one equivalent of the malonate to avoid disubstitution. However, while no disubstituted product was observed, the desired product was formed as part of an inseparable 3:2 mixture of regioisomers **176** and **177**, along with remaining starting materials (Scheme 2.28).



Scheme 2.28 – S_NAr reactions of dichloro-nitropyridines

Therefore, it was decided to switch to 2,5-dichloro-3-nitropyridine (**178**), in which only the chloride at the desired substitution position is activated by the nitro group. Following a modified literature procedure nitropyridine **179** was isolated in 66 % yield.[91]

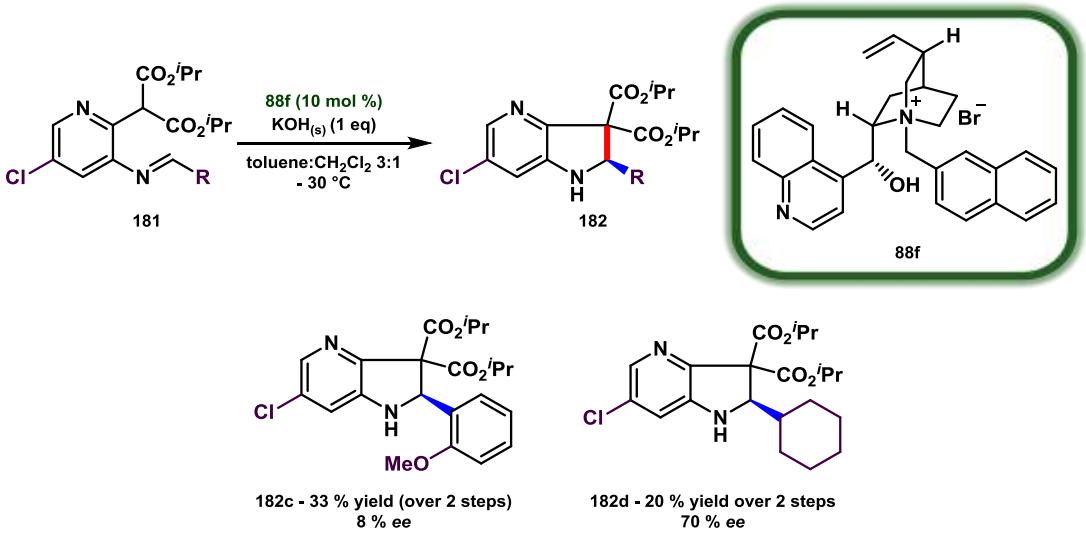
Fearing that the hydrogenative reduction of the nitro group employed in the previous synthesis would result in hydrodehalogenation of the chloro substituent we instead turned to a zinc reduction protocol.[92] This proceeded in good yield and left the chloro substituent intact, while also proceeding at a faster rate than the hydrogenation process. Unfortunately, imine formation proved problematic with only a small selection of aldehydes forming the desired imines at room temperature (Scheme 2.29).



Scheme 2.29 – Imine formations using chloro-aminopyridine 180

Raising the reaction temperature for unreactive aldehydes to 50 °C was successful in forcing the reaction to go to completion, but also resulted in significant formation of cyclized material, exemplified by substrates **181-a** and -**b**. Pleasingly, imines **181-c** and -**d** formed at room temperature, with only trace quantities of cyclized material observed. These imines were taken forward without further purification in a "one-pot" cyclization process.

Cyclization of these imines occurred in lower yields when compared to examples with an unsubstituted pyridine ring, with the reaction failing to reach full conversion (Scheme 2.30).



Scheme 2.30 – Asymmetric cyclization of pyridines bearing a chlorine substituent

The imine bearing an aromatic group, **181c**, cyclized with only 8 % *ee*. In contrast, cyclohexane-substituted azaindoline **182d** was formed in a vastly improved 70 % *ee*. The reason for this marked difference in enantioselectivity is not immediately apparent. Cyclization of crude phenyl-substituted imine **181a** resulted in an inseparable mixture of cyclized material and remaining imine. HPLC analysis showed the cyclized material was racemic; suggesting that the lack of enantioinduction observed in **181c** is general to imines bearing aromatic groups in this system. Given that cyclization of **181d** affords enantioenriched material it is unlikely that this is a steric effect, but the exact nature of the

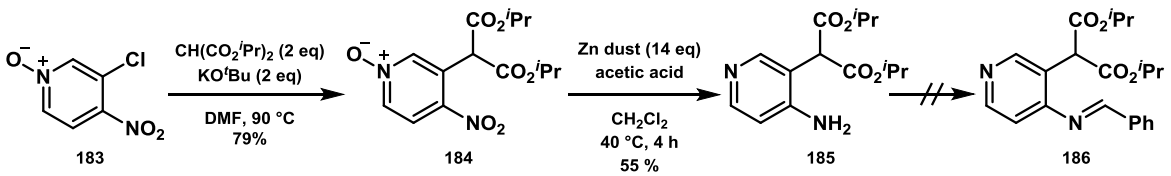
catalyst-substrate interaction leading towards these observations is not immediately apparent.

Despite the setbacks faced during the synthesis of chloride-substituted azaindolines the asymmetric synthesis of 4-azaindolines has been successful, showing tolerance of a wide variety of substituents on the imine and generating a variety of highly functionalized azaindolines in good yields with moderate to excellent degrees of enantiocontrol. The next stage of this investigation was to determine whether this process could be extended to the other azaindoline isomers.

2.6. Synthesis of the isomeric azaindolines

2.6.1. 5-azaindoline synthesis

Investigations previously carried out in our group had attempted the synthesis of 5-azaindolines prior to the initial development of the 4-azaindoline system.[86] This synthesis initially progressed smoothly; S_NAr of commercially available pyridine *N*-oxide **183**, afforded nitroarene **184** in 79 % yield (Scheme 2.31). Reduction of the nitro group and removal of the *N*-oxide functionality could be achieved concurrently in 55 % yield, utilizing zinc in acetic acid.



Scheme 2.31 – Attempted synthesis of 5-azaindolines

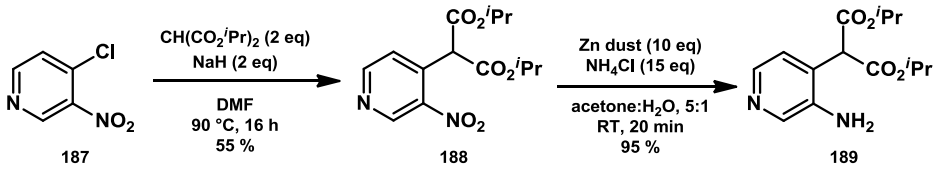
However, in a similar manner as observed in the chlorine-substituted 4-azaindoline system (Chapter 2.5.3) the imine formation step failed to go to completion over several days, with higher temperatures resulting in either a mixture of products or complete conversion to the

azaindoline. This can be attributed to the reduced nucleophilicity of aminopyridine **185**, caused by the electron-withdrawing nature of the pyridine nitrogen situated *para* to the amine group. This is analogous to the rationale behind the proton transfer observed during carbolithiation to form 5- and 7-azaindolines (Chapter 2.1.2).

With this previous knowledge it is clear that attempted synthesis of 7-azaindolines would likely be similarly futile as the pyridine nitrogen being situated in an *ortho* relationship with the amine will result in a similar deactivation of the aminopyridine. Therefore, our efforts to apply our optimized cyclization procedures to the synthesis of isomeric azaindolines focused exclusively on the 6-azaindoline scaffold, which should not face this problem.

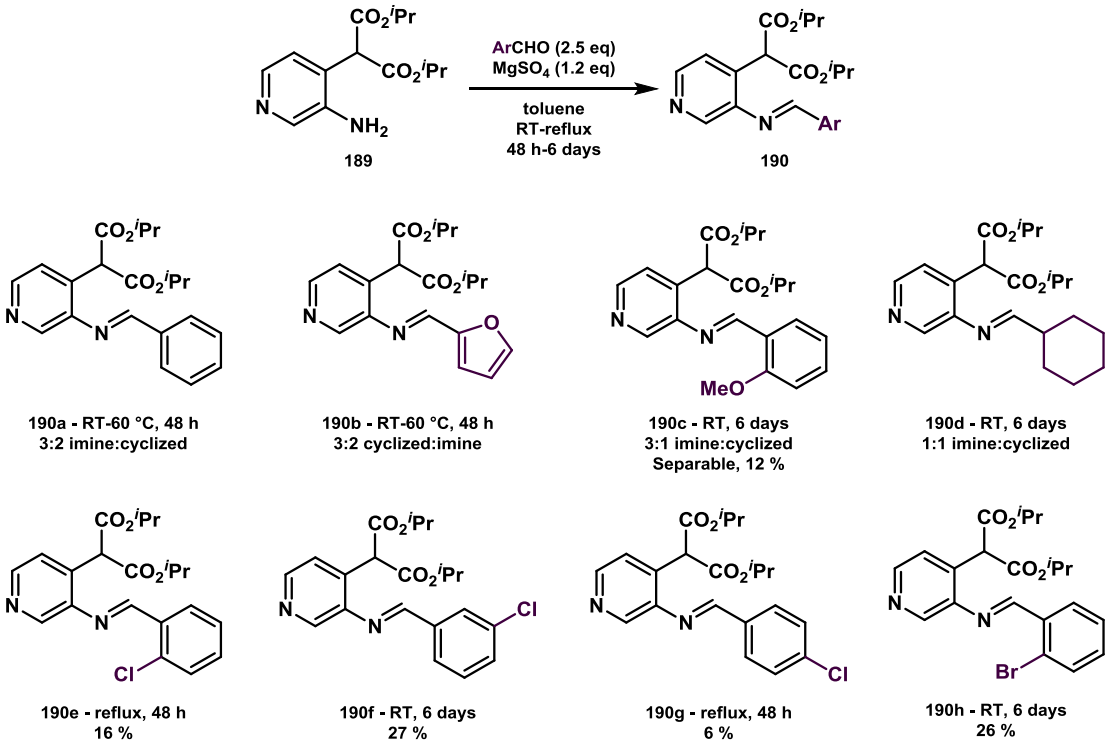
2.6.2. 6-azaindoline synthesis

The now familiar synthetic route to the required aminopyridine **189** was employed (Scheme 2.32), with zinc chosen for the reduction step over palladium due to the more favourable reaction rate.



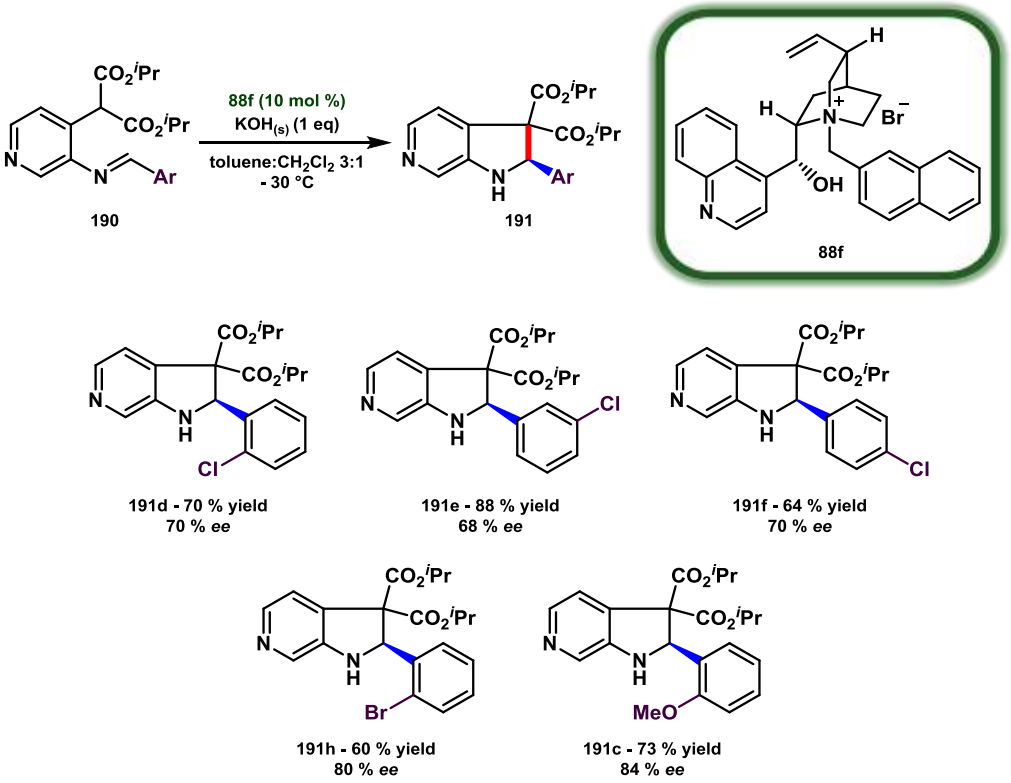
Scheme 2.32 – Synthesis of aminopyridine 189

Imine formation proved to be less straightforward than anticipated, with substrates that had been facile to synthesize in the 4-azaindoline system leading to exceptionally low yields even with prolonged reaction times, or in several cases failing to go to completion (Scheme 2.33). Increasing the reaction temperature resulted in undesired cyclization to the azaindoline with more reactive substrates (**190a**-**d**), or failed to aid conversion for chloro-substituted aldehydes (**190-e** and **-g**).



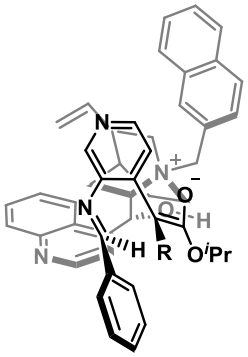
Scheme 2.33 – 6-azaindolines – synthesis of imine precursors

The cyclization conditions were then applied to the imines which had been successfully isolated (Scheme 2.34). Similar patterns were observed as for the 4-azaindolines, with *ortho* and *para* substituents on the aryl groups typically giving higher *ee* values than *meta* substituents. Enantioselectivities were typically around 10 % lower than the equivalent 4-azaindoline, with the exception of the *meta*-chloro-substituted 6-azaindoline **191e**, which exhibited an identical *ee*. The azaindoline bearing a *para*-chloro group was worst affected with a drop to 70 % *ee*.



Scheme 2.34 – Asymmetric synthesis of 6-azaindolines

The decrease in selectivity may be rationalized with reference to the proposed stereochemical model. The position of the nitrogen in the pyridine ring is now too distal from the positively charged area of the catalyst to participate in ion-pairing interactions (Scheme 2.35). This could potentially lead to alternative modes of binding which result in lower selectivities.



192 - R = $CO_2{}^iPr$

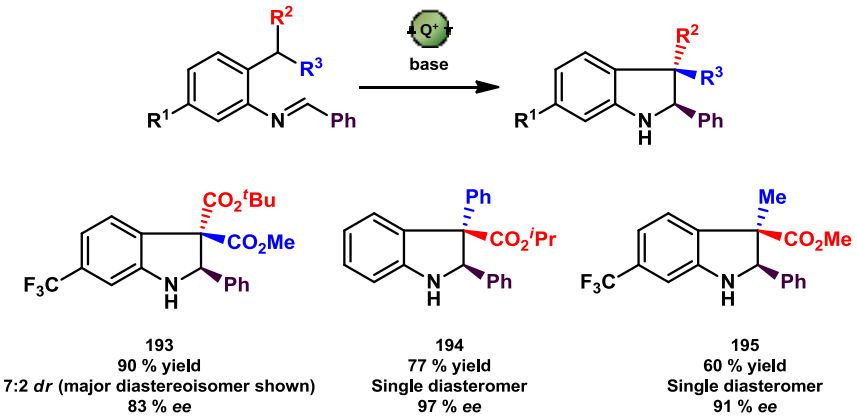
Scheme 2.35 – Rationale for diminished selectivity in the synthesis of 6-azaindolines

Thus, the asymmetric cyclization of 6-azaindolines proceeded in good yields and with moderate *ee* further extending the scope of the cyclization process.

2.7. Diastereo- and enantio-selective synthesis of 4-azaindolines

2.7.1. Concept

By replacing one of the ester groups of the azaindoline substrate with an alternative electron-withdrawing group the cyclization process can be utilized to form diastereomeric products. At the time of embarking on this project preliminary work had been carried out on the indoline system (Scheme 2.36).[60,85] The simplest modification, utilizing two different ester groups **193**, resulted in good enantioselectivity but a modest *dr* of 7:2. On the other hand, replacing one ester with a phenyl group **194** resulted in the formation of a single diastereomer in excellent *ee*. Diastereoselective cyclization of a precursor bearing only a single electron-withdrawing group was also successful, with methyl-substituted derivative **195** obtained in 91% *ee* and as a single diastereoisomer, albeit in reduced yield.

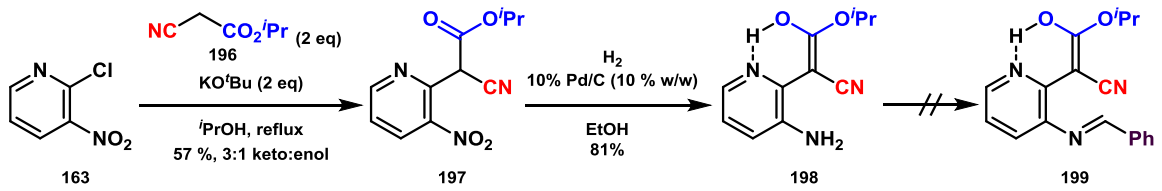


Scheme 2.36 – Diastereoselective cyclizations – concept and previous work

Work on extending the scope and probing the mechanism of this process is ongoing in our group and as part of this effort we wished to examine the potential of the azaindoline system to participate in diastereo- and enantio-selective reactions.

2.7.2. *Substrate synthesis – isopropyl cyanoacetate system*

Initial efforts in this area focused on the synthesis of a derivative bearing an ester and a nitrile group as preparations of similar substrates had been demonstrated in the literature, allowing required nitropyridine **197** to be accessed *via* a modified literature procedure.[93] S_NAr of 2-chloro-3-nitropyridine proceeded in 57 % yield with the product observed to be a 3:1 mixture of keto and enol forms by ^{1}H-NMR spectroscopy. Reduced product **198** showed a preference for the enol form, with the keto tautomer undetectable by ^{1}H-NMR spectroscopy. Surprisingly, treatment of **198** under standard imine formation conditions returned mostly aminopyridine. Presumably the nitrogen lone pair is sufficiently involved with the conjugated system of the enol to reduce its nucleophilicity and prevent attack on an aldehyde.



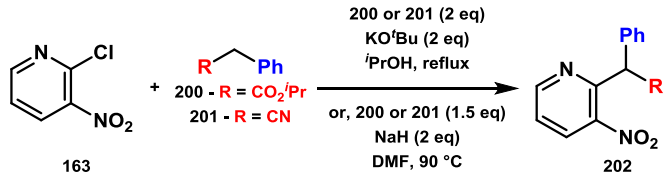
Scheme 2.37 – Attempted synthesis of imine 199

With the failure of this substrate to form the desired imine an alternative nucleophile had to be sought to make the desired imine precursor.

2.7.3. *Substrate synthesis – aromatic substitution*

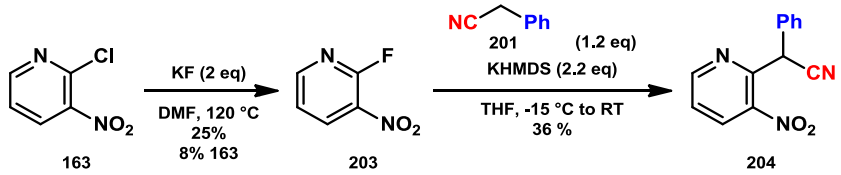
Attention turned to two alternative nucleophiles, isopropyl phenylacetate (**200**) and phenylacetonitrile (**201**). Attempts to utilize the same conditions as for the isopropyl cyanoacetate S_NAr reaction met with failure for both substrates, returning mostly starting material (Scheme 2.38). Switching to NaH in DMF again failed to convert with **200**, while **201** formed a complex mixture of products. The inactivity of **200** suggested it was a poorer

nucleophile than both **196** and **201**, so efforts to develop an efficient substitution reaction mainly focused on **201** as the nucleophile.



Scheme 2.38 – Attempted S_NAr reactions to form nitropyridine 202

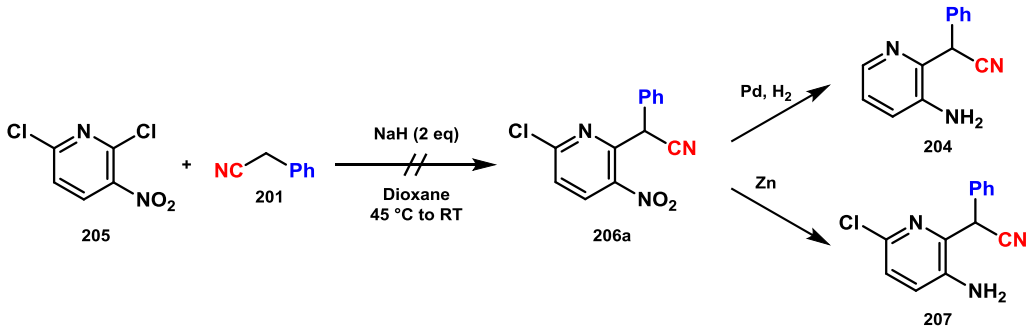
Literature precedent suggested that fluoronitrobenzenes could participate in S_NAr reactions with phenylacetate-derived nucleophiles using KHMDS as a base.[94] This procedure was ineffective when chloronitropyridine **163** was used. Therefore, fluoronitropyridine **203** was synthesized using KF in DMF in the hope that the reaction would proceed with the more reactive aryl fluoride.[95] Conversion to the aryl fluoride was incomplete after 16 hours, with approximately 14 % starting material remaining. Purification by Kugelrohr distillation could only reduce this to 8 % as the boiling points of the aryl halides were very similar, leading to a 25 % yield of fluoropyridine **203**. Pleasingly, a S_NAr reaction with phenylacetonitrile afforded the desired nitropyridine **204** in 36 % yield (Scheme 2.39). However, the low overall yield of this process meant that alternative conditions were sought.



Scheme 2.39 – Synthesis of nitropyridine 204 from fluoronitropyridine 203

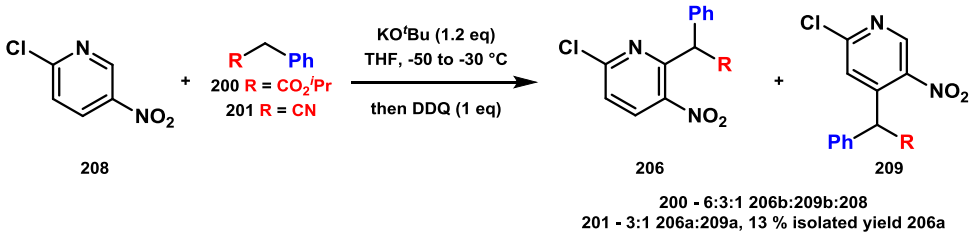
A search of the patent literature revealed a published synthesis of chloro-substituted derivative **206** utilizing NaH in dioxane.[96] This approach was attractive as access to both desired aminopyridine **204** and chloro-substituted aminopyridine **207** should be possible by utilizing divergent conditions for reduction of the nitro functionality (Scheme 2.40).

Unfortunately, the reaction did not perform satisfactorily in our hands, forming a complex mixture of products. The authors suggested that the salt of the product precipitated during the reaction and could be filtered off, but this was not observed during our attempts at the reaction.



Scheme 2.40 – Attempted S_NAr of dichloronitropyridine 206

An alternative approach to chloro-nitropyridine **206** is to utilize oxidative nucleophilic substitution of hydrogen (ONSH).[97] As this reaction proceeds through a dearomatized intermediate and there is no leaving group on the nucleophile to restore aromaticity, a stoichiometric oxidant has to be employed to achieve this. Both **201** and the less nucleophilic **200** reacted successfully under these conditions, employing DDQ as the oxidant (Scheme 2.41).

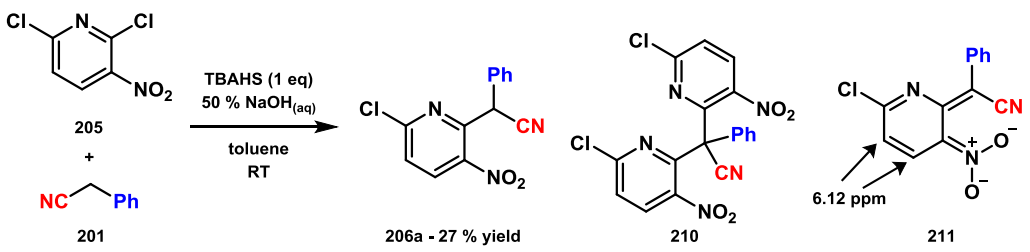


Scheme 2.41 – Vicarious nucleophilic substitution route to 206

200 yielded an inseparable 6:3:1 mixture of the desired product **206b**, its isomer **209b** and starting material **208**. Use of phenylacetonitrile (**201**) resulted in complete conversion, also with a 3:1 ratio of regioisomers. Separation by chromatography proved exceptionally

difficult and only a 13 % isolated yield of **206a** could be achieved so this route too was abandoned.

Given the prevailing use of phase-transfer catalysis during this thesis it is perhaps unsurprising that this became our port of call in times of struggle. Phase-transfer catalyzed S_NAr reactions with carbanions are well known with Mąkosza having demonstrated that phase-transfer reactions closely related to the desired transformation require the use of stoichiometric "catalyst." This is because the product of the reaction is of a higher acidity than the starting material and forms a salt with the catalyst, hence preventing catalyst turnover and leading to poor conversion to the desired product.[98] Applying Mąkosza's conditions to the synthesis of **206a** resulted in the formation of a mixture of products with a 27 % yield of the desired nitropyridine (Scheme 2.42). The impurities formed could not be isolated and analysis of the crude NMR spectrum proved challenging. However, the crude ^{1}H-NMR spectrum showed that phenylacetonitrile was remaining, along with a coupled pair of aromatic doublets attributed to **210**. As the product is highly acidic it seemed reasonable to assume that the product would be deprotonated under the reaction conditions and may participate in a further S_NAr reaction with **205**. This conclusion is supported by the integration of the aromatic peaks assumed to be from the resultant disubstituted product **210** revealing there was an approximately 1:1 ratio of **210** and phenylacetonitrile.



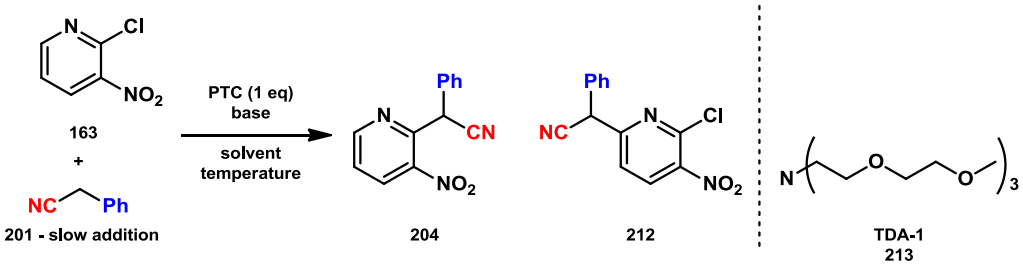
Scheme 2.42 – Phase-transfer catalyzed synthesis of 206a and proposed side-products

As further impurities remained unidentified we treated product **206a** under the same reaction conditions to test its stability. On sampling the reaction no **206a** was observed, instead there was a new set of peaks in the ^{1}H-NMR spectrum, which were also present in the spectrum of the crude reaction mixture previously. However, when the reaction was worked up in an attempt to identify the product ^{1}H-NMR spectroscopy revealed the reappearance of **206a**. Given that the new peaks showed unusually low shifts for an aromatic compound and the regeneration of the product on workup it can be assumed that this product is salt **211**, presumably associated with the phase-transfer catalyst, although the sodium salt cannot be ruled out.

Thus, two problems were potentially responsible for the modest yield achieved in the phase-transfer catalyzed reaction. One was the formation of the double S_NAr product **210**, which should be easily alleviated by slow addition of the chloronitropyridine. As this modification may result in disubstitution of **205**, it seemed prudent to return to reactions employing mono-chloro-substituted nitropyridine **163**. The second problem was salt formation which we envisaged could be avoided by moving away from cationic phase-transfer catalysts to formally neutral variants.

Examination of the literature revealed that the "trident" catalyst TDA-1[99] (**213**), essentially an acyclic equivalent of a crown-ether, had been successfully employed in S_NAr reactions with chloropyridines, albeit utilizing more reactive alkoxide nucleophiles.[100] A small screen was carried out, initially based on these literature conditions (Table 4). Utilizing the exact conditions in the literature procedure led to complete consumption of starting material and formation of desired product **204** in 38 % yield (entry **1**). Mass spectrometry indicated the presence of a vicarious nucleophilic substitution product, assumed to be **212**, given both the

tendency of ONSH to occur in the *ortho*-position to activating groups, and ^{1}H-NMR chemical shifts suggesting substitution had most likely occurred adjacent to the pyridine nitrogen. Alternative neutral phase-transfer catalysts such as 18-crown-6 and PEG-400 led to reduced or zero conversion (entries **2** and **3**).



Entry	PTC	Base	Solvent	Temp.	Outcome
1	TDA-1	KOH (4 eq), K_2CO_3 (1 eq)	Toluene	RT	38 % **204**, **212** present by MS
2	18-crown-6	KOH (4 eq), K_2CO_3 (1 eq)	Toluene	RT	Incomplete conversion
3	PEG-400	KOH (4 eq), K_2CO_3 (1 eq)	Toluene	RT	No conversion
4	TDA-1	KOH (4 eq)	Toluene	RT	Complete conversion
5	TDA-1	K_2CO_3 (2 eq)	Toluene	RT	No conversion
6	TDA-1	KOH (2 eq)	Toluene	RT	Incomplete conversion
7	TDA-1	KOH (4 eq)	THF	RT	Complete conversion, faster rate
8	TDA-1	KOH (4 eq)	Toluene	Reflux	Complex mixture
9	TDA-1	KOH (4 eq)	THF	50 °C	67 % **204**, no **212** observed

Table 4 – Screen of neutral phase-transfer catalysts for synthesis of nitropyridine 204

For the TDA-1 reaction, use of KOH alone also led to consumption of starting material (entry **4**), whereas no conversion was seen with K_2CO_3 (entry **5**), suggesting it has little role to play in the reaction and was insufficiently basic to deprotonate **201** at room temperature. Reducing the stoichiometry of KOH led to incomplete conversion (entry **6**). The reaction progressed more rapidly when carried out in a more polar solvent such as THF (entry **7**). Given that ONSH typically occurs at lower temperatures the best way to minimise formation

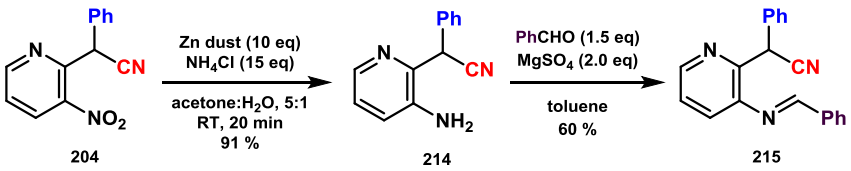
of assumed impurity **212** would be to carry out the reaction at elevated temperatures. Disappointingly the use of the optimized conditions in toluene at reflux led to a complex mixture of products and incomplete conversion of **163** (entry **8**). However, when the optimized conditions were used with THF at 50 °C, complete conversion was observed with no indication of the presence of **212** by mass spectrometry (entry **9**).

The final process improvement required was the removal of TDA-1, which was problematic to completely separate by chromatography. Pleasingly this issue was solved by carrying out a final wash with pH 6 phosphate buffer during the workup. This removed the more strongly basic catalyst, while leaving the nitrogen of the pyridine ring unprotonated. This process afforded **204** in a practically useful 67 % yield on a multigram scale.

Unfortunately these conditions did not extend to the use of isopropyl phenylacetate (**200**) as a nucleophile, with only starting materials returned. However, with **204** in hand, progress towards a diastereoselective cyclization of azaindolines could now continue.

2.7.4. Completion of substrate synthesis

After the challenges of developing the S_NAr reaction the remainder of the synthesis of imine **215** was more facile (Scheme 2.43).



Scheme 2.43 – Completion of synthesis of imine 215

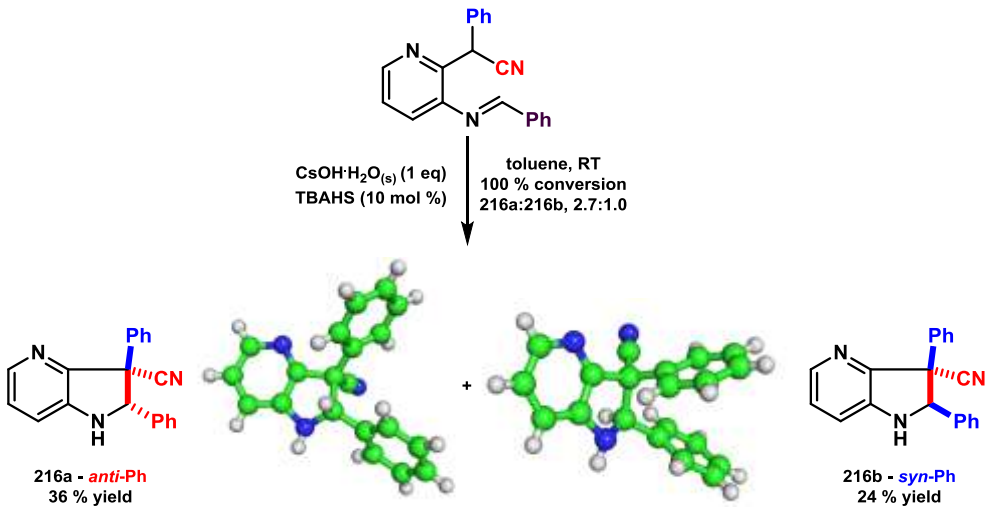
The previously employed zinc reduction conditions afforded the required aminopyridine **214** in excellent yield, and subsequent imine formation also proceeded smoothly. Due to the

high insolubility of the imine product in ether purification was achieved *via* straightforward trituration, with imine **215** isolated in 60 % yield.

With a robust synthesis of imine **215** developed the diastereoselective cyclization could now be investigated.

2.7.5. Racemic diastereoselective cyclization

The cyclization was initially tested using the racemic phase-transfer catalyst tetrabutylammonium bisulfate (TBAHS). Treatment of imine **215** with 10 mol % TBAHS and one equivalent of $CsOH{\cdot}H_2O$ resulted in complete conversion to cyclized product **216** as a 2.7:1.0 mixture of diastereomers, as determined by ^{1}H-NMR analysis of the crude reaction mixture (Scheme 2.44). Separation of the diastereomers by chromatography was challenging, hence accounting for the sub-optimal isolated yield. Recrystallization of the pure diastereomers and analysis by single crystal X-ray diffraction revealed that the major diastereomer **216a** exhibited an *anti* relationship between the two phenyl groups.[87]



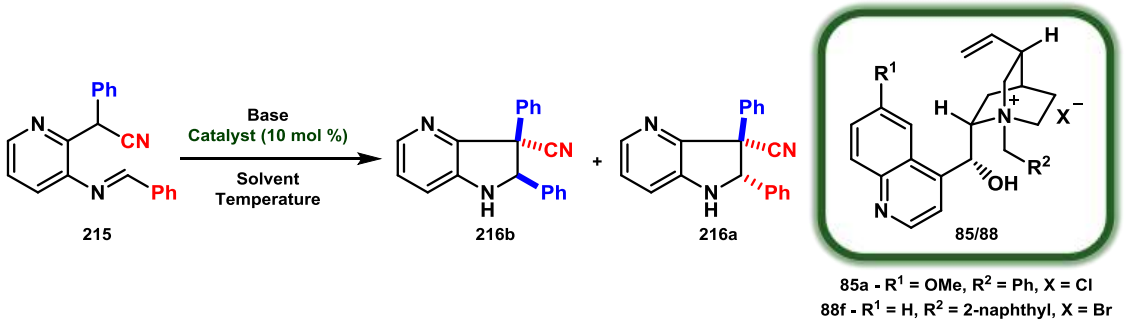
Scheme 2.44 – Racemic phase-transfer catalyzed cyclization of imine 215

Whilst the level of diastereoselectivity was modest the reactivity observed was encouraging and asymmetric cation-directed catalysis was subsequently investigated.

2.7.6. Cation-directed diastereo- and enantio-selective cyclization

The diastereoselective cyclization was first trialled under the same conditions developed in Chapter 0 (Table 5). Hence, cyclization utilizing catalyst **88f** and one equivalent of solid KOH in a 3:1 mixture of toluene and CH_2Cl_2 at -30 °C afforded the diastereomer **216b** with the phenyl groups in a *syn*-relationship as the major product, the opposite to that seen in the racemic cyclization (entry **1**). The diastereoselectivity was modest with ^{1}H NMR analysis of the crude reaction mixture showing a 1.5:1.0 ratio of isomers. Enantioselectivity was also modest, with the major diastereomer having an *ee* of 54 % and the minor 24 %. Further reduction of the reaction temperature in an effort to improve stereoselectivity resulted in incomplete conversion (entry **2**). Concurrent work in our group on the equivalent indoline system had demonstrated that a single diastereomer could be obtained utilizing *N*-benzylquininium chloride (**85a**) as the catalyst and cesium hydroxide as the base.[101] Use of these conditions led to a marginally reduced *dr* and an *ee* of 30 % (entry **3**). While these results were disappointing, given the success with these conditions in the closely related indoline system we decided to proceed with altering them in an attempt to improve selectivity. Removing CH_2Cl_2 led to a small decrease in diastereoselectivity and had no effect on enantioselectivity (entry **4**). Given the minimal effect of removing CH_2Cl_2 it was decided to use toluene alone as the solvent as this made screening operationally simpler. Using a large excess of base resulted in a complete loss of diastereocontrol and a small drop in *ee* (entry **5**). Slight diastereocontrol was restored by use of substoichiometric base, though this resulted in a halving of *ee* (entry **6**). Returning to KOH as the base led to exactly the same degree of enantiocontrol as $CsOH{\cdot}H_2O$ but again saw no preference for either diastereomer (entry **7**). Although small effects were seen on selectivity through choice of base and its

stoichiometry these were often within measurement errors for the integration of ^{1}H NMR peaks (up to 10 %).



85a - R^1 = OMe, R^2 = Ph, X = Cl
88f - R^1 = H, R^2 = 2-naphthyl, X = Br

Entry	Catalyst	Base	Solvent	Temp.	dr (216b:216a)[a]	ee (216b) (%)[b]
1	**88f**	KOH (1 eq)	Toluene:CH_2Cl_2, 3:1	-30 °C	1.5:1.0	54
2	**88f**	KOH (1 eq)	Toluene:CH_2Cl_2, 3:1	-50 °C	Incomplete conversion	
3	**85a**	CsOH·H_2O (1 eq)	Toluene:CH_2Cl_2, 3:1	-30 °C	1.3:1.0	30
4	**85a**	CsOH·H_2O (1 eq)	Toluene	-30 °C	1.1:1.0	30
5	**85a**	CsOH·H_2O (5 eq)	Toluene	-30 °C	1.0:1.0	24
6	**85a**	CsOH·H_2O (0.2 eq)	Toluene	-30 °C	1.5:1.0	14
7	**85a**	KOH (1 eq)	Toluene	-30 °C	1.0:1.0	30

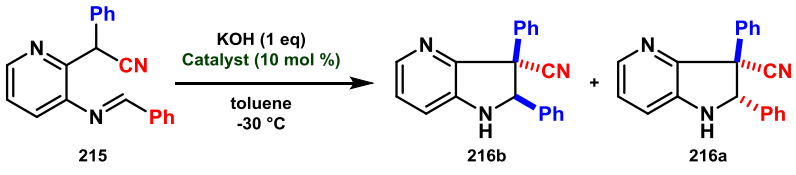
a) determined by analysis of crude ^{1}H NMR spectra, b) determined by chiral HPLC

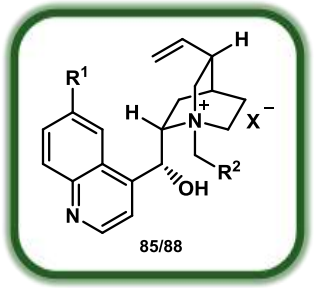
Table 5 – Initial screening of conditions for diastereoselective cyclization

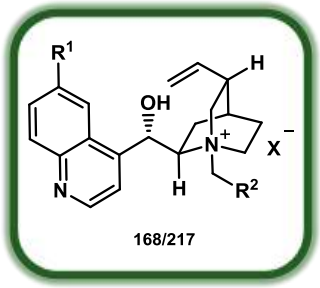
It seemed at this stage that the choice of catalyst was likely to have a far more dramatic effect on stereoselectivity and so we decided to embark on a screen of catalysts. Despite the inferior performance of KOH in terms of diastereoselectivity it was chosen as the base for screening due to its lower hygroscopicity making it easier to handle in the small quantities required for screening.

The first catalyst to be screened was cinchonidine-derived catalyst **88e** (Table 6). This improved on the diastereoselectivity previously achieved with the quinine-derived catalyst by a factor of two, although *ee* decreased by the same factor (entries **1** and **2**). Switching to the pseudoenantiomeric equivalents of these catalysts, **217a** and **168b**, led to a further

increase in diastereoselectivity, with both approaching a 3:1 ratio in favour of **216b** (entries **3** and **4**). Catalyst **168b** exhibited a superior enantioselectivity with an *ee* of 40 % for the major diastereomer. Increasing the steric bulk of the quaternizing group resulted in an improved diastereomeric ratio when anthracenyl-substituted catalysts **85b** and **88c** were employed, with a two-fold improvement of diastereocontrol (compare entries **1** and **5**, and **2** and **6**).







85a - R^1 = OMe, R^2 = Ph, X = Cl
85b - R^1 = OMe, R^2 = 9-anthracenyl, X = Cl
88c - R^1 = H, R^2 = 9-anthracenyl, X = Cl
88e - R^1 = H, R^2 = Ph, X = Cl

168b - R^1 = H, R^2 = Ph, X = Cl
168c - R^1 = H, R^2 = 9-anthracenyl, X = Cl
217a - R^1 = OMe, R^2 = Ph, X = Br
217b - R^1 = OMe, R^2 = 9-anthracenyl, X = Cl

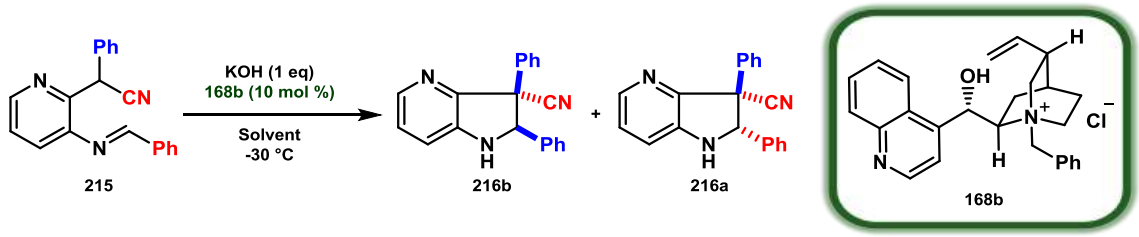
Entry	Catalyst	dr (216b:216a)[a]	ee (*syn*) (%)[b]
1	**85a**	1.0:1.0	30
2	**88e**	1.8:1.0	16
3	**217a**	2.7:1.0	-22
4	**168b**	2.8:1.0	-40
5	**85b**	2.1:1.0	10
6	**88c**	4.5:1.0	28
7	**217b**	4.2:1.0	0
8	**168c**	Incomplete conversion	

a) determined by analysis of crude ^{1}H NMR spectra, b) determined by chiral HPLC

Table 6 – Diastereoselective cyclization catalyst screen

Interested to determine if improvements from switching to the pseudoenantiomeric catalysts and increase in steric bulk would be cumulative, we screened catalyst **217b** and gratifyingly a four-fold enhancement of diastereoselectivity was observed (compare entries **1** and **7**). Unfortunately, no enantioselectivity was observed with this catalyst. If the pattern observed was to continue with catalyst **168c** then it should lead to the highest *dr* obtained thus far. Disappointingly when this catalyst was used the reaction failed to go to completion after three days (entry **8**).

As hypothesized, the choice of catalyst had a more profound effect on *dr* than the previous parameters screened. Now that improvements had been made a screen of solvents was carried out, utilizing catalyst **168b**, which had the best balance between diastereo- and enantio-selectivity (Table 7).



Entry	Solvent	dr (216b:216a)[a]	ee (216b) (%)[b]
1	Toluene	2.8:1.0	-40
2	Di*iso*propylether[c]	1.0:1.0	ND[d]
3	Hexane:CH_2Cl_2 1:1[c]	1.9:1.0	ND
4	Chlorobenzene	2.3:1.0	-4
5	Acetonitrile	1.0:5.3	0

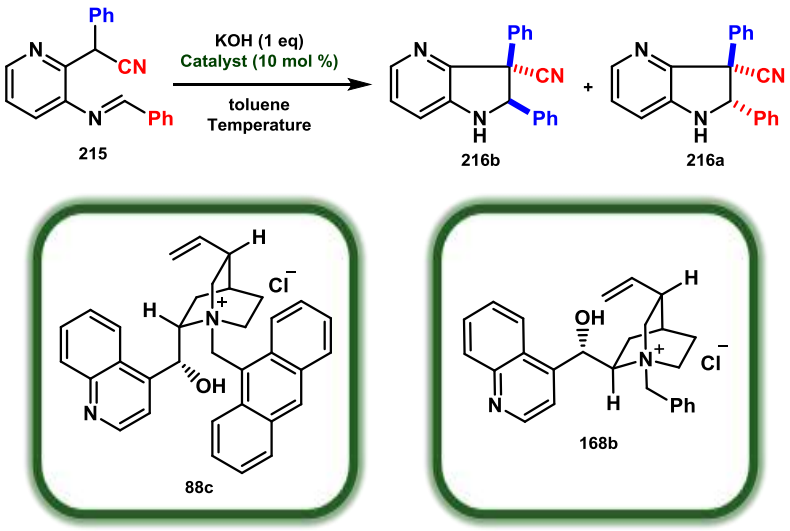
a) determined by analysis of crude ^{1}H NMR spectra, b) determined by chiral HPLC, c) incomplete conversion, d) ND = not determined

Table 7 – Diastereoselective cyclization solvent screen

An ethereal solvent led to a 1:1 mixture of diastereoisomers and did not go to completion after four days (entry **2**). A biphasic mixture of hexane and CH_2Cl_2 also resulted in partial conversion, though did restore a degree of diastereoselectivity (entry **3**). Chlorobenzene proved to be less diastereoselective than toluene and also degraded enantioselectivity to an almost non-existent level (entry **4**).

Acetonitrile produced a result that at the time seemed rather anomalous. Although the *dr* of 5.3:1.0 was the highest achieved thus far it was unexpectedly in favour of the *anti*-phenyl isomer **216a**.

Given that diastereoselectivity was not improving significantly it was decided to focus on enantioselectivity. Past work in the group has shown that careful optimization of temperature is required to obtain the highest possible enantioselectivity in phase-transfer-catalyzed reactions. Therefore, it was decided to carry out a temperature screen, utilizing two catalysts to ensure the results were general. It transpired that the diastereoselectivities obtained from this screen were rather intriguing. Both catalysts exhibited an increasing preference for the *anti* diastereomer **216a** as the temperature of the reaction was raised (Table 8). This suggested that the reaction may be a reversible process, with equilibration between the two diastereomers. Thus, at lower temperatures the kinetically favoured product is obtained, whereas at room temperature equilibration occurs, leading to formation of the thermodynamically favoured product. This process has been postulated previously in our group for reactions conducted with tetrabutylammonium catalysts but past work with *cinchona*-derived catalysts always led to the kinetically favoured product, which is formed as a single diastereomer even when the reaction is carried out at room temperature.[85]

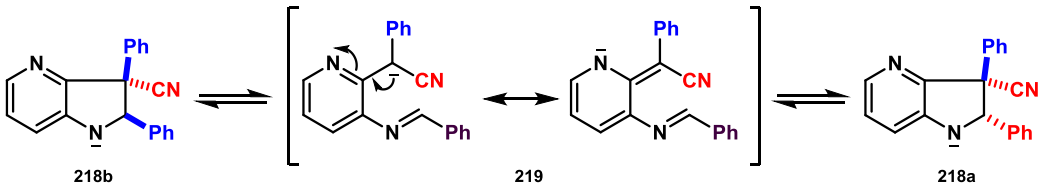


Entry	Catalyst	Temp.	dr (216b:216a)[a]	ee (216b) (%)[b]
1	**88c**	-30 °C	4.5:1.0	28
2	**88c**	-10 °C	3.0:1.0	18
3	**88c**	RT	1.0:2.0	0
4	**168b**	-30 °C	2.8:1.0	-40
5	**168b**	-10 °C	1.0:2.0	-46
6	**168b**	RT	1.0:3.0	0

a) determined by analysis of crude ^{1}H NMR spectra, b) determined by chiral HPLC

Table 8 – Diastereoselective cyclization temperature screen

A possible explanation for the difference between the two systems lies with the nitrogen on the pyridine ring. This nitrogen can offer extra stabilization of anionic intermediate **219**, which is not available to the nitrogen anion of azaindoline **218**, hence making the reverse reaction more favourable than in the equivalent benzene-derived substrate.



Scheme 2.45 – Reversibility of azaindoline formation and potential stabilization of anionic intermediate

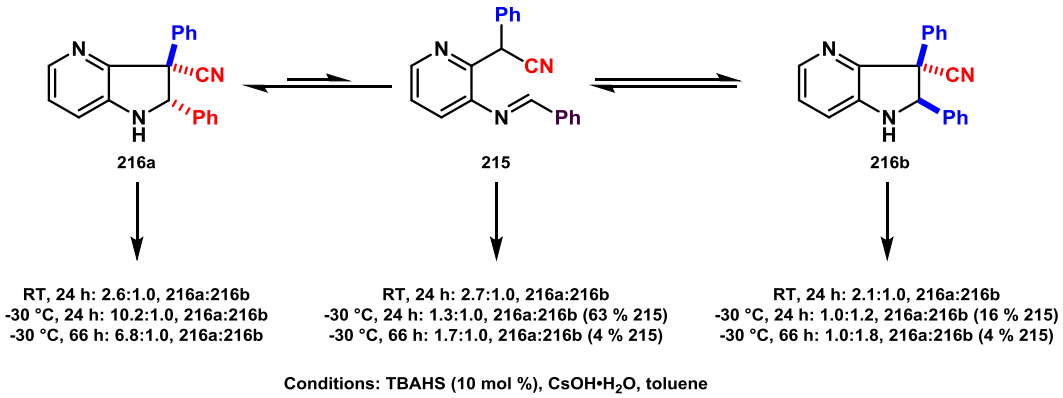
This explanation would also help account for the anomalous result observed with acetonitrile, as the use of a polar solvent for the reaction will disrupt ion-pairing interactions between the anionic reacting species and the positively charged phase-transfer catalyst. This results in azaindolinie anions **218** which are more reactive and hence more likely to undergo equilibration, leading to a preference for the thermodynamically favoured product, even at lower temperatures.

Having postulated that reversibility of the reaction may be responsible for the observed diastereoselectivity we wished to confirm this experimentally and also investigate how important this effect was in determining the diastereoselectivity of the reaction.

2.7.7. Equilibration studies

First of all, the reversibility of the reaction using an achiral phase-transfer catalyst was tested. Imine **215** and pure samples of each diastereomer were treated with $CsOH{\cdot}H_2O$ and the *dr* measured after 24 hours (Scheme 2.46). In all cases equilibration was observed, with the *anti* phenyl diastereomer **216a** the major product. When the same reactions were performed at -30 °C equilibration was also observed but was markedly slower. Equilibration of *anti* phenyl isomer **216a** for 24 h at -30 °C resulted in a *dr* of 10.2:1.0 in favour of *anti* phenyl isomer **216a**, compared to a *dr* of only 2.6:1.0 at room temperature. Similarly equilibration of *syn* phenyl isomer **216b** at -30 °C resulted in a 1.8:1.0 mixture of **216b**:**216a** after 66 h, in contrast to the same experiment at room temperature, which resulted in a product distribution favouring *anti* phenyl isomer **216a**. Further proof of equilibration came with the presence of imine **215** being detected in reaction samples from equilibration of *syn*-phenyl isomer **216b**. The formation of *anti*-phenyl isomer **216a** as the thermodynamic product of the reaction would be expected, as the nitrile group (A value 0.2) is significantly

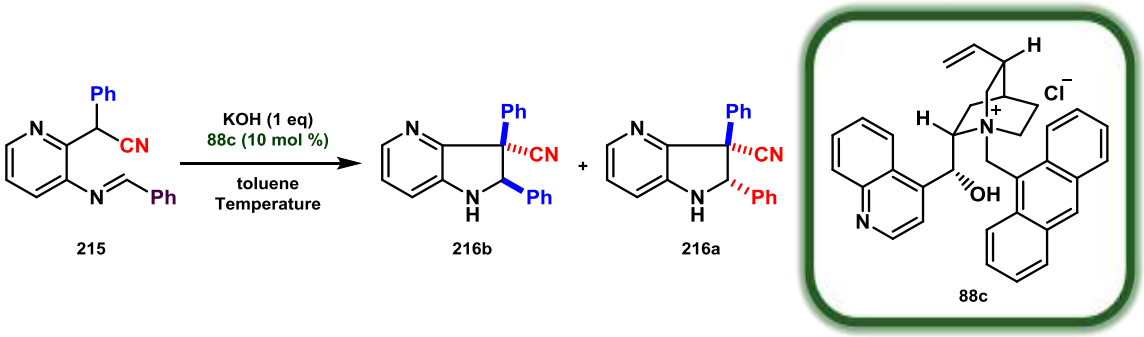
less bulky than the phenyl group (A value 3.1).[90] Hence, thermodynamic conditions favour the lower energy isomer where the phenyl groups are orientated away from each other. The modest *dr* obtained under thermodynamic control suggests that the difference in ground state energy between the two diastereomers is relatively low.



Scheme 2.46 – Equilibration under achiral phase-transfer catalysis

Having demonstrated the reversibility of the process and confirmed that *anti*-phenyl isomer **216a** is the thermodynamic product of the reaction the effect of equilibration with *cinchona* alkaloid-derived phase-transfer catalysts was examined (Table 9). The reaction of imine **215** at room temperature, using **88c** as the catalyst and KOH as the base, was monitored over one day by taking reaction aliquots and analysing them by ^{1}H-NMR spectroscopy. This revealed that at room temperature after an initial induction period of two to three hours, where no reaction was observed, the kinetically favoured *syn*-phenyl isomer **216b** was observed in modest *dr*. Over the course of the reaction the reversibility of the process allowed the thermodynamically favoured *anti*-phenyl isomer to predominate, with a 1.5:1.0 *dr* observed after 24 hours. Monitoring of the process under conditions which should favour the kinetic isomer at -30 °C proved more challenging as the induction period proved lengthier and hence the reaction was not monitored during the timeframe in which equilibration was taking place. The *dr* of the reaction was unchanged from its value at 24

hours after a further 5 days. This experiment confirmed that lower temperatures favoured formation of the kinetic product, but unveiled nothing about whether or not the reaction was reversible at -30 °C with *cinchona*-derived catalysts.



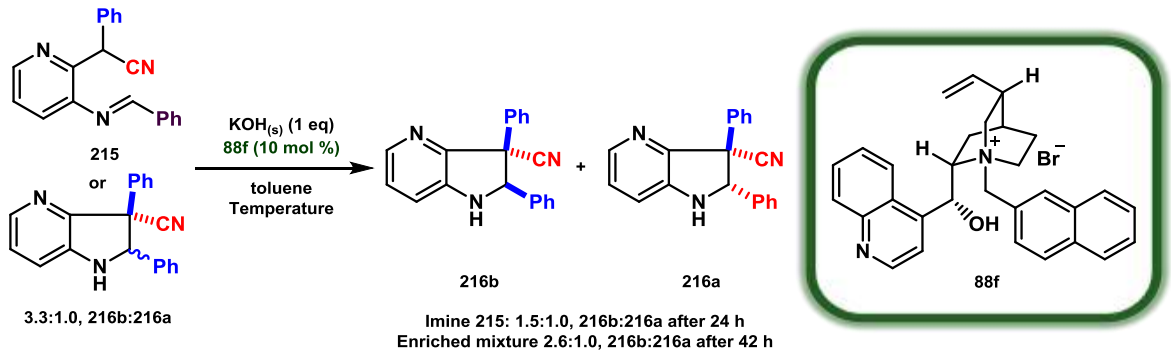
Temp.	Time	dr (216b:216a)[a]	Imine 215 (%)[a]
RT	2 h	-	100
RT	3 h	3.5:1.0	66
RT	6 h	1.3:1.0	0
RT	8 h	1.0:1.2	0
RT	24 h	1.0:1.5	0
-30 °C	8 h	-	100
-30 °C	24 h	3.8:1.0	0
-30 °C	6 days	3.9:1.0	0

a) Determined by ^{1}H NMR analysis of reaction aliquots

Table 9 – Equilibration under chiral phase-transfer catalysis

In an effort to elucidate whether the reaction was reversible at -30 °C an enriched mixture of diastereomers, with a 3.3:1.0 ratio in favour of the kinetic product **216b**, was submitted at -30 °C to one equivalent of solid KOH and catalyst **88f**, which had previously led to a 1.5:1.0 *dr* of **216b**:**216a**. After 42 hours, degradation in *dr* to 2.6:1.0 was observed (Scheme 2.47). This confirms that the reaction is reversible at -30 °C with *cinchona*-derived phase-transfer catalysts. However, the rate of equilibration is markedly slower than with

TBAHS; if it was assumed equilibration was occurring at a constant rate then it would take the marginally enriched mixture approximately five days to reach the *dr* value obtained by reaction of the imine. The contrast between rates of equilibration of the two classes of phase-transfer catalyst may be be governed by accessibility of the ammonium cation. As the tetrabutylammonium cation is less accessible than the *cinchona* alkaloid cation this means that ion-pairing is less tight and, as postulated for the use of polar solvents (Chapter 2.7.6), the azaindoline anion is more reactive and hence more prone to equilibration.



Scheme 2.47 – Reversibility study with chiral catalyst 88f

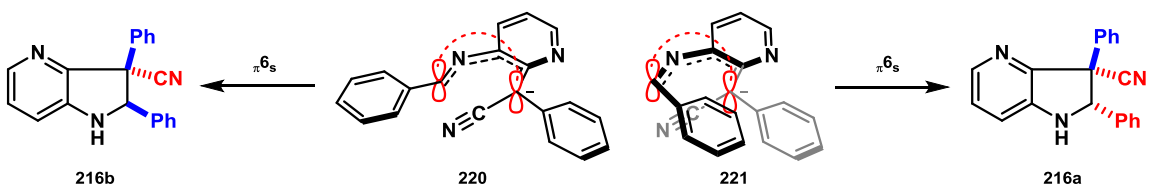
Given the slower equilibration with *cinchona*-derived catalysts and that the timescale of the asymmetric reaction was typically 24 hours or lower, it can be suggested that equilibration, while a contributing factor, is not the main reason for the modest diastereoselectivities obtained. Therefore, the reason for low diastereoselectivity must be due to a relatively low difference in energy between the transition states which lead to the two diastereomers. To ascertain why this is the case the mechanism of the cyclization must be considered.

2.7.8. Mechanistic considerations

The catalyst dependency of diastereoselectivity of the cyclization of **215** makes it clear that catalyst-substrate interactions must play a role in determining the transition state energy of the stereodetermining step. However, which of the many possible interactions are crucial is

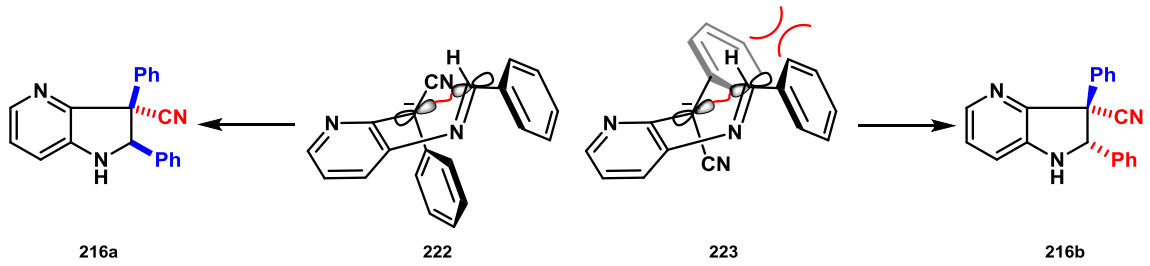
not immediately apparent without a detailed binding model between catalyst and substrate, which is a significant technical challenge.

Looking at the mechanistic aspects without consideration of the catalyst is still worthwhile. As previously discussed the two possible mechanisms for this reaction are a pericyclic pathway and an anionic pathway, which are challenging to distinguish. Considering the pericyclic pathway first; if the imine reacts in the *trans* configuration the orientation of the enolate will likely be such that the nitrile group points towards the imine, hence avoiding an unfavourable clash between the two phenyl groups in the transition state (**220**, Scheme 2.48). In this case disrotatory 6π-electrocyclization would be expected to yield the observed *syn*-phenyl isomer of the kinetic product. However, this process should be highly diastereoselective when the reaction is under kinetic control, which does not match our observations. Also, if the transition state is analogous to that of the indoline work, then computational evidence suggests that the pericyclic process proceeds through the *cis*-imine.[85] This would inevitably lead to a higher energy intermediate, that is likely to exist in a helical state to avoid steric clashes, rather than an idealized planar intermediate (**221**, Scheme 2.48). More tellingly, disrotatory cyclization would result in the incorrect stereochemical relationship for the observed kinetic product. Therefore, it seems unlikely that the reaction is proceeding *via* the electrocyclic mechanism.



Scheme 2.48 – Transition states for *cis*- and *trans*-imine 215 *via* a pericyclic mechanism

The anionic Mannich-type process has been proposed to progress through the *trans*-imine intermediate in the indoline system.[85] The difference in energy between the transition states leading to the two diastereomers is likely to be smaller than in the pericyclic case as the large steric clash between the phenyl groups shown in **221** will no longer occur. Given the modest diastereoselectivity observed, the transition state interactions resulting in the kinetic preference for the *syn*-phenyl product are likely to be rather subtle. One possibility is that this preference may arise from a steric clash between the two equatorially situated phenyl groups in transition state **223**, disfavouring formation of the *anti* phenyl isomer **216b** (Scheme 2.49).

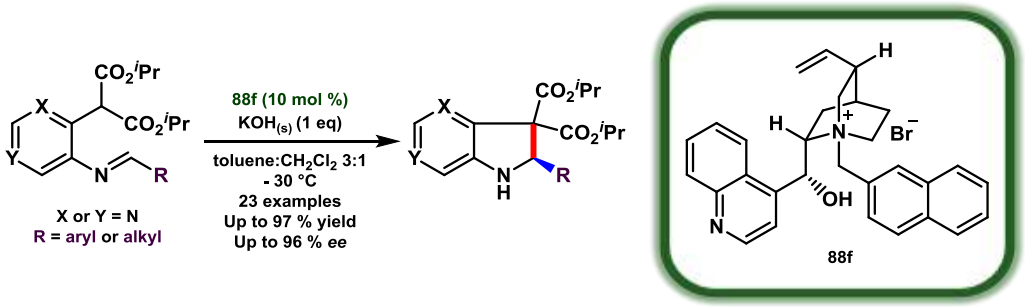


Scheme 2.49 – Transition states of *trans*-imine 215 *via* an anionic mechanism

These considerations are vastly simplified, as they do not account for the role of the phase-transfer catalyst, which has been demonstrated to have a significant effect on diastereoselectivity. However, the conclusion that can be reached, regardless of both reaction mechanism and substrate-catalyst interactions, is that the relative energy differences between both the transition states of the reaction and the ground states of products are low enough that neither kinetic nor thermodynamic control can be utilized to obtain high levels of diastereoselectivity for this reaction manifold.

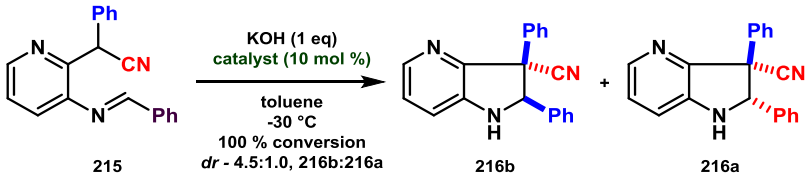
2.8. Conclusions

The asymmetric synthesis of densely functionalized azaindoline products has been achieved by cation-directed catalysis. This constitutes one of only a handful of methods to synthesize azaindolines asymmetrically. While access to the entire isomeric family of azaindolines was not possible the route is most effective for the synthesis of 4-azaindolines, reports of which are rarest in the literature. Hence this methodology towards 4- and 6-azaindolines complements existing processes in the literature towards the synthesis of 5- and 7-azaindolines. The reaction tolerates a range of aryl and alkyl substituents, and proceeds with high yields and good to excellent *ee* (Scheme 2.50).



Scheme 2.50 – Chiral cation-directed cyclizations to form 4- and 6-azaindolines

The reaction could also be extended to a substrate bearing two different electron-withdrawing groups. Cyclization occurred smoothly, but both diastereoselectivity and enantioselectivity proved to be modest (Scheme 2.51).



Scheme 2.51 – Diastereoselective cyclization

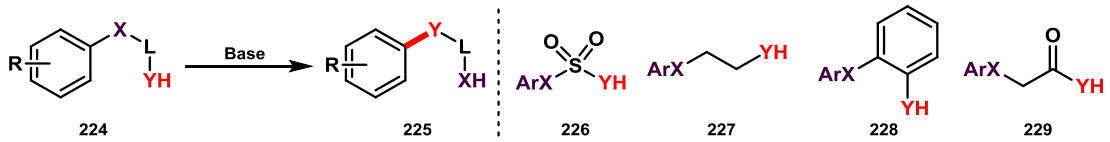
Having successfully demonstrated the utility of chiral cation-directed catalysis in extending our pre-existing methodology to new heterocyclic targets we now intended to apply the

same principles to new reaction manifolds. In particular, we were interested in employing the concept of cation-directed catalysis towards the development of novel asymmetric rearrangements.

3. Development of a cation-directed Truce-Smiles rearrangement

3.1. Background and Aims

Rearrangement reactions are a powerful tool in organic chemistry as they have the potential to allow the formation of complex products, which could be otherwise challenging to synthesize from simple and readily accessible precursors.[16] One group of rearrangements are collectively known as Smiles rearrangements, after Samuel Smiles, who was the principal developer of the field during the 1930s.[102] A Smiles rearrangement involves an intramolecular nucleophilic aromatic substitution where a reactive nucleophile, such as the anion of **Y** generated upon deprotonation of **224**, attacks the aromatic ring at the *ipso* position resulting in the expulsion of a more stable anion **X**, which is subsequently protonated on work up to form **225**. The formal outcome is the migration of the aryl group from heteroatom **X** to heteroatom **Y** (Scheme 3.1).

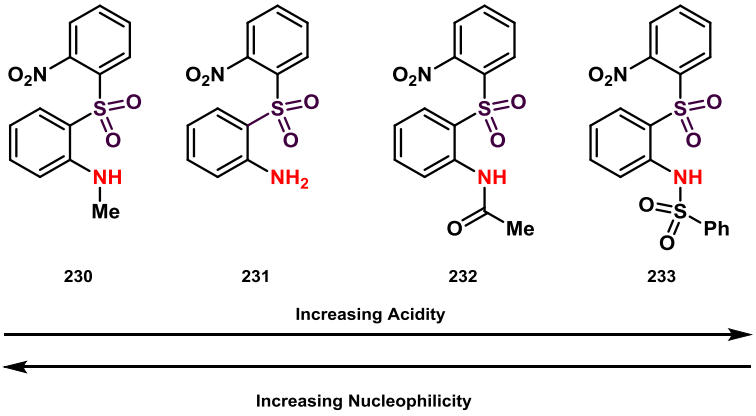


Scheme 3.1 – General representation of the Smiles rearrangement and typical linking groups

The most common linking groups, **L**, comprise of sulfones (**226**) or groups with carbon backbones, which can be unsaturated (**227**), part of an aromatic ring (**228**) or contain ketones or amides (**229**). The linking group is typically one or two atoms in length but on rare occasions can extend to a length of three atoms. The nature of the linking group can have profound effects on the rate of the reaction, particularly in the case of **228** when the

aromatic ring is substituted, however these effects are not simple to predict as both steric and electronic factors compete for influence.[102]

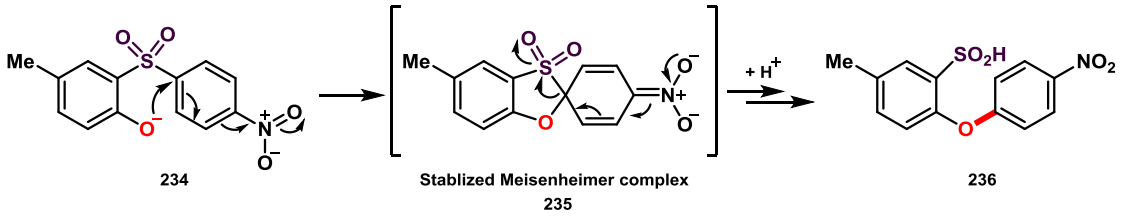
The nucleophile **Y** is generally O^-, S^- or RN^- and the leaving group **X** is usually S, SO, SO_2, O or COO. Clearly the attacking **Y** group must be more nucleophilic than leaving group anion **X** otherwise the reaction will reverse. For example if **Y** is O and is attached to an alkyl linker then rearrangement will be observed when **X** is SO_2 or SO but not when **X** is S.[102] Another factor of paramount importance is the delicate balance between the acidity of **XH** and the nucleophilicity of $\mathbf{X}^-$. This is best demonstrated when **Y** is a substituted amine (Scheme 3.2).[103]



Scheme 3.2 – Effect of amine substituents on the Smiles rearrangement

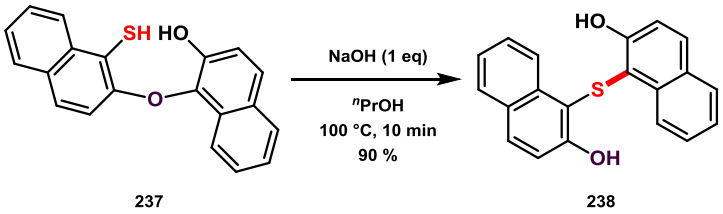
The first step of the rearrangement involves deprotonation of the aniline. Hence while both aniline **231** and acetamide **232** rearrange smoothly under standard conditions (1 M NaOH, 100 °C, 30 min), *N*-methyl aniline **230** requires a higher concentration of base to effect the rearrangement due to the less acidic nature of the methylated aniline. In contrast deprotonation of *N*-benzylmethanesulfonamide **233** is facile but the resulting anion is too weakly nucleophilic to initiate the rearrangement.

As the Smiles rearrangement is an intramolecular nucleophilic aromatic substitution it usually requires strongly electron-withdrawing substituents, such as nitro groups, *ortho* and/or *para* to the **X** substituent. These facilitate the initial nucleophilic attack by increasing the electrophilicity of the *ipso* carbon and stabilizing the transition state leading towards Meisenheimer intermediate **235** (Scheme 3.3).[104,105]



Scheme 3.3 – Nitro group activation of a Smiles rearrangement

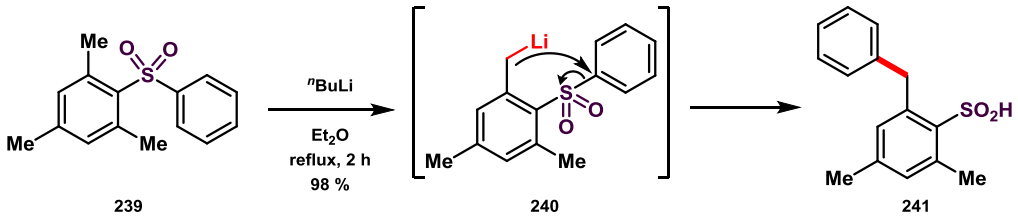
Somewhat surprisingly, the first rearrangement disclosed by Smiles is a rare example of a Smiles rearrangement without activation with a strongly electron-withdrawing group.[106] *Iso*-β-naphthol sulfide (**237**) undergoes Smiles rearrangement to 2-naphthol 1-sulfide (**238**) (Scheme 3.4).



Scheme 3.4 – First Smiles rearrangement

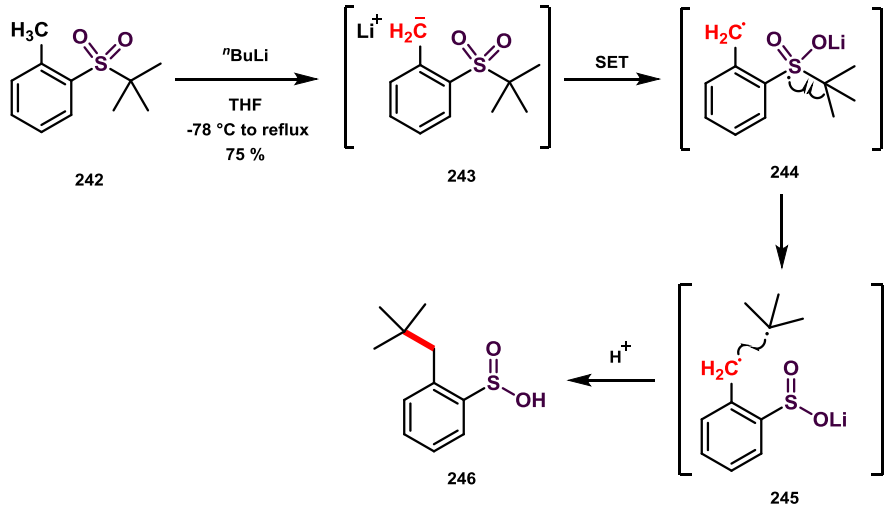
Given the exceptional nature of this transformation, Smiles proved to be remarkably prescient in anticipating that the use of strongly electron-withdrawing groups in place of the β-hydroxyl group would be particularly effective in facilitating the rearrangement. Without investigating this hypothesis he would have been unlikely to have made the strides he did towards the more typical variant of the Smiles reaction, which opened up avenues towards further substrates for this transformation.

One area which Smiles did not explore was the possibility of using a carbanion as the nucleophilic species in the rearrangement. This is unsurprising as in his era the strong organolithium bases required to form the required carbanions were not the ubiquitous synthetic tool they have become today.[107] The potential of these reagents to initiate a Smiles rearrangement was first recognised by William Truce. In 1958 he published a communication detailing the metallation and rearrangement of mesityl phenyl sulfone (**239**).[108] On treating the sulfone with a slight excess of ^{n}BuLi in refluxing ether he observed what was rather charmingly described as a "flocculent precipitate," which after hydrolysis and work up, yielded rearrangement product **241** (Scheme 3.5).



Scheme 3.5 – The first Truce-Smiles rearrangement

Truce subsequently developed several variants of the reaction,[109] perhaps the most notable of which was the development of the first Smiles or Truce-Smiles rearrangement that involved migration of an alkyl group instead of an aryl group.[110] This reaction is proposed to be mechanistically distinct from the Smiles rearrangement and instead proceeds *via* an electron-transfer/radical-anion combination process (Scheme 3.6).



Scheme 3.6 – Alkyl Truce-Smiles rearrangement

At this point it is worth nothing that the original definition of a Truce-Smiles rearrangement refers to rearrangements where:

a) The nucleophile was a carbanion;

b) The rearrangement required no activating groups on the migrating aromatic ring (indeed activating nitro groups are likely to result in side reactions due to addition of the organolithium to the nitro group).

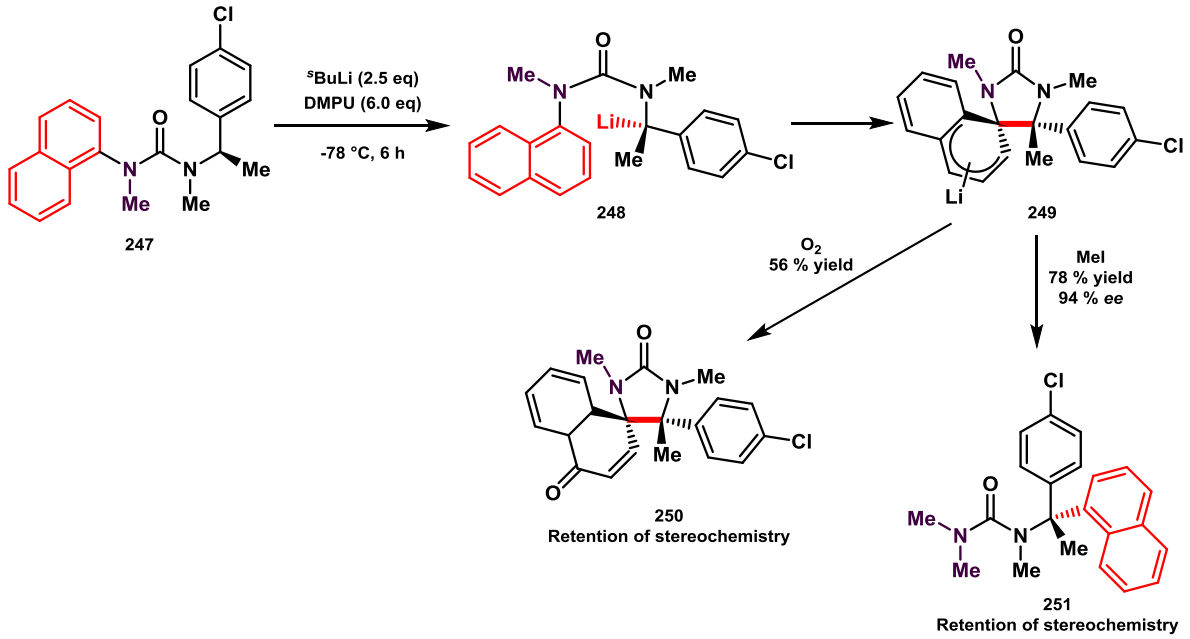
More recently the definition has widened to rearrangements which only satisfy the first of these conditions,[109a] perhaps reflecting the greater challenge of effecting the rearrangement with carbon nucleophiles. During this thesis the term "Truce-Smiles rearrangement" is used to refer to this broader class of reactions.

In spite of this definition encompassing a wider array of transformations, relatively few reports of Truce-Smiles rearrangements appear in the literature since the initial work of Truce. This is perhaps surprising given the value of a reaction which allows the formation of a carbon-carbon bond at the expense of a carbon-heteroatom bond, providing access to substrates which may have proved challenging to synthesize utilizing other carbon-carbon

bond-forming strategies. A comprehensive review in 2008[109a] notes that there were no reports of Truce-Smiles rearrangements between 1982 and 2000. Since then interest in exploring the reaction has reappeared. Several of these studies are particularly relevant to the work described later in this chapter and will be discussed in detail at a more appropriate juncture.

Perhaps the most significant recent development in this area is a series of aryl-transfer reactions developed by Clayden.[111] Although not described as such in his communications, these reactions fit the definition of the Truce-Smiles rearrangement used throughout this thesis (indeed, as activation of the transferred aryl group is not required, the reaction also fits the stricter original definition). In contrast to the reactions developed by Truce, which involve migration of the aryl group from sulfur to carbon, these reactions involve transfer of the aryl group from nitrogen to carbon. While an isolated example of this type of transfer had previously been reported[112] Clayden's work represents a significant step forward as it is wide-reaching in scope and capable of producing highly functionalized products, which can undergo further synthetic transformations. The initial publication concerns the rearrangement of lithiated ureas[111a] and also provides mechanistic evidence that the reaction proceeds *via* a Meisenheimer intermediate **249**, as originally proposed by Truce (Scheme 3.7).[109b] After lithiation of urea **247** the carbanion attacks at the *ipso* position forming Meisenheimer intermediate **249**. In cases where the methyl group α- to the urea in **247** is replaced with hydrogen, rearrangement is fast. However in the disubstituted case significant starting material remained, with longer reaction times or increases in temperature leading to the elimination of the urea. This problem was solved by the addition of DMPU as a cosolvent. This additive increases the reactivity of the organolithium by

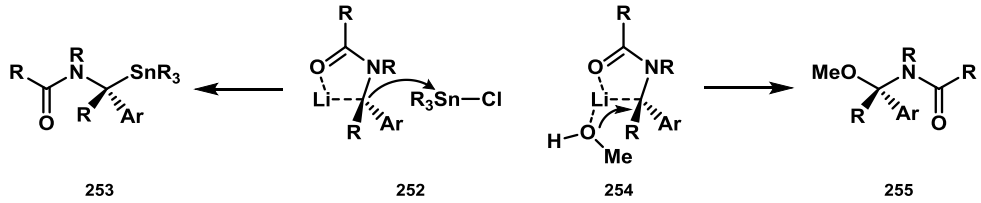
coordinating lithium, forming a highly reactive solvent-separated ion-pair.[113] Intermediate **249** was then quenched with water or an electrophile to yield the aryl-transfer products **251**, typically in 70-90 % yields. If chiral starting materials are used, as in the reaction depicted, the rearrangement proceeds in a stereospecific manner with retention of stereochemistry. If the reaction was exposed to oxygen instead of quenching with water then enone **250** is formed, also with retention of stereochemistry. This provides evidence for the existence of dearomatized intermediate **249**.



Scheme 3.7 – Mechanism of the Clayden-Truce-Smiles rearrangement

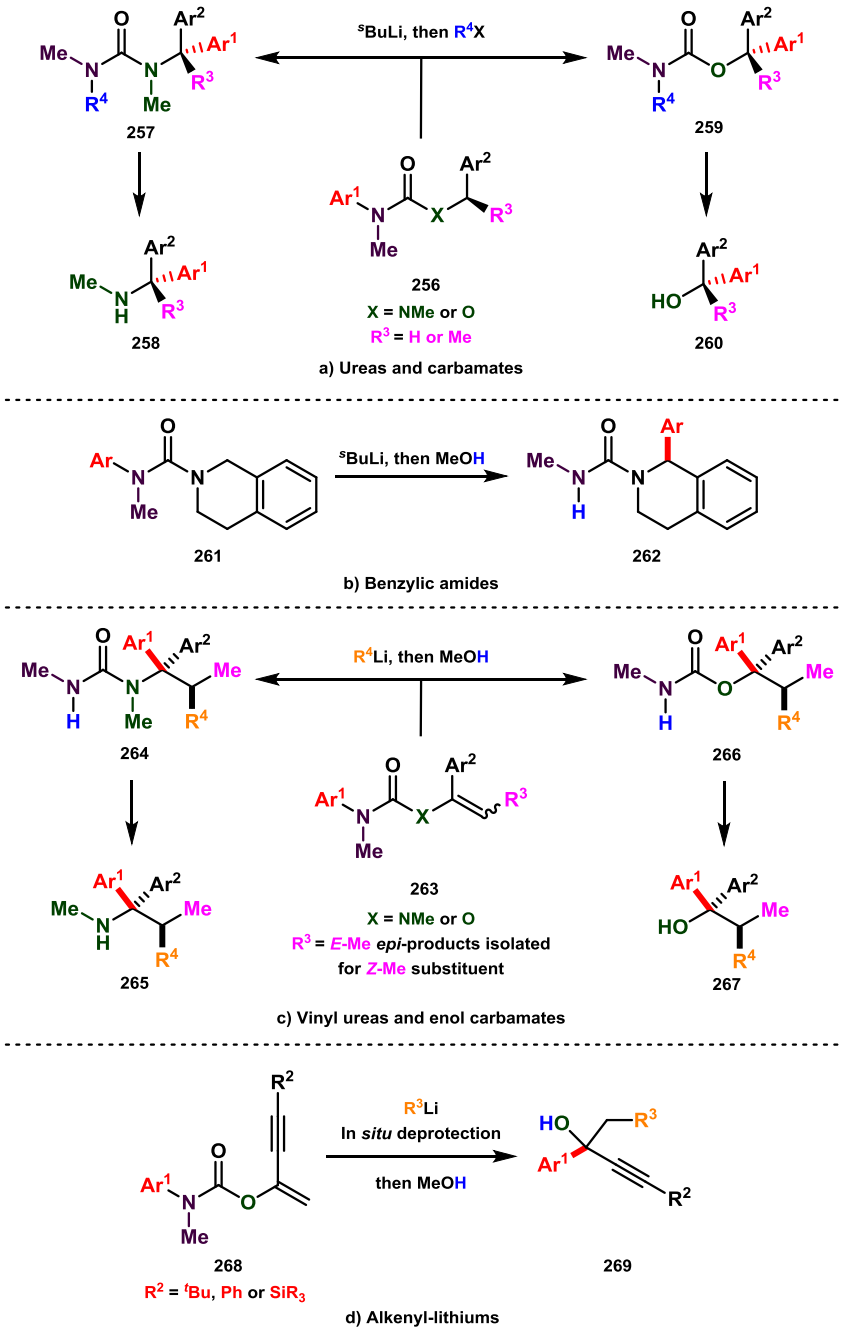
The observed stereochemical retention is most likely due to the fact that tertiary and secondary benzyl-lithiums α- to nitrogen are configurationally stable over the timescale of the reaction at -78 °C and the emperically observed tendency of lithium-complexing electrophiles to undergo substitution reactions with benzyl lithiums with retention. In contrast, non-complexing or highly reactive electrophiles typically undergo inversion.[114] This difference is proposed to be due to non-complexing electrophiles, such as stannyl-halides, avoiding the steric bulk of the complexed lithium cation, leading to antarafacial attack and

inversion (**252**, Scheme 3.8), whereas complexing electrophiles react suprafacially because lithium delivers the electrophile in an intramolecular-type process, leading to retention (**254**, Scheme 3.8).



Scheme 3.8 – Stereochemical outcome of reactions of benzyl lithiums with complexing and non-complexing electrophiles

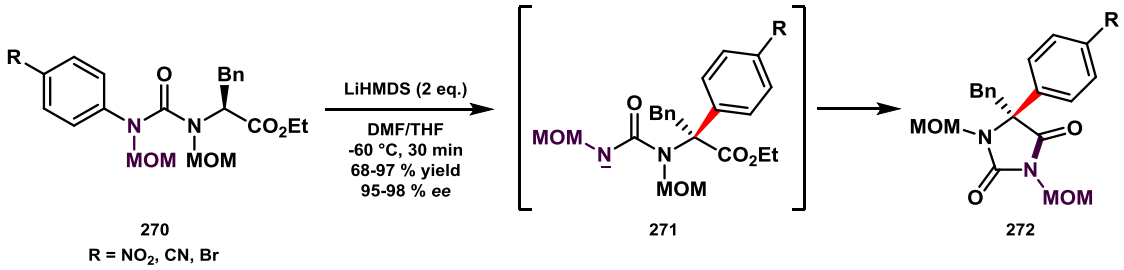
Since this initial publication, Clayden has expanded this work to include carbamates **256** (Scheme 3.9 a),[111c] cyclic amines **261** (Scheme 3.9 b),[111b] and vinylureas[111d] and enol carbamates **263** (Scheme 3.9 c),[111e] allowing access to a variety of highly substituted, enantioenriched amines and alcohols on subsequent hydrolysis. In particular, the use of vinylureas and enol carbamates allows the organic portion of the organolithium reagent to be incorporated into the product during the carbolithiation step, further improving the reaction scope. The diastereoselectivity in these reactions arises from *syn*-carbolithiation, followed by the stereochemically retentive migration observed in the previous work. The aryl group adjacent to the lithiated carbon can also be replaced by an alkyne (Scheme 3.9 d).[111e]



Scheme 3.9 – Scope of the Clayden-Truce-Smiles rearrangement

Kawabata has also developed an ester-enolate variation of the Clayden-Truce-Smiles rearrangement (Scheme 3.10).[115] This is distinct from Clayden's work in that it proceeds *via* deprotonation of an amino acid ester with a strong base, such as Li- or K-HMDS. This reintroduces the requirement for activation of the migrating aryl group, with electron-withdrawing substituents such as *p*-Br, *p*-CN or *p*-NO_2 utilized to activate the *ipso* carbon towards nucleophilic attack. When unsubstituted migrating aryl groups were

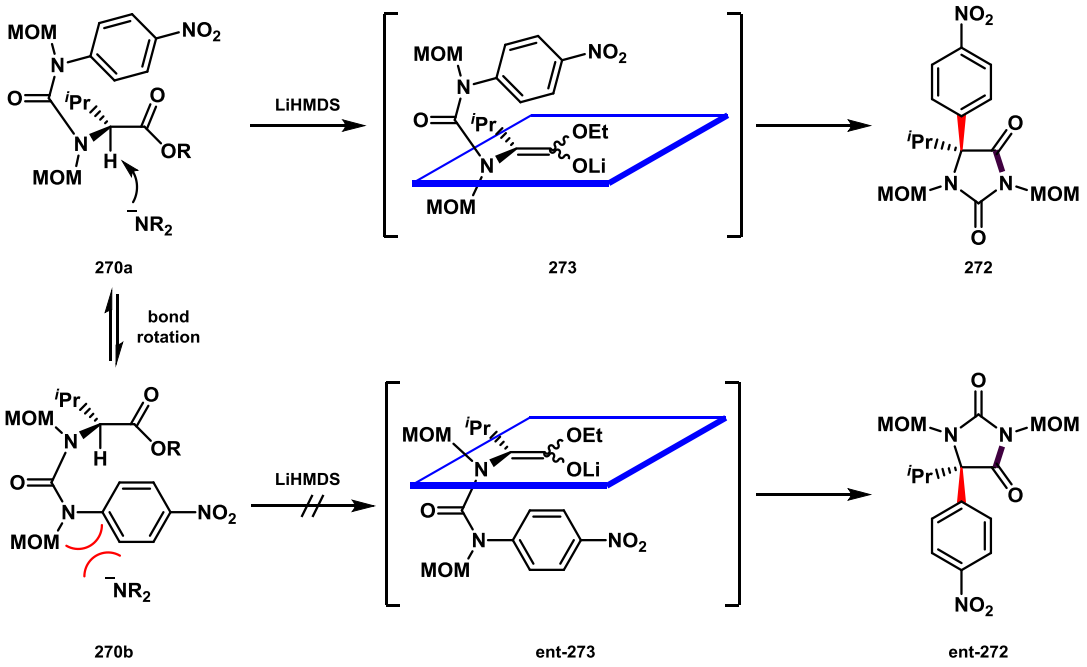
employed the desired product was formed, but the reaction did not go to completion, with 40 % of the starting material recovered. The anion of the rearranged product **271** is spontaneously trapped by the ester, forming hydantoins **272**.



Scheme 3.10 – Kawabata's ester-enolate Clayden-Truce-Smiles rearrangement

As with Clayden's work, the stereochemical integrity of the starting material is retained throughout the course of the reaction. As this rearrangement involves formal deprotonation of ester **270** to form the metal enolate the mechanism which governs the stereochemical outcome is different to Clayden's approach, a fact further highlighted by the observation that the reaction proceeds with inversion rather than retention of configuration at the stereocentre (Scheme 3.11). The enolate intermediate **273** possesses axial chirality due to the differing substituents on the nitrogen group.[116] While racemization of these enolates is facile, the rearrangement process is fast enough that formation of hydantoin **272** takes place before significant racemization of **273** can occur. Therefore the authors propose that the stereochemical outcome of the reaction is governed by the deprotonation step, with deprotonation occurring from conformer **270a** (determined by molecular modelling studies to be the most stable conformer) where the hydrogen is antiperiplanar to the bulky MOM-protected N-aryl amide substituent and eclipsed by the smaller N-MOM substituent. This renders the hydrogen more accessible to the bulky base than conformer **270b**, where approach of the base is hindered by the bulkier substituent eclipsing the hydrogen. Thus the

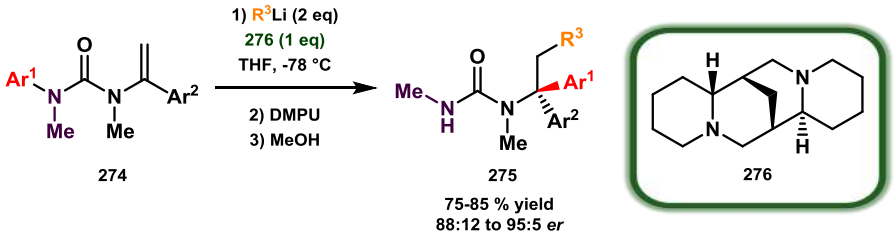
reaction proceeds through enolate **273**, which leads to inversion of the stereocentre in hydantoin **272**.



Scheme 3.11 – Stereochemical model for formation of hydantoin 272

Clayden has published a complementary aproach utilizing his lithiation chemistry and starting from either amino nitriles or the enolate of free amino acids, forming similar hydantoin products.[117] This allows for different substituents to be employed on the migrating aryl group and in contrast to Kawabata's method results in retention of stereochemistry of the amino acid as previously discussed.

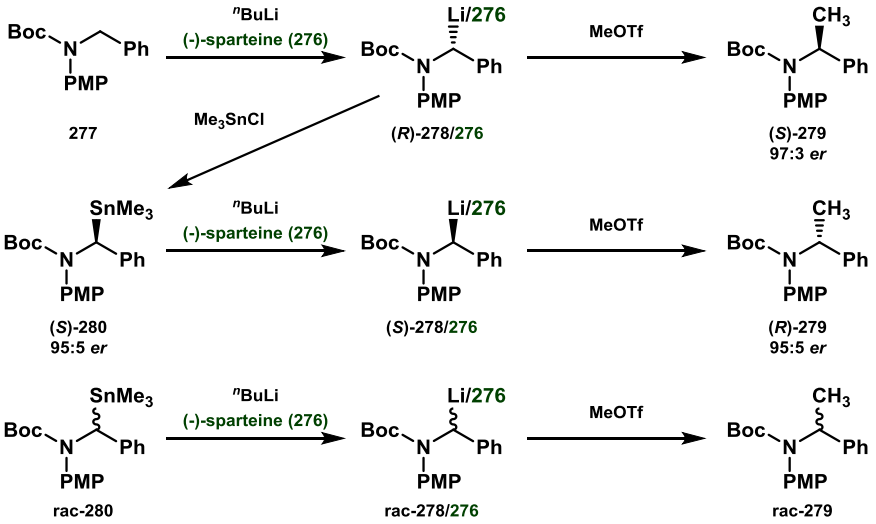
To the best of our knowledge the only example of the synthesis of enantioenriched products from achiral starting materials which involves the Truce-Smiles rearrangement was published by Clayden in 2013 (Scheme 3.12).[111f] This example involved regio- and enantioselective carbolitiation of vinylurea **274** in the presence of (-)-sparteine (**276**), a chiral lithium-coordinating ligand. This ensures that carbolithiation occurs from one face of the alkene.



Scheme 3.12 – Asymmetric Clayden-Truce-Smiles rearrangement

As with the systems which already had the desired stereochemical configuration installed, the carbolithiated intermediate is configurationally stable over the reaction timescale and the Clayden-Truce-Smiles rearrangement proceeds with retention of configuration of the stereocentre formed in the carbolithiation step to yield enantioenriched tertiary ureas **275**.

Precedent for both the configurational stability of the carbolithiated product and the non-stereodetermining nature of the final substitution can be found in the work of Beak (Scheme 3.13).[114a] He showed that lithiation and substitution of benzylamine **277** with a Me group in the presence of (-)-sparteine formed (*S*)-**279**. If the final substitution step controls the stereochemical outcome of the reaction then treatment of lithiated species **278**, generated from lithiodestannylation of (*S*)-**280**, should result in a final product of (*S*)-**279**, as observed in the initial sequence. Instead the product is the enantiomer (*R*)-**279**, formed through inversion. Further confirmation that the carbolithiation is the stereodetermining step was obtained by subjecting racemic tin intermediate **280** to the same sequence, which resulted in racemic **279**. The configurational stability of the complex between the lithiated intermediate **278** and sparteine is immediately apparent from this sequence as no erosion of enantiomeric excess is seen during the conversion of (*S*)-**278** to (*R*)-**279**. The extent of this stability was probed by allowing the reaction to proceed for ten hours before addition of methyl triflate instead of the standard thirty minutes. This had no effect on *ee*, showing the complex was configurationally stable long past the timeframe of the reaction.



Scheme 3.13 – Stereochemistry of asymmetric carbolithiations

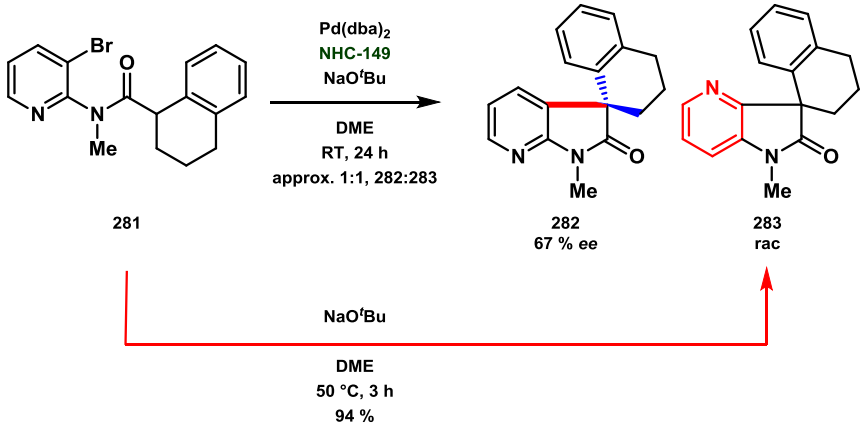
While Clayden has elegantly demonstrated the use of a Truce-Smiles reaction as part of an asymmetric process, there still remain no examples in the literature of an enantioselective process in which the Truce-Smiles rearrangement itself functions as the stereodetermining step. The remainder of this Chapter will describe the investigations carried out in our laboratory towards the fulfilment of this goal.

3.2. Initial inspiration and concept – Aza-oxindole Truce-Smiles/SNAr system

3.2.1. Background and initial blueprint

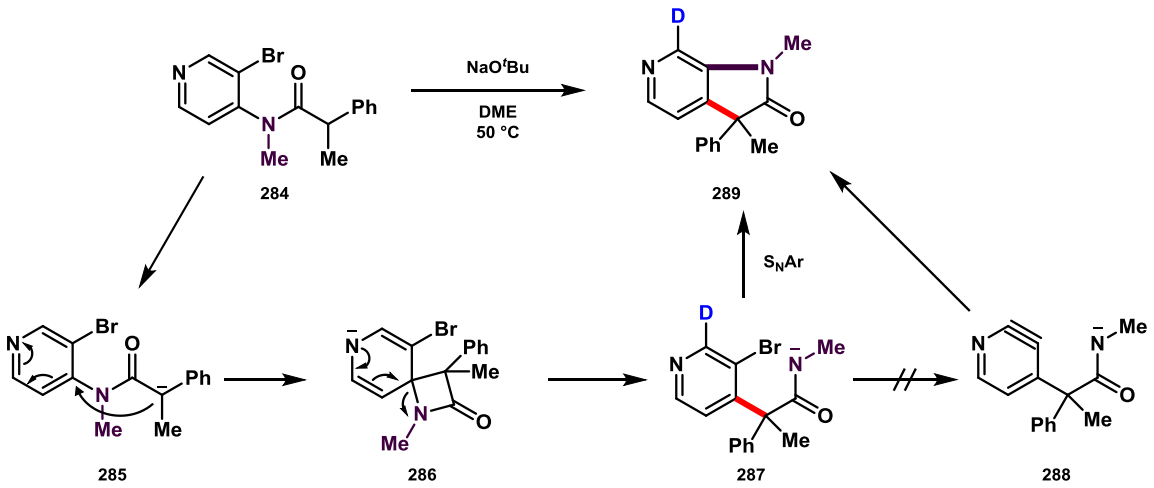
The initial inspiration for this project came during our investigations into the asymmetric synthesis of azaindolines described in Chapter 1. During our research into methods of azaindoline synthesis we were intrigued by an unexpected reaction observed by Kündig during his synthesis of aza-oxindoles *via* C-H activation methods (Chapter 2.1.3).[75a] While attempting to synthesise aza-oxindole **282** using this methodology, a 1:1 mixture of the desired product and its regioisomer **283** was isolated.[118] The racemic nature of **283** suggested that the Pd/chiral ligand complex was not involved in the transformation and

indeed treatment of amide precursor **281** with base alone led to the exclusive formation of the regioisomeric product **283** in 94 % yield (Scheme 3.14).



Scheme 3.14 – Unexpected formation of aza-oxindole 282

This methodology proved to be applicable in the synthesis of a range of aza-oxindoles and is proposed to proceed *via* a Truce-Smiles rearrangement, aided by the electron-withdrawing nature of the pyridine nitrogen, to form deprotonated amide intermediate **287** (Scheme 3.15). A subsequent electronically disfavoured intramolecular S_NAr reaction leads to aza-oxindole **289**.

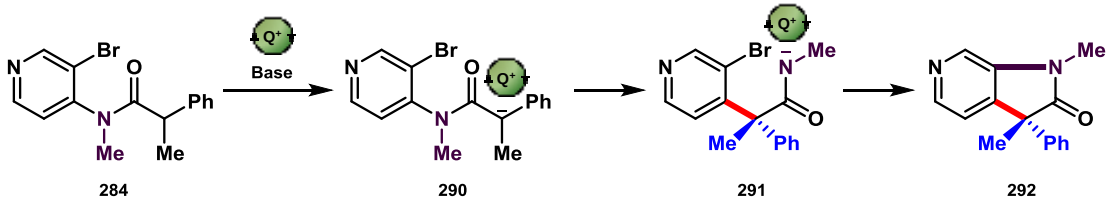


Scheme 3.15 – Proposed mechanism of formation of aza-oxindole 289

The final step could also be seen to proceed through benzyne intermediate **288** but this possibility was ruled out by studies with a deuterium labelled precursor, which show that a

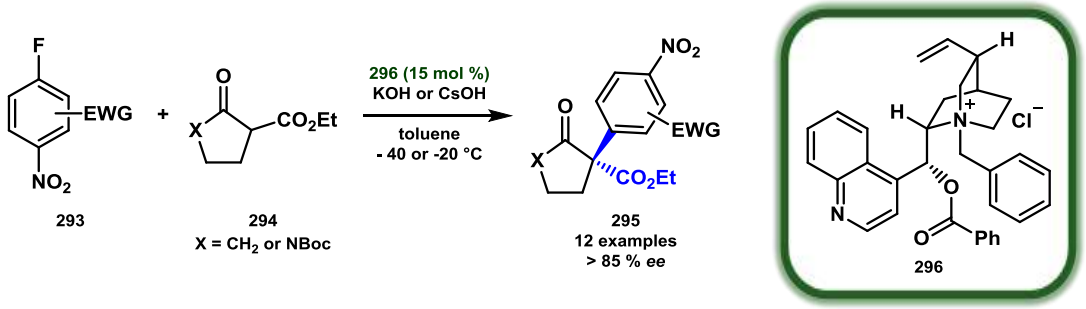
deuterium between the nitrogen and halogen remains incorporated in the final product, thus ruling out the involvement of a benzyne intermediate.

As the reaction proceeds *via* anionic intermediate **285** this opens up the possibility of utilizing cation-directed catalysis, in particular the use of chiral phase-transfer catalysis, to control the stereochemical outcome of the nucleophilic aromatic substitution step of the Truce-Smiles rearrangement, hence developing the first catalytic asymmetric variant of this type of reaction (Scheme 3.16).



Scheme 3.16 – Blueprint for a catalytic asymmetric Truce-Smiles reaction

Enantioselective nucleophilic aromatic substitution reactions which utilize asymmetric phase-transfer catalysis as the means of imparting stereocontrol have been reported by Jørgensen for the substitution of activated aryl fluoride electrophiles with β-keto esters **294**, employing novel benzoyl-protected *cinchona* alkaloid catalyst **296**.[119] This serves as a strong precedent for investigating the application of this methodology to the Truce-Smiles rearrangement (Scheme 3.17).

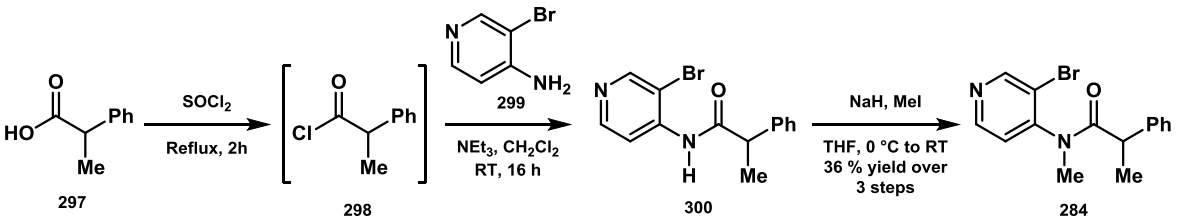


Scheme 3.17 – Jørgensen's asymmetric phase-transfer catalyzed S_NAr reaction

With a blueprint for the development of a catalytic asymmetric Truce-Smiles rearrangement in hand our efforts turned to applying this to the synthesis of aza-oxindoles.

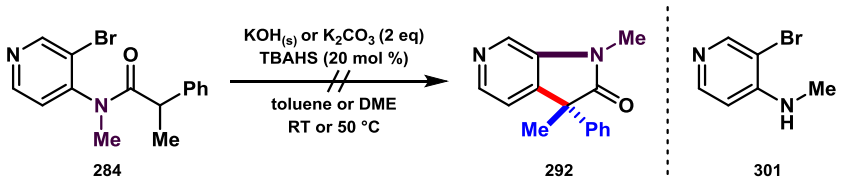
3.2.2. Investigation of an aza-oxindole system

To examine whether the Truce-Smiles reaction could be efficiently catalyzed under a phase-transfer regime we first synthesized amide **284**, using procedures reported by Kündig.[118] Formation of acid chloride **298**, amide coupling and *N*-methylation furnished Truce-Smiles precursor **284** in 36 % yield over three steps (Scheme 3.18).



Scheme 3.18 – Synthesis of Truce-Smiles precursor 284

284 was then treated with KOH, employing TBAHS as the phase-transfer catalyst. Disappointingly this resulted in no conversion to the desired rearranged product **292**, with only starting material observed by TLC. Furthermore an increase in reaction temperature to 50 °C resulted in partial hydrolysis to amine **301** suggesting that the amide is unstable under the hydroxide-initiated phase-transfer conditions (Scheme 3.19). Switching the solvent to DME had the same outcome. Using K_2CO_3 as base in an effort to avoid hydrolysis returned starting material. The lack of formation of product, regardless of the base employed, is likely to be due to a failure to deprotonate the substrate, as the characteristic colour change associated with deprotonation to form a conjugated system was not observed under any of these conditions.

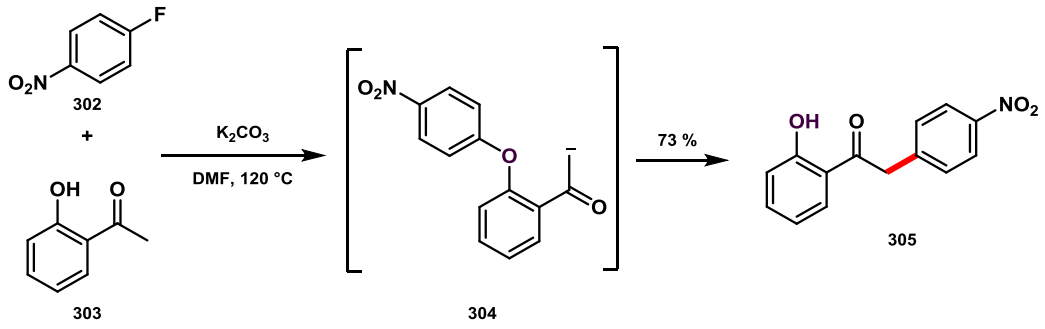


Scheme 3.19 – Attempted phase-transfer catalyzed Truce-Smiles rearrangement of 284

Although our investigations with this system were not fruitful due to a lack of reactivity, we still felt the concept of a phase-transfer catalyzed Truce-Smiles rearrangement was a plausible one and thus reexamined the literature in pursuit of a precursor which would be more amenable to the reaction conditions typically employed in phase-transfer processes. Our experience so far suggested that this precursor must undergo facile deprotonation with a hydroxide or carbonate base and should avoid functionality which may be prone to hydrolysis under basic conditions.

3.3. 2-Hydroxyphenyl ketone Truce-Smiles system

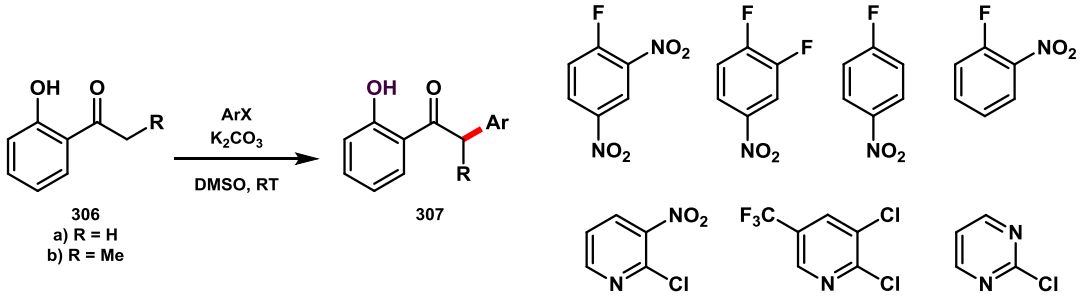
The first alternative system which presented itself as suitable for further investigation was a variant of the Truce-Smiles reaction first reported by Mitchell and Bavarian in 2004.[120] Upon attempting a S_NAr reaction of phenol **303** with 4-fluoronitrobenzene (**302**) the expected aryl ether product was not observed. Instead the enolate of the S_NAr product **304** was formed and underwent subsequent Truce-Smiles rearrangement to yield phenol **305** (Scheme 3.20).



Scheme 3.20 – Homologous enolate Truce-Smiles rearrangement

This system is unusual in that it possesses a three-atom linking unit instead of the usual one- or two-atom variants. For this reason the authors refer to the reaction as a "homologous enolate" Truce-Smiles rearrangement.

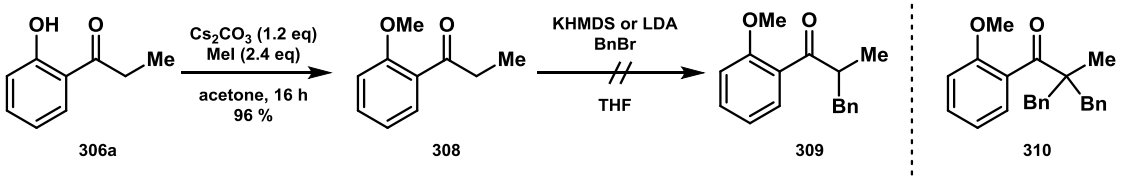
Subsequent work by Snape[121] and Ma[122] has extended the scope of this reaction, showing that it can be carried out using a range of electron-poor aryl halides under mild conditions (Scheme 3.21). Snape also confirmed that the reaction proceeds *via* the Truce-Smiles mechanism and not S_NAr of the enolate by treating acetophenone under the same reaction conditions, which resulted in the return of starting material.[121]



Scheme 3.21 – Scope of the homologous enolate Truce-Smiles rearrangement

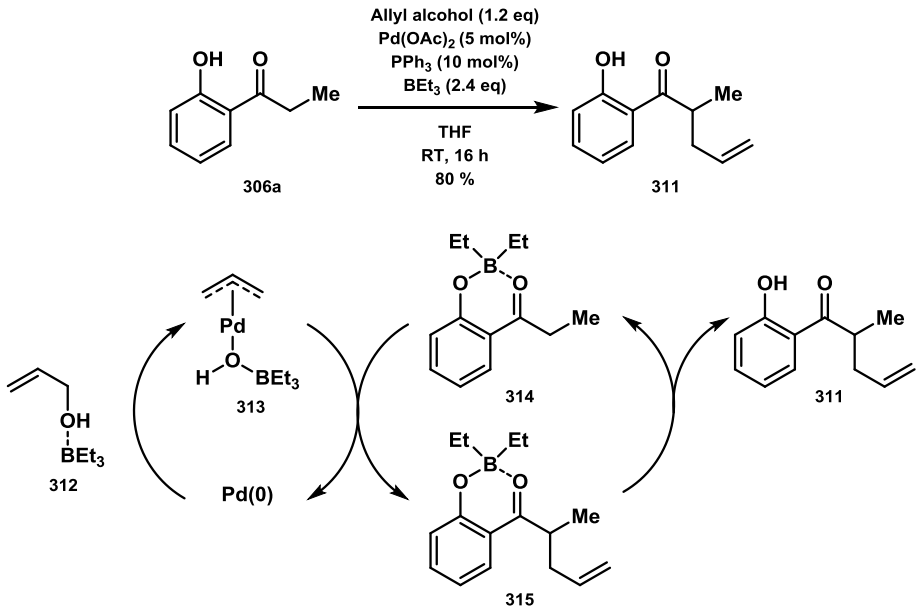
It is these mild conditions which make this system attractive, as they open up the possibility of the reaction occurring under a phase-transfer catalyzed regime. However, as discussed previously (Chapter 2.7.3), phase-transfer catalyzed S_NAr reactions with carbanions which form more acidic products than the starting material require the use of stoichiometric phase-transfer catalysts.[98] While no literature precedent exists for such a system it also seems likely that the phenol anion of the product would have a similar effect. Although the formation of a phenolic product is unavoidable in this system the presence of an acidic proton α- to the ketone of product **307** can be avoided by formation of a quaternary stereocentre. While remaining cognizant of the likely requirement for stoichiometric catalysis, we decided to investigate the viability of a phase-transfer catalyzed Truce-Smiles

rearrangement of alkylated **307**. To achieve this, protected phenol **308** was synthesized by methylation of commercially available phenol **306a**.[123] Unfortunately alkylation of **308** by deprotonation with either LDA or KHMDS, followed by treatment with benzyl bromide, failed to produce the desired alkylated product, with MS evidence indicating the presence of starting material **306a** and dialkylated product **310**. Slow addition failed to alleviate formation of **310** (Scheme 3.22).



Scheme 3.22 – Attempted benzylation of 308

Thus, an alternative strategy involving triethylborane-mediated palladium-catalyzed allylation of **306a**, afforded **311** in good yield (Scheme 3.23).[124]

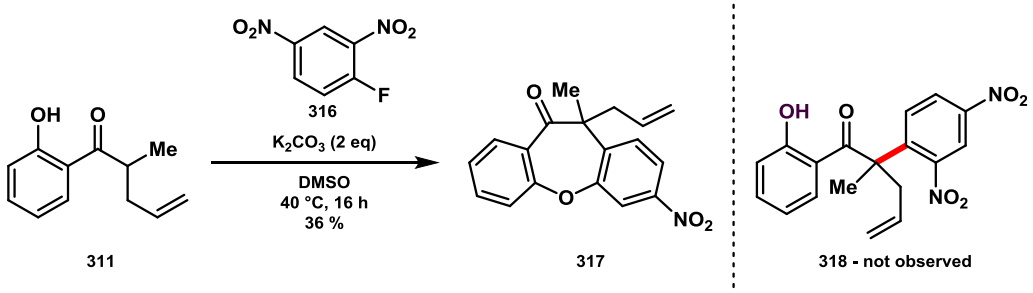


Scheme 3.23 – Allylation of 306a

This procedure had the added benefit of removing the need for a protecting group strategy, allowing access to allylated substrates in a single step. Mechanistically the reaction proceeds

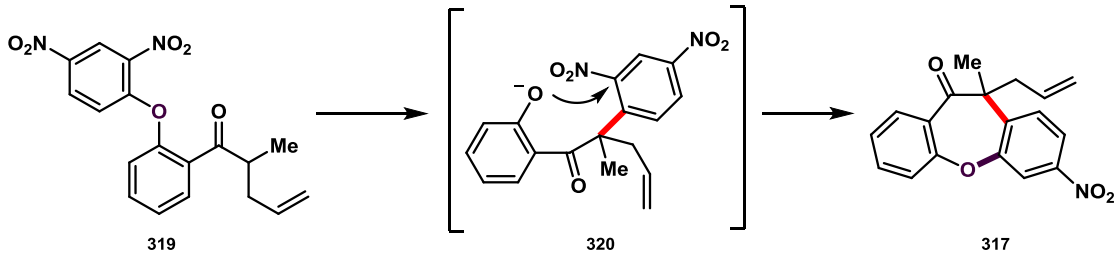
via oxidative addition of allyl alcohol, possibly aided by coordination of BEt_3. The resultant allyl palladium species then reacts with the enol form of **314** to produce intermediate **315**, which is subsequently protonated to form the desired phenol **311**.

With the required alkylated substrate successfully synthesized the Truce-Smiles product was first obtained under basic conditions, without the use of a phase-transfer catalyst. 2,4-Dinitrofluorobenzene (**316**) was chosen as the electrophile in the S_NAr step as Jørgensen's work had shown that 4-nitrofluorobenzene was unreactive in phase-transfer catalyzed systems and that a stronger electrophile was required for substitution to take place.[119a] The reaction conditions developed by Snape[121] were employed. Conversion was poor at room temperature but an increase in temperature to 40 °C furnished a single product in 36 % yield. Surprisingly, this was not the expected Truce-Smiles rearrangement product **318** but was instead identified as dihydro oxepin **317** (Scheme 3.24).



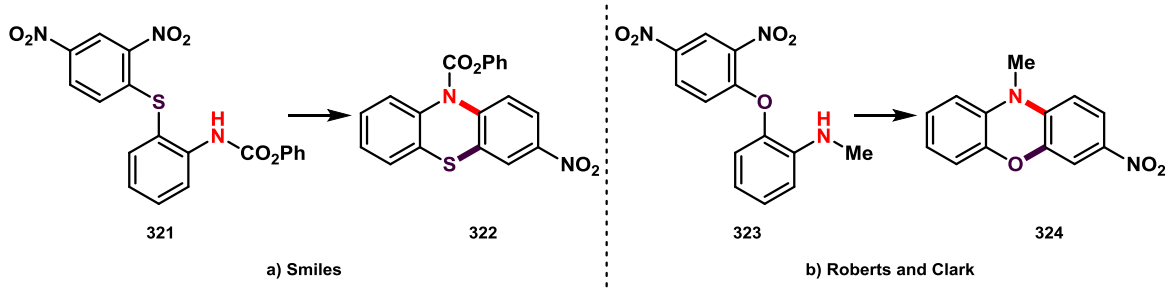
Scheme 3.24 – Unexpected formation of dihydro oxepin 317

This unanticipated product could be seen to arise from the expected Truce-Smiles rearrangement and, instead of the desired trapping as the lactone, an electronically disfavoured intramolecular S_NAr reaction with NO_2^- as a leaving group (Scheme 3.25).



Scheme 3.25 – Truce-Smiles rearrangement and subsequent S_NAr to form 317

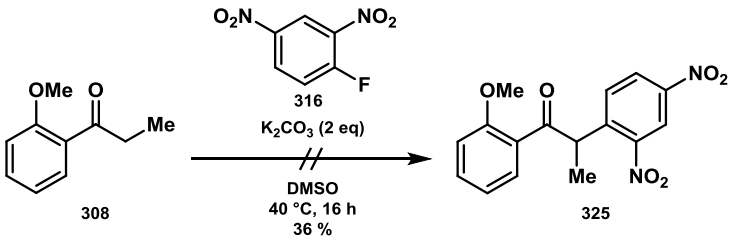
While somewhat uncommon due to the challenges of starting material synthesis (or indeed dangers, as some examples involve potentially explosive tri-nitro-substituted aromatics) there is precedent for this type of aromatic substitution being employed in the formation of heterocycles. Smiles has reported similar reactions with sulfur nucleophiles resulting from an initial Smiles rearrangement[125] and Roberts and Clark subsequently reported the phenol analogue of this reaction resulting in the formation of phenoxazines (Scheme 3.26).[126] Both of these reactions use nitrogen nucleophiles in the initial rearrangement step. To the best of our knowledge, the synthesis of **317** is the first example of this process using a carbanionic nucleophile; ie the Truce-Smiles variant of the reaction.



Scheme 3.26 – Precedent for Truce-Smiles rearrangement followed by S_NAr

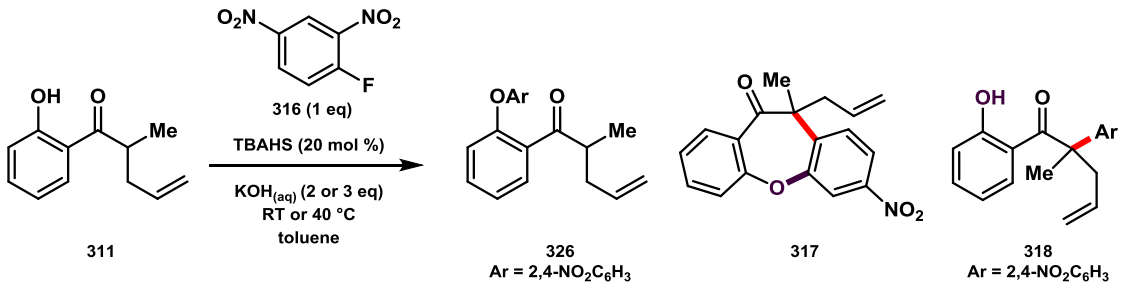
In order to confirm that the reaction proceeds *via* the rearrangement mechanism and not as a direct S_NAr reaction of ketone **311** we employed previously synthesized methyl-protected phenol **308**. When subjected to the same conditions no formation of S_NAr product **325** was observed, which supports a reaction mechanism which proceeds *via* S_NAr by the phenol

followed by subsequent Truce-Smiles rearrangement and intramolecular S_NAr (Scheme 3.27).



Scheme 3.27 – Methylated substrate under reaction conditions

Screening was then carried out to determine effective conditions to form the product using TBAHS as a phase-transfer catalyst (Scheme 3.28). As with the reaction under simple basic conditions only trace conversion was observed at room temperature when two equivalents of aqueous KOH were employed as the base and either catalytic or stoichiometric TBAHS as the phase-transfer catalyst. At 40 °C the use of two equivalents of aqueous KOH and catalytic TBAHS resulted in complete conversion to S_NAr product **326**, which was isolated in 23 % yield. This suggested that under these conditions the initial S_NAr reaction was occurring smoothly but the rearrangement was not initiated. Utilizing three equivalents of aqueous KOH resulted in a mixture of starting material **311**, S_NAr product **326** and rearrangement product **317**. This implied that the final intramolecular S_NAr step was not proceeding effectively under phase-transfer catalyzed conditions. The fact that starting material is remaining suggests that the initial S_NAr step is not turning over catalytically.



Scheme 3.28 – Initial screening of phase-transfer conditions

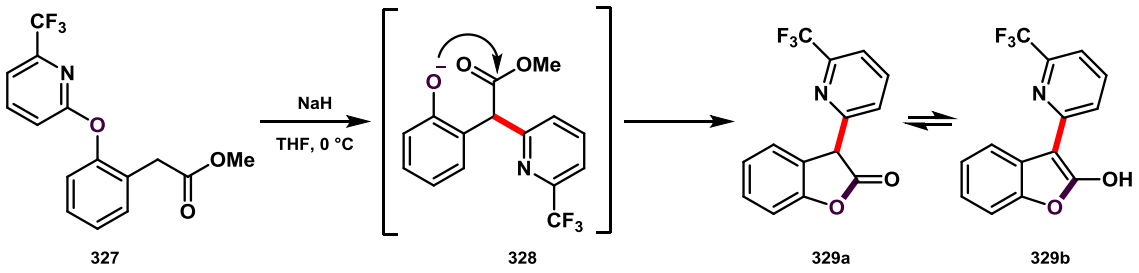
A potential reason for this is that the acidic phenol of Truce-Smiles rearrangement product **318**, which has not undergone cyclization to **317**, may sequester the phase-transfer catalyst, preventing it from assisting in the S_NAr of starting material **311**. However, we were unable to isolate **318** to confirm this theory.

The results from these initial forays show that phase-transfer catalysis can be used to initiate Truce-Smiles rearrangements and hence utilizing chiral cations to control the stereochemical outcome of these rearrangements may be a viable strategy. They also highlight several considerations which must be taken into account when selecting a suitable substrate for this endeavour, particularly the requirement that the final product must contain no protons which are more acidic than those of the starting material. The serendipitous discovery of an intramolecular trapping process of the leaving group of the Truce-Smiles product revealed a feasible solution to this problem, which had coincidentally been built in to the first system we had investigated (Chapter 3.2.2). However, the demands of forming a seven-membered ring resulted in the reaction failing to proceed to completion under phase-transfer conditions. Therefore alternative intramolecular traps for the Truce-Smiles product were sought.

3.4. Truce-Smiles rearrangements with intramolecular traps

3.4.1. Benzofuranone Truce-Smiles/lactonization system

Further examination of the literature revealed a promising substrate where trapping might be more facile. While attempting to formylate the ester enolate of **327** Erickson and McKennon observed an unexpected Truce-Smiles rearrangement to form intermediate **328**, followed by trapping of the phenol anion by the ester group to form benzofuranone **329** (Scheme 3.29).[127]



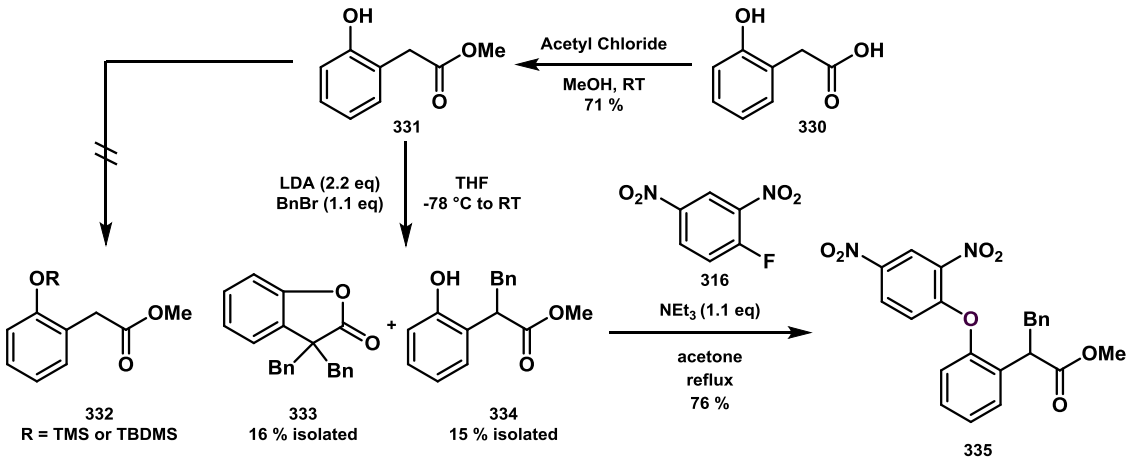
327 328 329a 329b

Scheme 3.29 – Truce-Smiles rearrangement and lactonization to form benzofuranone 329

This system is attractive because the formation of a five-membered lactone would be expected to be more favourable than a demanding electronically disfavoured S_NAr to form a seven-membered ring. As previously the use of a substrate which will form a quaternary stereocentre is required. This is not only due to the undesired acidic proton in **329a** but also because of the formation of tautomeric product **329b**, which may result in epimerization of the newly formed stereocentre during catalytic asymmetric reactions.

Synthesis of a suitable substrate began by esterification of 2-hydroxyphenylacetic acid (**330**).[128] Unfortunately, the allylation conditions used in Chapter 3.3 are unsuitable for this substrate due to the lack of a chelating group for boron. Hence we returned to alkylation with benzyl bromide. Attempts to silyl-protect phenol **331** prior to carrying out the benzylation were ineffective, with the reactions failing to go to completion and both TMS and TBDMS protecting groups proving too acid-labile to survive attempts at chromatography. Therefore unprotected ester **331** was subjected to the alkylation conditions using two equivalents of LDA and benzyl bromide (Scheme 3.30). This resulted in the formation of dibenzylated lactone **333** as the major product of the reaction. This was a stubborn product to separate from the desired alkylated product **334** as its low solubility made purification by chromatography problematic. Taking advantage of this low solubility to remove the lactone *via* trituration proved more effective, allowing **334** to be isolated in 15 % yield with only a trace quantity of the lactone impurity remaining. Despite the

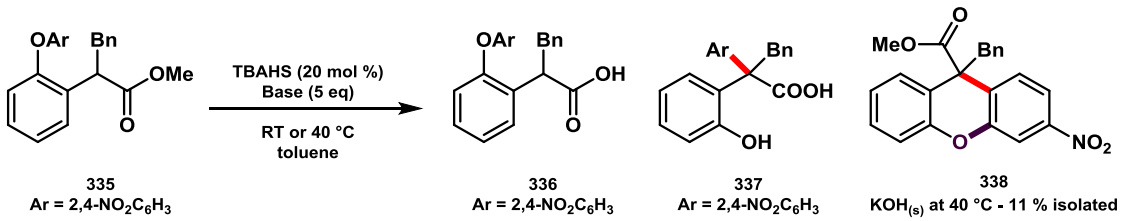
inefficient nature of this procedure, starting materials were easily accessible and the reaction could be carried out on a large enough scale to obtain sufficient material to investigate the Truce-Smiles rearrangement process. S_NAr reaction of phenol **334** was achieved in good yield using NEt_3 in refluxing acetone,[129] the use of a mild base allowing conversion to the desired Truce-Smiles precursor **335** in good yield without inducing the rearrangement itself.



Scheme 3.30 – Synthesis of Truce-Smiles precursor 335

335 was now subjected to phase-transfer catalysis, using 20 mol % of TBAHS as the catalyst (Scheme 3.31). As with the system investigated in Chapter 3.3 only limited conversion was observed at room temperature. Treatment of **335** with five equivalents of aqueous KOH at 40 °C resulted in complete conversion to material which remained on the baseline during TLC analysis. This polar material could not be isolated but we speculate that it may have arisen from hydrolysis of either the starting material or the desired lactone to form **336** and **337**, respectively. Hydrolysis of the starting material to form **336** is more likely as the formation of acidic products, such as those of hydrolysis, was previously shown to prevent catalytic turnover. In an effort to avoid hydrolysis, aqueous KOH was replaced with solid KOH. Disappointingly, the assumed hydrolysis products still dominated; however a less polar

product was also observed and was successfully isolated, albeit in low yield. The product was identified as xanthene **338**, which arises from the same Truce-Smiles rearrangement/S_NAr mechanism proposed previously (Scheme 3.25, Chapter 3.3), suggesting that for this substrate this alternative process is in competition with the desired lactonization.



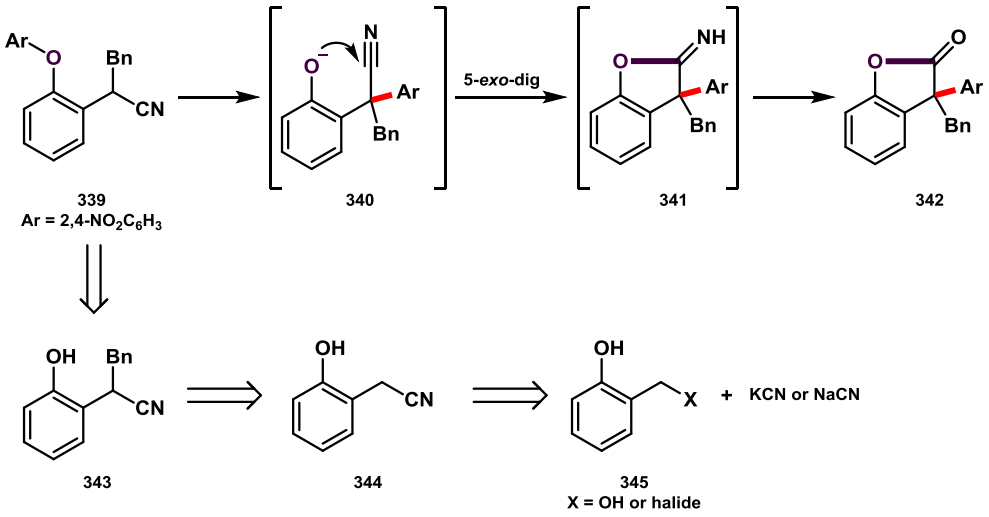
Scheme 3.31 – Phase-transfer catalyzed reaction of aryl ether 335

Given the problems with hydrolysis of the methyl ester under phase-transfer conditions an alternative system was required which does not contain this problematic functional group. Therefore we decided to pursue a system where a nitrile could be used as an alternative trapping group for the phenol anion of the Truce-Smiles product.

3.4.2. Substrate modification – nitrile/isopropyl ester substituted system

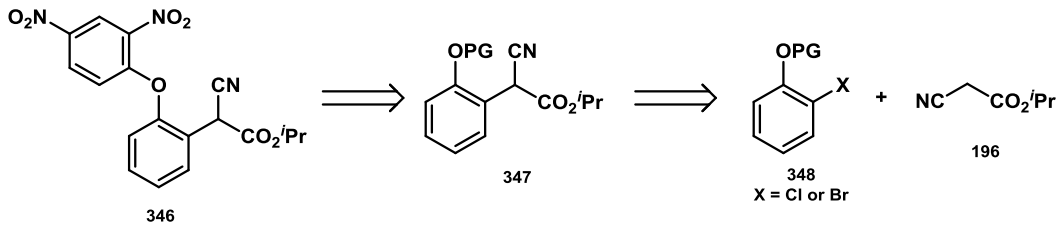
It could be envisaged that a system where the methyl ester group was replaced by a nitrile group would provide an alternative trap for the resulting phenol anion *via* a 5-*exo*-dig cyclization to form **341** (Scheme 3.32). This would ultimately form lactone **342** either after acidic work up or *via in situ* hydrolysis. This hydrolysis is not problematic as it does not result in the formation of an acidic product. The desired cyclization would be expected to proceed under milder conditions than the electronically disfavoured S_NAr reaction to form the xanthene. However, this system is not without its caveats as it may suffer from unwanted cyclization of the phenol anion during the alkylation step of substrate synthesis. Thus, the synthetic route requires protection of the phenol, which had proved problematic during

work on the benzofuranone system (Chapter 3.4.1). Another caveat is that synthesis of sufficient quantities of 2-hydroxyphenylacetonitrile (**344**) to trial protecting group strategies would require the use of large quantities of cyanide salts.[130]



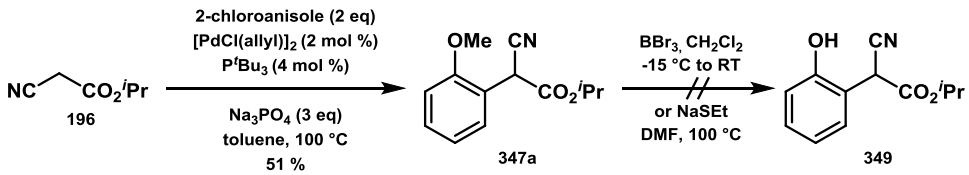
Scheme 3.32 – Proposed phase-transfer catalyzed Truce-Smiles/5-*exo*-dig trapping and substrate retrosynthesis

In an effort to avoid this procedure we turned to an alternative substrate **346**, which could instead be synthesized by an α-arylation procedure developed by Hartwig (Scheme 3.33).[131] While this modification will result in reduced nucleophilicity of the carbanion in the Truce-Smiles rearrangement it will test the validity of the substrate synthesis. Furthermore, given our knowledge that carbanions can react smoothly in S_NAr reactions (Chapter 2.7.3), it did not seem unreasonable to assume that the anion of **346** would be nucleophilic enough to undergo rearrangement, allowing the testing of competition between cyclization onto the nitrile to form an imine and intramolecular S_NAr to form a xanthene in the final step of the reaction. In an effort to avoid hydrolysis a bulkier isopropyl ester group, which in our experience is resistant to hydrolysis under phase-transfer conditions would be employed.



Scheme 3.33 – Alternative substrate retrosynthesis

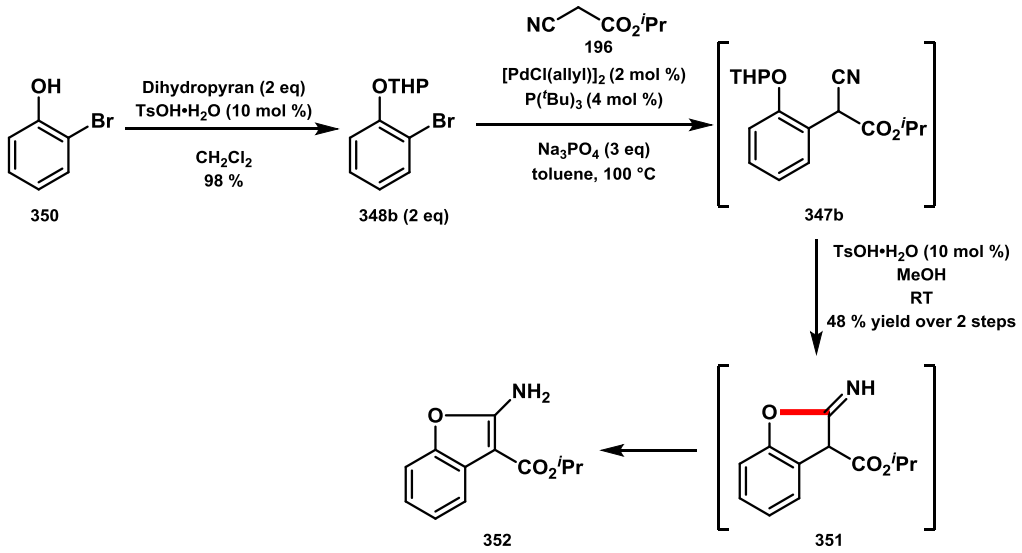
Efforts towards the synthesis of substrate **346** began with a methyl ether protecting group, as this allowed the initial α-arylation conditions to most closely mirror those developed by Hartwig[131] and the required starting materials were commercially available. We speculated that under the conditions typically used for deprotection, cyclization onto the nitrile group may be avoided. If this was not the case then alternative conditions, such as the use of sodium ethanethiolate, could be employed. α-Arylation of isopropyl cyanoacetate (**196**) with 2-chloroanisole, utilizing palladium allyl chloride dimer as the catalyst and tri-*tert*-butyl phosphine as the ligand proceeded smoothly, albeit with a reduced yield due to dehydrohalogenation of 2-chloroanisole. Hartwig has shown that use of a bulkier pentaphenylferrocenyl ligand can circumvent this problem,[131] but this was deemed unnecessary due to the prohibitively high cost of this ligand. Altering the procedure to use an excess of 2-chloroanisole ensured that the majority of the isopropyl cyanoacetate was consumed, with **347a** isolated in 51 % yield after recrystallization (Scheme 3.34).



Scheme 3.34 – α-arylation and subsequent attempts at deprotection of aryl methyl ether

Deprotection of **347a** was initially attempted using BBr_3 but did not result in formation of the desired phenol **349**. Inspection of the crude ^1H NMR spectrum showed that the

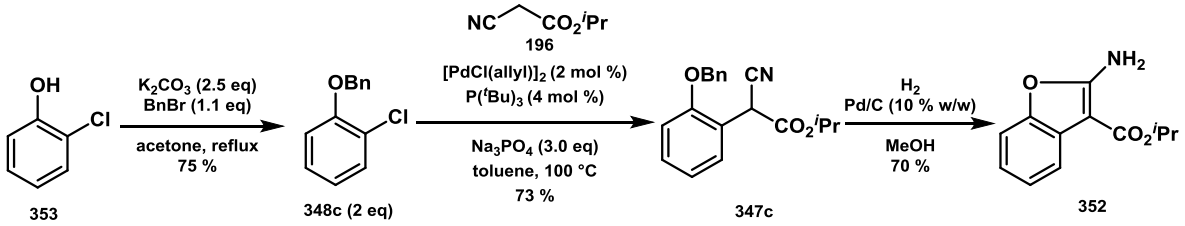
isopropyl ester peaks did not integrate to a sufficient value, suggesting that the ester may be unstable to the reaction conditions. Employing sodium ethanethiolate, without use of an activating Lewis acid, was attempted,[132] but disappointingly these conditions returned only starting material. Therefore alternative protecting groups for the phenol were investigated. THP-protected aryl bromide **348b** was prepared in near quantitative yield[133] and participated smoothly as an arylating agent under the same conditions as 2-chloroanisole (Scheme 3.35). The crude product was then subjected to tosic acid in methanol to remove the protecting group prior to purification. Rather than yielding the desired phenol, amino-benzofuran **352** was obtained instead in 48 % overall yield.



Scheme 3.35 – THP-protection strategy and formation of amino-benzofuran 352

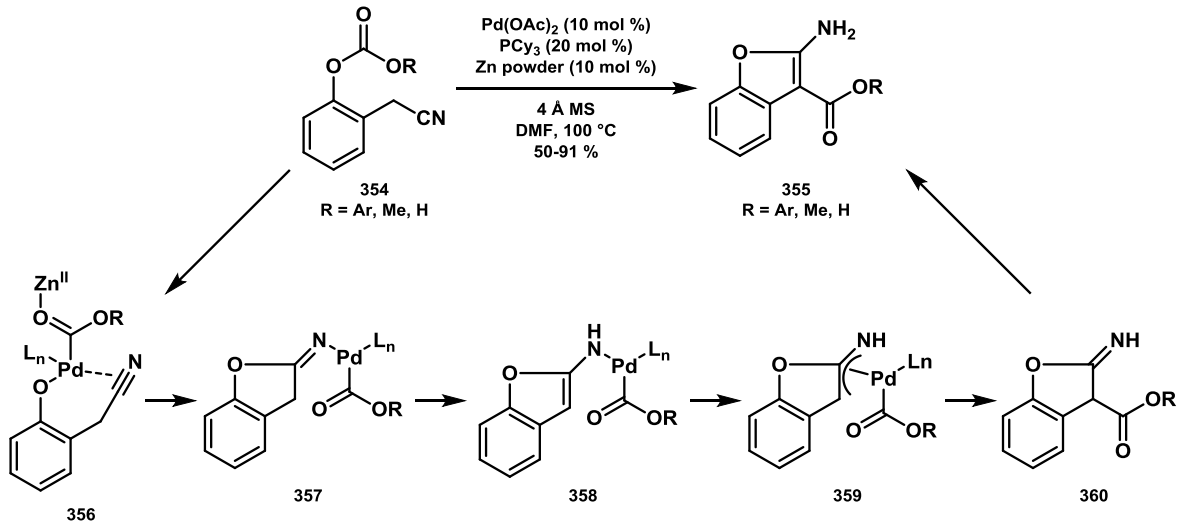
This product arises from cyclization onto the nitrile group and subsequent proton transfer to form the benzofuran. This result demonstrates that acidic conditions are effective in catalysing cyclization onto the nitrile group and thus the deprotection step to form the phenol must occur under neutral conditions. Hence, the next protecting group to be investigated was the benzyl group as this can be cleaved by palladium-catalyzed hydrogenolysis under neutral conditions.

Synthesis of the required aryl halide **348c** was achieved in 75 % yield[134] and α-arylation proceeded smoothly to afford **347c**. Disappointingly, palladium on carbon-catalyzed hydrogenative deprotection once again resulted in the formation of benzofuran **352** in good yield (Scheme 3.36).



Scheme 3.36 – Bn-protection strategy

A literature search to investigate whether this constituted an efficient synthesis of this type of product revealed an alternative approach by palladium-catalyzed cycloisomerization published by Ohe (Scheme 3.37).[135]



Scheme 3.37 – Cycloisomerization approach to amino-benzofurans

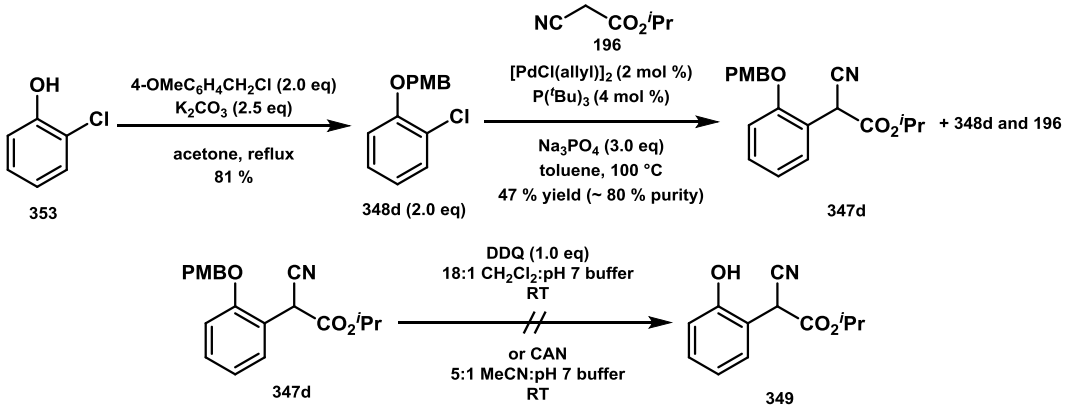
The mechanism proposed by the authors involves oxidative addition of palladium into the acyl group facilitated by activation of the carbonyl group with zinc (**356**). Oxypalladation of the nitrile group results in intermediate **357**, which after isomerization, forms aza-allyl

palladium complex **359**. Subsequent reductive elimination and tautomerism forms the aminobenzofuran product **355**.

Our conditions represent an approach with possibly increased scope, as there is no requirement to carry out the demanding oxidative addition in the first step. Hence, esters which zinc may prove insufficient to activate in Ohe's approach may cyclize efficiently under the hydrogenative conditions.

Adding palladium to our list of unsuitable deprotection conditions left little room for manoeuvre, with the only obvious remaining option the *para*-methoxybenzyl protecting group, which can be removed under oxidative conditions.

PMB protection of phenol **353**[134] proceeded in 81 % yield and the product **348d** was subjected to the α-arylation conditions (Scheme 3.38).



Scheme 3.38 – Attempted PMB protecting group strategy

Unfortunately α-arylation failed to reach completion and the insolubility of both **348d** and product **347d** rendered separation of the compounds an insurmountable challenge as both chromatography and recrystallization failed to yield pure product. The crude product (approx. 80 % purity by analysis of the ^{1}H NMR spectrum) was subjected to oxidative

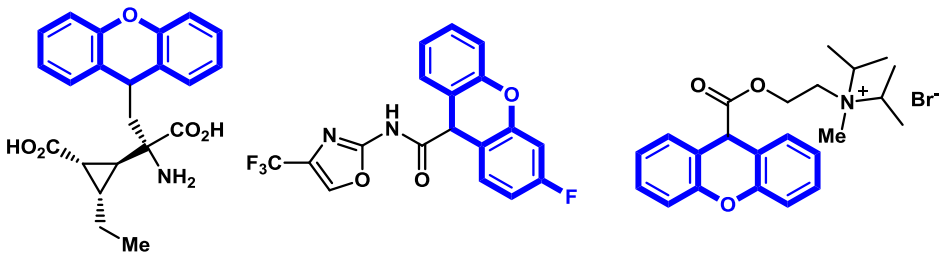
deprotection conditions utilizing either CAN or DDQ, in the hope that the deprotected products would be more straightforward to isolate. In both cases only starting material was observed by TLC and hence this route was abandoned.

These results show that a protecting group strategy is unsuitable for the synthesis of desired substrate **349** and by analogy synthesis of previously proposed substrate **339** by such an approach would also not be viable. Given this lack of success it was decided instead to further investigate our serendipitous discovery of a phase-transfer catalyzed Truce-Smiles rearrangement/S_NAr reaction to form oxacycles, with the aim of developing an asymmetric variant of this novel reaction. While phase-transfer reactions to form seven-membered rings had previously been unsuccessful (Chapter 3.3), the formation of six-membered rings had shown more promise, highlighted by the isolation of xanthene products from phase-transfer catalyzed reactions (Chapter 3.4.1). Therefore, the synthesis of xanthenes *via* rearrangement processes now became the focus of our investigations.

3.5. Synthesis of xanthenes via a Truce-Smiles/S_NAr reaction

3.5.1. Background and concept

Xanthene derivatives most commonly find use as dyes[136] and fluorescent probes[137] but are also found in several bioactive molecules such as antimuscarinics[138] and metabotropic glutamate receptor agonists (Scheme 3.39).[139] While these molecules typically contain achiral xanthene units, some examples such as **365** are chiral, with their activity being tested in the racemic form. Reports of the synthesis of enantionriched xanthenes with stereocentres situated at the 9-position are rare[140] and to the best of our knowledge no catalytic asymmetric methods exist for their synthesis.



364 365 366

Metabotropic glutamate receptor agonists
Receptor may have role in psychiatric/neurological disorders

Antimuscarinic
Used to treat excessive sweating
of gut, intestines or bladder

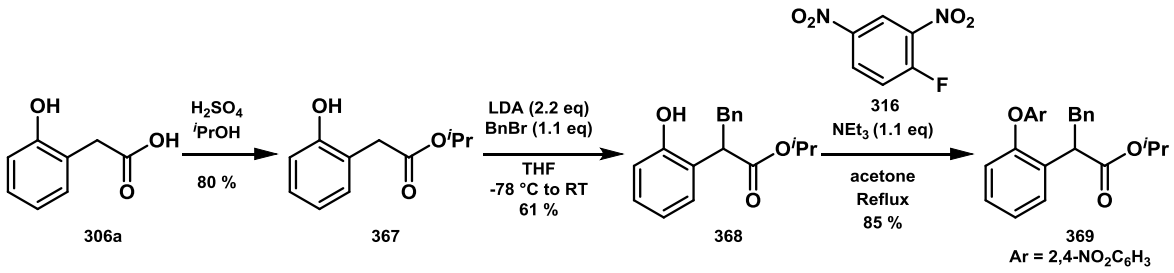
Scheme 3.39 – Bioactive xanthenes

The work described in Chapter 3.4.1 forms the basis for a synthesis of xanthenes with all-carbon quaternary stereocentres at the 9-position, however, the substrate utilized is not suitable for the exclusive formation of xanthenes because of the competing lactonization to form benzofuranones and the suspected hydrolysis of the methyl ester and/or benzofuranone under the reaction conditions employed. To prevent these issues from occurring it was decided to begin the synthesis from a substrate containing an isopropyl ester as this resists hydrolysis under basic phase-transfer conditions and should prove more resistant to lactonization than the methyl ester, favouring formation of the desired xanthene.

3.5.2. Benzyl/isopropyl ester substituted system – achiral phase-transfer catalysis

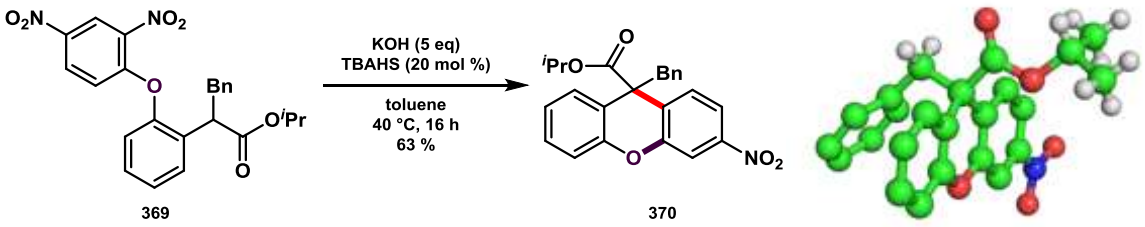
The required substrate was synthesized by an analogous route to that employed with the methyl ester substrate **355** (Chapter 3.4.1). Esterification of 2-hydroxyphenylacetic acid (**306a**)[141] was followed by subjection of the ester to the same alkylation conditions used previously (Scheme 3.40). This reaction provided evidence that the isopropyl ester was indeed resistant to lactonization, as the lactone formation, which had plagued the methyl ester, was not observed. This procedure afforded the desired phenol **367** in a far more

synthetically useful 61 % yield. S_NAr to form the required Truce-Smiles precursor **369** again proceeded smoothly, utilizing NEt_3 in refluxing acetone.



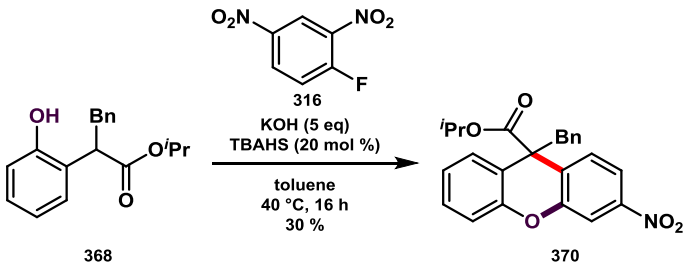
Scheme 3.40 – Synthesis of Truce-Smiles precursor 369

With the required substrate in hand the phase-transfer conditions developed in Chapter 3.4.1 were trialled with alkylated ester **369**. Pleasingly this resulted in complete conversion of the starting material and a 63 % isolated yield of the desired xanthene **370**, the structure of which was further confirmed by single crystal X-ray diffraction (aromatic H atoms omitted for clarity) (Scheme 3.41).[87]



Scheme 3.41 – Synthesis of xanthene 370

The reaction can also be carried out in a one-pot process where S_NAr to afford **369** is followed by xanthene formation (Scheme 3.42).



Scheme 3.42 – One-pot synthesis of xanthene 370

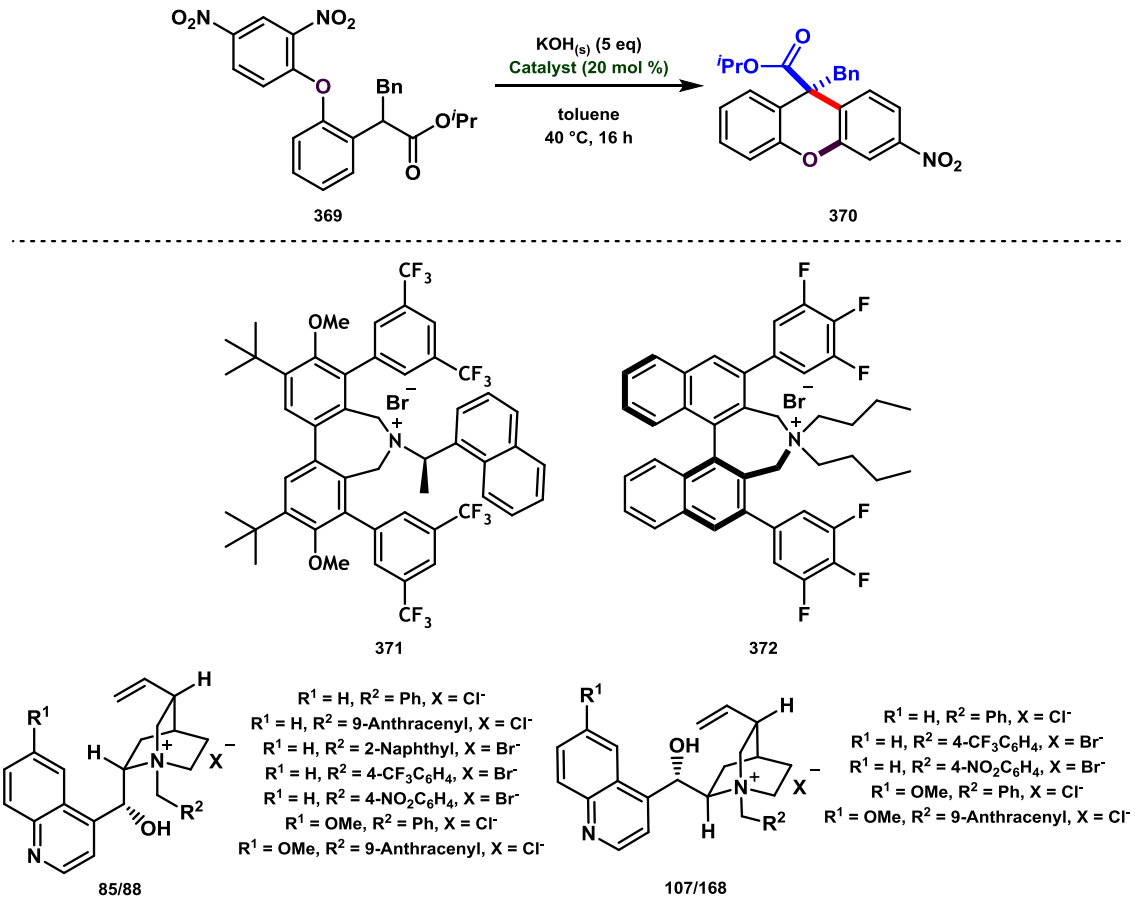
While this was successful it resulted in a reduced overall yield, thus subsequent work continued to use the two-step protocol.

When the reaction was carried out in the absence of TBAHS no formation of the product is observed with only starting material returned. This confirms that the presence of the phase-transfer catalyst is essential for the reaction to occur.

Having shown the reaction proceeds smoothly with a racemic phase-transfer catalyst, attention was now turned towards chiral phase-transfer catalysts in an effort to control the stereochemical outcome of the reaction.

3.5.3. Benzyl/isopropyl ester substituted system – chiral cation-directed catalysis

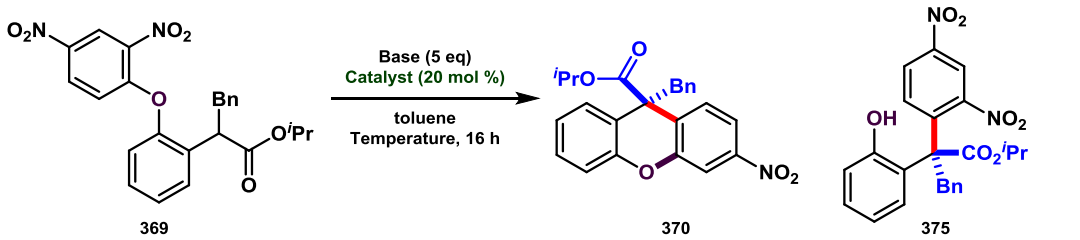
Attempts to utilize phase-transfer catalysts disclosed by Maruoka (**371**)[142] and Lygo (**372**)[143] as an alternative to the *cinchona* alkaloid scaffold resulted in no conversion to the desired product (Scheme 3.43). Returning to the *cinchona*-derived catalysts we initially decided to screen catalysts with a free hydroxyl group. The utility of such catalysts could not be fully examined in Jørgensen's asymmetric S_NAr reactions as the free hydroxyl group in the catalyst reacted with the aryl fluoride resulting in the formation of a new catalyst in *situ*.[119b] When this catalyst was synthesized independently and used in the S_NAr reaction it resulted in low enantioselectivities. Truce-Smiles precursor **369** already has the aryl group installed so this issue will not be faced. Disappointingly, these catalysts resulted in at best trace conversion to xanthene **370** and analysis of analytical preparative TLC samples of the product by HPLC showed that racemic product was being formed during the reaction (Scheme 3.43).



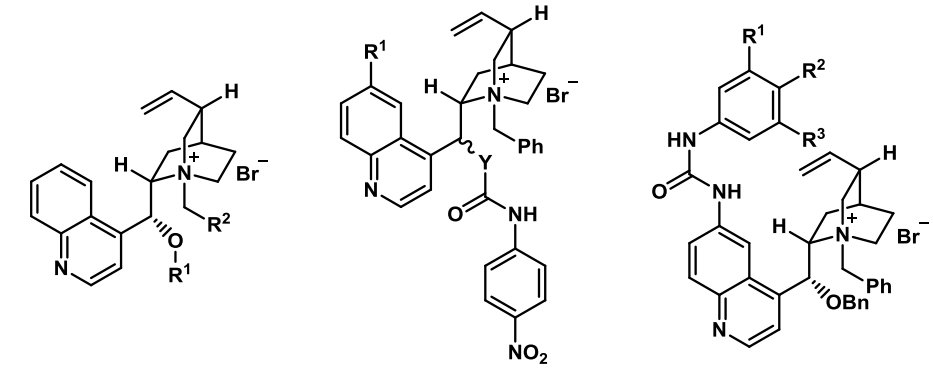
Scheme 3.43 – Chiral catalysts ineffective in xanthene formation

We now turned to catalysts where the hydroxyl group of the alkaloid catalyst was substituted. The ideal starting point would have been the *O*-benzoyl-substituted catalysts developed by Jørgensen,[119] however as these are prone to hydrolysis even at sub-zero temperatures they are unlikely to survive the elevated temperature required to initiate the Truce-Smiles rearrangement. A variety of alternative *O*-substituted catalysts were screened (Table 10), with the majority of these showing improved conversion over the catalysts with a free alcohol. However conversions were still modest, approximately 12 % when measured by crude ^{1}H NMR spectroscopy (entry **1**). Much more encouraging was that a preference for one enantiomer was observed, with a 14 % enantiomeric excess when commercially available catalyst **88b** was employed (entry **1**), proving that the principle of imparting enantioselectivity using a chiral cation was indeed valid. A variety of catalysts were then

screened in an effort to improve the conversion and enantioselectivity of the reaction. Carrying out the reaction with Cs_2CO_3 as the base resulted in similar conversion with a marginal drop in *ee* (entry **2**) and the crude NMR spectra showed additional unidentified impurities compared to when KOH was employed, so KOH remained the base of choice.



369 370 375



88 b - R^1 = Allyl, R^2 = Ph
88 - dR^1 = Allyl, R^2 = 9-anthracenyl

373a - R^1 = H, Y = (*S*)-NH
373b - R^1 = OMe, Y = (*R*)-O

374a - R^1 = R^3 = H, R^2 = NO_2
374b - R^1 = R^3 = CF_3, R^2 = H

Entry	Conditions	Outcome	ee (%)[a]
1	$KOH_{(s)}$, **88b**, 40 °C	Trace **370** (12 % conversion)[b]	14
2	$Cs_2CO_{3(s)}$, **88b**, 40 °C	Trace **370**	12
3	$KOH_{(s)}$, **88d**, 40 °C	Trace **370,** trace **375**[c]	30[c]
4	$KOH_{(s)}$, **373a**, 40 °C	No reaction	-
5	$KOH_{(s)}$, **373b**, 40 °C	No reaction	-
6	$KOH_{(s)}$, **374a**, 40 °C	Trace **370**	6
7	$KOH_{(s)}$, **374b**, 40 °C	Trace **370**	10

a) determined by chiral HPLC analysis of preparative TLC, b) determined by crude ^{1}H NMR spectroscopy, c) HPLC showed second set of peaks with 30 % *ee* - see text for discussion

Table 10 – Chiral catalyst screen

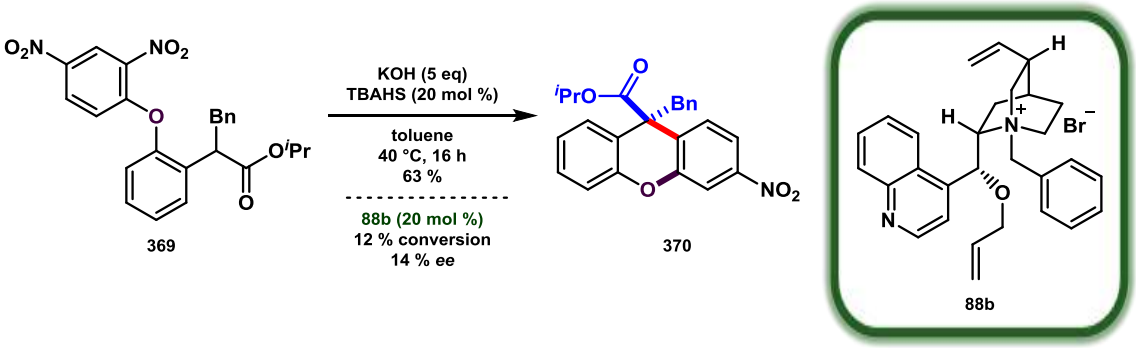
Altering the quaternizing group of the catalyst to a bulkier anthracenyl unit resulted in a two-fold improvement in *ee* to 30 % (entry **3**). However, the HPLC trace contained a second set of peaks which also integrated to an *ee* of 30 %. Due to the low conversion of the reaction this second product could not be positively identified, however we believe it to be the intermediate Truce-Smiles rearrangement product **375**. This product may arise because, while beneficial to the enantioselectivity, the bulkier anthracenyl aromatic group sterically inhibits the final intramolecular S_NAr step to form xanthene **370**.

In another approach, bifunctional phase-transfer catalysts bearing urea or carbamate groups were also employed as these types of groups are known to participate in hydrogen bonding interactions with nitro groups, facilitating Michael additions[144] and the nitro-Mannich reaction.[145] It was hoped that similar non-bonding interactions would occur with the nitro group in **369**, hence stabilizing the transition state and improving catalytic activity. The reaction proved intolerant of introduction of these groups onto the alcohol moiety (entries **4** and **5**); this may be because the greater bulk of these groups compared to the allyl unit creates an environment which is too sterically congested to allow access to the ammonium cation, preventing formation of the tight ion pair required for efficient phase-transfer catalysis to occur. Placement of the urea functionality on the quinoline ring of the catalyst proved more effective (compare entries **4** and **5**, and **6** and **7**) although conversion was still limited. A small degree of enantiocontrol was observed and the slight improvement in *ee* when bis-CF_3 catalyst **374b** was employed suggests that the urea group does exert some influence on the stereochemical outcome of the reaction, though synthesis of further derivatives of these catalysts would be required to probe whether this is a steric or an electronic effect.

At this stage of screening it was abundantly clear that the main issue faced was low conversion to the xanthene product due to the lack of activity of the chiral phase-transfer catalysts in this reaction. It is unclear from the experiments currently undertaken which step of the process the asymmetric catalysts are ineffective at expediting, though given that both steps are nucleophilic aromatic substitutions it is likely that the lack of activity applies to both steps. Modifications to this substrate to improve the nucleophilicity of the carbanion could potentially alleviate this, although as described in chapter 3.1 such compounds are inherently less basic, and therefore deprotonation of the substrate may become problematic. However, the synthesis of enantioenriched products using chiral phase-transfer catalysts, coupled with the good conversion observed in the racemic reaction shows that the concept of performing an asymmetric Truce-Smiles reactions utilizing chiral-cation directed catalysis is viable.

3.6. Conclusions and future work

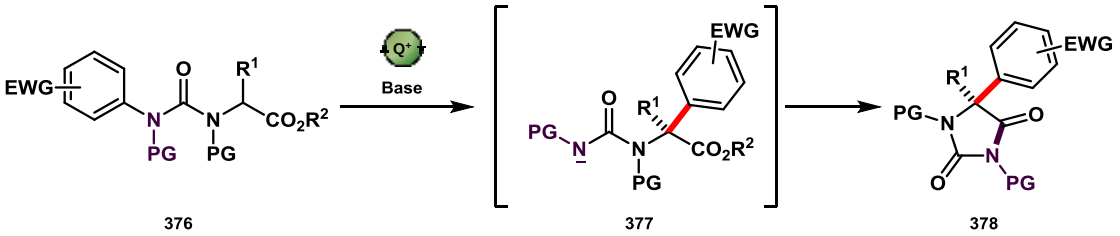
In conclusion, asymmetric Truce-Smiles rearrangements *via* chiral cation-directed catalysis have been shown to be a viable concept; with reactions proceeding smoothly under racemic conditions, provided the resulting anion is trapped in a subsequent intramolecular cyclization reaction (Scheme 3.44).



Scheme 3.44 – Proof of concept for cation-directed asymmetric Truce-Smiles reaction

Confirmation of asymmetric induction in this process has been obtained, however improvement of the levels of enantioselectivity has been hindered by the lack of activity of the chiral phase-transfer catalysts employed to facilitate the reaction.

Efforts towards potentially more reactive substrates with nitrile substituents, which would ultimately form lactones, have met with failure due to the lack of a suitable protecting group strategy to build the required substrates. Hence, future work towards improving the reactivity of the substrate must encompass more dramatic alterations. One option may be to move towards a modification of Kawabata's ester enolate Truce-Smiles rearrangement.[115] Kawabata's system lacks the required acidity for facile deprotonation under phase-transfer conditions, but by moving from an alanine to a phenyl glycine-derived substrate this problem may be circumvented (Scheme 3.45). However, as with any Truce-Smiles rearrangement system, the trade-off between acidity and the nucleophilicity of the resulting carbanion must be considered, and some subtle engineering of the system may be required to achieve the optimum balance.

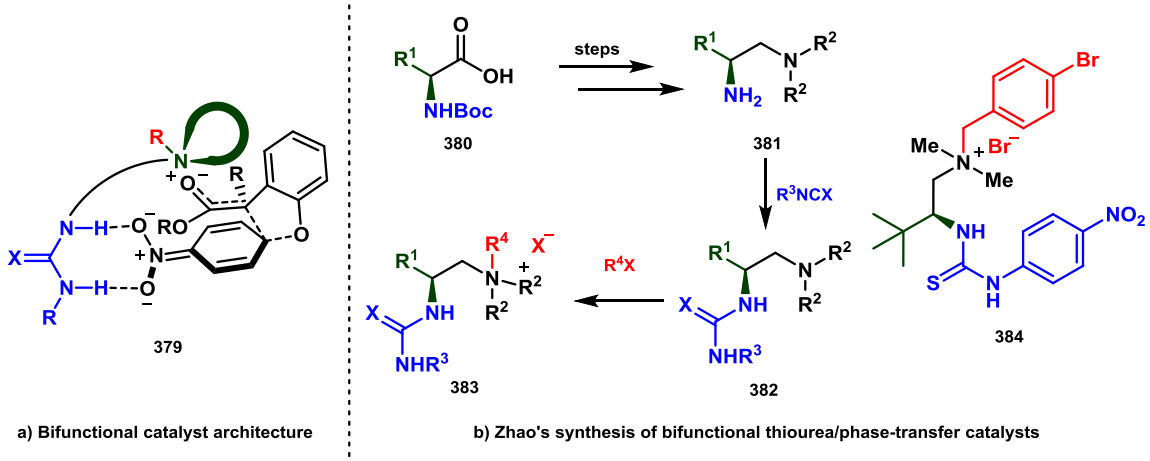


Scheme 3.45 – Potential asymmetric Truce-Smiles rearrangement by modification of Kawabata system

As alluded to in Chapter 3.5.2, another potential approach lies in the development of a new phase-transfer catalyst. While the *cinchona* alkaloids are often excellent chiral phase-transfer catalysts, this work and the work of Jørgensen[119] have shown that, when weaker electrophiles are employed, they suffer from a lack of activity in S_NAr reactions when compared to tetra-alkylammonium salts. Opportunities to systematically modify these

catalysts to address the issues are also limited; both enantioselectivity and activity can hinge on exceptionally specific substrate-catalyst interactions. For example, it is often observed that the catalytic activities of a *cinchona* alkaloid and its pseudoenantiomer are markedly different.[146] As such it would be attractive to develop a new series of phase-transfer catalysts for use in this reaction. One avenue towards this goal is to undertake a quantitative structure-activity relationship (QSAR) approach. This methodology has been developed and demonstrated by Denmark who synthesized a library of catalysts[147] and then examined their activity and selectivity in the alkylation of glycine-derived Schiff bases.[57] Application of this strategy towards a new reaction would be a useful test of its utility, and if successful could overcome the problems of low activity and selectivity faced during our efforts to develop an asymmetric Truce-Smiles rearrangement. From a wider perspective, and practical point of view, it may perhaps be more useful to use an intermolecular process such as Jørgensen's S_NAr reaction as a benchmark for new catalysts, since intermolecular S_NAr reactions are far more prevalent than the intramolecular case of the Truce-Smiles rearrangement. To undertake such a study a blueprint for an easily modifiable phase-transfer catalyst architecture, from which a library of catalysts can be synthesized and evaluated, must be proposed. One possibility is a bifunctional catalyst which contains a chiral environment around the ammonium cation to impart stereoselectivity and a hydrogen bond donor moiety connected to this catalyst by a modifiable linking unit (Scheme 3.46 a). This hydrogen bond donor may activate the electrophile towards attack, while also influencing the stereochemical outcome of the reaction. The quaternizing group should also be easily modifiable, allowing the steric and electronic properties of the catalyst, which in Denmark's study had approximately equal influence on stereoselectivity, to be easily tuned. Zhao has recently disclosed the synthesis of a series of bifunctional catalysts derived from

chiral amino acids, of which **384** is an example, which closely fit this description and can be synthesized in a modular fashion (Scheme 3.46 b).[148] If active, these catalysts would be perfectly suited to a detailed QSAR study of asymmetric S_NAr reactions, potentially leading to highly enantioselective transformations.

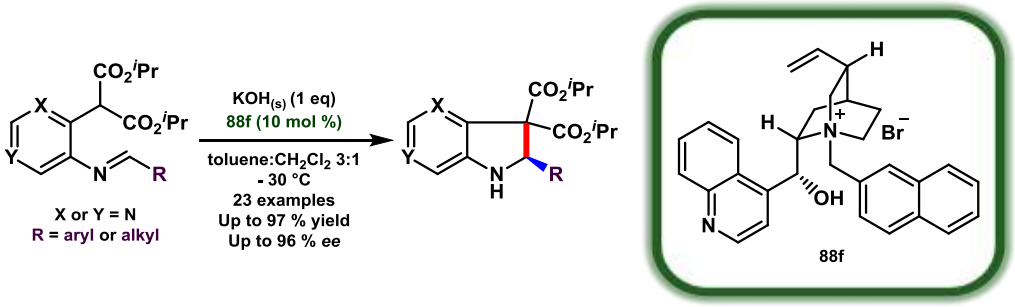


Scheme 3.46 – Potential new catalyst architecture

4. Overview

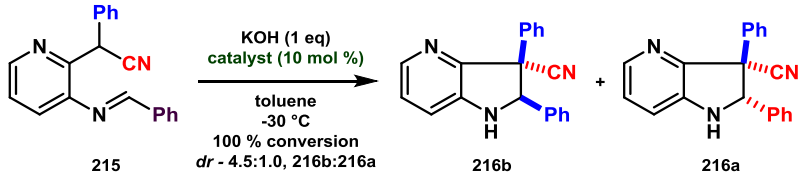
4.1. Asymmetric cyclizations to form azaindolines

Chiral cation-directed catalysis has been shown to be an effective method for the asymmetric synthesis of azaindolines, compounds for which few general synthetic routes have been developed. Densely functionalized 4- and 6-azaindolines could be generated in high yields and enantioselectivities using *cinchona* alkaloid-derived phase-transfer catalyst **88f** (Scheme 4.1)



Scheme 4.1 – Chiral cation-directed synthesis of 4- and 6- azaindolines

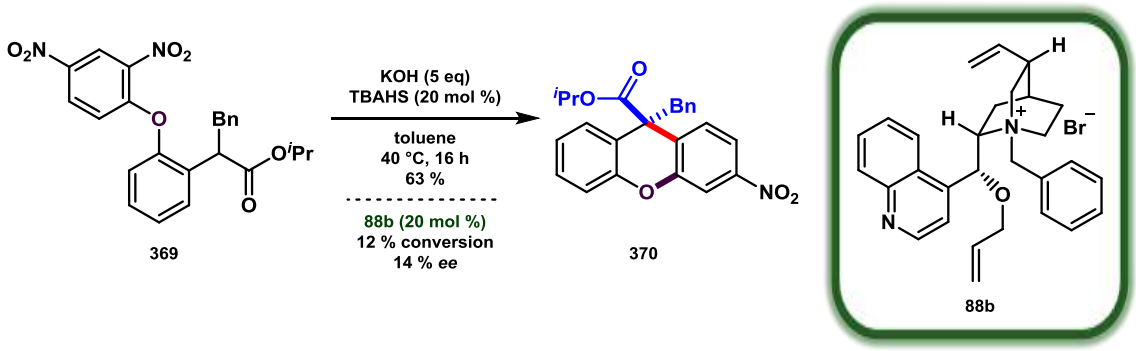
More complex azaindolines, bearing two contiguous stereocentres, one of which is all carbon and quaternary, were successfully synthesized (Scheme 4.2). However, the observed, diastereoselectivity and enantioselectivity of this process was significantly lower than the malonate system. This highlights that small changes in substrate structure can have a large influence on stereoselectivity during phase-transfer catalyzed processes.



Scheme 4.2 – Chiral cation-directed synthesis of azaindolines bearing contiguous stereocentres

4.2. Asymmetric rearrangements to form xanthenes

Chiral cation-directed catalysis could also be applied to asymmetric rearrangement processes, an area which has hitherto not been tested. The synthesis of xanthenes by initiating a Truce-Smiles rearrangement followed by an intramolecular S_NAr was discovered during these investigations (Scheme 4.3). This process was successfully catalyzed by achiral phase transfer catalysts. Screening of chiral phase-transfer catalysts demonstrated that low levels of asymmetric induction could be achieved, but conversion was poor. Further catalyst development and reaction optimization is required to transform this process into an efficient synthetic methodology.



Scheme 4.3 – Chiral cation-directed synthesis of xanthenes *via* a rearrangement process

4.3. Outlook

Chiral cation-directed catalysis is an effective tool in the field of asymmetric organocatalysis. Consultation of the literature reveals a vast array of processes in which it can be used to effect highly enantioselective transformations.[47] This thesis has highlighted that established methodologies can be directed towards the synthesis of new targets, but, despite the variety of reactions already explored, there remain areas which can be developed further. While only briefly discussed during this thesis, recent advances such as the development of bifunctional phase-transfer catalysts demonstrate that, even thirty years after the first

highly asymmetric phase-transfer-catalyzed reactions were disclosed, chiral cation-directed catalysis is still a vibrant area of research with much to offer the synthetic community.

5. Experimental

5.1. General Experimental Procedures

5.1.1. General Information

Unless otherwise indicated, all reactions were carried out under a positive pressure of argon or nitrogen (balloon pressure) in washed and oven-dried glassware. Unless otherwise indicated reaction mixtures were degassed using a 3 × pump/fill cycle.

5.1.2. Solvents and Reagents

Tetrahydrofuran, dichloromethane, and toluene were purified by pressurized filtration through activated silica columns, employing the method of Grubbs.[149] Unless otherwise indicated, solvents were used as supplied (analytical or HPLC grade) without further purification. "Petrol" or "petroleum ether" refers to the fraction of petroleum ether boiling in the range 40−60 °C. Where mixtures of solvents are specified, the stated ratios are volume:volume. pH 6 Buffer solution was prepared by the addition of sodium hydroxide (0.1 M aq., 56 mL) to potassium dihydrogen phosphate (0.1 M aq., 500 mL). Reagents were used directly as supplied by major chemical suppliers, or purified by procedures described by Perrin and Armarego.[150] The group library of *cinchona* alkaloid-derived quaternary ammonium salts were synthesized by the method of Corey[151] or by similar methods known in the literature.

5.1.3. Chromatography

Flash column chromatography was carried out using VWR silica gel (40−63 μm particle size).

Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} 0.25 mm precoated aluminium plates. Visualization was carried out under ultra-violet irradiation (254 nm) and by appropriate heating with potassium permanganate or vanillin. Potassium permanganate solution was prepared by dissolving potassium permanganate (2.5 g), potassium carbonate (13 g) and sodium hydroxide (0.63 g) in water (250 mL). Vanillin solution was prepared by dissolving vanillin (15 g) in ethanol (250 mL) and conc. sulfuric acid (2.5 mL).

5.1.4. NMR Spectroscopy

NMR spectra were recorded on Bruker AV400 (^{1}H: 400 MHz, ^{13}C: 101 MHz), Bruker AVII Cryo 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) or Bruker AVII 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) spectrometer. Chemical shifts are quoted in ppm, based on appearance rather than interpretation, and are referenced to the residual non-deuterated solvent peak. ^{1}H NMR spectra are reported as follows: δ_H (spectrometer frequency, solvent): chemical shift/ppm (number of protons, multiplicity*, J-coupling constant(s),* ***assignment***). ^{13}C NMR spectra are reported as follows: δ_C (spectrometer frequency, solvent): chemical shift/ppm (***assignment***). Multiplets are abbreviated as follows: br. – broad; s – singlet; d – doublet; t – triplet; q – quartet; sept – septet; m – multiplet; apt. – apparent. Compound multiplets are reported in the order of decreasing coupling constant magnitude. Spectral assignment was aided by the results of DEPT, COSY, HMBC and HSQC experiments where appropriate.

5.1.5. *IR Spectroscopy*

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

5.1.6. *Mass Spectrometry*

Mass spectra were recorded on a Micromass LCT Premier spectrometer under conditions of electrospray ionization (ESI). Accurate masses (HRMS) were recorded on a Bruker MicroTOF spectrometer under conditions of ESI, and on a Micromass GCT spectrometer under conditions of field ionization (FI). Quoted accurate mass values refer to the monoisotopic mass and are calculated for the lightest isotope. Masses are reported in daltons (Da).

5.1.7. *Polarimetry*

Optical rotations were recorded on Perkin-Elmer 241 and 341 polarimeters with a path length of 1 dm, and are reported in $deg \cdot dm^{-1} cm^3 g^{-1}$. Values are measured at the sodium D line (589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C.

5.1.8. *Melting Points*

All melting points were measured on a Gallenkamp MF-370 melting point apparatus or a Reichert melting point stage, and are uncorrected. Temperatures are reported in °C.

5.1.9. *HPLC*

Analytical chiral HPLC was performed on a Dionex Ultimate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment,

DAD-3000 diode-array detector, equipped with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø x 25 cm) and corresponding guard column (0.4 cm ø x 1 cm). Wavelengths (λ) are reported in nm, retention times (t_R) are reported in seconds and solvent flow rates are reported in mL/min.

5.1.10. Naming, numbering and depiction of compounds

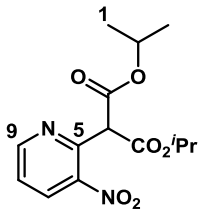
Where given, systematic compound names are those generated by ChemBioDraw Ultra 12.0 following IUPAC conventions. The numbering of atoms for spectral assignment purposes is arbitrary and not necessarily consistent with the IUPAC names.

Chiral nonracemic and racemic molecules are depicted according to the Maehr convention:[152] absolute stereochemistry is indicated by solid wedged (—) and hatched wedged (⋯) bonds, and relative stereochemistry is indicated by solid bold (—) and hatched bold (⋯) bonds.

5.2. Experimental procedures

5.2.1. Cation-directed asymmetric synthesis of azaindolines

Preparation of diisopropyl 2-(3-nitropyridin-2-yl) malonate (164)



Diisopropyl malonate (7.17 mL, 37.8 mmol) was added to a stirred suspension of K_2CO_3 (5.23 g, 37.8 mmol) in DMF (60 mL) at RT. The mixture was heated to 90 °C and stirred for 30 min. 2-Chloro-3-nitropyridine (3.00 g, 18.9 mmol) was added and the resulting dark brown solution stirred at 90 °C for 16 h, when complete consumption of the starting material was observed by NMR spectroscopy. The crude reaction mixture was concentrated *in vacuo* and diluted with ethyl acetate:methanol (5:1, 100 mL) and saturated aqueous NH_4Cl (100 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate:methanol (5:1, 2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:1) to yield nitropyridine **164** (4.66 g, 79 %) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.81 (1H, dd, *J* 4.8, 1.5, **H9**), 8.47 (1H, dd, *J* 8.3, 1.5, **H7**), 7.52 (1H, dd, *J* 8.2, 4.7, **H8**), 5.46 (1H, s, **H4**), 5.18 (2H, sept, *J* 6.2, **H2**), 1.28 (12H, d, *J* 6.1, **H1**).

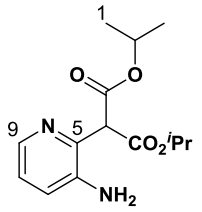
^{13}C (101 MHz, $CDCl_3$): δ 166.0 (**C3**), 152.9 (**C9**), 149.3 (**C5**), 144.9 (**C6**), 133.1 (**C7**), 123.7 (**C8**), 69.9 (**C2**), 59.6 (**C4**), 21.5 (**C1**).

HRMS (ESI): found 333.1055; $[C_{14}H_{18}N_2O_6Na]^+$ $(M + Na)^+$ requires 333.1057.

IR: ν_{max} (neat)/cm^{-1}: 2983 (C-H aromatic), 2937 (C-H aliphatic), 1719 (C=O), 1630, 1603, 1583, 1523 (NO_2), 1380 (NO_2).

MP: 69-71 °C.

Preparation of diisopropyl 2-(3-aminopyridin-2-yl) malonate (165)



Nitropyridine **164** (602 mg, 1.94 mmol) was added to a stirred suspension of palladium black (60 mg, 10 % wt/wt) in ethanol (15 mL). The mixture was degassed and placed under an atmosphere of hydrogen for 6 h. The reaction mixture was filtered through Celite®, eluting with CH_2Cl_2, and concentrated *in vacuo*. The crude product was then passed through a plug of silica eluting with diethyl ether. This solution was concentrated *in vacuo* to yield aminopyridine **165** (543 mg, 99 %) as a pale yellow solid. NB: Product is unstable in air and must be used immediately or stored under argon.

^{1}H (400 MHz, $CDCl_3$): δ 7.99 (1H, dd, *J* 4.6, 1.5, **H9**), 7.05 (1H, dd, *J* 8.1, 1.6, **H8**), 6.99 (1H, dd, *J* 8.1, 1.5, **H7**), 5.11 (2H, sept, *J* 6.3, **H2**), 4.88 (1H, s, **H4**), 4.22 (2H, br. s, **NH**), 1.28 (6H, d, *J* 6.3, **H1**), 1.24 (6H, d, *J* 6.3, **H1**).

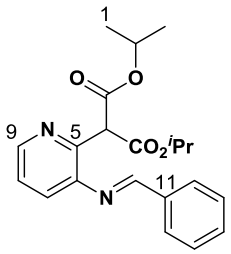
^{13}C (101 MHz, $CDCl_3$): δ 167.8 (**C3**), 142.1 (**C5**), 140.2 (**C6**), 139.5 (**C9**), 124.3 (**C8**), 123.9 (**C7**), 69.7 (**C2**), 60.5 (**C4**), 21.6 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 303.1318; $[C_{14}H_{20}N_2O_4Na]^+$ $(M + Na)^+$ requires 303.1315.

IR: ν_{max} (neat)/cm^{-1}: 3359 (N-H), 2983 (C-H aromatic), 2936 (C-H aliphatic), 1725 (C=O), 1634 (N-H), 1583, 1104.

MP: 95-97 °C.

Preparation of (*E*)-diisopropyl 2-(3-(benzylideneamino)pyridin-2-yl)malonate (166a)



Freshly distilled benzaldehyde (472 µL, 4.65 mmol) was added to a solution of aminopyridine **165** (869 mg, 3.10 mmol) in toluene (30 mL) containing anhydrous $MgSO_4$ (1.12 g, 9.30 mmol) at RT. The suspension was stirred for 24 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was recrystallized from diethyl ether and 40-60 petrol to yield imine **166a** (702 mg, 62 %) as yellow crystals.

^{1}H (400 MHz, $CDCl_3$): δ 8.46 (1H, dd, *J* 4.7, 1.5, **H9**), 8.43 (1H, s, **H10**), 7.90-7.88 (2H, m, **H12**), 7.53-7.45 (3H, m, **H13** and **H14**), 7.40 (1H, dd, *J*, 7.9, 1.6, **H7**), 7.30 (1H, dd, *J* 8.0, 4.6, **H8**), 5.32 (1H, s, **H4**), 5.12 (2H, sept, *J* 6.3, **H2**), 1.25 (6H, d, *J* 6.2, **H1**), 1.19 (6H, d, *J* 6.2, **H1'**).

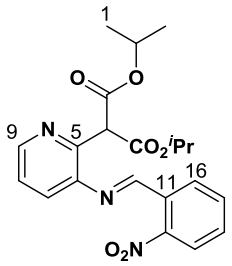
^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 161.8 (**C10**), 149.5 (**C5**), 146.7 (**C9**), 145.5 (**C6**), 135.8 (**C11**), 132.0 (**C14**), 129.1 (**C12**), 128.8 (**C13**), 124.4 (**C7**), 123.7 (**C8**), 69.1 (**C2**), 57.6 (**C4**), 21.7 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 369.1809; $[C_{21}H_{25}N_2O_4]^+$ $(M + H)^+$ requires 369.1809.

IR: ν_{max} (neat)/cm^{-1}: 2981 (C-H aromatic), 2936 (C-H aliphatic), 1731 (C=O), 1629 (C=N), 1102.

MP (diethyl ether): 79-82 °C.

Preparation of (*E*)-diisopropyl 2-(3-((2-nitrobenzylidene)amino)pyridin-2-yl)malonate (166b)



Recrystallized 2-nitrobenzaldehyde (272 mg, 1.80 mmol) was added to a solution of aminopyridine **165** (336 mg, 1.20 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (180 mg, 1.50 mmol) at RT. The solution was stirred for 24 h and the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:1) to yield imine **166b** (319 mg, 64 %) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.95 (1H, s, **H10**), 8.51 (1H, dd, *J* 4.8, 1.3, **H9**), 8.30 (1H, dd, *J* 7.8, 1.3, **H16**), 8.11 (1H, dd, *J* 8.2, 0.9, **H13**), 7.76 (1H, t, *J* 7.3, **H15**), 7.66 (1H, td, *J* 8.1, 1.5, **H14**), 7.53 (1H, dd *J* 8.1, 1.5, **H7**) 7.35 (1H, dd, *J* 7.8, 4.8, **H8**), 5.29 (1H, s, **H4**), 5.12 (2H, spt, *J* 6.3, **H2**), 1.24 (6H, d, *J* 6.3, **H1**), 1.21 (6H, d, *J* 6.3, **H1'**).

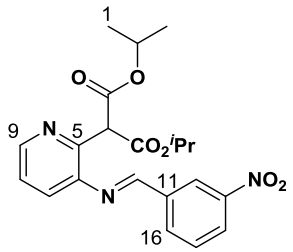
^{13}C (101 MHz, $CDCl_3$): δ 167.2 (**C3**), 157.7 (**C10**), 149.6 (**C5**), 149.3 (**C12**), 147.6 (**C9**), 144.9 (**C6**), 133.8 (**C15**), 131.8 (**C14**), 130.7 (**C11**), 130.0 (**C16**), 125.0 (**C7**), 124.6 (**C13**), 124.0 (**C8**), 69.3 (**C2**), 58.0 (**C4**), 21.6 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 436.1485; $[C_{21}H_{23}N_3O_6Na]^+$ ($M + Na^+$) requires 436.1479.

IR: ν_{max} (neat)/ cm^{-1}: 2983, 2935, 1736 (C=O), 1624 (C=N), 1528 (NO_2), 1349 (NO_2), 1104.

MP: 111-114 °C.

Preparation of (*E*)-diisopropyl 2-(3-((3-nitrobenzylidene)amino)pyridin-2-yl)malonate (166c)



Recrystallized 3-nitrobenzaldehyde (211 mg, 1.40 mmol) was added to a solution of aminopyridine **165** (225 mg, 0.80 mmol) in toluene (8 mL) containing anhydrous $MgSO_4$ (193 mg, 1.60 mmol) at RT. The solution was stirred for 40 h and the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:1) to yield imine **166c** (228 mg, 69 %) as a dark yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.70 (1H, s, **H12**), 8.54 (1H, s, **H10**), 8.50 (1H, d, *J* 4.6, **H9**), 8.36 (1H, dt, *J* 8.1, 1.0, **H14**), 8.25 (1H, dd, *J* 7.7, 0.9, **H16**), 7.68 (1H, t, *J* 8.0, **H15**), 7.45 (1H, dd *J* 8.1, **H7**) 7.33 (1H, dd, *J* 8.1, 4.8, **H8**), 5.30 (1H, s, **H4**), 5.12 (2H, spt, *J* 6.1, **H2**), 1.25 (6H, d, *J* 6.3, **H1**), 1.20 (6H, d, *J* 6.3, **H1'**).

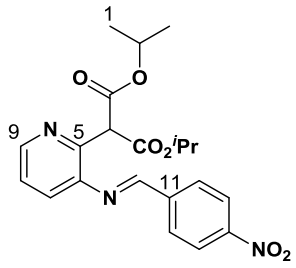
^{13}C (101 MHz, $CDCl_3$): δ 167.2 (**C3**), 158.9 (**C10**), 149.8 (**C5**), 148.7 (**C13**), 147.6 (**C9**), 144.5 (**C6**), 137.3 (**C11**), 134.3 (**C16**), 130.0 (**C15**), 126.2 (**C14**), 124.3 (**C7**), 123.8 (**C8**), 123.7 (**C12**), 69.3 (**C2**), 58.0 (**C4**), 21.6 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 436.1470; $[C_{21}H_{23}N_3O_6Na]^+$ ($M + Na^+$) requires 436.1479.

IR: ν_{max} (neat)/ cm^{-1}: 2964, 2880, 1736 (C=O), 1629 (C=N), 1533 (NO_2), 1353 (NO_2), 1103.

MP: 100-102 °C.

Preparation of (*E*)-diisopropyl 2-(3-((4-nitrobenzylidene)amino)pyridin-2-yl)malonate (166d)



Recrystallized 4-nitrobenzaldehyde (242 mg, 1.60 mmol) was added to a solution of aminopyridine **165** (300 mg, 1.07 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (320 mg, 2.63 mmol) at RT. The suspension was stirred for 48 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:1) to yield imine **166d** (195 mg, 35 %) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.55 (1H, s, **H10**), 8.51 (1H, d, *J* 4.8, **H9**), 8.33 (2H, d, *J* 8.3, **H13**), 8.07 (2H, d, *J* 8.3, **H12**), 7.46 (1H, d, *J* 7.8 **H7**), 7.33 (1H, dd, *J* 7.8, 4.8, **H8**), 5.29 (1H, s, **H4**), 5.11 (2H, sept, *J* 6.3, **H2**), 1.25 (6H, d, *J* 6.3, **H1**), 1.19 (6H, d, *J* 6.1, **H1'**).

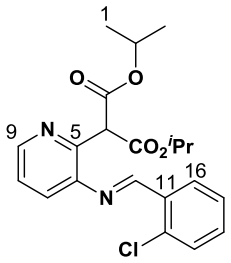
^{13}C (101 MHz, $CDCl_3$): δ 167.1 (**C3**), 158.9 (**C10**), 150.0 (**C14**) 149.6 (**C5**), 147.8 (**C9**), 144.4 (**C6**), 141.0 (**C11**), 129.7 (**C12**), 124.2 (**C7**), 124.0 (**C13**), 123.8 (**C8**), 69.2 (**C2**), 57.9 (**C4**), 21.6 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 436.1482; $[C_{21}H_{23}N_3O_6Na]^+$ $(M + Na)^+$ requires 436.1479.

IR: ν_{max} (neat)/cm^{-1}: 2983 (C-H aromatic), 2937 (C-H aliphatic), 1730 (C=O), 1631 (C=N), 1523 (NO_2), 1346 (NO_2), 1103.

MP: 118-121 °C.

Preparation of (*E*)-diisopropyl 2-(3-((2-bromobenzylidene)amino)pyridin-2-yl)malonate (166e)



2-Chlorobenzaldehyde (178 µL, 2.50 mmol) was added to a solution of aminopyridine **165** (300 mg, 1.61 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (386 mg, 4.83 mmol) at RT. The suspension was stirred for 24 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:1) to yield imine **166e** (229 mg, 54 %) as bright yellow crystals.

^{1}H (400 MHz, $CDCl_3$): δ 8.92 (1H, s, **H10**), 8.48 (1H, dd, *J* 4.8, 1.5, **H9**), 8.24 (1H, d, *J* 8.1, **H16**), 7.47-7.43 (3H, m, **H7**, **H13** and **H14**), 7.39-7.35 (1H, m, **H15**), 7.32 (1H, dd, *J* 8.3, 4.8, **H8**), 5.31 (1H, s, **H4**), 5.13 (2H, sept, *J* 6.3, **H2**), 1.25 (6H, d, *J* 6.1, **H1**), 1.21 (6H, d, *J* 6.3, **H1'**).

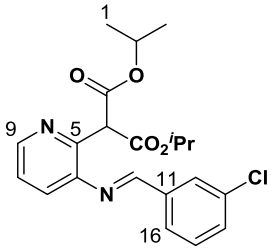
^{13}C (101 MHz, $CDCl_3$): δ 167.2 (**C3**), 158.2 (**C10**), 149.7 (**C5**), 147.1 (**C9**), 145.2 (**C6**), 136.2 (**C12**), 132.8 and 132.7 (**C11** and **C13**), 130.0 (**C15**), 128.9 (**C16**), 127.2 (**C14**), 124.6 (**C7**), 123.8 (**C8**), 69.1 (**C2**), 57.8 (**C4**), 21.6 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 403.1416; $[C_{21}H_{24}ClN_2O_4]^+$ $(M + H)^+$ requires 403.1419.

IR: ν_{max} (neat)/cm^{-1}: 2982 (C-H aromatic), 2934 (C-H aliphatic), 1737 (C=O), 1622 (C=N), 1104.

MP: 76-78 °C.

Preparation of (*E*)-diisopropyl 2-(3-((3-chlorobenzylidene)amino)pyridin-2-yl)malonate (166f)



Recrystallized 3-chlorobenzaldehyde (236 µL, 2.08 mmol) was added to a solution of aminopyridine **165** (291 mg, 1.04 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (626 mg, 5.20 mmol) at RT. The suspension was stirred for 24 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was recrystallized from diethyl ether and 40-60 petrol to yield imine **166f** (162 mg, 39 %) as white crystals.

^{1}H (400 MHz, $CDCl_3$): δ 8.48 (1H, dd, *J* 4.8, 1.5, **H9**), 8.39 (1H, s, **H10**), 7.92 (1H, apt. t, *J* 1.8, **H12**), 7.76-7.71 (1H, m, **H16**), 7.51-7.45 (1H, m, **H14**), 7.44-7.37 (2H, m, **H7** and **H15**), 7.30 (1H, dd, *J* 8.1, 4.8, **H8**), 5.30 (1H, s, **H4**), 5.12 (2H, sept, *J* 6.3, **H2**), 1.26 (6H, d, *J* 6.3, **H1**), 1.21 (6H, d, *J* 6.3, **H1'**).

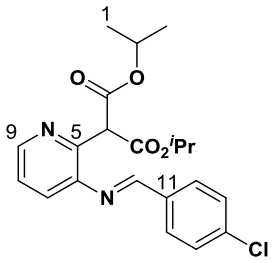
^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 160.1 (**C10**), 149.7 (**C5**), 147.1 (**C9**), 144.9 (**C6**), 137.5 (**C11**), 135.0 (**C13**), 131.9 (**C14**), 130.1 (**C15**), 128.5 (**C12**), 127.5 (**C16**), 124.3 (**C7**), 123.7 (**C8**), 69.2 (**C2**), 57.7 (**C4**), 21.7 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 425.1237; $[C_{21}H_{23}ClN_2O_4Na]^+$ $(M + Na)^+$ requires 425.1239.

IR: ν_{max} (neat)/ cm^{-1}: 2963 (C-H aromatic), 2935 (C-H aliphatic), 1738 (C=O), 1622 (C=N), 1047.

MP (diethyl ether:40-60 petrol): 83-85 °C.

Preparation of (*E*)-diisopropyl 2-(3-((4-chlorobenzylidene)amino)pyridin-2-yl)malonate (166g)



Recrystallized 4-chlorobenzaldehyde (222 mg, 1.61 mmol) was added to a solution of aminopyridine **165** (300 mg, 1.07 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (320 mg, 2.68 mmol) at RT. The suspension was stirred for 48 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:1) to yield imine **166g** (171 mg, 40 %) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.46 (1H, d, *J* 4.6, **H9**), 8.40 (1H, s, **H10**), 7.83 (2H, d, *J* 7.8, **H13**), 7.45 (2H, d, *J* 7.8, **H12**), 7.40 (1H, d, *J* 8.0, **H7**), 7.29 (1H, dd, *J* 7.8, 4.5, **H8**), 5.29 (1H, s, **H4**), 5.11 (2H, sept, *J* 6.2, **H2**), 1.24 (6H, d, *J* 6.3, **H1**), 1.19 (6H, d, *J* 6.3, **H1'**).

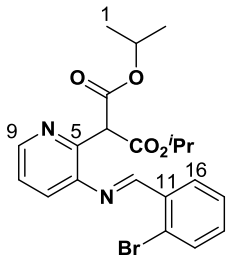
^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 160.2 (**C10**), 149.6 (**C5**), 146.9 (**C9**), 145.1 (**C6**), 138.1 (**C14**), 134.3 (**C11**), 130.2 (**C13**), 129.2 (**C12**), 124.3 (**C7**), 123.7 (**C8**), 69.1 (**C2**), 57.7 (**C4**), 21.6 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 425.1237; $[C_{21}H_{23}ClN_2O_4Na]^+$ $(M + Na)^+$ requires 425.1239.

IR: ν_{max} (neat)/cm^{-1}: 2983 (C-H aromatic), 2942 (C-H aliphatic), 1736 (C=O), 1627 (C=N), 1102.

MP: 122-125 °C.

Preparation of (*E*)-diisopropyl 2-(3-((2-bromobenzylidene)amino)pyridin-2-yl)malonate (166h)



2-Bromobenzaldehyde (206 µL, 1.76 mmol) was added to a solution of aminopyridine **165** (248 mg, 0.88 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (318 mg, 2.64 mmol) at RT. The suspension was stirred for 48 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:1) to yield imine **166h** (243 mg, 62 %) as a yellow crystalline solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.85 (1H, s, **H10**), 8.48 (1H, dd, *J* 4.7, 1.4, **H9**), 8.22 (1H, dd, *J* 7.8, 1.8, **H16**), 7.62 (1H, dd, *J* 7.8, 1.3, **H13**), 7.46 (1H, dd, *J* 8.1, 1.5, **H7**), 7.41 (1H, apt. t, *J* 7.3, **H15**) 7.37-7.31 (2H, m, **H8** and **H14**), 5.31 (1H, s, **H4**), 5.12 (2H, sept, *J* 6.2, **H2**), 1.24 (6H, d, *J* 6.3, **H1**), 1.20 (6H, d, *J* 6.3, **H1'**).

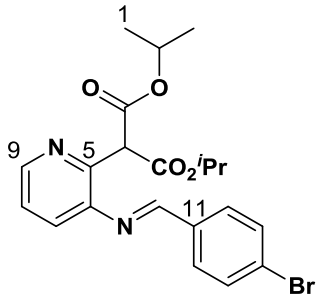
^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 160.6 (**C10**), 149.7 (**C5**), 147.2 (**C9**), 145.1 (**C6**), 134.1 (**C11**), 133.3 (**C13**), 133.0 (**C14**), 129.4 (**C16**), 127.8 (**C15**), 126.3 (**C12**), 124.7 (**C7**), 123.8 (**C8**), 69.1 (**C2**), 57.8 (**C4**), 21.7 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 447.0918; $[C_{21}H_{24}BrN_2O_4]^+$ $(M + H)^+$ requires 447.0914.

IR: ν_{max} (neat)/cm^{-1}: 2982 (C-H aromatic), 2934 (C-H aliphatic), 1735 (C=O), 1620 (C=N), 1104.

MP: 78-81 °C.

Preparation of (*E*)-diisopropyl 2-(3-((4-bromobenzylidene)amino)pyridin-2-yl)malonate (166i)



Recrystallized 4-bromobenzaldehyde (386 mg, 2.14 mmol) was added to a solution of aminopyridine **165** (300 mg, 1.07 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (386 mg, 3.21 mmol) at RT. The suspension was stirred for 48 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:1) to yield imine **166i** (351 mg, 73 %) as a pale yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.46 (1H, dd, *J* 4.68, 1.5, **H9**), 8.39 (1H, s, **H10**), 7.76 (2H, d, *J* 8.3, **H12**), 7.61 (2H, d, *J* 8.3, **H13**), 7.40 (1H, dd, *J* 8.0, 1.5, **H7**), 7.29 (1H, dd, *J* 7.8, 4.8, **H8**), 5.28 (1H, s, **H4**), 5.11 (2H, sept, *J* 6.3, **H2**), 1.24 (6H, d, *J* 6.3, **H1**), 1.19 (6H, d, *J* 6.3, **H1'**).

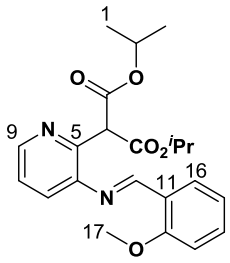
^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 160.3 (**C10**), 149.6 (**C5**), 147.0 (**C9**), 145.1 (**C6**), 134.7 (**C11**), 130.4 (**C13**), 126.7 (**C12**), 124.3 (**C14**), 123.9 (**C7**), 123.7 (**C8**), 69.1 (**C2**), 57.7 (**C4**), 21.7 (**C1**), 21.7 (**C1'**).

HRMS (ESI): found 447.0912; $[C_{21}H_{24}BrN_2O_4]^+$ $(M + H)^+$ requires 447.0914.

IR: ν_{max} (neat)/cm^{-1}: 3068 (C-H aromatic), 2983 (C-H aromatic), 2935 (C-H aliphatic), 1736 (C=O), 1632 (C=N), 1104.

MP: 104-107 °C.

Preparation of (*E*)-diisopropyl 2-(3-((2-methoxybenzylidene)amino)pyridin-2-yl)malonate (166j)



2-Methoxybenzaldehyde (219 mg, 1.61 mmol) was added to a solution of aminopyridine **165** (300 mg, 1.07 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (161 mg, 1.34 mmol) at RT. The suspension was stirred for 24 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was recrystallized from ethyl acetate and 40-60 petrol to yield imine **166j** (181 mg, 42 %) as white crystals.

^{1}H (400 MHz, $CDCl_3$): δ 8.90 (1H, s, **H10**), 8.43 (1H, dd, *J* 4.8, 1.5, **H9**), 8.15 (1H, dd, *J* 7.8, 1.8, **H16**), 7.46 (1H, apt. td, *J* 7.6, 1.8, **H14**), 7.42 (1H, dd *J* 7.8, 1.5, **H7**) 7.27 (1H, dd, *J* 8.1, 4.8, **H8**), 7.03 (1H, apt. t, *J* 7.6, **H15**), 7.03 (1H, d, *J* 8.1, **H13**), 5.33 (1H, s, **H4**), 5.12 (2H, sept, *J* 6.3, **H2**), 3.90 (3H, s, **H17**), 1.24 (6H, d, *J* 6.3, **H1**), 1.20 (6H, d, *J* 6.3, **H1'**).

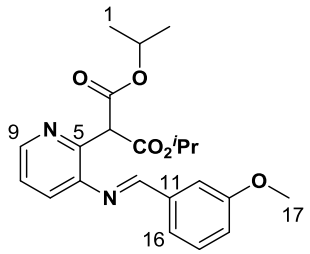
^{13}C (101 MHz, $CDCl_3$): δ 167.2 (**C3**), 159.7 (**C12**), 157.6 (**C10**), 149.6 (**C5**), 146.4 (**C9**), 146.2 (**C6**), 133.4 (**C14**), 130.0 (**C16**), 124.6 (**C7**) 124.3 (**C11**), 123.6 (**C8**), 120.9 (**C15**), 111.1 (**C13**), 69.0 (**C2**), 58.0 (**C4**), 55.5 (**C17**), 21.6 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 399.1906; $[C_{22}H_{27}N_2O_5]^+$ $(M + H)^+$ requires 399.1914.

IR: ν_{max} (neat)/cm^{-1}: 2892 (C-H aromatic), 2934 (C-H aliphatic), 1737 (C=O), 1613 (C=N), 1248, 1104.

MP (ethyl acetate:40-60 petrol): 92-94 °C.

Preparation of (*E*)-diisopropyl 2-(3-((3-methoxybenzylidene)amino)pyridin-2-yl)malonate (166k)



Freshly distilled 3-methoxybenzaldehyde (216 µL, 1.76 mmol) was added to a solution of aminopyridine **165** (248 mg, 0.88 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (254 mg, 2.11 mmol) at RT. The suspension was stirred for 48 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 2:1) to yield imine **166k** (235 mg, 67 %) as a cream solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.45 (1H, d, *J* 4.6, **H9**), 8.40 (1H, s, **H10**), 7.51 (1H, d, *J* 1.3, **H12**), 7.44-7.35 (3H, m, **H7**, **H15** and **H16**), 7.30 (1H, dd, *J* 8.1, 4.8, **H8**), 7.08-7.06 (1H, m, **H14**), 5.29 (1H, s, **H4**), 5.11 (2H, sept, *J* 6.3, **H2**), 3.90 (3H, s, **H17**), 1.24 (6H, d, *J* 6.3, **H1**), 1.18 (6H, d, *J* 6.3, **H1'**).

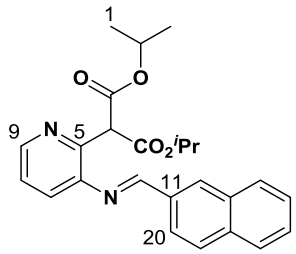
^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 161.6 (**C10**), 160.0 (**C13**), 149.6 (**C5**), 146.7 (**C9**), 145.4 (**C6**), 137.2 (**C11**), 129.7 (**C15**), 124.4 (**C7**), 123.6 (**C8**), 122.5 (**C16**), 118.8 (**C14**), 112.4 (**C12**), 69.1 (**C2**), 57.8 (**C4**), 55.4 (**C17**), 21.6 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 399.1918; $[C_{22}H_{27}N_2O_5]^+$ $(M + H)^+$ requires 399.1914.

IR: ν_{max} (neat)/cm^{-1}: 2891 (C-H aromatic), 2936 (C-H aliphatic), 1730 (C=O), 1628 (C=N), 1309, 1268, 1103.

MP: 44-47 °C.

Preparation of (*E*)-diisopropyl 2-(3-((naphthalen-2-ylmethylene)amino)pyridin-2-yl)malonate (166m)



Recrystallized 2-naphthaldehyde (836 mg, 3.75 mmol) was added to a solution of aminopyridine **165** (420 mg, 1.50 mmol) in toluene (15 mL) containing anhydrous $MgSO_4$ (322 mg, 1.88 mmol) at RT. The suspension was stirred for 48 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was recrystallized from diethyl ether and 40-60 petrol to yield imine **166m** (208 mg, 33 %) as white crystals.

^{1}H (400 MHz, $CDCl_3$): δ 8.59 (1H, s, **H10**), 8.48 (1H, dd, *J* 4.8, 1.5, **H9**), 8.22-8.12 (2H, m, **H12** and **H20**), 7.96-7.87 (3H, m, **H14**, **H17** and **H19**), 7.57 (2H, apt. quin d, *J* 7.1, 1.5, **H15** and **H16**), 7.46 (1H, dd, *J* 8.1, 1.5, **H7**), 7.32 (1H, dd, *J* 8.1, 4.8, **H8**), 5.40 (1H, s, **H4**), 5.13 (2H, sept, *J* 6.3, **H2**), 1.26 (6H, d, *J* 6.3, **H1**), 1.21 (6H, d, *J* 6.3, **H1'**).

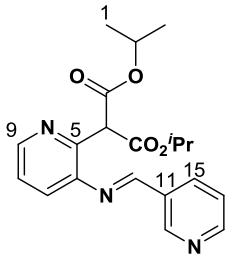
^{13}C (101 MHz, $CDCl_3$): δ 167.4 (**C3**), 161.6 (**C10**), 149.7 (**C5**), 146.7 (**C9**), 145.5 (**C6**), 135.3 (**C11**), 133.6 (**C13**), 133.0 (**C18**), 132.1 (**C20**), 128.9 and 128.8 (**C14** and **C17**), 128.0 (**C19**), 127.9 and 126.8 (**C15** and **C16**), 124.3 (**C7**), 123.8 (**C12**), 123.7 (**C8**), 69.1 (**C2**), 57.7 (**C4**), 21.7 (**C1**), 21.6 (**C1'**).

HRMS (ESI): found 441.1785; $[C_{25}H_{26}N_3O_4Na]^+$ $(M+Na)^+$ requires 441.1785.

IR: ν_{max} (neat)/cm^{-1}: 2982 (C-H aromatic), 2935 (C-H aliphatic), 1736 (C=O), 1621 (C=N), 1104.

MP (diethyl ether:40-60 petrol): 119-121 °C.

Preparation of (*E*)-diisopropyl 2-(3-((pyridin-3-ylmethylene)amino)pyridin-2-yl)malonate (166n)



Pyridine-3-carboxaldehyde (101 µL, 1.61 mmol) was added to a solution of aminopyridine **165** (300 mg, 1.07 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (161 mg, 1.34 mmol) at RT. The solution was stirred for 40 h and the reaction mixture was filtered and concentrated *in vacuo*. The crude product was recrystallized from diethyl ether and 40-60 petrol to yield imine **166n** (237 mg, 60 %) as orange crystals.

^{1}H (400 MHz, $CDCl_3$): δ 8.99 (1H, d, *J* 1.8, **H12**), 8.72 (1H, dd, *J* 4.8, 1.5, **H13**), 8.49 (1H, s, **H10**), 8.47 (1H, dd, *J* 4.8, 1.5, **H9**), 8.27 (1H, dt, *J* 8.0, 1.8, **H15**), 7.42 (2H, m, **H7** and **H14**), 7.31 (1H, dd, *J* 8.0, 4.8, **H8**), 5.28 (1H, s, **H4**), 5.10 (2H, spt, *J* 6.3, **H2**), 1.23 (6H, d, *J* 6.3, **H1**), 1.18 (6H, d, *J* 6.3, **H1'**).

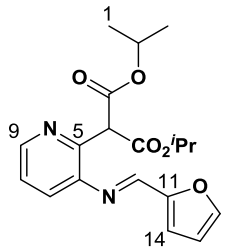
^{13}C (101 MHz, $CDCl_3$): δ 167.2 (**C3**), 158.8 (**C10**), 152.6 (**C13**), 151.1 (**C12**), 149.7 (**C5**), 147.1 (**C9**), 144.9 (**C6**), 135.1 (**C15**), 131.4 (**C11**), 124.3 (**C7**), 123.9 (**C14**), 123.7 (**C8**), 69.2 (**C2**), 57.8 (**C4**), 21.6 (**C1**), 21.7 (**C1'**).

HRMS (ESI): found 370.1764; $[C_{20}H_{24}N_3O_4]^+$ ($M+H^+$) requires 370.1761.

IR: ν_{max} (neat)/ cm^{-1}: 2983, 2937, 1736 (C=O), 1630 (C=N), 1104.

MP (diethyl ether:40-60 petrol): 83-85 °C.

Preparation of (*E*)-diisopropyl 2-(3-((furan-2-ylmethylene)amino)pyridin-2-yl)malonate (166o)



Freshly distilled furfural (177 µL, 2.14 mmol) was added to a solution of aminopyridine **165** (300 mg, 1.07 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (155 mg, 1.29 mmol) at RT. The suspension was stirred for 40 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was recrystallized from cold diethyl ether and 40-60 petrol to yield imine **166o** (190 mg, 50 %) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.44 (1H, dd, *J* 4.7, 1.6, **H9**), 8.21 (1H, s, **H10**), 7.62 (1H, d, *J* 1.3, **H12**), 7.32 (1H, dd, *J* 8.1, 1.5, **H7**), 7.26 (1H, dd, *J* 8.1, 4.5, **H8**), 7.02 (1H, d, *J* 3.2, **H14**), 6.56 (1H, dd, *J* 3.4, 1.6, **H13**), 5.31 (1H, s, **H4**), 5.11 (2H, sept, *J* 6.3, **H2**), 1.24 (6H, d, *J* 6.3, **H1**), 1.19 (6H, d, *J* 6.3, **H1'**).

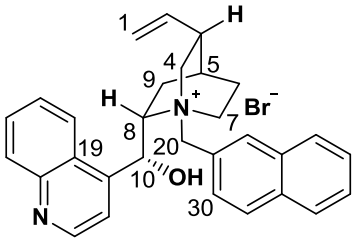
^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 152.2 (**C11**), 149.6 (**C10**), 149.3 (**C5**), 146.6 (**C9**), 146.1 (**C12**) 145.7 (**C6**), 124.4 (**C7**), 123.6 (**C8**), 116.5 (**C14**), 112.4 (**C13**), 69.0 (**C2**), 57.3 (**C4**), 21.6 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 381.1422; $[C_{19}H_{22}N_2O_5Na]^+$ $(M+Na)^+$ requires 381.1421.

IR: ν_{max} (neat)/cm^{-1}: 2983 (C-H aromatic), 2933 (C-H aliphatic), 1735 (C=O), 1626 (C=N), 1104.

MP (diethyl ether:40-60 petrol): 90-93 °C.

Preparation of (8*S*, 9*R*) *N*-(2-naphthylmethyl)cinchonidinium bromide (88f)



According to a modified literature procedure[151] a mixture of (-)-cinchonidine (500 mg, 1.69 mmol) and 2-(bromomethyl)naphthalene (466 mg, 2.11 mmol) in toluene (20 mL) was heated to 80 °C and stirred for 6 h. The resulting pink mixture was cooled to RT and then 20 mL of ether was added over 2 min. The resulting slurry was stirred for 15 min, filtered and washed with ether. The product was dried under vacuum to yield phase transfer catalyst **88f** (664 mg, 76 %) as a white solid. A sample for analysis was obtained by flash column chromatography (5 % methanol in CH_2Cl_2).

^{1}H (400 MHz, DMSO-d_6): δ 9.01 (1H, d, *J* 4.3, **H13**), 8.37 (1H, d, *J* 8.5, **H18**), 8.35 (1H, s, **H22**), 8.17-8.09 (2H, m, **H24** and **H27**), 8.08-8.00 (2H, m, **H25** and **H26**), 7.89-7.83 (3H, m, **H12**, **H16**, **H30**), 7.80-7.74 (1H, m, **H17**), 7.68-7.62 (2H, m, **H15** and **H29**), 6.81 (1H, d, *J* 4.5, **OH**), 6.64 (1H, br. d, *J* 3.5, **H10**), 5.70 (1H, ddd, *J* 17.3, 10.6, 6.4, **H2**), 5.37 (1H, d, *J* 12.3, **H20**), 5.25 (1H, d, *J* 12.6, **H20'**), 5.19 (1H, d, *J* 17.3, $\mathbf{H1_{trans}}$), 4.96 (1H, d, *J* 10.5, $\mathbf{H1_{cis}}$), 4.45-4.31 (1H, m, **H7**), 4.01 (1H, t, *J* 8.7, **H8**), 3.92-3.82 (1H, m, **H4**), 3.44-3.38 (2H, m, **H4'** and **H7'**), 2.66 (1H, br. s, **H3**), 2.17-2.05 (2H, m, **H6** and **H9**), 2.00 (1H, d, *J* 2.5, **H5**), 1.86-1.71 (1H, m, **H6'**), 1.34-1.29 (1H, m, **H9'**).

^{13}C (101 MHz, DMSO-d_6): δ 151.0 (**C13**), 148.5 (**C14**), 146.2 (**C11**), 139.0 (**C2**), 134.8 (**C22**), 134.2 (**C28**), 133.4 (**C23**), 131.1 (**C19**), 130.7 (**C16**), 130.3 (**C30**), 129.2 (**C25**), 129.2 (**C26**) 128.5, 128.4 and 128.1 (**C15**, **C24** and **C27**), 127.7 (**C17**), 126.4 (**C29**), 125.2 (**C21**),

124.6 (**C18**), 121.0 (**C12**), 117.3 (**C1**), 68.4 (**C8**), 65.0 (**C10**), 63.7 (**C20**), 60.2 (**C4**), 51.6 (**C7**), 37.8 (**C3**), 26.8 (**C5**), 25.1 (**C6**), 21.9 (**C9**).

HRMS (ESI): found 435.2425; $[C_{30}H_{31}N_2O]^+$ (M) requires 435.2421.

IR: ν_{max} (neat)/cm^{-1}: 3163, 2359, 2339, 832, 764, 750

MP: 226-230 °C.

$[\alpha]_D^{22}$ -154 (*c* = 0.3, $CHCl_3$).

General Experimental Procedures

General Procedure A: Base-Catalyzed Racemic Cyclization

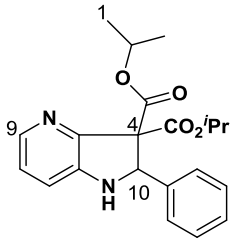
$CsOH{\cdot}H_2O$ (2.0 eq.) was added to a stirred solution of the requisite imine **166** (1.0 eq.) in toluene (10 mg mL^{-1}). Unless otherwise stated, the reaction mixture was stirred for 16 h at RT. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.2 mL mg^{-1} imine) and then extracted with CH_2Cl_2 (3 × 0.2 mL mg^{-1} imine). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 1:1, unless otherwise stated).

General Procedure B: Asymmetric Cyclization

A solution of **88f** (0.1 eq.) and imine **166** (1.0 eq.) in 3:1 toluene:CH_2Cl_2 (25 mg mL^{-1}) was cooled to -30 °C and stirred for 30 min. Powdered KOH (1.0 eq.) was then added. Unless otherwise stated the reaction mixture was stirred for 24 h at -30 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.2 mL mg^{-1} imine) and extracted with CH_2Cl_2 (3 × 0.2 mL mg^{-1} imine). The combined organic layers were dried

($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:2, unless otherwise stated).

Preparation of (±)-diisopropyl 2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167a)



Following **General Procedure A**; the reaction of imine **166a** (25 mg, 0.07 mmol) and $CsOH{\cdot}H_2O$ (24 mg, 0.14 mmol) in toluene (3 ml) yielded azaindoline **rac-167a** (22 mg, 88 %) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.08 (1H, dd, *J* 4.8, 1.3, **H9**), 7.46-7.42 (2H, m, **H13**), 7.31-7.28 (3H, m, **H12** and **H14**), 7.07 (1H, dd, *J* 8.0, 4.8, **H8**), 6.97 (1H, dd, *J* 8.0, 1.4, **H7**), 5.89 (1H, d, *J* 2.4, **H10**), 5.21 (1H, sept, *J* 6.3, **H2**), 4.54 (1H, sept, *J* 6.3, **H2'**), 4.18 (1H, br. s, **NH**), 1.34 (3H, d, *J* 6.3, **H1**), 1.31 (3H, d, *J* 6.3, **H1**), 1.04 (3H, d, *J* 6.6, **H1'**), 0.53 (3H, d, *J* 6.3, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 168.1 (**C3**), 166.7 (**C3'**), 146.0 (**C5**), 145.0 (**C6**), 140.9 (**C9**), 139.4 (**C11**), 128.8 (**C14**), 128.7 (**C12**), 128.4 (**C13**), 124.1 (**C8**), 116.0 (**C7**), 70.6 (**C2**), 69.7 (**C2'**), 69.2 (**C4**), 67.2 (**C10**), 22.1 (**C1**) 21.9 (**C1**), 21.8 (**C1'**), 21.1 (**C1'**).

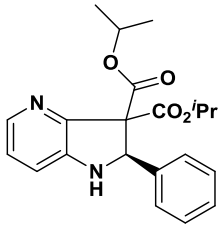
HRMS (ESI): found 369.1816; $[C_{21}H_{25}N_2O_4]^+$ $(M + H)^+$ requires 369.1809.

IR: ν_{max} (neat)/cm^{-1}: 3354 (N-H), 2982 (C-H aromatic), 2937 (C-H aliphatic), 1718 (C=O), 1106.

MP: 104-108 °C.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 249 nm); t_R 7.5 min, 10.1 min.

Preparation of (*R*)-diisopropyl 2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167a)

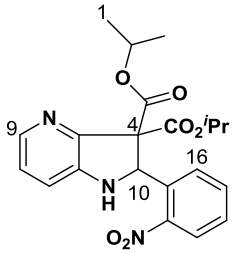


Following **General Procedure B**; the reaction of imine **166a** (30 mg, 0.08 mmol), **88f** (4.0 mg, 7.8 μmol) and KOH (4.5 mg, 0.08 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) yielded azaindoline **167a** (29 mg, 97 %, 94 % *ee*) as a white solid with identical spectroscopic properties to **rac-167a**.

$[\alpha]_D^{22}$ +75 (*c* = 1.0, $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 249 nm); t_R (major) = 7.6 min, t_R (minor) = 10.4 min.

Preparation of (±)-diisopropyl 2-(2-nitrophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167b)



Following **General Procedure A**; the reaction of imine **166b** (30 mg, 0.073 mmol), $CsOH.H_2O$ (25 mg, 0.15 mmol) in toluene (3.0 ml) yielded azaindoline **rac-167b** (14 mg, 49 %) as a bright yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.12 (1H, dd, *J* 4.8, 1.3, **H9**), 7.88 (1H, dd, 8.1, 1.3, **H13**), 7.71 (1H, dd, *J* 8.1, 1.3, **H16**), 7.52 (1H, td, *J* 7.8, 1.3, **H15**), 7.44 (1H, td, *J* 8.1, 1,5, **H14**), 7.08 (1H, dd, *J* 8.1, 4.8, **H8**), 6.99 (1H, dd, *J* 8.3, 1.3, **H7**), 6.55 (1H, d, *J* 3.5, **H10**), 5.19 (1H, spt, *J* 6.3, **H2**), 4.60 (1H, spt, *J* 6.3, **H2'**), 4.33 (1H, d, *J* 3.3, **NH**), 1.30 (3H, d, *J* 6.3, **H1**), 1.28 (3H, d, 6.3, **H1**), 1.07 (3H, d, *J* 6.3, **H1'**), 0.52 (3H, d, *J* 6.3, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.4 (**C3**), 166.4 (**C3'**), 149.3 (**C12**), 145.7 (**C5**), 144.1 (**C6**), 141.1 (**C9**), 134.9 (**C11**), 134.9 (**C14**), 132.9 (**C15**), 129.0 (**C16**), 124.1 (**C13**), 124.0 (**C8**), 115.9 (**C7**), 70.6 (**C2**), 69.6 (**C2'**), 69.1 (**C4**), 60.3 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.2 (**C1'**), 20.6 (**C1'**).

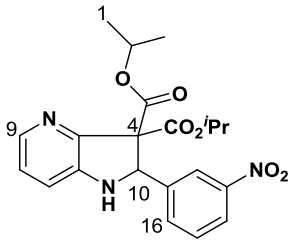
HRMS (ESI): found 436.1485; $[C_{21}H_{23}N_3O_6Na]^+$ (M + Na^+) requires 436.1479.

IR: ν_{max} (neat)/ cm^{-1}: 3357 (N-H), 2977, 2930, 1727 (C=O), 1528 (NO_2), 1358 (NO_2), 1266, 1102, 733.

MP: 111-114 °C.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 244 nm); t_R 10.4 min, 12.8 min.

Preparation of (±)-diisopropyl 2-(3-nitrophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167c)



Following **General Procedure A**; the reaction of imine **166c** (48 mg, 0.12 mmol), CsOH.H_2O (40 mg, 0.24 mmol) in toluene (4.8 ml) yielded azaindoline **rac-167c** (22 mg, 46 %) as a yellow foam.

^{1}H (400 MHz, $CDCl_3$): δ 8.39 (1H, s, **H12**), 8.15 (1H, dt, *J* 8.1, 1.1, **H14**), 8.10 (1H, dd, *J* 4.8, 1.5, **H9**), 7.86 (1H, d, *J* 7.8, **H16**), 7.50 (1H, t, *J* 8.0, **H15**), 7.10 (1H, dd, *J* 8.1, 4.6, **H8**), 7.04 (1H, dd, *J* 8.1, 1.3, **H7**), 6.02 (1H, d, *J* 3.3, **H10**), 5.23 (1H, spt, *J* 6.3, **H2**), 4.54 (1H, spt, *J* 6.1, **H2'**), 4.35 (1H, d, *J* 3.0, **NH**), 1.36 (3H, d, *J* 6.3, **H1**), 1.33 (3H, d, 6.3, **H1**), 0.99 (3H, d, *J* 6.1, **H1'**), 0.54 (3H, d, *J* 6.1, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 166.2 (**C3'**), 148.1 (**C13**), 145.3 (**C5**), 144.2 (**C6**), 141.2 (**C9**), 141.1 (**C11**), 134.3 (**C16**), 129.3 (**C15**), 124.0 (**C8**), 123.2 (**C14**), 123.2 (**C12**), 116.4 (**C7**), 70.7 (**C2**), 69.8 (**C2'**), 68.9 (**C4**), 65.7 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.3 (**C1'**), 20.7 (**C1'**).

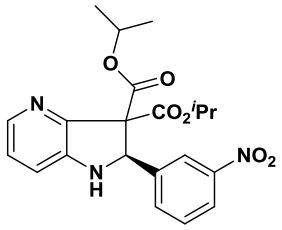
HRMS (ESI): found 414.1661; $[C_{21}H_{24}N_3O_6]^+$ (M + H^+) requires 414.1660.

IR: ν_{max} (neat)/ cm^{-1}: 3357 (N-H), 2984, 2937, 1722 (C=O), 1531 (NO_2), 1350 (NO_2), 1270, 1104, 753.

MP: 55-59 °C.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 254 nm); t_R 8.5 min, 11.5 min.

Preparation of (*R*)-diisopropyl 2-(3-nitrophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167c)

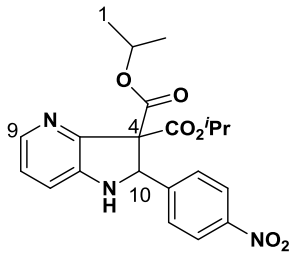


Following **General Procedure B**; the reaction of imine **166c** (40 mg, 0.097 mmol), **88f** (5.0 mg, 9.7 μmol) and KOH (5.5 mg, 0.10 mmol) in toluene:CH_2Cl_2 (1.2:0.4 mL) yielded azaindoline **167c** (22 mg, 55 %, 48 % *ee*) with identical spectroscopic properties to **rac-167**.

$[\alpha]_D^{22}$: +24.9 ° (c 1.1 $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 254 nm); t_R (major) = 8.4 min, t_R (minor) = 11.5 min.

Preparation of (±)-diisopropyl 2-(4-nitrophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167d)



Following **General Procedure A**; the reaction of imine **166d** (34 mg, 0.08 mmol) and $CsOH{\cdot}H_2O$ (27 mg, 0.16 mmol) in toluene (3 ml) yielded azaindoline **rac-167d** (14 mg, 41 %) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.17 (2H, d, *J* 7.8, **H13**), 8.11 (1H, d, *J* 4.8, **H9**), 7.71 (2H, d, *J* 8.3, **H12**), 7.10 (1H, ddd, *J* 7.8, 4.8, 0.8, **H8**), 7.04 (1H, d, *J* 8.1, **H7**), 6.02 (1H, s, **H10**), 5.23 (1H, sept, *J* 6.2, **H2**), 4.55 (1H, sept, *J* 6.2, **H2'**), 4.29 (1H, br. s, **NH**), 1.34 (6H, apt t, *J* 6.8, **H1**), 1.02 (3H, d, *J* 6.3, **H1'**), 0.54 (3H, d, *J* 6.1, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.4 (**C3**), 166.1 (**C3'**), 147.9 (**C14**) 146.2 (**C11**), 145.4 (**C5**), 144.1 (**C6**), 141.3 (**C9**), 129.1 (**C12**), 124.0 (**C8**), 123.3 (**C13**), 116.3 (**C7**), 70.7 (**C2**), 69.8 (**C2'**), 68.9 (**C4**), 65.8 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.3 (**C1'**), 20.7 (**C1'**).

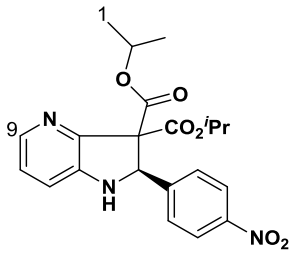
HRMS (ESI): found 414.1660; $[C_{21}H_{24}N_3O_6]^+$ $(M + H)^+$ requires 414.1660.

IR: ν_{max} (neat)/cm^{-1}: 3357 (N-H), 2982 (C-H aromatic), 2935 (C-H aliphatic), 1720 (C=O), 1589 (NO_2), 1380 (NO_2), 1271, 1105, 756.

MP: 117-122 °C.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 254 nm); t_R 10.8 min, 14.5 min.

Preparation of (*R*)-diisopropyl 2-(4-nitrophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167d)

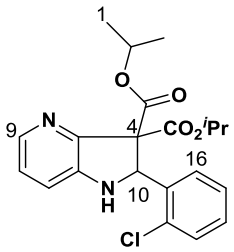


Following **General Procedure B**; the reaction of imine **166d** (30 mg, 0.07 mmol), **88f** (3.5 mg, 6.8 µmol) and KOH (4.0 mg, 0.07 mmol) in toluene:CH_2Cl_2 (1.2:0.4 mL) for 36 h yielded azaindoline **167d** (27 mg, 90 %, 90 % *ee*) as a yellow solid with identical spectroscopic properties to **rac-167d**.

$[\alpha]_D^{22}$ +25 (*c* = 0.8, $CHCl_3$).

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 254 nm); t_R (major) = 11.0 min, t_R (minor) = 14.9 min.

Preparation of (±)-diisopropyl 2-(2-chlorophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167e)



Following **General Procedure A**; the reaction of imine **166e** (28 mg, 0.07 mmol) and $CsOH{\cdot}H_2O$ (24 mg, 0.14 mmol) in toluene (3 ml) yielded azaindoline **rac-167e** (18 mg, 64 %) as a pale yellow solid.

^{1}H (400 MHz, $CDCl_3$):, 8.07 (1H, dd, *J* 4.8, 1.3, **H9**), 7.41 (1H, dd, *J* 7.6, 2.0, **H13**), 7.33 (1H, dd, *J* 7.7, 1.4, **H16**), 7.24-7.13 (2H, m, **H14** and **H15**), 7.04 (1H, dd, *J* 7.8, 4.8, **H8**), 6.94 (1H, dd, *J* 8.1, 1.3, **H7**), 6.44 (1H, d, *J* 2.5, **H10**), 5.17 (1H, sept, *J* 6.6, **H2**), 4.59 (1H, sept, *J* 6.2, **H2'**), 4.22 (1H, d, *J* 2.5, **NH**), 1.31 (3H, d, *J* 6.3, **H1**), 1.26 (3H, d, *J* 6.3, **H1**), 1.09 (3H, d, *J* 6.3, **H1'**), 0.58 (3H, d, *J* 6.1, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.4 (**C3**), 166.2 (**C3'**), 145.4 (**C5**), 144.3 (**C6**), 140.6 (**C9**), 137.7 (**C11**), 134.3 (**C12**), 129.4, 129.3 and 129.3 (**C13**, **C15** and **C16**), 127.0 (**C14**), 123.9 (**C8**), 115.4 (**C7**), 70.4 (**C2**), 69.4 (**C2'**), 68.6 (**C4**), 62.0 (**C10**), 21.5 (**C1** × 2), 21.4 (**C1'**) 20.5 (**C1'**).

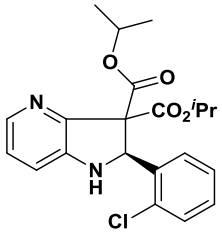
HRMS (ESI): found 403.1315; $[C_{21}H_{24}ClN_2O_4]^+$ $(M + H)^+$ requires 403.1419.

IR: ν_{max} (neat)/cm^{-1}: 3356 (N-H), 2983 (C-H aromatic), 2938 (C-H aliphatic), 1719 (C=O), 1268, 1104, 732.

MP: 122-126 °C.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 254 nm); t_R 8.2 min, 17.6 min.

Preparation of (*S*)-diisopropyl 2-(2-chlorophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167e)

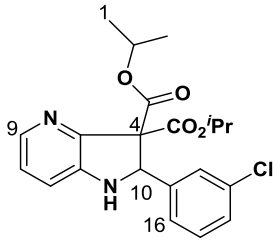


Following **General Procedure B**; the reaction of imine **166e** (50 mg, 0.12 mmol), **88f** (6.0 mg, 12.0 µmol) and KOH (7.0 mg, 0.12 mmol) in toluene:CH_2Cl_2 (1.5:0.5 mL) yielded azaindoline **167e** (40 mg, 80 %, 96 % *ee*) as a pale yellow solid with identical spectroscopic properties to **rac-167e**.

$[\alpha]_D^{22}$ +117 (*c* = 1.7, $CHCl_3$).

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 254 nm); t_R (minor) = 8.2 min, t_R (major) = 17.6 min.

Preparation of (±)-diisopropyl 2-(3-chlorophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167f)



Following **General Procedure A**; the reaction of imine **166f** (33 mg, 0.08 mmol), $CsOH{\cdot}H_2O$ (27 mg, 0.16 mmol) in toluene (3 ml) yielded azaindoline **rac-167f** (23 mg, 70 %) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 8.08 (1H, dd, *J* 4.8, 1.3, **H9**), 7.48 (1H, apt. t, *J*, 1.8, **H12**), 7.35 (1H, apt. dt, *J* 7.1, 1.3, **H14**), 7.26-7.20 (2H, m, **H15** and **H16**), 7.04 (1H, dd, *J* 8.1, 4.8, **H8**), 6.98 (1H, dd, *J* 8.1, 1.5, **H7**), 5.87 (1H, s, **H10**), 5.21 (1H, sept, *J* 6.3, **H2**), 4.58 (1H, sept, *J* 6.1, **H2'**), 4.24 (1H, br s, **NH**), 1.34 (3H, d, *J* 6.3, **H1**), 1.31 (3H, d, 6.3, **H1**), 1.04 (3H, d, *J* 6.1, **H1'**), 0.61 (3H, d, *J* 6.1, **H1'**).

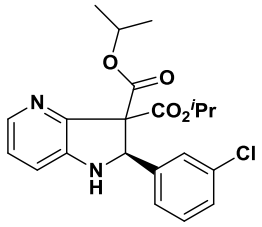
^{13}C (101 MHz, $CDCl_3$): δ 167.5 (**C3**), 166.2 (**C3'**), 145.5 (**C5**), 144.4 (**C6**), 140.9 and 140.8 (**C9** and **C11**), 134.1 (**C13**), 129.6 (**C15**), 128.4 (**C16**), 128.3 (**C12**), 126.2 (**C14**), 123.9 (**C8**), 115.9 (**C7**), 70.4 (**C2**), 69.5 (**C2'**), 68.8 (**C4**), 66.1 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.3 (**C1'**), 20.7 (**C1'**).

HRMS (ESI): found 425.1237; $[C_{21}H_{23}ClN_2O_4Na]^+$ $(M + Na)^+$ requires 425.1239.

IR: ν_{max} (neat)/ cm^{-1}: 3357 (N-H), 2983 (C-H aromatic), 2938 (C-H aliphatic), 1717 (C=O), 1271, 1104, 732.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 214 nm); t_R 6.5 min, 8.1 min.

Preparation of (*R*)-diisopropyl 2-(3-chlorophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167f)

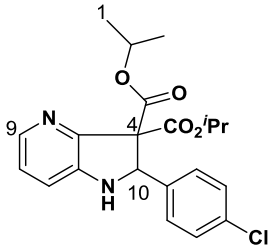


Following **General Procedure B**; the reaction of imine **166f** (36 mg, 0.09 mmol), **88f** (4.5 mg, 8.7 µmol) and KOH (5.0 mg, 0.09 mmol) in toluene:CH_2Cl_2 (1.2:0.4 mL) yielded azaindoline **167f** (31 mg, 86 %, 68 % *ee*) as a yellow oil with identical spectroscopic properties to **rac-167f**.

$[\alpha]_D^{22}$: +50 (c 1.1 $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 214 nm); t_R (major) = 6.4 min, t_R (minor) = 8.1 min.

Preparation of (±)-diisopropyl 2-(4-chlorophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167g)



Following **General Procedure A**; the reaction of imine **166g** (35 mg, 0.09 mmol) and $CsOH{\cdot}H_2O$ (30 mg, 0.18 mmol) in toluene (3 ml) yielded azaindoline **rac-167g** (25 mg, 70 %) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.10 (1H, dd, *J* 4.8, 1.3, **H9**), 7.42 (2H, d, *J* 8.6, **H12**), 7.31-7.25 (2H, m, **H13**), 7.08 (1H, dd, *J* 8.1, 4.8, **H8**), 6.99 (1H, dd, *J* 8.1, 1.0, **H7**), 5.88 (1H, d, 1.8, **H10**), 5.21 (1H, sept, *J* 6.2, **H2**), 4.58 (1H, sept, *J* 6.3, **H2'**), 4.14 (1H, br. s, **NH**), 1.34 (3H, d, *J* 6.3, **H1**), 1.31 (3H, d, *J* 6.3, **H1**), 1.06 (3H, d, *J* 6.1, **H1'**), 0.60 (3H, d, *J* 6.1, **H1'**).

^{13}C (101 MHz, $CDCl_3$): 167.5 (**C3**), 166.2 (**C3'**), 145.5 (**C5**), 144.4 (**C6**), 140.8 (**C9**), 137.3 (**C11**), 134.2 (**C14**), 129.4 (**C12**), 128.4 (**C13**), 123.9 (**C8**), 115.8 (**C7**), 70.4 (**C2**), 69.5 (**C2'**), 68.8 (**C4**), 66.0 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.4 (**C1'**), 20.7 (**C1'**).

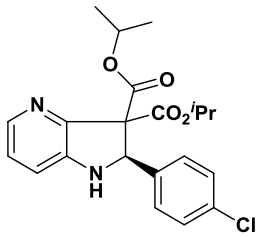
HRMS (ESI): found 403.1237; $[C_{21}H_{23}ClN_2O_4Na]^+$ $(M + Na)^+$ requires 403.1239.

IR: ν_{max} (neat)/cm^{-1}: 3357 (N-H), 2983 (C-H aromatic), 2935 (C-H aliphatic), 1720 (C=O), 1271, 1103, 756.

MP: 152-155 °C.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 248 nm); t_R 8.0 min, 9.5 min.

Preparation of (*R*)-diisopropyl 2-(4-chlorophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167g)

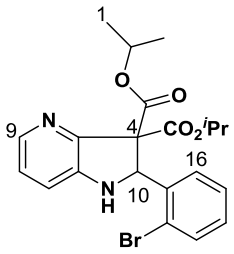


Following **General Procedure B**; the reaction of imine **166g** (23 mg, 0.06 mmol), **88f** (3.0 mg, 5.8 µmol) and KOH (3.5mg, 0.06 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) for 36 h yielded azaindoline **167g** (22 mg, 96 %, 88 % *ee*) as a white solid with identical spectroscopic properties to **rac-167g**.

$[\alpha]_D^{22}$ +105 (*c* = 0.7, $CHCl_3$).

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 248 nm); t_R (major) = 8.1 min, t_R (minor) = 9.6 min.

Preparation of (±)-diisopropyl 2-(2-bromophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167h)



Following **General Procedure A**; the reaction of imine **166h** (50 mg, 0.11 mmol) and $CsOH{\cdot}H_2O$ (37 mg, 0.22 mmol) in toluene (5 ml) with purification by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:3) yielded azaindoline **rac-167h** (17 mg, 34 %) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): 8.07 (1H, d, *J* 4.8, **H9**), 7.52 (1H, d, *J* 8.1, **H13**), 7.37 (1H, dd, *J* 7.8, 1.5, **H16**), 7.20 (1H, apt. t, *J* 7.3, **H15**), 7.10 (1H, apt. td, *J* 7.6, 1.3, **H14**), 7.05 (1H, dd, *J* 8.1, 4.8, **H8**), 6.92 (1H, d, *J* 8.1, **H7**), 6.41 (1H, d, *J* 2.3, **H10**), 5.17 (1H, sept, *J* 6.3, **H2**), 4.59 (1H, sept, *J* 6.3, **H2'**), 4.25 (1H, br. s, **NH**), 1.31 (3H, d, *J* 6.3, **H1**), 1.26 (3H, d, *J* 6.3, **H1**), 1.10 (3H, d, *J* 6.3, **H1'**), 0.58 (3H, d, *J* 6.3, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.3 (**C3**), 166.1 (**C3'**), 145.2 (**C5**), 144.3 (**C6**), 140.6 (**C9**), 139.4 (**C11**), 132.6 (**C13**), 129.7 and 129.6 (**C15** and **C16**), 127.7 (**C14**), 124.7 (**C12**), 123.9 (**C8**), 115.3 (**C7**), 70.4 (**C2**), 69.4 (**C2'**), 68.6 (**C4**), 64.5 (**C10**), 21.5 (**C1**), 21.5 (**C1**), 21.4 (**C1'**), 20.5 (**C1'**).

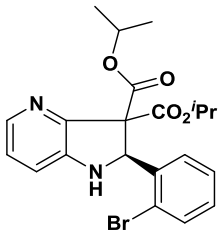
HRMS (ESI): found 447.0914; $[C_{21}H_{24}BrN_2O_4]^+$ $(M + H)^+$ requires 447.0914

IR: ν_{max} (neat)/cm^{-1}: 3368 (N-H), 2982 (C-H aromatic), 2935 (C-H aliphatic), 1721 (C=O), 1260, 1105, 730.

MP: 196 -200 °C.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 217 nm); t_R 8.1 min, 26.4 min.

Preparation of (*S*)-diisopropyl 2-(2-bromophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167h)

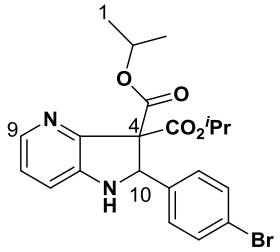


Following **General Procedure B**; the reaction of imine **166h** (50 mg, 0.11 mmol), **88f** (5.5 mg, 11.0 μmol) and KOH (6.0 mg, 0.11 mmol) in toluene:CH_2Cl_2 (1.50:0.50 mL) with purification by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:3) yielded azaindoline **167h** (43 mg, 86 %, 86 % *ee*) as a yellow solid with identical spectroscopic properties to **rac-167h**. An sample for analysis by single crystal XRD was obtained by recrystallization by vapour diffusion from ethyl acetate and pentane.

$[\alpha]_D^{22}$ +142 (*c* = 1.0, $CHCl_3$).

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 217 nm); t_R (minor) = 8.3 min, t_R (major) = 27.4 min.

Preparation of (±)-diisopropyl 2-(4-bromophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167i)



Following **General Procedure A**; the reaction of imine **166i** (50 mg, 0.11 mmol) and $CsOH{\cdot}H_2O$ (37 mg, 0.22 mmol) in toluene (5 ml) yielded azaindoline **rac-167i** (25 mg, 50 %) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.08 (1H, dd, *J* 4.8, 1.3, **H9**), 7.42 (2H, d, *J* 8.3, **H13**), 7.35 (2H, d, *J* 8.3, **H12**), 7.06 (1H, dd, *J* 8.1, 1.3, **H7**), 6.97 (1H, dd, *J* 8.1, 4.8, **H8**), 5.85 (1H, d, 2.8, **H10**), 5.20 (1H, sept, *J* 6.2, **H2**), 4.57 (1H, sept, *J* 6.3, **H2'**), 4.20 (1H, d, *J* 2.3, **NH**), 1.33 (3H, d, *J* 6.3, **H1**), 1.31 (3H, d, *J* 6.3, **H1**), 1.04 (3H, d, *J* 6.3, **H1'**), 0.59 (3H, d, *J* 6.1, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.6 (**C3**), 166.3 (**C3'**), 145.5 (**C5**), 144.4 (**C6**), 140.8 (**C9**), 137.9 (**C11**), 131.3 (**C13**), 129.8 (**C12**), 123.9 (**C8**), 122.3 (**C14**), 115.9 (**C7**), 70.4 (**C2**), 69.5 (**C2'**), 68.7 (**C4**), 66.1 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.4 (**C1'**), 20.7 (**C1'**).

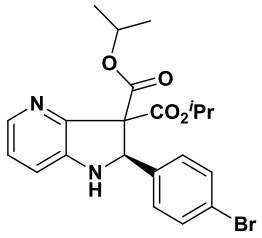
HRMS (ESI): found 447.0911; $[C_{21}H_{24}BrN_2O_4]^+$ $(M + H)^+$ requires 447.0914

IR: ν_{max} (neat)/cm^{-1}: 3354 (N-H), 2982 (C-H aromatic), 2937 (C-H aliphatic), 1716 (C=O), 1268, 1104.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 254 nm); t_R 6.5 min, 12.5 min.

MP: 47-51 °C.

Preparation of (*R*)-diisopropyl 2-(4-bromophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167i)

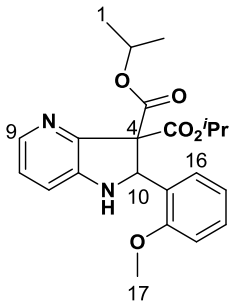


Following **General Procedure B**; the reaction of imine **166i** (30 mg, 0.07 mmol), **88f** (3.5 mg, 6.8 µmol) and KOH (4.0 mg, 0.07 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) for 36 h yielded azaindoline **167i** (16 mg, 65 %, 88 % *ee*) as a yellow solid with identical spectroscopic properties to **rac-167i**.

$[\alpha]_D^{22}$ +101 (*c* = 0.8, $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 254 nm); t_R (major) = 6.3 min, t_R (minor) = 12.3 min.

Preparation of (±)-diisopropyl 2-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167j)



Following **General Procedure A**; the reaction of imine **166j** (50 mg, 0.13 mmol) and $CsOH{\cdot}H_2O$ (44 mg, 0.26 mmol) in toluene (5 ml) yielded azaindoline **rac-167j** (21 mg, 42 %) as a white solid.

^{1}H (400 MHz, $CDCl_3$): 8.04 (1H, dd, *J* 4.8, 1.4, **H9**), 7.38 (1H, dd, *J* 7.6, 1.5, **H16**), 7.24 (1H, apt. td, *J* 7.6, 1.5, **H14**), 7.03 (1H, dd, *J* 8.1, 4.8, **H8**), 6.93 (1H, dd, *J* 8.1, 1.5, **H7**), 6.87 (1H, apt. td, *J* 7.6, 0.8, **H15**), 6.83 (1H, d, *J* 8.1, **H13**), 6.24 (1H, s, **H10**), 5.18 (1H, sept, *J* 6.3, **H2**), 4.57 (1H, sept, *J* 6.3, **H2'**), 4.04 (1H, br. s, **NH**), 3.17 (3H, s, **H17**), 1.28-1.31 (6H, m, **H1**), 1.02 (3H, d, *J* 6.3, **H1'**), 0.54 (3H, d, *J* 6.3, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.9 (**C3**), 166.4 (**C3'**), 157.6 (**C12**), 146.8 (**C5**), 144.6 (**C6**), 140.1 (**C9**), 129.2 (**C14**), 128.4 (**C16**), 128.0 (**C11**), 123.5 (**C8**), 120.4 (**C15**), 115.4 (**C7**), 110.2 (**C13**), 69.8 (**C2**), 68.7 (**C2'**), 68.0 (**C4**), 61.2 (**C10**), 55.2 (**C17**), 21.6 (**C1**), 21.6 (**C1**), 21.3 (**C1'**), 20.6 (**C1'**).

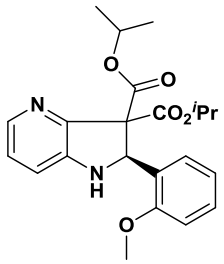
HRMS (ESI): found 399.1911; $[C_{22}H_{27}N_2O_5]^+$ $(M + H)^+$ requires 399.1914.

IR: ν_{max} (neat)/cm^{-1}: 3359 (N-H), 2982 (C-H aromatic), 2938 (C-H aliphatic), 1722 (C=O), 1447, 1262, 1108, 756.

MP: 131-134 °C.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 217 nm); t_R 10.3 min, 16.1 min.

Preparation of (*R*)-diisopropyl 2-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167j)

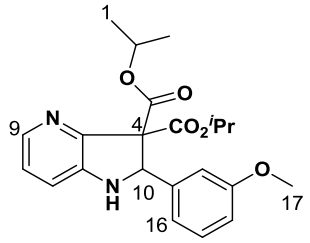


Following **General Procedure B**; the reaction of imine **166j** (30 mg, 0.08 mmol), **88f** (4.0 mg, 7.8 μmol) and KOH (4.5 mg, 0.08 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) yielded azaindoline **167j** (30 mg, 63 %, 93 % *ee*) as a white solid with identical spectroscopic properties to **rac-167j**.

$[\alpha]_D^{22}$ +134 (*c* = 0.7, $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 217 nm); t_R (major) = 10.3 min, t_R (minor) = 16.2 min.

Preparation of (±)-diisopropyl 2-(3-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167k)



Following **General Procedure A**; the reaction of imine **166k** (31 mg, 0.08 mmol) and $CsOH{\cdot}H_2O$ (27 mg, 0.16 mmol) in toluene (3 ml) yielded azaindoline **rac-167k** (17 mg, 55 %) as an orange oil.

^{1}H (400 MHz, $CDCl_3$): 8.06 (1H, dd, *J* 4.8, 1.0, **H9**), 7.20 (1H, apt. t, *J* 8.3, **H15**), 7.07-7.01 (3H, m, **H8**, **H12** and **H16**), 6.96 (1H, dd, *J* 7.8, 1.0, **H7**), 6.82 (1H, dd, *J* 8,1, 2.3, **H14**), 5.86 (1H, s, **H10**), 5.20 (1H, sept, *J* 6.3, **H2**), 4.56 (1H, sept, *J* 6.3, **H2'**), 4.19 (1H, br. s, **NH**), 3.76 (3H, s, **H17**), 1.33 (3H, d, *J* 6.3, **H1**), 1.30 (3H, d, *J* 6.3, **H1**), 1.03 (3H, d, *J* 6.3, **H1'**), 0.58 (3H, d, *J* 6.3, **H1'**).

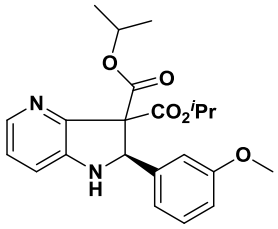
^{13}C (101 MHz, $CDCl_3$): δ 167.7 (**C3**), 166.3 (**C3'**), 159.5 (**C13**), 145.7 (**C5**), 144.6 (**C6**), 140.5 (**C9**), 140.4 (**C11**), 129.3 (**C15**), 123.8 (**C8**), 120.3 (**C16**), 115.6 (**C7**), 114.1 (**C14**), 113.4 (**C12**), 70.2 (**C2**), 69.2 (**C2'**), 68.7 (**C4**), 66.8 (**C10**), 55.3 (**C17**), 21.6 (**C1**), 21.5 (**C1**) 21.4 (**C1'**), 20.7 (**C1'**).

HRMS (ESI): found 399.1918; $[C_{22}H_{27}N_2O_5]^+$ $(M + H)^+$ requires 399.1914.

IR: ν_{max} (neat)/cm^{-1}: 3358 (N-H), 2982 (C-H aromatic), 2938 (C-H aliphatic), 1715 (C=O), 1465, 1265, 1104.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 208 nm); t_R 9.5 min, 17.5 min.

Preparation of (*R*)-diisopropyl 2-(3-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167k)

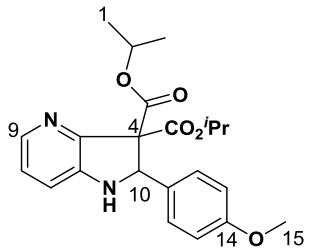


Following **General Procedure B**; the reaction of imine **166k** (30 mg, 0.08 mmol), **88f** (4.0 mg, 7.8 µmol) and KOH (4.5 mg, 0.08 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) yielded azaindoline **167k** (19 mg, 65 %, 90 % *ee*) as an orange oil with identical spectroscopic properties to **rac-167k**.

$[\alpha]_D^{22}$ +85 (*c* = 1.2, $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 208 nm); t_R (major) 9.5 min, t_R (minor) = 17.5 min.

Preparation of (±)-diisopropyl 2-(3-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167l)



Freshly distilled butyraldehyde (557 µL, 6.10 mmol) was added to a solution of aminopyridine (170 mg, 0.61 mmol) in toluene (30 mL) containing anhydrous $MgSO_4$ (88 mg, 0.73 mmol) at RT. The suspension was stirred for 16 h and then the reaction mixture was filtered and concentrated *in vacuo* and excess aldehyde removed under high vacuum. The product was carried forward to the cyclization reactions without further purification.

Following **General Procedure A**; crude imine (50 mg, 0.15 mmol) and $CsOH{\cdot}H_2O$ (50 mg, 0.30 mmol) in toluene (5 ml) yielded azaindoline **rac-167l** (15 mg, 22 % over 2 steps) as an orange oil.

^{1}H (400 MHz, $CDCl_3$): 8.05 (1H, dd, *J* 4.8, 1.3, **H9**), 7.32 (2H, d, *J* 8.6, **H12**), 7.03 (1H, dd, *J* 7.8, 4.8, **H8**), 6.93 (1H, dd, *J* 8.1, 1.3, **H7**), 6.80 (1H, d, *J* 8.6, **H13**), 5.80 (1H, d, *J* 1.8, **H10**), 5.17 (1H, sept, *J* 6.3, **H2**), 4.55 (1H, sept, *J* 6.3, **H2'**), 4.17 (1H, br. s, **NH**), 3.76 (3H, s, **H15**), 1.32 (3H, d, *J* 6.3, **H1**), 1.28 (3H, d, *J* 6.3, **H1**), 1.04 (3H, d, *J* 6.3, **H1'**), 0.59 (3H, d, *J* 6.3, **H1'**).

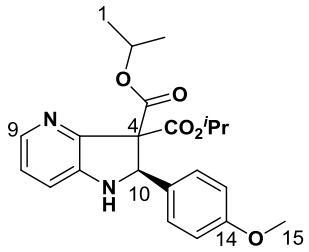
^{13}C (101 MHz, $CDCl_3$): δ 167.7 (**C3**), 166.3 (**C3'**), 159.7 (**C14**), 145.5 (**C5**), 144.7 (**C6**), 140.4 (**C9**), 131.0 (**C11**), 129.1 (**C12**), 123.8 (**C8**), 115.5 (**C7**), 113.6 (**C13**), 70.1 (**C2**), 69.2 (**C2'**), 68.7 (**C4**), 66.3 (**C10**), 55.3 (**C15**), 21.6 (**C1**), 21.5 (**C1**) 21.4 (**C1'**), 20.8 (**C1'**).

HRMS (ESI): found 339.1914; $[C_{22}H_{27}N_2O_5]^+$ $(M + H)^+$ requires 339.1915.

IR: ν_{max} (neat)/cm^{-1}: 3358 (N-H), 2982 (C-H aromatic), 2937 (C-H aliphatic), 1714 (C=O), 1512, 1464, 1246, 1103, 731.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 247 nm); t_R 8.8 min, 15.7 min.

Preparation of (*R*)-diisopropyl 2-(3-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167l)

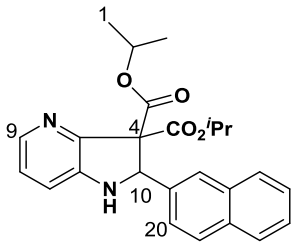


The required imine was prepared following the procedure for **rac-167l**. Following **General Procedure B**; crude imine (50 mg, 0.13 mmol), **88f** (6.5 mg, 13.0 µmol) and KOH (7.0 mg, 0.13 mmol) in toluene:CH_2Cl_2 (1.2:0.4 mL) yielded azaindoline **167l** (32 mg, 46 % over 2 steps, 75 % *ee*) as an orange oil with identical spectroscopic properties to **rac-167l**.

$[\alpha]_D^{22}$ +96 (*c* = 0.7, $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 247 nm); t_R (major) = 8.8 min, t_R (minor) = 16.0 min.

Preparation of (±)-diisopropyl 2-(naphthalen-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167m)



Following **General Procedure A**; the reaction of imine **166m** (28 mg, 0.07 mmol) and $CsOH{\cdot}H_2O$ (23 mg, 0.14 mmol) in toluene (3 ml) yielded azaindoline **rac-167m** (14 mg, 50 %) as a white solid.

^{1}H (400 MHz, $CDCl_3$): 8.09 (1H, dd, *J* 4.8, 1.3, **H9**), 7.93 (1H, s, **H12**), 7.79 (2H, dd, *J* 6.1, 3.3, **H14** and **H17**), 7.74 (1H, d, *J* 8.3, **H19**), 7.52 (1H, d, *J* 8.6, **H20**) 7.48-7.39 (2H, m, **H15** and **H16**), 7.08 (1H, dd, *J* 8.1, 4.8, **H8**), 6.99 (1H, dd, *J* 7.8, 1.5, **H7**), 6.05 (1H, s, **H10**), 5.23 (1H, sept, *J* 6.3, **H2**), 4.40 (1H, sept, *J* 6.2, **H2'**), 4.30 (1H, br. s, **NH**), 1.33 (6H, m, **H1**), 0.92 (3H, d, *J* 6.3, **H1'**), 0.19 (3H, d, *J* 6.3, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.8 (**C3**), 166.4 (**C3'**), 145.7 (**C5**), 144.6 (**C6**), 140.7 (**C9**), 136.3 (**C11**), 133.4 and 133.0 (**C13** and **C18**), 128.0, 127.9 and 127.5 (**C14**, **C17** and **C19**), 127.1 (**C12**), 126.2 and 126.1 (**C15** and **C16**), 125.8 (**C20**), 123.8 (**C8**), 115.7 (**C7**), 70.3 (**C2**), 69.2 (**C2'**), 68.9 (**C4**), 66.9 (**C10**), 21.7 (**C1**) 21.5 (**C1**), 21.3 (**C1'**), 20.4 (**C1'**).

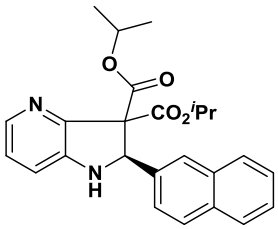
HRMS (ESI): found 419.1963; $[C_{25}H_{26}N_2O_4]^+$ $(M + H)^+$ requires 419.1965.

IR: ν_{max} (neat)/cm^{-1}: 3361 (N-H), 2983 (C-H aromatic), 2936 (C-H aliphatic), 1719 (C=O), 1270, 1106, 754.

MP: 119-121 °C.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 223 nm); t_R 10.9 min, 16.2 min.

Preparation of (*R*)-diisopropyl 2-(naphthalen-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167m)

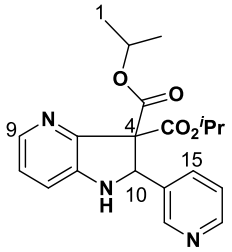


Following **General Procedure B**; the reaction of imine **166m** (50 mg, 0.12 mmol), **88f** (6.0 mg, 12.0 µmol) and KOH (7.0 mg, 0.12 mmol) in toluene:CH_2Cl_2 (1.5:0.5 mL) for 48 h yielded azaindoline **167m** (39 mg, 78 %, 90 % *ee*) as a white solid with identical spectroscopic properties to **rac-167m**.

$[\alpha]_D^{22}$ +85 (*c* = 1.2, $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 223 nm); t_R (major) = 11.0 min, t_R (minor) = 17.0 min.

Preparation of (±)-diisopropyl 2-(pyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167n)



Following **General Procedure A**; the reaction of imine **166n** (50 mg, 0.14 mmol), $CsOH.H_2O$ (47 mg, 0.28 mmol) in toluene (5.0 ml) with purification by flash column chromatography (ethyl acetate:40-60 petrol, 3:1) yielded azaindoline **rac-167n** (25 mg, 50 %) a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 8.71 (1H, s, **H12**), 8.53 (1H, d, *J* 4.0, **H13**), 8.09 (1H, dd, *J* 4.8, 1.5, **H9**), 7.78 (1H, dt, *J* 7.8, 1.8, **H15**), 7.23 (1H, dd, *J* 7.8 4.8, **H14**), 7.08 (1H, dd, *J* 8.1, 4.8, **H8**), 7.00 (1H, dd, *J* 8.1 1.3, **H7**), 5.92 (1H, s, **H10**), 5.21 (1H, spt, *J* 6.1, **H2**), 4.56 (1H, spt, *J* 6.1, **H2'**), 4.30 (1H, br s, **NH**), 1.34 (3H, d, *J* 6.3, **H1**), 1.31 (3H, d, 6.3, **H1**), 1.02 (3H, d, *J* 6.1, **H1'**), 0.55 (3H, d, *J* 6.3, **H1'**).

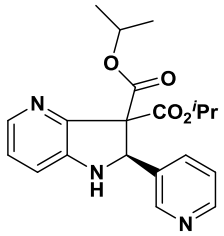
^{13}C (101 MHz, $CDCl_3$): δ 167.4 (**C3**), 166.2 (**C3'**), 149.6 and 149.6 (**C12** and **C13**), 145.3 (**C5**), 144.4 (**C6**), 141.1 (**C9**), 135.5 (**C15**), 134.1 (**C11**), 124.0 (**C8**), 123.3 (**C14**) 116.2 (**C7**), 70.6 (**C2**), 697 (**C2'**), 68.8 (**C4**), 64.3 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.3 (**C1'**), 20.8 (**C1'**).

HRMS (ESI): found 370.1760; $[C_{20}H_{24}N_3O_4]^+$ ($M+H^+$) requires 370.1761.

IR: ν_{max} (neat)/ cm^{-1}: 3358 (N-H), 2982, 2938, 1719 (C=O), 1269, 1105.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 249 nm); t_R 8.5min, 9.2 min.

Preparation of (*R*)-diisopropyl 2-(pyridin-3-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167n)

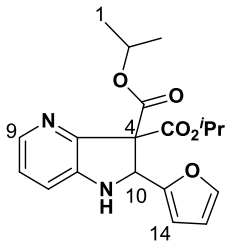


Following **General Procedure B**; the reaction of imine **166n** (30 mg, 0.081 mmol), **88f** (4.0 mg, 8.1 µmol) and KOH (4.5 mg, 0.081 mmol) in toluene:DCM (0.9:0.3 mL) for 36 h with purification by flash column chromatography (ethyl acetate:40-60 petrol, 3:1) yielded azaindoline **167n** (19 mg, 63 %, 68 % *ee*) with identical spectroscopic properties to **rac-167n.**

$[\alpha]_D^{22}$: +51.3 ° (c 1.0 $CHCl_3$).

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 249 nm); t_R (major) = 8.5 min, t_R (minor) = 9.3 min.

Preparation of (±)-diisopropyl 2-(furan-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167o)



Following **General Procedure A**; the reaction of imine **166o** (50 mg, 0.14 mmol) and $CsOH{\cdot}H_2O$ (47 mg, 0.28 mmol) in toluene (5 ml) with purification by flash column chromatography (40-60 petrol:diethyl ether, 1:2) yielded azaindoline **rac-167o** (38 mg, 76 %) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.09 (1H, dd, *J* 4.8, 1.5, **H9**), 7.33 (1H, m, **H12**), 7.05 (1H, dd, *J* 8.0, 4.9, **H8**), 6.96 (1H, dd, *J* 7.8, 1.3, **H7**), 6.33 (1H, d, *J* 3.3, **H14**), 6.30 (1H, dd, *J* 3.3, 1.8, **H13**), 5.88 (1H, s, **H10**), 5.17 (1H, sept, *J* 6.3, **H2**), 4.79 (1H, sept, *J* 6.1, **H2'**), 4.16 (1H, br. s, **NH**), 1.32 (3H, d, *J* 6.3, **H1**), 1.26 (3H, d, 6.3, **H1**), 1.14 (3H, d, *J* 6.1, **H1'**), 0.89 (3H, d, *J* 6.1, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.2 (**C3**), 166.0 (**C3'**), 152.0 (**C11**), 145.4 (**C5**), 144.0 (**C6**), 142.5 (**C12**), 141.0 (**C9**), 123.7 (**C8**), 116.3 (**C7**), 110.4 (**C14**), 108.7 (**C13**), 70.4 (**C2**), 69.4 (**C2'**), 67.6 (**C4**), 61.0 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.4 (**C1'**), 21.3 (**C1'**).

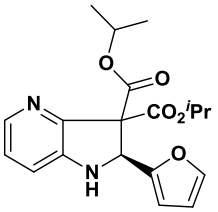
HRMS (ESI): found 359.1600; $[C_{19}H_{23}N_2O_5]^+$ $(M+H)^+$ requires 359.1601.

IR: ν_{max} (neat)/cm^{-1}: 3358 (N-H), 2982 (C-H aromatic), 2938 (C-H aliphatic), 1719 (C=O), 1269, 1105.

MP: 121-123 °C.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 249 nm); t_R 8.0 min, 9.4 min.

Preparation of (*S*)-diisopropyl 2-(furan-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167o)

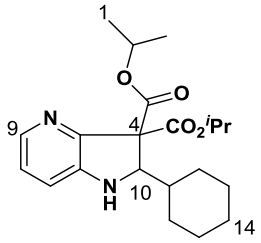


Following **General Procedure B**; the reaction of imine **166o** (30 mg, 0.08 mmol), **88f** (4.0 mg, 7.8 μmol) and KOH (4.5 mg, 0.08 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) with purification by flash column chromatography (40-60 petrol:diethyl ether, 1:2) yielded azaindoline **167o** (28 mg, 93 %, 94 % *ee*) as a white solid with identical spectroscopic properties to **rac-167o**.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 249 nm); t_R (minor) = 8.3 min, t_R (major) = 9.7 min.

$[\alpha]_D^{22}$ +84 (*c* = 1.1, $CHCl_3$).

Preparation of (±)-diisopropyl 2-cyclohexyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167p)



Freshly distilled cyclohexanecarbaldehyde (242 µL, 1.59 mmol) was added to a solution of aminopyridine **165** (260 mg, 0.93 mmol) in toluene (30 mL) containing anhydrous $MgSO_4$ (135 mg, 1.12 mmol) at RT. The suspension was stirred for 36 h and then the reaction mixture was filtered and concentrated *in vacuo*. The product was carried forward to the cyclization reactions without further purification.

Following **General Procedure A**; the reaction of crude imine (40 mg, 0.11 mmol) and $CsOH{\cdot}H_2O$ (37 mg, 0.22 mmol) in toluene (4 ml) yielded azaindoline **rac-167p** (24 mg, 53 % over 2 steps) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.98 (1H, dd, *J* 4.8, 1.3, **H9**), 6.97 (1H, dd, *J* 7.8, 4.8, **H8**), 6.89 (1H, dd, *J* 7.8, 1.3, **H7**), 5.22-5.05 (2H, m, **H2**), 4.37 (1H, dd, *J* 8.1, 1.5, **H10**), 3.99 (1H, br. s, **NH**), 1.94 (1H, d, *J* 12.6, **H14**), 1.83-1.65 (6H, m, **H11**, **H12**, **H13** and **H14'**), 1.35-1.32 (12H, m, **H1** and **H1'**), 1.21-0.90 (4H, m, **H12'** and **H13'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.9 (**C3**), 167.2 (**C3'**), 148.4 (**C5**), 144.2 (**C6**), 140.2 (**C9**), 123.4 (**C8**), 116.0 (**C7**), 69.9 (**C2**), 69.7 (**C2'**), 69.5 (**C10**), 66.2 (**C4**), 39.9 (**C11**), 31.0 (**C12**), 29.2 (**C13**), 25.9 (**C14**), 21.7 (**C1**), 21.6 (**C1**), 21.6 (**C1'**), 21.5 (**C1'**).

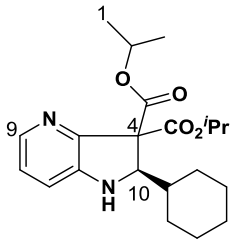
HRMS (ESI): found 375.2273; $[C_{21}H_{31}N_2O_4]^+$ $(M + H)^+$ requires 375.2278.

IR: ν_{max} (neat)/cm^{-1}: 3364 (N-H), 2979 (C-H aromatic), 2923 (C-H aliphatic), 2851 (C-H aliphatic), 1718 (C=O), 1441, 1263, 1233, 1207, 1104, 796.

MP: 81-85 °C.

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 249 nm); t_R 5.0 min, 6.4 min.

Preparation of (*R*)-diisopropyl 2-(4-nitrophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167p)

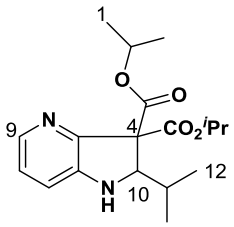


The required imine was prepared following procedure for **rac-167p**. Following **General Procedure B**; the reaction of crude imine (35 mg, 0.09 mmol), **88f** (4.5 mg, 8.7 μmol) and KOH (5.0 mg, 0.09 mmol) in toluene:CH_2Cl_2 (1.2:0.4 mL) yielded azaindoline **167p** (27 mg, 66 % over 2 steps, 96 % *ee*) as a white solid with identical spectroscopic properties to **rac-167p**.

$[\alpha]_D^{22}$ +88 (*c* = 1.4, $CHCl_3$).

Chiral HPLC: (Chiralpak OD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 249 nm); t_R (major) = 4.9 min, t_R (minor) = 6.4 min.

Preparation of (±)-diisopropyl 2-isopropyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167q)



Freshly distilled isobutyraldehyde (557 µL, 6.10 mmol) was added to a solution of aminopyridine **165** (170 mg, 0.61 mmol) in toluene (30 mL) containing anhydrous $MgSO_4$ (88 mg, 0.73 mmol) at RT. The suspension was stirred for 16 h and then the reaction mixture was filtered and concentrated *in vacuo* and excess aldehyde removed under high vacuum. The product was carried forward to the cyclization reactions without further purification.

Following **General Procedure A**; the reaction of crude imine (50 mg, 0.15 mmol) and $CsOH{\cdot}H_2O$ (50 mg, 0.30 mmol) in toluene (5 ml) yielded azaindoline **rac-167q** (44 mg, 65 % over 2 steps) as a pale yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.00 (1H, dd, *J* 4.8, 1.0, **H9**), 6.98 (1H, dd, *J* 8.1, 4.8, **H8**), 6.90 (1H, dd, *J* 7.8, 1.0, **H7**), 5.23-5.06 (2H, m, **H2**), 4.37 (1H, dd, *J* 7.8, 1.0, **H10**), 3.98 (1H, br. s, **NH**), 2.00 (1H, sept, *J* 6.6, **H11**), 1.28 (12H, m, **H1** and **H1'**), 1.08 (3H, d, *J* 6.6, **H12**), 0.98 (3H, d, *J* 6.6, **H12'**).

^{13}C (101 MHz, $CDCl_3$): δ 168.0 (**C3**), 167.2 (**C3'**), 148.3 (**C5**), 144.3 (**C6**), 140.3 (**C9**), 123.5 (**C8**), 115.9 (**C7**), 70.5 (**C10**), 69.9 (**C2**), 69.5 (**C2'**), 66.3 (**C4**), 30.3 (**C11**), 21.6 (**C1**), 21.6 (**C1**), 21.6 (**C1'**), 21.5 (**C1'**), 21.0 (**C12**), 19.2 (**C12'**).

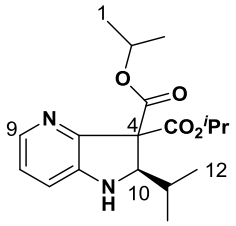
HRMS (ESI): found 335.1963; $[C_{18}H_{27}N_2O_4]^+$ $(M + H)^+$ requires 335.1965.

IR: ν_{max} (neat)/cm^{-1}: 3367 (N-H), 2981 (C-H aromatic), 2936 (C-H aliphatic), 2876 (C-H aliphatic), 1719 (C=O), 1466, 1264, 1233, 1027.

MP: 96-100 °C.

Chiral HPLC: (Chiralpak IC, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 249 nm); t_R 8.3 min, 11.0 min.

Preparation of (*R*)-diisopropyl 2-isopropyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167q)

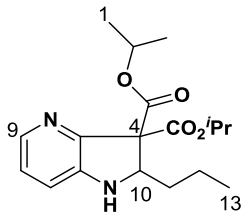


The required imine was prepared following procedure for **rac-167q**. Following **General Procedure B**; the reaction ofcrude imine (50 mg, 0.15 mmol), **88f** (7.5 mg, 15.0 μmol) and KOH (8.5 mg, 0.15 mmol) in toluene:CH_2Cl_2 (1.2:0.4 mL) yielded azaindoline **167q** (31 mg, 46 % over 2 steps, 86 % *ee*) as a pale yellow solid with identical spectroscopic properties to **rac-167q**.

$[\alpha]_D^{22}$ +88 (*c* = 1.6, $CHCl_3$).

Chiral HPLC: (Chiralpak IC, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 249 nm); t_R (major) = 8.3 min, t_R (minor) = 11.0 min.

Preparation of (±)-diisopropyl 2-propyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-167r)



Freshly distilled butyraldehyde (557 µL, 6.10 mmol) was added to a solution of aminopyridine **165** (170 mg, 0.61 mmol) in toluene (30 mL) containing anhydrous $MgSO_4$ (88 mg, 0.73 mmol) at RT. The suspension was stirred for 16 h and then the reaction mixture was filtered and concentrated *in vacuo* and excess aldehyde removed under high vacuum. The product was carried forward to the cyclization reactions without further purification.

Following **General Procedure A**; the reaction of crude imine (50 mg, 0.15 mmol) and $CsOH{\cdot}H_2O$ (50 mg, 0.30 mmol) in toluene (5 ml) yielded azaindoline **rac-167r** (15 mg, 22 % over 2 steps) as a pale yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.03 (1H, dd, *J* 4.8, 1.0, **H9**), 6.99 (1H, dd, *J* 8.1, 4.8, **H8**), 6.89 (1H, dd, *J* 7.8, 1.0, **H7**), 5.21-5.07 (2H, m, **H2**), 4.57 (1H, dd, *J* 9.7, 3.1, **H10**), 3.99 (1H, br. s, **NH**), 1.71-1.63 (1H, m, **H11**), 1.60-1.47 (2H, m, **H11'** and **H12**), 1.46-1.38 (1H, m, **H12**'), 1.35-1.21 (12H, m, **H1** and **H1'**), 0.98 (3H, t, *J* 7.1, **H13**).

^{13}C (101 MHz, $CDCl_3$): δ 167.6 (**C3**), 167.0 (**C3'**), 147.1 (**C5**), 144.3 (**C6**), 140.5 (**C9**), 123.6 (**C8**), 116.4 (**C7**), 69.8 (**C2**), 69.5 (**C2'**), 66.3 (**C4**), 63.4 (**C10**), 34.1 (**C11**), 21.7 (**C1**), 21.6 (**C1**), 21.6 (**C1'**), 21.6 (**C1'**), 20.0 (**C12**), 13.9 (**C13**).

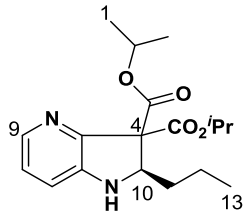
HRMS (ESI): found 335.1956; $[C_{18}H_{27}N_2O_4]^+$ $(M + H)^+$ requires 335.1965.

IR: ν_{max} (neat)/cm^{-1}: 3367 (N-H), 2982 (C-H aromatic), 2937 (C-H aliphatic), 2875 (C-H aliphatic), 1719 (C=O), 1439, 1266, 1181, 1105, 753.

MP: 115-118 °C.

Chiral HPLC: (Chiralpak IC, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 249 nm); t_R 9.4 min, 10.9 min.

Preparation of (*R*)-diisopropyl 2-propyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (167r)

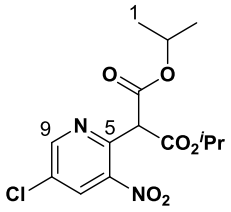


The required imine was prepared following procedure for **rac-167r**. Following **General Procedure B**; the reaction of crude imine (50 mg, 0.15 mmol), **88f** (7.5 mg, 15.0 μmol) and KOH (8.5 mg, 0.15 mmol) in toluene:CH_2Cl_2 (1.2:0.4 mL) yielded azaindoline **167r** (31 mg, 46 % over 2 steps, 75 % *ee*) as a pale yellow solid with identical spectroscopic properties to **rac-167r**.

$[\alpha]_D^{22}$ +102 (*c* = 1.6, $CHCl_3$).

Chiral HPLC: (Chiralpak IC, 15 % IPA, 85 % hexane, 1.0 $mL.min^{-1}$, λ = 249 nm); t_R (major) = 9.3 min, t_R (minor) = 10.9 min.

Preparation of diisopropyl 2-(5-chloro-3-nitropyridin-2-yl) malonate (179)



According to a modified literature procedure,[91] diisopropyl malonate (5.88 mL, 31.2 mmol) in DME (15 mL) was added to a stirred suspension of 60 % NaH (1.25 g, 31.2 mmol) in DME (40 mL) at RT. The mixture was stirred at RT for 1 h. 2-5-Dichloro-3-nitropyridine (3.00 g, 15.6 mmol) was added and the resulting dark brown solution stirred at RT for 16 h. The crude reaction mixture was diluted with water (100 mL) and acidified to pH 2 with 1 M HCl. The mixture was extracted with ether (3 × 150 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 5:1 to 1:2) and the resulting yellow oil was further purified by distillation of the remaining diisopropyl malonate to yield nitropyridine **179** (3.53 g, 66 %) as an orange oil.

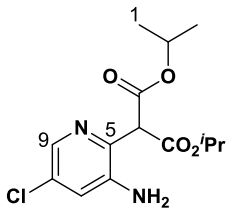
^{1}H (400 MHz, $CDCl_3$): δ 8.77 (1H, d, *J* 2.2, **H9**), 8.48 (1H, d, *J* 2.5, **H7**), 5.42 (1H, s, **H4**), 5.17 (2H, sept, *J* 6.3, **H2**), 1.28 (12H, d, *J* 6.6, **H1**).

^{13}C (101 MHz, $CDCl_3$): δ 165.7 (**C3**), 151.9 (**C9**), 147.3 (**C5**), 144.6 (**C6**), 132.8 (**C7**), 132.1 (**C8**), 70.2 (**C2**), 59.2 (**C4**), 21.6 (**C1**).

HRMS (ESI): found 345.0845; $[C_{14}H_{18}ClN_2O_6]^+$ $(M + H)^+$ requires 345.0848.

IR: ν_{max} (neat)/cm^{-1}: 2983 (C-H aromatic), 2937 (C-H aliphatic), 2360, 1733 (C=O), 1557, 1533 (NO_2), 1375 (NO_2), 1102.

Preparation of diisopropyl 2-(5-chloro-3-aminopyridin-2-yl) malonate (180)



According to a modified literature procedure,[92] NH_4Cl (3.53 g, 66.6 mmol) and zinc dust (2.88 g, 44.0 mmol) were added to a solution of nitropyridine **179** (1.50 g, 4.35 mmol) in acetone:water (50:10 mL). The mixture was stirred for 20 min, filtered through Celite®, extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield aminopyridine **180** (1.00 g, 72%) as a yellow oil.

NB: Product is unstable and must be used immediately or stored under argon in a freezer.

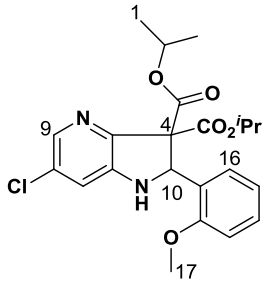
Unable to obtain pure proton/carbon spectral data due to decomposition.

Diagnostic ^{1}H NMR peak: δ 4.35 (2H, br. s, **NH_2**).

HRMS (ESI): found 315.1109; $[C_{14}H_{20}ClN_2O_4]^+$ $(M + H)^+$ requires 315.1106.

IR: ν_{max} (neat)/cm^{-1}: 3360 (N-H), 2982 (C-H aromatic), 2330, 1721 (C=O), 1253, 1180, 1098.

Preparation of (±)-diisopropyl 6-chloro-2-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-182c)



Freshly distilled 2-methoxybenzaldehyde (208 mg, 1.53 mmol) was added to a solution of aminopyridine **180** (322 mg, 1.02 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (147 mg, 1.22 mmol) at RT. The suspension was stirred for 24 h and then the reaction mixture was filtered and concentrated *in vacuo*. The product was carried forward to the cyclization reactions without further purification.

Following **General Procedure A**; the reaction of crude imine (100 mg, 0.23 mmol) and $CsOH{\cdot}H_2O$ (77 mg, 0.46 mmol) in toluene (3 ml) with purification by flash column chromatography (40-60 petrol:diethyl ether, 4:1 to 1:1) yielded azaindoline **rac-182c** (47 mg, 44 % over 2 steps) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.94 (1H, d, *J* 2.0, **H9**), 7.33 (1H, dd, *J* 7.7, 1.4, **H16**), 7.24 (1H, m, **H14**), 6.89 (1H, d, *J* 2.2, **H7**), 6.85 (2H, m, **H13** and **H15**), 6.26 (1H, d, *J* 1.7, **H10**), 5.16 (1H, spt, *J* 6.3, **H2**), 4.56 (1H, spt, *J* 6.3, **H2'**), 4.18 (1H, s, **NH**), 3.75 (3H, s, **H17**), 1.34-1.24 (6H, m, **H1**), 1.01 (3H, d, *J* 6.4, **H1'**), 0.53 (3H, d, *J* 6.4, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.5 (**C3**), 166.1 (**C3'**), 157.6 (**C12**), 145.4 (**C5**), 145.0 (**C6**), 138.2 (**C9**), 132.4 (**C8**), 129.5 (**C16**), 128.5 (**C14**), 127.4 (**C1**), 120.5 (**C15**), 114.9 (**C7**), 110.4 (**C13**), 70.2 (**C2**), 69.0 (**C2'**), 67.3 (**C4**), 62.0 (**C10**), 55.2 (**C17**), 21.6 (**C1**), 21.6 (**C1**), 21.3 (**C1'**), 20.6 (**C1'**).

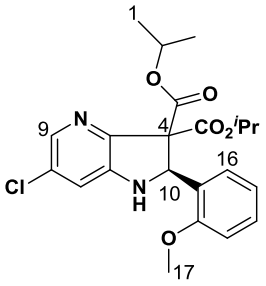
HRMS (ESI): found 455.1329; $[C_{22}H_{25}ClN_2O_5Na]^+$ $(M + Na)^+$ requires 455.1344.

IR: ν_{max} (neat)/cm^{-1}: 3356 (N-H), 2981 (C-H aromatic), 2937 (C-H aliphatic), 1719 (C=O), 1586, 1435, 1246, 1105, 1026, 787.

MP: Decomposed at 170 °C.

Chiral HPLC: (Chiralpak IC, 25 % IPA, 75 % hexane, 1.0 mL.min^{-1}, λ = 220 nm); t_R 13.0 min, 20.5 min.

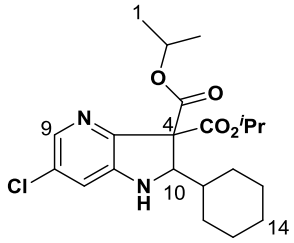
Preparation of (*R*)-diisopropyl 6-chloro-2-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (182-c)



The required imine was prepared following procedure for **rac-182c**. Following **General Procedure B**; the reaction of crude imine (50 mg, 0.12 mmol), **88f** (6.0 mg, 12 μmol) and KOH (6.5 mg, 0.12 mmol) in toluene:CH_2Cl_2 (1.5:0.5 mL) with purification by flash column chromatography (40-60 petrol:diethyl ether, 4:1 to 1:1) yielded azaindoline **182c** (18 mg, 33 % over 2 steps, 8 % *ee*) as a white solid with identical spectroscopic properties to **rac-182c**.

Chiral HPLC: (Chiralpak IC, 25 % IPA, 75 % hexane, 1.0 mL.min^{-1}, λ = 220 nm; t_R (minor) = 17.6 min, t_R (major) = 27.3 min.

Preparation of (±)-diisopropyl 6-chloro-2-cyclohexyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (rac-182d)



Freshly distilled cyclohexanecarbaldehyde (193 µL, 1.59 mmol) was added to a solution of aminopyridine **180** (333 mg, 1.06 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (153 mg, 1.27 mmol) at RT. The suspension was stirred for 24 h and then the reaction mixture was filtered and concentrated *in vacuo*. The product was carried forward to the cyclization reactions without further purification.

Following **General Procedure A**; the reaction of crude imine (100 mg, 0.24 mmol) and $CsOH{\cdot}H_2O$ (61 mg, 0.48 mmol) in toluene (3 ml) with purification by flash column chromatography (40-60 petrol:diethyl ether, 3:1) and further purification by trituration with petrol yielded azaindoline **rac-182d** (4 mg, 4 % over 2 steps) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.92 (1H, d, *J* 1.6, **H9**), 6.87 (1H, d, *J* 1.6, **H7**), 5.20-5.06 (2H, m, **H2**), 4.44 (1H, d, *J* 7.25, **H10**), 1.90 (1H, d, *J* 12.6, **H12**), 1.83-1.57 (H, m, **H11**, **H13** and **H14'**), 1.34-1.07 (16H, **H1**, **H1'**, **H12'** and **H13'**), 1.07-0.96 (1H, m, **H14'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.5 (**C3**), 166.8 (**C3'**), 146.1 (**C5**), 145.0 (**C6**), 138.3 (**C9**), 132.3 (**C8**), 115.6 (**C7**), 70.3 (**C2**), 69.9 (**C2'**), 69.8 (**C10**), 65.4 (**C4**), 39.9 (**C11**), 31.0 (**C12**), 28.9 (**C14**), 25.9 (**C13**), 21.7 (**C1**), 21.6 (**C1**), 21.6 (**C1'**), 21.5 (**C1'**).

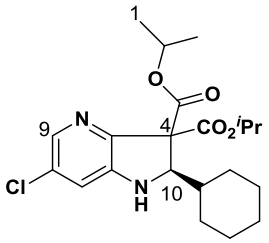
HRMS (ESI): found 431.1702; $[C_{21}H_2ClN_2O_4Na]^+$ $(M + Na)^+$ requires 431.1708.

IR: ν_{max} (neat)/cm^{-1}: 3363 (N-H), 2981 (C-H aromatic), 2927 (C-H aliphatic), 2853 (C-H aliphatic), 2361, 2340, 1715 (C=O), 1590, 1267, 1104.

MP: 153-154 °C.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 340 nm); t_R 9.4 min, 10.5 min.

Preparation of (*R*)-diisopropyl 6-chloro-2-cyclohexyl-1*H*-pyrrolo[3,2-*b*]pyridine-3,3(2*H*)-dicarboxylate (182-d)

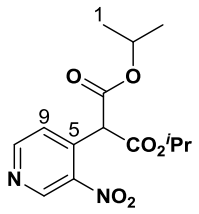


The required imine was prepared following procedure for **rac-182d**. Following **General Procedure B**; the reaction of crude imine (50 mg, 0.12 mmol), **88f** (6.0 mg, 12 μmol) and KOH (6.5 mg, 0.12 mmol) in toluene:CH_2Cl_2 (1.5:0.5 mL) with purification by flash column chromatography (40-60 petrol:diethyl ether, 6:1) yielded azaindoline **182d** (10 mg, 20 % over 2 steps, 70 % *ee*) as an orange oil with identical spectroscopic properties to **rac-182d**.

$[\alpha]_D^{22}$ +12 (*c* = 0.5, $CHCl_3$).

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 249 nm); t_R (major) = 9.4 min, t_R (minor) = 10.5 min.

Preparation of diisopropyl 2-(3-nitropyridin-4-yl) malonate (188)



Diisopropyl malonate (5.89 mL, 31.0 mmol) was added to a stirred suspension of NaH (60 % in mineral oil) (1.24 g, 31.0 mmol) in DMF (30 mL) at RT. The mixture was heated to 90 °C and stirred for 20 min. 2-Chloro-5-nitropyridine (2.45 g, 15.5 mmol) was added as a solution in DMF (20 mL) and the resulting dark red solution stirred at 90 °C for 16 h. The reaction was quenched with saturated aqueous ammonium chloride solution (50 mL) and extracted with ethyl acetate:methanol 5:1 (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1 to 1:2) to yield a yellow oil (3.61 g). The product was then crystallized in the freezer using 40-60 petrol. The crystals were collected by filtration and washed with cold 40-60 petrol to yield nitropyridine **188** (2.63 g, 55 %) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 9.26 (1H, s, **H7**), 8.83 (1H, d, *J* 5.1, **H8**), 7.50 (1H, d, *J* 5.1, **H9**), 5.28 (1H, s, **H4**), 5.12 (2H, sept, *J* 6.3, **H2**), 1.28 (12H, apt. dd *J* 7.6, 6.3, **H1**).

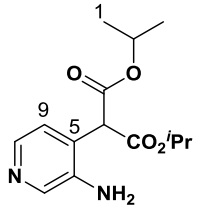
^{13}C (101 MHz, $CDCl_3$): δ 165.5 (**C3**), 153.8 (**C8**), 146.3 (**C7**), 144.9 (**C6**), 137.2 (**C5**), 125.1 (**C9**), 70.7 (**C2**), 54.3 (**C4**), 21.6 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 333.1054; $[C_{14}H_{18}N_2O_6Na]^+$ $(M + Na)^+$ requires 333.1057.

IR: ν_{max} (neat)/cm^{-1}: 2984 (C-H aromatic), 2937 (C-H aliphatic), 2361, 1731 (C=O), 1605, 1532 (NO_2), 1353 (NO_2), 1237, 1101.

MP (40-60 petrol): 48-52 °C.

Preparation of diisopropyl 2-(3-aminopyridin-4-yl) malonate (189)



According to a modified literature procedure,[92] NH_4Cl (2.30 g, 43.4 mmol) and zinc dust (1.89 g, 28.9 mmol) were added to a solution of nitropyridine **188** (898 mg, 2.89 mmol) in acetone:water (25:5 mL). The mixture was stirred for 20 min, filtered through Celite®, extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield aminopyridine **189** (773 mg, 95 %) as a yellow solid. NB: Product is unstable in air and must be used immediately or stored under argon in a freezer.

^{1}H (400 MHz, $CDCl_3$): δ 8.11 (1H, s, **H7**), 8.00 (1H, d, *J* 4.8, **H8**), 7.08 (1H, d, *J* 4.6, **H9**), 5.08 (2H, sept, *J* 6.2, **H2**), 4.53 (1H, s, **H4**), 4.21 (2H, br. s, **NH_2**), 1.24 (12H, m, **H1**).

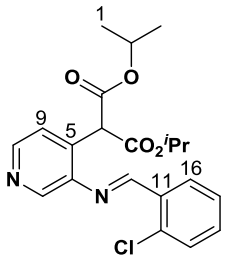
^{13}C (101 MHz, $CDCl_3$): δ 167.0 (**C3**), 141.8 (**C6**), 140.2 (**C8**), 139.7 (**C7**), 126.6 (**C5**), 125.1 (**C9**), 70.1 (**C2**), 55.4 (**C4**), 21.6 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 281.1486; $[C_{14}H_{21}N_2O_4]^+$ $(M + H)^+$ requires 281.1495.

IR: ν_{max} (neat)/cm^{-1}: 3362 (N-H), 2983 (C-H aromatic), 2935 (C-H aliphatic), 1722 (C=O), 1635 (N-H), 1566, 1098, 729.

MP: 67-72 °C.

Preparation of (*E*)-diisopropyl 2-(3-((2-chlorobenzylidene)amino)pyridin-4-yl)malonate (190e)



2-Chlorobenzaldehyde (352 µL, 3.13 mmol) was added to a solution of aminopyridine **189** (350 mg, 1.25 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (181 mg, 1.50 mmol). The suspension was heated at reflux for 48 h and then the reaction mixture was allowed to cool to RT, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (diethyl ether:40-60 petrol, 1:1) to yield imine **190e** (78 mg, 16 %) as an orange oil.

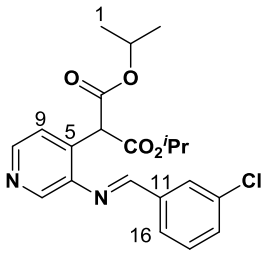
^{1}H (400 MHz, $CDCl_3$): δ 8.90 (1H, s, **H10**), 8.52 (1H, br s, **H8**), 8.35 (1H, br s, **H7**), 8.23 (1H, d, *J* 7.8, **H16**), 7.48-7.33 (4H, m, **H9**, **H13**, **H14** and **H15**), 5.23 (1H, s, **H4**), 5.07 (2H, sept, *J* 6.3, **H2**), 1.25 (6H, d, *J* 6.6, **H1**), 1.19 (6H, d, *J* 6.4, **H1**).

^{13}C (126 MHz, $CDCl_3$): δ 166.8 (**C3**), 158.5 (**C10**), 147.8 (**C8**), 146.0 (**C6**), 139.1 (**C7**), 136.4 (**C5**), 136.2 (**C11**) 132.8 (**C14**), 132.6 (**C12**), 130.0 (**C16**), 128.9 (**C13**), 127.7 (**C16**), 127.1 (**C15**), 69.7 (**C2**), 53.0 (**C4**), 21.6 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 403.1405; $[C_{21}H_{24}ClN_2O_4]^+$ $(M + H)^+$ requires 403.1419.

IR: ν_{max} (neat)/cm^{-1}: 2981 (C-H aromatic) 2934 (C-H aliphatic), 1729 (C=O), 1620 (C=N), 1225, 1099, 759.

Preparation of (*E*)-diisopropyl 2-(3-((3-chlorobenzylidene)amino)pyridin-4-yl)malonate (190f)



3-Chlorobenzaldehyde (304 µL, 2.68 mmol) was added to a solution of aminopyridine **189** (300 mg, 1.07 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (154 mg, 1.28 mmol) at RT. The suspension was stirred for 6 days and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (diethyl ether: 40-60 petrol, 1:1) to yield imine **190f** (118 mg, 27 %) as an orange oil.

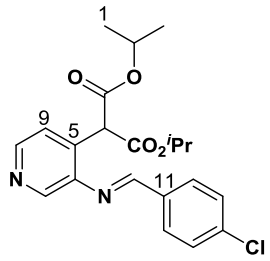
^{1}H (500 MHz, $CDCl_3$): δ 8.52 (1H, d, *J* 5.0, **H8**), 8.41 (1H, s, **H10**), 8.32 (1H, s, **H7**), 7.95 (1H, apt. t, *J* 1.6, **H12**), 7.76 (1H, d, *J* 7.6, **H16**), 7.50 (1H, ddd, *J* 7.9, 1.9, 1.0, **H14**), 7.45-7.42 (2H, m, **H9** and **H15**), 5.22 (1H, s, **H4**), 5.08 (2H, sept, *J* 6.3, **H2**), 1.26 (6H, d, *J* 6.6, **H1**), 1.21 (6H, d, *J* 6.0, **H1**).

^{13}C (126 MHz, $CDCl_3$): δ 166.8 (**C3**), 160.2 (**C10**), 147.7 (**C8**), 145.7 (**C6**), 138.7 (**C7**), 137.3 (**C11**), 136.6 (**C5**), 135.1 (**C13**), 132.0 (**C14**), 130.1 (**C15**), 128.5 (**C12**), 127.7 (**C16**), 123.3 (**C9**), 69.8 (**C2**), 53.0 (**C4**), 21.6 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 403.1415; $[C_{21}H_{24}ClN_2O_4]^+$ $(M + H)^+$ requires 403.1419.

IR: ν_{max} (neat)/cm^{-1}: 2982 (C-H aromatic) 2936 (C-H aliphatic), 1727 (C=O), 1629 (C=N), 1196, 1100, 684.

Preparation of (*E*)-diisopropyl 2-(3-((4-chlorobenzylidene)amino)pyridin-4-yl)malonate (190g)



4-Chlorobenzaldehyde (439 mg, 3.13 mmol) was added to a solution of aminopyridine **189** (350 mg, 1.25 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (181 mg, 1.50 mmol). The suspension was heated at reflux for 48 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (diethyl ether:40-60 petrol, 1:1) to yield imine **190g** (31 mg, 6 %) as an orange oil.

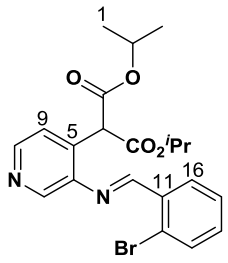
^{1}H (400 MHz, $CDCl_3$): δ 8.51 (1H, d, *J* 5.1, **H8**), 8.41 (1H, s, **H10**), 8.31 (1H, br s, **H7**), 7.86 (2H, d, *J* 8.3, **H13**), 7.46 (2H, d, *J* 8.6 **H12**), 5.21 (1H, s, **H4**), 5.06 (2H, sept, *J* 6.3, **H2**), 1.24 (6H, d, *J* 6.4, **H1**), 1.19 (6H, d, *J* 6.1, **H1**).

^{13}C (126 MHz, $CDCl_3$): δ 166.8 (**C3**), 160.3 (**C10**), 147.7 (**C8**), 145.9 (**C6**), 138.9 (**C7**), 138.2 (**C14**), 136.2 (**C5**) 134.2 (**C11**), 130.4 (**C13**), 129.2 (**C12**), 123.2 (**C9**), 69.7 (**C2**), 53.1 (**C4**), 21.6 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 425.1227; $[C_{21}H_{23}ClN_2O_4Na]^+$ $(M + Na)^+$ requires 425.1239.

IR: ν_{max} (neat)/cm^{-1}: 2980 (C-H aromatic) 2932 (C-H aliphatic), 1727 (C=O), 1620 (C=N), 1230, 1104, 754.

Preparation of (*E*)-diisopropyl 2-(3-((2-bromobenzylidene)amino)pyridin-4-yl)malonate (190h)



2-Bromobenzaldehyde (404 µL, 2.58 mmol) was added to a solution of aminopyridine **189** (288 mg, 1.03 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (149 mg, 1.24 mmol) at RT. The suspension was stirred for 6 days and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 1:1) to yield imine **190h** (120 mg, 26 %) as an orange oil.

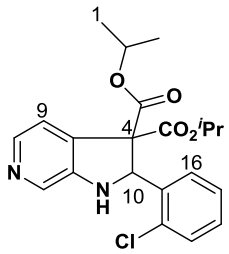
^{1}H (400 MHz, $CDCl_3$): δ 8.85 (1H, s, **H10**), 8.53 (1H, d, *J* 5.1, **H8**), 8.35 (1H, s, **H7**), 8.23 (1H, dd, *J* 7.7, 1.9, **H16**), 7.64 (1H, dd, *J* 8.0, 1.1, **H13**), 7.47-7.40 (2H, m, **H9** and **H15**), 7.36 (1H, apt. td, *J* 7.8, 1.8, **H14**), 5.23 (1H, s, **H4**), 5.08 (2H, sept, *J* 6.3, **H2**), 1.24 (6H, d, *J* 6.3, **H1**), 1.20 (6H, d, *J* 6.3, **H1**).

^{13}C (101 MHz, $CDCl_3$): δ 166.8 (**C3**), 160.9 (**C10**), 147.7 (**C8**), 145.9 (**C6**), 139.1 (**C7**), 136.3 (**C5**), 134.0 (**C11**), 133.4 and 133.1 (**C13** and **C14**), 129.4 (**C16**), 127.8 (**C15**), 126.4 (**C12**), 123.3 (**C9**), 69.8 (**C2**), 53.1 (**C4**), 21.6 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 447.0902; $[C_{21}H_{24}BrN_2O_4]^+$ $(M + H)^+$ requires 447.0914.

IR: ν_{max} (neat)/cm^{-1}: 2981 (C-H aromatic), 2936 (C-H aliphatic), 1728 (C=O), 1620 (C=N), 1097, 757.

Preparation of (±)-diisopropyl 2-(2-chlorophenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (rac-191e)



Following **General Procedure A**; the reaction of imine **190e** (30 mg, 0.07 mmol) and $CsOH{\cdot}H_2O$ (24 mg, 0.14 mmol) in toluene (3 ml) with purification by flash column chromatography (diethyl ether: 40-60 petrol, 1:1) yielded azaindoline **rac-191e** (11 mg, 37 %) as an orange oil.

^{1}H (400 MHz, $CDCl_3$): 8.39-7.98 (2H, br. m, **H7** and **H8**), 7.41 (1H, br. s, **H9**), 7.33 (1H, dd, *J* 8.2, 1.3, **H13**), 7.24 (1H, dd, *J* 7.9, 1.6, **H16**), 7.20 (1H, apt. td, *J* 7.6. 1.6, **H14**), 7.16-7.10 (1H, m, **H15**), 6.43 (1H, s, **H10**), 5.10 (1H, sept, *J* 6.3, **H2**), 4.59 (1H, sept, *J* 6.2, **H2'**), 4.27 (1H, br. s, **NH**), 1.30 (3H, d, *J* 6.6, **H1**), 1.20 (3H, d, *J* 6.6, **H1**), 1.08 (3H, d, *J* 6.0, **H1'**), 0.65 (3H, d, *J* 6.3, **H1'**).

^{13}C (126 MHz, $CDCl_3$): δ 166.8 (**C3**), 166.0 (**C3'**), 147.2 (**C6**),* 140.5 (**C8**),* 137.5 (**C14**), 134.0 (**C11**), 132.2 (**C7**),* 131.3 (**C5**),* 129.6 (**C14**), 129.4 (**C13**), 128.5 (**C16**), 127.2 (**C15**), 122.7 (**C9**),* 70.5 (**C2**), 69.9 (**C2'**), 69.0 (**C4**), 62.0 (**C10**), 21.5 (**C1**), 21.4 (**C1**), 21.3 (**C1'**), 20.4 (**C1'**).

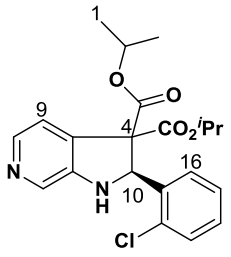
* Pyridine ring peaks weak and broad (possible restricted rotation)

HRMS (ESI): found 403.1403; $[C_{21}H_{24}ClN_2O_4]^+$ $(M + H)^+$ requires 403.1419.

IR: ν_{max} (neat)/cm^{-1}: 3376 (N-H), 2982 (C-H aromatic), 2936 (C-H aliphatic), 1730 (C=O), 1257, 1104.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 209 nm); t_R 7.0 min, 14.7 min.

Preparation of (*S*)-diisopropyl 2-(3-chlorophenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (191e)



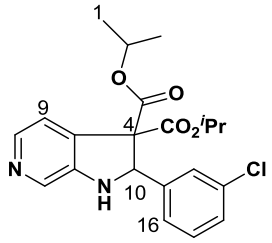
Following **General Procedure B**; the reaction of imine **190e** (55 mg, 0.13 mmol), **88f** (6.5 mg, 13 µmol) and KOH (7.0 mg, 0.13 mmol) in toluene:CH_2Cl_2 (1.5:0.5 mL) with purification by flash column chromatography (diethyl ether:40-60 petrol, 1:1) yielded azaindoline **191e** (35 mg, 70 %, 70 % *ee*) as a white solid with identical spectroscopic properties to **rac-191e**.

$[\alpha]_D^{22}$ +200 (*c* = 1.0, $CHCl_3$).

MP: 102-104 °C.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 251 nm); t_R (minor) = 6.7 min, t_R (major) = 14.3 min.

Preparation of (±)-diisopropyl 2-(3-chlorophenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (rac-191f)



Following **General Procedure A**; the reaction of imine **190f** (34 mg, 0.08 mmol) and $CsOH{\cdot}H_2O$ (28 mg, 0.17 mmol) in toluene (3 ml) with purification by flash column chromatography (diethyl ether) yielded azaindoline **rac-191f** (21 mg, 62 %) as a colourless oil.

^{1}H (400 MHz, $CDCl_3$): 8.15-8.13 (2H, m, **H7** and **H8**), 7.45 (1H, apt. t, *J* 1.9, **H12**), 7.38 (1H, d, *J* 4.7, **H9**), 7.33 (1H, d, *J* 7.6, **H14**), 7.29-7.19 (2H, m, **H15** and **H16**), 5.77 (1H, s, **H10**), 5.15 (1H, sept, *J* 6.3, **H2**), 4.57 (1H, sept, *J* 6.3, **H2'**), 4.38 (1H, br. s, **NH**), 1.32 (3H, d, *J* 6.3, **H1**), 1.28 (3H, d, *J* 6.3, **H1**), 1.03 (3H, d, *J* 6.3, **H1'**), 0.66 (3H, d, *J* 6.3, **H1'**).

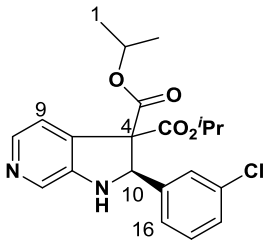
^{13}C (126 MHz, $CDCl_3$): δ 167.2 (**C3**), 165.9 (**C3'**), 146.9 (**C6**), 140.6 (**C8**), 135.8 (**C5**), 134.2 (**C13**), 132.8 (**C11**), 131.5 (**C7**), 129.7 (**C15**), 128.6 (**C16**), 128.2 (**C12**), 126.0 (**C14**), 121.6 (**C9**), 70.5 (**C2**), 70.1 (**C2'**), 69.7 (**C4**), 65.8 (**C10**), 21.7 (**C1**), 21.5 (**C1**), 21.3 (**C1'**), 20.6 (**C1'**).

HRMS (ESI): found 403.1416; $[C_{21}H_{24}ClN_2O_4]^+$ $(M + H)^+$ requires 403.1419.

IR: ν_{max} (neat)/cm^{-1}: 3359 (N-H), 2981 (C-H aromatic), 2937 (C-H aliphatic), 1727 (C=O), 1263, 1109, 755.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 209 nm); t_R 7.4 min, 9.2 min.

Preparation of (*R*)-diisopropyl 2-(3-chlorophenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (191f)

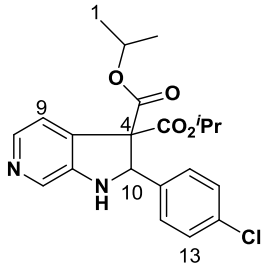


Following **General Procedure B**; the reaction of imine **190f** (34 mg, 0.08 mmol), **88f** (4.0 mg, 7.8 µmol) and KOH (4.5 mg, 0.08 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) with purification by flash column chromatography (diethyl ether) yielded azaindoline **191f** (30 mg, 88 %, 68 % *ee*) as a colourless oil with identical spectroscopic properties to **rac-191f**.

$[\alpha]_D^{22}$ +82 (*c* = 1.0, $CHCl_3$).

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 209 nm); t_R (minor) = 7.4 min, t_R (major) = 9.2 min.

Preparation of (±)-diisopropyl 2-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (rac-191g)



Following **General Procedure A**; the reaction of imine **190g** (5 mg, 0.01 mmol) and $CsOH{\cdot}H_2O$ (4 mg, 0.02 mmol) in toluene (250 µL) with purification by flash column chromatography (ethyl acetate:40-60 petrol, 1:1) yielded azaindoline **rac-191g** (3 mg, 60 %) as an orange oil.

^{1}H (400 MHz, $CDCl_3$): 8.21-8.03 (2H, br. m, **H7** and **H8**), 7.41-7.33 (3H, m, **H9** and **H12**), 7.29-7.20 (2H, m, **H13**), 5.77 (1H, s, **H10**), 5.15 (1H, sept, *J* 6.3, **H2**), 4.56 (1H, sept, *J* 6.3, **H2'**), 4.27 (1H, br. s, **NH**), 1.33 (3H, d, *J* 6.3, **H1**), 1.29 (3H, d, *J* 6.3, **H1**), 1.04 (3H, d, *J* 6.3, **H1'**), 0.64 (3H, d, *J* 6.3, **H1'**).

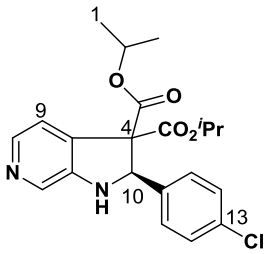
^{13}C (126 MHz, $CDCl_3$): δ 167.2 (**C3**), 166.0 (**C3'**), 146.9 (**C6**), 140.8 (**C8**), 137.1 (**C11**), 134.4 (**C14**), 132.7 (**C7**), 131.7 (**C5**), 129.3 (**C12**), 128.5 (**C13**), 121.6 (**C9**), 70.5 (**C2**), 70.0 (**C2'**), 68.6 (**C4**), 66.6 (**C10**), 21.6 (**C1**), 21.5 (**C1**), 21.3 (**C1'**), 20.6 (**C1'**).

HRMS (ESI): found 403.1407; $[C_{21}H_{24}ClN_2O_4]^+$ $(M + H)^+$ requires 403.1419.

IR: ν_{max} (neat)/cm^{-1}: 3364 (N-H), 2982 (C-H aromatic), 2936 (C-H aliphatic), 1726 (C=O), 1262, 1104.

Chiral HPLC: (Chiralpak IC, 25 % IPA, 75 % hexane, 1.0 mL.min^{-1}, λ = 220 nm); t_R 13.0 min, 20.5 min.

Preparation of (*R*)-diisopropyl 2-(3-chlorophenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (191g)

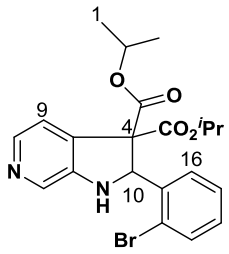


Following **General Procedure B**; the reaction of imine **190g** (25 mg, 0.06 mmol), **88f** (4.0 mg, 7.8 µmol) and KOH (3.5 mg, 0.06 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) with purification by flash column chromatography (ethyl acetate:40-60 petrol, 1:1) yielded azaindoline **191g** (16 mg, 64 %, 70 % *ee*) as an orange oil with identical spectroscopic properties to **rac-191g**.

$[\alpha]_D^{22}$ +89 (*c* = 0.5, $CHCl_3$).

Chiral HPLC: (Chiralpak IC, 25 % IPA, 75 % hexane, 1.0 mL.min^{-1}, λ = 220 nm); t_R (major) = 12.9 min, t_R (minor) = 20.4 min.

Preparation of (±)-diisopropyl 2-(2-bromophenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (rac-191h)



Following **General Procedure A**; the reaction of imine **190h** (66 mg, 0.15 mmol) and $CsOH{\cdot}H_2O$ (50 mg, 0.30 mmol) in toluene (5 ml) with purification by flash column chromatography (40-60 petrol: diethyl ether, 1:2 to 0:1) yielded azaindoline **rac-191h** (12 mg, 18 %) as a pale yellow solid.

^{1}H (300 MHz, $CDCl_3$):, 8.19-8.06 (2H, m, **H8** and **H7**) 7.53 (1H, dd, *J* 8.0, 0.8, **H13**), 7.44 (1H, d, *J* 5.0, **H9**), 7.23-7.08 (3H, m, **H14**, **H15** and **H16**), 6.44 (1H, d, *J* 1.0, **H10**), 5.11 (1H, sept, *J* 6.3, **H2**), 4.68-4.53 (2H, sept, m, **H2'** and **NH**), 1.31 (3H, d, *J* 6.3, **H1**), 1.22 (3H, d, *J* 6.3, **H1**), 1.10 (3H, d, *J* 6.3, **H1'**), 0.63 (3H, d, *J* 6.3, **H1'**).

^{13}C (126 MHz, $CDCl_3$): δ 166.8 (**C3**), 166.0 (**C3'**), 147.0 (**C6**), 140.6 (**C8**), 139.2 (**C11**), 132.8 (**C15**), 132.2 (**C5**), 131.3 (**C7**), 129.9 (**C13**), 128.6 (**C12**), 127.9 (**C14**), 124.5 (**C16**), 122.5 (**C9**), 70.5 (**C2**), 70.0 (**C2'**), 69.1 (**C4**), 64.7 (**C10**), 21.5 (**C1**), 21.5 (**C1**), 21.3 (**C1'**), 20.4 (**C1'**).

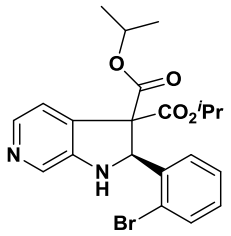
HRMS (ESI): found 447.0904; $[C_{21}H_{24}BrN_2O_4]^+$ $(M + H)^+$ requires 447.0914.

IR: ν_{max} (neat)/cm^{-1}: 3368 (N-H), 2982 (C-H aromatic), 2935 (C-H aliphatic), 1721 (C=O), 1260, 1105, 730.

MP: 74-76 °C.

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 209 nm); t_R 8.1 min, 17.6 min.

Preparation of (*S*)-diisopropyl 2-(2-bromophenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (191h)

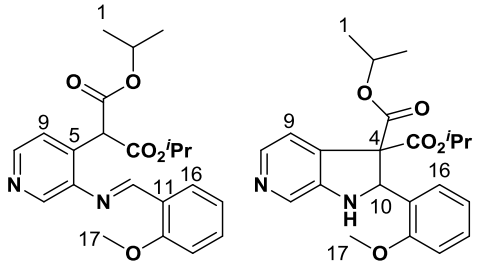


Following **General Procedure B**; the reaction of imine **190h** (43 mg, 0.10 mmol), **88f** (5.0 mg, 9.7 μmol) and KOH (5.5 mg, 0.10 mmol) in toluene:CH_2Cl_2 (1.2:0.4 mL) with purification by flash column chromatography (40-60 petrol:diethyl ether, 1:2 to 0:1) yielded azaindoline **191h** (26 mg, 60 %, 80 % *ee*) as a pale yellow solid with identical spectroscopic properties to **rac-191h**.

$[\alpha]_D^{22}$ +127 (*c* = 0.7, $CHCl_3$).

Chiral HPLC: (Chiralpak AD-H, 15 % IPA, 85 % hexane, 1.0 mL.min^{-1}, λ = 209 nm); t_R (minor) = 8.1 min, t_R (major) = 17.6 min.

Preparation of 2-(3-((2-methoxybenzylidene)amino)pyridin-4-yl)malonate (190c) and (±)-diisopropyl 2-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (rac-191c)



2-Methoxybenzaldehyde (365 mg, 2.68 mmol) was added to a solution of aminopyridine **189** (300 mg, 1.03 mmol) in toluene (10 mL) containing anhydrous $MgSO_4$ (154 mg, 1.28 mmol) at RT. The suspension was stirred for 3 days and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 1:2 to 0:1) to yield imine **190c** (52 mg, 12 %) as an orange oil* and azaindoline **rac-191c** (81 mg, 19 %) as a white solid.

*Due to the instability of this imine it was used immediately after purification and full characterization was not possible. Characteristic peaks observed in crude ^{1}H NMR: 8.90 (1H, s, **H10**), 5.27 (1H, s, **H4**).

rac-191c

^{1}H (400 MHz, $CDCl_3$): 8.04 (1H, d, *J* 4.8, **H8**), 8.00 (1H, s, **H7**), 7.30 (1H, d, *J* 4.8, **H9**), 7.20-7.15 (2H, m, **H14** and **H16**), 6.79-6.76 (2H, m, **H13** and **H15**), 6.18 (1H, s, **H10**), 5.05 (1H, sept, *J* 6.3, **H2**), 4.53 (1H, sept, *J* 6.2, **H2'**), 4.30 (1H, br. s, **NH**), 3.68 (3H, s, **H17**), 1.25 (3H, d, *J* 6.3, **H1**), 1.17 (3H, d, *J* 6.3, **H1**), 0.99 (3H, d, *J* 6.3, **H1'**), 0.55 (3H, d, *J* 6.1, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 167.4 (**C3**), 166.2 (**C3'**), 157.2 (**C12**), 147.6 (**C6**), 140.0 (**C8**), 133.0 (**C5**), 131.4 (**C7**), 129.5 (**C14**), 128.5 (**C16**), 128.0 (**C11**), 121.8 (**C9**), 120.5 (**C15**),

110.5 (**C13**), 70.0 (**C2**), 69.1 (**C2'**), 68.4 (**C4**), 61.0 (**C10**), 55.2 (**C17**), 21.5 (**C1**), 21.4 (**C1**), 21.3 (**C1'**), 20.5 (**C1'**).

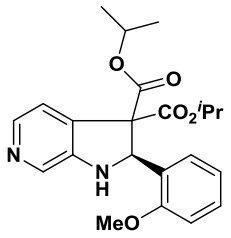
HRMS (ESI): found 399.1916; $[C_{22}H_{27}N_2O_5]^+$ $(M + H)^+$ requires 399.1914.

IR: ν_{max} (neat)/cm^{-1}: 3371 (N-H), 3051 (C-H aromatic), 2981 (C-H aromatic), 2936 (C-H aliphatic), 1730 (C=O), 1492, 1463 1259, 1105, 755.

MP: 120-124 °C.

Chiral HPLC: (Chiralpak IC, 25 % IPA, 75 % hexane, 1.0 $mL.min^{-1}$, λ = 209 nm); t_R 14.3 min, 24.8 min.

Preparation of (*R*)-diisopropyl 2-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3,3(2*H*)-dicarboxylate (191c)

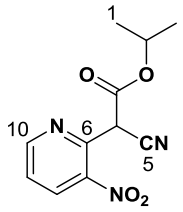


The required imine was prepared following procedure for imine **190c**. Following **General Procedure B**; reaction of crude imine (40 mg, 0.10 mmol), **88f** (5.0 mg, 9.7 μmol) and KOH (5.5 mg, 0.10 mmol) in toluene:CH_2Cl_2 (0.9:0.3 mL) with purificatiuon by flash column chromatography (diethyl ether) yielded azaindoline **191c** (29 mg, 73 %, 84 % *ee*) as a white solid with identical spectroscopic properties to **rac-191c**.

$[\alpha]_D^{22}$ +157 (*c* = 1.3, $CHCl_3$).

Chiral HPLC: (Chiralpak IC, 25 % IPA, 75 % hexane, 1.0 $mL.min^{-1}$, λ = 209 nm); t_R (major) = 14.5 min, t_R (minor) = 25.2 min.

Preparation of iso-propyl 2-cyano-2-(3-nitropyridin-2-yl)acetate (197)



According to a modified literature procedure,[93] isopropyl cyanoacetate (787 µL, 6.30 mmol) was added to a stirred solution of KO^{t}Bu (707 mg, 6.30 mmol) in anhydrous isopropyl alcohol (30 mL). The resulting suspension was stirred for 30 min and 2-chloro-3-nitropyridine (500 mg, 3.15 mmol) was added as a solid. The brown solution was refluxed for 16 h when the reaction was complete by TLC. The reaction was concentrated *in vacuo*, quenched with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (diethyl ether:40-60 petrol, 1:1 to 5:1) to yield nitropyridine **197** (362 mg, 46 %) as a deep orange oil. The product was isolated as a 3:1 mixture of keto:enol forms.

^{1}H (400 MHz, $CDCl_3$): δ 8.92 (1H, dd, *J* 4.6, 1.4, **H10**), 8.56 (1H, dd, *J* 8.3, 1.3, **H8**), 7.66 (1H, dd, *J* 8.3, 4.8 **H9**), 5.83 (1H, s, **H4**), 5.12 (1H, m, **H2**), 1.33 (6H, m, **H1**).

Enol form: δ 15.42 (1H, br s, **OH**), 8.03 (1H, dd, *J* 7.8, 1.4, **H10**), 7.86 (1H, m, **H8**), 6.74 (1H, dd, *J* 7.8, 6.2, **H9**), 5.12 (2H, m, **H2**), 1.33 (6H, m, **H1**).

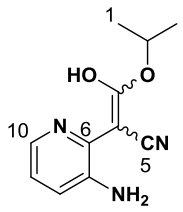
^{13}C (101 MHz, $CDCl_3$)*: 162.5 (**C3**), 153.6 (**C10**), 147.6 (**C6**), 145.4 (**C7**), 133.9 (**C8**), 125.2 (**C9**), 113.4 (**C5**), 72.5 (**C2**), 45.8 (**C4**), 21.5 (**C1**).

* Peaks from enol form also observed in spectra are not quoted as full assignment was not possible (quaternary peaks in baseline).

HRMS (ESI): found 272.0642; $[C_{11}H_{11}N_3O_4Na]^+$ ($M+Na^+$) requires 272.0642.

IR: ν_{max} (neat)/ cm^{-1}: 2984, 2938, 2202 (C≡N), 1745 (C=O), 1635, 1579, 1535 (NO_2), 1352 (NO_2), 1288, 1261, 1103.

Preparation of 2-(3-aminopyridin-2-yl)-3-hydroxy-3-isopropoxyacrylonitrile (198)



Nitropyridine **197** (328 mg, 1.32 mmol) was added to a stirred suspension of 10 % Pd/C (33 mg, 10 % wt/wt) in ethanol (15 mL). The mixture was degassed and placed under an atmosphere of hydrogen for 14 h. The reaction mixture was filtered over Celite® and concentrated *in vacuo*. The resultant oil solidified on standing to yield aminopyridine **198** (263 mg, 92 %) as a light orange solid. This was used in subsequent reactions without any further purification.

^{1}H (400 MHz, $CDCl_3$): δ 14.85 (1H, br s, **OH**), 7.20 (1H, apt t, *J* 5.8, **H10**), 6.79 (1H, d, *J* 7.8, **H8**), 6.62 (1H, apt. t, *J* 6.8, **H9**), 5.08 (1H, spt, *J* 6.8, **H2**), 4.91 (2H, br s, **NH_2**), 1.32 (6H, d, *J* 6.3, **H1**).

^{13}C (101 MHz, $CDCl_3$): 171.5 (**C3**), 144.1 (**C6**), 138.4 (**C7**), 123.6 (**C10**), 122.7 (**C5**), 120.4 (**C9**), 114.7 (**C8**), 67.8 (**C2**), 58.0 (**C4**), 22.1 (**C1**).

HRMS (ESI): found 242.0902; $[C_{11}H_{13}N_3O_4Na]^+$ ($M+Na^+$) requires 292.0900.

IR: ν_{max} (neat)/ cm^{-1}: 3137 (NH_2), 2985, 2939, 2209 (C≡N), 1739, 1615, 1582, 1542, 1281, 1104.

MP: 116-122 °C

Preparation of 2-fluoro-3-nitropyridine (203)

According to a modified literature procedure,[95] KF (1.10 g, 18.9 mmol), was added to a solution of 2-chloro-3-nitropyridine (1.50 g, 9.5 mmol) in DMF (5 mL) and heated to 120 °C. The mixture was stirred for 16 h then cooled, diluted with diethyl ether (10 mL) and quenched with water (10 mL). The organic layer was separated, then the aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic extracts washed with water (3 × 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. This yielded a dark orange oil which was purified by kugelrohr distillation to yield fluoropyridine **203** as a yellow oil (341 mg, 25 % yield, 92 % purity, remainder starting material).

^{1}H (400 MHz, $CDCl_3$): δ 8.58-8.49 (2H, m, **H3** and **H5**), 7.49-7.40 (1H, m, **H4**).

^{13}C* (101 MHz, $CDCl_3$): δ 152.5 (d, *J* 15 **C5**), 136.8 (**C4**), 122.2 (d, *J* 6, **C3**).

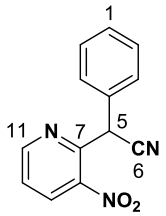
*Quaternary carbons not visible.

^{19}F (377 MHz, $CDCl_3$): δ -67.3 (**Ar-F**).

BP: 110 °C at 10 mm Hg.

Data in accordance with literature.[153]

Preparation of 2-(3-nitropyridin-2-yl)-2-phenylacetonitrile (204)



Method A: According to a modified literature procedure,[94] a solution of fluoropyridine **203** (176 mg, 1.1 mmol) and phenylacetonitrile (154 µL, 1.33 mmol) in THF (15 mL) was cooled to -15 °C. KHMDS (0.5 M in toluene, 4.88 mL, 2.44 mmol) was added and the reaction mixture was allowed to warm to RT, stirred for 1 h, quenched with saturated aqueous ammonium chloride solution (10 mL) and then extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:ethyl acetate, 5:1) to yield nitropyridine **204** (97 mg, 36 %) as a yellow solid.

Method B: According to a modified literature procedure,[100] tris(2-(2-methoxyethoxy)ethyl)amine (6.05 mL, 18.9 mmol) and phenylacetonitrile (2.40 mL, 20.8 mmol) were added to a stirred suspension of KOH (2.24 g, 75.6 mmol) in THF (50 mL). The mixture was then heated to 50 °C and stirred for 10 min. A solution of 2-chloro-3-nitropyridine (3.00 g, 18.9 mmol) in THF (15 mL) was added over 1 h *via* syringe pump and the mixture stirred for a further 15 minutes, when complete consumption of the starting material was observed by TLC. The reaction was cooled to RT, quenched with saturated aqueous ammonium chloride solution (80 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with pH 6 phosphate buffer (2 × 250 mL) to remove TDA-1. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column

chromatography (40-60 petrol:diethyl ether, 3:1 to 0:1) to yield nitropyridine **204** (3.01 g, 67 %) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.96 (1H, dd, *J* 4.8, 1.5, **H11**), 8.40 (1H, dd, *J* 8.3, 1.5, **H9**), 7.55 (1H, dd, *J* 8.2, 4.6, **H10**), 7.48 (2H, dd, *J* 8.1, 1.8, **H3**), 7.40-7.30 (3H, m, **H1** and **H2**), 6.33 (1H, s, **H5**).

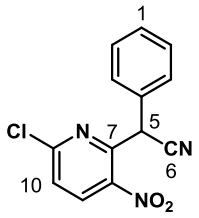
^{13}C (101 MHz, $CDCl_3$): δ 153.7 (**C11**), 149.6 (**C7**), 143.9 (**C8**), 133.9 (**C9**), 133.3 (**C4**), 129.3 (**C2**), 128.9 (**C1**), 128.4 (**C3**), 124.2 (**C10**), 118.1 (**C6**), 42.0 (**C5**).

HRMS (ESI): found 262.0583; $[C_{13}H_9N_3O_2Na]^+$ $(M + Na)^+$ requires 262.0587.

IR: ν_{max} (neat)/cm^{-1}: 3082 (C-H aromatic), 2248 (C≡N), 1594 (C=C aromatic), 1568, 1528 (NO_2), 1491, 1348 (NO_2), 700.

MP: 89-92 °C.

Preparation of 2-(6-chloro-3-nitropyridin-2-yl)-2-phenylacetonitrile (206a)



Method A: According to a modified literature procedure,[97b] a solution of potassium *tert*-butoxide (778 mg, 6.95 mmol) was dissolved in THF (15 mL) and cooled to -50 °C. Phenylacetonitrile (698 µL, 6.31 mmol) and 2-chloro-5-nitropyridine (1.00 g, 6.31 mmol) were then added and the reaction mixture stirred at -50 °C for 2 h. A solution of DDQ (1.72 g, 7.58 mmol) in DMF (3 mL) was added and the mixture stirred for 5 min. The crude reaction mixture was filtered through Celite® using CH_2Cl_2 as the eluent. The filtered reaction mixture was diluted with further CH_2Cl_2 (25 mL) and quenched with water (20 mL).The organic layer was separated, then the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 20:1 to 1:1) to yield nitropyridine **206a** (283 mg, 13 %).

Method B: According to a modified literature procedure,[97b] a solution of 50 % $NaOH_{(aq)}$ (82µL, 1.56 mmol) was added to a stirred suspension of TBAHS (530 mg, 1.56 mmol), 2,6-dichloro-3-nitropyridine (300 mg, 1.65 mmol) and phenylacetonitrile (186 µL, 1.56 mmol) in toluene (5 mL). The mixture was allowed to stir at RT for 6 h, then quenched with saturated aqueous ammonium chloride solution (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 2:1) to yield nitropyridine **206a** (114 mg, 27 %).

^{1}H (400 MHz, DMSO-d_6): δ 7.76 (1H, d, *J* 8.6, **H9**), 7.06 (1H, d, *J* 8.6, **H10**), 6.66-6.46 (5H, m, **H1**, **H2** and **H3**), 5.58 (1H, s, **H5**).

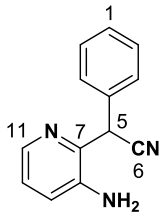
^{13}C (101 MHz, DMSO-d_6): δ 154.0 (**C11**), 150.3 (**C7**), 144.7 (**C8**), 138.8 (**C9**), 134.5 (**C4**), 130.0 (**C2**), 129.5 (**C1**), 128.1 (**C3**), 126.7 (**C10**), 119.4 (**C6**), 42.2 (**C5**).

HRMS (ESI): found 296.0198; $[C_{13}H_8ClN_3O_2Na]^+$ $(M + Na)^+$ requires 296.0197.

IR: ν_{max} (neat)/cm^{-1}: 3078 (C-H aromatic), 2249 (C≡N), 1581 (C=C aromatic), 1565, 1525 (NO_2), 1370 (NO_2), 1182, 1158, 871, 717, 695.

MP: 87-90 °C.

Preparation of 2-(3-aminopyridin-2-yl)-2-phenylacetonitrile (214)



According to a modified literature procedure,[92] NH_4Cl (6.33 g, 118 mmol) and zinc dust (5.19 g, 79.4 mmol) were added to a solution of nitropyridine **204** (1.88 g, 7.9 mmol) in acetone:water (50:10 mL). The mixture was stirred for 20 min, filtered through Celite®, extracted with CH_2Cl_2 (3 × 80 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was then passed through a plug of silica using CH_2Cl_2 as an eluent. This solution was concentrated *in vacuo* to yield aminopyridine **214** (1.49 g, 91 %) as a pale orange solid. NB: Product is unstable in air and must be stored under argon in freezer.

^{1}H (400 MHz, $CDCl_3$): δ 8.12 (1H, dd, *J* 4.7, 1.4, **H11**), 7.29-7.49 (5H, m, **H1**, **H2**, and **H3**) 7.13 (1H, dd, *J* 8.1, 4.8, **H10**), 6.99 (1H, dd, *J* 8.1, 1.3, **H9**), 5.44 (1H, s, **H5**), 3.58 (2H, br. s, **NH_2**).

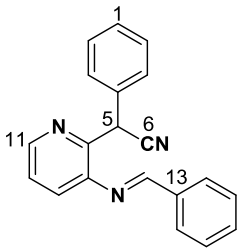
^{13}C (101 MHz, $CDCl_3$): δ 140.1 (**C11**), 140.1 and 139.7 (**C7** and **C8**) 132.9 (**C4**), 129.4 (**C3**), 128.9 (**C1**), 127.5 (**C2**), 124.6 and 124.5 (**C9** and **C10**), 118.1 (**C6**), 42.8 (**C5**).

HRMS (ESI): found 232.0841; $[C_{13}H_{11}N_3Na]^+$ $(M + Na)^+$ requires 232.0845.

IR: ν_{max} (neat)/cm^{-1}: 3362 (N-H), 3062 (C-H aromatic), 2247 (C≡N), 1633 (N-H), 1584 (C=C aromatic), 1452, 648.

MP: 117-121 °C.

Preparation of (*E*)-2-(3-(benzylideneamino)pyridin-2-yl)-2-phenylacetonitrile (215)



Freshly distilled benzaldehyde (180 µL, 1.50 mmol) was added to a solution of aminopyridine **214** (235 mg, 1.12 mmol) in toluene (25 mL) containing anhydrous $MgSO_4$ (270 mg, 2.24 mmol) at RT. The suspension was stirred for 24 h and then the reaction mixture was filtered and concentrated *in vacuo*. The crude product was washed with diethyl ether to yield imine **215** (200 mg, 60 %) as an orange solid. Product was contaminated with trace benzaldehyde.

^{1}H (400 MHz, $CDCl_3$): δ 8.54 (1H, d, *J* 4.3, **H11**), 8.37 (1H, s, **H12**), 7.95 (2H, d, *J* 6.8, **H14**), 7.61-7.46 (5H, m, **H2**, **H15** and **H16**), 7.39 (1H, d, *J*, 8.1, **H9**), 7.35-7.17 (4H, m, **H1**, **H3** and **H10**), 6.07 (1H, s, **H5**).

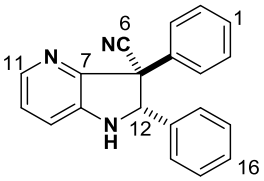
^{13}C (101 MHz, $CDCl_3$): δ 162.6 (**C12**), 150.0 (**C7**), 147.5 (**C11**), 144.4 (**C8**), 135.5 and 135.1 (**C4** and **C13**), 132.4 (**C16**), 129.2 (**C14**), 129.1 (**C15**), 129.0, 128.9 and 128.0 (**C1**, **C2** and **C3**), 125.7 (**C9**), 124.3 (**C10**), 119.5 (**C6**), 40.7 (**C5**).

HRMS (ESI): found 320.1161; $[C_{20}H_{15}N_3Na]^+$ $(M + Na)^+$ requires 320.1156.

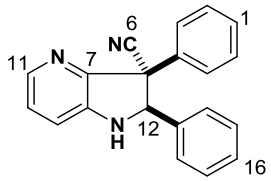
IR: ν_{max} (neat)/cm^{-1}: 3061 (C-H aromatic), 2246 (C≡N), 1626 (C=N), 1577 (C=C aromatic), 1453, 1434, 754, 694.

MP (diethyl ether): 116-120 °C.

Preparation of (±)-2,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carbonitrile (216)



216a



216b

$CsOH{\cdot}H_2O$ (113 mg, 0.67 mmol) was added to a stirred solution of imine **215** (200 mg, 0.67 mmol) in toluene (10 mL). The reaction mixture was stirred for 16 h at RT and quenched with saturated aqueous ammonium chloride solution (5 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The diastereomeric products (*dr* 2.7:1.0 **216a**:**216b** by crude ^{1}H NMR) were separated by flash column chromatography (40-60 petrol:ethyl acetate, 10:1 to 1:1) to yield azaindoline **216a** 72 mg (36 %) as a pale yellow solid and azaindoline **206b** 48 mg (24 %) as a pale yellow solid. Single crystals of each isomer for X-ray analysis were obtained by recrystallization by vapour diffusion using ethyl acetate and pentane.

216a

^{1}H (500 MHz, DMSO-d_6): δ 7.81 (1H, dd, *J* 4.3, 2.1, **H11**), 7.51-7.43 (3H, m, **H14** and **H16**), 7.38-7.37 (3H, m, **H1** and **H3**), 7.33-7.31 (2H, m, **H15**), 7.26-7.21 (4H, m, **H2**, **H9** and **H10**), 6.95 (1H, d, *J* 2.2, **H12**), 5.21 (1H, d, *J* 2.2, **NH**).

^{13}C (126 MHz, DMSO-d_6): δ 148.1 (**C7**), 146.2 (**C8**), 140.6 (**C11**), 138.1 and 138.0 (**C4** and **C13**), 129.8, 129.6, 129.3, 129.2, 128.3 and 128.1 (6 × **CH_{Ar}**), 125.7 (**C10**), 119.1 (**C6**), 117.3 (**C9**), 75.2 (**C5**), 59.3 (**C12**).

HRMS (ESI): found 320.1154; $[C_{20}H_{15}N_3Na]^+$ $(M + Na)^+$ requires 320.1158.

IR: ν_{max} (neat)/cm^{-1}: 3359 (N-H), 3062 (C-H aromatic), 2982, 2244 (C≡N), 1723, 1582 (C=C aromatic), 1437, 1267, 1101, 730, 700.

MP*: 138-141 °C.

216b

^{1}H (500 MHz, $CDCl_3$): δ 8.16 (1H, dd, *J* 4.6, 1.5, **H11**), 7.24-7.12 (7H, m, **H9**, **H10** and 5 × $\mathbf{H_{Ar}}$), 7.11-7.00 (3H, m, 3 × $\mathbf{H_{Ar}}$), 6.70 (2H, d, *J* 7.3, 2 × $\mathbf{H_{Ar}}$), 5.63 (1H, d, *J* 2.8, **H12**), 4.30 (1H, br. s, **NH**).

^{13}C (126 MHz, $CDCl_3$): δ 148.8 (**C7**), 144.5 (**C8**), 142.1 (**C11**), 135.1 (**C4**), 133.1 (**C13**), 129.0, 128.6, 128.1, 128.0, 127.7 and 127.4 (6 × $\mathbf{CH_{Ar}}$), 124.5 (**C10**), 120.5 (**C6**), 117.3 (**C9**), 73.2 (**C5**) 56.3 (**C12**).

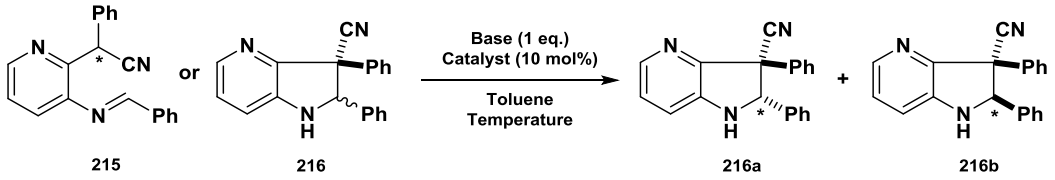
HRMS (ESI): found 320.1148; $[C_{20}H_{15}N_3Na]^+$ (M + Na^+) requires 320.1158.

IR: ν_{max} (neat)/cm^{-1}: 3354 (N-H), 3063 (C-H aromatic), 3030 (C-H aromatic), 2243 (C≡N), 1719, 1583 (C=C aromatic), 1438, 1105, 791, 698.

MP*: 176-178 °C.

*Melting points measured prior to recrystallization.

Equilibration Experiments



215 216 216a 216b

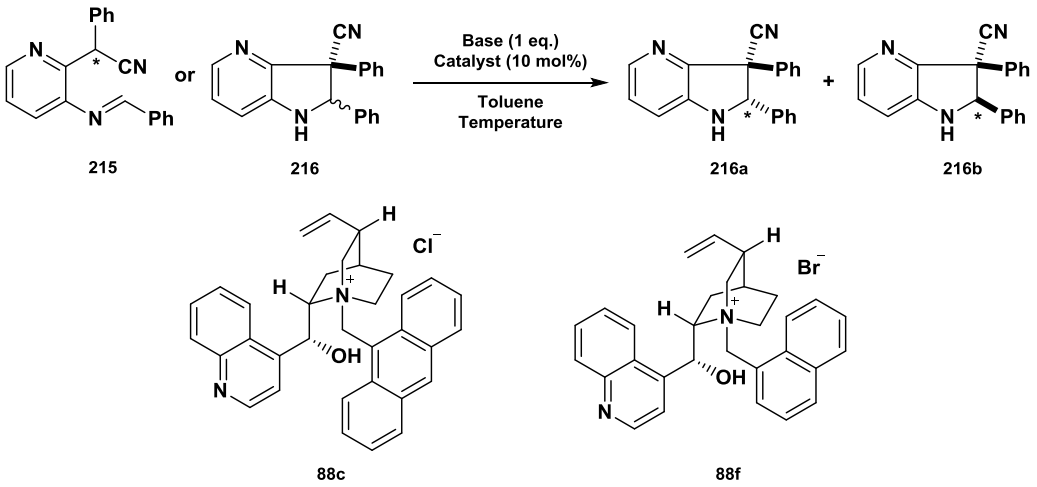
In all experiments, solid base (1 eq.) was added to a stirred mixture of imine **215** or azaindoline **216** (as a single diastereoisomer or mixture of diastereoisomers) and phase transfer catalyst (1 eq.) in toluene (25 mg mL^{-1}) at the required temperature. At various points aliquots were taken and worked up by quenching into NH_4Cl, extraction with diethyl ether and filtration through a pipette containing a short plug of silica. After concentrating this reaction sample *in vacuo* the diastereomeric ratio was measured by integration of the crude ^1H NMR spectra (**216b**: H* - δ = 5.64, **216a**: H* - δ = 5.14). On completion of the reaction it was quenched with NH_4Cl, extracted with CH_2Cl_2 and filtered through a pipette containing a short plug of silica. The final *dr* was measured in the same fashion. In some reactions imine **215** (H* - δ = 6.07) was observed.

Tetrabutylammonium bisulfate catalyzed reaction

All reactions used $CsOH{\cdot}H_2O$ as the base.

Starting material	Temperature (° C)	Time (h)	*Anti*-Ph **216a**:*Syn*-Ph **216b**	Imine **215** (%)
Imine **215**	RT	24	**2.7**:1.0	0
Syn-Ph **216b**	RT	24	**2.1**:1.0	0
Anti-Ph **216a**	RT	24	**2.6**:1.0	0
Imine **215**	-30	24	**1.3:**1.0	63
		66	**1.7**:1.0	4
Syn-Ph **216b**	-30	24	1.0:**1.2**	16
		66	1.0:**1.8**	4
Anti-Ph **216a**	-30	24	**10.2**:1.0	0
		66	**6.8**:1.0	0

Asymmetric reactions



88c 88f

Base: KOH, catalyst: N-anthracenylmethyl cinchonidinium chloride (**88c**)

Starting material	Temperature (° C)	Time (h)	*Anti*-Ph **216a**:*Syn*-Ph **216b**	Imine **215** (%)
Imine **215**	RT	2	-	100
		3	1.0:**3.5**	66
		6	1.0:**1.3**	0
		8	**1.2**:1.0	0
		24	**1.5**:1.0	0
Imine **215**	-30	8	-	100
		24	1.0:**3.8**	0
		144	1.0:**3.9**	0
1:**3.4** *Anti*-Ph **216a**:*Syn*-Ph **216b**	-30	22	1:**3.3**	0
		168	1:**3.3**	0

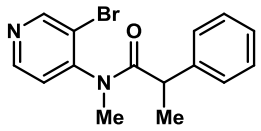
Base: KOH, catalyst: N-2-naphthylmethyl cinchonidinium bromide (**88f**)

Starting material	Temperature (° C)	Time (h)	1:**3.4** *Anti*-Ph **216a**:*Syn*-Ph **216b**	Imine (%)
Imine **215**	-30	24	1.0:**1.5**	0
1:**3.4** *Anti*-Ph **216a**:*Syn*-Ph **216b**	-30	42	1.0:**2.6**	0

Results show that equilibration occurs at -30 °C but is slow to reach the equilibration position found when reaction took place with imine. This suggests that while equilibration occurs with asymmetric phase transfer catalysts and will have an effect on diastereoselectivity that this effect is small in comparison to the inherent selectivity of the cyclization.

5.2.2. Cation-directed asymmetric Truce-Smiles rearrangement

Preparation of *N*-(3-bromopyridin-4-yl)-*N*-methyl-2-phenylpropanamide (284)



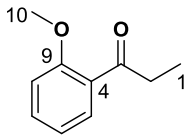
According to a literature procedure,[118] $SOCl_2$ (251 µL, 3.45 mmol) was added to 2-phenylpropionic acid (236 µL, 1.73 mmol) and the mixture heated at reflux for 3 h. The mixture was cooled to RT and the remaining $SOCl_2$ removed in *vacuo*. The resulting crude acid chloride was dissolved in CH_2Cl_2 (2 mL) and then added to a solution of 4-amino-3-bromopyridine (300 mg, 1.73 mmol) and triethylamine (482 µL, 3.46 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred for 16 h at RT, passed through a small pad of silica eluting with CH_2Cl_2, and concentrated *in vacuo*. The crude amide was dissolved in THF (6 mL) and added to a suspension of NaH (60 % dispersed in mineral oil, 76 mg, 1.90 mmol) in THF (6 mL) at 0 °C. The suspension was stirred for 1 h then cooled to 0 °C when MeI (118 µL, 1.90 mmol) was added. The reaction mixture was stirred for 24 h at RT, quenched with brine (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:ethyl acetate, 2:1) to yield amide **284** (188 mg, 34 % over 3 steps) as a yellow oil. The amide exists as a mixture of rotamers and specific assignments have not been made.

^{1}H (400 MHz, $CDCl_3$): δ 8.90 (1H, br s), 8.71 (0.3H, s,), 8.66 (0.4H, d, *J* 5.0) 8.37 (1H, d *J* 5.0), 7.33 (0.8H, d, *J* 5.1), 7.26-7.17 (4.3H, m), 6.96-6.91 (2.9H, m), 6.60 (0.9H, d, *J* 5.1), 3.53 (0.5H, q, *J* 7.1), 3.28 (1.2H, q *J* 6.7), 3.21-3.13 (4.7H, m), 1.49-1.39 (5.2H, m).

LRMS (ESI): found 319.1; $[C_{15}H_{16}BrN_2O]^+$ $(M + H)^+$ requires 319.0.

Data in accordance with literature.[118]

Preparation of 1-(2-methoxyphenyl)propan-1-one (308)



According to a literature procedure,[123] 2'-hydroxypropiophenone (4.55 mL, 27.7 mmol), Cs_2CO_3 (11.0 g, 33.8 mmol) and MeI (4.10 mL, 65.8 mmol) in acetone (100 mL) were stirred in a sealed flask at RT for 16 h. The reaction mixture was concentrated *in vacuo*, partitioned between ethyl acetate (50 mL) and water (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:ethyl acetate, 30:1 to 5:1) to yield aryl methyl ether **308** (4.39 g, 96 %) as an orange oil.

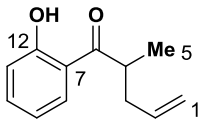
^{1}H (400 MHz, $CDCl_3$): δ 7.69 (1H, dd, *J* 7.7, 1.3, **H5**), 7.51-7.40 (1H, m, **H7**), 7.05-6.91 (2H, m, **H6** and **H8**), 3.90 (3H, s, **H10**), 3.00 (2H, q, *J* 7.2, **H2**), 1.17 (3H, t, *J* 7.2, **H1**).

^{13}C (101 MHz, $CDCl_3$): δ 203.5 (**C3**), 158.5 (**C9**), 133.1 (**C7**) 130.2 (**C5**), 128.5 (**C4**), 120.6 (**C6**), 111.5 (**C8**), 55.6 (**C10**), 37.0 (**C2**), 8.4 (**C1**).

LRMS (ESI): found 165.1; $[C_{10}H_{13}O_2]^+$ $(M + H)^+$ requires 165.1.

Data in accordance with literature.[154]

Preparation of 1-(2-hydroxyphenyl)-2-methylpent-4-en-1-one (311)



According to a literature procedure,[124] a Schlenk flask containing $Pd(OAc)_2$ (38 mg, 0.17 mmol) and PPh_3 (87 mg, 0.33 mmol) was placed under an argon atmosphere. THF (15 mL), allyl alcohol (272 µL, 4.00 mmol), 2'-hydroxypropiophenone (500 µL, 3.33 mmol) and BEt_3 (1 M in hexane, 8.00 mL, 8 mmol) were added sequentially and the suspension stirred for 4 h at RT. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with 1 M HCl (20 mL) and brine (20 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 15:1) to yield allylated product **311** (630 mg, 99 %) as a yellow oil.

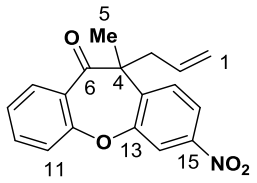
^{1}H (400 MHz, $CDCl_3$): δ 12.52 (0.3 H, s, **OH**), 7.80 (1H, dd, *J* 8.1, 1.7, **H8**), 7.49 (1H, ddd, *J* 8.5, 7.0, 1.6, **H10**), 7.01 (1H, dd, *J* 8.3, 1.0, **H11**), 6.92 (1H, ddd, *J* 8.2, 7.2, 1.2, **H9**), 5.86-5.71 (1H, m, **H2**), 5.14-4.99 (2H, m, **H1**), 3.66-3.53 (1H, m, **H4**), 2.64-2.52 (1H m, **H3**), 2.30-2.19 (1H, m, **H3'**), 1.25 (3H, d, *J* 6.9, **H5**).

^{13}C (101 MHz, $CDCl_3$): δ 209.9 (**C6**), 163.2 (**C12**), 136.4 (**C10**) 135.4 (**C2**), 129.8 (**C8**), 118.9 (**C9**), 118.8 (**C11**), 118.5 (**C7**), 117.1 (**C1**), 39.9 (**C4**), 37.7 (**C3**), 17.3 (**C5**).

HRMS (ESI): found 213.0888; $[C_{12}H_{14}O_2Na]^+$ $(M + Na)^+$ requires 213.0886.

IR: ν_{max} (neat)/cm^{-1}: 2976, 1634 (C=O), 1485, 1445, 1283, 1160, 977, 752.

Preparation of 2-(2,4-dinitrophenyl)-1-(2-hydroxyphenyl)-2-methylpent-4-en-1-one (317)



K_2CO_3 (144 mg, 1.06 mmol)) was added to a stirred solution of phenol **311** (100 mg, 0.53 mmol) and 2,4-dinitrofluorobenzene (96 mg, 0.53 mmol) in DMSO (1.0 mL). The mixture was heated to 40 °C and stirred for 16 h. The reaction mixture was allowed to cool to RT, then quenched with 1 M HCl (1.0 mL), and extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was adsorbed onto silica then purified by flash column chromatography (15:1 40-60 petrol:diethyl ether) to yield dihydro oxepin **317** (68 mg, 36 %) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 8.06 (1H, d, *J* 2.5, **H14**), 8.01-7.96 (2H, m, **H8** and **H16**), 7.53 (1H, ddd, *J* 8.2, 7,2, 2.0, **H10**), 7.46 (1H, d, *J* 8.8, **H17**), 7.32 (1H, dd, *J* 8.1, 1.0, **H11**), 7.20-7.15 (1H, m, **H9**), 5.49-5.29 (1H, m, **H2**), 4.92-4.84 (2H, m, **H1**), 2.92 (1H, dd, *J* 13.9, 7.3, **H3**), 2.62 (1H, dd, *J* 13.7, 7.3 **H3'**), 1.65 (3H, s, **H5**).

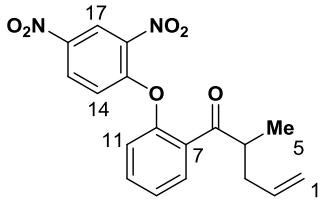
^{13}C (125 MHz, $CDCl_3$): δ 193.1 (**C6**), 157.0 (**C11**), 156.5 (**C14**) 147.6 (**C5**), 138.9 (**C18**), 135.1 (**C10**), 132.5 (**C2**), 131.8 (**C16**), 129.2 (**C17**), 124.7 (**C7**), 124.4 (**C9**), 120.8 (**C11**), 120.5 (**C8**), 118.4 (**C1**), 117.3 (**C14**), 55.7 (**C4**), 39.2 (**C3**), 20.6 (**C5**).

HRMS (FI): found 309.0973; $[C_{18}H_{56}NO_4\bullet]^+$ $(M\bullet)^+$ requires 309.1001.

IR: ν_{max} (neat)/cm^{-1}: 3079 (C-H aromatic), 2985, 1678 (C=O), 1640 (C=C), 1523 (NO_2), 1472, 1446, 1407 1347 (NO_2), 1288, 1230, 756.

MP: 121-122 °C

Preparation of 1-(2-(2,4-dinitrophenoxy)phenyl)-2-methylpent-4-en-1-one (326)



Aqueous KOH (50 % w/w, 8 µL, 0.22 mmol) was added to a stirred solution of phenol **311** (20 mg, 0.11 mmol) and TBAHS (6.5 mg, 0.02 mmol) in toluene (0.5 mL). After 15 min 2,4-dinitrofluorobenzene (20 mg, 0.11 mmol) was added and the mixture was heated to 40 °C and stirred for 5 h. The reaction mixture was quenched with 1M HCl (0.5 mL) and extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 5:1) to yield aryl ether **326** (9 mg, 23 %) as a yellow oil.

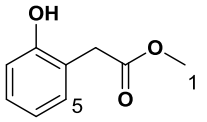
^{1}H (500 MHz, $CDCl_3$): δ 8.81 (1H, d, *J* 2.7, **H17**), 8.24 (1H, dd, *J* 9.3, 2.7, **H15**), 7.64 (1H, dd, *J* 7.7, 1.6, **H8**), 7.53 (1H, apt. td, *J* 7.7, 1.7, **H10**), 7.37 (1H, apt. td, *J* 7.6, 1.1, **H9**), 7.07 (1H, dd, *J* 8.1, 0.9, **H11**), 6.84 (1H, d, *J* 9.3, **H14**), 5.60 (1H, ddt, *J*, 17.1, 10.0, 7.1, **H2**), 5.01-4.85 (2H, m, **H1**), 3.35-3.16 (1H, m, **H4**), 2.13-2.29 (1H, m, **H3**), 2.14-1.95 (1H, m, **H3'**), 1.05 (3H, d, *J* 6.9, **H5**).

^{13}C (125 MHz, $CDCl_3$): δ 204.5 (**C6**), 156.3 (**C13**), 150.8 (**C12**) 141.5 (**C16**), 139.0 (**C18**), 135.1 (**C2**), 133.4 (**C10**), 132.8 (**C7**), 130.2 (**C8**), 128.9 (**C15**), 127.0 (**C9**), 122.2 (**C17**), 121.1 (**C11**), 118.3 (**C14**), 117.2 (**C1**), 44.7 (**C4**), 37.1 (**C3**), 16.1 (**C5**).

HRMS (ESI): found 379.0900; $[C_{18}H_{16}N_2O_6Na]^+$ $(M + Na)^+$ requires 379.0901.

IR: ν_{max} (neat)/cm^{-1}: 3081 (C-H aromatic) 2361, 2341, 1691 (C=O), 1640 (C=C), 1574 (C=C), 1535 (NO_2), 1344 (NO_2), 1268 (C-O ether).

Preparation of methyl 2-(2-hydroxyphenyl)acetate (331)



According to a literature procedure,[128] a solution of HCl in methanol was prepared by the addition of acetyl chloride (5 mL) to methanol (50 mL). 2-Hydroxyphenylacetic acid (10.0 g, 65.7 mmol) was added, the mixture was stirred for 3 h at RT and then left to stand for 15 h. The reaction mixture was concentrated *in vacuo*, dissolved in ether (50 mL) and saturated aqueous sodium bicarbonate was added until effervescence ceased. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated in *vacuo*. The crude product was purified by recrystallization from diethyl ether/40-60 petrol (2 crops) to yield ester **331** (7.72 g, 71 %) as a white solid.

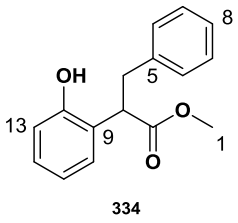
^{1}H (400 MHz, $CDCl_3$): δ 7.38 (1H, s, **OH**), 7.21 (1H, apt. td, *J* 7.7, 1.5, **H7**), 7.11 (1H, dd, *J* 7.5, 1.3, **H5**), 6.95 (1H, dd, *J* 8.1, 1.0, **H8**), 6.90 (1H, apt. td, *J* 7.5, 1.1, **H6**), 3.76 (3H, s, **H1**), 3.70 (2H, s, **H3**).

^{13}C (101 MHz, $CDCl_3$): δ 174.4 (**C2**), 155.2 (**C9**), 131.0 (**C5**), 129.3 (**C7**), 121.0 (**C6**), 120.5 (**C4**), 117.7 (**C8**), 52.8 (**C3**), 37.7 (**C1**).

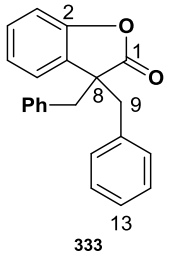
LRMS (ESI): found 167.1; $[C_9H_{11}O_3]^+$ $(M + H)^+$ requires 167.1.

Data in accordance with literature.[155]

Preparation of methyl 2-(2-hydroxyphenyl)-3-phenylpropanoate (334) and 3,3-dibenzylbenzofuran-2(3*H*)-one (333)



334



333

^{n}BuLi (1.6 M in hexanes, 16.6 mL, 26.6 mmol) was added to a stirred solution of diisopropylamine (4.05 mL, 28.9 mmol) in THF (25 mL) at -78 °C. The mixture was stirred for 15 min then allowed to warm to 0 °C. A solution of phenol **331** (2.0 g, 12.0 mmol) in THF (5 mL) was added and the mixture was stirred at 0 °C for 1 h. Benzyl bromide (1.58 mL, 13.3 mmol) was added and the mixture was allowed to warm to RT and then stirred for 16 h. The reaction mixture was quenched with 1 M HCl (25 mL), stirred for 15 min and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was adsorbed onto silica and purified by flash column chromatography (40-60 petrol:ethyl acetate, 12:1) to yield dibenzylated lactone **333** (602 mg, 16 %) as a white solid, and phenol **334** as a yellow oil, contaminated by lactone **333**. The oil was triturated thrice with ether to remove the lactone, affording pure phenol **334** (448 mg, 15 %).

334

^{1}H (400 MHz, $CDCl_3$): δ 7.90 (1H, s, **OH**), 7.28-7.10 (6H, m, **ArCH**, **H12**), 7.01 (1H, dd, *J* 7.7, 1.6, **H10**), 6.94 (1H, dd, *J* 8.1, 1.2, **H13**), 6.84 (1H, apt. td, *J* 7.5, 1.2, **H11**), 3.99 (1H, dd, *J* 9.1, 6.9, **H3**), 3.64 (3H, s, **H1**), 3.47 (1H, dd, *J* 13.7, 9.1, **H4**), 3.25 (1H, dd, *J* 13.6, 7.0 **H4'**).

^{13}C (101 MHz, $CDCl_3$): δ 176.8 (**C2**), 154.9 (**C10**), 138.6 (**C5**), 130.2 (**C14**), 129.2 (**C12**), 128.9 (**C6**), 128.4 (**C7**), 126.6 (**C8**), 123.7 (**C9**), 120.8 (**C13**), 118.1 (**C11**), 52.7 (**C1**), 51.8 (**C3**), 37.5 (**C4**).

HRMS (ESI): found 279.0994; $[C_{16}H_{16}O_3Na]^+$ $(M + Na)^+$ requires 279.0992.

IR: ν_{max} (neat)/cm^{-1}: 3371 (br, O-H) 3063 (C-H aromatic), 1705 (C=O), 1507 (C=C), 1231, 752, 700.

333

^{1}H (400 MHz, $CDCl_3$): δ 7.24-7.03 (9H, m, **ArCH**), 7.00-6.84 (4H, m, **ArCH**), 6.76-6.62 (1H, m, **H3**), 3.40 (2H, d, *J* 13.3, **H9**), 3.25 (2H, d, *J* 13.3, **H9'**).

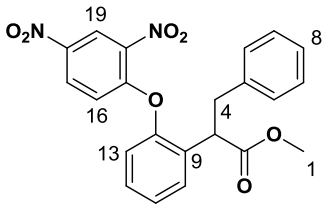
^{13}C (101 MHz, $CDCl_3$): δ 178.8 (**C1**), 152.9 (**C2**), 135.0 (**C10**), 130.1 (**C11**), 128.8 (**C6**), 128.4 (**C7**), 128.1 (**C12**), 124.7 (**C4**), 127.0 (**C13**), 123.6 (**C5**), 110.5 (**C3**), 55.9 (**C8**), 44.1 (**C9**).

HRMS (ESI): found 337.1196; $[C_{22}H_{18}O_2Na]^+$ $(M + Na)^+$ requires 337.1199.

IR: ν_{max} (neat)/cm^{-1}: 3029 (C-H aromatic) 2360, 1792 (C=O), 1462 (C=C), 881, 758, 699.

MP: Decomposed at 172-174 °C.

Preparation of methyl 2-(2-(2,4-dinitrophenoxy)phenyl)-3-phenylpropanoate (335)



According to a modified literature procedure,[129] NEt_3 (230 µL, 1.65 mmol) was added to a stirred solution of phenol **334** (384 mg, 1.50 mmol) and 2,4-dinitrofluorobenzene (335 mg, 1.80 mmol) in acetone (10 mL). The mixture was heated to reflux for 3 h, allowed to cool to RT, and then concentrated *in vacuo*. The residue was treated with 1 M HCl (10 mL) and extracted with diethyl ether (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was adsorbed onto silica and purified by flash column chromatography (40-60 petrol:ethyl acetate, 10:1) to yield aryl ether **335** (417 mg, 66 %) as a yellow oil.

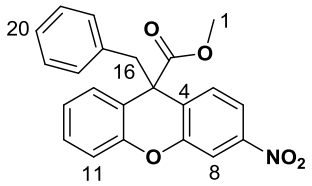
^{1}H (400 MHz, $CDCl_3$): δ 8.82 (1H, d, *J* 2.7, **H19**), 8.14 (1H, dd, *J* 9.3, 2.7, **H17**), 7.65-7.52 (1H, m, **H11**), 7.39-7.31 (2H, m, **H10** and **H12**), 7.15-7.09 (3H, m, **H7** and **H8**), 7.02 (2H, dd, *J* 6.7, 2.8, **H6**), 6.99-6.93 (1H, m, **H13**), 6.56 (1H, d, *J*, 9.3, **H16**), 4.23 (1H, dd, *J* 8.8, 6.9, **H3**), 3.55 (3H, s, **H1**), 3.42 (1H, dd, *J* 13.7, 6.9, **H4**), 3.08 (1H, dd, *J* 13.6, 8.9, **H4'**).

^{13}C (101 MHz, $CDCl_3$): δ 173.0 (**C2**), 155.6 (**C15**) 151.0 (**C14**), 141.5 (**C18**), 139.2 (**C20**), 138.4 (**C5**), 131.1 (**C9**), 130.2 (**C11**), 129.3 (**C12**), 129.1 (**C6**), 128.6 (**C17**), 128.4 (**C7**), 127.0 (**C10**), 126.5 (**C8**), 121.9 (**C19**), 120.7 (**C13**), 117.8 (**C16**), 52.2 (**C1**), 46.2 (**C3**), 38.7 (**C4**).

HRMS (ESI): found 445.1003; $[C_{22}H_{18}N_2O_7Na]^+$ $(M + Na)^+$ requires 445.1006.

IR: ν_{max} (neat)/cm^{-1}: 3111 (C-H aromatic), 1734 (C=O), 1608 (C=C), 1580 (C=C), 1537 (NO_2), 1343 (NO_2), 1266 (C-O ether), 741.

Preparation of isopropyl 9-benzyl-3-nitro-9*H*-xanthene-9-carboxylate (338)



Powdered KOH (20 mg, 0.35 mmol) was added to a stirred solution of Truce-Smiles precursor **335** (30 mg, 0.09 mmol) and TBAHS (5 mg, 0.014 mmol) in toluene (1.5 mL). The mixture was heated to 40 °C for 16 h, then allowed to cool to RT, quenched with 1M HCl (1 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:ethyl acetate, 8:1) to yield xanthene **338** (3 mg, 11 %) as a yellow gum.

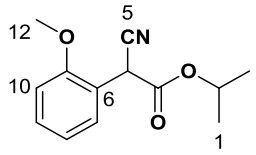
^{1}H (400 MHz, $CDCl_3$): δ 7.96 (1H, dd, *J* 8.6, 2.5, **H6**), 7.72 (1H, d, *J* 2.5, **H8**), 7.38 (1H, d, *J*, 8.6, **H5**), 7.33-7.28 (2H, m, **H12** and **H14**), 7.20 (1H, td, *J* 7.6, 1.2, **H13**), 7.05 (1H, tt, *J* 7.6, 1.2, **H20**), 6.94-6.87 (3H, m, **H11** and **H19**), 6.29-6.13 (2H, m, **H18**), 3.75 (3H, s, **H1**), 3.52 (1H, d, *J* 13.5, **H16**), 3.45 (1H, d, *J* 13.5, **H16'**).

^{13}C (125 MHz, $CDCl_3$): δ 173.3 (**C2**), 151.0 (**C9**) 149.9 (**C10**), 147.9 (**C7**), 134.8 (**C17**), 130.0 (**C18**), 129.3 (**C14**), 128.6 (**C5**), 128.3 (**C4**) 127.7 (**C19**), 127.2 (**C12**), 126.8 (**C20**), 124.2 (**C13**), 120.2 (**C15**), 117.5 (**C6**), 116.7 (**C11**), 112.1 (**C8**), 53.2 (**C1**), 52.3 (**C3**), 48.8 (**C16**).

HRMS (FI): found 375.1116; $[C_{22}H_{17}NO_5\bullet]^+$, $(M\bullet)^+$ requires 375.1107.

IR: ν_{max} (neat)/cm^{-1}: 3030 (C-H aromatic), 1736 (C=O), 1529 (NO_2), 1483 (C=C), 1421 (C=C), 1350 (NO_2), 1254 (C-O ether), 956, 731.

Preparation of isopropyl 2-cyano-2-(2-methoxyphenyl)acetate (347a)



According to a modified literature procedure,[131] Na_3PO_4 (3.88 g, 23.6 mmol) and $[PdCl(allyl)]_2$ (58 mg, 0.16 mmol) were added to a flame dried Schlenk flask and placed under an argon atmosphere. $P(^tBu)_3$ (76 µL, 0.32 mmol), isopropyl cyanoacetate (989 µL, 7.88 mmol), 2-chloroanisole (2.00 ml, 15.8 mmol) and toluene (20 mL) were added and the mixture heated to 100 °C for 4 h. The mixture was allowed to cool to RT, diluted with ethyl acetate, filtered through Celite®, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1) to yield α-arylated product **347a** (1.46 g, 80 % purity, 64 %) as a pale yellow solid. This was either used crude or purified by recrystallization from warm diethyl ether/40-60 petrol to yield pure **347a** as a white solid (80 % recovery).

^1H (400 MHz, $CDCl_3$): δ 7.43-7.33 (2H, m, **H7** and **H9**), 7.01 (1H, apt. td, *J* 7.5, 1.1, **H8**), 6.93 (1H, d, *J* 8.1, **H10**), 5.10 (1H, spt, *J* 6.3, **H2**), 4.99 (1H, s, **H4**), 3.86 (3H, s, **H12**), 1.28 (6H, apt. dd, *J* 11.1, 6.2, **H1**).

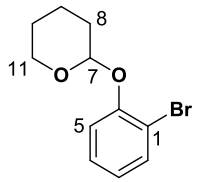
^{13}C (101 MHz, $CDCl_3$): δ 164.7 (**C3**), 156.5 (**C11**), 130.7 (**C7**), 129.4 (**C9**), 121.1 (**C8**), 119.3 (**C6**), 116.0 (**C5**), 111.1 (**C10**), 71.0 (**C2**), 55.7 (**C12**), 38.5 (**C4**), 21.5 (**C1**), 21.5 (**C1'**).

HRMS (ESI): found 256.0952; $[C_{13}H_{15}NO_3Na]^+$ $(M + Na)^+$ requires 256.0944.

IR: ν_{max} (neat)/cm^{-1}: 2941 (C-H aromatic), 2365 (C≡N), 1732 (C=O), 1632, 1486 (C=C), 1275 (C=C), 1248 (C-O ether), 1063, 1024, 746, 685.

MP: (diethyl ether/40-60 petrol) 51 °C.

Preparation of 2-(2-bromophenoxy)tetrahydro-2*H*-pyran (348b)



According to a literature procedure,[133] a solution of 2-bromophenol (15.0 mL, 58 mmol), dihydropyran (10.58 mL, 116 mmol) and pyridinium *p*-toluenesulfonate (1.46 g, 5.80 mmol) in CH_2Cl_2 (100 mL) was stirred for 16 h at RT. The mixture was washed with saturated aqueous ammonium chloride (50 mL), water (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield THP protected phenol **348b** (14.66 g, 98 %) as a yellow oil.

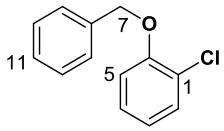
^{1}H (400 MHz, $CDCl_3$): δ 7.56 (1H, dd, *J* 7.6, 1.1, **H2**), 7.27-7.22 (1H, m, **H4**), 7.21-7.15 (1H, m, **H5**), 6.94-6.86 (1H, m, **H3**), 5.55 (1H, s, **H7**), 3.99-3.85 (1H, m, **H11**), 3.71-3.59 (1H, m, **H11'**), 2.23-2.08 (1H, m, **H8**), 2.06-1.97 (1H, m **H8'**), 1.94-1.48 (4H, m, **H9** and **H10**).

^{13}C (101 MHz, $CDCl_3$): δ 153.4 (**C6**), 133.3 (**C2**), 128.4 (**C4**), 122.8 (**C3**), 116.6 (**C5**), 113.1 (**C1**), 96.6 (**C7**), 61.8 (**C11**), 30.2 (**C8**), 25.3 (**C10**), 18.3 (**C9**).

LRMS (ESI): found 257.1; $[C_{11}H_{14}BrO_2]^+$ $(M + H)^+$ requires 257.1.

Data in accordance with literature.[156]

Preparation of 1-(benzyloxy)-2-chlorobenzene (348c)



According to a literature procedure,[134] 2-chlorophenol (4.00 mL, 38.6 mmol) and benzyl bromide (5.04 mL, 42.5 mmol) were added to a stirred suspension of K_2CO_3 (13.30 g, 96.5 mmol) in acetone (50 mL). The mixture was heated to reflux and stirred for 16 h. The suspension was allowed to cool to RT, filtered, concentrated in *vacuo* and partitioned between ethyl acetate (25 mL) and water (20 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 9:1) to yield benzyl-protected phenol **348c** (6.36 g, 75 %) as a clear, colourless oil.

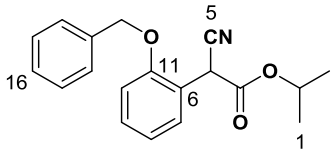
^{1}H (400 MHz, $CDCl_3$): δ 7.50 (2H, d, *J* 7.3, **H9**), 7.44-7.39 (3H, m, **H10** and **H2**), 7.35 (1H, t, *J* 7.1, **H11**), 7.21 (1H, t, *J* 8.3, **H4**), 6.99 (1H, d, *J* 8.1, **H5**), 6.93 (1H, t, *J* 7.7, **H3**), 5.18 (2H, s, **H7**).

^{13}C (101 MHz, $CDCl_3$): δ 154.2 (**C6**), 136.6 (**C8**), 130.4 (**C2**), 128.6 (**C10**), 128.0 (**C11**), 127.7 (**C4**), 127.1 (**C9**), 123.3 (**C1**), 121.7 (**C3**), 114.1 (**C5**), 70.8 (**C7**).

LRMS (ESI): found 241.1; $[C_{13}H_{11}ClONa]^+$ $(M + Na)^+$ requires 241.1.

Data in accordance with literature.[157]

Preparation of isopropyl 2-(2-(benzyloxy)phenyl)-2-cyanoacetate (347c)



According to a modified literature procedure,[131] Na_3PO_4 (3.92 g, 23.9 mmol) and $[PdCl(allyl)]_2$ (59 mg, 0.16 mmol) were added to a flame dried Schlenk flask and placed under an argon atmosphere. $P(^tBu)_3$ (77 µL, 0.32 mmol), isopropyl cyanoacetate (1.00 mL, 7.9 mmol), benzyl-protected chlorophenol **348c** (3.48 g, 15.9 mmol) and toluene (20 mL) were added and the mixture heated to 100 °C for 8 h. The mixture was allowed to cool to RT, diluted with ethyl acetate, filtered through Celite®, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether 3:1) to yield α-arylated product **347c** (1.89 g, 95 % purity, 73 %) as a pale yellow solid. This was either used crude or purified by recrystallization from warm diethyl ether/40-60 petrol to yield pure **347c** as a white solid (53 % recovery).

^{1}H (400 MHz, $CDCl_3$): δ 7.50-7.32 (7H, m, **H7**, **H9** and **ArCH**), 7.08-6.98 (2H, m, **H8** and **H10**), 5.19-5.09 (2H, m, **H12**), 5.08-4.98 (2H, m, **H2** and **H4**), 1.02 (6H, d, *J* 6.4, **H1**).

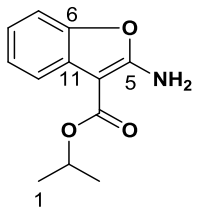
^{13}C (101 MHz, $CDCl_3$): δ 164.6 (**C3**), 155.7 (**C11**), 136.2 (**C13**), 130.7 (**C7**), 129.6 (**C9**), 128.7 (**C15**), 128.2 (**C16**), 127.4 (**C14**), 121.4 (**C8**), 119.6 (**C6**), 116.0 (**C5**), 112.2 (**C10**), 71.1 (**C2**), 70.4 (**C12**), 38.7 (**C4**), 21.4 (**C1**).

HRMS (ESI): found 332.1264; $[C_{19}H_{19}NO_3Na]^+$ $(M + Na)^+$ requires 332.1257.

IR: ν_{max} (neat)/cm^{-1}: 2983 (C-H aromatic), 2360 (C≡N), 1739 (C=O), 1601, 1494, (C=C) 1452 (C=C), 1250 (C-O ether), 1145, 1050, 957, 760, 682.

MP: (diethyl ether/40-60 petrol) 96 °C.

Preparation of isopropyl 2-aminobenzofuran-3-carboxylate (352)



Method A: According to a modified literature procedure,[131] Na_3PO_4 (3.83 g, 23.2 mmol) and $[PdCl(allyl)]_2$ (57 mg, 0.16 mmol) were added to a flame dried Schlenk flask and placed under an argon atmosphere. $P(^tBu)_3$ (77 µL, 0.32 mmol), isopropyl cyanoacetate (1.07 mL, 5.6 mmol), THP-protected chlorophenol **348b** (2.0 g, 7.8 mmol) and toluene (25 mL) were added and the mixture heated to 100 °C for 4 h. The mixture was allowed to cool to RT, diluted with ethyl acetate, filtered through Celite®, and concentrated in *vacuo*. The crude product was dissolved in methanol (20 mL) then *p*-toluenesulfonic acid (148 mg, 0.78 mmol) was added and the mixture stirred for 16 h. The mixture was quenched with 5 % aqueous sodium bicarbonate (20 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 3:1) to yield aminobenzofuran **352** (835 mg, 49 %) as a yellow oil.

Method B: Benzyl-protected phenol **347c** (830 mg, 2.68 mmol) was added to a stirred suspension of 10 % Pd/C (83 mg, 10 % w/w) in methanol (25 mL). The mixture was degassed and placed under an atmosphere of hydrogen for 18 h. The reaction mixture was filtered through Celite®, eluting with CH_2Cl_2, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:diethyl ether, 1:1) to yield aminobenzofuran **352** (406 mg, 70 %) as a yellow oil.

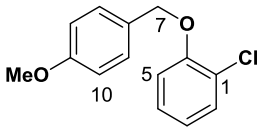
^{1}H (400 MHz, $CDCl_3$): δ 7.67 (1H, d, *J* 7.6, **H10**), 7.26-7.18 (2H, m, **H7** and **H8**), 7.11-7.05 (1H, m, **H9**), 5.98 (2H, br s, **NH_2**), 5.27 (1H, spt, *J* 6.3, **H2**), 1.42 (6H, d, *J* 6.4, **H1**).

^{13}C (101 MHz, $CDCl_3$): δ 165.9 (**C5**), 164.4 (**C3**), 149.1 (**C6**), 127.0 (**C11**), 124.0 (**C8**), 121.5 (**C9**), 119.5 (**C10**), 112.8 (**C4**), 109.7 (**C7**), 67.1 (**C2**), 22.4 (**C1**).

HRMS (ESI): found 242.0795; $[C_{12}H_{13}NO_3Na]^+$ $(M + Na)^+$ requires 242.0788.

IR: ν_{max} (neat)/cm^{-1}: 3442 (N-H), 3313 (N-H), 2979 (C-H aromatic), 2360, 1664 (C=O), 1628, 1532 (C=C), 1478 (C=C), 1238 (C-O ether), 1098, 1039, 758, 744.

Preparation of 1-(benzyloxy)-2-chlorobenzene (348d)



According to a literature procedure,[134] 2-chlorophenol (2.91 mL, 28.1 mmol) and *p*-methoxybenzyl chloride (4.20 mL, 30.9 mmol) were added to a stirred suspension of K_2CO_3 (9.71 g, 70.3 mmol) in acetone (35 mL). The mixture was heated to reflux and stirred for 16 h. The suspension was allowed to cool to RT, filtered, concentrated in *vacuo* and partitioned between ethyl acetate (20 mL) and water (15 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was washed with 40-60 petrol to yield PMB-protected phenol **348d** (5.68 g, 81 %) as a cream solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.50 (2H, d, *J* 7.3, **H9**), 7.44-7.39 (3H, m, **H10** and **H2**), 7.35 (1H, t, *J* 7.1, **H11**), 7.21 (1H, t, *J* 8.3, **H4**), 6.99 (1H, d, *J* 8.1, **H5**), 6.93 (1H, t, *J* 7.7, **H3**), 5.18 (2H, s, **H7**).

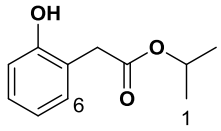
^{13}C (101 MHz, $CDCl_3$): δ 154.2 (**C6**), 136.6 (**C8**), 130.4 (**C2**), 128.6 (**C10**), 128.0 (**C11**), 127.7 (**C4**), 127.1 (**C9**), 123.3 (**C1**), 121.7 (**C3**), 114.1 (**C5**), 70.8 (**C7**).

HRMS (ESI): found 271.0496; $[C_{14}H_{13}ClO_2Na]^+$ $(M + Na)^+$ requires 271.0505.

IR: ν_{max} (neat)/cm^{-1}: 2965 (C-H aromatic), 2360, 1576, 1241, 1132, 1026, 995 753.

MP: 121-123 °C

Preparation of isopropyl 2-(2-hydroxyphenyl)acetate (367)



According to a literature procedure[141] a solution of 2-hydroxyphenylacetic acid (5.0 g, 32.9 mmol) in H_2SO_4 (5.0 mL) and isopropylalcohol (50 mL) was stirred at reflux for 6 h. The mixture was allowed to cool to RT, poured onto ice and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with sodium bicarbonate (80 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:ethyl acetate, 4:1) to yield ester **367** (5.12 g, 80 %) as a yellow solid.

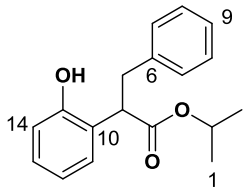
^{1}H (400 MHz, $CDCl_3$): δ 7.86 (1H, s, **OH**), 7.20 (1H, apt. td, *J* 7.8, 1.7, **H8**), 7.10 (1H, d, *J* 7.3, **H6**), 6.97 (1H, d *J* 8.1, **H9**), 6.89 (1H, apt. td, *J* 7.4, 1.1, **H7**), 5.05 (1H, spt, *J* 6.6, **H2**), 3.66 (2H, s, **H4**), 1.27 (6H, d, *J* 6.3, **H1**).

^{13}C (101 MHz, $CDCl_3$): δ 173.8 (**C3**), 155.4 (**C10**), 131.0 (**C6**), 129.2 (**C8**), 128.8 (**C7**), 120.8 (**C5**), 117.9 (**C9**), 69.9 (**C2**), 38.7 (**C4**), 21.7 (**C1**).

LRMS (ESI): found 195.1; $[C_{11}H_{14}O_3]^+$ $(M + H)^+$ requires 195.1.

Data in accordance with literature.[158]

Preparation of isopropyl 2-(2-hydroxyphenyl)-3-phenylpropanoate (368)



^{n}BuLi (1.6 M in hexanes, 14.16 mL, 22.7 mmol) was added to a stirred solution of diisopropylamine (3.46 mL, 24.7 mmol) in THF (25 mL) at -78 °C, and the mixture was stirred for 15 min. A solution of phenol **367** (2.0 g, 10.3 mmol) in THF (15 mL) was added and the mixture stirred for a further 15 min. Benzyl bromide (1.35 mL, 11.2 mmol) was added and the mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was quenched with 1 M HCl (25 mL), stirred for 15 min and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was adsorbed onto silica and purified by flash column chromatography (40-60 petrol:diethyl ether, 6:1) to yield phenol **368** as a yellow oil (1.79 g, 61 %).

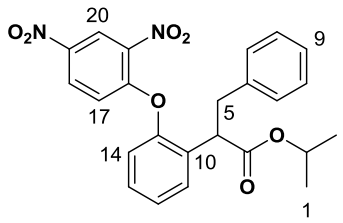
^{1}H (400 MHz, $CDCl_3$): δ 7.90 (1H, s, **OH**), 7.30-7.15 (6H, m, **ArCH**, **H13**), 7.05-6.95 (2H, m, **H11** and **H14**), 6.84 (1H, apt. td, *J* 7.3, 1.2, **H12**), 4.93 (1H, spt, *J* 6.4, **H2**), 3.94-3.82 (1H, m, **H4**), 3.47 (1H, dd, *J* 13.5, 10.3, **H5**), 3.11 (1H, dd, *J* 13.7, 6.6, **H5'**), 1.15 (3H, d, *J* 6.4, **H1**), 0.99 (3H, d, *J* 6.4, **H1'**).

^{13}C (101 MHz, $CDCl_3$): δ 176.4 (**C3**), 155.5 (**C11**), 138.4 (**C6**), 130.5 (**C15**), 129.3 (**C13**), 129.1 (**C7**), 128.4 (**C8**), 126.6 (**C9**), 123.6 (**C10**), 120.6 (**C14**), 118.6 (**C12**), 69.9 (**C2**), 53.3 (**C4**), 37.6 (**C5**), 21.5 (**C1**), 21.3 (**C1'**).

HRMS (ESI): found 307.1305; $[C_{18}H_{20}O_3Na]^+$ $(M + Na)^+$ requires 307.1310.

IR: ν_{max} (neat)/cm^{-1}: 3366 (br, O-H) 3064 (C-H aromatic), 2360, 1701 (C=O), 1495 (C=C), 1273, 1103, 750, 669.

Preparation of isopropyl 2-(2-(2,4-dinitrophenoxy)phenyl)-3-phenylpropanoate (369)



According to a modified literature procedure,[129] NEt_3 (527 µL, 3.78 mmol) was added to a stirred solution of phenol **368** (979 mg, 3.44 mmol) and 2,4-dinitrofluorobenzene (611 mg, 3.28 mmol) in acetone (40 mL). The mixture was heated to reflux for 3 h, then allowed to cool to RT, and concentrated in *vacuo*. The residue was treated with 1 M HCl (40 mL) and extracted with diethyl ether (80 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was adsorbed onto silica and purified by flash column chromatography (40-60 petrol:diethyl ether, 2:1) to yield aryl ether **369** (1.41 g, 91 %) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 8.83 (1H, d, *J* 2.7, **H20**), 8.14 (1H, dd, *J* 9.3, 2.7, **H18**), 7.68-7.59 (1H, m, **H12**), 7.38-7.31 (2H, m, **H11** and **H13**), 7.16-7.10 (3H, m, **H8** and **H9**), 7.07-7.02 (2H, m, **H7**), 6.98-6.94 (1H, m, **H14**), 6.59 (1H, d, *J*, 9.3, **H17**), 4.89 (1H, spt, *J* 6.3, **H2**), 4.17 (1H, dd, *J* 8.3, 7.3, **H4**), 3.38 (1H, dd, *J* 13.6, 7.2, **H5**), 3.07 (1H, dd, *J* 13.7, 8.6, **H5'**), 1.07 (3H, d, *J* 6.1, **H1**), 1.04 (3H, d, *J* 6.1, **H1'**).

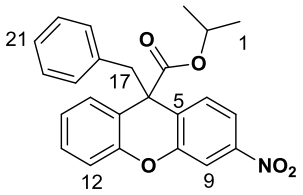
^{13}C (101 MHz, $CDCl_3$): δ 172.0 (**C3**), 155.8 (**C16**), 151.0 (**C15**), 141.2 (**C19**), 139.2 (**C21**), 138.4 (**C6**), 131.4 (**C10**), 130.0 (**C12**), 129.2 (**C13**), 129.1 (**C7**), 128.6 (**C18**), 128.3 (**C8**),

127.0 (**C11**), 126.5 (**C9**), 121.9 (**C20**), 120.7 (**C14**), 117.9 (**C17**), 68.7 (**C2**), 46.3 (**C4**), 38.9 (**C5**), 21.5 (**C1**).

HRMS (ESI): found 473.1319; $[C_{24}H_{22}N_2O_7Na]^+$ $(M + Na)^+$ requires 473.1319.

IR: ν_{max} (neat)/cm^{-1}: 3111 (C-H aromatic), 2982 (C-H aromatic), 1802, 1725 (C=O), 1610 (C=C), 1581 (C=C), 1538 (NO_2), 1344 (NO_2), 1268 (C-O ether), 1148.

Preparation of isopropyl 9-benzyl-3-nitro-9H-xanthene-9-carboxylate (370)



Method A: Powdered KOH (42 mg, 0.75 mmol) was added to a stirred solution of Truce-Smiles precursor **369** (67 mg, 0.15 mmol) and TBAHS (10 mg, 0.030 mmol) in toluene (2.5 mL). The mixture was heated to 40 °C for 16 h, then allowed to cool to RT, quenched with 1 M HCl (2 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40-60 petrol:ethyl acetate, 7:1) to yield xanthene **370** (38 mg, 63 %) as a yellow solid. A single crystal for XRD analysis was grown *via* vapour diffusion from ethyl acetate and hexane.

Method B: An equivalent procedure generating Truce-Smiles precursor **369** in *situ*, employed phenol **368** (54 mg, 0.19 mmol), 2,4-dinitrofluorobenzene (35 mg, 0.19 mmol), powdered KOH (64 mg, 1.14 mmol) and TBAHS (13 mg, 0.038 mmol) in toluene to yield xanthene **370** (23 mg, 30 %).

^{1}H (500 MHz, MeOD): δ 7.89 (1H, dd, *J* 8.6, 2.4, **H7**), 7.57 (1H, d, *J* 2.4, **H9**), 7.47 (1H, d, J8.5,**H6**), 7.29 (1H, dd, *J* 7,7, 1.6, **H15**), 7.23-7.17 (1H, m, **H13**), 7.12 (1H, apt. td, *J* 7.7, 1.3, **H14**), 6.89 (1H, tt, *J* 7.4, 1.1, **H21**), 6.81 (1H, dd, *J* 8.2, 1.1, **H12**), 6.77-6.69 (2H, m, **H20**), 6.15-6.08 (2H, m, **H19**), 5.04 (1H, spt, *J* 6.3, **H2**), 3.42 (1H, d, *J* 13.9, **H17**), 3.36 (1H, d, 13.7, **H17'**), 1.01 (6H, apt. dd, *J* 8.6, 6.3, **H1**).

^{13}C (125 MHz, MeOD): δ 172.2 (**C3**), 151.1 (**C10**), 150.2 (**C11**), 148.0 (**C8**), 135.4 (**C18**), 129.8 (**C19**), 129.3 (**C15**), 129.0 (**C6**) 128.7 (**C5**), 127.3 (**C13**), 127.2 (**C20**), 126.3 (**C21**),

123.9 (**C14**), 120.7 (**C16**), 117.2 (**C7**), 117.2 (**C12**), 111.3 (**C9**), 69.7 (**C2**), 52.3 (**C4**), 48.0 (**C17**)*, 20.2 (**C1**).

* Overlaps with solvent peaks, assigned by HSQC cross-peak.

HRMS (FI): found 403.1414; $[C_{24}H_{21}NO_5\bullet]^+$, $(M\bullet)^+$ requires 403.1420.

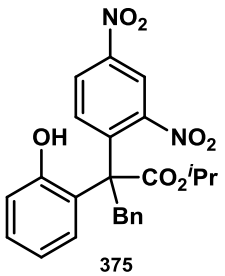
IR: ν_{max} (neat)/cm^{-1}: 3030 (C-H aromatic), 1727 (C=O), 1527 (NO_2), 1483 (C=C), 1422 (C=C), 1349 (NO_2), 1254 (C-O ether), 1078, 702.

MP: (prior to recrystallization) 121 °C.

Chiral HPLC: (Chiralpak IC, 10 % IPA, 90 % hexane, 1.0 $mL.min^{-1}$, λ = 255 nm); t_R 5.8 min, 6.6 min.

Chiral HPLC: (Chiralpak IC, 2 % IPA, 98 % hexane, 1.0 $mL.min^{-1}$, λ = 255 nm); t_R 8.8 min, 12.3 min.*

*During screening of catalysts an unidentified product was observed by chiral HPLC with the same enantiomeric excess as **370**, this product was inseparable by chromatography and is proposed to be **375**.

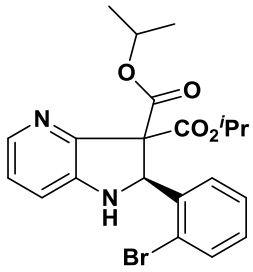


375

Chiral HPLC: (Chiralpak IC, 2 % IPA, 98 % hexane, 1.0 $mL.min^{-1}$, λ = 255 nm); t_R 9.8 min, 11.0 min.

5.2.3. Crystallographic Data

167h



167h

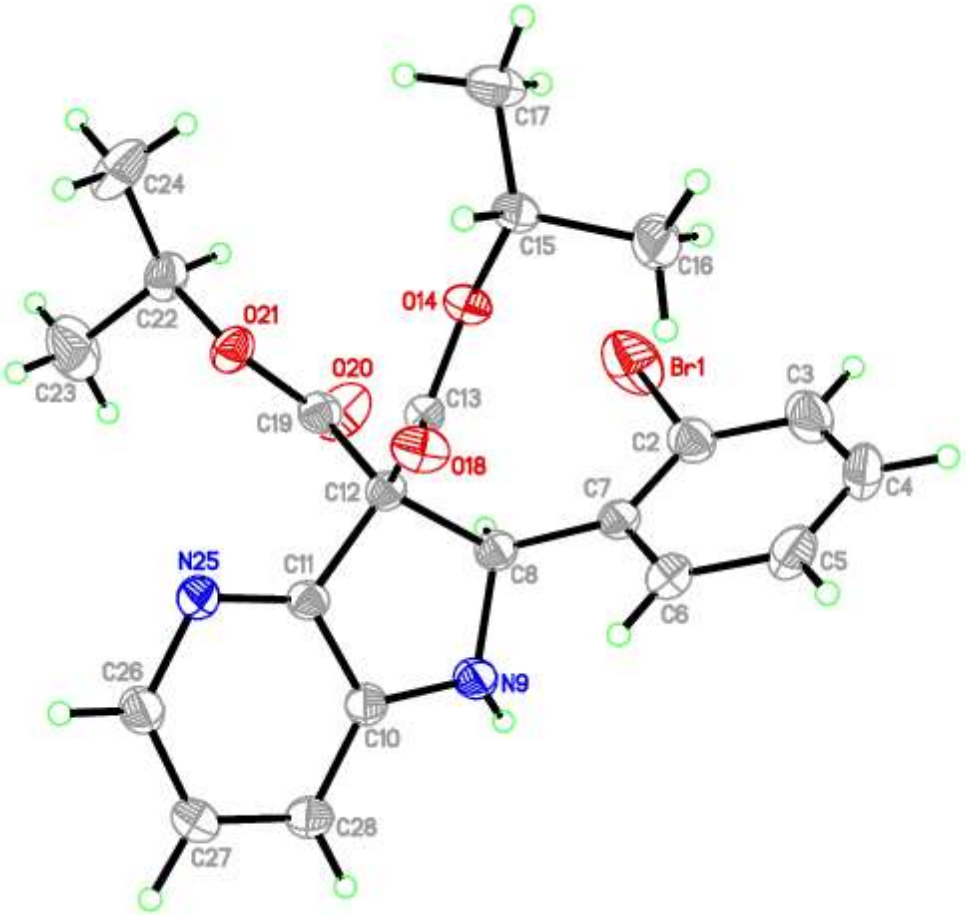
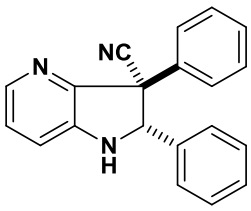


Table 1. Crystal data and structure refinement for 6418.

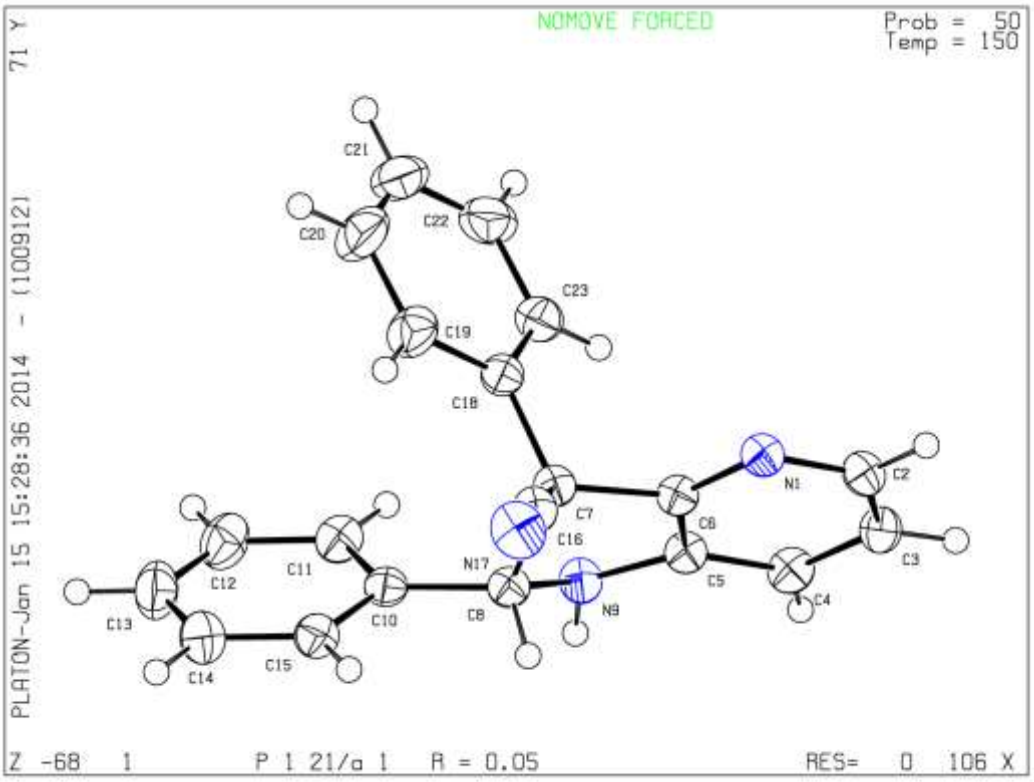
Identification code	6418	
Empirical formula	C21 H23 Br1 N2 O4	
Formula weight	447.33	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 12.20190(10) Å	α= 90°.
	b = 15.59050(10) Å	β= 90°.
	c = 21.63620(10) Å	γ = 90°.
Volume	4115.93(5) Å^3	
Z	8	
Density (calculated)	1.444 Mg/m^3	
Absorption coefficient	2.967 mm^{-1}	
F(000)	1840	
Crystal size	0.09 x 0.05 x 0.03 mm^3	
Theta range for data collection	3.494 to 76.789°.	
Index ranges	-15<=h<=15, -19<=k<=19, -27<=l<=27	
Reflections collected	91277	
Independent reflections	8640 [R(int) = 0.031]	
Completeness to theta = 76.789°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.91 and 0.82	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8640 / 108 / 525	
Goodness-of-fit on F^2	1.0028	
Final R indices [I>2sigma(I)]	R1 = 0.0205, wR2 = 0.0509	
R indices (all data)	R1 = 0.0212, wR2 = 0.0513	
Absolute structure parameter	-0.030(7)	
Largest diff. peak and hole	0.26 and -0.49 e.Å^{-3}	

216a



216a

216a - ellipsoid plot



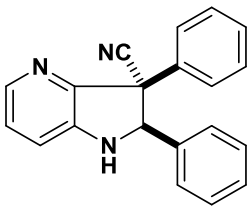
Crystal data

$C_{20}H_{15}N_3$	2
M_r = 297.36	D_x = 1.238 Mg m^{-3}
Monoclinic, $P2_1/a$	Melting point: see SI K
Hall symbol: -P 2yab	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 11.6533 (2) Å	Cell parameters from 3807 reflections
b = 10.6806 (2) Å	θ = 5–27°
c = 13.6153 (3) Å	μ = 0.08 mm^{-1}
β = 109.7256 (8)°	T = 150 K
V = 1595.18 (5) Å^3	Prism, pale_clear_colourless
Z = 4	0.70 × 0.10 × 0.10 mm
F(000) = 624	

Data collection

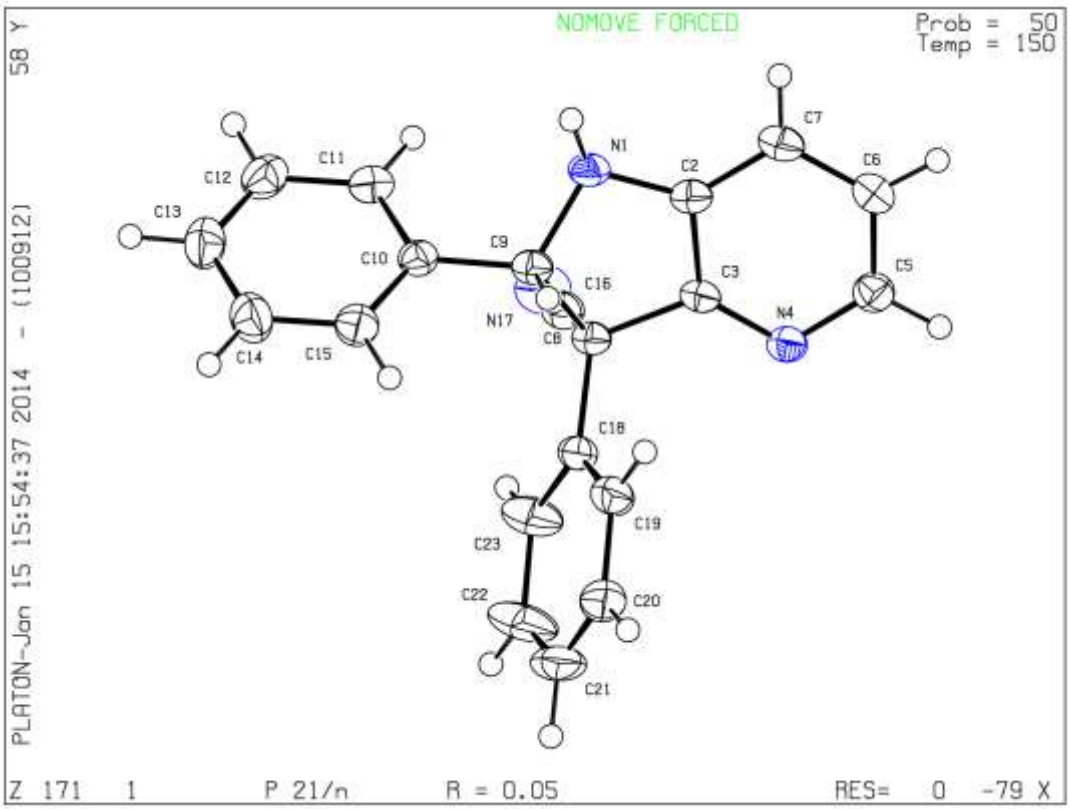
Nonius KappaCCD diffractometer	3639 independent reflections
Radiation source: ?	2830 reflections with $I > 2.0\sigma(I)$
graphite	R_{int} = 0.027
Detector resolution: ? pixels mm^{-1}	θ_{max} = 27.5°, θ_{min} = 5.1°
ω scans	h = −15 15
Absorption correction: multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)	k = −13 13
T_{min} = 0.99, T_{max} = 0.99	l = −17 17
23646 measured reflections	

216b



216b

216b - ellipsoid plot

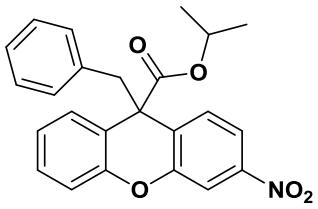


Crystal data

$C_{20}H_{15}N_3$	1
M_r = 297.36	D_x = 1.245 Mg m^{-3}
Monoclinic, $P2_1/n$	Melting point: please see SI K
Hall symbol: -P 2yn	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 9.2699 (2) Å	Cell parameters from 3620 reflections
b = 17.2089 (3) Å	θ = 1–1°
c = 10.2868 (2) Å	μ = 0.08 mm^{-1}
β = 104.8563 (9)°	T = 150 K
V = 1586.14 (5) Å^3	Block, pale_clear_amber
Z = 4	0.60 × 0.40 × 0.40 mm
F(000) = 624	

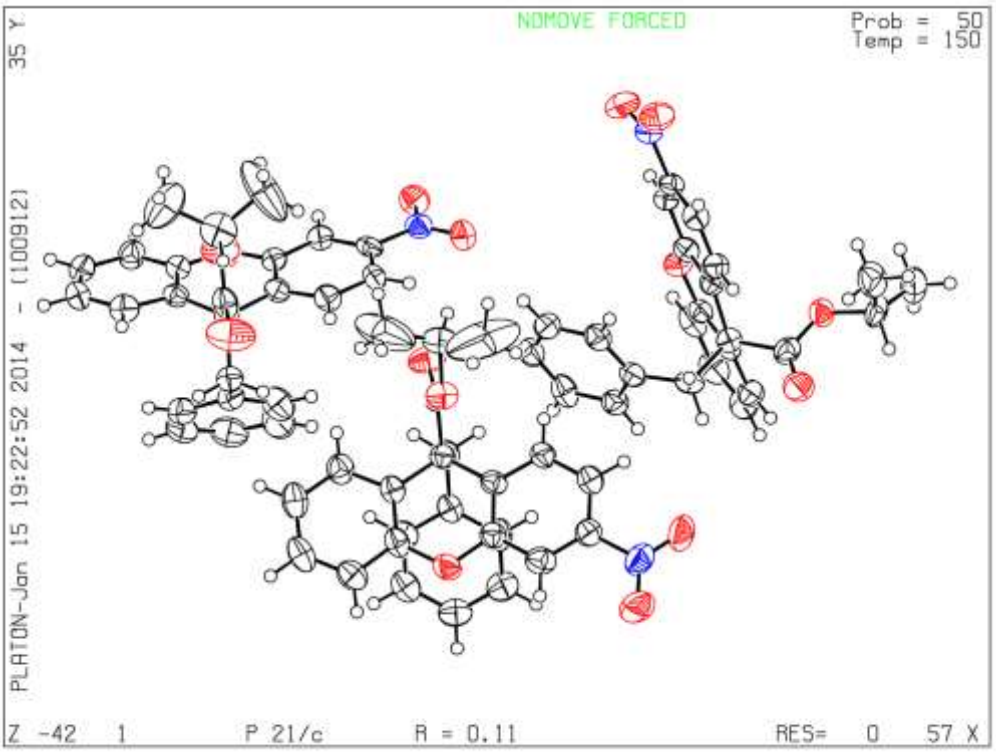
Data collection

Nonius KappaCCD diffractometer	4415 independent reflections
Radiation source: ?	3285 reflections with $I > 2.0\sigma(I)$
graphite	R_{int} = 0.023
Detector resolution: ? pixels mm^{-1}	θ_{max} = 29.6°, θ_{min} = 5.2°
ω scans	h = −12 12
Absorption correction: multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)	k = −23 17
T_{min} = 0.97, T_{max} = 0.97	l = −14 14
16471 measured reflections	



270

270 - ellipsoid plot



Crystal data

$C_{24}H_{21}NO_5$	?
M_r = 403.43	D_x = 1.315 Mg m^{-3}
Monoclinic, $P2_1/c$	Melting point: ? K
Hall symbol: -P 2yc	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 10.0946 (2) Å	Cell parameters from 7638 reflections
b = 20.3715 (6) Å	θ = 5–27°
c = 29.7911 (10) Å	μ = 0.09 mm^{-1}
β = 93.5269 (16)°	T = 150 K
V = 6114.7 (3) Å^3	Plate, clear_pale_col
Z = 12	0.50 × 0.30 × 0.10 mm
F(000) = 2544	

Data collection

Nonius KappaCCD diffractometer	12560 independent reflections
Radiation source: ?	5873 reflections with $I > 2.0\sigma(I)$
graphite	R_{int} = 0.062
Detector resolution: ? pixels mm^{-1}	θ_{max} = 27.5°, θ_{min} = 5.1°
ω scans	h = −11 12
Absorption correction: multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)	k = −23 26
T_{min} = 0.97, T_{max} = 0.99	l = −38 38
19265 measured reflections	

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