CHIRAL COUNTER-ION CONTROLLED ASYMMETRIC ELECTROCYCLIC REACTIONS

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A dissertation presented in partial fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

of the

University of Oxford

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May 2012

Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory between October 2008 and April 2012. The dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

Peter Knipe

Acknowledgements

It has been an enormous pleasure to work under the tutelage of Dr Martin Smith. I am privileged to have benefitted from his fierce intelligence, perspicacious insight and enthusiastic support in all my endeavours, and to be one of the few lucky souls to have witnessed his dancing.

I am also extremely grateful to my industrial supervisor, Dr Paul Brennan, for his helpful suggestions and enthusiastic support, and to Pfizer and the EPSRC for generously supporting my research.

Organic chemistry can be a cruel mistress, and the past years would have been intolerable without a kind and supportive group of friends and colleagues. My heartfelt thanks are therefore extended to everyone who has made the Smith group such an excellent place to work:

From the good old days: to Dr Hannah Lingard, for first welcoming me into the group (although, admittedly, not until the afternoon); to Dr Sam Thompson, whose impressive all-day hangovers always make mine feel better; to Dr Eleanor Maciver, for a fun collaboration; and to Dr Abhishek Kothari, Dr Chris Jones, Dr Pranjal Baruah and Dr Rhian Thomas – you all made the early days of my DPhil bearable! I was fortunate to begin my doctorate at the same time as Dr Stephen Wallace (he won, obviously), whose encyclopaedic knowledge of named reactions served him in good stead during our drinking games in Tijuana, and will doubtless continue to serve him in his future career.

A great many talented undergraduate students have passed through the Smith group since I began. Thanks to Jana Franke, Joe Marshall, Dai Yeo, Laura Manicassamy, Toby Mullins, Diana Bowtell and Chris Wood, and to my students Peter "Mini-Pete" (figurative) Davey and Josh "Mini-Josh" (literal) Bailey. I'm certain you'll all excel wherever you end up.

The current members of the Smith group have been exceptionally supportive during the last few years. I am extremely appreciative to Dr Meiling "The Machine" Li, Dr Phil Woods and Dr Russell Driver for their wisdom in the lab, and advice whilst writing this thesis. Thanks also to the DPhils: Craig "Capability" Johnston, Caroline Stovold, Alan Lamb, Roly Armstrong and Emily Kiss, and to Krishna Sharma, Melissa D'Ascenzio, Paul Brian, Art Cernijenko and Dan Finnemore – you all make the lab a great place to work.

The CRL is a world-class place to practice chemistry, and my sincere thanks go to all the support and analytical staff who have made it such a pleasure to work here.

I must also particularly thank again those who helped to proof-read this thesis: thanks to Martin, Phil, Sam, Hannah and Craig for their useful input and suggestions.

I could never have achieved what I have without the love and support of my parents, my staggeringly intelligent big brother David, and my amazing granny.

Finally, and most importantly, I would like to thank the beautiful Dr Rachel Ruddock, whose patience, understanding and love have made my time in Oxford the best of my life; I can't wait to see where life takes us together.

Abbreviations

2D	two-dimensional
Å	Ångstroms
Ac	acetyl
aq.	aqueous
Ar	*denotes a generic aromatic system*
BAIB	bis(acetoxy)iodobenzene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
box	bisoxazoline
Bu	butyl
°C	degrees celsius
c	concentration
cal	calories
cat.	catalytic/catalyst
cf.	*confer*
conc.	concentration
conv.	conversion
COSY	correlation spectroscopy
Cy	cyclohexyl
d	days
Da	daltons
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
EI	electron-impact ionization
eq.	equivalents
ESI	electrospray ionization

Et	ethyl
EWG	*electron-withdrawing group*
FI	field ionization
$\Delta G^{\ddagger}$	activation Gibbs free energy
g	grams
[H]	*denotes a generic reduction reaction*
h	hours
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazide
hOe	heteronuclear Overhauser effect
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	hertz
i	*iso*
IPA	*iso*-propanol
IR	infra-red
IUPAC	International Union of Pure and Applied Chemistry
k	kilo-
L	litres
LA	Lewis acid
LDA	lithium diisopropylamide
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	molecular sieves
MS	mass spectrometry
Ms	methanesulfonyl
n	normal
n	*denotes a generic integer*
n	nano-

N/A	not applicable
ND	not determined
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NR	no reaction
NTPA	N-trifluoromethanesulfonyl phosphoramide
[O]	*denotes a generic oxidation reaction*
o	*ortho-*
ONSH	oxidative nucleophilic substitution of hydrogen
p	*para-*
PCC	pyridinium chlorochromate
PEG	polyethylene glycol
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
PTC	phase-transfer catalysis
pybox	pyridine bisoxazoline
Q^+	*denotes a quaternary cation*
quant.	quantitative
R	*denotes a generic substituent*
RT	room temperature
§	see section
s	seconds
s	solid
SM	starting material
S_NAr	nucleophilic aromatic substitution
t	*tertiary*
tert	*tertiary*
T	temperature
t	time
TBA	tribromoacetic acid
TBS	*tert*-butyldimethylsilyl
temp.	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
triflate	trifluoromethanesulfonate
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	toluenesulfonyl
v	volume
VNS	vicarious nucleophilic substitution
vs.	*versus*
wt%	weight percent
$_{\gamma}\mathbf{N}_{s/a}$	*This label describes the components of a pericyclic reaction according to their symmetry (γ = ω, σ, π etc.), the number of electrons in the component that participate in the pericyclic process (N), and the facial selectivity of orbital overlap (s = suprafacial or a = antarafacial).*

Abstract

The aim of this project was to develop new catalytic methods to control asymmetry in electrocyclic reactions, and to apply these methods to generate complex molecules. Initial efforts were directed towards the catalysis of anionic 8π electrocyclizations (Chapter 2 and Figure i).

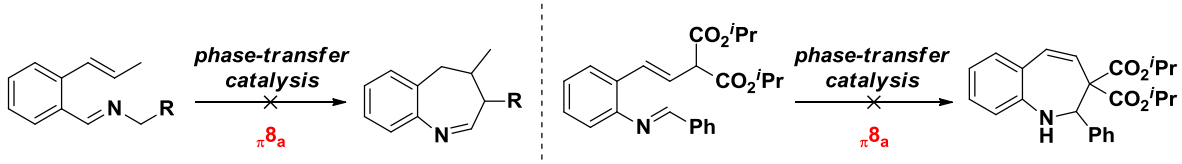


Figure i. Attempted 8π electrocyclization reactions.

8π electrocyclization was not achieved due to issues with alkene geometry and anion stability. Our efforts were then directed towards using phase-transfer catalysis to generate complex polycyclic compounds *via* a cascade electrocyclization-1,4-addition (Chapter 3 and Figure ii).

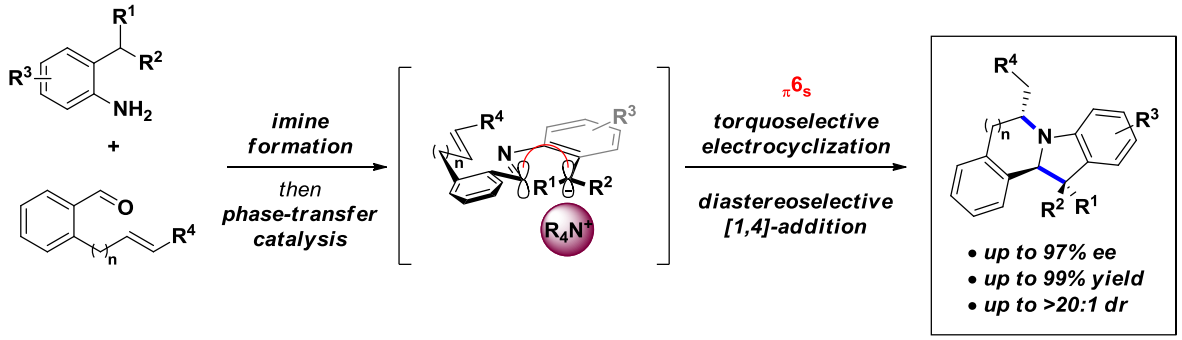


Figure ii. Cascade electrocyclization-1,4-addition methodology.

Pyrrolidines and indolizidines were generated in excellent yield from simple starting-materials with high levels of stereocontrol. Finally, we investigated the catalysis of a 6π [1,6]-electrocyclization to generate dihydroquinolones (Chapter 4 and Figure iii).

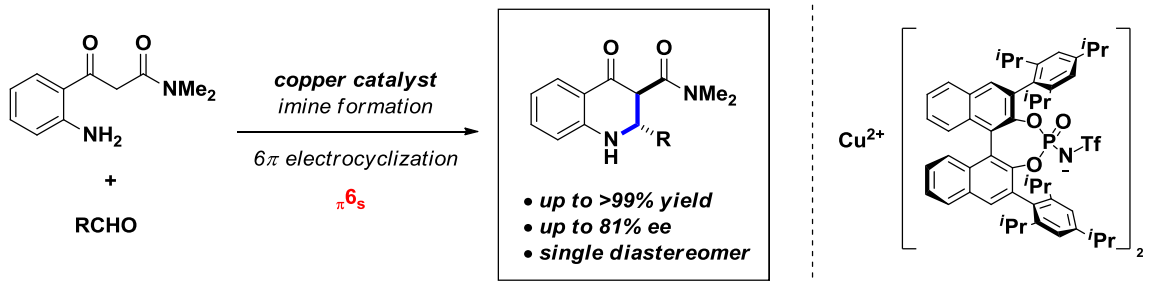


Figure iii. Copper(II) catalysed [1,6]-electrocyclic reaction generating dihydroquinolones.

A novel BINOL-derived copper(II) catalyst was developed, and afforded dihydroquinolones directly from their amine and aldehyde precursors with good yields and enantioselectivities.

CONTENTS

1. INTRODUCTION

1.1 Electrocyclization

1.1.1 Historical Context

In the past sixty years, explaining the stereochemical outcome of pericyclic reactions has progressed from being one of organic chemistry's greatest mysteries to one of its most triumphant success stories. In 1962, prior to their now-familiar rationalization by Woodward and Hoffmann, Doering was driven to describe pericyclic reactions as having "*no mechanism*".[1] In the same year, Oosterhoff prophesied the developments later that decade, noting that "… *the stereochemical difference between the thermal and photo induced ring closure* [of precalciferol] *may be found in the symmetry characteristics of the highest occupied π orbital of the conjugated hexatriene system*".[2] This simple concept – that the stereochemistry of concerted bond formation is dependent on the symmetry of the orbitals involved – independently underpinned the development of the Woodward-Hoffmann rules.[3]

In 1965, in a series of seminal papers, Woodward and Hoffmann outlined a set of rules that explained the stereochemical outcome of every known cycloaddition, sigmatropic rearrangement and electrocyclization;[4–8] such was the power of these results that they were able to predict the behaviour of many pericyclic processes that had not yet been observed. Whilst these predictions were initially based in the symmetry of the HOMO, Longuet-Higgins subsequently used state correlation diagrams to show that the results obtained by Woodward and Hoffmann could be more rigorously derived from the symmetry of all orbitals involved in the pericyclic process.[9] In the years that followed, these ideas were generalized to the ubiquitous Woodward-Hoffmann rules, which provide a simple and general prediction of the stereochemical outcome of all pericyclic reactions:[10–12]

"A ground-state pericyclic change is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components is odd" [*]

This treatment also leads to a complementary prediction for reactions carried out under photochemical conditions:

"A pericyclic change in the first electronically excited state is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components is even"

An alternative derivation of this result has been proposed by Zimmerman[13–15] and Dewar,[16] where the assertion that the transition states for allowed pericyclic reactions must possess Hückel or Möbius aromaticity leads to the same selection rules and stereochemical predictions as the orbital symmetry approach, without the requirement that the system has high levels of molecular symmetry.

Regardless of the derivation, the predictive power of these rules is irrefutable, and has undoubtedly been a major factor in the rapid uptake of pericyclic reactions within the community of synthetic organic chemistry.[12]

1.1.2 Definitions

Electrocyclic reactions are a sub-class of pericyclic reactions, formally defined as "…*the formation of a σ-bond between the termini of a fully conjugated linear π-electron system and a decrease by one in the number of π-bonds…".*[17] Application of the Woodward-Hoffmann rules to this sub-class leads to a remarkably simple set of predictions: all thermal electrocyclizations of systems possessing (4n) π-electrons will proceed antarafacially and may therefore be described as conrotatory; conversely, thermal electrocyclizations of systems possessing (4n+2) π-electrons will proceed suprafacially and are described as disrotatory (Figure 1.1).

[*] *q and r denote integers; s and a indicate suprafacial and antarafacial orbital interactions respectively.*

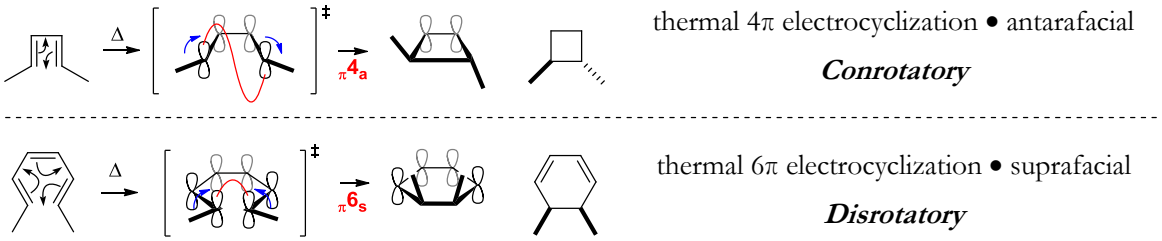


Figure 1.1. Representative thermal electrocyclizations (*arrows indicate direction of rotation of terminal groups*).

Although these rules are typically demonstrated with reference to uncharged homonuclear polyenes they apply equally to charged and heteroatom-containing species.[7,12,18]

1.1.3 Strategies to Control Absolute Stereochemistry

The Woodward-Hoffmann rules establish unambiguously the relative stereochemistry of the two sp^3 centres formed during an electrocyclic ring closure. They do not, however, have any influence on the absolute stereochemistry of the products formed. In order to achieve enantioselective electrocyclization it is necessary to control the torquoselectivity * of the electrocyclic ring-closure (Figure 1.2).

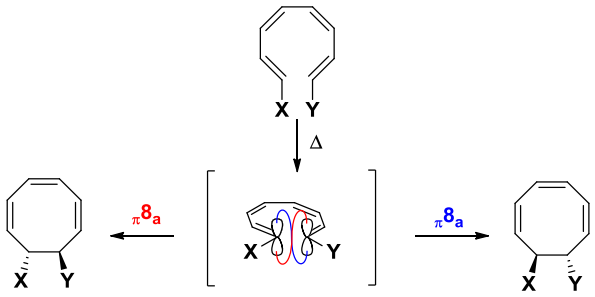


Figure 1.2. Torquoselectivity in an 8π electrocyclic ring closure.

Numerous strategies have been employed in order to achieve torquoselectivity in electrocyclic ring closures;[19] the vast majority employ substrate or chiral auxiliary control,

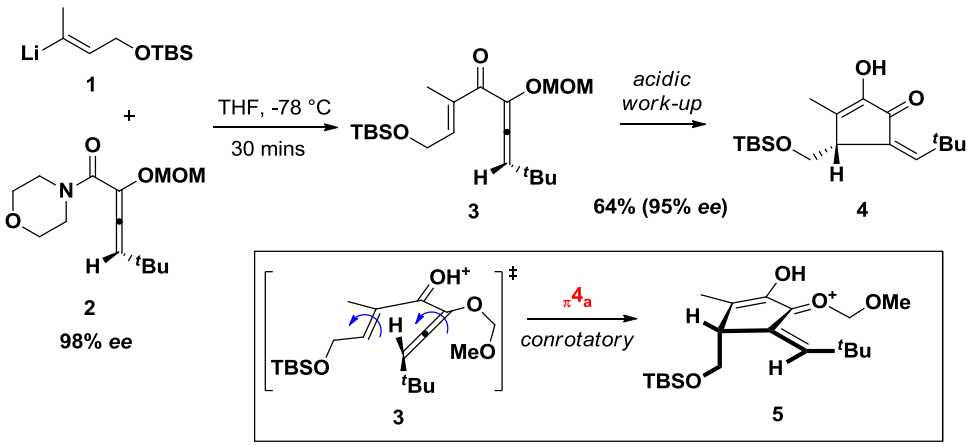
* *IUPAC define torquoselectivity as "the preference for 'inward' or 'outward' rotation of substituents in conrotatory or disrotatory electrocyclic ring opening reactions".*[17] *We extend this definition to describe the absolute direction of rotation of substituents in an electrocyclic ring closure in a manner consistent with – but not identical to – the IUPAC definition.*

however in the past decade there has been a rapid increase in the number of catalytic asymmetric methods available.

1.1.3.1 Substrate Control *

There are a great many examples of the use of an existing chiral centre to direct the absolute stereochemistry of the product obtained from electrocyclic reactions. Generally the transmission of chirality is through steric interactions, although stereoelectronics can also have a significant effect.

Tius has demonstrated the use of intramolecular steric interactions to direct torquoselectivity in the 4π Nazarov reaction.[20,21] Chiral allenyl ketone **3** undergoes a conrotatory 4π electrocyclic ring closure on acidic work-up; the absolute stereochemistry of the resulting cyclopentenone is a direct consequence of the steric clash between the bulky ^{t}Bu group and the trisubstituted alkene (Scheme 1.1).[22]

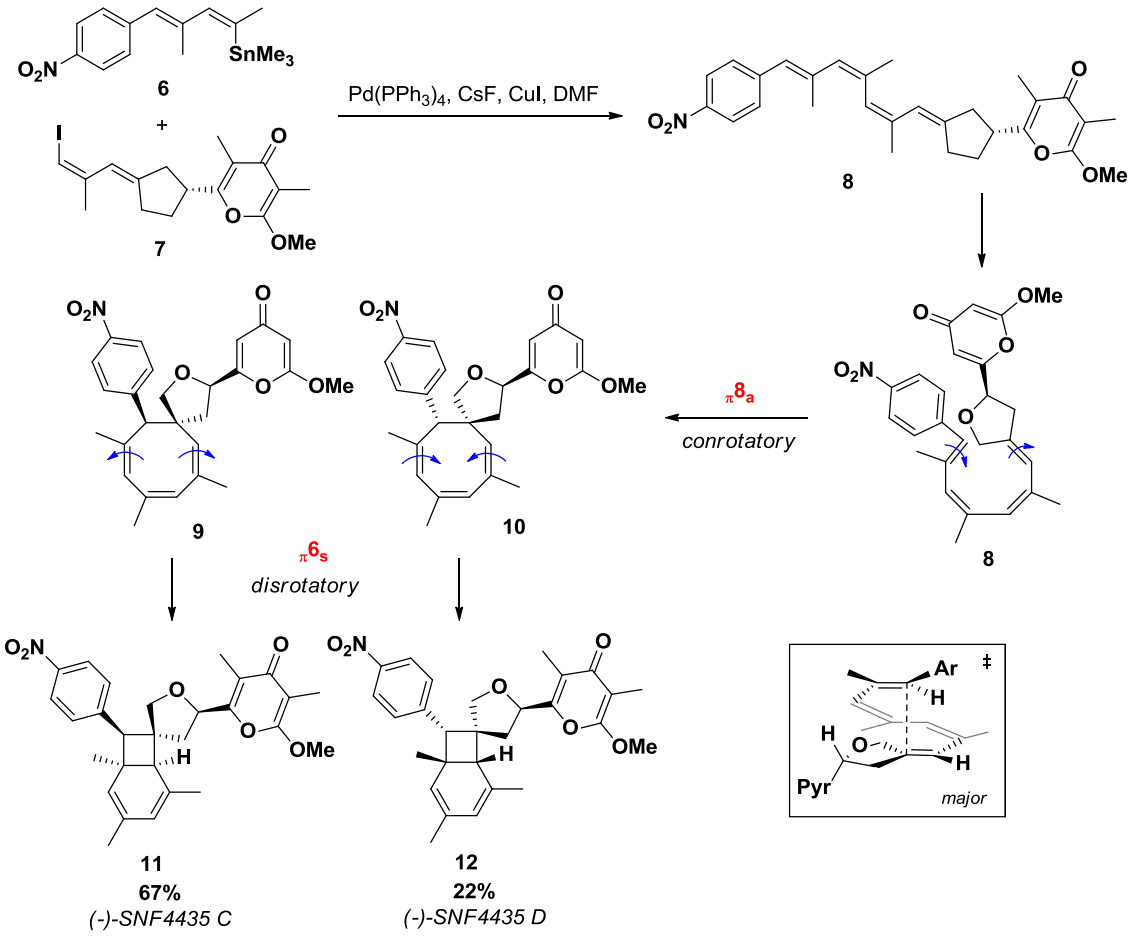


Scheme 1.1. Tius' axial-to-centre chirality transfer in the Nazarov reaction.

The potential for electrocyclic reactions to generate high levels of molecular complexity has been extensively demonstrated, nowhere more so than in numerous biomimetic 8π-6π cascades.[23] In Trauner's synthesis of diastereomeric polyketides (−)-SNF4435 C and (+)-SNF4435 D, the

* *Note that substrate control due to the presence of a chiral auxiliary is considered in the following section,* vide infra.

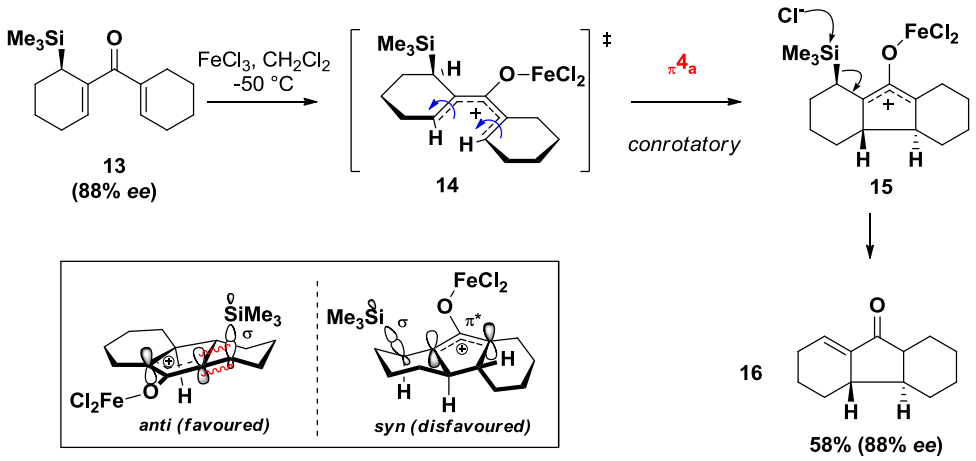
requisite tetraene **8** is generated *in situ* by a Stille coupling reaction, followed by a spontaneous 8π-6π electrocyclic cascade of **8** under the same conditions (Scheme 1.2).[24] Overall the reaction generates four new stereocentres, two of which are all-carbon quaternary, with modest levels of diastereoselectivity (~ 3:1), as a direct consequence of substrate-induced torquoselectivity in the initial 8π reaction. The major stereoisomer **11** is consistent with a helical transition state in which the 4-pyrone substituent is projected away from the bulk of the molecule, minimizing steric repulsion (Scheme 1.2, *inset*).



Scheme 1.2. Trauner's biomimetic total synthesis of SNF4435 C and D.

Denmark utilized a chiral silane to control torquoselectivity in the 4π Nazarov reaction of dinvinyl ketone **13**.[25–27] Upon treatment of enantiomerically-enriched silyl divinyl ketone **13** with iron(III) chloride, the product tricycle **16** was obtained in moderate yield with complete

transmission of asymmetry from the starting material, after concomitant elimination of the silicon group (Scheme 1.3). The stereochemical outcome is rationalized on the basis of a product-like transition state; the allowed conrotatory electrocyclization can afford two different diastereomeric cationic intermediates, termed *syn* and *anti*, but stabilization of this cation by the electron-rich C-Si σ bond is only possible in the *anti* case, and so only the *anti* product **16** is obtained (Scheme 1.3, *inset*).



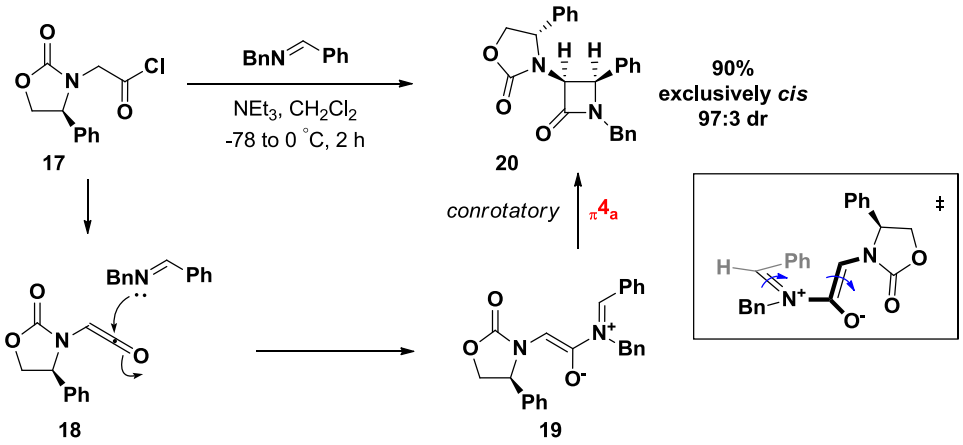
Scheme 1.3. Denmark's chiral silane-controlled torquoselective Nazarov reaction.

1.1.3.2 Chiral Auxiliary Control

Substrate control directed by a chiral centre already present in the molecule is not always a convenient way to achieve torquoselectivity, particularly when this chiral centre is absent from the structure that is ultimately desired. In such cases, chiral auxiliaries may be employed as removable directing-groups for torquoselective electrocyclization.

This approach has been applied extensively to the Staudinger reaction, where nucleophilic addition of an imine to a ketene generates an intermediate zwitterion, which undergoes conrotatory 4π electrocyclization to afford the corresponding β-lactam.[28] Chiral oxazolidone auxiliaries have been particularly successful in this application.[29–40] In 1985 Evans demonstrated that such an auxiliary performed admirably in the Staudinger reaction, giving exclusively the

cis-substituted β-lactam **20** with diastereoselectivities of up to 97:3 and yields of up to 90% (Scheme 1.4).[30] The stereochemistry of the resulting lactam is consistent with a transition state where the auxiliary adopts a conformation minimizing allylic strain and the large phenyl group is projected away from the bulk of the molecule (Scheme 1.4, *inset*).



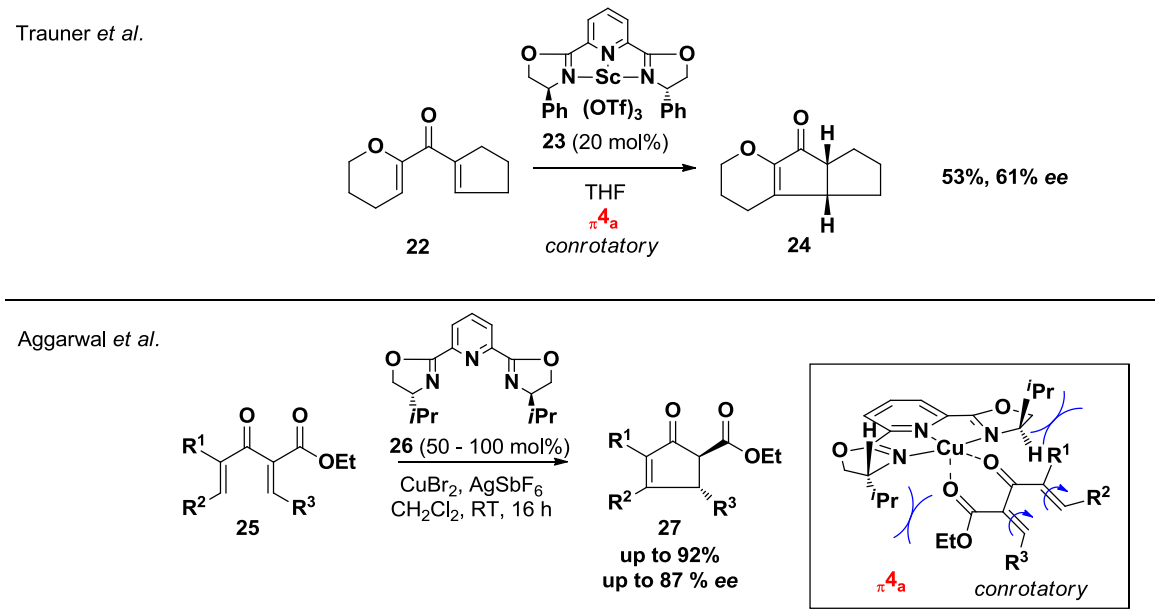
Scheme 1.4. Evans' auxiliary-controlled torquoselective Staudinger reaction.

Whilst the use of auxiliaries is certainly a powerful and reliable method for asymmetric induction, their impact on step- and atom-economy means they are generally disfavoured in synthesis if catalytic asymmetric methodologies are available.

1.1.3.3 Chiral Catalyst Control

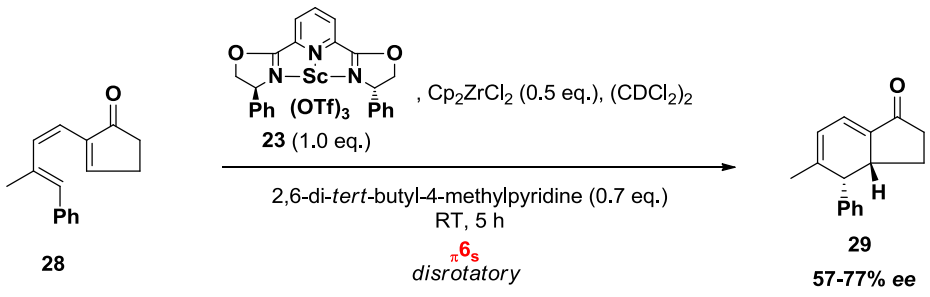
The use of catalysts to control torquoselectivity is a field dominated by the use of chiral acids to induce cationic cyclization in the presence of a closely-associated chiral counter-anion. The first examples of such catalysis were disclosed independently by Trauner[41,42] and Aggarwal,[43] who both utilized Lewis acids with chiral C_2-symmetric bisoxazoline ligands to invoke torquoselective 4π Nazarov reactions of divinyl ketones **22** and **25** respectively (Scheme 1.5). Although neither group probed the precise interaction between the catalyst and substrate, Aggarwal proposed a transition state where bidentate chelation of the metal causes a steric clash between the bulky ^{t}Pr groups on the catalyst and the alkene substituents (Scheme 1.5, *inset*). Lewis acids have

subsequently been used extensively in the catalysis of the Nazarov reaction.[44–49] A limitation of this methodology, however, is the requirement for heteroatomic substitution to achieve the required bidentate binding.



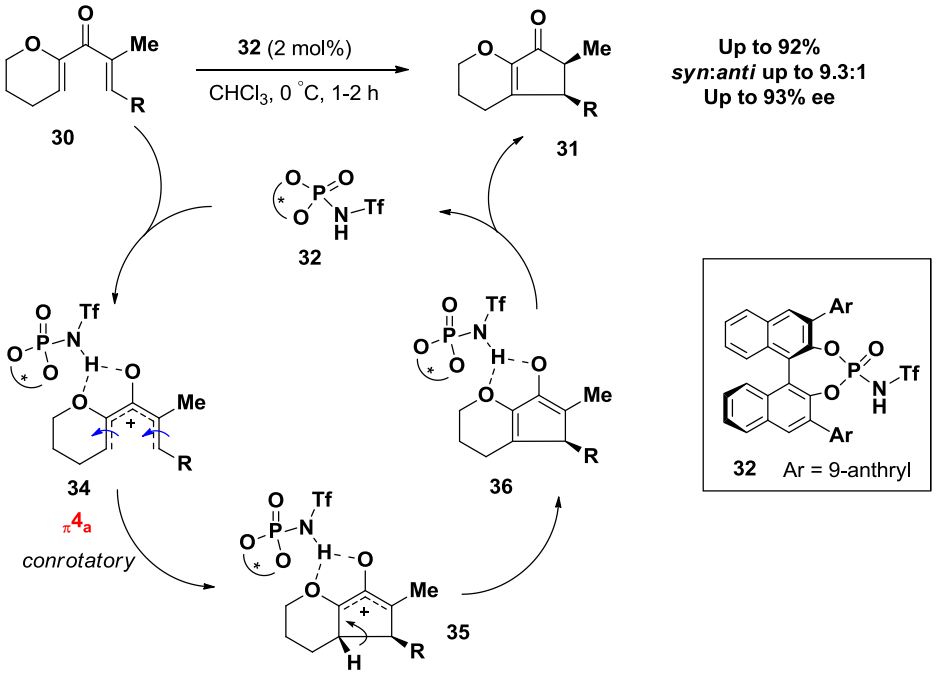
Scheme 1.5. Lewis acid-catalysed asymmetric Nazarov reactions.

Trauner has employed the same Sc(III)/pybox catalyst system in the only example of a catalytic asymmetric 6π [1,6]-electrocyclization (Scheme 1.6).[50] Whilst the reaction requires a stoichiometric quantity of catalyst and gave only modest enantioselectivity, it provides proof-of-principle that catalysis of such "neutral" electrocyclizations is viable (*cf.* the Nazarov reaction, where the species undergoing electrocyclization is formally cationic).[51]



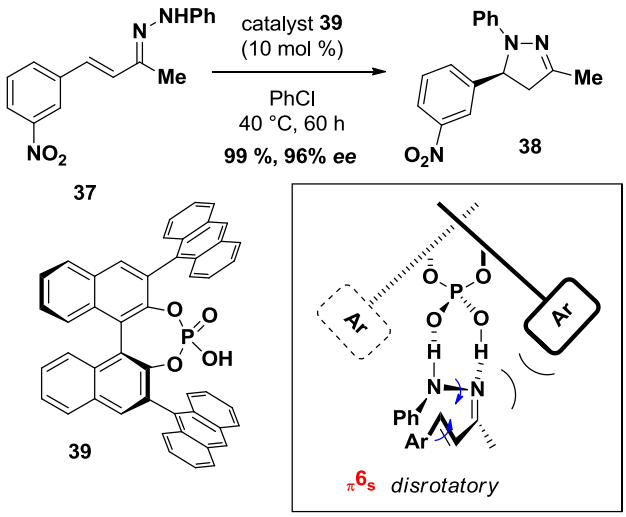
Scheme 1.6. Trauner's asymmetric 6π [1,6]-electrocyclization.

Whilst the use of Lewis acids is most prevalent, Brønsted acids have also been demonstrated to be effective in the asymmetric catalysis of electrocyclic reactions. Rueping has utilized chiral *N*-triflyl phosphoramide (NTPA) **32** in the asymmetric Nazarov reaction, achieving outstanding enantioselectivities of up to 93% ee with very low catalyst loading (Scheme 1.7).[52,53] The authors propose a mechanism involving bifurcated hydrogen-bonded intermediate **34**, although the exact substrate-catalyst interaction leading to asymmetric induction is not indicated. More recently a tandem Nazarov-halogenation procedure has been developed as an extension of this work.[54]



Scheme 1.7. Rueping's Brønsted acid-catalysed asymmetric Nazarov reaction.

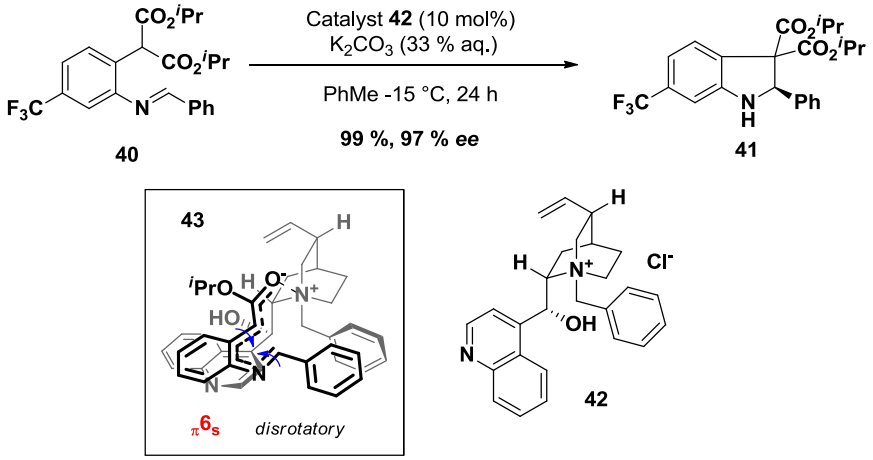
Chiral Brønsted acids have also been applied to the asymmetric catalysis of 6π electrocyclizations. In 2009, List *et al.* disclosed the electrocyclic ring closure of α,β-unsaturated hydrazones **37** to the corresponding optically-active pyrazoline **38**; BINOL-derived phosphoric acid **39** gave up to 99% yield and 96% ee with modest catalyst loading of 10 mol% (Scheme 1.8).[55,56]



Scheme 1.8. List's Brønsted acid catalysed asymmetric 6π electrocyclization.

The observed absolute stereochemical outcome is consistent with the model proposed by Goodman for the BINOL-derived phosphoric acid-catalysed Strecker[57] and related reactions.[58] The phosphoric acid acts both as a Brønsted acid and base, simultaneously activating the amine portion of the hydrazone by deprotonation, and the imine portion by protonation. The torquoselectivity is therefore controlled by the developing steric clash with the large aromatic groups on the catalyst, and so cyclization occurs with the *N*-Ph group moving away from the catalyst bulk (Scheme 1.8, *inset*).

The only catalytic asymmetric 6π electrocyclization of an anionic system is the work of Smith *et al.*[59] Inspired by the work of Speckamp,[60,61] the authors investigated the deprotonation-cyclization of benzaldimines to the corresponding indolines. This was achieved under mild conditions: employing aqueous potassium carbonate and *N*-benzylcinchonidinium chloride **42** as a chiral phase-transfer catalyst the desired indoline **41** was obtained in 99% yield and 97% ee (Scheme 1.9).

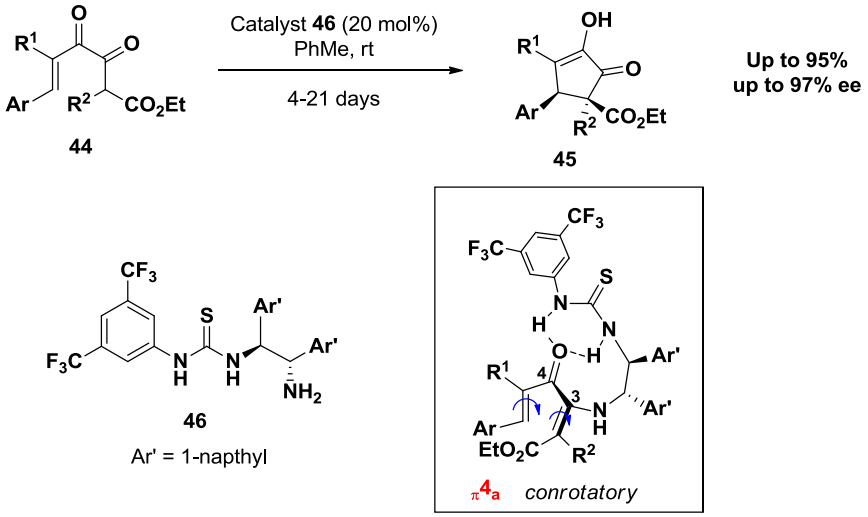


Scheme 1.9. Smith's phase-transfer catalysed asymmetric 6π electrocyclization.*

The sense of asymmetric induction is consistent with the model proposed by Corey and Lygo for related phase-transfer catalysed processes:[62,63] coordination of the enolate to the least hindered quadrant of the ammonium cation, coupled with non-covalent π-stacking interactions leads to a tight ion pair resembling **43**, where disrotatory electrocyclization occurs with the phenyl ring moving away from the substrate bulk.

A major advantage of the chiral auxiliary method discussed in the previous section is that the source of chirality is covalently bound, and therefore in fixed close proximity to the site of electrocyclization. Such covalent interactions have also been used catalytically; Tius employed chiral aminothiourea **46** in the Nazarov reaction of α,β-unsaturated 1,2-diones **44**, achieving up to 95% yield and 97% ee, although requiring rather long reaction times (Scheme 1.10).[64–66]

* *Note that in the model for asymmetric induction an ester group has been omitted for clarity.*



Scheme 1.10. Tius' organocatalytic Nazarov reaction.

The authors propose that the torquoselectivity observed is a consequence of the catalyst imposing a torsion upon the C3-C4 bond, favouring a single mode of conrotation.

Whilst the strategies outlined show remarkable creativity, there remain very few electrocyclic reactions amenable to asymmetric catalysis, with the vast majority of studies directed towards the Nazarov reaction.

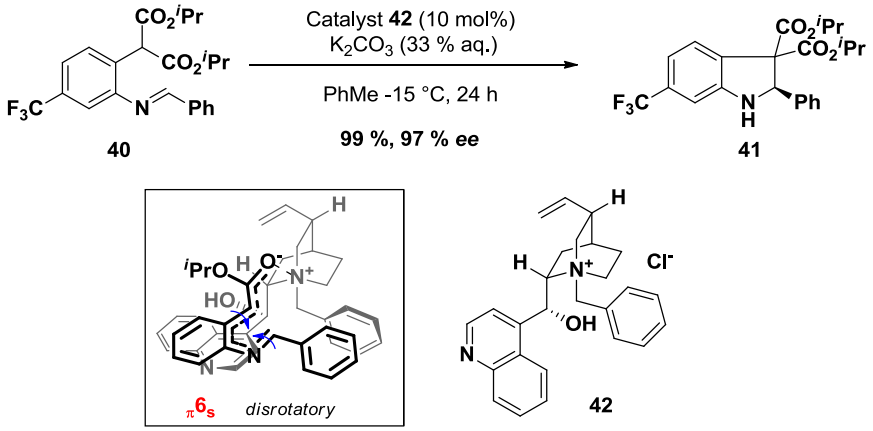
1.2 Aims of the Project: Developing New Catalytic Asymmetric Electrocyclic Reactions

We hope to expand the field of asymmetric electrocyclization: we are interested in the development of new catalytic methods to control torquoselectivity in electrocyclic reactions, the deployment of known methodologies to electrocyclic manifolds that remain untouched by catalysis, and the application of these methods to generating highly complex stereodefined molecules.

2. 8Π ELECTROCYCLIZATION

2.1 Introduction

We hoped to apply the experience gained within our research group in the field of catalytic asymmetric 6π electrocyclization to the 8π domain. In the 6π series, deprotonation of the malonate substrate *in situ* generates the requisite anion possessing the six conjugated π-electrons necessary for the electrocyclization to occur, whilst the presence of a chiral counter-ion directs the torquoselectivity of the ring-closure (Scheme 2.1).[59]



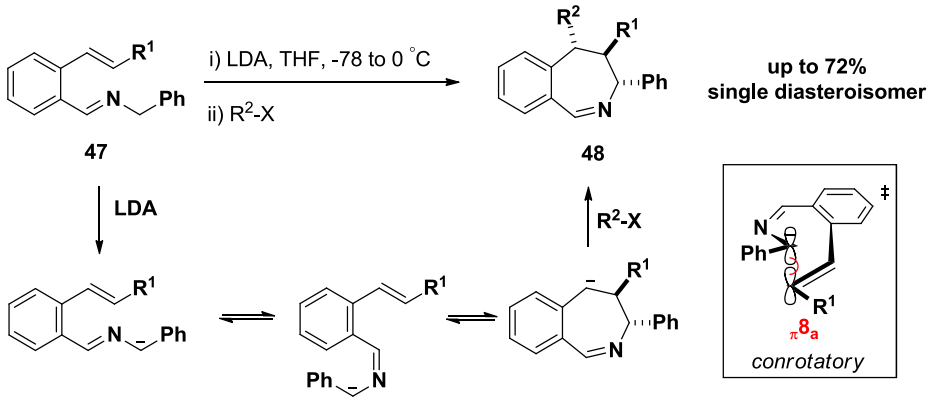
Scheme 2.1.

It follows that necessary conditions for the use of this methodology are that the species undergoing electrocyclization is anionic (so that the counter-ion remains tightly bound to it), and that its precursor is sufficiently acidic to be deprotonated under the mild phase-transfer conditions.

2.2 *o*-Vinyl Benzaldimines

We were interested in the 8π electrocyclic reaction reported by Würthwein *et al.* in 2004, where *N*-benzylstyryl Schiff base **47** was deprotonated using LDA and, upon warming above

−10 °C, cyclized to afford 7-membered arylimine **48** in good yield (Scheme 2.2).[67] Exposure of the corresponding (*Z*)-alkene to the same reaction conditions gave a *syn* diastereomeric relationship between the Ph and R^1 substituents, attesting to the fact that the reaction is electrocyclic, and therefore subject to the Woodward-Hoffmann rules; the helical transition state is a consequence of the conrotatory nature of the reaction (Scheme 2.2, *inset*).



Scheme 2.2. Würthwein's racemic 8π electrocyclization using strong base.

The reaction is not immediately amenable to phase-transfer conditions since a strong base is required to remove the benzylic proton ($pK_a \approx 25$ in DMSO[68,69]). We therefore envisaged a related system in which the benzylic proton is acidified by the positioning of appropriate electron-withdrawing groups. Given the successful use of malonates under phase-transfer conditions within our research group, our initial target was malonate **49** (Figure 2.1).

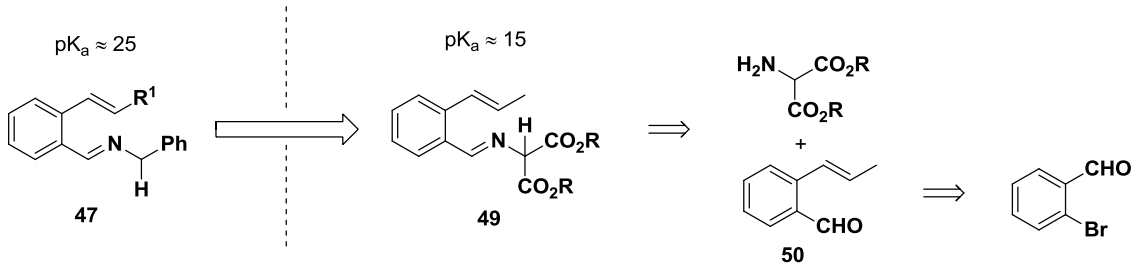
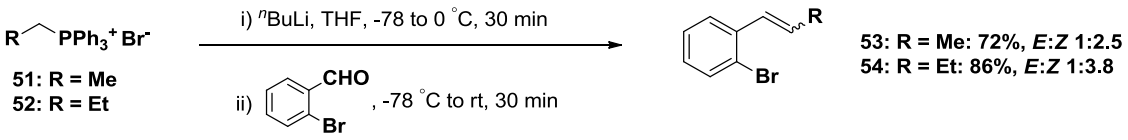


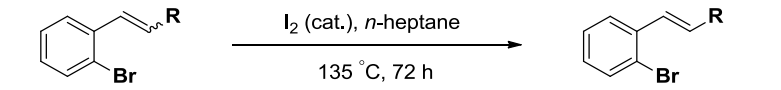
Figure 2.1. Phase-transfer catalysed electrocyclization – substrate design and retrosynthesis.

The synthetic route to **49** was based on the route followed by Würthwein *et al.* Wittig olefination of 2-bromobenzaldehyde with the ylides formed *in situ* from salts **51** and **52** afforded bromostyrenes **53** and **54** in good yields, but with poor stereoselectivity in favour of the *Z*-isomers (Scheme 2.3).



Scheme 2.3.

Although the isomers were inseparable by column chromatography, it was possible to convert the majority of the material to the thermodynamically-favoured (*E*)-stereochemistry by iodine-catalysed isomerization;[70] a solution of the mixed alkene isomers was dissolved in *n*-heptane and heated to 130 °C in a sealed tube for 72 h, which gave isomerically-enriched products **53** and **54** in excellent yields after purification and with satisfactory *E*:*Z* ratios of up to 16:1 and 21:1 respectively (Scheme 2.4).

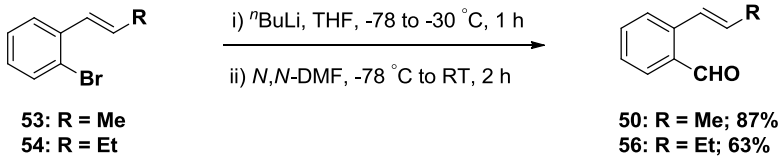


53: R = Me: *E*:*Z* 1:2.5
54: R = Et: *E*:*Z* 1:3.8

53: R = Me: 90%, *E*:*Z* 16:1
54: R = Et: quant., *E*:*Z* 21:1

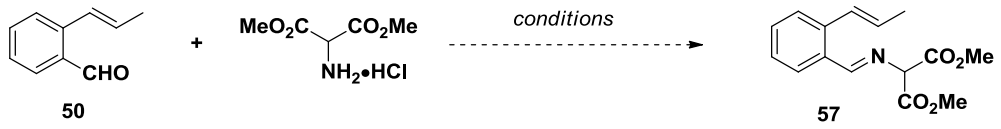
Scheme 2.4.

Formation of the desired aldehydes **50** and **56** was achieved by a tandem lithium-halogen exchange-formylation procedure.[71] This proceeded in good yield in both cases, and with no degradation of the *E*:*Z* ratio (Scheme 2.5).



Scheme 2.5.

With these aldehydes in hand our attention turned to forming the desired malonyl imine **57**. Unfortunately, the steric bulk of the amine and the tempered electrophilicity of the conjugated aldehyde led to poor conversion under all conditions attempted. The use of 4 Å molecular sieves in methanol gave the best crude conversion (Table 2.1, entry 2), however no imine was observed after column chromatography, and 2D-TLC analysis confirmed the instability of the imine with respect to hydrolysis on silica gel.



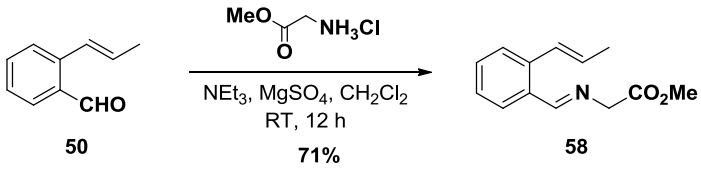
Entry[i]	Conditions[ii]	Outcome (conversion)[iii]
1[72]	$MgSO_4$, CH_2Cl_2, RT, 16 h	No reaction
2	4 Å MS, MeOH, RT, 16 h	SM (30%), Imine (50%), Unknown (20%)
3	4 Å MS, CH_2Cl_2, RT, 16 h	No reaction
4	$MgSO_4$, MeOH, RT, 16 h	SM (70%), Unknown (30%), imine (trace)
5[73]	$MgSO_4$, NEt_3, CH_2Cl_2, RT, 16 h	SM (70%), Imine (30%)
6[74]	Na_2CO_3, H_2O, 40 °C (45 min) *then* RT (16 h)	No reaction

[i] *References given where literature procedures were followed.* [ii] *All reactions were carried out on 20−100 mg scale (aldehyde) at a concentration of ~0.1 M in the solvent indicated.* [iii] *Determined by TLC, MS and crude ^1H NMR spectral analysis. Imine formation is determined by the appearance of a diagnostic singlet at 8.72 ppm.*

Table 2.1.

All other attempts to effect this transformation gave poorer conversion; in the absence of a quantitative method of forming the imine, or means to purify it, we decided to explore the synthesis of alternative substrates.

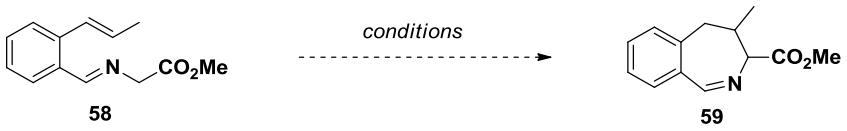
Greater success was enjoyed in the synthesis of glycine-derived imine **58**, which was formed with complete conversion and 71% isolated yield from aldehyde **50** and glycine methyl ester hydrochloride (Scheme 2.6).



Scheme 2.6.

We were optimistic about the deployment of this substrate under the phase-transfer conditions envisaged for the electrocyclization: such glycine-derived Schiff bases are ubiquitous in phase-transfer catalysed asymmetric alkylation studies.[63,75–77] The imine was extremely unstable with respect to hydrolysis, and therefore could not be purified by column chromatography,[*] but was formed in sufficient purity for use crude in the electrocyclization studies that follow (Table 2.2).

[*] *When attempted, column chromatography afforded only the aldehyde* ***50****. 2D-TLC analysis confirmed the instability of imine* ***58*** *on silica gel.*



Entry[i]	Conditions	Outcome[ii]
1[59]	Cs_2CO_3, PhMe, RT, 16 h	Aldehyde **50** recovered[iii]
2	Bu_4NBr, aq. K_2CO_3, PhMe, RT, 16 h	Aldehyde **50** recovered[iii]
3[67]	LDA, THF, −40 °C to RT, H^+ quench, 90 min	Aldehyde **50** recovered[iii]
4[67]	LDA, THF, −40 °C to RT, MeI quench, 90 min	Aldehyde **50** recovered + unidentified aliphatic side-product

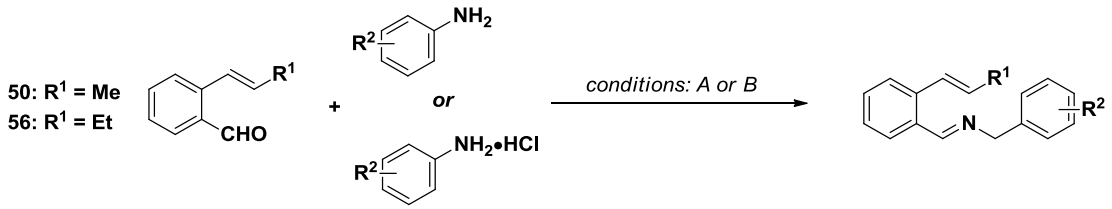
[i] *References given where literature procedures were followed.* [ii] *Determined by ^1H NMR analysis of the reaction mixture.* [iii] *TLC analysis indicated the aldehyde **50** was formed during acidic work-up. Its formation is indicative of imine **58** failure to react.*

Table 2.2.

The cyclization of imine **58** was initially attempted under conditions that had been successful in previous studies within the group. However, treatment with caesium carbonate in toluene gave no reaction, and the aldehyde **50** was recovered after acidic work-up (Table 2.2, entry 1). Similarly, treatment under racemic phase-transfer catalysed conditions did not induce cyclization (Table 2.2, entry 2). Given these failures, we attempted to carry out the reaction under the strong basic conditions employed racemically by Würthwein *et al*: disappointingly, as with the weaker bases, no reaction was observed and the aldehyde **50** was recovered, both when H^+ and MeI were employed as electrophiles to trap the product anion (Table 2.2, entries 3 & 4).

The failure of glycine-derived imine **58** to react was perhaps not surprising: the electrocyclic ring-closure of benzylamine-derived imines **47** is rationalized on the basis of stabilization of the cyclic anion relative to the open-chain compound due to the nodal properties of the HOMO placing negative charge on the electronegative nitrogen.[78,79] It follows that by acidifying the substrate (in order to achieve deprotonation under phase-transfer conditions) the electrocyclic ring-closure is disfavoured, since the open-chain enolate anion is much more stable than the cyclic benzyl anion.

With this in mind, we proceeded to synthesize imines **60**-**65**, derived from benzylamine and aryl-substituted benzylamines, in the hope that these substrates might prove sufficiently acidic to undergo deprotonation under phase-transfer conditions, and the resulting anions sufficiently high in energy for electrocyclic ring-closure to remain favourable. Imine formation for **60**,**61**, **64** and **65** was carried out using 3 Å molecular sieves in dichloromethane, giving yields of 85−93%. **62** and **63** were formed from benzylamine salts, and were therefore formed under triethylamine buffered conditions in 94−99% yield (Table 2.3).

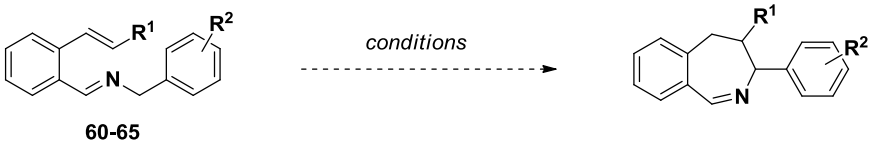


Entry	R^1	R^2	Conditions[i]	Product	Yield / %[ii]
1	Me	H	A	**60**	92
2	Et	H	A	**61**	93
3	Et	2-NO_2	B	**62**	99
4	Et	3-NO_2	B	**63**	94
5	Me	2-CF_3	A	**64**	85
6	Me	4-CF_3	A	**65**	92

[i] *A: Amine (1.0 eq.), aldehyde (1.0 eq.), 3 Å MS, CH_2Cl_2 (0.25 M), RT, 16 h. B: Amine (1.0 eq.), aldehyde (1.1 eq.), triethylamine (1.1 eq.), CH_2Cl_2 (0.1 M), RT, 16 h.* [ii] *For isolated material.*

Table 2.3.

We initially attempted to cyclize these imines under phase-transfer conditions, employing 50% aqueous sodium hydroxide and tetra-*n*-butylammonium bromide in toluene; unfortunately the substrates uniformly failed to cyclize (Table 2.4, entries 1−5). Surprisingly, even under the strong base conditions previously reported[67] only unsubstituted benzylimines **60** and **61** cyclized (Table 2.3, entries 6−7) – the other substrates resulting only in recovered starting material (Table 2.4, entries 8−11).



60-65

Entry	R^1	R^2	Conditions[i]	Product	Yield / % [iii]
1	Et	H	A	No reaction[ii]	-
2	Me	2-CF_3	A	No reaction[ii]	-
3	Me	4-CF_3	A	No reaction[ii]	-
4	Et	2-NO_2	A	No reaction[ii]	-
5	Et	4-NO_2	A	No reaction[ii]	-
6	Et	H	B	**66**	73
7	Me	H	B	**67**	38
8	Me	2-CF_3	B	No reaction[ii]	-
9	Me	4-CF_3	B	No reaction[ii]	-
10	Et	2-NO_2	B	No reaction[ii]	-
11	Et	4-NO_2	B	No reaction[ii]	-

[i] *All reactions were carried out on 20−50 mg scale at a concentration of 0.04−0.1 M. A: NBu_4Br, NaOH (50% aq.), PhMe, RT, 16 h. B: LDA, THF, −40 °C to RT, H^+ quench, 90 min.* [ii] *Determined by analysis of the crude ^1H NMR spectrum.* [iii] *For isolated material.*

Table 2.4.

These results indicate that even minimal stabilization of the open-chain anion leads to poor reactivity, rendering phase-transfer catalysis ineffective in this transformation: paradoxically substrate acidicification to allow deprotonation under phase-transfer conditions necessarily renders it inert to cyclization.

2.3 α,β-Unsaturated Malonate Benzaldimines

Re-examining the substrate employed successfully in the group's investigation of 6π electrocyclization, we hoped to devise a closely-related 8π analogue that would display the same reactivity.

We envisaged α,β-unsaturated malonate **69** as a vinylogous analogue of the malonate system (**68**) previously investigated in the 6π series (Figure 2.2); deprotonation would afford a delocalized anion that could undergo electrocyclization either through the carbon α- or γ- to the esters. We hoped that the 8π helical transition state **70**, imposed by the Woodward-Hoffmann rules, would be favoured over the 6π planar transition state **72**, since it would place the reacting centres in closer proximity with less allylic strain, allowing the 8π mode to dominate. This is the case in the numerous 8π-6π cascade electrocyclizations, where the 8π reaction invariably occurs prior to the 6π.[23]

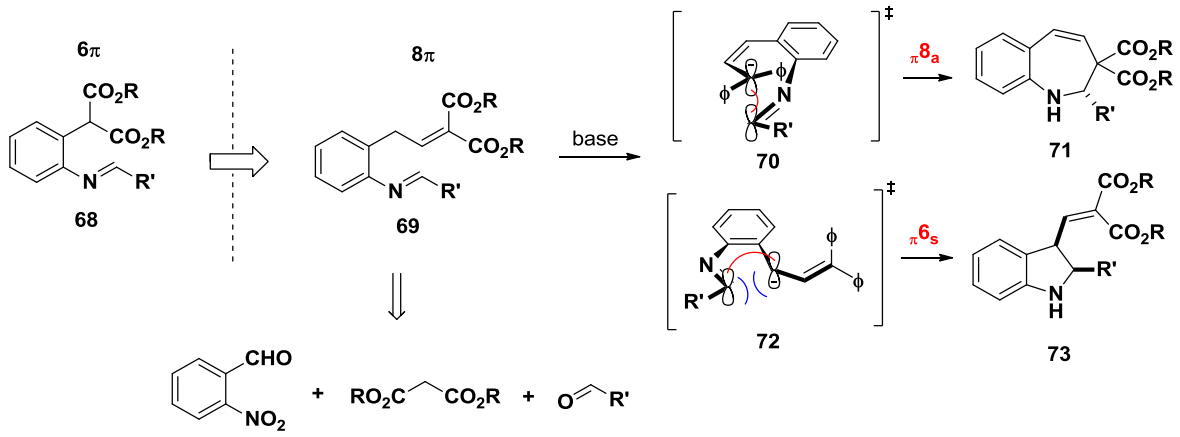
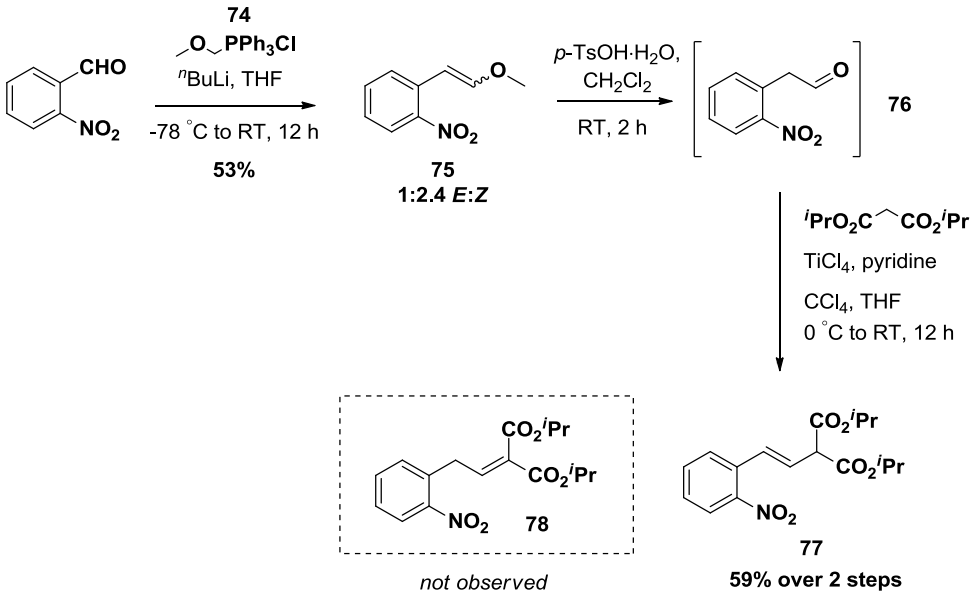


Figure 2.2. 8π electrocyclization: substrate design and retrosynthesis.

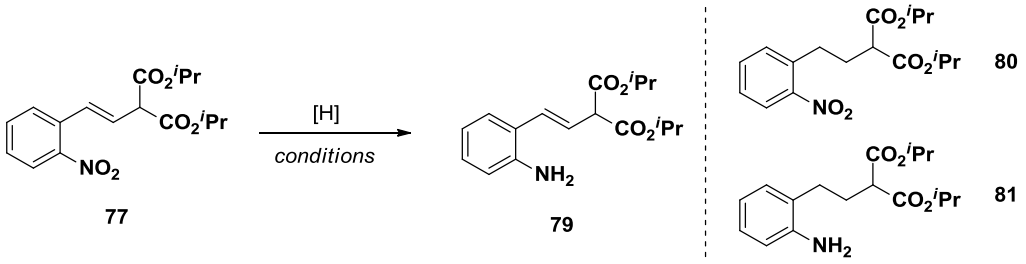
We hoped to access the aniline precursor to **69** by reduction of the corresponding nitroarene, formed from 2-nitrobenzaldehyde *via* an aldehyde homologation and Knoevenagel condensation.

Treatment of 2-nitrobenzaldehyde with Wittig salt **74** gave access to enol ether **75** in a moderate 53% yield, and as an inconsequential mixture of alkene isomers. Acidic hydrolysis of the enol ether followed by Knoevenagel condensation of the crude aldehyde **76** with diisopropyl malonate afforded nitroarene **77** in 59% over two steps (Scheme 2.7). Although we had planned to form alkene isomer **78**, the formation of **77** was not deemed to be problematic, since the deprotonation of its corresponding imine ought to generate the same delocalized anion as **78**.



Scheme 2.7.

Attempts to reduce the aromatic nitro group using catalytic palladium on carbon and molecular hydrogen were unsuccessful due to facile reduction of the alkene and formation of the saturated aniline **81** in good yield. Efforts to slow this reduction and isolate the desired unsaturated aniline **79** before further reduction had occurred were unsuccessful: when the reaction was carried out in ethyl acetate the reaction slowed considerably, but only afforded saturated nitroarene **80** and aniline **81**, indicating that the alkene is reduced more rapidly than the nitro group under these conditions (Table 2.5, entries 1 & 2). Similarly, use of metallic iron failed to cleanly reduce the aromatic nitro group, giving poor reactivity at room temperature, and an intractable mixture of products when heated to reflux (Table 2.5, entries 3 & 4). Finally the mild tin(II) chloride reduction conditions introduced by Bellamy were found to be highly effective, and gave the aniline **79** in 63% yield (Table 2.5, entry 5).[80]

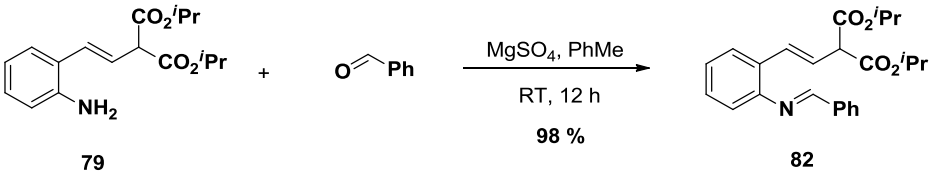


Entry	Conditions	Outcome[i] (yield[ii])
1	H_2, Pd/C, EtOH, RT, 60 min	**81** (89%)
2	H_2, Pd/C, EtOAc, RT, 60 min	**80** (35%), **81** (33%)
3	Fe^0, AcOH, EtOH, reflux, 60 min	Complex mixture
4	Fe^0, AcOH, EtOH, RT, 60 min	No reaction, recovered **77**
5	$SnCl_2 \cdot 2H_2O$, EtOAc, 70 °C, 60 min	**79** (63%)

[i] *Determined by crude ^1H NMR, MS and TLC analysis.* [ii] *Where quoted, yields relate to pure isolated material.*

Table 2.5.

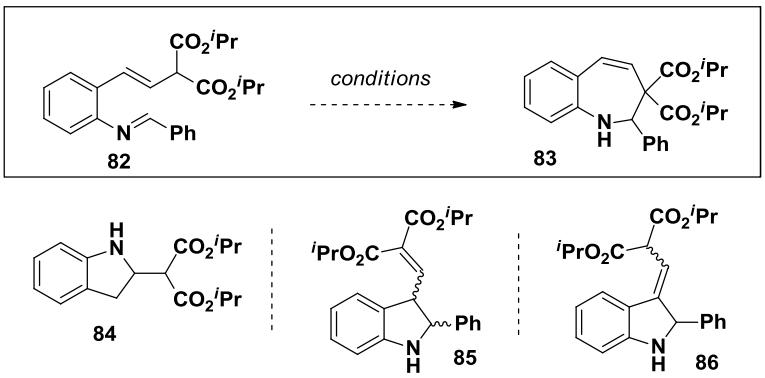
Imine formation with this aniline was facile, and proceeded in almost quantitative yield to afford benzaldimine **82**, the substrate for our studies into asymmetric 8π electrocyclization (Scheme 2.8).

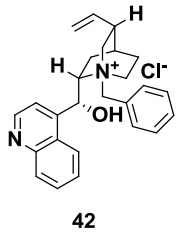


Scheme 2.8.

Attempts to induce electrocyclic ring-closure of this substrate were extensive,[*] and are summarized in Table 2.6.

[*] *For a full account, see Appendix 8.1, p. 276*





42

Entry	Conditions[i]				Outcome[ii, iii]
	Reagent/catalyst	Solvent	T / °C	t / h	
1	Cs_2CO_3 (1.1 eq.)	PhMe	RT	16	**82** (75%), unknown (25%)
2	cat. **42** (0.1 eq.), K_2CO_3 (33% aq.)	1:1 PhMe:CH_2Cl_2	RT	16	**82** (100%)
3	LDA (1.2 eq.)	THF	−78 °C to RT	4	**82** (100%)
4	$Zn(OAc)_2$ (0.1 eq.)	MeOH	RT	16 h	**86** (trace), **85** (30%), unknown (70%)[iv]
5	$Sc(OTf)_3$ (0.1 eq.)	THF	RT	16 h	**86** (50%), **85** (50%)
6	$ZnBr_2$ (0.1 eq.)	CH_2Cl_2	RT	16 h	**85** (50%), unknown (50%)[iv]

[i] *All reactions were carried out on 20−50 mg scale at concentrations of 0.1 M in the solvent indicated.* [ii] *Where indicated, product ratios are determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Values are approximate.* [iii] *"Unknown" indicates compounds or mixture of compounds visible in the ^{1}H NMR spectrum of the crude reaction mixture that could not be isolated by chromatography, and whose identity was not established.* [iv] *Although not observed in the crude ^{1}H NMR spectrum, styrene **86** was isolated in small quantities after silica gel chromatography, presumably due to acid-catalyzed formation on silica gel.*

Table 2.6.

In particular, aqueous potassium carbonate was found to be completely ineffective under phase-transfer catalysed conditions (Table 2.6, entry 2), whilst caesium carbonate alone gave some reactivity, but afforded only a mixture of multiple unidentified species as a minor component of the crude reaction mixture. Surprisingly the use of LDA also afforded only recovered imine, indicating that deprotonation alone is not sufficient to induce cyclization in this case.

We hoped that the use of an acid catalyst might stabilize the product anion on nitrogen, favouring the cyclization. Lewis acids, particularly scandium(III) triflate, zinc(II) acetate and zinc(II) bromide, were successful in inducing 6π [1,5]-electrocyclic ring closure, affording a mixture of isomeric indolines **85** (as an inseparable 3:1 mixture of diastereoisomers) and **86**, albeit with modest conversion. Interestingly, in some cases **86** was not present in the crude reaction mixture, but was isolated with **85** after silica gel chromatography, suggesting its formation by isomerization on the column. This made isolation of either isomer extremely challenging, with the unfortunate consequence that this process could not be used reliably for the formation of vinylindolines **85**.

Although the precise reason for the failure of this substrate to undergo 8π electrocyclization remains unknown, we speculate that the necessity for double-bond isomerization prior to the 8π ring-closure means that the 6π cyclization (which has no such requirement) outcompetes (Figure 2.3).

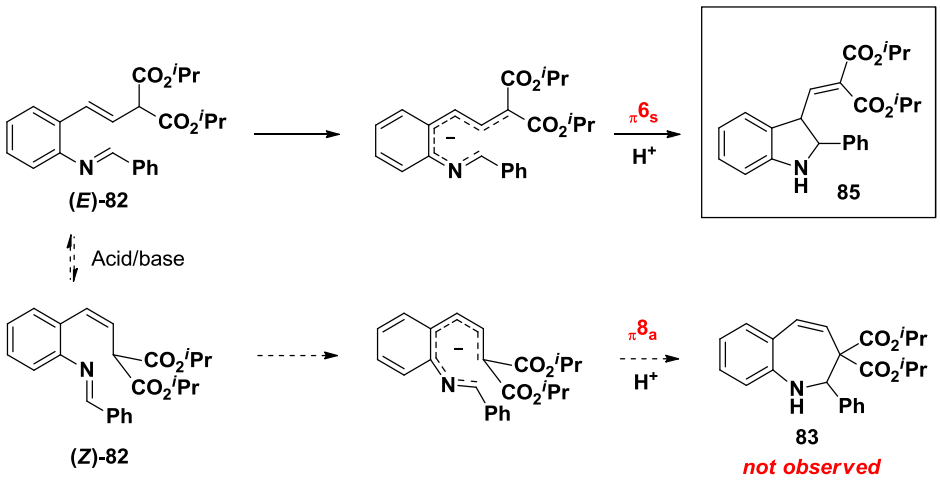


Figure 2.3.

This would explain the observed periselectivity[17] in the Lewis-acid catalysed process, but fails to explain the dearth of electrocyclization under basic conditions.

2.4 "Extended Malonate" Benzaldimines

We hoped that by placing a substituent at the benzylic position, formation of the (*Z*)-configured 8π anion might be favoured (Figure 2.4, *inset*), and therefore lead to 8π electrocyclization in preference to the 6π reaction observed above. Although the possibility of reaction by the alternative 6π mode would still be possible, the inclusion of a substituent at the benzylic position would prevent alkene isomerization in the product (*cf.* Table 2.6), and at least render this a useful 6π process (Figure 2.4).

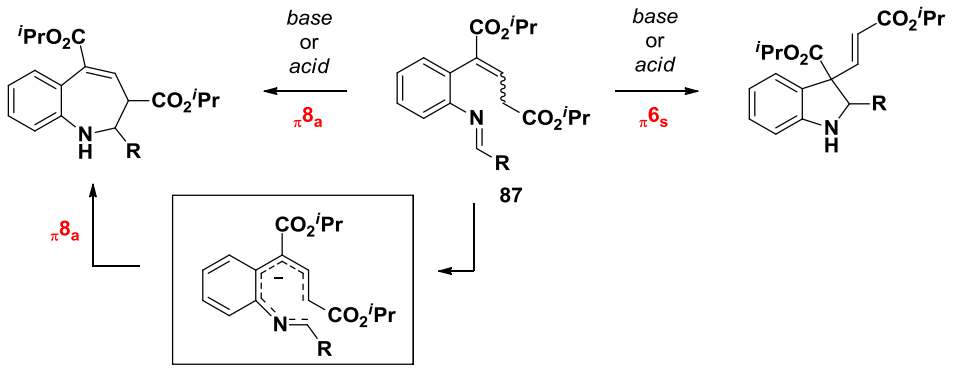
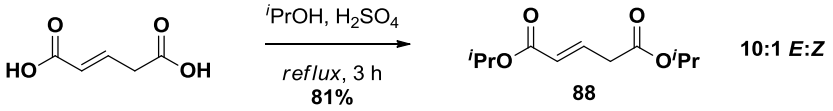


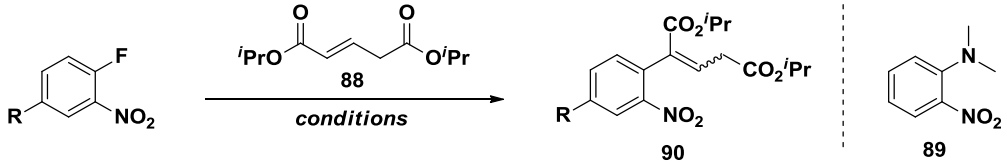
Figure 2.4. Proposed substrate for 8π electrocyclization, and potential alternative 6π pathway.

We therefore set about synthesizing "extended malonate" **87**. We hoped to achieve synthesis of the aniline by a similar S_NAr/reduction pathway as employed by co-workers in the related 6π studies.[59] Thus, double Fischer esterification of glutaconic acid afforded a 10:1 *E*:*Z* mixture of diisopropyl glutaconate **88** in 81% yield, which would be employed as a nucleophile in the subsequent S_NAr reaction (Scheme 2.9).



Scheme 2.9.

Unfortunately, treatment of 2-fluoronitrobenzene with diester **88** in the presence of potassium carbonate in DMF at 80 °C afforded none of the desired S_NAr product; only nitroaniline **89** was obtained, the result of solvent decomposition and subsequent nucleophilic addition (Table 2.7, entry 1).



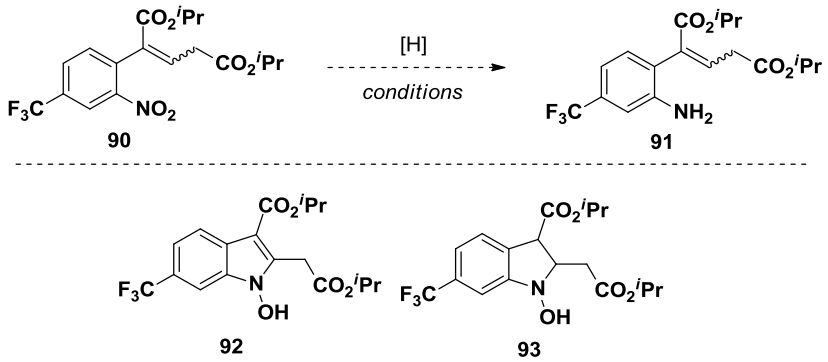
Entry	R	Conditions	Product (yield[i])
1	H	Arene (1 eq.), diester (2 eq.), K_2CO_3 (2 eq.), DMF, 80 °C, 8 h	**89** (43%)
2	H	Arene (1.25 eq.), diester (1 eq.), LDA (1.25 eq.), DMPU (3.0 eq.), THF, −78 °C, 30 min	No reaction
3	CF_3	Arene (1.25 eq.), diester (1 eq.), LDA (1.25 eq.), DMPU (3.0 eq.), THF, −78 °C, 30 min	**90** (52%)
4	CF_3	Arene (3 eq.), diester (1 eq.), LDA (3 eq.), DMPU (3 eq.) 4Å MS, THF, −78 °C, 15 min	**90** (80%)

[i] *Yields quoted for isolated material.*

Table 2.7.

An alternative procedure, employing LDA and carried out in the presence of DMPU for increased nucleophilicity, returned starting material.[81] Switching the electrophilic component to 4-fluoro-3-nitrobenzotrifluoride gave much-improved reactivity, affording the desired S_NAr product in 52% yield at the first attempt. Gratifyingly, by shortening the reaction time to just 15 minutes, addition of molecular sieves, and employing a three-fold excess of the arene and base, the yield was improved to 80%. Surprisingly no over-addition was observed, even in the presence of excess base and electrophile.

Subsequent attempts to reduce the aromatic nitro group were unsuccessful due to the propensity for intramolecular 1,4-addition leading to indoline and indole by-products (Table 2.8).



Entry[i]	Conditions[ii]				Outcome[iii]
	Reagent/catalyst	Solvent	T / °C	t	
1	H_2, Pd/C (10 wt%)	EtOH	RT	6 h	Mostly **90**, trace **91** (crude)[iv]
2	NH_4CO_2H, Pd/C (10 wt%)	MeOH/EtOAc 10:1	50	2 h	No reaction
3	H_2, PtO_2 (10 wt%)	EtOH	RT	1 h; 2.5 h	**93** (1 h); **93** and **92** (2.5 h)[iv]
4	H_2, Pd black (10 wt%)	EtOH	RT	1 h	Complex mixture
5[80]	$SnCl_2 \cdot 2H_2O$	EtOAc	70	16 h	**92** (80%)
6[82]	Zn, NH_4Cl	Acetone/H_2O 5:1	RT	15 min	**93** (60%)
7[83]	In, HCl	H_2O/THF 1:10	RT	20 min	Complex mixture
8[84]	Sm, NH_4Cl, *ultrasound*	MeOH	RT	20 min	No reaction
9	Fe, HCl (3 eq.)	EtOH/H_2O 4:1	RT	1 h	**91** and trace **93** (crude)[v] ***91** not isolated*

[i] *References given where literature procedures were followed.* [ii] *All reactions were carried out on 20−50 mg scale at concentrations of ~0.1 M in the solvent indicated.* [iii] *Where quoted, yields are for isolated material.* [iv] *Determined by TLC and MS analysis.* [v] *Determined by ^{1}H NMR analysis.*

Table 2.8.

Under heterogeneous catalytic hydrogenation conditions, none of the desired aniline was observed (Table 2.8, entries 1−4), although MS evidence indicated that Adams' catalyst[85] led to the formation of *N*-hydroxyindole **92** and *N*-hydroxyindoline **93**; this suggested that the rate of 1,4-addition of the intermediate hydroxylamine was faster than reductive cleavage of the remaining N-O bond, hence that this was not a viable reduction method for obtaining the aniline. The mild tin(II) chloride reduction, successful in the previous malonate system (*vide supra*), was ineffective in forming aniline **91**, instead giving an excellent 80% yield of hydroxyindole **92**. Metal reductions employing zinc, indium and samarium were also unsuccessful (Table 2.8, entries 6−8), although the zinc reaction afforded hydroxyindoline **93** in reasonable yield. Béchamp reduction[86] also failed to provide access to the aniline: the presence of the amine as a minor component was indicated by MS and tentatively by ^{1}H NMR analysis of the crude mixture, however all attempts to isolate this material afforded only hydroxyindoline **93**.

Thus we were unable to obtain a sample of aniline **91**, and studies into the electrocyclization of the resulting imine were discontinued.

2.5 Biaryl Benzaldimines

In a further attempt to achieve enantioselective 8π electrocyclization, we set about the synthesis of ring-constrained substrate **94**. Here the issues of alkene geometry and periselectivity are nullified by the presence of an additional aromatic ring (Figure 2.5).

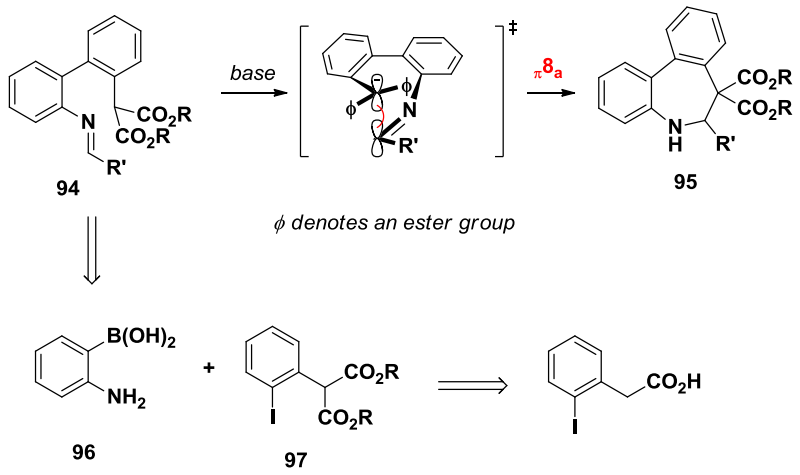
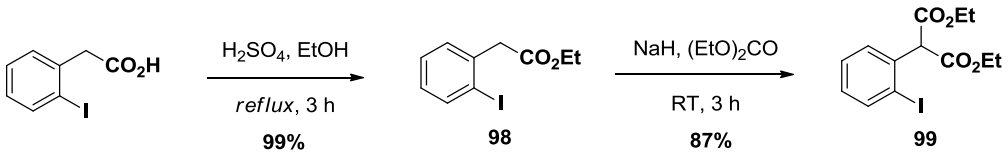


Figure 2.5.

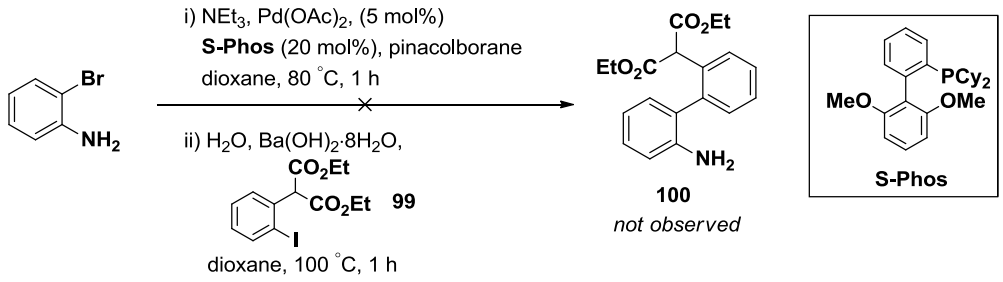
We hoped to form the key aryl-aryl bond *via* a Stille cross-coupling reaction between fragments **96** and **97**, the latter being formed in two precedented steps from 2-iodophenylacetic acid.[87]

Fischer esterification of 2-iodophenylacetic acid proceeded cleanly in ethanol to give the desired ester **98** in 99% isolated yield. The subsequent acylation with diethyl carbonate and sodium hydride afforded Suzuki coupling partner **99** in 87% yield (Scheme 2.10).



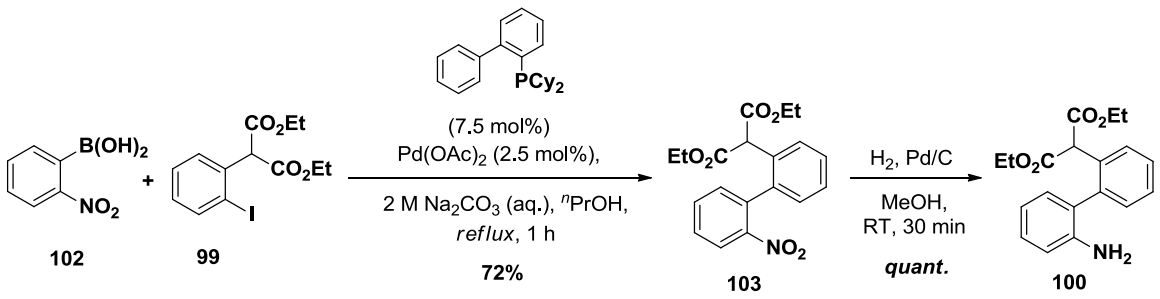
Scheme 2.10.

We initially hoped to couple iodoarene **99** directly with 2-bromoaniline by *in situ* formation of the corresponding boronic ester followed by Suzuki cross-coupling, by analogy to a literature procedure (Scheme 2.11).[88]



Scheme 2.11.

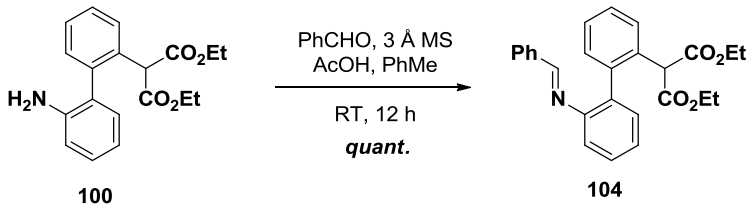
In our hands this afforded none of the desired biaryl **100**, however coupling of nitrarylboronic acid **102** proceeded smoothly to afford **103** in 72% yield; the nitro group was subsequently reduced using catalytic palladium on carbon under hydrogen pressure in quantitative yield (Scheme 2.12).



Scheme 2.12.

The subsequent imine formation was initially carried out using magnesium sulfate in toluene, but this reaction gave just 50% conversion after 16 h; the imine was extremely prone to hydrolysis on silica gel* so an alternative imine formation was sought in order to avoid purification issues. Switching to 3 Å molecular sieves as a dessicant, and employing acetic acid to catalyse the reaction afforded the imine **104** cleanly with no trace of residual starting material (Scheme 2.13).

* *Determined by 2D-TLC.*



Scheme 2.13.

It is noteworthy that the imine displayed axial chirality: NMR analysis indicated that the ester groups were anisochronous, implying that the molecule exhibits restricted rotation on the NMR timescale. Surprisingly the atropisomers were at least partially separable by chiral HPLC, implying a lifetime for rotation about the biaryl axis at room temperature of at least the order of minutes (Figure 2.6).

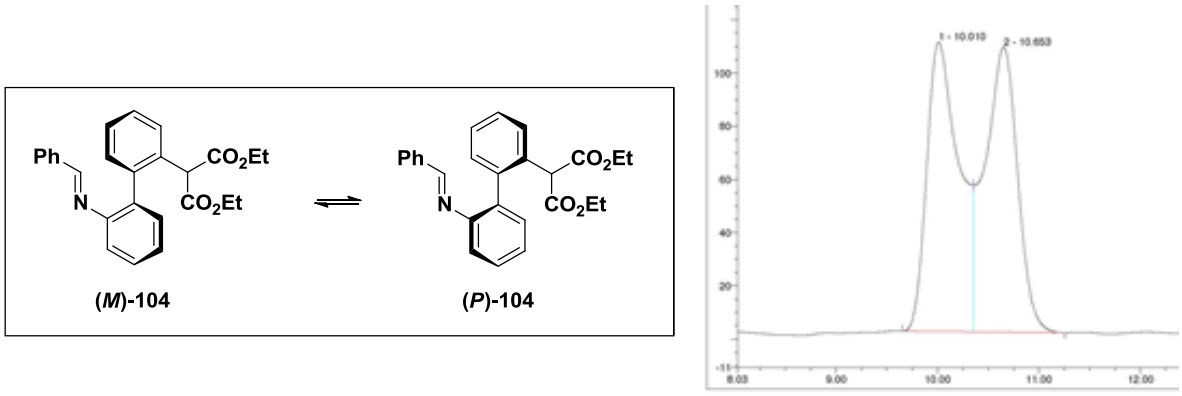
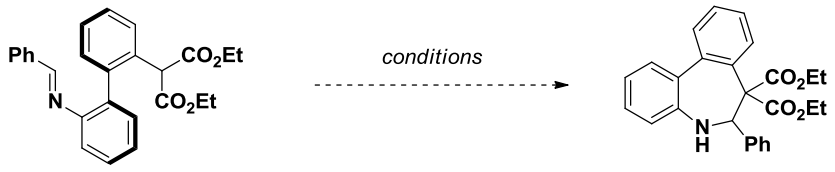


Figure 2.6. Atropisomerism of **104**; chiral HPLC trace of racemic **104**.

This axial chirality is intriguing since it implies that any asymmetric cyclization process must override the inherent preference of the molecule by resolving the atropisomers.

Attempts to induce electrocyclization were carried out under basic conditions and, to our surprise, uniformly gave no reaction. The imine failed to react even under forcing conditions: employing strong base, elevated temperature and extended reaction times, no reactivity was observed (Table 2.9).

The reason for this lack of reactivity is not well understood, but may be a consequence of the severe steric clash between the approaching imine and malonyl anion in the transition state leading to the cyclized product.



(±)-104 105

Entry	Conditions[i]	Outcome[ii]
1	Cs_2CO_3 (1.5 eq.), PhMe, RT, 16 h	No reaction
2	NBu_4Cl (0.1 eq.), 30% K_2CO_3 (aq), PhMe/CH_2Cl_2 5:1, RT, 16 h	No reaction
3	NaH (1.1 eq.), CH_2Cl_2, RT, 16 h	No reaction
4[iii]	NaH (1.1 eq.), PhMe, RT (24 h)	No reaction
	then 60 °C (24 h)	No reaction
	then 85 °C (48 h)	No reaction
5	K_2CO_3 (1.2 eq.), *N*,*N*-DMF, RT, 16 h	No reaction
6	NaH (1.2 eq.), *N*,*N*-DMF, RT, 16 h	No reaction

[i] *All reactions were carried out on 50−150 mg scale at a concentration of ~0.1 M in the solvent indicated.* [ii] *Determined by MS, TLC and ^{1}H NMR analysis.* [iii] *Aliquots removed for analysis after the indicated time periods.*

Table 2.9.

With no trace of reactivity, it was clear that asymmetric electrocyclization of this biaryl substrate was not a viable reaction, and correspondingly it was not further explored.

2.6 Conclusions

The asymmetric catalysis of 8π electrocyclic reactions is an inherently challenging task. In our studies the necessary presence of three conjugated (*Z*)-configured double-bonds has been a constant and significant problem. Unless these elements are placed under ring-constraint (§ 2.5), the natural thermodynamic preference for (*E*)-configuration undoubtedly disfavours the 8π

process, preventing propinquity of the reacting termini of the 8π system. In the case where cyclization was observed (§ 2.3), the competing 6π pathway was dominant, due – at least in part – to the fact that the 6π process did not require any double bond isomerization prior to cyclization.

Our ring-constraint approach to address this issue was unsuccessful: the (*Z*)-stereochemistry was enforced by use of a biaryl system, but this inevitably led to issues of restricted rotation about the aryl-aryl axis, a factor that may have contributed to the failure of this substrate to react.

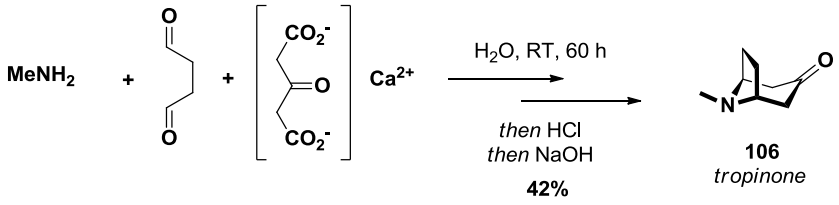
The first catalytic asymmetric 8π electrocyclic reaction remains elusive.

3. CASCADES[89]*

3.1 Introduction

Cascade reactions have the potential to generate molecular complexity with remarkable efficiency: by contrast with stepwise chemical synthesis, where each reaction is followed by purification and isolation of the product, cascade reactions involve multiple discrete sequential intramolecular reaction steps carried out in "one-pot", and without the need for purification of intermediates. The advantages of cascade reactions are clear: by removing the need to isolate and purify intermediates solvent use is minimized and labour costs abated. Waste is also reduced by the removal of multiple purification steps, making processes more sustainable and environmentally-benign.

Robinson was an early pioneer in the field of biomimetic cascade synthesis. In his landmark 1917 synthesis of tropinone, a mixture of methylamine, succinaldehyde and calcium acetonedicarboxylate underwent a remarkable series of imine formation, Mannich and decarboxylation reactions leading ultimately to the target molecule **106**, which was obtained in 42% yield in a single step (Scheme 3.1).[90]

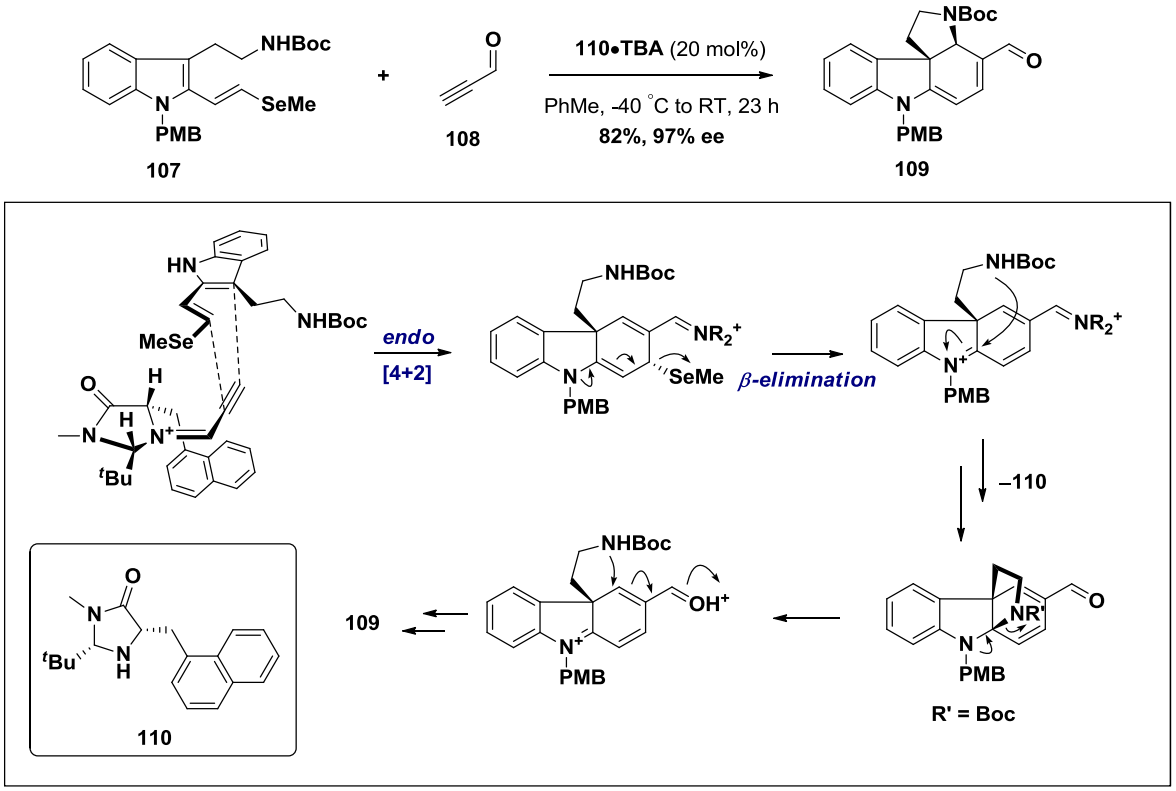


Scheme 3.1.

Although organic synthesis has progressed significantly, cascade reactions remain prominent in the generation of complex molecules.[23,91–95] The field of asymmetric organocatalytic cascade

* *The work presented in this chapter was carried out as a collaborative effort with Dr Eleanor Maciver.*[111]

reactions has emerged only in the past few years,[96–98] but has already been used to spectacular effect by Macmillan *et al.* in the total synthesis of six members of the *Strychnos*, *Aspidosperma* and *Kopsia* families of alkaloid natural products (Scheme 3.2).[99]



Scheme 3.2.

Imidazolidinone salt **110**·TBA* catalysed the *endo*-selective Diels-Alder cycloaddition between tryptamine-derived indole selenide **107** and propynal **108**. A series of acid-catalysed elimination and addition reactions ensued, ultimately leading to aldehyde **109** – a key intermediate in the synthesis of all six natural products – in 82% yield and 97% ee. This intermediate **109** allowed the synthesis of (−)-strychnine – "*for its molecular size…the most complex substance known*"[100] – in just 12 synthetic steps.

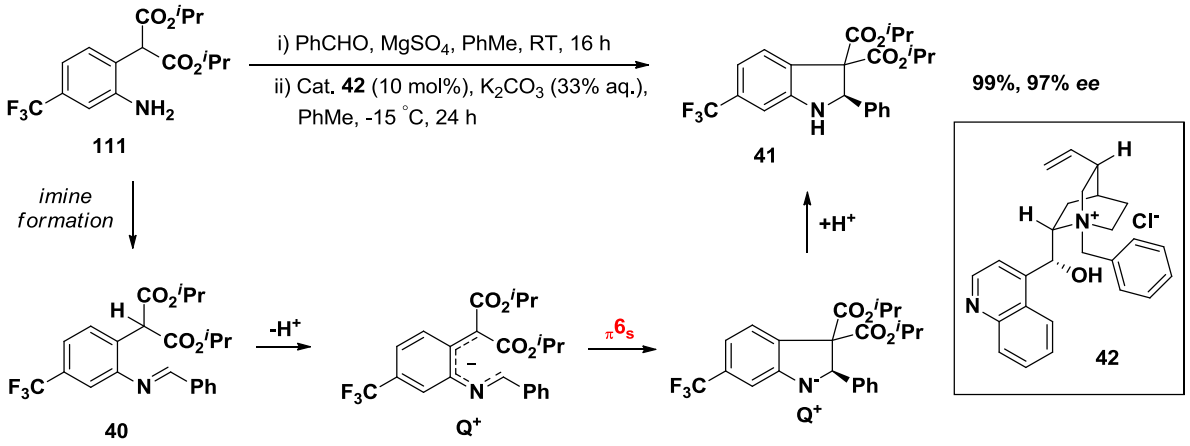
* *TBA = tribromoacetic acid*

Cascades of electrocyclic reactions have been implicated in the biosynthesis of several marine polyketide natural products, typically through sequential 8π-6π electrocyclic ring-closures (*cf.* Scheme 1.2, p. 8).[23]

The development of an organocatalytic cascade reaction incorporating an asymmetric electrocyclization is therefore an interesting and topical synthetic challenge.

3.2 Concept and Aims

Work within the group had demonstrated the efficacy of phase-transfer catalysis as a route to enantiomerically-enriched indolines.[59] The prototypical reaction in this study was the cyclization of malonate imine **40** in the presence of *N*-benzylcinchonidinium chloride **42** and aqueous potassium carbonate. Imines were typically formed from aniline **111** immediately prior to cyclization and used without purification, such that the overall process has been dubbed a two-step "pseudo one-pot" protocol (Scheme 3.3).



Scheme 3.3. Q denotes the quaternary cation component of catalyst **42**.

We hoped to expand considerably on this powerful methodology; it was anticipated that i) by differentiating between the two acidifying groups at the benzylic carbon (**112**, R^1 & R^2) it would be possible to form an all-carbon quaternary stereocentre at this position; and ii) by tethering a

conjugate electrophile onto the aromatic aldehyde **113** it would be possible to form a second ring *via* 1,4-addition of the intermediate *N*-anion (Figure 3.1). There is potential, therefore, for this process to generate two new rings and three new asymmetric centres in a single cascade synthetic operation.

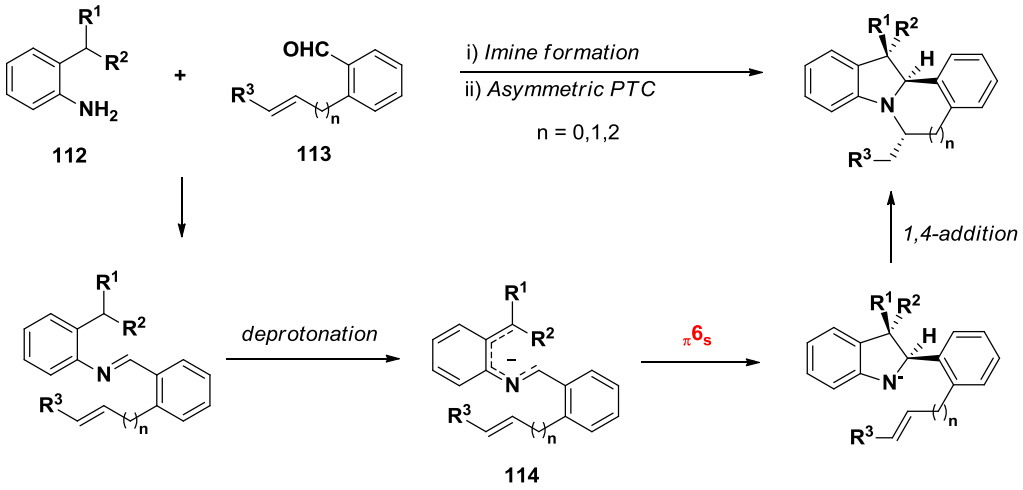


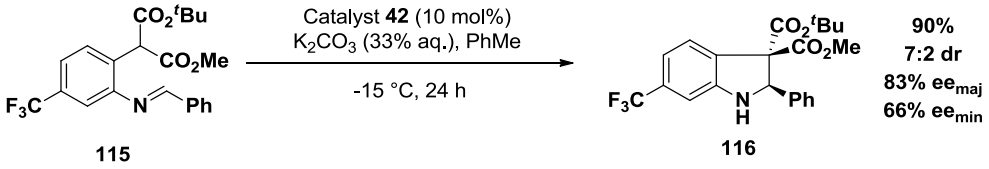
Figure 3.1.

The generation of all-carbon quaternary remains a difficult and central problem in the field of synthetic organic chemistry.[101–104] The generation of such a centre in a catalytic asymmetric cascade process would therefore constitute powerful and valuable methodology.

3.2.1 Diastereoselective Electrocyclization

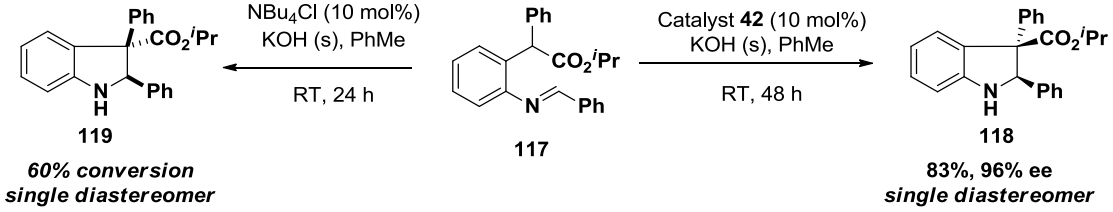
The formation of a quaternary stereocentre during the electrocyclization requires that the process must be not only enantioselective, but also diastereoselective. In order to achieve diastereoselectivity there are several attributes which aniline **112** must necessarily possess: i) R^1 and R^2 must be sufficiently anion-stabilizing to allow deprotonation at the benzylic position under the mild phase-transfer conditions we hoped to employ; and ii) R^1 and R^2 must be sufficiently different from one another that there is a strong preference for a particular stereoisomer of anionic intermediate **114**. Early forays into diastereoselective electrocyclization

within the group involved the use of two different esters, and whilst this satisfied the first of the above requirements, it clearly did not satisfy the second. Cyclization of mixed malonates **115** under phase-transfer conditions yielded a 7:2 mixture of diastereoisomers (Scheme 3.4).



Scheme 3.4.

We hoped to improve this diastereoselectivity by substituting one of the esters for an alternative electron-withdrawing group. Initial studies by an undergraduate co-worker demonstrated the potential of α-phenyl esters as viable substrates for this process.[105] Electrocyclization of **117** employing *N*-benzylcinchonidinium chloride **42** and solid powdered potassium hydroxide afforded **118** in 83% yield and 96% ee as a single diastereoisomer (Scheme 3.5).



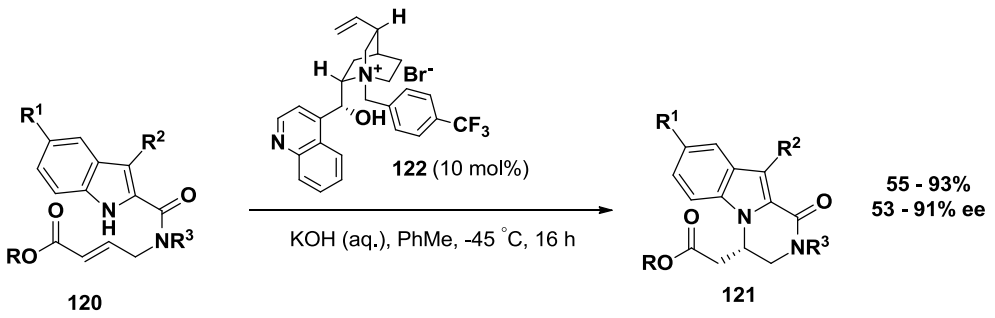
Scheme 3.5.

An intriguing catalyst-dependent diastereoselectivity issue was noted: when achiral tetrabutylammonium chloride was used, there was a complete switch in stereochemical outcome, with sole formation of the epimeric product **119**. This behaviour was attributed to more efficient catalysis by tetrabutylammonium chloride enabling formation of thermodynamic products.[106]

Since the reactivity and selectivity of this α-phenyl ester under phase-transfer catalysed conditions had been demonstrated, we hoped it would provide similarly impressive results when incorporated into the cascade.

3.2.2 Diastereoselective 1,4-Addition

We were confident that achieving diastereoselectivity in the 1,4-addition step would be possible, since catalyst control in a related process has been demonstrated by Umani-Ronchi *et al.*;[107] deprotonation of a number of indoles **120** under PTC conditions in the presence of catalyst **122** led to dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones **121** in good yields and with modest to high enantioselectivities (Scheme 3.6).



Scheme 3.6.

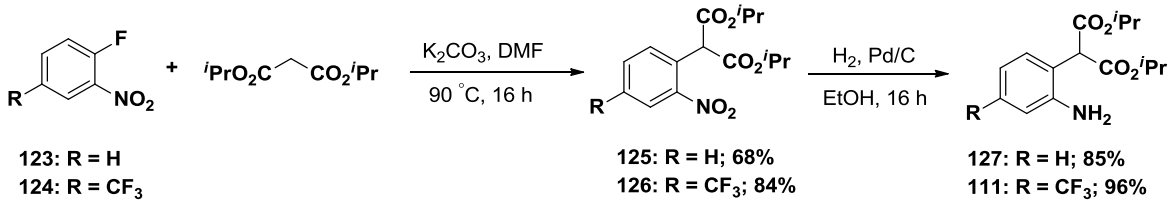
In our studies the indoline nucleophile, formed by asymmetric electrocyclization, will be chiral, so substrate control is also expected.

3.3 Results and Discussion

3.3.1 Synthesis of Anilines

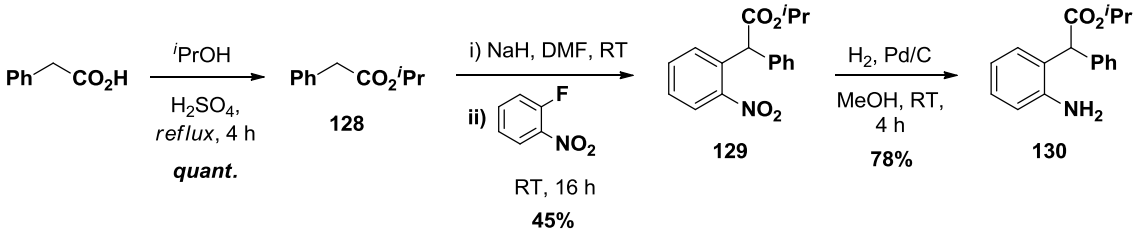
The general procedure for the synthesis of malonate-substituted anilines was identical to the work previously published.[59] Nucleophilic aromatic substitution of 2-fluoronitrobenzenes **123** and **124** by diisopropyl malonate gave the desired aromatic malonates **125** and **126** in moderate to

good yields, and subsequent reduction using hydrogen gas and palladium on carbon afforded anilines **127** and **111** in excellent yield (Scheme 3.7).



Scheme 3.7.

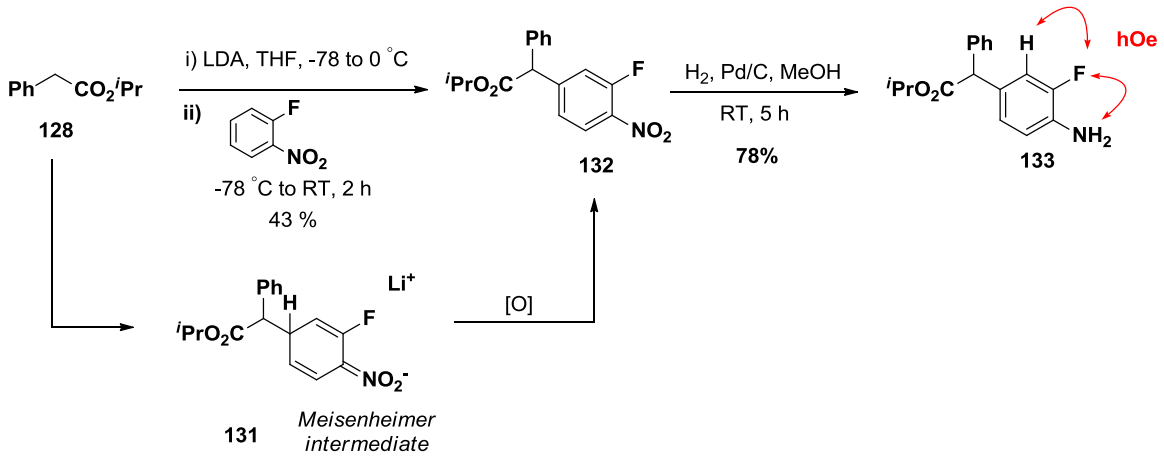
α-Phenyl ester-substituted nitroarene **129** was similarly formed by nucleophilic aromatic substitution (S_NAr) with *iso*-propyl phenylacetate **128** (formed by a quantitative Fischer esterification of phenylacetic acid), in a moderate and capricious 45% yield (Scheme 3.8). Reduction of **129** using hydrogen gas and palladium on carbon gave the corresponding aniline **130** in a respectable 78% yield.



Scheme 3.8.

S_NAr yields were frequently impacted by a difficult work-up and purification procedure, so an alternative protocol was sought. It was hoped that by employing the LDA/tetrahydrofuran conditions, used successfully in the synthesis of diester **90** (*cf.* Table 2.7, p. 30), nitroarene **129** might be obtained in a cleaner fashion. However, under these conditions an unexpected vicarious nucleophilic substitution (VNS) reaction took place, affording *para*-substituted nitroarene **132** in a modest 43% yield.

VNS reactions are generally carried out using nucleophiles that possess a leaving group, whose elimination serves to quench the anionic Meisenheimer intermediate **131**,[108] or are quenched with a separate oxidant.[109*] In our case both these sources of oxidation are absent, so it is presumed the Meisenheimer intermediate **131** is oxidised by adventitious oxygen or a second nitroarene (Scheme 3.9).



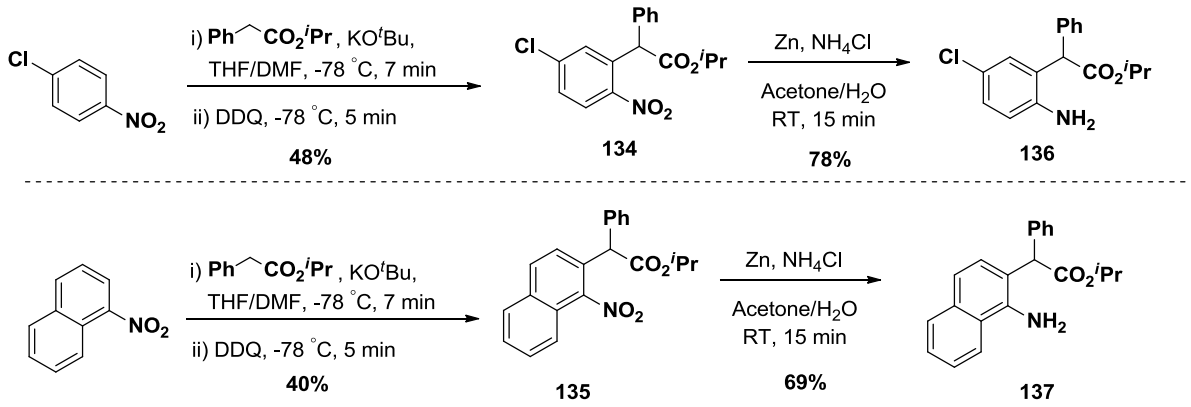
Scheme 3.9. Formation of undesired aniline **133** by VNS. *Red arrows indicate hOe enhancements.*

The nitroarene **132** was reduced using palladium on carbon to afford the corresponding aniline **133** in 78% yield, at which point the regiochemistry of the VNS reaction was unambiguously determined by ^{19}F-decoupled ^{1}H and ^{1}H-^{19}F HOESY NMR experiments which demonstrated that the addition had occurred *para*- to the nitro group, rendering it unsuitable as a substrate for our cascades. Thus the original route to aniline **130** (Scheme 3.8) was followed in all subsequent studies.

Whilst the reaction sequence discussed above was unexpected and, ultimately, unfruitful, it did draw our attention to VNS as a possible route to other substituted nitroarenes. Mąkosza *et al.* have demonstrated that the addition of α-phenyl ester enolates to nitroarenes followed by oxidation with DDQ is a viable method to generate substituted nitroarenes.[109] Whilst the

[*] *The process involving a separate oxidant is also known as "Oxidative Nucleophilic Substitution of Hydrogen" (ONSH).*

majority of substrates undergo *para*-addition, a few notable exceptions were known to favour the *ortho*-substitution we required; treatment of 4-chloronitrobenzene and 1-nitronaphthalene with *iso*-propyl phenylacetate and potassium *tert*-butoxide followed by DDQ oxidation was reported to afford the corresponding *ortho*-substituted products **134** and **135** in 78% and 75% yield respectively. Although the reaction involved a difficult work-up to remove the DDQ residue, the extreme rapidity of the reaction (complete after just 12 minutes) made this method synthetically useful. The *ortho*-substituted nitroaromatics **134** and **135** were obtained in moderate yields, and were rapidly reduced using zinc dust and ammonium chloride to afford the corresponding anilines **136** and **137** (Scheme 3.10).[82]



Scheme 3.10.

3.3.2 Synthesis of Aldehydes

Where possible, aldehydes were synthesised by known literature procedures. Aldehydes bearing the general structure **138** are termed cinnamyl aldehydes, and in our proposed cascade will ultimately lead to [5,5]-fused bicyclic products, whilst those with the general structure **139** are termed homocinnamyl aldehydes and will lead to [5,6]-fused bicycles (Figure 3.2).

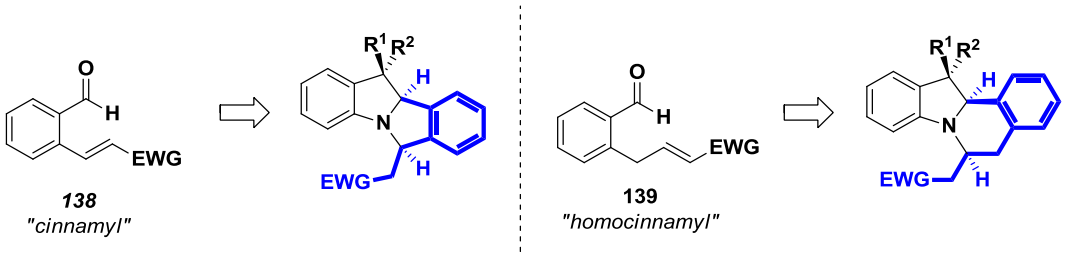
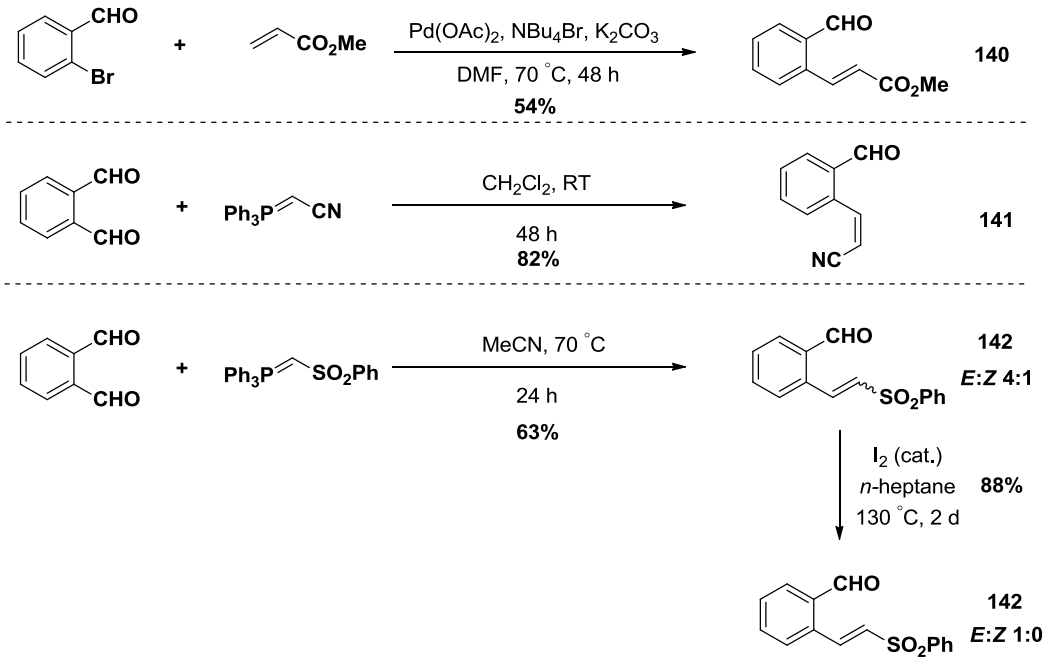


Figure 3.2.

3.3.2.1 Cinnamyl Aldehydes

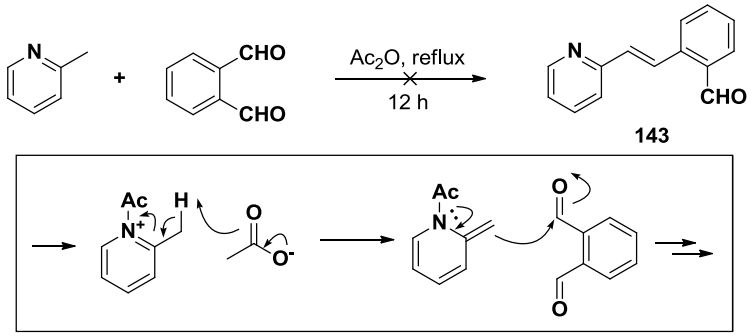
Ester **140** was formed *via* a precedented Heck reaction,[110] whilst nitrile **141** and sulfone **142** were formed by Wittig olefination reactions, all in good yields (Scheme 3.11).[111] Only the sulfone **142** was obtained as an inseparable mixture of geometrical isomers, but could be converted to the (*E*)-isomer exclusively by catalytic isomerization with iodine.



Scheme 3.11.

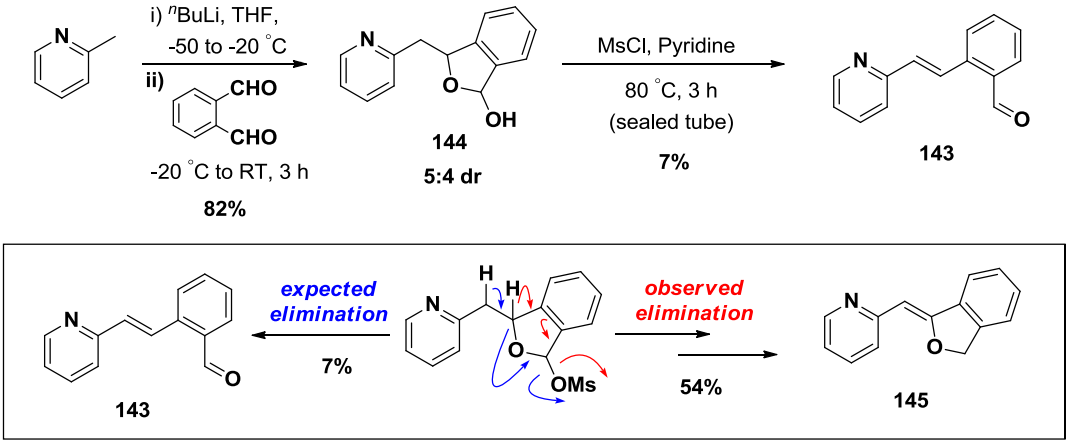
We initially attempted to synthesise pyridine-containing aldehyde **143** in a single step directly from 2-picoline and phthaldialdehyde by analogy to a literature protocol (although the literature

reaction involved only a mono-aldehyde).[112] Trace amounts of the desired aldehyde **143** were observed by ^{1}H NMR, yet we were unable to isolate a pure sample (Scheme 3.12).



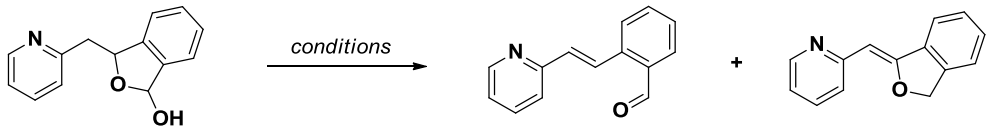
Scheme 3.12.

Therefore, we attempted to form this substrate through a stepwise aldol reaction-β-elimination protocol. Treatment of 2-picoline with *n*-butyllithium and addition of phthaldialdehyde afforded the aldol product **144** in 82% yield as the hemi-acetal isomer, and a 5:4 mixture of diastereomers. However, subsequent attempts to activate the secondary alcohol and carry out an elimination reaction did not afford the desired aldehyde **143** cleanly. Treatment of the hemi-acetal with methanesulfonyl chloride in the presence of pyridine gave the aldehyde in just 7% yield, with dihydroisobenzofuran **145** formed in 54% yield, the result of deprotonation at the benzylic position, rather than α- to the pyridine (Scheme 3.13).



Scheme 3.13.

Such reactivity is precedented, and has been demonstrated to proceed *via* an *iso*-benzofuran intermediate.[113] Attempts to carry out the elimination under acidic conditions also failed: treatment of the acetal with *para*-toluenesulfonic acid and sulfuric acid gave only recovered starting material, whilst trifluoroacetic acid cleanly afforded the dihydroisobenzofuran **145** in 70% yield (Table 3.1).



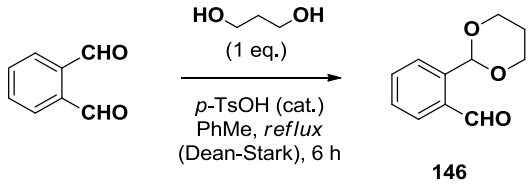
144 **143** **145**

Entry	Conditions	Outcome[i]
1	MsCl, pyridine, 80 °C, sealed tube, 3 h	**143** (7%), **145** (54%)
2	*p*-TsOH, CH_2Cl_2, RT, 16 h	SM[ii]
3	H_2SO_4, H_2O, RT, 16 h	SM[ii]
4	TFA, CH_2Cl_2, RT, 16 h	70% **145**

[i] *Where quoted, yields are for isolated material.* [ii] *Determined by crude ^1H NMR analysis.*

Table 3.1.

It was therefore necessary to mono-protect the phthaldialdehyde to prevent hemi-acetal formation and the subsequent problems associated with *iso*-benzofuran formation. Treatment of phthaldialdehyde with propane-1,3-diol in the presence of toluenesulfonic acid provided the desired mono-protected aldehyde **146** in 85% isolated yield (Scheme 3.14).

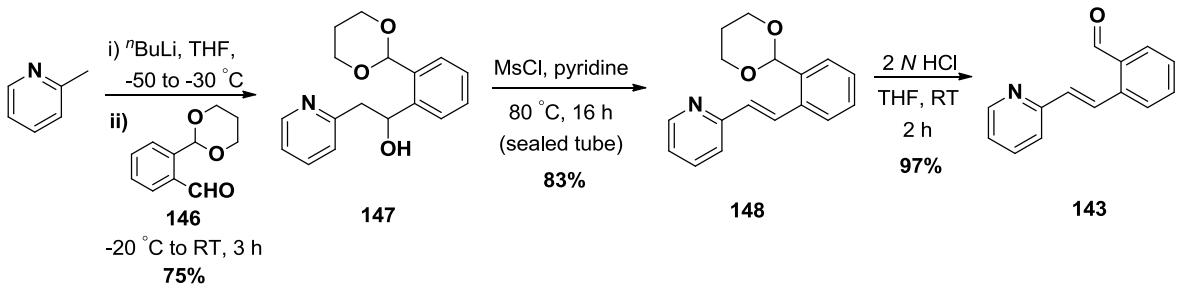


146

85%

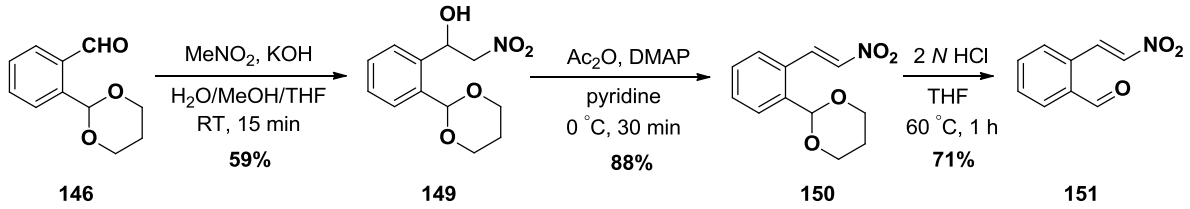
Scheme 3.14.

Deprotonation of 2-picoline with *n*-butyllithium as before, followed by quenching with mono-protected aldehyde **146**, afforded the desired secondary alcohol **147** cleanly in 75% yield, which was activated with methanesulfonyl chloride, and underwent smooth basic elimination to give alkene **148** in 83% yield solely as the (*E*)-isomer. Final deprotection of the acetal in aqueous acid afforded the pyridyl aldehyde **143** cleanly in 97% yield (Scheme 3.15).



Scheme 3.15.

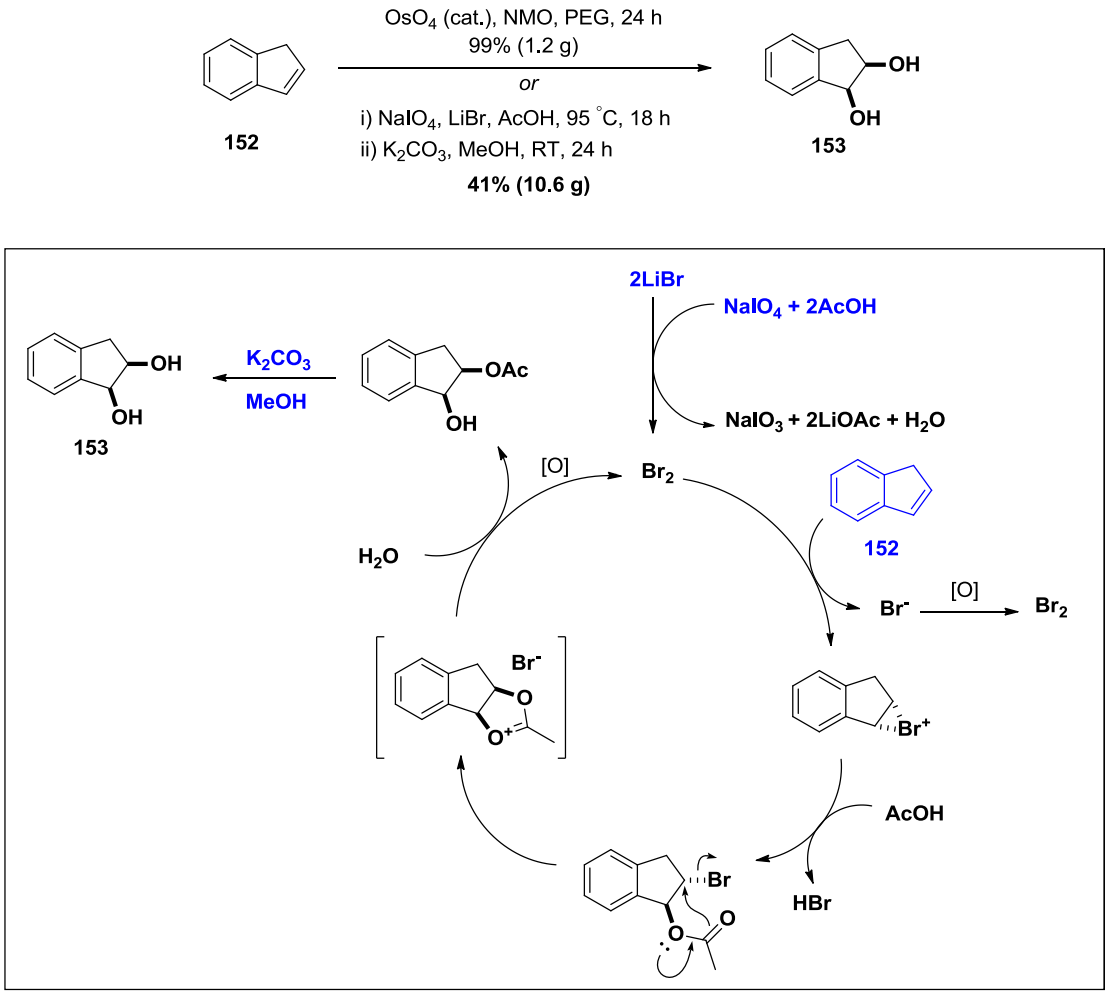
Nitrostyryl aldehyde **151** was formed by a similar route; treatment of protected aldehyde **146** with nitromethane and potassium hydroxide afforded Henry addition product **149** in 59% yield. The secondary alcohol was activated with acetic anhydride in the presence of DMAP, and underwent smooth basic elimination to the (*E*)-styrene **150** in 88% yield as a single stereoisomer. Final deprotection of the acetal with aqueous acid afforded the aldehyde **151** in 71% yield (Scheme 3.16).



Scheme 3.16.

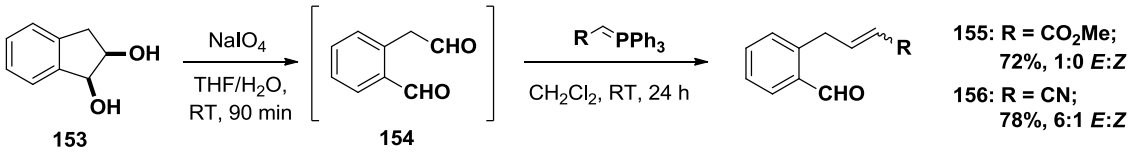
3.3.2.2 Homocinnamyl Aldehydes

Methyl ester and sulfone aldehydes **155** and **156** were accessible in three steps from indene **152** *via* an oxidative cleavage-Wittig olefination protocol. The initial dihydroxylation of indene **152** was carried out on a small scale by a literature procedure employing osmium tetroxide and *N*-methylmorpholine-*N*-oxide, with excellent yields of up to 99%.[114] We hoped to avoid the use of the highly toxic Os(VIII) species when carrying out this reaction on a larger scale, and therefore opted for a lower-yielding but more benign protocol employing sodium periodate and lithium bromide in a "catalytic Prévost-Woodward reaction" (Scheme 3.17)[115] which afforded the diol **153** in 41% yield on a 10 g scale.



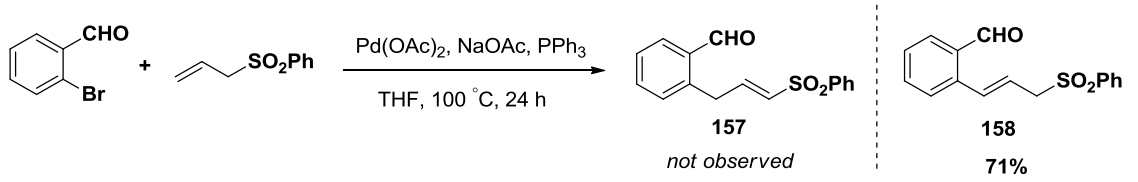
Scheme 3.17. Inset: catalytic cycle for catalytic Prévost-Woodward reaction.

Oxidative cleavage of the diol **153** was achieved with sodium periodate in tetrahydrofuran/water followed by dehydration with anhydrous magnesium sulfate, cleanly affording the homophthaldialdehyde **154** in quantitative yield. Due to its instability the aldehyde could not be purified, but its formation was verified by ^{1}H NMR spectroscopy. The dialdehyde **154** was used immediately in the subsequent Wittig olefination reactions to afford aldehydes **155** and **156** in 72% and 78% yields over two steps (Scheme 3.18).



Scheme 3.18.

The synthesis of sulfone **157** has been reported *via* a Heck reaction-isomerization procedure,[116] although in our hands the protocol afforded only styrene **158**, the isomer where the alkene sits in conjugation with the aromatic ring (Scheme 3.19).*

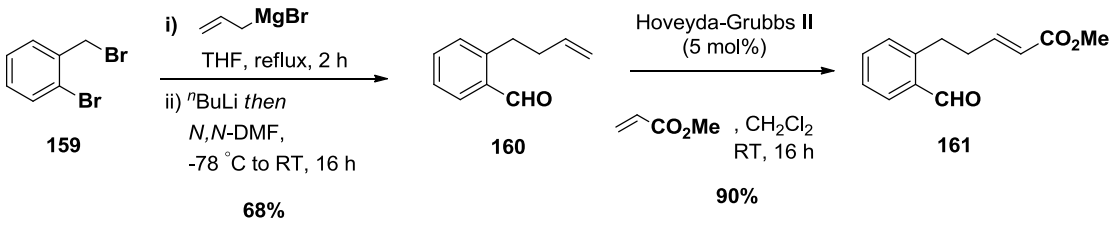


Scheme 3.19.

3.3.2.3 Miscellaneous Aldehydes

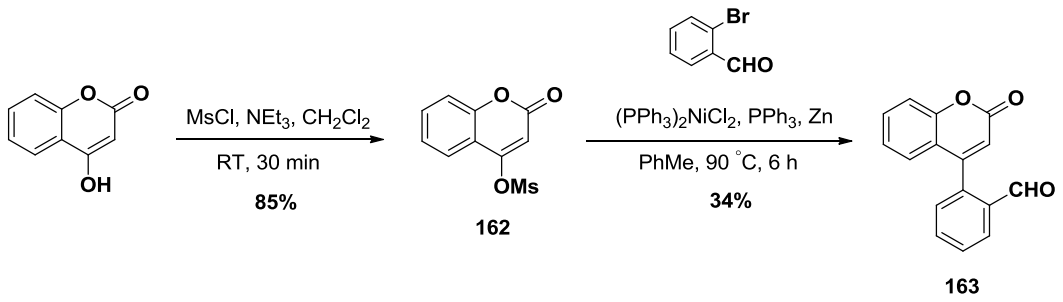
The synthesis of aldehyde **161** (which would ultimately result in a [5,7]-fused ring system after our cascade process) was achieved in three steps from 2'-bromobenzyl bromide **159** by a tandem substitution-formylation procedure followed by alkene metathesis (Scheme 3.20).[111]

* *Since no spectroscopic data was provided for the sulfone **157** we were unable to determine whether it was mis-assigned in the original paper, or the reaction had demonstrated different selectivity in our hands.*



Scheme 3.20.

Finally, we envisioned the possibility of forming complex spirocyclic structures in our cascade protocol. To this end, we synthesised coumarin-derived aldehyde **163** in two steps from commercially-available 4-hydroxycoumarin and 2-bromobenzaldehyde. The 4-hydroxycoumarin was activated with methanesulfonyl chloride and subjected to nickel-catalysed Ullmann-like reductive cross-coupling conditions in the presence of zinc powder, affording the desired aldehyde **163** in moderate yield (Scheme 3.21).



Scheme 3.21.

With a modest library of aldehydes in hand (Figure 3.3), we proceeded to investigate the proposed cascade process.

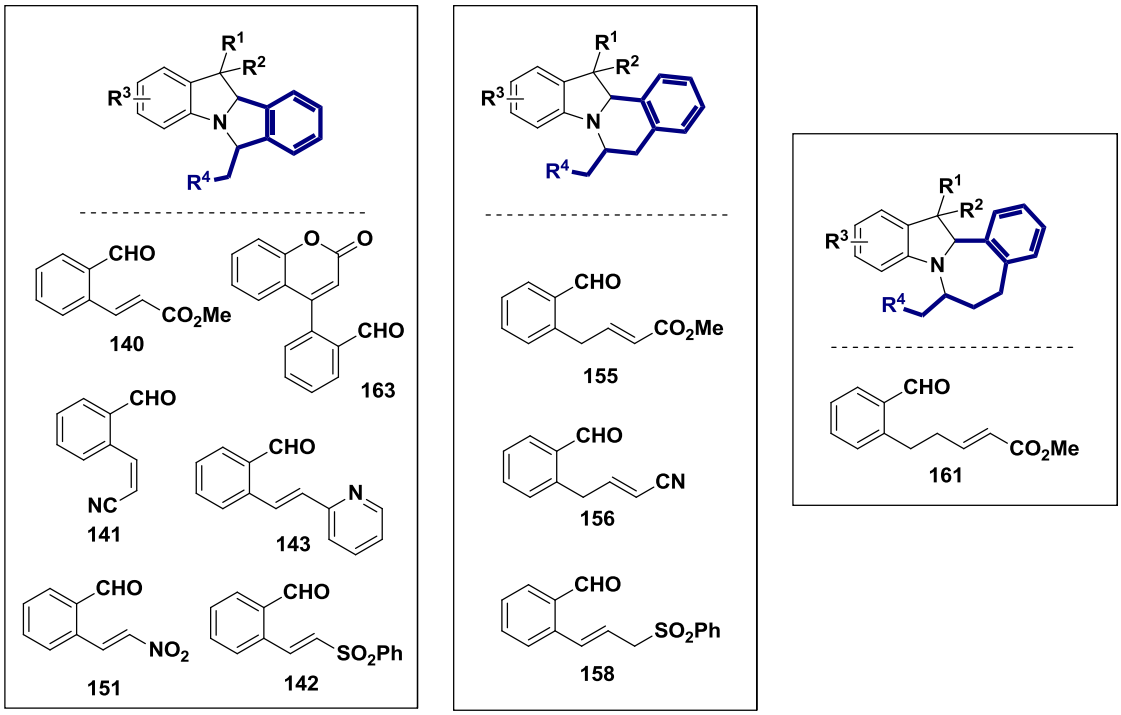
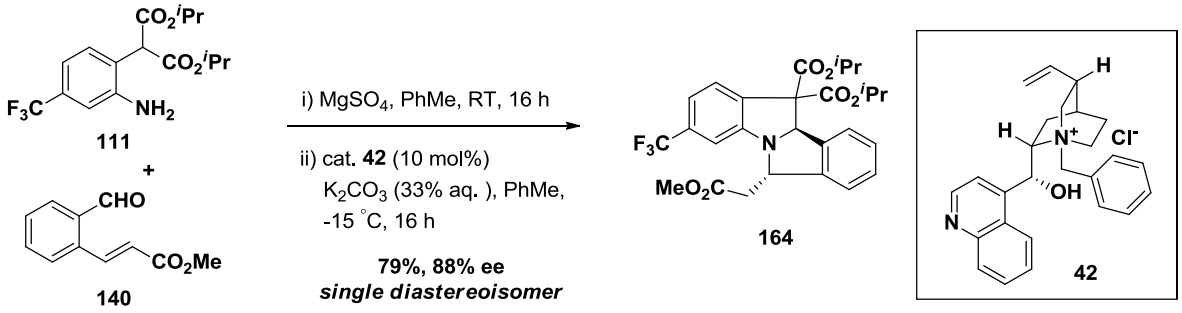


Figure 3.3. Library of cascade aldehydes.

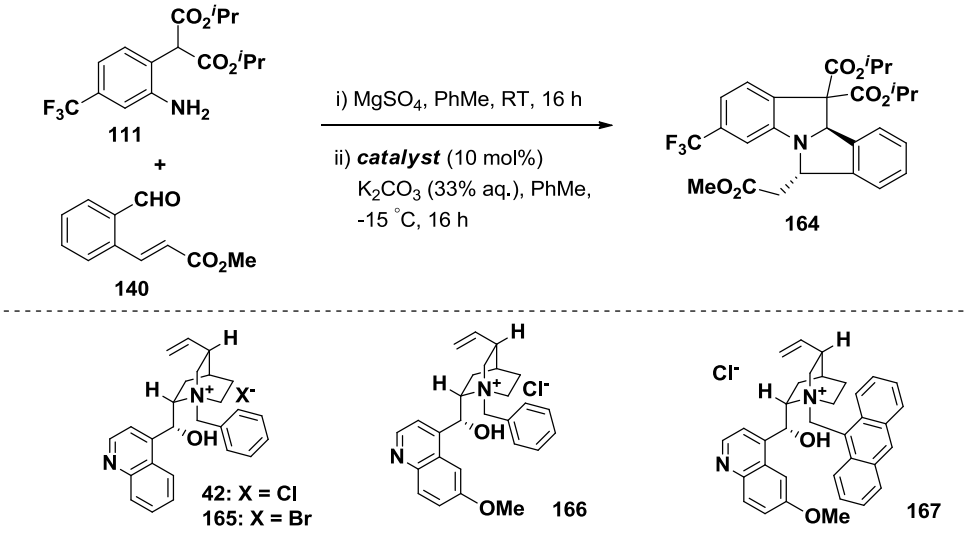
3.3.3 Reaction Optimization

Our initial studies into catalytic enantioselective electrocyclic cascades were focused on the simplest case where the benzylic electron-withdrawing groups were identical, such that only two diastereomeric products could be formed. Thus aniline **111** and aldehyde **140** were exposed to imine formation conditions followed by the electrocyclization conditions optimized in earlier work, employing *N*-benzylcinchonidinium chloride **42** and aqueous potassium carbonate, and we were delighted to obtain the cascade product **164** as a single diastereoisomer in 79% yield and 88% ee (Scheme 3.22).



Scheme 3.22.

A short screen was undertaken under these conditions to determine the optimum catalyst for the process (Table 3.2). The counter-ion was found to have a surprisingly large influence on the enantioselectivity, with *N*-benzylcinchonidinium bromide **165** giving a 10% reduction in ee relative to the chloride **42** (Table 3.2, entries 1 & 2). Quininium catalyst **166** gave an improvement in enantioselectivity, but significantly reduced the yield of the cascade product, whilst *N*-anthracenyl catalyst **167** was found to reduce both the yield and enantioselectivity (Table 3.2, entries 3 & 4). We therefore opted to proceed employing our initial catalyst, *N*-benzylcinchonidinium chloride **42**, since it was deemed to offer the best combination of high yield and good enantioselectivity, and had been used to great effect in earlier studies.[59]

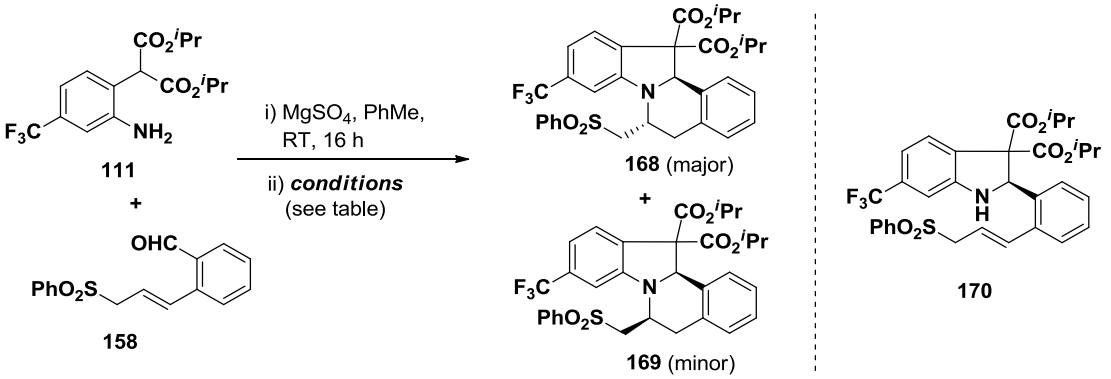


Entry	Catalyst[i]	Yield / %[ii]	ee / %[iii]
1	**42**	79	88
2	**165**	77	78
3	**166**	57	95
4	**167**	63	70

[i] *All reactions were carried out on 50 or 100 mg scale (aniline) at 0.05 M concentration.* [ii] *Yields for isolated material. In all cases only a single diastereomer was observed by ^{1}H NMR analysis of the crude reaction mixture.* [iii] *Determined by chiral HPLC.*

Table 3.2. Catalyst screening. *For experimental details, see p. 190.*

Cascade reactions forming a [5,6]-fused ring system (employing the homocinnamyl aldehydes, *vide supra*) required further optimization. Due to the ease of its synthesis, these studies were initially focused on sulfonyl aldehyde **158** (Table 3.3). However, we were acting under the mistaken belief that the compound was the α,β-unsaturated isomer **157** (as stated in the paper describing its synthesis[116]); key results from the optimization studies were therefore repeated for methyl ester aldehyde **155** to demonstrate their general validity (see Table 3.4). *Note that all optimization studies on sulfone **158** (Table 3.3) were carried out by a co-worker,[111] and are presented only for completeness.*



Entry	Base	T / °C	Solvent (conc. / M)	dr 168:169	ee[ii] / %
1	K_2CO_3 (33% aq.)	−15	PhMe (0.15)	N/A[iii]	N/A[iii]
2	$CsOH{\cdot}H_2O$ (s)	−15	PhMe (0.15)	2:1	30
3	$CsOH{\cdot}H_2O$ (s)	−50	PhMe (0.15)	N/A[iii]	N/A[iii]
4	$CsOH{\cdot}H_2O$ (s)	−50 *then* RT	PhMe (0.15)	3:2	20
5	KOH (s)	−50 *then* RT	PhMe (0.15)	2:3	80
6	KOH (s)	−78 *then* RT	PhMe (0.05)	1:1	84

[i] *All reactions were carried on 50 mg scale (aniline) using 10 mol% N-benzylcinchonidinium chloride* ***42****.* [ii] *ee quoted is for diastereomer* ***168*** *only due to the availability of racemic standards. Determined by chiral HPLC.* [iii] *Only* ***170****, the product of electrocyclization without subsequent 1,4-addition, was observed.*

Table 3.3. Temperature and base screen.

The conditions proven successful in the formation of [5,5]-fused rings were unfruitful in this series, and yielded only **170**, the product of 6π electrocyclization followed by protonation, with no subsequent 1,4-addition (Table 3.3, entry 1). In the presence of weak carbonate bases it is believed that this protonation is essentially irreversible, causing the cascade to stall at the indoline intermediate **170**.

It was hoped that solid hydroxide bases would give greater reactivity due to their increased basicity; we were delighted to discover that use of solid cesium hydroxide monohydrate in place of aqueous potassium carbonate induced the electrocyclization, double bond isomerization and subsequent 1,4-addition to afford diastereomeric products **168** and **169** with complete conversion

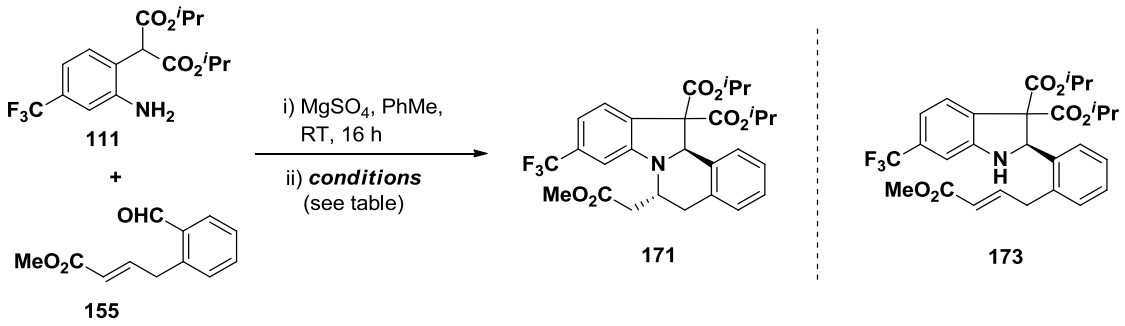
and a 2:1 diastereomeric ratio, albeit with a disappointing 30% enantiomeric excess (Table 3.3, entry 2).

In addition to its increased reactivity, the use of solid base allowed a reduction in temperature below −15 °C, which was the practical lower limit for systems involving aqueous potassium carbonate due to freezing of the aqueous layer. However, cooling to −50 °C gave only the mono-cyclized product **170** (Table 3.3, entry 3); it was clear that whilst the electrocyclization was rapid even at very low temperatures, the barrier to 1,4-addition was higher and so the process required more energy. Since the ee was determined during the electrocyclization step, we hoped that by maintaining a low temperature initially until the electrocyclization was complete – followed by warming to induce 1,4-addition – we might obtain cascade products but with improved ee. This was initially unsuccessful (Table 3.3, entry 4), but a switch of base to powdered potassium hydroxide dramatically improved the enantioselectivity of the process to 80% ee (Table 3.3, entry 5). This may be rationalized on the basis of the greater solubility of Cs^+ in organic solvents relative to K^+: such solubility would allow Cs^+ to act as a counter-ion to the anionic substrate in place of the chiral quaternary ammonium species, leading to racemic cyclization.

Finally, a slight reduction in initial temperature to −78 °C and greater dilution gave a highly enantioselective and high-yielding process, affording [5,6]-cascade product **168** in 84% ee, although the diastereoselectivity was poor (Table 3.3, entry 6).[*]

Once the true identity of sulfone **158** as the styrene isomer had been determined, it was necessary to prove that these optimization studies were generally relvant. Methyl ester aldehyde **155** was therefore exposed to selected conditions, and it was demonstrated that the optimized conditions were equally applicable (Table 3.4).

[*] *Note that results presented in Table 3.3 are selected examples only; for a more complete discussion of these aspects, see ref.* [111]



Entry[i]	Base	T / °C	ee[ii] / %	Yield / %
1	K_2CO_3 (33% aq.)	−15	N/A[iii]	N/A[iii]
2	KOH (s)	−15	84	64
3	KOH (s)	−78 *then* RT	91	88

[i] *All reactions were carried on 50 mg scale at a concentration of 0.05 M (aniline) in toluene, using 10 mol% N-benzylcinchonidinium chloride* ***42****.* [ii] *Determined by chiral HPLC.* [iii] *Only* ***173****, the product of electrocyclization without subsequent 1,4-addition, was observed.*

Table 3.4. Temperature and base screen. *For full experimental details, see p. 192.*

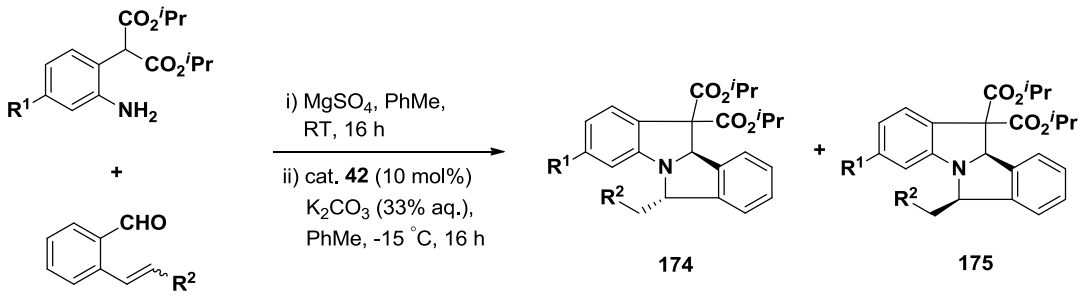
It was clearly shown that the reaction conditions favoured for the sulfone were generally applicable, providing an impressive 91% ee for the methyl ester substrate, obtained as a single diastereoisomer (Table 3.4, entry 3).

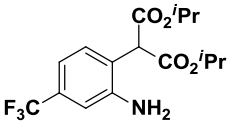
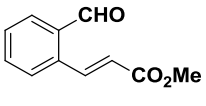
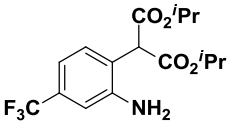
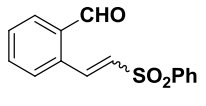
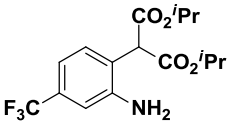
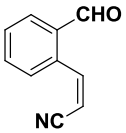
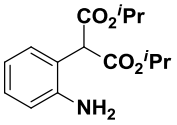
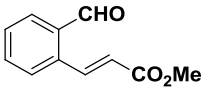
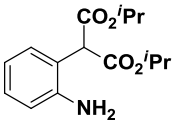
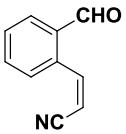
3.3.4 Reaction Scope and Limitations

The primary focus of this thesis is on α-phenyl ester substrates whose cyclization generates an additional, all-carbon quaternary stereocentre. In general, cascades involving malonate anilines ***111*** *and* ***127*** *were carried out by a co-worker;*[111] *the results of these reactions are presented for completeness, but only minimal discussion and comment will be provided.*

3.3.4.1 [5,5]-Malonate Cascades

Employing the optimized procedure for [5,5]-cascades (§ 3.3.3) it was shown that the cascade reaction is tolerant of sulfone and nitrile electron-withdrawing groups, in addition to the ester already demonstrated. These results are summarised in Table 3.5.



Entry	Aniline	Aldehyde	Yield / %	dr 174:175	ee[i] / %
1	 **111**	 **140**	79	>20:1	88
2[ii]	 **111**	 **142 (4:1 *E*:*Z*)**	87	2:1	85 (major) 91 (minor)
3	 **111**	 **141**	70	>20:1	97
4[iii]	 **127**	 **140**	49	>20:1	52
5	 **127**	 **141**	89	>20:1	73

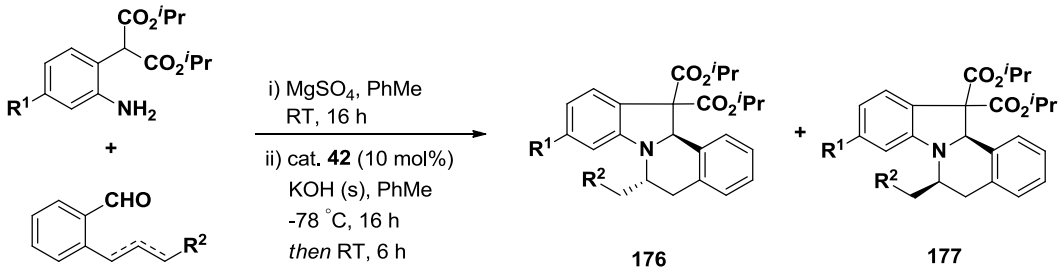
[i] *Determined by chiral HPLC.* [ii] *It was demonstrated that use of the exclusively (E)-alkene isomer had no effect on the diastereoselectivity of this cascade.*[111] [iii] *Due to substrate solubility issues this reaction was carried out in 1:1 $CHCl_3$:PhMe; the lower enantioselectivity reflects the poorer ion-binding in this more-polar solvent mixture.*

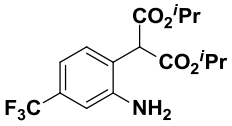
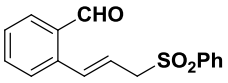
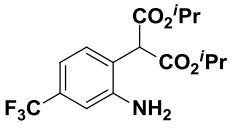
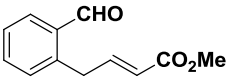
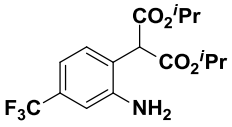
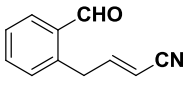
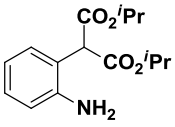
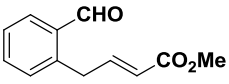
Table 3.5.

Malonates lacking the aryl CF_3 group tended to give lower enantioselectivities, and the sulfone gave lower diastereoselectivity.

3.3.4.2 [5,6]-Malonate Cascades

Similarly, adopting the optimized procedure of [5,6]-cascades (§ 3.3.3), it was demonstrated that sulfone, methyl ester and nitrile groups were tolerated in the cascade (Table 3.6).



Entry	Aniline	Aldehyde	Yield / %	dr 176:177	ee[i] / %
1	 **111**	 **158**	91	3:2	83 (major) 87 (minor)
2	 **111**	 **155**	88	>20:1	91
3	 **111**	 **156**	99	3:2	93 (major) 90 (minor)
4	 **127**	 **155**	45	>20:1	80

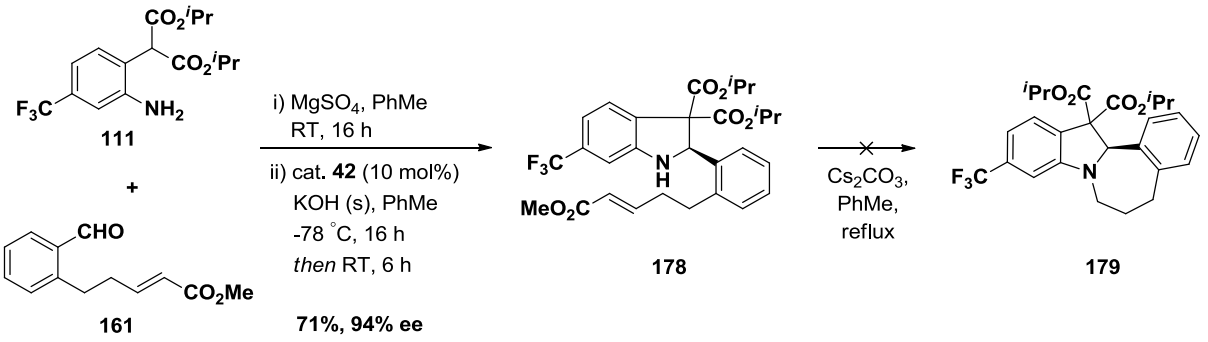
[i] *Determined by chiral HPLC.*

Table 3.6.

Diastereoselectivities were lower than in the [5,5]-cascades, but enantioselectivities and yields were generally excellent.

3.3.4.3 [5,7]-Malonate Cascades

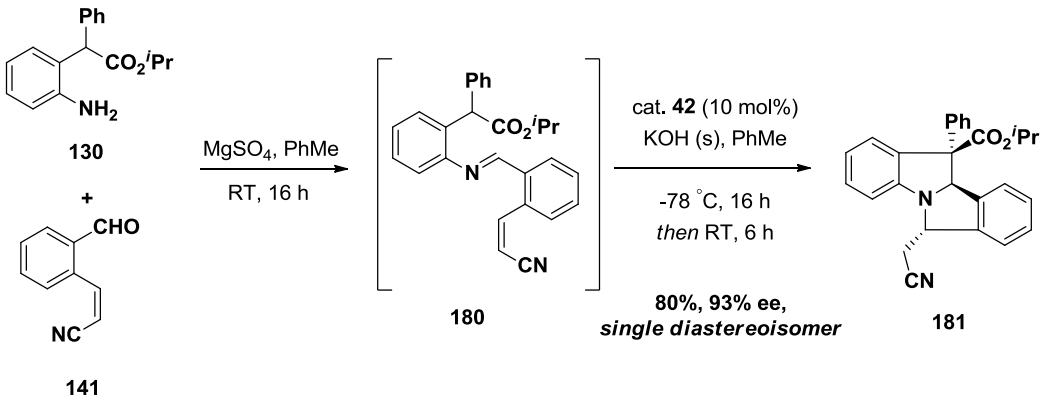
Attempts to induce a cascade electrocyclization 1,4-addition employing methyl ester aldehyde **161** were not successful. Although electrocyclization was facile, the subsequent 1,4-addition was extremely slow, such that even when refluxed in toluene in the presence of cesium carbonate, no addition was observed and the indoline **178** could be isolated (Scheme 3.23).



Scheme 3.23.

3.3.4.4 [5,5]-α-Phenyl Ester Cascades

We initially focused efforts on the cascade cyclization of **180**, the imine formed from aldehyde **130** and aniline **141**. Previous experience with the electrocyclization of α-phenyl ester substrates had indicated that they are unreactive when aqueous base was employed.[105] We therefore took, as a starting point for our cascades, the conditions optimized for the formation of [5,6]-fused ring systems, employing anhydrous powdered potassium hydroxide as a base. Gratifyingly, treatment of imine **180** under these conditions afforded the desired [5,5]-fused system in 80% yield as a single diastereoisomer in 93% ee (Scheme 3.24).



Scheme 3.24.

We were particularly delighted with the diastereoselectivity achieved in this process, since there is potential for the formation of four unique diastereoisomers, only one of which was observed by ^{1}H NMR analysis of the crude reaction mixture. The relative configuration of the product was determined by nOe analysis, and is consistent with X-ray crystal data obtained for subsequent products (Figure 3.4).

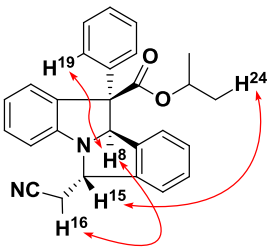
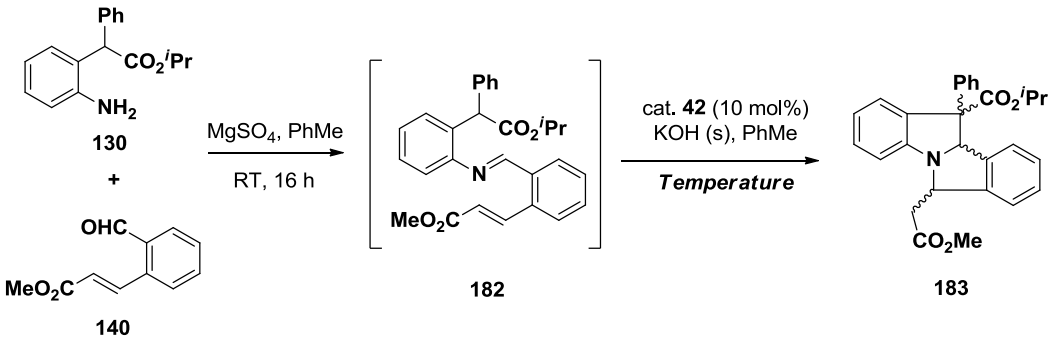


Figure 3.4. nOe data for nitrile **181** (*arrows indicate observed nOe enhancements*).

The absolute stereochemistry is assumed to be analogous to that obtained in earlier studies and for subsequent products whose absolute stereochemistry was determined by single crystal X-ray diffraction.

Given this initial success, we proceeded to the related cascade involving methyl ester aldehyde **140**. Imine formation was quantitative by TLC, and verified by ^{1}H NMR analysis of the

crude reaction mixture. Exposure of the imine to the phase-transfer catalysed cascade conditions did not lead to the desired bicycle **183**; after 16 h at −78 °C and 6 h at RT, crude ^{1}H NMR revealed an inseparable mixture of predominantly unreacted imine, along with several unidentified products of cyclization (Table 3.7). Since the reaction had not even approached completion, it was repeated both at room temperature and at 40 °C. When carried out at 40 °C conversion was improved, but the cyclized product was obtained as a 2.4:1.0 mixture of inseparable diastereoisomers, whose apparent incompatibility with silica gel chromatography led to their isolation (as a mixture) in only 9% combined yield.



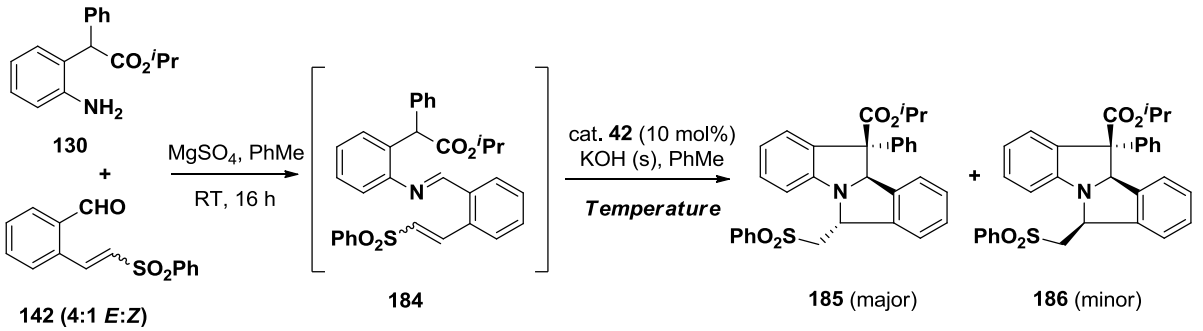
Entry	Temperature / °C	Conversion[i] / %	Isolated Yield / %
1	-78 (16 h) *then* RT (6 h)	28	-
2	RT (48 h)	39	-
3	40 °C (16 h)	64	9 (2.4:1.0 dr[ii])

[i] *Determined by analysis of the crude ^{1}H NMR spectrum.* [ii] *Obtained as an inseparable mixture of diastereoisomers.*

Table 3.7.

The poor conversion observed with this substrate is not well understood; even at elevated temperatures complete consumption of the imine was not observed, implying that the electrocyclization was sluggish, despite the apparent lack of involvement of the methyl ester in this step of the cascade.

We proceeded to investigate the reactivity of sulfone **184** under our cascade conditions. Imine formation was quantitative under our standard protocol, and conditions to induce a stereoselective cascade were then investigated (Table 3.8).



Entry	Temperature / °C	Conversion[i] / %	Isolated Yield	dr[i] 185:186	ee[ii] / %
1	-78 (16 h) *then* RT (6 h)	65	-	1:1	-
2	-30 (16 h) *then* RT (3 h)	40	-	3:2	-
3	-15 (16 h) *then* RT (3 h)	35	-	1:1	-
4	RT (16 h)	100	36	2:1	-
5[iii]	RT (16 h)	100	76	9:1	89

[i] *Determined by analysis of the crude ^{1}H NMR spectrum.* [ii] *Determined by chiral HPLC.* [iii] *Reaction was carried out under strictly anhydrous conditions.*

Table 3.8.

As ever, we initially applied the conditions optimized for the [5,6]-cascades. Cyclization did occur, but with incomplete conversion; 35% of the imine remained unreacted (Table 3.8, entry 1). The diastereoselectivity was disappointing, nevertheless we proceeded to incrementally increase the initial reaction temperature (at which we expected the electrocyclization – but not the 1,4-addition – to occur) to improve the consumption of imine. No such improvement was observed at either −30 °C or −15 °C (Table 3.8, entries 2 & 3), leading to the conclusion that both the electrocyclization and the 1,4-addition were occurring once the reaction had been raised

to room temperature. This was supported by the complete conversion obtained when the reaction was carried out at room temperature throughout, which also gave a slight improvement in dr (Table 3.8, entry 4).* It was noted (by TLC analysis) that after complete consumption of the imine **184** both diastereoisomers were present in approximately equal quantities, but that over time one isomer became predominant. This process seemed to be impeded by adventitious water which caused the solid potassium hydroxide to coagulate, preventing efficient catalysis. Carrying out the reaction under strictly anhydrous conditions in a Schlenk tube allowed catalysis to continue for a greater length of time, and gave sulfone pyrrolizidine **185** as the major diastereomer in 76% yield, with 9:1 dr and an excellent 89% ee (Table 3.8, entry 5).

It is presumed that the process by which conversion to the major diastereomer occurs is by reversible 1,4-addition, leading to the thermodynamic epimer (Figure 3.5).

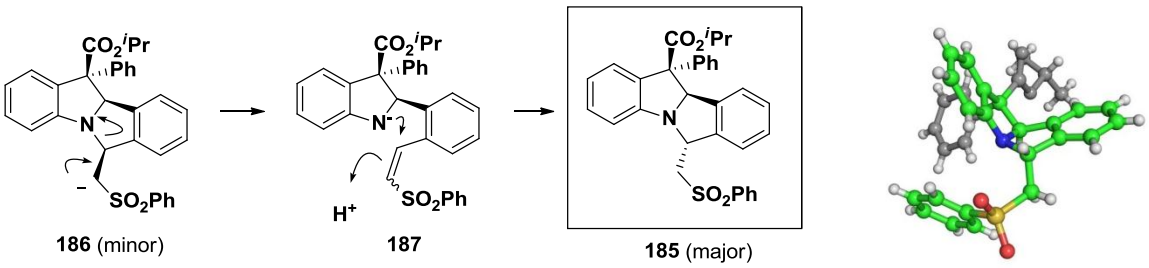


Figure 3.5. Proposed mechanism of epimerization and single crystal X-ray structure of **185**.

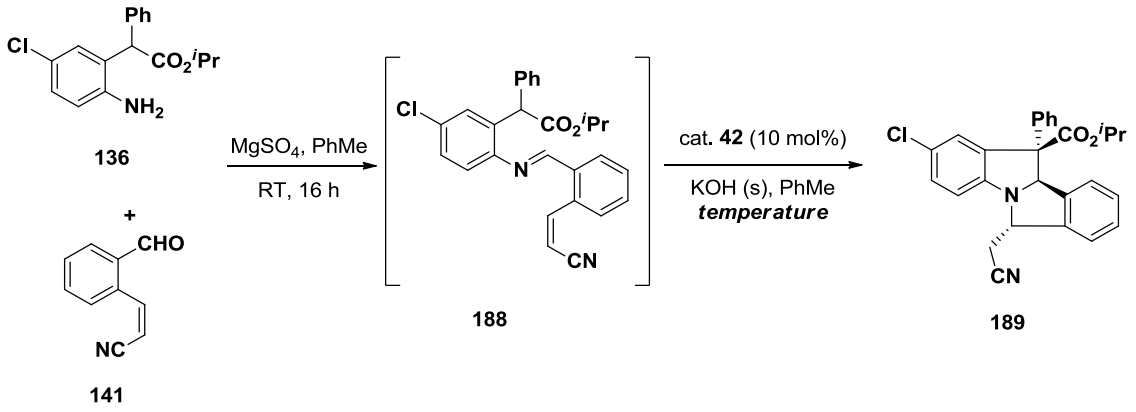
Single-crystal X-ray structure rendered using PyMOL.[117]

The relative and absolute stereochemistry of the major stereoisomer was confirmed by single crystal X-ray diffraction, and is consistent with previous work.

We proceeded to investigate cascades involving chloroaniline **136**, to determine whether substitution was well tolerated. Treatment of chloroaniline **136** with aldehyde **141** under our

* *Although the conversion was good and the crude ^{1}H NMR clean, isolated yields were hampered by product decomposition; upon standing, in $CDCl_3$, and on silica the sulfone (yellow in colour when formed) turned a rich green colour. Attempts to separate diastereomers by column chromatography therefore led to decomposition on silica, where the green decomposition product remained, and explains the disparity between conversion and isolated yield.*

cascade conditions proceeded much more smoothly than sulfone **184**, similarly to nitrile **180**. Imine formation was quantitative, and a short temperature screen led rapidly to an extremely efficient and stereoselective cascade (Table 3.9).



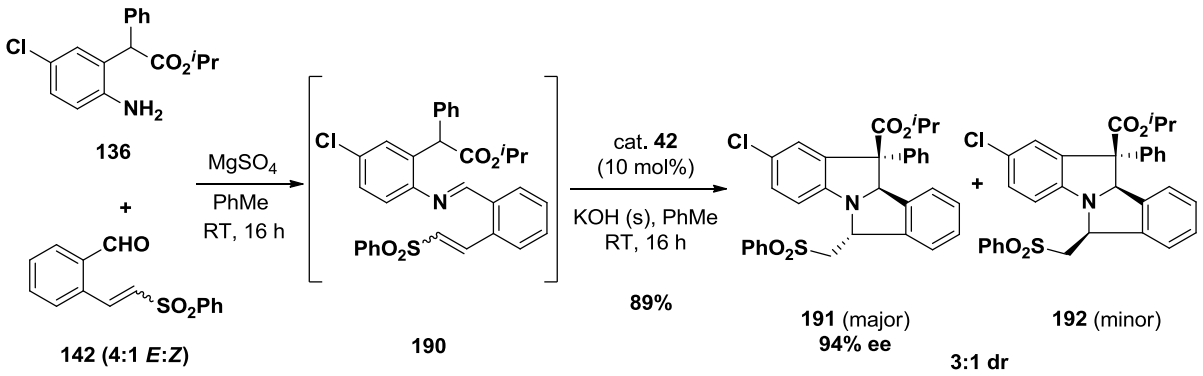
Entry	Temperature / °C	Isolated Yield / %	ee[i] / %
1	−78 (16 h) *then* RT (6 h)	90	95
2	−30 (16 h) *then* RT (6 h)	89	97

[i] *Determined by chiral HPLC.*

Table 3.9.

Gratifyingly, the [5,5]-fused cascade product **189** was obtained as a single diastereoisomer in up to 90% yield and up to 97% ee. These results represent a process that is more enantioselective that any of the simpler malonate substrates, and gives a single diastereoisomer where up to four are possible.

This chlorinated aniline **136** was also employed in conjunction with sulfone aldehyde **187**. As with previous examples, the imine formation was trivial. Exposure of this imine **190** to the conditions optimized for the related sulfone **184** gave excellent results (Scheme 3.25)



Scheme 3.25.

Although the observed diastereoselectivity was poorer than in earlier examples, the same thermodynamic epimerization behaviour was observed as in the previous sulfone case, with early formation of a near-equal mixture of diastereoisomers, and with an increasing bias to the major diastereoisomer over time. Extended reaction times did not appear to increase the diastereoselectivity, so the observed 3:1 dr is thought to be a thermodynamic ratio. The cyclization was achieved in an excellent 89% combined yield and 94% ee (major diastereomer).

The identity of the minor diastereoisomer **192** was determined by nOe enhancements, which confirmed our supposition that it possessed the same relative configuration between C7 and C8 as all previous examples, but was epimeric at C15 (Figure 3.6).

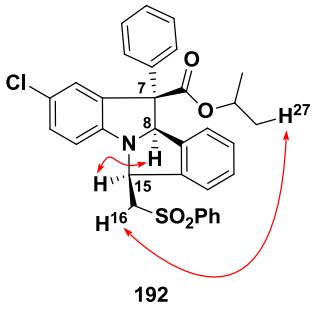
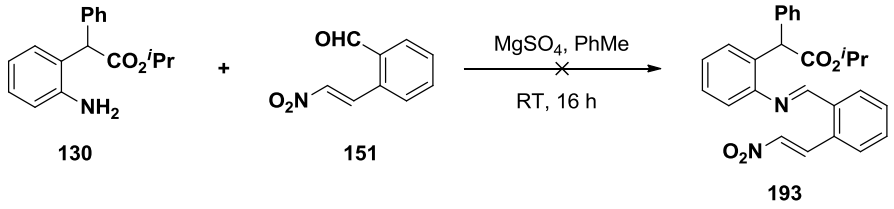


Figure 3.6. nOe data for sulfone **192** (*arrows indicate observed nOe enhancements*).

This is in accordance with our retro-1,4-addition hypothesis for the change in dr over time (see Figure 3.5).

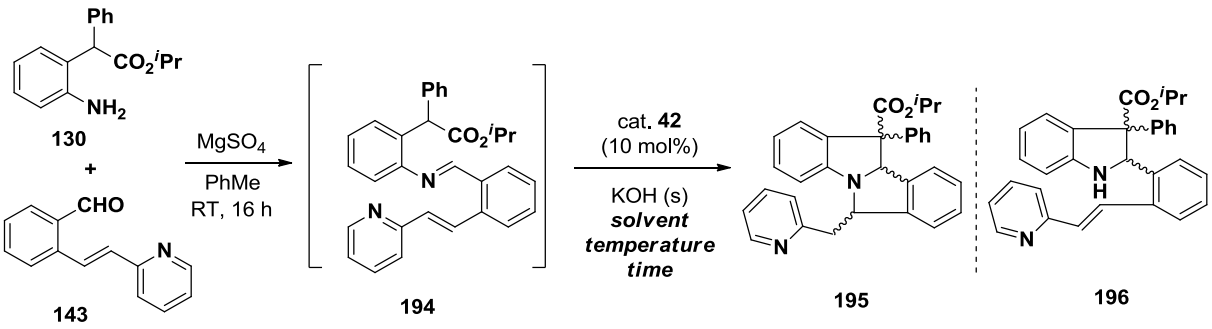
We hoped to further expand on the functional-group tolerance of the process by incorporating a nitro group as the electron-withdrawing component of the 1,4-acceptor. However, attempts to apply our cascade methodology to nitroaldehyde **151** failed at the imine formation stage. Upon combining the aldehyde **151** and aniline **130** in toluene an immediate and dramatic colour change was observed (even in the absence of magnesium sulfate), where the solution turned deep red/black within minutes. TLC and crude ^{1}H NMR analysis revealed a complex and intractable mixture of products, and as a consequence this substrate was not pursued further (Scheme 3.26).



Scheme 3.26.

The uncontrolled reactivity observed is perhaps unsurprising; nitro-olefins are known to undergo spontaneous 1,4-addition with anilines, and polymerization processes may occur even at room temperature in the absence of any reagent or catalyst.[118]

Whilst nitroaldehyde **151** failed due to the high reactivity of the nitro-olefin, we suspected that pyridine **143** might prove a difficult substrate for the opposite reason – the poor electrophilicity of the α,β-unsaturated pyridine. Imine formation with this substrate was quantitative, although attempts to induce its cascade cyclization were problematic. Anticipating the lower reactivity of the α,β-unsaturated pyridine as a 1,4-acceptor, our initial studies were carried out at room temperature (Table 3.10).



Entry	Temperature	Solvent (conc. / M)	Outcome (conv. / %[i])	dr[i]
1	RT (16 h)	PhMe (0.1)	**195** (100%)	5:2:1:1
2	RT (48 h)	PhMe (0.1)	**195** (100%)	5:2:1:1
3	50 °C (16 h)	PhMe (0.1)	**195** (100%)	7:1:3:1
4	0 °C (16 h) *then* RT (6 h)	PhMe (0.1)	**196** (~30%) **195** (~30%)	*ND*[ii]
5	RT (16 h)	CH_2Cl_2 (0.1)	**196** (~39%) **195** (~61%)	4:9:4:1
6	RT (16 h)	THF (0.1)	**195** (100%)	9:0:0:1
7	RT (16 h)	$^iPr_2O$ (0.1)	*decomposition*	*ND*
8	RT (16 h)	PhMe (0.03)	**196** (62%) **195** (38%)	5:10:6:1

[i] *Determined by integration of the characteristic diastereotopic doublets corresponding to the ^{i}Pr group in the crude ^{1}H NMR spectrum. Values are approximate.* [ii] *Obtained as a complex mixture of imine, indoline and pyrrolizidine material.*

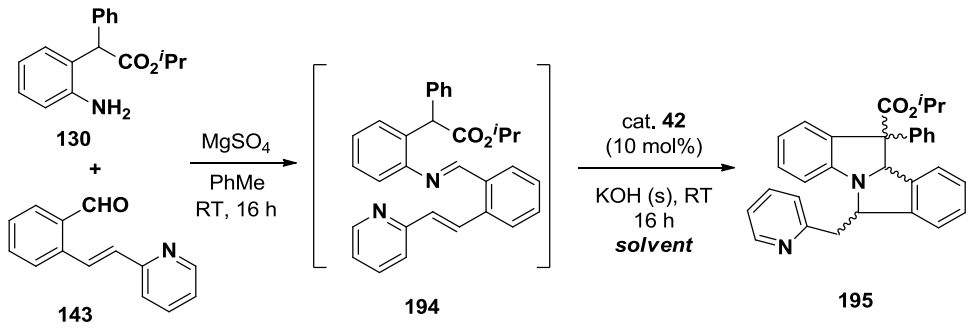
Table 3.10.

Although cyclization was observed, we were disappointed to obtain an inseparable mixture of the four possible diastereoisomers of the product pyrrolizidine **195**.[*] Given prior success in thermodynamic equilibration of diastereomers, we allowed the reaction to continue for 48 h, however this had no influence on the dr. Similarly, increasing the reaction temperature to 50 °C did not greatly improve the diastereoselectivity (Table 3.10, entry 3). As expected, cooling led to very poor reactivity, with ~40% imine remaining when cyclization was carried out at 0 °C with

[*] *The crude mixture of compounds was determined to be a mixture of diastereomeric products by the presence of characteristic coupling patterns corresponding to the protons α- and β- to the pyridine in the crude ^{1}H NMR spectrum.*

subsequent warming to room temperature (Table 3.10, entry 4), and although the dr could not be determined from the crude mixture, it did not appear to be significantly different from the room temperature case.

A short solvent screen led to the discovery that tetrahydrofuran alone gave respectable diastereoselectivity. Disappointingly the product **195** was obtained in racemic form, although it is perhaps unsurprising that tetrahydrofuran would prevent tight ion-pairing between the substrate and catalyst under phase-transfer conditions. We hoped that by employing a mixed tetrahydrofuran/toluene solvent system we might be able to obtain both good diastereo- and enantioselectivity; unfortunately this was not the case (Table 3.11).

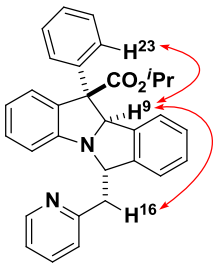


Entry	THF:PhMe v:v	dr[i]	ee_{maj}[ii] / %
1	1:0	92:8	0
2	10:1	86:14	0
3	5:1	85:15	0
4	2:1	77:23	0
5	1:1	75:25	0
6	1:2	73:27	0
7	1:5	62:38	0
8	1:10	59:41	0
9	0:1	56:45	0

[i] *Determined by analysis of the crude mixture by ^{1}H NMR spectroscopy. Quoted as ratio of major isomer to sum of all minor isomers.*
[ii] *Determined by chiral HPLC.*

Table 3.11.

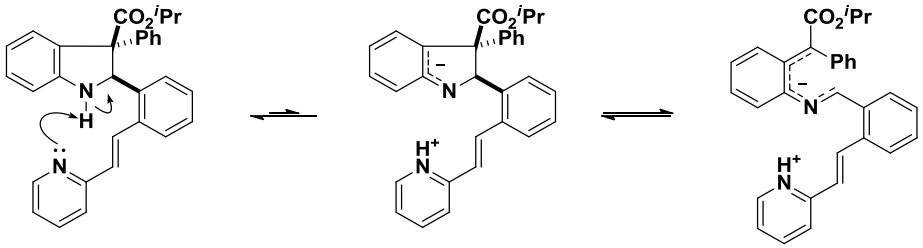
There was a clear trend towards better diastereoselectivity with increasing tetrahydrofuran content – probably due to increased reversibility leading to the thermodynamic product – but the pyrrolizidine was racemic in all cases, even when the reaction was carried out in pure toluene. The major diastereomer of **195** was identified by NOESY experiments (Figure 3.7).



195 (major)

Figure 3.7. nOe data for major diastereomer of pyridine **195** (*arrows indicate observed nOe enhancements*).

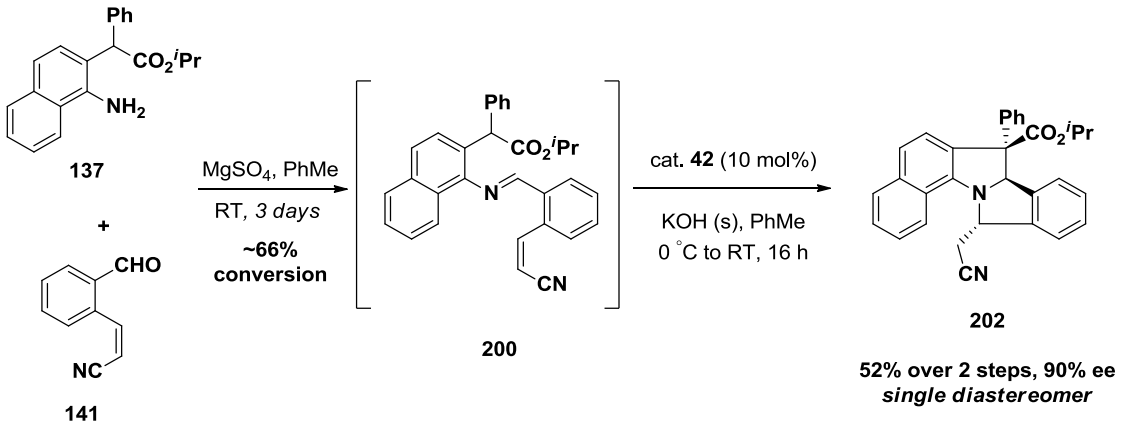
It was surprising to find such poor stereoselectivity in this substrate; although the sulfones gave poorer selectivity than their nitrile counterparts (*vide supra*), only two diastereomers were ever observed, corresponding to epimerization at the site of 1,4-addition. Generally, the electrocyclization step was reliably exquisite in its diastereoselectivity, never contributing any minor diastereoisomer to the distribution of products. However, in the pyridine case either the electrocyclization remains under kinetic control with much lower diastereoselectivity, or is reversible leading to thermodynamic products. The latter has been shown not to occur under asymmetric phase-transfer conditions in earlier studies,[105] but it is possible that the presence of the pyridine as an internal base could favour such a process (Figure 3.8). Re-cyclization of the zwitterion **198** would proceed in the absence of a chiral counter-ion, and therefore lead to racemic product.



197 **198** **199**

Figure 3.8. Possible mechanism for pyridine-catalysed retro-electrocyclization

Enantioselectivity in this substrate thus proved elusive, so our attention and efforts were redirected towards other interesting systems. Amine **137** poses an interesting challenge, with 1,6-disubstitution making the aniline extremely hindered and unreactive. Formation of the required imine with aniline **137** and nitrile aldehyde **141** was problematic. The extreme steric bulk of the aniline renders the amine unusually non-nucleophilic; after 36 h only ~65% conversion to the imine was achieved.* Nonetheless, the crude mixture was subjected to phase-transfer catalysed cyclization conditions, albeit with a diminished potential yield over the two steps. Initial attempts to carry out the electrocyclization at −30 °C followed by warming to room temperature to induce 1,4-addition led to a 50:50 mixture of pyrrolizidine **202** and unreacted imine **200**. However, increasing the initial temperature to 0 °C followed by warming to room temperature led smoothly to the formation of pyrrolizidine **202** as a single diastereoisomer in 52% yield from the aniline **137**, and with 90% ee (Scheme 3.27).

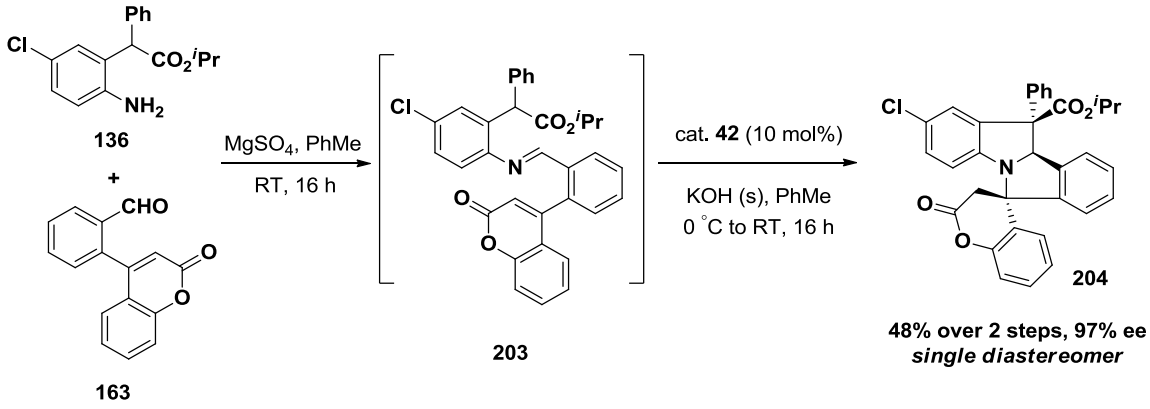


Scheme 3.27.

The moderate yield over two steps is a reflection of the difficult imine formation step, and represents ~80% yield for the cascade cyclization. We were delighted to achieve such high selectivities and relatively good yield for such a bulky molecule, proving the compatibility of our tight ion-pairing approach even to hindered substrates.

* *Determined by ^{1}H NMR analysis of the crude reaction mixture.*

The final and perhaps most-challenging [5,5]-cascade attempted involved coumarin-derived aldehyde **163**; here, the intermediate indoline must perform a de-aromatizing 1,4-addition to the coumarin, in the process generating a spirocyclic product **204** (Scheme 3.28).



Scheme 3.28.

Treatment of the aldehyde **163** with chloroaniline **136** cleanly gave the corresponding imine **203**, which gratifyingly underwent electrocyclization at 0 °C and subsequent 1,4-addition upon warming to room temperature to afford **204** in 48% yield over two steps as a single diastereoisomer, and in 97% ee. The moderate yield is a result of some residual electrocyclized material which failed to undergo 1,4-addition. The relative configuration of the [5,5,6]-spirocyclic product was determined by nOe analysis (Figure 3.9).

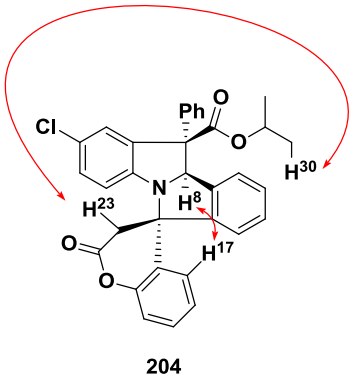
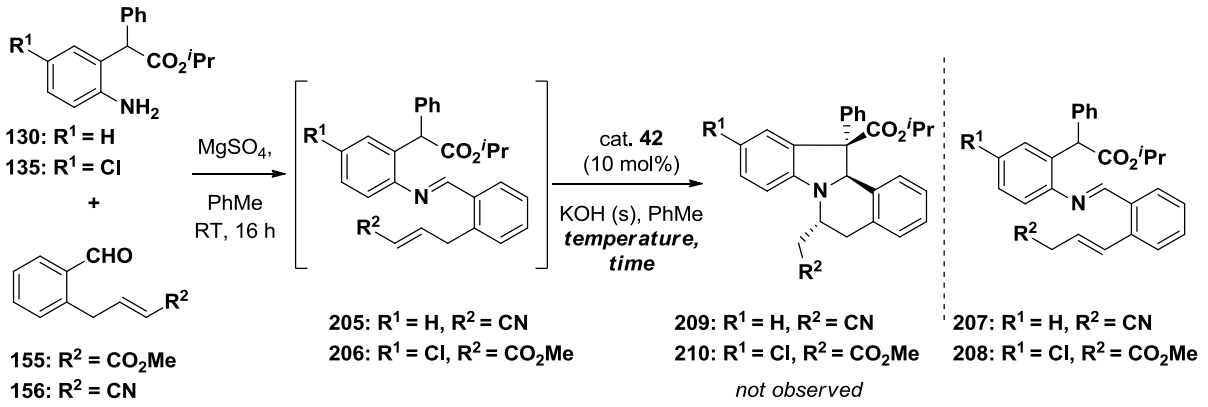


Figure 3.9. nOe data for spirocycle **204** (*arrows indicate observed nOe enhancements*).

3.3.4.5 [5,6]-α-Phenyl Ester Cascades

Having enjoyed success in the synthesis of pyrrolizidine products by asymmetric phase-transfer catalysis, our attention turned to the analogous indolizidines. Studies in the malonate series (§ 3.3.4.2) had indicated that this was a more challenging transformation than the [5,5]-system. Nonetheless, we proceeded to investigate this cascade reaction by our tandem imine formation-cascade cyclization protocol. We chose nitrile **156** as a suitable electron-withdrawing group since in previous studies it generally gave the highest conversion and cleanest reactivity.



Entry	X	R	Temperature / °C	Conversion[i] / %
1	H	CN	−78 (16 h) *then* RT (6 h)	80% **207**, 20% **205**
2	H	CN	RT (16 h)	100% **207** (30% isolated)
3	Cl	CO_2Me	RT (16 h)	80% **208**, 20% **206**

[i] *Determined by ^{1}H NMR analysis of the crude reaction mixture. Values are approximate.*

Table 3.12.

Imine formation occurred cleanly after 16 h, and initially the cyclization conditions optimized for the malonate [5,6]-cascade were employed (Table 3.12, entry 1). Unfortunately the only product identified after 16 h at −78 °C then 6 h at room temperature was alkene-isomerized imine **207**. Similarly, when the reaction was carried out at room temperature for 16 h only imine **207** was isolated (Table 3.12, entry 2). Despite multiple repetitions of this reaction, cyclized

material was not observed in the crude ^{1}H NMR spectrum at any stage. The unexpected stability of imine **207** under the reaction conditions is not well understood, but may be a consequence of the electron-donating properties of the styrene tempering the imine's electrophilicity,* or a steric interaction preventing cyclization. Regardless of the cause, cyclization of **205** was not achieved.

We subsequently attempted cyclization of **206**, the imine derived from aniline **136** and aldehyde **155**, hoping that the problems encountered above were unique to that substrate. Unfortunately, under the room temperature conditions, again only the isomerized imine **208** was observed (Table 3.12, entry 3).†

Having demonstrated both the scope and limitations of our cascade methodology, this study was concluded and the results published.[89]

3.4 Conclusions and Future Work

3.4.1 Overview and Conclusions

We have developed a practical, high-yielding and highly enantio- and diastereoselective cascade route to fused [5,5]-and [5,6]-bicyclic pyrrolizidines and indolizidines under phase-transfer catalysed conditions. A convenient "pseudo one-pot" protocol gave access to the products directly from their aniline and aldehyde precursors without purification of the intermediate imine (Figure 3.10).

* *In our electrocyclic reaction, the electrophilicity of the imine may be considered a metric for the stability of the product anion.*
† *By ^{1}H NMR analysis of the crude reaction mixture.*

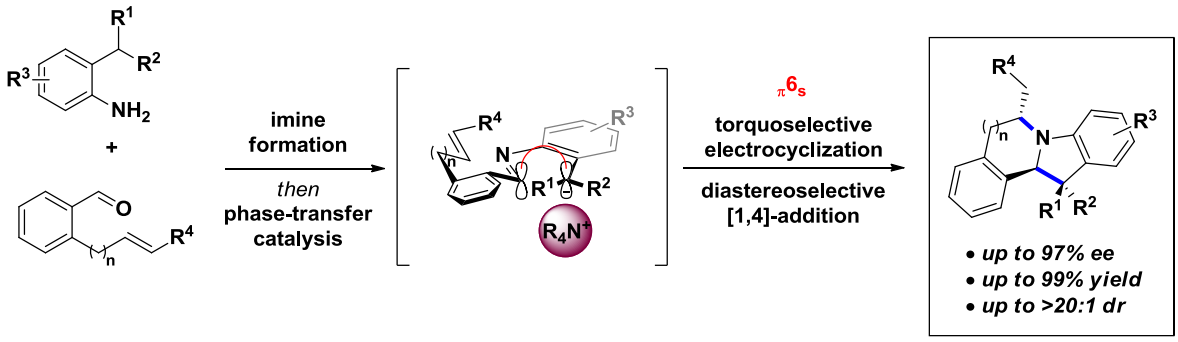


Figure 3.10.

Preferential binding of the *N*-benzylcinchonidinium cation to one face of the prochiral substrate anion gave high levels of torquoselectivity in the electrocyclic ring-closure reaction, and where two stereocentres were formed in this step the diastereoselectivity was uniformly exquisite. The subsequent conjugate addition also proceeded with generally excellent diastereoselectivity, although some substrates (particularly sulfones) tended to give lower selectivities; we postulate that this is due to conflicting kinetic and thermodynamic preferences in the [1,4]-addition.

The cyclization of malonates gave access to both [5,5]- and [5,6]-fused bicyclic ring systems, tolerating the presence of sulfone, ester and nitrile electron-withdrawing groups at the R^4 position (Figure 3.10).

The cyclization of α-phenyl ester substrates was more challenging: methyl esters were not tolerated at the R^4 position due to instability of the products, and imine formation was not possible for nitro-olefins. Pyridine-substituted pyrrolizidine **196** was successfully generated, but in racemic form. The formation of [5,6]-fused rings was not achieved in this series, and we speculate this is due to rapid isomerization of the alkene and subsequent conjugative stabilization of the imine **207** (Figure 3.11).

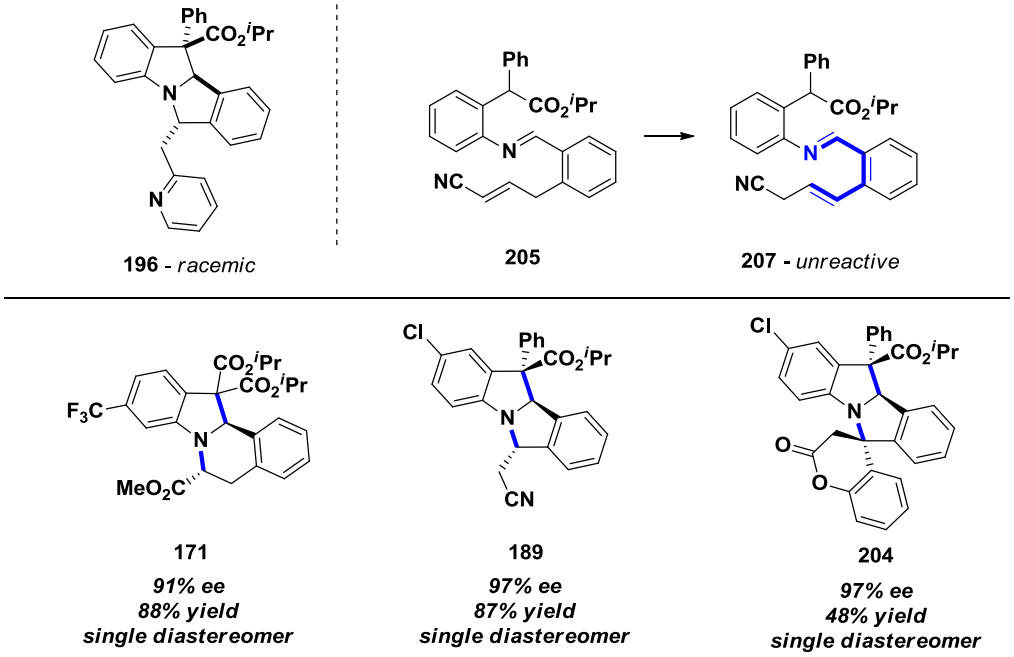


Figure 3.11. Limitations and scope of this methodology.

Despite these limitations, the cascade cyclization of α-phenyl ester substrates provided the highest enantioselectivities observed in this study (**189** and **204**, 97% ee), gave access to the greatest levels of molecular complexity (**204**), and in the process generated all-carbon quaternary stereocentres, the synthesis of which would otherwise be exceptionally challenging (Figure 3.11).

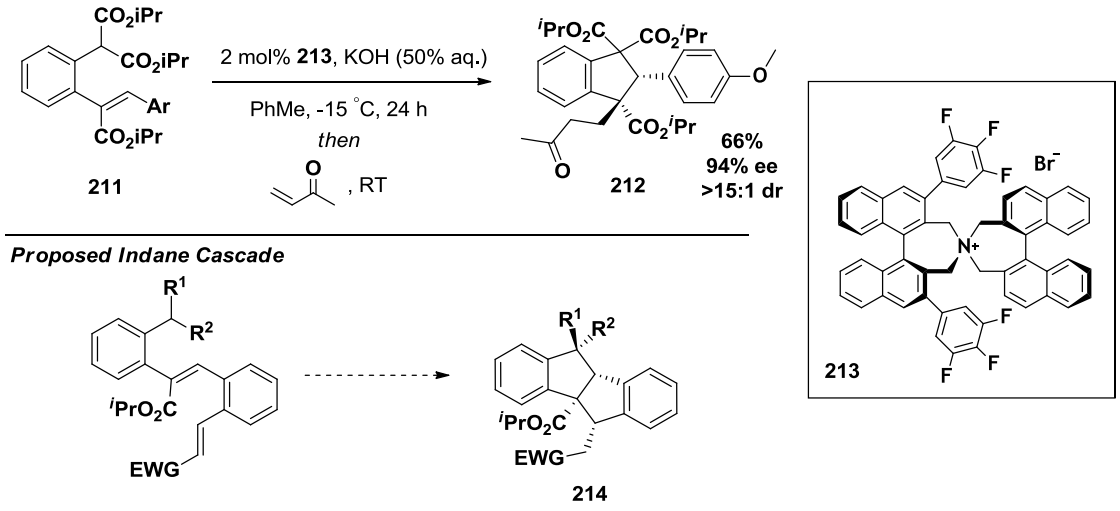
In summary, phase-transfer catalysis provides a viable and powerful methodology for the asymmetric and diastereoselective synthesis of highly functionalized pyrrolizidine and indolizidines, capable of generating all-carbon quaternary stereogenic centres with up to 97% ee.

3.4.2 Future Work

We have demonstrated the powerful strategy of carrying out multiple stereoselective reactions under the influence of a single chiral phase-transfer catalyst, and the potential to generate highly complex molecular architectures rapidly in a single synthetic operation.

A co-worker has demonstrated the efficacy of phase-transfer catalysis in a highly enantioselective all-carbon 6π electrocyclic manifold (Scheme 3.29);[119] it is clear that the

carbanion produced in this process could be employed in a similar manner to the aza-anion in this cascade study, trapping with intra- or intermolecular electrophiles to generate further complexity in a single step. Preliminary results have demonstrated that the electrocyclization of **211**, and trapping of the resulting cyclized anionic species with methyl vinyl ketone affords indane **212** with extremely high levels of diastereocontrol. These results augur well for the use of tandem phase-transfer mediated processes in the asymmetric synthesis of complex, polyfunctionalized indanes **214**.



Scheme 3.29.

Combining this carba-electrocyclic reaction with cascade methodology has the potential to form densely-functionalized indano-indanes containing multiple all-carbon quaternary stereocentres.

More broadly-speaking, given the ability of asymmetric phase-transfer catalysis to mediate a large number of processes under similar reaction conditions,[75–77] there are surprisingly few examples of multiple reactions carried out in one-pot. Although there are a small number of phase-transfer catalysed tandem inter-intramolecular reactions,[120–125] to our knowledge the current study constitutes the only example of an intramolecular cascade. There is therefore great scope to combine other modes of reactivity to generate complexity *via* cascades; an interesting

example closely related to this study would be the combination of our electrocyclic methodology with epoxidation and alkylation reactions to generate hydroxypyrrolizidines **216** from the corresponding cascade precursor **215** (Figure 3.12).

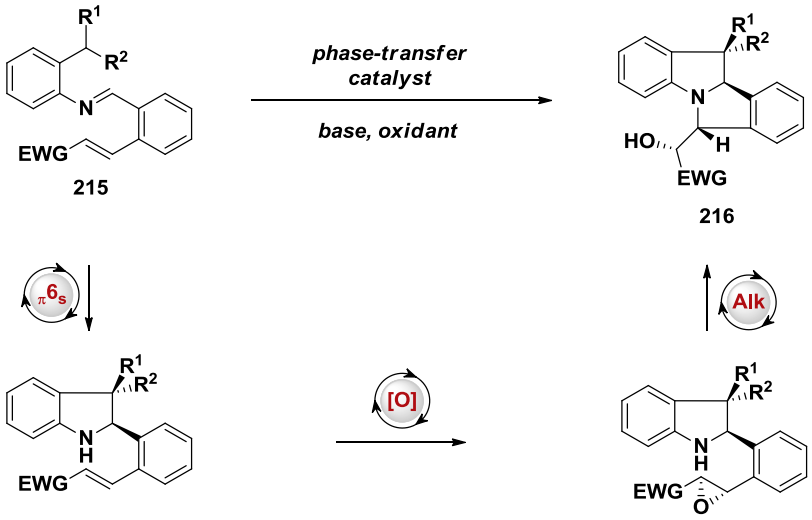


Figure 3.12. A potential phase-transfer catalysed electrocyclization-epoxidation-alkylation reaction.

The potential combinations of phase-transfer catalysed processes are too numerous to detail, but the success of this study bodes well for the future combination of multiple reactions in the generation of highly complex stereodefined targets.

4. 6π [1,6]-ELECTROCYCLIZATIONS

4.1 Phase-Transfer Catalysis of 6π [1,6]-Electrocyclic Reactions

4.1.1 Background

In their uncatalysed form, thermal 6π electrocyclic reactions typically require heating to overcome the considerable activation energy for the disrotatory ring-closure – temperatures of 100–200 °C are generally required.[126,127] Whilst clearly a powerful method of generating carbon-carbon bonds in a stereospecific manner, the harsh reaction conditions make such reactions unsuitable for thermally-unstable molecules.

The effect of substituents on the rates of [1,6]-electrocyclic reactions have been extensively studied over the past 40 years.[50,51,126–139] Of particular note is the recent computational study disclosed by Fu, Liu *et al.,*[138] where the authors comprehensively computed the activation Gibbs free energies ($\Delta G^{\ddagger}$) for the 6π thermal electrocyclic ring-closure reactions of all possible permutations of disubstituted hexatriene **221** (Figure 4.1). This led to the conclusion, corroborated by the experimental findings of Magomedov[135] and Funk,[137] that appropriate captodative substitution could give rise to remarkably facile electrocyclic reactions.

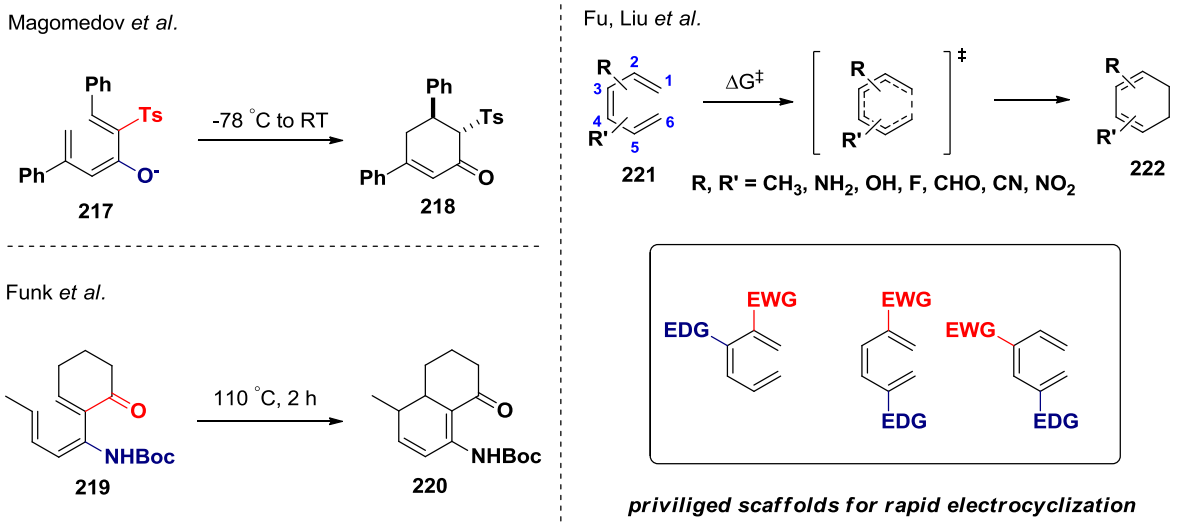
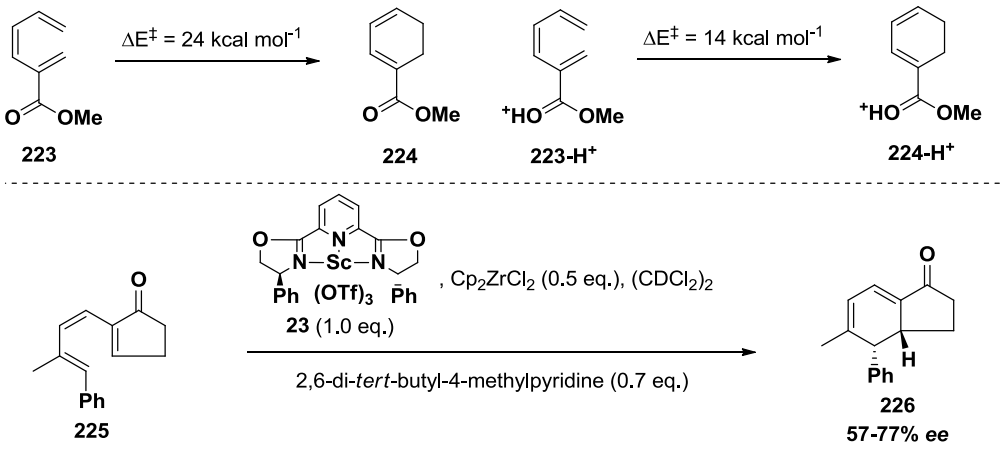


Figure 4.1. Strategies to accelerate 6π [1,6]-electrocyclization.

Trauner and Bergman recently pioneered the catalysis of hexatriene electrocyclizations. DFT calculations indicated that the activation energy for the electrocyclization of hexatriene **223** could be lowered by 10 kcal mol^{-1} by protonation of the ester, clearly demonstrating that acid catalysis is a viable strategy.[51] This theory was confirmed experimentally, where up to 55-fold rate acceleration was observed in the presence of a Lewis acid, and has been applied with moderate success to the catalytic asymmetric electrocyclization of triene **225** to generate hexadiene **226** (Scheme 4.1 and *cf.* Scheme 1.6, p. 11).[50]



Scheme 4.1. Trauner's pioneering catalysis of 6π [1,6]-electrocyclizations.

4.1.2 Concept and Substrate Design

We therefore envisaged that our 6π [1,5]-electrocyclization methodology – employed in the formation of indolines from aldimines **228**, and the related cascades (see chapter 3) – might be amenable to the catalysis of a [1,6]-process (Figure 4.2).

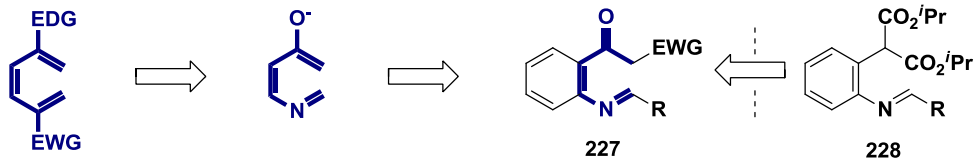


Figure 4.2. Concept development for catalytic [1,6]-azaelectrocyclization.

We rationalized that the presence of a nitrogen atom at the 2-position of **227** in the electrocyclic ring-closure would be functionally equivalent to an EWG-substituted carbon at that site, since it has a similar ability to stabilise negative charge in the transition state and product. We envisioned an electrocyclization under phase-transfer mediated basic conditions (Figure 4.3).

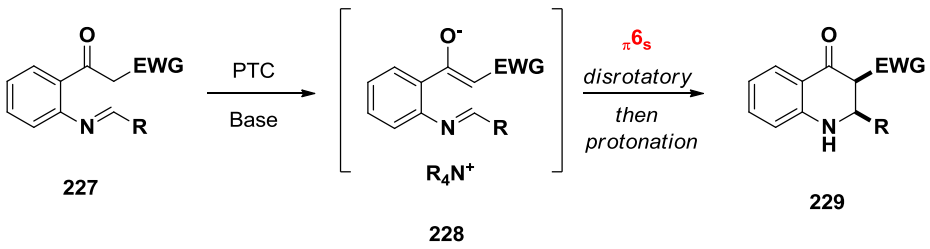


Figure 4.3. Basic phase-transfer catalysed electrocyclization.

It is interesting to note the similarity of this process to the 4π electrocyclic Staudinger β-lactam synthesis;[28] were the nitrogen protonated, this could be considered a vinylogous Staudinger reaction (Figure 4.4).

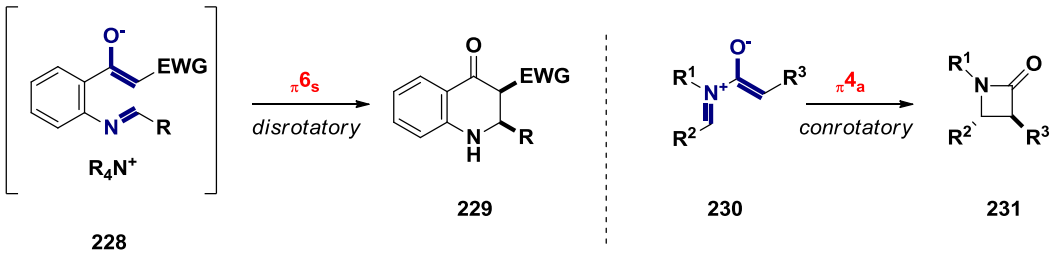
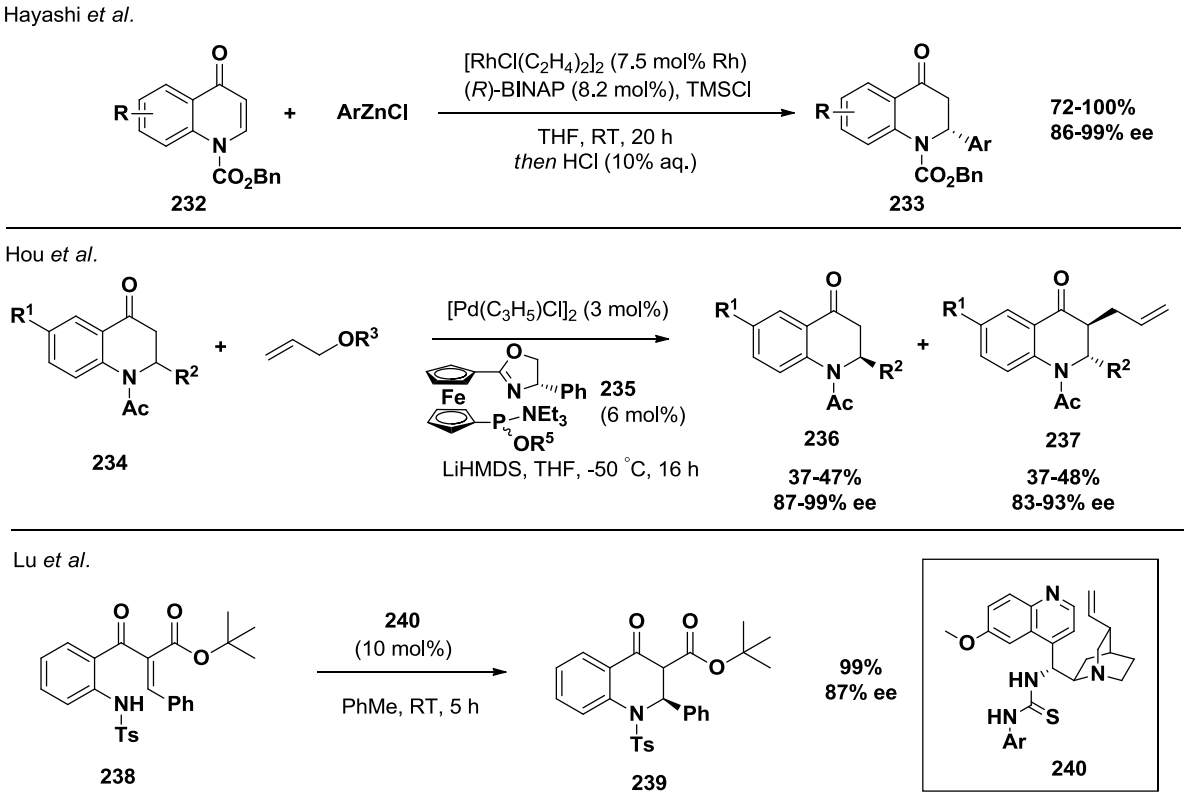


Figure 4.4. Comparison between envisaged electrocyclization and Staudinger reaction.

Whilst the products formed by the proposed 6π electrocyclic process cannot claim the extraordinary therapeutic effects of the β-lactams,[140] 2-aryldihydroquinolones have demonstrated potent cytotoxic effects in almost all tumour cell lines.[141,142] The asymmetric synthesis of 2-substituted dihydroquinolones has been the subject of surprisingly few studies (Scheme 4.2).[143–145]



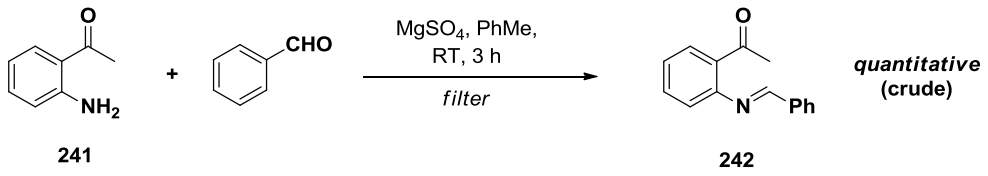
Scheme 4.2. Strategies for the asymmetric synthesis of dihydroquinolones.

Hayashi and Lu employed inter- and intramolecular 1,4-addition approaches respectively, whilst Hou achieved asymmetry *via* a palladium-catalysed kinetic resolution in the synthesis of dihydroquinolones.

We aim to develop a novel tandem imine formation-electrocyclization approach to the asymmetric synthesis of these heterocycles, which should prove complementary to the strategies outlined above.

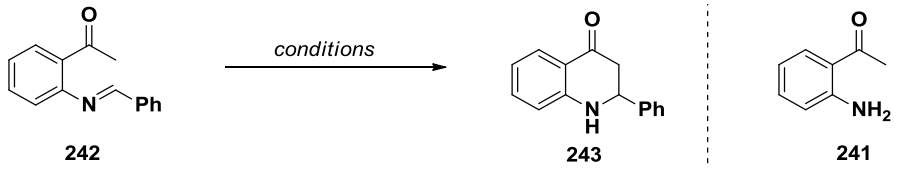
4.1.3 Results and Discussion

Although it was suspected that an electron-withdrawing group would be necessary to facilitate enolization of the substrate under phase-transfer conditions, we hoped that unsubstituted ketone **241** might be sufficiently acidic. The imine was formed in one step from commercially-available 2'-aminoacetophenone and benzaldehyde (Scheme 4.3); reaction at room temperature in the presence of oven-dried magnesium sulfate led to quantitative formation of imine **242**, which was readily hydrolysed in chloroform, on silica and on standing, and was therefore used crude in the subsequent cyclization reactions.



Scheme 4.3.

As expected, exposure of this imine to basic phase-transfer conditions, using both aqueous and solid base, gave no cyclized product and partial hydrolysis of the imine (Table 4.1).



242 243 241

Entry	Conditions[i]	Outcome[ii]
1	*N*-Benzylcinchonidinium chloride **42** (10 mol%), KOH (s), PhMe, RT, 16 h	20% SM, 80% **241**
2	L-Proline, DMF, RT, 48 h	45% SM, 55% **241**
3	LiHMDS, THF, –78 °C to RT, 16 h	80% SM, 20% **241**

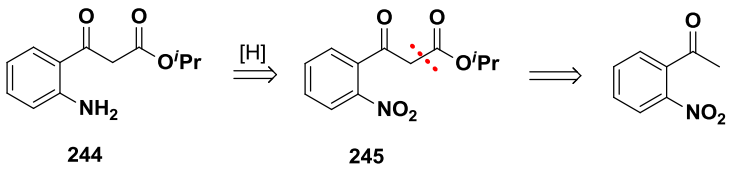
[i] *All reactions were carried out on 50−100 mg scale at ~0.1 M in the solvent indicated.* [ii] D*etermined on the basis of* ^{1}*H NMR analysis of the crude reaction mixture. Values are approximate.*

Table 4.1.

After failure under phase-transfer conditions, we attempted to carry out this cyclization using proline, hoping to achieve asymmetry *via* a chiral enamine intermediate. This also failed, yielding only recovered SM and aniline **241**, the product of imine hydrolysis.

Surprisingly, even by adding a stoichiometric quantity of LiHMDS we were unable to obtain cyclized product **243**. It was clear, therefore, that this substrate had little potential for use in catalytic asymmetric electrocyclization studies.

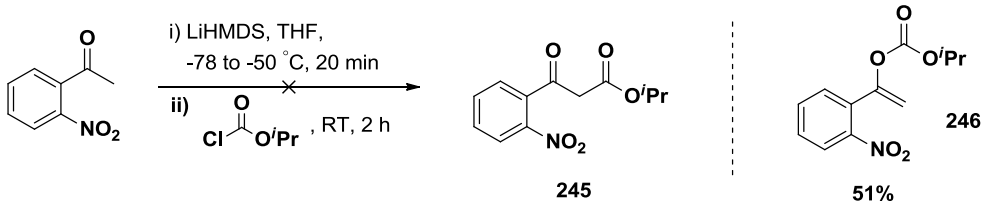
We believed that by increasing the acidity of the proton α- to the ketone it might be possible to deprotonate the substrate under the mild phase-transfer conditions previously used within the group to great effect.[59] We therefore initially focused on the synthesis of β-keto ester substrate **244** since it bears a strong resemblance to the malonates previously investigated, which we hoped to form by the route outlined in Figure 4.5.



244 245

Figure 4.5. Retrosynthetic approach to ester **244**.

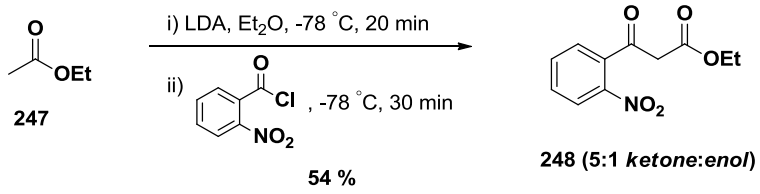
C-carboxylation of 2'-nitroacetophenone was unsuccessful, and the only product obtained upon treatment with base and isopropyl chloroformate was enol carbonate **246**, the product of *O*-carboxylation (Scheme 4.4)



245 246 51%

Scheme 4.4.

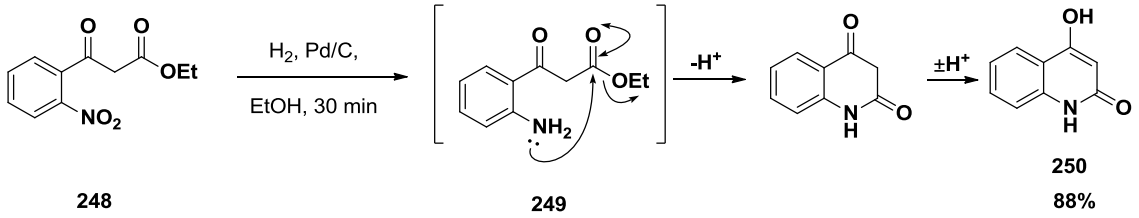
As an alternative approach, deprotonation of ethyl acetate with LDA and quenching the resulting enolate with 2'-nitrobenzoyl chloride afforded β-keto ester **248** in 54% yield as a 5:1 mixture of ketone and enol tautomeric forms respectively (Scheme 4.5).



Scheme 4.5.

Reduction of the nitro group was carried out using palladium on activated carbon under an atmosphere of hydrogen, with crude ^{1}H NMR and MS analysis indicating complete consumption of starting material and formation of the desired aniline **249**. All attempts to purify this material were unsuccessful, and led to the formation of hydroxyquinolone **250**; when the neat crude

material was left to stand for just two hours, or used immediately under imine formation conditions, the hydroxyquinolone was similarly formed (Scheme 4.6).



Scheme 4.6.

Unavoidable lactam formation rendered this aniline **249** useless in the synthesis of the desired corresponding imines, and therefore this substrate was not pursued further.

We turned our attention to the positioning of alternative electron-withdrawing groups α- to the ketone. We hoped to form nitroketone **251** *via* a Henry reaction, followed by oxidation of the resultant secondary alcohol to the corresponding ketone, and chemoselective reduction of the aromatic nitro group (Figure 4.6)

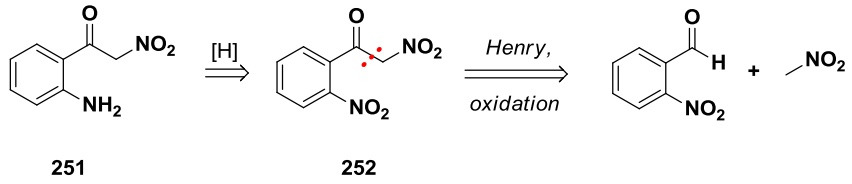
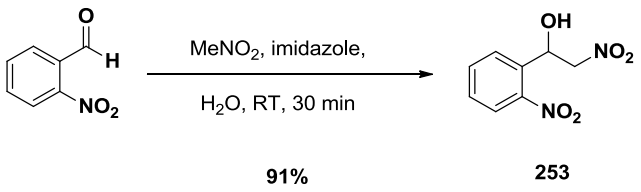


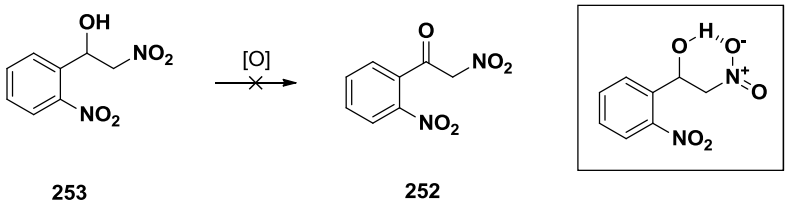
Figure 4.6. Retrosynthetic approach to nitroketone **251**.

Treatment of 2'-nitrobenzaldehyde with imidazole and nitromethane in water afforded alcohol **253** in an excellent 91% yield (Scheme 4.7).



Scheme 4.7.

Unfortunately alcohol **253** proved resilient to oxidation; treatment under a number of oxidation conditions led to either returned starting material or, in the case of the Swern oxidation, a complex mixture of products (Table 4.2).



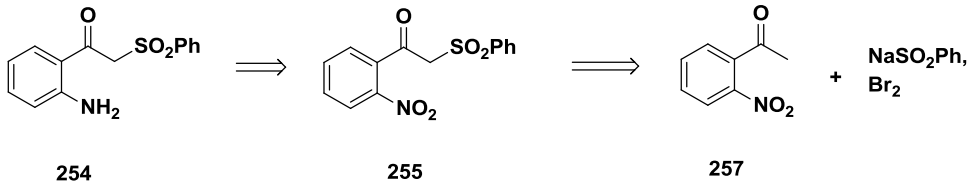
Entry[i]	Conditions[ii]	Outcome[iii]
1	PCC, 3 Å MS, CH_2Cl_2, RT, 18 h	Returned SM
2[146]	DMSO, oxalyl chloride, CH_2Cl_2 *then* NEt_3, −78 to 0 °C, 45 min	Complex mixture
3[147]	TEMPO (cat.), BAIB, CH_2Cl_2, RT, 16 h	Returned SM
4	MnO_2, CH_2Cl_2, RT, 16 h	Returned SM
5	TPAP (cat.), NMO, 4Å MS, CH_2Cl_2/MeCN, RT, 16 h	Returned SM

[i] *References given where literature procedures were followed.* [ii] *All reactions were carried out on a 100 mg scale.* [iii] *Determined by TLC, MS and ^{1}H NMR analysis of the crude reaction mixture.*

Table 4.2.

The failure to oxidize the alcohol may be a consequence of the presence of strong stabilizing intramolecular hydrogen bonding rendering it inert (Table 4.2, *inset*).

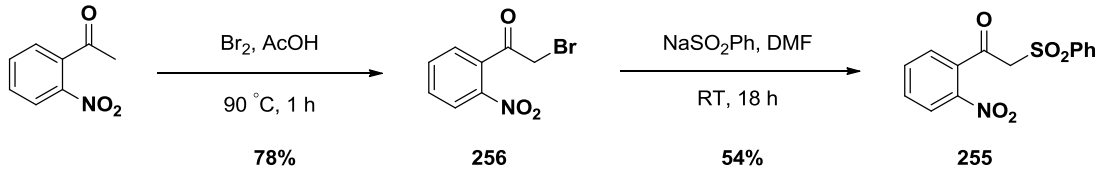
We next considered the use of a sulfone α- to the ketone. We hoped to form this substrate by bromination and subsequent sulfonylation of 2'-nitroacetophenone, followed by reduction to afford the aniline **254** (Figure 4.7).



254 255 257

Figure 4.7. Retrosynthetic approach to sulfonyl ketone **254**.

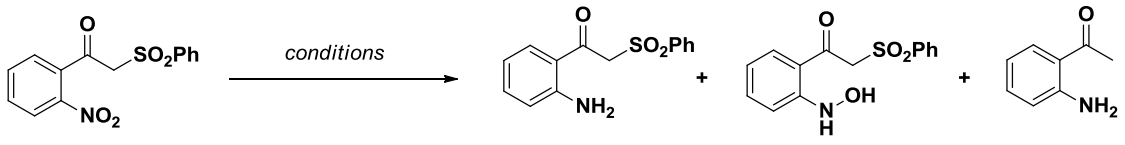
Bromination of 2'-nitroacetophenone was carried out according to a literature procedure:[148] heating to 90 °C in acetic acid in the presence of molecular bromine afforded the product **256** in 78% yield. Treatment with sodium benzenesulfinate in *N*,*N*-DMF gave the desired sulfone **255** in a moderate 54% yield (Scheme 4.8)



256 **255**

Scheme 4.8.

Reduction of the nitro group was initially attempted using palladium on carbon under an atmosphere of hydrogen. This reaction proved extremely slow; after 20 h only the hydroxylamine **259** was observed by MS (Table 4.3, entry 1).



255 **254** **259** **241**

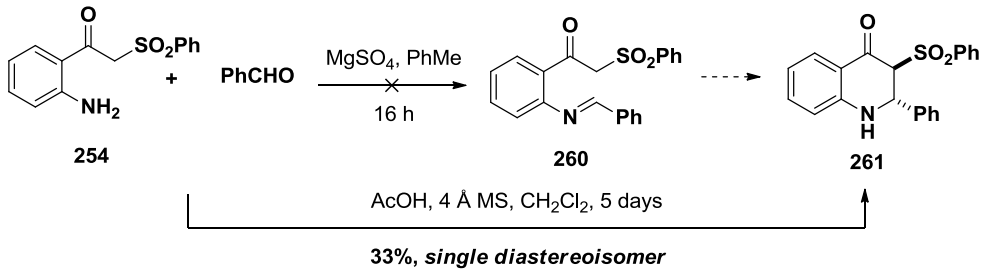
Entry	Conditions	Outcome (yield[i])
1	Pd/C, H_2, MeOH, RT, 20 h	**259**[ii]
2	Zn dust, AcOH, CH_2Cl_2, RT, 20 min	**254** (37%), **241** (51%)
3	PtO_2, H_2, MeOH, RT, 4 h	**254** (87%)

[i] *Where quoted, yields are for isolated material.* [ii] *Observed by MS only.*

Table 4.3.

Treatment of nitro compound **255** with zinc dust in acetic acid for just 20 min afforded aniline **254** in a meagre but acceptable 37% yield, with a 51% yield of 2'-aminoacetophenone, the product of reductive cleavage of the C-S bond. However, Adam's catalyst proved to be the reagent of choice for this reaction, cleanly converting nitroarene **255** to aniline **254** in just four hours with no reductive C-S cleavage observed.

With aniline **254** in hand, we proceeded to investigate formation of the imine. Previous studies into the synthesis of indolines had favoured a mild imine formation reaction, utilizing magnesium sulfate as a Lewis acid and dessicant in toluene at room temperature. Under these conditions aniline **154** sadly failed to react with benzaldehyde, returning only starting material. This led us to explore alternative methods of imine formation; treatment of aniline **254** with benzaldehyde in dichloromethane in the presence of acetic acid and 4 Å molecular sieves initially appeared to give no reaction – even after 48 h – and so the reaction was abandoned. However, it was subsequently noted that after a further 3 days left unattended the reaction mixture had turned a lurid yellow colour, and analysis revealed this was due to formation of the cyclized product **261** in 33% yield as a single diastereoisomer (Scheme 4.9).



Scheme 4.9.

The curious time-dependence of this reaction was presumed to be a concentration effect; evaporation of dichloromethane left the aniline and aldehyde in neat acetic acid at very high concentration. The intermediate imine **260** was not observed by ^{1}H NMR at any stage, suggesting that cyclization occurs rapidly on the iminium intermediate **258** *via* the enol tautomer

262. The stereochemistry of **261** was determined to be *anti* by single crystal X-ray diffraction. Assuming formation of the (*E*)-enol **262**, the diastereoselectivity may be explained either by a direct (and non-pericyclic) Mannich reaction, or by electrocyclization followed by acid-catalysed epimerization (Figure 4.8).

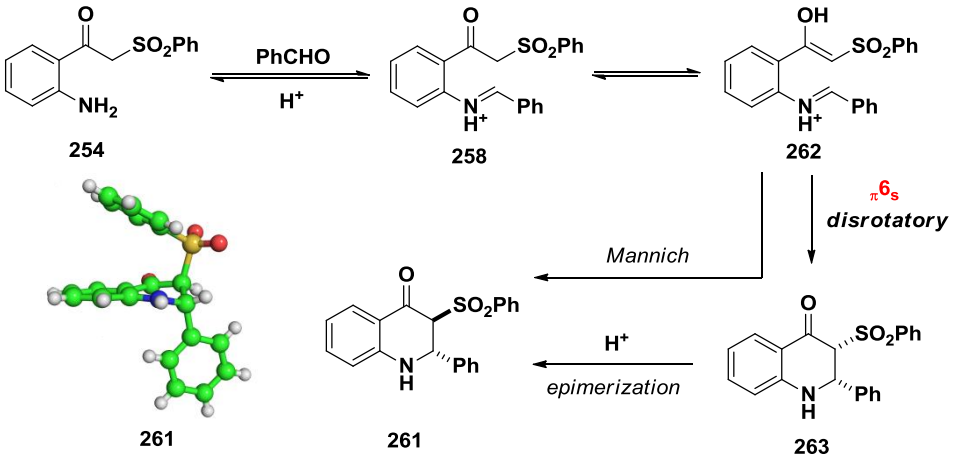


Figure 4.8. Mechanistic proposal for the tandem imine formation-cyclization of sulfone **261**.

Single-crystal X-ray structure rendered using PyMOL.[117]

Despite the successful formation of cyclized material, this substrate did not appear to be amenable to phase-transfer catalysis, since this necessarily requires formation and isolation of imines, and subsequent controlled and catalytic enolate formation. Thus the acid-catalysed process outlined in Figure 4.8, and particularly the spontaneous formation and cyclization of the reactive enol-iminium intermediate **262**, preclude any asymmetric induction employing chiral counter-cations since no substrate-catalyst binding could reasonably be expected.

At this stage we were still seeking a substrate that would undergo electrocyclization under phase-transfer conditions. Spontaneous formation of the enol **262** allowed its cyclization to occur under acidic imine-formation conditions; we therefore proceeded to investigate a less acidic substrate, where enol formation under acidic conditions might be avoided, but enolate formation under basic conditions might be expected. Given the successful cyclization of sulfone

254 we decided to temper its acidity with minimal alteration to the substrate by forming thioether **264** (Figure 4.9).

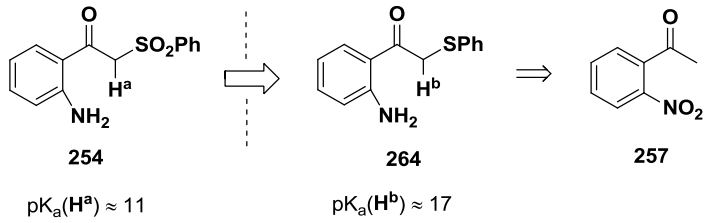
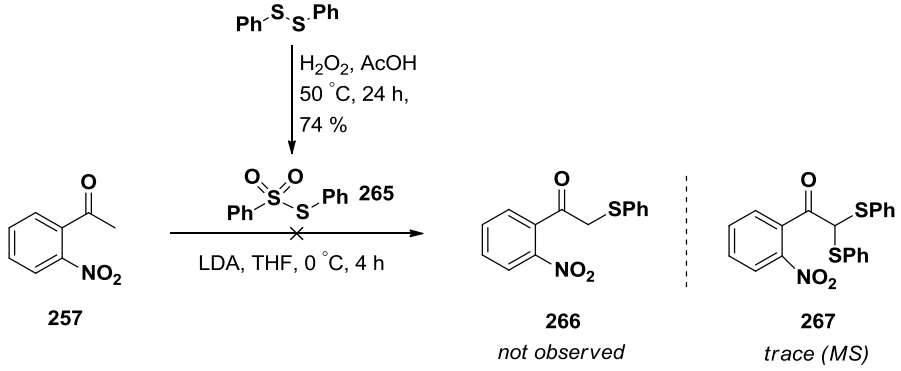


Figure 4.9. *pKa values are estimated by analogy to structurally-related compounds.*[68]

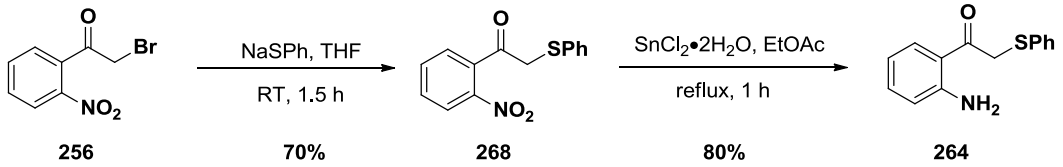
Initially, we attempted to form nitro thioether **266** directly from 2'-nitroacetophenone **257** using LDA and *S*-phenyl benzene thiosulfonate **265** (formed by oxidation of diphenyl disulphide), as reported by Trost for alkyl ketones.[149] Unfortunately MS analysis of the reaction mixture revealed only starting material and double addition product **267** (Scheme 4.10).



Scheme 4.10.

We therefore resolved to form the substrate by nucleophilic substitution of bromoketone **256**, in a similar manner to the formation of sulfone **255** above. Thus, treatment of 2-bromo-2'-nitroacetophenone **256** with sodium thiophenolate in tetrahydrofuran afforded the desired α-thiophenyl ketone **268** in 70% yield (Scheme 4.11). Reduction of the nitro group under the conditions employed for the earlier sulfone substrate was ineffective, and produced a

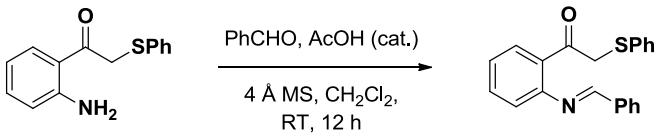
multitude of unidentified products. However, refluxing the nitroarene in the presence of tin(II) chloride dihydrate afforded the desired aniline **264** cleanly in 80% yield.



256 **70%** **268** **80%** **264**

Scheme 4.11.

Our efforts were then directed towards imine formation. Anhydrous magnesium sulfate was ineffective to this end, but treatment of the aniline with benzaldehyde in the presence of acetic acid and 4 Å molecular sieves afforded the imine **269** as the major component of the reaction mixture (Scheme 4.12).

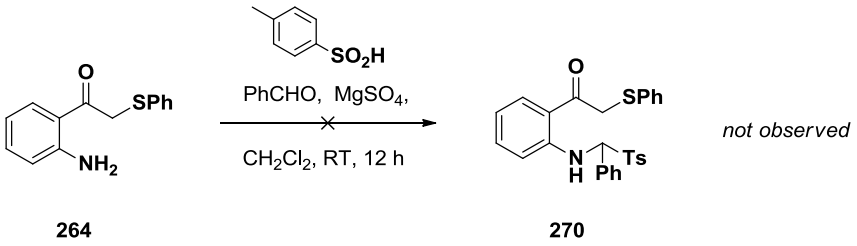


264 ***up to ~60% conversion*** **269**

Scheme 4.12.

However, further purification was not possible due to the instability of the imine **269** with respect to hydrolysis. This imine formation was exceedingly capricious, with the level of ~60% product purity achieved only once.[*] We hoped to counter these issues of purification by formation of masked imine **270**; elimination under basic conditions would generate the imine **269** *in situ* during our phase-transfer catalysed electrocyclization (Scheme 4.13).

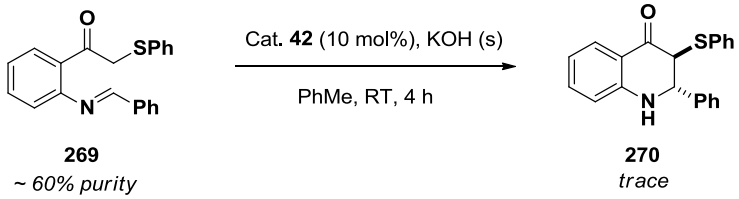
[*] *Determined by ^{1}H NMR analysis of the crude reaction mixture.*



Scheme 4.13.

Unfortunately this reaction resulted only in recovered starting material, and was not further pursued.

Nonetheless, we proceeded to expose the imine formed above (in 60% purity) to phase-transfer catalysed cyclization conditions, to determine whether the reaction was worthy of further investigation. Treatment of imine **269** in toluene with *N*-benzylcinchonidinium chloride **42** (10 mol%) and solid potassium hydroxide led to consumption of the crude starting material, and led to a complex mixture of products which could not be obtained in pure form even after multiple attempts *via* column chromatography. Cyclized product **270** was obtained,[*] but was inseparable from aniline **264** and another unidentified compound (Scheme 4.14).



Scheme 4.14.

We were growing increasingly frustrated with issues of purification: the necessity of imine formation prior to cyclization (since the imines are formed under acidic conditions, and the cyclization carried out in base) – combined with the instability of the imines with respect to hydrolysis – meant that we were consistently unable to obtain a pure sample of the substrate for

[*] *Although the cyclized product was not obtained in sufficient purity for characterization or analysis, its formation was determined by retrospective comparison with the pure compound obtained subsequently under acidic conditions.*

electrocyclization. Subequently, we were unable to investigate the cyclization with any degree of rigour, since difficult and often intractable mixtures of products were obtained.

4.2 Acid-Catalysed Tandem Imine Formation-Electrocyclization

4.2.1 Background and Concept Development

In all studies towards asymmetric electrocyclization of imines within our laboratory, mild imine formation conditions have been employed.[59,89] This was necessary, since more harsh imine formation conditions (such as azeotropic removal of water in toluene in the presence of an acid catalyst) often led to partial or complete formation of the cyclized product, prior to use of the asymmetric phase-transfer catalyst under basic conditons. Even silica gel is sufficiently acidic to induce some cyclization reactions, leading to reduced enantioselecivities due to the presence of residual racemic cyclized material prior to the asymmetric step.[111,150]

The implication is that these reactions can generally occur under acidic as well as basic conditions. Since the imine formation is also acid-catalyzed, there is an obvious opportunity to carry out both the imine formation and cyclization in a single process. Given the ubiquity of chiral acids in asymmetric catalysis,[151] we were hopeful that an acid could be found to catalyse this two-step procedure and induce asymmetry in the [1,6]-electrocyclization of **273** to form **274** (Figure 4.10).

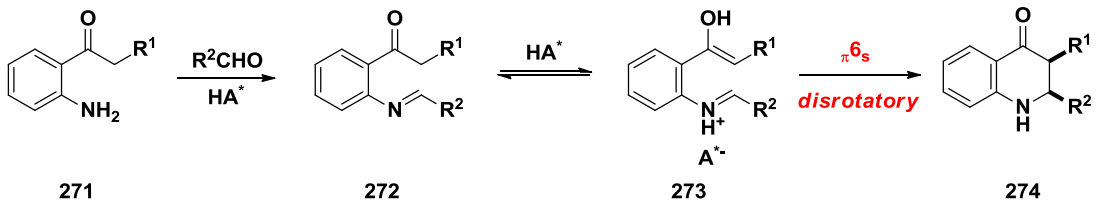


Figure 4.10. Acid catalysis of 6π [1,6]-electrocyclization. *HA* is representative of a generic chiral acid.*

We were encouraged to find excellent precedent for such reactivity. Both Lewis and chiral Brønsted acids have been employed in closely-related three-component coupling reactions.

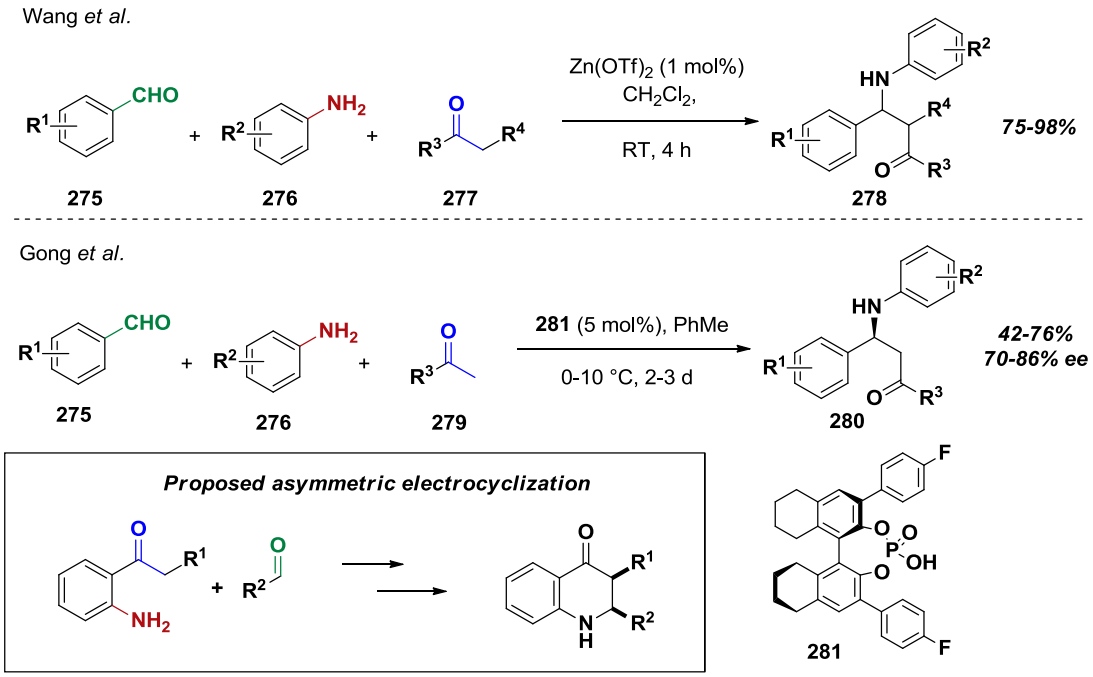


Figure 4.11. Precedent for acid-catalysed imine formation and cyclization.

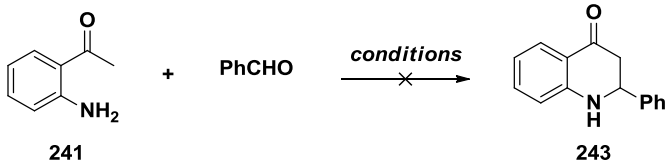
Wang employed zinc(II) triflate to catalyse the racemic coupling of a range of anilines **276**, aromatic aldehydes **275** and enolizable ketones **277** to form β-amino ketones **278** in up to 98% yield; we were hopeful that in our case, similar conditions might be adopted in the presence of a chiral ligand to induce asymmetry in the proposed electrocyclization.[152] More recently, Gong utilized chiral phosphoric acid **281** to effect a similar three-component coupling, affording products **280** in up to 76% yield and 86% ee.[*153] We were therefore optimistic in applying both Lewis and Brønsted acid catalysis to our electrocyclization manifold.

4.2.2 Initial Findings

We initially investigated the simplest case for our electrocyclization studies, where commercially-available 2'-aminoacetophenone is employed as the keto-aniline component of the

[*] *Where cyclic aliphatic ketones were employed in this reaction, ee's of up to 98% were achieved.*

reaction. We were hopeful that an additional electron-withdrawing group would not be necessary, given the successful use of acetophenone as the ketone component in the studies of Gong *et al* (*cf.* Figure 4.11).



241 243

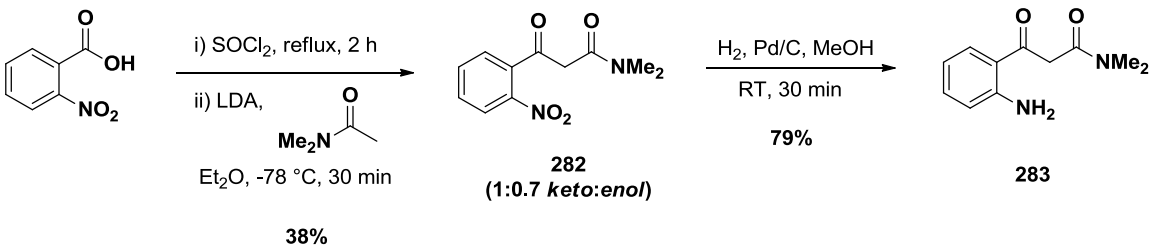
Entry	Conditions[i]	Outcome[ii]
1	$Zn(OTf)_2$ (10 mol%), CH_2Cl_2, RT, 16 h	No reaction
2	$Sc(OTf)_3$ (10 mol%), CH_2Cl_2, RT, 16 h	No reaction
3	Diphenyl phosphate (10 mol%), CH_2Cl_2, RT, 16 h	No reaction

[i] *All reactions were carried out with 1 eq. aniline and 2 eq. benzaldehyde at 0.2 M (aniline), on a scale of 25−50 mg (aniline).* [ii] *Determined by TLC, MS and ^{1}H NMR analysis of the crude reaction mixture.*

Table 4.4.

When treated with benzaldehyde and Lewis or Brønsted acids, 2'-aminoacetophenone **241** was unfortunately unreactive (Table 4.4). This was surprising, given the successful reaction of similar substrates in an intermolecular sense in the three-component couplings outlined above; we had expected that since the reaction was intramolecular, product formation would be accelerated.

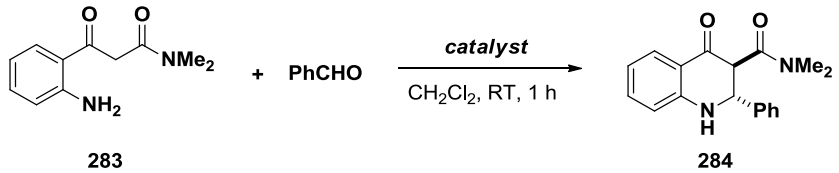
There is also significant precedent for the addition of 1,3-dicarbonyl compounds to imines under Lewis and Brønsted acid catalysis:[152,154] we hoped that by modifying the ketone component of our reaction we might be able to favour formation of the enol and increase reactivity as a consequence. Although previous attempts to form a β-keto ester substrate had been fraught with difficulty (§ 4.1.3) we were able to form β-keto amide substrate **283** by a simple three-step procedure (Scheme 4.15)



Scheme 4.15.

2-Nitrobenzoyl chloride was formed *in situ* from 2-nitrobenzoic acid, and reacted with the lithium enolate of *N*,*N*-dimethylacetamide to form β-keto amide **282** in a moderate 38% yield, and as a mixture of tautomers. Reduction of the nitro group proceeded cleanly in 79% yield to afford aniline **283**, a bench-stable crystalline solid that did not suffer from any of the unwanted cyclization observed for the ester (*cf.* Scheme 4.6, p. 89).

With the aniline in hand we proceeded to probe its reactivity under acidic reaction conditions. In the presence of benzaldehyde and a catalytic quantity of zinc(II) triflate, copper(II) triflate, scandium(III) triflate or diphenyl phosphate in dichloromethane, the aniline cleanly underwent imine formation and cyclization to form *trans*-dihydroquinolone **284** (Table 4.5).



Entry[i]	Catalyst (loading)	Conversion / %[ii]
1	$Zn(OTf)_2$ (10 mol%)	100
2	$Cu(OTf)_2$ (10 mol%)	100
3	$Sc(OTf)_3$ (10 mol%)	100
4	$(PhO)_2PO_2H$ (20 mol%)	~80

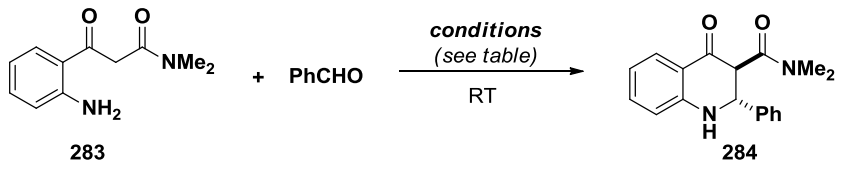
[i] *All reactions were carried out on a 25 mg scale (aniline) at RT in CH_2Cl_2 at a concentration of 0.1 M with 2 eq. of benzaldehyde. Yields not determined.* [ii] *Determined by ^1H NMR analysis of the crude reaction mixture after 1 h.*

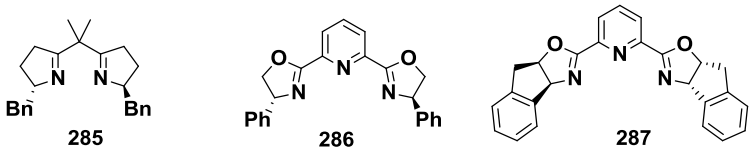
Table 4.5.

With the desired reactivity proven, we progressed to investigate the potential for asymmetric induction under Lewis and Brønsted acid-catalysed conditions in turn.

4.2.3 Lewis Acid Catalysis

The focus of our studies was primarily on metal triflate Lewis acids, since these have been extensively employed in asymmetric catalysis in combination with chiral nonracemic (often oxazoline) ligands.[155–163]





Entry[i]	Solvent[ii]	Catalyst[iii]	Ligand (eq.)	Conversion (time) [iv]	ee / % [v]
1[164]	1:1 THF:PhMe	$Sc(OTf)_3$	**285** (0.11)	~75% (15 min) 100% (2 h)	0
2[164]	1:1 THF:PhMe	$Sc(OTf)_3$	**286** (0.11)	~75% (15 min) 100% (2 h)	0
3[164]	1:1 THF:PhMe	$Cu(OTf)_2$	**285** (0.11)	~50% (16 h)	0
4[164]	1:1 THF:PhMe	$Cu(OTf)_2$	**286** (0.11)	~50% (16 h)	0
5[164]	1:1 THF:PhMe	$Zn(OTf)_2$	**285** (0.11	0% (16 h)	-
6[164]	1:1 THF:PhMe	$Zn(OTf)_2$	**286** (0.11)	0% (16 h)	-
7[42]	MeCN	$Sc(OTf)_3$	**286** (0.2)	100% (20 min)	8
8[165]	CH_2Cl_2	$Sc(OTf)_3$ (0.01 eq.)	**286** (0.025)	100% (3 h)	0
9[165]	CH_2Cl_2	$Sc(OTf)_3$ (0.01 eq.)	**287** (0.025)	100% (3 h)	3

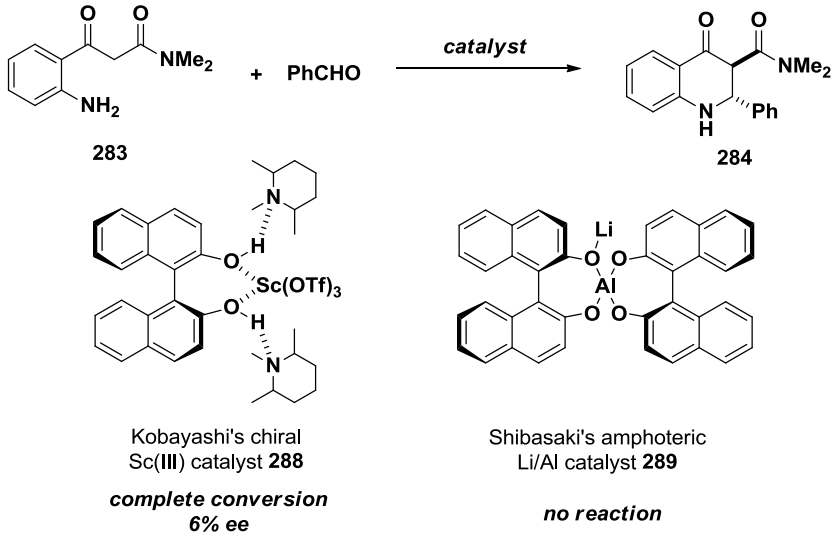
[i] *References given where literature procedures were followed.* [ii] *All reactions were carried out on 25−50 mg scale (aniline) with 2.0 eq. aldehyde at RT. Unless stated otherwise, all reactions were carried out using 0.1 eq. catalyst.* [iii] *In all cases the catalyst and ligand were stirred for 1−3 h in the presence of powdered 3 or 4 Å molecular sieves prior to adding the aniline and aldehyde.* [iv] *Values determined by TLC analysis, and are approximate only.* [v] *Determined by chiral HPLC.*

Table 4.6. Catalyst screen. *For full details, see experimental section, p. 238.*

Aniline **283** and benzaldehyde were treated with scandium(III), copper(II) and zinc(II) triflates in the presence of chiral bisoxazoline (box) **285** and pyridine bisoxazoline (pybox) **286**, under conditions employed by Evans for the asymmetric Diels-Alder cycloaddition of quinones (Table 4.6, entries 1−6).[164] No asymmetric induction was observed, and surprisingly the addition of ligands significantly retarded the copper(II) and zinc(II)-mediated processes (*cf.* Table 4.5). Performing the Sc(III) catalysed process in dichloromethane also gave essentially racemic

product, both with pybox **286** and indapybox **287** (Table 4.6, entries 8−9), whilst acetonitrile gave a very small degree of asymmetric induction (Table 4.6, entry 7).

Kobayashi's BINOL-derived chiral scandium(III) catalyst **288** (formed *in situ* from BINOL, scandium(III) triflate and *cis*-1,2,6-trimethylpiperidine) gave good reactivity, but only 6% ee,[166] while Shibasaki's amphoteric BINOL-derived lithium/aluminium catalyst **289** failed to catalyse the reaction (Scheme 4.16).[167]



Scheme 4.16. Kobayashi and Shibasaki's chiral Lewis acids. *For full conditions see experimental section, p.239.*

By considering the mechanism for this transformation, we believed that the use of chiral Lewis acids to induce asymmetry was inherently flawed, since the chiral ligands are positioned much too far away from the site of bond formation. We propose that acid-catalysed imine formation is followed by binding of the metal to the bidentate 1,3-dicarbonyl, acidifying the methylene position. Inter- or intramolecular proton transfer to the imine leads to zwitterionic iminium scandium enolate **291**, which undergoes 6π electrocyclization and thermodynamic epimerization to afford the observed dihydroquinolone (Figure 4.12).

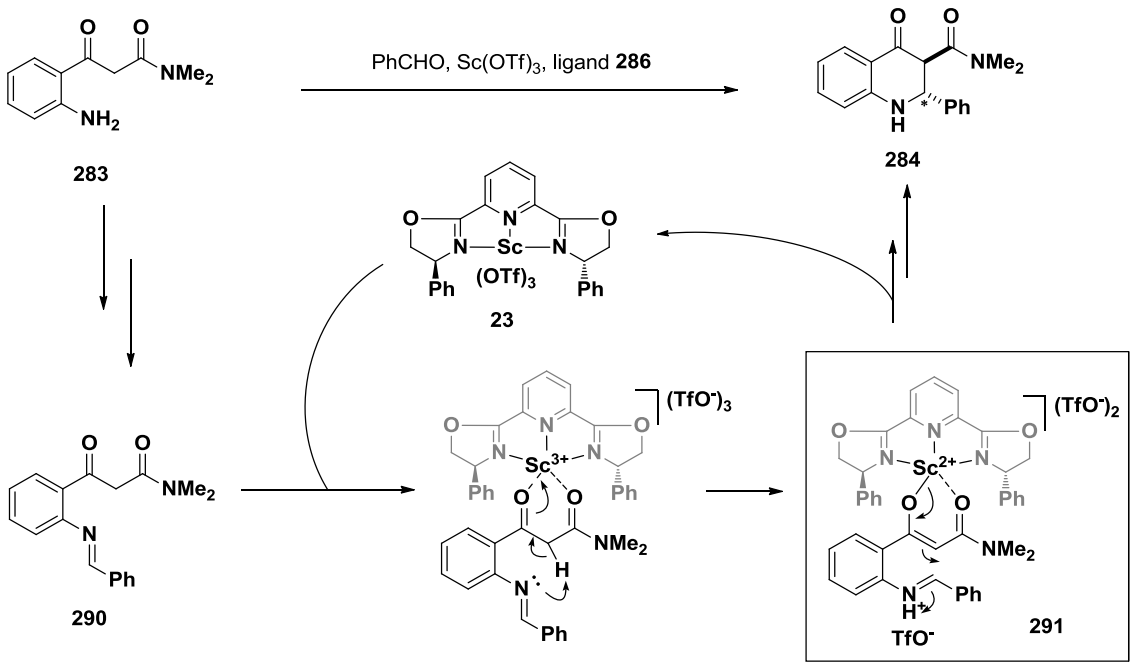


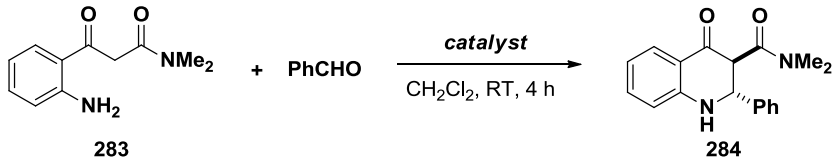
Figure 4.12. Proposed mechanism for Lewis-acid catalysed cyclization.

The stereocentre that determines the absolute stereochemistry of the product is not the central carbon of the 1,3-dicarbonyl (since this site is subject to acid-catalyzed epimerization), but the benzylic position (*). It is difficult to imagine that the stereodirecting groups on the ligand would have any impact on the facial selectivity of addition to the iminium (i.e. the torquoselectivity), and so the failure to achieve significant levels of enantioselectivity is not surprising.

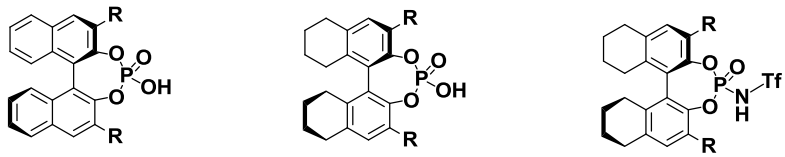
We were hopeful that Brønsted acid catalysis might provide improved enantioselectity: by placing a chiral counter-anion in close proximity to the iminium intermediate, we expected that greater levels of asymmetric induction may be achieved.

4.2.4 Brønsted Acid Catalysis

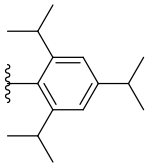
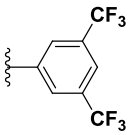
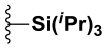
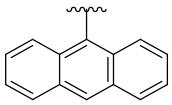
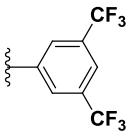
Early studies had indicated diphenyl phosphate was a competent catalyst for this reaction, so a variety of BINOL-derived chiral phosphoric acids were screened (Table 4.7).[*168–171]



283 284



39, 292-295 296 297

Entry	Catalyst[i]	R	ee / % [ii]
1	**292**		35
2	**293**		-6
3	**294**		-9
4	**295**		6
5	**39**		8
6	**296**		-18
7	**297**		1

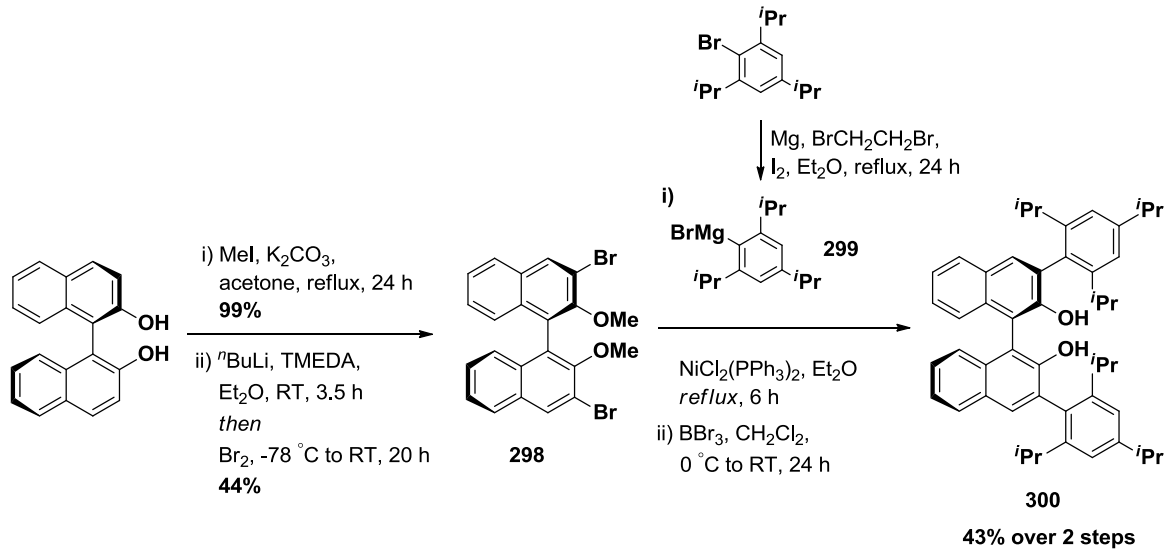
[i] *All reactions were carried out at RT on a 10 mg scale (aniline) with 2.0 eq. benzaldehyde and 5 mol% catalyst in dichloromethane at an aniline concentration of 0.1 M. All reactions went to completion (TLC) after 4 h. Yields not determined.* [ii] *Determined by chiral HPLC.*

Table 4.7. Chiral Brønsted acid screen. *For full details, see experimental section, p. 241.*

[*] *Thanks to the Prof. Darren Dixon group for use of their library of chiral phosphoric acids during this screen.*

All catalysts were found to be active, although surprisingly giving different major enantiomers of the product (despite having the same sense of axial chirality), most noticably **292** and **296**. Catalyst **292** (TRIP) gave the highest levels of enantioselectivity, affording the dihydroquinolone in 35% ee, and was therefore the focus of further study.*

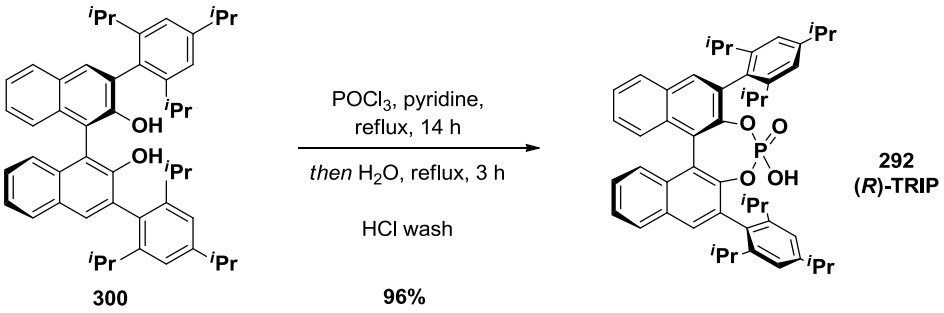
We set about synthesizing useful quantities of TRIP to allow further reaction optimization. Following literature procedures, key diol **300** was accessible in four linear steps from commercially-available (*R*)-BINOL, in an overall yield of 19% (Scheme 4.17).[172,173] Formation of Grignard reagent **299** under the literature protocol was initially challenging, but use of mechanically-activated magnesium turnings and iodine as an additional initiator led to smooth formation of the Grignard and successful Kumada coupling.[174]



Scheme 4.17.

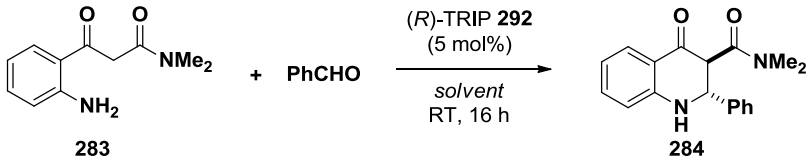
Final formation of the phosphoric acid was achieved under the conditions reported by List, avoiding the use of silica gel chromatography which has been reported to cause partial formation of the calcium salt (Scheme 4.18).

* *Although yields were not determined since the screen was carried out on an analytical scale, all reactions went to completion and could reasonably be expected to be high-yielding once scaled up.*



Scheme 4.18.

With large quantities of the chiral acid in hand, optimization of the Brønsted acid-catalysed cyclization procedure was commenced; the role of solvent on the enantioselectivity of the reaction was examined (Table 4.8).



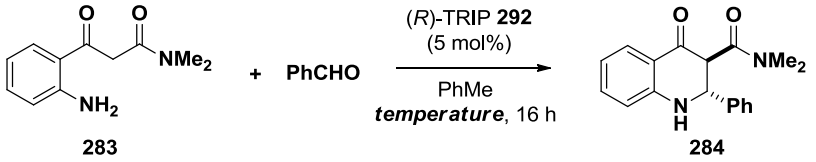
Entry[i]	Solvent	Aniline conc. / M	ee / % [ii]
1	CH_2Cl_2	0.05	14
2	CH_2Cl_2	0.10	14[iii]
3	CH_2Cl_2	0.20	11
4	MeCN	0.10	8
5	MeOH	0.10	−7[iv]
6	THF	0.10	2
7	Et_2O	0.10	8
8	iPr_2O	0.10	~20[v]
9	PhMe	0.10	40
10	PhCl	0.10	40

[i] *All reactions were carried out at RT on a 10 mg scale (aniline) with 2.0 eq. benzaldehyde and 5 mol% catalyst, and were analysed after 16 h. Yields not determined.* [ii] *Determined by chiral HPLC.* [iii] *This value differs from that obtained previously (Table 4.7) but is used for comparison since experiments in this table were carried out concurrently.* [iv] *Unidentified contaminant present in HPLC trace; ee value may be inaccurate.* [v] *ee value approximate due to poor conversion leading to high noise/signal ratio in HPLC trace.*

Table 4.8. Solvent screen. *For full details, see experimental section, p. 241.*

Concentration had only a minimal influence on enantioselecivity (Table 4.8, entries 1−3), whilst the solvent itself had a larger effect. Polar, protic and ethereal solvents (entries 4−8) gave poor enantioselectivies (with the exception of diisopropyl ether, where substrate insolubility led to very low conversion), whilst toluene and chlorobenzene improved ee to 40%. Toluene was therefore employed in subsequent studies, at an aniline concentration of 0.1 M.

The influence of temperature on enantioselectivity was also investigated (Table 4.9).



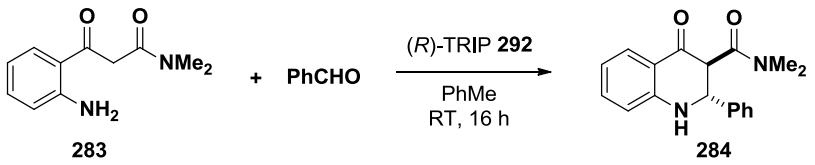
Entry	Temperature / °C [i]	ee / % [ii]
1	40	*decomposed*
2	RT (~20)	40
3	0	58
4	−30	68
5	−78	30[iii]

[i] *All reactions were carried out on a 10 mg (aniline) scale with 2.0 eq. benzaldehyde and 5 mol% catalyst at an aniline concentration of 0.1 M in toluene, and were analysed after 16 h. Yields not determined.* [ii] *Determined by chiral HPLC.* [iii] *ee value approximate due to poor conversion leading to high noise/signal ratio in HPLC trace.*

Table 4.9. Temperature screen. *For full details, see experimental section, p. 241.*

As expected for a catalytic asymmetric process, reducing temperature tended to improve enantioselectvity. Surprisingly, even moderate warming to 40 °C led to decomposition, and none of the desired cyclized product was obtained. Cooling to –78 °C gave extremely poor conversion, with only trace quantities of the product observed by TLC after 16 h. –30 °C was therefore determined to be the optimal temperature for the transformation, affording **284** in a much-improved 68% ee (Table 4.9, entry 4).

We also probed the effect of catalyst loading on enantioselectivity (Table 4.10)



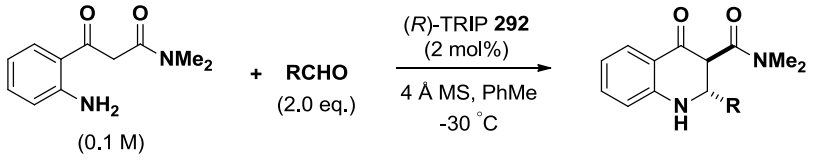
Entry	Catalyst loading / mol% [i]	ee / % [ii]	Conversion / % [iii]
1	10	34	100
2	5	24[iv]	76
3	2	30	85
4	1	22	34

[i] *All reactions were carried out at RT on a 50 mg (aniline) scale with 2.0 eq. benzaldehyde, at an aniline concentration of 0.1 M in toluene, and were analysed after 16 h. Yields not determined.* [ii] *Determined by chiral HPLC.* [iii] *Determined by ^{1}H NMR analysis of the crude reaction mixture.* [iv] *This value differs from that obtained previously (Table 4.9) but is used for comparison since experiments in this table were carried out concurrently.*

Table 4.10. Catalyst loading screen. *For full details, see experimental section, p. 241.*

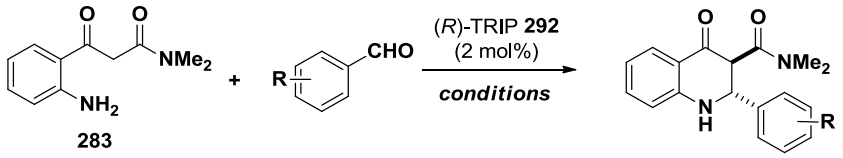
Reducing the catalyst loading to 2 mol% was well-tolerated, maintaining good conversion and enantioselectivity comparable to that obtained at 10 mol% (Table 4.10, entry 3).

It was also observed that the addition of 4 Å molecular sieves tended to improve the consistency of cyclization reactions. Our optimized procedure is therefore summarized in Scheme 4.11.



Scheme 4.19. Optimized procedure for TRIP-catalysed formation of dihydroquinolones.

Unfortunately, application of this complete procedure to benzaldehyde and isomers of chlorobenzaldehyde on a preparative scale revealed that it was prohibitively slow, and in some cases gave no reaction at all (Table 4.11). By warming to 0 °C and switching to chlorobenzene reactivity was regained, but enantiomeric excesses were unimpressive.



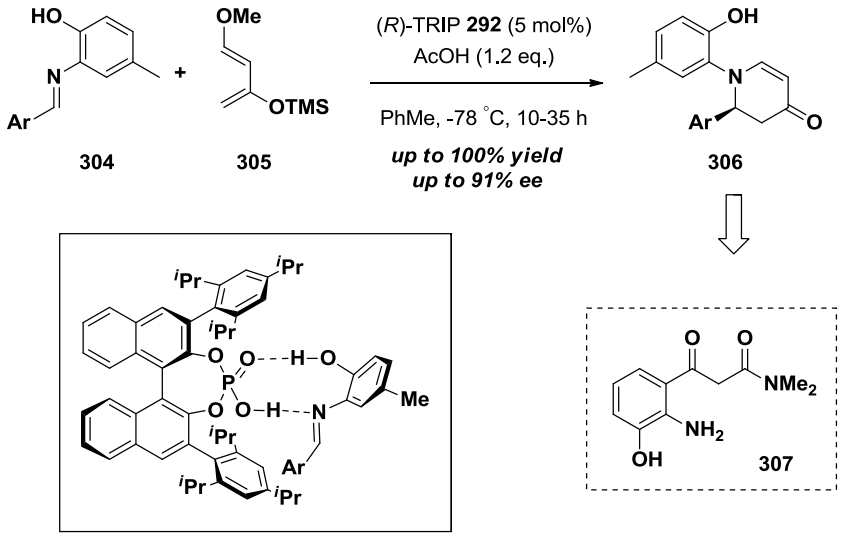
Entry[i]	R	–30 °C in PhMe		0 °C in PhCl		Product
		Conv. / % (time) [ii]	ee / % [iii]	Conv. / % (time) [ii]	ee / % [iii]	
1	H	50 (4 d)	51	100 (2 d)	4	**284**
2	2-Cl	65 (4 d)	16	100 (2 d)	5	**301**
3	3-Cl	NR (4 d)	-	100 (2 d)	12	**302**
4	4-Cl	NR (4 d)	-	100 (2 d)	11	**303**

[i] *All reactions were carried out on a 50 mg scale (aniline) with 2.0 eq. aldehyde and 2 mol% (R)-TRIP at an aniline concentration of 0.1 M in the presence of 4 Å MS. Yields not determined.* [ii] *Determined by ^{1}H NMR analysis of the crude reaction mixture.* [iii] *Determined by chiral HPLC.*

Table 4.11. Scope of the reaction. *For full details, see experimental section, p. 242.*

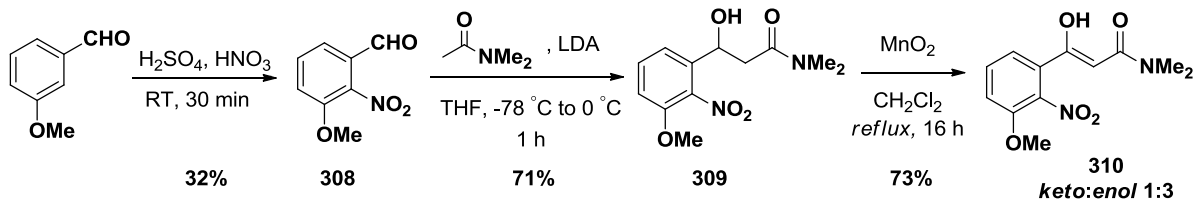
We were therefore faced with two possible strategies for improvement: either to improve the inherent selectivity of the process such that good enantioselectivity could be obtained at higher temperatures whilst maintaining conversion, or to increase the activity of the catalyst so that the reaction would proceed at cryogenic temperatures, where better enantioselectivity could be expected. We initially planned to follow the former strategy; hopeful that a small modification of the substrate might significantly increase levels of asymmetric induction.

Akiyama *et al.* have proposed that the presence of an *ortho*-hydroxyl group in related cycloaddition and Mannich processes leads to a bidentate catalyst-substrate interaction, affording enantioselectivities of up to 91% in the cycloaddition of *ortho*-hydroxy Schiff bases **304** with Danishefsky's diene **305** (Scheme 4.20).[168,175,176] We hoped that a structurally analogous substrate (**307**) would improve the enantioselectivity of our electrocyclization through the same interaction.



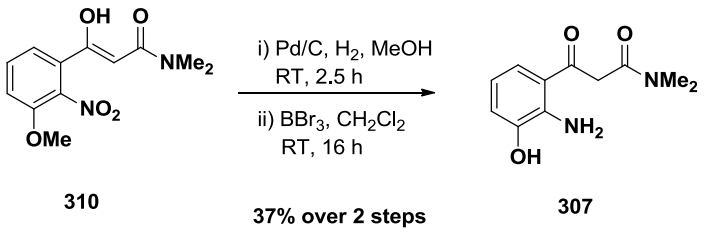
Scheme 4.20.

The synthesis of **307** was slightly more involved than the previous unsubstituted aniline, since the corresponding benzoic acid is not commercially-available (*cf.* Scheme 4.15). Nitration of *meta*-anisaldehyde, followed by aldol addition of *N*,*N*-dimethylacetamide and oxidation of the resulting alcohol **309** afforded intermediate 1,3-dicarbonyl compound **310**, primarily in its *enol* tautomeric form in 17% yield over 3 steps (Scheme 4.21).



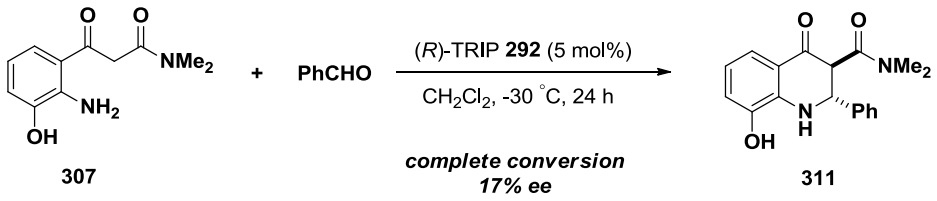
Scheme 4.21.

Reduction of the nitro group and demethylation of the phenol were carried out sequentially – without purification of the intermediate methyl ether – affording aniline **307** in 37% overall yield (Scheme 4.22).



Scheme 4.22.

Aniline **307** was extremely polar, and could not be dissolved in either toluene or chlorobenzene, so the cyclization reaction was attempted in dichloromethane (Scheme 4.23).



Scheme 4.23.

Although this substrate was reactive, cleanly affording the desired product after 24 h, the enantioselectivity achieved was not a significant improvement on that obtained on the earlier substrate that lacked the phenol *OH* (17% *vs.* 14% ee, *cf.* Table 4.8). Given the greater difficulty in the synthesis of this substrate and its poor solubility, it was not considered further.

We decided instead to pursue the synthesis of a more active catalyst, allowing reactivity to be maintained even at cryogenic temperatures, where better enantioselectivity had been observed.

4.2.5 A Unified Lewis Acid-Chiral Counteranion Strategy

4.2.5.1 Concept

Metal triflate catalysts have tended to give better reactivity than the phosphoric acids in our tandem imine formation-electrocyclization procedure (§ 4.2.3), whilst the chiral phosphoric acids tended to give better enantioselectivity but poorer conversion (§ 4.2.4). We can rationalize this

behaviour on the basis of the presumed reactive intermediates in each case (Figure 4.13 and *cf.* Figure 4.12). It is expected that the zwitterionic metal enolate-iminium species formed under metal triflate-catalysed conditions (Figure 4.12, *LA Catalysis*) would be more reactive than the corresponding cationic enol-iminium (Figure 4.12, *TRIP Catalysis*), since the quenching of charge-separation provides an additional driving force for cyclization. It is also clear why TRIP tends to give better enantioselectivity, since it places the chiral counter-anion in close proximity to the newly-forming asymmetric centre, whilst in the metal-catalysed process only the achiral triflate anion occupies this position.

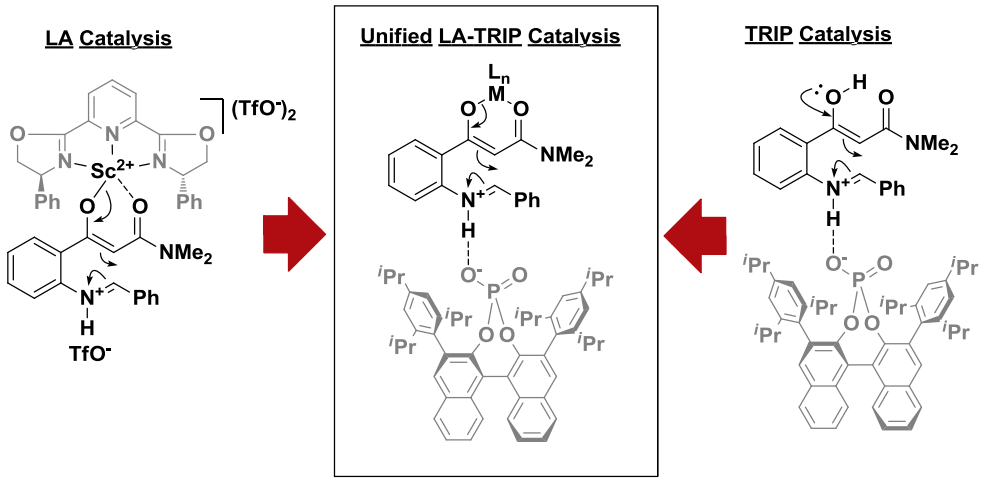
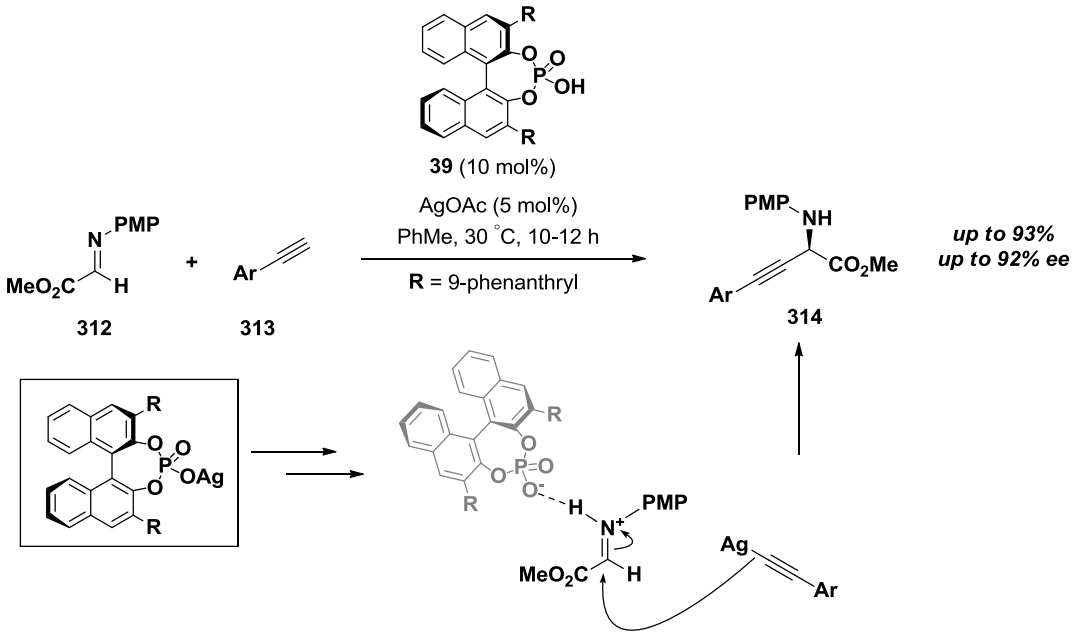


Figure 4.13. A dual-activation strategy for enantioselective electrocyclization.

We envisaged an ideal process, in which the zwitterionic metal enolate-iminium species is formed, providing good reactivity, but where the counter-anion is chiral, providing control of enantioselectivity (Figure 4.13, *inset*).

The use of metal salts of TRIP and related BINOL-derived organic acids for catalysis *via* a dual-activation mechanism was first considered by Rueping *et al.* for the addition of terminal alkynes to *N*-aryl aldimines.[177,178] A mechanism is proposed wherein the silver phosphate is formed *in situ* (Scheme 4.24, *inset*); Ag^+ then activates the alkyne **313** as a nucleophile, liberating

phosphoric acid **39** which serves to protonate the imine **312** and direct the asymmetric addition reaction (Scheme 4.24).



Scheme 4.24. Rueping's "dual-catalysis" approach to asymmetric alkynylation of imines.

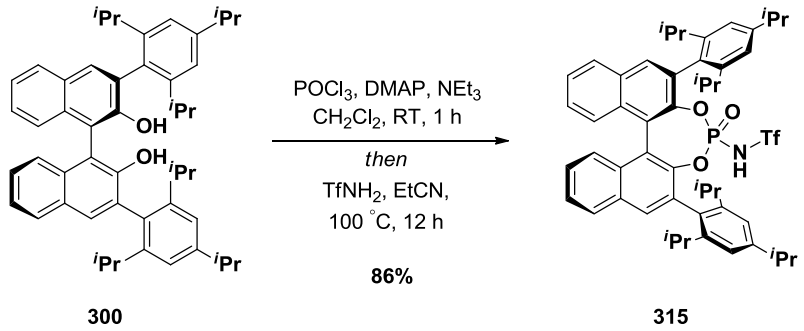
Such a mechanism is clearly relevant to our proposed strategy, where intramolecular addition of a metal enolate would replace the intermolecular addition of a silver acetylide. The use of chiral organic acid metal salts in asymmetric catalysis has emerged rapidly in the past five years, and is the subject of several recent review articles.[179–182] Specifically, such salts have been employed both for the activation of imines[177,183–185] and for the formation of reactive enolates,[186–188] suggesting that they are well-suited to our [1,6]-electrocyclization.

4.2.5.2 Catalyst Synthesis

We therefore set about the synthesis of a chiral transition metal salt capable of catalysing our transformation. Rather than using TRIP itself, we opted instead to use *N*-triflylphosphoramide (NTPA) **315** (Scheme 4.25) as the chiral organic acid component of our catalyst. These NTPA catalysts were developed in 2006 by Yamamoto as a more acidic alternative to the more conventional BINOL-derived phosphoric acids (with Rueping suggesting the NTPA is *ca.* five

orders of magnitude more acidic than the corresponding acid),[189] and we hoped they would display reactivity comparable to the achiral metal triflates (*vide supra*).[190] We chose copper as the transition metal component, since the route to copper(II)-BINOL phosphate compounds was already established.[191,192]

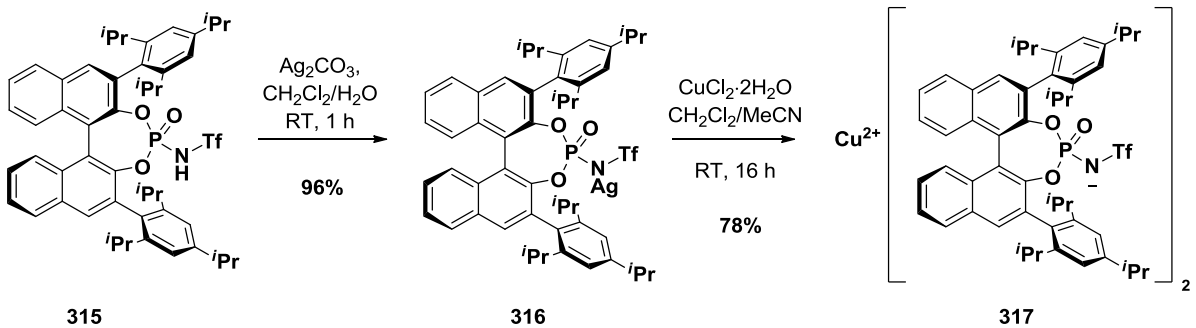
Accordingly, copper(II) NTPA **317** was synthesized in three steps from **300** (a common intermediate from the synthesis of (*R*)-TRIP, see Scheme 4.17). Treatment of diol **300** with phosphoryl chloride and quenching with trifluoromethanesulfonamide afforded NTPA **315** in 86% yield (Scheme 4.25).



300 **315**

Scheme 4.25.

Formation of the halophilic silver salt **316** was achieved with silver carbonate, and subsequent salt metathesis with copper(II) chloride dihydrate delivered copper(II) NTPA **317** in 75% yield over both steps (Scheme 4.26).

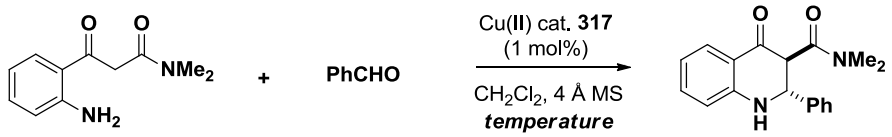


315 **316** **317**

Scheme 4.26.

4.2.5.3 Reaction Optimization

We were pleased to discover that copper(II) salt **317** was an extremely active catalyst in the sequential imine formation-electrocyclization protocol. Upon treating aniline **283** and benzaldehyde with 1 mol% catalyst in dichloromethane, conversion to dihydroquinolone **284** was complete after 1 h, in 17% ee (Table 4.12).



283 **284**

Entry[i]	Temp. / °C	Conv. / % (time) [ii]	ee / % [iii]
1	RT	100 (1 h)	17
2	−30	84 (16 h)	40
3	−50	25 (16 h)	39
4	−78	~5 (48 h)	26

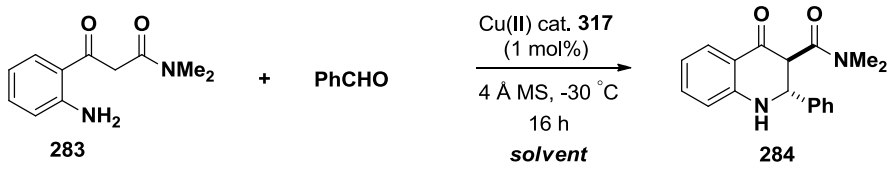
[i] *All reactions were carried out on a 25 mg scale (aniline) with 2.0 eq. aldehyde and 1 mol% catalyst* ***317*** *at an aniline concentration of 0.1 M. Yields not determined.* [ii] *Determined by* ^{1}*H NMR analysis of the crude reaction mixture.* [iii] *Determined by chiral HPLC.*

Table 4.12. Temperature screen. *For full details, see experimental section, p. 242.*

As expected, cooling led to slower conversion but better enantioselectivity; however, in comparison with the TRIP-catalysed process the rate of reaction was sufficient that good conversion could be attained at –30 °C, with a reasonable ee of 40%; further cooling led to an intolerably slow reaction. This conversion is impressive relative to that obtained under phosphoric acid catalysis, where only 34% product formation was achieved under similar conditions (Table 4.10, entry 4).

A screen of solvents indicated that tetrahydrofuran was preferable (Table 4.13, entry 5), giving much greater enantioselectivity than dichloromethane or, more surprisingly, chlorobenzene (which had performed well in the TRIP-catalysed protocol, Table 4.8). The

reactions attempted in acetonitrile and methanol gave only recovered starting material (Table 4.13, entries 2 & 4).

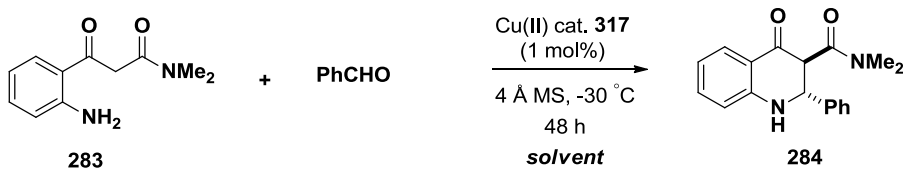


Entry[i]	Solvent	Conv. / % [ii]	ee / % [iii]
1	CH_2Cl_2	84	40
2	MeCN	NR	-
3	PhCl	55	4
4	MeOH	NR	-
5	THF	70	52

[i] *All reactions were carried out on a 25 mg scale (aniline) with 2.0 eq. aldehyde and 1 mol% catalyst* ***317*** *at an aniline concentration of 0.1 M in the presence of 4 Å MS, and were analysed after 16 h. Yields not determined.* [ii] *Determined by* ^{1}*H NMR analysis of the crude reaction mixture.* [iii] *Determined by chiral HPLC.*

Table 4.13. Solvent screen. *For full details, see experimental section, p. 242.*

Whilst tetrahydrofuran gave the best ee, we hoped that by employing a mixed solvent system, or by adjusting the reaction concentration, we might be able to improve the enantioselectivity further. By using a 1:1 volume:volume mixture of tetrahydrofuran and toluene a 7% improvement in ee was achieved (Table 4.14 entry 3), but adding more toluene proved detrimental to enantioselectivity (Table 4.14 entries 4 & 5).



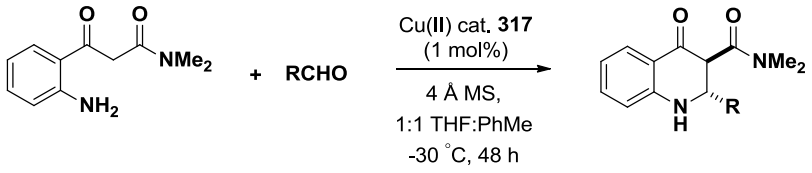
Entry[i]	Solvent ratio THF:PhMe v/v	Aniline conc. / M	ee / % [iii]
1	1:0	0.1	52
2	10:1	0.1	54
3	1:1	0.1	59
4	1:10	0.1	27
5	1:0	0.05	51

[i] *All reactions were carried out on a 25 mg (aniline) scale with 2.0 eq. aldehyde and 1 mol% catalyst* ***317*** *in the presence of 4 Å MS, and were analysed after 48 h. Yields not determined. All reactions went to completion (TLC,* ^{1}*H NMR).* [iii] *Determined by chiral HPLC.*

Table 4.14.

Concentration was found to have no significant effect on enantioselectivity (Table 4.14, entries 1 & 5), although the reaction carried out at higher concentration appeared to reach completion more rapidly; subsequent studies were therefore carried out at 0.2 M.

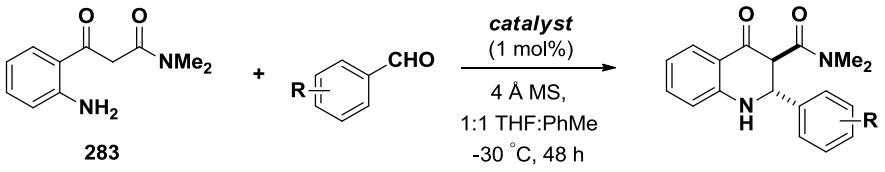
Our optimized procedure for catalysis of tandem imine formation-[1,6]-electrocyclization under copper(II) salt catalysis is therefore summarized in Scheme 4.27.

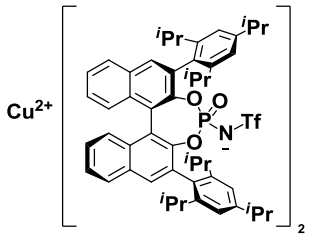


Scheme 4.27. Optimized procedure for copper(II) NTPA **317**-catalysed formation of dihydroquinolones

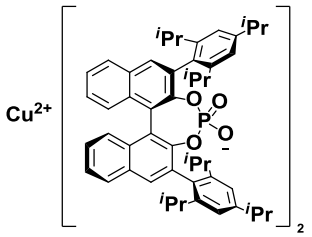
4.2.5.4 Reaction Scope

We initially applied these conditions to a number of aromatic aldehydes, to determine the scope of the reaction (Table 4.15).





317



318

Entry[i]	R	Catalyst	Yield / % [ii]	ee / % [iii]	Product
1	H	**317**	90	66	**284**
2	H	**318**	74	57	**284**
3[iv]	2-Cl	**317**	90	23	**301**
4	3-Cl	**317**	90	55	**302**
5	4-Cl	**317**	83	36	**303**
6	2-NO_2	**317**	17	42	**319**
7	3-NO_2	**317**	64	41	**320**
8	4-NO_2	**317**	73	23	**321**

[i] *All reactions were carried out on a 50 mg scale (aniline) with 2.0 eq. aldehyde and 1 mol% catalyst in the presence of 4 Å MS, and were analysed after 48 h.* [ii] *All yields are for isolated pure product.* [iii] *Determined by chiral HPLC.* [iv] *In this case an additional 2.0 eq. aldehyde and 1 mol% catalyst were added after 24 h.*

Table 4.15.

The majority of reactions were clean and high-yielding, with the clear exception of the 2-nitrobenzaldehyde derived product **319** (Table 4.15, entry 5). *Meta*-substitution gave the best enantioselectivites (Table 4.15, entries 4 & 7), although these were inferior to the parent benzaldehyde (Table 4.15, entry 1). For comparison, (*R*)-TRIP-derived catalyst **318** was also tested (Table 4.15, entry 2), and gave slightly lower enantioselectivity and poorer reactivity compared to the NTPA-derived catalyst.

The relative stereochemistry of *para*-chlorobenzaldehyde derived compound **303** was determined by single crystal X-ray diffraction of the racemate, and all other products are assumed to be analogous (Figure 4.14).

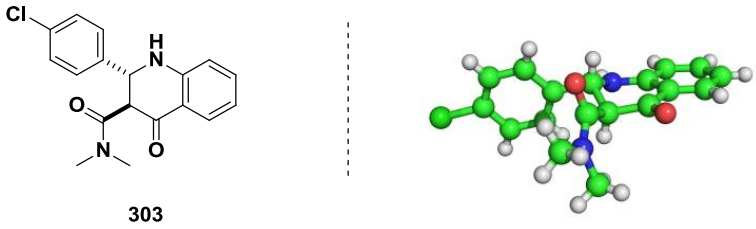
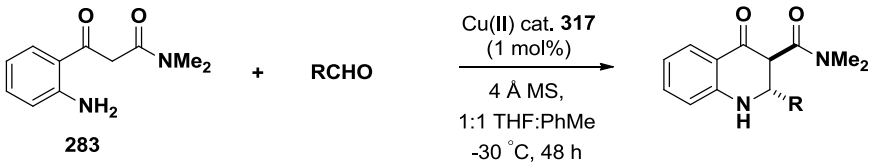
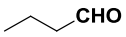
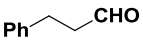
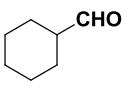
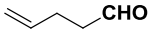


Figure 4.14. Relative stereochemistry of dihydroquinolone **303**. *Single-crystal X-ray structure rendered using PyMOL.*[117]

Alkyl aldehydes were also effective in this transformation, and afforded the 2-alkyldihydroquinolones in reliably high yield (Table 4.16).



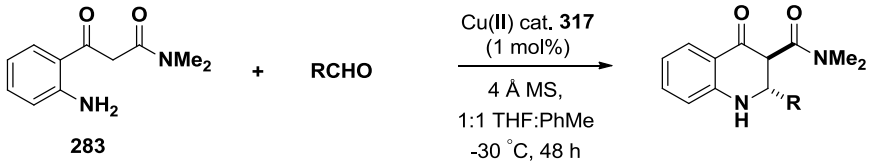
Entry[i]	RCHO	Yield / % [ii]	ee / % [iii]	Product
1		100	76	**322**
2		100	19	**323**
3		94	81	**324**
4		100	65	**325**
5		92	58	**326**
6		87	81	**327**
7		98	35	**328**

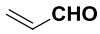
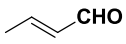
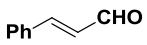
[i] *All reactions were carried out on a 50 mg scale (aniline) with 2.0 eq. aldehyde and 1 mol% catalyst **317** in the presence of 4 Å MS, and were analysed after 48 h.* [ii] *All yields are for isolated pure product.* [iii] *Determined by chiral HPLC.*

Table 4.16.

Alkyl aldehydes generally gave superior enantioselectivities to their aryl counterparts. With the exception of *iso*-butyraldehyde (Table 4.16, entry 2), bulky substituents tended to display the highest enantioselectivities, with pivaldehyde and cyclohexanal both affording products in high yield and 81% ee (Table 4.16, entries 3 & 6).

We hoped to expand the methodology further by incorporating α,β-unsaturated aldehydes (Table 4.17).



Entry[i]	RCHO	Yield / % [ii]	ee / % [iii]	Product
1		34	8	**329**
2		75	7	**330**
3		81	19	**331**

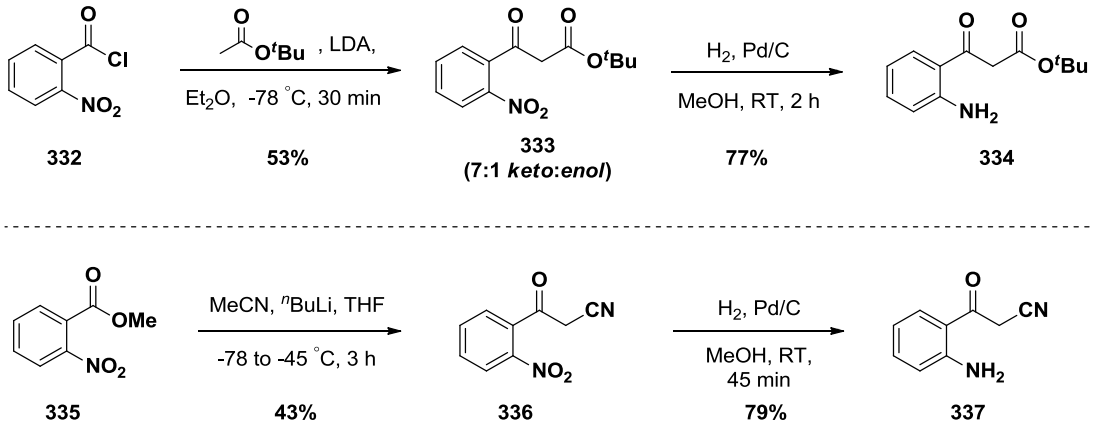
[i] *All reactions were carried out on a 50 mg scale (aniline) with 2.0 eq. aldehyde and 1 mol% catalyst* ***317*** *in the presence of 4 Å MS, and were analysed after 48 h.* [ii] *All yields are for isolated pure product.* [iii] *Determined by chiral HPLC.*

Table 4.17.

Unfortunately this functionality was not well tolerated. Although conversion was complete, acrolein gave low yields; multiple by-products were formed, possibly the result of competing 1,4-addition pathways (Table 4.17, entry 1). Although yields improved when *trans*-crotonaldehyde and *trans*-cinnemaldehyde were employed, enantioselectivities were uniformly poor (Table 4.17, entries 2 & 3).

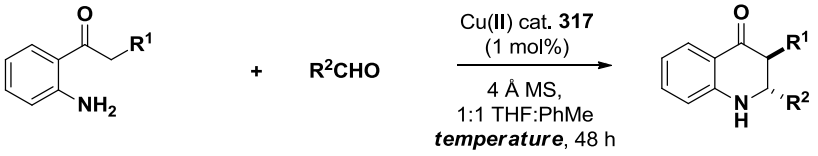
Other electron-withdrawing groups α- to the ketone were less successful than the dimethyl amide. We examined the parent 2'-aminoacetophenone, as well as the sulfone and thioether substrates formed previously (*cf.* Scheme 4.8 and Scheme 4.11), and *tert*-butyl ester **334** and nitrile

337. The latter compounds were both accessible in two steps from 2-nitrobenzoic acid derivatives (Scheme 4.28).



Scheme 4.28.

None of these substrates proved to be as successful as the dimethyl amide **283** on which the preceding studies were focused (Table 4.18).



Entry[i]	T / °C	R^1	R^2	Yield / % [ii]	ee / % [iii]	Product
1	RT	SO_2Ph	Ph	10% conv. [iv]	0	**261**
2	-30	$CO_2{}^tBu$	Ph	34	37	**338**
3	-30	CN	Ph	63 (4:1 dr)	0	**339**
4	RT	SPh	Ph	NR[v]	-	-
5	RT	H	Ph	NR[v]	-	-
6	RT	H	nBu	NR[v]	-	-

[i] *All reactions were carried out on a 25−50 mg scale (aniline) with 2.0 eq. aldehyde and 1 mol% catalyst* ***317*** *in the presence of 4 Å MS, and were analysed after 48 h.* [ii] *Yields are for isolated pure product.* [iii] *Determined by chiral HPLC.* [iv] *Determined by* ^1H *NMR analysis of the crude mixture.* [v] *Partial imine formation observed by* ^1H *NMR analysis.*

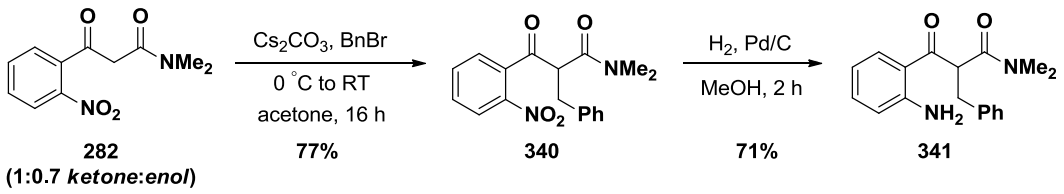
Table 4.18.

Although the sulfone, ester and nitrile substrates did undergo the desired reaction, they were prohibitively slow. Even when carried out at room temperature the sulfone reached only 10% conversion; although the ester and nitrile were sufficiently reactive to proceed at –30 °C, neither reached completion after 48 h and yields were correspondingly low. More significantly, enantioselectivities were also poor, with only the ester giving a non-racemic product. This suggests that chelation of the metal by both the ketone and the second electron-withdrawing group is an important factor in enantiocontrol, since we would expect the β-keto amide and ester to form chelates, whilst the β-keto sulfone and nitrile would not (*cf.* Figure 4.13). However, this is not an entirely satisfactory explanation, since we expect that the majority of stereocontrol is controlled by the chiral counter-anion associated with the iminium cation, which should be independent of the electron-withdrawing group.

Interestingly nitrile compound **339** (Table 4.18, entry 3) is the only product formed in this study where a minor diastereomer has been observed; this is not surprising, since we would not expect a large unfavourable steric interaction between the nitrile and phenyl ring-substituents due to the nitrile's diminutive steric influence.

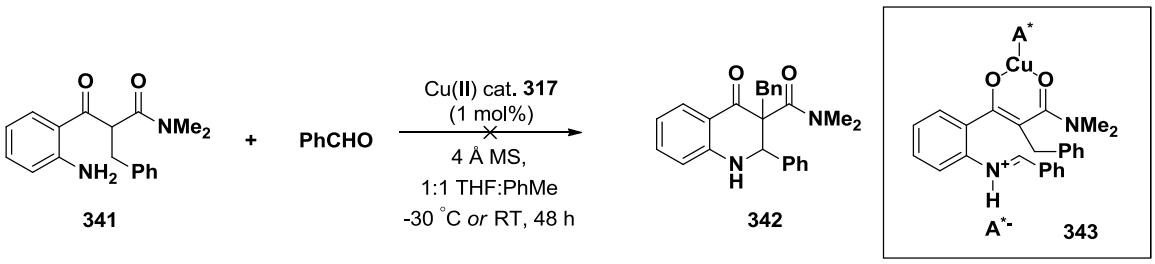
Less acidic compounds failed to cyclize (Table 4.18, entries 4−6); analysis of the crude reaction mixtures by ^{1}H NMR indicated that imine formation had (at least partially) occurred, but cyclization had not. We attribute their failure to cyclize to their lower propensity to form the necessary metal enolate intermediate.

We also hoped to employ our [1,6]-electrocyclization procedure to generate all-carbon quaternary stereocentres – this could be achieved either by substitution α- to the ketone in the aniline substrate, or by using a ketone in place of the aldehydes previously employed. Correspondingly, benzyl substrate **341** was synthesized in two steps from **282**: treatment of **282** with benzyl bromide in the presence of caesium carbonate and subsequent hydrogenation afforded the racemic aniline **341** in 55% yield from **282** (Scheme 4.29).



Scheme 4.29.

Treatment of this aniline **341** with benzaldehyde under our optimized reaction conditions at −30 °C gave no reaction; similarly, when the reaction was performed at room temperature no products were observed (Scheme 4.30)

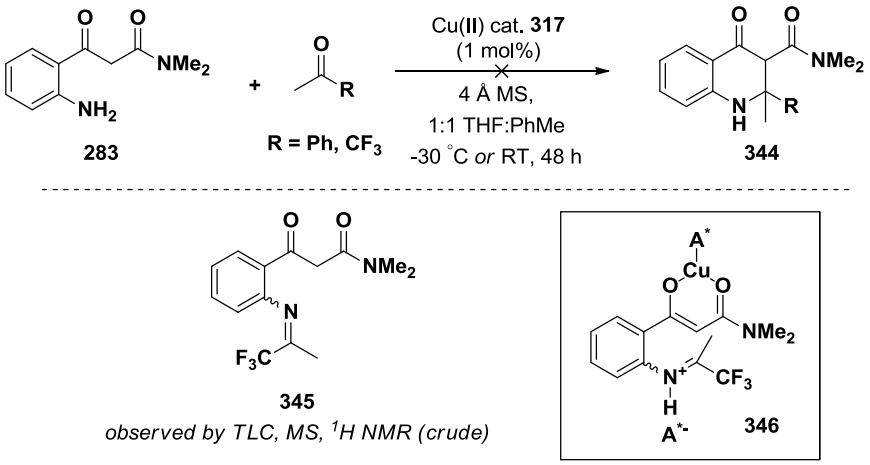


Scheme 4.30.

The failure to react may be a consequence of the extreme steric congestion of the necessary iminium-enolate intermediate **343** preventing it reaching the required conformation for cyclization to occur, or disfavouring its formation altogether (Scheme 4.30, *inset*). It was possible to obtain the racemic product **342** when 10 mol% scandium(III) triflate was employed at room temperature – suggesting substrate **341** is merely slow to react, not completely inert – but such high catalyst loadings are not acceptable for the chiral copper(II) NTPA **317** (molecular weight: 1830 Da) catalysed process.

Ketones were also extremely slow to react. Treatment of aniline **283** with acetophenone at -30 °C or room temperature gave no reactivity, whilst with the more electrophilic

1,1,1-trifluoroacetone, partial imine formation was observed.* In this case only the aniline could be isolated, since the imines hydrolysed completely during chromatography (Scheme 4.31).



Scheme 4.31.

Since imine formation was observed, it is clear that the failure to generate cyclized material is not solely due to the poorer electrophilicity of the ketone relative to the aldehydes, but once again may be a consequence of the steric encumbrance of intermediate **346** (Scheme 4.31, *inset*).

The problems encountered in the generation of quaternary stereocentres were disappointing, yet this methodology does provide a new and practical route to enantiomerically-enriched 2-alkyl and 2-aryl dihydroquinolones.

4.3 Conclusions and Future Work

4.3.1 Overview and Conclusions

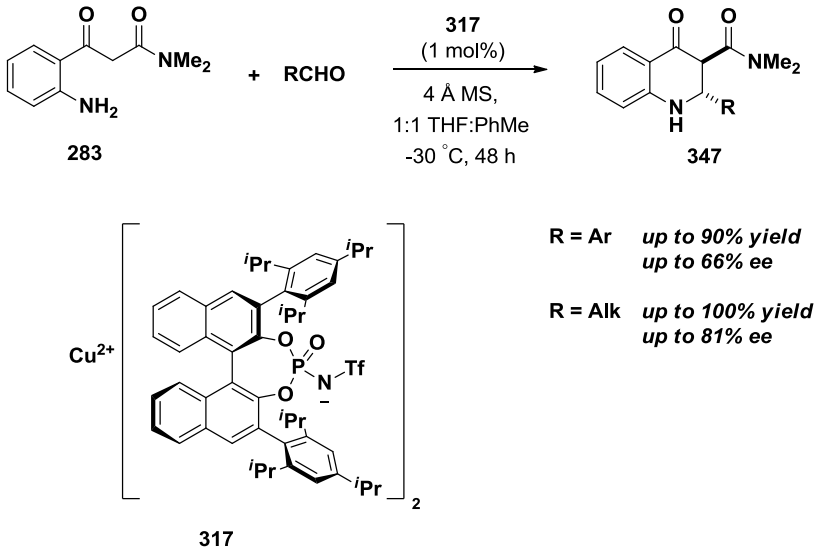
Previous studies within the group and within this thesis have demonstrated the efficacy of phase-transfer catalysis under basic conditions to enact asymmetric electrocyclic reactions; however, it has been shown that this strategy is ineffective in the current [1,6]-electrocyclization study. The instability of the imines with respect to hydrolysis – coupled with the poor

* *TLC, MS and crude ^{1}H NMR*

nucleophilicity of the amines – meant that the pure samples of the required imine intermediates could not be obtained.

A tandem acid-catalyzed imine formation-cyclization protocol was proposed, which would negate the issues associated with imine isolation. Correspondingly, a variety of chiral Lewis and Brønsted acids were investigated: transition metal triflates proved particularly reactive, but did not give significant levels of stereoselectivity when used in combination with chiral ligands, whilst chiral phosphoric acids gave promising stereoselectivity but lower reactivity.

A synergy of the reactivity of Lewis acids and the selectivity of Brønsted acids was therefore pursued, and chiral BINOL-derived copper(II) catalyst **317** was synthesized. Under optimized conditions, this catalyst afforded *trans*-dihydroquinolones **347** in generally excellent yields and with moderate to good enantioselectivity (Scheme 4.32) directly from aniline **283**.



Scheme 4.32. Tandem imine formation-electrocyclization overview.

A variety of aldehydes were examined, with alkyl aldehydes generally giving higher yields and better enantioselectivities. Bulky alkyl groups gave the highest enantioselectivities

(R = cyclohexyl and ^{t}Bu – 81% ee), although this was not always the case (R = ^{i}Pr – 19% ee *vs.* R = ^{n}Bu – 65% ee), but the reason for this behaviour is not yet understood.

Reactivity and enantioselectivity were highest for the dimethyl amide aniline **283**. Ester, sulfone and nitrile electron-withdrawing groups all gave some reactivity, but yields and enantioselectivities were disappointing.

In our attempts to generate quaternary stereogenic centres, it was determined that ketones were not reactive under our optimized conditions, nor were substrates with additional substitution α- to the ketone. We attribute this failure to the steric congestion of the enolate-iminium intermediates **348** and **349** disfavouring their formation, or preventing their subsequent cyclization (Figure 4.15).

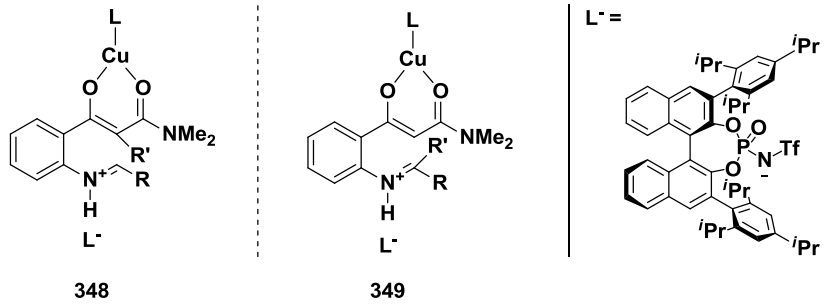
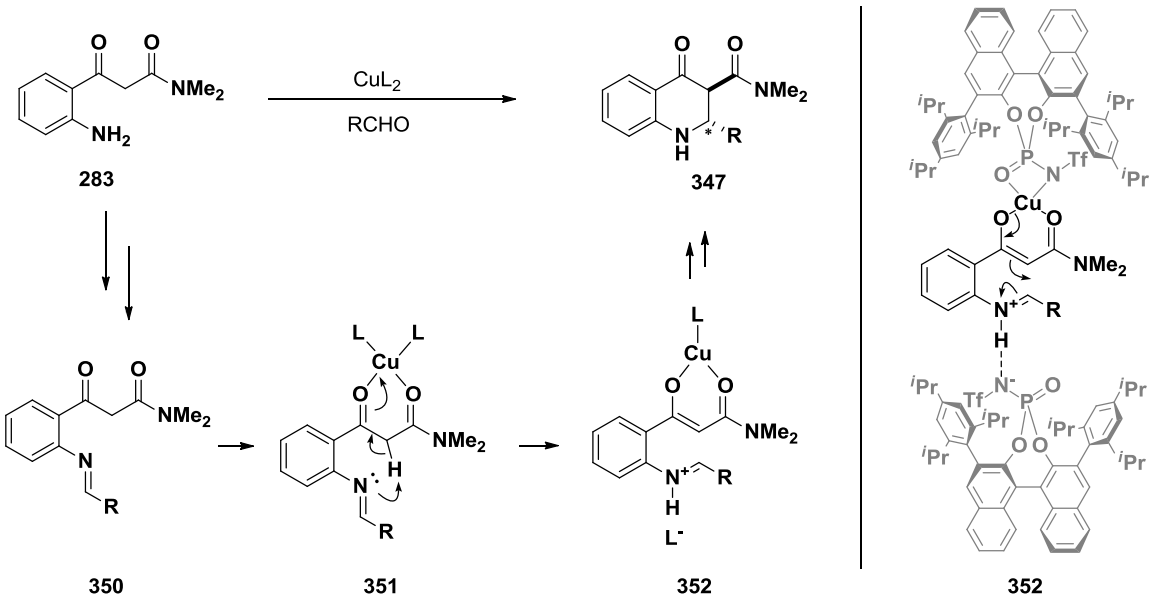


Figure 4.15. Attempted formation of quaternary stereogenic centres.

A mechanism for the transformation is proposed, whereby (following acid-catalysed imine formation) binding of the metal complex to the 1,3-dicarbonyl acidifies the α-proton; deprotonation (either inter- or intramolecular) affords copper(II) enolate-iminium species **352**, which upon 6π electrocyclization and epimerization affords the dihydroquinolone **347** and regenerates the catalyst (Scheme 4.33).



Scheme 4.33. Mechanistic proposal.

In summary, we have developed a high-yielding and operationally-simple asymmetric synthesis of 2-aryl and 2-alkyl dihydroquinolones mediated by a novel copper(II) *N*-triflylphosphoramidate **317**. The copper(II) salt is a highly efficient catalyst (giving up to 81% ee at 1 mol% loading) and plays multiple roles in the reaction, catalysing imine formation, activating the 1,3-dicarbonyl as its metal enolate and the imine *via* protonation, and crucially inducing asymmetry in the [1,6]-electrocyclization. This methodology provides a complementary strategy to the phase-transfer catalysed process developed within the group, and we remain hopeful that by further optimization and catalyst development it will be possible to achieve greater enantioselectivity, and to broaden the scope of this potentially powerful transformation.

4.3.2 Future Work

We would like to expand the scope of this [1,6]-electrocyclization to allow greater variation of electron-withdrawing groups, and to tolerate ketones as well as aldehydes.

The mechanism by which copper(II) salt **317** catalyses the transformation would provide strategic guidance when attempting to expand the scope: although we have postulated a

mechanism that is consistent with experimental observations, it is possible that an entirely different one is in operation. The tools available to probe the mechanism are somewhat limited by the use of paramagnetic copper(II), since this makes it impossible to follow the reaction by NMR and identify intermediates. It would therefore be useful to synthesize the analogous zinc(II) salt, since this would be non-paramagnetic, and since zinc(II) triflate has been shown to be a competent catalyst. Kinetic studies and DFT calculations may aid further elucidation of the reaction mechanism, although the presumed pre-equilibrium between the aniline and aldehyde and imine **350** would complicate such a study.

We are also interested in applying this mode of catalysis to other electrocyclic transformations. The reaction studied bears a remarkable similarity to the Staudinger β-lactam synthesis (Figure 4.16 and *cf.* Figure 4.4).

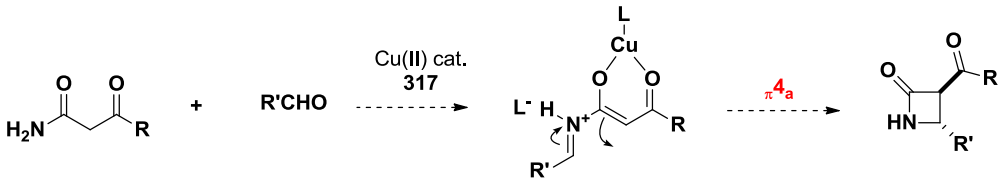


Figure 4.16. Proposed catalytic asymmetric Staudinger β-lactam synthesis.

Asymmetric catalysis of this 4π electrocyclic process is unprecedented, and would be an extremely valuable contribution to the synthesis of these biologically-relevant species.[140]

5. OVERVIEW AND EPILOGUE

5.1 8π Electrocyclization

The asymmetric catalysis of 8π electrocyclic reactions is an extremely challenging synthetic problem. We hoped to employ the mild phase-transfer methodology developed within the group for 6π reactions, but this was surprisingly ineffective in the 8π domain, even for **82**, whose structural similarity to the 6π substrates is apparent (Figure 5.1).

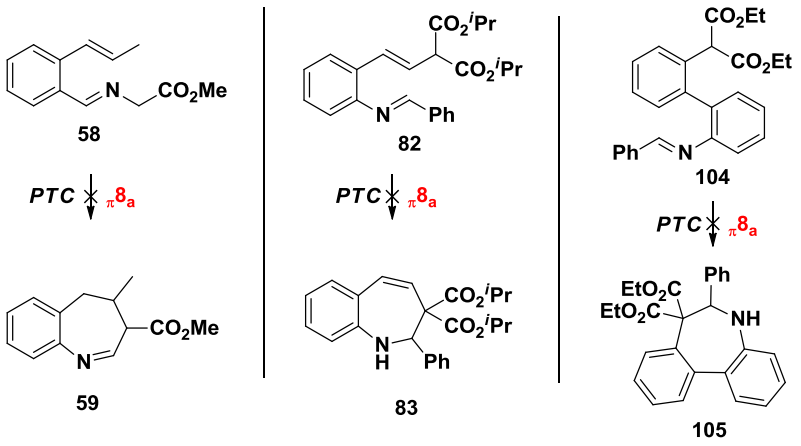


Figure 5.1. Attempted phase-transfer catalysed 8π electrocyclizations.

Double bond geometry was believed to be a major factor contributing to the poor reactivity observed. In all but the biaryl substrate, *in situ* double bond isomerization was required before cyclization could occur, and undoubtedly retarded the desired 8π reaction.

The stability of the deprotonated substrate may be significant; the stabilization of this anion required to allow deprotonation under phase-transfer conditions may also render it inert to cyclization, with the open-chain anion thermodynamically favoured. Phase-transfer catalysis may therefore be inherently ill-suited to this transformation.

5.2 Cascades

Through a collaborative effort a high-yielding, operationally simple and highly enantio- and diastereoselective cascade synthesis of pyrrolizidines and indolizidines has been developed (Figure 5.2).

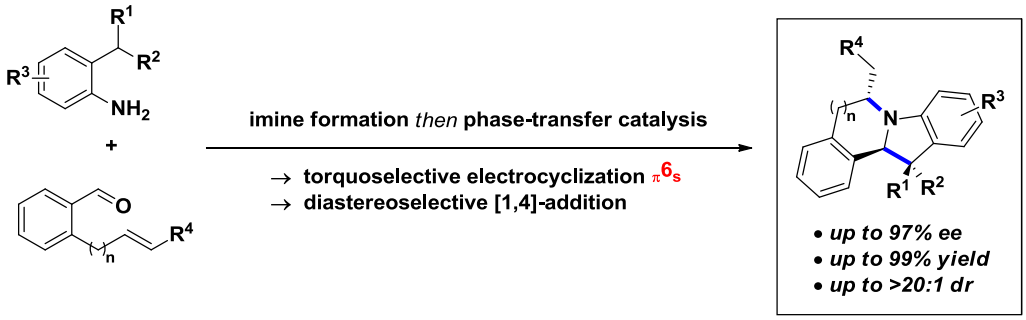


Figure 5.2. Asymmetric electrocyclization-1,4-addition cascades.

The process is the only reported example of an intramolecular cascade reaction carried out under asymmetric phase-transfer conditions, and demonstrates the power of this methodology to catalyse multiple stereoselective steps in one pot.

5.3 6π [1,6]-Electrocyclization

We initially hoped to apply the phase-transfer methodology used to great effect in the cascade process (*vide supra*) to catalyse [1,6]-electrocyclic reactions. The isolation of imines after their synthesis (under acidic conditions) was problematic, and led us to the concept of carrying out both the imine formation and cyclization under the same asymmetric acidic conditions. Screening led to the development of copper(II) catalyst **317**, combining the attributes of achiral metal triflates and chiral BINOL-derived Brønsted acids (Figure 5.3).

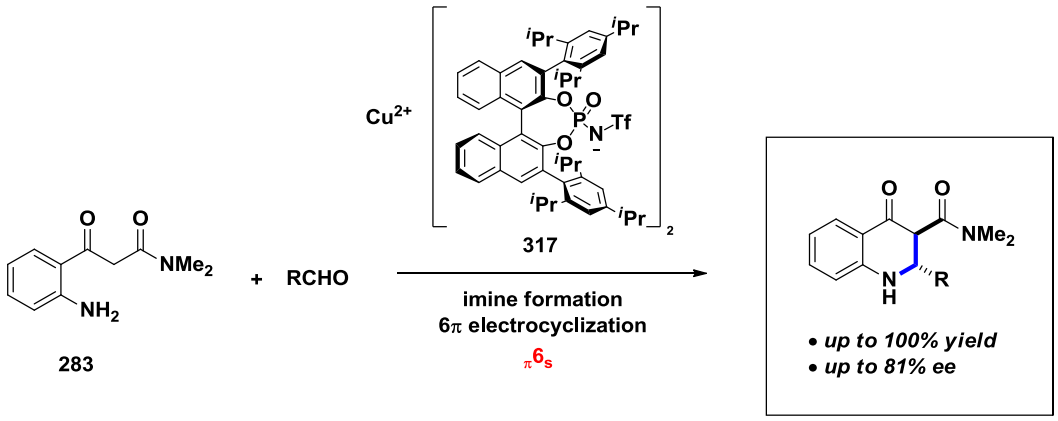


Figure 5.3. Catalytic asymmetric synthesis of trans-dihydroquinolones.

Tandem imine formation-cyclization reactions were carried out in excellent yields, and with up to 81% ee at catalyst loadings of just 1 mol%. Although work to expand the scope of this reaction is still ongoing, this mode of catalysis may provide a new and powerful means to control asymmetry in the electrocyclization of zwitterionic species, including the Staudinger β-lactam synthesis.

5.4 Epilogue

There is no single, generally-applicable approach to the asymmetric catalysis of electrocyclic reactions. However, it is our hope that we have developed strategies with which the synthetic chemist may attack the problem of enantioselective electrocyclization, and that these powerful reactions will play a growing role in asymmetric synthesis.

6. EXPERIMENTAL

6.1 General Experimental Procedures

6.1.1 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.

6.1.2 Solvents and Reagents

Tetrahydrofuran, dichloromethane, diethyl ether, methanol, toluene and acetonitrile were purified by pressurized filtration through activated silica columns, employing the method of Grubbs *et al.*[193] 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. Triethylamine was distilled over calcium hydride and stored over potassium hydroxide under an inert argon atmosphere. pH 7 buffer solution was prepared by the addition of sodium hydroxide (0.1 M aq., 291 mL) to potassium dihydrogen phosphate (0.1 M aq., 500 mL). Unless otherwise indicated, all aqueous solutions used were saturated. Reagents were used directly as supplied by major chemical suppliers, or purified by procedures described by Perrin and Armarego.[194]

6.1.3 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, ammonium molybdate or ninhydrin.

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). Ammonium molybdate solution was prepared by dissolving ammonium molybdate (5 g) and ceric sulfate (0.2 g) in 5% aqueous sulfuric acid (100 mL). Ninhydrin solution was prepared by dissolving ninhydrin (0.3 g) in *n*-butanol (100 mL) and adding acetic acid (3 mL).

6.1.4 NMR Spectroscopy

NMR spectra were recorded on a Bruker AV400 (^{1}H: 400 MHz, ^{13}C: 101 MHz, ^{19}F: 377 MHz), Bruker AVII Cryo 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz), Bruker AVII 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz, ^{19}F: 470 MHz), Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 126 MHz, ^{31}P: 202 MHz) or Bruker DPX300 (^{1}H: 300 MHz, ^{13}C: 75 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 spectra are reported as follows: δ_H (*spectrometer frequency, solvent*): *chemical shift/ppm* (*number of protons, multiplicity, J-coupling constant(s), assignment*). ^{13}C 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*; m – *multiplet*. Compound multiplets are reported in the order of decreasing coupling constant magnitude. Spectral assignment was aided by the results of DEPT, COSY, HMBC, HSQC and NOESY experiments where appropriate.

6.1.5 IR Spectroscopy

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

6.1.6 Mass Spectrometry

Mass spectra were recorded on a Micromass LCT Premier spectrometer under conditions of electrospray ionization (ESI). Accurate masses (HRMS) were recorded on Bruker MicroTOF and Micromass GCT spectrometers under conditions of ESI and field ionization (FI) respectively. MALDI spectra were recorded on a Waters MALDI Micro MX. Masses are reported in daltons (Da).

6.1.7 Polarimetry

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

6.1.8 Melting Points

All melting points were measured on a Gallenkamp MF-370 melting point apparatus or a Reichert melting point stage, and are uncorrected. Solvents are reported in parentheses where solids were purified by recrystallization. Temperatures are reported in °C.

6.1.9 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.

6.1.10 Naming, Numbering and Depiction of Compounds

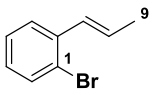
Where given, systematic compound names are those generated by ChemBioDraw Ultra 12.0 following IUPAC conventions. The numbering of atoms for discussion and spectral assignment purposes is arbitrary and not necessarily consistent with the IUPAC names.

Chiral nonracemic and racemic molecules are depicted according to the Maehr convention:[195] absolute stereochemistry is indicated by solid wedged (▬) and hatched wedged (⋯) bonds, and relative stereochemistry is indicated by solid bold (▬) and hatched bold (⋯) bonds.

6.2 8π Electrocyclization

6.2.1 Synthesis of Substrates

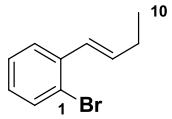
(*E*)-1-Bromo-2-(prop-1-enyl)benzene (53)



This compound was prepared according to a literature procedure.[67] *n*-Butyllithium (1.6 M in hexanes, 25 mL, 40 mmol), was added dropwise to a stirred suspension of ethyltriphenylphosphonium bromide (15 g, 40 mmol) in tetrahydrofuran (100 mL) at −78 °C. The solution was warmed to 0 °C for 30 min, turning a deep red/orange colour, then cooled to −78 °C. 2-Bromobenzaldehyde (1.42 mL, 26 mmol) was added dropwise and the mixture stirred for 30 min, then warmed to RT and stirred for a further 30 min. The mixture was diluted with petrol (300 mL), causing the triphenylphosphine oxide to precipitate. The solution was poured off the unwanted side-product, filtered and concentrated *in vacuo*, and purified by flash column chromatography (silica gel, petrol:diethyl ether, 25:1) to afford 1-bromo-2-(prop-1-enyl)benzene **53** as a mixture of *E* and *Z* isomers (3.68 g, 72%, *E*/*Z* = 2:5). The mixture of isomers (3.68 g, 18.7 mmol) and iodine (9 mg, 0.036 mmol) were dissolved in *n*-heptane and heated to 130 °C for 72 h. The solution was allowed to cool to RT, the solvent removed *in vacuo*, and the crude

product purified by flash column chromatography (silica gel, petrol:diethyl ether, 25:1) to afford predominantly (*E*)-bromo-2-(prop-1-enyl)benzene **53** (3.31 g, 90%, *E*/*Z* = 16:1) as a yellow oil. *Data is consistent with that reported in the literature.*[196] δ_H (400 MHz, $CDCl_3$): 7.53 (1H, dd, *J* 8.0, 1.1, H2), 7.48 (1H, dd, *J* 7.7, 1.3, H5), 7.25 (1H, t, *J* 7.8, H4), 7.06 (1H, td, *J* 7.7, 1.5, H3), 6.72 (1H, dq, *J* 15.6, 1.4, H7), 6.20 (1H, dq, *J* 15.5, 6.7, H8), 1.94 (3H, dd, *J* 6.7, 1.7, H9). δ_C (101 MHz, $CDCl_3$): 137.7 (C6), 132.8 (C2), 129.9 (C7), 129.4 (C8), 128.1 (C3), 127.4 (C4), 126.8 (C5), 123.0 (C1), 18.7 (C9). HRMS (FI): found 195.9888; C_9H_9Br $[M\bullet]^+$ requires 195.9888. ν_{max} (film): 3060, 3034, 2964, 1698, 1652 1466, 1435, 802 cm^{-1}.

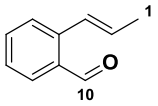
(*E*)-1-Bromo-2-(but-1-enyl)benzene (54)



This compound was prepared by analogy to a literature procedure.[67] *n*-Butyllithium (1.6 M in hexanes, 24 mL, 39 mmol), was added dropwise to a stirred suspension of propyltriphenylphosphonium bromide (15 g, 39 mmol) in tetrahydrofuran (150 mL) at −78 °C. The solution was warmed to 0 °C for 30 min, turning a deep red/orange colour, then cooled to −78 °C. 2-Bromobenzaldehyde (4.2 mL, 35 mmol) was added dropwise and the mixture stirred for 30 min, then warmed to RT and stirred for a further 30 min. The mixture was diluted with petrol (500 mL), causing the triphenylphosphine oxide to precipitate. The solution was poured off the unwanted side-product, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, petrol:diethyl ether, 25:1) to afford 1-bromo-2-(but-1-enyl)benzene **54** as a mixture of *E* and *Z* isomers (6.46 g, 86% *E*/*Z* = 1:3.8). A portion of the mixture of isomers (4.0 g, 18.9 mmol) and iodine (9 mg, 0.036 mmol) were dissolved in *n*-heptane and heated to 130 °C for 72 h. The solution was allowed to cool to RT, the solvent removed *in vacuo*, and the crude product purified by flash column chromatography (silica gel, petrol:diethyl

ether, 25:1) to afford predominantly (*E*)-bromo-2-(but-1-enyl)benzene **54** (4.0 g, quant., *E*/*Z* = 21:1) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 7.54 (1H, dd, *J* 8.0, 1.0, H2), 7.50 (1H, dd, *J* 7.7, 1.3, H5), 7.26 (1H, t, *J* 7.5, H4), 7.06 (1H, t, *J* 7.6, H3), 6.72 (1H, d, *J* 15.7, H7), 6.23 (1H, dt, *J* 15.7, 6.5, H8), 2.29 (2H, m, H9), 1.13 (3H, t, *J* 7.5, H10). δ_C (101 MHz, $CDCl_3$): 137.7 (C6), 135.7 (C8), 132.8 (C2), 128.1 (C3), 127.7 (C7), 127.4 (C4), 126.8 (C5), 123.2 (C1), 26.2 (C9), 13.5 (C10). HRMS (FI): found 210.0042; $C_{10}H_{11}Br$ $[M\bullet]^+$ requires 210.0044. ν_{max} (film): 3060, 3009, 2966, 2874, 1699, 1646, 1464, 1435, 1068, 964, 747 cm^{-1}.

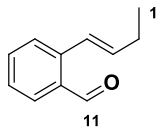
(*E*)-2-(Prop-1-enyl)benzaldehyde (50)



This compound was prepared according to a literature procedure.[67] *n*-Butyllithium (1.6 M in hexanes, 7.12 mL, 11.4 mmol) was added to a stirred solution of bromostyrene **53** (1.12 g, 5.7 mmol) in dry tetrahydrofuran (20 mL) at −78 °C. The solution was stirred for 30 min, then warmed to −30 °C and stirred for a further 30 min. The solution was cooled to −78 °C and *N*,*N*-dimethylformamide (0.88 mL, 11.4 mmol) in dry tetrahydrofuran (5 mL) was added dropwise. The solution was stirred at −78 °C for 1 h before being warmed to RT and stirred for a further 1 h. Brine (20 mL) was added to the reaction mixture and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petrol:diethyl ether, 50:1) to afford (*E*)-2-(prop-1-enyl)benzaldehyde **50** as a pale yellow oil (0.73 g, 87%, *E*/*Z* = 16:1). *Data is consistent with that reported in the literature.*[67] δ_H (400 MHz, $CDCl_3$):10.29 (1H, s, H10), 7.80 (1H, d, *J* 7.7, H8), 7.55−7.48 (2H, m, H5 & H6), 7.36 (1H, t, *J* 7.8, H7), 7.20 (1H, d, *J* 15.4, H3), 6.18 (1H, dqd, *J* 15.2, 6.8, 1.5, H2), 1.97 (3H, d, *J* 6.6, H1). δ_C (101 MHz, $CDCl_3$): 192.5 (C10), 140.9 (C4), 133.7 (C6), 132.5 (C9), 132.0 (C2), 130.8 (C8), 127.5 (C5), 127.0(2) (C3), 126.9(8) (C7), 18.9 (C1).

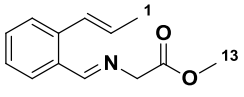
HRMS (FI): found 146.0730; $C_{10}H_{10}O$ $[M\bullet]^+$ requires 146.0732. ν_{max} (film): 3062, 3023, 2852), 2734, 1697, 1596, 1188, 754 cm^{-1}.

(*E*)-2-(But-1-enyl)benzaldehyde (56)



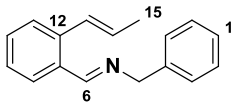
This compound was prepared according to a literature procedure.[67] *n*-Butyllithium (1.6 M in hexanes, 4.3 mL, 6.9 mmol) was added to a stirred solution of bromostyrene **54** (1.5 g, 7.0 mmol) in dry tetrahydrofuran (20 mL) at −78 °C. The solution was stirred for 30 min, then warmed to −30 °C and stirred for a further 30 min. The solution was cooled to −78 °C and *N,N*-dimethylformamide (0.58 mL, 7.5 mmol) in dry tetrahydrofuran (10 mL) was added dropwise. The solution was stirred at −78 °C for 1 h before being warmed to RT and stirred for a further 1 h. Brine (20 mL) was added, and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography (silica gel, petrol:diethyl ether, 50:1) to afford (*E*)-2-(but-1-enyl)benzaldehyde **56** as a pale yellow oil (708 mg, 63%, E/Z = 21:1). δ_H (400 MHz, $CDCl_3$): 10.30 (1H, s, H11), 7.81 (1H, d, *J* 8.0, H9), 7.55−7.49 (2H, m, H6 & H7), 7.40−7.34 (1H, m, H8), 7.17 (1H, d, *J* 15.7, H4), 6.20 (1H, dt, *J* 15.6, 6.5, H3), 2.31 (2H, dt, *J* 7.4, 7.1, H2), 1.13 (3H, t, *J* 7.5, H1). δ_C (101 MHz, $CDCl_3$): 192.6 (C11), 141.1 (C5), 139.0 (C3), 133.7 (C7), 132.6 (C10), 130.7 (C9), 127.5 (C6), 127.0 (C8), 124.7 (C4), 26.4 (C2), 13.4 (C1). HRMS (FI): found 160.0885; $C_{11}H_{12}O$ $[M\bullet]^+$ requires 160.0888. ν_{max} (film): 3063, 2933, 2875, 1692, 1645, 1566, 1160, 801 cm^{-1}.

Methyl 2-((*E*)-2-((*E*)-prop-1-enyl)benzylideneamino)acetate (58)



This compound was prepared by a modified literature procedure.[73] Triethylamine (78 μL) was added to a stirred solution containing aldehyde **50** (50 mg, 0.34 mmol, *E*:*Z* 16:1), glycine methyl ester hydrochloride (64.5 mg, 0.68 mmol) and $MgSO_4$ (120 mg) in dichloromethane (5 mL), and the resulting mixture stirred for 12 h at RT. The reaction mixture was diluted slowly with petrol (10 mL) and filtered. The solution was washed with water (5 mL) and the aqueous layer extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford methyl 2-((*E*)-2-((*E*)-prop-1-enyl)benzylideneamino)acetate **58** (52 mg, 71%, *E*:*Z* 16:1) without further purification as a red oil. δ_H (400 MHz, C_6D_6): 8.57 (1H, s, H10), 8.39 (1H, d, *J* 7.8, H8), 7.45 (1H, d, *J* 7.5, H5), 7.29 (1H, t, *J* 7.2, H6), 7.23 (1H, t, *J* 7.5, H7), 7.05 (1H, d, *J* 15.6, H3), 6.04 (1H, dq, *J* 15.4, 6.8, H2), 4.31 (2H, s, H11), 3.53 (3H, s, H13), 1.85 (3H, dd, *J* 6.6, 1.4, H1). δ_C (101 MHz, C_6D_6): 170.1 (C12), 163.5 (C10), 139.2 (C4), 133.3 (C9), 132.9 (C2), 130.8 (C6), 129.8 (C8), 128.5 (C3), 127.2 (C7), 127.1 (C5), 62.3 (C11), 51.3 (C13), 18.7 (C1). HRMS (ESI): found 240.0998; $C_{13}H_{15}NNaO_2$ $[M+Na]^+$ requires 240.0998. ν_{max} (film): 3026, 2953, 1747 (C=O), 1698, 1640, 1437, 1272, 1199 cm^{-1}.

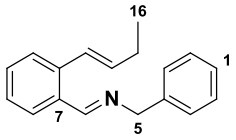
(*E*)-1-Phenyl-*N*-(2-((*E*)-prop-1-enyl)benzylidene)methanamine (60)



This compound was prepared according to a literature procedure.[67] Benzylamine (112 μL, 1.0 mmol) was added to a stirred mixture of styryl aldehyde **50** (150 mg, 1.0 mmol) and activated 3 Å molecular sieves (0.5 g) in dichloromethane (5 mL), and stirred for 16 h. The reaction mixture was filtered, and the solvent removed *in vacuo* to afford (*E*)-*N*-(2-((*E*)-prop-1-enyl)benzylidene)-1-phenylmethanamine **60** (216 mg, 92%, *E*/*Z* = 16:1) as a yellow oil without further purification. *Data is consistent with that reported in the literature.*[67] δ_H (400 MHz, $CDCl_3$): 8.76 (1H, s, H6), 7.95 (1H, d, *J* 7.7, H8), 7.48−7.32 (5H, m, H1, H3, H10 & H11), 7.31−7.23 (3H, m, H2 & H9), 6.90

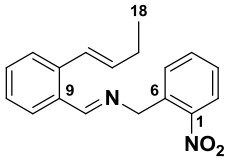
(1H, d, *J* 15.7, H13), 6.10 (1H, dq, *J* 15.4, 6.7, H14), 4.87 (2H, s, H5), 1.95 (3H, dd, *J* 6.6, 1.5, H15). δ_C (101 MHz, $CDCl_3$): 160.7 (C6), 139.5 (C4), 138.6 (C7), 132.7 (C12), 130.4 (CH), 130.1 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 127.0 (CH), 126.9 (CH), 65.4 (C5), 18.9 (C15). ν_{max} (film): 3061, 3027, 2962, 2911, 2877, 1637 (C=N), 1448, 964, 753 cm^{-1}.

(*E*)-*N*-(2-((*E*)-But-1-enyl)benzylidene)-1-phenylmethanamine (61)



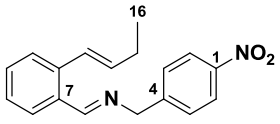
This compound was prepared according to a literature procedure.[67] Benzylamine (170 μL, 1.56 mmol) was added to a stirred mixture of styryl aldehyde **56** (250 mg, 1.56 mmol) and activated 3 Å molecular sieves (0.75 g) in dichloromethane (5 mL), and stirred for 16 h. The reaction mixture was filtered, and the solvent removed *in vacuo* to afford (*E*)-*N*-(2-((*E*)-but-1-enyl)benzylidene)-1-phenylmethanamine **61** (360 mg, 93%, *E*/*Z* = 21:1) as a yellow oil without further purification. δ_H (400 MHz, $CDCl_3$): 8.76 (1H, s, H6), 7.94 (1H, d, *J* 7.7, H8), 7.46−7.24 (8H, m, H1, H2, H3, H9, H10, H11), 6.88 (1H, d, *J* 15.7, H13), 6.13 (1H, dt, *J* 15.7, 6.5, H14), 4.86 (2H, s, H5), 2.90 (2H, m, H15), 1.13 (3H, t, *J* 7.4, H16). δ_C (101 MHz, $CDCl_3$): 160.7 (C6), 139.4 (C4), 139.0 (C7), 138.6 (C12), 137.0 (C14), 130.3 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.0 (CH), 126.9(6) (CH), 126.9(2) (CH), 125.5 (C13), 65.4 (C5), 26.4 (C15), 13.6 (C16). HRMS (ESI): found 250.1598; $C_{18}H_{20}N$ $[M+H]^+$ requires 251.1590. ν_{max} (film): 3061, 2964, 2844, 1638 (C=N), 1493, 965, 800, 697 cm^{-1}.

(*E*)-*N*-(2-((*E*)-But-1-enyl)benzylidene)-1-(2-nitrophenyl)methanamine (62)



This compound was prepared according to a modified literature procedure.[73] Triethylamine (96 μL, 0.69 mmol) was added to a stirred suspension of 2-nitrobenzylamine hydrochloride (130 mg, 0.69 mmol) and magnesium sulfate (250 mg) in dichloromethane (5 mL) and stirred for 1 h. Styryl aldehyde **56** (100 mg, 0.63 mmol) was added, and the resulting mixture stirred for 12 h. Water (5 mL) was added, and the aqueous layer extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford (*E*)-*N*-(2-((*E*)-but-1-enyl)benzylidene)-1-(2-nitrophenyl)methanamine **62** (180 mg, 99%, *E*/*Z* = 21:1) as a red oil without further purification. δ_H (400 MHz, $CDCl_3$): 8.82 (1H, s, H8), 8.07 (1H, dd, *J* 8.1, 1.0, H2), 7.97 (1H, d, *J* 7.7, H10), 7.76 (1H, d, *J* 7.8, H5), 7.63 (1H, td, *J* 7.6, 0.9, H4), 7.48−7.42 (2H, m, H3 & H13), 7.39 (1H, t, *J* 7.6, H12), 7.30 (1H, t, *J* 7.5 H11), 6.91 (1H, d, *J* 15.6, H15), 6.15 (1H, dt, *J* 15.6, 6.5, H16), 5.18 (2H, s, H7), 2.30 (2H, dq, *J* 7.4, 7.1, H17), 1.13 (3H, t, *J* 7.5, H18). δ_C (101 MHz, $CDCl_3$): 162.2 (C8), 148.0 (C1), 138.9 (C14), 137.3 (C16), 135.7 (C9), 133.5 (C4), 132.4 (C6), 130.7 (C12), 130.3 (C5), 127.7 (C10/C11), 127.6 (C10/C11), 127.1 (C3/C13), 127.0 (C3/C13), 125.4 (C15), 124.7 (C2), 61.7 (C7), 26.4 (C17), 13.6 (C18). . HRMS (ESI): found 295.1441; $C_{18}H_{19}N_2O_2$ $[M+H]^+$ requires 295.1441. ν_{max} (film): 3063, 3026, 2965, 2931, 2873, 1637 (C=N), 1347, 966, 728 cm^{-1}

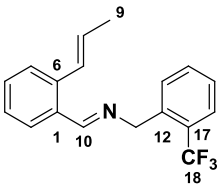
(*E*)-*N*-(2-((*E*)-But-1-enyl)benzylidene)-1-(4-nitrophenyl)methanamine (63)



This compound was prepared according to a modified literature procedure.[73] Triethylamine (96 μL, 0.69 mmol) was added to a stirred suspension of 4-nitrobenzylamine hydrochloride (130 mg,

0.69 mmol) and magnesium sulfate (250 mg) in dichloromethane (5 mL) and stirred for 1 h. Styryl aldehyde **56** (100 mg, 0.63 mmol) was added, and the resulting mixture stirred for 12 h. Water (5 mL) was added, and the aqueous layer extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford (*E*)-*N*-(2-((*E*)-but-1-enyl)benzylidene)-1-(4-nitrophenyl)methanamine **63** (172 mg, 94%, *E*/*Z* = 21:1) as a red oil without further purification. δ_H (400 MHz, $CDCl_3$): 8.80 (1H, s, H6), 8.22 (2H, d, *J* 8.7, H2), 7.96 (1H, d, *J* 8.1, H8), 7.56 (2H, d, *J* 8.3, H3), 7.45 (1H, d, *J* 7.4, H11), 7.39 (1H, t, *J* 7.6, H10), 7.30 (1H, t, *J* 7.5, H9), 6.90 (1H, d, *J* 15.7, H13), 6.14 (1H, dt, *J* 15.5, 6.5, H14), 4.93 (2H, s, H5), 2.30 (2H, dq, *J* 7.3, 7.1, H15), 1.13 (3H, t, *J* 7.4, H16). δ_C (101 MHz, $CDCl_3$): 161.9 (C6), 147.4 (C1/C4), 147.0 (C1/C4), 138.9 (C12), 137.3 (C14), 132.2 (C7), 130.8 (C10), 128.4 (C3), 127.7 (C8), 127.2 (C9), 127.1 (C11), 125.4 (C13), 123.7 (C2), 64.4 (C5), 26.4 (C15), 13.6 (C16). HRMS (ESI): found 295.1445; $C_{18}H_{19}N_2O_2$ $[M+H]^+$ requires 295.1441. ν_{max} (film): 3108, 2965, 2873, 1638 (C=N), 1377, 1109, 754 cm^{-1}.

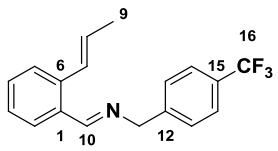
(*E*)-*N*-(2-((*E*)-Prop-1-en-1-yl)benzylidene)-1-(2-(trifluoromethyl)phenyl)methanamine (64)



This compound was prepared by analogy to a literature procedure.[67] 2-(Trifluoromethyl)benzylamine (96 μL, 0.68 mmol) was added to a stirred mixture of styryl aldehyde **50** (100 mg, 0.68 mmol, *E*:*Z* 10:1) and activated 3 Å molecular sieves (0.25 g) in dichloromethane (2 mL), and stirred for 16 h. The reaction mixture was filtered, and the solvent removed *in vacuo* to afford (*E*)-*N*-(2-((*E*)-but-1-enyl)benzylidene)-1-phenylmethanamine **64** (176 mg, 85%, *E*:*Z* 10:1) as a yellow oil without further purification. δ_H (500 MHz, d_8-toluene): 8.53 (1H, s, H10), 8.11 (1H, dd, *J* 7.7,

1.4, H2), 7.66 (1H, d, *J* 7.8, H5), 7.46 (1H, d, *J* 7.9, H16), 7.28 (1H, d, *J* 7.3, H13), 7.17−7.13 (2H, m, H4 & H14), 7.10 (1H, t, *J* 7.5, H3), 6.94−6.87 (2H, m, H7 & H15), 5.88 (1H, dq, *J* 15.7, 6.6, H8), 4.91 (2H, s, H11), 1.73 (3H, dd, *J* 6.6, 1.7, H9). δ_C (126 MHz, d_8-toluene):* 161.1 (C10), 139.3 (C12), 139.1 (C6), 133.1 (C1), 132.0 (C14), 130.6 (C4), 130.1 (C5), 129.5 (C8), 128.5 (C2), 128.4 (C7), 127.2 (C13), 127.1 (C3), 126.8 (C15), 125.8 (q, *J* 5.7, C16), 125.4 (q, *J* 274, C18), 61.3 (C11), 18.7 (C9). δ_F (470 MHz, d_8-toluene): -64.8. HRMS (ESI): found 304.1307; $C_{18}H_{17}F_3N$ $[M+H]^+$ requires 304.1308. ν_{max} (film): 3028, 2915, 1639 (C=N), 1311, 1111, 765, 656 cm^{-1}.

(*E*)-*N*-(2-((*E*)-Prop-1-en-1-yl)benzylidene)-1-(4-(trifluoromethyl)phenyl)methanamine (65)



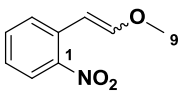
This compound was prepared by analogy to a literature procedure.[67] 4-(Trifluoromethyl)benzylamine (98 μL, 0.68 mmol) was added to a stirred mixture of styryl aldehyde **50** (100 mg, 0.68 mmol, *E*:*Z* 10:1) and activated 3 Å molecular sieves (0.25 g) in dichloromethane (2 mL), and stirred for 16 h. The reaction mixture was filtered, and the solvent removed *in vacuo* to afford (*E*)-*N*-(2-((*E*)-but-1-enyl)benzylidene)-1-phenylmethanamine **65** (191 mg, 92%, *E*:*Z* 10:1) as a yellow oil without further purification. δ_H (500 MHz, d_8-toluene): 8.51 (1H, s H10), 8.13 (1H, dd, *J* 7.7, 1.5, H2), 7.40 (2H, d, *J* 8.2, H14), 7.29 (1H, dd, *J* 7.5, 0.8, H5), 7.18−7.09 (4H, m, H3, H4 & H13), 6.92 (1H, dq, *J* 15.5, 1.7, H7), 5.89 (1H, dq, *J* 15.5, 6.6, H8), 4.46 (2H, s, H11), 1.76 (3H, dd, *J* 6.6, 1.8, H9). δ_C (126 MHz, d_8-toluene):† 160.7 (C10), 144.5 (C12), 139.0 (C6), 133.0 (C1), 130.7 (C4), 129.6 (C8), 128.2 (C13), 127.3 (C5), 127.2 (C3), 125.4 (q, *J* 3.7, C14), 125.1 (q, *J* 273, C16), 64.7 (C11), 18.7 (C9). δ_F (470 MHz, d_8-toluene): -67.0. HRMS (ESI): found 304.1305;

* *Note that the expected ^{13}C quartet corresponding to C17 was not observed due to low intensity or co-incidence with the residual solvent peaks.*

† *Note that the expected ^{13}C quartet corresponding to C15 was not observed due to low intensity or co-incidence with the residual solvent peaks.*

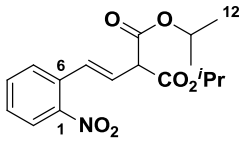
$C_{18}H_{17}F_3N$ $[M+H]^+$ requires 304.1308. ν_{max} (film): 3026, 2880, 1638 (C=N), 1322, 1118, 1109, 1065, 819, 757 cm^{-1}.

1-(2-Methoxyvinyl)-2-nitrobenzene (75)



This compound was prepared according to a literature procedure.[197] *n*-Butyllithium (1.6 M in hexanes, 19 mL, 30 mmol) was added dropwise to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (10 g, 30 mmol) in tetrahydrofuran (40 mL) at −78 °C. The mixture was warmed to 0 °C for 30 min, turning a deep orange colour, then cooled to −78 °C. 2-nitrobenzaldehyde (2.94 g, 19 mmol) was added, and the solution stirred at −78 °C for 1 h, allowed to warm to RT and stirred for a further 12 h. The mixture was diluted with petrol (150 mL), causing the triphenylphosphine oxide to precipitate out of solution. The supernatant liquid was poured off the unwanted side-product, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, petrol:diethyl ether, 25:1) to afford 1-(2-methoxyvinyl)-2-nitrobenzene **75** (1.83 g, 53%, E/Z = 5:2) as a yellow oil. *Data is consistent with that reported in the literature.*[197] δ_H (400 MHz, $CDCl_3$): 8.07 (1H, d, *J* 8.0, (*Z*)-H2), 7.91 (1H, d, *J* 8.0, (*E*)-H2), 7.81 (1H, d, *J* 8.1, (*Z*)-H5), 7.52−7.44 (3H, m, (*E*)-H4, (*E*)-H5 & (*Z*)-H3), 7.30−7.23 (2H, m, (*E*)-H3 & (*Z*)-H4), 7.06 (1H, d, *J* 12.8, (*E*)-H7), 6.40 (1H, d, (*E*)-H8), 6.31 (1H, d, *J* 7.2, (*Z*)-H7), 5.70 (1H, d, *J* 7.3, (*Z*)-H8), 3.80 (3H, s, (*Z*)-H9), 3.74 (2H, s, (*E*)-H9). δ_C (101 MHz, $CDCl_3$): 152.4 ((*E*)-C8), 150.8 ((*Z*)-C8), 147.3 ((*E*)-C1), 144.9 ((*Z*)-C1), 132.9 ((*E*)-C4), 132.2 ((*Z*)-C3), 131.9 ((*E*)-C6), 131.1 ((*Z*)-C2), 129.8 ((*Z*)-C6), 127.1 ((*E*)-C5), 126.2 ((*E*)-C3), 126.2 ((*Z*)-C4), 125.0 ((*E*)-C2), 124.2 ((*Z*)-C5), 100.3 ((*E*)-C7), 99.0 ((*Z*)-C7), 61.0 ((*Z*)-C9), 56.6 ((*E*)-C9). HRMS (FI): found 179.0586; $C_9H_9NO_3$ $[M\bullet]^+$ requires 179.0582. ν_{max} (film): 3071, 3011, 2938, 2837, 1633, 1522 (NO_2), 1310 (NO_2), 938, 743 cm^{-1}.

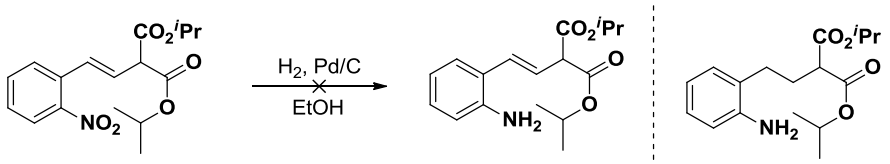
(*E*)-Diisopropyl 2-(2-nitrostyryl)malonate (77)



This compound was prepared by modified literature procedures.[198,199] *para*-Toluenesulfonic acid monohydrate (2.2 g, 11.6 mmol) was added to a stirred solution of masked aldehyde **75** (1.83 g, 11 mmol) in dichloromethane (100 mL) at RT. The reaction was stirred for 2 h then filtered, washed with water (100 mL) and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford sufficiently pure 2-(2-nitrophenyl)acetaldehyde **76** to be carried forward. In a separate reaction vessel, tetrahydrofuran (20 mL) was added dropwise to a solution of titanium(IV) chloride (2.24 mL, 20.9 mmol) in carbon tetrachloride (5 mL) at 0 °C, causing a bright yellow precipitate to form. Di*iso*propyl malonate (2.92 mL, 15.5 mmol) and the freshly prepared 2-(2-nitrophenyl)acetaldehyde **76** in tetrahydrofuran (20 mL) were added. Pyridine (3.36 mL, 42 mmol) in tetrahydrofuran (6 mL) was then added dropwise over a period of 1 h, causing formation of a brick red/black precipitate, and the resulting mixture was allowed to warm to RT and stirred for a further 12 h. Water (50 mL) was added and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) to afford (*E*)-diisopropyl 2-(2-nitrostyryl)malonate **77** (2.0 g, 59% over 2 steps) as a dark orange oil. δ_H (400 MHz, $CDCl_3$): 7.97 (1H, dd, *J* 8.2, 0.8, H2), 7.66 (1H, dd, *J* 7.9, 0.9, H5), 7.59 (1H, t, *J* 7.1, H4), 7.43 (1H, t, *J* 7.7, H3), 7.11 (1H, d, *J* 15.8, H7), 6.42 (1H, dd, *J* 15.8, 8.8, H8), 5.10 (2H, septet, *J* 6.2, H11), 4.19 (1H, d, *J* 8.8, H9), 1.29 (12H, d, *J* 6.2, H12). δ_C (101 MHz, $CDCl_3$): 167.2 (C10), 143.8

(C1), 133.2 (C4), 132.4 (C6), 130.1 (C7), 129.0 (C5), 128.6 (C3), 126.6 (C8), 124.6 (C2), 69.6 (C11), 55.9 (C9), 21.6 (C12). HRMS (ESI): found 358.1260; $C_{17}H_{21}NNaO_6$ $[M+Na]^+$ requires 358.1260. ν_{max} (film): 2983, 2938, 2878, 1726 (C=O), 1528 (NO_2), 1349 (NO_2), 1105 cm^{-1}.

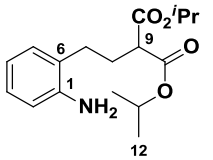
Attempted formation of (*E*)-Diisopropyl 2-(2-aminostyryl)malonate (79) I



77 79 81

Nitroarene **77** (60 mg, 0.18 mmol) was added to a stirred suspension of palladium on carbon (10 wt%, 6 mg) in ethanol (2 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen, then stirred vigorously for 60 min. The reaction mixture was filtered over Celite® and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) to afford aniline **81** (48 mg, 89%) as a red oil.

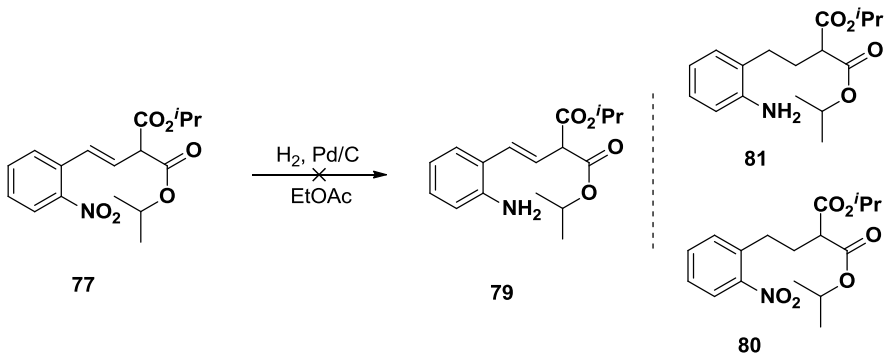
*Diisopropyl 2-(2-aminophenethyl)malonate (**81**)*



δ_H (500 MHz, $CDCl_3$): 7.08−7.02 (2H, m, H3 & H5), 6.74−6.70 (2H, m, H2 & H4), 5.09 (2H, septet, *J* 6.3, H11), 3.35 (1H, t, *J* 7.1, H9), 2.59−2.54 (2H, m H7), 2.15−2.09 (2H, m, H8), 1.27 (6H, d, *J* 6.3), 1.26 (6H, d, *J* 6.2, H12). δ_C (126 MHz, $CDCl_3$): 169.1 (C10), 144.1 (C1), 129.9 (C5), 127.5 (C3), 125.2 (C6), 118.6 (C2/C4), 115.8 (C2/C4), 69.0 (C11), 51.6 (C9), 29.5 (C7), 28.1 (C8), 21.6(5) & 21.5(6) (C12). HRMS (ESI): found 330.1677; $C_{17}H_{25}NNaO_4$ $[M+Na]^+$ requires

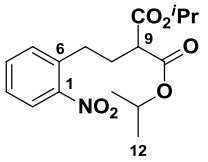
330.1676. ν_{max} (film): 3464 (NH_2), 3384 (NH_2), 2982 (CH), 2939 (CH), 1729 (C=O), 1103, 750 cm^{-1}.

Attempted formation of (*E*)-Diisopropyl 2-(2-aminostyryl)malonate (79) II



Nitroarene **77** (20 mg, 0.06 mmol) was added to a stirred suspension of 10 wt% palladium on carbon (2 mg) in ethyl acetate (1 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen, then stirred vigorously for 60 min. The reaction mixture was filtered over celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) to afford nitroarene **80** (7 mg, 35%) as a colourless oil and aniline **81** (6 mg, 33%) as a red oil.

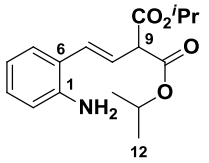
*Diisopropyl 2-(2-nitrophenethyl)malonate (**80**)*



δ_H (500 MHz, $CDCl_3$): 7.93 (1H, dd, *J* 8.1, 1.1, H2), 7.54 (1H, td, *J* 7.5, 1.2, H4), 7.41−7.35 (2H, m, H3 & H5), 5.08 (2H, septet, *J* 6.3, H11), 3.35 (1H, t, *J* 7.4, H9), 2.98−2.93 (2H, m, H7), 2.25 (2H, td, *J* 7.9, 7.6, H8), 1.27 (12H, d, *J* 6.2, H12). δ_C (126 MHz, $CDCl_3$): 169.6 (C10), 149.2 (C1), 136.0 (C6), 133.1 (C4), 132.1 (C5), 127.4 (C3), 124.8 (C2), 69.0 (C11), 51.9 (C9), 30.5 (C7), 29.4 (C8), 21.6(4) (C12), 21.5(5) (C12'). HRMS (ESI): found 360.1424; $C_{17}H_{23}NNaO_6$ $[M+Na]^+$

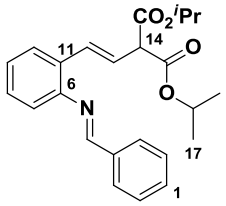
requires 360.1418. ν_{max} (film): 2983 (CH), 2878 (CH), 1727 (C=O), 1528 (NO_2), 1350 (NO_2), 1103, 747 cm^{-1}.

(*E*)-Diisopropyl 2-(2-aminostyryl)malonate (79)



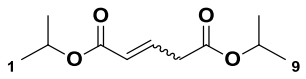
This compound was prepared by to a literature procedure.[80] Nitroarene **77** (300 mg, 0.89 mmol) was dissolved in ethyl acetate (5 mL), and tin(II) chloride dihydrate (1 g, 4.5 mmol) was added to this stirred solution. The reaction mixture was heated to 70 °C and stirred vigorously for 1 h. After cooling to RT the mixture was diluted with ethyl acetate (30 mL) and Rochelle's salt (aq., 50 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 25 mL), and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:3) to afford (*E*)-diisopropyl 2-(2-aminostyryl)malonate **79** (172 mg, 63%) as a colourless oil. δ_H (400 MHz, $CDCl_3$): 7.28 (1H, dd, *J* 7.4, 1.7, H5), 7.09 (1H, td, *J* 7.6, 1.5, H4), 6.76 (1H, td, *J* 7.5, 0.8, H3), 6.68 (1H, dd, *J* 8.0, 0.9, H2), 6.62 (1H, d, *J* 15.8, H7), 6.28 (1H, dd, *J* 15.8, 9.0, H8), 5.10 (2H, sept, H11), 4.12 (1H, dd, *J* 8.9, 0.8, H9), 3.80 (2H, br s, $-NH_2$), 1.28 (12H, dd, *J* 6.3, 1.1, H12). δ_C (101 MHz, $CDCl_3$): 167.7 (C10), 143.8 (C1), 130.8 (C7), 129.0 (C5), 127.9 (C3), 123.0 & 122.7 (C6 & C8), 118.9 (C4), 116.1 (C2), 69.3 (C11) 56.6 (C9), 21.6 (C12). HRMS (ESI): found 328.1519; $C_{17}H_{23}NNaO_4$ $[M+Na]^+$ requires 328.1519. ν_{max} (film): 3462 (NH_2), 3381 (NH_2), 1726 (C=O), 1623, 1282, 1103, 751 cm^{-1}.

Diisopropyl 2-(2-((*E*)-benzylideneamino)styryl)malonate (82)



Benzaldehyde (181 μL, 1.8 mmol) was added to a RT solution of aniline **79** (375 mg, 1.2 mmol) in toluene (5 mL) with magnesium sulfate (0.8 g), and the reaction mixture stirred for 12 h. The mixture was filtered, and the solvent and any unreacted benzaldehyde removed *in vacuo*, to afford diisopropyl 2-(2-((*E*)-benzylideneamino)styryl)malonate **82** (473 mg, 98%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$): 8.38 (1H, s, H5), 7.97−7.92 (2H, m, H3), 7.63 (1H, dd, *J* 7.7, 1.3, H10), 7.58−7.48 (3H, m, H1 & H2), 7.30 (1H, td, *J* 7.6, 1.4, H8), 7.22 (1H, td, *J* 7.5, 1.0, H9), 7.09 (1H, d, *J* 16.0, H12), 6.96 (1H, dd, *J* 7.8, 1.1, H7), 6.45 (1H, dd, *J* 16.1, 9.0, H13), 5.07 (2H, septet, *J* 6.2, H16), 4.16 (1H, dd, *J* 9.0, 0.9, H14), 1.25 (12H, d, *J* 6.2, H17). δ_C (101 MHz, $CDCl_3$): 167.7 (C15), 160.3 (C5), 149.8 (C6), 136.4 (C11), 131.5 (C1), 131.2 (C12), 129.0 (C4), 128.9(4) (C8), 128.9(2) (C3), 128.8 (C2), 126.1 (C10), 126.0 (C9), 121.9 (C13), 118.4 (C7), 69.2 (C16), 56.7 (C14), 21.6 (C17). HRMS (ESI): found 416.1827; $C_{24}H_{27}NNaO_4$ $[M+Na]^+$ requires 416.1832. ν_{max} (film): 3060, 3028, 2982, 1728 (C=O), 1627 (C=N), 1455, 1283, 1259, 1202, 973, 750 cm^{-1}

Diisopropyl glutaconate (88)

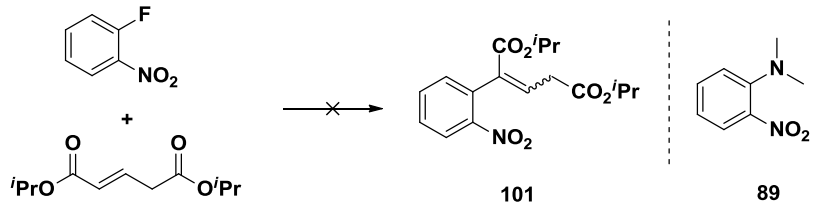


Concentrated sulfuric acid (0.5 mL) was added to a stirred solution of glutaconic acid (500 mg, 3.85 mmol, mixture of *E*/*Z* isomers) in *iso*-propanol (5 mL), and the mixture was heated to reflux. After 3 h the reaction mixture was allowed to cool to RT and poured into ice water (5 mL), and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with water (5 mL), sodium bicarbonate (aq., 2 x 5 mL) and brine

(5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford diester **88** (664 mg, 81%, *E*:*Z* 10:1) as a yellow oil, requiring no further purification.

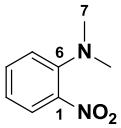
Major (E) Isomer: δ_H (400 MHz, $CDCl_3$): 6.99 (1H, dt, *J* 15.0, 7.5, H5), 5.90 (1H, dt, *J* 15.7, 1.6, H4), 5.12−5.00 (2H, m, H2 & H8), 3.19 (2H, dd, *J* 7.2, 1.6, H6), 1.26 (6H, d, *J* 6.3, H1/H9), 1.26 (6H, d, *J* 6.2, H1/H9). δ_C (400 MHz, $CDCl_3$): 169.4 & 165.4 (C3 & C7), 139.5 (C5), 125.0 (C4), 68.6 & 67.8 (C2 & C8), 37.7 (C6), 21.8 & 21.7 (C1 & C9). HRMS (ESI+): found 237.1098; $C_{11}H_{18}NaO_4$, $[M+Na]^+$ requires 237.1097. ν_{max} (film): 2982 (C=C), 2939 (C=C), 1716 (C=O), 1104, 986, 823 cm^{-1}.

Attempted formation of diisopropyl 2-(2-nitrophenyl)pent-2-enedioate (101)



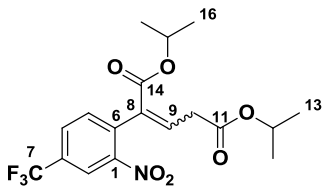
This reaction was carried out by analogy to a literature procedure. Potassium carbonate (98 mg, 0.71 mmol) was added to a solution of diisopropyl glutaconate **88** (152 mg, 0.71 mmol) in *N*,*N*-dimethylformamide (1 mL) and warmed to 80 °C. After 15 min the reaction mixture was cooled to RT and 1-fluoro-2-nitrobenzene (37 μL, 0.35 mmol) was added, and the reaction warmed to 80 °C. After 12 h the reaction mixture was allowed to cool to RT and ammonium chloride (aq., 5 mL) was added, and the aqueous layer extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) to afford *N*,*N*-dimethyl-2-nitroaniline **89** (25 mg, 43%) as a yellow oil.

*N,N-Dimethyl-2-nitroaniline (**89**)*



Data is consistent with that reported in the literature.[200] δ_H (400 MHz, $CDCl_3$): 7.77 (1H, dd, *J* 8.2, 1.5, H2), 7.40 (1H, ddd, *J* 8.5, 7.1, 1.5, H4), 7.03 (1H, dd, *J* 8.4, 0.6, H5), 6.83 (1H, ddd, *J* 8.2, 7.2, 1.0, H3), 2.90 (6H, s, H7). δ_C (101 MHz, $CDCl_3$): 146.2 (C1), 139.3 (C6), 133.2 (C4), 126.7 (C2), 118.1 (C5), 117.9 (C3), 42.4 (C7). ν_{max} (film): 2932 (CH), 2881 (CH), 2809 (CH), 1511 (NO_2), 1343 (NO_2), 1288, 742 cm^{-1}.

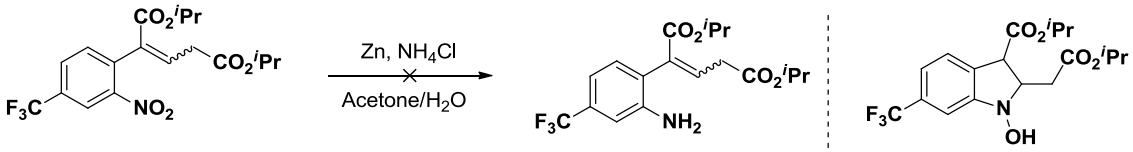
Diisopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)pent-2-enedioate (90)



This reaction was carried out by analogy to a literature procedure.[81] *n*-Butyllithium (1.21 M in hexanes, 1.69 mL, 2.04 mmol) was added to a stirred −78 °C solution of diisopropylamine (291 μL, 2.04 mmol) in tetrahydrofuran (10 mL). The resulting solution was stirred for a 15 min before warming to 0 °C; after a further 15 min stirring the reaction mixture was cooled to −78 °C and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 0.78 mL, 6.4 mmol) was added, followed by diisopropyl glutaconate **88** (600 mg, 2.04 mmol) in tetrahydrofuran (10 mL). The reaction mixture was warmed to −30 °C and stirred for a further 30 min; this mixture was then added *via* insulated cannula to a stirred −30 °C suspension of activated 4Å molecular sieves (1.0 g) and 4-fluoro-3-nitrobenzotrifluoride **124** (855 μL, 6.1 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred for 15 min before adding ammonium chloride (aq., 25 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude yellow residue was purified by flash column chromatography

(silica gel, petrol:diethyl ether, 15:1) to afford nitroarene **90** (661 mg, 80%) as a white crystalline solid. δ_H (400 MHz, $CDCl_3$): 8.44 (1H, s, H2), 7.91 (1H, d, *J* 7.9, H4), 7.50 (1H, d, *J* 7.8, H5), 7.29 (1H, t, *J* 8.1, H9), 5.07 (1H, septet, *J* 6.1, H12/H15), 5.03 (1H, septet, *J* 6.2, H12/H15), 3.03 (2H, s, *J* 8.1, H10), 1.24 (6H, d, *J* 6.3, H13/H16), 1.21 (6H, d, *J* 6.2, H13/H16). δ_C (126 MHz, $CDCl_3$): 168.8 (C11), 163.6 (C14), 148.5 (C1), 135.6 (C9), 134.2 (C6), 133.7 (C8), 133.3 (C5), 131.9 (q, *J* 34.4, C3), 129.9 (q, *J* 3.4, C4), 122.7 (q, *J* 273, C7), 122.2 (q, *J* 3.8, C2), 69.5 & 69.1 (C12 & C15), 35.5 (C10), 21.7 & 21.4 (C13 & C16). δ_F (377 MHz, $CDCl_3$): -63.1. MP: 62−64 °C. ν_{max} (film): 2984 (CH), 2940 (CH), 1728 (C=O), 1572 (NO_2), 1324 (NO_2), 1178, 1021 cm^{-1}. HRMS (ESI): found 426.1119; $C_{18}H_{20}F_3NNaO_6$ $[M+Na]^+$ requires 426.1135.

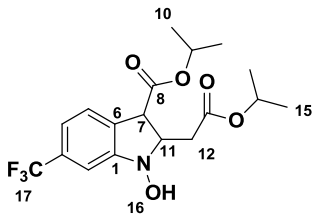
Attempted formation of diisopropyl 2-(2-amino-4-(trifluoromethyl)phenyl)pent-2-enedioate (91) I



90 **91** **93**

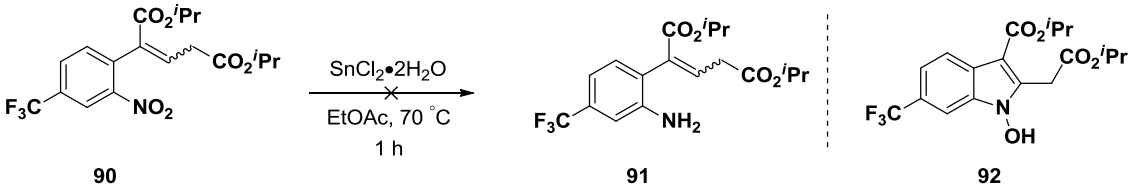
This reaction was carried out by analogy to a literature procedure.[82] Zinc dust (82 mg, 1.25 mmol) was added to a stirred suspension of ammonium chloride (112 mg, 1.88 mmol) and nitroarene **90** (50 mg, 0.125 mmol) in acetone/water (5:1, 0.5 mL). After 15 min the reaction mixture was filtered over Celite®, diluted with water (5 mL) and the aqueous layer extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 4:1) to afford *N*-hydroxyindoline **93** (29 mg, 60%) as a pale yellow oil, and as the only identifiable product of the reaction.

*(±)-Isopropyl 1-hydroxy-2-(2-isopropoxy-2-oxoethyl)-6-(trifluoromethyl)indoline-3-carboxylate (**93**)*



This compound was isolated after chromatography in ~90% purity with an unidentified contaminant. δ_H (400 MHz, $CHCl_3$): 7.42 (1H, d, *J* 7.8, H5), 7.24 (1H, d , *J* 8.1, H4), 7.22 (1H, s, H2), 6.83 (1H, d, H16), 5.16 (1H, septet, *J* 6.0, H9/H14), 5.06 (1H, septet, *J* 6.3, H9/H14), 4.23 (1H, ddd, *J* 10.3, 6.5, 5.1, H11), 3.88 (1H, d, *J* 10.2, H7), 2.92 (1H, dd, *J* 14.9, 5.0, H12), 2.83 (1H, dd, *J* 14.9, 6.7, H12'), 1.34 (6H, d, *J* 6.2, H10/H15), 1.27 (3H, d, *J* 6.1, H10/H15), 1.26 (3H, d, *J* 6.0, H10/H15). δ_C (101 MHz, $CHCl_3$):* 171.4 (C8/C13), 169.1 (C8/C13), 152.2 (C1), 128.0 (C6), 124.6 (C5), 119.9 (q, *J* 3.2, C4), 110.7 (q, *J* 4.1, C2), 70.0 (C11), 69.5 (C9/C14), 68.7 (C9/C14), 49.9 (C7), 38.0 (C12), 21.9 (C10/C15), 21.7(8) (C10/C15), 21.7(6) (C10/C15). δ_F (377 MHz, $CHCl_3$): -62.4. HRMS (ESI): found 412.1325; $C_{18}H_{22}F_3NNaO_5$ $[M+Na]^+$ requires 412.1342. ν_{max} (film): 3409 (OH), 2984 (CH), 2939 (CH), 1731 (C=O), 1321, 1165, 1106, 822 cm^{-1}.

Attempted formation of diisopropyl 2-(2-amino-4-(trifluoromethyl)phenyl)pent-2-enedioate (91) II



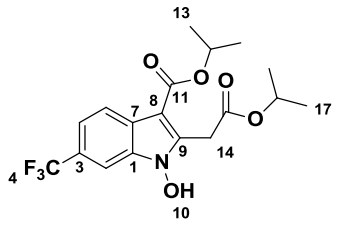
90 **91** **92**

This reaction was carried out by analogy to a literature procedure.[80] Tin(II) chloride dihydrate (242 mg, 1.08 mmol) was added to a stirred solution of nitroarene **90** (72 mg, 0.21 mmol) in ethyl acetate (1.5 mL) and heated to 70 °C. After 16 h the reaction mixture was allowed to cool to RT and Rochelle's salt (aq., 5 mL) was added, and the resulting biphasic mixture stirred vigorously for 1

* *The expected ^{13}C quartet peaks corresponding to C3 and C17 were not observed due to their low intensity.*

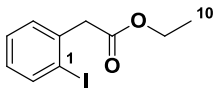
h. The aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, diethyl ether:petrol, 2:1) to afford hydroxyindole **92** (55 mg, 80%) as a white crystalline solid.

*Isopropyl 1-hydroxy-2-(2-isopropoxy-2-oxoethyl)-6-(trifluoromethyl)-1H-indole-3-carboxylate (**92**)*



δ_H (400 MHz, C_6D_6): 9.06 (1H, br s, H10), 8.41 (1H, d, *J* 8.4, H6), 7.87 (1H, s, H2), 7.51 (1H, d, *J* 8.3, H5), 5.32 (1H, septet, *J* 6.1, H12), 4.89 (1H, septet, *J* 6.3, H16), 4.33 (2H, s, H14), 1.27 (6H, d, *J* 6.2, H13), 1.03 (6H, d, *J* 6.2, H17). δ_C (101 MHz, C_6D_6): 171.3 (C15), 164.4 (C11), 138.6 (C9), 132.2 (C1), 128.3 (C7), 125.4 (Ar C*), 125.1 (Ar C*), 124.9 (Ar C*), 122.6 (C6), 118.8 (q, *J* 3.2, C5), 106.7 (q, *J* 4.4, C2), 101.8 (C8), 70.2 (C16), 67.5 (C12), 31.1 (C14), 22.0 (C13), 21.3 (C17). HRMS (ESI): found 410.1170; $C_{18}H_{20}F_3NNaO_5$ $[M+Na]^+$ requires 410.1186. ν_{max} (film): 3134 (OH), 2991 (CH), 1735 (C=O), 1649, 1276, 1195, 1103, 1053, 1016, 820 cm^{-1}. MP: 62-65 °C ($CDCl_3$).

Ethyl 2-(2-iodophenyl)acetate (98)

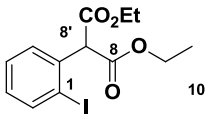


This compound was prepared according to a literature procedure.[201] Concentrated sulfuric acid (0.6 mL) was added to a stirred solution of 2-iodophenylacetic acid (2.0 g, 7.6 mmol) in ethanol

* *The ^{13}C quartet peaks corresponding to C3 and C4 were not fully identified due to their low intensity and co-incidence with the residual solvent peaks. The peaks denoted "ArC" are presumed to be components of these multiplets that lie outwith the residual solvent peak.*

(6 mL) and heated to reflux for 3 h. The solution was cooled to RT and water (20 mL) was added, and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with water (10 mL), sodium bicarbonate solution (10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, hexane:ethyl acetate, 4:1), affording ethyl 2-(2-iodophenyl)acetate **98** (2.20 g, 99%) as a white crystalline solid. δ_H (400 MHz, $CDCl_3$): 7.87 (1H, d, *J* 7.9, H2), 7.38−7.25 (2H, m, H4 & H5), 6.97 (1H, td, *J* 7.4, 2.0, H3), 4.20 (2H, q, *J* 7.1, H9), 3.80 (2H, s, H7), 1.29 (3H, t, *J* 7.2, H10). δ_C (101 MHz, $CDCl_3$): 170.5 (C8), 139.5 (C2), 137.8 (C6), 130.6 (C4), 128.8 (C3), 128.4 (C5), 101.0 (C1), 61.1 (C9), 46.3 (C7), 14.2 (C10). ν_{max} (film): 3057 (CH), 2981 (CH), 1736 (C=O), 1160, 1029, 1016 cm^{-1}. MP 30−32 °C. *Data is consistent with that reported in the literature.*[201]

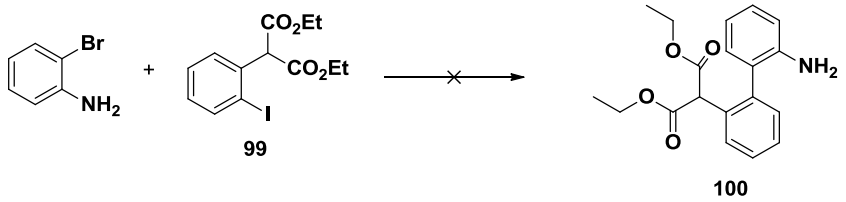
Diethyl 2-(2-iodophenyl)malonate (99)



This compound was prepared according to a literature procedure.[201] Sodium hydride (60 wt% dispersion in mineral oil, 1.22 g, 30.5 mmol) was added to a stirred solution of ethyl iodophenyl acetate **98** (2.21 g, 7.6 mmol) in diethyl carbonate (40 mL) at RT. The resulting solution was stirred for 3 h, and ammonium chloride (aq., 80 mL) was added, and the aqueous layer extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) to afford diethyl 2-(2-iodophenyl)malonate **99** (2.38 g, 87%) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 7.87 (1H, dd, *J* 8.0, 1.0, H2), 7.47 (1H, dd, *J* 7.8, 1.5, H5), 7.37 (1H, td, *J* 7.6, 1.0, H4), 7.01 (1H, td, *J* 7.6, 1.4, H3), 5.12 (1H, s, H7), 4.31−4.19 (4H, m, H9 & H9'), 2.82 (6H, t, *J* 7.1, H10 & H10'). δ_C (101 MHz,

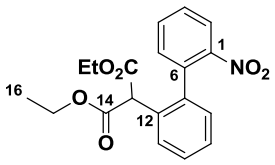
$CDCl_3$): 167.8 (C8 & C8'), 139.6 (C2), 136.4 (C6), 129.8 & 129.6 (C3 &C5), 128.5 (C4), 101.7 (C1), 62.2 & 62.0 (C9 & C9'), 14.0 (C10 & C10'). ν_{max} (film): 3061 (CH), 2983 (CH), 1754 (C=O), 1733 (C=O), 1369, 1031, 745 cm^{-1}. *Data is consistent with that reported in the literature.*[201]

Attempted formation of diethyl 2-(2'-aminobiphenyl-2-yl)malonate (100)



This reaction was attempted by analogy to a literature procedure.[88] Triethylamine (322 μL, 2.32 mmol), palladium(II) acetate (6.5 mg, 0.029 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 48 mg, 0.12 mmol) were added to a stirred RT solution of 2-bromoaniline (100 mg, 0.58 mmol) in 1,4-dioxane (1 mL). Pinacolborane (254 μL, 1.75 mmol) was added dropwise and the resulting mixture was warmed to 80 °C. After 1 h the reaction mixture was allowed to cool to RT and water (0.25 mL), barium hydroxide octahydrate (553 mg, 1.75 mmol) and malonate **99** (211 mg, 0.58 mmol) were added. The reaction mixture was warmed to 100 °C for 1 h, then allowed to cool to RT and filtered over Celite®, washing with dichloromethane (10 mL). Brine (5 mL) was added to the filtrate, and the aqueous phase extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. *^{1}H NMR and MS analysis of the crude reaction mixture did not indicate formation of the desired biaryl.* The residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1 → 2:1), affording 2-bromoaniline (24 mg, 24%) as the only identifiable compound.

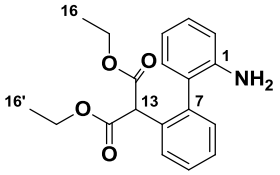
Diethyl 2-(2'-nitrobiphenyl-2-yl)malonate (103)



This compound was prepared according to a modified literature procedure.[87] Aryl iodide **99** (620 mg, 1.7 mmol) and 2-nitrobenzeneboronic acid (300 mg, 1.8 mmol) were dissolved in *n*-propanol (30 mL) and stirred for 30 min. Palladium(II) acetate (10 mg, 0.04 mmol), (2-biphenyl)dicyclohexylphosphine (47 mg, 0.13 mmol) and sodium carbonate solution (2 M aq., 0.86 mL, 1.7 mmol) were added, and the reaction mixture was heated to reflux for 1 h. The heat source was removed and water (100 mL) was added to the reaction mixture before it was allowed to cool. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organic extracts were washed with sodium bicarbonate solution (50 mL) and brine (50 mL), stirred with charcoal, dried over anhydrous magnesium sulfate, filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) to afford diethyl 2-(2'-nitrobiphenyl-2-yl)malonate **103** (440 mg, 72%) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 8.07 (1H, dd, *J* 8.1, 1.2, H2), 7.71 (1H, d, *J* 7.9, H8), 7.64 (1H, td, *J* 7.5, 1.2, H4), 7.57 (1H, td, *J* 7.8, 1.4, H3), 7.45 (1H, td, *J* 7.7, 1.2, H9), 7.38−7.30 (2H, m, H5 & H10), 7.12 (1H, dd, *J* 7.5, 0.9, H11), 4.40 (1H, s, H13), 4.22−4.10 (4H, m, H15 & H15'), 1.21 (3H, t, *J* 7.1, H16), 1.20 (3H, t, *J* 7.0, H16'). δ_C (101 MHz, $CDCl_3$):* 169.5 & 168.2 (C14 &C14'), 138.0 (Ar C), 132.6 (Ar CH), 132.5 (Ar CH), 131.1 (Ar C), 129.4 (Ar CH), 129.0 (Ar CH), 128.5 (2 x Ar CH), 127.0 (Ar C), 124.4 (Ar CH), 120.9 (C8), 61.9 & 61.8 (C15 & C15'), 54.6 (C13), 14.0 & 13.9 (C16 & C16'). HRMS (ESI): found 380.1106; $C_{19}H_{19}NO_6Na$ $[M+Na]^+$ requires 380.1105. ν_{max} (film): 3064 (CH), 2982 (CH), 2934 (CH), 1750 (C=O), 1731 (C=O), 1527 (NO_2), 1390 (NO_2), 1142, 1027, 751 cm^{-1}.

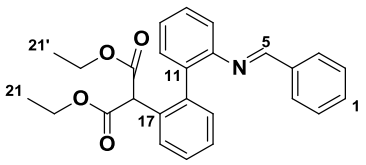
Diethyl 2-(2'-aminobiphenyl-2-yl)malonate (100)

* *Note that the ^{13}C peak corresponding to C1 was not observed.*



Nitroarene **103** (312 mg, 0.87 mmol) was added to a stirred suspension of 10 wt% palladium on carbon (30 mg) in methanol (10 mL). The reaction mixture was purged under vacuum, placed under an atmosphere of hydrogen, and stirred vigorously for 30 min, then filtered over Celite® and concentrated *in vacuo*. The crude product was then dissolved in diethyl ether (10 mL) and acidified with hydrochloric acid (2 M aq., 2 x 5 mL); the organic layer was discarded, and the aqueous layer made basic by a dropwise addition of NaOH (3 M aq.). The aqueous layer was extracted with dichloromethane (3 x 10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, affording diethyl 2-(2'-aminobiphenyl-2-yl)malonate **100** (286 mg, 100%) as a yellow oil requiring no additional purification. δ_H (400 MHz, C_6D_6): 7.64−7.58 (1H, m, H8), 7.46−7.38 (2H, m, H9 & H10), 7.31−7.26 (1H, m, H11), 7.20 (1H, td, *J* 7.7, 1.5, H3), 7.00 (1H, dd, *J* 7.5, 1.4, H5), 6.82 (1H, td, *J* 7.4, 0.8, H4), 6.77 (1H, d, *J* 8.0, H2), 4.67 (1H, s, H13), 4.24−4.09 (4H, m, H15 & H15'), 3.92−2.60 (2H, br s, NH_2), 1.24 (3H, t, *J* 7.1, H16), 1.19 (3H, t, *J* 7.1, H16'). δ_C (101 MHz, C_6D_6): 168.6 (C14 & C14'), 154.6 (C1), 139.1 (C12), 132.3 (C7), 130.6 (CH), 130.5 (CH), 129.4 (CH), 129.0 (CH), 128.5 (CH), 128.2 (CH), 118.4 (C4), 116.0 (C6), 115.3 (C2), 61.7 & 61.6 (C15 & C15'), 54.3 (C13), 14.0 & 13.9 (C16 & C16'). ν_{max} (film): 3207 (NH_2), 3067, 2980, 2932, 1731 (C=O), 1678, 1208, 755 cm^{-1}. HRMS (ESI): found 350.1359; $C_{19}H_{21}NNaO_4$ $[M+Na]^+$ requires 350.1363.

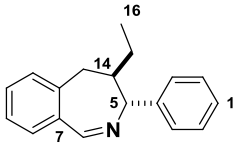
(*E*)-Diethyl 2-(2'-(benzylideneamino)biphenyl-2-yl)malonate (104)



This compound was prepared according to a modified literature procedure.[202] Benzaldehyde (31 μL, 0.31 mmol) was added to a stirred solution of aniline **100** (100 mg, 0.31 mmol) and flame-dried 3 Å molecular sieves (200 mg) in toluene (1 mL) at RT. Acetic acid (70 μL, 1.2 mmol) was added dropwise, and the reaction mixture stirred for 12 h. Solid potassium carbonate (200 mg) and water (10 mL) were added, and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* without further purification to afford (*E*)-diethyl 2-(2'-(benzylideneamino)biphenyl-2-yl)malonate **104** (132 mg, 100%) as a yellow oil. δ_H (400 MHz, C_6D_6): 8.22 (1H, s, H5), 8.11 (1H, dd, *J* 7.9, 1.1, H13), 7.74 (2H, m, H3), 7.45 (1H, dd, *J* 7.4, 1.5, H7), 7.34 (1H, dd, *J* 7.5, 1.4, H10), 7.25−7.31 (2H, m, H14 & H15), 7.16−7.23 (2H, m, H8 & H9), 7.15−7.10 (3H, m, H1 & H2), 6.98 (1H, dd, *J* 7.8, 1.2, H16), 5.33 (1H, s, H18), 4.01−3.84 (4H, m, H20 & H20'), 0.91 (3H, t, *J* 7.1, H21), 0.88 (3H, t, *J* 7.1, H21'). δ_C (101 MHz, C_6D_6): 168.8 (C19), 168.4 (C19'), 160.8 (C5), 150.6 (C6), 141.2 (C12), 136.7 (C4), 135.4 (C11/C17), 132.5 (C11/C17), 131.6 (Ar CH), 131.3 (Ar CH), 130.6 (Ar CH), 129.5 (Ar CH), 129.3 (C2/C3), 129.2 (Ar CH), 128.6 (C2/C3), 127.8 (2 x Ar CH), 126.1 (Ar CH), 118.8 (C7), 61.3 & 61.2 (C20 & C20'), 55.3 (C18), 13.9 & 13.8 (C21 & C21'). HRMS (ESI): found 416.1850; $C_{26}H_{26}NO_4$ $[M+H]^+$ requires 416.1850; ν_{max} (film): 3061 (CH), 3024 (CH), 1749 (C=O), 1732 (C=O), 1627 (C=N), 1261, 1030, 752 cm^{-1}. HPLC (Chiralpak OD-H, 5% IPA, 95% hexane, 1.0 $mL.min^{-1}$, λ = 210) $t_R(1)$= 10.0, $t_R(2)$ = 10.6.

6.2.2 Cyclization Reactions

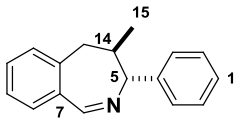
(±)-*trans*-4-Ethyl-3-phenyl-4,5-dihydro-3*H*-benzo[*c*]azepine (66)



This compound was prepared by analogy to a literature procedure.[67] LDA was prepared *in situ* by the dropwise addition of *n*-butyllithium (1.54 M in hexanes, 114 μL, 0.17 mmol) to a stirred solution

of diisopropylamine (27 μL, 0.19 mmol) in tetrahydrofuran (3 mL) at −40 °C. The solution was cooled to −78 °C and imine **61** (40 mg, 0.16 mmol) in tetrahydrofuran (1 mL) was added dropwise over 30 min. The resulting mixture was stirred for a further 1 h, then warmed to 0 °C and stirred for a further 30 min. The reaction mixture was poured into saturated sodium bicarbonate solution (20 mL) and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the crude product was purified by flash column chromatography (Silica gel, petrol:ethyl acetate, 10:1) to afford *trans*-4-ethyl-3-phenyl-4,5-dihydro-3*H*-benzo[*c*]azepine **66** (29 mg, 73%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$): 8.64 (1H, d, *J* 2.0, H6), 7.41−7.31 (7H, m, 7 x Ar CH), 7.30−7.23 (2H, m, 2 x Ar CH), 3.80 (1H, dd, *J* 10.7, 1.8, H5), 2.86 (1H, dd, *J* 13.9, 7.1, H13), 2.68 (1H, dd, *J* 13.9, 1.2, H13'), 2.54 (1H, m, H14), 1.29−1.10 (2H, m, H15), 0.89 (3H, t, *J* 7.4, H16). δ_C (101 MHz, $CDCl_3$):* 170.0 (C6), 143.6 (C12), 138.7 (C7), 135.1 (C4), 129.9 (Ar CH), 128.4 (Ar CH), 128.3 (Ar CH), 128.0 (Ar CH), 127.0 (Ar CH), 126.6 (Ar CH), 70.5 (C5), 54.7 (C13), 33.7 (C14), 23.0 (C15), 12.0 (C16). HRMS (ESI): found 250.1591; $C_{18}H_{20}N^+$ $[M+H]^+$ requires 250.1590. ν_{max} (film): 3060, 3025, 2956, 2869, 1616 (C=N), 1456, 1377, 757, 701 cm^{-1}.

(±)-*trans*-4-Methyl-3-phenyl-4,5-dihydro-3*H*-benzo[*c*]azepine (67)

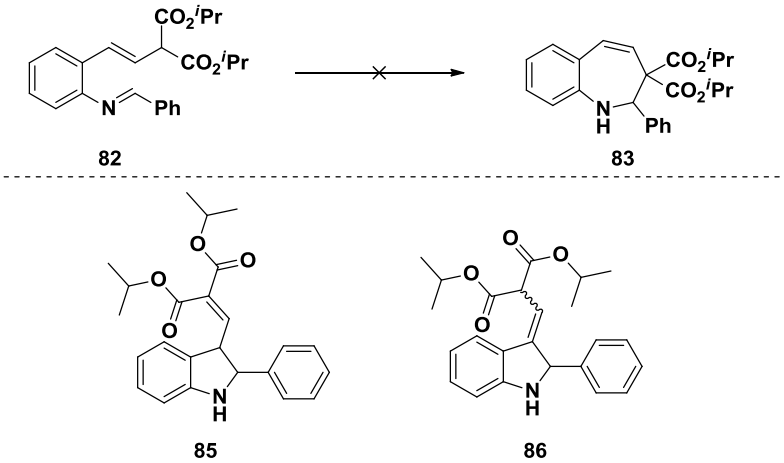


This compound was prepared according to a literature procedure.[67] LDA was prepared *in situ* by the dropwise addition of *n*-butyllithium (1.55 M in hexanes, 295 μL, 0.45 mmol) to a stirred solution of diisopropylamine (60 μL, 0.45 mmol) in tetrahydrofuran (8 mL) at −40 °C. The solution was cooled to −78 °C and imine **60** (100 mg, 0.42 mmol) in tetrahydrofuran (1 mL) was added

* *Note that one of the expected aromatic CH peaks in the ^{13}C spectrum was not observed.*

dropwise over 30 min. The resulting mixture was stirred for a further 1 h, then warmed to 0 °C and stirred for a further 30 min. The reaction mixture poured into saturated sodium bicarbonate solution (20 mL) and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 10:1) to afford racemic *trans*-4-methyl-3-phenyl-4,5-dihydro-3*H*-benzo[*c*]azepine **67** (38 mg, 38%) as a pale yellow oil. *Data is consistent with that reported in the literature.*[67] δ_H (400 MHz, $CDCl_3$): 8.65 (1H, d, *J* 2.1, H6), 7.42−7.32 (7H, m, 7 x Ar CH), 7.30−7.24 (2H, m, 2 x Ar CH), 3.63 (1H, dd, *J* 11.0, 2.1, H5), 3.01 (1H, dd, *J* 13.5, 7.4, H13), 2.86 (1H, m, H14), 2.42 (1H, dd, *J* 13.5, H13'), 0.86 (3H, d, *J* 6.8, H15). δ_C (101 MHz, $CDCl_3$): 163.1 (C6), 143.7 (C12), 138.2 (C4), 135.1 (C7), 129.8 (Ar CH), 129.73 (Ar CH), 128.3 & 128.3 (C2 & C3), 127.5 (Ar CH), 126.9 (Ar CH), 126.6 (Ar CH), 71.7 (C5), 48.2 (C14), 38.4 (C13), 17.6 (C15). ν_{max} (film): 3062, 3028, 2957, 2927, 2868, 1647, 1619 (C=N), 1453, 701, 664 cm^{-1}.

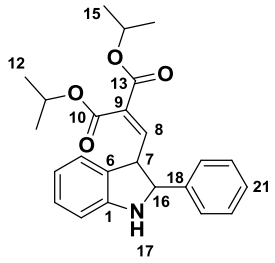
Attempted formation of diisopropyl 2-phenyl-1*H*-benzo[*b*]azepine-3,3(2*H*)-dicarboxylate (83)



Scandium(III) triflate (13 mg, 0.025 mmol) was added in one portion to a stirred RT solution of imine **82** (100 mg, 0.25 mmol) in tetrahydrofuran (2.5 mL). After 16 h complete consumption of the imine was apparent by TLC. The reaction mixture was concentrated *in vacuo* and purified

by flash column chromatography (silica gel, petrol:ethyl acetate, 20:1 → 10:1) to afford **85** (42 mg, 42%, 3:1 dr) as a pale yellow oil and **86** (18 mg, 18%) as bright yellow oil.

*(±)-Diisopropyl 2-((2-phenylindolin-3-yl)methylene)malonate (**85**)*



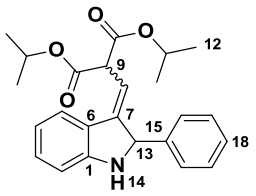
This compound was obtained as an inseparable mixture of diastereomers even after multiple attempts to separate by column chromatography. Complete ^{1}H and ^{13}C spectral assignment of the aromatic region was therefore not possible.

Selected NMR Data: Major diastereomer. δ_H (d_8-toluene, 500 MHz): 7.18 (1H, d, *J* 10.3, H8), 6.68 (1H, td, *J* 7.4, 0.9, H4), 6.44 (1H, d, *J* 7.8, H2), 5.02 (1H, septet, *J* 6.3, H11/H14), 4.92 (1H, septet, *J* 6.2, H11/H14), 4.34−4.27 (2H, m, H7 & H16), 3.40 (1H, br s, H17), 1.05 (3H, d, *J* 6.3, H12/H15), 1.03 (3H, d, *J* 6.3, H12/H15), 0.99 (3H, d, *J* 6.3, H12/H15), 0.85 (3H, d, *J* 6.3, H12/H15). δ_C (d8-PhMe, 126 MHz): 164.5 (C10/C13), 163.3 (C10/C13), 151.0 (C1), 145.4 (C8), 119.5 (C4), 109.3 (C2), 69.8 (C16), 68.9 (C11/C14), 68.8 (C11/C14), 53.3 (C7), 21.5(9) (C12/C15), 21.5(6) (C12/C15), 21.4(6) (C12/C15), 21.4 (C12/C15).

Selected NMR Data: Minor diastereomer. δ_H (d_8-toluene, 500 MHz): 6.76 (1H, d, *J* 11.2, H8), 6.68 (1H, td, *J* 7.4, 1.0, H4), 6.47 (1H, d, *J* 7.8, H2), 5.19 (1H, septet, *J* 6.3, H11/H14), 4.80 (1H, d, *J* 9.0, H16), 4.79 (1H, septet, *J* 6.3, H11/H14), 4.65 (1H, dd, *J* 11.1, 8.8, H7), 3.40 (1H, br s, H17), 1.17 (6H, app. T, *J* 6.2, H12/H15), 0.89 (3H, d, *J* 6.2, H12/H16), 0.85 (3H, d, *J* 6.2, H12/H16). δ_C (d8-PhMe, 126 MHz): 165.0 (C10/C13), 162.9 (C10/C13), 151.4 (C1), 145.3 (C8), 119.6 (C4), 109.3 (C2), 68.6 (C11/C14), 68.3 (C11/C14), 67.5 (C16), 47.9 (C7), 21.7 (C12/C15), 21.4 (C12/C15), 21.4 (C12/C15).

The following data was obtained for the mixture of diastereomers: HRMS (ESI): found 394.1999; $C_{24}H_{28}NO_4$ $[M+H]^+$ requires 394.2013. ν_{max} (film): 3368 (NH), 3056 (CH), 2981 (CH), 2934 (CH), 1714 (C=O), 1605, 1274, 1107, 751 cm^{-1}.

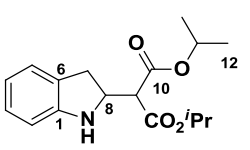
*(±)- (E)-Diisopropyl 2-((2-phenylindolin-3-ylidene)methyl)malonate (**86**)*



*This compound was obtained only in ~80% purity,[*] with isomer **85** as the main contaminant.*

δ_H (500 MHz, C_6D_6): 7.37 (1H, d, *J* 7.3, H5), 7.29−7.09 (6H, m, H3, H16, H17, H18), 6.77−6.72 (2H, m, H4 & H8), 6.42 (1H, d, *J* 7.9, H2), 5.45 (1H, d, *J* 2.8, H13), 5.12 (1H, septet, *J* 6.0, H11), 4.91 (1H, septet, *J* 6.3, H11'), 4.40 (1H, d, *J* 9.8, H9), 3.44 (1H, br s, H14), 1.11 (6H, d, *J* 6.3, H12), 1.03 (3H, d, *J* 6.3, H12), 0.92 (3H, d, *J* 6.3, H12). δ_C (400 MHz, $CDCl_3$):[†] 167.6 (C10), 167.1 (C10'), 152.9 (C1), 146.8 (C7), 142.7 (C6), 130.5 (C18), 129.1 (C16/C17), 127.9 (C16/C17), 126.8 (C15), 121.4 (C5), 119.0 (C4), 110.5 (C8), 110.2 (C2), 69.2 (C11), 68.6 (C11'), 65.0 (C13), 52.8 (C9), 21.5(2) (C12), 21.5(0) (C12), 21.4(2) (C12), 21.3(6) (C12). ν_{max} (film): 3306 (NH), 3059 (CH), 2980 (CH), 2926 (CH), 1723 (C=O), 1626, 1580, 1258, 1099, 744, 698 cm^{-1}. HRMS (ESI): found 394.2020; $C_{24}H_{28}NO_4$ $[M+H]^+$ requires 394.2013.

*(±)-Diisopropyl 2-(indolin-2-yl)malonate (**84**)*



[*] *Determined by ^1H NMR analysis of the sample after column chromatography.*
[†] *The ^{13}C peak corresponding to C3 was not observed, and is presumed to co-incide with the residual solvent peaks.*

*This compound was formed unintentionally in small quantities during attempts to induce 8π electrocyclization of imine **82** under basic conditions. A pure sample was obtained from aniline **79** by base-catalyzed 1,4-addition as follows:*

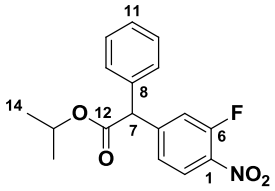
Potassium carbonate (5 mg, 0.04 mmol) was added to a stirred RT solution of aniline **79** (50 mg, 0.16 mmol) in propan-2-ol (2 mL). After 16 h the reaction mixture was diluted with dichloromethane (10 mL) and water (10 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 8:2) to afford diisopropyl 2-(indolin-2-yl)malonate **84** (43 mg, 86%) as a pale yellow oil. δ_H (500 MHz, $CDCl_3$): 7.07 (1H, d, *J* 7.3, H5), 7.02 (1H, t, *J* 7.6, H3), 6.70 (1H, t, *J* 7.3, H4), 6.61 (1H, t, *J* 7.9, H2), 5.13−5.04 (2H, m, H11 & H11'), 4.41 (1H, q, *J* 8.8, H8), 3.50 (1H, d, *J* 8.8, H9), 3.18 (1H, dd, *J* 15.7, 8.9, H7), 2.89 (1H, dd, *J* 15.7, 8.5, H7'), 1.29−1.23 (12H, m, H12). δ_C (126 MHz, $CDCl_3$): 168.1 (C10), 167.3 (C10'), 150.0 (C1), 127.6 (C6), 127. 5 (C5), 124.6 (C3), 118.8 (C4), 109.2 (C2), 69.3 (C11), 69.1 (C11'), 58.2(3) (C9), 58.1(8) (C8), 34.1 (C7), 21.6 (C12), 21.5(5) (C12), 21.5(2) (C12). HRMS (ESI): found 328.1506; $C_{17}H_{23}NNaO_4$ $[M+Na]^+$ requires 328.1519. ν_{max} (film): 3387 (NH), 2981 (CH), 2936 (CH), 1723 (C=O), 1611, 1102, 747 cm^{-1}.

6.1 Cascades

This work was carried out as a collaborative project with a co-worker. Spectral data and synthetic protocols for compounds synthesized exclusively by Dr. Maciver are not duplicated here. For details regarding these compounds, see ref. [111].

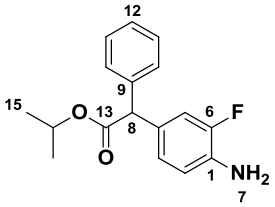
6.1.1 Synthesis of Substrates

(±)-*iso*-Propyl 2-(3-fluoro-4-nitrophenyl)-2-phenylacetate (132)



n-Butyllithium (1.6 M in hexanes, 35.4 mL, 56.6 mmol) was added dropwise to a stirred -78 °C solution of diisopropylamine (8.0 mL, 29 mmol) in tetrahydrofuran (150 mL). The solution was warmed to 0 °C for 15 min then cooled to −78 °C. DMPU (20 mL) was added, then isopropyl phenylacetate **128** (10.0 mL, 57 mmol) was added slowly and the resulting mixture warmed to RT. After 1 h the reaction mixture was cooled to −78 °C and 2-fluoronitrobenzene (2.98 mL, 28.2 mmol) was added dropwise. After 1 h the reaction mixture was allowed to warm to RT and stirred for a further 1 h. Ammonium chloride (aq., 150 mL) was added, and the aqueous layer extracted with dichloromethane (3 x 100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude yellow residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 25:1) to afford nitroarene **132** (3.62 g, 43%) as a pale yellow oil. *Data is consistent with that reported in the literature.*[109] δ_H (500 MHz, $CDCl_3$): 8.02 (1H, app. T, $^3J_{H\text{-}H}$ 8.1, $^4J_{H\text{-}F}$ 8.1, H2), 7.41−7.32 (3H, m, H10 & H11), 7.31−7.23 (4H, m, H3, H5 & H9), 5.10 (1H, septet, *J* 6.3, H13), 5.02 (1H, s, H7), 1.27 (3H, d, *J* 6.3, H14), 1.23 (3H, s, *J* 6.3, H14'). δ_C (126 MHz, $CDCl_3$): 170.3 (C12), 155.4 (d, *J* 265, C6), 147.8 (d, *J* 7.8, C4), 136.8 (C8), 136.7 (d, *J* 19.2, C1), 129.1 (C10), 128.3 (C9), 128.0 (C11), 126.1 (d, *J* 2.4, C2), 124.8 (C3), 118.7 (d, *J* 21.8, C5), 69.6 (C13), 56.7 (C7), 21.7 (C14), 21.5 (C14'). δ_F (470 MHz, $CDCl_3$): -116.5. ν_{max} (neat): 3065 (CH), 2983 (CH), 2937 (CH), 1728 (C=O), 1526 (NO_2), 1349 (NO_2), 1104, 732, 702 cm^{-1}. HRMS (ESI+): found 340.0944; $C_{17}H_{16}FNNaO_4$, $[M+Na]^+$ requires 340.0956.

(±)-*iso*-Propyl 2-(4-amino-3-fluorophenyl)-2-phenylacetate (133)



Palladium on carbon (10 wt%, 0.36 g) was added to a stirred RT solution of nitroarene **132** (3.57 g, 11.9 mmol) in methanol (35 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen (balloon pressure). The resulting mixture was stirred vigorously for 5 h, filtered over Celite® and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) to afford aniline **133** (2.5 g, 78%) as a yellow crystalline solid. δ_H (500 MHz, $CDCl_3$): 7.34−7.24 (5H, m, H10-H12), 6.98 (1H, dd, $^3J_{H\text{-}F}$ 12.2, $^4J_{H\text{-}H}$ 2.0, H5), 6.88 (1H, dd, *J* 8.2, 1.9, H3), 6.73 (1H, dd, $^4J_{H\text{-}F}$ 9.1, $^3J_{H\text{-}H}$ 8.2, H2), 5.08 (1H, septet, *J* 6.3, H14), 4.85 (1H, s, H8), 3.13 (2H, br s, H7), 1.24 (3H, d, *J* 6.2, H15), 1.23 (3H, d, *J* 6.3, H15'). δ_C (126 MHz, $CDCl_3$): 172.0 (C13), 151.5 (d, *J* 239, C6), 138.9 (C9), 133.3 (d, *J* 13.4, C1), 129.6 (d, *J* 6.7, C4), 128.5 (C10/C11), 128.4 (C10/C11), 127.1 (C12), 124.6 (d, *J* 3.0, C3), 116.8 (d, *J* 3.8, C2), 115.6 (d, *J* 20.0, C5), 68.6 (C14), 56.2 (C8), 21.7 (C15), 21.6 (C15'). δ_F (470 MHz, $CDCl_3$): -134.5. ν_{max} (neat): 3458 (NH_2), 3365 (NH_2), 2982 (CH), 1716 (C=O), 1517, 1227, 1175, 1101, 700 cm^{-1}. HRMS (ESI+): found 310.1213; $C_{17}H_{18}NNaO_2$, $[M+Na]^+$ requires 310.1214. MP: 29−31 °C (petrol/diethyl ether).

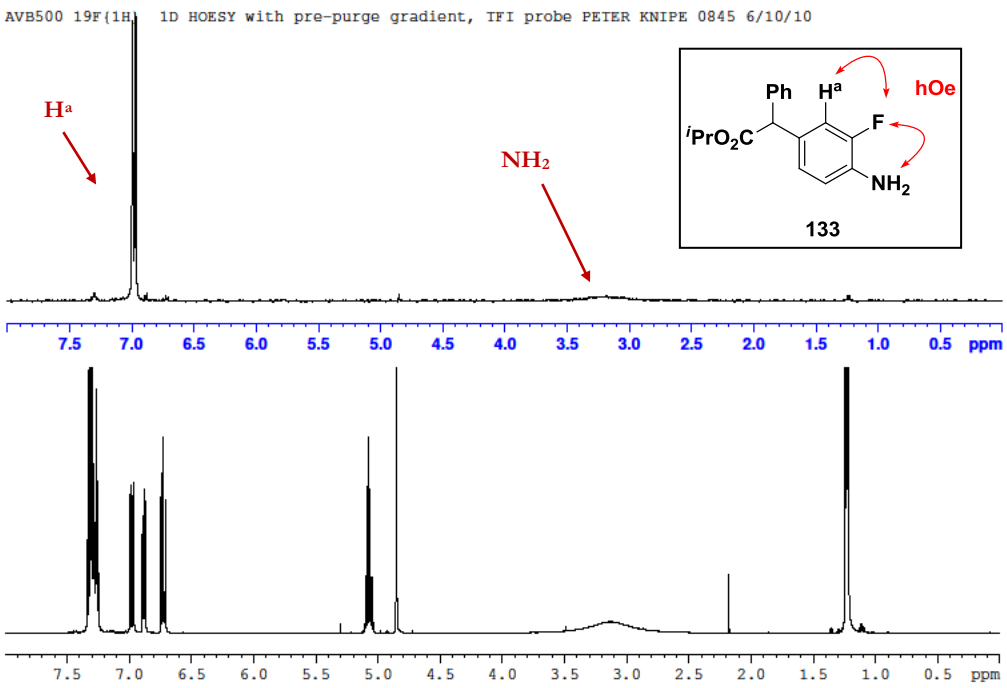
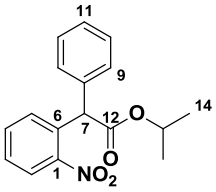


Figure 6.1. 1D hOe analysis of **133** (19F irradiated at −134.54 ppm, mixing time = 1 s).

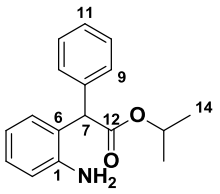
(±)-*iso*-Propyl 2-(2-nitrophenyl)-2-phenylacetate (129)



Sodium hydride (60% dispersion in mineral oil, 1.10 g, 27.5 mmol) was added in three portions over 30 min to a stirred solution of isopropyl-2-phenylacetate (5.0 g, 28 mmol) in *N*,*N*-dimethylformamide (50 mL) at 0 °C. After a further 30 min 2-fluoronitrobenzene (1.95 mL, 18.5 mmol) was added dropwise and the solution allowed to rise to RT. After 16 h the reaction was diluted with diethyl ether (200 mL), ammonium chloride (aq., 50 mL) was added and the organic phase washed with 10% aqueous magnesium sulfate solution (3 x 50 mL). The aqueous washes were extracted with diethyl ether (50 mL) and the combined organic layers dried

over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 50:1) and subsequent recrystallization (petrol/ethyl acetate) to afford nitroarene **129** (2.48 g, 45%) as a white crystalline solid. *Data is consistent with that reported in the literature.*[109] δ_H (400 MHz, $CDCl_3$): 8.03 (1H, dd, *J* 8.0, 1.4, H2), 7.50 (1H, td, *J* 7.6, 1.4, H4), 7.44−7.32 (4H, m, H3, H10, H11), 7.27 (2H, d, *J* 6.6, H9), 7.13 (1H, dd, *J* 7.8, 1.0, H5), 5.63 (1H, s, H7), 5.11 (1H, septet, *J* 6.3, H13), 1.30 (3H, d, *J* 6.1, H14), 1.18 (3H, d, *J* 6.3, H14'). δ_C (101 MHz, $CDCl_3$): 170.8 (C12), 148.9 (C1), 136.8 (C8), 134.2 (C6), 133.1 (C4), 131.6 (C5), 129.2 (C10), 129.0 (C9), 128.1 (C3), 127.8 (C11), 124.8 (C2), 69.2 (C13), 53.4 (C7), 21.7 (C14), 21.4 (C14'). ν_{max} (neat): 2980 (CH), 2360, 1727 (C=O), 1524 (NO_2), 1453 cm^{-1}. HRMS (ESI+): found 322.1049; $C_{17}H_{17}NO_4Na$, $[M+Na]^+$ required 322.1050. MP: 69−74 °C (petrol/ethyl acetate).

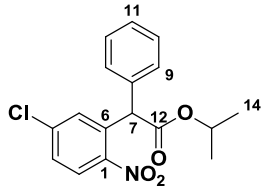
(±)-*iso*-Propyl 2-(2-aminophenyl)-2-phenylacetate (130)



A RT suspension of nitroarene **129** (3.57 g, 11.9 mmol) and palladium on activated carbon (350 mg) in degassed methanol (35 mL) was stirred vigorously under an atmosphere of hydrogen (balloon pressure). After 2.5 h the reaction mixture was filtered over Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) and subsequent recrystallization (diethyl ether/petrol) to afford aniline **130** (2.50 g, 78%) as an off-white crystalline solid. δ_H (300 MHz, $CDCl_3$): 7.29−7.15 (5H, m, H9, H10 & H11), 7.08−7.00 (2H, m, H3 & H5), 6.70 (1H, td, *J* 7.5, 1.1, H4), 6.61 (1H, d, *J* 7.9, H2), 5.03 (1H, septet, *J* 6.3, H13), 4.90 (1H, s, H7), 3.59 (2H, br s, NH_2), 1.17 (6H, t, *J* 6.7, H14). δ_C (75 MHz, $CDCl_3$): 172.1 (C12), 144.6 (C1), 137.1 (C8), 129.3 (C5), 128.8 (C9/C10), 128.6

(C9/C10), 128.4 (C3/C11), 127.4 (C3/C11), 123.5 (C6), 118.9 (C4), 116.8 (C2), 68.8 (C13), 53.5 (C7), 21.8 (C14), 21.7 (C14'). ν_{max} (neat): 3442, 2982, 2935, 1722 (C=O), 1637 (Ar C=C), 1451 cm^{-1}. HRMS (ESI+): found 292.1313; $C_{17}H_{19}NO_2Na$, $[M+Na]^+$ requires 292.1313. MP: 74−78 °C (diethyl ether/petrol).

(±)-*iso*-Propyl 2-(5-chloro-2-nitrophenyl)-2-phenylacetate (134)

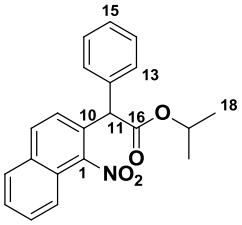


This compound was prepared according to a literature procedure.[109] *Iso*-propyl phenylacetate (2.26 g, 12.7 mmol) in tetrahydrofuran (25 mL) was added to a stirred suspension of potassium *tert*-butoxide (1.42 g, 12.7 mmol) in tetrahydrofuran (100 mL) at −78 °C, and the resulting yellow solution stirred for three minutes. 1-Chloro-4-nitrobenzene (4.00 g, 25.4 mmol) in tetrahydrofuran (25 mL) was added over a period of one minute, and the solution stirred for a further 3 minutes. DDQ (3.45 g, 15.2 mmol) in *N,N*-dimethylformamide (25 mL) was added and the solution stirred for a further 5 minutes before ammonium chloride (aq., 50 mL) was added and the reaction mixture allowed to warm to RT. The crude mixture was poured into water (1 L) and extracted with ethyl acetate (3 x 250 mL), the combined organic extracts washed with brine (250 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.* The resulting crude product was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 50:1) and subsequent recrystallization (ethyl acetate/petrol) to afford nitroarene **134** (2.03 g, 48%) as a white crystalline solid. *Data is consistent with that reported in the literature.*[109] δ_H (400 MHz, $CDCl_3$): 8.02 (1H, d, *J* 8.7, H2), 7.46−7.35 (4H, m), 7.28−7.24 (2H, m), 7.05 (1H, d, *J* 2.2, H5), 5.63 (1H, s, H7), 5.10 (1H, septet, *J* 6.3, H13), 1.29 (3H, d, *J* 6.2, H14), 1.17 (3H, d, *J*

* *The separation of aqueous and organic layers was exceptionally difficult due to their very dark (almost black) colouration. Upon close inspection the organic layer could be distinguished from the aqueous by its slight purple hue.*

6.2, H14'). δ_C (101 MHz, $CDCl_3$): 170.4 (C12), 147.1 (C1), 139.8 (C4), 136.3 & 135.9 (C6 & C8), 131.8 (Ar CH) 129.2 & 129.1 (C9 & C10), 128.3 (Ar CH), 128.2 (Ar CH), 126.4 (Ar CH), 69.5 (C13), 53.5 (C7), 21.7 (C14), 21.4 (C14'). HRMS (ESI+): found 356.0652; $C_{17}H_{16}{}^{35}ClNO_4Na$, $[M(^{35}Cl)+Na]^+$ requires 326.0660. ν_{max} (neat): 2981, 1731 (C=O), 1516 (NO_2) 1339 (NO_2), 1106, 713 cm^{-1}. MP: 94−99 °C (ethyl acetate/petrol).

(±)-*iso*-Propyl 2-(1-nitronaphthalen-2-yl)-2-phenylacetate (135)

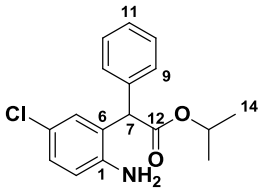


This compound was prepared according to a literature procedure.[109] *Iso*-propyl phenylacetate (2.26 g, 12.7 mmol) in tetrahydrofuran (25 mL) was added to a stirred suspension of potassium *tert*-butoxide (1.42 g, 12.7 mmol) in tetrahydrofuran (100 mL) at −78 °C, and the resulting yellow solution stirred for three minutes. 1-Nitronaphthalene (4.32 g, 25.4 mmol) in tetrahydrofuran (25 mL) was added over a period of one minute, and the solution stirred for a further 3 minutes. DDQ (3.45 g, 15.2 mmol) in *N,N*-dimethylformamide (25 mL) was added and the solution stirred for a further 5 minutes before ammonium chloride (aq., 50 mL) was added and the reaction mixture was allowed to warm to RT. The crude mixture was poured into water (1 L) and extracted with ethyl acetate (3 x 250 mL), the combined organic extracts washed with brine (250 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.*[*] The resulting crude product was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 35:1) and subsequent recrystallization (ethyl acetate/petrol) to afford nitroarene **135** (1.76 g, 40%) as a pale pink crystalline solid. *Data is consistent with that reported in the literature.*[109] δ_H

[*] *The separation of aqueous and organic layers was exceptionally difficult due to their very dark (almost black) colouration. Upon close inspection the organic layer could be distinguished from the aqueous by its slight purple hue.*

(500 MHz, $CDCl_3$): 7.90 (1H, d, *J* 8.8, H8), 7.87 (1H, d, *J* 8.0, H6), 7.76 (1H, d, *J* 8.4, H3), 7.63 (1H, t, *J* 7.6, H4), 7.58 (1H, t, *J* 7.5, H5), 7.52 (1H, d, *J* 8.5, H9), 7.30−7.40 (5H, m, H13, H14 & H15), 5.23 (1H, s, H11), 5.14 (1H, sept, *J* 6.3, H17), 1.28 (3H, d, *J* 6.3, H18), 1.26 (3H, d, *J* 6.3, H18'). δ_C (126 MHz, $CDCl_3$): 170.3 (C16), 147.6 (C1), 137.0 (C10), 132.8 (C7), 130.5 (C8), 128.9 (C14), 128.7 (C4), 128.4 (C13), 128.1 (C12), 128.0 (C6), 127.7 (C15), 127.5 (C5), 126.4 (C9), 124.2 (C2), 121.8 (C3), 69.5 (C17), 51.8 (C11), 21.6 & 21.6 (C18 & C18'). ν_{max} (neat): 3028, 2985, 1716 (C=O), 1497 (NO_2), 1289 (NO_2), 1239, 1097, 748, 697 cm^{-1}. HRMS (ESI+): found 372.1198; $C_{21}H_{19}NO_4Na$, $[M+Na]^+$ requires 372.1206. MP: 152−159 °C (ethyl acetate/petrol).

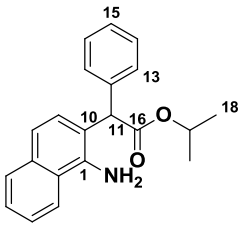
(±)-*iso*-Propyl 2-(2-amino-5-chlorophenyl)-2-phenylacetate (136)



This compound was prepared by analogy to a literature procedure.[82] Zinc dust (2.43 g, 37.1 mmol) and ammonium chloride (2.93 g, 54.8 mmol) were added to a stirred RT solution of nitroarene **134** (1.25 g, 3.75 mmol) in 5:1 acetone:water (100 mL). After 10 minutes the heterogeneous reaction mixture was filtered over Celite®, and diluted with ethyl acetate (100 mL). The crude mixture was washed with water (100 mL) and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by recrystallization (ethyl acetate/petrol) to afford aniline **136** (888 mg, 78%) as a pale yellow crystalline solid. δ_H (400 MHz, $CDCl_3$): 7.39−7.26 (5H, m, H9, H10 &H11), 7.13 (1H, s, H5), 7.08 (1H, d, *J* 8.4, H3), 6.62 (1H, d, *J* 8.6, H2), 5.12 (1H, sept, *J* 6.1, H13), 4.93 (1H, s, H7), 3.80 (2H, br s, NH_2), 1.29−1.24 (6H, m, H14). δ_C (101 MHz, $CDCl_3$): 171.5 (C12), 143.3 (C1), 136.3 (C8), 129.1 (C5), 128.8 & 128.7 (C9 & C10), 128.2 (C3), 127.7 (C11), 124.9 (C6), 123.5 (C4), 117.8 (C2), 69.1

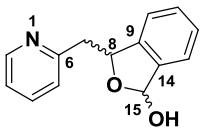
(C13), 53.4 (C7), 21.7 & 21.6 (C14 & C14'). HRMS (ESI+): found 326.0906; $C_{17}H_{18}{}^{35}ClNO_2Na$, $[M(^{35}Cl)+Na]^+$ requires 326.0918. ν_{max} (neat): 3477 (N-H), 3374 (N-H), 2983, 2932, 1720 (C=O), 1493, 1201, 1093, 813, 698 cm^{-1}. MP: 118−121 °C (ethyl acetate/petrol).

(±)-*iso*-Propyl 2-(1-aminonaphthalen-2-yl)-2-phenylacetate (137)



This compound was prepared by analogy to a literature procedure.[82] Zinc dust (1.89 g, 29.1 mmol) and ammonium chloride (2.28 g, 43.0 mmol) were added to a stirred RT solution of nitroarene **135** (1.00 g, 2.87 mmol) in 5:1 acetone:water (60 mL). After 10 minutes the heterogeneous reaction mixture was filtered over Celite®, and diluted with ethyl acetate (60 mL). The crude mixture was washed with water (60 mL) and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 15:1) to afford aniline **137** (633 mg, 69%) as a white solid. δ_H (400 MHz, $CDCl_3$): 7.82−7.77 (2H, m, H3 & H6), 7.49−7.43 (2H, m, H4 & H5), 7.38−7.25 (7H, m, H8, H9, H13, H14 & H15), 5.21 (1H, s, H11), 5.15 (1H, sept, *J* 6.1, H17), 4.35 (2H, br s, NH_2), 1.29 (3H, d, *J* 6.3, H18), 1.24 (3H, d, *J* 6.2, H18'). δ_C (101 MHz, $CDCl_3$): 172.2 (C16), 140.0 (C1), 137.3 (C12), 133.6 (C7), 128.7 & 128.6 (C13 & C14), 128.5 (C6), 127.5 (Ar CH), 127.3 (Ar CH), 125.8 (Ar CH), 125.1 (Ar CH), 123.9 (C2), 120.6 (C3), 118.5 (C8), 117.0 (C10), 68.9 (C17), 53.9 (C11), 21.8 (C18), 21.7 (C18'). HRMS (ESI+): found 320.1641; $C_{21}H_{22}NO_2$, $[M+H]^+$ requires 320.1645. ν_{max} (neat): 3481 (NH_2), 3397 (NH_2), 3059, 2981, 2930, 1712 (C=O), 1699, 1641, 1198, 1098, 801, 738, 709 cm^{-1}. MP: 109−111 °C.

(±)-3-(Pyridin-2-ylmethyl)-1,3-dihydroisobenzofuran-1-ol (144)



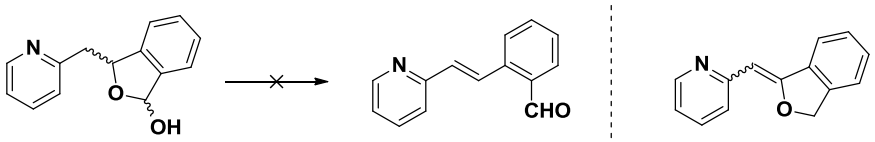
This compound was prepared by analogy to a literature procedure.[203] 2-Picoline (3.7 mL 37 mmol) was added slowly to a stirred −50 °C solution of *n*-butyllithium (1.6 M in hexanes, 24 mL, 39 mmol) in tetrahydrofuran (200 mL) and the temperature was raised to −20 °C for 5 min before cooling back to −50 °C. This solution was then added *via* insulated cannula to a separate flask containing phthaldialdehyde (5.49 g, 41 mmol) in tetrahydrofuran (50 mL) at −50 °C. The reaction was raised to −20 °C and stirred for 2 hours, then warmed to RT and stirred for a further hour. Sodium bicarbonate (aq., 100 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude solid residue was purified by flash column chromatography (silica gel, methanol:chloroform, 3:97) to afford hemi-acetal **144** (6.89 g, 82%) as a yellow crystalline solid, and an inseparable 5:4 mixture of diastereoisomers.

Selected NMR Data – Major diastereomer. δ_H (400 MHz, $CDCl_3$): 8.52 (1H, dq, *J* 5.0, 0.8, H2), 6.40 (1H, s, H15), 5.51 (1H, dd, *J* 8.6, 3.5, H8). δ_C (101 MHz, $CDCl_3$): 148.8 (C2), 101.2 (C15), 82.1 (C8), 45.5 (C7).

Selected NMR Data - Minor diastereoisomer. δ_H (400 MHz, $CDCl_3$): 8.49 (1H, dq, *J* 4.8, 0.8, H2), 6.49 (1H, s, H15), 5.62 (1H, dd, *J* 9.4, 3.7, H8). δ_C (101 MHz, $CDCl_3$): 149.0 (C2), 100.7 (C15), 81.9 (C8), 44.9 (C7).

HRMS (ESI+): found 250.0842; $C_{14}H_{13}NNaO_2$, $[M+Na]^+$ requires 250.0838. ν_{max} (neat): 3140 (OH), 3073 (CH), 3048 (CH), 2871, 1595 (C=N), 1568 (C=N), 1477, 1459, 1034, 755 cm^{-1}. MP: 95−100 °C (chloroform).

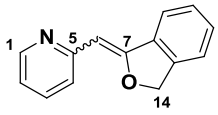
Attempted formation of (*E*)-2-(2-(pyridin-2-yl)vinyl)benzaldehyde (143)



144 **143** **145**

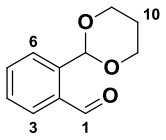
Trifluoroacetic acid (1.68 mL, 22 mmol) was added to a stirred RT solution of hemi-acetal **144** (500 mg, 2.20 mmol) in dichloromethane (25 mL). After 3 h sodium bicarbonate (aq., 25 mL) was added and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, 98:2, dichloromethane:methanol) to afford **145** (320 mg, 70%) as a yellow crystalline solid.

*2-(Isobenzofuran-1(3H)-ylidenemethyl)pyridine (**145**)*



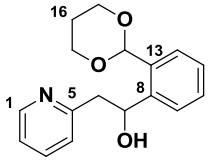
The data obtained is consistent with that reported in the literature.[204] δ_H (400 MHz, $CDCl_3$): 8.56 (1H, d, *J* 5.6, H1), 8.47 (1H, d, *J* 8.5, H4), 8.09 (1H, t, *J* 8.1, H3), 7.88 (1H, d, *J* 7.3, H9), 7.54 (1H, td, *J* 7.2, 1.1, H11), 7.49 (1H, td, *J* 7.4, 0.8, H10), 7.44 (1H, d, *J* 7.4, H12), 7.34 (1H, ddd, *J* 7.1, 6.2, 0.9, H2), 6.78 (1H, s, H6), 5.67 (2H, s, H14). δ_C (101 MHz, $CDCl_3$): 167.1 (C7), 151.2 (C5), 143.0 (C3), 140.8 (C8), 140.2 (C1), 132.4 (C13), 131.9 (C11), 129.2 (C10), 124.8 (C4), 122.7 (C9), 121.2 (C12), 120.1 (C2), 88.0 (C6), 77.2 (C14). ν_{max} (neat): 3052 (CH), 2445, 1752, 1676, 1185, 1122, 1053, 768 716 cm^{-1}. MP: 110−116 °C (dichloromethane).

2-(1,3-Dioxan-2-yl)benzaldehyde (146)



This compound was prepared according to a literature procedure.[205] A solution of *2*-phthalaldehyde (5.57g, 41 mmol), propane-1,3-diol (3.0 mL, 42 mmol) and *para*-toluenesulfonic acid monohydrate (78 mg, 0.41 mmol) in toluene (50 mL) was heated for 6 hours under reflux with azeotropic removal of water *via* a Dean-Stark apparatus. The mixture was allowed to cool and sodium carbonate (aq., 3 mL) and water (30 mL) were added. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 8.5:1.5) to afford 2-(1,3-dioxan-2-yl)benzaldehyde **146** (6.80 g, 85%) as a pale yellow oil. *Data is consistent with that reported in the literature.*[206] δ_H (400 MHz, $CDCl_3$): 10.53 (1H, s, *H1*), 7.92 (1H, dd, *J* 7.7, 1.2, *H6*), 7.69 (1H, d, *J* 7.4, *H3*), 7.59 (1H, td, *J* 7.5, 1.3, *H4*), 7.49 (1H, t, *J* 7.5, *H5*), 6.02 (1H, s, *H8*), 4.28 (2H, dd, *J* 10.8, 5.0, *H9*), 4.04 (1H, td, *J* 12.4, 2.4, *H9'*), 2.33−2.20 (1H, m, *H10*), 1.49 (1H, d, *J* 13.6). δ_C (101 MHz, $CDCl_3$): 192.32 (*C1*), 139.64 (*C7*), 133.78 (*C2*), 133.54 (*C4*), 129.72 (*C6*), 129.23 (*C5*), 127.25 (*C3*), 100.14 (*C8*), 67.66 (*C9*), 25.65 (*C10*). HRMS (ESI+): found 215.0682; $C_{11}H_{12}NaO_3$, $[M+Na]^+$ requires 215.0679. ν_{max} (neat): 2967 (CH), 2857 (CH), 1690 (C=O), 1601, 1377, 1091, 988, 760 cm^{-1}.

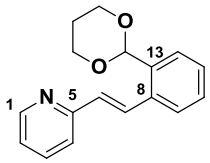
(±)-1-(2-(1,3-Dioxan-2-yl)phenyl)-2-(pyridin-2-yl)ethanol (147)



This compound was prepared by analogy to a literature procedure.[203] 2-Picoline (0.47 mL, 4.7 mmol) was added dropwise to a stirred solution of *n*-butyllithium (3.1 mL, 1.6 M in hexanes, 5.0 mmol)

in tetrahydrofuran (25 mL) at −50 °C. The temperature was raised to −20 °C for 5 minutes, and cooled to −50 °C. This cooled solution was then added *via* insulated cannula to a separate reaction vessel containing 2-(1,3-dioxan-2-yl)benzaldehyde **146** (1.0 g, 5.2 mmol) in tetrahydrofuran (10 mL) at −50 °C. The reaction mixture was warmed to -20 °C and after 2 h was warmed to RT and stirred for a further hour. Sodium bicarbonate solution (50 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 25 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, dichloromethane:methanol, 97:3) to afford 1-(2-(1,3-dioxan-2-yl)phenyl)-2-(pyridin-2-yl)ethanol **147** (1.01 g, 75%) as a grey crystalline solid. δ_H (400 MHz, $CDCl_3$): 8.56 (1H, d, *J* 4.2, *H1*), 7.68−7.59 (3H, m, *H3, H9* & *H12*), 7.37 (1H, td, *J* 7.5, 1.2, *H11*), 7.30 (1H, td, *J* 7.5, 1.1, *H10*), 7.18 (1H, dd, *J* 7.5, 5.0, *H2*), 7.10 (1H, d, *J* 7.7, *H4*), 5.74 (1H, s, *H14*), 5.54 (1H, dd, *J* 9.2, 3.0, *H7*), 5.45 (1H, br s, *H17*), 4.30−4.18 (1H, m, *H15*), 4.01−3.90 (2H, m, *H15'*), 3.22 (1H, dd, *J* 14.7, 3.0, *H6*), 3.13 (1H, dd, *J* 14.8, 9.2, *H6'*), 2.27−2.14 (1H, m, *H16*), 1.42 (1H, dq, *J* 13.4, 1.2). δ_C (101 MHz, $CDCl_3$): 160.29 (*C5*), 148.71 (*C1*), 141.77 (*C8*), 136.80 (*C3*), 134.81 (*C13*), 129.10 (*C11*), 127.27 (*C10*), 126.30 & 126.05 (*C9* & *C12*), 123.61 (*C4*), 121.62 (*C2*), 100.04 (*C14*), 69.45 (*C7*), 67.49 & 67.33 (*C15* & *C15'*), 45.44 (*C6*), 25.68 (*C16*). HRMS (ESI+): found 308.1254; $C_{17}H_{19}NNaO_3$, $[M+Na]^+$ requires 308.1257. ν_{max} (neat): 3342 (OH), 2939 (CH), 2853 (CH), 1598 (C=N), 1571 (C=N), 1110, 1010, 757 cm^{-1}. MP: 89−92 °C (dichloromethane).

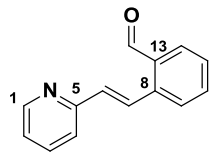
(*E*)-2-(2-(1,3-Dioxan-2-yl)styryl)pyridine (148)



This compound was prepared by analogy to a literature procedure.[203] A solution of secondary alcohol **147** (4.0 g, 14 mmol), methanesulfonyl chloride (2.16 mL, 28 mmol) and pyridine (11.2 mL,

140 mmol) were heated to 80 °C for 16 h. The volatiles were removed *in vacuo* and the remaining residue was dissolved in diethyl ether (100 mL), washed with sodium bicarbonate (aq., 50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, dichloromethane:methanol, 200:1) to afford styrene **148** (3.10 g, 83%) as a brown oil. δ_H (400 MHz, $CDCl_3$): 8.62 (1H, d, *J* 4.1, H2), 8.05 (1H, d, *J* 15.9, H8), 7.70−7.64 (3H, m, H4 & 2 x Ar CH), 7.41 (1H, d, *J* 7.8, H5), 7.39−7.30 (2H, m, 2 x Ar CH), 7.15 (1H, dd, *J* 6.7, 5.2, H3), 7.08 (1H, d, *J* 16.0, H7), 5.82 (1H, s, H15), 4.30 (2H, dd, *J* 11.0, 4.8, H16), 4.06 (2H, dd, *J* 12.2, 1.1, H16'), 2.29 (1H, tdt, *J* 12.6, 12.5, 5.3, H17), 1.47 (1H, d, *J* 13.5, H17'). δ_C (101 MHz, $CDCl_3$): 155.9 (C6), 149.7 (C2), 136.5 (C4), 136.2 (C9), 135.1 (C14), 130.4 (C7), 130.0 (C8), 129.0 (Ar CH), 128.2 (Ar CH), 126.5 (Ar CH), 126.3 (Ar CH), 122.1 (C3), 122.0 (C5), 100.1 (C15), 67.5 (C16), 25.8 (C17). HRMS (ESI+): found 290.1152; $C_{17}H_{17}NNaO_2$, $[M+Na]^+$ requires 290.1151. ν_{max} (neat): 3054 (CH), 2966 (CH), 2852 (CH), 1584 (C=N), 1562 (C=N), 1485, 1106, 987, 775, 742 cm^{-1}.

(*E*)-2-(2-(Pyridin-2-yl)vinyl)benzaldehyde (143)



Method I

This reaction was attempted by analogy to a literature procedure.[112] Acetic anhydride (0.70 mL, 7.4 mmol) was added to a stirred mixture of 2-picoline (0.37 mL, 3.7 mmol) and phthaldialdehyde (500 mg, 3.7 mmol) and the reaction mixture was heated to reflux. After 12 h the reaction was allowed to cool to RT and crushed ice was added. Sodium hydroxide solution (10% aq.) was added dropwise with stirring until the reaction mixture reached pH 8. The

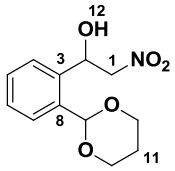
aqueous layer was extracted with dichloromethane (3 x 10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Attempts to purify the crude material by flash column chromatography (silica gel, petrol:diethyl ether, 8.5:1.5) were unsuccessful. *The desired product* ***143*** *was observed as a minor component of the crude product* ^{1}H *NMR spectrum by its characteristic peaks at 10.39, 8.63 and 8.47 ppm (*vide infra*), but could not be obtained in pure form.*

Method II

Hydrochloric acid (2 *N* aq., 20 mL) was added dropwise to a stirred RT solution of (*E*)-2-(2-(1,3-dioxan-2-yl)styryl)pyridine **148** (487 mg, 1.82 mmol) in tetrahydrofuran (40 mL). After 2 h sodium bicarbonate was added to neutralize the solution, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 3:1) to afford (*E*)-2-(2-(pyridin-2-yl)vinyl)benzaldehyde **143** (370 mg, 97%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$): 10.39 (1H, s, *H14*), 8.63 (1H, dq, *J* 4.8, 0.8, H1), 8.47 (1H, d, *J* 16.0, H7), 7.87 (1H, dd, *J* 7.7, 1.3, H12), 7.76 (1H, d, *J* 7.8, H9), 7.69 (1H, td, *J* 7.7, 1.8, H3), 7.60 (1H, td, *J* 7.6, 1.2, H10), 7.52−7.45 (2H, m, H4 & H11), 7.19 (1H, ddd, *J* 7.5, 4.8, 1.1, *H2*), 7.13 (1H, d, *J* 16.0, H6). δ_C (101 MHz, $CDCl_3$):[*] 192.38 (C14), 155.16 (C5), 149.75 (C1), 139.29 (C8), 136.64 (C3), 133.31 (C6), 131.77 (C12), 128.76 (C7), 128.25 (C11), 127.47 (C9), 122.63 (C2), 122.20 (C4). HRMS (ESI+): found 232.0737; $C_{14}H_{11}NNaO$, $[M+Na]^+$ requires 232.0733. ν_{max} (neat): 3061 (CH), 2859 (CH), 2741 (RC(O)-H), 1691 (C=O), 1584 (C=N), 1566 (C=N), 990, 773, 740 cm^{-1}.

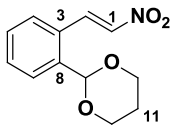
(±)-1-(2-(1,3-Dioxan-2-yl)phenyl)-2-nitroethanol (149)

[*] *The peak corresponding to* C13 *is not observed, presumably due to its co-incidence with another peak in the* ^{13}C *spectrum.*



This compound was prepared by analogy to a literature procedure.[207] Potassium hydroxide (1.75 g, 31 mmol) in water (10 mL) was added in one portion to a stirred solution of aldehyde **146** (4.0 g, 20.8 mmol) and nitromethane (3.36 mL, 62.4 mmol) in tetrahydrofuran (50 mL) and methanol (25 mL), fitted with a large stirrer bar. The resulting solution formed a gel which was stirred vigorously for a further 15 min before ammonium chloride (aq., 100 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 80 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude crystalline material was purified by recrystallization (ethyl acetate/petrol) to afford alcohol **149** (3.13 g, 59%) as a white crystalline solid. δ_H (400 MHz, $CDCl_3$): 7.63 (1H, d, *J* 7.6, H4), 7.47−7.40 (2H, m, H5 & H7), 7.35 (1H, td, *J* 7.5, 1.2, H6), 6.19 (1H, dt, *J* 9.8, 2.8, H2), 5.61 (1H, s, H9), 4.79 (1H, dd, *J* 12.9, 2.2, H1'), 4.55 (1H, dd, *J* 12.9, 9.9, H1), 4.28 (2H, td, *J* 10.8, 5.3, H10), 4.00 (2H, tdd, *J* 12.1, 8.2, 2.5, H10'), 2.94 (1H, d, *J* 3.2, H12), 2.32 (1H, tdt, *J* 13.0, 12.6, 5.0, H11), 1.50 (1H, d, *J* 13.7, H11'). δ_C (101 MHz, $CDCl_3$): 137.3 (C8), 135.0 (C3), 129.7 (C5), 128.5 (C6), 127.8 (C7), 126.8 (C4), 102.6 (C9), 81.3 (C1), 67.7, 67.6, 67.5 (C2, C10 & C10'), 25.5 (C11). HRMS (ESI+): found 276.0847; $C_{12}H_{15}NNaO_5$, $[M+Na]^+$ requires 276.0842. ν_{max} (neat): 3430 (OH), 2969 (CH), 2936 (CH), 2861 (CH), 1739, 1554 (NO_2), 1348 (NO_2), 1116, 751 cm^{-1}. MP: 125−131 °C (ethyl acetate/petrol).

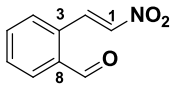
(*E*)-2-(2-(2-Nitrovinyl)phenyl)-1,3-dioxane (150)



This compound was prepared by analogy to a literature procedure.[207] Acetic anhydride (224 μL, 2.36 mmol) and DMAP (39 mg, 0.32 mmol) were added to a stirred 0 °C solution of alcohol **149**

(400 mg, 1.60 mmol) in pyridine (40 mL). After 30 min sodium bicarbonate (aq., 50 mL) was added and the aqueous layer extracted with dichloromethane (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 8:1) to afford styrene **150** (331 mg, 88%) as a grey crystalline solid and a single stereoisomer. δ_H (400 MHz, $CDCl_3$): 8.75 (1H, d, *J* 13.7, H2), 7.60 (1H, d, *J* 7.6, H4), 7.56 (1H, d, *J* 7.7, H7), 7.52−7.45 (2H, m, H1 & H5), 7.40 (1H, t, *J* 7.5, H6), 5.66 (1H, s, H9)< 4.32 (2H, dd, *J* 11.5, 4.6, H10), 4.03 (2H, t, *J* 12.1, H10'), 2.34 (1H, qt, *J* 12.6, 5.3, H11), 1.52 (1H, d, *J* 13.7, H11'). δ_C (101 MHz, $CDCl_3$): 138.4 (C3), 137.6 & 137.5 (C1 & C2), 131.5 (C5), 129.5 (C6), 128.6 (C8), 128.1 (C4), 127.6 (C7), 101.3 (C9), 67.7 (C10), 25.6 (C11). HRMS (ESI+): found 258.0740; $C_{12}H_{13}NNaO_4$, $[M+Na]^+$ requires 258.0737. ν_{max} (neat): 2973 (CH), 2859 (CH), 1635, 1505 (NO_2), 1336 (NO_2), 1106, 1089, 958, 765 cm^{-1}. MP: 66−69 °C (petrol/ethyl acetate).

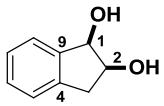
(*E*)-2-(2-Nitrovinyl)benzaldehyde (151)



Hydrochloric acid (2M aq., 12 mL, 24 mmol) was added to a stirred solution of acetal **150** (610 mg, 2.60 mmol) in tetrahydrofuran (40 mL) and warmed to 60 °C. After 1 h the reaction was quenched cautiously with sodium bicarbonate (aq., 20 mL) and the aqueous layer was extracted with dichloromethane (3 x 20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The solid residue was purified by recrystallization (ethyl acetate/petrol) to afford aldehyde **151** (331 mg, 71%) as a white crystalline solid. *Data is consistent with that reported in the literature.*[208] δ_H (400 MHz, $CDCl_3$): 10.20 (1H, s, H9), 8.95 (1H, d, *J* 13.6, H2), 7.94 (1H, d, *J* 7.3, H7), 7.71 (2H, app. pentet, *J* 7.0, H5 & H6), 7.63 (1H, d, *J* 7.3, H4), 7.48 (1H, d, *J* 13.6, H1). δ_C (101 MHz, $CDCl_3$): 192.2 (C9), 139.7 (C1), 136.7 (C2), 134.8 (C7), 134.4 (C3), 134.1 (C5), 131.6 (C6), 131.0 (C8), 128.6 (C4). HRMS (ESI+): found 377.0742;

$C_{18}H_{14}N_2NaO_6$, $[2M+Na]^+$ requires 377.0744. ν_{max} (neat): 3102 (CH), 2977 (CH), 1684 (C=O), 1550 (NO_2), 1343 (NO_2), 1197, 965, 760 cm^{-1}. MP: 90−94 °C (ethyl acetate/petrol).

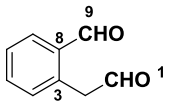
(±)-2,3-Dihydro-1*H*-indene-1,2-diol (153)



This compound was prepared according to a literature procedure.[115] Indene (2.5 mL, 22 mmol), sodium metaperiodate (1.38 g, 6.48 mmol) and lithium bromide (375 mg, 4.32 mmol) were dissolved in acetic acid (30 mL) and heated to reflux for 18 h. Water (100 mL) was added to the purple solution, and the aqueous layer extracted with ethyl acetate (3 x 100 mL). The combined organic layers washed with sodium thiosulfate solution (aq., 50 mL), water (50 mL) and sodium bicarbonate solution (aq., 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude intermediate was dissolved in methanol (150 mL), Potassium carbonate (4.46 g, 32.3 mmol) was added and the mixture stirred for 24 h. The solvent was removed *in vacuo*, water (50 mL) was added and the aqueous layer was extracted exhaustively with 3:1 chloroform:*iso*-propanol (5 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, dichloromethane:methanol, 97:3) to afford the *syn* diol **153** (1.50 g, 46%) as a white amorphous solid. *Data is consistent with that reported in the literature.* [115] δ_H (300 MHz, $CDCl_3$): 7.44−7.36 (1H, m, Ar-H), 7.32−7.20 (3H, m, Ar-H), 4.92 (1H, s, H1), 4.46−4.36 (1H, m, H2), 3.17 (1H, br s, OH), 3.14−2.99 (2H, m, H3 & OH), 2.92 (1H, dd, *J* 16.3, 3.6, H3'). δ_C (126 MHz, $CDCl_3$): 142.0 (C4/C9), 140.2 (C4/C9), 128.8 (C5/C6/C7/C8), 127.2 (C5/C6/C7/C8), 125.3 (C5/C6/C7/C8), 125.0 (C5/C6/C7/C8), 76.0 (C1), 73.5 (C2), 38.5 (C3). HRMS (ESI+): found 173.0573; $C_9H_{10}O_2Na$ $[M+Na]^+$ requires

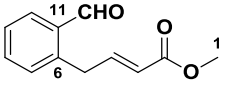
173.0573. ν_{max} (neat): 3418 (br), 1642. MP: 100−105 °C (dichloromethane). *On a larger scale yields dropped slightly: 20 mL indene (176 mmol) afforded 10.6 g indene-1,2-diol* ***153*** *(71 mmol, 40%).*

Homophthaldialdehyde (154)



This compound was prepared according to a literature procedure.[209] Sodium metaperiodate (1.29 g, 6.0 mmol) in water (50 mL) was added to a stirred RT solution of indene-1,2-diol **153** (750 mg, 5.0 mmol) in tetrahydrofuran (25 mL). After 90 min the tetrahydrofuran was removed *in vacuo* and sodium chloride was added to the aqueous solution until it became saturated. The organic layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and dried *in vacuo*. The solid residue was then dissolved in dichloromethane (100 mL) and anhydrous magnesium sulfate (10 g) was added. The heterogeneous suspension was stirred vigorously for 2 h, then filtered and concentrated *in vacuo* to afford the crude aldehyde **154** (721 mg, quant.) as a pale brown oil. *Product formation was verified by ^{1}H NMR spectroscopy, which was in accordance with literature values.*[210] δ_H (200 MHz, $CDCl_3$): 10.06 (1H, s, H9), 9.81 (1H, t, *J* 1.1, H1), 7.86 (1H, dd, *J* 7.0, 2.0, H7), 7.67−7.50 (2H, m, H5 & H6), 7.27 (1H, dd, *J* 6.5, 2.1, H4), 4.16 (2H, s, H2). *Due to its instability this dialdehyde was generally formed and used immediately as part of a two-step oxidative cleavage-Wittig protocol, vide infra.*

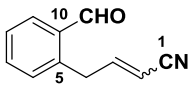
(*E*)-Methyl 4-(2-formylphenyl)but-2-enoate (155)



This compound was prepared by analogy to a literature procedure.[209] Sodium metaperiodate (1.19 g, 5.56 mmol) in water (50 mL) was added to a stirred RT solution of diol **153** (700 mg, 4.67 mmol)

in tetrahydrofuran (25 mL). After 90 min the organic solvent was removed *in vacuo* and the remaining aqueous solution saturated with sodium chloride (~15 g). The aqueous layer was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford crude *iso*-chroman-1,3-diol, which was immediately redissolved in dichloromethane (50 mL) and stirred with anhydrous magnesium sulfate (2.5 g). After 2 h the mixture was filtered and concentrated *in vacuo* to afford crude homophthaldialdehyde **154** (pure by ^{1}H NMR) in quantitative yield. The crude aldehyde was dissolved in dichloromethane (5 mL) and added to a stirred RT solution of methyl triphenylphosphoranylidene acetate (1.57 g, 4.70 mmol) in dichloromethane (5 mL). After 24 h the solvent was removed *in vacuo* and the crude mixture purified by flash column chromatography (silica gel, petrol:diethyl ether, 15:1) to afford aldehyde **155** (686 mg, 72%) as a pale yellow oil. *Data is consistent with that reported in the literature.*[211] δ_H (500 MHz, $CDCl_3$): 10.15 (1H, s, H12), 7.84 (1H, d, *J* 7.6, H7), 7.56 (1H, dd, *J* 7.6, 7.5, H9), 7.47 (1H, t, *J* 7.5, H8), 7.28 (1H, d, *J* 7.6, H10), 7.15 (1H, dt, *J* 15.6, 6.5, H4), 5.73 (1H, d, *J* 15.6, H3), 3.99 (2H, d, *J* 6.5, H5), 3.70 (3H, s, H1). δ_C (126 MHz, $CDCl_3$): 192.5 (C12), 166.7 (C2), 147.0 (C11), 139.6 (C4), 134.0 (C9), 133.8 (C7), 133.7 (C6), 131.4 (C10), 127.5 (C8), 122.2 (C3), 51.5 (C1), 35.3 (C5). ν_{max} (neat): 2734, 2860, 2851, 1723, 1697, 1655, 1600, 1575 cm^{-1}. HRMS (ESI+): found 227.0697; $C_{12}H_{12}O_3Na$, $[M+Na]^+$ requires 227.0679.

4-(2-Formylphenyl)but-2-enenitrile (156)



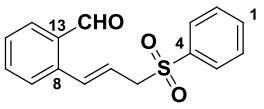
This compound was prepared by analogy to a literature procedure.[209] Sodium metaperiodate (2.55 g, 11.9 mmol) in water (100 mL) was added to a stirred RT solution of diol **153** (1.50 g, 10 mmol) in tetrahydrofuran (50 mL). After 90 min the organic solvent was removed *in vacuo* and the remaining aqueous solution saturated with sodium chloride (~30 g). The aqueous layer was

extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford crude *iso*-chroman-1,3-diol, which was immediately redissolved in dichloromethane (100 mL) and stirred with anhydrous magnesium sulfate (5 g). After 2 h the mixture was filtered and concentrated *in vacuo* to afford crude homophthaldialdehyde **154** (pure by ^{1}H NMR) in quantitative yield. The crude aldehyde was dissolved in dichloromethane (10 mL) and added to a stirred RT solution of triphenylphosphylidene acetonitrile (3.38 g, 11 mmol) in dichloromethane (10 mL). After 24 h the solvent was removed *in vacuo* and the crude mixture purified by flash column chromatography (silica gel, petrol:diethyl ether, 15:1) to afford aldehydes (*E*)-**156** (1.15 g, 67%) and (*Z*)-**156** (192 mg, 11%) as colourless oils.

*(E)-**156***: δ_H (500 MHz, $CDCl_3$): 10.09 (1H, s, H11), 7.84 (1H, dd, *J* 7.5, 1.6, H6), 7.59 (1H, td, *J* 7.5, 1.6, H8) 7.53 (1H, td, *J* 7.5, 1.0, H7), 7.27 (1H, dd, *J* 6.9, 1.6, H9), 6.90 (1H, dt, *J* 16.4, 6.5, H3), 5.25 (1H, dt, *J* 16.4, 1.8, H2), 3.99 (2H, dd, *J* 6.5, 1.8, H4). δ_C (126 MHz, $CDCl_3$): 192.8 (C11), 153.3 (C3), 137.9 (C10), 135.4 (C6), 134.1 (C7), 133.7 (C5), 131.5 (C9), 128.0 (C8), 117.2 (C1), 100.9 (C2), 36.6 (C4). ν_{max} (neat): 3057, 3925, 2859, 2360, 2342, 1697, 1631, 1601 cm^{-1}. HRMS (ESI+): found 194.0575; $C_{11}H_9NONa$, $[M+Na]^+$ requires 194.0576.

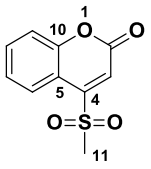
*(Z)-**156***: δ_H (500 MHz, $CDCl_3$): 10.15 (1H, s, H11), 7.83 (1H, dd, *J* 7.5, 0.9, H6), 7.59 (1H, td, *J* 7.5, 1.3, H8), 7.51 (1H, t, *J* 7.5, H7), 7.40 (1H, d, *J* 7.5, H9), 6.71 (1H, dt, *J* 10.8, 7.5, H3), 5.39 (1H, d, *J* 10.8, H2), 4.19 (2H, d, *J* 7.5, H4). δ_C (126 MHz, $CDCl_3$): 193.1 (C11), 152.2 (C3), 138.4 (C10), 135.2 (C6), 134.3 (C8), 133.6 (C5), 131.6 (C9), 127.8 (C7), 116.0 (C1), 100.1 (C2), 35.7 (C4). ν_{max} (neat): 3021, 2917, 2849, 2360, 2342, 1697, 1602 cm^{-1}. HRMS (ESI+): found 194.0578; $C_{11}H_9NONa$, $[M+Na]^+$ requires 194.0576.

(*E*)-2-(3-(Phenylsulfonyl)prop-1-en-1-yl)benzaldehyde (158)



This compound was prepared according to a literature procedure.[116] A mixture of 2-bromobenzaldehyde (1.0 g, 5.4 mmol), allylphenylsulfone (980 mg, 5.4 mmol), sodium acetate (1.3 g, 16.2 mmol), triphenylphosphine (140 mg, 0.5 mmol) and palladium(II) acetate (60 mg, 0.3 mmol) in tetrahydrofuran (10 mL) was stirred in a sealed tube at 100 °C for 24 h. The resulting mixture was filtered through Celite®, concentrated *in vacuo* and purified by flash column chromatography (silica gel, petrol:ethyl acetate, 5:1) to afford aldehyde **158** (1.1 g, 71%) as a yellow solid.* δ_H (500 MHz, $CDCl_3$): 10.00 (1H, s, H14), 7.90 (2H, d, *J* 7.8, H3), 7.77 (1H, d, *J* 7.8, H9/H12), 7.65 (1H, t, *J* 7.7, H1), 7.58−7.45 (5H, m, Ar C-*H*), 7.27 (1H, d, *J* 15.7, H7), 6.11 (1H, dt, *J* 15.7, 7.7, H6), 4.05 (2H, d, *J* 7.7, H5). δ_C (126 MHz, $CDCl_3$): 192.2 (C14), 138.3 (C4/C8), 137.9 (C4/C8), 135.8 (C7), 133.9 (C1), 133.9 (Ar CH), 132.7 (C13), 132.5 (Ar CH), 129.2 (C2/C3), 128.6 (Ar CH), 128.4 (C2/C3), 127.7 (Ar CH), 120.4 (C6), 60.6 (C5). ν_{max} (neat): 3064, 2730, 1694, 1596, 1568 cm^{-1}. HRMS (ESI+): found 309.0558; $C_{16}H_{14}O_3SNa$ $[M+Na]^+$ requires 309.0556. MP: 72−75 °C.

2-Oxo-2*H*-chromen-4-yl methanesulfonate (162)

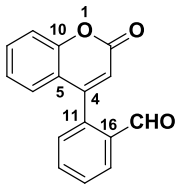


This compound was prepared by analogy to a literature procedure.[212] Methanesulfonyl chloride (2.63 mL, 34 mmol), was added in one portion to a stirred RT solution of 4-hydroxycoumarin (5.0 g, 31 mmol) and triethylamine (6.4 mL, 46 mmol) in dichloromethane (120 mL). After 30 min the reaction was diluted with dichloromethane (200 mL), water (100 mL) was added and

* *Although the reference reports the synthesis of the isomeric compound **157** where the alkene sits in conjugation with the sulfone, in our hands only the styrenic compound **158** was isolated.*

the organic layer washed with hydrochloric acid (1 M, 100 mL), sodium bicarbonate (aq., 100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid residue was purified by a single recrystallization from hot toluene to afford 4-hydroxycoumarin methanesulfonate **162** (6.36 g, 85%) as a white crystalline solid.* δ_H (400 MHz, $CDCl_3$): 7.74 (1H, dd, *J* 7.9, 1.5, H6), 7.64 (1H, ddd, *J* 8.5, 7.2, 1.4, H8), 7.40−7.32 (2H, m, H7 & H9), 6.53 (1H, s, H3), 3.40 (3H, s, H11). δ_C (101 MHz, $CDCl_3$): 160.5 (C4), 157.2 (C2), 153.6 (C10), 133.5 (C8), 124.7 (C7), 122.9 (C6), 117.2 (C9), 114.7 (C5), 103.5 (C3), 39.2 (C11). ν_{max} (neat): 3070, 3035, 3011, 2933, 1720 (C=O), 1368 (S=O), 1330 (S=O), 1173, 899, 867 cm^{-1}. HRMS (ESI+): found 262.9981; $C_{10}H_8O_5SNa$, $[M+Na]^+$ requires 262.9985. MP: 113−117 °C (toluene).

2-(2-Oxo-2*H*-chromen-4-yl)benzaldehyde (163)



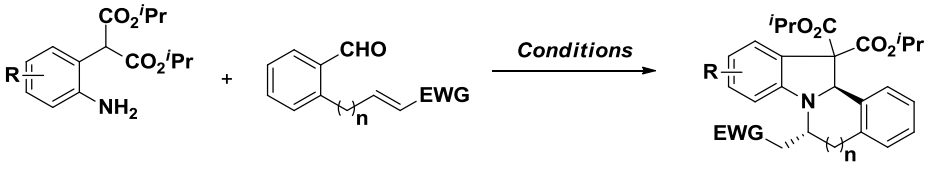
This compound was prepared by analogy to a literature procedure.[213] A stirred suspension of 4-methoxycoumarin methanesulfonate **162** (500 mg, 2.08 mmol), bis(triphenylphosphine)nickel(II) chloride† (272 mg, 0.42 mmol), triphenylphosphine (217 mg, 0.84 mmol) and zinc dust (340 mg, 5.2 mmol) in dry toluene (12 mL) was warmed to 90 °C. 2-Bromobenzaldehyde (0.29 mL, 2.5 mmol) was added dropwise over 3 h and the mixture stirred for a further 3 h until the starting material was consumed. The reaction mixture was allowed to cool to RT, diluted with dichloromethane (50 mL) and filtered over Celite®. Hydrochloric acid (5% aq., 25 mL) was added and the aqueous layer extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and

* *Note: trace amounts of this compound were observed to cause irritation on contact with skin.*

† *This compound was used as supplied or prepared according to ref.* [233]

concentrated *in vacuo*. The resulting crude mixture was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 4:1) to afford aldehyde **163** (175 mg, 34%) as an off-white crystalline solid. δ_H (400 MHz, $CDCl_3$): 9.91 (1H, s, H17), 8.11 (1H, dd, *J* 7.7, 1.2, H15), 7.78 (1H, app. td, *J* 7.5, 1.5, H13), 7.71 (1H, app. t, *J* 7.9, H14), 7.56 (1H, ddd, *J* 8.4, 7.2, 1.4, H8), 7.42 (2H, app. t, *J* 8.5, H6 & H12), 7.18 (1H, ddd, *J* 7.9, 7.3, 0.9, H7), 7.01 (1H, dd, *J* 7.9, 1.5, H9), 6.40 (1H, s, H3). δ_C (101 MHz, $CDCl_3$): 190.0 (C17), 160.0 (C2), 153.5 & 153.3 (C4 & C10), 137.2 (C11), 134.5 (C13), 133.8 (C16), 132.4 (C7), 130.1 (C14), 129.9 (C6), 129.7 (C15), 126.5 (C9), 124.6 (C8), 120.0 (C5), 117.4 (C12), 116.5 (C3). ν_{max} (neat): 2857, 2759, 1698 (C=O), 1605, 1370, 1183, 937, 866, 775, 752 cm^{-1}. HRMS (ESI+): found 273.0522; $C_{16}H_{10}O_3Na$, $[M+Na]^+$ requires 273.0522. MP: 107−111 °C.

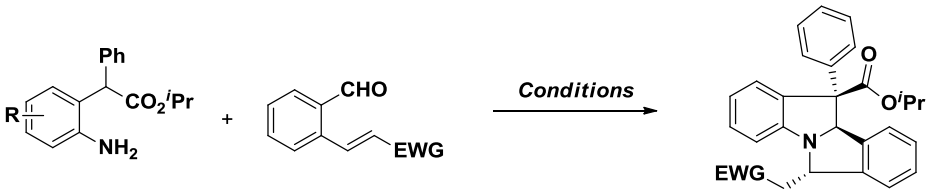
6.1.2 General Procedures for the Cascade Cyclization of Malonate Substrates



General Procedure 1 *(asymmetric). The appropriate aniline (1.0 eq.), the appropriate aldehyde (1.0 eq.)* and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (0.05 M concentration of imine), *the appropriate catalyst (0.1 eq.)* was added and the solution was stirred at −15 °C for 30 min. Pre-cooled potassium carbonate (33% aq., 0.25 mL / mL toluene) was added to the reaction and stirred for 16 h at −15 °C before adding ammonium chloride (aq., 50 mL/mmol imine) and extracting the aqueous layer with dichloromethane (3 x 50 mL/mmol imine). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 2 *(asymmetric). The appropriate aniline (1.0 eq.), the appropriate aldehyde (1.0 eq.)* and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (0.05 M concentration of imine), (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **42** (0.1 eq.) was added and the mixture was cooled to −78 °C for 30 min before adding anhydrous freshly-ground potassium hydroxide (10 eq.). The reaction was stirred at −78 °C for 16 h and then allowed to warm to RT and stirred for a further 6 h before adding ammonium chloride (aq., 50 mL/mmol imine) and extracting the aqueous layer with dichloromethane (3 x 50 mL/mmol imine). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography.

6.1.3 General Procedures for the Cascade Cyclization of α-Phenyl Ester Substrates

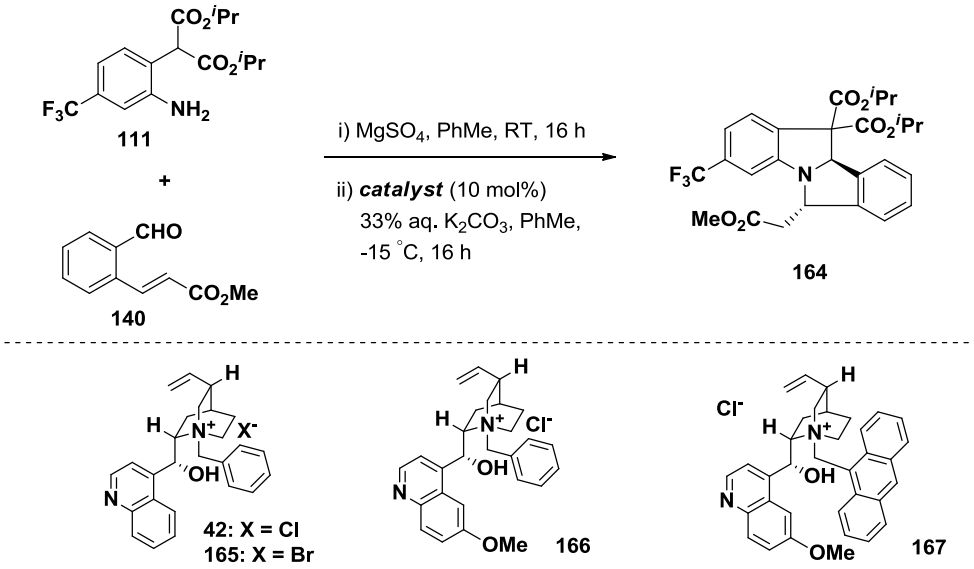


General Procedure 3 *(asymmetric). The appropriate aniline (1.0 eq.), the appropriate aldehyde (1.0 eq.)* and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered over Celite® and concentrated *in vacuo*. The crude imine was then redissolved in toluene (0.1 M concentration of imine), cooled to *the appropriate temperature* and (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **42** (0.1 eq.) and anhydrous freshly-ground potassium hydroxide (10 eq.) added. After 16 h the mixture was allowed to warm to RT and stirred for a further 6 h. Ammonium chloride (aq., 50 mL/mmol imine) was added, and the reaction mixture diluted with dichloromethane (50 mL/mmol imine). The aqueous layer was extracted with dichloromethane (3 x 50 mL/mmol imine), and the combined organic

extracts dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 4 *(racemic). The appropriate aniline (1.0 eq.), the appropriate aldehyde (1.0 eq.)* and magnesium sulfate (5.0 eq.) were stirred for 16 h at RT in toluene (0.1 M concentration of aniline). The resulting mixture was filtered over Celite® and concentrated *in vacuo*. The crude imine was then redissolved in tetrahydrofuran (0.1 M concentration of imine) and potassium *tert*-butoxide (2.0 eq.) was added to the stirred solution at RT. After 45 min ammonium chloride (aq., 50 mL/mmol imine) was added and the reaction mixture was diluted with dichloromethane (50 mL/mmol imine). The aqueous layer was extracted with dichloromethane (3 x 50 mL/mmol imine), and the combined organic extracts dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography to afford the racemic cyclized product.*

6.1.4 Catalyst Screening



Catalyst screening was carried out exclusively on trifluoromethyl malonate substrate **111** and methyl ester aldehyde **140** according to ***general procedure 1***. *For discussion, see p. 56*.

* *Note that diastereomeric products formed under racemic reaction conditions that were not formed under asymmetric conditions were not spectroscopically assigned.*

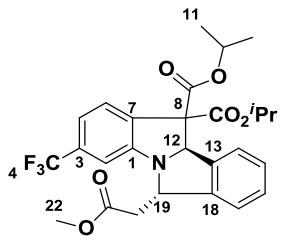
Cat. 42. **164** was prepared according to ***general procedure 1***: aniline **111** (100 mg, 0.29 mmol), aldehyde **140** (66 mg, 0.29 mmol), (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **42** (12 mg, 0.028 mmol), chromatography (silica gel, hexane:ethyl acetate, 20:1). **164** (119 mg, 79%, 88% ee, >20:1 dr) was obtained as a colourless oil.

Cat. 165. **164** was prepared according to ***general procedure 1***: aniline **111** (100 mg, 0.29 mmol), aldehyde **140** (66 mg, 0.29 mmol), *N*-benzylcinchonidinium bromide **165** (13.5 mg, 0.029 mmol), chromatography (silica gel, hexane:ethyl acetate, 20:1). **164** (116 mg, 77%, 78% ee, >20:1 dr) was obtained as a colourless oil.

Cat. 166. **164** was prepared according to ***general procedure 1***: aniline **111** (50 mg, 0.14 mmol), aldehyde **140** (33 mg, 0.14 mmol), *N*-benzylquininium chloride **166** (6.5 mg, 0.014 mmol), chromatography (silica gel, hexane:ethyl acetate, 20:1). **164** (43 mg, 57%, 95% ee, >20:1 dr) was obtained as a colourless oil.

Cat. 167. **164** was prepared according to ***general procedure 1***: aniline **111** (50 mg, 0.14 mmol), aldehyde **140** (33 mg, 0.14 mmol), *N*-anthracenylcinchonidinium chloride **167** (7.5 mg, 0.014 mmol), chromatography (silica gel, hexane:ethyl acetate, 20:1). **164** (47 mg, 63%, 70% ee, >20:1 dr) was obtained as a colourless oil.

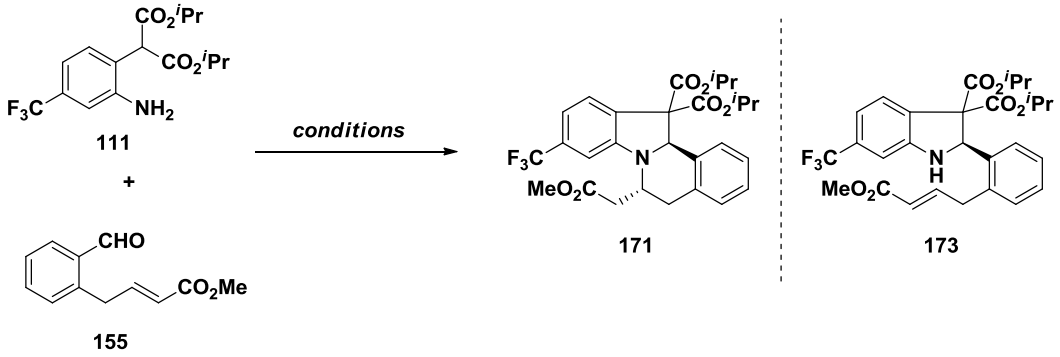
Pyrrolizidine ***164***



δ_H (400 MHz, $CDCl_3$): 7.65 (1H, d, *J* 7.8, H6), 7.50−7.47 (1H, m, H15), 7.34−7.30 (2H, m, H14, H16), 7.22−7.17 (2H, m, H5, H17), 7.04 (1H, s, H2), 6.15 (1H, s, H12), 5.52 (1H, t, *J* 6.4,

H19), 5.29 (1H, septet, *J* 6.3, H10), 4.61 (1H, septet, *J* 6.3, H10'), 3.75 (3H, s, H22), 3.01 (1H, dd, *J* 16.7, 6.4, H20), 2.37 (1H, dd, *J* 16.8, 6.4, H20), 1.42 (6H, d, *J* 6.3, H11), 0.84 (6H, d, *J* 6.3, H11'). δ_C (101 MHz, $CDCl_3$): 172.7 (C9/C21), 168.3 (C9/C21), 167.0 (C9/C21), 149.5 (C1/C7/C13/C18), 144.2 (C1/C7/C13/C18), 135.9 (C1/C7/C13/C18), 135.0 (C1/C7/C13/C18), 131.7 (q, *J* 32, C4), 128.8 (C14/C15/C16/C17), 127.8 (C14/C15/C16/C17), 126.6 (C6), 124.5 (C14/C15/C16/C17), 123.9 (q, *J* 282, C3), 122.9 (C14/C15/C16/C17), 118.1 (q, *J* 4, C5), 122.2 (q, *J* 4, C2), 76.3 (C12), 70.2 (C10), 70.1 (C10'), 66.9 (C8), 61.0 (C19), 51.8 (C22), 39.0 (C20), 21.7 (C11), 21.6 (C11), 21.1 (C11), 21.0 (C11). δ_F (376 MHz, $CDCl_3$): -62.5. HRMS (ESI+): found 542.1741; $C_{27}H_{28}F_3NO_6Na$ $[M+Na]^+$ required 542.1761. ν_{max} (neat): 2983 (CH), 1729 (C=O), 1632 cm^{-1}. Chiral HPLC (Chiralpak OD-H, 1.5% IPA, 98.5% hexane, 1.0 $mL.min^{-1}$, λ = 271): t_R (major) = 6.9, t_R (minor) = 9.1. $[\alpha]_D^{25.0}$ +14.0 (c = 1.36, $CHCl_3$).

6.1.5 Temperature and Base Screen



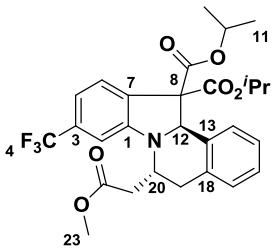
This short screen was performed as a validation of the results obtained in Table 3.3, and was carried out exclusively on trifluoromethyl malonate substrate **111** and methyl ester aldehyde **155**. *For discussion, see p. 59.*

Table 3.4 (p. 59), entry 1. *This reaction was carried out according to* ***general procedure 1***: aniline **111** (50 mg, 0.14 mmol), aldehyde **155** (29 mg, 0.14 mmol), (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **42** (12 mg, 0.028 mmol). *Crude ^1H NMR analysis revealed only formation of* ***173****, the product of electrocyclization without subsequent 1,4-addition.*

Table 3.4 (p. 59), entry 2. *This reaction was carried out according to a modification of* ***general procedure 1***: aniline **111** (50 mg, 0.14 mmol), aldehyde **155** (29 mg, 0.14 mmol), (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **42** (12 mg, 0.028 mmol), ***powdered potassium hydroxide*** (used in place of aqueous potassium carbonate, 81 mg, 1.44 mmol). **171** (49 mg, 64%, 84% ee) was obtained as pale oil.

Table 3.4 (p. 59), entry 3. *This reaction was carried out according to* ***general procedure 2***: aniline **111** (50 mg, 0.14 mmol), aldehyde **155** (29 mg, 0.14 mmol). **171** (68 mg, 88%, 91% ee) was obtained as pale oil.

Indolizidine ***171***

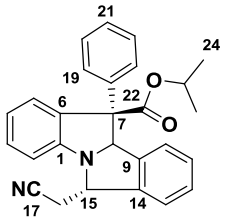


δ_H (500 MHz, $CDCl_3$): 7.64 (1H, d, *J* 7.9, H6), 7.44 (1H, d, *J* 6.6, H14), 7.30−7.22 (3H, m, H15, H16, H17), 6.94 (1H, d, *J* 7.9, H5), 6.72 (1H, s, H2), 5.52 (1H, s, H12), 5.28 (1H, septet, *J* 6.3, H10), 4.82 (1H, sept, *J* 6.3, H10), 4.53−4.46 (1H, m, H20), 3.70 (3H, s, H23), 3.18 (1H, dd, *J* 15.1, 5.2, H19), 3.04 (1H, dd, *J* 15.1, 1.9, H19), 2.53 (1H, d, *J* 15.8, H21), 2.12 (1H, dd, *J* 15.9 10.3, H21), 1.40 (3H, d, *J* 6.3, H11), 1.38 (3H, d, *J* 6.3, H11), 0.95 (3H, d, *J* 6.3, H11), 0.81 (3H, d, *J* 6.3, H11). δ_C (126 MHz, CDCl3): 172.2 (C22), 168.4 (C9), 166.8 (C9), 148.3 (C7), 134.5 (C18), 133.4 (C13), 132.2 (q, J 32, C4), 130.3 (C1), 128.9 (C15/C16/C17), 127.3 (C15/C16/C17), 126.5 (C15/C16/C17), 126.0 (C6), 125.3 (C14), 124.3 (q, J 272, C3), 114.3 (q, J 4, C5), 103.4 (q, J 4, C2), 70.3 (C10), 69.8 (C10), 65.5 (C8), 65.2 (C12), 51.7 (C23), 47.8 (C20), 36.6 (C21), 33.6 (C19), 21.7 (C11), 21.6 (C11), 21.2 (C11), 21.1 (C11). δ_F (376 MHz, CDCl3): –62.6. HRMS (ESI+): found 556.1916; $C_{28}H_{30}NNaF_3O_6$ $[M+Na]^+$ requires 556.1917. ν_{max} (neat): 2984, 2939, 1732,

1614. Chiral HPLC (Chiralpak IC, 1 % IPA, 99 % hexane, 1.0 mL.min^{-1}, λ = 288) t_R (major) = 12.5, t_R (minor) = 17.7. $[\alpha]_D^{25.0}$ +8.0 (c = 1.10, $CHCl_3$).

6.1.6 Cyclization Reactions

Pyrrolizidine 181



Asymmetric: prepared according to ***general procedure 3***. Aniline **130** (50 mg, 0.186 mmol), aldehyde **141** (26 mg, 0.184 mmol), T = −78 °C, chromatography (silica gel, dichloromethane:hexane, 1:1). The product pyrrolizidine **181** (61 mg, 80%, 93% ee, >20:1 dr) was obtained as a white solid.

Racemic: prepared according to ***general procedure 4***. Aniline **130** (50 mg, 0.186 mmol), aldehyde **141** (26 mg, 0.184 mmol), chromatography (silica gel, dichloromethane:hexane, 1:1). **181** was obtained: 48 mg, 64% combined yield of diastereomers; 18 mg, 24% yield of desired diastereoisomer.

δ_H (400 MHz, $CDCl_3$): 7.60 (2H, d, *J* 7.4, H19), 7.48−7.39 (3H, m), 7.38−7.32 (4H, m), 7.29 (1H, t, *J* 8.2, H3), 7.13 (2H, t, *J* 6.9, H2 & H5), 6.95 (1H, t, *J* 7.5, H4), 5.65 (1H, d, *J* 2.4, H8), 4.91 (1H, td, *J* 5.7, 2.5, H15), 4.60 (1H, septet, *J* 6.2, H23), 2.95 (1H, dd, *J* 16.6, 5.6, H16), 2.89 (1H, dd, *J* 16.7, 5.8, H16'), 0.79 (3H, d, *J* 6.2, H24), 0.49 (3H, d, *J* 6.3, H24'). δ_C (101 MHz, $CDCl_3$): 170.4 (C22), 153.2 (C1), 142.5 (Ar C), 140.9 (Ar C), 139.2 (Ar C), 134.2 (C6), 129.4 (C3), 128.6 (Ar CH), 128.6 (Ar CH), 128.5 (Ar CH), 128.5 (C19), 127.3 (Ar CH), 126.4 (C5), 123.1 (Ar CH), 122.6 (Ar CH), 121.8 (C4), 118.0 (C17), 112.7 (C2), 81.8 (C8), 68.4 (C23), 67.0 (C7), 66.9 (C15), 27.4 (C16), 21.0 (C24), 20.6 (C24'). HRMS (ESI+): found 431.1727;

$C_{27}H_{24}N_2O_2Na$, $[M+Na]^+$ requires 431.1730. ν_{max} (neat): 3029, 2979, 2933, 2162, 1719 (C=O), 1599, 1479, 1210, 1103, 754, 699 cm^{-1}. MP: 61−64 °C. Chiral HPLC (Chiralpak IA, 10% IPA, 90% hexane, 1.0 mL.min^{-1}, λ = 207): t_R (major) = 22.2, t_R (minor) = 14.3. $[\alpha]_D^{25.0}$ −29.8 (c = 0.57, $CHCl_3$).

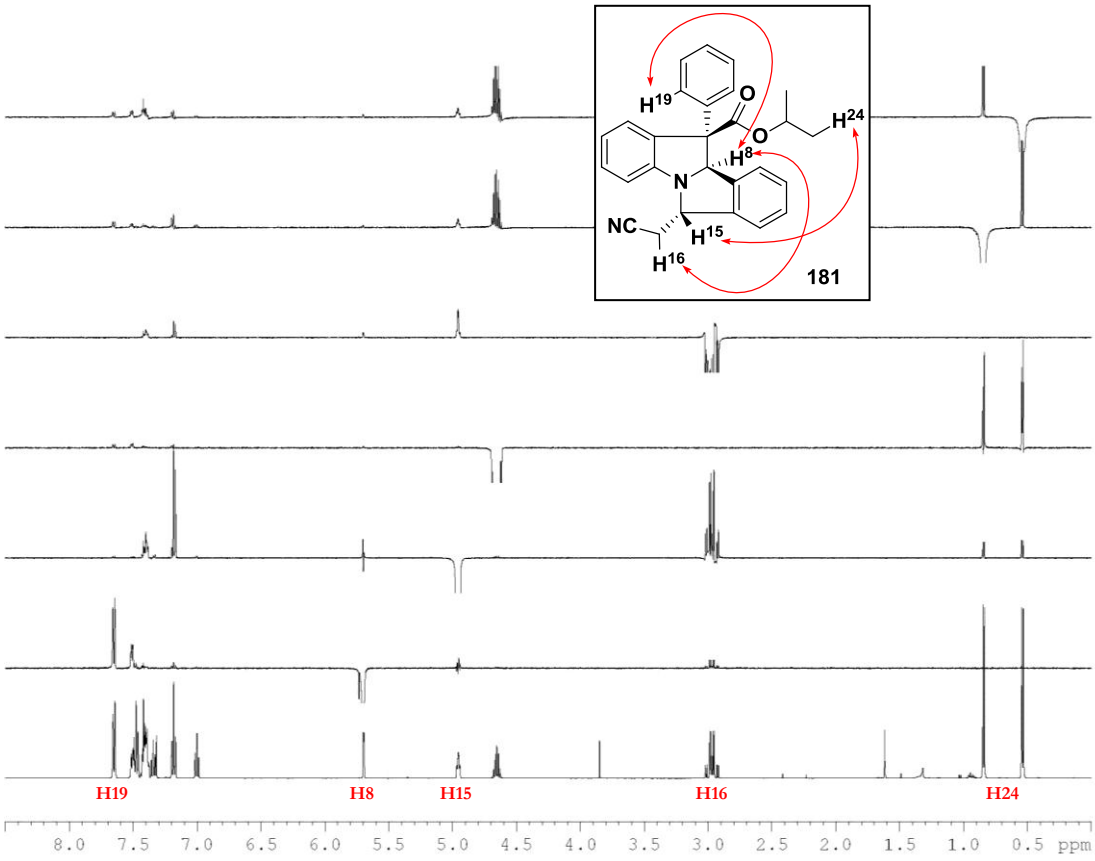
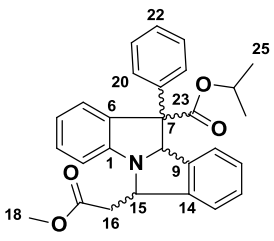


Figure 6.2. 1D nOe data for pyrrolizidine **181** (mixing time = 0.8 s).

Pyrrolizidine 183



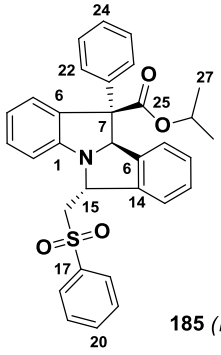
Attempted asymmetric: prepared according to ***general procedure 3***. Aniline **130** (50 mg, 0.186 mmol), aldehyde **140** (35 mg, 0.185 mmol), T = 40 °C, chromatography (silica gel, petrol:ethyl acetate 4:1). The product pyrrolizidine **183** (7 mg, 9%, 2.4:1 dr) was obtained as a colourless oil. *This compound is tentatively identified on the basis of ^{1}H NMR and MS evidence alone: the coupling pattern between H15 and the diasteretopic protons H16 and H16', and the presence of the weakly coupled H8 proton are deemed diagnostic of cyclized material, and the presence of two such spin systems is indicative of the formation of two inseparable diastereoisomers.*

Selected ^{1}H NMR data – Major Diastereoisomer. δ_H (400 MHz, $CDCl_3$): 5.81 (1H, s, H8), 5.43 (1H, dd, *J* 8.5, 4.9, H15), 4.79 (1H, septet, *J* 6.4, H24), 3.13 (1H, dd, *J* 16.1, 4.0, H16), 2.35 (1H, dd, *J* 16.1, 8.6, H16'), 0.93 (3H, d, *J* 6.2, H25), 0.79 (3H, d, *J* 6.3, H25').

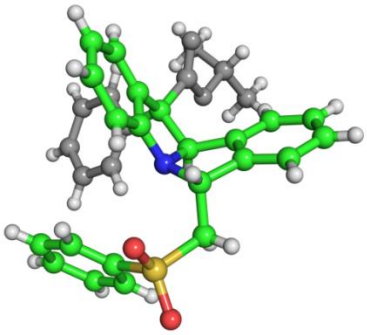
Selected ^{1}H NMR data – Minor Diastereoisomer. δ_H (400 MHz, $CDCl_3$): 5.61 (1H, dd, *J* 2.1, 0.7, H8) 5.13 (1H, ddd, *J* 1.7, 6.0, 7.3, H15), 4.71 (1H, septet, *J* 6.4, H24), 2.81 (1H, dd, *J* 15.6, 5.8, H16), 2.85 (1H, dd *J* 15.4, 7.4, H16'), 0.90 (3H, d, *J* 6.2, H25), 0.56 (3H, d, *J* 6.3, H25').

HRMS (ESI+): found 464.1841; $C_{28}H_{27}NNaO_4$, $[M+Na]^+$ requires 464.1838.

Pyrrolizidine 185



185 *(major)*



Asymmetric: prepared according to ***general procedure 3***. Aniline **130** (50 mg, 0.186 mmol), aldehyde **142** (51 mg, 0.187 mmol), T = RT, chromatography (silica gel,

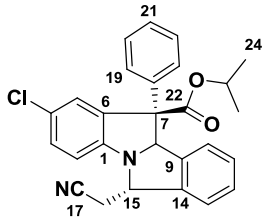
petrol:ethyl acetate, 10:1). The product pyrrolizidine **185** (69 mg, 70%, 89% ee, 8.5:1 dr.[*]) was obtained as a white solid.

Racemic: Prepared according to ***general procedure 4***. Aniline **130** (50 mg, 0.186 mmol), aldehyde **142** (51 mg, 0.187 mmol), chromatography (silica gel, petrol:ethyl acetate, 10:1). **185** was obtained: 58 mg, 60% combined yield of diastereomers; 12 mg, 12% yield of desired diastereoisomer.

Major diastereoisomer. δ_H (400 MHz, $CDCl_3$): 7.91 (2H, d, *J* 7.3, H18), 7.49 (1H, app. t, *J* 7.5, H20), 7.41 (1H, d, *J* 7.4, H10), 7.39−7.33 (3H, m, H11 & H19), 7.33−7.24 (7H, m, H12, H13, H22, H23 & H24), 7.22 (1H, d, *J* 7.0, H3), 7.17 (2H, app. d, *J* 8.4, H2 & H5), 6.89 (1H, app. td, *J* 7.4, 0.9, H4), 5.36 (1H, dd, *J* 7.4, 4.7, H15), 5.31 (1H, s, H8), 4.85 (1H, septet, *J* 6.3, H26), 3.63 (1H, dd, *J* 14.8, 7.9, H16). 3.55 (1H, dd, *J* 14.9, 4.5, H16'), 1.03 (3H, d, *J* 6.2, H27), 0.70 (3H, d, *J* 6.2, H27'). δ_C (101 MHz, $CDCl_3$): 170.4 (C25), 152.6 (C1), 143.4 (Ar C), 141.1 (Ar C), 140.3 (Ar C), 139.3 (Ar C), 133.5 (C20), 132.1 (C17), 129.1 (Ar CH), 128.9 (Ar CH), 128.7 (Ar CH), 128.3 (Ar CH), 128.2 (Ar CH), 127.7 (Ar CH), 127.6 (Ar CH), 127.0 (Ar CH), 126.6 (C5), 123.6 (C10), 123.1 (C11), 121.1 (C4), 112.9 (C2), 80.0 (C8), 68.9 (C26), 65.4 (C7), 65.1 (C15), 62.6 (C16), 21.4 (C27), 21.0 (C27'). HRMS (ESI+): found 524.1886; $C_{32}H_{30}NO_4S$, $[M+H]^+$ requires 524.1890. ν_{max} (neat): 3036, 2987, 2931, 1731 (C=O), 1598, 1299 (S=O), 1077, 690, 607 cm^{-1}. MP: 142−144 °C. Chiral HPLC (Chiralpak IA, 10% IPA, 90% hexane, 1.0 $mL.min^{-1}$, λ = 239): t_R (major) = 19.5, t_R (minor) = 13.7. $[\alpha]_D^{25.0}$ +41.3 (*c* = 0.45, $CHCl_3$). *For crystallographic data, see Appendix 8.2, p. 280.*

Pyrrolizidine 189

[*] *Diastereomeric ratio determined by integration of characteristic H16 peaks in the crude ^1H NMR spectrum.*

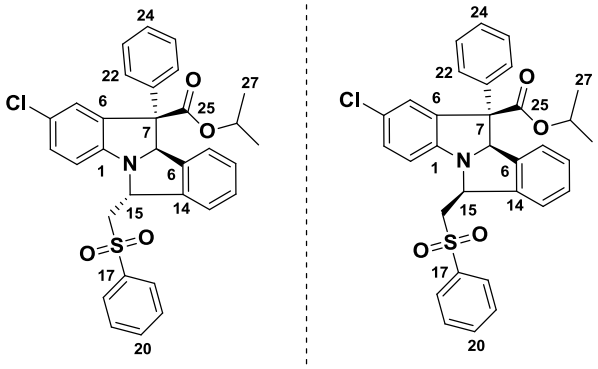


Asymmetric: Prepared according to ***general procedure 3***. Aniline **136** (50 mg, 0.165 mmol), aldehyde **141** (26 mg, 0.165 mmol), T = −30 °C, chromatography (silica gel, hexane:ethyl acetate, 10:1). The product pyrrolizidine **189** (64 mg, 87%, 97% ee, >20:1 dr) was obtained as a yellow solid.

Racemic: Prepared according to ***general procedure 4***. Aniline **136** (50 mg, 0.165 mmol), aldehyde **141** (26 mg, 0.165 mmol), chromatography (silica gel, hexane:ethyl acetate, 10:1). **189** was obtained: 72 mg, 95% combined yield of diastereomers; 14 mg, 19% yield of desired diastereoisomer.

δ_H (400 MHz, $CDCl_3$): 7.58 (2H, d, *J* 7.4, H19), 7.48−7.41 (3H, m), 7.40−7.31 (4H, m), 7.25 (1H, dd, *J* 8.4, 2.1, H3), 7.12 (1H, d, *J* 2.1, H5), 7.07 (1H, d, *J* 8.5, H2), 5.69 (1H, d, *J* 2.3, H8), 4.88 (1H, td, *J* 5.7, 2.3, H15), 4.64 (1H, sept, *J* 6.3, H23), 2.93 (1H, dd, *J* 16.7, 5.3, H16), 2.84 (1H, dd, *J*, 16.7, 6.2, H16), 0.86 (3H d, *J* 6.2, H24), 0.54 (3H, d, *J* 6.3, H24'). δ_C (101 MHz, $CDCl_3$): 169.9 (C22), 151.8 (C1), 141.9 (Ar C), 140.7 (Ar C), 138.7 (Ar C), 136.1 (Ar C), 129.4 (C3), 128.8 (Ar CH), 128.7 (Ar CH), 128.7 (C20), 128.2 (C19), 127.5 (Ar CH), 126.5 (Ar C), 126.4 (C5), 123.3 (Ar CH), 122.6 (Ar CH), 118.0 (C17), 113.5 (C2), 82.1 (C8), 68.8 (C23), 66.9 (C15), 66.8 (C7), 27.3 (C16), 21.1 (C24), 20.6 (C24'). HRMS (ESI+): found 465.1327; $C_{27}H_{23}{}^{35}ClN_2O_2Na$, $[M(^{35}Cl)+Na]^+$ requires 465.1340. ν_{max} (neat): 3060, 3029, 2981, 2934, 2881, 2250 (C≡N), 1723 (C=O), 1475, 1218, 1105, 757, 700 cm^{-1}. MP: 142−151 °C. Chiral HPLC (Chiralpak IA, 3% IPA, 97% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 22.2, t_R (minor) = 20.3. $[\alpha]_D^{25.0}$ −9.0 (*c* = 2.1, $CHCl_3$).

Pyrrolizidines 191 (major) & 192 (minor)



Asymmetric: prepared according to ***general procedure 3.*** Aniline **136** (0.165 mmol, 50 mg), aldehyde **142** (45 mg, 0.165 mmol), T = 0 °C, chromatography (silica gel, hexane:ethyl acetate, 20:1). The product pyrrolizidine was obtained as a mixture of *major* (**191**, 53 mg, 58%, 94% ee) and *minor* (**192**, 29 mg, 31%[*]) diastereoisomers.

Racemic: Prepared according to ***general procedure 4.***. Aniline **136** (50 mg, 0.165 mmol), aldehyde **142** (45 mg, 0.165 mmol), chromatography (silica gel, hexane:ethyl acetate, 20:1). The product pyrrolizidine was obtained as a mixture of diastereomers: 68 mg, 74% combined yield of diastereomers; 7 mg, 8% yield of desired diastereoisomer **191**.

Major (as drawn): δ_H (400 MHz, $CDCl_3$): 7.89 (2H, d, *J* 7.3, H18), 7.51 (1H, t, *J* 6.9, H20), 7.41−7.34 (3H, m, H11 & H19), 7.33−7.21 (7H, m), 7.20−7.13 (3H, m, H2 & 2 x Ar CH), 5.35-5.30 (2H, m, H8 & H15), 4.89 (1H, septet, *J* 6.3, H26), 3.58 (1H, dd, *J* 15.0, 8.3, H16), 3.52 (1H, dd, *J* 14.9, 4.3, H16'), 1.09 (3H, d, *J* 6.3, H27), 0.76 (3H, d, *J* 6.2, H27'). δ_C (101 MHz, $CDCl_3$): 169.8 (C25), 151.1 (C1), 142.8 (Ar C), 140.7 (Ar C), 140.3 (Ar C), 138.8 (Ar C), 133.7 (Ar C), 133.6 (C20), 129.1 (Ar CH), 129.0 (C19), 129.0 (Ar CH), 128.5 (Ar CH), 128.3 (Ar CH), 127.7 (C18), 127.3 (Ar CH), 127.2 (Ar CH), 126.6 (Ar CH), 125.9 (C4), 123.8 (C11), 123.0 (Ar CH), 113.8 (C2), 80.0 (C8), 69.3 (C26), 65.2 (C15), 65.1 (C7), 62.3 (C16), 21.4 (C27), 21.0 (C27').

[*] *The ee of the minor diastereoisomer could not be determined since a racemic sample of this isomer was not generated.*

HRMS (ESI+): found 580.1322; $C_{32}H_{28}{}^{35}ClNO_4SNa$, $[M(^{35}Cl)+Na]^+$ requires 580.1320. ν_{max} (neat): 3036, 2987, 2931, 1731 (C=O), 1598, 1299 (S=O), 1077, 690, 607 cm^{-1}. MP: 192−194 °C. Chiral HPLC (Chiralpak OD-H, 20% IPA, 80% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 13.0, t_R (minor) = 11.2. $[\alpha]_D^{25.0}$ +64.2 (c = 0.85, $CHCl_3$).

*Minor:** δ_H (500 MHz, $CDCl_3$): 8.01 (2H d, *J* 7.3, H18), 7.74 (1H, t, *J* 7.4, H20), 7.65 (2H, t, *J* 7.6, H19), 7.46−7.41 (4H, m, H22 & H23), 7.40−7.30 (3H, m, H12, H13 & H24), 7.30−7.25 (1H, m, H11), 7.20 (1H, dd, *J* 8.4, 2.2, H3), 7.18 (1H, d, *J* 2.2, H10), 7.12 (1H, d, *J* 2.2, H5), 6.60 (1H, d, *J* 8.5, H2), 5.55 (1H, d, H8), 5.49 (1H, d, *J* 6.6, H15), 4.68 (1H, septet, *J* 6.3, H26), 3.65 (1H, dd, *J* 15.4, 1.7, H16), 3.22 (1H, dd, *J* 15.4, 6.7, H16'), 0.91 (3H, d, *J* 6.3, H27), 0.82 (3H, d, *J* 6.3, H27'). δ_C (126 MHz, $CDCl_3$): * 170.1 (C25), 146.2 (C1), 143.7 (Ar C), 141.3 (Ar C), 139.4 (Ar C), 138.7 (Ar C), 136.2 (Ar C), 134.0 (C20), 129.5 (C19), 129.4 (C3), 128.7 (C23), 128.3 (C18), 127.9 (C11), 127.8 (C22), 127.6 (C12/C24), 127.0 (C5), 126.5 (C4), 123.7 (C13), 122.5 (C10), 116.0 (C2), 81.9 (C8), 68.7 (C26), 66.7 (C7), 58.7 (C16), 57.7 (C15), 21.3 (C27), 21.0 (C27'). HRMS (ESI+): found 580.1320; $C_{32}H_{28}{}^{35}ClNO_4SNa$, $[M(^{35}Cl)+Na]^+$ requires 580.1320. ν_{max} (neat): 3063, 2980, 1723 (C=O), 1600, 1472, 1308 (S=O), 1210, 1103, 911 cm^{-1}.

* *Note that a ^{13}C peak corresponding to either C12 or C24 was not observed, presumably due to overlap with another peak.*

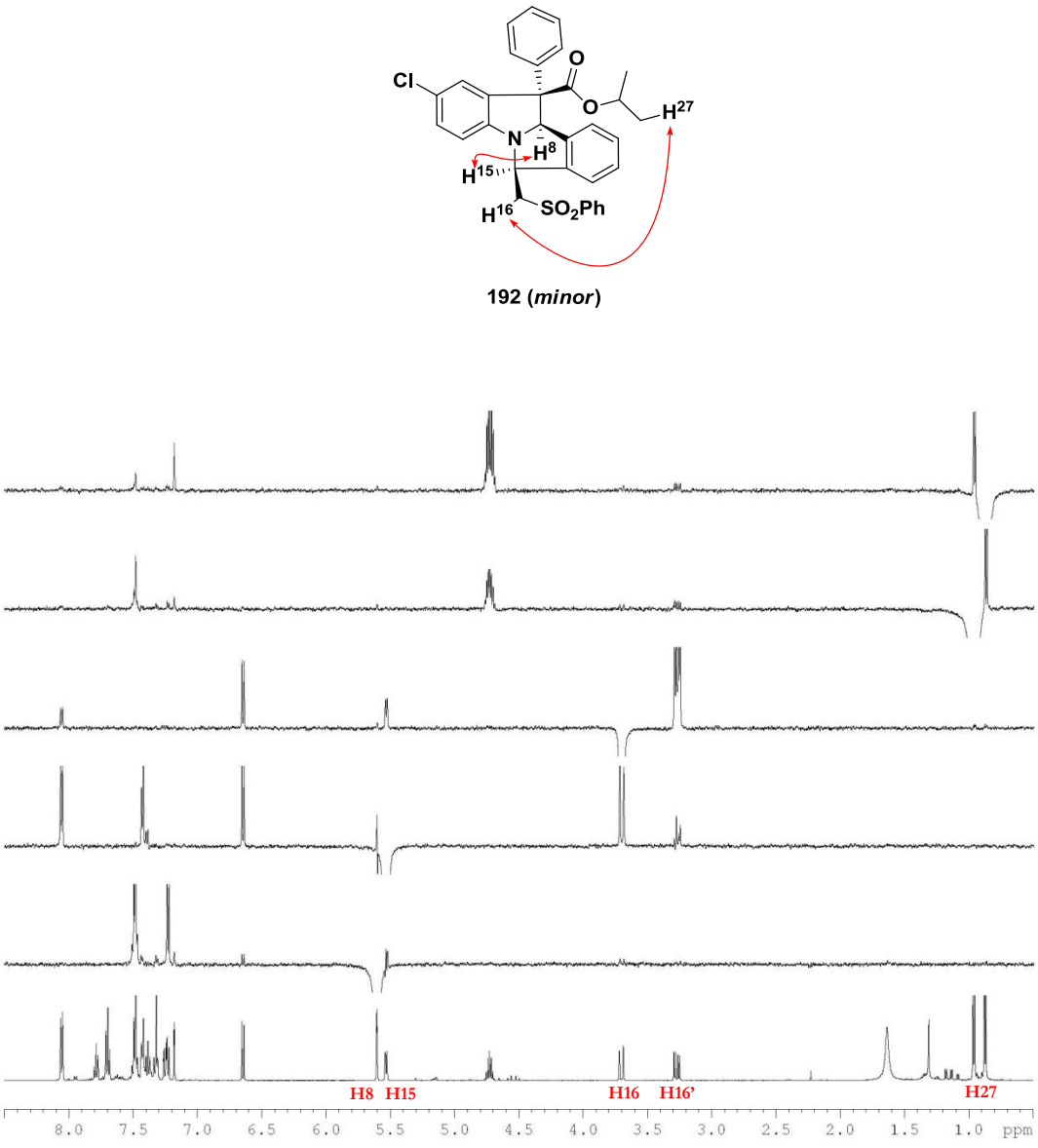
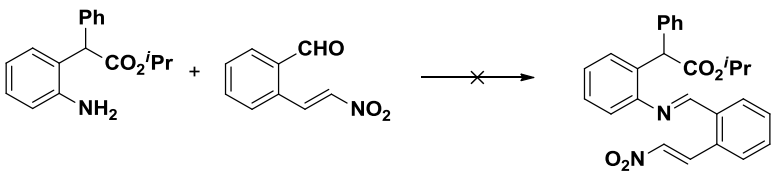


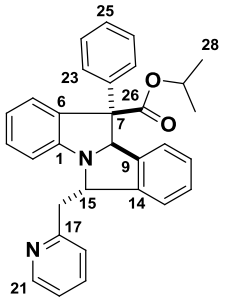
Figure 6.3. 1D nOe data for the minor diastereomer **192** (mixing time = 0.8 min).

Attempted formation of *iso*-propyl 2-(2-((*E*)-(2-((*E*)-2-nitrovinyl)benzylidene)amino)phenyl)-2-phenylacetate (193)



Magnesium sulfate (120 mg, 0.93 mmol) was added to a stirred RT solution of (*E*)-2-(2-nitrovinyl)benzaldehyde **151** (33 mg, 0.186 mmol) and aniline **130** (50 mg, 0.186 mmol) in toluene (2 mL) and a deep red/black colour was observed after several minutes. After 16 h the black reaction mixture was filtered and concentrated *in vacuo*. *TLC and NMR analysis of the crude product revealed a highly complex mixture of products which were not identified.*

Pyrrolizidine 195



Aniline **130** (88 mg, 0.33 mmol), aldehyde **143** (68 mg, 0.33 mmol) and magnesium sulfate (196 mg, 1.65 mmol) were stirred for 16 h at RT in toluene (3.5 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in tetrahydrofuran (6 mL) and (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride **42** (14 mg) and anhydrous freshly-ground potassium hydroxide (180 mg, 3.3 mmol) were added. The solution blackened, and after 16 h was ammonium chloride (aq., 5 mL) was added and the aqueous layer extracted with dichloromethane (3 x 5 mL). *^{1}H NMR analysis of the crude product revealed a 92:8 mixture of diastereoisomers.* The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 4:1) to afford **195** (88 mg, 58%, 0% ee_{major}) as yellow foam, and a 92:8 mixture of diastereomers. A pure sample of the major diastereomer was obtained by trituration of the mixed material (dichloromethane/hexane). δ_H (500 MHz, $CDCl_3$): 8.71 (1H, d, *J* 4.2, H21), 7.62 (1H, td, *J* 7.6, 11.7, H19), 7.30 (1H, d, *J* 7.7, H18), 7.23 -7.15 (5H, m, H5, H20, H24 & H25), 7.07−7.00 (3H, m, H3, H12 & H13), 6.87 (2H, d, *J* 6.2, H23), 6.77−6.71 (2H, m, H4 & H11), 6.22 (1H, s, H8), 6.15 (1H, d, *J* 7.9, H2), 5.79 (1H, d, *J* 7.9, H10), 5.20−5.11 (2H, m, H15

& H27), 3.25 (1H, dd, *J* 13.2, 4.3, H16), 3.11 (1H, dd, *J* 13.2, 9.7, H16'), 1.32 (3H, d, *J* 6.2, H28), 1.18 (3H, d, *J* 6.3, H28'). δ_H (126 MHz, $CDCl_3$): 172.9 (C26), 159.4 (C17), 154.2 (C1), 149.2 (C21), 143.1 (C14), 139.9 (C22), 139.3 (C9), 136.5 (C19), 130.0 (C6), 129.1 (C3), 128.8 (C23), 127.8 (C24), 127.6 (C5), 127.1 (C12), 127.0 (C25), 126.4 (C11), 125.1 (C18), 124.4 (C10), 122.3 (C13), 121.6 (C20), 120.2 (C4), 111.1 (C2), 75.7 (C8), 70.9 (C15), 69.3 (C27), 65.9 (C7), 46.5 (C16), 21.5 (C28), 21.4 (C28'). HRMS (ESI+): found 461.2223; $C_{31}H_{29}N_2O_2$ $[M+H]^+$ requires 461.2224. ν_{max} (neat): 3062 (CH), 2984 (CH), 2948 (CH), 1725 (C=O), 1590 (C=N), 1474, 1237, 1105, 754, 707 cm^{-1}.

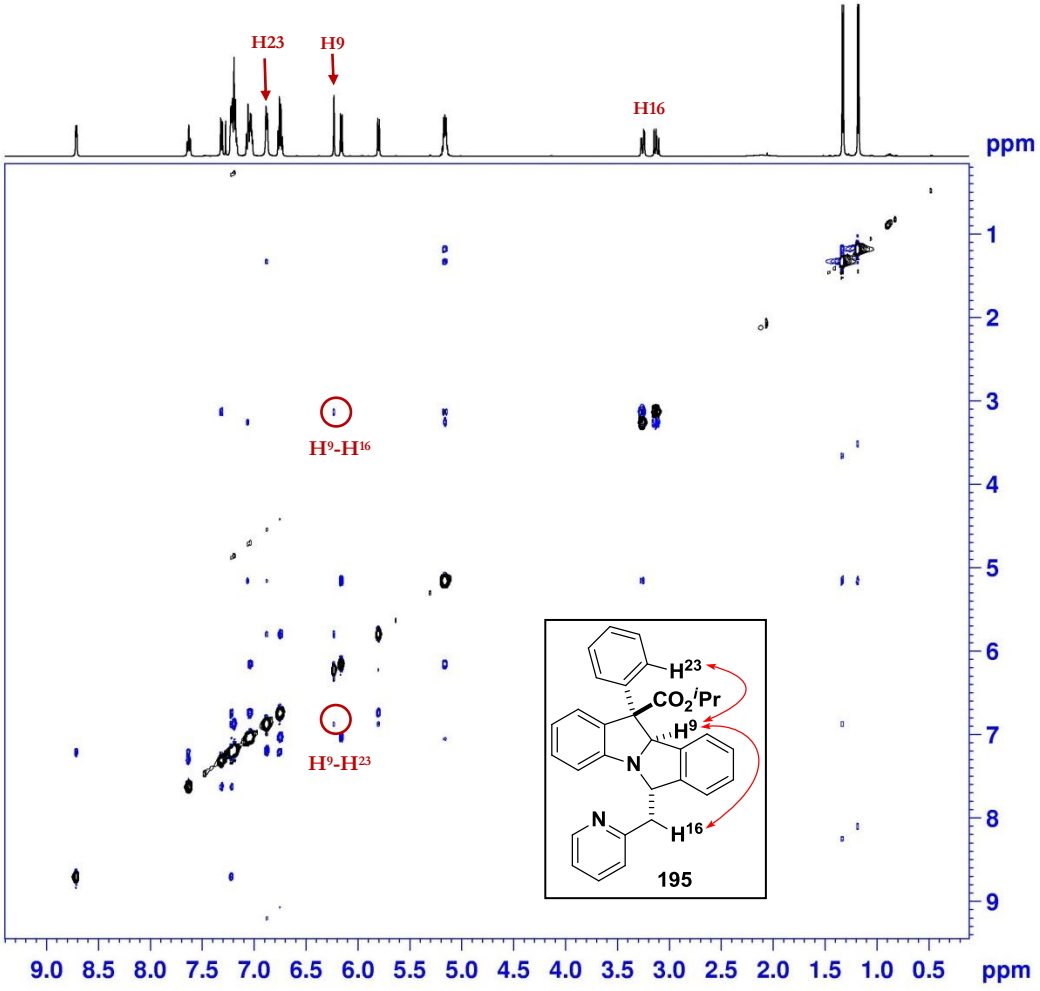
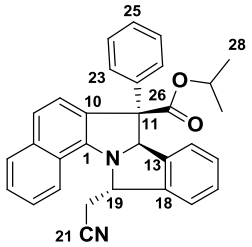


Figure 6.4. NOESY correlations for the major diastereomer of **195** (mixing time = 0.8 s)

Pyrrolizidine 202



Asymmetric: prepared according to ***general procedure 3***. Aniline **137** (50 mg, 0.156 mmol), aldehyde **141** (25 mg, 0.159 mmol),* T = 0 °C, chromatography (silica gel, hexane:ethyl acetate, 20:1). The product pyrrolizidine **202** (37 mg, 52%, 90% ee, >20:1 dr) was obtained as a white solid.

Racemic: prepared according to ***general procedure 4***. Aniline **137** (50 mg, 0.156 mmol), aldehyde **141** (25 mg, 0.156 mmol),* chromatography (silica gel, hexane:ethyl acetate, 20:1). **202** was obtained: 31 mg, 43% combined yield of diastereomers.†

δ_H (500 MHz, $CDCl_3$): 8.00 (1H, d, *J* 8.3, H3), 7.90 (1H, d, *J* 8.0, H6), 7.59−7.54 (2H, m, H4 & Ar CH), 6.54−7.47 (4H, m, H24, H25 & Ar CH), 7.42−7.32 (5H, m, H23 & 3 x Ar CH), 7.31−7.26 (2H, m, 2 x Ar CH), 5.94 (1H, s, H12), 5.36 (1H, t, *J* 4.5, H19), 4.74 (1H, septet, *J* 6.3, H27), 3.26−3.16 (2H, m, H20 & H20'), 0.98 (3H, d, *J* 6.2, H28), 0.52 (3H, d, *J* 6.3, H28'). δ_C (126 MHz, $CDCl_3$):‡ 170.5 (C26), 148.4 (C1), 143.8 (C22), 140.4 (Ar C), 139.2 (Ar C), 135.0 (C7), 129.2 (C6), 128.8 (Ar CH), 128.7 (Ar CH), 128.4 (C23), 128.1 (C24), 127.2 (Ar CH), 125.9 (Ar CH), 125.6 (Ar CH), 124.3 (Ar CH), 123.6 (C10), 123.5 (Ar CH), 122.8 (C3), 122.6 (Ar CH), 122.6 (Ar CH), 117.3 (C21), 82.3 (C12), 68.9 (C27), 66.6 (C11), 65.6 (C19), 28.1 (C20), 21.3 (C28), 20.7 (C28'). HRMS (ESI+): found 481.1875; $C_{31}H_{26}N_2O_2Na$, $[M+H]^+$ requires 481.1886. ν_{max} (neat): 3056, 2979, 2916, 2248 (C≡N), 1718 (C=O), 1573, 1341, 1178, 1095, 1086, 761,

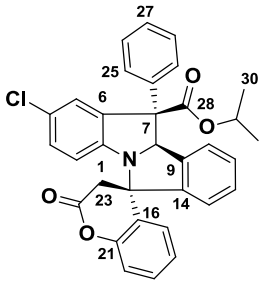
* *Note that this substrate was stirred for 72 h during the imine formation stage.*

† *In this case a pure racemic sample of the diastereomer formed in the asymmetric reaction could not be isolated, but it was possible to identify the relevant enantiomers from the chiral HPLC trace of the mixture of diastereomers.*

‡ *One fully substituted aromatic C not observed and assumed to be overlapping with another peak.*

693 cm^{-1}. MP: 158−163 °C. Chiral HPLC (Chiralpak OD-H, 10% IPA, 90% hexane, 1.0 $mL.min^{-1}$, λ = 251): t_R (major) = 10.5, t_R (minor) = 11.8. $[\alpha]_D^{25.0}$ −84.6 (c = 1.3, $CHCl_3$).

Pyrrolizidine 204



Asymmetric: prepared according to ***general procedure 3***. Aniline **136** (50 mg, 0.165 mmol), aldehyde **163** (41 mg, 0.164 mmol), T = 0 °C, chromatography (silica gel, petrol:ethyl acetate, 20:1). The product pyrrolizidine **204** (40 mg, 48%, 97% ee, >20:1 dr) was obtained as an off-white solid.

Racemic: prepared according to ***general procedure 4***. Aniline **136** (50 mg, 0.165 mmol), aldehyde **163** (41 mg, 0.164 mmol), chromatography (silica gel, petrol:ethyl acetate, 20:1). **204** was obtained: 45 mg, 51% combined yield of diastereomers.*

δ_H (500 MHz, $CDCl_3$): 7.69 (1H, dd, *J* 7.7, 1.6, H17), 7.58−7.51 (4H, m, H25 & H26), 7.45 (1H, app. tt, *J* 7.2, 1.6, H27), 7.43−7.39 (1H, m, H19), 7.39−7.27 (6H, m, H5, H11-H13, H20), 7.24−7.17 (3H, m, H3, H10, H18), 6.52 (1H, d, *J* 8.4, H2), 5.94 (1H, s, H8), 4.91 (1H, septet, *J* 6.3, H29), 3.49 (1H, d, *J* 15.4, H23), 2.89 (1H, d, *J* 15.8, H23'), 1.04 (3H, d, *J* 6.3, H30), 0.93 (3H, d, *J* 6.4, H30'). δ_C (126 MHz, $CDCl_3$): 170.2 (C28), 167.4 (C22), 150.1 (C1), 146.0 (C21), 145.0 (Ar C), 142.4 (Ar C), 138.6 (Ar C), 135.5 (Ar C), 129.7 (C19), 129.3 (Ar C), 129.1 (C3), 129.0 (Ar CH), 128.9 (C26), 128.5 (Ar CH), 127.7 (C25), 127.6 (Ar CH), 127.6 (C27), 127.2 (C4), 126.5 (C17), 125.2 (C18), 123.4 (Ar CH), 122.4 (C10), 117.5 (C20), 115.7 (C2), 82.4 (C8), 69.4 (C29),

* *In this case a pure racemic sample of the diastereomer formed in the asymmetric reaction could not be isolated, but it was possible to identify the relevant enantiomers from the chiral HPLC trace of the mixture of diastereomers.*

67.8 (C7/C15), 66.5 (C7/C15), 38.7 (C23), 21.2 (C30), 21.0 (C30'). HRMS (ESI+): found 558.1440; $C_{33}H_{26}{}^{35}ClNO_4Na$, $[M(^{35}Cl)+Na]^+$ requires 558.1443. ν_{max} (neat): 3028, 2981, 2929, 1776 (C=O), 1724 (C=O), 1471, 1227, 1193, 758 cm^{-1}. MP: 133−135 °C. Chiral HPLC (Chiralpak IC, 3% IPA, 97% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 10.5, t_R (minor) = 16.4. $[\alpha]_D{}^{25.0}$ +158.6 (c = 0.43, $CHCl_3$).

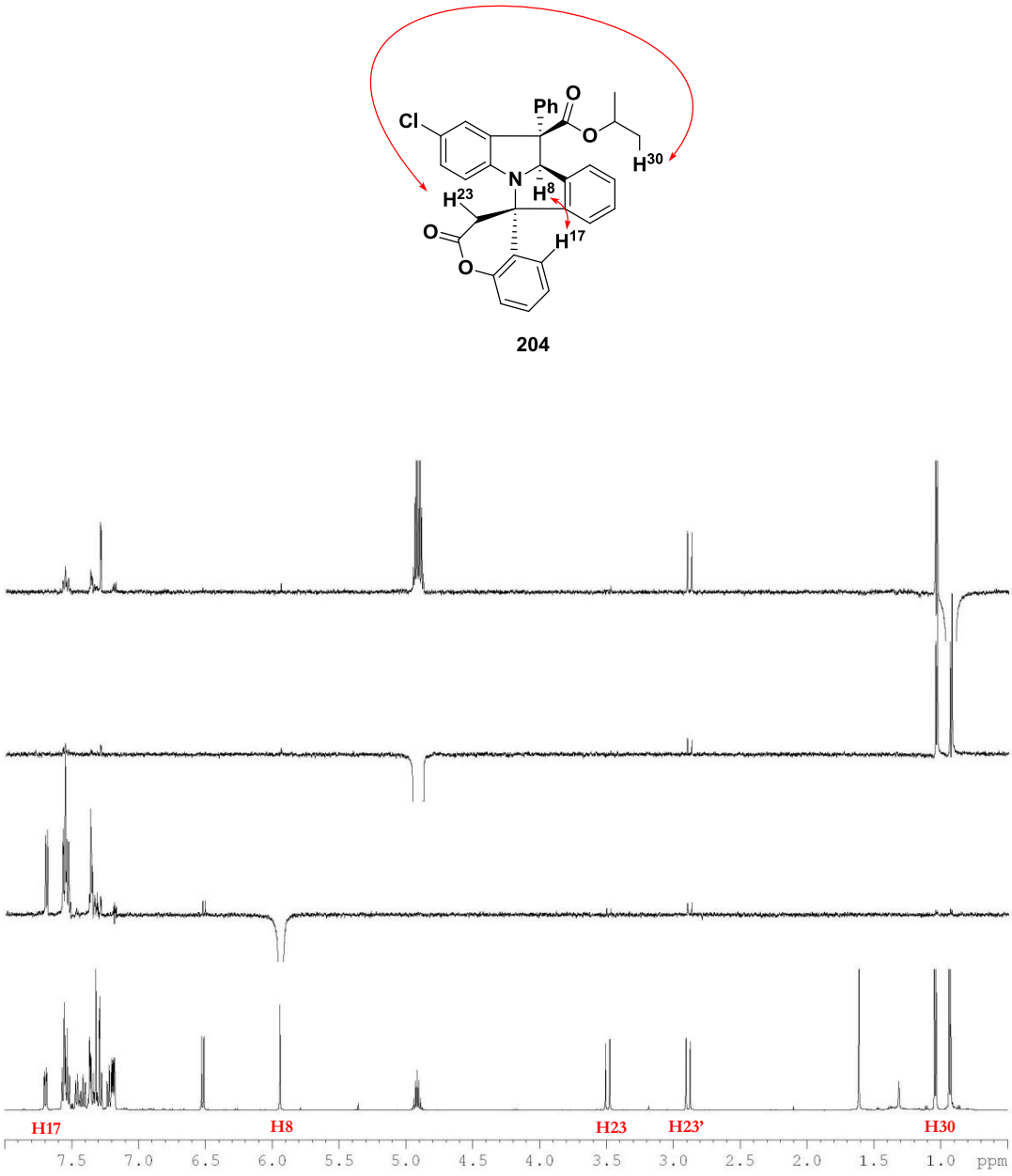
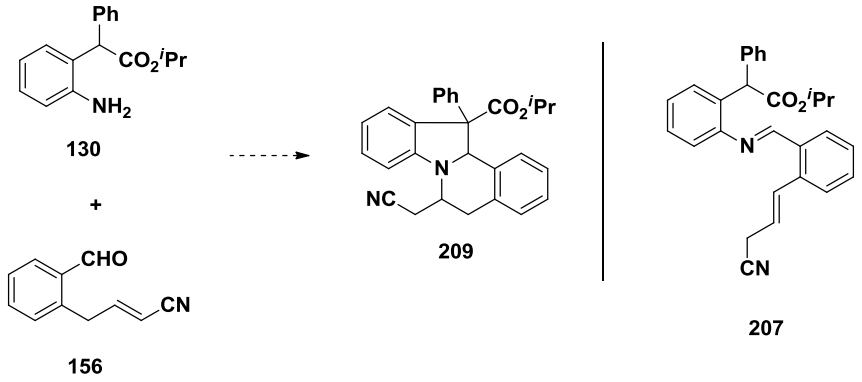


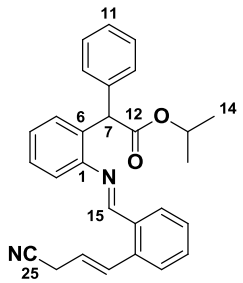
Figure 6.5. 1D nOe data for pyrrolizidine **204** (mixing time = 0.8 s).

Attempted synthesis of indolizidine 209



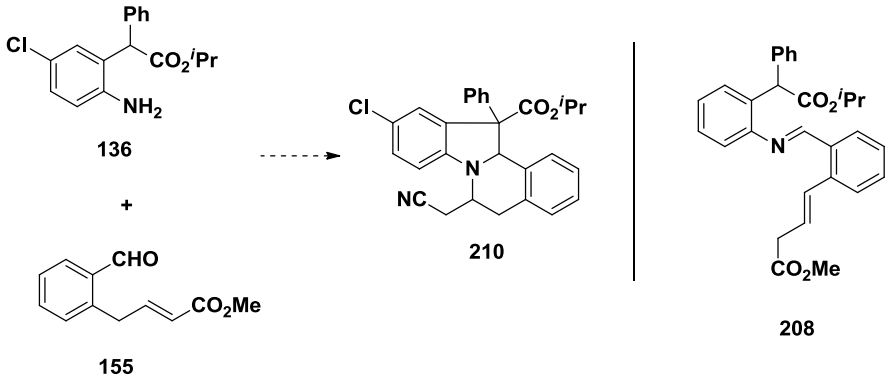
A RT suspension of aldehyde **156** (32 mg, 0.186 mmol), aniline **130** (50 mg, 0.186 mmol) and magnesium sulfate (112 mg, 0.93 mmol) in toluene (2.5 mL) was stirred for 16 h, when TLC and MS analysis indicated consumption of the starting materials. The reaction mixture was filtered over Celite® and concentrated *in vacuo*. The crude imine was redissolved in toluene (2 mL), (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **42** (8 mg, 0.019 mmol) and freshly-ground potassium hydroxide (104 mg, 1.86 mmol) were added and the reaction was stirred at RT. After 16 h ammonium chloride (aq., 10 mL) was added and the reaction mixture was diluted with dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. *Crude ^{1}H NMR analysis indicated complete conversion to imine **207**.* The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 10:1 → 5:1) to afford imine **207** (15 mg, 30%) as a pale orange oil, and as the sole product.

*iso-Propyl 2-(2-((E)-(2-((E)-3-cyanoprop-1-en-1-yl)benzylidene)amino)phenyl)-2-phenylacetate (**207**)*



δ_H (400 MHz, $CDCl_3$): 8.60 (1H, s, H15), 8.09 (1H, d, *J* 7.0, H17), 7.48−7.38 (4H, m, H18−H20, H22), 7.36−7.24 (6H, m, 6 x Ar CH), 7.21−7.18 (2H, m, 2 x Ar CH), 7.01 (1H, d, *J* 7.8, H2), 5.90 (1H, dt, *J* 15.6, 5.8, H23), 5.58 (1H, s, H7), 4.99 (1H, septet, *J* 6.3, H13), 3.30 (2H, dd, *J* 5.8, 1.6, H24), 1.14 (3H, d, *J* 6.2, H14), 1.09 (3H, d, *J* 6.2, H14'). δ_C (101 MHz, $CDCl_3$): 172.2 (C12), 158.5 (C15), 150.3 (C1), 138.4 (Ar C), 137.1 (Ar C), 133.6 (Ar C), 133.2 (Ar C), 132.4 (C22), 131.2 (C19), 129.4 (Ar CH), 129.1 (C9/C10), 128.8 (Ar CH), 128.5 (C9/C10), 128.4 (Ar CH), 128.3 (Ar CH), 127.6 (Ar CH), 127.0 (Ar CH), 126.2 (Ar CH), 121.1 (C23), 117.5 (C2), 117.2 (C25), 68.3 (C13), 52.6 (C7), 21.6 (C14), 21.5 (C14'), 21.0 (C24). ν_{max} (film): 3062 (CH), 3028 (CH), 2980 (CH), 2934 (CH), 2252 (C≡N), 1725 (C=O), 1623 (C=N), 1591, 1195, 1105, 1032, 765 cm^{-1}. HRMS (ESI): found 445.1869; $C_{28}H_{26}N_2NaO_2$ $[M+Na]^+$ requires 445.1886.

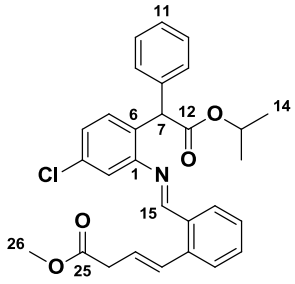
Attempted synthesis of indolizidine 210



A RT suspension of aldehyde **155** (40 mg, 0.165 mmol), aniline **136** (50 mg, 0.165 mmol) and magnesium sulfate (112 mg, 0.93 mmol) in toluene (2 mL) was stirred for 16 h, when TLC and MS analysis indicated consumption of the starting materials. The reaction mixture was filtered over Celite® and concentrated *in vacuo*. The crude imine was redissolved in toluene (2 mL), (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **42** (8 mg, 0.019 mmol) and freshly-ground potassium hydroxide (92 mg, 1.65 mmol) were added and the reaction was stirred at RT. After 16 h ammonium chloride (aq., 10 mL) was added and the reaction mixture was diluted with dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL)

and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. *Crude ^{1}H NMR analysis indicated ~80% conversion to imine* ***208****, and no cyclized products. Imine* ***208*** *was not isolated after attempted chromatography due to decomposition on silica gel, therefore only diagnostic ^{1}H NMR peaks visible in the crude mixture are given.*

*(E)-Methyl 4-(2-((E)-((5-chloro-2-(2-isopropoxy-2-oxo-1-phenylethyl)phenyl)imino)methyl)phenyl)but-3-enoate (**208**)*



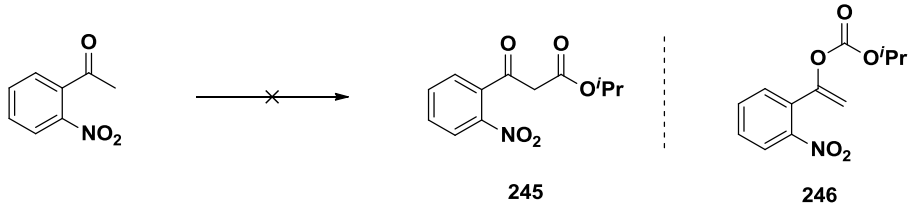
Selected ^{1}H NMR Data. δ_H (200 MHz, $CDCl_3$): 8.68 (1H, s, H15), 6.19 (1H, dt, *J* 15.0, 7.5, H23), 5.58 (1H, s, H7), 5.00 (1H, septet, *J* 6.3, H13), 3.72 (3H, s, H26), 1.13 (6H, t, *J* 6.4, H14).

HRMS (ESI): found 512.1579; $C_{29}H_{28}ClNNaO_4$ $[M+Na]^+$ requires 512.1599.

6.1 [1,6] Electrocyclization

6.1.1 Synthesis of Substrates

Attempted formation of *iso*-propyl 3-(2-nitrophenyl)-3-oxopropanoate (245)

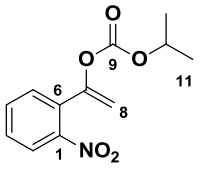


245 **246**

This reaction was carried out by analogy to a literature procedure.[214] *n*-Butyllithium (1.53 M in hexanes, 9.21 mL, 14.1 mmol) was added dropwise to a stirred −78 °C solution of

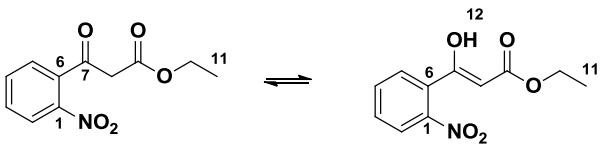
hexamethyldisilazane (2.98 mL, 14.1 mmol) in tetrahydrofuran (10 mL), and the temperature was raised to −50 °C. After 20 min the solution was cooled to −78 °C and 2'-nitroacetophenone (500 μL, 4.7 mmol) in tetrahydrofuran (2.5 mL) was added dropwise. After 1 h *iso*-propyl chloroformate (1.0 M in toluene, 7.05 mL, 7.05 mmol) was added in one portion, and the mixture was allowed to warm slowly to RT. After 2 h ammonium chloride (aq., 20 mL) was added and the aqueous layer extracted with diethyl ether (3 x 20 mL). The crude oil was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 10:1) to afford enol carbonate **246** (600 mg, 51%) as a pale yellow oil.

*iso-Propyl (1-(2-nitrophenyl)vinyl) carbonate (**246**)*



δ_H (300 MHz, $CDCl_3$): 7.78 (1H, d, *J* 8.0, H2), 7.55−7.50 (2H, m, H4 & H5), 7.44 (1H, m, H3), 5.34 (1H, d, *J* 2.5, H8), 5.17 (1H, d, *J* 2.5, H8'), 4.76 (1H, septet, *J* 6.3, H10), 1.19 (6H, d, *J* 6.2, H11). δ_C (75 MHz, $CDCl_3$): 152.0 (C7), 150.5 (C9), 147.8 (C1), 132.7 & 131.7 (C4 & C5), 130.1 (C3 & C6), 124.2 (C2), 105.7 (C8), 73.2 (C10), 21.5 (C11). ν_{max} (film): 2986 (CH), 2939 (CH), 1755 (carbonate), 1529 (NO_2), 1354 (NO_2), 1223, 1098, 910 cm^{-1}. HRMS (ESI+): found 274.0685; $C_{12}H_{13}NNaO_5$ $[M+Na]^+$ requires 274.0686.

Ethyl 3-(2-nitrophenyl)-3-oxopropanoate (248)



This compound was prepared by analogy to a literature procedure.[215] *n*-Butyllithium (1.6 M in hexanes, 47 mL, 75 mmol) was added dropwise to a stirred −78 °C solution of diisopropylamine

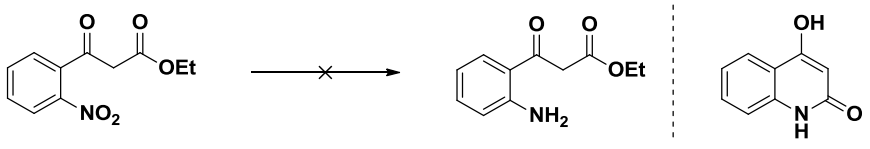
(10.6 mL, 75 mmol) in diethyl ether (100 mL), and the solution warmed to 0 °C for 15 min before cooling back to −78 °C. Ethyl acetate (6.4 mL, 65 mmol) was added, and the reaction mixture stirred for a further 20 min before adding 2-nitrobenzoyl chloride (9.3 g, 50 mmol) in diethyl ether (25 mL) dropwise. The resulting solution was stirred for 30 min and poured into 1 M aqueous hydrochloric acid (150 mL). The aqueous layer was extracted with diethyl ether (3 x 100 mL) and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 20:1 → 10:1) to afford ester **248** (6.4 g, 54%, 5:1 ketone:enol) as a white crystalline solid. *Data is consistent with that reported in the literature.*[216]

NMR Data: Ketone. δ_H (400 MHz, $CDCl_3$): 8.13 (1H, dd, *J* 8.3, 0.8, H2), 7.75 (1H, td, *J* 7.5, 1.0, H4), 7.63 (1H, ddd, *J* 8.3, 7.5, 1.4, H3), 7.50 (1H, dd, *J* 7.6, 1.5, H5), 4.13 (2H, q, *J* 7.2, H10), 3.86 (2H, s, H8), 1.20 (3H, t, *J* 7.2, H11). δ_C (101 MHz, $CDCl_3$): 194.7 (C7), 166.6 (C9), 145.4 (C1), 136.7 (C6), 134.6 (C4), 131.0 (C3), 128.1 (C5), 124.2 (C2), 61.6 (C10), 49.0 (C8), 14.0 (C11).

Selected NMR Data: Enol.[*] δ_H (400 MHz, $CDCl_3$): 12.29 (1H, s, H12), 7.58 (1H, dd, *J* 7.7, 1.8, H2), 5.40 (1H, s, H8), 4.25 (2H, q, *J* 7.1, H10), 1.31 (3H, t, *J* 7.2, H11). δ_C (101 MHz, $CDCl_3$): 172.2 (C7), 169.9 (C9), 132.7 (Ar CH), 131.1 (Ar CH), 130.1 (Ar CH), 129.5 (Ar C), 124.4 (Ar CH), 92.0 (C8), 60.7 (C10), 14.2 (C11).

MP (mixture of tautomers): 32−34 °C

Attempted formation of ethyl 3-(2-aminophenyl)-3-oxopropanoate (249)

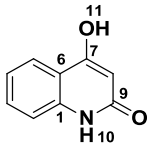


248 **249** **250**

[*] *Some enol peaks are absent since they were concealed by peaks corresponding to the major ketone tautomer.*

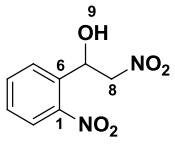
Palladium on activated carbon (10 wt%, 50 mg) was added to a stirred RT solution of nitroarene **248** (500 mg, 2.11 mmol) in ethanol (10 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen (balloon pressure). The resulting mixture was stirred vigorously for 30 min, filtered over Celite® and the solvent removed *in vacuo*. Upon standing for several hours, the crude aniline (obtained as a yellow oil, observed by crude ^{1}H NMR) spontaneously formed a white solid, which was purified by single recrystallization (ethanol) to afford hydroxyquinolone **250** (299 mg, 88%) as a white crystalline solid.

*4-Hydroxyquinolin-2(1H)-one (**250**)*



Data is consistent with that reported in the literature.[217] δ_H (400 MHz, d_6-DMSO): 11.33 (1H, br s, H10/H11), 11.21 (1H, br s, H10/H11), 7.77 (1H, dd, *J* 8.0, 1.2, H2), 7.48 (1H, ddd, *J* 8.3, 7.2, 1.3, H3), 7.25 (1H, d, *J* 8.1, H5), 7.13 (1H, ddd, *J* 8.1, 7.2, 0.9, H4), 5.75 (1H, s, H8). δ_C (101 MHz, d_6-DMSO): 164.4 (C9), 163.3 (C7), 140.0 (C1), 131.7 (C3), 123.5 (C4/C5), 121.9 (C4/C5), 115.95 & 115.83 (C2 & C6), 99.1 (C8). MP: 340−348 °C (ethanol).

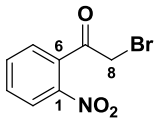
2-Nitro-1-(2-nitrophenyl)ethanol (253)



This compound was prepared according to a literature procedure.[218] Nitromethane (1.07 mL, 19.8 mmol) was added to a stirred solution of 2-nitrobenzaldehyde (1.00 g, 6.62 mmol) and imidazole (112 mg, 1.66 mmol) in water (12 mL). After 30 min the aqueous reaction mixture was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts dried over

anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 3:2) to afford alcohol **253** (1.28 g, 91%) as a yellow crystalline solid. *Data is consistent with that reported in the literature.*[219] δ_H (400 MHz, $CDCl_3$): 8.09 (1H, d, *J* 8.2, H2), 7.97 (1H, d, *J* 7.8, H5), 7.76 (1H, t, *J* 7.7, H4), 7.57 (1H, t, *J* 7.8, H3), 6.06 (1H, dt, *J* 8.6, 2.8, H7), 4.89 (1H, dd, *J* 13.9, 2.2, H8), 4.57 (1H, dd, *J* 13.9, 9.1, H8'), 3.17 (1H, d, *J* 4.2, H9). δ_C (101 MHz, $CDCl_3$):* 134.4 (C4), 133.9 (C6), 129.7 (C3), 128.7 (C5), 125.0 (C2), 80.0 (C8), 66.8 (C7). MP: 42−43 °C (petrol/diethyl ether). ν_{max} (film): 3533 (OH), 1608, 1558 (NO_2), 1547 (NO_2), 1346 (NO_2), 1098, 800, 755 cm^{-1}.

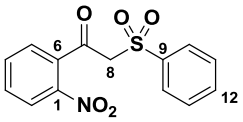
2-Bromo-2'-nitroacetophenone (256)



This compound was prepared according to a literature procedure.[148] Bromine (1.93 mL, 37 mmol) and 2'-nitroacetophenone (5.0 mL, 37 mmol) in acetic acid (50 mL) were heated to 90 °C for 1 h, after which the reaction mixture was poured into ice water, and the resulting precipitate collected by filtration, washed with copious amounts of water and dried under vacuum, affording 2-bromo-2'-nitroacetophenone **256** (7.09 g, 78%) as a yellow crystalline solid.† *Data is consistent with that reported in the literature.*[220] δ_H (400 MHz, $CDCl_3$): 8.22 (1H, dd, *J* 8.3, 0.9, H2), 7.80 (1H, td, *J* 7.5, 1.1, H4), 7.69 (1H, td, *J* 7.9, 1.4, H3), 7.51 (1H, dd, *J* 7.6, 1.4, H3), 7.51 (1H, dd, *J* 7.6, 1.4, H5), 4.31 (2H, s, H8). δ_C (101 MHz, $CDCl_3$): 194.3 (C7), 145.3 (C1), 135.0 (C6), 134.7 (C4), 131.3 (C3), 129.1 (C5), 124.4 (C2), 33.8 (C8). ν_{max} (film): 3015 (CH), 2938 (CH), 1720 (C=O), 1526 (NO_2), 1389 (NO_2), 1190, 996, 790, 695 cm^{-1}. MP: 53−56 °C (ethyl acetate).

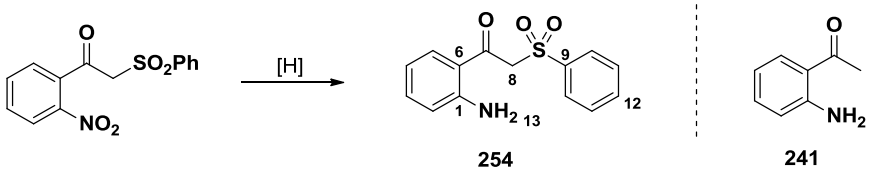
1-(2-Nitrophenyl)-2-(phenylsulfonyl)ethanone (255)

* *Note that the peak corresponding to C1 was not observed.*
† *Note: This compound is highly lachrymatory.*



This compound was prepared by analogy to a literature procedure.[221] Sodium benzenesulfinate (6.01 g, 37 mmol) was added to a stirred RT solution of 2-bromo-2'-nitroacetophenone **256** (1.55 g, 6.4 mmol) in *N*,*N*-dimethylformamide (50 mL). After 18 h the reaction mixture was diluted with diethyl ether (150 mL) and washed with 10% magnesium sulfate solution (3 x 50 mL). The combined aqueous washings were extracted with diethyl ether (2 x 50 mL) and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude solid was purified by flash column chromatography (silica gel, petrol:ethyl acetate 4:1 → 3:2) to afford sulfone **255** (1.06 g, 54%) as a yellow solid. δ_H (400 MHz, $CDCl_3$): 8.16 (1H, d, *J* 8.2, H2), 7.92 (2H, d, *J* 7.9, H10), 7.82 (1H, t, *J* 7.5, H4), 7.74−7.65 (2H, m, H3 & H12), 7.65−7.47 (3H, m, H5 & H11), 4.62 (2H, s, H8). δ_C (101 MHz, $CDCl_3$): 189.8 (C7), 145.2 (C1), 138.8 (C9), 136.3 (C6), 135.0 (C4), 134.4 (C12), 131.6 (C3), 129.4 (C11), 129.0 (C5), 128.4 (C10), 124.3 (C2), 66.7 (C8). ν_{max} (film): 2942 (CH), 1697 (C=O), 1572 (NO_2), 1344 (NO_2), 1155, 746, 711 cm^{-1}. HRMS (ESI): found 328.0245; $C_{14}H_{11}NNaO_5S$ $[M+Na]^+$ requires 328.0250. MP: 80−84 °C (petrol/ethyl acetate).

1-(2-Aminophenyl)-2-(phenylsulfonyl)ethanone (254)

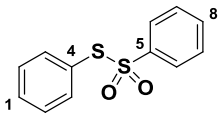


Method I: Zinc dust (1.6 g, 24 mmol) was added to a stirred solution of sulfone **255** (508 mg, 1.7 mmol) and acetic acid (4 mL) in dichloromethane (50 mL). After 3 h the reaction mixture was filtered and concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 4:1) to afford aniline **254** (168 mg, 37%) as a

white crystalline solid. *2'-Aminoacetophenone* ***241*** *(117 mg, 51%) was also obtained as a colourless oil, with* ^{1}H *and* ^{13}C *NMR data in agreement with literature values.*

Method II: Platinum(IV) oxide (7.5 mg) was added to a stirred RT solution of nitroarene **255** (161 mg, 0.53 mmol) in methanol (2 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen (balloon pressure). The resulting mixture was stirred vigorously for 4 h, filtered over Celite® and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 4:1 → 3:2) to afford aniline **254** (126 mg, 87%) as a white crystalline solid. δ_H (400 MHz, $CDCl_3$): 7.92 (2H, d, *J* 7.5, H10), 7.69−7.63 (2H, m, H5 & H12), 2.55 (2H, t, *J* 7.8, H11), 7.23 (1H, t, *J* 8.5, H3), 6.67−6.62 (2H, m, H2 & H4), 6.29 (2H, br s, H13), 4.70 (2H, s, H8). δ_C (101 MHz, $CDCl_3$): 188.7 (C7), 151.5 (C1), 139.0 (C9), 135.7 (C3), 134.1 (C12), 132.3 (C5), 129.1 (C11), 128.5 (C10), 117.3 (C2/C4), 117.0 (C6), 116.1 (C2/C4), 64.2 (C8). ν_{max} (film): 3483 (NH_2), 3360 (NH_2), 3003 (CH), 2970 (CH), 1739 (C=O), 1631, 1366, 1230, 1217, 752 cm^{-1}. HRMS (ESI): found 298.0507; $C_{14}H_{13}NNaO_3S$ $[M+Na]^+$ requires 298.0508. MP: 114−116 °C (ethyl acetate/petrol).

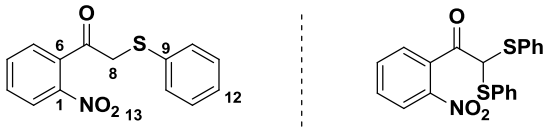
S-Phenyl benzenethiosulfonate (265)



This compound was prepared according to a literature procedure.[222] Aqueous hydrogen peroxide solution (27% w/w, 1.65 mL, 14.1 mmol) was added dropwise to a stirred 50 °C solution of diphenyl disulfide (1.5 g, 6.9 mmol) in acetic acid (2.75 mL) and the resulting mixture stirred for 24 h at this temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (silica gel, petrol:diethyl ether, 50:1 → 10:1) to afford thiosulfonate **265** (1.28 g, 74%) as a white crystalline solid. *Data is consistent with that reported in the literature.*[149] δ_H (400 MHz, $CDCl_3$): 7.62−7.55 (3H, m, H6 & H8), 7.48 (1H, tt, *J* 6.1, 2.7, H1), 7.42 (2H, t, *J* 7.9,

H7), 7.39−7.32 (4H, m, H2 & H3). δ_C (101 MHz, $CDCl_3$): 142.9 (C5), 136.6 (C3), 133.6 (C8), 131.4 (C1), 129.4 (C7), 128.8 (C2), 127.8 (C4), 127.6 (C6). MP: 40−43 °C (diethyl ether).

1-(2-Nitrophenyl)-2-(phenylthio)ethanone (266)



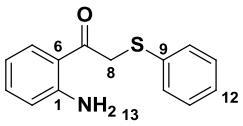
266 **267**

Method I. This reaction was carried out by analogy to a literature procedure.[149] *n*-Butyllithium (1.54 M in hexane, 1.08 mL, 1.66 mmol) was added to a stirred −78 °C solution of diisopropylamine (233 μL, 1.66 mmol) in tetrahydrofuran (2 mL), and the resulting mixture warmed to 0 °C. After 15 min the reaction mixture was cooled to −78 °C and 2'-nitroacetophenone (250 mg, 1.51 mmol) in tetrahydrofuran (2 mL) was added dropwise over 10 min. The reaction mixture was warmed to 0 °C, then added *via* cannula to a stirred 0 °C solution of *S*-phenyl benzene thiosulfonate (378 mg, 1.51 mmol) in tetrahydrofuran (2 mL), and stirred for a further 4 h at this temperature. *TLC revealed that most of the ketone remained unreacted, and MS indicated that the only product formed was* ***267****, the result of double addition. This method was not further pursued.*

Method II. This reaction was carried out by analogy to a literature procedure.[223] Sodium thiophenolate (415 mg, 3.2 mmol) was added in one portion to a stirred RT solution of bromoketone **256** (700 mg, 2.9 mmol) in tetrahydrofuran (20 mL). After 1.5 h the reaction mixture was diluted with diethyl ether (100 mL) and pH 7 buffer solution (50 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts washed with brine (50 mL) dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 10:1) to afford thioether **266** (550 mg, 70%) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 8.14 (1H, d, *J* 7.9, H2), 7.65 (1H, td, *J* 7.5, 1.1, H4), 7.59 (1H, td, *J* 7.8, 1.4,

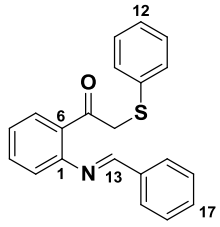
H3), 7.32−7.19 (6H, m, H5, H10, H11, H12), 4.12 (2H, s, H8). δ_C (101 MHz, $CDCl_3$): 197.1 (C7), 145.4 (C1), 136.1 (C9), 134.2 (C4), 134.1 (C6), 130.7 (C3), 130.0 (C10/C11), 129.1 (C10/C11 & C5), 127.2 (C12), 124.1 (C2), 43.7 (C8). HRMS (ESI): found 296.0351; $C_{14}H_{11}NNaO_3S$ $[M+Na]^+$ requires 296.0352. ν_{max} (neat): 3063 (CH), 1699 (C=O), 1523 (NO_2), 1344 (NO_2), 737, 690 cm^{-1}.

1-(2-Aminophenyl)-2-(phenylthio)ethanone (264)



This compound was prepared by analogy to a literature procedure.[80] Tin(II) chloride dihydrate (1.23 g, 5.5 mmol) was added to a stirred solution of nitroarene **266** (300 mg, 1.1 mmol) in ethyl acetate (10 mL) and heated to reflux. After 1 h the reaction mixture was allowed to cool to RT and Rochelle's salt solution (aq., 20 mL) was added. The resulting biphasic mixture was stirred vigorously for 1 h, and the aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:diethyl ether, 8.5:1.5) and subsequent recrystallization (ethyl acetate/petrol) to afford aniline **264** (213 mg, 80%) as a yellow crystalline solid. δ_H (400 MHz, $CDCl_3$): 7.70 (1H, dd, *J* 8.0, 1.1, H5), 7.41 (2H, d, *J* 7.2, H10), 7.32−7.26 (3H, m, H3 & H11), 7.22 (1H, t, *J* 7.3, H12), 6.69−6.62 (2H, m, H2 & H4), 6.28 (2H, br s, H13), 4.32 (2H, s, H8). δ_C (101 MHz, $CDCl_3$): 196.0 (C7), 151.0 (C1), 135.4 (C9), 134.9 (C3), 131.3 (C5), 130.1 (C10), 129.0 (C11), 126.8 (C12), 117.5 (C2), 116.3 (C6), 115.8 (C4), 42.3 (C8). ν_{max} (film): 3482 (NH_2), 3344 (NH_2), 2911 (CH), 1657 (C=O), 1610, 1575, 1547, 1197, 1026, 737 cm^{-1}. HRMS (ESI): found 266.0613; $C_{14}H_{13}NNaOS$ $[M+Na]^+$ requires 266.0610. MP: 71−74 °C (ethyl acetate/petrol).

(*E*)-1-(2-(Benzylideneamino)phenyl)-2-(phenylthio)ethanone (269)

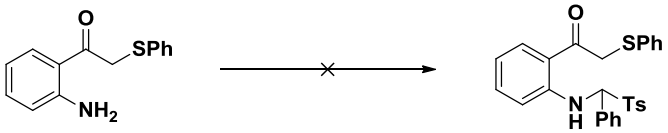


Benzaldehyde (33 μL, 0.31 mmol) was added to a stirred RT suspension of aniline **264** (50 mg, 0.21 mmol), activated 4 Å powdered molecular sieves (200 mg) and acetic acid (6 μL, 0.1 mmol) in dichloromethane (2.5 mL). After 24 h the reaction mixture was filtered over Celite® and concentrated *in vacuo*. The crude material thus obtained (54 mg) consisted of imine **269** (~36 mg [calculated*], ~55%) and residual aniline **264** (~19 mg [calculated*], ~38%). *Further purification was not possible due to facile imine hydrolysis. Product formation was determined on the basis of MS and ^{1}H NMR analysis of the crude mixture.*

*Selected NMR data – Imine **269**.* δ_H (200 MHz, $CDCl_3$): 8.40 (1H, s, H13), 7.90 (2H, dd, *J* 7.5, 2.0, H15), 7.78 (1H, dd, *J* 7.7, 1.5, H5), 7.02 (1H, dd, *J* 7.9, 0.9, H12), 4.50 (2H, s, H8).

HRMS (ESI+): found 354.0914; $C_{21}H_{17}NNaOS$, $[M+Na]^+$ requires 354.0923

Attempted formation of 1-(2-((phenyl(tosyl)methyl)amino)phenyl)-2-(phenylthio)ethanone (270)

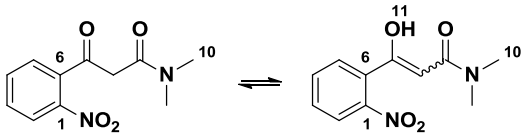


This reaction was attempted by analogy to a literature procedure.[224] *para*-Toluenesulfinic acid (80 mg, 0.51 mmol), benzaldehyde (84 μL, 0.82 mmol) and anhydrous magnesium sulfate (80 mg, 0.7 mmol) were added to a stirred RT solution of aniline **264** (100 mg, 0.41 mmol) in dichloromethane (4 mL). After 12 h the reaction mixture was filtered over Celite® and

* *Mass yield calculated from molar ratio of imine:aniline in crude ^{1}H NMR spectrum.*

concentrated *in vacuo*. *^{1}H NMR and MS analysis of the crude reaction mixture indicated only unreacted starting materials.*

N,*N*-Dimethyl-3-(2-nitrophenyl)-3-oxopropanamide (282)



This compound was prepared by analogy to a literature procedure.[215] A solution of 2-nitrobenzoic acid (1.67 g, 10 mmol) in thionyl chloride (3 mL) was heated to reflux for two hours. The resulting brown solution was cooled to RT and the solvent removed *in vacuo* to afford the crude acid chloride. *n*-Butyllithium (1.6 M in hexanes, 12.5 mL, 20 mmol) was added dropwise to a solution of diisopropylamine (2.82 mL, 20 mmol) in diethyl ether (25 mL) at −78 °C and the mixture allowed to warm to 0 °C for 15 min before cooling back to −78 °C. *N*,*N*-Dimethyl acetamide (1.20 mL, 13 mmol) was added dropwise to the reaction mixture, and after 20 min a solution of the crude 2-nitrobenzoyl chloride in diethyl ether (10 mL) was added over 5 min. After a further 30 min the reaction mixture was quenched cautiously with hydrochloric acid (1 *N*, 30 mL) and the organic layer extracted with diethyl ether (2 x 10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 2:1 → 1:1) to afford **282** (870 mg, 38%, 10:7, *ketone*:*enol*) as a yellow amorphous solid.

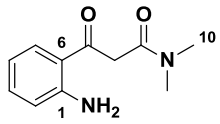
Selected NMR Data – Ketone.[*] δ_H ($CDCl_3$, 400 MHz): 8.12 (1H, dd, *J* 8.2, 0.7, H2), 4.00 (2H, s, H8), 3.11 (3H, s, H10), 2.97 (3H, s, H10'). δ_C ($CDCl_3$, 101 MHz): 196.2 (C7), 48.7 (C8), 37.9 (C10), 35.5 (C10').

[*] *Full structural characterization was not possible for this compound since the ketone and enol tautomers were inseperable; selected characteristic ^{1}H and ^{13}C peaks are therefore presented.*

Selected NMR Data – Enol. δ_H ($CDCl_3$, 400 MHz): 16.39 (1H, br s, H11), 7.84 (1H, dd, *J* 7.9, 0.9, H2), 5.52 (1H, s, H8), 3.05 (6H, s, H10). δ_C ($CDCl_3$, 101 MHz): 166.2 (C7), 88.6 (C8).

ν_{max} (neat): 2937 (CH), 1720 (ketone), 1636 (amide), 1526 (NO_2), 1360 (NO_2), 1163, 800, 779 cm^{-1}. HRMS (ESI+): found 259.0697; $C_{11}H_{12}N_2NaO_4$, $[M+Na]^+$ requires 259.0689.

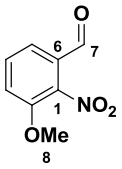
3-(2-Aminophenyl)-*N*,*N*-dimethyl-3-oxopropanamide (283)



Palladium on activated carbon (10 wt%, 50 mg) was added to a stirred RT solution of nitroarene **282** (500 mg, 2.43 mmol) in methanol (10 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen (balloon pressure). The resulting mixture was stirred vigorously for 30 min, filtered over Celite® and the solvent removed *in vacuo*. The crude residue was purified by single recrystallization from hot toluene to afford **283** as a yellow crystalline solid (394 mg, 79%). δ_H ($CDCl_3$, 400 MHz): 7.76 (1H, dd, *J* 8.4, 1.4, H5), 7.28 (1H, ddd, *J* 8.3, 7.0, 1.4, H3), 6.69−6.64 (2H, m, H2 & H4), 6.30 (2H, br s, NH_2), 4.10 (2H, s, H8), 3.04 (3H, s, H10), 3.02 (3H, s, H10'). δ_C ($CDCl_3$, 101 MHz):* 195.8 (C7), 167.7 (C9), 150.8 (C1), 134.9 (C3), 131.7 (C5), 117.3 & 116.0 (C2 & C4), 46.6 (C8), 38.1 (C10), 35.6 (C10'). HRMS (ESI+): found 229.0954; $C_{11}H_{14}N_2NaO_2$, $[M+Na]^+$ requires 229.0947. ν_{max} (neat): 3440 (NH_2), 3329 (NH_2), 3071 (CH), 2975 (CH), 2933 (CH), 1647 (ketone), 1614 (amide), 1393, 1145, 756 cm^{-1}. MP: 126−128 °C (toluene).

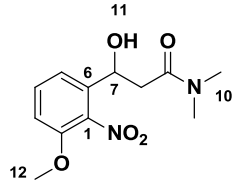
3-Methoxy-2-nitrobenzaldehyde (308)

* *The ^{13}C peak corresponding to C6 was not observed, and is presumed to coincide with another peak.*



This compound was prepared according to a literature procedure.[225] *m*-Anisaldehyde (9.0 mL, 74 mmol) was added slowly to a 0 °C mixture of sulfuric acid (20 mL) and nitric acid (50 mL). The mixture was stirred for a further 30 min at RT, poured cautiously into ice water (500 mL) and extracted with dichloromethane (3 x 250 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatograpy (silica gel, petrol:ethyl acetate, 20:1 → 4:1), and the product further purified by recrystallization (toluene) to afford 3-methoxy-2-nitrobenzaldehyde **308** (4.2 g, 32%) as a white crystalline solid. *Data is consistent with that reported in the literature.*[226] δ_H (400 MHz, $CDCl_3$): 9.95 (1H, s, H7), 7.63 (1H, t, *J* 8.0, H4), 7.51 (1H, dd, *J* 7.7, 1.1, H5), 7.35 (1H, dd, *J* 8.4, 0.9, H3), 3.96 (3H, s, H8). δ_C (101 MHz, $CDCl_3$):* 186.9 (C7), 151.1 (C2), 131.7 (C4), 128.2 (C1), 122.0 (C5), 118.4 (C3), 56.9 (C8). ν_{max} (neat): 3100 (CH), 2958 (CH), 2872 (CH), 1702 (C=O), 1489 (NO_2), 1275 (NO_2), 835, 739 cm^{-1}. HRMS (EI/FI): found 181.0368; $C_8H_7NO_4$, $[M]^{\bullet+}$ requires 181.0375. MP: 94−99 °C (toluene).

(±)-3-Hydroxy-3-(3-methoxy-2-nitrophenyl)-*N*,*N*-dimethylpropanamide (309)

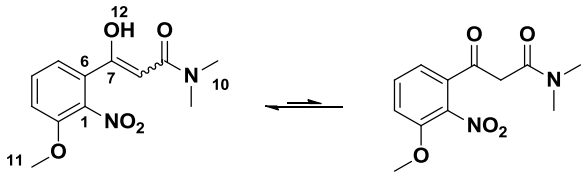


n-Butyllithium (1.6 M in hexanes, 6.9 mL, 11.0 mmol) was added dropwise to a stirred solution of diisopropylamine (1.56 mL, 11.0 mmol) in tetrahydrofuran (10 mL) at −78 °C. After 15 min the solution was allowed to warm to 0 °C, and after a further 15 min was cooled

* *The ^{13}C peak corresponding to C6 was not observed.*

to -78 °C. Dimethyl acetamide (1.02 mL, 11.04 mmol) was added, and the reaction mixture stirred for a further 20 min, then added dropwise *via* cannula to a stirred −78 °C solution of aldehyde **308** (1.0 g, 5.5 mmol) in tetrahydrofuran (10 mL), and the reaction mixture was allowed to warm to 0 °C. After 30 min ammonium chloride (aq., 25 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude solid was purified by a single recrystallization (dichloromethane/petrol) to afford secondary alcohol **309** (1.05 g, 71%) as an off-white crystalline solid. δ_H (400 MHz, $CDCl_3$): 7.46 (1H, t, *J* 7.8, H4), 7.30 (1H, d, *J* 7.8, H5), 6.98 (1H, dd, *J* 8.5, 0.9, H3), 5.23 (1H, d, *J* 2.3, H11), 5.09 (1H, dt, *J* 9.9, 2.3, H7), 3.90 (3H, s, H12), 2.97 (3H, s, H10), 2.95 (3H, s, H10'), 2.83 (1H, dd, *J* 16.3, 2.4, H8), 2.55 (1H, dd, *J* 16.4, 9.9, H8'). δ_C (101 MHz, $CDCl_3$):* 171.8 (C9), 150.4 (C2), 136.1 (C1), 131.3 (C4), 118.8 (C5), 111.5 (C3), 66.5 (C7), 56.5 (C12), 40.7 (C8), 37.1 & 35.3 (C10 & C10'). ν_{max} (neat): 3474 (OH), 3095 (CH), 2946 (CH), 1632 (amide), 1522 (NO_2), 1370 (NO_2), 1058, 798 cm^{-1}. HRMS (ESI+): found 291.0951; $C_{12}H_{16}N_2O_5Na$, $[M+Na]^+$ requires 291.0953. MP: 148−151 °C (dichloromethane/petrol).

3-Hydroxy-3-(3-methoxy-2-nitrophenyl)-*N*,*N*-dimethylacrylamide (310)

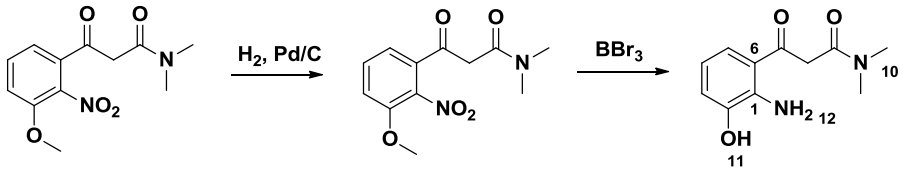


Manganese dioxide (4.1 g, 47 mmol) was added to a stirred solution of secondary alcohol **309** (500 mg, 1.94 mmol) in dichloromethane (20 mL) and heated to reflux. After 16 h the heterogeneous mixture was allowed to cool to RT and the crude mixture passed through filter paper. The resulting black mixture was purified by flash column chromatography (silica gel, methanol:dichloromethane, 2:98) to afford **310** (379 mg, 73%) as a yellow crystalline solid

* *The ^{13}C peak corresponding to C6 was not observed.*

composed of a 3:1 mixture of enol:ketone tautomeric forms.* δ_H (400 MHz, $CDCl_3$): 15.42 (1H, s, H12), 7.45 (1H, t, *J* 8.1, H4), 7.22 (1H, dd, *J* 7.9, 0.9, H5), 7.11 (1H, d, *J* 8.4, H3), 5.58 (1H, s, H8), 3.91 (3H, s, H11), 3.03 (6H, s, H10). δ_C (101 MHz, $CDCl_3$): 171.5 (C7), 167.8 (C9), 151.0 (C2), 130.9 (C4), 129.8 (C1), 121.2 (C6), 120.1 (C5), 114.1 (C3), 88.7 (C8), 56.6 (C11), 38.1 & 35.6 (C10 & C10'). ν_{max} (neat): 2949 (CH), 1600 (amide), 1535 (NO_2), 1372 (NO_2), 1122, 1053, 801 cm^{-1}. HRMS (ESI+): found 289.0795; $C_{12}H_{14}N_2O_5Na$, $[M+Na]^+$ requires 289.0795. MP: 141−143 °C (dichloromethane).

3-(2-Amino-3-hydroxyphenyl)-*N*,*N*-dimethyl-3-oxopropanamide (307)



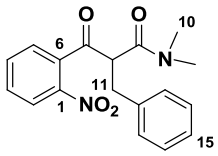
310 **353** **307**

Palladium on activated carbon (10 wt%, 20 mg) was added to a stirred RT solution of nitroarene **310** (200 mg, 0.75 mmol) in methanol (4 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen (balloon pressure). After 2.5 h the reaction mixture was filtered over Celite® and concentrated *in vacuo* to afford the crude *O*-methyl aniline **353** as a yellow oil. The residue was dissolved in dichloromethane (10 mL) and cooled to 0 °C, and boron tribromide (1.0 M in dichloromethane, 2.66 mL, 2.66 mmol) was added dropwise to this stirred solution. The resulting mixture was allowed to warm to RT and stirred for a further 16 h. Water (10 mL) was added and the aqueous layer was exhaustively extracted with 3:1 chloroform:*iso*-propanol (6 x 10 mL) and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, dichloromethane:methanol, 98:2) to afford aminophenol **307** (62 mg, 37%) as a yellow solid. δ_H (400 MHz, d_6-DMSO): 9.72 (1H, s, H11),

** The ^1H and ^{13}C data presented is for the major (enol) tautomer. The presence of the ketone as a minor component is asserted on the basis of the characteristic CH_2 peak (4.03 ppm) in the ^1H and ketone peak (192.2 ppm) in the ^{13}C spectra.*

7.19 (1H, dd, *J* 8.3, 0.9, H5), 6.81 (1H, dd, *J* 7.5, 0.9, H3), 6.73 (2H, br s, H12), 6.40 (1H, t, *J* 7.9, H4), 4.05 (2H, s, H8), 2.95 (3H, s, H10), 2.84 (3H, s, H10'). δ_C (101 MHz, d_6-DMSO): 197.5 (C7), 168.6 (C9), 145.4 (C2), 142.0 (C1), 122.9 (C5), 117.6 (C3), 117.4 (C6), 114.6 (C4), 46.8 (C8), 38.2 (C10), 35.6 (C10'). HRMS (ESI+): found 245.0901; $C_{11}H_{14}N_2O_3Na$, $[M+Na]^+$ requires 245.0897. ν_{max} (neat): 3450 (NH_2), 3331 (NH_2 and OH), 2934 (CH), 1641 (ketone), 1612 (amide), 1550, 1147, 851, 741 cm^{-1}. MP: 225−228 °C (dichloromethane).

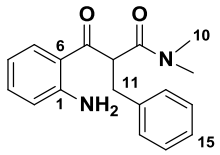
(±)-2-Benzyl-*N*,*N*-dimethyl-3-(2-nitrophenyl)-3-oxopropanamide (340)



This compound was prepared according to a modified literature procedure.[227] Caesium carbonate (0.759 g, 2.66 mmol) was added to a stirred solution of nitroarene **282** (550 mg, 2.66 mmol) in acetone (5 mL) at 0 °C and the resulting mixture allowed to warm to RT. Benzyl bromide (275 μL, 2.66 mmol) was added dropwise and the reaction was stirred for 16 h. The reaction mixture was diluted with dichloromethane (25 mL) and ammonium chloride (aq., 15 mL) was added, and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 3:1) to afford **340** (587 mg, 77%) as a viscous yellow oil, which crystallized upon prolonged standing to a yellow solid. δ_H ($CDCl_3$, 400 MHz): 8.16 (1H, dd, *J* 8.3, 0.8, H2), 7.73 (1H, dt, *J* 7.5, 1.1, H4), 7.60 (1H, ddd, *J* 8.2, 7.5, 1.3, H3), 7.53 (1H, dd, *J* 7.6, 1.3, H5), 7.36−7.16 (5H, m, H13-H15), 4.50−4.44 (1H, m, H8), 3.31 (2H, d, *J* 7.8, H11), 2.75 (3H, s, H10), 2.44 (3H, s, H10'). δ_C ($CDCl_3$, 101 MHz): 198.2 (C7), 168.8 (C9), 145.1 (C1), 138.1 (C12), 136.9 (C6), 134.6 (C4), 130.3 (C3), 129.0 (C5), 129.0 & 128.5 (C13 & C14), 126.8 (C15), 124.1 (C2), 57.3 (C8), 37.4 (C10), 35.8 (C11), 35.7 (C10'). HRMS (ESI+): found 349.1159; $C_{18}H_{18}N_2NaO_4$, $[M+Na]^+$

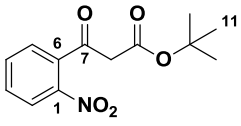
requires 349.1159. ν_{max} (neat): 3062 (CH), 3030 (CH), 2930 (CH), 1719 (ketone) 1626 (amide), 1526 (NO_2), 1343 (NO_2), 750, 692 cm^{-1}. MP: 62−66 °C (chloroform).

(±)-3-(2-Aminophenyl)-2-benzyl-*N*,*N*-dimethyl-3-oxopropanamide (341)



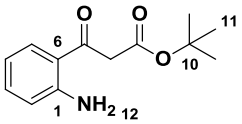
Palladium on activated carbon (10 wt%, 28 mg) was added to a stirred RT solution of nitroarene **340** (280 mg, 0.86 mmol) in methanol (5 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen (balloon pressure). The resulting mixture was stirred vigorously for two hours, filtered over Celite® and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 3:2) to afford **341** as a yellow crystalline solid (180 mg, 71%). δ_H ($CDCl_3$, 400 MHz): 7.58 (1H, d, *J* 8.2, H5), 7.30−7.18 (6H, m, H3, H13-H15), 6.67 (1H, d, *J* 8.3, H2), 6.60 (1H, t, *J* 7.5, H4), 6.33 (2H, br s, NH_2), 4.68 (1H, dd, *J* 8.6, 5.3, H8), 3.45 (1H, dd, *J* 13.9, 8.5, H11), 3.22 (1H, dd, *J* 13.9, 5.2, H11'), 2.93 (3H, s, H10), 2.78 (3H, s, H10'). δ_C ($CDCl_3$, 101 MHz): 197.4 (C7), 169.6 (C9), 151.3 (C1), 139.6 (C12), 134.6 (C3), 130.0 (C5), 129.1 & 129.1 (C13 & C14), 126.5 (C15), 117.7 (C2), 116.6 (C6), 115.8 (C4), 54.5 (C8), 37.1 (C10), 35.9 (C10'), 35.8 (C11). HRMS (ESI+): found 319.1413; $C_{18}H_{20}N_2NaO_2$, $[M+Na]^+$ requires 319.1417. ν_{max} (neat): 3433 (NH_2), 3314 (NH_2), 3032 (CH), 2934 (CH), 1651 (ketone), 1614 (amide), 1484, 1257, 749, 696 cm^{-1}. MP: 103−109 °C (chloroform).

tert-Butyl 3-(2-nitrophenyl)-3-oxopropanoate (333)



This compound was prepared by analogy to a literature procedure.[215] *n*-Butyllithium (1.6 M in hexanes, 30.3 mL, 48.5 mmol) was added to a stirred solution of diisopropylamine (6.84 mL, 48.5 mmol) in diethyl ether (60 mL) at −78 °C. The stirring solution was allowed to warm to 0 °C and was cooled to −78 °C after 15 min. *tert*-Butyl acetate (5.6 mL, 42 mmol) was added and the mixture was stirred for a further 20 min before adding 2-nitrobenzoyl chloride (4.29 mL, 32.3 mmol). The resulting turbid mixture was stirred for 30 min, hydrochloric acid (1 M aq., 100 mL) was added and the aqueous layer extracted with diethyl ether (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 20:1) to afford **333** (4.55 g, 53%) as a viscous orange oil composed of a 7:1 mixture of ketone:enol tautomeric forms.* δ_H (400 MHz, $CDCl_3$): 8.15 (1H, dd, *J* 8.2, 0.9, H2), 7.75 (1H, td, *J* 7.5, 1.1, H4), 7.63 (1H, ddd, *J* 8.2, 7.5, 1.3, H3), 7.51 (1H, dd, *J* 7.6, 1.3, H5), 3.79 (2H, s, H8), 1.37 (9H, s, H11). δ_C (101 MHz, $CDCl_3$): 195.2 (C7), 165.7 (C9), 145.5 (C1), 136.9 (C6), 134.4 (C4), 130.8 (C3), 128.3 (C5), 124.2 (C2), 82.4 (C10), 50.4 (C8), 27.8 (C11). ν_{max} (neat): 2980 (CH), 2935 (CH), 1731 (ketone), 1703 (ester), 1574 (NO_2), 1346 (NO_2), 1150, 853, 748 cm^{-1}. HRMS (ESI+): found 288.0843; $C_{13}H_{15}NO_5Na$, $[M+Na]^+$ requires 288.0842.

tert-Butyl 3-(2-aminophenyl)-3-oxopropanoate (334)

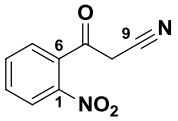


Palladium on activated carbon (10 wt%, 100 mg) was added to a stirred RT solution of nitroarene **333** (1.0 g, 3.8 mmol) in methanol (20 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen (balloon pressure). The resulting mixture was stirred vigorously for 2.5 h, filtered over Celite® and the solvent removed *in vacuo*. The

* *The ^1H and ^{13}C data presented is for the major (ketone) tautomer. The presence of the enol as a minor component is asserted on the basis of characteristic OH (12.45 ppm) and C=CH (5.33) peaks in the ^1H spectrum.*

crude residue was purified flash column chromatography (silica gel, petrol:ethyl acetate, 8:2) to afford aniline **334** (681 mg, 77%) as a pale yellow oil.* δ_H ($CDCl_3$, 400 MHz): 7.61 (1H, d, *J* 7.3, H5), 7.28 (1H, td, *J* 7.7, 0.5, H3), 6.68−6.62 (2H, m, H2 & H4), 6.28 (2H, br s, H12), 3.87 (2H, s, H8), 1.47 (9H, s, H11). δ_C ($CDCl_3$, 101 MHz):† 195.0 (C7), 167.3 (C9), 150.7 (C1), 134.8 (C3), 131.4 (C5), 117.3 & 115.8 (C2 & C4), 81.7 (C10), 48.2 (C8), 28.0 (C11). HRMS (ESI+): found 258.1106; $C_{13}H_{17}NNaO_3$, $[M+Na]^+$ requires 258.1101. ν_{max} (film): 3468 (NH_2), 3351 (NH_2), 2979 (CH), 1724 (C=O), 1646 (ester), 1616, 1368, 1138, 947, 748 cm^{-1}.

3-(2-Nitrophenyl)-3-oxopropanenitrile (336)



This compound was prepared according to a literature procedure.[228] Acetonitrile (1.74 mL, 33.1 mmol) was added dropwise to a stirred −78 °C solution of *n*-butyllithium (1.49 M in hexanes, 22 mL, 33.1 mmol) in tetrahydrofuran (20 mL). After 1 h methyl-2-nitrobenzoate (2.34 mL, 16.6 mmol) was added dropwise over 15 min, and the resulting mixture was stirred for a further 1 h before warming to −45 °C. After 2 h the reaction mixture was warmed to 0 °C and ammonium chloride (aq., 50 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 5:1 → 1:1) to afford nitroarene **336** (1.34 g, 43%) as a red crystalline solid. *Data is consistent with that reported in the literature.*[229] δ_H ($CDCl_3$, 400 MHz): 8.26 (1H, d, *J* 8.3, H2), 7.85 (1H, td, *J* 7.5, 0.8, H4), 7.74 (1H, td, *J* 7.9, 1.9, H3), 7.48 (1H, dd, *J* 7.5, 0.9, H5), 3.91 (2H, s, H8). δ_C ($CDCl_3$, 101 MHz): 190.0 (C7), 145.1 (C1), 135.2 (C4), 134.7 (C6), 131.9 (C3), 127.6 (C5), 124.7 (C2), 113.3 (C9), 32.5 (C8).

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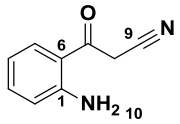
* *This compound is prone to RT decomposition to 4-hydroxyquinolin-2(1H)-one, and must be stored at −18 °C under argon.*
† *The ^{13}C peak corresponding to C6 was not observed.*

ν_{max} (neat): 2971 (CH), 2908 (CH), 2268 (C≡N), 1718 (C=O), 1524 (NO_2), 1340 (NO_2), 1216, 1004, 743, 702 cm^{-1}. MP: 88−90 °C (ethyl acetate).

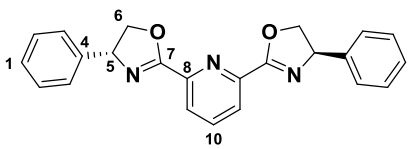
3-(2-Aminophenyl)-3-oxopropanenitrile (337)



Palladium on activated carbon (10 wt%, 30 mg) was added to a stirred RT solution of nitroarene **336** (300 mg, 1.58 mmol) in methanol (6 mL). The reaction mixture was purged under vacuum and placed under an atmosphere of hydrogen (balloon pressure). After 45 min the reaction mixture was filtered over Celite® and concentrated *in vacuo*. The crude residue was purified by passing over a short pad of silica gel, eluting with copious amounts of 1:1 petrol:ethyl acetate, and concentrated *in vacuo* to afford aniline **337** (199 mg, 79%) as a white crystalline solid. *Data is consistent with that reported in the literature.*[230] δ_H ($CDCl_3$, 400 MHz): 7.46 (1H, d, *J* 8.2, H5), 7.34 (1H, t, *J* 7.7, H3), 6.72−6.64 (2H, m, H2 & H4) 6.34 (2H, br s, H10), 4.07 (2H, s, H8). δ_C ($CDCl_3$, 101 MHz): 188.1 (C7), 151.2 (C1), 135.9 (C3), 130.4 (C5), 117.7 (C2/C4), 116.2 (C2/C4), 115.2 (C6/C9), 114.4 (C6/C9), 30.1 (C8). ν_{max} (neat): 3476 (NH_2), 3364 (NH_2), 2945 (CH), 2258 (C≡N), 1647 (C=O), 1617, 1544, 1451, 1208, 1158, 742 cm^{-1}. MP: 78−81 °C (dichloromethane).

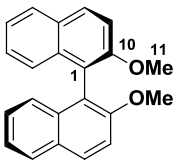
6.1.2 Synthesis of Catalysts

2,6-Bis(4-(*R*)-phenyloxazolin-2-yl)pyridine (286)



This compound was prepared according to a literature procedure.[231] A stirred neat mixture of (*R*)-phenylglycinol (4.85 g, 35.4 mmol) and dimethyl-2,6-pyridine dicarboxylate (3.45 g, 17.7 mmol) was heated to 120 °C. After 16 h the crude mixture was allowed to cool to RT and dissolved in dichloromethane (20 mL). Triethylamine (10 mL) and *para*-toluenesulfonyl chloride (6.80 g, 35.4 mmol) were added, and the mixture was heated to reflux. After 20 h the reaction mixture was allowed to cool to RT, and water (20 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude solid residue obtained was purified by single recrystallization (ethanol) to afford (*R*)-phenyl PyBOX **286** (4.63 g, 71%) as a white crystalline solid. *Data is consistent with that reported in the literature.*[232] δ_H (400 MHz, $CDCl_3$): 8.36 (2H, d, *J* 7.9, H9), 7.93 (1H, t, *J* 7.8, H10), 7.41−7.28 (10H, m, H1, H2 & H3), 5.47 (2H, dd, *J* 10.3, 8.6, H5), 4.94 (2H, dd, *J* 10.3, 8.7, H6), 4.44 (2H, t, *J* 8.6, H6'). δ_C (101 MHz, $CDCl_3$): 163.5 (C7), 146.8 (C8), 141.7 (C4), 137.5 (C10), 128.8 (C2/C3), 127.8 (C1), 126.8 (C2/C3), 126.3 (C9), 75.5 (C6), 70.4 (C5). MP: 153−156 °C (ethanol).

(*R*)-Dimethyl BINOL (354)

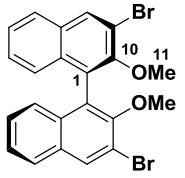


This compound was prepared according to a literature procedure.[172] Acetone (200 mL) was added to a flask containing (*R*)-BINOL* (14 g, 49 mmol) and warmed until all of the diol was dissolved. Potassium carbonate (22.8 g, 166 mmol) and iodomethane (18.4 mL, 293 mmol) were added, and the resulting mixture was heated under reflux for 24 h. The mixture was allowed to cool to RT and concentrated *in vacuo* to a volume of approximately 50 mL. Water (500 mL) was added, and the mixture stirred for 8 h at RT. The solid residue was obtained by filtration, and washed with

* (*R*)-BINOL was purchased from AK Scientific, Union City, CA, USA.

water (3 x 200 mL) to afford **354** (15.3 g, 99%) as a white powder. *Data is consistent with that reported in the literature.*[172] δ_H (400 MHz, $CDCl_3$): 8.00 (2H, d, *J* 9.0, H8), 7.89 (2H, d, *J* 8.1, H3), 7.48 (2H, d, *J* 9.1, H9), 7.34 (2H, ddd, *J* 8.1, 6.8, 1.2, H4), 7.23 (2H, ddd, *J* 8.4, 6.8, 1.4, H5), 7.13 (2H, d, *J* 8.2, H6), 3.78 (6H, s, H11). δ_C (101 MHz, $CDCl_3$): 155.0 (C10), 134.0 (C2), 129.4 (C8), 129.2 (C7), 127.9 (C3), 126.3 (C5), 125.3 (C6), 123.5 (C4), 119.6 (C1), 114.3 (C9), 56.9 (C11). MP = 230−235 °C (diethyl ether/petrol). $[\alpha]_D^{20.0}$ +56.6 (*c* = 1.0, $CHCl_3$). ν_{max} (neat): 3048 (CH), 3021 (CH), 2956 (CH), 2933 (CH), 1619, 1591, 1250, 1065, 811 cm^{-1}.

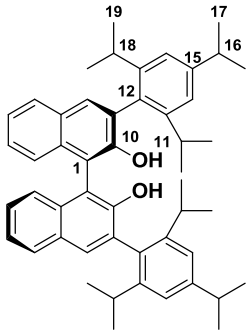
(*R*)-3,3-Dibromo-dimethyl BINOL (298)



This compound was prepared according to a literature procedure.[172] *n*-Butyllithium (1.6 M in hexanes, 35 mL, 56 mmol) was slowly added to a stirred RT solution of tetramethylenediamine (5.21 mL, 35 mmol) in diethyl ether (250 mL). After 1 h (*R*)-dimethyl BINOL **354** (5.0 g, 16 mmol) was added, and the mixture was stirred for a further 3.5 h before cooling to −78 °C. Bromine (4.1 mL, 80 mmol) was added, and the mixture was allowed to warm to RT and stirred for a further 20 h. Sodium sulfite (aq., 80 mL) was added, and the biphasic mixture stirred for 1 h, before the aqueous phase was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 1:0 → 20:1) and subsequent recrystallization (dichloromethane/petrol), affording (*R*)-3,3'-dibromo-dimethyl BINOL **298** as a white crystalline solid (3.33 g, 44%). *Data is consistent with that reported in the literature.*[172] δ_H (400 MHz, $CDCl_3$): 8.28 (2H, s, H8), 7.83 (2H, d, *J* 8.2, H3), 7.43 (2H, ddd, *J* 8.0, 7.1, 1.0, H4), 7.28 (2H, ddd, *J* 8.4, 7.0, 1.3, H5), 7.09 (2H, d, *J* 8.5,

H6), 3.52 (6H, s, H11). δ_C (101 MHz, $CDCl_3$): 152.5 (C10), 133.1 (C2), 133.0 (C8), 131.4 (C7), 127.1 (C3), 126.9 (C5), 126.5 (C1), 125.9 (C4), 125.8 (C6), 117.5 (C9), 61.1 (C11). MP: 182-187 °C (dichloromethane/petrol). $[\alpha]_D^{20.0}$ -14.0 (*c* = 1.0, $CHCl_3$). ν_{max} (neat): 3056 (CH), 1575, 1493, 1328, 1043, 750 cm^{-1}.

(*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-BINOL (300)



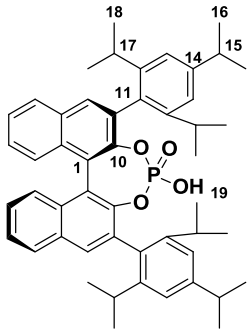
This compound was prepared according to a literature procedure.[173] Mechanically-activated magnesium turnings (1.26 g, 52 mmol) were covered with diethyl ether (~ 3 mL) and further activated by the addition of a single crystal of iodine. 2-Bromo-1,3,5-triisopropylbenzene (6.86 mL, 26 mmol), diethyl ether (35 mL) and 1,2-dibromoethane (0.1 mL) were added separately and simultaneously *via* syringe in a manner that maintained the exothermic reaction, and the grey solution was heated to reflux for a further 24 h. The resulting Grignard solution was filtered over a short pad of cotton wool and used without further purification in the subsequent step.

In a separate flask, dibromoarene **298** (2.00 g, 4.26 mmol) and bis(triphenylphosphine)nickel(II) chloride* (277 mg, 0.42 mmol) were suspended in diethyl ether (25 mL). The Grignard solution was added dropwise to the suspension, and the mixture heated to reflux for 6 h. The resulting brown solution was allowed to cool to RT and hydrochloric acid (1.0 M aq., 30 mL), and the aqueous layer was extracted with diethyl ether (3 x 25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

* *This compound was prepared according to* L. M. Venanzi, *J. Chem. Soc.,* **1958**, *719*.

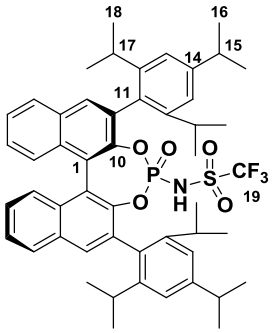
The crude product of the Kumada coupling was dissolved in anhydrous dichloromethane (100 mL) and cooled to 0 °C. Boron tribromide (1.0 M in dichloromethane, 29.7 mL, 29.7 mmol) was added dropwise, and the resulting clear solution allowed to warm to RT and stirred for a further 24 h. Water (40 mL) was added, and the aqueous layer extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude brown residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 100:1), and the resulting yellow solid was triturated with hexanes, affording diol **300** (1.26 g, 43% over two steps) as a white powder. *Data is consistent with that reported in the literature.*[173] δ_H (400 MHz, $CDCl_3$): 7.89 (2H, d, *J* 7.9, H3), 7.79 (2H, s, H8), 7.42−7.37 (2H, m, H4), 7.36−7.29 (4H, m, H5 & H6), 7.16 (2H, s, H14), 7.14 (2H, s, H14'), 4.94 (2H, s, H11), 2.98 (2H, septet, *J* 6.9, H16), 2.86 (2H, septet, *J* 6.8, H18), 2.71 (2H, septet, *J* 6.8, H18'), 1.33 (12H, d, *J* 6.9, H17), 1.22 (6H, d, *J* 6.8, H19) 1.13 (6H, d, *J* 7.0, H19), 1.11 (6H, d, *J* 7.0, H19'), 1.05 (6H, d, *J* 6.8, H19'). δ_C (101 MHz, $CDCl_3$): 150.6 (C10), 149.1 (C15), 147.8 (C13), 147.7 (C13'), 133.4 (Ar C), 130.6 (C8), 130.4 (Ar C), 129.1 (Ar C), 129.0 (Ar C), 128.2 (C3), 126.6 (C5/C6), 124.5 (C5/C6), 123.8 (C4), 121.2 (C14), 121.2 (C14'), 113.1 (C1), 34.3 (C16), 30.9 (C18), 30.8 (C18'), 24.3 (C17/C19), 24.3 (C17/C19), 24.1 (C17/C19), 24.0 (C17/C19), 23.9 (C17/C19), 23.7 (C17/C19). MP: 268−274 °C (ethyl acetate/hexanes). $[\alpha]_D^{20.0}$ +68.9 (*c* = 1.0, $CHCl_3$). ν_{max} (neat): 3524 (OH), 2960 (CH), 2928 (CH), 2869 (CH), 1739, 1364, 1230, 1217, 749 cm^{-1}.

(*R*)-TRIP (292)



This compound was prepared according to a literature procedure.[173] Phosphoryl chloride (198 μL, 2.12 mmol) was added to a solution of diol **300** (500 mg, 0.72 mmol) in pyridine (1.5 mL) and the mixture heated to reflux. After 14 h the reaction was allowed to cool to RT, water (1.5 mL) was added and the reaction mixture was heated to reflux. After 3 h the reaction was allowed to cool to RT and the aqueous reaction mixture extracted with dichloromethane (2 x 5 mL). The combined organic extracts were washed thoroughly with hydrochloric acid (1N aq., 3 x 5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to (*R*)-TRIP **292** (522 mg, 96%) as a white solid. *Data is consistent with that reported in the literature.*[173] δ_H (400 MHz, $CDCl_3$):* 7.90 (2H, d, *J* 8.2, H3), 7.82 (2H, s, H8), 7.54−7.48 (2H, m, H4), 7.38−7.31 (4H, m, H5 & H6), 6.96 (2H, d, *J* 1.0, H13), 6.94 (2H, d, *J* 1.2, H13'), 2.84 (2H, septet, *J* 6.8, H15), 2.65 (2H, septet, *J* 6.7, H17), 2.59 (2H, septet, *J* 6.6, H17), 1.24 (12 H, d, *J* 6.9, H16), 1.02 (6H, d, *J* 6.8, H18), 1.00 (6H, d, *J* 6.8, H18), 0.93 (6H, d, *J* 6.8, H18), 0.73 (6H, d, *J* 6.6, H18). δ_C (101 MHz, $CDCl_3$): 148.1 (C12/C14), 148.0 (C12/C14), 147.4 (C12/C14), 146.2 (d, *J* 9.4, C10), 132.5(1) (C2/C7/C11), 132.4(7) (C8), 132.3 (d, *J* 3.2, C9), 131.7 (C2/C7/C11), 130.8 (C2/C7/C11), 128.1 (C3), 127.4 (C5/C6), 126.1 (C5/C6), 125.4 (C4), 122.2 (C1), 121.1 (C13), 120.1 (C13'), 34.2 (C15), 30.9 (C17), 30.6 (C17), 26.2 (C18), 25.0 (C18), 24.1 (C16), 24.0 (C16), 23.3 (C18), 22.9 (C18). δ_P (162 MHz, $CDCl_3$): -2.25. ν_{max} (neat): 3572 (OH), 2960 (CH), 2869 (CH), 1606, 1410, 1280, 1197, 905, 729 cm^{-1}.

N-Triflylphosphoramide 315

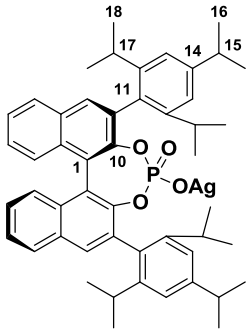


* *Note that the expected broad singlet corresponding to H19 was not observed in the ^1H NMR spectrum.*

This compound was prepared according to a literature procedure.[190] Triethylamine (707 μL, 5.07 mmol), phosphoryl chloride (81 μL, 0.87 mmol) and 4-dimethylaminopyridine (177 mg, 1.45 mmol) were added to a stirred RT solution of bis(aryl) BINOL **300** (500 mg, 0.72 mmol) in dichloromethane (3.5 mL). After 1 h propionitrile (3.5 mL) and trifluoromethanesulfonamide (216 mg, 1.45 mmol) were added, and the mixture heated to 100 °C. After 12 h water (5 mL) was added, and the aqueous layer extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with sodium bicarbonate solution (aq., 5 mL) and hydrochloric acid (4 M, 2 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The solid residue was purified by flash column chromatography (silica gel, hexanes: dichloromethane:diethyl ether, 1:1:1), to afford the product as a mixture of the free acid and calcium salt. This residue was dissolved in dichloromethane (25 mL), washed with hydrochloric acid (4.0 M aq., 2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford triflamide **315** (545 mg, 86%) as a pale orange powder. *Data is consistent with that reported in the literature.*[190] *This compound was obtained as a 10:1 inseperable mixture of the desired NTPA and phosphoric acid TRIP.* δ_H (500 MHz, $CDCl_3$): 8.00−7.95 (4H, m, H3 & H8), 7.57 (2H, t, *J* 7.4, H4), 7.39−7.27 (4H, m, H5 & H6), 7.18 (1H, d, *J* 1.6, H13), 7.13 (2H, d, *J* 0.9, 2 x H13), 7.06 (1H, d, *J* 1.6, H13), 3.00−2.90 (2H, m, 2 x H15), 2.80−2.69 (2H, m, 2 x H17), 2.66 (1H, septet, *J* 6.9, H17), 2.58 (1H, septet, *J* 6.7, H17), 1.32−1.24 (15H, m, 12 x H16 & 3 x H18), 1.24−1.13 (12H, m, 12 x H18), 1.11 (3H, d, *J* 6.8, 3 x H18), 1.00 (3H, d, *J* 6.8, 3 x H18), 0.96 (3H, d, *J* 6.8, 3 x H18). δ_C (126 MHz, $CDCl_3$): 149.7 (C14), 149.1 (C14'), 147.9 (C12), 147.8 (C12), 147.1 (C12), 146.6 (C12), 145.4 (d, *J* 11.0, C10), 144.7 (d, *J* 9.0, C10'), 133.2 (C8), 133.0 (C8'), 132.3 (d, *J* 2.9, C9), 132.1 (C7), 131.6 (C2), 131.2 (C2'), 130.5 (d, *J* 4.4, C9'), 130.1 (C11), 129.9 (C11), 128.4(1) (C3), 128.3(6) (C3'), 127.3 (C6), 126.8 (C5), 126.7 (C5'), 126.4(0) (C4), 126.3(5) (C4'), 121.8 (C13), 121.2 (2 x C13), 121.1 (C1), 120.4 (C13), 118.8 (q, *J* 322, C19), 34.5 (C15), 34.3 (C15'), 31.4 (C17), 31.0(4) (C17), 30.9(7) (C17), 30.5 (C17), 26.9 (C16/C18), 26.7 (C16/C18), 25.4 (C16/C18), 25.1 (C16/C18), 24.1 (C16/C18), 24.0 (C16/C18), 23.9(1) (C16/C18), 23.8(7)

(C16/C18), 23.0 (C16/C18), 22.9 (C16/C18), 22.8 (C16/C18), 22.6 (C16/C18). δ_F (470 MHz, $CDCl_3$): 77.4. δ_P (202 MHz, $CDCl_3$): -1.98. MP: 170−175 °C (dichloromethane). $[\alpha]_D^{20.0}$ -24.1 (*c* = 1.0, $CHCl_3$). ν_{max} (neat): 2961 (CH), 2870 (CH), 1738, 1364, 1227, 975, 751 cm^{-1}. HRMS (ES-): found 882.3572; $C_{51}H_{56}F_3NO_5PS$, $[M-H]^-$ requires 882.3574.

Silver(I) TRIP (355)

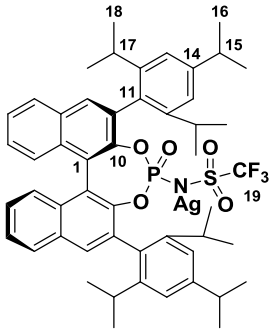


This compound was prepared by analogy to a literature procedure.[191] *Where possible, all steps of this procedure were carried out in the dark.* Silver(I) carbonate (37 mg, 0.13 mmol) and water (3 mL) were added to a stirred solution of (*R*)-TRIP **292** (200 mg, 0.27 mmol) in dichloromethane (3 mL). The resulting biphasic solution was stirred vigorously for 1 h, diluted with dichloromethane (10 mL) and water (10 mL) and the organic layer extracted with dichloromethane (3 x 10 mL). The organic extracts were filtered over Celite® and concentrated *in vacuo* to afford silver salt **355** (220 mg, 96%) as a white solid which was stored in the dark. *Data is consistent with that reported in the literature.*[191] δ_H (500 MHz, $CDCl_3$): 7.88 (2H, d, *J* 8.2, H3), 7.83 (2H, s, H8), 7.47 (2H, t, *J* 7.6, H4), 7.37 (2H, d, *J* 8.5, H6), 7.30 (2H, t, *J* 7.5, H5), 7.02 (2H, br s, H13), 6.96 (2H, br s, H13), 2.83 (2H, septet, *J* 6.8, H15), 2.76−2.61 (4H, m, H17), 1.23 (6H, d, *J* 6.9, H16), 1.21−1.08 (24H, m, H16 & H18), 0.94 (6H, d, *J* 6.8, H18). δ_C (126 MHz, $CDCl_3$):* 148.7 (C14), 147.8 (C12), 147.5 (C12), 147.3 (d, *J* 9.1, C10), 132.6 (Ar C), 132.4 (Ar C), 131.8 (C8), 130.6 (Ar C), 128.1 (C3), 127.4 (C6), 125.8 (C5), 125.1 (C4), 122.4 (d, *J* 1.9, C1), 120.4 (C13), 119.4 (C13), 33.8 (C15), 30.9

* *Note that one of the expected fully-substituted aromatic carbon ^{13}C peaks was not observed, and is assumed to be co-incident with another peak.*

(C17), 30.8 (C17), 26.6 (C18), 25.0 (C18), 24.4 (C18), 24.1 (C16), 23.9 (C18), 23.8 (C16). δ_P (202 MHz, $CDCl_3$): 14.1. ν_{max} (neat): 2960 (CH), 2867 (CH), 1606, 1410, 1246, 1086, 750, 734 cm^{-1}. MP: 244−247 °C ($CDCl_3$). $[\alpha]_D^{20.0}$ +8.6 (c = 1.0, $CHCl_3$).

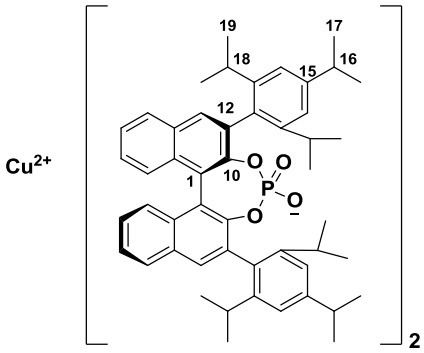
Silver(I) NTPA (316)



This compound was prepared by analogy to a literature procedure.[191] *Where possible, all steps of this procedure were carried out in the dark.* Silver(I) carbonate (31.2 mg, 0.113 mmol) and water (2 mL) were added to a stirred solution of triflamide **315** (200 mg, 0.226 mmol) in dichloromethane (2 mL). The resulting biphasic solution was stirred vigorously for 1 h, diluted with dichloromethane (5 mL) and water (5 mL) and the organic layer extracted with dichloromethane (3 x 5 mL). The organic extracts were filtered over Celite® and concentrated *in vacuo* to afford silver salt **316** (214 mg, 96%) as a pale grey powder which was stored in the dark. δ_H (500 MHz, $CDCl_3$): 7.97 (1H, d, *J* 8.3, H3), 7.95 (1H, s, H8), 7.91 (1H, d, *J* 7.9, H3'), 7.90 (1H, s, H8'), 7.53 (1H, t, *J* 7.4, H4), 7.49 (1H, ddd, *J* 8.0, 5.8, 2.2, H4'), 7.36−7.27 (5H, m, 2 x H5, 2 x H6, H13), 7.14 (1H, s, H13), 7.06 (1H, s, H13), 7.03 (1H, s, H13), 3.04−2.94 (1H, m, H15), 2.94−2.85 (2H, m, 2 x H15/H17), 2.85−2.77 (2H, m, 2 x H15/H17), 2.67 (1H, septet, *J* 6.7, H15/H17), 1.34−1.22 (24H, m, 24 x H16/H18), 1.20 (3H, d, *J* 6.7, 3 x H16/H18), 1.15 (3H, d, *J* 6.8, 3 x H16/H18), 1.02 (3H, d, *J* 6.7, 3 x H16/H18), 0.91 (3H, d, *J* 6.8, 3 x H16/H18). δ_C (126 MHz, $CDCl_3$): 151.4 (C14), 148.5 (C14'), 148.4 (C12), 147.6 (2 x C12), 147.2 (C12), 146.9 (d, *J* 11.0, C10), 145.4 (d, *J* 9.0, C10'), 132.9 (C8), 132.7 (Ar C), 132.3 (Ar C), 132.1 (Ar C), 132.1 (C11),

131.5 (C8'), 131.3 (Ar C), 131.3 (C11'), 130.8 (Ar C), 130.7 (Ar C), 128.3 (C3), 128.1 (C3'), 127.5 (C5), 127.4 (C5'), 126.4 (C6), 126.0 (C6'), 125.8 (C4), 125.5 (C4'), 123.0 (C1), 121.7(3) (C13), 121.6(6) (C13), 121.2 (C1'), 120.4 (2 x C13'), 34.3 (C15), 34.2 (C15'), 31.6 (C17), 31.0 (C17), 30.8 (2 x C17), 26.9 (C16/C18), 26.6 (C16/C18), 25.2 (C16/C18), 25.2 (2 x C16/C18), 24.8 (C16/C18), 24.3 (C16/C18), 24.1 (C16/C18), 24.8 (C16/C18), 23.3 (2 x C16/C18), 22.2 (C16/C18). δ_P (202 MHz, $CDCl_3$): 6.81. δ_F (470 MHz, $CDCl_3$): -77.87. MP: 236−242 °C (dichloromethane). $[\alpha]_D^{20.0}$ -38.9 (c = 0.61, $CHCl_3$). ν_{max} (neat): 2962 (CH), 1364, 1314, 1194, 974 cm^{-1}. HRMS (MALDI+): found 1010.12; $C_{51}H_{58}AgF_3NO_6PS$, $[M+H_3O]^+$ requires 1010.28; *isotope pattern consistent with Ag(I) salt.*

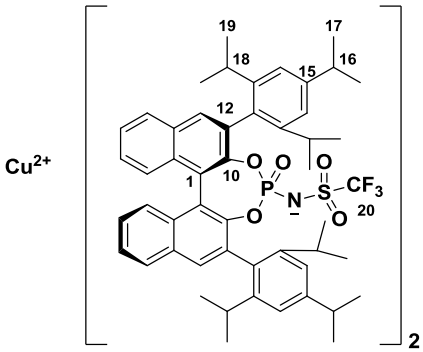
Copper(II) TRIP Salt (318)



This compound was prepared by analogy to a literature procedure.[192] *Where possible, all steps of this procedure were carried out in the dark.* Copper(II) chloride dihydrate (41 mg, 0.24 mmol) was added to a stirred RT solution of silver salt **355** (435 mg, 0.51 mmol) in acetonitrile:dichloromethane (1:1 v/v, 10 mL). After 16 h the reaction mixture was filtered over Celite® and concentrated *in vacuo*. The solid residue was redissolved in dichloromethane (25 mL) and filtered over Celite®, washing with dichloromethane (5 mL), and the solvent removed *in vacuo* to afford **318** (314 mg, 79%) as a green/grey solid. *Note that due to the paramagnetic nature of the copper(II) ion it was not possible to carry out NMR analysis of this compound.* MP: 244−248 °C (dichloromethane). $[\alpha]_D^{20.0}$ -36.3 (c = 0.29, $CHCl_3$). ν_{max} (neat): 2960 (CH), 2869 (CH), 1607, 1072, 874, 749 cm^{-1}.

m/z (ESI$^+$): * 1590 ([M+Na]$^+$, 10%), 1568 ([M+H]$^+$, 58%), 797 (TRIP$^-$+2Na)$^+$, 775 ([TRIP$^-$+H+Na]$^+$, 89%).

Copper(II) NTPA Salt (317)



This compound was prepared by analogy to a literature procedure.[192] *Where possible, all steps of this procedure were carried out in the dark.* Copper(II) chloride dihydrate (9.5 mg, 0.056 mmol) was added to a stirred RT solution of silver salt **316** (100 mg, 0.101 mmol) in acetonitrile:dichloromethane (1:1 v/v, 2 mL). After 16 h the reaction mixture was filtered over Celite® and concentrated *in vacuo*. The solid residue was redissolved in dichloromethane (5 mL) and filtered over Celite®, washing with dichloromethane (1 mL), and the solvent removed *in vacuo* to afford **317** (72 mg, 78%) as a green/grey solid. *Note that due to the paramagnetic nature of the copper(II) ion it was not possible to carry out NMR analysis of this compound.* MP: 241−244 °C (dichloromethane). $[\alpha]_D^{20.0}$ -33.8 (*c* = 0.29, $CHCl_3$). ν_{max} (neat): 2961 (CH), 2871 (CH), 1196, 1146, 999, 751 cm^{-1}. *m/z* (ESI$^+$):† 1850 ([M+Na]$^+$, 71%), 1828 ([M+H]$^+$, 53%), 928.3 ([NTPA$^-$+2Na]$^+$, 100%).

6.1.3 Screening Asymmetric Lewis Acidic Conditions

Table 4.6 (p. 102), entries 1−6. These reactions were carried out by analogy to a literature protocol, according to the following general procedure:[164]

* *"TRIP$^-$" refers to the conjugate base anion of the neutral phosphoric acid **292**.*
† *"NTPA$^-$" refers to the conjugate base anion of the neutral N-triflylphosphoramide **315**.*

A suspension of *the appropriate metal triflate* (0.012 mmol), *the appropriate ligand* (0.013 mmol) and 4 Å powdered molecular sieves (30 mg) in tetrahydrofuran (1 mL) was stirred for 2 h at RT. Amine **283** (25 mg, 0.12 mmol) in toluene (1 mL) and benzaldehyde (24 μL, 0.24 mmol) were added, and the reaction was monitored by TLC. *Conversion was determined approximately by TLC. HPLC analysis was carried out on pure samples of the product **284** isolated by small-scale preparative TLC.*

Table 4.6 (p. 102), entry 7. This reaction was carried out by analogy to a literature procedure.[42]

A suspension of scandium(III) triflate (12 mg, 0.024 mmol), (*R*)-phenylpybox **286** (18 mg, 0.049 mmol) and 3 Å powdered molecular sieves (150 mg) in acetonitrile (3 mL) was stirred vigorously for 80 min. Aniline **283** (50 mg, 0.24 mmol) and benzaldehyde (49 μL, 0.48 mmol) were added, and the reaction was monitored by TLC. After 20 min TLC indicated consumption of the starting material; the reaction mixture was concentrated *in vacuo* and ^{1}H NMR analysis of the crude material indicated complete conversion to the product. The crude residue was purified by column chromatography (silica gel, 99:1, dichloromethane:methanol) to afford dihydroquinolone **284** (66 mg, 93%, 8% ee) as a yellow crystalline solid. *For spectroscopic data, see page 246.*

Table 4.6 (p. 102), entries 8 & 9. These reactions were carried out by analogy to a literature protocol, according to the following general procedure:[165]

A suspension of scandium(III) triflate (1.2 mg, 0.0024 mmol), *the appropriate ligand* (0.060 mmol) and 4 Å powdered molecular sieves (25 mg) in dichloromethane (1 mL) was stirred for 3 h at RT. Aniline **283** (50 mg, 0.24 mmol) and benzaldehyde (49 μL, 0.48 mmol) were added, and the reaction was monitored by TLC. *Conversion was determined approximately by TLC. HPLC analysis was carried out on pure samples of the product **284** isolated by small-scale preparative TLC.*

*Kobayashi's "chiral scandium catalyst" **288** (Scheme 4.16, p. 103). This reaction was carried out by analogy to a literature procedure.*[166]

Trimethylpiperidine was prepared by an Eschweiler-Clarke methylation: a mixture of *cis*-2,6-dimethylpiperidine (2.5 g, 22 mmol), formic acid (5 mL) and formaldehyde (37% aq., 5 mL) was heated to reflux for 2 h, when MS indicated complete consumption of the secondary amine. Sodium hydroxide (aq, 3 N, 10 mL) was added, and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and carefully concentrated *in vacuo*. The crude product was purified by distillation (BP: 142 °C, atmospheric pressure) to afford *cis*-1,2,6-trimethylpiperidine **356** (1.9 g, 68%) as a colourless oil.

cis-1,2,6-Trimethylpiperidine **356** (15 mg, 0.24 mmol) was added to a stirred −78 °C suspension of scandium(III) triflate, (*S*)-BINOL (16.6 mg, 0.12 mmol) and 4 Å molecular sieves (50 mg) in dichloromethane (1 mL) at −78 °C. After 30 min aniline **283** (100 mg, 0.49 mmol) and benzaldehyde (73 μL, 0.58 mmol) were added and the reaction mixture allowed to warm to RT. After 16 h, TLC and MS analysis indicated complete consumption of the starting material. *HPLC analysis was carried out on pure samples of the product **284** isolated by small-scale preparative TLC.* The dihydroquinolone was obtained in 6% ee.

*Shibasaki's amphoteric Li/Al-BINOL catalyst **289** (Scheme 4.16, p. 103). This reaction was carried out by analogy to a literature procedure.*[167]

(*R*)-BINOL (1.43 g, 5.0 mmol) in tetrahydrofuran (20 mL) was added to a stirred, 0 °C suspension of lithium aluminium hydride (95 mg, 2.5 mmol) in tetrahydrofuran (5 mL). After 30 min the stirrer was removed and the solid residue allowed to settle. The supernatant solution was used immediately as a 0.1 M stock solution of catalyst **289**.

Catalyst solution **289** (0.48 mL, 0.048 mmol) was added to a stirred 0 °C solution of aniline **283** (50 mg, 0.24 mmol) and benzaldehyde (49 μL, 0.48 mmol) in tetrahydrofuran (1 mL), and

the reaction mixture was allowed to warm to RT overnight. *TLC and MS analysis indicated no product formation, and the reaction was not further investigated.*

6.1.4 Screening Asymmetric Brønsted Acidic Conditions

Catalyst Screen (Table 4.7, p. 105).

Benzaldehyde (10 μL, 0.1 mmol) was added to a stirred RT solution of aniline **283** (10 mg, 0.05 mmol) and *the appropriate Brønsted acid* (5 mol%) in dichloromethane (0.5 mL). *TLC and MS indicated all reactions had reached completion after 4 h. HPLC analysis was carried out on pure samples of the product **284** isolated by small-scale preparative TLC.*

Solvent Screen (Table 4.8, p. 107).

Benzaldehyde (10 μL, 0.1 mmol) was added to a stirred RT solution of aniline **283** (10 mg, 0.05 mmol) and (*R*)-TRIP **292** (1.8 mg, 2.4 μmol) in *the appropriate solvent* at *the concentration indicated. After 16 h HPLC analysis was carried out on pure samples of the product **284** isolated by small-scale preparative TLC.*

Temperature Screen (Table 4.9, p. 108).

Benzaldehyde (10 μL, 0.1 mmol) was added to a stirred solution of aniline **283** (10 mg, 0.05 mmol) and (*R*)-TRIP **292** (1.8 mg, 2.4 μmol) in toluene (0.5 mL), *at the appropriate temperature. After 16 h HPLC analysis was carried out on pure samples of the product **284** isolated by small-scale preparative TLC.*

Catalyst Loading Screen (Table 4.10, p. 109).

Benzaldehyde (49 μL, 0.48 mmol) was added to a stirred RT solution of aniline **283** (50 mg, 0.24 mmol) and *the appropriate quantity* of (R)-TRIP **292** in toluene (2.5 mL). After 16 h the catalyst was removed by passing the reaction mixture over a short pad of silica and washing with

dichloromethane, and the solvents and unreacted benzaldehyde removed *in vacuo*. *^{1}H NMR analysis was carried out on the crude material. HPLC analysis was carried out on pure samples of the product* ***284*** *isolated by small-scale preparative TLC.*

Scope Study (Table 4.11, p. 110).

The appropriate aldehyde (2.0 eq., 0.48 mmol) was added to a stirred suspension of aniline **283** (50 mg, 0.24 mmol), (*R*)-TRIP **292** (3.6 mg, 4.8 μmol) and oven-dried 4 Å molecular sieves (50 mg) in *the appropriate solvent* at *the appropriate temperature*. *Reactions monitored by TLC and MS for consumption of aniline.* After *the indicated time period* the catalyst was removed by passing the reaction mixture over a short pad of silica and washing with dichloromethane, and the solvents removed *in vacuo*. *^{1}H NMR analysis was carried out on the crude material. HPLC analysis was carried out on pure samples of the product isolated by small-scale preparative TLC.*

6.1.5 Screening Asymmetric Cu(II)-NTPA Catalysed Conditions

Temperature Screen (Table 4.12, p. 116).

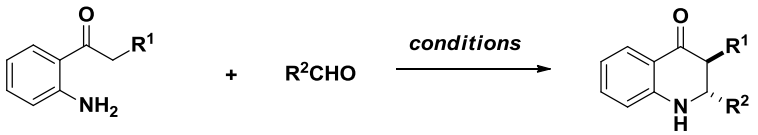
Benzaldehyde (25 μL, 0.25 mmol) was added to a stirred suspension of aniline **283** (25 mg, 0.12 mmol), oven-dried 4 Å molecular sieves (25 mg) and copper catalyst **317** (2.2 mg, 1.2 μmol) in dichloromethane (1.25 mL) at *the appropriate temperature*. After *the indicated time period* the reaction was diluted with dichloromethane (100 mL) and filtered over a short plug of silica to remove the catalyst, and the solvents removed *in vacuo*. *^{1}H NMR analysis was carried out on the crude material. HPLC analysis was carried out on pure samples of the product* ***284*** *isolated by small-scale preparative TLC.*

Solvent Screen (Table 4.14, p. 118).

Benzaldehyde (25 μL, 0.25 mmol) was added to a stirred −30 °C suspension of aniline **283** (25 mg, 0.12 mmol), oven-dried 4 Å molecular sieves (25 mg) and copper catalyst **317** (2.2 mg, 1.2 μmol) in *the appropriate solvent* at *the indicated concentration*. After *the indicated time period* the

reaction was diluted with dichloromethane (100 mL) and filtered over a short plug of silica to remove the catalyst, and the solvents removed *in vacuo*. *^{1}H NMR analysis was carried out on the crude material. HPLC analysis was carried out on pure samples of the product* ***284*** *isolated by small-scale preparative TLC.*

6.1.6 General Procedures for the Copper(II) NTPA (317)-Catalysed Asymmetric Synthesis of Dihydroquinolones



General Procedure 5 *(asymmetric). The appropriate aldehyde (2.0 eq.)* was added to a stirred -30 °C suspension of *the appropriate aniline (1.0 eq.)*, oven-dried 4 Å molecular sieves (*1 mg / 1 mg aniline*) and copper catalyst **317** (*0.01 eq.*) in 1:1 tetrahydrofuran:toluene (v:v, *0.2 M concentration of aniline*). After 48 h the product dihydroquinolone was obtained by work-up procedure A or B.*

Work-up procedure A. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel.

Work-up procedure B. The reaction mixture was poured into dichloromethane (200 mL / mmol aniline) and passed over a short plug of silica gel to remove the catalyst. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel.

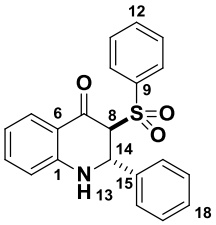
General Procedure 6 *(racemic). The appropriate aldehyde (2.0 eq.)* was added to a stirred RT solution of *the appropriate aniline* (~5 mg, ~12 μmol) in dichloromethane (0.15 mL). *After 2 h*

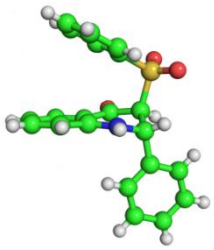
* *Work-up procedure A should be employed where TLC and MS indicate that the reaction has gone to completion, with no residual aniline remaining. Otherwise, work-up procedure B is necessary to prevent further reaction at RT, which would give mis-representative yields and enantioselectivities. Quenching these reactions with acid or base is not possible, since both the free acid and salt forms of the catalyst are active.*

small-scale preparative TLC afforded an analytical quantity of the racemic dihydroquinolone, sufficient to provide a racemic standard for HPLC analysis. Yields not determined.

6.1.7 Cyclization Reactions

(±)-2-Phenyl-3-(phenylsulfonyl)-2,3-dihydroquinolin-4(1*H*)-one (261)





Method I. Benzaldehyde (10 μL, 0.1 mmol) was added to a stirred solution of aniline **254** (25 mg, 0.09 mmol), oven-dried 4 Å molecular sieves (100 mg) and acetic acid (25 μL) in dichloromethane (1 mL) and the resulting mixture stirred for 2 days, after which TLC analysis suggested no product formation. The reaction mixture was left to stand for a further 3 days, after which time a bright yellow colour was observed. The mixture was filtered over Celite®, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 0.5% methanol in dichloromethane) to afford dihydroquinolone **261** (11 mg, 33%) as a bright yellow crystalline solid.

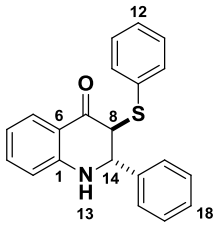
Method II. Benzaldehyde (74 μL, 0.72 mmol) was added to a stirred suspension of aniline **254** (100 mg, 0.36 mmol) and oven-dried magnesium sulfate (400 mg, 3.3 mmol) in toluene (5 mL) and the solution heated to reflux. After 4 h the reaction mixture was allowed to cool to RT and filtered over Celite®, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 0.5% methanol in dichloromethane) to afford dihydroquinolone **261** (124 mg, 94%) as a yellow crystalline solid.

Method III – Attempted asymmetric synthesis. This reaction was carried out according to ***general procedure 5*** at RT, not −30 °C. Aniline **254** (25 mg, 0.09 mmol), benzaldehyde (19 μL,

0.18 mmol). *Work-up procedure B* was employed. The product dihydroquinolone **261** was obtained in ~10% conversion (crude ^{1}H NMR) and as the racemate. *HPLC analysis was carried out on a pure analytical sample of the product isolated by small-scale preparative TLC.*

δ_H ($CDCl_3$, 400 MHz): 7.83 (2H, d, *J* 7.3, H10), 7.66 (1H, dd, *J* 8.0, 1.5, H5), 7.58 (1H, ddt, *J* 8.0, 6.8, 1.1, H12), 7.45 (2H, t, *J* 7.8, H11), 7.31 (1H, ddd, *J* 8.4, 7.0, 1.5, H3), 7.28−7.19 (5H, m, H16, H17 & H18), 6.69 (1H, ddd, *J* 7.9, 7.1, 0.8, H4), 6.61 (1H, d, *J* 8.3, H2), 5.74 (1H, s, H13), 5.04 (1H, br s, H8), 4.12 (1H, d, *J* 1.3, H14). δ_C ($CDCl_3$, 101 MHz): 182.7 (C7), 149.3 (C1), 139.1 (C15), 137.5 (C9), 136.9 (C3), 134.2 (C12), 129.2(8) & 129.2(6) (C10 & C17), 128.8 (C11), 128.3 (C18), 127.6 (C5), 125.8 (C16), 118.3 (C6), 118.1 (C4), 115.4 (C2), 74.8 (C8), 54.6 (C14). ν_{max} (neat): 3374 (NH), 3063 (CH), 2929 (CH), 1708, 1660, 1613, 1517, 1309 (S=O), 1151 (S=O), 1082, 718 cm^{-1}. HRMS (ESI+): found 386.0817; $C_{21}H_{17}NNaO_3S$, $[M+Na]^+$ requires 386.0821. MP: 50−56 °C (dichloromethane). HPLC (Chiralpak IA, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 245): $t_R(1)$ = 8.1, $t_R(2)$ = 27.0. *For crystallographic data, see Appendix 8.2, p. 282.*

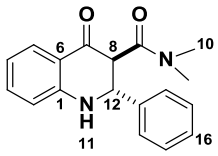
(±)-2-Phenyl-3-(phenylthio)-2,3-dihydroquinolin-4(1*H*)-one (270)



Benzaldehyde (34 μL, 0.33 mmol) was added to a stirred RT solution of aniline **264** (40 mg, 0.16 mmol) and scandium(III) triflate (8 mg, 0.016 mmol) in dichloromethane (1.5 mL). After 16 h the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 4:1 → 2:1) to afford dihydroquinolone **270** (38 mg, 72%) as a yellow solid.

δ_H ($CDCl_3$, 300 MHz): 7.75 (1H, dd, *J* 7.9, 1.2, H5), 7.40−7.35 (2H, m, H10), 7.30 (1H, ddd, *J* 8.2, 7.1, 1.3, H3), 7.22−7.15 (8H, m, H11, H12, H16, H17 & H18), 6.71 (1H, t, *J* 7.6, H4), 6.66 (1H, d, *J* 8.2, H2), 4.87 (1H, dd, *J* 4.3, 2.9, H14), 4.77 (1H, br s, H13), 4.00 (1H, d, *J* 4.8, H8). δ_C ($CDCl_3$, 75 MHz): 188.3 (C7), 148.8 (C1), 139.6 (C15), 135.7 (C3), 133.2 (C9), 132.8 (C10), 129.0 (C11/C16/C17), 128.9 (C11/C16/C17), 128.3 (C12/C18), 128.2 (C5), 127.9 (C12/C18), 126.5 (C11/C16/C17), 118.3 (C4), 117.8 (C6), 115.0 (C2), 61.2 (C14), 57.7 (C8). ν_{max} (neat): 3392 (NH), 3059 (CH), 2923 (CH), 1656, 1609, 1495, 1154, 746, 696 cm^{-1}. HRMS (ESI+): found 354.0914; $C_{21}H_{17}NNaOS$, $[M+Na]^+$ requires 354.0923.

N,N-Dimethyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (284)



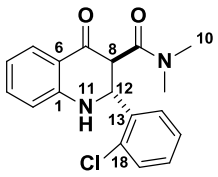
Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), benzaldehyde (49 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, dichloromethane:methanol, 100:1). The product dihydroquinolone **284** (64 mg, 90%, 66% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H ($CDCl_3$, 400 MHz): 7.89 (1H, dd, *J* 7.9, 1.5, H5), 7.55 (2H, dd, *J* 7.7, 1.7, H14), 7.39−7.33 (4H, m, H3, H15, H16), 6.79 (1H, t, *J* 7.5, H4), 6.70 (1H, d, *J* 8.2, H2), 5.25 (1H, d, *J* 12.9, H12), 4.50 (1H, br s, H11), 4.15 (1H, d, *J* 13.1, H8), 2.87 (3H, s, H10), 2.85 (3H, s, H10'). δ_C ($CDCl_3$, 101 MHz): 189.6 (C7), 167.9 (C9), 151.2 (C1), 139.7 (C13), 135.7 (C3), 128.7 (C14), 128.6 (C16), 128.0 (C5), 127.6 (C15), 118.6 (C6), 118.5 (C4), 115.8 (C2), 60.7 (C12), 57.6 (C8), 37.5 (C10), 35.5 (C10'). HRMS (ESI+): found 317.1261; $C_{18}H_{18}N_2NaO_2$, $[M+Na]^+$ requires 317.1260. ν_{max} (neat): 3282 (NH), 3034 (CH), 2940 (CH), 1659 (ketone), 1632 (amide), 1510, 1481, 1331, 1303,

760, 662 cm^{-1}. MP: 203−208 °C (dichloromethane). HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 8.2, t_R (minor) = 15.1. $[\alpha]_D^{20.0}$ +60.4 (c = 1, $CHCl_3$).

2-(2-Chlorophenyl)-*N,N*-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (301)



Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), 2-chlorobenzaldehyde (54 μL, 0.48 mmol). *After 48 h incomplete conversion was observed by TLC analysis. An additional aliquot of o-chlorobenzaldehyde (54 μL, 0.48 mmol) and catalyst **317** (4.4 mg, 2.4 μmol) was added, and the reaction stirred for a further 24 h. Work-up procedure A* was employed: chromatography (silica gel, dichloromethane:methanol, 100:1). The product dihydroquinolone **301** (71 mg, 90%, 23% ee, >20:1 dr) was obtained as a yellow foam.

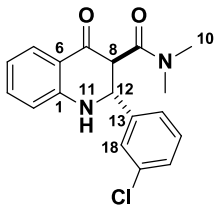
Racemic: Scandium(III) triflate (6 mg, 0.012 mmol) was added to a stirred RT solution of aniline **283** (25 mg, 0.12 mmol) and 2-chlorobenzaldehyde (27 μL, 0.24 mmol) in dichloromethane (1 mL). After 1 h the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (silica gel, petrol:ethyl acetate, 1:1) to afford **301** (34 mg, 86%) as a yellow foam.

δ_H (400 MHz, $CDCl_3$): 7.85 (1H, dd, *J* 8.0, 1.0, H5), 7.48−7.43 (1H, m, H15), 7.43−7.38 (1H, m, H16), 7.34 (1H, ddd, *J* 8.3, 7.1, 1.4, H3), 7.29−7.23 (2H, m, H14 & H17), 6.77 (1H, t, *J* 7.6, H4), 6.69 (1H, d, *J* 8.3, H2), 5.63 (1H, d, *J* 11.6, H12), 4.58 (1H, s, H11), 4.44 (1H, d, *J* 11.6, H8), 3.07 (3H, s, H10), 2.89 (3H, s, H10'). δ_C (101 MHz, $CDCl_3$):* 189.4 (C7), 167.4 (C9), 150.9 (C1), 136.6 (C13), 135.8 (C3), 133.9 (C18), 130.6 (C16), 129.6 (C17), 128.7 (C15), 128.0 (C5),

* *The ^{13}C peak corresponding to C6 was not observed.*

127.2 (C14), 118.3 (C4), 115.8 (C2), 56.5 (C12), 54.5 (C8), 37.7 (C10), 35.7 (C10'). HRMS (ESI+): found 351.0874; $C_{18}H_{17}{}^{35}ClN_2NaO_2$, $[M(^{35}Cl)+Na]^+$ requires 351.0871. ν_{max} (neat): 3328 (NH), 2924 (CH), 2854 (CH), 1639 (ketone), 1608 (amide), 1479, 1324, 1057, 757 cm^{-1}. MP: 173-175 °C (dichloromethane). HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 7.3, t_R (minor) = 11.6. $[\alpha]_D^{20.0}$ +69.2 (c = 1, $CHCl_3$).

2-(3-Chlorophenyl)-*N*,*N*-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (302)



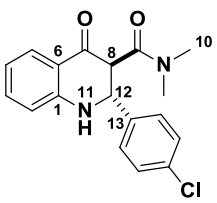
Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), 3-chlorobenzaldehyde (54 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 0.75% methanol in dichloromethane). The product dihydroquinolone **302** (66 mg, 83%, 55% ee, >20:1 dr) was obtained as a yellow foam.

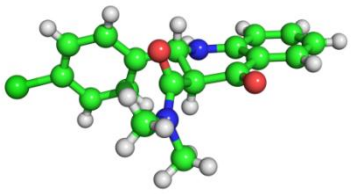
Racemic: Scandium(III) triflate (6 mg, 0.012 mmol) was added to a stirred RT solution of aniline **283** (25 mg, 0.12 mmol) and 3-chlorobenzaldehyde (27 μL, 0.24 mmol) in dichloromethane (1 mL). After 1 h the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (silica gel, petrol:ethyl acetate, 1:1) to afford **302** (28 mg, 71%) as a yellow crystalline solid.

δ_H (400 MHz, $CDCl_3$): 7.87 (1H, dd, *J* 8.0, 1.1, H5), 7.59 (1H, s, H18), 7.42 (1H, dt, *J* 6.7, 1.7, H16), 7.36 (1H, ddd, *J* 8.3, 7.0, 1.4, H3), 7.33−7.28 (2H, m, H14 & H15), 6.80 (1H, t, *J* 7.5, H4), 6.72 (1H, d, *J* 8.4, H2), 5.23 (1H, d, *J* 13.0, H12), 4.51 (1H, s, H11), 4.10 (1H, d, *J* 12.9, H8), 2.87 (6H, s, H10). δ_C (101 MHz, $CDCl_3$): 189.2 (C7), 167.6 (C9), 150.9 (C1), 141.9 (C13), 135.8 (C3),

134.5 (C17), 130.0 (C14/C15), 128.8 (C14/C15), 128.0 (C5), 127.5 (C18), 126.3 (C16), 118.7 (C4), 118.6 (C6), 115.9 (C2), 60.1 (C12), 57.4 (C8), 37.6 (C10), 35.6 (C10'). HRMS (ESI+): found 351.0871; $C_{18}H_{17}{}^{35}ClN_2NaO_2$, $[M(^{35}Cl)+Na]^+$ requires 351.0871. ν_{max} (neat): 3282 (NH), 2924 (CH), 2854 (CH), 1632 (ketone), 1608 (amide), 1327, 1162, 747 cm^{-1}. MP: 232−235 °C (dichloromethane). HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 245): t_R (major) = 7.9, t_R (minor) = 14.7. $[\alpha]_D^{20.0}$ +80.0 (c = 1, $CHCl_3$).

2-(4-Chlorophenyl)-*N*,*N*-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (303)





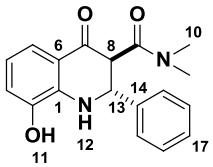
Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), 4-chlorobenzaldehyde (72 mg, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 0.75% methanol in dichloromethane). The product dihydroquinolone **303** (71 mg, 90%, 59% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: Scandium(III) triflate (6 mg, 0.012 mmol) was added to a stirred RT solution of aniline **283** (25 mg, 0.12 mmol) and 4-chlorobenzaldehyde (27 μL, 0.24 mmol) in dichloromethane (1 mL). After 1 h the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (silica gel, petrol:ethyl acetate, 1:1) to afford **303** (31 mg, 79%) as a yellow crystalline solid.

δ_H (400 MHz, $CDCl_3$): 7.86 (1H, d, *J* 8.0, H5), 7.49 (2H, d, *J* 7.8, H14), 7.35 (1H, t, *J* 7.7, H3), 7.32 (2H, d, *J* 7.8, H15), 6.80 (1H, t, *J* 7.6, H4), 6.72 (1H, d, *J* 8.2, H2), 5.20 (1H, d, *J* 12.9, H12), 4.53 (1H, s, H11), 4.07 (1H, d, *J* 13.1, H8), 2.86 (6H, s, H10). δ_C (101 MHz, $CDCl_3$): 189.3 (C7),

167.6 (C9), 151.1 (C1), 138.4 (C13), 135.8 (C3), 134.3 (C16), 129.1 (C14), 128.8 (C15), 128.0 (C5), 118.7 (C4), 118.6 (C6), 115.9 (C2), 60.0 (C12), 57.6 (C8), 37.5 (C10), 35.6 (C10'). HRMS (ESI+): found 351.0866; $C_{18}H_{17}{}^{35}ClN_2NaO_2$, $[M(^{35}Cl)+Na]^+$ requires 351.0871. ν_{max} (neat): 3328 (NH), 2924 (CH), 2855 (CH), 1662 (ketone), 1628 , 1607 (amide), 1507, 1484, 1134, 1107, 765 cm^{-1}. MP: 198−200 °C (dichloromethane). HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 7.8, t_R (minor) = 19.1. $[\alpha]_D^{20.0}$ +51.4 (c = 0.5, $CHCl_3$). *For crystallographic data, see Appendix 8.2, p.* ***Error! Bookmark not defined.***.

8-Hydroxy-*N*,*N*-dimethyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (311)

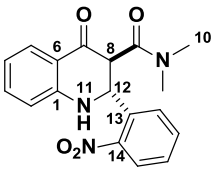


Benzaldehyde (9 μL, 0.09 mmol) was added to a stirred −30 °C suspension of aniline **307** (5 mg, 0.022 mmol) and (*R*)-TRIP (1 mg, 1.3 μmol) in dichloromethane. After 24 h the solvent was removed *in vacuo* and the residue purified by flash column chromatography (silica gel, 5% methanol in dichloromethane) to afford dihydroquinolone **311** (6 mg, 88%, 17% ee, >20:1 dr) as a yellow crystalline solid.

δ_H (500 MHz, $CDCl_3$): 7.52 (2H, dd, *J* 7.6, 1.8, H15), 7.40 (1H, dd, *J* 8.2, 1.2, H5), 7.36−7.31 (3H, m, H16 & H17), 7.05 (1H, br s, H11), 6.88 (1H, dd, *J* 7.6, 1.2, H3), 6.55 (1H, t, *J* 7.9, H4), 5.12 (1H, d, *J* 12.9, H13), 4.96 (1H, br s, H12), 4.16 (1H, d, *J* 13.2, H8), 2.85 (3H, s, H10), 2.82 (3H, s, H10). δ_C (126 MHz, $CDCl_3$): 189.6 (C7), 168.8 (C9), 143.4 (C2), 141.8 (C1), 139.7 (C14), 128.6 (C17), 128.5 (C16), 127.6 (C15), 119.5 (C3), 119.2 (C5), 118.8 (C6), 117.3 (C4), 60.6 (C13), 57.7 (C8), 37.7 (C10'), 35.7 (C10). ν_{max} (neat): 3379 (NH), 3199 (OH), 2929 (CH), 1669 (ketone), 1612 (amide), 1505, 1270, 735, 702 cm^{-1}. HRMS (ESI+): found 333.1219;

$C_{18}H_{18}N_2NaO_3$, $[M+Na]^+$ requires 333.1210. $[\alpha]_D^{20.0}$ +33.6 (c = 0.33, $CHCl_3$). MP: 202−207 °C ($CDCl_3$). HPLC (Chiralpak ODH, 50% IPA, 50% hexane, 1.0 mL.min^{-1}, λ = 229): t_R(minor) = 3.8, t_R(major) = 5.3.

_N,N_-Dimethyl-2-(2-nitrophenyl)-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (319)



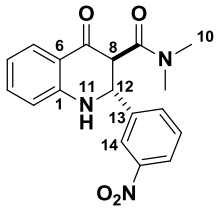
Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), 2-nitrobenzaldehyde (72 mg, 0.48 mmol). *Work-up procedure B* was employed: chromatography (silica gel, 0.5% methanol in dichloromethane). The product dihydroquinolone **319** (14 mg, 17%, 42% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.85 (1H, d, *J* 8.0, H5), 7.80 (1H, d, *J* 8.1, H15), 7.71 (1H, d, *J* 7.8, H18), 7.59 (1H, t, *J* 7.6, H17), 7.47 (1H, t, *J* 7.7, H16), 7.38 (1H, t, *J* 7.8, H3), 6.82 (1H, t, *J* 7.6, H4), 6.75 (1H, d, *J* 8.2, H2), 5.66 (1H, d, *J* 11.6, H12), 4.80 (1H, d, *J* 11.4, H8), 3.05 (3H, s, H10), 2.88 (3H, s, H10'). δ_C (101 MHz, $CDCl_3$): 188.6 (C7), 167.0 (C9), 150.8 & 150.4 (C1 & C14), 135.9 (C3), 133.8 (C13), 132.7 (C17), 129.2 (C18), 129.0 (C16), 127.9 (C5), 124.6 (C15), 119.0 (C4), 118.5 (C6), 116.1 (C2), 55.6 (C8), 55.1 (C12), 37.6 (C10), 35.7 (C10'). HRMS (ESI+): found 362.1120; $C_{18}H_{17}N_3NaO_4$, $[M+Na]^+$ requires 362.1111. ν_{max} (neat): 3361 (NH), 2930 (CH), 1640 (ketone), 1611 (amide), 1528 (NO_2), 1355 (NO_2), 1155, 762 cm^{-1}. MP: 202−204 °C (dichloromethane). $[\alpha]_D^{20.0}$ +61.8 (c = 1, $CHCl_3$). HPLC (Chiralpak ODH, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 246): t_R(major) = 9.4, t_R(minor) = 13.6.

***N,N*-Dimethyl-2-(3-nitrophenyl)-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide**

(320)



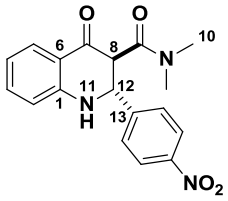
Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), 3-nitrobenzaldehyde (72 mg, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 0.5% methanol in dichloromethane). The product dihydroquinolone **320** (53 mg, 64%, 41% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, d_6-DMSO): 8.43 (1H, t, *J* 1.9, H14), 8.20 (1H, ddd, *J* 8.3, 2.3, 0.9, H16), 8.00 (1H, d, *J* 7.7, H18), 7.71−7.63 (2H, m, H5 & H17), 7.37 (1H, ddd, *J* 8.4, 7.0, 1.5, H3), 7.22 (1H, br s, H11), 6.87 (1H, d, *J* 8.3, H2), 6.70 (1H, t, *J* 7.6, H4), 5.13 (1H, d, *J* 13.2, H12), 4.70 (1H, d, *J* 13.3, H8), 2.84 (3H, s, H10), 2.67 (3H, s, H10'). δ_C (101 MHz, d_6-DMSO): 190.2 (C7), 168.4 (C9), 152.7 (C1), 148.4 (C15), 143.3 (C13), 136.3 (C3), 136.0 (C18), 130.7 (C17), 127.6 (C5), 123.9 (C16), 123.9 (C14), 118.2 (C6), 117.8 (C4), 117.1 (C2), 59.8 (C12), 56.2 (C8), 37.8 (C10), 35.7 (C10'). HRMS (ESI+): found 362.1107; $C_{18}H_{17}N_3NaO_4$, $[M+Na]^+$ requires 362.1111. ν_{max} (neat): 3262 (NH), 2922 (CH), 2853 (CH), 1664 (ketone), 1625 (amide), 1531 (NO_2), 1347 (NO_2), 766, 731, 705 cm^{-1}. MP: 231−234 °C (dichloromethane). $[\alpha]_D^{20.0}$ +65.5 (c = 1, $CHCl_3$). HPLC (Chiralpak ODH, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 245): t_R(major) = 12.5, t_R(minor) = 20.6.

***N,N*-Dimethyl-2-(4-nitrophenyl)-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide**

(321)

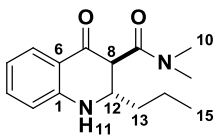


Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), 4-nitrobenzaldehyde (72 mg, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 0.5% methanol in dichloromethane). The product dihydroquinolone **321** (60 mg, 73%, 23% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 8.21 (2H, d, *J* 8.8, H15), 7.89 (1H, dd, *J* 8.0, 1.4, H5), 7.78 (2H, d, *J* 8.7, H14), 7.40 (1H, ddd, *J* 8.2, 7.2, 1.5, H3), 6.85 (1H, t, *J* 7.2, H4), 6.75 (1H, d, *J* 8.2, H2), 5.39 (1H, d, *J* 12.9, H12), 4.51 (1H, br s, H11), 4.11 (1H, d, *J* 12.9, H8), 2.89 (3H, s, H10), 2.87 (3H, s, H10').). δ_C (101 MHz, $CDCl_3$): 188.5 (C7), 167.1 (C9), 150.7 (C1), 148.0 (C16), 147.1 (C13), 136.0 (C3), 128.9 (C14), 128.0 (C5), 123.9 (C15), 119.2 (C4), 118.7 (C6), 116.0 (C2), 60.0 (C12), 57.5 (C8), 37.6 (C10), 35.6 (C10'). HRMS (ESI+): found 362.1115; $C_{18}H_{17}N_3NaO_4$, $[M+Na]^+$ requires 362.1111. ν_{max} (neat): 3245 (NH), 3058 (CH), 2923 (CH), 2854 (CH), 1665 (ketone), 1630 (amide), 1513 (NO_2), 1480, 1344 (NO_2), 858, 745, 662 cm^{-1}. MP: 248−253 °C (dichloromethane). $[\alpha]_D^{20.0}$ +30.3 (*c* = 1, $CHCl_3$). HPLC (Chiralpak ODH, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 245): t_R(major) = 12.2, t_R(minor) = 31.0.

N,N-Dimethyl-4-oxo-2-propyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (322)

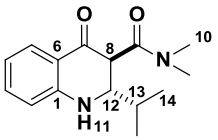


Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), *n*-butyraldehyde (43 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 1% methanol in dichloromethane). The product dihydroquinolone **322** (64 mg, 100%, 76% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.82 (1H, dd, *J* 8.0, 1.1, H5), 7.31 (1H, t, *J* 8.2, H3), 6.72 (1H, t, *J* 7.5, H4), 6.69 (1H, d, *J* 8.3, H2), 4.39 (1H, br s, H11), 4.14 (1H, ddd, *J* 12.4, 7.9, 3.3, H12), 3.72 (1H, d, *J* 12.7, H8), 3.08(4) (3H, s, H10), 3.07(6) (3H, s, H10'), 1.75−1.55 (2H, m, H13), 1.53−1.42 (2H, m, H14), 0.99 (3H, t, *J* 7.2, H15). δ_C (101 MHz, $CDCl_3$): 190.2 (C7), 168.6 (C9), 151.1 (C1), 135.5 (C3), 127.9 (C5), 118.6 (C6), 118.0 (C4), 1115.9 (C2), 55.4 (C8), 55.1 (C12), 37.7 (C10), 35.7 (C10' & C11), 18.4 (C13), 14.0 (C14). ν_{max} (neat): 3284 (NH), 2959 (CH), 2873 (CH), 1664 (ketone), 1611 (amide), 1519, 1484, 1198, 1154, 772 cm^{-1}. HRMS (ESI+): found 283.1416; $C_{15}H_{20}N_2NaO_2$, $[M+Na]^+$ requires 283.1417. MP: 106−108 °C (dichloromethane). HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 237): t_R (major) = 5.4, t_R (minor) = 10.0. $[\alpha]_D^{20.0}$ +280.3 (*c* = 1, $CHCl_3$).

2-i*so*-Propyl-*N*,*N*-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (323)

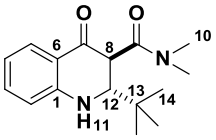


Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), *n*-butyraldehyde (44 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 0.5% methanol in dichloromethane). The product dihydroquinolone **323** (64 mg, 100%, 19% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.81 (1H, d, *J* 7.9, H5), 7.31 (1H, t, *J* 8.1, H3), 6.74−6.68 (2H, m, H2 & H4), 4.26 (1H, br s, H11), 4.07 (1H, dd, *J* 12.5, 2.8, H12), 3.84 (1H, d, *J* 12.4, H8), 3.10 (3H, s, H10), 3.07 (3H, s, H10'), 2.04 (1H, septet of doublets, *J* 6.9, 2.8, H13), 1.10 (3H, d, *J* 7.1, H14), 0.95 (3H, d, *J* 6.9, H14'). δ_C (101 MHz, $CDCl_3$): 190.5 (C7), 168.6 (C9), 151.4 (C1), 135.5 (C3), 127.8 (C5), 118.4 (C6), 117.8 (C4), 115.9 (C2), 59.7 (C12), 53.2 (C8), 37.6 (C10), 35.7 (C10'), 28.9 (C13), 19.7 (C14), 15.7 (C14'). ν_{max} (neat): 3319 (NH), 2959 (CH), 2934 (CH), 1663 (ketone), 1631 (amide), 1514, 1484, 1302, 1146, 1094, 769, 755 cm^{-1}. HRMS (ESI+): found 283.1418; $C_{15}H_{20}N_2NaO_2$, $[M+Na]^+$ requires 283.1417. MP: 130−136 °C (dichloromethane). HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 245): t_R (major) = 5.5, t_R (minor) = 9.7. $[\alpha]_D^{20.0}$ +36.5 (*c* = 1, $CHCl_3$).

2-(*Tert*-butyl)-*N,N*-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (324)



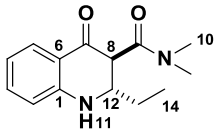
Asymmetric: prepared according to ***general procedure 5***. Aniline **284** (50 mg, 0.24 mmol), pivaldehyde (52 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 1% methanol in dichloromethane). The product dihydroquinolone **324** (62 mg, 94%, 81% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.67 (1H, dd, *J* 8.3, 1.4, H5), 7.24 (1H, ddd, *J* 8.2, 7.2, 1.3, H3), 6.62−6.56 (2H, m, H2 & H4), 4.60 (1H, br s, H11), 3.96 (1H, d, *J* 5.4, H8), 3.76 (1H, dd, *J* 5.2, 2.1, H12), 3.25 (3H, s, H10), 2.97 (3H, s, H10'), 0.98 (9H, s, H14). δ_C (101 MHz, $CDCl_3$): 190.1 (C7), 169.4 (C9), 150.9 (C1), 135.9 (C3), 127.4 (C5), 116.7 (C4), 116.5 (C6), 115.2 (C2), 62.3

(C12), 49.6 (C8), 38.1 (C10), 36.2 (C10'), 29.7 (C13), 26.4 (C14). ν_{max} (neat): 3343 (NH), 2918 (CH), 1613 (amide), 1529, 1485, 1445, 1143, 1054, 906, 758 cm^{-1}. HRMS (ESI+): found 297.1572; $C_{16}H_{22}N_2NaO_2$, $[M+Na]^+$ requires 297.1573. MP: 124−128 °C (dichloromethane). HPLC (Chiralpak IA, 30% IPA, 70% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 7.7, t_R (minor) = 5.6. $[\alpha]_D^{20.0}$ +616.6 (c = 0.11, $CHCl_3$).

2-Ethyl-*N*,*N*-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (325)

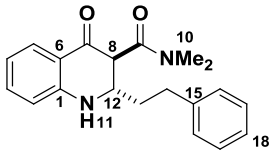


Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), *n*-butyraldehyde (34 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 1% methanol in dichloromethane). The product dihydroquinolone **325** (60 mg, 100%, 65% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.80 (1H, dd, *J* 7.9, 1.4, H5), 7.30 (1H, ddd, *J* 8.3, 7.1, 1.4, H3), 6.74−6.68 (2H, m, H2 & H4), 4.44 (1H, br s, H11), 4.09 (1H, ddd, *J* 12.6, 7.3, 3.1, H12), 3.73 (1H, d, *J* 12.6, H8), 3.07 (3H, s, H10), 3.06 (3H, s, H10'), 1.75 (1H, dqd, *J* 14.7, 7.3, 3.2, H13), 1.62 (1H, ddq, *J* 14.4, 7.2, 7.2, H13'), 1.03 (3H, t, *J* 7.5, H14). δ_C (101 MHz, $CDCl_3$): 190.3 (C7), 168.6 (C9), 151.3 (C1), 135.5 (C3), 127.8 (C5), 118.5 (C6), 117.9 (C4), 115.8 (C2), 56.2 (C12), 54.8 (C8), 37.7 (C10), 35.6 (C10'), 26.2 (C13), 9.3 (C14). ν_{max} (neat): 3288 (NH), 2970 (CH), 2875 (CH), 1660 (ketone), 1625, 1610 (amide), 1517, 1483, 1155, 1046, 767 cm^{-1}. MP: 124−128 °C (dichloromethane). HRMS (ESI+): found 269.1262; $C_{14}H_{18}N_2NaO_2$, $[M+Na]^+$ requires 269.1260. HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 5.7, t_R (minor) = 9.8. $[\alpha]_D^{20.0}$ +278.8 (c = 1, $CHCl_3$).

_N,N_-Dimethyl-4-oxo-2-phenethyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (326)

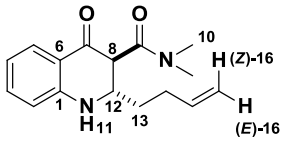


Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), 3-phenypropionaldehyde (64 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 1% methanol in dichloromethane). The product dihydroquinolone **326** (72 mg, 92%, 58% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.81 (1H, dd, *J* 8.0, 1.4, H5), 7.28−7.37 (3H, m, H3 & H17), 7.27−7.22 (3H, m, H16 & H18), 6.73 (1H, t, *J* 7.5, H4), 6.55 (1H, d, *J* 8.3, H2), 4.32−4.19 (2H, m, H11 & H12, *H12 appears as a ddd, J 12.4, 7.8, 3.0*), 3.74 (1H, d, *J* 12.5, H8), 3.06 (3H, s, H10), 3.03 (3H, s, H10'), 2.85 (1H, ddd, *J* 14.0, 8.8, 5.5, H14), 2.79 (1H, ddd, *J* 13.8, 9.0, 7.2, H14'), 2.09−1.90 (2H, m, H13 & H13'). δ_C (101 MHz, $CDCl_3$): 190.0 (C7), 168.4 (C9), 151.0 (C1), 141.0 (C15), 135.5 (C3), 128.7 (C16), 128.4 (C17), 127.8 (C5), 126.4 (C18), 118.6 (C6), 118.1 (C4), 115.7 (C2), 55.6 (C12), 55.4 (C8), 37.6 (C10), 35.7 (C10'), 35.0 (C13), 32.1 (C14). ν_{max} (neat): 3325 (NH), 3026 (CH), 2929 (CH), 1629, 1609 (amide), 1483, 1343, 1153, 1114, 754, 699 cm^{-1}. HRMS (ESI+): found 345.1573; $C_{20}H_{22}N_2NaO_2$, $[M+Na]^+$ requires 345.1573. MP: 54−56 °C (dichloromethane). HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 27.4, t_R (minor) = 17.9. $[\alpha]_D^{20.0}$ +187.7 (*c* = 1, $CHCl_3$).

2-(But-3-en-1-yl)-_N,N_-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (328)

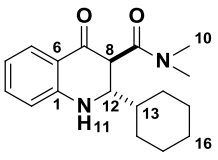


Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), 4-pentenal (57 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 0.5% methanol in dichloromethane). The product dihydroquinolone **328** (65 mg, 98%, 35% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.82 (1H, d, *J* 8.0, H5), 73 (1H, ddd, *J* 8.9, 6.6, 1.2, H3), 6.73 (1H, ddt, *J* 8.9, 6.6, 1.2, H3), 6.73 (1H, ddt, *J* 8.0, 7.2, 0.7, H4), 6.78 (1H, d, *J* 8.3, H2), 5.86 (1H, ddt, *J* 17.0, 10.3, 6.7, H15), 5.12 (1H, d, *J* 17.1, (*Z*)-H16), 5.04 (1H, d, *J* 10.1, (*E*)-H16), 4.50 (1H, br s, H11), 4.17 (1H, ddd, *J* 12.1, 8.5, 3.3, H12), 3.73 (1H, d, *J* 12.5, H8), 3.08 (3H, s, H10), 3.07 (3H, s, H10'), 2.31−2.19 (2H, m, H14), 1.86−1.77 (1H, m, H13), 1.76−1.65 (1H, m, H13'). δ_C (101 MHz, $CDCl_3$): 190.0 (C7), 168.5 (C9), 151.1 (C1), 137.6 (C15), 135.5 (C3), 127.9 (C5), 118.6 (C6), 118.1 (C4), 115.8 (C2/C16), 115.7 (C2/C16), 55.3 (C8), 55.2 (C12), 37.7 (C10), 35.7 (C10'), 32.4 (C13), 29.7 (C14). HRMS (ESI+): found 295.1412; $C_{16}H_{20}N_2NaO_2$, $[M+Na]^+$ requires 295.1417. MP: 146−150 °C (dichloromethane). ν_{max} (neat): 3325 (NH), 3075 (CH), 2927 (CH), 1631, 1610 (amide), 1483, 1346, 1154, 912, 759 cm^{-1}. $[\alpha]_D^{20.0}$ +143.7 (*c* = 1, $CHCl_3$). HPLC (Chiralpak ODH, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 245): t_R(major) = 5.5, t_R(minor) = 9.6.

2-Cyclohexyl-*N*,*N*-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (327)

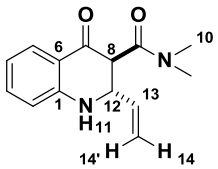


Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), cyclohexanecarboxaldehyde (58 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 0.5% methanol in dichloromethane). The product dihydroquinolone **327** (63 mg, 87%, 81% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.81 (1H, dd, *J* 7.9, 1.1, H5), 7.31 (1H, t, *J* 7.6, H3), 6.74−6.66 (2H, m, H2 & H4), 4.31 (1H, br s, H11), 4.03 (1H, d, *J* 11.1, H12), 3.89 (1H, d, *J* 11.9, H8), 3.10 (3H, s, H10), 3.07 (3H, s, H10'), 1.90−1.57 (6H, m, H13 & 5 x H14/H15/H16), 1.41−1.11 (5H, m, 5 x H14/H15/H16). δ_C (126 MHz, $CDCl_3$): 190.7 (C7), 168.7 (C9), 151.2 (C1), 135.4 (C3), 127.7 (C5), 118.4 (C6), 117.8 (C4), 115.8 (C2), 59.5 (C12), 52.5 (C8), 39.2 (C13), 37.7 (C10), 35.7 (C10'), 30.4 (C14/C15/C16), 26.7 (C14/C15/C16), 26.4 (C14/C15/C16), 26.3(5) (C14/C15/C16), 26.2(9) (C14/C15/C16). ν_{max} (neat): 3339 (NH), 2927 (CH), 2853 (CH), 1634, 1612 (amide), 1484, 1398, 759, 731 cm^{-1}. HRMS (ESI+): found 323.1731; $C_{18}H_{24}N_2NaO_2$, $[M+Na]^+$ requires 323.1731. MP: 140−142 °C (dichloromethane). $[\alpha]_D^{20.0}$ +334.0 (*c* = 1, $CHCl_3$). HPLC (Chiralpak ODH, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 245): t_R(major) = 5.4, t_R(minor) = 9.8.

_N,N_-Dimethyl-4-oxo-2-vinyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (329)

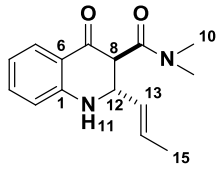


Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), acrolein (32 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, petrol:ethyl acetate, 1:1). The product dihydroquinolone **329** (20 mg, 34%, 8% ee, >20:1 dr) was obtained as a yellow glassy solid.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.83 (1H, dd, *J* 8.0, 1.3, H5), 7.34 (1H, ddd, *J* 8.3, 7.0, 1.4, H3), 6.76 (1H, t, *J* 7.9, H4), 6.71 (1H, d, *J* 8.3, H2), 5.97 (1H, ddd, *J* 17.2, 10.4, 6.7, H13), 5.51 (1H, d, *J* 17.2, H14'), 5.28 (1H, d, *J* 10.4, H14), 4.70 (1H, dd, *J* 12.6, 6.6, H12), 4.37 (1H, br s, H11), 3.79 (1H, d, *J* 12.7, H8), 3.06 (3H, s, H10), 3.05 (3H, s, H10). δ_C (101 MHz, $CDCl_3$):* 189.5 (C7), 167.9 (C9), 150.9 (C1), 136.6 (C13), 135.6 (C3), 127.9 (C5), 118.6 (C14), 118.4 (C4), 115.9 (C2), 58.1 (C12), 56.0 (C8), 37.7 (C10), 35.6 (C10'). ν_{max} (neat): 3309 (NH), 2931 (CH), 1634, 1611 (amide), 1583, 1506, 1329, 1155, 761 cm^{-1}. HRMS (ESI+): found 267.1102; $C_{14}H_{16}N_2NaO_2$, $[M+Na]^+$ requires 267.1104. HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 $mL.min^{-1}$, λ = 245): t_R (major) = 6.7, t_R (minor) = 11.3. $[\alpha]_D^{20.0}$ +5.2 (c = 1, $CHCl_3$).

N,N-Dimethyl-4-oxo-2-((*E*)-prop-1-en-1-yl)-1,2,3,4-tetrahydroquinoline-3-carboxamide (330)



Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), *trans*-crotonaldehyde (40 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, petrol:ethyl acetate, 1:1). The product dihydroquinolone **330** (47 mg, 75%, 7% ee, >20:1 dr) was obtained as a yellow foam.

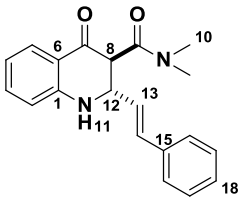
Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.83 (1H, dd, *J* 8.0, 1.5, H5), 7.32 (1H, ddd, *J* 8.3, 7.1, 1.4, H3), 6.74 (1H, t, *J* 7.7, H4), 6.68 (1H, d, *J* 8.1, H2), 5.94 (1H, dq, *J* 15.2, 6.6, H14), 5.54 (1H, ddq, *J* 15.3,

* *Note that the ^{13}C peak corresponding to C6 was not observed.*

7.5, 1.6, H13), 4.63 (1H, dd, *J* 12.6, 7.4, H12), 4.28 (1H, br s, H11), 3.78 (1H, d, *J* 12.6, H8), 3.07 (3H, s, H10), 3.05 (3H, s, H10'), 1.73 (3H, dd, *J* 6.5, 1.5, H15). δ_C (126 MHz, $CDCl_3$):189.8 (C7), 168.1 (C9), 151.0 (C1), 135.5 (C3), 130.6 (C14), 129.3 (C13), 127.9 (C5), 118.6 (C6), 119.2 (C4), 115.7 (C2), 57.9 (C12), 56.1 (C8), 37.7 (C10), 35.6 (C10'), 17.9 (C15). ν_{max} (neat): 3304 (NH), 2935 (CH), 1631, 1608 (amide), 1504, 1482, 1435, 1154, 961, 758 cm^{-1}. HRMS (ESI+): found 281.1261; $C_{15}H_{18}N_2NaO_2$, $[M+Na]^+$ requires 281.1260. MP: 118−122 °C (dichloromethane). HPLC (Chiralpak OD-H, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 259): t_R (major) = 12.6, t_R (minor) = 6.3. $[\alpha]_D^{20.0}$ -22.0 (*c* = 1, $CHCl_3$).

_N,N_-Dimethyl-4-oxo-2-((_E_)-styryl)-1,2,3,4-tetrahydroquinoline-3-carboxamide (331)



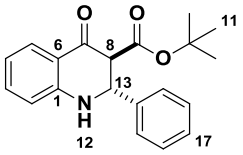
Asymmetric: prepared according to ***general procedure 5***. Aniline **283** (50 mg, 0.24 mmol), *trans*-cinnemaldehyde (60 μL, 0.48 mmol). *Work-up procedure A* was employed: chromatography (silica gel, 0.5% methanol in dichloromethane). The product dihydroquinolone **331** (63 mg, 81%, 19% ee, >20:1 dr) was obtained as a yellow foam.

Racemic: prepared according to ***general procedure 6***.

δ_H (400 MHz, $CDCl_3$): 7.86 (1H, dd, *J* 7.8, 1.1, H5), 7.41 (2H, d, *J* 7.4, H16), 7.39−7.33 (3H, m, H3 & H17), 7.31−7.27 (1H, m, H18), 6.85 (1H, d, *J* 16, H14), 6.79 (1H, t, *J* 7.5, H4), 6.74 (1H, d, *J* 8.2, H2), 6.31 (1H, dd, *J* 16.0, 7.1, H13), 4.89 (1H, dd, *J* 12.6, 7.1, H12), 4.42 (1H, br s, H11), 3.88 (1H, d, *J* 12.6, H8), 3.06 (3H, s, H10), 3.02 (3H, s, H10'). δ_C (126 MHz, $CDCl_3$): 189.5 (C7), 167.9 (C9), 151.0 (C1), 136.2 (C15), 135.7 (C3), 133.5 (C14), 128.6 (C17), 128.1 (C18), 127.9 (C5), 127.5 (C13), 126.6 (C16), 118.7 (C6), 118.5 (C4), 115.9 (C2), 57.9 (C12), 56.3 (C8),

37.7 (C10), 35.7 (C10'). ν_{max} (neat): 3304 (NH), 3026 (CH), 2930 (CH), 1632, 1609 (amide), 1482, 1326, 1154, 965, 752, 694 cm^{-1}. HRMS (ESI+): found 343.1410; $C_{20}H_{20}N_2NaO_2$, $[M+Na]^+$ requires 343.1417. MP: 78−81 °C (dichloromethane). HPLC (Chiralpak IA, 30% IPA, 70% hexane, 1.0 mL.min^{-1}, λ = 245): t_R (major) = 16.2, t_R (minor) = 10.8. $[\alpha]_D^{20.0}$ -35.1 (c = 1, $CHCl_3$).

tert-Butyl 4-oxo-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (338)

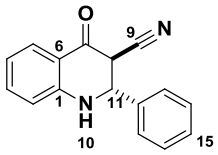


Asymmetric: prepared according to ***general procedure 5***. Aniline **334** (100 mg, 0.42 mmol), benzaldehyde (86 μL, 0.84 mmol). *Work-up procedure B* was employed: chromatography (silica gel, petrol:ethyl acetate, 20:1). The product dihydroquinolone **338** (47 mg, 34%, 37% ee, >20:1 dr) was obtained as a yellow oil, and as a 10:1 mixture of ketone:enol tautomeric forms.

Racemic: prepared according to ***general procedure 6***.

Ketone: δ_H (400 MHz, $CDCl_3$): 7.88 (1H, d, *J* 8.0, 1.2, H5), 7.51 (2H, dd, *J* 7.6, 1.7, H15), 7.42−7.31 (4H, m, H3, H16 & H17), 6.80 (1H, td, *J* 7.2, 0.7, H4), 6.69 (1H, d, *J* 8.1, H2), 4.97 (1H, d, *J* 13.1, H13), 4.54 (1H, br s, H12), 3.76 (1H, d, *J* 13.1, H8), 1.29 (9H, s, H11). δ_C (101 MHz, $CDCl_3$): 189.2 (C7), 167.2 (C9), 150.8 (C1), 138.5 (C14), 135.7 (C3), 128.9 (C17), 128.7 (C16), 127.9 (C5), 127.8 (C15), 118.6 (C4), 118.4 (C6), 115.7 (C2), 81.8 (C10), 61.8 (C8), 60.6 (C13), 27.8 (C11). HRMS (ESI+): found 346.1402; $C_{20}H_{21}NNaO_3$, $[M+Na]^+$ requires 346.1414. ν_{max} (film): 3342 (NH), 2979 (CH), 2932 (CH), 1725 (C=O), 1665, 1611, 1482, 1334, 1296, 1148, 910, 730 cm^{-1}. $[\alpha]_D^{20.0}$ +35.4 (c = 1, $CHCl_3$). HPLC (Chiralpak ADH, 5% IPA, 95% hexane, 1.0 mL.min^{-1}, λ = 245): t_R(minor) = 8.3, t_R(major) = 15.8.

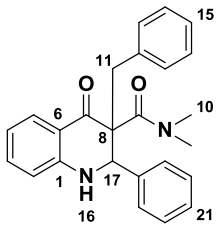
4-Oxo-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carbonitrile (339)



Attempted asymmetric synthesis: prepared according to ***general procedure 5***. Aniline **337** (50 mg, 0.31 mmol), benzaldehyde (64 μL, 0.62 mmol). *Work-up procedure B* was employed: chromatography (silica gel, petrol:ethyl acetate, 4:1). The product dihydroquinolone **339** (49 mg, 63%, *racemic*, 4:1 dr) was obtained as a yellow crystalline solid. *Although the diastereomers were inseparable by column chromatography, a pure sample of the major diastereomer was obtained by single recrystallization (dichloromethane/petrol).*

Major (as drawn): δ_H (400 MHz, d6-acetone): 7.78 (1H, d, *J* 7.6, H5), 7.68 (2H, d, *J* 6.5, H13), 7.52−7.41 (4H, m, H3, H14, H15), 7.02 (1H, d, *J* 8.3, H2), 6.81 (1H, t, *J* 7.6, H4), 6.59 (1H, br s, H10), 4.99 (1H, d, *J* 13.1, H11), 4.55 (1H, d, *J* 13.2, H8). δ_C (101 MHz, d6-acetone): 184.4 (C7), 152.2 (C1), 138.6 (C12), 136.5 (C3), 129.6 (C15), 129.2 (C14), 128.3 (C13), 127.8 (C5), 118.5 (C4), 117.0 (C6/C9), 116.9 (C2), 115.5 (C6/C9), 60.9 (C11), 48.1 (C8). HRMS (ESI+): found 271.0839; $C_{16}H_{12}N_2NaO$, $[M+Na]^+$ requires 271.0842. ν_{max} (film): 3350 (NH), 2891 (CH), 2252 (C≡N), 1661, 1609, 1481, 1455, 1335, 752, 705 cm^{-1}. MP: 164−168 °C (dichloromethane/petrol). HPLC (Chiralpak AS, 50% IPA, 50% hexane, 1.0 mL.min^{-1}, λ = 245): $t_R(1)$ = 8.6, $t_R(2)$ = 11.4.

(±)-3-Benzyl-*N*,*N*-dimethyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (342)



Benzaldehyde (7 μL, 0.07 mmol) was added to a stirred RT solution of aniline **341** (10 mg, 0.033 mmol) and scandium(III) triflate (2 mg, 4 μmol) in dichloromethane (0.5 mL). After 16 h the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, petrol:ethyl acetate, 4:1) to afford dihydroquinolone **342** (9 mg, 69%) as a yellow solid. δ_H ($CDCl_3$, 500 MHz): 7.74 (1H, dd, *J* 7.9, 1.3, H5), 7.40−7.34 (4H, m, H3, H13 & H21), 7.34-7.30 (2H, m, H14), 7.16−7.10 (5H, m, H15, H19, H20), 6.79 (1H, t, *J* 7.6, H4), 6.71 (1H, d, *J* 8.2, H2), 5.37 (1H, s, H17), 4.72 (1H, br s, H16), 3.21 (1H, d, *J* 13.3, H11), 3.14 (1H, d, *J* 13.2 H11'), 2.88 (3H, br s, H10), 2.68 (3H, br s, H10). δ_C ($CDCl_3$, 126 MHz):* 168.5 (C9), 149.7 (C1), 137.2 (C12/C18), 137.1 (C12/C18), 135.5 (C3), 131.4 (C19), 128.9 (C21), 128.7 (C13), 128.2 (C5), 127.9 (C14), 127.5 (C20), 126.4 (C15), 118.8 (C6), 118.3 (C4), 115.4 (C2), 63.9 (C8), 63.7 (C17), 38.6 (C10), 37.6 (C10'), 34.8 (C11). MP: 214−220 °C (ethyl acetate/petrol). HRMS (ESI+): found 407.1714; $C_{25}H_{24}N_2NaO_2$, $[M+Na]^+$ requires 407.1730. ν_{max} (neat): 3328 (NH), 2924 (CH), 2853 (CH), 1738, 1636, 1609, 1154, 728, 697 cm^{-1}.

* *The ^{13}C peak corresponding to C7 was not observed.*

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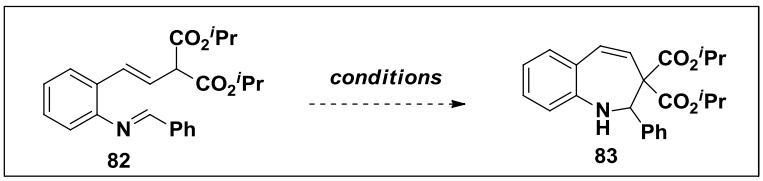
8. APPENDICES

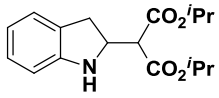
8.1 Conditions Screened for the 8π Electrocyclic Ring-Closure of Malonate 82

These results are summarized in Table 2.6, p. 27.

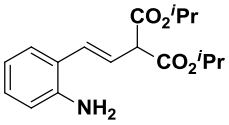
Initial investigations to induce 8π electrocyclization were focused on deprotonation under basic conditions (Table 8.1), since we hoped to employ phase-transfer catalysis to control the process asymmetrically.

The use of weak carbonate bases was unsuccessful, both in the presence and absence of phase-transfer catalysts (Table 8.1, entries 1−3 & 6). Whilst at elevated temperatures and in the presence of a phase-transfer catalyst solid caesium carbonate did consume starting material, the products formed were numerous and could not be identified. They lacked the characteristic *Z*-alkene peaks that would correspond with formation of the product **83**, and did not correspond to any of the products of 6π electrocyclization later observed under acidic conditions. Similarly, hydroxide bases gave numerous unidentified products (Table 8.1, entries 4, 5 & 7), with the exception of aqueous sodium hydroxide in methanol, which afforded aniline **79** and 1,4-addition product **84**. Surprisingly LDA gave no reaction at all, suggesting that the enolate formed is relatively stable (Table 8.1, entry 8).

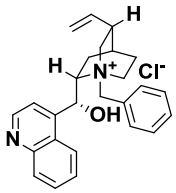




84



79



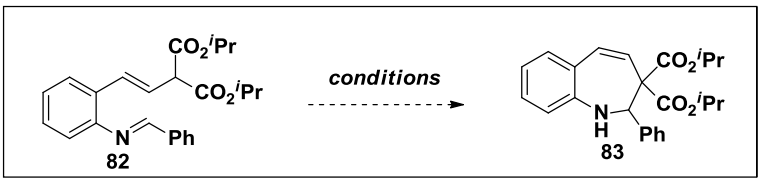
42

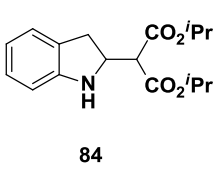
Entry	Conditions[i]				Outcome[ii, iii]
	Reagent/catalyst	Solvent	T / °C	t / h	
1	Cs_2CO_3 (1.1 eq.)	PhMe	RT	16	**82** (75%), unknown (25%)
2	Cs_2CO_3 (1.1 eq.)	PhMe	70	1	**82** (30%), **84** (10%), unknown (60%)
3	Cs_2CO_3 (1.1 eq.)	10:1 PhMe:DMF	RT	16	**84** (10%), unknown (90%)
4	$CsOH·H_2O$	CH_2Cl_2	RT	16	complex mixture
5	NaOH (50% aq.)	MeOH	RT	16	**82** (40%), **84** (30%), **79** (30%)
6	**42** (0.1 eq.), K_2CO_3 (33% aq.)	1:1 PhMe:CH_2Cl_2	RT	16	**82** (100%)
7	N^nBu_4Cl (0.1 eq.), NaOH (50% aq.)	1:1 PhMe:CH_2Cl_2	RT	16	**82** (10%), unknown (90%)
8	LDA (1.2 eq.)	THF	−78 to RT	4	**82** (100%)

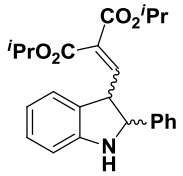
[i] *All reactions were carried out on 20−50 mg scale at concentrations of 0.1 M in the solvent indicated.* [ii] *Where indicated, product ratios are determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Values are approximate.* [iii] *"Unknown" indicates compounds or mixture of compounds visible in the ^{1}H NMR spectrum of the crude reaction mixture that could not be isolated by chromatography, and whose identity was not established.*

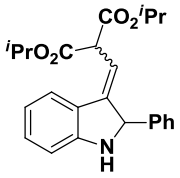
Table 8.1. Basic conditions employed in the attempted 8π electrocyclization of **82**.

Given the failure of basic conditions to afford any of the desired cyclized product, we proceeded to investigate the use of Lewis acids to catalyse the process (Table 8.2).









Entry	Conditions[i]				Outcome[ii, iii]
	Reagent/catalyst	Solvent	T / °C	t / h	
1	$Zn(OAc)_2$ (0.1 eq.)	MeOH	RT	16 h	**86** (trace), **85** (30%), unknown (70%)[iv]
2	$Zn(OAc)_2$ (0.1 eq.)	PhMe	RT	16 h	**82** (100%)
3	AcOH (1.0 eq.)	MeOH	RT	16 h	**82** (100%)
4	$Sc(OTf)_3$ (0.1 eq.)	MeOH	RT	16 h	**85** (50%), unknown (50%)[iv]
5	$Sc(OTf)_3$ (0.1 eq.)	THF	RT	16 h	**86** (50%), **85** (50%)
6	$Sc(OTf)_3$ (0.1 eq.), NEt_3 (1.0 eq.)	THF	RT	16 h	**82** (100%)
7	$Sc(OTf)_3$ (0.1 eq.)	CH_2Cl_2	RT	16 h	**86** (20%), **85** (50%)
8	$Sc(OTf)_3$ (0.1 eq.)	THF	−20	24 h	**82** (100%)
9	$BF_3{\cdot}OEt_2$ (1.5 eq.)	THF	RT	16 h	**82** (100%)
10	BCl_3 (1.5 eq.)	THF	RT	16 h	**82** (90%), unknown (10%)
11[73]	AgOAc (0.1 eq.), PPh_3 (0.11 eq.), $^iPr_2NEt$ (0.3 eq.)	THF	RT	16 h	**82** (19%) **84** (81%),
12	$ZnBr_2$ (0.1 eq.)	CH_2Cl_2	RT	16 h	**85** (50%), unknown (50%)[iv]
13	$ZnBr_2$ (0.1 eq.)	CH_2Cl_2	−78	16 h	**82** (>95%), **85** (trace)
14	$ZnBr_2$ (0.1 eq.)	CH_2Cl_2	−20	16 h	**85** (50%), unknown (50%)[iv]
15	$ZnBr_2$ (0.1 eq.)	THF	−20	16 h	**82** (100%)
16	$ZnBr_2$ (0.1 eq.)	MeOH	−20	16 h	**85** (30%), unknown (70%)

17	$Zn(OAc)_2$ (0.1 eq.)	THF	−20	16 h	**82** (100%)
18	$Zn(OAc)_2$ (0.1 eq.)	CH_2Cl_2	−20	16 h	**82** (100%)

[i] *All reactions were carried out on 20−50 mg scale at concentrations of 0.1 M in the solvent indicated.* [ii] *Where indicated, product ratios are determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Values are approximate.* [iii] *"Unknown" indicates compounds or mixture of compounds visible in the ^{1}H NMR spectrum of the crude reaction mixture that could not be isolated by chromatography, and whose identity was not established.* [iv] *Although not observed in the crude ^{1}H NMR spectrum, styrene **86** was isolated after silica gel chromatography, presumably due to acid-catalyzed formation on silica.*

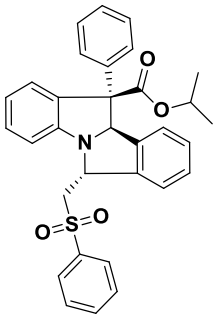
Table 8.2. Acidic conditions employed in the attempted 8π electrocyclization of **82**.

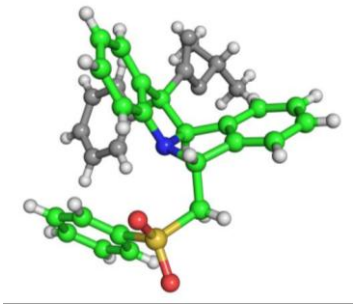
Acid catalysis was equally unsuccessful in the formation of 8π electrocyclized product **83**, although generally gave cleaner reactions than the base-catalyzed conditions. Several Lewis acids (scandium(III) triflate, zinc(II) acetate, zinc(II) bromide) gave cyclized products, although they were 5-membered isomeric indolines **85** and **86**, the product of [1,5]-electrocyclization (Table 8.2, entries 1, 4, 5, 7, 12−14, 16). However, attempts to use this as a general route to vinylindolines **85** were unsuccessful, since isomerization to **86** was spontaneous on silica gel leading to poor yields and low purity of isolated products.

8.2 Crystallographic Data

Key data and refinement for structures are presented here. Further data may be found in the attached digital appendix.

Pyrrolizidine 185 (for preparation and spectroscopic data, see p. 196)



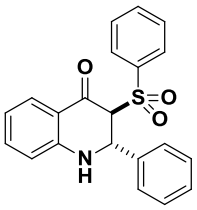


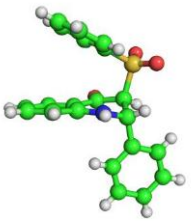
Key data and refinement for the crystal structure of 185

Identification code	6338
Empirical formula	C32 H29 N1 O4 S1
Formula weight	523.65
Temperature	150 K
Wavelength	1.54180 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 9.3165(1) Å α = 90° b = 14.3322(1) Å β = 90° c = 19.7050(1) Å γ = 90°
Volume	2631.13(4) $Å^3$
Z	4
Density (calculated)	1.322 Mg/m^3
Absorption coefficient	1.407 mm^{-1}

F (000)	1104
Crystal size	0.24 x 0.06 x 0.06 mm^3
Theta range for data collection	3.814 to 76.872°
Index ranges	−11<=h<=11, −17<=k<=18, −24<=l<=24
Reflections collected	43647
Independent reflections	5518 [R(int) = 0.024)
Completeness to theta = 76.872°	99.6%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.92 and 0.78
Refinement method	Full-matrix least-squared on F^2
Data/restraints/parameters	5498 / 0 / 344
Goodness-of-fit on F^2	1.0057
Final R indices [I>2sigma(I)]	R1 = 0.0237, wR2 = 0.0619
R indices (all data)	R1 = 0.0239, wR2 = 0.0621
Absolute structure parameter	0.001(9)
Largest diff. peak and hole	0.26 and −0.41 e.$Å^{-3}$

(±)-2-Phenyl-3-(phenylsulfonyl)-2,3-dihydroquinolin-4(1*H*)-one (261) (for preparation and spectroscopic data, see p. 244)



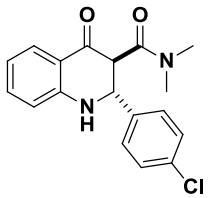


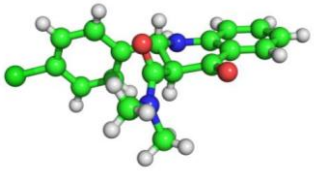
Key data and refinement for the crystal structure of 261

Identification code	PCK 261
Empirical formula	C21 H17 N1 O3 S1
Formula weight	363.43
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P b n 21
Unit cell dimensions	a = 8.78330(10) Å α = 90° b = 14.8824(2) Å β = 90° c = 26.8484(3) Å γ = 90°
Volume	3509.53(7) $Å^3$
Z	7
Density (calculated)	1.376 Mg/m^3
Absorption coefficient	0.205 mm^{-1}
F (000)	1104
Crystal size	0.12 x 0.10 x 0.06 mm^3

Theta range for data collection	5.226 to 27.487°
Index ranges	−11<=h<=11, −19<=k<=19, −34<=l<=34
Reflections collected	7927
Independent reflections	7510 [R(int) = 0.046)
Completeness to theta = 27.487°	99.1%
Max. and min. transmission	0.99 and 0.85
Refinement method	Full-matrix least-squared on F^2
Data/restraints/parameters	7510 / 1 / 469
Goodness-of-fit on F^2	0.9389
Final R indices [I>2sigma(I)]	R1 = 0.2477, wR2 = 0.6238
R indices (all data)	R1 = 0.2708, wR2 = 0.6466
Largest diff. peak and hole	11.76 and −1.22 e.$Å^{-3}$

2-(4-Chlorophenyl)-*N*,*N*-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (303) (for preparation and spectroscopic data, see p. 249)





Key data and refinement for the crystal structure of 303

Identification code	PCK 303
Empirical formula	C18 H17 C11 N2 O2
Formula weight	328.80
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/n
Unit cell dimensions	a = 12.5878(2) Å α = 90.04° b = 9.3875(2) Å β = 98.3672(8)° c = 14.5609(3) Å γ = 90.05°
Volume	1702.32(6) $Å^3$
Z	4
Density (calculated)	1.283 Mg/m^3
Absorption coefficient	0.235 mm^{-1}
F (000)	688
Crystal size	0.5 x 0.4 x 0.4 mm^3
Theta range for data collection	5.226 to 27.487°

Index ranges	−15<=h<=16, −12<=k<=10, −18<=l<=18
Reflections collected	12589
Independent reflections	3898 [R(int) = 0. 028)
Completeness to theta = 27.487°	99.8%
Max. and min. transmission	0.91 and 0.91
Refinement method	Full-matrix least-squared on F^2
Data/restraints/parameters	3898 / 0 / 93
Goodness-of-fit on F^2	3.3784
Final R indices [I>2sigma(I)]	R1 = 0.0237, wR2 = 0.0619
R indices (all data)	R1 = 0.0615, wR2 = 0.1020
Largest diff. peak and hole	0.34 and −0.51 e.$Å^{-3}$