Declaration

This dissertation describes work carried out at the University Chemical Laboratory, Cambridge between October 2007 and September 2008 and the Chemical Research Laboratory, Oxford between October 2008 and April 2011. The dissertation is the result of my own work and only includes work which is the outcome of a collaboration where it is specifically indicated in the text.

Eleanor E. Maciver

Acknowledgements

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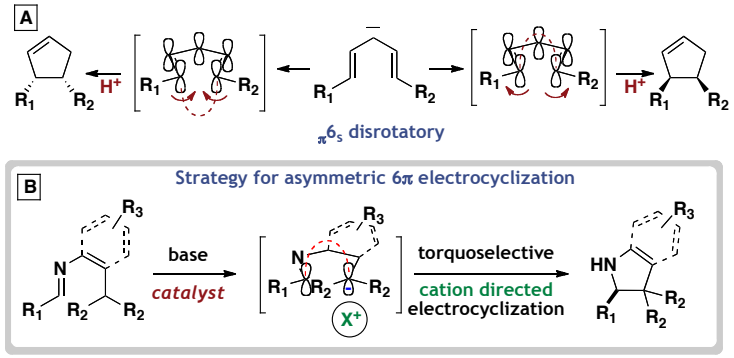
Abstract: Asymmetric electrocyclic reactions *(Eleanor Maciver, DPhil, Lincoln College)*

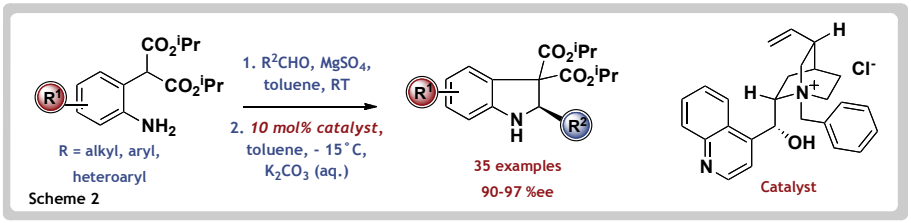
■ **Introduction:** Pericyclic reactions are a class of transformations that comprise sigmatropic rearrangements, group transfer reactions, cycloadditions and electrocyclic reactions. Since Woodward and Hoffmann rationalized the mechanism and stereochemistry of pericyclic reactions they have become powerful synthetic tools. Whilst sigmatropic rearrangements and cycloadditions are cornerstones of contemporary synthetic methodology, many electrocyclic reactions are not fully exploited currently; there are no general methods for the asymmetric catalysis of electrocyclic reactions and as a consequence, opportunities for exerting stereocontrol in these manifolds are limited. We aim to establish general methods for the asymmetric catalysis of 6π electrocyclic reactions. Our initial studies are focused on a pentadienyl anion moiety due to the greater ease of cyclization observed with such systems in comparison to the corresponding neutral hexatriene systems.

■ **Stereocontrol:** Pericyclic reactions are by their nature stereospecific, **scheme 1A.** In order to achieve enantioselectivity in the ring-closing process, we planned to block one π-face of the pentadienyl anion and rely on the stereospecificity of the reaction to direct the stereochemical outcome, **scheme 1B**. One way to accomplish this would be to exploit tight ion-pairing in an organic solvent, using a chiral counterion to select one of the two planar faces of a pentadienyl anion.



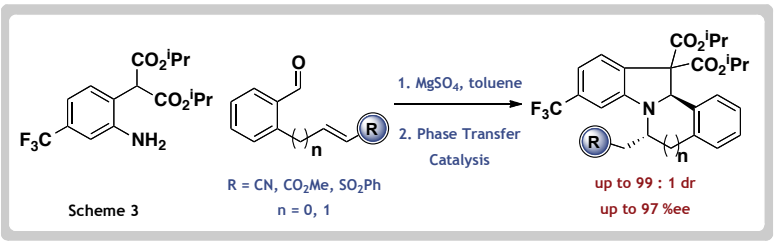
Scheme 1

■ **Asymmetric electrocyclization:** We prepared a series of benzaldimines in three efficient steps *via* a modification of a literature procedure. We envisaged that deprotonation of the malonate portion would furnish the desired planar 6π system which would cyclize to give the corresponding indoline derivatives. Formation of the imine and immediate treatment under optimized phase-transfer catalysis conditions allowed us to access our test indoline (where R^1 = *m*-CF_3 and R^2 = Ph) in 87 % yield and 94 % ee over two steps, **scheme 2**. Using this optimized procedure we expanded the scope of the reaction to allow substitution at all positions on both aryl rings with electron-withdrawing and donating substituents and the use of alkyl/heteroaryl aldehydes, **scheme 2**, in up to 90 % yield and with ee's from 90 – 98 %. From a mechanistic perspective, there are two pathways to consider: an anionic intramolecular Mannich-type reaction *via* 5-(*enolexo*)-*endo* trig, which is stereoelectronically disfavoured by Baldwin's rules or an electrocyclic process which does not suffer from the stereoelectronic constraints of an anionic process. We have expanded the scope of this reaction by introducing a different functional group in place of one of the esters used in our initial work. This has allowed us to develop a highly diastereo- and enantioselective electrocyclization reaction.



Scheme 2

■ **Electrocyclization cascade reactions:** Our current interests are focused on using our methodology to build more complex polycyclic systems with control over more than one stereocentre in a single transformation. We aim to exploit the chiral amine produced in the electrocyclization step by building a 1,4-acceptor into the aldehyde providing an intramolecular trap for the amine. Initial investigations into this cascade reaction have given us some promising results, **scheme 3**, with only a single diastereoisomer of product obtained in up to 97 % ee for a range of substrates. Relative configuration has been confirmed by X-ray crystallography.



Scheme 3

■ **Conclusions:** This transformation offers a glimpse into the potential of asymmetric electrocyclic reactions, and we anticipate that this approach can be expanded to encompass other electrocyclic manifolds.

Abbreviations

Ac	Acetyl
aq	Aqueous
Ar	Aromatic (generic)
Boc	*t*-Butoxycarbonyl
Bn	Benzyl
Bu	Butyl
cal	Calorie
cat.	Catalyst
COSY	Correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	Di*iso*butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
eq	Equivalents
Et	Ethyl
EWG	Electron-withdrawing group
g	Grams
h	Hours
NaHMDS	Sodium hexamethyldisilazide
HMBC	Heteronuclear multiple-bond correlation
HMQC	Heteronuclear multiple-quantum correlation
HRMS	High resolution mass spectrometry
Hz	Hertz
i	*iso*
IPA	Isopropylalcohol
IR	Infra-red
k	Kilo
L	Litres
LCMS	Liquid chromatography mass spectrometry
LDA	Lithium di*iso*propylamide
LHMDS	Lithium hexamethyldisilazide
m	Milli
m	*meta*
M	Mol dm^{-3}
Me	Methyl
Min	Minutes
Mol	Mole
MVK	Methyl vinylketone
n	*neo*
N	Normal
TBS	Tertiary-

	butyldimethylsilyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	*ortho*
p	*para*
Ph	Phenyl
ppm	Parts per milion
Pr	Propyl
***p*TSA**	*Para*-toluenesulfonic acid
Q	Quaternary ammonium salt (generic)
RT	Room temperature
S_NAr	Nucleophilic aromatic substitution
T	Tertiary
TBAC	Tetrabutylammonium chloride
tert	Tertiary
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
Tol	Toluene
Ts	Toluenesulfonyl
UV	Ultra-violet
˚C	Degrees celcius
$_\pi2_s$	two π-electrons, suprafacial
$_\pi4_a$	four π-electrons, antarafacial
$_\pi6_s$	six π-electrons, suprafacial
$_\pi8_a$	eight π-electrons, antarafacial
μ	micro

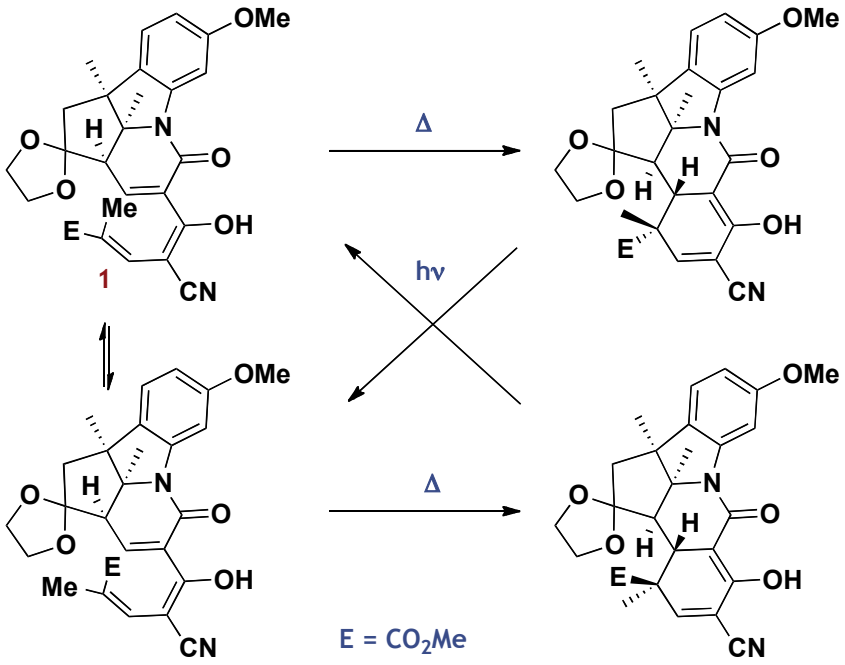
Contents

1. Introduction

1.1 Pericyclic reactions

There are three classes into which most reactions in organic chemistry fall: ionic, radical and pericyclic. The latter class has only been well understood since the late 1960s; in contrast ionic and radical reactions were relatively well understood by the 1950s.[1] Pericyclic reactions are a class of transformations that comprise sigmatropic rearrangements, group transfer reactions, cycloadditions and electrocyclic reactions. A pericyclic reaction is defined as one that proceeds through a cyclic transition state with bond formation and breaking occurring simultaneously.[2] Interest in pericyclic reactions came from the observation of a number of so-called "no mechanism" reactions such as the Diels-Alder cycloaddition. This was a well-known reaction before the 1960s but its mechanism was not understood; the lack of directionality in the attempted use of conventional curly arrows did not sit well with chemists.[1]

Woodward's interest in the topic arose during his much-celebrated synthesis of vitamin B_{12}.[3] The desired late-stage cyclization of cyano-enol **1** would not occur under basic conditions but during an attempt to obtain the melting point of **1** the desired product was formed as a mixture of diastereoisomers, scheme **1**.



Electrocyclization during Woodward's B_{12} Synthesis

Scheme 1

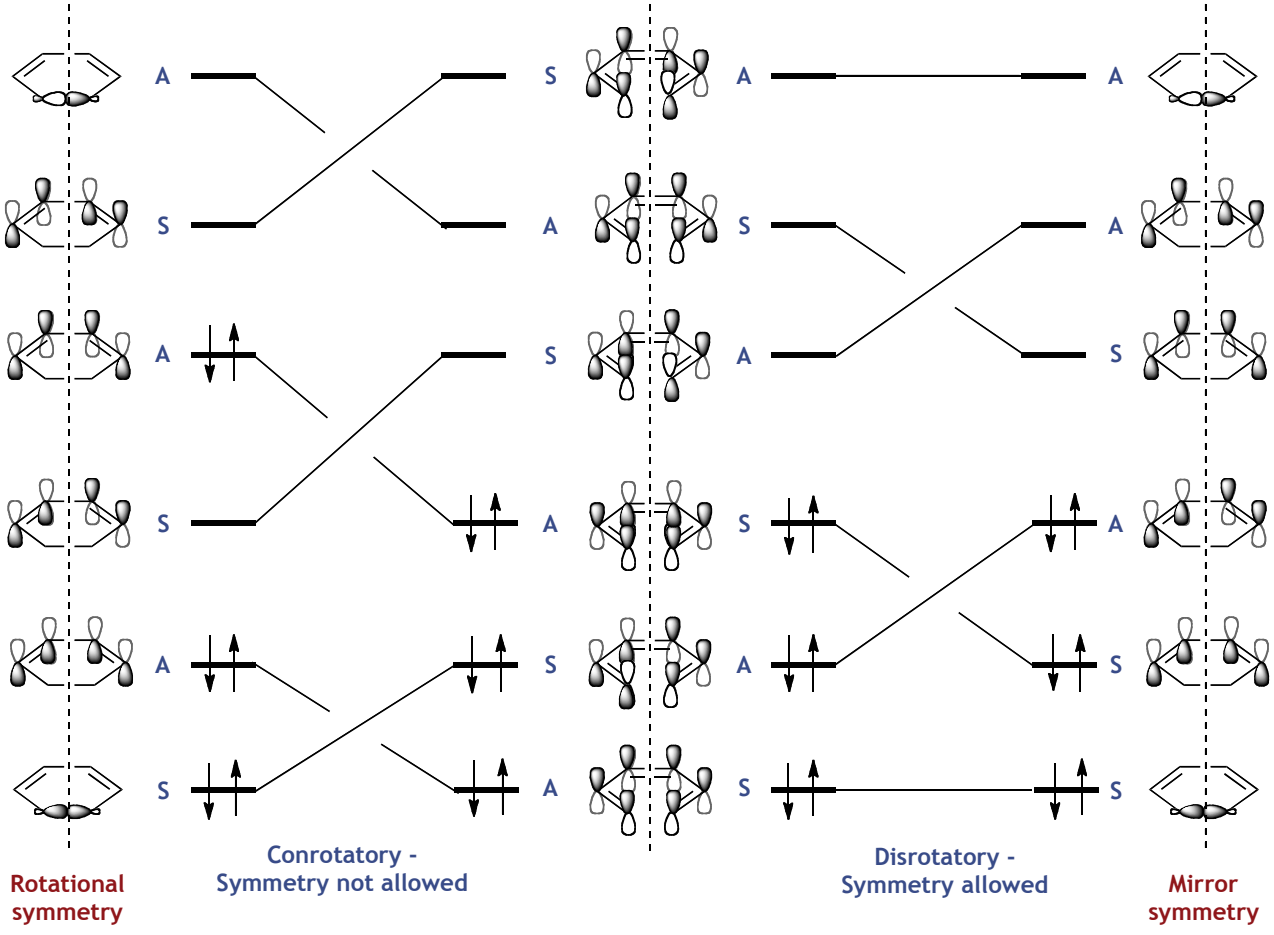
This in itself is perhaps not remarkable; an ionic process could simply have required a higher temperature to proceed. However, further study led to the conclusion that each diastereoisomer was produced by the stereospecific cyclization of a single geometrical isomer of the olefin, which was isomerizing upon heating, scheme **1**. Furthermore, the irradiation of these products resulted in the re-formation of the cyano enolate as the opposite geometrical isomer to that used in the forward thermal reaction. We would now recognise these processes as a thermal disrotatory and photochemical conrotatory 6π electrocyclization respectively.[4]

Earlier work by Vogel had reported strikingly similar stereospecificity in the ring opening of cyclobutenes,[5] the only difference being that the specificity was exactly opposite to that of Woodward's cyclohexadiene ring opening. These results, along with a range of other "no mechanism" examples such as the Diels-Alder reaction led Woodward, in collaboration with Hoffmann, to delineate a set of rules that governed this class of reactions.[4]

The basic rationale behind these rules is derived from the conservation of orbital symmetry during concerted reactions, which dictates that only orbital components of the correct parity can overlap.[4] One of the more compelling and complete explanations we can give for the selectivity of these reactions is to construct an orbital correlation diagram.[6] The main assumption in these

diagrams is that an orbital in the starting material must become an orbital in the product with the same symmetry. These diagrams can only accurately be constructed for systems that have well-defined symmetry such that all the molecular orbitals involved in the process can be readily depicted and the relevant symmetry elements exist.

Our work is focused on the subclass of pericyclic reactions called electrocyclizations, which are characterized by the formation of a ring from an open chain conjugated system whereby the π system is shortened by two atoms with concomitant formation of a new σ-bond. It is however, important to note that the term electrocyclic existed before pericyclic reactions had been rationalized and is therefore not always synonymous with the term pericyclic.[1] The correlation diagram for the electrocyclization of hexatriene, scheme **2**, shows that for the pericyclic process to be allowed it must proceed *via* a disrotatory mechanism.



6π Hexatriene Correlation Diagram

Scheme 2

There are two possible types of symmetry available to the hexatriene system: rotational and mirror symmetry. In the case where mirror symmetry is conserved the corresponding product

molecular orbitals have the correct symmetry for the electrons to occupy the ground state. In the case where rotational symmetry is conserved during the bond forming process the electrons must occupy an excited state in order to populate orbitals with the same symmetry as in the starting material. This leads to the rule that under thermal conditions a 6π hexatriene reaction proceeds *via* a disrotatory mechanism as this has mirror symmetry. Conversely, conrotatory cyclizations have rotational symmetry and are therefore not allowed for a thermal 6π process.

The stereochemical rules that result from the construction of a correlation diagram also apply to less symmetrical systems. The Woodward Hoffmann rules pertain to overlap of orbitals with the correct symmetry and in a system where the symmetry is perturbed only the orbital *coefficients* are affected, not the orbital parity. Therefore although the correlation diagram would be difficult to represent accurately for an unsymmetrical system, the selectivity arising from a symmetric system of the same electronic configuration would accurately predict its stereoselectivity. Similar diagrams can be constructed for 4π systems to rationalize the conrotatory mode of cyclization and hence explain the opposite selectivities observed by Vogel and Woodward.

Whilst it is important to understand the logical derivation of the Woodward Hoffmann rules it is not always desirable to construct these complicated diagrams and so the simplified rules are more often applied:[i/i]

A thermal pericyclic change is symmetry allowed when the total number of $(4q+2)_s$ *and* $(4r)_a$ *components is odd.*

and

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

Since Woodward and Hoffmann rationalized the mechanism and stereochemistry of pericyclic reactions they have become powerful synthetic tools. Whilst sigmatropic rearrangements and cycloadditions are cornerstones of contemporary synthetic methodology, electrocyclic reactions are not fully exploited; there are few methods for the asymmetric catalysis of electrocyclic reactions and as a consequence, opportunities for exerting stereocontrol in these systems are limited.

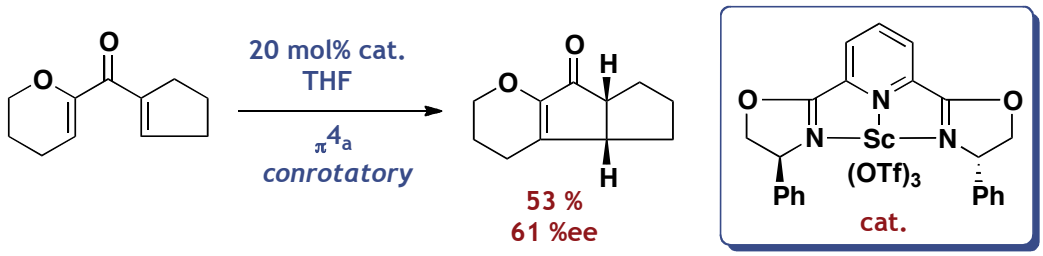
[i] 'q' and 'r' are integer values; 's' denotes suprafacial overlap of orbitals; 'a' denotes antarafacial overlap of orbital

1.2 Literature

In this introduction I have tried to highlight the examples which inspired and directed the work undertaken without reproducing a comprehensive literature review of the field. For a current in-depth review of asymmetric electrocyclizations a recently published review[7] by Smith *et al*. is particularly useful.

1.2.1 Asymmetric 4π Nazarov

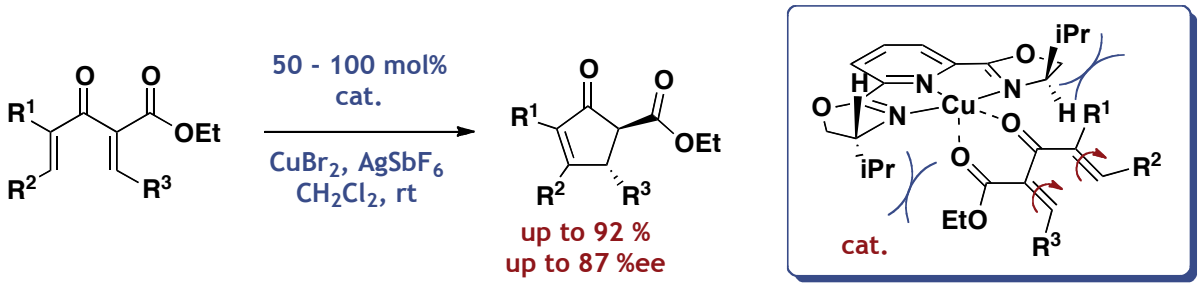
One of the more extensively studied electrocyclizations is the Nazarov reaction; a thermal 4π conrotatory process which involves the conversion of divinyl ketones to cyclopentenones, often requiring activation by an acid. One of the earliest catalytic asymmetric Nazarov reactions, reported by Trauner *et al*., is catalyzed by a chiral scandium Lewis acid, scheme **3**.[8]



Scheme 3

Trauner exploited the bidentate binding properties of α-oxygenated dienones in this reaction to facilitate more selective binding to the catalyst. The alkoxy substituent is also known to render the substrate highly reactive, possibly by lowering the activation energy for cation formation; reactions of such substrates can occur in a matter of minutes at room temperature under optimized conditions.

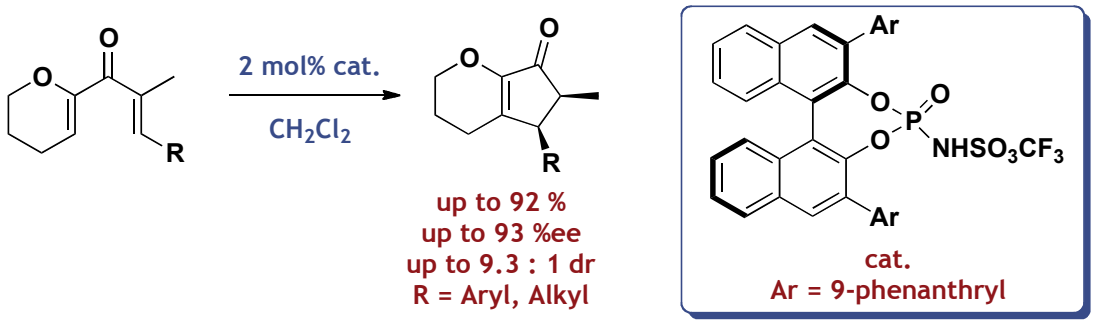
In the same year Aggarwal *et al*., published a similar manifold involving the catalysis of a Nazarov reaction with a chiral Lewis acid, this time using copper as the Lewis acidic metal,[9] scheme **4**.



Scheme 4

Aggarwal rationalized that to employ this mode of catalysis a 1,3-dicarbonyl was required; however, the inclusion of an electron-withdrawing ester into the substrate should effectively slow down the Nazarov reaction (by destabilising the intermediate cation). Although the yields and ees reported are good, the reaction requires stoichiometric amounts of the catalyst to maintain these high yields; reduction to 50 mol% catalyst loading reduces the yield to 56 % with no change in the ee. This is possibly due to catalyst inhibition by the product 1,3-dicarbonyl as this would bind in a similar way to the starting material. The ligand transfers stereochemistry by distorting the plane of the cationic intermediate of the Nazarov reaction to favour one mode of conrotation over the other. The ability to distort the planarity of the electrocyclization precursor would make a similar mode of catalysis appropriate for our research. More recent work by Eisenberg,[10] Togni[11] and Ma[12] using similar Lewis acid based catalysis has greatly improved on these pioneering results.

The first organocatalytic asymmetric Nazarov cyclization was reported by Rueping *et al*. in 2007, using a chiral Brønsted acid derived from BINOL, scheme **5**.[13]



Scheme 5

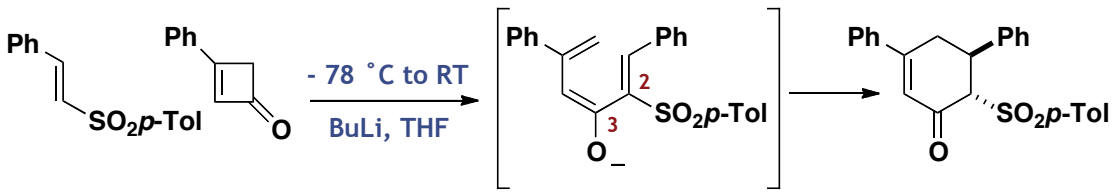
Rueping employs a similar substrate to Trauner's earlier work, relying on the reactivity of an α-alkoxy dienone. In terms of catalysis it is proposed that the Brønsted acid protonates the ketone moiety which promotes the formation of the cyclopentadienyl cation. The cation is then stabilized by formation of an ion-pairing adduct with the phosphate anion. Subsequent electrocyclization then favours one direction of rotation over another as the chiral phosphate anion will bind preferentially to one side of the pentadienyl cation. The second stereocentre is determined by protonation of the enolate. The low catalyst loading required for this transformation and high ees make it a useful route to substituted cyclopentenones and demonstrates the many improvements in the area of asymmetric Nazarov reactions.

Although our research is not in the area of 4π Nazarov electrocyclizations (as this particular reaction manifold is reasonably well established) the modes of catalysis employed in these examples and the wealth of other literature not discussed here provide precedent for the catalysis of electrocyclic reactions. In particular, the use of Lewis acid and tight ion-pairing catalysis provide useful insight into possible modes of catalysis for our own work.

1.2.2 [1,6] 6π electrocyclizations

Our work has focused on the development of a 6π electrocyclization, electronically similar to that observed by Woodward in the synthesis of vitamin B_{12}. The lack of any general methods for asymmetric induction in these systems and the obvious utility of such reactions made this an exciting research prospect.

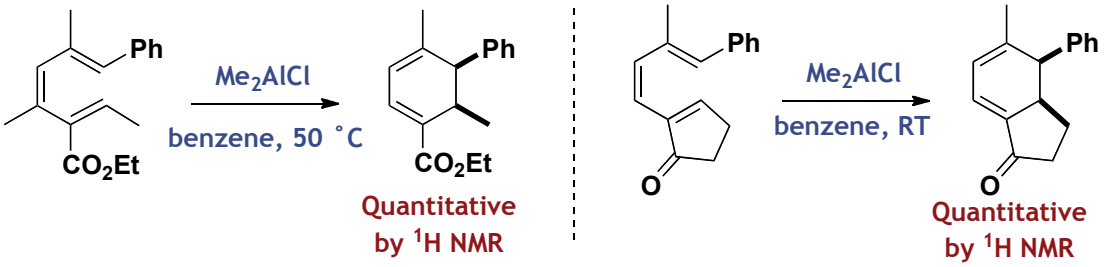
One of the problems associated with electrocyclization reactions is that high temperatures are often required to promote the forward reaction. However, it has been shown by Magomedov *et al*. that the use of donor and acceptor substituents at the C3 and C2 positions around the hexatriene ring system significantly reduces the barrier to electrocyclization,[14] scheme **6**. This hypothesis has been backed up with theoretical calculations by Fu *et al*.[15] which suggest that a variety of substitution patterns of captodative donor and acceptor substituents lower the barrier to electrocyclization in such systems.



Scheme 6

The lowering of the activation energy by the inclusion of these stabilising groups around the ring system allows lower temperatures to be used to effect the transformations. Lower temperatures may also prevent double bond isomerization, leading to a more stereocontrolled process.

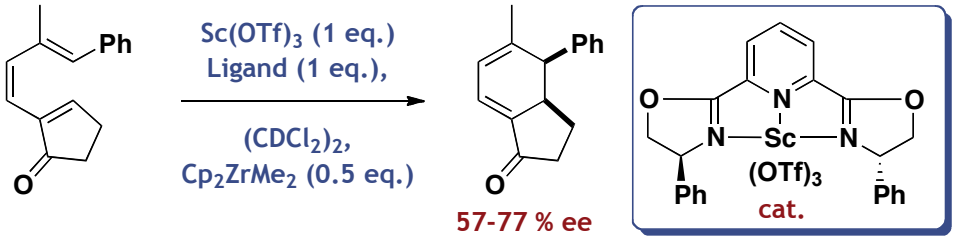
Trauner *et al*.[16] have shown that a combination of stabilizing groups and Lewis acid catalysis can be used to promote 6π electrocyclizations under mild conditions, scheme **7**. The inclusion of a carbonyl at the 2-position is known to lower the activation energy of a hexatriene reaction by up to 10 kcal/mol. This in itself does not allow the reaction to proceed; a Lewis acid catalyst can bind to the carbonyl making it more electron-withdrawing and further reducing the activation energy. It is this interaction that allows the reaction to proceed at low temperatures.



Scheme 7

The ability to accelerate the electrocyclization using a Lewis acid catalyst suggested that such processes could be controlled by asymmetric Lewis acids which could therefore promote enantioselectivity.

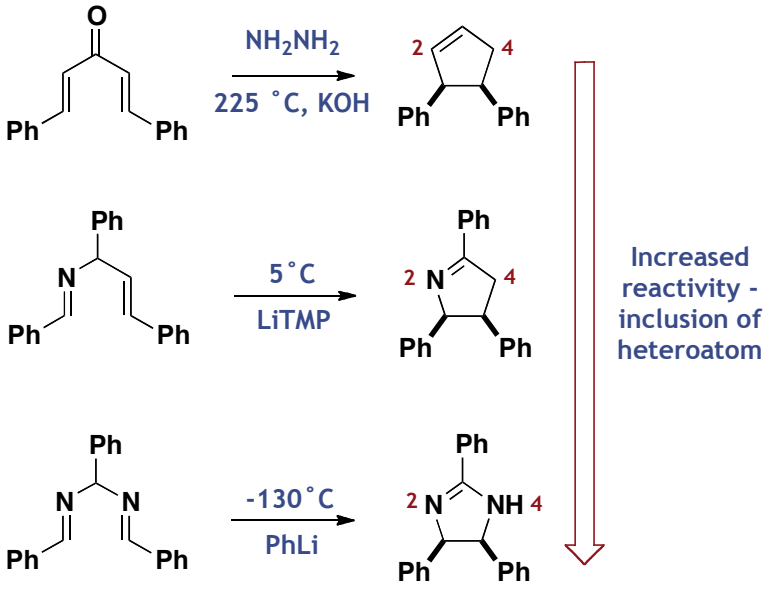
Recently Trauner *et al*.[17] published the same system using a PyBOX ligand with scandium(III) as the Lewis acid catalyst to promote enantioselectivity in the electrocyclic process, scheme **8**. Although the asymmetric variant was published after we began our work, the earlier promising results provided insight into possible modes of catalysis.



Scheme 8

1.2.3 [1,5] 6π electrocyclizations

Our work focusses on the isoelectronic [1,5]-electrocyclization; this is the cyclization of a 6π pentadienyl anion to form a five-membered ring. As with the hexatriene manifold, the inclusion of anion-stabilizing groups has been shown to lower the activation energy of the reaction. This can be demonstrated by comparing the rates of electrocyclization of a range of pentadienyl anions, scheme **9**.[18]



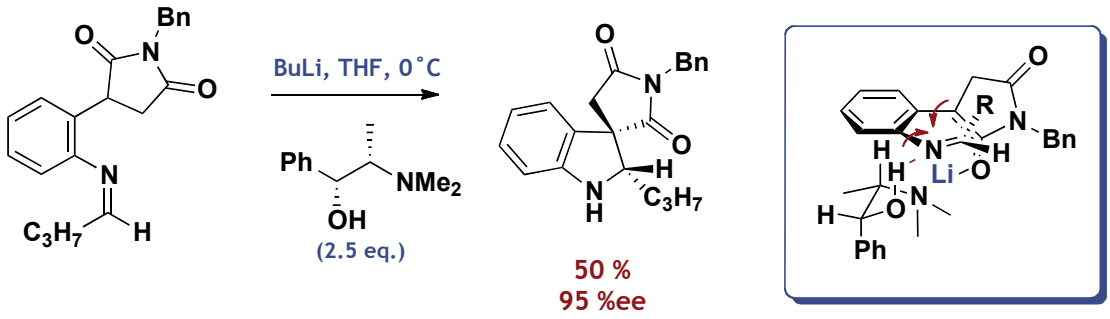
Scheme 9

The inclusion of a heteroatom at the 2- and 4- position of the carbon backbone of the pentadienyl anion has a marked effect on the rate of reaction, possibly due to the stabilization of the product anion.

The consideration of these factors, both the hexatriene data and that directly relating to [1,5]-electrocyclizations, allows us to design a substrate that should be amenable to electrocyclization under mild conditions such that we can explore asymmetric induction.

1.2.4 Asymmetric 6π electrocyclizations

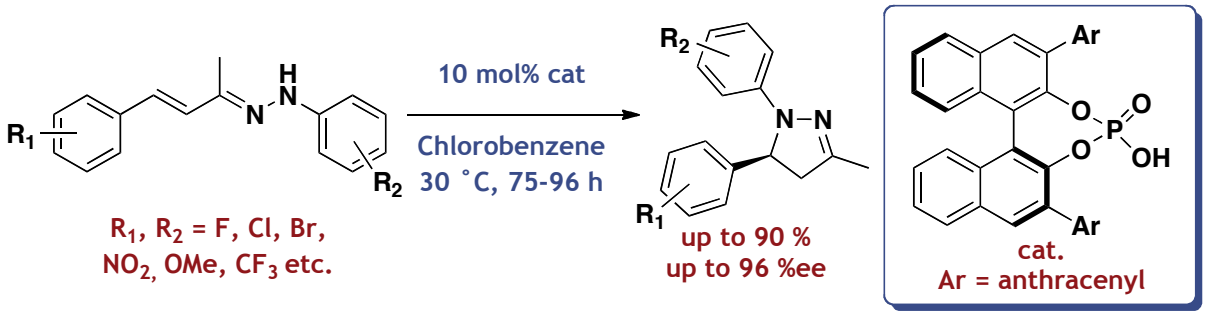
There are very few examples of asymmetric variants of 6π electrocyclizations despite the utility of these powerful carbon-carbon bond forming reactions. These examples were limited to the [1,5]-electrocyclization manifold when we began our research. In the 1980s Speckamp published a number of papers[19] on such systems culminating in the process outlined in scheme **10**.[20] This reaction involves the cyclization of a 6π system azapentadienyl anion to furnish an indoline product.



Scheme 10

This reaction is carried out by pre-mixing of *N*-methylephedrine with BuLi and subsequent addition of the substrate. The use of a stong base would almost certainly deprotonate the alcohol functionality meaning the reaction must involve the alkoxide deprotonating the amide.The binding mode proposed simultaneously relies on the interaction of *N*-methylephedrine with both the lithium cation and with the imine portion of the substrate *via* hydrogen-bonding to transfer stereochemical information. The high ee reported makes this a very attractive manifold; however the reaction is highly substrate specific and replacing the propyl group with a butyl group reduces the ee to 38 %. The ability to effect an electrocyclic process at low temperatures under reasonably mild conditions is attributed to the inclusion of nitrogen into the 6π-system. It is also interesting to note that the anion can be formed by the relatively facile deprotonation of an α-amido benzylic proton. It was this encouraging precedent that led to our proposed study of a [1,5]-electrocyclization. The ability to effect the reaction at low temperatures would make such a process amenable to modern asymmetric catalysis methodologies.

More recently in 2009 List *et al*. published another catalytic asymmetric 6π electrocyclization to form a variety of substituted pyrazoline rings, scheme **11**.[21]



Scheme 11

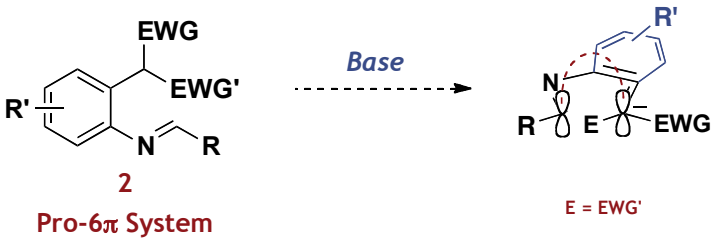
The proposed mode of asymmetric induction is similar to that employed by Rueping in his Nazarov reaction (scheme **5**) and relies on the tight ion-pairing of the chiral phosphoric acid derivative with the protonated imine portion of the substrate to transfer stereochemical information.

These few examples give a glimpse of the potential for asymmetric catalysis in 6π electrocyclization reactions and electrocyclizations in general. It is interesting to note that all catalytic asymmetric examples given so far do not fully utilise the stereospecificity of an electrocyclization; they create one stereocentre during the electrocyclization process. It is of course possible to utilise the inherent specificity of the process and create two stereocentres as a single diastereoisomer during an electrocyclization. The use of pericyclic processes to create otherwise troublesome quaternary carbon centres is well known; by developing a general route to asymmetric induction during an electrocyclization process we hope to enable these powerful reactions to be exploited more fully in organic synthesis.

2. Development of a catalytic asymmetric [1,5]-electrocyclization

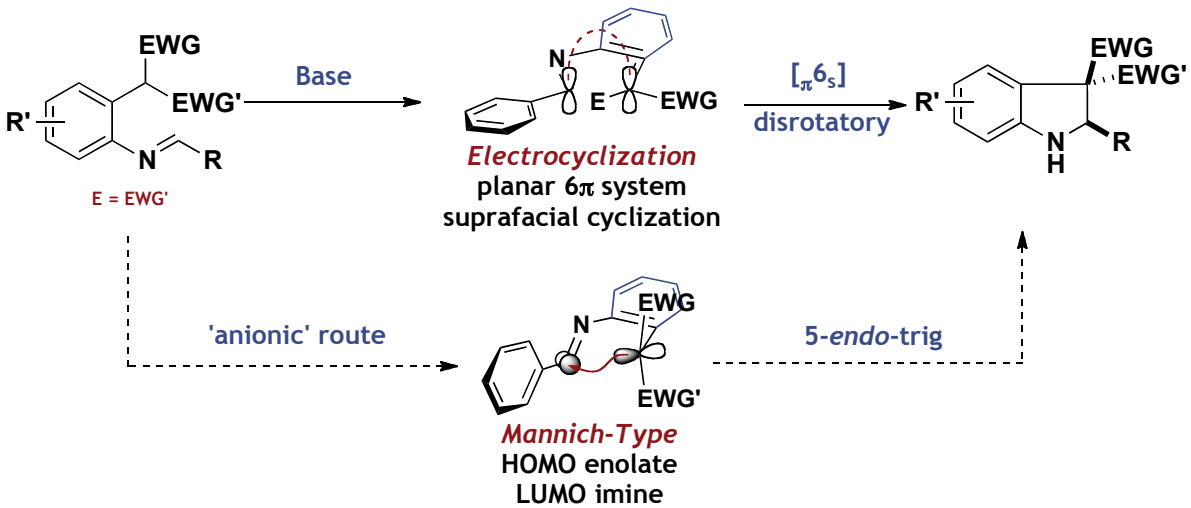
2.1 Project aims

The aim of this project was the development of methodology for the asymmetric catalysis of [1,5]-electrocyclization reactions that facilitate the assembly of complex, highly functionalized molecules. To accomplish this we envisaged the assembly of a 'pro-6π system' **2**, scheme **12**,[22] that could subsequently be diversified with ease.



Scheme 12

As discussed in the introduction, rationale for the inclusion of a heteroatom in our system for the initial investigation was that it would lower the temperature required for cyclization compared to an analogous all-carbon system,[18] giving greater scope for controlling asymmetric induction in the process. The use of two electron-withdrawing groups in the proposed scaffold should allow facile deprotonation at the benzylic position to furnish the desired 6π system and again we hoped that the use of mild conditions would allow for control of asymmetric induction.

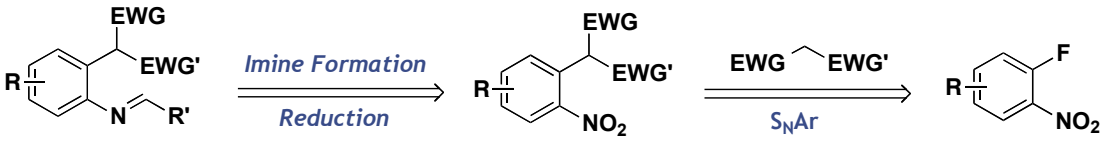


Scheme 13

Once the deprotonation has taken place the cyclization could be interpreted as an intramolecular Mannich-type reaction but this would constitute a 5-*endo*-trig cyclization which would be disfavoured by Baldwin's rules,[23] scheme **13**. Hence we rationalized that the proposed reaction seemed likely to take place *via* the electrocyclic route, as this process does not suffer from the same stereoelectronic constraints.

2.2 Retrosynthesis

Synthesis of the desired imine for our studies was proposed by a modification of a literature procedure by Goetz *et al*.[22] An S_NAr reaction with commercially available aryl fluorides, facilitated by the adjacent nitro group, reduction of the nitro group and subsequent imine formation would furnish the desired electrocyclization precursor, scheme **14**.



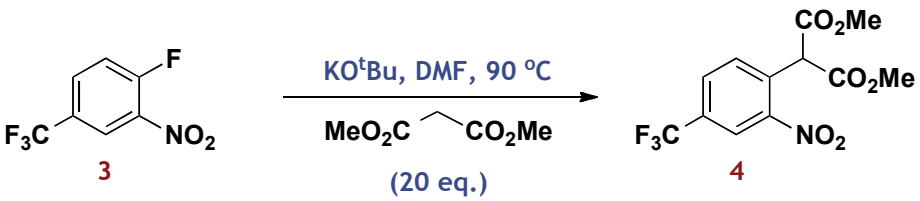
Scheme 14

It was envisaged that a range of electron-withdrawing groups and substituted aryl rings could be incorporated during the S_NAr step and use of different aldehydes for the imine formation would allow easy diversification of the system.

2.3 Construction of the pro-6π system

2.3.1 S_NAr

For the initial S_NAr reaction it was proposed that the inclusion of a trifluoromethyl group on the aromatic ring would help promote the reaction due to the extra electron-withdrawing effect, scheme **15**.



Scheme 15

Treatment of dimethyl malonate with potassium *tert*-butoxide at 90 °C in dimethylformamide and subsequent addition of commercially available aryl fluoride **3** afforded the desired nitro compound **4**. It was, however, inseparable from the excess of dimethyl malonate either by flash column chromatography or recrystallization. Subsequent modification and optimization of the literature procedure, table **1**, led to a much-improved reaction.

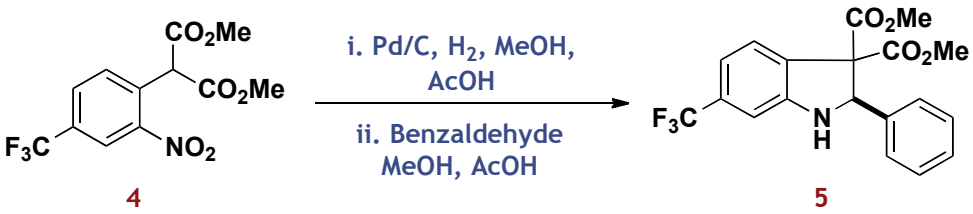
Aryl fluoride (eq.)	Dimethyl malonate (eq.)	Base	Yield
1	20	KO^tBu	Inseparable
1	20	K_2CO_3	Inseparable
1	5	K_2CO_3	Inseparable
1	1	K_2CO_3	91 %

Table 1

Use of potassium carbonate with one equivalent of dimethyl malonate allowed facile purification of the product *via* recrystallization from toluene.

2.3.2 Nitro reduction and imine formation

With the desired nitro compound **4** in hand we moved on to explore reduction of the nitro group and subsequent imine formation; our initial attempts focused on a tandem process reported for a similar substrate by Goetz *et al*.,[22] scheme **16**.

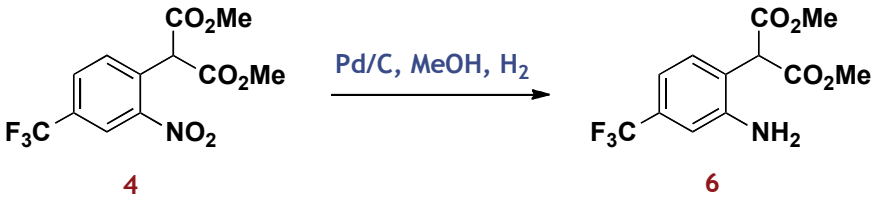


Scheme 16

Treatment of nitro compound **4** with palladium on carbon and hydrogen in methanol : acetic acid, 50 : 1, removal of the palladium and subsequent addition of benzaldehyde afforded the cyclized product **5** in 62 % yield. Formation of the product was verified by ^{1}H NMR and the connectivity of the ring system was verified by HMBC; strong correlation between the benzylic proton and the malonate carbon in the product was observed.

Although this was not the intended product, this result was promising as it demonstrated that the imine was susceptible to the desired cyclization reaction. We hoped that it would be possible to isolate the intermediate imine in order to study the electrocyclization reaction. We rationalized that our substrate bearing a trifluoromethyl group would be more reactive than the substrate reported in the literature to deprotonation at the benzylic position and hence required milder imine formation conditions.

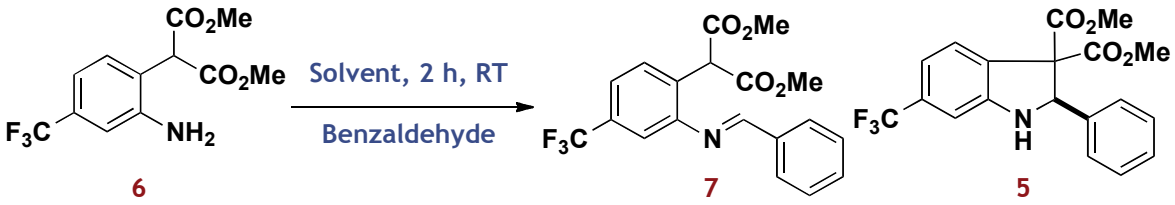
Treatment of the nitro compound **4** with palladium on carbon in methanol under a positive pressure of hydrogen afforded the desired product **6** in an isolated yield of 91 %, scheme **17**.



Scheme 17

The product was verified by ^{1}H NMR with the appearance of a peak corresponding to two amine protons and a large shift in the aromatic protons around 1.6 ppm upfield.

With aniline **6** in hand we investigated a number of different conditions for imine formation. As the mechanism of imine formation is reversible, a dehydrating agent was necessary in all cases, table **2**.



6 7 5

Solvent	Dehydrating agent	Ratio of products[a] (7 : 5)[b]	
MeOH	$MgSO_4$	Not observed	Complete
	4Å Sieve	1	2
Dichloromethane	$MgSO_4$	1.7	1.1
	4Å Sieve	1	1
Toluene	$MgSO_4$	2.8	0.7
	4Å Sieve	Not observed	Complete

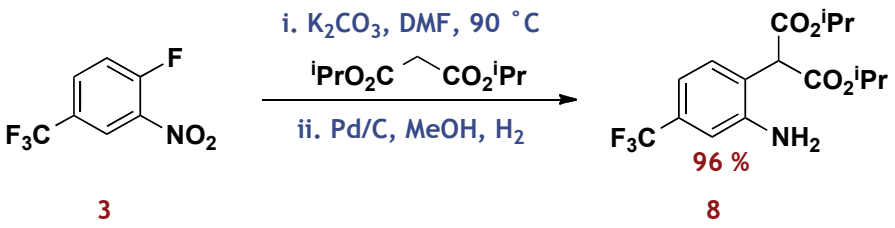
a) Treatment of aniline **6** (20 mg) with benzaldehyde (1 eq.) and a dehydrating agent as shown in solvent (0.3 mL) for 2 h afforded the ratio of products.

b) The ratio of products was determined by ^{1}H NMR analysis.

Table 2

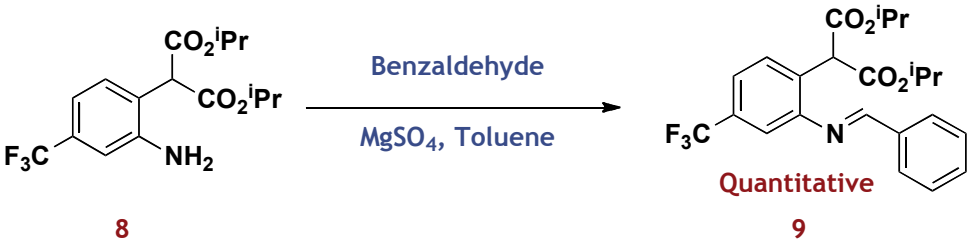
During the imine formation reaction using various drying agents and solvents we observed a range of ratios of the desired imine **7** and the cyclized product **5**. The best results were observed using magnesium sulfate as the dehydrating agent and toluene as the solvent. In methanol using magnesium sulfate the extent of unwanted cyclization is higher than in both other solvents. If the cyclization is pericyclic we would not expect the solvent to affect the cyclization; however as the cyclization necessarily involves a deprotonation we would expect a polar protic solvent (like methanol) to favour the cyclization. Likewise methanol may hydrogen-bond to the imine activating it for the cyclization; both of these rationalizations would also be valid for a non-pericyclic pathway. Although these results vindicated our choice of substrate (as it indicates the cyclization is facile), the inability to isolate the imine as the sole product or even purify the resulting mixture by chromatography (further cyclization occurred on silica) meant that this substrate was too reactive for our study.

We envisaged that a more sterically hindered malonate might slow down the cyclization reaction and allow access to the desired imine in pure form. Therefore this study was continued using isopropyl esters, scheme **18**.



Scheme 18

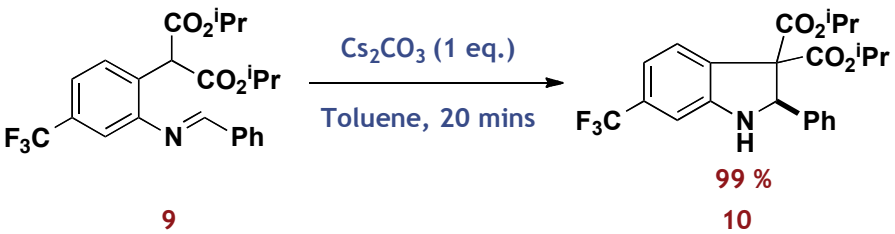
The initial S_NAr and reduction worked well with the new isopropyl esters allowing imine formation to be investigated. Isolated aniline **8** was treated under the previously optimised conditions for imine formation, scheme **19**, to afford the desired imine **9** in quantitative yield.



Scheme 19

2.4 [1,5]-Electrocyclization

With a high-yielding route to a stable pro-6π system in hand, investigation of the [1,5]-electrocyclization reaction was possible. Initial focus on the achiral cyclization led to the investigation of a number of solvent and base systems, many of which were amenable to the cyclization. The most reliable and practical of these was the use of cesium carbonate in toluene, scheme **20**. Reducing the amount of base to 0.1 equivalent still effects the transformation cleanly and completely within five hours.

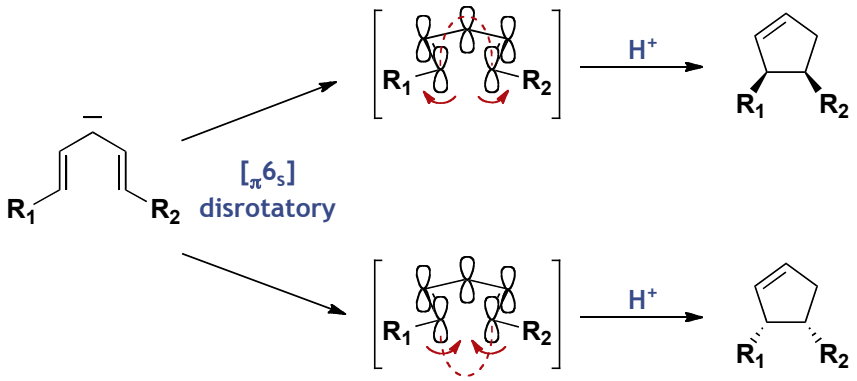


Scheme 20

The facile nature of this cyclization validated our original substrate design and with this promising result in hand we turned our attention to exploration of asymmetric catalysis of the process.

2.5 Asymmetric induction

During a 6π electrocyclization reaction the bond forming process can occur on either the top or bottom face of the π-system.[1] These processes are the two possible disrotatory pathways and each one gives a single enantiomer of product, scheme **21**.

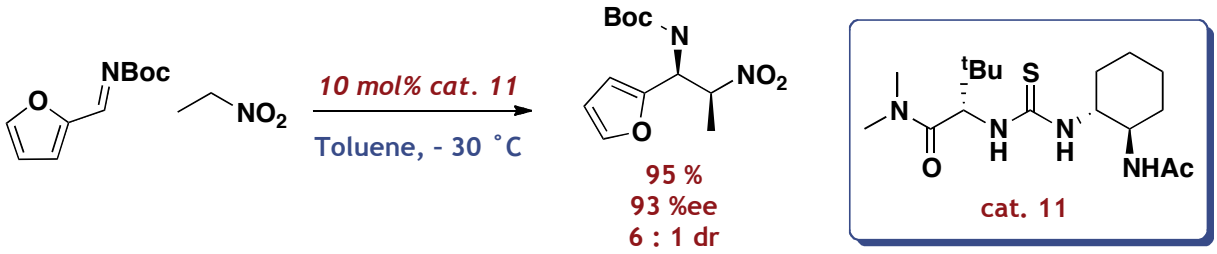


Scheme 21

In order to induce asymmetry in the electrocyclic process we need to favour one direction of rotation of the orbitals over the other. As discussed in the previous chapter there were a number of possible methods for asymmetric induction to be considered.

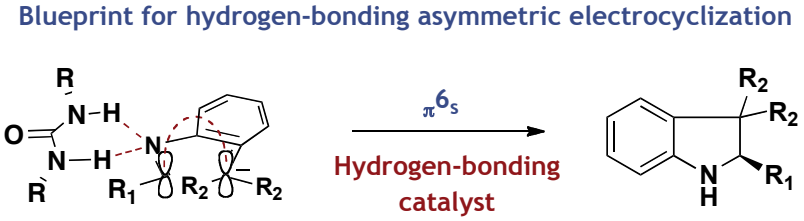
2.5.1 Hydrogen-bonding catalysis

Hydrogen-bonding catalysts have been reported to induce high levels of enantioselectivity in Mannich type reactions,[24] scheme **22**.



Scheme 22

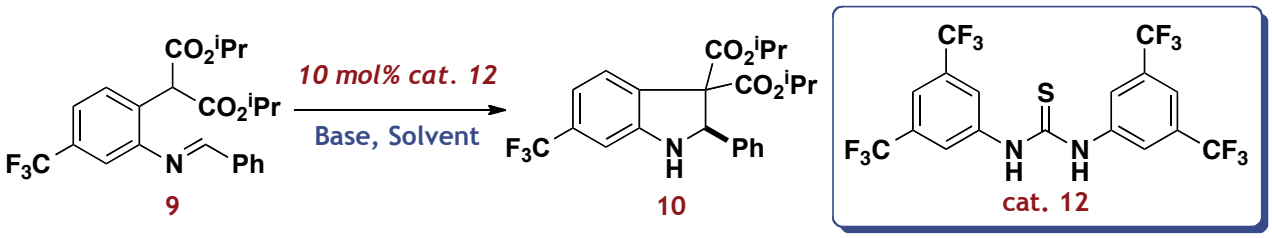
It is thought that the mode of catalysis involves hydrogen-bonding of the thiourea moiety to imine in the transition state. This activates the imine toward nucleophilic attack and promotes transfer of the stereochemistry. The build up of charge on the imine nitrogen is expected in the forward direction during our cyclization. This similarity led us to propose the use of hydrogen-bonding catalysis to induce stereochemistry in the electrocyclization reaction, scheme **23**.



Scheme 23

For asymmetric induction the R groups on the catalyst must be of sufficient steric bulk to force the bond forming process to occur on the top face (as drawn) and rotate the phenyl group away from the bulk of the catalyst. By tailoring these groups we hoped to be able to induce asymmetry into the electrocyclic process.

In order to investigate the viability of hydrogen-bonding catalysis an achiral thiourea catalyst, **12**,[25] was studied, table **3**. Potassium carbonate and triethylamine were screened as bases as well as cesium carbonate because they give only limited conversion to the product without the use of a catalyst.



Base, Solvent[a]	Catalysed[b]	Background[b]
Cs_2CO_3, $CHCl_3$	Full conversion	Full conversion
Cs_2CO_3, Toluene	Full conversion	Full conversion
K_2CO_3, $CHCl_3$	52 % / 18 %[c]	7 %
K_2CO_3, Toluene	75 % / 23 %[c]	15 %
NEt_3, $CHCl_3$	24 %	17 %
NEt_3, Toluene	24 %	6 %

a) Treatment of the imine **9** with one equivalent of base and 10 mol% of catalyst in the given solvent afforded the cyclized product **10** in the reported yields which are the average of two identical experiments.

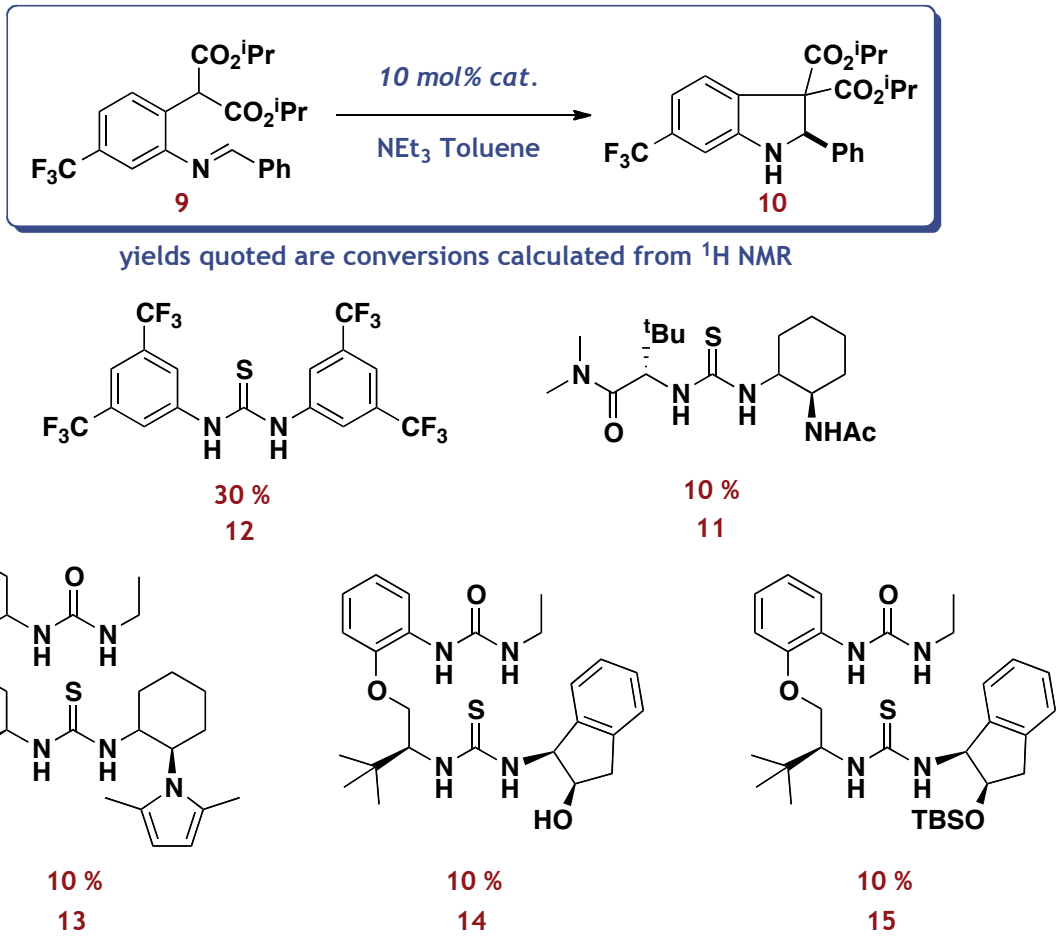
b) Conversions are quoted from the analysis of ^{1}H NMR.

c) Where two values are quoted the range of conversion was too large for an average to be taken

Table 3

The potassium carbonate results were not consistent across repeated runs; potassium carbonate was ground by hand and it is possible that differences in particle size may have an effect on its solubility. Hence two separate values are reported instead of an average of the two runs. When cesium carbonate was used as a base the product was obtained in near quantitative yields after a reaction time of just 1 hour in both the catalysed and uncatalysed reactions. It was therefore apparent that the background reaction in this case was too fast.

Using triethylamine as a base the reaction rate was significantly increased in the presence of the catalyst suggesting that this might be a possibility for the use of asymmetric catalysts. As the background reaction in toluene using triethylamine as the base was slower than in chloroform we decided to screen a number of chiral hydrogen-bonding catalysts using toluene and triethylamine as the conditions, scheme **24**. These asymmetric catalysts were kindly provided by co-workers: Dr Chris Jones and Dr Rhian Thomas. Jacobsen's catalyst **11** has become well-used in the area of hydrogen-bonding catalysis;[24] catalysts **13 – 15** were developed within the group and have been shown to out-compete Jacobsen's catalyst in a Mannich reaction.[26]

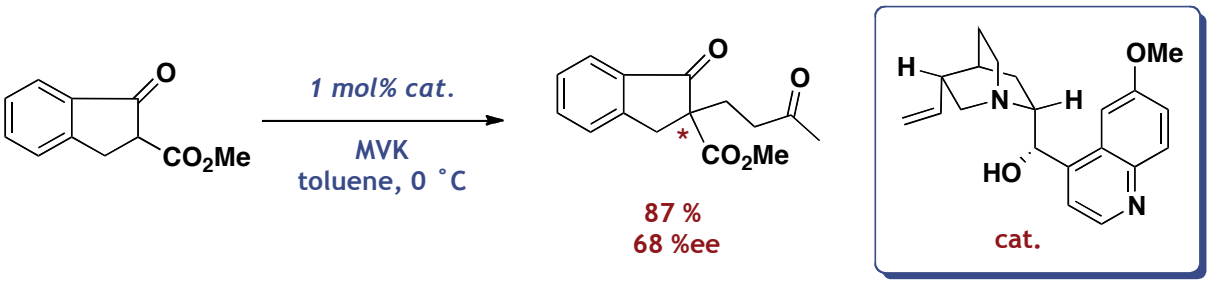


Scheme 24

As it can be seen from these experiments the only catalyst that gave any rate acceleration was the original achiral catalyst **12**. This can be rationalized by considering the larger steric bulk of the chiral catalysts which may prevent binding to the imine portion of the starting material. Alternatively, the electron deficient nature of the bis-trifluoromethyl aryl groups increase the hydrogen-bonding potential of the thiourea moiety of catalyst **12** and enhance the catalytic activity.

2.5.2 Cinchona alkaloid catalysis

As hydrogen-bonding catalysis appeared unsuitable for our system, we turned our attention away from the prospect of imine activation towards catalysis that would exploit the anionic nature of the process. The ability of cinchona alkaloids to act as catalysts has been exploited in a number of reactions[27] and was first introduced as an organocatalyst by Wynberg *et al.*[28] in the 1970s, scheme **25**.

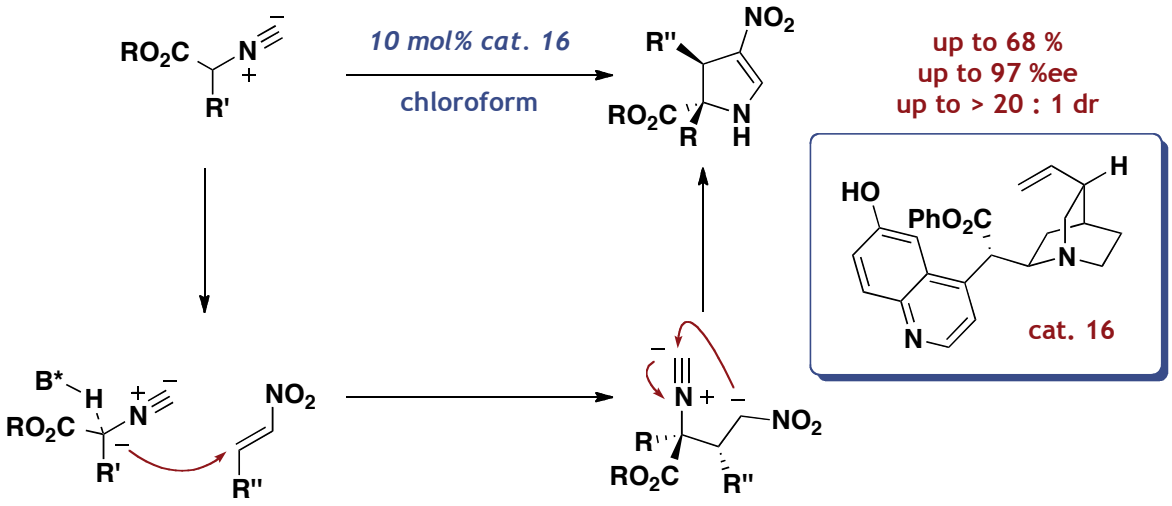


Scheme 25

The Michael reaction was carried out with a number of substrates all possessing two electron-withdrawing groups at the desired nucleophilic centre with methyl vinyl ketone as the electrophile. Enantiomeric excess was not calculated for all examples but similarly high optical rotations for all substrates was observed leading the authors to propose similar enantioselectivities had been induced in the process.

These remarkable early results, some of the earliest asymmetric Michael additions reported, led Wynberg *et al*. to attempt to rationalize the mode of catalysis utilised by cinchona alkaloids in the early 1980s.[28] They proposed that the catalysts behave in a bifunctional manner with the amine portion acting as a base and the hydroxy moiety behaving as a hydrogen-bond donor. These interactions allow the catalyst to preorganise the nucleophile by both hydrogen-bonding and ion-pairing, with the now charged ammonium nitrogen, giving greater enantiomeric excesses than catalysts whereby the hydroxy group is blocked by alkylation etc.

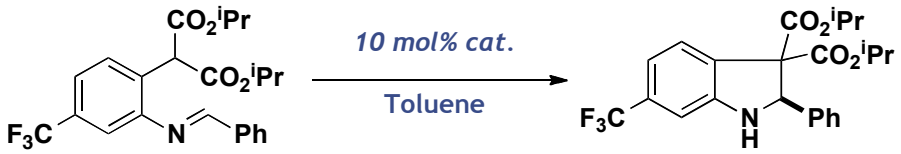
More recently the use of quinine-derived bases to catalyse a formal [3+2] cycloaddition of isocyanoesters and nitro olefins has recently been reported,[29] scheme **26**.



Scheme 26

The quinine derived base **16** forms a tight ion-pair with the isocyanoester as it is deprotonated and transfers stereochemistry in the initial attack on the nitro olefin setting the two contiguous stereocentres.

We hoped that the ability of the cinchona alkaloids to form a tight ion-pairs should make it a good candidate for catalysing the electrocyclization – by forming a tight ion-pair with the deprotonated malonate, table **4**.



9 10

Catalyst	24 h, RT	24 h, 60 °C	72 h, 60 °C
-	10 %	12 %	12 %
Quinine	10 %	38 %	72 %
Cinchonine	12 %	22 %	100 %

a) Conversions are quoted from the analysis of ^{1}H NMR.

Table 4

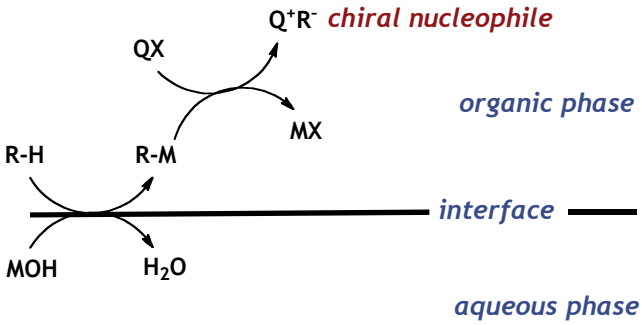
The results over a 72 hour period of heating with cinchonine and quinine were both promising due to the much higher conversions achieved in comparison to the background reaction. HPLC analysis of the reaction products after purification by column chromatography revealed no enantiomeric excess. This is possibly due to weaker ion-pairing than expected at the elevated temperatures required or low facial recognition by the catalyst resulting in racemic material.

2.5.3 Phase-transfer catalysis

We reasoned that despite the disappointing asymmetric induction with cinchona alkaloids we could still hope to effect a similar mode of catalysis with a greater propensity for tight ion-pairing such as phase-transfer catalysis. Phase-transfer catalysis, which relies on the principle of tight ion-pairing, has become an increasingly powerful method for inducing asymmetry in organic processes in recent years.

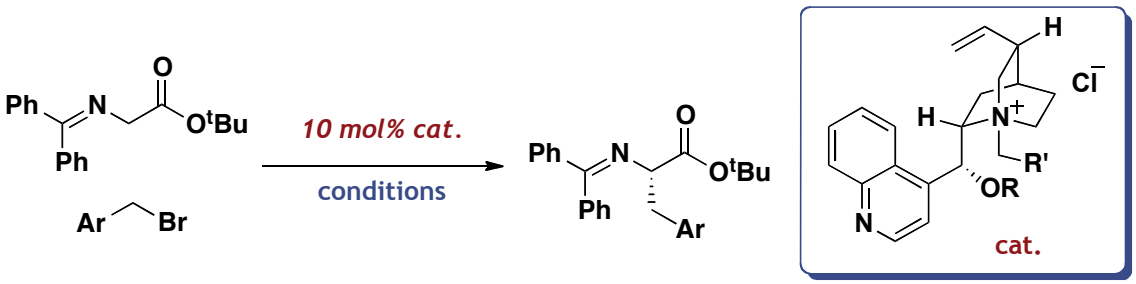
The term phase-transfer catalysis was first used in the 1970s by Storks to explain the need for tetraalkylammonium or phosphonium salts in a number of reactions involving biphasic mixtures.[30] The ability of these catalysts to bring otherwise insoluble anions into an organic environment *via* a tight ion-pairing enhances the nucleophilicity or basicity of the anion allowing reactions that are otherwise sluggish or do not occur to happen. The robust nature of these types of reactions mean they have become common in organic synthesis and have found many applications in industry.

The obvious extension of this methodology to utilize asymmetric cations (most commonly ammonium cations) was developed more recently and has been widely published; a number of excellent reviews by Maruoka *et al*. cover the range of reactions in depth.[31] Commonly asymmetric phase-transfer catalysis involves the generation of a prochiral nucleophile, thought to be deprotonated at the phase boundary, accompanied by swift ion exchange with a chiral cation. This takes the prochiral nucleophile into the organic layer whilst the tight ion-pair should bind preferentially to one face of the nucleophile forcing it to react with an electrophile on the other face, providing enantioenriched material,[31] scheme **27**.



Scheme 27

A large number of asymmetric phase-transfer reactions using glycine imines have been investigated leading to the development of a large range of catalysts many around the cinchona alkaloid scaffold. However, until the development of a catalyst bearing an anthracenyl group on the quaternary nitrogen the enantioselectivities for these reactions were relatively low,[31] scheme **28**.



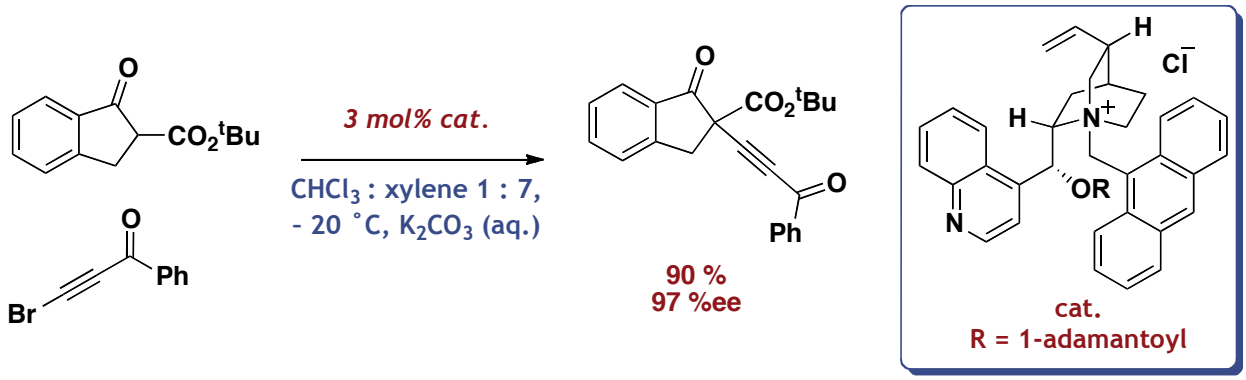
1. Conditions: $CHCl_3$, RT, $NaOH_{(aq.)}$, 20 h; Catalyst: R = H, R' = Ph; Result: 82 %, 62 %ee
2. Conditions: Toluene, 20 °C, $KOH_{(aq.)}$, 18 h; Catalyst: R = H, R' = Anthracenyl; Result: 68 % 91 %ee
3. Conditions: Toluene, - 78 °C, $CsOH_{(s.)}$, 23 h; Catalyst: R = allyl, R' = Anthracenyl; Result: 84 % 94 %ee

Scheme 28

The higher ees reported by Lygo *et al.*[32] **(2)** using their anthracenyl catalyst was a significant development for asymmetric phase-transfer catalysis, showing that tailoring of the catalyst scaffold can be used to greatly improve enantioselectivities. At the same time Corey *et al.*[33] **(3)** published a similar catalyst system which varies from the Lygo version by capping the free hydroxy with an allyl group. Interestingly, Corey's system also required the lowering of the temperature from RT to – 78 °C to obtain a high ee and required a liquid-solid base biphasic mixture. The introduction of solid-liquid phase-transfer also expanded the scope of asymmetric phase-transfer catalysis allowing previously poor enantioselectivities to be improved upon by removing the temperature constraints imposed by an aqueous layer. These catalysts and other

variations have since been widely exploited due to the greater enantioselectivities they often offer.[31]

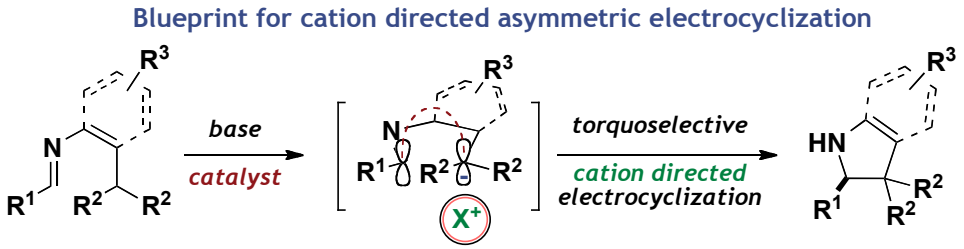
We were particularly interested in examples whereby 1,3-dicarbonyl compounds were deprotonated with subsequent addition to an electrophile in high enantiomeric excess as this was a close analogy to our substrate, scheme **29**.[34]



Scheme 29

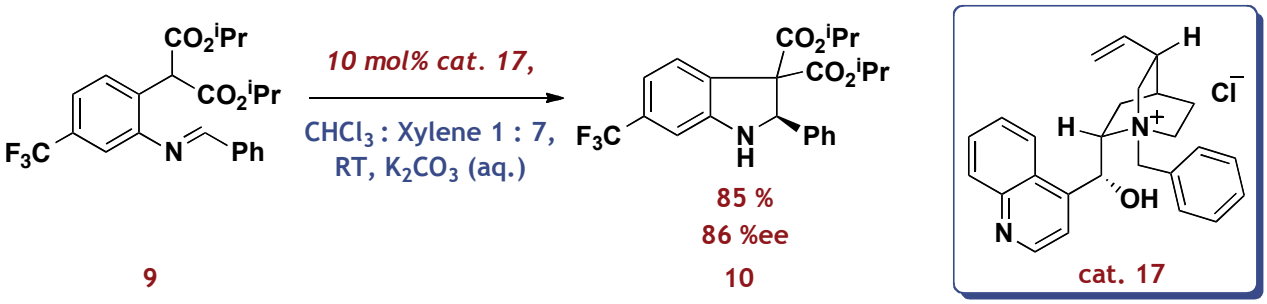
The high enantioselectivities reported lead to the conclusion that binding of the deprotonated 1,3-dicarbonyl is highly specific and it was hoped that this specificity could be exploited in our own system by using similar catalysis.

In our case we hoped that the chiral cation would preferentially bind one or other prochiral π-face; this would force the bond-forming process to occur on the face opposite the cation, moving the substituents away from the bulk of the catalyst to predominantly afford one enantiomer of the product, scheme **30**.



Scheme 30

Our initial attempts at inducing asymmetry focused on using commercially available catalyst **17** under modified literature conditions;[34] this proved to be pleasingly effective, scheme **31**.



Scheme 31

Optimization of the modified literature conditions was undertaken with an initial solvent screen, table **5**, to determine the role solvent plays in the reaction, and to hopefully allow the use of lower boiling point solvents than xylene as above.[35]

Solvent	Yield (%)	ee (%)
Hexane	85	84
Xylene	80	86
Toluene	81	86
THF	81	80
DCM	88	76

All reaction conditions are as described in scheme **31** with the exception of varying solvents used as shown.

Table 5

From table **5** above we can see that the reaction is tolerant of a range of solvents with the exception of using solely chlorinated solvents which afforded significantly lower enantioselectivities. We decided in this case to switch to the use of toluene, as no reduction in enantioselectivity was observed for this solvent when compared to the original xylene : chloroform mix, and it was easier to remove from the reaction mixture.[35]

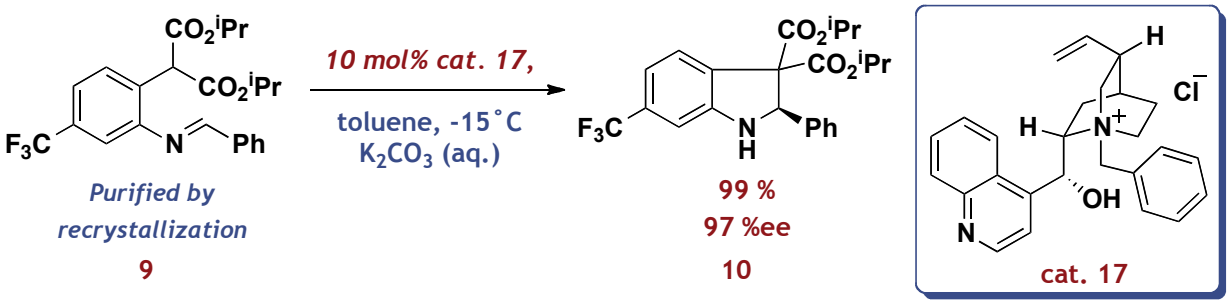
A screen of temperatures was also undertaken, since asymmetric phase-transfer reactions are frequently carried out at reduced temperatures, and we hoped this would allow us to improve the observed enantiomeric excess, table **6**.

Temperature	Catalyst Loading	ee (%)
0 ˚C	10 mol%	89
- 15 ˚C	10 mol%	93
- 15 ˚C	1 mol%	88

All reaction conditions are as described in scheme **31** with the exception of temperature and catalyst loading used as shown.

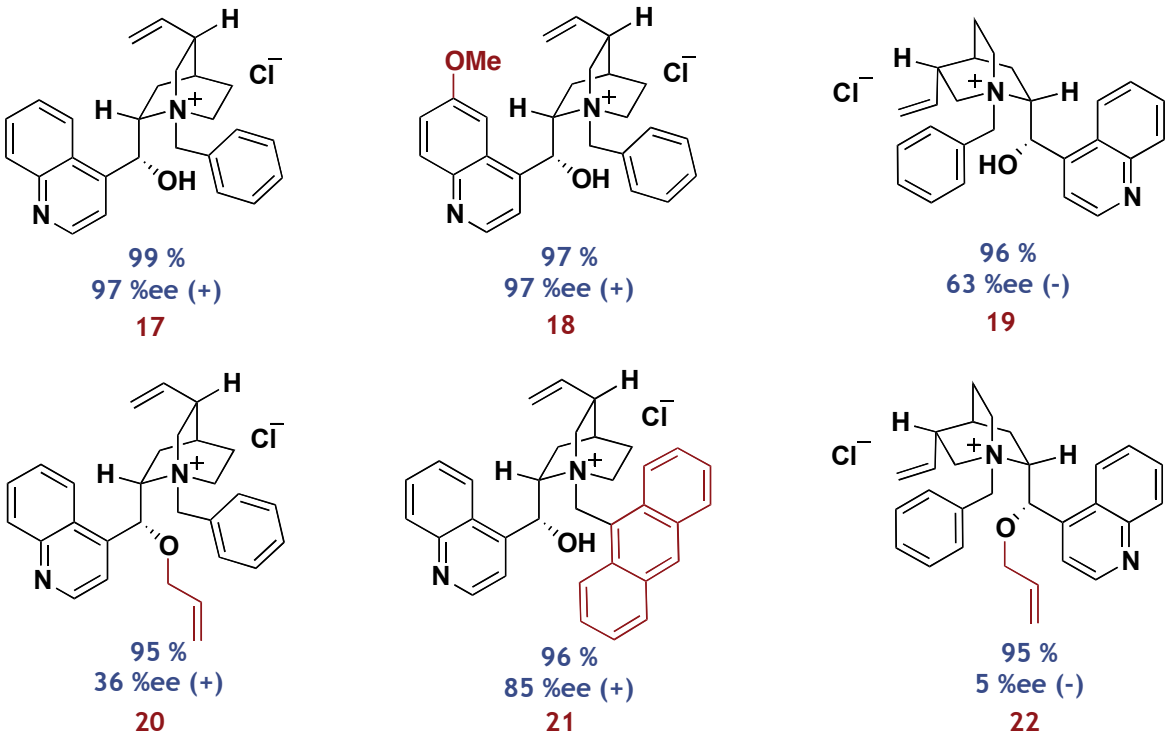
Table 6

These initial results were extremely promising however, we noticed that upon purification by silica gel chromatography the imine **9** was contaminated by 2-6 % of the cyclized material.[35] This would have a detrimental effect on the observed level of asymmetric induction, so we purified the imine more rigorously by recrystallization and were pleased to observe a significant increase in ee with this material, scheme **32**.



Scheme 32

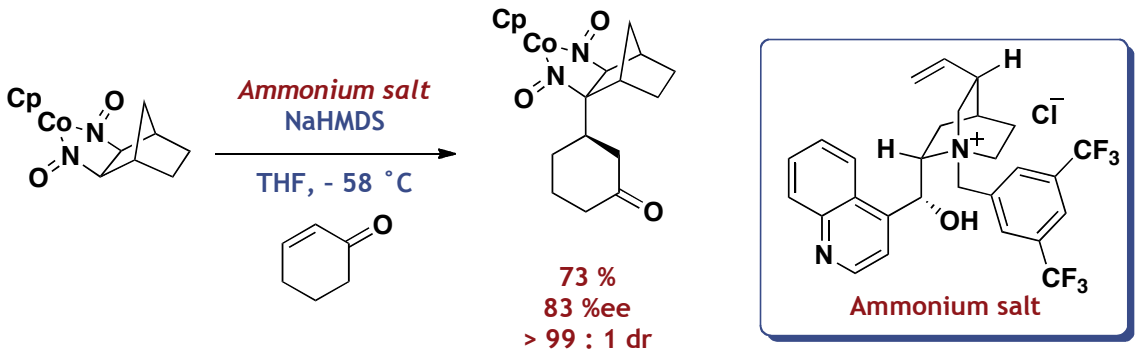
We believe that this result is indicative of the limit of this particular asymmetric process as no cyclized material could be observed prior to reaction by ^{1}H NMR spectroscopy. We then turned our attention to optimization of the catalyst; we screened a number of relatively inexpensive commercially available phase-transfer catalysts for this process. The catalysts studied are all based on the cinchona alkaloid scaffold using recrystallized imine under the conditions shown above (in scheme **32**), scheme **33**.



Scheme 33

The yields for all catalysts are consistently good but the asymmetric induction varies greatly. The cinchonidine **17** and quinine **18** derived catalysts which vary only by the presence of a methoxy group on the quinoline ring give very similar results. However, when the benzyl group is replaced by an anthracenyl group **21** which is often shown to give higher ees in the literature, we saw a significant drop in ee; presumably steric clashes with the larger anthracenyl group gives rise to poorer binding in the case of our substrate. The *pseudo*-enantiomeric cinchonidinium catalyst **19** gave the opposite enantiomer as expected but with a reduced ee of 63 %. It is not uncommon to observe different asymmetric induction between the cinchonidine and cinchonine catalyst as they are not enantiomers. A possible reason for this can be attributed to the conformation of the quinuclidine ring. Calculations on the analagous anthracenyl catalyst **21**[37] have shown that in the lowet energy conformation of the catalyst the allyl group on the quinuclidine ring points towards the binding pocket in the cinchonidine derived catalyst. In the cinchonine derived catalyst the allyl group points away from the binding pocket. It is possible that this extra steric interaction is the cause of greater selectivity in the cinchonidine catalyst **17** *vs* **19**. The enantiomers of these catalysts are not commercially available nor are they simple to synthesize often resulting in a higher ee being reported for one enantiomer of a substrate over the other.

In both cases where the free hydroxy group is capped with an allyl group, **20** & **22,** we see a marked drop in ee. A recent paper by Toste *et al.*[36] demonstrates the possible use of the free hydroxy to act as a base when deprotonated and induce asymmetry into a reaction probably *via* the same tight ion-pairing invoked in phase-transfer reactions, scheme **34**.

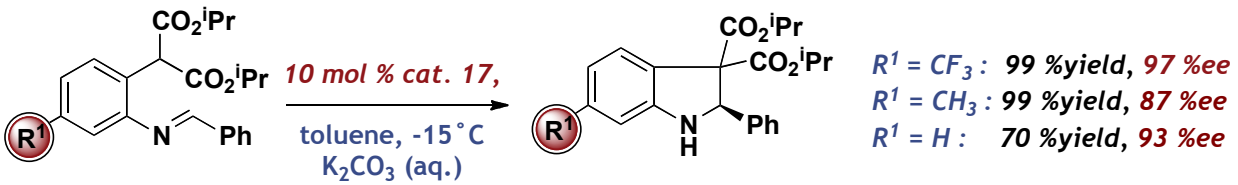


Scheme 34

Pre-mixing the NaHMDS and the phase-transfer ammonium catalyst (1 : 1.3 stoichiometry) before adding them to a mixture of the cobalt complex and electrophile should ensure that the only base present is the chiral ammonium species. The high enantioselectivities and diastereoselectivities suggest that the chiral ammonium species forms a tight ion-pair once deprotonation has occurred in order to transfer stereochemical information.

In our case we could rely on this deprotonation event to preorganise the substrate into the preferred binding conformation with catalyst. The overall conclusion from our catalyst screen is that the original catalyst **17** gives the best ee and yield (with the quinidine derivative **18** a very close second) and so in our further development of this methodology catalyst **17** was used.[35]

With optimised conditions in hand we turned our attention to substrate diversity and synthesized a range of benzaldimines using the route described. We initially varied substitution around the left hand aromatic ring, recrystallizing the imines to give us representative results, scheme **35**.

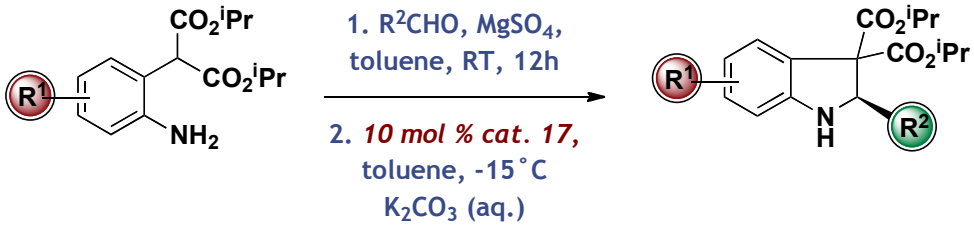


Scheme 35

These results demonstrate that the reaction is tolerant of different substituents on the aniline portion of the molecule with high yields and good ees maintained for the substrates tested. The drop in ee for R^1=CH_3 could be attributed to poorer selectivity in the binding process with the more electron rich arene, nevertheless we were satisfied with the generality of this approach. Unfortunately the purification of these imines by recrystallization was not a trivial task and required that large amounts (usually ~1 g) of the imine were synthesized in order to effect the crystallization. Our overall aim was to design a catalytic asymmetric electrocyclization that was sufficiently general and operationally simple that it would be employed by the wider chemical community.

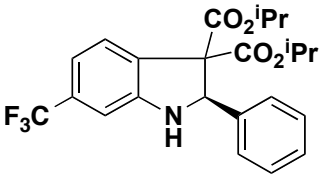
2.5.4 A pragmatic one-pot solution

Fortunately the crude imine products before any purification were clean by ^{1}H NMR spectroscopy leading us to believe we could develop a *pseudo*-one-pot procedure to circumvent the problems associated with column chromatography and recrystallization. Synthesis of different anilines was accomplished *via* the same route as for aniline **8** using commericially available starting materials; these syntheses are described fully in the experimental section. Treatment of anilines under imine formation conditions gave quantitative conversion to the desired imine. Filtration of the reaction to remove magnesium sulfate and concentration *in vacuo* afforded the crude imine cleanly. This imine was subsequently re-dissolved and treated directly under our optimized asymmetric conditions, scheme **36**.

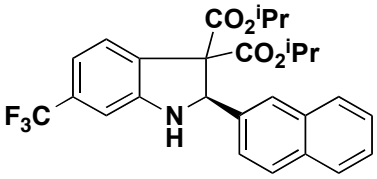


Scheme 36

We were delighted to find that this procedure could be used to generate a wide variety of substituted indolines in excellent ees and yields, schemes **37** – **43**.[35] Enantiomeric excesses were measured by stationary phase chiral HPLC.



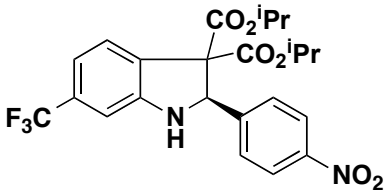
94 % ee,
89 % yield
10



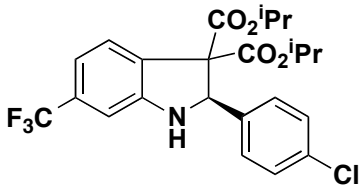
92 % ee,
92 % yield
23

Scheme 37

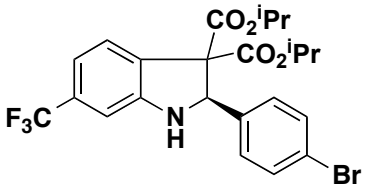
A small drop in ee is observed for our test substrate but this seems a reasonable compromise for the greatly simplified laboratory procedure. Larger aromatic rings are well tolerated, scheme **37**, naphthaldehyde derivative **23** was obtained in 92 %ee.



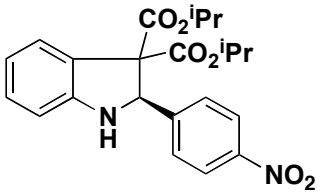
98 % ee,
75 % yield
24



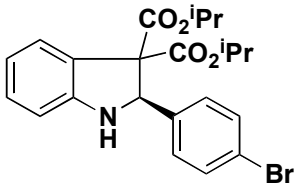
93 % ee,
69 % yield
25



93 % ee,
80 % yield
26



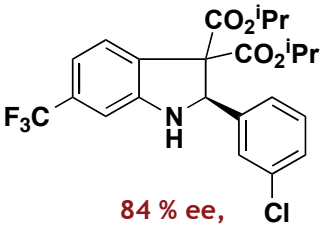
89 % ee,
89 % yield
27



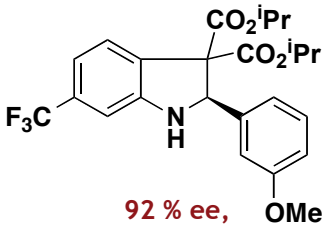
90 % ee,
70 % yield
28

Scheme 38

Para-substituted aldehydes generally affording the highest ees with a range of substituents tolerated, **24** – **26**, scheme **38**. The removal of the trifluoromethyl group from the left hand ring leads to a slight drop in enantiomeric excess, **27** & **28**, but with good ees still reported for these substrates.



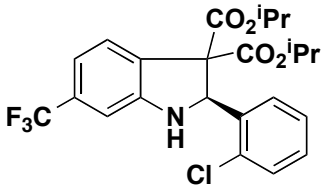
84 % ee,
86 % yield
29



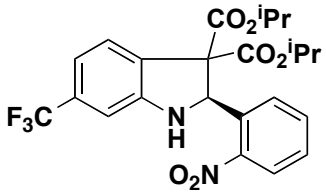
92 % ee,
76 % yield
30

Scheme 39

Meta-substitution is also well tolerated with high ees reported for both substrates, **29** & **30**, scheme **39**.



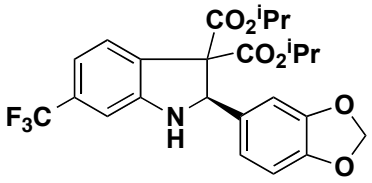
91 % ee,
78 % yield
31



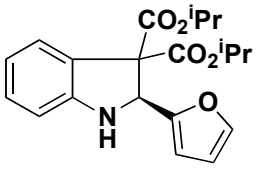
76 % ee,
89 % yield
32

Scheme 40

Pleasingly *ortho*-substitution was well tolerated, **31** & **32**, scheme **40**; perhaps unsurprisingly *ortho*-substitution may be sensitive to the size of the group with a chloro group **31** giving a much higher ee than that of the nitro group **32**.



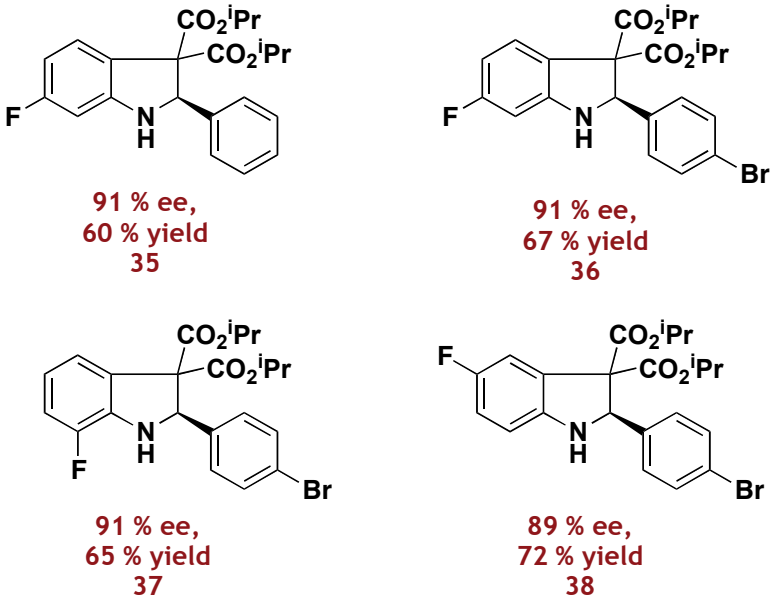
85 % ee,
90 % yield
33



86 % ee,
68 % yield
34

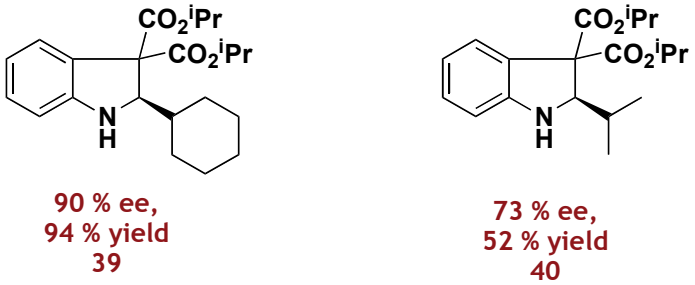
Scheme 41

Electron-rich aromatic rings, **33**, and heteroaromatic aldehydes, **34**, are also tolerated well, scheme **41**; although these electron rich substrates do tend to show lower enantiomeric excesses than electron-poor derivatives.



Scheme 42

We have shown that it is possible to replace the trifluoromethyl group and still maintain high ees and yields in this process so we turned our attention to demonstrating the tolerance of our reaction to substitution patterns on the left-hand aromatic ring. Using commercially available starting materials we were able to install fluoro substitution in the 2, 3 and 4 positions, scheme **42**. These substrates show a remarkable tolerance for substitution around this aromatic ring with a negligible variation of only 2 %ee between sites.



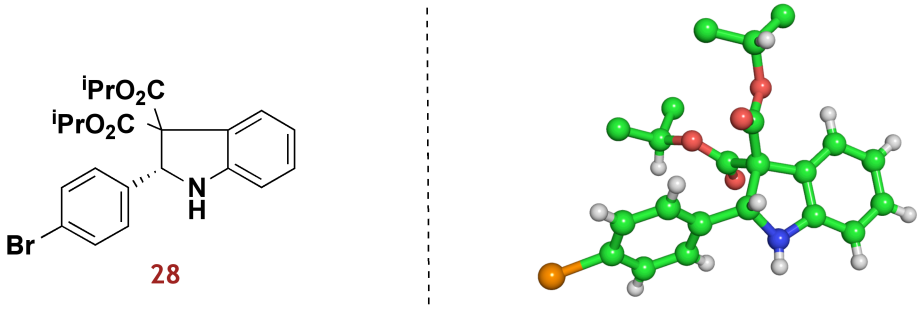
Scheme 43

Lastly, we were delighted to be able to include a number of alkyl aldehydes into the study with some very high ees and yields considering the other modes of activity available to such systems, scheme **43**. These transformations under our standard conditions gave lower ees than the aromatic derivatives, but switching to solid-liquid phase-transfer and lowering the temperature ($CsOH{\cdot}H_2O$, – 50 °C)[33] allowed us to obtain the higher ees reported above, **39** & **40**. To

conclude, we have shown that this process is tolerant of a wide variety of substituents from alkyl, aryl and heteroaryl aldehydes to varying *ortho*-, *meta*- and *para*-substitution.

2.5.5 Stereochemical model

The absolute configuration as drawn is taken by analogy to the X-ray crystal structure of compound **28**, scheme **44**. The absolute stereochemistry is assumed to be the same for all compounds.

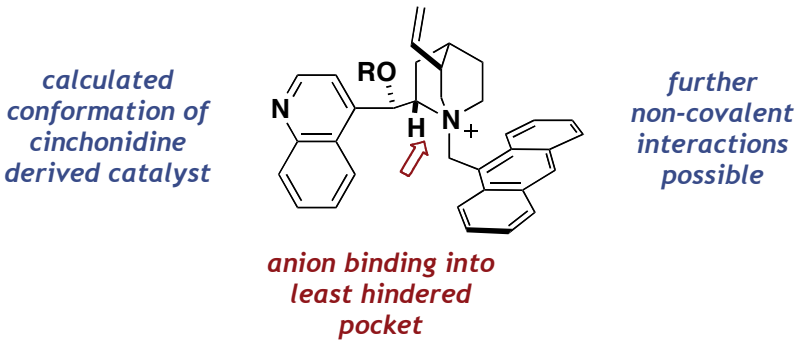


Scheme 44

We were keen to understand the sense of induction we have observed; in order to do this we turned out attention to a number of papers which discuss cinchona alkaloid derived phase-transfer catalysts and their interactions with anions. Notably, Lygo *et al.*[37/38] have developed a model for binding by mapping functional group tolerance in the catalyst scaffold along with theoretical modelling and Corey *et al*. have published a crystal structure of *p*-nitrophenoxide binding to a cinchonidine derived catalyst.[33] Although these discussions relate to the alkylation of glycine imines the binding principles can hopefully be applied to rationalize our observed stereochemistry.

A series of structure activity relationship studies by Lygo *et al*. suggest that the quinoline ring, the aromatic capping of the nitrogen and alkylation on the free hydroxy are important in phase-transfer catalysis.[38] When the quinoline ring is switched for other aromatic rings the enantioselectivity drops and if alkyl groups are used, significantly lower ees are observed. A similar trend is noticed when varying the group capping the nitrogen; if alkyl groups are used almost racemic material is obtained, likewise in the case whereby phenyl (not benzyl) caps the

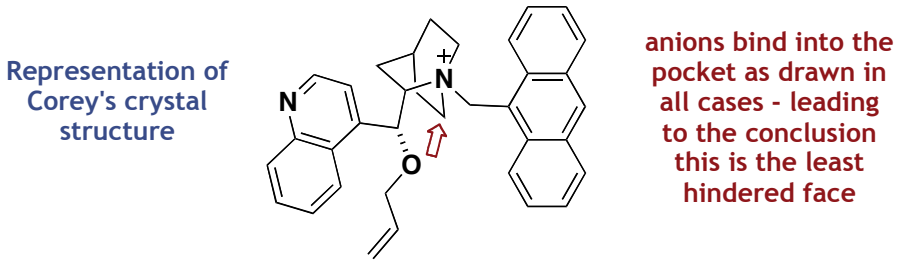
nitrogen. These observations along with a number of docking studies[37] build a picture of binding to cinchona alkaloid derived catalysts, scheme **45**.



Scheme 45

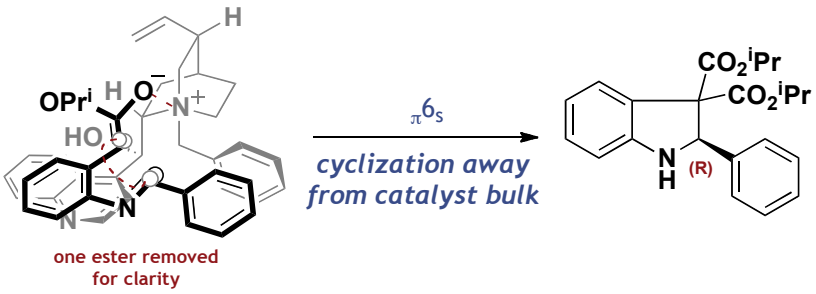
The anion is proposed to bind into the least hindered pocket with further order imposed by extra non-covalent interactions.

The crystal structure published by Corey *et al*. along with crystal structures of the cloride and bromide derivatives also give rise to the rationale that anions bind to the catalyst *via* the least hindered face of the nitrogen cation, scheme **46**.[33]



Scheme 46

With these studies in mind and with the absolute configuration of our substrate in hand we rationalized the sense of stereoinduction observed for binding to a phase-transfer catalyst, scheme **47**.

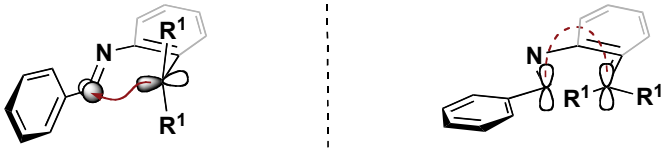


Scheme 47

We propose that as well as ion-pairing into the least hindered quadrant of the catalyst, non-covalent interations between the aromatic rings of the catalyst and our substrate effectively block one π-face of the anion. This forces the bond-forming process to occur on the face drawn and the aromatic ring from the original aldehyde to rotate away from the bulk of the catalyst to give the absolute stereochemistry observed. The main problems with this model arise from the need to include a second bulky ester which from the representation would be sterically clashing with the catalyst. Secondly the model does not explain the role of the hydroxy group which we have seen experimentally has a great effect on the stereocontrol. It is possible that the imine or an ester provide a secondary hydrogen-bonding interaction with the free hydroxy group. Work is ongoing to determine the role of the hydroxy group and produce a more accurate understanding of the interactions.

2.6 Mechanistic discussion

As previously touched upon there are two viable mechanistic pathways for this reaction: an intramolecular Mannich reaction or by the proposed pericyclic process, scheme **48**. We were keen to develop an understanding of which mechanism was operating under our newly developed reaction conditions.



5-endo-trig Mannich
HOMO enolate,
LUMO imine

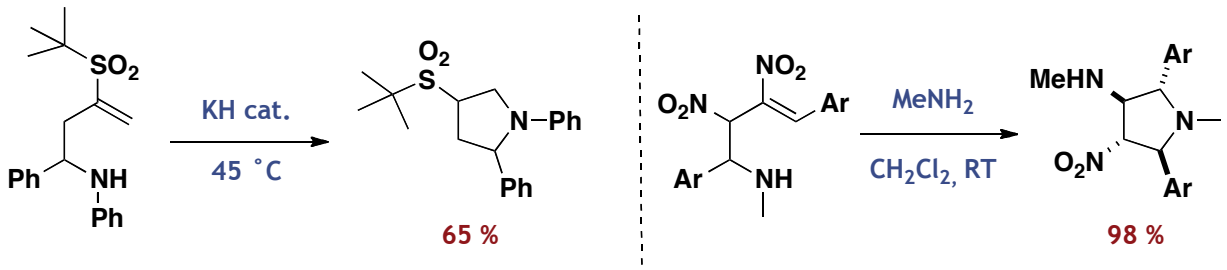
Pericyclic
Planar 6π system,
suprafacial
cyclization

Scheme 48

We have already discussed how asymmetric induction might occur in the pericyclic process. For the anionic process to be rendered asymmetric the catalyst must distinguish between one or other of the prochiral faces of the imine. It is not clear how this could be achieved given the assumption that the catalyst should form a tight ion-pair with the malonate anion as phase-transfer catalysts are known to do. It is possible to envisage some form of hydrogen-bonding *via* the catalyst hydroxy group to the imine but the introduction of a stronger hydrogen-bond donor into the cinchona scaffold and even the use of standard hydrogen-bonding catalysts leads usually to retardation of the reaction and at best racemic material is formed. Our understanding of the asymmetric induction does not constitute any proof that the process is pericyclic.

2.6.1 Kinetic vs thermodynamic control

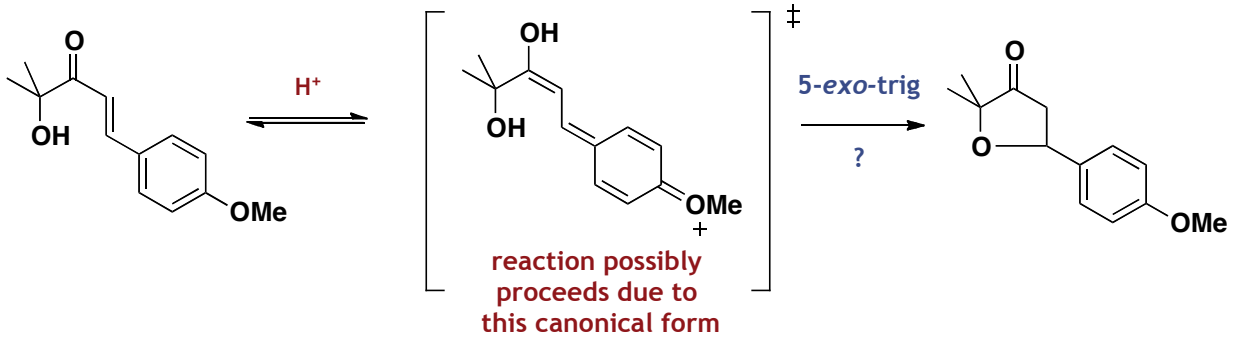
The 5-*endo*-trig Mannich process is kinetically disfavoured by Baldwin's rules whereas the electrocyclization process does not suffer from such stereoelectronic contraints. Baldwin's rules are based on the theory that for a reaction to occur kinetically orbital overlap in the correct (reaction) geometry must be possible. However, there are a range of literature examples in which an apparent 5-*endo*-trig cyclization occurs contrary to the rules set out by Baldwin.[39] With these examples there are a number of common features such as the nucleophile being a heteroatom, scheme **49**;[40/41] a proposed diffuse lone pair is often cited as the reason these reactions can occur despite stereoelectronic constraints.



Scheme 49

In both cases the reactions are quite substrate specific; in the sulfone case[40] the use of stronger bases such as LDA led to recovery of starting material and the corresponding sulfoxide derivatives could not be made to cyclize. In the nitro case[41] the actual presursors, 1,4-diaromatic 2,3-dinitrobutadienes undergo a 1,4-addition with a variety of primary amines to provide the precursor as drawn. However, only the use of 1,4-aromatic 2,3-dinitrobutadiene substrates resulted in the desired cyclization; primary alkyl groups or no substituents at the 1 and 4 position were not tolerated.

Another common feature is the occurance of reversed substituent effect in a 1,4-addition manifold. The explanation for the apparent breaking of Baldwin's rules in this case falls to the contribution of a canonical form which facilitates a 5-*exo*-trig pathway, scheme **50**.[42]

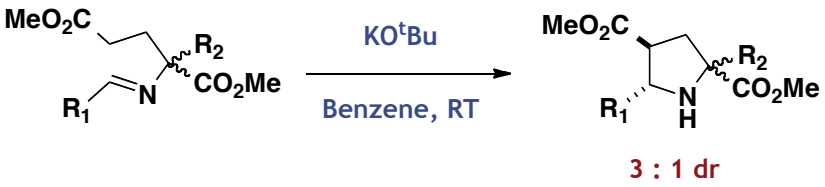


Scheme 50

This reaction proceeds much faster with electron donating groups on the aromatic ring which is contrary to the intermolecular case whereby electron-withdrawing groups enhance the rate of reaction. Substituent effects for 1,4-addition reactions under acidic conditions have been studied extensively and suggest that the reaction proceeds *via* protonation and the canonical form then

facilitates a 5-*exo*-trig cyclization. Whether the reaction proceeds *via* the canonical form described or due to the less stereoelectronically defined nature of the imine electrophile is unclear; other base mediated reactions show similar reactivity and the reason in that case is less convincingly due to the canonical form and more likely a product of the diffuse nature of heteroatom lone pairs.[39]

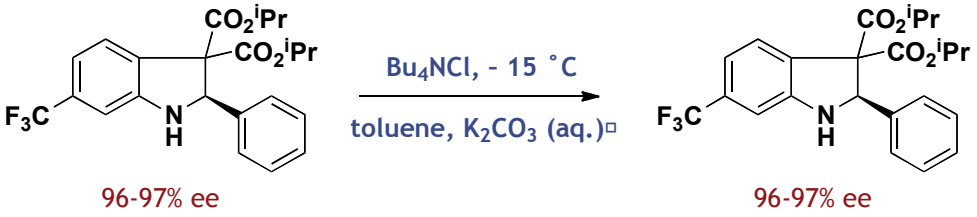
As is clear from our results we do not observe a reversed substituent effect, the reaction works well with all aromatic and alkyl groups. Likewise, our cyclization does not involve the trapping of a heteroatom nucleophile onto an electrophile. However, there are examples in which substrates containing an imine electrophile and a carbon nucleophile that cannot rely on either of these common explanations for non-Baldwin behaviour just like in our system, scheme **51**.[43]



Scheme 51

Whether this system is under kinetic or thermodynamic control is not discussed by the authors. In any case this substrate lacks the required functionality to proceed *via* the alternative pericyclic pathway that is present in our work.

We have observed high ees in our process; this would suggests the reaction is under kinetic control. Baldwin's rules can only be applied when the system is under kinetic control although as we have seen there are probably still some exceptions to this rule making it difficult to conclusively say the reaction in pericyclic because it is under kinetic control. However, we undertook a number of experiments to probe the extent of this kinetic control under different conditions. We took enantioenriched material and treated it under achiral phase-transfer conditions, scheme **52**.

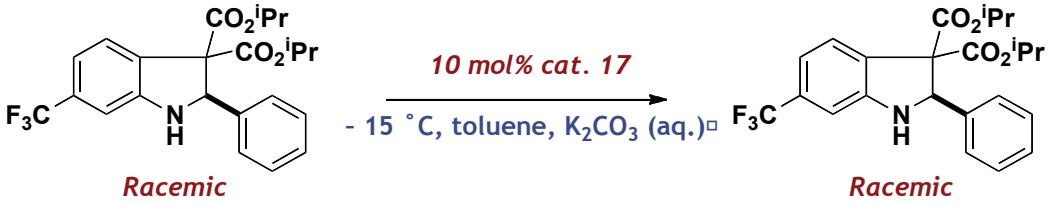


96-97% ee 96-97% ee

Scheme 52

At – 15 ˚C, as with our asymmetric process, no appreciable change in ee was observed. This suggests that under the conditions used the reaction is not reversible and is therefore under kinetic control.

Likewise taking racemic starting material and treating it under our asymmetric conditions at - 15 ˚C no asymmetric induction was observed, scheme **53**.

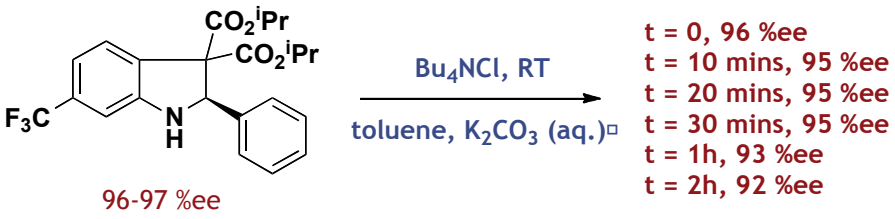


Racemic *Racemic*

Scheme 53

This again suggests that under our asymmetric conditions the reaction is under kinetic control. Repeating this reaction at room temperature also gave no asymmetric induction.

However, when enantioenriched material was treated under racemic phase-transfer conditions at room temperature some enantioerosion was observed, scheme **54**.

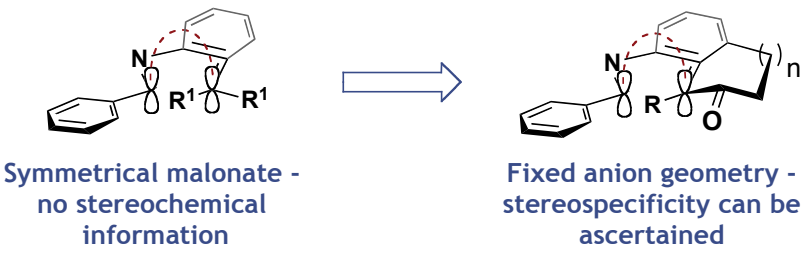


Scheme 54

This result suggests that when using the achiral catalyst at room temperature the reaction is reversible and therefore the reaction under these conditions is thermodynamically controlled. The implication of these differing results is that the achiral catalyst and the cinchona alkaloid derived catalyst do not operate under the same mechanism, this will be discussed in greater detail later in the chapter.

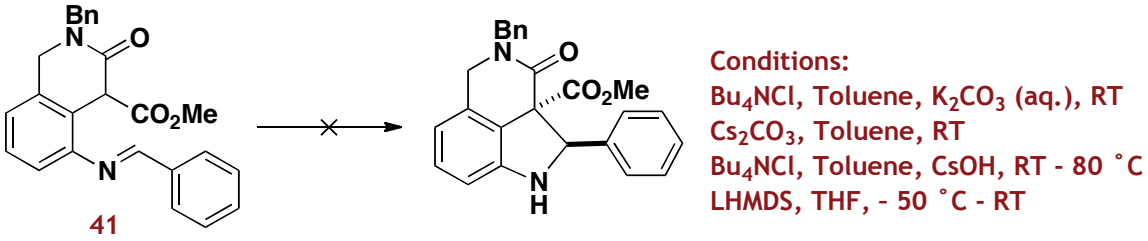
2.6.2 Stereospecificity

We were also interested in determining whether the reaction is stereospecific, as it must be for the pericyclic mechanism. All of the substrates we have discussed so far lack the stereochemical markers required to determine whether this is the case. To do this we would need to generate two contiguous stereocentres and know the absolute geometry about the anion before cyclization occured, scheme **55**.



Scheme 55

One way to do this would be to constrain the malonate portion of the molecule into a ring system such that the geometry upon deprotonation is known; the diastereoselectivity during the ring closing process should allow us to determine whether the process is disrotatory as required (provided the imine does not isomerize under the reaction conditions). To do this we produced imine **41** and treated it under a variety of cyclization conditions, scheme **56**.

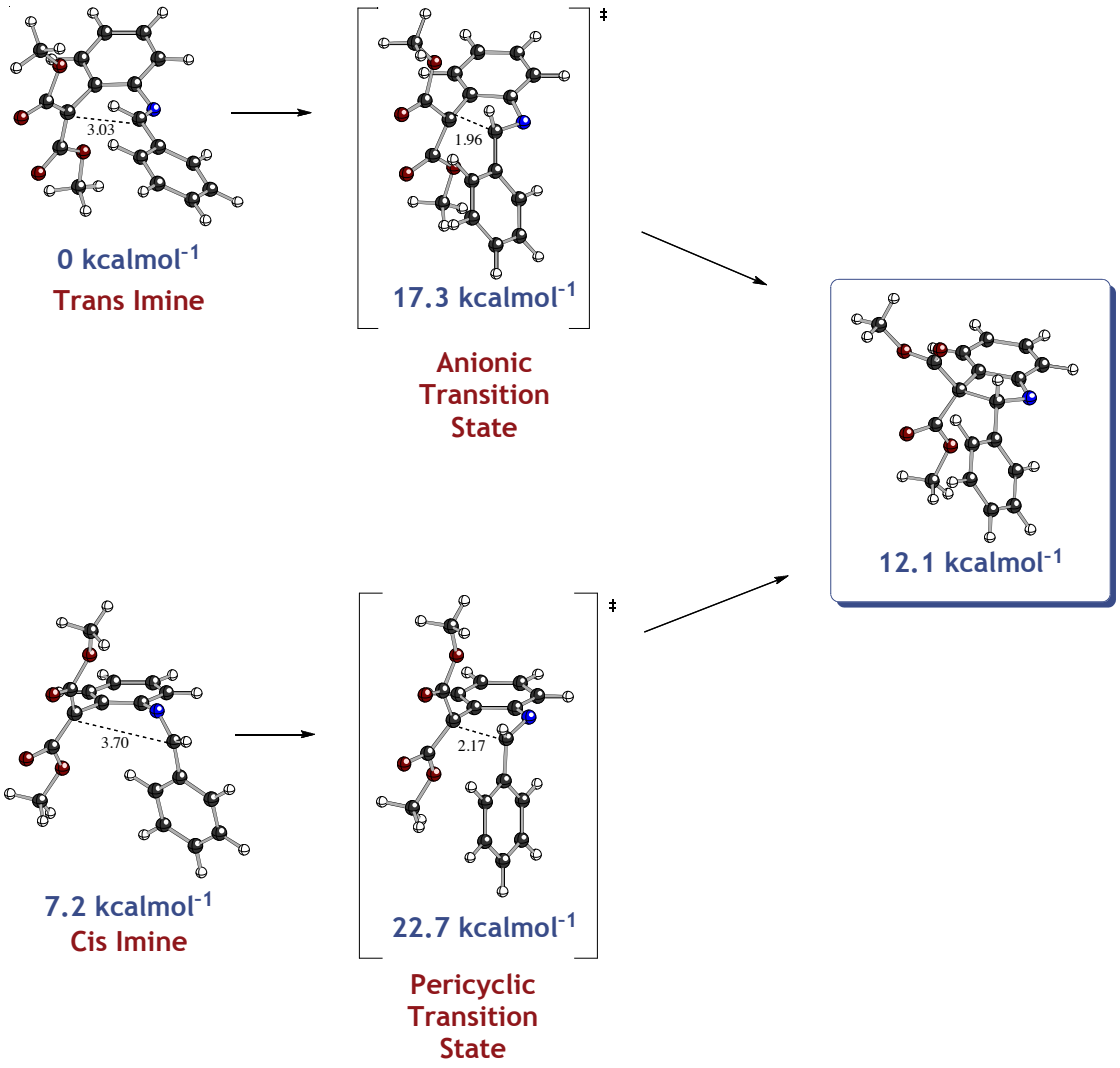


Scheme 56

Unfortuntely the substrate was not amenable to cyclization, probably due to the extra strain in the system imposed by tethering the malonate into a ring. Further attempts by co-workers to expand the six-membered ring and hence relieve the strain are still ongoing.

2.6.3 Theoretical calculations

Although we have have shown the reaction to be under kinetic control this does not constitute proof that the pericyclic process is occuring as opposed to the disfavoured Mannich process. We are currently working in collaboration with Professor D. Tantillo and P. Painter at UC Davis to produce an accurate theoretical model of our system.[44] Calculations were carried out using density functional methods (DFT-B3LYP/6-31+G(d,p)) and the energies reported are Gibbs Free Energies at room temperature and non zeropoint corrected electronic energies. The nature of the transition state was probed by Nucleus Independaent Chemical Shifts to determine whether there is any current build up as the reaction proceeds; this would be the case if a pericyclic pathway is in operation and not for the anionic pathway. Initial results suggest that the process is finely balanced between the pericyclic and anionic pathways, scheme **57**.

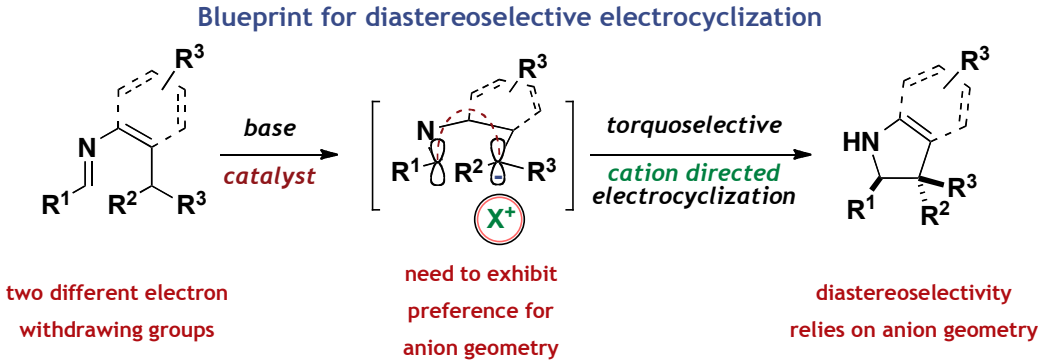


Scheme 57

If the imine geometry is *trans*- the reaction by these calculations should proceed *via* an anionic pathway. Conversely, if the imine geometry is *cis*- the reaction should proceed through a pericyclic transition state. We have nOe evidence that the imine geometry is *trans*- in solution on an NMR timescale but this does not rule out the possibility of imine isomerization under the reaction conditions. However, no modelling of the chiral counterion and its effect on the reaction have been possible to date making it difficult to say unequivocally which process is actually occuring.

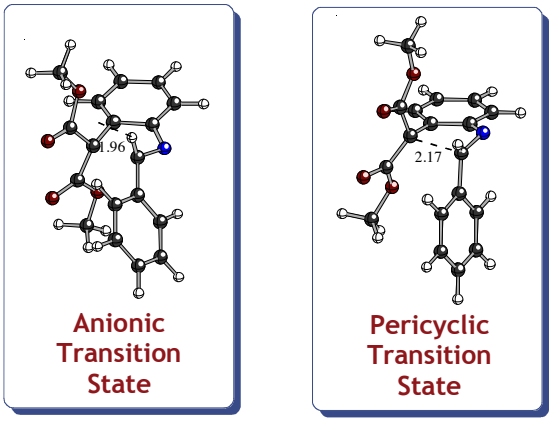
2.7 Diastereoselective electrocyclization

Up to now our methodology has allowed us to produce a single stereocentre in high ee. However, as discussed in the introduction, the ability to produce two stereocentres during an electrocyclization process has yet to be fully exploited. This was therefore one goal for our methodology; the production of two contiguous sterecentres in high enantioselectivity and diastereoselectivity. To do this we would need to synthesize a substrate with two different groups at the malonate centre, scheme **58**.



Scheme 58

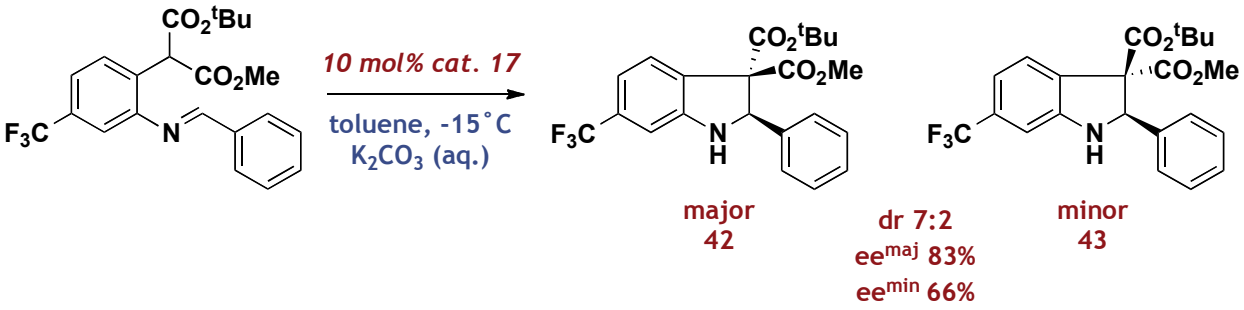
In a purely pericyclic process diastereoselectivity would rely on the preference for geometry about the anion formed as the reaction is stereospecific. However, as discussed, we do not know the mechanism of the reaction and therefore should consider the transition state; both the pericyclic and anionic transition states calculated show the malonate and imine in a similar configuration, scheme **59**.[44]



Scheme 59

In both of these calculated transition states the malonate lies almost perpendicular to the left hand aromatic ring with the imine aromatic ring nearly parallel to the malonate. Unlike our idealised electrocyclization transition state these calculated models suggest that the anion must show some preference for orientation with respect to the imine aromatic ring.

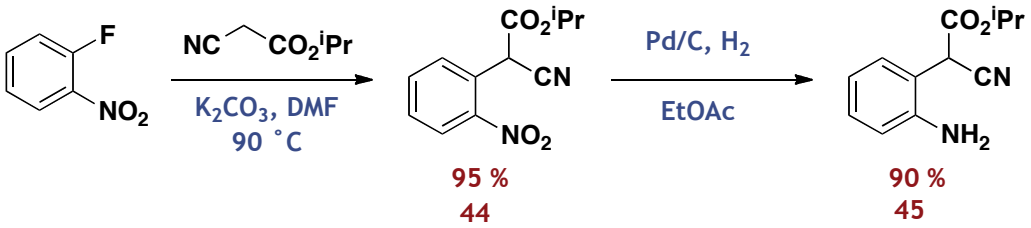
Our initial attempt at diastereoselectivity, using an unsymmetrical malonate as the smallest perturbation to our previous work, gave modest dr and reasonable ees, scheme **60**.[35]



Scheme 60

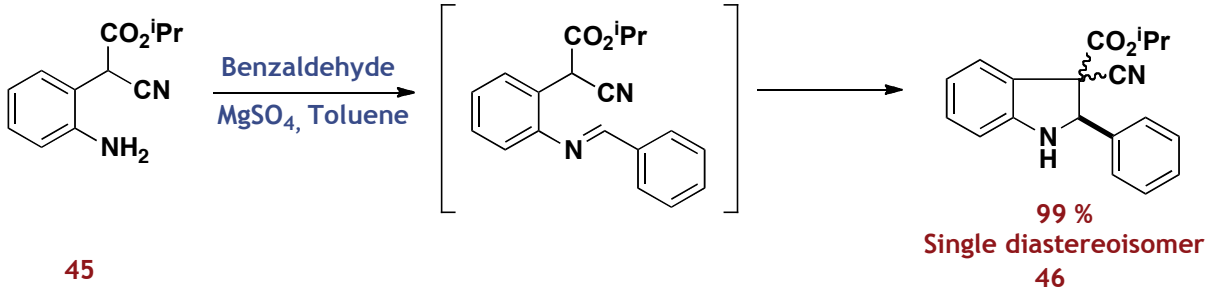
In this case we were relying on either the anion geometry having some preference due to the large steric bulk of the *t*-butyl ester or the same steric bulk prefering to sit away from the imine aromatic ring in the transition state. The relative configuration of the two diastereoisomers was confirmed by nOe studies. The selectivity was not as high as we had hoped and so we turned our attention away from steric bias to the use of electronically different substituents which would hopefully give greater selectivity.

To do this we returned to our original substrate synthesis and in place of the malonate for S_NAr we used isopropylcyanoacrylate to give us two electronically different electron-withdrawing groups, scheme **61**. This was followed by reduction under hydrogenation condition proceeded well in the presence of the cyano functional group to give aniline **45**.



Scheme 61

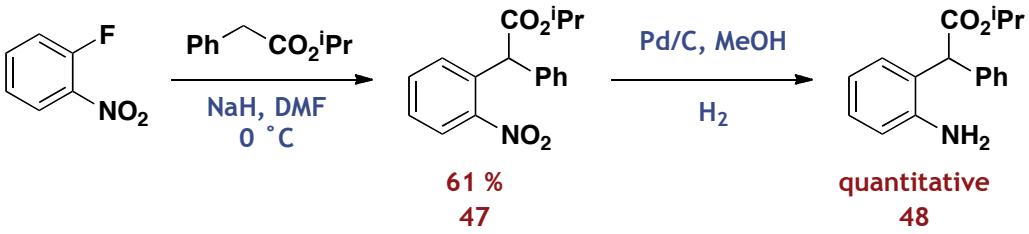
Excitingly, replacing one of the esters with a cyano group gave the desired indoline **46** as a single diastereoisomer, scheme **62**.



Scheme 62

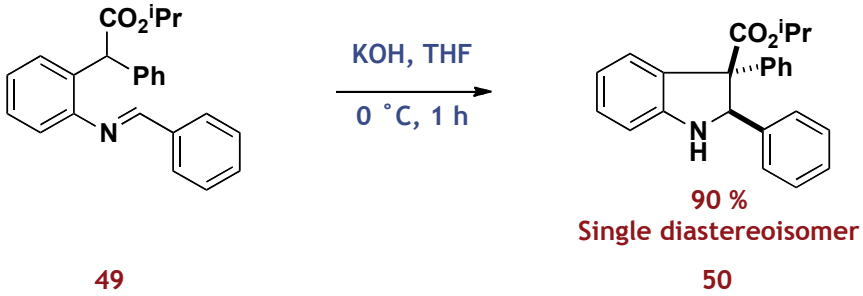
Unfortunately this cyclization was completely uncontrollable as we saw earlier with the dimethyl malonate substrate; attempts to cool the reaction, use of less acidic drying agents and a one-pot imine formation/asymmetric phase-transfer reaction were unsuccessful. However, this did lead us to believe that varying the electronic nature of the groups would furnish the high diastereoselectivities desired.

This theory was tested in collaboration with an undergraduate co-worker[45] who successfully synthesized a substrate which replaced one of the esters with a phenyl ring using modified S_NAr conditions, scheme **63**.



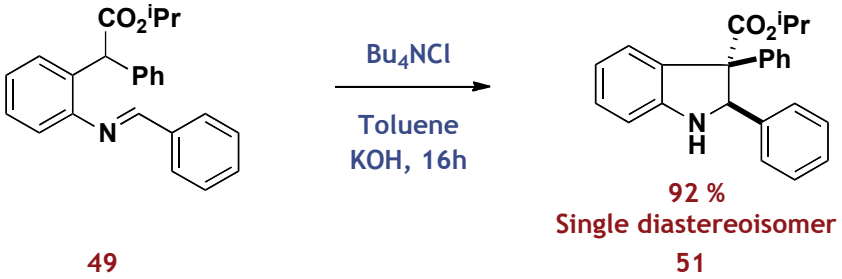
Scheme 63

It was hoped that the less electron-withdrawing nature of the phenyl ring would temper the reactivity of the substrate but still produce high diastereoselectivity. We were delighted to find that this was the case by using a slight variation of literature conditions, scheme **64**.[46]



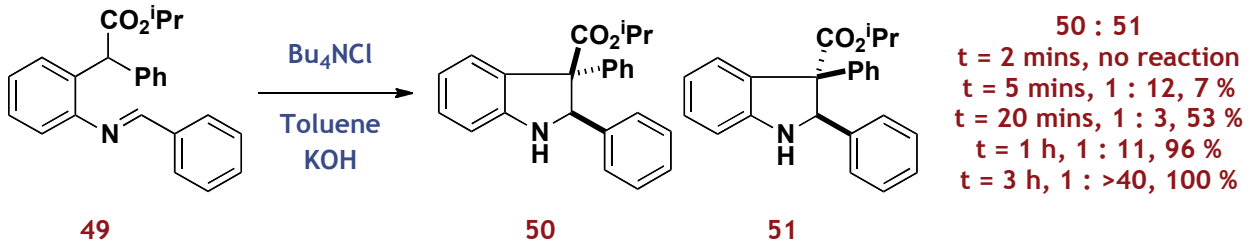
Scheme 64

These literature conditions involved the cyclization of a similar substrate with only a single ester withdrawing group to give racemic material. We rationalized that this would be a good place to begin work on this system which is much less electron-withdrawing than previous work. Interestingly the opposite diastereoisomer, **51**, can be obtained by treating the imine under racemic phase-transfer conditions, scheme **65**.



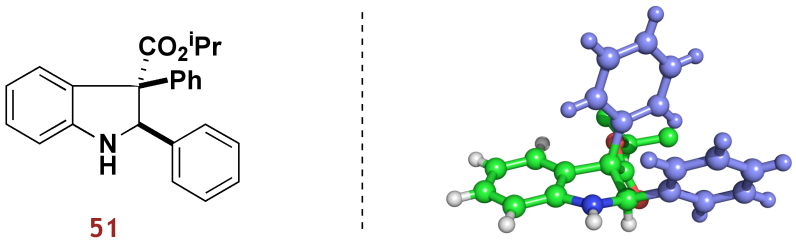
Scheme 65

Treatment of the first diastereoisomer **50** under prolonged reaction times or higher temperatures led to a degradation of the diastereoselectivity. Therefore, we proposed that the reaction with NBu_4Cl is under thermodynamic control, suggesting that this catalyst can effect the retroelectrocyclization. In collaboration with a co-worker we tested this hypothesis by stopping the achiral phase-transfer reaction at various time intervals, scheme **66**.



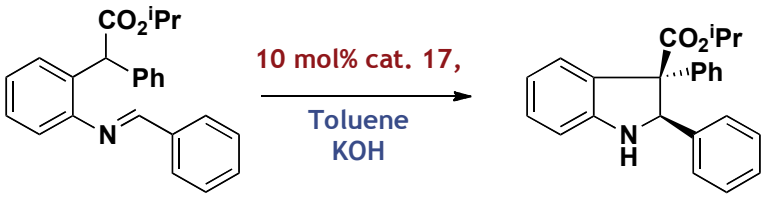
Scheme 66

The appearance and subsequent consumption of small amounts of the proposed kinetic isomer suggests that this catalyst can effect the retroelectrocyclization and that the final product of this reaction is the thermodynamic isomer. We considered that the reason for greater thermodynamic stability of diastereoisomer **51** is due to π–π stacking of the aromatic rings. The relative configuration of the isomers was confirmed by X-ray crystallography of the thermodynamic isomer, scheme **67**.



Scheme 67

Excitingly, treatment of imine **49** under asymmetric phase-transfer reaction conditions yielded the desired indoline as a single diastereoisomer in 96 %ee, scheme **68**.



single diastereoisomer
96 %
96 %ee

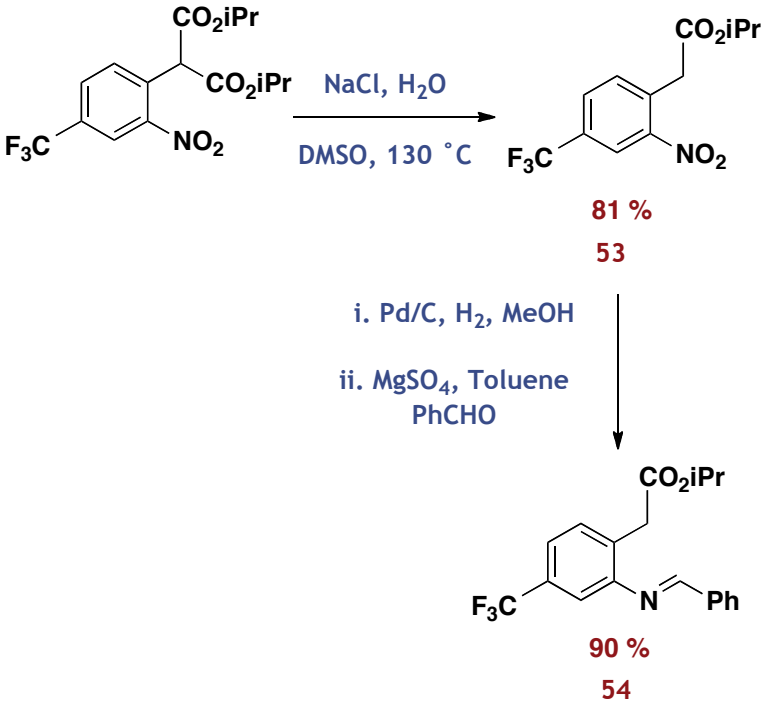
49

50

Scheme 68

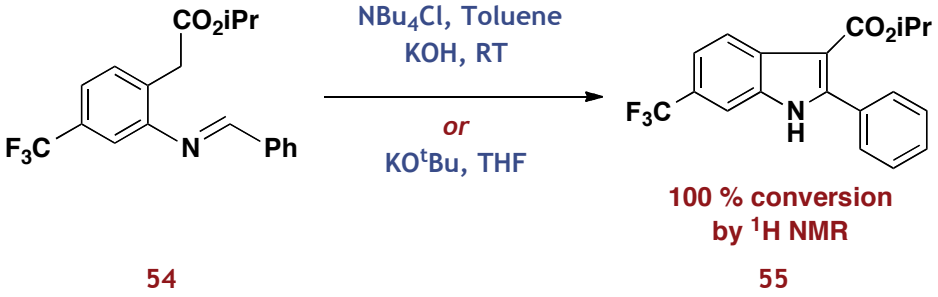
The product in this case was solely the kinetic isomer **50**; longer reaction times did not provide any of the thermodynamic isomer suggesting that the cinchona alkaloid phase-transfer catalyst is not capable of affecting the retroelectrocyclization in the same way as NBu_4Cl.

With this promising system in hand we turned our attention to developing other systems that would exhibit diastereoselectivity. My initial attempts focused on a system with only a single ester as the electron-withdrawing group as a similar subsrate had been reported to cyclize under racemic reaction conditions to give a single diastereoisomer.[46] This substrate could be readily made by introducing a decarboxylation step[47] between the S_NAr and reduction step in our initial sequence, scheme **69**.



Scheme 69

Pleasingly, the decarboxylation furnished nitro compound **53** in high yields, subsequent reduction and imine formation afforded the desired substrate **54**. To the best of our knowledge this is one of the only examples of decarboxylation of an *iso*propyl ester under Krapcho type conditions. However, treatment under achiral phase-transfer conditions or with KO^{t}Bu afforded only the indole product **55**, scheme **70**.

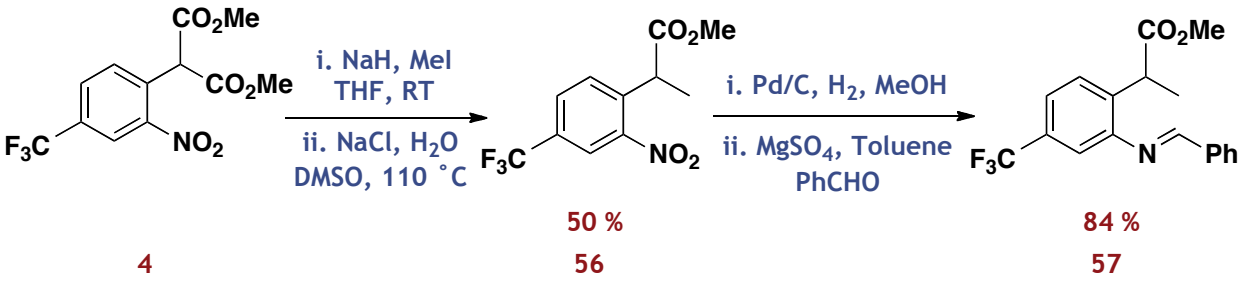


Scheme 70

Literature precedent for a similar racemic cyclization led us to believe this substrate would be a reasonable candidate for our study.[46] However, given the results of our attempted racemic

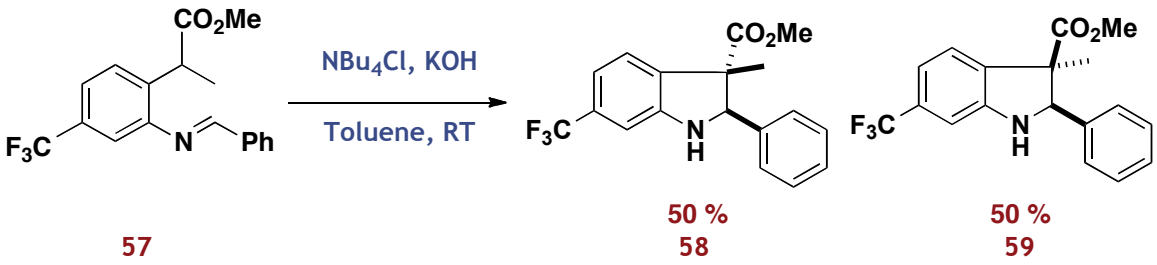
cyclizations and the propensity for indoles to form from dihydroindoles we decided to move on from this substrate.

As previous results had proven that an aryl group could be used to replace one electron-withdrawing group we turned our attention to studying whether an alkyl group would also be tolerated at this position. We also hoped that this would block the ability to oxidise the product to the indole as above. Our initial efforts focused on a methyl group which was introduced by a S_N2 reaction[48] and subsequent decarboxylation,[49] scheme **71**. It was this decarboxylation step that led to the use of methyl rather than isopropyl esters for this substrate as decarboxylation of the latter proved problematic. The usual reduction and imine formation proceeded as with previous work to afford the desired imine **57**.



Scheme 71

Treatment of the imine under achiral phase-transfer reaction conditions afforded the desired indoline as a mixture of diastereoisomers, scheme **72**.

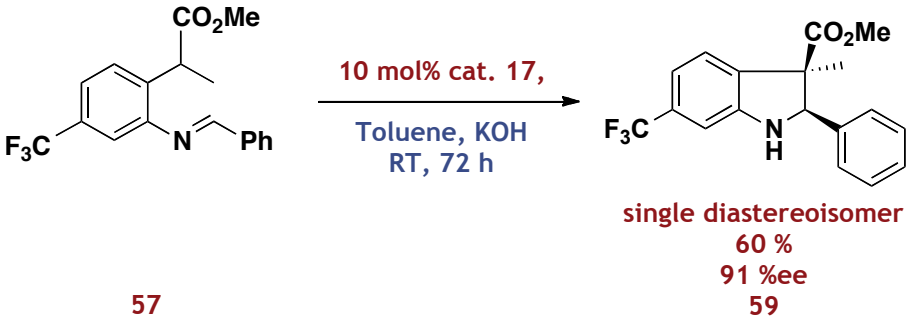


Scheme 72

Although this result is a little disappointing we rationalized that, if we can assume that under these conditions the reaction is under thermodynamic control, we are isolating a thermodynamic

mixture of products. With the phenyl derivative, the π–π stacking in the thermodynamic product could give that diastereoisomer its lower energy; in the case with a methyl group no such interaction can occur leaving the diastereoisomer possibly similar in energy.

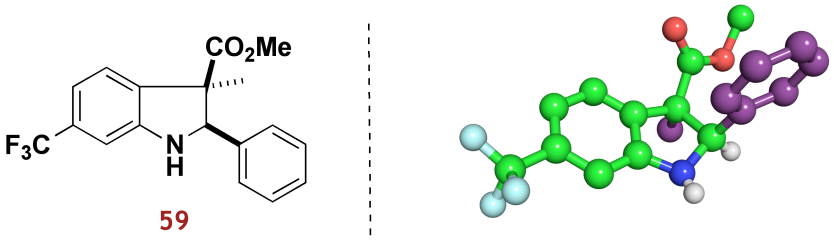
We were delighted to find that upon treatment with cinchona alkaloid catalyst **17** the reaction yielded a single diastereoisomer in 91 %ee, scheme **73**.



Scheme 73

As the reaction is most likely under kinetic control, if the reaction is pericyclic in nature the ester and phenyl ring would both sit pointing outwards (as drawn in the imine form) and subsequent cyclization would give the desired diastereoisomer. However, considering our calculated transition state model both the pericyclic and anionic pathways would result in a similar transition state.

The relative configuration of this presumed kinetic isomer was confirmed by X-ray crystallography with absolute stereochemistry taken by analogy to our earlier work, scheme **74**.



Scheme 74

In conclusion, we have developed a highly diastereoselective electrocyclization manifold that is tolerant of different substitution patterns. The ability to control which diastereoisomer is formed simply by choice of catalyst may provide insight into some of the mechanistic aspects of this process. In addition to this we have demonstrated that our initial asymmetric induction methodology can be readily applied to other systems allowing us to create two contiguous stereocentres with complete diastereoselectivity and consistently high enantioselectivities.

2.8 Phase-transfer catalysis mechanisms

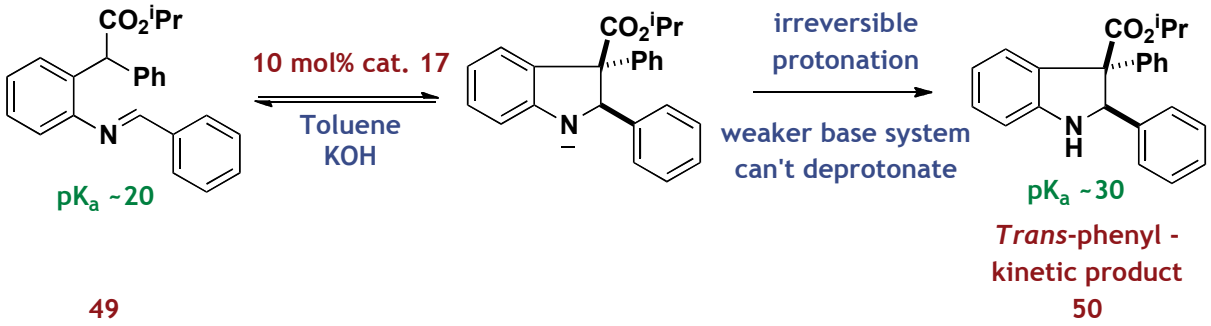
It is currently believed that there are two different mechanisms under which phase-transfer reactions can operate, depending on a number of factors.[50] The interface mechanism[51] describes phase-transfer reactions whereby the substrate is deprotonated at the phase boundary and the catalyst then takes this anion *via* tight ion-pairing into the organic solvent for the reaction to occur. The extraction mechanism is when the catalyst itself enters the aqueous phase and brings 1 eq. of base back into the organic phase to deprotonate the substrate directly in the organic phase (for solid cases this means the catalyst brings 1 mole of base from the solid phase into solution in the same way).

From the literature, the mechanism that is operating can be rationalized by a number of factors:[50] 1) Catalyst structure - the more organophilic the catalyst, the greater propensity for extraction-type mechanism. Conversely, the more electrostatically available[ii] a catalyst, the better it is at interfacial-type mechanisms; 2) Stirring speed - an interface mechanism reaction will be strongly dependant on stirring speed whilst the extraction mechanism does not always rely on

[ii] Electrostatically available refers to the steric hinderance about the cation centre which determines how easy it is to ion-pair to the catalyst. For example NMe_4^+ is considered to be very electrostatically available whereas $N(C_8H_{18})_4$ is not very electrostatically available.

stirring speed. The extraction mechanism operates at $pK_a < 16$ and $23 < pK_a < 37$; whilst the interface mechanism operates at $16 < pK_a < 23$. Whilst this rationalization was constructed for systems that are stoichiometric in base it offers insight into some of the trands in reactivity we have observed.

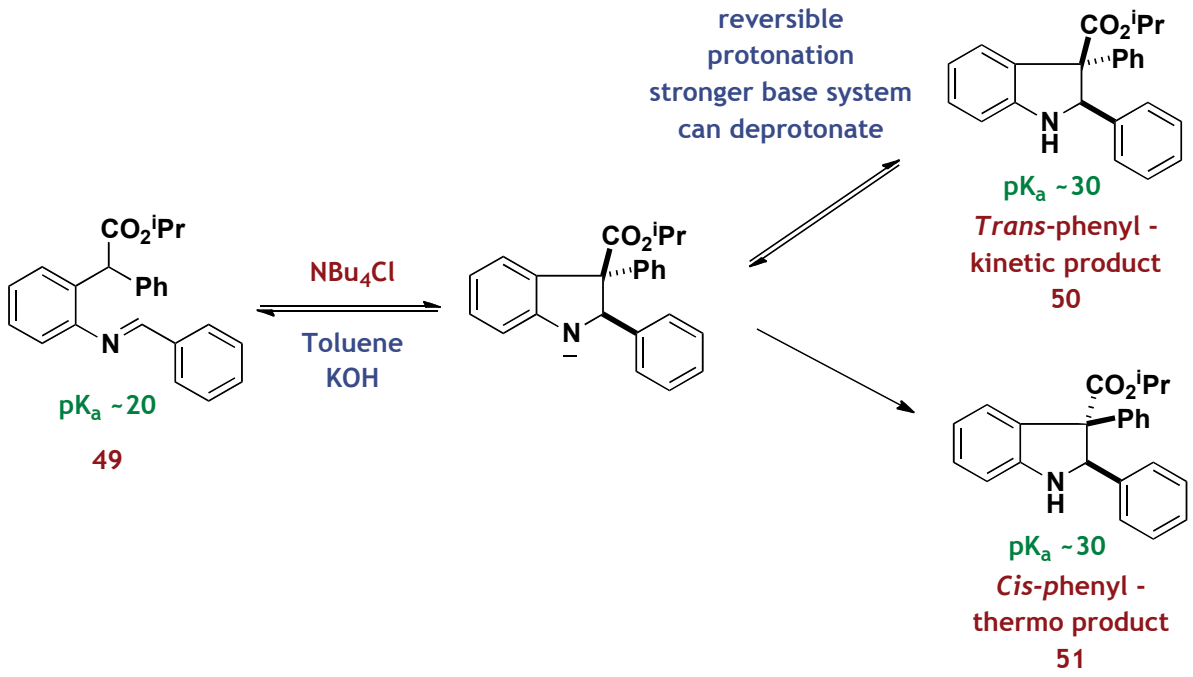
We postulate that the cinchona alkaloid catalyst (chiral and non-racemic) is a phase-transfer catalyst that can only operate under the 'interface' mechanism at pK_as between 16 and 23. This suggests that protonation of the indoline would be essentially irreversible, scheme **75**; the deprotonation of the indoline could still occur but given its predicted pK_a the concentration of the deprotonated indoline would be vanishingly small resulting in an essentially irreversible cyclization.



Scheme 75

This may explain the high levels of selectivity observed in all cases when using these cinchona alkaloid derived catalysts.

The NBu_4Cl catalyst is a more powerful catalyst in the sense that it can operate under both the 'extraction' and 'interface' mechanisms. Hence, it can operate at pK_as up to 37.[50] This allows these type of catalysts to deprotonate the indoline product and effect the retroelectrocyclization in the way cinchona alkaloid-type catalysts cannot, scheme **76**.



Scheme 76

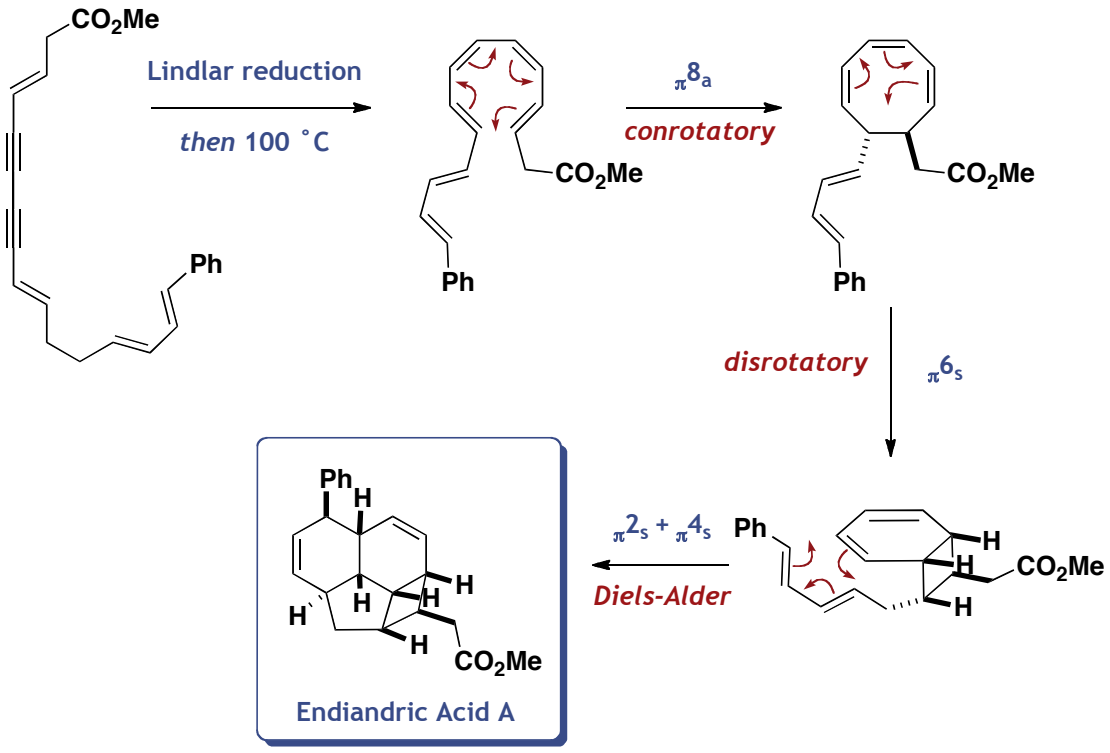
This may also explain the selectivity observed when using NBu_4Cl as a catalyst; in this case selectivity relies on the reversibility of the electrocyclization step. In the phenyl case above we have shown that the reaction goes *via* the kinetic product by sampling the reaction at short time intervals; this is consistant with this hypothesis that the thermodynamic product is formed under these conditions.

With the alkyl derived imine **57** we obtain a mixture of diastereoisomers upon treatment with NBu_4Cl which is likely a thermodynamic mixture given the nature of the catalyst. It is possible that the π–π interactions in the phenyl derivative are strong enough to make the *cis*-phenyl product significantly lower in energy. This favourable interaction would not occur with the alkyl derivative meaning the two diastereoisomers may be closer in energy and hence a mixture is observed under thermodynamic conditions.

3. [1,5]-Electrocyclization cascade reactions

3.1 Cascade reactions

Cascade reactions have become powerful tools in organic synthesis;[52] the ability to produce complex structures in a single synthetic step, often with high diastereoselectivity and enantioselectivity has undoubtedly provided the impetus for their study. Cascade reactions are common in nature and have therefore been exploited in numerous biomimetic natural product syntheses. Until recently, pericyclic reactions were considered to be relatively rare in nature; during the last 15 years there has been increasing evidence that they do occur with greater frequency than once thought.[53] A large portion of the electrocyclizations proposed biomimetically occur as cascade-type processes allowing the formation of complex polycyclic systems in a single step,[54] scheme **78**.



Scheme 78

The biosynthesis of the Endiandric acids was proposed by Black *et al*;[55] the ground breaking biomimetic synthesis of the Endiandric acids by Nicolaou *et al*.[56] highlights the powerful electrocyclization/electrocyclization/Diels-Alder cascade, scheme **78**. The production of Endiandric acid A in a single synthetic step, from a relatively simple starting material, as a single

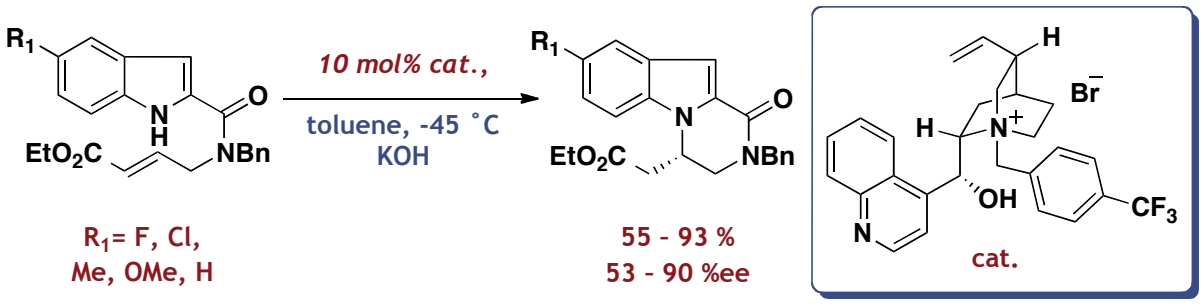
stereoisomer (along with by-products Endiandric acid D & E, which are earlier precursors of Endiandric acid A) demonstrates the utility of cascade processes which incorporate pericyclic reactions for generating highly complex scaffolds.

It is the ability to exert control over numerous stereocentres in a single transformation and the production of complex polycyclic systems that inspired our interest in developing cascade reactions involving our electrocyclization methodology.

3.2 Electrocyclization / 1,4-addition cascade

The aim of this project is the development of a cascade reaction incorporating our current asymmetric [1,5]-electrocyclization methodology to furnish complex polycyclic compounds. We hoped to exploit the current reaction manifold by utilising the product anion formed during the electrocyclization. The anion formed is thought to be localised on the nitrogen adjacent to the newly formed stereocentre and could therefore act as a 'chiral nucleophile' in a further reaction.

An interesting paper by Ronchi *et al*.[57] provided us with further inspiration for this work, scheme **79**.

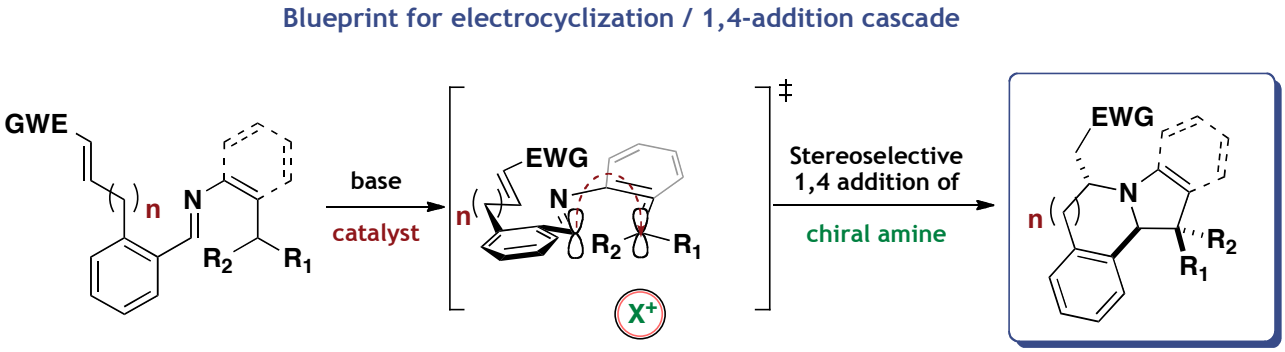


Scheme 79

By tethering a conjugate acceptor to an indole ring they were able to effect a 1,4-addition of the indole nitrogen under asymmetric phase-transfer conditions. The reaction proceeded with modest to high ees and good yields for a wide variety of substrates. Moreover this approach allowed the generation of a range of *N*-substituted indoles which are of interest to the pharmaceutical industry due to their wide variety of biological activity.[58]

With this in mind we proposed to effect a 1,4-addition by tethering an electrophile into the aldehyde. Imine formation was planned using the conditions used previously. The resulting

imine will then be treated under our optimized phase-transfer conditions facilitating an electrocyclization / 1,4-addition cascade, scheme **80**.

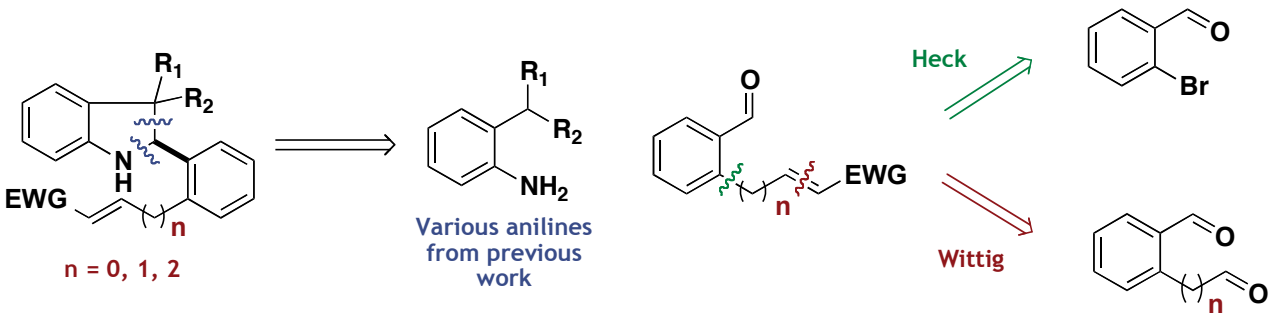


Scheme 80

Treatment of the imine under phase-transfer conditions should effect the electrocyclization in high enantioselectivity. The subsequent 1,4-addition will hopefully proceed with good diastereoselectivity due either to the presence of a chiral counterion or the chiral environment about the amine nucleophile.

3.2.1 Retrosynthetic analysis

Retrosynthetic analysis leads back to the now familiar aniline portion from our previous work and to a range of aldehyde 1,4-acceptors. In order to synthesize the desired aldehyde components for our cascade reaction we took a number of approaches depending on literature precedent and availability of starting materials, scheme **81**.



Scheme 81

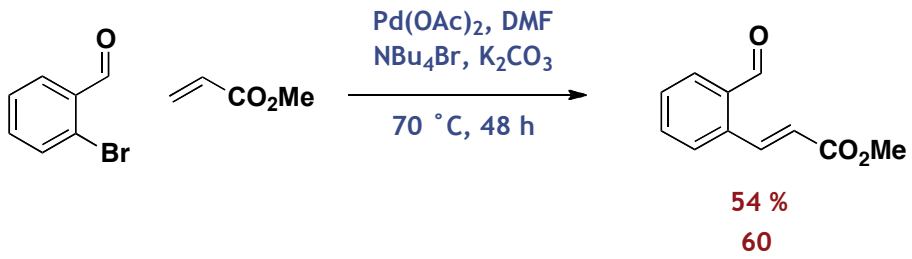
Aldehydes were envisaged *via* either Wittig or Heck reactions; specific details regarding conditions and literature precedent for each aldehyde will appear in the sections that follow.

3.3 Five-membered ring cascades

The title refers to the size of the ring formed during the proposed 1,4-addition step of the cascade and this nomenclature will be used throughout the section.

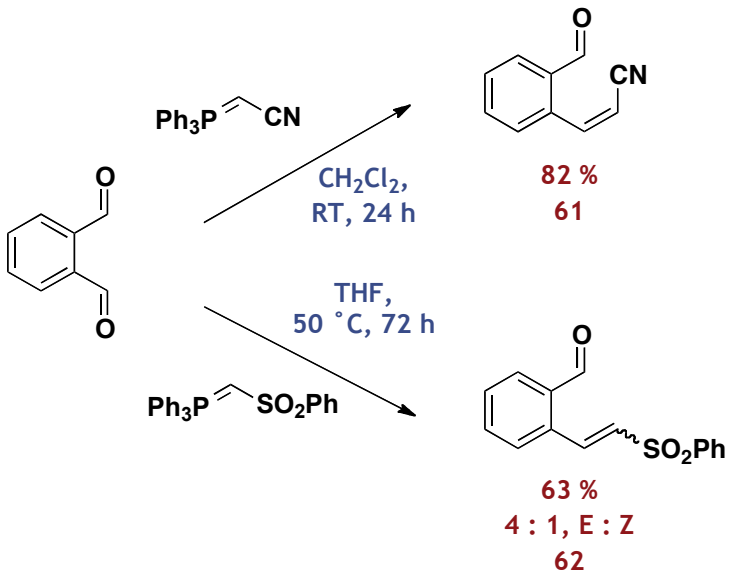
3.3.1 Aldehyde synthesis

Aldehyde **60** was the first synthesized according to literature precedent *via* a Heck reaction,[59] scheme **82**.



Scheme 82

The sulfone and cyano aldehydes were synthesized using the alternative Wittig chemistry from commercially available phthaldialdehyde. The cyano aldehyde **61** was prepared from a literature procedure[60] and the sulfone aldehyde **62** was synthesized by analogy, scheme **83**.

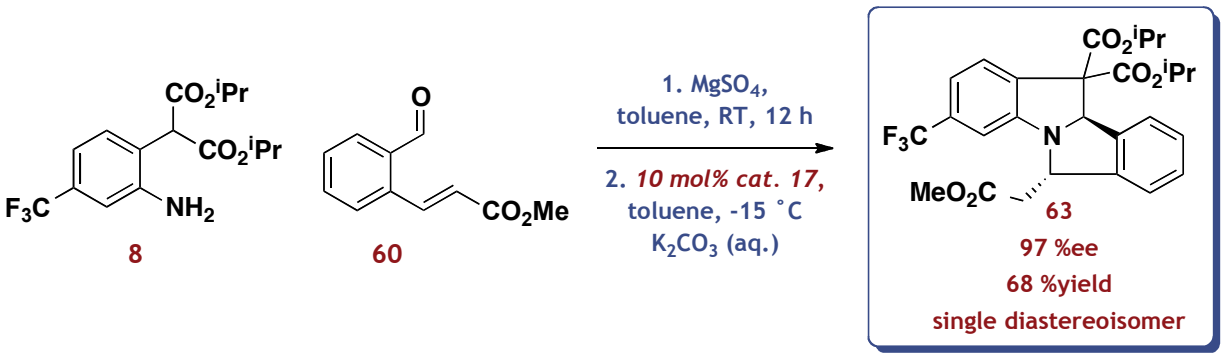


Scheme 83

Perhaps suprisingly the cyano aldehyde **61** was obtained in good yield as the *cis*-isomer. The sulfone derived aldehyde **62** was isolated as an inseparable mixture of geometric isomers; the *trans*-isomer is the major isomer as expected.

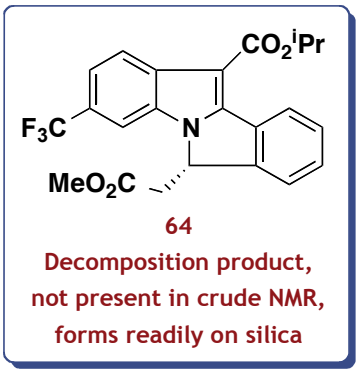
3.3.2 Malonate aniline derivatives

For our initial study we focused on using the malonate-derived aniline **8** from our initial work, allowing us to create two stereocentres and two rings in a single synthetic transformation. We were delighted to find that methyl ester aldehyde **60** during our initial investigation furnished us with the desired polycyclic compound **63** as a single diastereoisomer in high enantioselectivity, scheme **84**.



Scheme 84

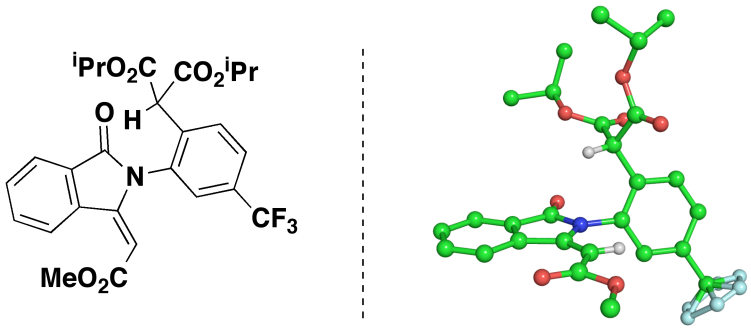
Unfortunately although the crude reaction showed nearly spotless material with the exception of the catalyst, purification of this compound proved difficult leading to a lower than desired yield. The product appears to be unstable to oxidation on silica as it was possible to isolate the corresponding indole derivative **64**, scheme **85**, upon column chromatography.



Scheme 85

Switching purification media to alumina or doping silica with triethylamine led to similar results. The best results were achieved by minimising the time spent on silica by using a short pad and relatively polar solvent system allowing isolation of the desired indoline in up to 68 %.

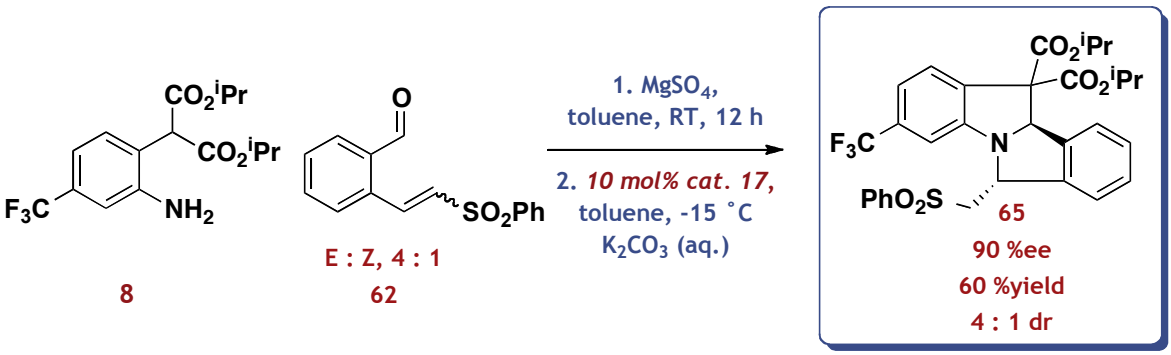
We have also found that the this product can be unstable when left at room temperature to similar oxidative decomposition. We discovered this attribute when trying to obtain a crystal structure of the product; crytals were grown from a mixture of petroleum ether and diethyl ether left open to air. The resulting X-ray crystal structure,[61] scheme **86**, was suprisingly different to our desired compound.



Scheme 86

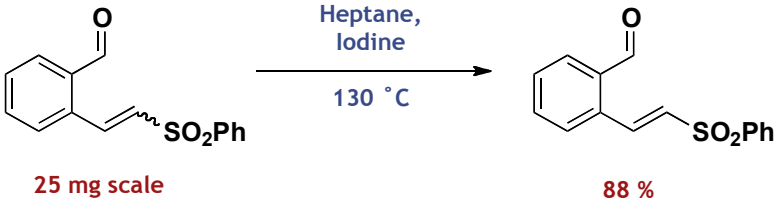
Although this is a different product to the indole derivative **64** it appears to be the product of an oxidative process and shows that for this particular example the product is unstable at room temperature in air. This occurs to a lesser degree at – 15 °C whereby the product can be stored for two to three weeks without appreciable decomposition but after two to three months has degraded entirely.

We were pleased to see that the sulfone aldehyde also proceeded to the desired indoline **65**, scheme **87**.



Scheme 87

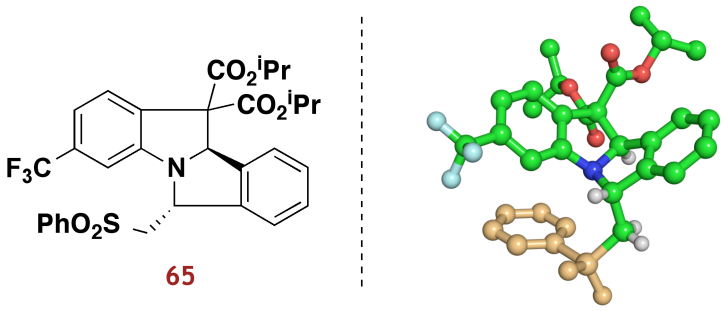
Pleasingly, high enantioselectivity was also observed for this substrate. The diastereoselectivity was significantly reduced (major diastereoisomer drawn) and we rationalized that this could be due to the mixture of geometrical isomers of the 1,4-acceptor. However, upon isomerization of aldehyde **62** to solely the *trans*-isomer, scheme **88**, similar diastereoselectivities in the cascade process were observed.



Scheme 88

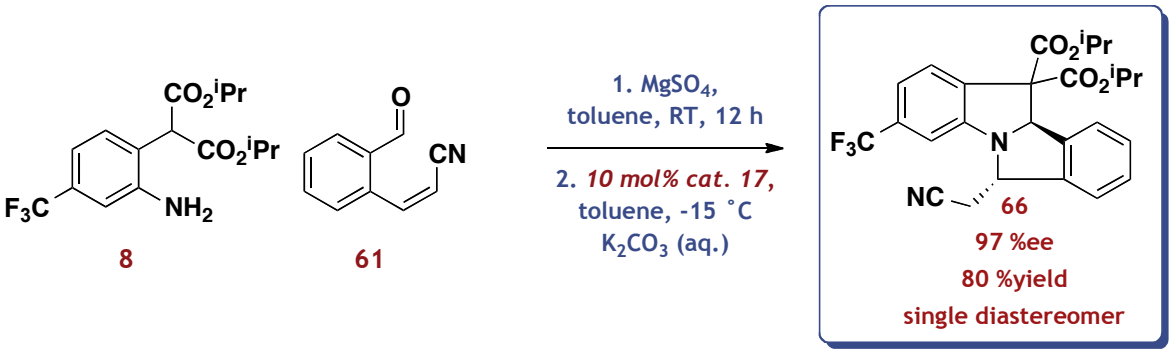
This led us to the conclusion that the 1,4-addition in this case must be less selective, possibly due to a slower rate of conjugate addition to these types of electrophiles.[62] This slower rate could allow a thermodynamic mixture of products to be formed whereas with the more reactive electrophile we are possibly observing solely the kinetic 1,4-addition product. The continued use of a mixture of geometrical isomers of the aldehyde was validated by this result and meant that the capricious isomerization reaction in this case could be avoided.

The relative configuration of the major diastereoisomer **65** was confirmed by X-ray crystallography, with absolute configuration being inferred from previous work, scheme **89**.



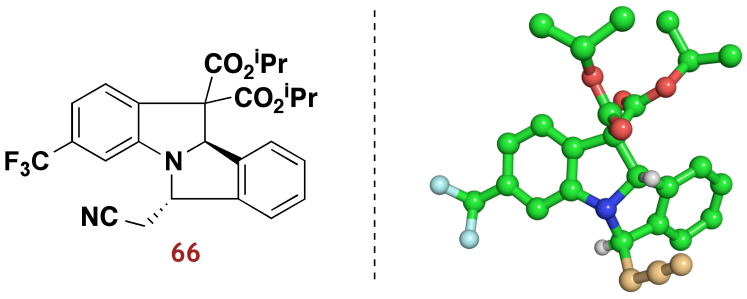
Scheme 89

The final aldehyde to test in this series, the cyano derivative, provided the best results, scheme **90**.



Scheme 90

The product indoline **66** was obtained as a single diastereoisomer in 97 %ee. The relative configuration of this compound was confirmed by X-ray crystallography of a racemic sample of **66**, scheme **91**.



Scheme 91

Relative stereochemistry is the same as the major diastereoisomer of the sulfone derivative and absolute stereochemistry is assumed by analogy to our initial electrocyclization work, The structure shown is the enantiomer of the expected major enantiomer due to the use of racemic

material for recrystallization. This similarity gave us confidence to infer the relative stereochemistry of the methyl ester which proved difficult to crystallize due to its propensity to oxidise as discussed.

As with our initial work, we began by using the trifluoromethyl substituted aniline **8**. However, we wanted to show it is possible to effect these reactions using other malonate-type anilines. To achieve this we repeated the cascade reaction with methyl ester aldehyde **60** and cyano aldehyde **61** with aniline **67**, scheme **92**. We rationalized that these aldehydes had given the best diastereoselectivities and were therefore more likely to do so with a different aniline.

Scheme 92

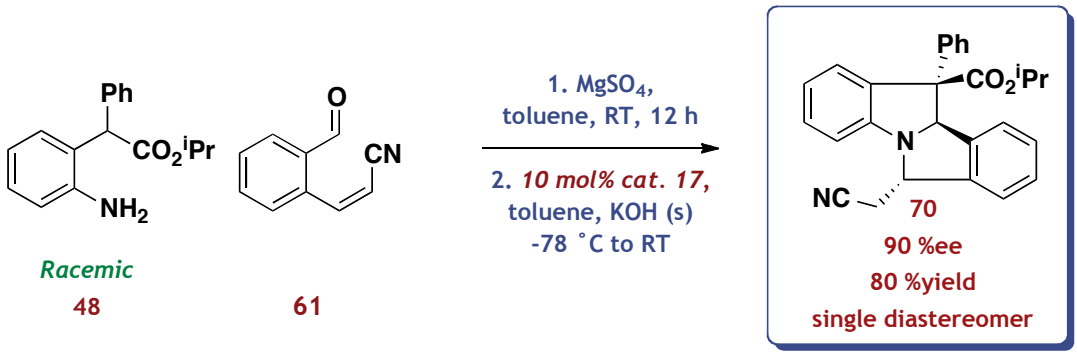
The diastereoselectivity remained high for both derivatives with a single diastereoisomer observed by ^{1}H NMR spectroscopy and upon isolation. However, we did observe a marked drop in ee for both substrates when the trifluoromethyl group was removed from the left hand aromatic ring. This is possibly due to poorer selectivity of binding to the catalyst; our model for binding proposed in the previous section relies on non-covalent interactions between the aromatic rings of the catalyst and substrate. The electronic differences associated with removing the trifluoromethyl group could be the reason for poorer binding; a broadly similar trend was observed with our initial work although the drop in ee was significantly smaller.

We propose that the initial electrocyclization is under kinetic control during these reactions with the secondary 1,4-addition being under thermodynamic control. This would account for the same relative configuration we observed for the major/sole diastereoisomer when different geometries of 1,4-acceptor were used. Moreover when the sulfone aldehyde was isomerized to solely the *trans*-isomer a similar mixture of distereoisomers was observed upon cyclization. This suggests that the second step is under thermodynamic control.

3.3.3 Diastereoselective electrocyclization cascades

With the promising results for the malonate derived aniline in hand we turned our attention to incorporating the work on diastereoselective electrocyclization into our cascade methodology. In this section all work containing the phenyl substrate **48** was undertaken by a co-worker and is presented to give a overview of the work.[63]

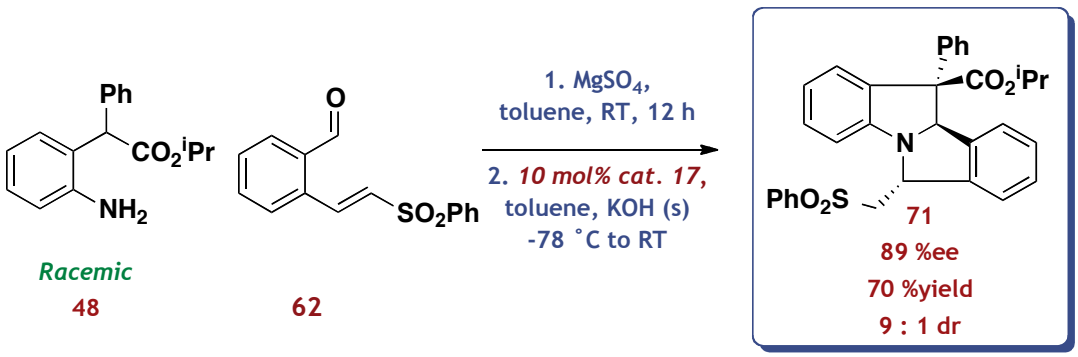
The incorporation of our diastereoselective electrocyclization methodology proceeded smoothly with the cyano aldehyde, scheme **93**.



Scheme 93

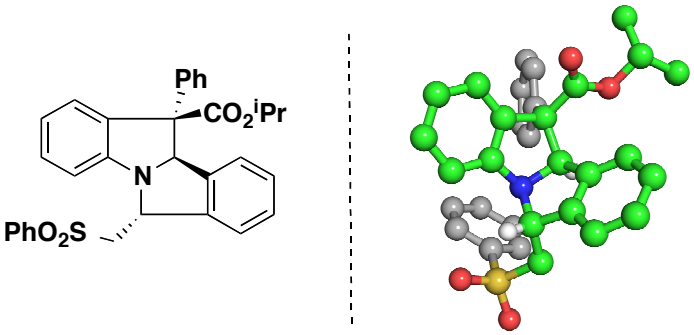
These exciting results, with high enantioselectivity and complete diastereocontrol over three stereocentres highlights the ability of cascade methodology to create complex materials from a simple starting material in a single step.

Inclusion of the sulfone aldehyde gave equally promising results, scheme **94**.



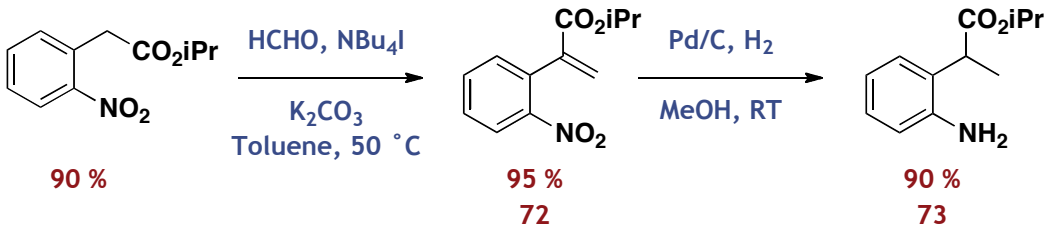
Scheme 94

The absolute and relative stereochemistry of the major diastereoisomer **71** was obtained by X-ray crystallography, scheme **95**. This again confirmed our belief that the absolute configuration is the same as for our initial electrocyclization methodology and the relative stereochemistry across the rings is the same as for the malonate derivatives.



Scheme 95

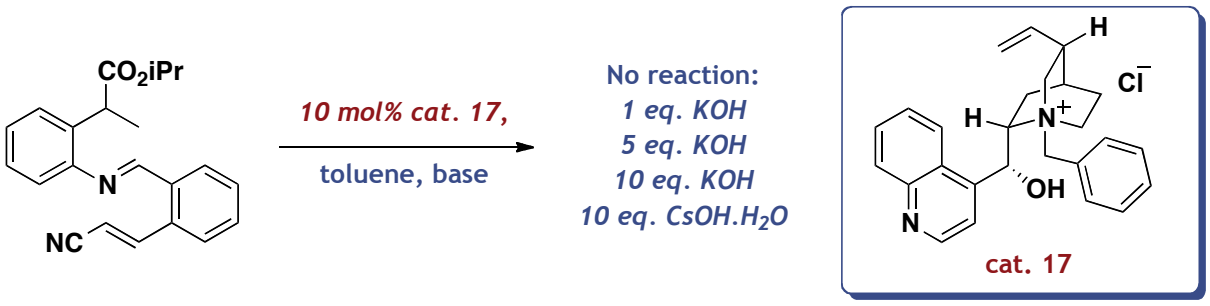
Our development of a diastereoselective electrocyclization also provided us with a methyl derivative which cyclized with complete diastereoselectivity and high enantioselectivity. However, the route to the precursor aniline was laborious and occasionally inconsistent. To that end, when we undertook to incorporate that substrate into our cascade sequence we also re-designed our route to the aniline, scheme **96**.



Scheme 96

This time, as with most of our work, an isopropyl ester was used in a high-yielding three step sequence. Esterification, Knoevenagel condensation[64] and reduction could all be effected on a large scale and with consistent yields; this represents a significant improvement on the previous route. This aniline differs from the one used during our diastereoselectivity studies; it is lacking a trifluromethyl group on the aromatic ring. We rationalized that as we had achieved excellent ees and diastereoselectivity with the phenyl system, which also does not contain the trifluoromethyl moeity, we hoped this would also be the case with our new methyl derivative.

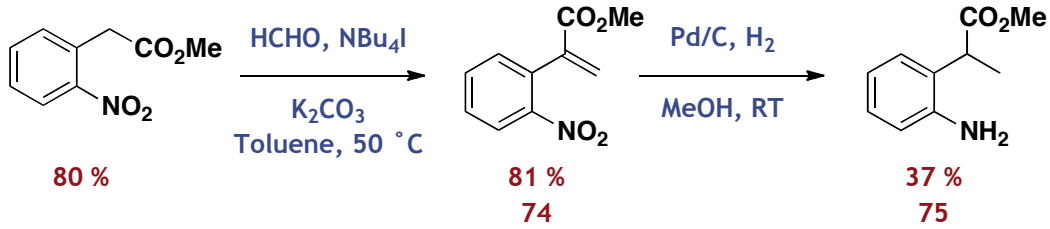
Imine formation with cyano derivative **61** proceeded smoothly under our standard conditions. This was followed by a number of attempts at cyclization under asymmetric phase-transfer conditions, scheme **97**.



Scheme 97

Unfortunately we were unable to effect the cyclization under any of the conditions attempted with only trace amounts of cyclized material after 72 hours by ^{1}H NMR spectroscopy. During our very early work we used methyl esters instead of isopropyl esters; the switch to the more sterically bulky isopropyl esters was promoted by the uncontrollably fast rate of cyclization when methyl esters were used (table **2**). We therefore hoped that switching back to a methyl ester might allow us to produce the desired cyclization.

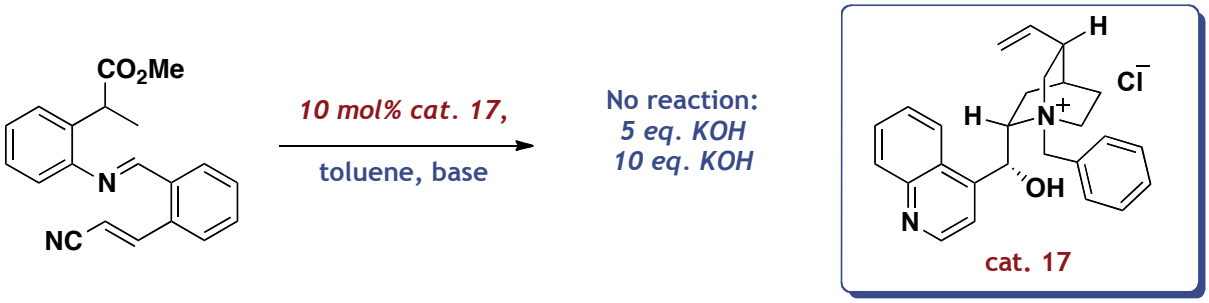
Therefore we repeated the new route to the corresponding methyl ester derivative, scheme **98**.



Scheme 98

Precursor synthesis proceeded smoothly with some poorer yields (this sequence was only carried out once and not optimized).

Imine formation with the cyano aldehyde was successful under our standard conditions. This was followed by attempts at cyclization which unfortunately failed, as with the previous substrate, scheme **99**.



Scheme 99

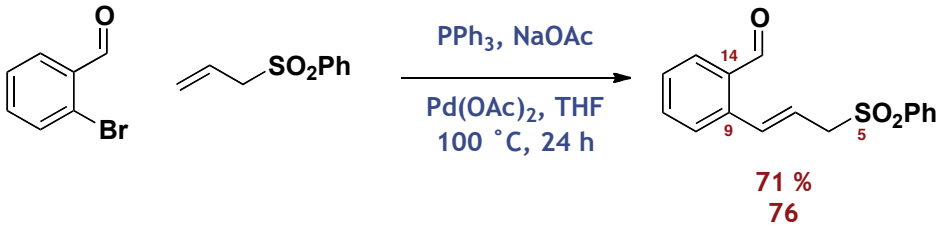
This led us to the conclusion that we have perhaps found the limit in terms of acidity of the benzylic proton. In the initial diastereoselectivity work (scheme **72** & **73)** the presence of a trifluoromethyl group on the aromatic ring would increase the acidity of the benzylic proton. In the new system the trifluoromethyl group was omitted due to availability of starting material and therefore the benzylic proton should be less acidic; the general trend in acidity for inductively withdrawing groups on a aromatic ring suggests that in comparison to an unsubstituted ring an inductively withdrawing group lowers the pK_a.[65] We propose that perhaps this small difference is the difference between whether the substrate can deprotonate and hence cyclize or not. Work to produce the analogous trifluoromethyl precursor for this cascade reaction and determine whether it will cyclize is ongoing. Attempts to affect this cyclization under racemic phase-transfer conditions, which generally can operate at higher pK_a's, resulted in decomposition of the material; this is possibly due to the use of a methyl ester which are known to be unstable under phase-transfer conditions.

3.4 Six-membered ring cascades

With these exciting results in hand we turned our attention to expanding the scope of the reaction to include the formation of a six-membered ring during the 1,4-addition step (as opposed to the five-membered ring case we have just seen). To do this a series of different aldehydes were synthesized; the aniline portion of the reaction remained the same.

3.4.1 Aldehyde synthesis

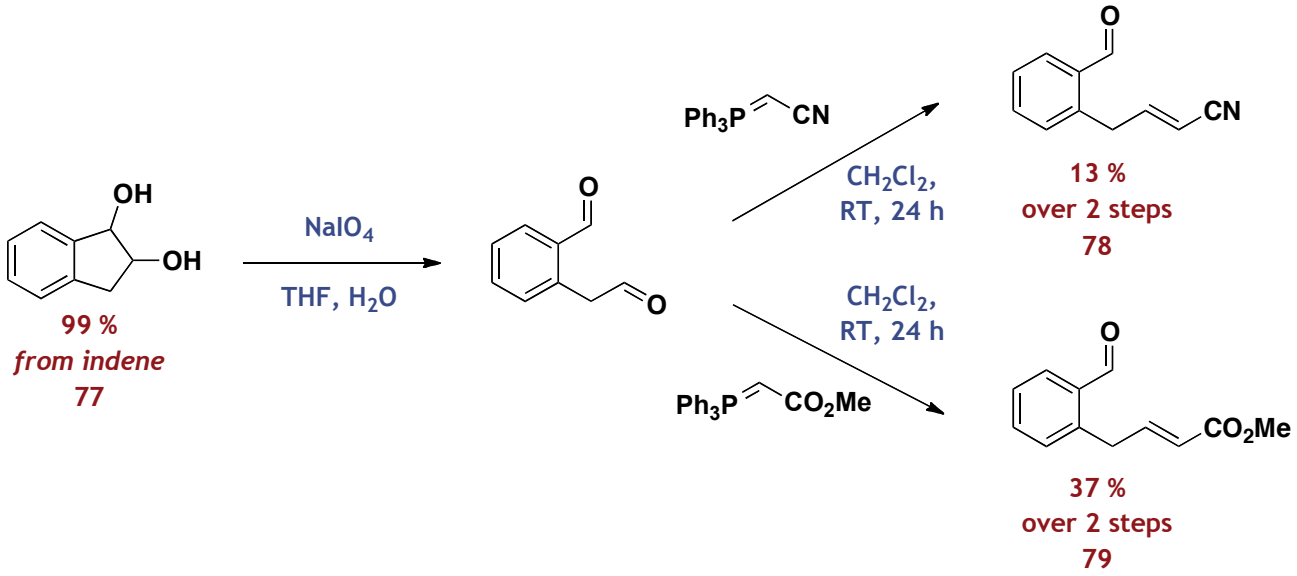
The sulfone derived aldehyde was the first attempted in this series due to literature precedent utilizing a tandem Heck isomerization reaction,[66] scheme **100**.



Scheme 100

Unfortunately the product we obtained was not the same as that reported in the literature but the regioisomer **76**. Initial doubt was cast by the relative shifts of the two alkene protons, these were opposite to that expected with an electron withdrawing group attached. This was confirmed by HMBS analysis which shows strong correlation between C9 and alkene proton H8. The lack of correltaion between the alkyl protons H6 and an aromatic carbon further suggest the proposed structure **76**.

The cyano aldehyde **78** and methyl ester aldehyde **79** in this sequence were synthesized using the alternative Wittig chemistry from homo-phthaldialdehyde. Homo-phthaldialdehyde was prepared by oxidative cleavage of indene.[67] The methyl ester derivative is a known compound[68] whilst the cyano derivative was synthesized by analogy, scheme **101**.



Scheme 101

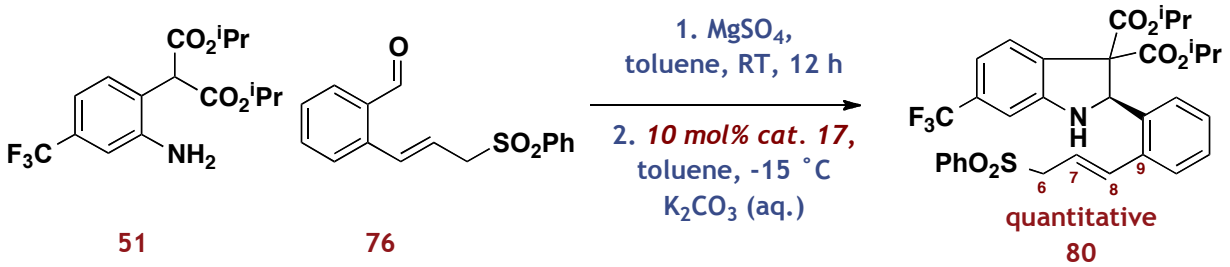
The poor yields are thought to be due to the unstable nature of the intermediate aldehyde formed, which was not isolated but its presence confirmed by ^{1}H NMR. This synthesis has been

improved[69/70] in collaboration with a co-worker to afford the cyano derivative **78** in 76 % and the ester derivative **79** in 52 % over two steps.

3.4.2 Malonate aniline derivatives

3.4.2.1 Optimization studies

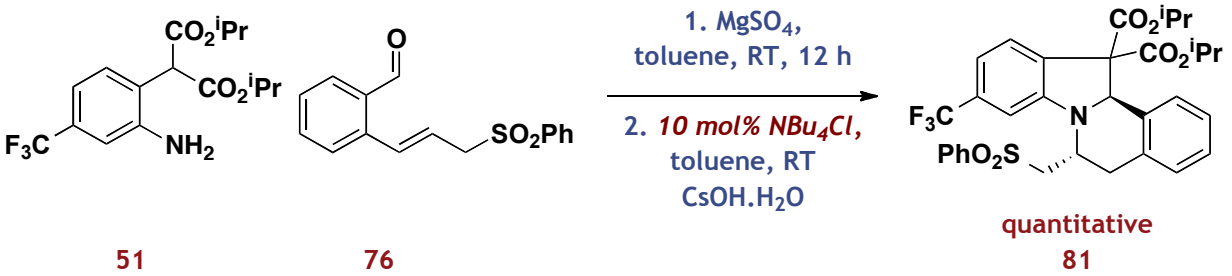
Initial work to develop a six-membered ring cascade focused on the use of sulfone aldehyde **76** as this was available in relatively high yields from commercially available starting materials and we had fortunately not deduced that the alkene was in the wrong position. Attempts to cyclize this six-membered ring derivative proved unsuprisingly more difficult than the previous five-membered ring examples. Imine formation proceeded smoothly followed by an initial attempt to effect the cyclization under our standard liquid-liquid phase-transfer conditions, scheme **102**.



Scheme 102

The initial electrocyclization occurred quantitatively but no second cyclization was observed under these conditions. In hindsight we can rationalise this due to the need for isomerization of the alkene to form a conjugate acceptor before the second cyclization can occur. Confirmation of structure **80** was provided by strong correlations in HMBC between H8 and C9 and the lack of any correlation between H6 and C9. Attempts to separate a racemic sample of compound **80** using chiral HPLC analysis were extensive but no suitable conditions were found. This unfortunately means no enantiomeric excess can be reported for this compound.

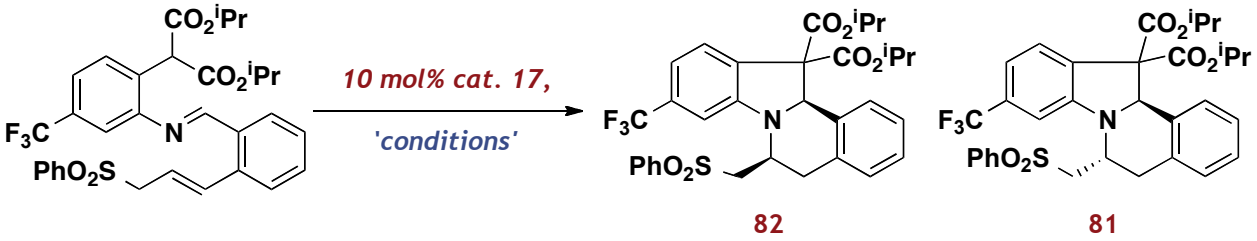
Fortuitously, the racemic reaction was run simultaneously and gave different results, scheme **103**, a single diastereoisomer of the desired product, **81**.



Scheme 103

This reaction was carried out at room temperature and under solid-liquid phase-transfer conditions. We rationalized that either the more basic nature of solid-liquid phase-transfer conditions or the higher temperature could be the driving force for isomerization and the second cyclization.

To determine whether this was the case we decided to screen a number of solid base systems. The use of cryogenic temperatures initially was to promote high enantioselectivity during the electrocyclization process with the hope that the second cyclization is under thermodynamic control as proposed for the 5-membered ring derivatives. By allowing the reaction to warm to room temperature we hoped to effect the isomerization and second cyclization, table **6**.



82 81

Entry	Base	Temperature (˚C)	dr (82 : 81)	ee[a] (%)
1	$CsOH·H_2O$	- 50 (24 h)	No second cyclization	-
2	$CsOH·H_2O$	- 50 then RT (4 h)	3 : 2	20
3	$CsOH·H_2O$	- 50 then RT (20 h)	1 : 2	20
4	$CsOH·H_2O$	- 15 (24 h)	2 : 1	30
5	KOH	- 50 then RT (6 h)	2 : 3	80
6	NaOH	- 50 then RT (6 h)	No second cyclization	-

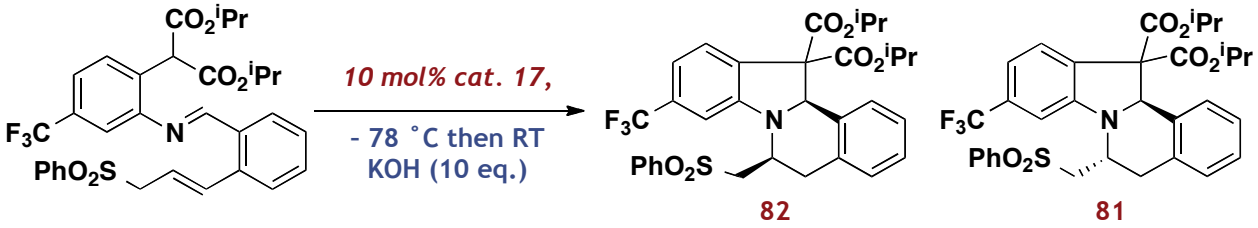
a. ees quoted are for diastereoisomer **81** due to availability of a racemic standard.

Table 6

Screening using $CsOH·H_2O$ led us to the conclusion that the electrocyclization does occur at the reduced temperature as predicted (entry 1) and subsequent warming will effect the desired isomerization/second cyclization completely (entry 2 & 3). However the complete diastereoselectivity of the racemic variant could not be replicated, with prolonged reaction times only affording a modest dr of 1 : 2 (entry 3). We hoped to determine whether the more basic solid-liquid phase-transfer system could effect the second cyclization at an intermediate temperature, between – 50 ˚C and RT. Conducting the entire reaction at – 15 ˚C gave the desired product as a 2 : 1 mixture of diastereoisomers (entry 4). This is in line with the previous two results, which after extended reaction times at RT equilibrated to favour diastereoisomer **81**. Unfortunately, in all the $CsOH·H_2O$ examples the ees were low; we rationalized that this may be due to the greater solubility of cesium bases facilitating deprotonation and cyclization in the absence of the chiral cation. We therefore turned our attention to screening other common solid bases amenable to phase-transfer catalysis.

The results show a marked increase in ee for potassium hydroxide (entry 5) and disappointingly no second cyclization for sodium hydroxide (entry 6). Prolonged reaction times did not increase the diastereoselectivity using potassium hydroxide, however due to the significant increase in enantioselectivity we continued our optimization using potassium hydroxide.

With a choice of base made we decided to further optimize the reaction conditions; we found that varying the equivalents of base had no effect on the enantioselectivity or diastereoselectivity of the process with the exception that lower base equivalents could be inconsistent. Therefore, the decision was made to continue with 10 equivalents of base for the remaining screens, and reduce the temperature to – 78 °C in order to maximise the enantioselectivity, table **7**.



Entry	Solvent	Concentration mmolmL^{-1}	ee[a] (%)	dr (82 : 81)
1	Toluene	0.10	44	1 : 1
2	Toluene	0.05	84	1 : 1
3	Toluene	0.02	No second cyclization	-
4	Toluene	0.10	54	2 : 3
5	9 : 1, Toluene : $CHCl_3$	0.10	50	2 : 3
6	1 : 1, Toluene : $CHCl_3$	0.10	No second cyclization	-

a. ees quoted are for diastereoisomer **81** due to availability of a racemic standard.

Table 7

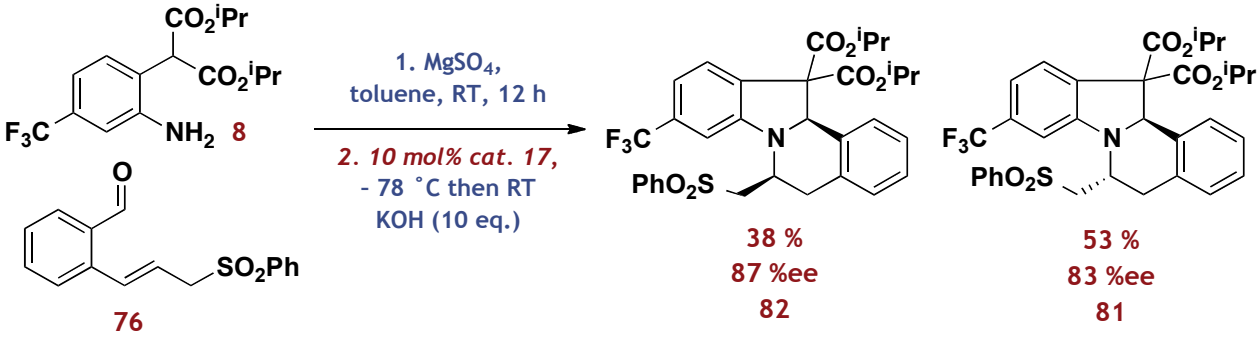
Very little difference in diastereoselectivity is observed for all entries so our main focus was on the enantioselectivity afforded. The screening of different solvents suggested, perhaps unsurprisingly, that pure toluene is the best solvent (entry 4). Concentration experiments yielded more interesting results, indicating that at low concentration (entry 3) there is not enough

catalyst/base/substrate interaction to effect the second cyclization. At higher concentrations (entry 1) the poorer enantioselectivity observed could be due to an increased background reaction. The highest enantioselectivity observed was at 0.05 $mmolmL^{-1}$ (entry 2) and therefore our optimized reaction will be carried out at a concentration of 0.05 $mmolmL^{-1}$.

Lastly, during our optimization studies we anecdotally noticed that more rigorously anhydrous KOH generally gives better enantioselectivities. Therefore during our work we were careful to prevent our powdered KOH from becoming wet.

3.4.2.2 Substrate scope

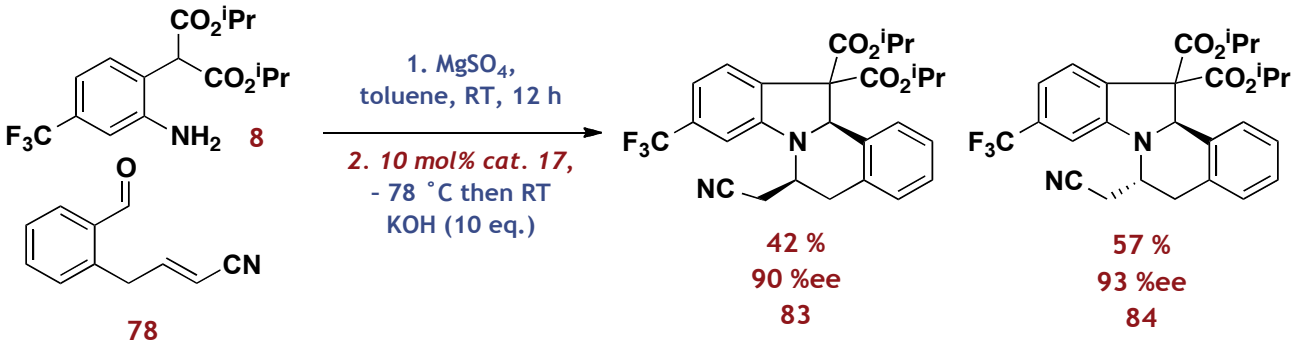
With optimized conditions in hand we turned to the exploration of substrate scope. Firstly the sulfone derivative under *pseudo* one-pot and optimized cyclization conditions gave promising results, scheme **104**.



Scheme 104

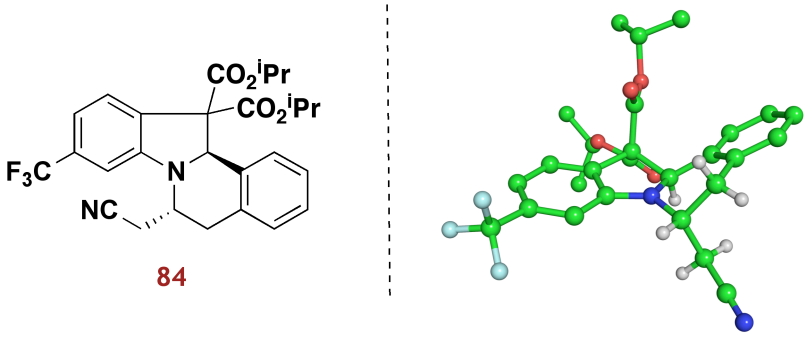
The high yields and enantioselectivity coupled with the separable nature of the diastereoisomers, **81** & **82**, make this an attractive process; creating two new rings and two stereocentres in a single step from simple starting materials. A racemic sample of **82** was obtained for HPLC analysis by stopping the racemic reaction after 1 hour which gave small amounts of the proposed kinetic isomer.

Extending this reaction to the cyano aldehyde provided even more pleasing results, scheme **105**. Stopping this reaction after the – 78 °C portion provided a mixture of singly clized and doubly cyclized product (no isomerization was needed for this aldehyde); this suggested that the second cyclization is slow in the six-membered ring case leading us to use the optimized conditions for the sulfone aldehyde from all other substrates despite the fact no isomerization is required.



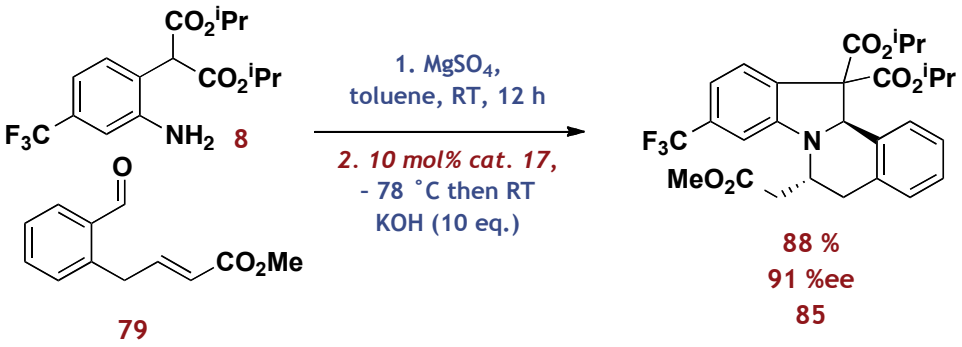
Scheme 105

Similarly high diastereoselectivity is observed for this substrate and an almost quantitative yield. The slightly higher enantioselectivities are perhaps not surprising; we observe similar differences in enantioselectivity with our five-membered ring series. It is possible the smaller size of cyano *vs* sulfone leads to greater steric clashes with the catalyst in the sulfone case. This in turn could lead to a relatively higher energy transition state for the preferred enantiomer (*vs* the other enantiomer) and therefore if Curtin Hammett kinetics are observed a lower enantioselectivity. The relative and absolute configuration of the major diastereoisomer **84** was confirmed by X-ray crystallography, scheme **106**. Other substrates are assumed to exhibit the same configuration accordingly.



Scheme 106

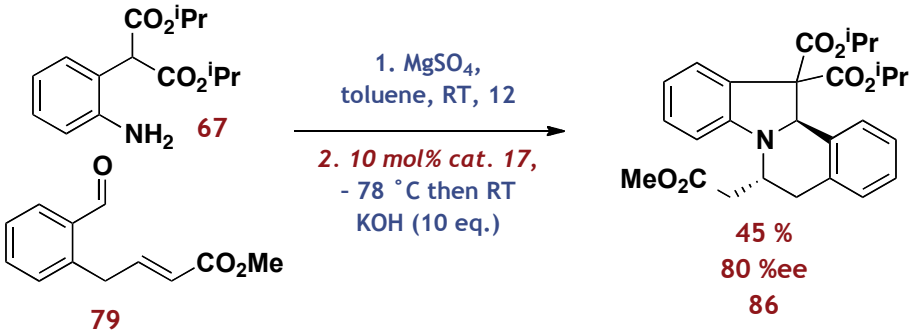
The final methyl ester aldehyde gave the most surprising results, scheme **107**.



Scheme 107

Complete diastereocontrol as well as high enantioselectivity was observed with this system to give indoline **85**. The yield reported for this substrate could be variable (down to 70 %) due to the same oxidation type process as observed for the five-membered ring derivative resulting in the corresponding indoline. This decomposition could be avoided to give the high yield reported by using a very short pad of silica and a polar solvent system allowing the removal of the catalyst without a significant amount of the oxidation occurring.

With this promising result we decided to effect the cyclization using aniline **67**, devoid of the trifluoromethyl group, as with the five-membered ring derivatives, scheme **108**.



Scheme 108

Substrate **86** shows lower enantioselectivity than the corresponding trifluoromethyl derivative **85**, the same trend as observed for the five-membered ring case. The lower yields here reflect the inability to purify the material without decomposition to the corresponding indole. It should be noted that in all cases the crude ^{1}H NMR spectrum shows only the desired indoline products with small amounts of catalyst as expected after the cascade reaction.

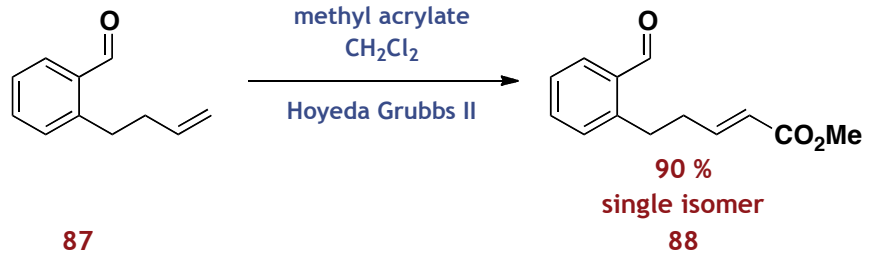
The six-membered ring substrates required substantially more optimization than the five-membered ring series; however, the high ees and separable nature of the diastereoisomers make this an attractive reaction manifold. The unexpected isomerization required for the sulfone derived aldehyde proceeded smoothly under the standard reaction conditions making this example as operationally simple as the rest. The possibility to exert near-perfect diastereocontrol by selection of the correct 1,4-acceptor would make this a useful route to similar structures. Efforts to extend this six-membered series to include a diastereoselective electrocyclization step, giving the chance to control three stereocentres, are currently ongoing.

3.5 Seven-membered ring cascades

In order to continue to expand the scope of the reaction we proposed to study the possibility of creating a seven-membered ring during the 1,4-addition step of the cascade. In a similar manner to the six-membered ring series we synthesized different aldehydes whilst the aniline portion of the reaction remained the same.

3.5.1 Aldehyde synthesis

Initial work focused on the methyl ester derived aldehyde which was synthesized *via* Grubbs metathesis with alkene **87** (a known compound),[71] scheme **109**.[72]

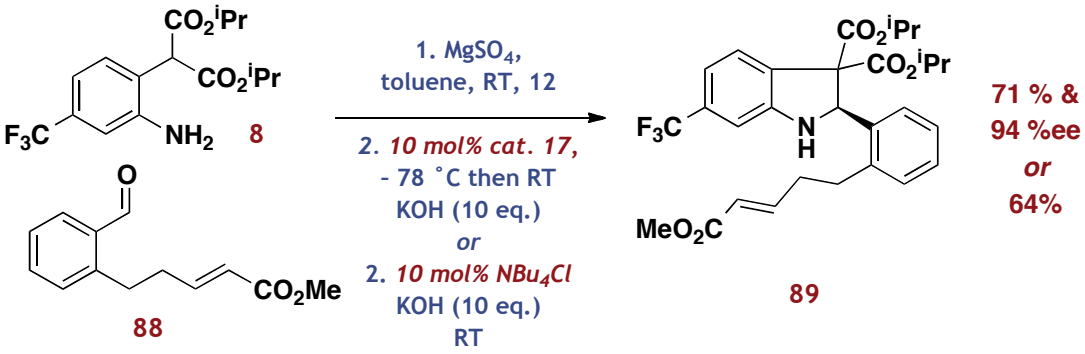


Scheme 109

This disconnection was chosen due to literature precedent for the alkene and similar cross metathesis reactions. The desired aldehyde **88** was obtained in high yield as a single geometrical isomer.

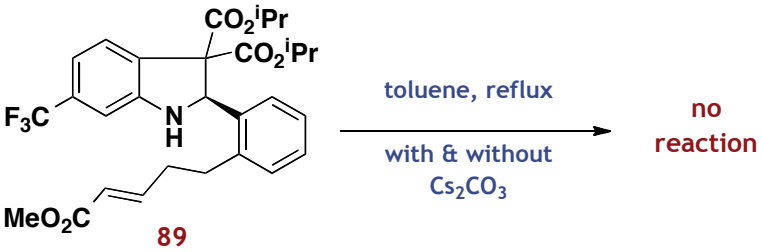
3.5.2 Cyclization

Imine formation proceeded smoothly under our standard conditions with quantitative conversion. Likewise, electrocyclization proceeded smoothly to give **89** under a variety of conditions however, the 1,4-addtion step did not occur under phase-transfer conditions, scheme **110**.



Scheme 110

This result is not suprising as five and six membered rings are generally more readily formed than seven-membered rings. Separation of a racemic sample provedAdditional attempts to promote the desired cyclization by heating with and without a base present were unsuccessful and led to recovery of the electrocyclized product **89**, scheme **111**.



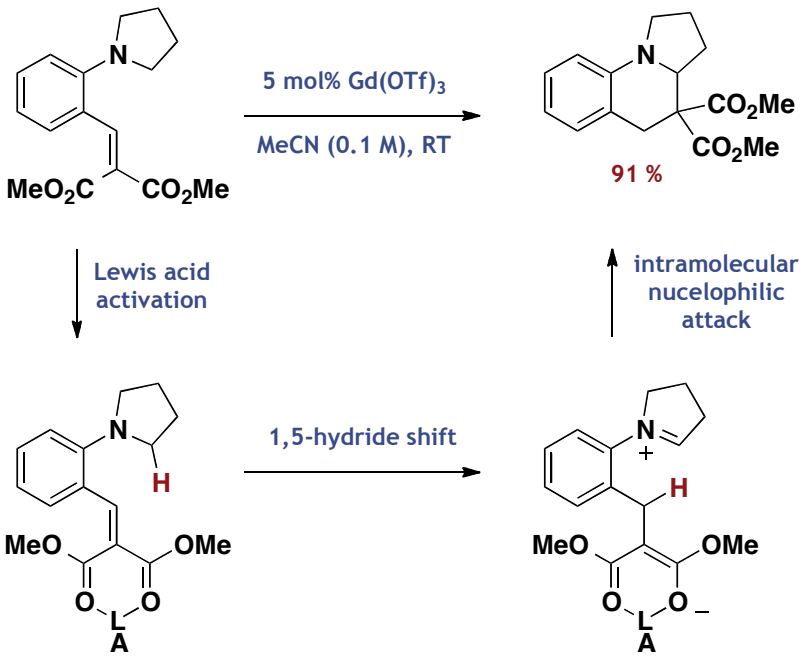
Scheme 111

We believe that this result indicates the limit of the potential of this cascade reaction; five- and six-membered rings are well tolerated, unfortunately this can not be expanded to encompass seven-membered rings.

3.6 Oxidation of methyl ester derivatives

Throughout this work we have seen that when using a methyl ester as our 1,4-acceptor, we often observe decomposition of the resulting cascade product. We originally proposed that the product was formed by an air-oxidation[73] followed by decarboxylation to give the indole; whilst this is still the most likely explanation there are other plausible mechanisms to be considered.

Recent work by Siedel *et al.*[74] has demonstrated the ability of hydrogen atoms α- to an amine to act as hydride doners. Initial work, scheme **112**,[75] suggested a 1,5-hydride shift was responsible for this reactivity. This reaction was originally reported by Reinhoudt *et al.*[76] in 1984 and has been rendered catalytic and asymmetric by Siedel *et al.* in more recent publications.



Scheme 112

The use of a Lewis acid to promote this reaction was essential (earlier work required refluxing between 80 and 120 °C) and is proposed to activate the conjugate acceptor towards the desired hydride shift.

In the case of our substrate a similar hydride shift could explain the observed decomposition to the indole derivative. It is possible that upon silica gel chromatography the malonate portion of the molecule is activated towards nucleophilic attack by the acidic nature of the silica similarly to the use of a Lewis acid reported by Seidel *et al.* Subsequent hydride shift *via* a non-pericyclic

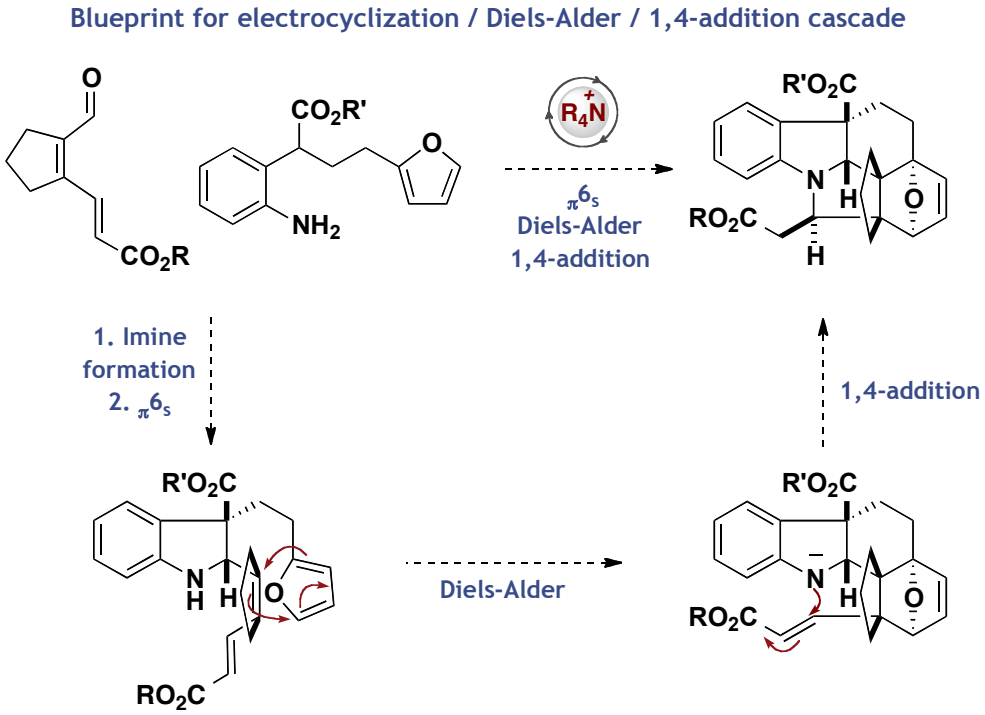
pathway could occur intramolecularly, the hydrogen and ester would already be in close proximity, followed by a fast decarboxylation.

This would not be a pericyclic hydride shift as no extended π-system is available to promote such a reaction; however, there are reports in the literature of similar hydride shift reactions whereby a pericyclic pathway is not available.[77] It is most common to observe a 1,2-shift in these non-pericyclic cases but larger shifts have been also been observed such as the one required in our system.

Although this rationale leads to the product observed with some literature precedent for the mechanism proposed it is still unclear why this decomposition occurs only with the methyl ester substrates. The sulfone and cyano substrates are remarkably stable; isolation of these substrates by silica chromatography and a number of crystallizations in air have not shown any decomposition of these substrates. The same problem occurs when considering the perhaps more likely *N*-oxidation in air followed by decarboxylation originaly proposed. This pathway does not provide an obvious reason for the distinction between the different conjugate acceptors that we have observed.

3.7 Electrocyclization / Diels-Alder cascade

In a large number of proposed biosynthetic electrocyclization reactions the reaction is accompanied by other pericyclic reactions, often cycloadditions. With this in mind we turned our attention to a cascade sequence involving a Diels-Alder reaction, scheme **113**.

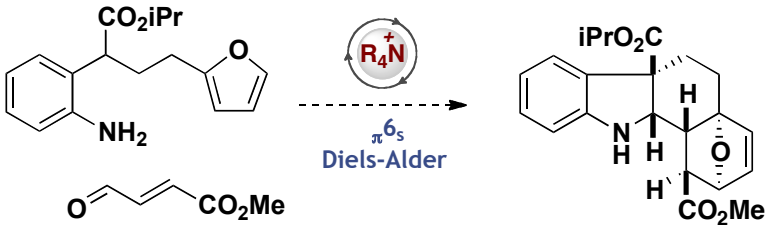


Scheme 113

Incorporation of furan (to act as a diene) into the aniline portion and extending the conjugated system on the aldehyde (to include a dienophile) should facilitate a Diels-Alder reaction after the electrocyclization has occurred. The reaction would proceed *via* imine formation followed by treatment under phase-transfer conditions. This should effect the electrocyclization which, if the facial selectivity is correct, would place the diene and dienophile onto the same side of the new ring, allowing the proposed Diels-Alder reaction to occur. Finally, we envisaged extending this to include our previous work by a final 1,4-addition step to create the final ring of the sequence. This ambitious project would furnish five new rings and seven stereocentres in a single synthetic transformation.

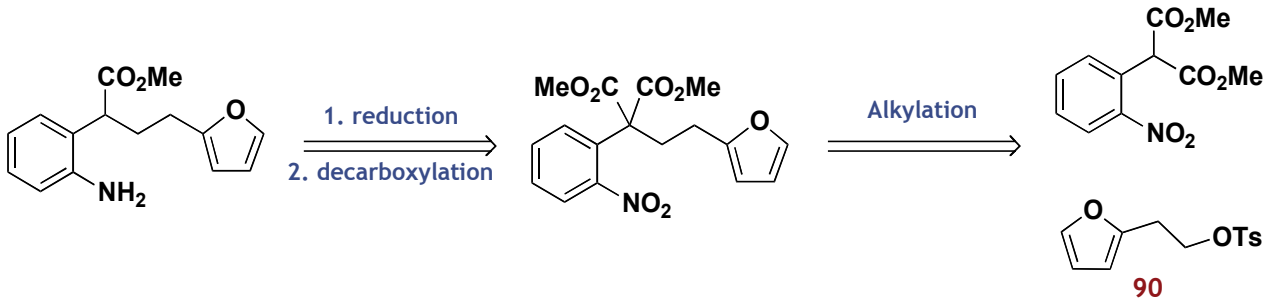
3.7.1 Retrosynthetic analysis

In the first instance we aimed to synthesize a substrate that would allow us to determine whether the Diels-Alder reaction could be effected after the initial electrocyclization, scheme **114**.



Scheme 114

This sequence removes the possibility for a final 1,4-addition allowing us to hopefully optimize the process for the Diels-Alder reaction. In terms of retrosynthesis the aldehyde portion of the cascade is a known compound; the forward synthesis will discussed in the following section. The aniline portion could be synthesized in a variety of ways; from our previous work on diastereoselective electrocyclization we know that alkylation of the aromatic malonate and subsequent decarboxylation can be successful, scheme **115**.

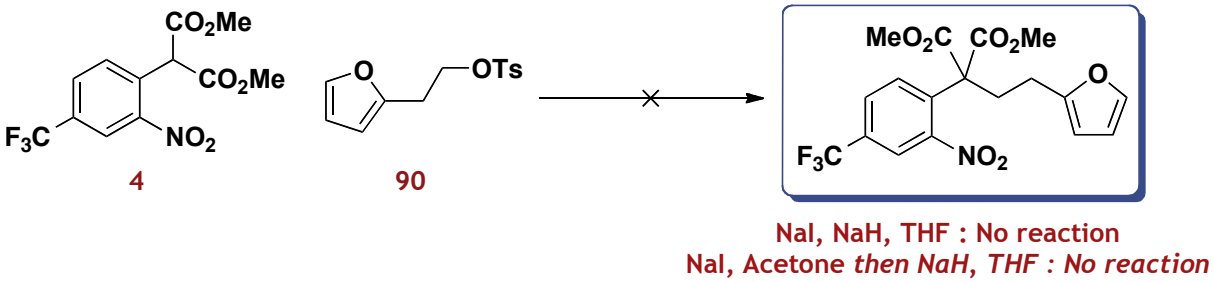


Scheme 115

The furan compound **90** is a known compound[78/79] and the choice of methyl over isopropyl ester is due to the relative ease of decarboxylation observed for our previous system.

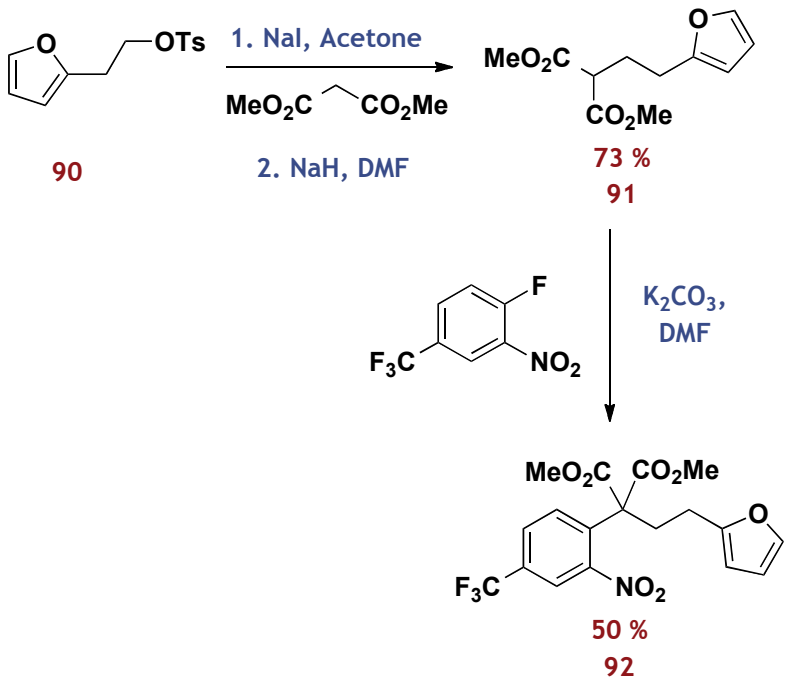
3.7.2 Substrate synthesis

Attempts to effect the initial desired alkylation unfortunately proved unsuccessful, scheme **116**.



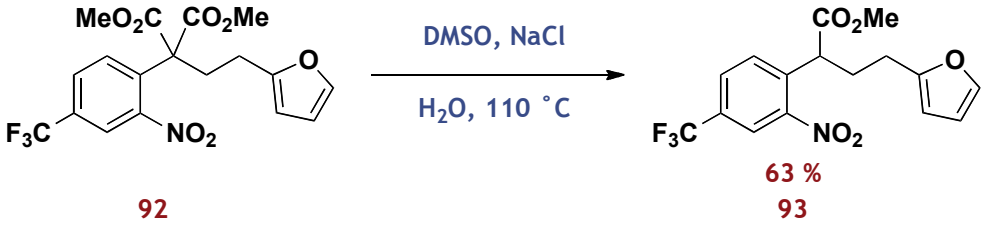
Scheme 116

Nitro-compound **4** was recovered and we propose that the tosylate is hydrolysed to the alcohol which is a volatile compound. These results are perhaps not surprising given the sterically demanding tertiary carbon nucleophile **4**; heating the reaction mixture had no effect on the outcome of the reaction. With this in mind we decided to reverse the order of these steps, scheme **117**, alkylating dimethylmalonate and using the resulting tertiary carbon nucleophile **91** to attempt the S_NAr reaction.



Scheme 117

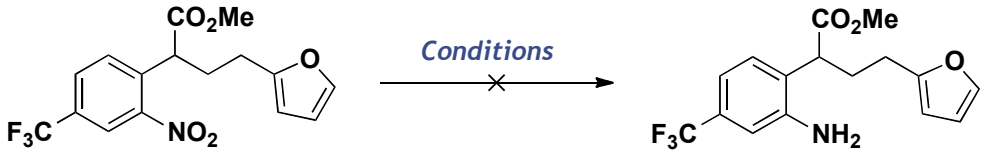
This worked surprisingly well; given the sterically demanding nature of the new S_NAr reaction we were pleased with a 50 % overall yield. Decarboxylation, using the procedure we optimized for the diastereoselectivity study, proceeded with a slightly disappointing yield, scheme **118**.



92 93

Scheme 118

However, we now had access to **93** in reliable yields, one reduction step away from the cascade precursor. Unfortunately multiple attempts to effect the reduction of this compound failed, table **8**.



93

Entry	Conditions	Product[a]	Furan reduction[b]	Methyl ester removal[c]
1	Pd/C, MeOH, H_2	none	complete	none
2	$Pd(OH)_2$, MeOH, H_2	20 %	some	none
3[80]	Pd/C, NH_2NH_2, EtOH	none	complete	complete
4[81]	PtO_2, EtOAc, H_2	none	complete	none
5[82]	$Pd(OH)_2$, EtOAc, NEt_3, H_2	none	none	complete

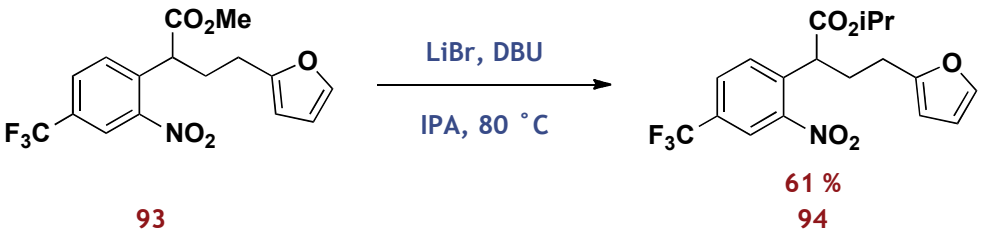
a. The product column in this table refers solely to the observation of the desired aniline. In most cases an inseperable mixture of unwanted compounds was observed. In all cases the nitro-compound **93** was not present.

b. Furan reduction refers to the lack of distinctive peaks in ^1H NMR between 6-7 ppm.

c. Refers to the lack of a methyl peak corresponding to the ester.

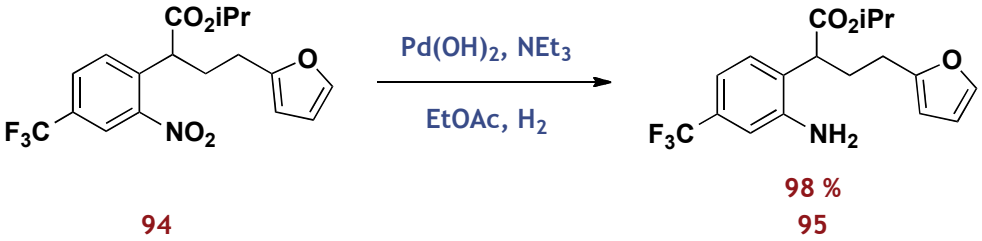
Table 8

The reduction of the furan ring so readily was disappointing as most of the conditions described were chosen since literature precedent had shown they were amenable to the presence of a furan ring. However, entry 5 shows that by poisoning the catalyst with triethylamine we can effectively stop any furan reduction. Our other problem seems to be related to the methyl ester which entirely disappears under many reaction conditions; whether this is due to hydrolysis or decarboxylation was not determined due to time constraints. We did not observe any oxindole formation which has a characteristic peak between 8–9 ppm in ^{1}H NMR spectroscopy. Having never encountered such problems with isopropyl esters under many different hydrogenation conditions, we decided to transesterify the substrate to determine whether this would solve our reduction problem, scheme **119**.[83]



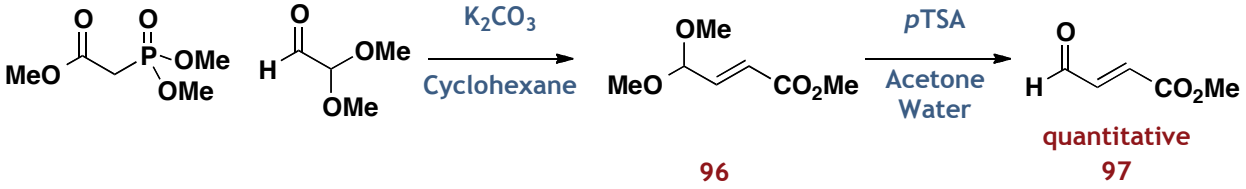
Scheme 119

Transesterification proceeded smoothly to give **94** and subsequent reduction was effected under the catalyst-poisoned conditions to protect the furan functional group, scheme **120**.



Scheme 120

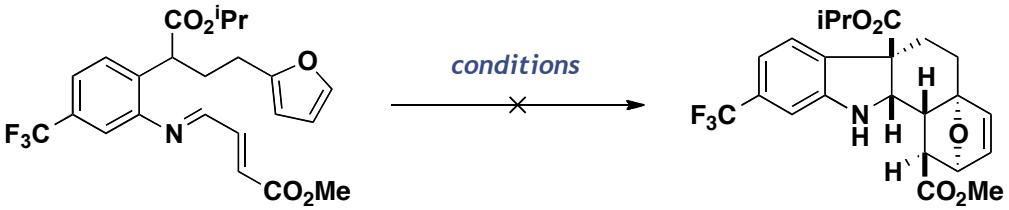
The success of this reduction allowed us access to enough material, albeit *via* the cumbersome transesterification route, to allow us to study the cascade. Aldehyde **97** was freshly prepared by deprotection of **96** (synthesized from commercially available starting material in one known step), scheme **121**.



Scheme 121

3.7.3 Cascade cyclization study

Subsequent imine formation under our standard conditions gave the desired cascade precursor with quantitative conversion (no purification was attempted at this stage due to possible stability issues). Attempts to cyclize the imine are outlined in table **9**.



Conditions	Catalyst	Result
RT, 10 eq. KOH	NBu_4Cl	complete decomposition
RT, 1 eq. KOH	NBu_4Cl	complete decomposition
RT, 10 eq. KOH	catalyst 17	complete decomposition
- 15 °C, 10 eq. KOH	catalyst 17	no reaction
0 °C, 10 eq. KOH	catalyst 17	no reaction

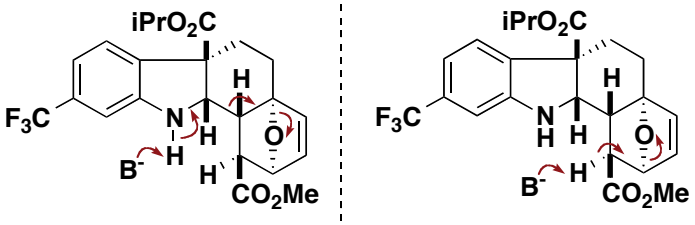
Table 9

Our initial attempts to effect the cascade under racemic phase-transfer conditions were chosen due to the proposed reversibility of the electrocyclization under these conditions. We did not know which diastereoisomer would be preferred under the asymmetric conditions and this could lead to the diene and dienophile being placed on opposite faces of the ring, preventing the Diels-Alder reaction. We rationalized that under the racemic conditions which we have shown to be reversible, some of the diastereoisomer with the correct configuration for the Diels-Alder reaction to occur would be formed and hopefully act as a thermodynamic sink. Unfortunately

under these conditions rapid decomposition of the material was observed with almost no aromatic protons in the crude NMR spectrum. No attempt was made to determine the products of this decomposition. The tetrabutylammonium catalyst can operate at higher pK_a's than those accessible to the cinchona alkaloid catalyst and we rationalised that this could be the cause of the decomposition. However, similar results were observed with the cinchona catalyst at room temperature. Reducing the temperature in the hope of controlling the reaction led only to recovery of the starting imine.

It is possible to envisage a number of decomposition pathways, scheme **122**, which perhaps suggest that the choice of diene might be an insurmountable issue in this motif.

Possible decomposition pathways

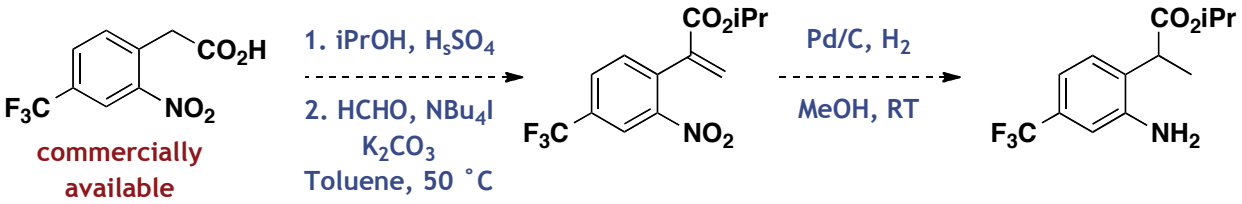


Scheme 122

4. Future work and conclusions

4.1 Future work

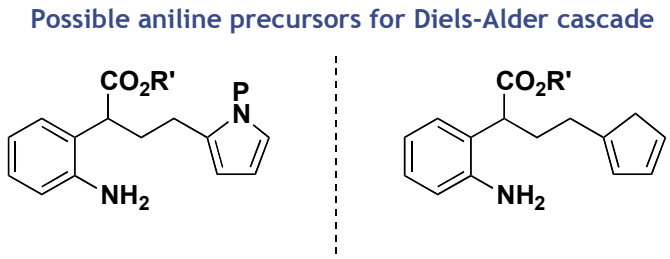
A number of aspects of the cascade methodology are currently still being researched. We are keen to incorporate our diastereoselective electrocyclization into the cascade methodology; in the case of the phenyl derivative this has been accomplished for some substrates. Our attempts to include the methyl derivative have so far been unsucessful but we hope to be able to include this motif shortly by introducing a trifluoromethyl group onto the aromatic ring as with our initial distereoselectivity substrate. To provide the desired starting material we plan to follow the more consistant second generation route with a trifluoromethyl group in the starting material, scheme **123**.



Scheme 123

We rationalized that the incorporation of the trifluoromethyl group could account for the difference in reactivity we observed using the non-trifluoromethyl derivative in the cascade process; conversely the diastereoselective electrocyclization had cyclized smoothly with a trifluoromethyl group.

Unfortunately, the Diels-Alder cascade failed to provide any conclusive products which we proposed was due to a number of possible decomposition pathways available to the product. These decomposition pathways, if they are the cause of the failed reaction, both result in breaking the oxygen bridging-ring which is formed by using a furan ring as the diene. To counter this problem we envisage the synthesis of a similar precursor whereby the furan is replaced with a different diene, scheme **124**.



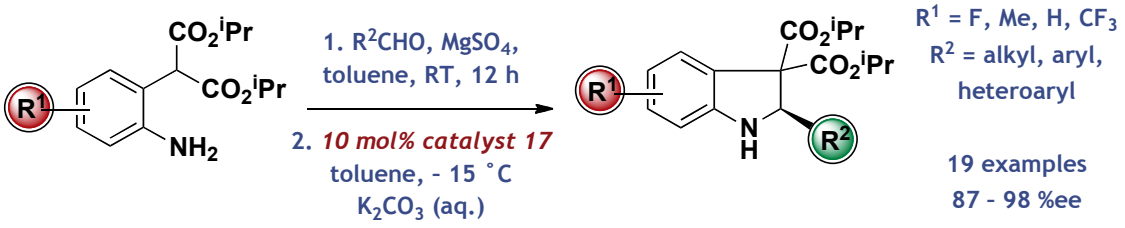
Scheme 124

Using the lessons learnt with the 1,4-addition cascade we would hope to include a trifluoromethyl group onto the aromatic scaffold in order to facilitate the initial electrocyclization.

4.2 Conclusions

The aim of this project was the development of new methodology that would facilitate the use of [1,5]-electrocyclization in a wider chemical context. These powerful carbon-carbon bond forming reactions have the potential to create two stereocentres in a stereospecific manner. Their lack of use in modern synthetic endeavours was thought to be due to the lack of methods for asymmetric catalysis of these reactions and the often harsh conditions required to force the reaction to proceed.

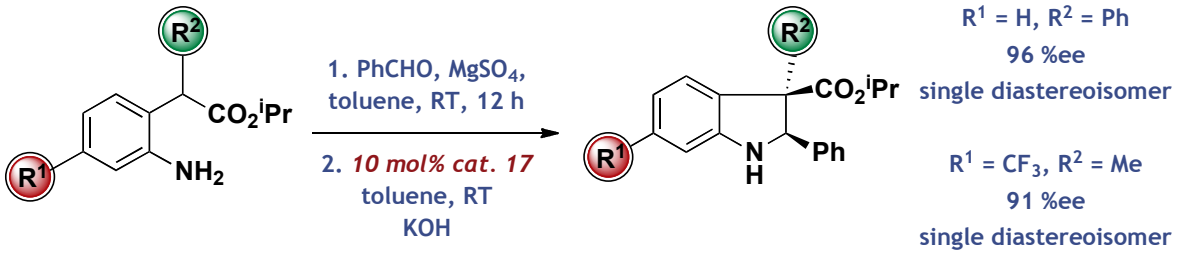
Our initial work allowed us to develop a highly enantioselective method for the synthesis of indolines *via* a proposed [1,5]-electrocyclization. This methodology prooved to be highly tolerant of different functional groups with 19 examples published in high ee, scheme **125**.



Scheme 125

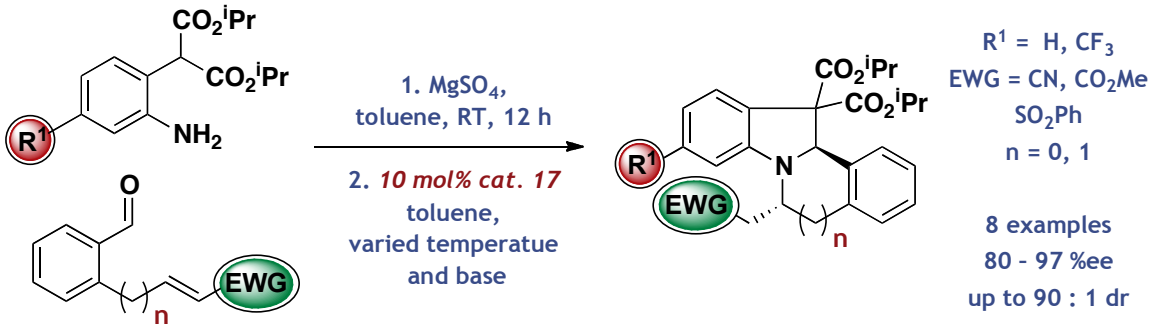
This work led us to investigate the nature of the reaction we had developed: is this process a [1,5]-electrocyclization or a Mannich reaction? We have been unable to conclusively answer this question and work in this area will be ongoing as more systems are developed within the group.

We successfully extended this methodology to incorporate diastereoselectivity into the electrocyclization step; complete diastereocontrol could be achieved under asymmetric conditions and in some cases we were able to choose which diastereoisomer was formed under racemic conditions, scheme **126**.



Scheme 126

The final chapter in this project was designed to show the utility of these reactions in creating more complex polycyclic compounds. Our initial efforts to incorporate a 1,4-addition reaction after the electrocyclization to utilize the 'chiral amine' nucleophile proved sucessful, scheme **127**.



Scheme 127

We are currently still working to include some of our diastereoselectivity methodology into this process.

Unfortunately we were unable to incorporate a similar Diels-Alder reaction after the electrocyclization step and will continue effort towards this end.

In conclusion we have developed a highly diastereoselective and enantioselective synthesis of functionalized indolines *via* a proposed electrocyclization reaction. We hope that the extension

of this methodology to include cascade processes gives a glimpse of their potential to be powerful tools in modern synthetic chemistry.

5. Experimental

5.1 General experimental procedures

5.1.1 Solvents and Reagents

THF, dichloromethane, toluene, methanol and acetonitrile were purified by filtration through activated alumina columns, employing the method of Grubbs *et al.* or: THF was distilled under an atmosphere of nitrogen from lithium aluminium hydride and calcium hydride in the presence of triphenylmethane or sodium metal in the presence of benzophenone; dichloromethane was distilled from calcium hydride; toluene was distilled from sodium under an atmosphere of nitrogen. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Petroleum ether refers to the fraction of petroleum ether boiling between 40 and 60 ˚C. Commercially available aldehydes were purified by distillation or crystallography according to the procedure in Perrin and Amarego. All other reagents and solvents were used as supplied, without prior purification. All water used experimentally was distilled and non-aqueous reactions were carried out under an atmosphere of argon in oven dried glassware.

5.1.2 Chromatography

Thin layer chromatography (TLC) was performed on glass or aluminium plates coated with Merck 60 F_{254} silica and visualization was achieved by UV light or by staining with ceric ammonium molybdate or potassium permanganate. Flash column chromatography was carried out using Merck Kieselgel (230-400 mesh) or silica gel 60 (0.043-0.063 mm, VWR).

5.1.3 Nuclear Magnetic Resonance Spectroscopy

NMR spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100 MHz), a Bruker Avance Cryo 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz), a Bruker AVB 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz), or a Bruker DPX 250 (^{1}H: 250 MHz and ^{13}C: 63 MHz) spectrometer. Chemical shifts are quoted in ppm and are referenced to the residual non-deuterated solvent peak, and are reported (based on appearance rather than interpretation) as follows: chemical shift δ/ppm (number of protons, multiplicity, coupling constant *J*/Hz, assignment) [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet]. ^{19}F spectra were run at 376 MHz on a Bruker Avance 400 with a QNP probe.

5.1.4 Infrared Spectroscopy

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer fitted with an attenuated total reflectance attachment with internal referencing or as thin films on sodium chloride plates on a Bruker Tensor 27 FTIR with internal calibration.

5.1.5 Mass Spectrometry

Accurate mass measurements were performed on a Finnigan MAT 900 XLT (ES+) at the EPSRC National Mass Spectrometry Service Centre at Swansea, or on a Bruker microTOF (ES+) at the University of Oxford. LCMS were performed on an Agilent MSD LC-MS APCI 120-1000 full gradient machine or an Agilent LC-MS APCI 1100.

5.1.6 Polarimetry

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm.

5.1.7 HPLC

Chiral HPLC was performed on an Agilent 1200 Series instrument or a Dionex 3000 system fitted with the appropriate Daicel Chiralpak column.

5.1.8 Naming and numbering of compounds

Compounds are named according to IUPAC guidelines and the numbers within names refer to the IUPAC system of numbering. In assigning the NMR spectra a separate numbering system was used as shown on individual compounds. Where compounds are characterized and do not have compound numbers from the results and discussion, such as those which appear only in general schemes, I have continued numbering but attempted to put the compound in the order it was discussed within the text.

5.2 Experimental procedures and data

General Procedures.

General Procedure 1. Asymmetric 'one pot' cyclization.

Aniline (1.0 eq.), aldehyde (1.5 eq.) and magnesium sulfate (5.0 eq.) were stirred in toluene (7.0 mL $mmol^{-1}$ aniline) for 9 h at RT. The reaction mixture was filtered, eluted with toluene (10 mL), concentrated *in vacuo* and redissolved in the *appropriate solvent* (7.0 mL $mmol^{-1}$ aniline). (8*S*, 9*R*)-*N*-Benzylcinchonidinium chloride (0.1 eq.) was added, and the resulting mixture was stirred for 30 minutes at the *appropriate temperature*. Potassium carbonate (3 M aq., 3.0 mL $mmol^{-1}$ aniline) pre-cooled to the *appropriate temperature* was added, and the reaction was stirred for 24 – 36 h at the *appropriate temperature*. The resulting solution was diluted with diethyl ether (20 mL $mmol^{-1}$ aniline), washed with water (20 mL $mmol^{-1}$ aniline) and the aqueous layer extracted with diethyl ether (2 x 30 mL $mmol^{-1}$ aniline). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and the resulting residue was purified using flash column chromatography.

General procedure 2. Asymmetric cyclization from recrystallized imines.

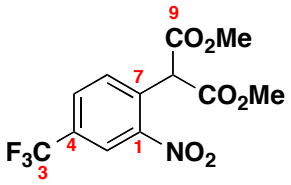
(8*S*, 9*R*)-*N*-Benzylcinchonidinium chloride (0.1 eq.) was added to a stirring solution of imine (1.0 eq.) in the *appropriate solvent* (7.0 mL $mmol^{-1}$ imine) and the resulting mixture was stirred for 30 minutes at the *appropriate temperature*. Aqueous potassium carbonate (3 M, 3.0 mL $mmol^{-1}$ imine) pre-cooled to the *appropriate temperature* was added, and the reaction was stirred for 24 h at the *appropriate temperature*. The resulting solution was diluted with diethyl ether (20 mL $mmol^{-1}$ aniline), washed with water (20 mL $mmol^{-1}$ aniline) and the aqueous layer extracted with diethyl ether (2 x 30 mL $mmol^{-1}$ aniline). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and the resulting residue was purified using flash column chromatography.

General procedure 3. One-pot imine formation / base catalyzed racemic cyclization.

Aniline (1.0 eq.), aldehyde (1.5 eq.) and magnesium sulfate (5.0 eq.) were stirred at RT in toluene (7.0 mL $mmol^{-1}$ aniline) for 9 h. The reaction mixture was filtered, eluted with toluene (10 mL) and concentrated *in vacuo*. The resulting residue was dissolved in toluene (3.0 mL $mmol^{-1}$ aniline) and stirred with cesium carbonate (1.0 eq.) for 4 h. The mixture was diluted

with water : acetic acid (10 mL, 20 : 1 v/v) and extracted with dichloromethane (3 x 15 mL), dried over magnesium sulfate, concentrated *in vacuo* and purified using flash column chromatography.

Dimethyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate

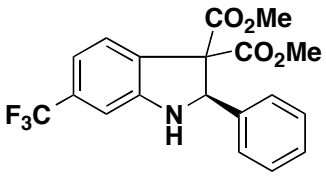


4

Dimethyl malonate (1.5 mL, 10.5 mmol) and potassium carbonate (1.4 g, 10.5 mmol) in DMF (30 mL) were stirred at 90 °C for 10 minutes and then cooled to room temperature. Arylfluoride **3** (1.5 mL, 7.0 mmol) was added to the mixture and subsequently heated at 90 °C for 3 h. After cooling to room temperature the mixture was diluted with 5 % HCl (10 mL) and the organic layer extracted with toluene (20 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid was recrystallised from toluene to afford a yellow crystalline solid **4** (2.3 g, 7.2 mmol, 73 %).

ν_{max} (neat): 3090, 2966, 1759, 1733, 1540, 1507. δ_H (400MHz, $CDCl_3$): 8.32 (1H, d, *J* 1.5, H2), 7.91 (1H, dd, *J* 8.3, *J* 1.5, H5), 7.72 (1H, d, *J* 8.3, H6), 5.38 (1H, s, H8), 3.82 (6H, s, H10). δ_C (100MHz, $CDCl_3$): 166.9 (C9), 148.8 (C1), 132.7 (C6), 132.0 (q, *J* 29, C4) 129.9 (q, *J* 3.5, C5), 122.5 (q, *J* 271, C3), 122.4 (q, *J* 3.8, C2), 53.8 (C8 and C10). δ_F (376MHz, $CDCl_3$): −63.4. LCMS (ES): 320.4 $[M]^-$ and 322.5 $[MH^+]$. HRMS (ES+): 322.0537 found; $C_{12}H_{10}F_3NO_6$ $[M+H]^+$ requires 322.0533. Mp: 39 – 41 ˚C.

Dimethyl 2-phenyl-6-(trifluoromethyl)indoline-3,3-dicarboxylate

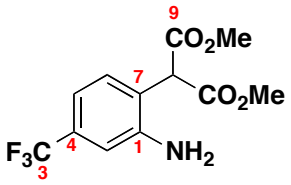


5

Nitro compound **4** (320 mg, 1.0 mmol) and palladium on carbon (wet degussa type, 32 mg, 10 wt%) were stirred in methanol : acetic acid, 50 : 1 (5 mL) with a positive pressure of H_2 for 2 h. The mixture was filtered through Celite™ and benzaldehyde (96 μL, 1.0 mmol) was added to the filtrate and stirred for 20 h. The mixture was concentrated *in vacuo* and the resulting residue purified using flash column chromatography (Petroleum ether : ethyl acetate, 7 : 1) to yield indoline **5** (235 mg, 0.62 mmol, 62 %) as a yellow solid.

ν_{max} (neat): 3335, 2951, 1758, 1726, 1624, 1601. δ_H (500MHz, $CDCl_3$): 7.48 (1H, d, *J* 8.0, H11), 7.36-7.39 (2H, m, H2), 7.28-7.31 (3H, m, H1/H3), 7.05 (1H, d, *J* 8.0, H10), 6.93 (1H, s, H7), 5.84 (1H, s, H5), 3.83 (3H, s, H15), 3.16 (3H, s, H15'). δ_C (125MHz, $CDCl_3$): 168.8 (C14), 167.5 (C14'), 150.9 (C12), 138.5 (C4), 132.2 (q, *J* 32, C9), 128.6 (C1), 128.3 (C3), 127.5 (11), 127.5 (C2), 126.9 (C6), 124.1 (q, *J* 271, C8), 116.0 (q, *J* 3.9, C10), 105.7 (q, *J* 3.9, C7), 68.9 (C13), 67.9 (C5), 53.4 (C15), 52.3 (C15'). δ_F (376MHz, $CDCl_3$): −62.9. LCMS (ES): 378.5 $[M]^-$ and 380.5 $[M+H]^+$. HRMS (ES+): 380.1105 found; $C_{19}H_{17}F_3NO_4$ $[M+H]^+$ requires 380.1104.

Dimethyl 2-(2-amino-4-(trifluoromethyl)phenyl)malonate

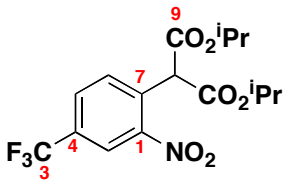


6

Nitro compound **4** (2.0 g, 6.4 mmol) and palladium on carbon (wet degussa type, 320 mg, 10 wt%) were stirred in methanol (40 mL) with a positive pressure of hydrogen for 24 h. The mixture was filtered through Celite™, washed with methanol (100 mL) and the solvent removed *in vacuo* to yield aniline **6** (1.7 g, 5.8 mmol, 91 %) as a yellow solid.

ν_{max} (neat): 3427, 3359, 2955, 2920, 1723, 1639. δ_H (500MHz, $CDCl_3$): 7.24 (1H, d, *J* 8.0, H6), 7.00 (1H, dd, *J* 8.0, *J* 1.1, H5), 6.95 (1H, d, *J* 1.1, H2), 4.68 (1H, s, H8), 3.77 (6H, s, H10). δ_C (125MHz, $CDCl_3$): 168.5 (C9), 145.9 (C1), 131.9 (C6), 131.6 (q, *J* 26, C4), 123.8 (q, *J* 217, C3), 122.0 (C7), 115.5 (q, *J* 3.0, C5), 114.2 (q, *J* 3.0, C2), 55.2 (C8), 53.1 (C10). δ_F (376MHz, $CDCl_3$): −61.0. LCMS (ES): 290.3 [M^-] and 292.5 [MH^+]. HRMS (ES+): 292.0790 found; $C_{12}H_{12}F_3NO_4$ $[M+H]^+$ requires 292.0791.

Diisopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate

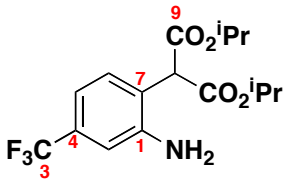


98

Potassium carbonate (7.6 g, 57.6 mmol) was added to a stirring solution of diisopropyl malonate (8.0 mL, 57.6 mmol) in DMF (160 mL), and the mixture was stirred at 90 ˚C for 10 mins before being cooled to room temperature. 1-Fluoro-2-nitro-4-(trifluoromethyl)benzene (8.0 mL, 57.6 mmol) was added and the mixture was heated at 90 ˚C for 3 h before being cooled to room temperature. The mixture was diluted with hydrochloric acid (5 % aq., 1.25 L), extracted with toluene (3 x 1.0 L), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid was recrystallized from petroleum ether to afford compound **98** (18.6 g, 84 % yield) as a yellow crystalline solid.

ν_{max} (neat): 2987, 1747, 1732, 1631, 1541, 1322. δ_H (400 MHz, $CDCl_3$): 8.34 (1H, d, *J* 1.5, H2), 7.92 (1H, dd, *J* 8.2, *J* 1.5, H5), 7.76 (1H, d, *J* 8.2, H6), 5.29 (1H, s, H8), 5.16 (2H, sept, *J* 6.3, H10), 1.33 (6H, d, *J* 6.3, H11), 1.31 (6H, d, *J* 6.3, H11). δ_C (100 MHz, $CDCl_3$): 166.1 (C9), 150.0 (C1), 132.4 (C6), 132.2 (C7), 131.7 (q, *J* 34, C4), 129.7 (q, *J* 3.5, C2), 122.6 (q, *J* 270, C3), 122.4 (q, *J* 3.9, C5), 70.5 (C8), 54.7 (C10), 21.5 (C11). δ_F (376 MHz, $CDCl_3$)" – 63.3. LCMS (ES+): 378.6 $[M+H]^+$. HRMS (ES+): found 378.1159; $C_{16}H_{18}F_3NO_6$ $[M+H]^+$ requires 378.1154. Mp: 40 – 42 ˚C.

Diisopropyl 2-(2-amino-4-(trifluoromethyl)phenyl)malonate

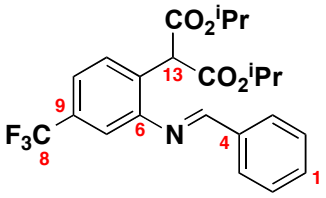


8

Palladium on carbon (200 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of diisopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate **98** (2.14 g, 5.68 mmol) in methanol (12 mL). The solution was degassed three times with argon using a pump-flood procedure and placed under hydrogen for 14 h. The mixture was filtered through Celite™, eluted with methanol (300 mL) and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether : diethyl ether, 6 : 1) to afford compound **8** (1.89 g, 96 % yield) as a pale yellow solid.

ν_{max} (neat): 3447, 3376, 2987, 1733, 1712, 1644. δ_H (500 MHz, $CDCl_3$): 7.25 (1H, d, *J* 7.9, H6), 6.98 (1H, d, *J* 7.9, H5), 6.93 (1H, s, H2), 5.09 (2H, sept, *J* 6.3, H10), 4.57 (1H, s, H8), 1.26 (6H, d, *J* 6.3, H11), 1.23 (6H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 167.6 (C9), 146.0 (C7), 131.9 (C6), 131.4 (q, *J* 32, C4), 123.8 (q, *J* 271, C3) 122.6 (C1), 115.3 (q, *J* 3.8, C2), 113.9 (q, *J* 3.5, C5), 69.9 (C10), 56.0 (C8), 21.5 (C11), 21.5 (C11). δ_F (376 MHz, $CDCl_3$): − 63.2. LCMS (ES+): 348.5 $[M+H]^+$. HRMS (ES+): found 348.1417; $C_{16}H_{20}F_3NO_4$ $[M+H]^+$ requires 348.1417.

(*E*)-Diisopropyl 2-(2-(benzylideneamino)-4-(trifluoromethyl)phenyl)malonate



9

Method 1. Isolation by silica gel chromatography

Palladium on carbon (200 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of diisopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate **98** (2.0 g, 5.2 mmol) in methanol (12 mL). The solution was degassed three times with argon using a pump-flood procedure and placed under hydrogen for 14 h. The mixture was filtered through Celite™, eluted with methanol (300 mL) and the solvent removed *in vacuo*. The resulting residue was redissolved in toluene (80 mL), treated with benzaldehyde (1.1 mL, 11.2 mmol) and magnesium sulfate (3.2 g, 26.8 mmol) then left to stir at RT for 24 h. The reaction mixture was filtered, concentrated *in vacuo* and the resulting residue was purified using flash column chromatography (petroleum ether : ethyl acetate, 5 : 1) to afford compound **9** (76 % yield, contaminated with approximately 3 % (±)-**10**) as a yellow solid.

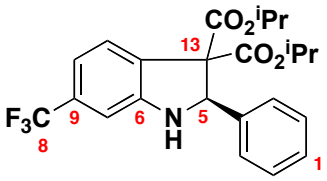
Method 2. Isolation by crystallization

Benzaldehyde (580 μL, 5.72 mmol) was added to a stirred slurry of diisopropyl 2-(2-amino-4-(trifluoromethyl)phenyl)malonate **8** (1.65 g, 4.77 mmol) and magnesium sulfate (2.86 g, 24.00 mmol) in toluene (15 mL) for 16 h. The solids were removed by filtration, washed with toluene (200 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 6 : 1) and recrystallized from petroleum ether, to afford compound **9** (1.51 g, 86 %) as a white crystalline solid.

ν_{max} (neat): 2985, 1748, 1720, 1628. δ_H (500 MHz, $CDCl_3$): 8.44 (1H, s, H5), 7.94 (2H, d, *J* 7.3, H3), 7.63 – 7.58 (1H, m, ArH), 7.56 – 7.46 (4H, m, ArH), 7.31 (1H, br, H11), 5.35 (1H, br, H13), 5.13 – 5.03 (2H, m, H15), 1.26 (6H, d, *J* 6.1, H16), 1.19 (6H, d, *J* 6.1, H16). δ_C (125 MHz, $CDCl_3$): 167.6 (C14), 161.9 (C5), 150.5 (C6), 135.7 (C4), 132.0 (C2), 131.9 (C12), 131.2 (q, *J* 33, C9), 129.5 (C1), 129.2 (C11), 128.8 (C3), 123.9 (q, *J* 272, C8), 122.6 (q, *J* 4, C10),

114.5 (q, *J* 3, C7), 69.4 (C15), 53.3 (C13), 21.6 (C16), 21.5 (C16). δ_F (376 MHz, $CDCl_3$): –62.8. LCMS (ES+): 436.6 $[M+H]^+$. HRMS (ES+): found 436.1730; $C_{23}H_{25}F_3NO_4$ $[M+H]^+$ requires 436.1730. Mp: 50 – 52 ˚C.

(*R*)-Diisopropyl 2-phenyl-6-(trifluoromethyl)indoline-3,3-dicarboxylate



10

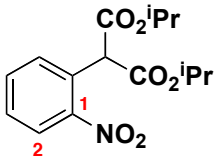
Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 87 % yield, 94 % ee.

Asymmetric: Prepared according to *general procedure 2* (109 mg imine, 0.25 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 99 % yield, 97 % ee, yellow oil.

Racemic: (±)-**10** was prepared according to *general procedure 3* (50 mg aniline, 0.12 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 84 % yield.

ν_{max} (neat): 3333, 2988, 2919, 1745, 1716, 1595. $[\alpha]_D^{18}$ + 159 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.52 (1H, d, *J* 7.9, H11), 7.37 (2H, dd, *J* 6.0, *J* 2.6, H3), 7.25 – 7.27 (3H, m, H1, H2), 7.05 (1H, dd, *J* 7.9, *J* 0.8, H10), 6.89 (1H, d, *J* 0.8, H7), 5.77 (1H, s, H5), 5.11 (1H, sept, *J* 6.3, H15), 4.51 (1H, sept, *J* 6.3, H15), 1.29 (3H, d, *J* 6.3, H16), 1.23 (3H, d, *J* 6.3, H16), 1.01 (3H, d, *J* 6.3, H16), 0.55 (3H, d, *J* 6.3, H16). δ_C (125 MHz, $CDCl_3$): 167.8 (C14), 166.6 (C14), 150.8 (C12), 139.0 (C4), 132.1 (q, *J* 32, C9), 128.5 (C11), 128.3 (C3), 127.8 (C2), 127.7 (C6), 127.6 (C1), 124.2 (q, *J* 271, C8), 115.8 (q, *J* 4, C10), 105.6 (q, *J* 4, C7), 70.1 (C15), 69.5 (C15), 68.4 (C13), 67.7 (C5), 21.5 (C16), 20.6 (C16). δ_F (376 MHz, $CDCl_3$): – 62.9. LCMS (ES+): 436.1 $[M+H]^+$. HRMS (ES+): found 436.1733; $C_{23}H_{25}F_3NO_4$ $[M+H]^+$ requires 436.1730. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 11.7, t_R (minor) = 16.2

Diisopropyl 2-(2-nitrophenyl)malonate

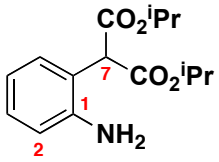


99

Diisopropyl malonate (6.8 mL, 36.0 mmol) was added to a stirred slurry of potassium carbonate (5.0 g, 36.0 mmol) in DMF at 90 ˚C. After 10 mins stirring, 1-fluoro-2-nitrobenzene (6.8 mL, 36.0 mmol) was added in one portion and allowed to stir for 5 h. The reaction mixture was diluted with dichloromethane (400 mL), partitioned with hydrochloric acid (5 % aq., 200 mL) and extracted with dichloromethane (2 x 200 mL). The organic layers were combined, over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was recrystallized from petroleum ether to afford compound **99** (7.6 g, 68 % yield) as a white crystalline solid.

ν_{max} (neat): 2983, 1730, 1529, 1349, 1100. δ_H (400 MHz, $CDCl_3$): 8.07 (1H, dt, *J* 8.4, 1.4, H2), 7.65 (1H, tt, *J* 7.7, *J* 1.2, H4), 7.55 – 7.49 (2H, m, H3, H5), 5.22 (1H, s, H7), 5.13 (2H, sept, *J* 6.3, C9), 1.30 (6H, d, *J* 6.2, H10), 1.27 (6H, d, *J* 6.3, H10). δ_C (100 MHz, $CDCl_3$): 166.8 (C8), 148.8 (C1), 133.4 (C6), 131.2 (C4), 129.1 (C5), 128.5 (C3), 125.2 (C2), 70.0 (C9), 54.9 (C7), 21.5 (C10). HRMS (ES+): found 322.1105; $C_{15}H_{19}NO_6Na$ $[M+Na]^+$ requires 332.1105. Mp: 58 – 60 ˚C.

Diisopropyl 2-(2-aminophenyl)malonate

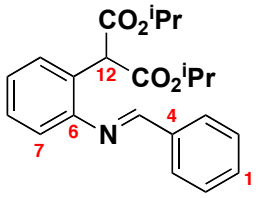


67

Palladium on carbon (100 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of diisopropyl 2-(2-nitrophenyl)malonate **99** (1.00 g, 3.23 mmol) in ethanol (12 mL). The solution was degassed three times with argon using a pump-flood procedure and placed under hydrogen for 14 h. The mixture was filtered through Celite™, eluted with methanol (300 mL) and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography (petroleum ether : diethyl ether, 6 : 1) to afford compound **67** (0.77 mg, 85 % yield) as a white solid.

ν_{max} (neat): 3371 (br), 2983, 1727, 1633, 1498, 1459, 1101, 833. δ_H (200 MHz, $CDCl_3$): 7.21 – 7.07 (2H, m, H3, H5), 6.80 (1H, dd, *J* 7.5, *J* 1.2, H4), 6.73 (1H, d, *J* 7.7, H2), 5.10 (2H, sept, *J* 6.3, H9), 4.57 (1H, s, H7), 4.12 (2H, br, NH), 1.26 (12H, ap t, *J* 6.3, H10). δ_C (100 MHz, $CDCl_3$): 168.3 (C8), 145.6 (C1), 131.3 (C5), 129.2 (C3), 119.5 (C6), 118.9 (C4), 117.5 (C2), 69.5 (C9), 56.1 (C7), 21.6 (10). HRMS (ES+): found 302.1363; $C_{15}H_{21}NO_4Na$ $[M+Na]^+$ requires 302.1363.

(*E*)-Diisopropyl 2-(2-(benzylideneamino)phenyl)malonate

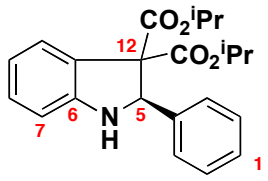


100

Benzaldehyde (1.20 mL, 11.83 mmol) was added to a stirred slurry of diisopropyl 2-(2-aminophenyl)malonate **67** (2.31 g, 8.28 mmol) and magnesium sulfate (4.97 g, 41.42 mmol) in toluene (20 mL). The reaction was stirred for 16 h at RT, the solids were removed by filtration, washed with dichloromethane (200 mL) and concentrated *in vacuo*. The resulting residue was recrystallized from petroleum ether to afford compound **100** (2.13 g, 70 %) as a white crystalline solid.

ν_{max} (neat): 2982, 1729, 1630, 1102, 766. δ_H (400 MHz, $CDCl_3$): 8.42 (1H, s, H5), 7.95 – 7.90 (2H, m, H3), 7.53 – 7.43 (4H, m, H9, H2, H1), 7.37 (1H, dt, *J* 7.6, 1.4, ArH), 7.27 (1H, dt, *J* 7.6, 1.2, ArH), 7.08 (1H, dd, *J* 7.8, 1.1, H7), 5.37 (1H, s, H12), 5.08 (2H, sept, *J* 6.3, H14), 1.25 (6H, d, *J* 6.3, H15), 1.19 (6H, d, *J* 6.3, H15). δ_C (100 MHz, $CDCl_3$): 168.2 (C13), 160.3 (C5), 150.0 (C6), 136.2 (C4), 131.5 (C10), 129.0 (C1), 129.0 (C3), 128.8 (C2/C8), 128.7 (C2/C8), 128.3 (C11), 126.2 (C9), 117.5 (C7), 69.0 (C14), 53.5 (C12), 21.6 (C15), 21.6 (C15). HRMS (ES+): found 390.1672; $C_{22}H_{25}NO_4Na$ $[M+Na]^+$ requires 390.1676. Mp: 55 – 57 ˚C.

(*R*)-Diisopropyl 2-phenylindoline-3,3-dicarboxylate



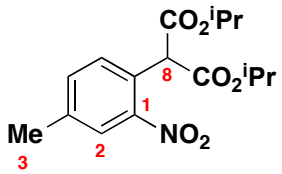
101

Asymmetric: Prepared according to *general procedure 2* (50 mg imine, 0.14 mmol), 0 ˚C, chloroform/toluene (1:1, v/v), reaction time: 36 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 70 % yield, 93 % ee.

Racemic: Cesium carbonate (126 mg, 0.39 mmol) was added to a stirred solution of recrystallized (*E*)-diisopropyl 2-(2-(benzylideneamino)phenyl)malonate **100** (109 mg, 0.30 mmol) in toluene (1.0 mL) and dichloromethane (0.5 mL). After stirring overnight the reaction was diluted with dichloromethane (10 mL), washed with ammonium chloride (sat. aq., 3 x 10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 10 : 1) to afford (±)-**101** (105 mg, 96 %) as a crystalline solid.

ν_{max} (neat): 3368, 2981, 1725, 1607, 1486, 1271, 1105, 747. $[\alpha]_D^{23}$ + 134 (*c* = 1.20, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.47 (1H, d, *J* 7.6, ArH), 7.44 – 7.38 (2H, m, ArH), 7.29 – 7.24 (3H, m, ArH), 7.20 (1H, dt, *J* 7.6, *J* 1.2, ArH), 6.84 (1H, dt, *J* 7.6, *J* 0.9, ArH), 6.72 (1H, d, *J* 7.9, H7), 5.73 (1H, d, *J* 1.6, H5), 5.12 (1H, sept, *J* 6.3, H14), 4.53 (1H, sept, *J* 6.3, H14), 4.15 (1H, br, NH), 1.31 (3H, d, *J* 6.3, H15), 1.26 (3H, d, *J* 6.3, H15), 1.03 (3H, d, *J* 6.3, H15), 0.57 (3H, d, *J* 6.3, H15). δ_C (100 MHz, $CDCl_3$): 168.5 (C13), 167.2 (C13), 150.7 (C6), 139.8 (C4), 129.8, 128.3, 128.2, 127.9, 127.2, 124.2 (C11), 119.1 (C9), 109.5 (C7), 69.6 (C14), 69.1 (C14), 68.7 (C12), 67.6 (C5), 21.6 (C15), 21.4 (C15), 20.6 (C15). HRMS (ES+): found 390.1676; $C_{22}H_{25}NO_4Na$ $[M+Na]^+$ requires 390.1676. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 18.3, t_R (minor) = 22.9.

Diisopropyl 2-(4-methyl-2-nitrophenyl)malonate

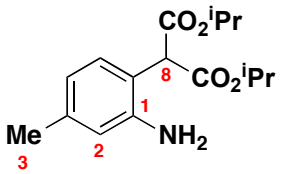


102

Diisopropyl malonate (1.22 mL, 6.45 mmol) was added to a stirred slurry of potassium carbonate (0.89 g, 6.45 mmol) in DMF at 90 ˚C. After 10 mins stirring, 4-fluoro-3-nitrotoluene (1.00 g, 6.45 mmol) was added in one portion and allowed to stir for 24 h. The reaction mixture was diluted with dichloromethane (100 mL), washed with hydrochloric acid (5 % aq., 50 mL) and extracted with dichloromethane (2 x 100 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 25 : 1) to afford compound **102** (1.01 g, 49 % yield) as a pale solid.

ν_{max} (neat): 2984, 2938, 1732, 1536, 1467, 1354, 1103, 972, 905. δ_H (400 MHz, $CDCl_3$): 7.84 (1H, s, H2), 7.43 (1H, dd, *J* 8.1, *J* 1.3, H5), 7.36 (1H, d, *J* 8.1, H6), 5.14 (1H, s, H8), 5.10 (2H, sept, *J* 6.3, H10), 2.42 (3H, s, H3), 1.26 (6H, d, *J* 6.3, H11), 1.24 (6H, d, *J* 6.3, H11). δ_C (100 MHz, $CDCl_3$): 167.0 (C9), 148.6 (C1), 139.7 (C4), 134.2 (C5), 130.9 (C6), 125.5 (C7, C2), 69.9 (C10), 54.6 (C8), 21.6 (C11), 20.8 (C3). HRMS (ES+): found 346.1264; $C_{16}H_{21}NO_6Na$ $[M+Na]^+$ requires 346.1261.

Diisopropyl 2-(2-amino-4-methylphenyl)malonate

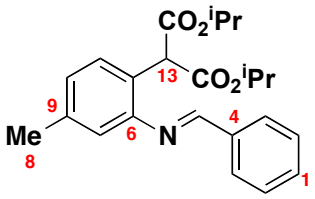


103

Palladium on carbon (300 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of diisopropyl 2-(4-methyl-2-nitrophenyl)malonate **103** (3.06 g, 9.47 mmol) in ethanol (30 mL). The solution was degassed three times with argon using a pump-flood procedure and placed under hydrogen for 14 h. The mixture was filtered through Celite™, eluted with methanol (300 mL) and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **103** (2.14 g, 77 % yield) as a white solid.

ν_{max} (neat): 3372, 2982, 1726, 1633, 1529, 1165, 1101. δ_H (400 MHz, $CDCl_3$): 7.05 (1H, d, *J* 7.7, H6), 6.60 (1H, dd, *J* 7.7, *J* 0.9, H5), 6.55 (1H, s, H2), 5.10 (2H, sept, *J* 6.3, H10), 4.54 (1H, s, H8), 4.07 (2H, br, NH), 2.26 (3H, s, H3), 1.28 (6H, d, *J* 6.3, H11), 1.24 (6H, d, *J* 6.3, H11). δ_C (100 MHz, $CDCl_3$): 168.4 (C9), 145.3 (C1), 139.1 (C4), 131.1 (C6), 119.9 (C5), 118.2 (C2), 116.6 (C7), 69.4 (C10), 55.7 (C8), 21.6 (C11), 21.1 (C3). HRMS (ES+): found 294.1691; $C_{16}H_{24}NO_4$ $[M+H]^+$ requires 294.1700.

(*E*)-Diisopropyl 2-(2-(benzylideneamino)-4-methylphenyl)malonate

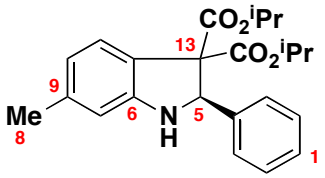


104

Benzaldehyde (940 μL, 9.20 mmol) was added to a stirring solution of aniline **103** (2.14 g, 7.67 mmol) and magnesium sulfate (4.60 g, 38.33 mmol) in toluene (25 mL). The reaction was stirred for 16 h at RT, the solids were removed by filtration, washed with dichloromethane (100 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 14 : 1) and recrystallized from petroleum ether to afford compound **104** (1.93 g, 66 %) as a yellow solid.

ν_{max} (neat): 2981, 1729, 1631, 1453, 1169, 1102, 693. δ_H (400 MHz, $CDCl_3$): 8.42 (1H, s, H5), 7.95 – 7.89 (2H, m, H3), 7.52 – 7.44 (3H, m, H2, H1), 7.35 (1H, d, *J* 7.8, H11), 7.10 (1H, dd, *J* 7.8, 0.9, H10), 6.90 (1H, d, *J* 0.9, H7), 5.33 (1H, s, H13), 5.08 (2H, sept, *J* 6.2, H15), 2.40 (3H, s, H8), 1.26 (6H, d, *J* 6.2, H16), 1.19 (6H, d, *J* 6.2, H16). δ_C (100 MHz, $CDCl_3$): 168.4 (C14), 160.0 (C5), 149.9 (C6), 138.9 (C9), 136.3 (C4), 131.4 (C1), 128.9 (C11), 128.7 (C3), 128.7 (C2), 127.0 (C10), 125.4 (C12), 118.2 (C7), 69.0 (C15), 53.2 (C13), 21.6 (C16), 21.6 (C16), 21.3 (C8). HRMS (ES+): found 382.2004; $C_{23}H_{28}NO_4$ $[M+H]^+$ requires 382.2013.

(*R*)-Diisopropyl 6-methyl-2-phenylindoline-3,3-dicarboxylate



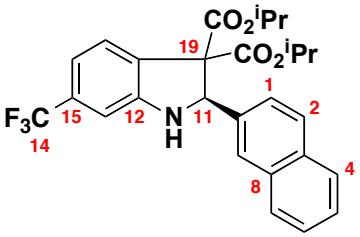
105

Asymmetric: Prepared according to *general procedure 2* (50 mg imine, 0.13 mmol), 0 ˚C, chloroform/toluene (1:1, v/v), reaction time: 72 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 99 % yield, 87 % ee.

Racemic: Silica gel (200 mg) was added to a stirred solution of (*E*)-diisopropyl 2-(2-(benzylideneamino)-4-methylphenyl)malonate **103** (75 mg, 0.20 mmol) in dichloromethane (10 mL). After stirring overnight the reaction was filtered through Celite™, washed with dichloromethane (100 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford (±)-**105** (61 mg, 81 %) as a colourless crystalline solid.

ν_{max} (neat): 3366, 2981, 1725, 1618, 1455, 1527, 1106, 910, 700. $[\alpha]_D^{23}$ + 135 (*c* = 0.95, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.45 –7.44 (2H, m, H2), 7.34 (1H, d, *J* 7.8, H11), 7.28 – 7.22 (3H, m, H1, H3), 6.66 (1H, d, *J* 7.8, H10), 6.55 (1H, s, H7), 5.72 (1H, s, H5), 5.11 (1H, sept, *J* 6.2, H15), 4.52 (1H, sept, *J* 6.2, H15), 4.09 (1H, br, NH), 2.32 (3H, s, H8), 1.30 (3H, d, *J* 6.2, H16), 1.25 (3H, d, *J* 6.2, H16), 1.02 (3H, d, *J* 6.2, H16), 0.56 (3H, d, *J* 6.2, H16). δ_C (100 MHz, $CDCl_3$): 168.6 (C14), 167.4 (C14), 150.9 (C6), 139.9 (C4/C9), 139.9 (C4/C9), 128.2 (C11), 128.0 (C3), 126.8 (C1, C2), 121.4 (C12), 120.1 (C10), 110.2 (C7), 69.5 (C15), 69.0 (C15), 68.4 (C13), 67.7 (C5), 21.6 (C8), 21.6 (C16), 21.6 (C16), 21.4 (C16), 20.6 (C16). HRMS (ES+): found 404.1824; $C_{23}H_{27}NO_4Na$ $[M+Na]^+$ requires 404.1832. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 225) t_R (major) = 11.0, t_R (minor) = 11.6.

(*R*)-Diisopropyl 2-(naphthalen-2-yl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



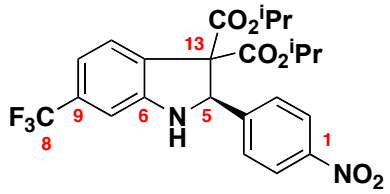
23

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 92 % yield, 92 % ee.

Racemic: (±)-**23** was prepared according to *general procedure 3* (50 mg aniline, 0.14 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 78 % yield, pale yellow solid.

ν_{max} (neat): 3354, 2984, 2937, 1745, 1719, 1616. $[\alpha]_D^{18}$ + 145 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.88 (1H, s, H9), 7.78 – 7.75 (2H, m, ArH), 7.73 (1H, d, *J* 8.6, ArH), 7.54 (1H, d, *J* 7.9, H17), 7.54 –7.50 (3H, m, ArH), 7.08 (1H, d, *J* 7.9, H16), 6.95 (1H, s, H13), 5.97 (1H, s, H11), 5.14 (1H, sept, *J* 6.3, H21), 4.39 (1H, sept, *J* 6.3, H21), 1.30 (3H, d, *J* 6.3, H22), 1.21 (3H, d, *J* 6.3, H22), 0.91 (3H, d, *J* 6.3, H22), 0.26 (3H, d, *J* 6.3, H22). δ_C (125 MHz, $CDCl_3$): 167.8 (C20), 166.7 (C20), 150.7 (C18), 136.2 (C12), 133.4, 133.0, 132.1 (q, *J* 32, C15), 128.1, 128.0, 127.8, 127.5, 127.5, 127.1, 126.2, 126.2, 125.2, 124.2 (q, *J* 271, C14), 116.0 (C13), 105.8 (C16), 70.2 (C21), 69.5 (C21), 68.5 (C19), 67.8 (C11), 21.6 (C22), 21.5 (C22), 21.2 (C22), 20.4 (C22). δ_F (376 MHz, $CDCl_3$): – 62.8. LCMS (ES+): 486.1 $[M+H]^+$. HRMS (ES+): found 508.1706; $C_{27}H_{26}F_3NO_4$ $[M+Na]^+$ requires 508.1705. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 27.5, t_R (minor) = 53.8.

(*R*)-Diisopropyl 2-(4-nitrophenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



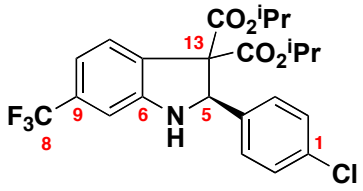
24

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 75 % yield, 98 % ee.

Racemic: (±)-**24** was prepared according to *general procedure 3* (29 mg aniline, 0.06 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 85 % yield, yellow solid.

ν_{max} (neat): 3376, 2990, 2939, 1742, 1716, 1618, 1596, 1515, 1468. $[\alpha]_D^{18}$ + 125 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 8.15 (2H, d, *J* 8.8, H3), 7.67 (2H, d, *J* 8.8, H2), 7.52 (1H, d, *J* 7.9, H11), 7.10 (1H, d, *J* 7.9, H10), 6.96 (1H, s, H7), 5.92 (1H, d, *J* 2.8, H5), 5.15 (1H, sept, *J* 6.3, H15), 4.52 (1H, sept, *J* 6.3, H15'), 4.39 (1H, d, *J* 2.8, NH), 1.33 (3H, d, *J* 6.3, H16), 1.28 (3H, d, *J* 6.3, H16), 1.00 (3H, d, *J* 6.3, H16), 0.57 (3H, d, *J* 6.3, H16). δ_C (125 MHz, $CDCl_3$): 167.5 (C14), 166.3 (C14), 150.2 (C12), 147.9 (C4), 146.1 (C1), 132.4 (q, *J* 125, C9), 129.1 (C2), 127.5 (C6), 127.2 (C11), 125.0 (q, *J* 271, C8), 123.4 (C3), 116.5 (q, *J* 4, C10), 106.3 (d, *J* 4, C7), 70.7 (C15), 70.0 (C15), 68.6 (C13), 66.8 (C5), 21.6 (C16), 21.3 (C16), 20.7 (C16), 14.0 (C16). δ_F (376 MHz, $CDCl_3$): – 62.9. LCMS (ES+): 481.5 $[M+H]^+$. HRMS (ES+): found 481.1584; $C_{23}H_{24}F_3N_2O_6$ $[M+H]^+$ requires 481.1581. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 27.2, t_R (minor) = 33.6.

(*R*)-Diisopropyl 2-(4-chlorophenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



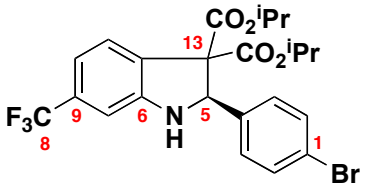
25

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 69 % yield, 93 % ee.

Racemic: (±)-**25** was prepared according to *general procedure 3* (50 mg aniline, 0.14 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 83 % yield, pale yellow oil.

ν_{max} (neat): 3332, 2984, 2941, 1743, 1717, 1620, 1599. $[\alpha]_D^{18}$ + 92 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.51 (1H, d, *J* 8.0, H11), 7.35 (2H, d, *J* 8.5, H2), 7.25 (2H, d, *J* 8.5, H3), 7.06 (1H, d, *J* 8.0, H10), 6.91 (1H, s, H7), 5.77 (1H, s, H5), 5.11 (1H, sept, *J* 6.3, H15), 4.55 (1H, sept, *J* 6.3, H15), 1.30 (3H, d, *J* 6.3, H16), 1.23 (3H, d, *J* 6.3, H16), 1.03 (3H, d, *J* 6.3, H16), 0.62 (3H, d, *J* 6.3, H16). δ_C (125 MHz, $CDCl_3$): 167.7 (C14), 166.5 (C14), 150.5 (C12), 137.4 (C1), 134.4 (C4), 132.1 (q, *J* 32, C9), 129.3 (C2/C3), 128.5 (C2/C3), 127.6 (C6), 127.4 (C11), 124.2 (q, *J* 271, C8), 116.1 (q, *J* 4, C7), 105.9 (q, *J* 4, C10), 70.3 (C15), 69.8 (C15), 68.4 (C13), 67.0 (C5), 21.6 (C16), 21.5 (C16), 21.3 (C16), 20.6 (C16). δ_F (376 MHz, $CDCl_3$): – 62.6. LCMS (ES+): 470.1/472.1 $[M+H]^+$. HRMS (ES+): found 492.1156; $C_{23}H_{23}{}^{(35)}ClF_3NO_4Na$ $[M+Na]^+$ requires 492.1160. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 10.4, t_R (minor) = 18.4.

(*R*)-Diisopropyl 2-(4-bromophenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



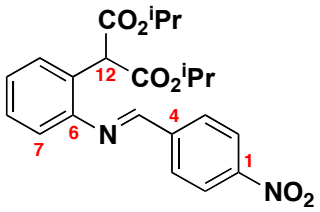
26

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 80 % yield, 93 % ee.

Racemic: (±)-**26** was prepared according to *general procedure 3* (20 mg aniline, 0.06 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 80 % yield, yellow oil.

ν_{max} (neat): 3333, 2985, 2939, 1743, 1717, 1619, 1599. $[\alpha]_D^{18}$ + 140 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.51 (1H, d, *J* 7.9, H11), 7.40 (2H, d, *J* 8.4, H2), 7.30 (2H, d, *J* 8.4, H3), 7.06 (1H, d, *J* 7.9, H10), 6.91 (1H, s, H7), 5.76 (1H, s, H5), 5.12 (1H, sept, *J* 6.3, H15), 4.55 (1H, sept, *J* 6.3, H15), 1.30 (3H, d, *J* 6.3, H16), 1.25 (3H, d, *J* 6.3, H16), 1.02 (3H, d, *J* 6.3, H16), 0.62 (3H, d, *J* 6.3, H16). δ_C (125 MHz, $CDCl_3$): 167.7 (C14), 166.5 (C14), 150.5 (C12), 137.9 (C1), 132.1 (q, *J* 32, C9), 131.4 (C3), 129.6 (C2), 127.6 (C6), 127.4 (C11), 124.1 (q, *J* 217, C8), 122.4 (C4), 116.1 (q, *J* 4, C10), 105.9 (q, *J* 4, C7), 70.3 (C15), 69.8 (C15), 68.4 (C13), 67.0 (C5), 21.5 (C16), 21.5 (C16), 21.3 (C16), 20.6 (C16). δ_F (376 MHz, $CDCl_3$): – 62.9. LCMS (ES+): 516.5 $[M(^{81}Br)+H]^+$. HRMS (ES+): found 514.0834; $C_{23}H_{24}{}^{(79)}BrF_3NO_4$ $[M+H]^+$ requires 514.0835. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 11.5, t_R (minor) = 22.3.

(*E*)-Diisopropyl 2-(2-(4-nitrobenzylideneamino)phenyl)malonate

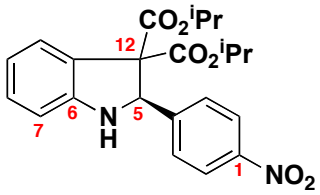


106

4-Nitrobenzaldehyde (65 mg, 0.43 mmol) was added to a stirred slurry of diisopropyl 2-(2-aminophenyl)malonate **67** (85 mg, 0.31 mmol) and magnesium sulfate (183 mg, 1.53 mmol) in toluene (2.0 mL). The reaction was stirred at RT for 16 h, the solids were removed by filtration, washed with dichloromethane (100 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 6 :1) to afford compound **106** (110 mg, 0.27 mmol, 88 %) as a yellow solid.

ν_{max} (neat): 2981, 1724, 1549, 1102, 896. δ_H (400 MHz, $CDCl_3$): 8.52 (1H, s, H5), 8.31 (2H, d, *J* 8.7, H2), 8.07 (2H, d, *J* 8.7, H3), 7.48 (1H, dd, *J* 7.6, *J* 1.4, H10), 7.38 (1H, dt, *J* 7.6, *J* 1.5, H9), 7.31 (1H, dt, *J* 7.6, *J* 1.3, H8), 7.12 (1H, dd, *J* 7.7, *J* 1.2, H7), 5.33 (1H, s, H12), 5.07 (2H, sept, *J* 6.2, H14), 1.25 (6H, d, *J* 6.2, H15), 1.19 (6H, d, *J* 6.2, H15). δ_C (100 MHz, $CDCl_3$): 168.4 (C13), 157.8 (C5), 149.8 (C1/C6), 149.2 (C1/C6), 141.9 (C4), 130.0 (C10), 129.7 (C8), 129.6 (C3), 129.5 (C11), 127.9 (C2), 124.4 (C9), 117.6 (C7), 69.6 (C14), 54.1 (C12), 22.0 (C15), 22.0 (C15). HRMS (ES+): found 413.1696; $C_{22}H_{25}N_2O_6$ $[M+H]^+$ requires 413.1707.

(*R*)-Diisopropyl 2-(4-nitrophenyl)indoline-3,3-dicarboxylate



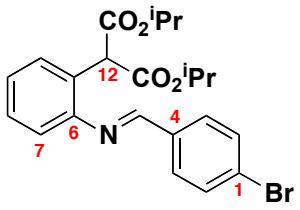
27

Asymmetric: Prepared according to *general procedure 1* (139 mg aniline, 0.50 mmol), – 15 ˚C, chloroform/toluene (5 : 1, v/v), reaction time: 36 h, chromatography (petroleum ether : diethyl ether, 4 : 1), 89 % yield, 89 % ee.

Racemic: Cesium carbonate (129 mg, 0.33 mmol) was added to a stirred solution of *(E)*-diisopropyl 2-(2-(4-nitrobenzylideneamino)phenyl)malonate **106** (110 mg, 0.27 mmol) in toluene (2 mL) and dichloromethane (1 mL). After stirring overnight the reaction was diluted with dichloromethane (10 mL), washed with ammonium chloride (sat. aq., 3 x 10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 4 : 1) to afford (±)-**27** (80 mg, 73 %) as a crystalline solid.

ν_{max} (neat): 3368, 2983, 1724, 1607, 1522, 1348, 1273, 1105, 749. $[\alpha]_D^{23}$ + 132 (*c* = 1.25, $CHCl_3$). δ_H (250 MHz, $CDCl_3$): 8.15 (2H, d, *J* 8.8, H2), 7.72 (2H, d, *J* 8.8, H3), 7.48 (1H, d, *J* 7.6, H10), 7.25 (1H, dt, *J* 7.7, *J* 1.0, H8), 6.89 (1H, dt, *J* 7.6, *J* 1.0, H9), 6.79 (1H, d, *J* 7.7, H7), 5.88 (1H, d, *J* 2.1, H5), 5.17 (1H, sept, *J* 6.3, H14), 4.55 (1H, sept, *J* 6.3, H14), 4.32 (1H, br, NH), 1.35 (3H, d, *J* 6.3, H15), 1.32 (3H, d, *J* 6.3, H15), 1.03 (3H, d, *J* 6.3, H15), 0.59 (3H, d, *J* 6.3, H15). δ_C (63 MHz, $CDCl_3$): 168.6 (C13), 167.4 (C13), 150.6 (C6), 148.1 (C4), 147.4 (C1), 130.5 (C10), 129.6 (C8), 127.2 (C2), 124.4 (C11), 123.7 (C3), 120.2 (C9), 110.4 (C7), 70.6 (C14), 70.0 (C14), 69.2 (C12), 67.1 (C5), 22.0 (C15), 22.0 (C15), 21.7 (C15), 21.1 (C15). HRMS (ES+): found 413.1695; $C_{22}H_{25}N_2O_6$ $[M+H]^+$ requires 413.1707. Chiral HPLC (Chiralpak OD, 8 % IPA, 92 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 14.0, t_R (minor) = 15.4.

(*E*)-Diisopropyl 2-(2-(4-bromobenzylideneamino)phenyl)malonate

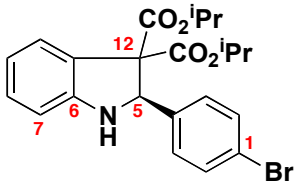


107

4-Bromobenzaldehyde (73 mg, 0.40 mmol) was added to a stirred slurry of diisopropyl 2-(2-aminophenyl)malonate **103** (79 mg, 0.28 mmol) and magnesium sulfate (170 mg, 1.42 mmol) in toluene (2 mL) the reaction was stirred at RT for 16 h, the solids were removed by filtration, washed with dichloromethane (100 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 8 : 1) to afford compound **107** (100 mg, 79 %) as a pale solid.

ν_{max} (neat): 2981, 1728, 1629, 1490, 1102, 1010, 823, 733. δ_H (400 MHz, $CDCl_3$): 8.37 (1H, s, H5), 7.78 (2H, d, *J* 8.4, H3), 7.60 (2H, d, *J* 8.4, H2), 7.46 (1H, dd, *J* 7.6, *J* 1.2, H10), 7.36 (1H, dt, *J* 7.6, *J* 1.4, H9), 7.28 (1H, dt, *J* 7.6, *J* 1.2, H8), 7.07 (1H, dd, *J* 7.7, *J* 0.9, H7), 5.34 (1H, s, H12), 5.08 (2H, sept, *J* 6.2, H14), 1.25 (6H, d, *J* 6.2, H15), 1.19 (6H, d, *J* 6.2, H15). δ_C (100 MHz, $CDCl_3$): 168.6 (C13), 159.2 (C5), 150.0 (C6), 135.5 (C4), 132.4 (C2), 130.7 (C10), 129.5 (C8), 129.4 (C3), 129.0 (C11), 127.0 (C9), 126.5 (C1), 117.8 (C7), 69.5 (C14), 54.0 (C12), 22.1 (C15), 22.0 (C15). HRMS (ES+): found 446.0947, $C_{22}H_{25}NO_4{}^{(79)}Br$; $[M+H]^+$ requires 446.0961. Mp: 140 – 142 ˚C (petroleum ether : diethyl ether).

(*R*)-Diisopropyl 2-(4-bromophenyl)indoline-3,3-dicarboxylate



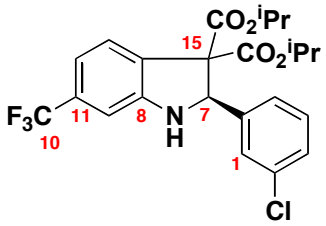
28

Asymmetric: prepared according to *general procedure 1* (279 mg aniline, 1.00 mmol), – 15 ˚C, chloroform/toluene (5 : 1, v/v), reaction time: 36 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 70 % yield, 90 % ee.

Racemic: Silica gel (200 mg) was added to a stirred solution of (*E*)-diisopropyl 2-(2-(4-bromobenzylideneamino)phenyl)malonate **107** (100 mg, 0.22 mmol) in dichloromethane (10 mL). After stirring overnight the reaction was filtered through Celite™, washed with dichloromethane (100 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 8 : 1) to afford (±)-**26** (86 mg, 86 %) as a crystalline solid.

ν_{max} (neat): 3386, 2982, 1724, 1606, 1485, 1272, 1104, 744. $[\alpha]_D^{23}$ + 180 (*c* = 1.00, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.45 (1H, dd, *J* 7.7, 0.8, H10), 7.40 (2H, d, *J* 8.5, H2), 7.34 (2H, d, *J* 8.5, H3), 7.20 (1H, dt, *J* 7.7, *J* 1.2, H8), 6.84 (1H, dt, *J* 7.7, *J* 0.9, H9), 6.73 (1H, d, *J* 7.7, H7), 5.71 (1H, s, H5), 5.13 (1H, sept, *J* 6.3, H14), 4.56 (1H, sept, *J* 6.3, H14), 4.14 (1H, br, NH), 1.31 (3H, d, *J* 6.3, H15), 1.27 (3H, d, *J* 6.2, H15), 1.04 (3H, d, *J* 6.2, H15), 0.63 (3H, d, *J* 6.2, H15). δ_C (100 MHz, $CDCl_3$): 168.4 (C13), 167.1 (C13), 150.4 (C6), 138.7 (C4), 131.3 (C2), 129.9 (C10), 129.8 (C8), 127.0 (C3), 124.1 (C1), 122.1 (C11), 119.3 (C9), 109.6 (C7), 69.8 (C14), 69.3 (C14), 68.6 (C12), 66.9 (C5), 21.6 (C15), 21.5 (C15), 21.4 (C15), 20.7 (C15). HRMS (ES+): found 446.0965; $C_{22}H_{25}NO_4{}^{(79)}Br$ $[M+H]^+$ requires 446.0961. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 16.9, t_R (minor) = 32.5.

(*R*)-Diisopropyl 2-(3-chlorophenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



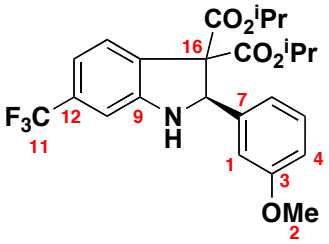
29

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 84 % yield, 86 % ee.

Racemic: (±)-**29** was prepared according to *general procedure 3* (50 mg aniline, 0.14 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 81 % yield, straw coloured oil.

ν_{max} (neat): 3338, 2983, 2921, 2851, 1743, 1717, 1621, 1595, 1574. $[\alpha]_D^{18}$ + 126 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.51 (1H, d, *J* 8.0, H13), 7.43 (1H, dd, *J* 1.8, *J* 1.8, H1), 7.30 (1H, d, *J* 7.5, H3/H5), 7.26 – 7.24 (1H, m, H3/H5), 7.23 (1H, dd, *J* 7.7, H4), 7.06 (1H, d, *J* 8.0, H12), 6.91 (1H, s, H9), 5.77 (1H, s, H7), 5.13 (1H, sept, *J* 6.3, H17), 4.56 (1H, sept, *J* 6.3, H17), 1.31 (3H, d, *J* 6.3, H18), 1.25 (3H, d, *J* 6.3, H18), 1.03 (3H, d, *J* 6.3, H18), 0.64 (3H, d, *J* 6.3, H18). δ_C (125 MHz, $CDCl_3$): 167.6 (C16), 166.5 (C16), 150.5 (C14), 140.9 (C2), 134.1 (C6), 132.2 (q, *J* 32, C11), 129.7 (C1/C3/C4/C5), 128.6 (C1/C3/C4/C5), 128.2 (C1/C3/C4/C5), 127.5 (C8), 127.4 (C13), 126.0 (C1,3,4,5), 124.1 (q, *J* 271, C10), 116.1 (q, *J* 3.8, C9), 105.9 (q, *J* 3.8, C12), 70.3 (C17), 69.8 (C17), 68.4 (C15), 67.0 (C7), 21.5 (C18), 21.5 (C18), 21.3 (C18), 20.6 (C18). δ_F (376 MHz, $CDCl_3$): – 62.6. LCMS (ES+): 470.1/472.1 $[M+H]^+$. HRMS (ES+): found 470.1347; $C_{23}H_{24}{}^{(35)}ClF_3NO_4$ $[M+H]^+$ requires 470.1340. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 11.6, t_R (minor) = 13.9.

(*R*)-Diisopropyl 2-(3-methoxyphenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



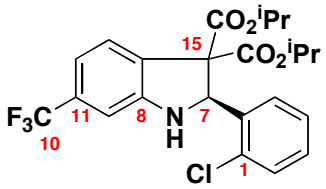
30

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reactiont ime: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 76 % yield, 92 % ee.

Racemic: (±)-**30** was prepared according to *general procedure 3* (50 mg aniline, 0.14 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 62 % yield, pale yellow oil.

ν_{max} (neat): 3373, 2983, 2939, 1722, 1597. $[\alpha]_D^{18}$ + 170 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.51 (1H, d, *J* 7.9, H14), 7.17 (1H, t, *J* 7.8, H5), 7.05 (1H, d, *J* 7.9, H13), 6.96 (1H, d, *J* 7.8, H4/H6), 6.93 (1H, t, *J* 2.4, H1), 6.90 (1H, s, H10), 6.80 (1H, dd, *J* 7.8, *J* 2.4, H4/H6), 5.76 (1H, s, H8), 5.11 (1H, sept, *J* 6.3, H18), 4.54 (1H, sept, *J* 6.3, H18), 3.74 (3H, s, H2), 1.29 (3H, d, *J* 6.3, H19), 1.24 (3H, d, *J* 6.3, H19), 1.02 (3H, d, *J* 6.3, H19), 0.60 (3H, d, *J* 6.3, H19). δ_C (125 MHz, $CDCl_3$): 167.8 (C17), 166.6 (C17), 159.5 (C3/C7), 150.7 (C15), 140.5 (C3/C7), 132.0 (q, *J* 32, C12), 129.4 (C5), 127.7 (C9), 127.5 (C14), 124.2 (q, *J* 271, C11), 120.1 (C1/C4/C6), 115.8 (q, *J* 4, C10), 114.2 (C1/C4/C6), 113.3 (C1/C4/C6), 105.7 (q, *J* 4, C13), 70.1 (C18), 69.5 (C18), 68.4 (C16), 67.7 (C8), 55.2 (C2), 21.5 (C19), 21.5 (C19), 21.3 (C19), 20.6 (C19). δ_F (376 MHz, $CDCl_3$): – 62.8. LCMS (ES+): 466.1 $[M+H]^+$. HRMS (ES+): found 488.1648; $C_{24}H_{26}F_3NO_5Na$ $[M+Na]^+$ requires 488.1655. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 17.5, t_R (minor) = 30.5.

(*S*)-Diisopropyl 2-(2-chlorophenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



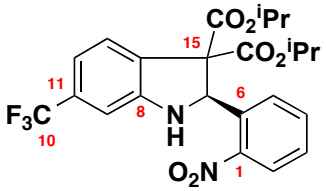
31

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 78 % yield, 91 % ee.

Racemic: (±)-**31** was prepared according to *general procedure 3* (50 mg aniline, 0.14 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 71 % yield, colourless oil.

ν_{max} (neat): 3377, 2984, 2939, 1724, 1618, 1598. $[\alpha]_D^{18}$ + 200 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.50 (1H, d, *J* 7.7, H13), 7.32 (1H, dd, *J* 8.0, *J* 1.2, H2/H5), 7.24 (1H, dd, *J* 8.5, *J* 1.7, H2/H5), 7.18 (1H, td, *J* 7.9, *J* 1.7, H3/H4), 7.11 (1H, td, *J* 7.5, *J* 1.2, H3/H4), 7.06 (1H, d, *J* 7.7, H12), 6.86 (1H, s, H9), 6.42 (1H, s, H7), 5.08 (1H, sept, *J* 6.3, H17), 4.57 (1H, sept, *J* 6.3, H17), 1.28 (3H, d, *J* 6.3, H18), 1.19 (3H, d, *J* 6.3, H18), 1.07 (3H, d, *J* 6.3, H18), 0.62 (3H, d, *J* 6.3, H18). δ_C (125 MHz, $CDCl_3$): 167.3 (C16), 166.5 (C16), 150.6 (C14), 137.7 (C8), 134.0 (C1), 132.2 (q, *J* 32, C11), 129.7, 129.5, 129.4, 128.5, 128.2, 127.3, 124.2 (q, *J* 271, C10), 115.8 (q, *J* 4, C9), 105.4 (q, *J* 4, C12), 71.3 (C17), 70.9 (C17), 68.7 (C15), 62.3 (C7), 21.5 (C18), 21.4 (C18), 21.3 (C18), 20.4 (C18). δ_F (376 MHz, $CDCl_3$): – 62.8. LCMS (ES+): 470.1 $[M+H]^+$. HRMS (ES+): found 492.1155; $C_{23}H_{23}{}^{(35)}ClF_3NO_4Na$ $[M+Na]^+$ requires 492.1160. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (minor) = 12.9, t_R (major) = 17.2.

(*R*)-diisopropyl 2-(2-nitrophenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



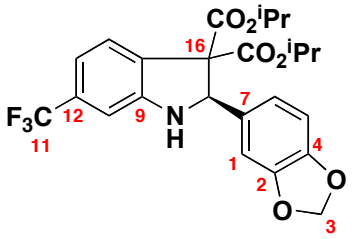
32

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 24 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 81 % yield, 76 % ee.

Racemic: (±)-**32** was prepared according to *general procedure 3* (50 mg aniline, 0.12 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 80 % yield, yellow oil.

ν_{max} (neat): 3377, 2985, 2360, 1729, 1618, 1532, 1467. $[\alpha]_D^{23}$ + 86 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.81 (1H, dd, *J* 8.0, *J* 1.3, H12), 7.53 – 7.50 (2H, m, H3, H4), 7.48 (1H, td, *J* 7.5, *J* 1.2, H2/H5), 7.42 (1H, td, *J* 8.0, *J* 1.4, H2/H5), 7.09 (1H, d, *J* 8.0, H13), 6.90 (1H, s, H9), 6.52 (1H, s, H7), 5.10 (1H, sept, *J* 6.3, H17), 4.58 (1H, sept, *J* 6.3, H17), 1.28 (3H, d, *J* 6.3, H18), 1.22 (3H, d, *J* 6.3, H18), 1.05 (3H, d, *J* 6.3, H18), 0.57 (3H, d, *J* 6.3, H18). δ_C (125 MHz, $CDCl_3$): 167.4 (C16), 166.6 (C16), 150.2 (C14), 149.4 (C1), 134.2 (C6), 132.9, 132.3 (q, *J* 31.6, C11), 129.4, 129.1, 127.9, 127.4 (C8), 124.1 (q, *J* 270, C10), 124.0, 116.2 (q, *J* 4, C12), 105.9 (q, *J* 3, C9), 70.7 (C17), 70.0 (C17), 69.0 (C15), 60.5 (C7), 21.4 (C18), 21.4 (C18), 21.0 (C18), 20.5 (C18). δ_F (470 MHz, $CDCl_3$): – 62.6. LCMS (ES–): 479.2 $[M–H]^-$. HRMS (ES+): found 503.1400; $C_{23}H_{23}F_3N_2O_6Na$ $[M+Na]^+$ requires 503.1400. Chiral HPLC (Chiralpak OD, 1 % IPA, 99 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 22.4, t_R (minor) = 51.9.

(*R*)-Diisopropyl 2-(benzo[*d*][1,3]dioxol-5-yl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



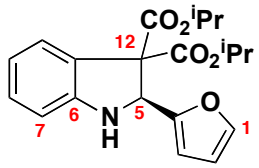
33

Asymmetric: Prepared according to *general procedure 1* (150 mg aniline, 0.43 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 10 : 1), 90 % yield, 85 % ee.

Racemic: (±)-**33** was prepared according to *general procedure 3* (50 mg aniline, 0.14 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 84 % yield, pale solid.

ν_{max} (neat): 3372, 2983, 2938, 2900, 1722, 1619, 1600. $[\alpha]_D^{18}$ + 91 (*c* = 1.00, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.50 (1H, d, *J* 7.9, H14), 7.05 (1H, d, *J* 7.9, H13), 6.89 (1H, s, H10), 6.88 (1H, dd, *J* 8.0, *J* 1.7, H6), 6.84 (1H, d, *J* 1.7, H1), 6.70 (1H, d, *J* 8.0, H5), 5.90 (2H, q, *J* 1.4, H3), 5.70 (1H, s, H8), 5.10 (1H, sept, *J* 6.3, H18), 4.63 (1H, sept, *J* 6.3, H18), 1.29 (3H, d, *J* 6.3, H19), 1.23 (3H, d, *J* 6.3, H19), 1.06 (3H, d, *J* 6.3, H19), 0.72 (3H, d, *J* 6.3, H19). δ_C (125 MHz, $CDCl_3$): 167.7 (C17), 166.6 (C17), 147.7, 147.5, 132.6, 132.1 (q, *J* 32, C12), 128.9, 127.7, 127.6, 124.2 (q, *J* 271, C11), 121.4, 116.1 (C10), 108.2, 108.0, 105.5 (C13), 101.1 (C3), 70.1 (C18), 69.5 (C18), 68.4 (C16), 67.5 (C8), 21.5 (C19), 21.5 (C19), 21.4 (C19), 20.8 (C19). δ_F (376 MHz, $CDCl_3$): – 62.8. LCMS (ES+): 480.1 $[M+H]^+$. HRMS (ES+): found 502.1443; $C_{24}H_{24}F_3NO_6Na$ $[M+Na]^+$ requires 502.1448. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (major) = 22.1, t_R (minor) = 29.9.

(*S*)-Diisopropyl 2-(furan-2-yl)indoline-3,3-dicarboxylate



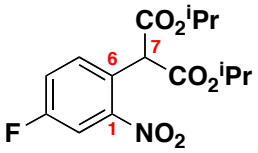
34

Asymmetric: Prepared according to *general procedure 1* (139 mg aniline, 0.50 mmol), – 15 ˚C, chloroform/toluene (5 : 1, v/v), reaction time: 36 h, chromatography (petroleum ether : diethyl ether, 6 :1), 68 % yield, 86 % ee.

Racemic: 2-Furaldehyde (34 μL, 0.41 mmol) was added to a stirred slurry of diisopropyl 2-(2-aminophenyl)malonate **8** (82 mg, 0.29 mmol) and magnesium sulfate (176 mg, 1.47 mmol) in toluene (2 mL). The reaction was stirred for 16 h at RT, the solids were removed by filtration, washed with dichloromethane (100 mL) and concentrated *in vacuo*. The residue was dissolved in dichloromethane (10 mL) and stirred with silica (approximately 200 mg). After stirring overnight the reaction was filtered through Celite™, washed with dichloromethane (100 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 4 : 1) to afford (±)-**32** (72 mg, 70 %) as a crystalline solid.

ν_{max} (neat): 3368, 2982, 1729, 1605, 1469, 1272, 1104, 746. $[\alpha]_D^{23}$ + 249 (*c* = 1.15, $CHCl_3$). δ_H (250 MHz, $CDCl_3$): 7.50 (1H, d, *J* 7.6, H1), 7.36 – 7.29 (1H, m, H10), 7.20 (1H, dt, *J* 7.5, *J* 1.2, H9), 6.87 (1H, dt, *J* 7.5, *J* 1.2, H8), 6.74 (1H, d, *J* 7.5, H7), 6.31 (2H, s, H3, H2), 5.79 (1H, d, *J* 1.8, H5), 5.12 (1H, sept, *J* 6.2, H14), 4.80 (1H, sept, *J* 6.2, H14), 4.13 (1H, br, NH), 1.32 (3H, d, *J* 6.2, H15), 1.25 (3H, d, *J* 6.2, H15), 1.16 (3H, d, *J* 6.2, H15), 0.92 (3H, d, *J* 6.2, H15). δ_C (63 MHz, $CDCl_3$): 168.4 (C13), 167.5 (C13), 153.3 (C6), 150.4 (C4), 142.6 (C1), 130.1 (C10), 127.5 (C8), 124.5 (C11), 119.9 (C9), 110.8 (C7), 110.5 (C2), 108.6 (C3), 70.2 (C14), 69.7 (C14), 68.0 (C12), 62.0 (C5), 22.0 (C15), 21.9 (C15), 21.9 (C15), 21.6 (C15). HRMS (ES+): found 358.1653; $C_{20}H_{24}NO_5$ $[M+H]^+$ requires 358.1649. Chiral HPLC (Chiralpak OD, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 254) t_R (minor) = 22.8, t_R (major) = 27.1.

Diisopropyl 2-(4-fluoro-2-nitrophenyl)malonate

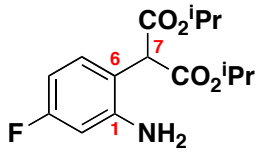


108

Diisopropyl malonate (1.30 mL, 6.92 mmol) was added to a stirred slurry of potassium carbonate (955 mg, 6.92 mmol) in DMF (12 mL) at 90 ˚C. After 10 mins, 1,4-difluoro-2-nitrobenzene (1.00 g, 6.29 mmol) was added in one portion and allowed to stir for 5 h at 90 ˚C. The reaction mixture was diluted with dichloromethane (150 mL), washed with hydrochloric acid (5 % aq., 150 mL) and extracted with dichloromethane (2 x 150 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromotography (petroleum ether : diethyl ether, 12 : 1) and recrystallized from petroleum ether to afford compound **108** (918 mg, 45 % yield) as a white crystalline solid.

ν_{max} (neat): 2985, 2939, 1733, 1541, 1356. δ_H (500 MHz, $CDCl_3$): 7.83 (1H, dd, *J* 8.2, *J* 2.8, H2), 7.60 (1H, dd, *J* 8.8, *J* 5.4, H4), 7.42 (1H, dt, *J* 8.4, *J* 2.5, H5), 5.23 (1H, s, H7), 5.17 (2H, sept, *J* 6.2, H9), 1.34 (6H, d, *J* 6.2, H10), 1.31 (6H, d, *J* 6.2, H10). δ_C (125 MHz, $CDCl_3$): 167.0 (C8), 162.1 (d, *J* 253, C3), 149.9 (d, *J* 8, C1), 133.4 (d, *J* 8, C5), 125.0 (d, *J* 4, C6), 121.1 (d, *J* 21, C4), 113.2 (d, *J* 26, C2), 70.7 (C9), 54.6 (C7), 22.0 (C10). δ_F (376 MHz, $CDCl_3$): – 110.0. HRMS (ES+): found 350.1009; $C_{15}H_{18}FNO_6Na$ $[M+Na]^+$ requires 350.1010.

Diisopropyl 2-(2-amino-4-fluorophenyl)malonate

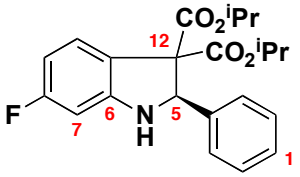


109

Palladium on carbon (30 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of diisopropyl 2-(4-fluoro-2-nitrophenyl)malonate **108** (300 mg, 0.92 mmol) in ethanol (8 mL). The solution was degassed three times using a pump-flood procedure and placed under hydrogen for 6 h. The reaction was filtered through Celite™, washed with methanol (30 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **108** (260 mg, 94 % yield) as a white solid.

ν_{max} (neat): 3380 (br), 2984 (br), 1726, 1509. δ_H (400 MHz, $CDCl_3$): 7.14 – 7.06 (1H, m, H5), 6.50 – 6.37 (2H, m, H2, H4), 5.15 – 5.03 (2H, m, H9), 4.51 (1H, s, H7), 4.25 (2H, br, NH), 1.28 (3H, d, *J* 6.2, H10), 1.28 (3H, d, *J* 6.2, H10), 1.24 (3H, d, *J* 6.2, H10), 1.22 (3H, d, *J* 6.2, H10). δ_C (100 MHz, $CDCl_3$): 168.1 (C8), 163.4 (d, *J* 245, C3), 147.4 (d, *J* 11, C1), 132.7 (d, *J* 10, C5), 115.1 (d, *J* 2, C6), 105.5 (d, *J* 22, C4), 104.0 (d, *J* 24, C2), 69.6 (C9), 55.5 (C7), 21.5 (C10). δ_F (376 MHz, $CDCl_3$): – 114.1. HRMS (ES+): found 320.1270; $C_{15}H_{20}FNNaO_4$ $[M+Na]^+$ requires 320.1269.

(*R*)-Diisopropyl 6-fluoro-2-phenylindoline-3, 3-dicarboxylate



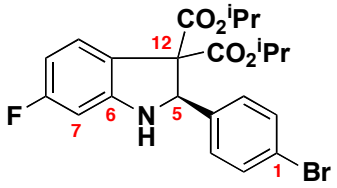
35

Asymmetric: Prepared according to *general procedure 1* (100 mg aniline, 0.34 mmol), – 15 ˚C, chloroform : toluene (1 : 1, v/v), reaction time: 20 h, chromatography (petroleum ether : ethyl acetate, 30 : 1), 60 % yield, 91 % ee.

Racemic: (±)-**35** was prepared according to *general procedure 3* (50 mg aniline, 0.17 mmol), – 15 ˚C, chloroform : toluene (1 : 1, v/v), reaction time: 20 h, chromatography (petroleum ether : ethyl acetate, 30 : 1), 53 % yield, pale yellow oil.

ν_{max} (neat): 3371 (br), 2983, 1726 (s), 1618, 1496, 1263, 1104. $[\alpha]_D^{25}$ + 186 (*c* = 1.00, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.43 – 7.40 (3H, m, Ar-H), 7.30 – 7.22 (3H, m, Ar-H), 6.50 (1H, dt, *J* 9.6, 2.2, H9), 6.39 (1H, dd, *J* 9.6, 2.2, H7), 5.75 (1H, s, H5), 5.12 (1H, sept, *J* 6.2, H14), 4.52 (1H, sept, *J* 6.2, H14), 1.30 (3H, d, *J* 6.2, H15), 1.25 (3H, d, *J* 6.2, H15), 1.02 (3H, d, *J* 6.2, H15), 0.56 (3H, d, *J* 6.2, H15). δ_C (100 MHz, $CDCl_3$): 168.3 (C13), 167.1 (C13), 164.6 (d, *J* 244, C8), 152.1 (d, *J* 12, C6), 139.3 (C4), 128.4 (C1), 128.3 (C2), 128.1 (d, *J* 11, C10), 127.9 (C3), 119.7 (C11), 105.6 (d, *J* 23, C9), 96.8 (d, *J* 26, C7), 69.8 (C14), 69.3 (C14), 68.1 (C5), 67.9 (C12), 21.5 (C15), 21.3 (C15), 20.6 (C15). δ_F (376 MHz, $CDCl_3$): – 113.2. HRMS (ES+): found 408.1576; $C_{22}H_{24}FNO_4Na$ $[M+Na]^+$ requires 408.1582. Chiral HPLC (Chiralpak OD, 4 % IPA, 96 % hexane, 1.0 mL.min^{-1}, λ = 272) t_R (major) = 9.7, t_R (minor) = 11.5.

(*R*)-Diisopropyl 2-(4-bromophenyl)-6-fluoroindoline-3, 3-dicarboxylate



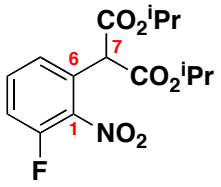
36

Asymmetric: Prepared according to *general procedure 1* (100 mg aniline, 0.34 mmol), – 15 ˚C, chloroform : toluene (1 : 1, v/v), reaction time: 20 h, chromatography (petroleum ether : ethyl acetate, 20 : 1), 67 % yield, 91 % ee.

Racemic: Aniline **109** (36 mg, 0.12 mmol), magnesium sulfate (73 mg, 0.61 mmol) and 4-bromobenzaldehyde (31 mg, 0.17 mmol) were stirred in toluene (2 mL) overnight. The mixture was filtered, concentrated *in vacuo* and the resulting residue was stirred with silica gel (50 mg) in dichloromethane (2 mL). After stirring overnight the reaction was filtered through Celite™, washed with dichloromethane (20 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 20 : 1) to afford compound (±)-**36** (27 mg, 58 %) as a crystalline solid.

ν_{max} (neat) 3366 (br), 2982, 1724 (s), 1496, 1182. $[\alpha]_D^{25}$ + 133 (*c* = 1.00, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.41 (2H, d, *J* 8.3, H2), 7.36 (1H, dd, *J* 8.3, 5.6, H10), 7.31 (2H, d, *J* 8.3, H3), 6.51 (1H, t, *J* 9.5, H9), 6.41 (1H, dd, *J* 9.5, 2.2, H7), 5.74 (1H, s, H5), 5.13 (1H, sept, *J* 6.2, H14), 4.56 (1H, sept, *J* 6.2, H14), 1.30 (3H, d, *J* 6.2, H15), 1.26 (3H, d, *J* 6.2, H15), 1.04 (3H, d, *J* 6.2, H15), 0.63 (3H, d, *J* 6.2, H15). δ_C (125 MHz, $CDCl_3$): 168.6 (C13), 167.5 (C13), 165.1 (d, *J* 245, C8), 152.2 (d, *J* 12, C6), 138.7 (C4), 131.8 (C2), 130.1 (C3), 128.4 (d, *J* 11, C10), 122.8 (C1), 120.0 (C11), 106.3 (d, *J* 23, C9), 97.5 (d, *J* 27, C7), 70.4 (C14), 70.1 (C14), 68.3 (C12), 67.9 (C5), 22.0 (C15), 22.0 (C15), 21.8 (C15), 21.1 (C15). δ_F (376 MHz, $CDCl_3$): – 112.0. HRMS (ES+): found 488.0659; $C_{22}H_{23}{}^{(81)}BrFNNaO_4$ $[M+Na]^+$ requires 488.0669. Chiral HPLC (Chiralpak OD, 4 % IPA, 96 % hexane, 1.0 mL.min^{-1}, λ = 272) t_R (major) = 9.6, t_R (minor) = 16.8.

Diisopropyl 2-(3-fluoro-2-nitrophenyl)malonate

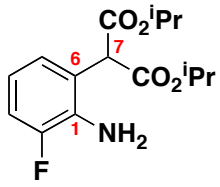


110

Diisopropyl malonate (1.00 mL, 5.40 mmol) was added to a stirred slurry of potassium carbonate (745 mg, 5.40 mmol) in DMF (12 mL) at 90 ˚C. After 10 mins, 1,3-difluoro-2-nitrobenzene (780 μL, 4.91 mmol) was added in one portion and the reaction was left to stir for 5 h. The reaction mixture was diluted with dichloromethane (80 mL), washed with hydrochloric acid (5 % aq., 80 mL) and extracted with dichloromethane (2 x 80 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromotography (petroleum ether : diethyl ether, 15 : 1) to afford compound **110** (1.08 g, 67 % yield) as a white crystalline solid.

ν_{max} (neat): 2985, 2939, 1734, 1617. δ_H (250 MHz, $CDCl_3$): 7.67 – 7.53 (1H, m, H3), 7.48 (1H, d, *J* 8.2, H5), 7.32 (1H, dd, *J* 8.3, 8.1, H4), 5.15 (2H, sept, *J* 6.2, H9), 4.80 (1H, s, H7), 1.35 (6H, d, *J* 6.2, H10), 1.31 (6H, d, *J* 6.2, H10). δ_C (100 MHz, $CDCl_3$): 166.5 (C8), 155.6 (d, *J* 259, C2), 132.7 (d, *J* 9, C1), 129.1 (C6), 126.6 (d, *J* 4, C3), 117.7 (C4/C5), 117.4 (C4/C5), 70.9 (C9), 53.7 (C7), 21.9 (C10). δ_F (376 MHz, $CDCl_3$): – 122.0. HRMS (ES+) found 350.1009; $C_{15}H_{18}FNO_6Na$ $[M+Na]^+$ requires 350.1010.

Diisopropyl 2-(2-amino-3-fluorophenyl)malonate

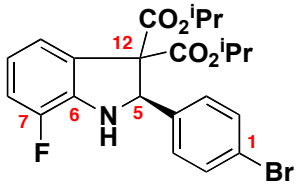


111

Palladium on carbon (20 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of diisopropyl 2-(3-fluoro-2-nitrophenyl)malonate **110** (200 mg, 0.61 mmol) in methanol (6 mL). The solution was degassed three times using a pump-flood procedure and placed under hydrogen for 6 h. The reaction was filtered through Celite™, washed with methanol (30 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **111** (168 mg, 93 % yield) as a white solid.

ν_{max} (neat) 3453, 3371, 2983, 2938, 1727, 1635, 1606. δ_H (400 MHz, $CDCl_3$): 7.03 – 6.85 (2H, m, H3, H5), 6.75 – 6.64 (1H, m, H4), 5.17 – 5.04 (2H, m, H9), 4.59 (1H, s, H7), 3.82 (2H, br, NH), 1.29 (3H, d, *J* 6.2, H10), 1.28 (3H, d, *J* 6.2, H10), 1.25 (3H, d, *J* 6.2, H10), 1.24 (3H, d, *J* 6.2, H10). δ_C (125 MHz, $CDCl_3$): 168.3 (C8), 153.1 (d, *J* 238, C2), 134.7 (d, *J* 14, C1), 126.9 (d, *J* 3, C5), 122.1 (C6), 118.6 (d, *J* 8, C4), 115.3 (d, *J* 19, C3), 70.2 (C9), 56.4 (C7), 22.0 (C10). δ_F (376 MHz, $CDCl_3$): – 134.0. HRMS (ES+): found 320.1270; $C_{15}H_{20}FNNaO_4$ $[M+Na]^+$ requires 320.1269.

(*R*)-Diisopropyl 2-(4-bromophenyl)-7-fluoroindoline-3, 3-dicarboxylate



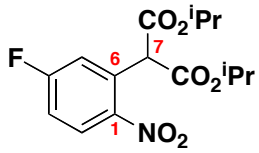
37

Asymmetric: Prepared according to *general procedure 1* (100 mg aniline, 0.34 mmol), – 15 ˚C, chloroform/toluene (1 : 1, v/v), reaction time: 20 h, chromatography (petroleum ether : ethyl acetate, 30 : 1), 65 % yield, 91 % ee.

Racemic: Aniline **111** (33 mg, 0.11 mmol), magnesium sulfate (67 mg, 0.56 mmol) and 4-bromobenzaldehyde (29 mg, 0.16 mmol) were stirred in toluene (2 mL) overnight. The mixture was filtered, concentrated *in vacuo* and the resulting residue was stirred with silica gel (50 mg) in dichloromethane (2 mL). After stirring overnight the reaction was filtered through Celite™, washed with dichloromethane (20 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 20 : 1) to afford (±)-**37** (27 mg, 54 %) as a crystalline solid.

ν_{max} (neat): 3311 (br), 2988, 1729 (s), 1690, 1355, 1187. $[\alpha]_D^{25}$ + 84 (*c* = 1.00, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.42 (2H, d, *J* 8.5, H2), 7.37 (2H, d, *J* 8.5, H3), 7.23 (1H, dd, *J* 7.6, 0.7, H8), 6.99 (1H, t, *J* 9.2, H10), 6.78 (1H, ddd, *J* 8.1, 7.8, 4.7, H9), 5.80 (1H, s, H5), 5.14 (1H, sept, *J* 6.2, H14), 4.55 (1H, sept, *J* 6.2, H14), 1.31 (3H, d, *J* 6.2, H15), 1.27 (3H, d, *J* 6.2, H15), 1.04 (3H, d, *J* 6.2, H15), 0.61 (3H, d, *J* 6.2, H15). δ_C (63 MHz, $CDCl_3$): 168.4 (C13), 167.2 (C13), 149.0 (d, *J* 241, C7), 138.5 (d, *J* 15, C6), 138.4 (C4), 131.8 (C2), 130.2 (C3), 127.8 (d, *J* 5, C11), 122.8 (C1), 122.7 (d, *J* 3, H10), 120.0 (d, *J* 6, C9), 116.5 (d, *J* 16, C8), 70.5 (C14), 70.1 (C14), 69.4 (d, *J* 2, C12), 68.1 (C5), 22.0 (C15), 22.0 (C15), 21.8 (C15), 21.1 (C15). δ_F (376 MHz, $CDCl_3$): – 135.0. HRMS (ES+): found 488.0667; $C_{22}H_{23}{}^{(81)}BrFNNaO_4$ $[M+Na]^+$ requires 488.0669. Chiral HPLC (Chiralpak OD, 3 % IPA, 97 % hexane, 1.0 mL.min^{-1}, λ = 272) t_R (major) = 7.1, t_R (minor) = 7.6.

Diisopropyl 2-(5-fluoro-2-nitrophenyl)malonate

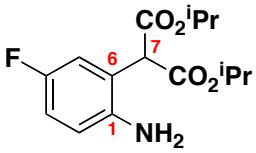


112

Diisopropyl malonate (910 μL, 4.79 mmol) was added to a stirred slurry of potassium carbonate (660 mg, 4.79 mmol) in DMF (9 mL) at 90 ˚C. After 10 mins, 2,4-difluoronitrobenzene (500 μL, 4.56 mmol) was added in one portion and the reaction left to stir for 5 h at 90 ˚C. The reaction mixture was diluted with dichloromethane (40 mL), washed with hydrochloric acid (5 % aq., 30 mL) and extracted with dichloromethane (2 x 40 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 50 : 1) to afford compound **112** (871 mg, 58 % yield) as a white solid.

ν_{max} (neat): 2985, 2939, 1748, 1732, 1623, 1590, 1532. δ_H (400 MHz, $CDCl_3$): 8.14 (1H, dd, *J* 9.0, 5.2, H2), 7.26 (1H, dd, *J* 9.0, 2.5, H3), 7.22 – 7.16 (1H, m, H5), 5.27 (1H, s, H7), 5.13 (2H, sept, *J* 6.2, H9), 1.32 – 1.24 (12H, m, H10). δ_C (63 MHz, $CDCl_3$): 166.7 (C8), 165.1 (d, *J* 258, C4), 145.4 (C1), 132.3 (d, *J* 10, C6), 128.4 (d, *J* 10, C2), 118.9 (d, *J* 25, C5), 116.5 (d, *J* 23, C3), 70.8 (C9), 55.3 (C7), 22.0 (C10). δ_F (376 MHz, $CDCl_3$): – 102.0. HRMS (ES+): found 350.1003; $C_{15}H_{18}FNO_6Na$ $[M+Na]^+$ requires 350.1010.

Diisopropyl 2-(2-amino-5-fluorophenyl)malonate

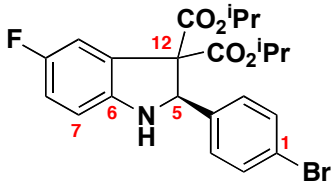


113

Palladium on carbon (30 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of diisopropyl 2-(5-fluoro-2-nitrophenyl)malonate **112** (300 mg, 0.92 mmol) in methanol (5 mL). The solution was degassed three times using a pump-flood procedure and placed under hydrogen for 5 h. The reaction was filtered through Celite™, washed with methanol (20 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 8 : 1) to afford compound **113** (188 mg, 69 % yield) as a white solid.

ν_{max} (neat): 3426, 3369, 2984, 2938, 1727 (s), 1635, 1505, 1239, 1101, 818. δ_H (250 MHz, $CDCl_3$): 7.04 (1H, dd, *J* 9.5, 2.9, H3), 6.90 (1H, dt, *J* 8.5, 2.9, H5), 6.71 (1H, dd, *J* 8.7, 5.0, H2), 5.15 (2H, sept, *J* 6.2, H9), 4.61 (1H, s, H7), 3.75 (2H, br, NH), 1.31 (12H, ap t, *J* 6.2, H10). δ_C (63 MHz, $CDCl_3$): 168.1 (C8), 156.7 (d, *J* 237, C4), 141.9 (C1), 121.4 (d, *J* 7, C6), 119.0 (d, *J* 7, C2), 117.8 (d, *J* 24, C5), 116.1 (d, *J* 22, C3), 70.2 (C9), 55.7 (C7), 22.0 (C10). δ_F (376 MHz, $CDCl_3$): – 126.3. HRMS (ES+): found 320.1265; $C_{15}H_{20}FNNaO_4$ $[M+Na]^+$ requires 320.1269.

(*R*)-Diisopropyl 2-(4-bromophenyl)-5-fluoroindoline-3, 3-dicarboxylate



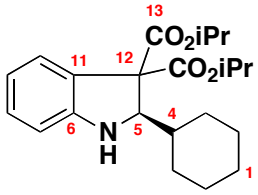
38

Asymmetric: Prepared according to *general procedure 1* (100 mg aniline, 0.34 mmol), – 15 ˚C, chloroform : toluene (1 : 1, v/v), reaction time: 20 h, chromatography (petroleum ether : ethyl acetate, 30 : 1), 72 % yield, 90 % ee.

Racemic: Aniline **113** (50 mg, 0.17 mmol), magnesium sulfate (73 mg, 0.61 mmol) and 4-bromobenzaldehyde (31 mg, 0.17 mmol) were stirred in toluene (2 mL) overnight. The mixture was filtered, concentrated *in vacuo* and the resulting residue was stirred with tetrabutylammonium chloride (3 mg, 0.02 mmol) in toluene : chloroform (1 : 1, 0.6 mL) for 0.5 h. To this stirred solution potassium carbonate (3M aq., 0.3 mL) was added, after stirring overnight the reaction was diluted with dichloromethane (5 mL), washed with ammonium chloride (sat. aq., 5 mL) and extracted with dichloromethane (2 x 10 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 15 : 1) to afford compound (±)-**38** (35 mg, 44 %) as a crystalline solid.

ν_{max} (neat): 3365 (br), 2983, 1725 (s), 1488, 1375, 1252, 1204, 1104. $[\alpha]_D^{25}$ + 118 (*c* = 1.00, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.41 (2H, d, *J* 8.3, H2), 7.34 (2H, d, *J* 8.3, H3), 7.17 (1H, dd, *J* 8.6, 2.5, H8), 6.91 (1H, dt, *J* 8.7, 2.5, H10), 6.48 (1H, dd, *J* 8.6, 4.3, H7), 5.71 (1H, s, H5), 5.14 (1H, sept, *J* 6.2, H14), 4.55 (1H, sept, *J* 6.2, H14), 4.02 (1H, br, NH), 1.31 (3H, d, *J* 6.2, H15), 1.29 (3H, d, *J* 6.2, H15), 1.04 (3H, d, *J* 6.2, H15), 0.63 (3H, d, *J* 6.2, H15). δ_C (125 MHz, $CDCl_3$): 167.9 (C13), 166.7 (C13), 157.0 (d, *J* 236, C9), 146.6 (C6), 138.3 (C4), 131.3 (C2), 129.7 (C3), 125.5 (C11), 122.2 (C1), 116.5 (d, *J* 24, C8), 114.1 (d, *J* 25, C10), 110.0 (C7), 70.1 (C14), 69.6 (C14), 68.6 (C12), 67.5 (C5), 21.6 (C15), 21.5 (C15), 21.3 (C15), 20.6 (C15). δ_F (376 MHz, $CDCl_3$): – 125.0. HRMS (ES+): found 466.0848; $C_{22}H_{24}BrFNO_4$ $[M+H]^+$ requires 466.0850. Chiral HPLC (Chiralpak OD, 4 % IPA, 96 % hexane, 1.0 mL.min^{-1}, λ = 272) t_R (major) = 10.0, t_R (minor) = 20.0.

(*R*)-diisopropyl 2-cyclohexylindoline-3,3-dicarboxylate



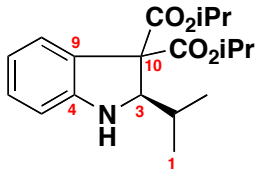
39

Asymmetric: Diisopropyl 2-(2-aminophenyl)malonate **67** (50 mg, 0.18 mmol), cyclohexanecarboxaldehyde (33 μL, 0.27 mmol) and magnesium sulfate (108 mg, 0.89 mmol) were stirred in toluene (1 mL) at RT for 7 h. The mixture was filtered to remove solids and concentrated *in vacuo*. The resulting oil was dissolved in toluene (0.7 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (8 mg, 0.02 mmol) was added and the mixture was stirred for 0.5 h at – 50 ˚C. $CsOH{\cdot}H_2O$ (301 mg, 1.79 mmol) was added and the reaction mixture was stirred at – 50 ˚C for 12 h before being diluted with ammonium chloride (sat. aq., 5 mL), extracted with dichloromethane (3 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether : diethyl ether, 10 : 1) to afford compound **39** (94 % yield, 90 % ee) as a pale yellow oil.

Racemic: (±)-**39** was prepared according to *general procedure 3* (100 mg aniline, 0.36 mmol), chromatography (petroleum ether : diethyl ether, 10 : 1), 13 % yield.

ν_{max} (neat): 3375, 3049, 2981, 2927, 2852, 1724, 1605. $[\alpha]_D^{29}$ + 157 (*c* = 1.00, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.36 (1H, d, *J* 7.6, H10), 7.11 (1H, td, *J* 7.7, *J* 0.8, H8), 6.75 (1H, t, *J* 7.6, H9), 6.65 (1H, d, *J* 7.7, H7), 5.13 (1H, sept, *J* 6.3, H14), 5.08 (1H, sept, *J* 6.3, H14), 3.36 (1H, d, *J* 5.9, H5), 1.86 (1H, d, *J* 9.7, H1), 1.78 (1H, d, *J* 10.1, H1), 1.64 (5H, m, H2, H3, H4), 1.23 (12H, m, H15), 1.08 (4H, m, H2, H3). δ_C (63 MHz, $CDCl_3$): 169.1 (C13), 168.7 (C13), 150.9 (C6), 129.9 (C10), 126.7 (C11), 126.4 (C8), 119.3 (C9), 110.1 (C7), 69.8 (C5/C14), 69.8 (C5/C14), 69.6 (C5/C14), 66.5 (C12), 40.7 (C4), 31.7 (C3), 29.0 (C2), 26.6 (C1), 22.1 (C15), 22.0 (C15). LCMS (ES–): 372.2 $[M–H]^-$. HRMS (ES–): found 372.2170; $C_{22}H_{30}NO_4$ $[M–H]^-$ requires 372.2180. Chiral HPLC (Chiralpak OD, 1.5 % IPA, 98.5% hexane, 1.0 mL.min^{-1}, λ = 225) t_R (major) = 9.5, t_R (minor) = 10.8.

(*R*)-Diisopropyl 2-isopropylindoline-3,3-dicarboxylate



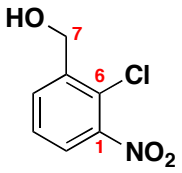
40

Asymmetric: Diisopropyl 2-(2-aminophenyl)malonate **67** (50 mg, 0.18 mmol), isobutyraldehyde (129 mg, 1.79 mmol) and magnesium sulfate (108 mg, 0.89 mmol) were stirred in toluene (1 mL) at RT for 7 h. The mixture was filtered to remove solids and concentrated *in vacuo*. The resulting oil was dissolved in toluene (0.7 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (8 mg, 0.02 mmol) was added and the mixture was stirred for 0.5 h at – 78 ˚C. $CsOH{\cdot}H_2O$ (301 mg, 1.79 mmol) was added and the reaction mixture was stirred at – 78 ˚C for 12 h before being diluted with ammonium chloride (sat. aq., 5 mL), extracted with dichloromethane (3 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether : diethyl ether, 20 : 1) to afford product **40** (52 % yield, 73 % ee) as a colourless oil.

Racemic: (±)-**40** was prepared according to *general procedure 3* (50 mg aniline, 0.18 mmol), chromatography (petroleum ether : diethyl ether, 50 : 1), 60 % yield.

ν_{max} (neat): 3376, 2923, 2853, 1713, 1605. $[\alpha]_D^{29}$ + 134 (*c* = 1.00, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 7.26 (1H, d, *J* 7.6, H5), 7.11 (1H, dd, *J* 7.6, *J* 7.6, H6/H7), 6.75 (1H, dd, *J* 7.6, *J* 7.6, H6/H7), 6.65 (1H, d, *J* 7.6, H8), 5.12 (1H, sept, *J* 6.3, H12), 5.07 (1H, sept, *J* 6.3, H12), 4.38 (1H, d, *J* 5.9, H3), 1.96 (1H, sept, *J* 5.9, H2), 1.30 (3H, d, *J* 6.3, H13), 1.26 (6H, d, *J* 5.9, H1), 1.23 (3H, d, *J* 6.3, H13), 1.06 (3H, d, *J* 6.5, H13), 0.86 (3H, d, *J* 6.3, H13). δ_C (100 MHz, $CDCl_3$): 168.7 (C11), 168.2 (C11), 150.5 (C4), 129.4 (C5 – C9), 126.2 (C5 – C9), 126.2 (C5 – C9), 118.9 (C5 – C9), 109.7 (C5 – C9), 69.7 (C12/C3), 69.4 (C12/C3), 69.3 (C12/C3), 66.2 (C10), 30.3 (C2), 21.6 (C1), 21.3 (C13), 18.3 (C13). LCMS (ES–): 332.2 $[M–H]^-$. HRMS (ES+): found 356.1834; $C_{19}H_{27}NO_4Na$ $[M+Na]^+$ requires 356.1832. Chiral HPLC (Chiralpak IA, 5 % EtOH, 95% heptane, 1.0 mL.min^{-1}, λ = 215) t_R (major) = 7.7, t_R (minor) = 6.9.

(2-Chloro-3-nitrophenyl)methanol

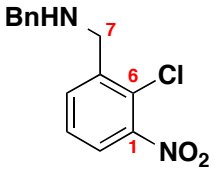


114

3-Nitro-2-chlorobenzoic acid (5.0 g, 25.0 mmol) was added to sodium borohydride (1.8 g, 50.0 mmol) in tetrahydrofuran (80 mL) over 1 h followed by addition of $BF_3 \cdot Et_2O$ (9.0 mL, 71.0 mmol) over 0.5 h at 0 ˚C. The reaction mixture was stirred for 5 h and cooled to 0 ˚C before concentrated hydrochloric acid (aq.) was added dropwise until effervescence ceased. The mixture was diluted with ethyl acetate (500 mL) and the organic layer was washed with sodium hydrogen carbonate (sat. aq., 200 mL), water (200 mL), hydrochloric acid (1M aq., 200 mL) and brine (sat. aq., 200 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford compound **114** (4.5 g, 97 % yield) as a crystalline solid.

ν_{max} (neat) 3272 (br), 1531, 1359, 1072. δ_H (400 MHz, $CDCl_3$): 7.80 (1H, d, *J* 7.7, H4), 7.73 (1H, d, *J* 8.0, H2), 7.45 (1H, dt, *J* 7.9, *J* 3.2, H3), 4.88 (2H, d, *J* 2.7, H7), 2.10 (1H, br, OH). δ_C (100 MHz, $CDCl_3$): 149.1 (C1), 141.8 (C5), 131.7 (C4), 127.8 (C3), 124.7 (C6), 124.4 (C2), 62.6 (C7). HRMS (ES+): found 209.9931; $C_7H_6ClNNaO_3$ $[M+Na]^+$ requires 209.9928.

***N*-Benzyl-1-(2-chloro-3-nitrophenyl)methanamine**

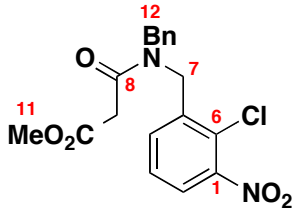


115

Dimethylsulfoxide (2.3 mL, 32.0 mmol) was added dropwise to a stirred solution of oxalyl chloride (1.4 mL, 16.0 mmol) in dichloromethane (70 mL) at – 78 ˚C over 15 mins. A solution of alcohol **114** (2.0 g, 10.7 mmol) in dichloromethane (20 mL) was added over 30 mins and left to stir at – 78 ˚C for 1 h. Triethylamine (7.2 mL, 53.0 mmol) was added and the reaction mixture was allowed to warm to RT over 1 h followed by the addition of water (200 mL) and extraction with dichloromethane (200 mL). The organic layer was washed with sodium hydrogen carbonate (sat. aq., 50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was stirred overnight with benzylamine (1.6 mL, 15.0 mmol) and sodium sulfate (7.6 g, 54.0 mmol) in dichloromethane (50 mL). The reaction mixture was filtered, concentrated *in vacuo* and redissolved in methanol (100 mL) to which sodium borohydride (203 mg, 5.4 mmol) was added in one portion. The reaction mixture was allowed to stir for 4 h, followed by addition of water (200 mL) and extraction with dichloromethane (2 x 200 mL). The organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 5 : 1) to afford compound **115** (2.1 g, 69 %) as a yellow oil.

ν_{max} (neat) 3346 (br), 3028, 2836, 1533, 1454, 1358, 1117, 739. δ_H (400 MHz, $CDCl_3$): 7.74 (1H, d, *J* 7.7, H4), 7.68 (1H, d, *J* 7.7, H3), 7.45 – 7.23 (6H, m, H2, ArH), 4.00 (2H, s, H7/$\underline{CH_2}$Ph), 3.85 (2H, s, H7/$\underline{CH_2}$Ph), 3.83 (1H, s, NH). δ_C (100 MHz, $CDCl_3$): 149.1 (C1), 141.0, 139.7 (C5), 132.9 (C4), 128.5, 128.1, 127.3, 127.1, 125.5 (C6), 123.6 (C2), 53.3 ($\underline{C}H_2$Ph), 50.3 (C7). HRMS (ES+): found 277.0741; $C_{14}H_{14}ClN_2O_2$ $[M+H]^+$ requires 277.0738.

Methyl 3-(benzyl(2-chloro-3-nitrobenzyl)amino)-3-oxopropanoate

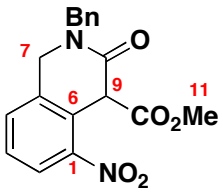


116

Methyl malonylchloride (1.4 mL, 10.3 mmol) was added to a stirred solution of amine **115** (711 mg, 2.6 mmol), triethylamine (1.1 mL, 7.7 mmol) and DMAP (31 mg, 0.3 mmol) in dichloromethane (5 mL) at 0 ˚C. The reaction mixture was allowed to warm to RT and stirred for 12 h. The reaction mixture was diluted with dichloromethane (15 mL), washed with potassium carbonate (10 % aq., 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 2 : 1) to afford compound **116** (606 mg, 63 %) as a yellow oil.

ν_{max} (neat) 3443 (br), 1651 (s), 1535, 1435, 1161. δ_H (400 MHz, $CDCl_3$): Major rotamer; 7.70 (2H, dd, *J* 7.9, *J* 1.8, H15), 7.48 – 7.32 (4H, m, H2/3/4/16), 7.18 (2H, d, *J* 7.9, H14), 4.78 (2H, s, H12/7), 4.49 (2H, s, H12/7) 3.78 (3H, s, H11), 3.62 (2H, s, H9). Minor rotamer; 7.75 (1H, d, *J* 7.6, H2/H4), 7.48 – 7.32 (4H, m, Ar-H), 7.27-7.24 (3H, m, Ar-H), 4.65 (2H, s, H12/7), 4.60 (2H, s, H12/7), 3.74 (3H, s, H11), 3.47 (2H, s, H9). δ_C (100 MHz, $CDCl_3$): Major rotamer; 168.2 (C8/C10), 167.1 (C8/C10), 149.1 (C1), 137.3 (C5/C13), 135.1 (C5/C13), 131.8, 129.2, 128.8, 128.2, 126.3, 125.3 (C6), 124.0, 52.7 (C11), 52.0 (C9), 46.8 (C7/12), 40.9 (C7/12). Minorrotamer; 167.6 (C8/C10), 166.9 (C8/C10), 149.1 (C1), 136.7 (C5/C13), 135.9 (C4/C13), 130.0, 128.8, 128.2, 127.9, 127.8, 125.0 (C6), 124.4, 52.6 (C11), 52.0 (C9), 49.2 (C7/C12), 49.0 (C7/C12). HRMS (ES^+): found 399.0715; $C_{18}H_{17}ClN_2NaO_5$ $[M+Na]^+$ requires 399.0718.

Methyl 2-benzyl-5-nitro-3-oxo-1, 2, 3, 4-tetrahydroisoquinoline-4-carboxylate

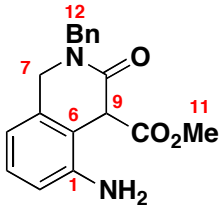


117

Nitro compound **116** (300 mg, 0.80 mmol) and potassium carbonate (121 mg, 0.88 mmol) were stirred in DMF (18 mL) at 90 ˚C for 18 h. The reaction mixture was cooled to RT, diluted with dichloromethane (50 mL), washed with ammonium chloride (sat. aq., 50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford compound **117** (122 mg, 45 %) as a colourless foam.

ν_{max} (neat) 2954, 2925, 1738, 1663, 1533, 1353; δ_H (400 MHz, $CDCl_3$): 7.91 (1H, d, *J* 7.8, H4), 7.46 (1H, t, *J* 7.8, H3), 7.39 (1H, d, *J* 7.8, H2), 7.37 – 7.22 (5H, m, Ar-H), 5.50 (1H, s, H9), 4.79 (2H, d, *J* 2.5, C$\underline{H_2}$Ph), 4.73 (1H, d, *J* 15.8, H7), 4.24 (1H, d, *J* 15.8, H7), 3.79 (3H, s, H11). δ_C (100 MHz, $CDCl_3$): 167.3 (C10), 163.5 (C8), 147.7 (C1), 135.6 (C5), 135.3, 130.7 (C4), 128.9, 128.7, 128.0, 127.9, 126.3 (C6), 124.3 (C2), 53.4 (C11), 51.5 (C9), 50.5 (C7/$\underline{CH_2}$Ph), 49.6 (C7/$\underline{CH_2}$Ph). HRMS (ES+): found 363.0950; $C_{18}H_{16}N_2NaO_5$ $[M+Na]^+$ requires 363.0951.

Methyl 5-amino-2-benzyl-3-oxo-1, 2, 3, 4-tetrahydroisoquinoline-4-carboxylate

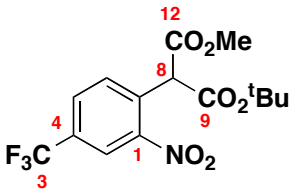


118

Nitro compound **117** (26 mg, 0.08 mmol) and palladium on carbon (2.6 mg, wet degussa type, 10 % palladium by weight) were stirred in methanol (0.75 mL) under a positive pressure of hydrogen for 4 h. The reaction mixture was filtered through Celite,™ concentrated *in vacuo* and purified by flash column chromatography (petroleum ether : ethyl acetate, 3 : 1) to afford compound **118** (16 mg, 68 %) as an orange solid.

ν_{max} (neat) 3446, 2263, 2953, 1733, 1652, 1601. δ_H (400 MHz, $CDCl_3$): 7.35 – 7.32 (4H, m, Ar-H), 7.30 –7.29 (1H, m, Ar-H), 7.06 (1H, t, *J* 7.9, H3), 6.66, (1H, d, *J* 7.9, H2/4), 6.53 (1H, d, *J* 7.9, H2/4), 5.02 (1H, d, *J* 15.3, H7), 4.79 (1H, s, H9), 4.64 (2H, t, *J* 15.2, H12), 4.11 (1H, d, *J* 15.3, H7), 3.72 (3H, s, H11). δ_C (100 MHz, $CDCl_3$): 169.3 (C8/C10), 165.5 (C8/C10), 144.4 (C1), 136.2 (C5/C6/C13), 132.4 (C5/C6/C13), 128.8, 128.7, 127.9, 127.6, 115.9, 115.5 (C5/C6/C13), 115.2, 53.0 (C9), 50.4 (C11), 50.3 (C7/C12), 50.3 (C7/C12). HRMS (ES^+): found 333.1203; $C_{18}H_{18}N_2NaO_3$ $[M+Na]^+$ requires 333.1210.

1-*tert*-Butyl 3-methyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate

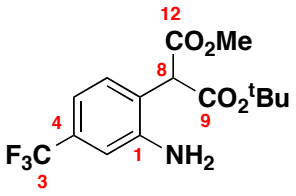


119

tert-Butyl methyl malonate (900 μL, 5.13 mmol) and potassium carbonate (675 mg, 5.13 mmol) in DMF (63 mL) were stirred at 90 ˚C for 10 minutes before being cooled to RT. 1-Fluoro-2-nitro-4-(trifluoromethyl)benzene (1.08 mL, 5.13 mmol) was added, and the mixture was subsequently heated at 90 ˚C for 6 h. The mixture was cooled to RT and diluted with hydrochloric acid (5 % aq., 250 mL) and extracted with petroleum ether (3 x 250 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether : ethyl acetate, 5 : 1) to afford compound **119** (1.51 g, 81 %) as a colourless liquid.

ν_{max} (neat): 3984, 1735, 1631, 1542, 1325. δ_H (400 MHz, $CDCl_3$): 8.34 (1H, s, H2), 7.90 (1H, d, *J* 8.0, H5), 7.72 (1H, d, *J* 8.0, H6), 5.27 (1H, s, H8), 3.82 (3H, s, H13), 1,48 (9H, s, H11). δ_C (100 MHz, $CDCl_3$): 167.4 (C12/C9), 165.4 (C12/C9), 148.9 (C1), 132.5 (C6), 132.2 (C7), 131.8 (q, *J* 34, C4), 129.8 (q, *J* 4, C2), 122.6 (q, *J* 270, C3), 122.5 (q, *J* 4, C5), 84.0 (C10), 55.1 (C13/C8), 53.2 (C13/C8), 27.8 (C11). δ_F (376 MHz, $CDCl_3$): – 63.1. LCMS (ES-): 362.2 $[M–H]^-$. HRMS (ES+): found 386.0817; $C_{15}H_{16}F_3NO_6Na$ $[M+Na]^+$ requires 386.0822.

1-*tert*-Butyl 3-methyl 2-(2-amino-4-(trifluoromethyl)phenyl)malonate

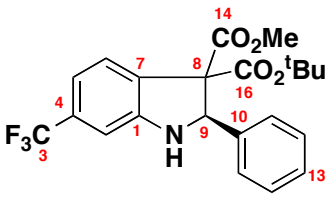


120

Nitro compound **119** (50 mg, 0.12 mmol) and palladium hydroxide (5 mg, 20 wt%) were stirred in methanol (1.5 mL) under a positive pressure of hydrogen for 48 h. The mixture was filtered through Celite™, washed with methanol (100 mL) and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether : ethyl acetate, 15 : 1) to afford compound **120** (34 mg, 84 %) an orange, yellow solid.

ν_{max} (neat): 3445, 3381, 3983, 1723, 1635. δ_H (400 MHz, $CDCl_3$): 7.24 (1H, d, *J* 8.0, H6), 7.00 (1H, d, *J* 8.0, H5), 6.95 (1H, s, H2), 4.59 (1H, s, H8), 3.77 (3H, s, H13), 1.47 (9H, s, H11). δ_C (100 MHz, $CDCl_3$): 169.0 (C12/C9), 167.1 (C12/C9), 146.0 (C1), 131.9 (C6), 131.9 (C7), 131.4 (q, *J* 33, C4), 124.0 (q, *J* 264, C3), 115.3 (q, *J* 4, C2), 114.0 (q, *J* 4, C5), 83.8 (C10), 56.5 (C13/C8), 52.9 (C13/C8), 27.9 (C11). δ_F (376 MHz, $CDCl_3$): – 62.5. LCMS (ES–): 331.94 $[M–H]^-$. HRMS (ES+): found 334.1246; $C_{15}H_{19}F_3NO_4$ $[M+H]^+$ requires 334.1261.

(2*R*)-3-*tert*-Butyl 3-methyl 2-phenyl-6-(trifluoromethyl)indoline-3,3-dicarboxylate



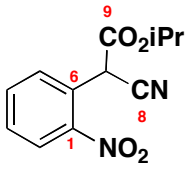
42/43

Asymmetric: Prepared according to *general procedure 1* (20 mg imine, 0.10 mmol), – 15 ˚C, toluene, reaction time: 17 h, chromatography (petroleum ether : diethyl ether, 50 : 1), 90 % yield, major 83 % ee, minor 66 % ee. Inseperable diastereisomers; ratio of diastereoisomers (major : minor, 7 : 2) by comparison of integrals of the methyl ester resonances (H15) in the ^{1}H NMR spectrum.

Racemic: (±)-**42/43** was prepared according to *general procedure 3* (25 mg aniline, 0.12 mmol), chromatography (petroleum ether : diethyl ether, 50 : 1), 68 % yield, yellow oil. Ratio of diastereoisomers (major : minor, 2.4 : 1) by comparison of H15 in ^{1}H NMR.

ν_{max} (neat): 3372, 2981, 2953, 2361, 2338, 1729. δ_H (250 MHz, $CDCl_3$): Major **42**; 7.50 (1H, d, *J* 7.8, H10), 7.36 – 7.30 (2H, m, H1/H2/H3), 7.27 – 7.25 (3H, m, H1/H2/H3), 7.07 (1H, d, *J* 7.8, H11), 6.93 (1H, s, H7) 5.78 (1H, s, H5), 4.35 (1H, br, NH), 3.17 (3H, s, H15), 1.49 (9H, s, H18). δ_H (400 MHz, $CDCl_3$): Minor **43**; 7.56 (1H, d, *J* 7.8, H10), 7.36 – 7.30 (2H, m, H1/H2/H3), 7.27 – 7.25 (3H, m, H1/H2/H3), 7.07 (1H, d, *J* 7.8, H11), 6.90 (1H, s, H7), 5.75 (1H, s, H5), 4.31 (1H, br, NH), 3.83 (3H, s, H15), 1.00 (9H, s, H18). δ_C (125 MHz, d^8-toluene): Major **42**; 167.7 (C14/C16), 167.3 (C14/C16), 151.7 (C6), 139.9 (C12), 132.2 (q, *J* 25, C9), 129.5, 127.5, 125.5, 125.2 (q, *J* 216, C8), 115.4 (C10), 105.8 (C7), 82.6 (C17), 81.6 (C13), 68.0 (C5), 51.4 (C15), 27.7 (C9). δ_C (125 MHz, d^8-toluene): Minor **43**; 169.0 (C14/C16), 165.6 (C14/C16), 151.5 (C), 139.9 (C12), 115.3 (C10), 105.5 (C7), 77.7 (C13), 70.1 (C17), 68.1 (C5), 52.5 (C15), 27.1 (C18). δ_F (376 MHz, $CDCl_3$): – 62.6. HRMS (ES–): found 444.1395; $C_{22}H_{22}F_3NO_4Na$ $[M–H]^-$ requires 444.1393. Chiral HPLC (Chiralpak IA, 10 % EtOH, 90% hexane, 1.0 mL/min, λ = 254); **minor diastereoisomer 43** t_R (major) = 11.4, t_R (minor) = 8.3; **major diastereoisomer 42** t_R (major) = 13.6, t_R (minor) = 17.0.

Isopropyl 2-cyano-2-(2-nitrophenyl)acetate

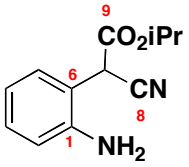


44

Isopropyl cyanoacetate (1.18 mL, 9.47 mmol) was added to a stirred slurry of potassium carbonate (1.31 g, 9.47 mmol) in DMF (20 mL) at 90 ˚C. After 10 mins stirring, 2-fluoro-nitrobenzene (1.00 g, 9.47 mmol) was added in one portion and allowed to stir for 24 h. The reaction mixture was diluted with dichloromethane (100 mL), washed with hydrochloric acid (5 % aq., 50 mL) and extracted with dichloromethane (2 x 100 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 7 : 1) to afford compound **44** (1.98 g, 84 % yield) as a yellow solid.

ν_{max} (neat): 2986, 2939, 2360, 2341, 1743, 1611, 1528, 1347. δ_H (400 MHz, $CDCl_3$): 8.22 (1H, d, *J* 8.2, H3/H4), 7.82 – 7.72 (2H, m, H2, H5), 7.68 – 7.68 (1H, m, H3/H4), 5.63 (1H, s, H7), 5.10 (1H, sept, *J* 6.3, H10), 1.32 (3H, d, *J* 6.3, H11), 1,29 (3H, d, *J* 6.3, H11). δ_C (100 MHz, $CDCl_3$): 163.0 (C9), 147.4 (C1), 134.5 (C2/C5), 131.1 (C2/C5), 130.6 (C3/C4), 126.0 (C3/C4), 125.4 (C6), 115.4 (C8), 72.3 (C10), 41.6 (C7), 21.4 (C11), 21.4 (C11). LCMS (ES+): 271.1 $[M+Na]^+$. HRMS (ES+): found 271.0685; $C_{12}H_{12}N_2O_4Na$ $[M+Na]^+$ requires 271.0689.

Isopropyl 2-(2-aminophenyl)-2-cyanoacetate

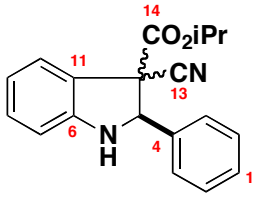


45

Palladium on carbon (50 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of nitro compound **44** (500 mg, 2.02 mmol) in ethyl acetate (8 mL). The solution was degassed three times with argon using a pump-flood procedure and placed under hydrogen for 16 h. The mixture was filtered through Celite™, eluted with ethyl acetate (300 mL) and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography (petroleum ether :ethyl acetate, 10 : 1) to afford compound **45** (440 mg, 99 % yield) as a colourless solid.

ν_{max} (neat): 3467, 3362, 2979, 2934, 2361, 2341, 1726, 1639. δ_H (400 MHz, $CDCl_3$): 7.37 (1H, d, *J* 7.7, H2), 7.19 (1H, t, *J* 7.7, H4), 6.86 (1H, t, *J* 7.7, H3), 6.77 (1H, d, *J* 7.7, H5), 5.05 (1H, sept, *J* 6.3, H9), 4.85 (1H, s, H6), 4.10 (2H, br, NH), 1.26 (6H, ap t, *J* 5.6, H16). δ_C (100 MHz, $CDCl_3$): 165.0 (C9), 144.5 (C6), 130.2 (C4), 129.2 (C2), 119.8 (C3), 117.9 (C5), 115.9 (C1/C7), 115.4 (C1/C7), 71.6 (C9), 41.0 (C6), 22.2 (C16), 21.4 (C16). LCMS (ES+): 219.1 $[M+H]^+$. HRMS (ES+) 241.0944: found; $C_{12}H_{14}N_2O_2Na$ $[M+H]^+$ requires 241.0947.

Isopropyl 3-cyano-2-phenylindoline-3-carboxylate

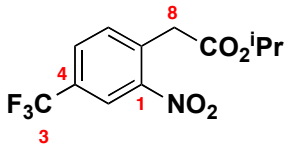


46

Benzaldehyde (93 μL, 0.92 mmol) was added to a stirred slurry of aniline **45** (100 mg, 0.46 mmol) and magnesium sulfate (275 mg, 2.29 mmol) in toluene (4 mL) for 16 h. The solids were removed by filtration, washed with toluene (20 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : diethyl ether, 6 : 1) to afford cyclized compound **46** (135 g, 99 %) as a yellow oil.

ν_{max} (neat): 3359, 3032, 3984, 2361, 2341, 1737, 1608. δ_H (400 MHz, $CDCl_3$): 7.62 – 7.52 (2H, m, ArH), 7.44 – 7.34 (3H, m, ArH), 7.33 – 7.23 (3H, m, ArH), 6.91 (1H, t, *J* 7.5, ArH) 6.95 (1H, d, *J* 7.9, ArH), 5.57 (1H, s, H5), 4.58 (1H, sept, *J* 6.3, H15), 4.23 (1H, br, NH), 1.05 (3H, d, *J* 6.3, H16), 0.66 (3H, d, *J* 6.3, H16). δ_C (100 MHz, $CDCl_3$): 165.5 (C14), 150.5 (C11), 135.8 (C6), 130.8, 129.1, 128.6, 127.5, 125.0, 120.4, 118.7 (CN), 110.8, 72.8 (C5), 71.0 (C15), 57.0 (C12), 21.3 (C16), 20.7 (C16). LCMS (ES+): 329.1 $[M+Na]^+$. HRMS (ES+): found 329.1250; $C_{19}H_{18}N_2O_2Na$ $[M+Na]^+$ requires 329.1260.

Isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acetate

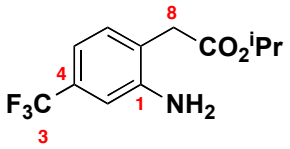


53

Nitro compound **98** (300 mg, 0.81 mmol), sodium chloride (47 mg, 0.81 mmol) and water (29 μL, 1.62 mmol) in dimethylsulfoxide (6 mL) were heated to 130 ˚C for 6 h. The mixture was then washed with water (60 mL), extracted with ethyl acetate (3 x 60 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford compound **53** (191 mg, 81 %) as a yellow solid.

ν_{max} (neat): 3096, 2987, 2925, 2851, 1715, 1630, 1575, 1538, 1503. δ_H (500 MHz, $CDCl_3$): 8.36 (1H, s, H2), 7.83 (1H, d, *J* 8.1, H5), 7.51 (1H, d, *J* 8.1, H6), 5.02 (1H, sept, *J* 6.1, H10), 4.05 (2H, s, H8), 1.23 (6H, d, *J* 6.1, H11). δ_C (125 MHz, $CDCl_3$): 168.6 (C9), 148.9 (C1), 134.2 (C6), 133.9 (C7), 131.3 (q, *J* 34, C4), 129.8 (q, *J* 4, C2), 122.7 (q, *J* 272, C3), 122.6 (q, *J* 4, C5), 69.5 (C10), 40.0 (C8), 21.6 (C11). δ_F (376 MHz, $CDCl_3$): –63.2. LCMS (ES–): 290.0 $[M–H]^-$. HRMS (ES+): found 309.1053: $C_{12}H_{17}F_3N_2O_4$ $[M+NH_4]^+$ requires 309.1057.

Isopropyl 2-(2-amino-4-(trifluoromethyl)phenyl)acetate

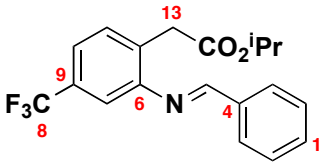


121

Nitro compound **53** (191 mg, 0.66 mmol) and palladium on carbon (19 mg, wet degussa type, 10 % palladium by weight) were stirred in methanol (4 mL) under a positive pressure of hydrogen for 4 h. The mixture was filtered through Celite™ and the methanol removed *in vacuo* to afford compound **121** (168 mg, 98 %) as an orange solid.

ν_{max} (neat): 3360, 3333, 2989, 2945, 1713, 1630, 1587. δ_H (500 MHz, $CDCl_3$): 7.16 (1H, d, *J* 7.5, H6), 6.96 (1H, d, *J* 7.5, H5), 6.92 (1H, s, H2), 4.99 (1H, sept, *J* 6.0, H10), 4.27 (2H, br, NH), 3.54 (2H, s, H8), 1.22 (6H, d, *J* 6.0, H11). δ_C (125 MHz, $CDCl_3$): 170.7 (C9), 145.9 (C1), 131.4 (C6), 130.7 (q, *J* 32, C4), 124.1 (q, *J* 270, C3), 123.1 (C7), 115.2 (q, *J* 4, C5), 112.8 (q, *J* 4, C2), 69.0 (C10), 38.8 (C8), 21.6 (C11). δ_F (376MHz, $CDCl_3$) – 63.0. LCMS (ES+): 262.5 $[M+H]^+$. HRMS (ES+): found 262.1049: $C_{12}H_{15}F_3NO_2$ $[M+H]^+$ requires 262.1049.

(*E*)-Isopropyl 2-(2-(benzylideneamino)-4-(trifluoromethyl)phenyl)acetate

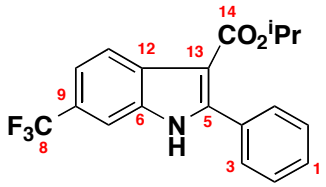


54

Aniline **121** (50 mg, 0.19 mmol), benzaldehyde (77 μL, 0.76 mmol), and magnesium sulfate (114 mg, 0.95 mmol) were stirred at RT in toluene (1.5 mL) for 24 h. The reaction mixture was filtered, concentrated *in vacuo* and the resulting residue was purified using flash column chromatography (petroleum ether : ethyl acetate, 5 : 1) to afford compound **54** (61 mg, 91 %) as a yellow solid.

ν_{max} (neat): 3066, 2988, 2940, 2925, 2877, 1725, 1627, 1610, 1577. δ_H (500 MHz, $CDCl_3$): 8.41 (1H, s, H5), 7.92 – 7.90 (2H, m, H2), 7.55 – 7.46 (4H, m, H1, H3, H7), 7.45 (1H, d, *J* 7.9, H10), 7.39 (1H, d, *J* 7.9, H11), 4.92 (1H, sept, *J* 6.3, H15), 3.80 (2H, s, H13), 1.10 (6H, d, *J* 6.3, H16). δ_C (125 MHz, $CDCl_3$): 170.6 (C14), 161.4 (C5), 151.1 (C6), 135.8 (C4), 132.9 (C12), 131.9 (C11), 130.9 (C1), 130.6 (q, *J* 32, C9), 129.1 (C2), 128.8 (C3), 124.0 (q, *J* 275, C8), 122.4 (q, *J* 4, C10), 114.5 (q, *J* 4, C7), 68.2 (C15), 37.9 (C13), 21.6 (C16). δ_F (376 MHz, $CDCl_3$): – 62.7. LCMS (ES+): 350.5 $[M+H]^+$. HRMS (ES+): found 350.1362: $C_{19}H_{19}F_3NO_2$ $[M+H]^+$ requires 350.1358.

Isopropyl 2-phenyl-6-(trifluoromethyl)-1*H*-indole-3-carboxylate

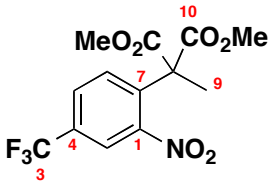


55

Aniline **121** (19 mg, 0.07 mmol), benzaldehyde (14 μL, 0.14 mmol) and magnesium sulfate (42 mg, 0.35 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.8 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (3 mg, 0.01 mmol) was added and the solution was stirred at RT for 30 minutes. Anhydrous potassium hydroxide (4 mg, 0.07 mmol) was added to the reaction and allowed to stir for 2 h at RT before diluting with ammonium chloride (sat. aq., 10 mL) and extracting with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **55** (12 mg, 50 %) as a clear oil.

ν_{max} (neat): 2982, 2936, 2361, 1672. δ_H (500 MHz, $CDCl_3$): 8.71 (1H, br. s, NH), 8.34 (1H, d, *J* 8.5, H11), 7.68 (1H, s, H7), 7.67 – 7.64 (2H, m, H1/H2/H3), 7.52 (1H, d, *J* 8.5, H10), 7.49 – 7.47 (3H, m, H1/H2/H3), 5.22 (1H, sept, *J* 6.2, H15), 1.30 (6H, d, *J* 6.2, H16). δ_C (125 MHz, $CDCl_3$): 164.2 (C14), 146.5 (C6), 134.0 (C4/C12/C13), 131.4 (C4/C12/C13), 130.1 (C4/C12/C13), 129.6 (C1), 129.6 (C2/C3), 128.2 (C2/C3), 125.2 (q, *J* 32, C9), 124.8 (q, *J* 272, C8), 122.7 (C11), 118.7 (q, *J* 3, C10), 108.4 (q, *J* 4, C7), 105.6 (C5), 67.4 (C15), 22.0 (C16). δ_F (470 MHz, $CDCl_3$): – 60.9. LCMS (ES+): 370.1 $[M+Na]^+$. HRMS (ES+): found 370.1025; $C_{19}H_{16}F_3NO_2Na$ $[M+Na]^+$ requires 370.1012.

Dimethyl 2-methyl-2-(2-nitro-4-(trifluoromethyl)phenyl)malonate

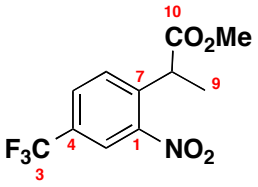


122

Sodium hydride (42 mg, 1.03 mmol) was added in one portion to a stirred solution of nitro compound **4** (300 mg, 0.93 mmol) and methyl iodide (332 μL, 4.67 mmol) in tetrahydrofuran (6 mL) at 0 ˚C. The reaction mixture was warmed to RT and stirred for 16 h before diluting with ammonium chloride (sat. aq., 20 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford **122** (328 mg, 98 %) as a yellow oil.

ν_{max} (neat): 3010, 2958, 2896, 2848, 1737, 1632. δ_H (500 MHz, $CDCl_3$): 8.30 (1H, s, H2), 7.87 (1H, d, *J* 8.3, H5), 7.52 (1H, d, *J* 8.3, H6), 3.76 (6H, s, H11), 2.04 (3H, s, H9). δ_C (125 MHz, $CDCl_3$): 169.5 (C10), 148.9 (C1), 138.0 (C7), 131.3 (q, *J* 35, C4), 130.2 (C6), 129.7 (q, *J* 4, C5), 123.2 (q, *J* 4, C2), 122.6 (q, *J* 273, C3), 59.2 (C8), 53.3 (C11), 23.5 (C9). δ_F (376 MHz, $CDCl_3$): – 63.1. LCMS (ES+): 336.1 $[M+H]^+$. HRMS (ES+): found 358.0498; $C_{13}H_{12}F_3NO_6Na$ $[M+Na]^+$ requires 358.0509.

Methyl 2-(2-nitro-4-(trifluoromethyl)phenyl)propanoate

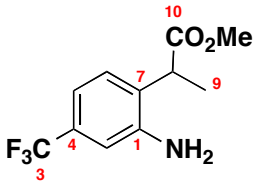


56

Nitro compound **122** (328 mg, 0.98 mmol), sodium chloride (172 mg, 2.94 mmol) and water (264 μL, 14.67 mmol) in dimethylsulfoxide (6 mL) were heated to 110 ˚C for 16 h. The mixture was then diluted with water (40 mL), extracted with dichloromethane (3 x 40 mL), dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford compound **56** (107 mg, 40 %) as a yellow oil.

ν_{max} (neat): 2994, 2956, 2892, 1742, 1655. δ_H (500 MHz, $CDCl_3$): 8.21 (1H, s, H2), 7.86 (1H, d, *J* 8.3, H5), 7.67 (1H, d, *J* 8.3, H6), 4.39 (1H, q, *J* 7.2, H8), 3.70 (3H, s, H11), 1.65 (3H, d, *J* 7.2, H9). δ_C (125 MHz, $CDCl_3$): 172.8 (C10), 148.2 (C1), 138.9 (C7), 130.8 (C6), 130.8 (q, *J* 34, C4), 129.7 (q, *J* 4, C5), 122.7 (q, *J* 274, C3), 122.2 (q, *J* 4, C2), 52.5 (C11), 41.2 (C8), 17.8 (C9). δ_F (376 MHz, $CDCl_3$): – 62.4. LCMS (ES+): 300.1 $[M+Na]^+$. HRMS (ES+): found 300.0448; $C_{11}H_{10}F_3NO_4Na$ $[M+Na]^+$ requires 300.0454.

Methyl 2-(2-amino-4-(trifluoromethyl)phenyl)propanoate

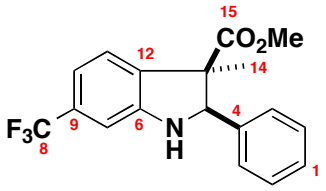


123

Palladium on carbon (3 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of nitro compound **56** (37 mg, 0.13 mmol) in methanol (1 mL). The solution was degassed three times with hydrogen using a pump-flood procedure and placed under hydrogen for 3 h. The mixture was filtered through Celite™, eluted with methanol (30 mL) and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **123** (36 mg, quantitative) as a pale yellow solid.

ν_{max} (neat): 2984, 2956, 1725, 1636. δ_H (500 MHz, $CDCl_3$): 7.25 (1H, d, *J* 8.2, H6), 7.02 (1H, d, *J* 8.2, H5), 6.92 (1H, s, H2), 4.20 (2H, br, NH), 3.83 (1H, q, *J* 7.2, H8), 3.69 (3H, s, H11), 1.56 (3H, d, *J* 7.2, H9). δ_C (125 MHz, $CDCl_3$): 174.3 (C10), 145.0 (C7), 130.3 (q, *J* 32, C4), 128.2 (C6), 127.8 (C1), 124.0 (q, *J* 271, C3), 115.4 (q, *J* 4, C5), 113.0 (q, *J* 4, C2), 52.3 (C11), 40.7 (C8), 15.6 (C9). δ_F (376 MHz, $CDCl_3$): – 62.8. LCMS (ES+): 270.1 $[M+Na]^+$. HRMS (ES+): found 248.0891; $C_{11}H_{13}F_3NO_2$ $[M+H]^+$ requires 248.0893.

(2*R*,3*R*)-Methyl 3-methyl-2-phenyl-6-(trifluoromethyl)indoline-3-carboxylate



59

Asymmetric: Aniline **123** (15 mg, 0.06 mmol), benzaldehyde (12 μL, 0.12 mmol) and magnesium sulfate (34 mg, 0.28 mmol) were stirred for 16 h at RT in toluene (0.4 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.6 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (2 mg, 0.01 mmol) was added and the solution was stirred at RT for 30 minutes. Anhydrous powdered potassium hydroxide (3 mg, 0.06 mmol) was added to the reaction and allowed to stir for 70 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracting with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford compound **59** (58 mg, 60 %, 91 % ee) as a single diastereoisomer.

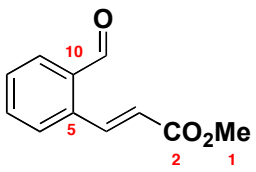
Racemic: Aniline **123** (15 mg, 0.06 mmol), benzaldehyde (12 μL, 0.12 mmol) and magnesium sulfate (34 mg, 0.28 mmol) were stirred for 16 h at RT in toluene (0.4 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.6 mL), tetrabutylammonium chloride (2 mg, 0.01 mmol) and anhydrous powdered potassium hydroxide (3 mg, 0.06 mmol) were added and the reaction left to stir for 16 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford separately diastereoisomer **58** (10 mg, 50 %) as a yellow oil and diastereoisomer **59** (10 mg, 50 %) as a yellow oil.

Diastereoisomer 59 (as drawn): ν_{max} (neat) 3370, 2926, 2853, 1732, 1684, 1652. $[\alpha]_D^{25}$ – 14 (*c* = 0.7, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.38 – 7.29 (5H, m, H1, H2, H3), 7.16 (1H, d, *J* 7.7, H11), 7.06 (1H, d, *J* 7.7, H10), 6.95 (1H, s, H7), 4.84 (1H, s, H5), 4.29 (1H, br, NH), 3.21 (3H, s, H16), 1.75 (3H, s, H14). δ_C (125 MHz, $CDCl_3$): 172.2 (C15), 150.6 (C12), 138.9 (C4), 135.0 (C6), 130.9 (q, *J* 32, C9), 128.4 (C1), 128.3 (C2/C3), 126.8 (C2/C3), 124.4 (C11), 124.3 (q, *J*

273, C8), 116.1 (q, *J* 4, C10), 105.6 (q, *J* 4, C7), 74.4 (C5), 58.0 (C13), 51.7 (C16), 24.5 (C14). δ_F (376 MHz, $CDCl_3$): – 62.4. LCMS (ES+): 336.1 $[M+H]^+$. HRMS (ES+): found 336.1204; $C_{18}H_{17}F_3NO_2$ $[M+H]^+$ requires 336.1206. Mp: 54 – 56 ˚C (dichloromethane : petroleum ether).

Diastereoisomer 58: ν_{max} (neat): 3372, 2954, 1732, 1632. δ_H (500 MHz, $CDCl_3$): 7.47 – 7.42 (2H, m, H1/H2/H3), 7.39 – 7.30 (3H, m, H1/H2/H3), 7.29 – 7.26 (1H, m, H11), 7.03 (1H d, *J* 7.6, H10), 6.94 (1H, s, H7), 5.66 (1H, s, H5), 3.85 (3H, s, H16), 1.04 (3H, s, H14). δ_C (125 MHz, $CDCl_3$): 161.2 (C15), 149.4 (C12), 138.3 (C4), 135.3 (C6), 131.1 (q, *J* 32, C9), 128.3 (C2/C3), 128.0 (C1), 127.5 (C2/C3), 124.4 (C11), 124.3 (q, *J* 271, C8), 116.0 (q, *J* 4, C10), 105.7 (q, *J* 4, C7), 68.7 (C5), 56.2 (C13), 52.7 (C16), 20.9 (C14). δ_F (376 MHz, $CDCl_3$): – 62.4. LCMS (ES+): 336.1 $[M+H]^+$. HRMS (ES+): found 336.1204; $C_{18}H_{17}F_3NO_2$ $[M+H]^+$ requires 336.1206.

(*E*)-Methyl 3-(2-formylphenyl)acrylate[59]

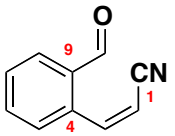


60

2-bromobenzaldehyde (500 mg, 2.7 mmol) in DMF (1.6 mL) was added to a stirring solution of methylacrylate (1.2 mL, 13.5 mmol), palladium acetate (61 mg, 0.3 mmol), tetrabutylammonium bromide (222 mg, 0.7 mmol), and potassium carbonate (298 mg, 2.2 mmol). The resulting mixture was heated to 70 ˚C for 48 h, cooled to RT, then filtered through Celite™ and washed with ethyl acetate. The organic layer was diluted with water (100 mL) and back extracted with ethyl acetate (3 x 100 mL), dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 50 : 1) to afford compound **60** (278 mg, 54 %) as a yellow solid. Data matches the published data.

ν_{max} (neat): 3068, 3002, 2953, 1719, 1635, 1596, 1569. δ_H (500 MHz, $CDCl_3$): 10.23 (1H, s, H11), 8.53 (1H, d, *J* 16.0, H4), 7.88 (1H, d, *J* 7.6, H9), 7.66 – 7.54 (3H, m, H6, H7, H8), 6.39 (1H, d, *J* 16.0, H3), 3.84 (3H, s, H1). δ_C (125 MHz, $CDCl_3$): 191.8 (C11), 166.6 (C2), 141.3 (C4), 136.5 (C10), 133.9 (C6/C7/C8), 133.8 (C5), 132.4 (C9), 129.9 (C6/C7/C8), 128.0 (C6/C7/C8), 122.7 (C3), 51.9 (C1). LCMS (ES+): 191.1 $[M+H]^+$. HRMS (ES+): found 213.0530; $C_{11}H_{10}O_3Na$ $[M+Na]^+$ requires 213.0522.

(*E*)-3-(2-Formylphenyl)acrylonitrile[60]

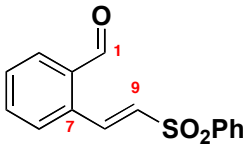


61

To a stirring solution of phthaldialdehyde (347 mg, 2.6 mmol) in dichloromethane (4 mL) was added 2-(triphenylphosphoranylidene)acetonitrile (780 mg, 2.6 mmol) and stirred for 24 h. The resulting solution was diluted with diethyl ether (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the resulting solid was purified by column chromatography (petroleum ether : ethyl acetate, 25 : 1) to afford compound **61** (332 mg, 82 %) as a white solid.

ν_{max} (neat): 3068, 3057, 2857, 2761, 2220, 1725, 1683, 1645, 1612, 1597. δ_H (400 MHz, $CDCl_3$): 10.11 (1H, s, H10), 8.03 (1H, d, *J* 11.9, H3), 7.91 (1H, d, *J* 7.6, H5), 7.89 (1H, d, *J* 7.6, H8), 7.71 (1H, dd, *J* 7.6, 7.6, H6), 7.65 (1H, dd, *J* 7.6, 7.6, H7), 5.66 (1H, d, *J* 11.9, H2). δ_C (100 MHz, $CDCl_3$): 192.7 (C10), 148.2 (C3), 134.6 (C6), 134.4 (C4), 134.1 (C8), 133.6 (C9), 130.5 (C7), 129.5 (C5), 116.7 (C1), 99.3 (C2). LCMS (ES+): 180.1 $[M+Na]^+$. HRMS (ES+): found 180.0419; $C_{10}H_7NONa$ $[M+Na]^+$ requires 180.0420.

2-(2-(Phenylsulfonyl)vinyl)benzaldehyde

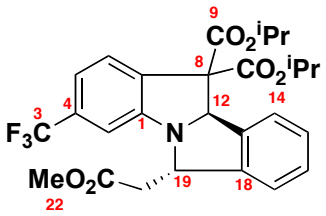


62

To a stirring solution of phthaldialdehyde (557 mg, 4.2 mmol) in acetonitrile (10 mL) was added triphenyl((phenylsulfonyl)methylene)phosphorane (1.7 g, 4.2 mmol). The resulting solution was heated to 70 ˚C for 72 h before being cooled, diluted with diethyl ether (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the resulting solid was purified by column chromatography (petroleum ether : ethyl acetate, 5 : 1) to afford compound **62** (707 mg, 63 %), an inseparable mixture of geometrical isomers, as a pale solid.

Major *(E)* isomer: ν_{max} (neat): 3066, 2959, 1774, 1697, 1615, 1595, 1568. δ_H (500 MHz, $CDCl_3$): 10.22 (1H, s, H1), 8.56 (1H, d, *J* 15.4, H8), 8.04 (2H, d, *J* 7.4, H11), 7.90 – 7.85 (1H, m, H3), 7.69 – 7.52 (6H, m, H4, H5, H6, H12, H13), 6.82 (1H, d, *J* 15.4, H9). δ_C (125 MHz, $CDCl_3$): 191.8 (C1), 140.3 (C10), 140.3 (C9) 134.1 (C2/C7), 134.1 (C2/C7), 134.0 (C8), 133.6 (C5/C13), 133.5 (C5/C13), 131.7 (C3/C4/C6/C11/C12), 130.7 (C3/C4/C6/C11/C12), 129.4 (C3/C4/C6/C11/C12), 128.4 (C3/C4/C6/C11/C12), 128.0 (C3/C4/C6/C11/C12). LCMS (ES+): 295.1 $[M+Na]^+$. HRMS (ES+): found 295.0406; $C_{15}H_{12}O_3SNa$ $[M+Na]^+$ requires 295.0399.

(6*S*,10b*R*)-Diisopropyl 6-(2-methoxy-2-oxoethyl)-3-(trifluoromethyl)-6*H*-isoindolo[2,1-*a*]indole-11,11(10b*H*)-dicarboxylate



63

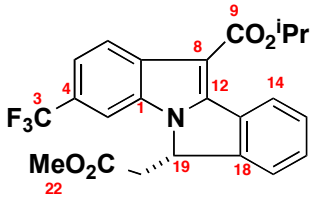
Asymmetric: Aniline **8** (100 mg, 0.29 mmol), aldehyde **60** (66 mg, 0.29 mmol) and magnesium sulfate (174 mg, 1.45 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine formed was then redissolved in toluene (2 mL), ((8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (12 mg, 0.03 mmol) was added and the solution was stirred at – 15 ˚C for 30 minutes. Pre-cooled potassium carbonate (33 %aq., 0.6 mL) was added to the reaction and allowed to stir for 16 h before diluting with ammonium chloride (sat. aq., 10 mL) and extracting with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **63** (91 mg, 61 %, 86 % ee) as a yellow oil.

Racemic: Aniline **8** (100 mg, 0.29 mmol), aldehyde **60** (66 mg, 0.29 mmol) and magnesium sulfate (174 mg, 1.45 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (1 mL), tetrabutylammonium chloride (8 mg, 0.03 mmol) and $CsOH{\cdot}H_2O$ (471 mg, 1.45 mmol) were added and the reaction left to stir for 6 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **63** (89 mg, 59 %).

ν_{max} (neat): 2983, 1729, 1632. $[\alpha]_D^{25}$ +14 (*c* = 1.36, $CHCl_3$). 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, H17, H5), 7.04 (1H, s, H2), 6.15 (1H, s, H12), 5.52 (1H, t, *J* 6.4, H19), 5.29 (1H, sept, *J* 6.3, H10), 4.61 (1H, sept, *J* 6.3, H10), 3.75 (3H, s, H22), 3.01 (1H, dd, *J* 16.8, 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 (100 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), 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. LCMS (ES+): 542.21 $[M+Na]^+$. HRMS (ES+): found 542.1741; $C_{27}H_{28}F_3NO_6Na$ $[M+Na]^+$ requires 542.1761. Chiral HPLC (Chiralpak OD-H, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, $\lambda = 272$) t_R (major) = 7.5, t_R (minor) = 10.1.

(*S*)-isopropyl 6-(2-methoxy-2-oxoethyl)-3-(trifluoromethyl)-6*H*-isoindolo[2,1-*a*]indole-11-carboxylate

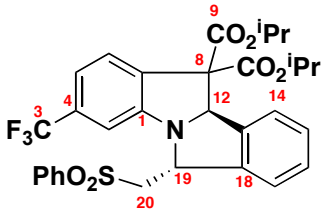


64

This compound was formed during the purification of indoline **63** by flash column chromatography in a variety of yields depending on the solvent system. Less polar solvent systems resulted in a larger yield of the indole **64** due to the greater length of time on silica. This compound is a bright yellow oil.

ν_{max} (neat): 2984, 2939, 1731, 1634, 1615. δ_H (500 MHz, $CDCl_3$): 8.84 (1H, d, *J* 7.2, H14), 8.37 (1H, d, *J* 8.5, H6), 7.65 (1H, s, H2), 7.58 – 7.54 (2H, m, H15, H16), 7.53 – 7.47 (2H, m, H5, H17), 5.85 (1H, dd, *J* 7.5, *J* 5.3, H19), 5.42 (1H, sept, *J* 6.3, H10), 3,81 (3H, s, H22), 3.23 (1H, dd, *J* 16.5, *J* 5.3, H20), 2.85 (1H, dd, *J* 16.5, *J* 7.5, H20), 1.52 (6H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 170.7 (C9/C21), 164.6 (C9/C21), 150.2 (C12), 146.6 (C18), 133.7 (C1), 132.0 (C7), 130.5 (C13), 129.8 (C17), 129.3 (C15/C16), 126.3 (C14), 124.9 (q, *J* 31.1 C4), 124.8 (q, *J* 271, C3), 123.5 (C6), 122.8 (C15/C16), 118.5 (q, *J* 4, C5), 107.1 (q, *J* 4, C2), 100.8 (C8), 67.7 (C10), 57.5 (C19), 52.4 (C22), 39.2 (C20), 22.4 (C11). LCMS (ES+): 454.2 $[M+Na]^+$. HRMS (ES+): found 454.1227; $C_{23}H_{20}F_3NO_4Na$ $[M+Na]^+$ requires 454.1237.

(6*R*,10b*R*)-Diisopropyl 6-((phenylsulfonyl)methyl)-3-(trifluoromethyl)-6*H*-isoindolo[2,1-*a*]indole-11,11(10b*H*)-dicarboxylate



65

Asymmetric: Aniline **8** (79 mg, 0.23 mmol), aldehyde **62** (62 mg, 0.23 mmol) and magnesium sulfate (137 mg, 1.14 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (1.5 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (10 mg, 0.02 mmol) was added and the solution was stirred at – 15 ˚C for 30 minutes. Pre-cooled potassium carbonate (33 % aq, 0.5 mL) was added to the reaction and allowed to stir for 16 h before diluting with ammonium chloride (sat. aq., 10 mL) and extracting with dichloromathane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 15 : 1) to afford the major diastereoisomer (61 mg, 43 %, 91 % ee) and the minor diastereoisomer (16 mg, 12 %, 87 % ee) of **65**.

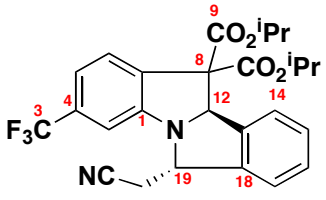
Racemic: Aniline **8** (25 mg, 0.07 mmol), aldehyde **62** (20 mg, 0.07 mmol) and magnesium sulfate (43 mg, 0.35 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (1 mL), tetrabutylammonium chloride (3 mg, 0.01 mmol) and $CsOH{\cdot}H_2O$ (131 mg, 0.40 mmol) were added and the reaction left to stir for 6 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford the major diastereoisomer (19 mg, 47 %) as a white solid and the minor diastereoisomer (7 mg, 17 %) of **65** as a white solid.

Major diastereomer (as drawn): ν_{max} (neat): 2984, 1730, 1618, 1590. $[\alpha]_D^{25}$ – 18 (*c* = 0.60, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.98 (2H, d, *J* 7.2, H22), 7.64 (1H, t, *J* 7.5, H24), 7.54 (2H, t, *J* 7.6, H23), 7.47 (1H, d, *J* 8.0, H6), 7.37 (1H, d, *J* 7.5, H14), 7.33 – 7.24 (3H, m, H15, H16, H17), 7.23 (1H, s, H2), 7.13 (1H, d, *J* 8.0, H5), 5.99 (1H, s, H12), 5.26 (1H, t, *J* 6.7, H19), 5.16 (1H, sept, *J* 6.3, H10), 4.74 (1H, sept, *J* 6.3, H10), 3.71 (1H, dd, *J* 15.7, *J* 6.7, H20), 3.57 (1H, dd, *J*

15.7, *J* 6.7, H20), 1.38 (3H, d, *J* 6.3, H11), 1.29 (3H, d, *J* 6.3, H11), 1.05 (3H, d, *J* 6.3, H11), 0.79 (3H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 167.8 (C9), 166.7 (C9), 152.9 (C1), 141.1 (C18), 140.0 (C21), 137.5 (C13), 133.9 (C24), 132.2 (q, *J* 32, C4), 131.6 (C7), 129.3 (C23), 129.1 (C16), 128.8 (C15), 127.8 (C22), 127.0 (C6), 124.0 (q, *J* 273, C3), 123.5 (C17), 123.2 (C14), 118.1 (q, *J* 4, C5), 109.4 (q, *J* 4, C2), 74.0 (C12), 70.3 (C10), 70.0 (C10), 67.4 (C8), 64.4 (C19), 63.2 (C20), 21.6 (C11), 21.5 (C11), 21.3 (C11), 20.9 (C11). δ_F (376 MHz, $CDCl_3$): – 62.3. LCMS (ES+): 624.1 $[M+Na]^+$. HRMS (ES+): found 624.1620; $C_{31}H_{30}F_3NO_6SNa$ $[M+Na]^+$ requires 624.1638. Chiral HPLC (Chiralpak OD-H, 2 % IPA, 98 % hexane, 1.0 mL.min^{-1}, λ = 262) t_R (major) = 34.2, t_R (minor) = 25.9. Mp: 144 – 146 ˚C (petroleum ether : diethyl ether).

Minor Diastereomer: ν_{max} (neat): 2985, 2938, 1726, 1641. $[\alpha]_D^{25}$ – 85 (*c* = 0.10, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 8.00 (2H, d, *J* 7.3, H22), 7.74 – 7.67 (2H, m, H14, H24), 7.65 – 7.59 (3H, m, H6, H23), 7.50 (1H, d, *J* 7.2, H17), 7.42 (1H, t, *J* 7.2, H16), 7.34 (1H, t, *J* 7.2, H15), 7.19 (1H, d, *J* 8.0, H5), 6.85 (1H, s, H2), 6.08 (1H, s, H12), 5.52 (1H, d, *J* 7.0, H19), 5.29 (1H, sept, *J* 6.3, H10), 4.50 (1H, sept, *J* 6.3, H10), 3.76 (1H, dd, *J* 15.6, *J* 1.5, H20), 3.01 (1H, dd, *J* 15.5, *J* 7.0, H20), 1.42 (3H, d, *J* 6.3, H11), 1.41 (3H, d, *J* 6.3, H11), 0.95 (3H, d, *J* 6.3, H11), 0.77 (3H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 167.9 (C9), 166.9 (C9), 148.4 (C1), 144.1 (C18), 139.1 (C21), 136.5 (C7), 134.3 (C13/C24), 134.0 (C13/C24), 132.0 (q, *J* 32, C4), 129.6 (C23), 129.6 (C16), 128.1 (C22), 128.0 (C15), 126.6 (C6), 124.2 (C14/C17), 124.1 (C14/C17), 123.9 (q, *J* 273, C3), 118.7 (q, *J* 4, C5), 112.0 (q, *J* 4, C2), 75.9 (C12), 70.2 (C10), 66.6 (C8), 58.6 (C20), 57.7 (C19), 21.7 (C11), 21.6 (C11), 21.2 (C11), 21.1 (C11). δ_F (376 MHz, $CDCl_3$): – 62.3. LCMS (ES+): 624.2 $[M+Na]^+$. HRMS (ES+): found 624.1628; $C_{31}H_{30}F_3NO_6SNa$ $[M+Na]^+$ requires 624.1638. Chiral HPLC (Chiralpak OD-H, 1.5 % IPA, 98.5 % hexane, 1.0 mL.min^{-1}, λ = 217) t_R (major) = 11.8, t_R (minor) = 13.9.

(6*S*,10b*R*)-Diisopropyl 6-(cyanomethyl)-3-(trifluoromethyl)-6*H*-isoindolo[2,1-*a*]indole-11,11(10b*H*)-dicarboxylate



66

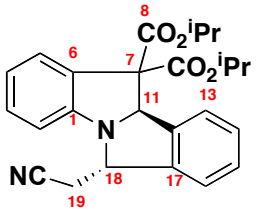
Asymmetric: Aniline **8** (50 mg, 0.14 mmol), aldehyde **61** (23 mg, 0.14 mmol) and magnesium sulfate (87 mg, 0.73 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo.* The imine was then redissolved in toluene (1 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (6 mg, 0.02 mmol) was added and the solution was stirred at – 15 ˚C for 30 minutes. Pre-cooled potassium carbonate (33 % aq, 0.3 mL) was added to the reaction and allowed to stir for 16 h before diluting with ammonium chloride (sat. aq., 10 mL) and extracting with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 15 : 1) to afford compound **66** (30 mg, 70 %, 97 % ee).

Racemic: Aniline **8** (25 mg, 0.07 mmol), aldehyde **61** (12 mg, 0.07 mmol) and magnesium sulfate (42 mg, 0.35 mmol) were stirred for 16 h at RT in toluene (0.4 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.7 mL), tetrabutylammonium chloride (3 mg, 0.01 mmol) and $CsOH{\cdot}H_2O$ (131 mg, 0.40 mmol) were added and the reaction left to stir for 6 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford compound **66** (32 mg, 91 %) as a white solid.

ν_{max} (neat): 2984, 2938, 2252, 1727, 1616, 1593. $[\alpha]_D^{25}$ – 7 (*c* = 0.75, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.59 (1H, d, *J* 8.0, H6), 7.45 (1H, d, *J* 7.1, H14), 7.41 – 7.33 (2H, m, H15, H16), 7.32 (1H, d, *J* 7.6, H17), 7.27 (1H, s, H2), 7.21 (1H, d, *J* 8.0, H5), 6.21 (1H, d, *J* 2.3, H12), 5.26 (1H, sept, *J* 6.3, H10), 4.91 (1H, td, *J* 5.6, *J* 2.4, H19), 4.57 (1H, sept, *J* 6.3, H10), 2.98 (1H, dd, *J* 16.7, *J*, 5.6, H20), 2.92 (1H, dd, *J* 16.7, *J* 5.6, H20) 1.42 (3H, d, *J* 6.3, H11), 1.38 (3H, d, *J* 6.3, H11), 0.91 (3H, d, *J* 6.3, H11), 0.68 (3H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 168.0 (C9),

167.0 (C9), 153.0 (C1), 140.6 (C18), 137.3 (C13), 133.6 (C7), 132.4 (q, *J* 32, C4), 129.1 (C15/C16), 128.8 (C15/C16), 127.0 (C6), 124.2 (C14), 124.0 (q, *J* 273, C3), 122.5 (C17), 118.9 (q, *J* 4, C5), 117.5 (C21), 109.4 (q, *J* 4, C2), 74.0 (C12), 70.5 (C10), 70.0 (C10), 67.9 (C8), 66.6 (C18), 27.5 (C20), 21.7 (C11), 21.6 (C11), 21.2 (C11), 20.8 (C11). δ_F (376 MHz, $CDCl_3$): –62.5. LCMS (ES+): 509.2 $[M+Na]^+$. HRMS (ES+): found 509.1647; $C_{26}H_{25}F_3N_2O_4Na$ $[M+Na]^+$ requires 509.1659. Chiral HPLC (Chiralpak OD-H, 2 % IPA, 98 % hexane, 1.0 $mL.min^{-1}$, λ = 221) t_R (major) = 16.8, t_R (minor) = 18.6. Mp: 109 – 111 ˚C (dichloromethane : petroleum ether).

(6*S*,10b*R*)-Diisopropyl 6-(cyanomethyl)-6*H*-isoindolo[2,1-*a*]indole-11,11(10b*H*)-dicarboxylate



68

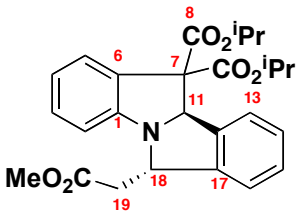
Asymmetric: Aniline **67** (50 mg, 0.18 mmol), aldehyde **61** (28 mg, 0.18 mmol) and magnesium sulfate (108 mg, 0.90 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo.* The imine was then redissolved in toluene (1 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (8 mg, 0.02 mmol) was added and the solution was stirred at – 30 ˚C for 30 minutes. Anhydrous powdered potassium hydroxide (81 mg, 1.44 mmol) was added to the reaction and allowed to stir for 16 h at – 30 ˚C before diluting with ammonium chloride (sat aq., 10 mL) and extracting with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 15 : 1) to afford compound **68** (67 mg, 89 %, 73 % ee).

Racemic: Aniline **67** (25 mg, 0.09 mmol), aldehyde **61** (13 mg, 0.09 mmol) and magnesium sulfate (54 mg, 0.45 mmol) were stirred for 16 h at RT in toluene (0.4 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.7 mL), tetrabutylammonium chloride (3 mg, 0.01 mmol) and $CsOH \cdot H_2O$ (131 mg, 0.40 mmol) were added and the reaction left to stir for 24 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **68** (36 mg, 96 %) as a colourless oil.

ν_{max} (neat): 2982, 2936, 2361, 2342, 1725, 1625, 1600. $[\alpha]_D^{25}$ + 43 (*c* = 2.1, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.50 (1H, d, *J* 7.7, H5), 7.46 (1H, d, *J* 6.5, H13), 7.37 – 7.32 (2H, m, H14, H15), 7.32 – 7.28 (2H, m, H3, H16), 7.10 (1H, d, *J* 7.9, H2), 6.96 (1H, td, *J* 7.6, *J* 0.9, H4), 6.16 (1H, d, *J* 2.4, H11), 5.25 (1H, sept, *J* 6.3, H9), 4.87 (1H, td, *J* 5.8, *J* 2.5, H18), 4.54 (1H, sept, *J* 6.3, H9), 2.93 (1H, d, *J* 5.8, H19), 2.92 (1H, d, *J* 5.8, H19), 1.41 (3H, d, *J* 6.3, H10), 1.37 (3H, d, *J*

6.3, H10), 0.89 (3H, d, *J* 6.3, H10), 0.68 (3H, d, *J* 6.3, H10). δ_C (125 MHz, $CDCl_3$): 168.7 (C8), 167.7 (C8), 152.7 (C6), 141.1 (C12), 137.8 (C17), 130.0 (C1/C3/C16), 129.9 (C1/C3/C16), 128.9 (C14/C15), 128.5 (C14/C15), 126.6 (C5), 124.2 (C13), 122.4 (C3/C16), 122.1 (C4), 117.9 (C20), 113.0 (C2), 74.8 (C11), 70.0 (C9), 69.5 (C9), 68.3 (C7), 66.8 (C18), 27.5 (C19), 21.7 (C10), 21.6 (C10), 21.2 (C10), 20.8 (C10). LCMS (ES+): 419.2 $[M+H]^+$. HRMS (ES+): found 441.1784; $C_{25}H_{26}N_2O_4Na$ $[M+Na]^+$ requires 441.1785. Chiral HPLC (Chiralpak IA, 3 % IPA, 97 % hexane, 1.0 mL.min^{-1}, λ = 272) t_R (major) = 23.8, t_R (minor) = 18.4.

(6*S*,10b*R*)-Diisopropyl 6-(2-methoxy-2-oxoethyl)-6*H*-isoindolo[2,1-*a*]indole-11,11(10b*H*)-dicarboxylate



69

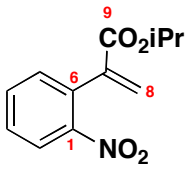
Asymmetric: Aniline **67** (75 mg, 0.27 mmol), aldehyde **60** (47 mg, 0.27 mmol) and magnesium sulfate (162 mg, 1.35 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo.* The imine was then redissolved in toluene (0.8 mL) and chloroform (0.8 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (11 mg, 0.03 mmol) was added and the solution was stirred at 0 ˚C for 30 minutes. Potassium carbonate (33 % aq, 0.5 mL) was added to the reaction and allowed to stir for 16 h at 0 ˚C before diluting with ammonium chloride (sat. aq., 10 mL) and extracting with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **69** (58 mg, 49 %, 52 % ee) as a yellow oil.

Racemic: Aniline **67** (25 mg, 0.09 mmol), aldehyde **60** (16 mg, 0.09 mmol) and magnesium sulfate (54 mg, 0.45 mmol) were stirred for 16 h at RT in toluene (0.4 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.3 mL) and chloroform (0.3 mL), tetrabutylammonium chloride (3 mg, 0.01 mmol) and anhydrous powdered potassium hydroxide (50 mg, 0.90 mmol) were added and the reaction left to stir for 16 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **69** (10 mg, 26 %).

ν_{max} (neat): 2983, 1729, 1632. $[\alpha]_D^{25}$ + 25 (*c* = 1.8, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.56 (1H, dd, *J* 7.7, *J* 0.8, H5), 7.49 (1H, t, *J* 4.4, H15), 7.32 – 7.28 (2H, m, H2, H13), 7.25 – 7.24 (1H, m, H3), 7.18 (1H, t, *J* 4.4, H14), 6.99 (1H, t, *J* 7.4, H4), 6.90 (1H, d, *J* 7.7, H16), 6.16 (1H, s, H11), 5.47 (1H, dd, *J* 8.1, *J* 5.3, H18), 5.27 (1H, sept, *J* 6.3, H9), 4.62 (1H, sept, *J* 6.3, H9), 3.73 (3H, s, H21), 3.11 (1H, dd, *J* 16.4, *J* 5.3, H19), 2.82 (1H, dd, *J* 16.4, *J* 8.4, H19), 1.41 (6H, d, *J* 6.3,

H10), 0.85 (3H, d, *J* 6.3, H10), 0.84 (3H, d, *J* 6.3, H10). δ_C (125 MHz, $CDCl_3$): 172.7 (C20), 168.8 (C8), 167.5 (C8), 144.0 (C17), 143.1 (C1), 137.9 (C6), 135.2 (C12), 132.4 (C4), 129.4 (C3), 128.6 (C2/C13), 127.8 (C2/C13), 126.4 (C5), 124.7 (C15), 123.0 (C14), 116.6 (C16), 75.9 (C11), 69.9 (C9), 69.8 (C9), 67.2 (C7), 61.5 (C18), 51.7 (C21), 38.6 (C19), 21.8 (C10), 21.6 (C10), 21.1 (C10), 21.0 (C10). LCMS (ES+): 452.2 $[M+Na]^+$. HRMS (ES+): found 474.1885; $C_{26}H_{29}NO_6Na$ $[M+Na]^+$ requires 474.1887. Chiral HPLC (Chiralpak OD-H, 2 % IPA, 98 % hexane, 1.0 $mL.min^{-1}$, $\lambda = 272$) t_R (major) = 14.5, t_R (minor) = 13.9.

Isopropyl 2-(2-nitrophenyl)acrylate

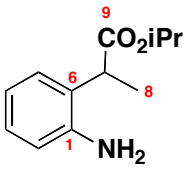


72

2-Nitro-isopropylphenyl acetic acid (730 mg, 3.27 mmol), paraformaldehyde (393 mg, 13.10 mmol), tetrabutylammonium iodide (48 mg, 0.13 mmol) and potassium carbonate (1.80 g, 13.04 mmol) were stirred in toluene (7 mL) at 50 ˚C for 16 h. The resulting solution was diluted with water (30 mL) and extracted with toluene (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford **72** (732 mg, 95 %) as a yellow liquid.

ν_{max} (neat): 2983, 2937, 1712, 1608. δ_H (500 MHz, $CDCl_3$): 8.11 (1H, dd, *J* 8.2, *J* 1.4, H5), 7.64 (1H, td, *J* 7.5, *J* 1.2, H3), 7.52 (1H, td, *J* 8.2, *J* 1.4, H4), 7.39 (1H, dd, *J* 7.6, *J* 1.3, H2), 6.53 (1H, s, H8), 5.86 (1H, s, H8), 5.05 (1H. sept, *J* 6.3, H10), 1.21 (6H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 164.2 (C9), 148.0 (C1), 140.5 (C7), 133.6 (C3), 133.2 (C6), 132.1 (C2), 129.2 (C4), 127.0 (C8), 124.5 (C5), 69.2 (C10), 21.5 (C11). LCMS (ES+): 258.1 $[M+Na]^+$. HRMS (ES+): found 258.0735; $C_{12}H_{13}NO_4Na$ $[M+Na]^+$ requires 258.0737.

Isopropyl 2-(2-aminophenyl)propanoate

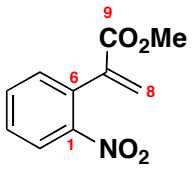


73

Palladium on carbon (20 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of **72** (200 mg, 0.85 mmol) in methanol (8 mL). The solution was degassed three times with hydrogen using a pump-flood procedure and placed under hydrogen for 3 h. The mixture was filtered through Celite™, eluted with methanol (50 mL) and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **73** (160 mg, 90 %) as a yellow oil.

ν_{max} (neat): 3448, 3376, 2980, 2938, 1718, 1629. δ_H (500 MHz, $CDCl_3$): 7.17 (1H, dd, *J* 7.7, *J* 1.3, H5), 7.07 (1H, td, *J* 7.6, *J* 1.4, H3), 6.78 (1H, td, *J* 7.5, *J* 1.2, H4), 6.70 (1H, dd, *J* 7.9, *J* 1.1, H2), 4.99 (1H, sept, *J* 6.3, H10), 4,03 (2H, br, NH), 3.77 (1H, q, *J* 7.1, H7), 1.53 (3H, d, *J* 7.1, H8), 1.22 (3H, d, *J* 6.3, H11), 1.17 (3H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 174.1 (C9), 144.7 (C6), 127.8 (C3), 127.5 (C5), 125.0 (C1), 119.0 (C4), 116.6 (C2), 68.3 (C10), 40.8 (C7), 21.7 (C11), 21,6 (C11), 15.7 (C8). LCMS (ES+): 208.1 $[M+H]^+$. HRMS (ES+): found 208.1331; $C_{12}H_{18}NO_2$ $[M+H]^+$ requires 208.1332.

Methyl 2-(2-nitrophenyl)acrylate[64]

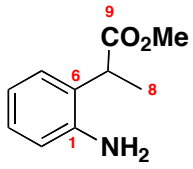


74

2-Nitro-methylphenyl acetic acid (3.4 g, 17.6 mmol), paraformaldehyde (2.1 g, 70.6 mmol), tetrabutylammonium iodide (261 mg, 0.7 mmol) and potassium carbonate (9.7 g, 70.6 mmol) were stirred in toluene (30 mL) at 50 ˚C for 16 h. The resulting solution was diluted with water (100 mL) and extracted with toluene (3 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford **74** (3.0 g, 81 %) as a yellow liquid. Data matches published data.

ν_{max} (neat): 3001, 2954, 1720, 1624, 1522, 1397. δ_H (500 MHz, $CDCl_3$): 8.09 (1H, dd, *J* 8.2, *J* 1.1, H5), 7.64 (1H, td, *J* 7.6, *J* 1.3, H3), 7.52 (1H, td, *J* 8.2, *J* 1.4, H4), 7.39 (1H, dd, *J* 7.6, *J* 1.4, H2), 6.52 (1H, s, H8), 5.87 (1H, s, H8), 3.70 (3H, s, H10). δ_C (125 MHz, $CDCl_3$): 165.2 (C9), 147.8 (C1), 139.8 (C7), 133.7 (C3), 132.9 (C6), 132.1 (C2), 129.4 (C4), 127.5 (C8), 124.5 (C5), 52.2 (C10). LCMS (ES+): 230.1 $[M+Na]^+$. HRMS (ES+): found 230.0425; $C_{10}H_9NO_4Na$ $[M+Na]^+$ requires 230.0424.

Methyl 2-(2-aminophenyl)propanoate

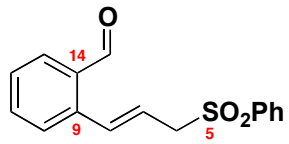


75

Palladium on carbon (50 mg, wet degussa type, 10 % palladium by weight) was added in one portion to a stirred solution of **74** (500 mg, 2.41 mmol) in methanol (15 mL). The solution was degassed three times with hydrogen using a pump-flood procedure and placed under hydrogen for 3 h. The mixture was filtered through Celite™, eluted with methanol (50 mL) and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **75** (160 mg, 37 %) as a pale oil.

ν_{max} (neat): 3445, 3374, 2980, 2951, 1720, 1627. δ_H (400 MHz, $CDCl_3$): 7.16 (1H, d, *J* 7.7, H5), 7.08 (1H, t, *J* 7.7, H3), 6.79 (1H, t, *J* 7.7, H4), 6.70 (1H, d, *J* 7.7, H2), 4.13 (1H, q, *J* 7.2, H7), 4.01 (br. NH), 3.67 (3H, s, H10), 1.54 (3H, d, *J* 7.2, H8). δ_C (100 MHz, $CDCl_3$): 171.1 (C9), 144.7 (C6), 128.0 (C3), 127.7 (C5), 124.7 (C1), 119.1 (C4), 116.7 (C2), 60.4 (C7), 40.5 (C10), 16.0 (C8). LCMS (ES+): 180.1 $[M+H]^+$. HRMS (ES+): found 180.1015; $C_{10}H_{14}NO_2$ $[M+H]^+$ requires 180.1019.

(*E*)-2-(3-(Phenylsulfonyl)allyl)benzaldehyde[66]

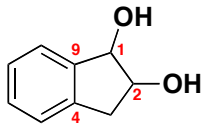


76

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 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 column chromatography (petroleum ether : ethyl acetate, 5 : 1) to afford compound **76** (1.1 g, 71 %) as a yellow solid.

ν_{max} (neat): 3064, 2730, 1694, 1596, 1568. δ_H (500 MHz, $CDCl_3$): 10.00 (1H, s, H15), 7.90 (2H, d, *J* 7.8, H3), 7.77 (1H, d, *J* 7.8, H10/H13), 7.65 (1H, t, *J* 7.7, H1), 7.58 – 7.45 (5H, m, ArH), 7.27 (1H, d, *J* 15.7, H8), 6.11 (1H, dt, *J* 15.7, 7.7, H7), 4.05 (2H, d, *J* 7.7, H6). δ_C (125 MHz, $CDCl_3$): 192.2 (C15), 138.3 (C4/C9), 137.9 (C4/C9), 135.8 (C6), 135.2, 133.9 (C1), 132.7, 132.5, 130.7, 129.9, 129.2, 128.6 (C14), 128.4, 127.7, 120.4 (C7), 60.6 (C8). LCMS (ES+): 227.1 $[M+Na]^+$. HRMS (ES+): found 309.0558; $C_{16}H_{14}O_3SNa$ $[M+Na]^+$ requires 309.0556.

2,3-Dihydro-1*H*-indene-1,2-diol[67]

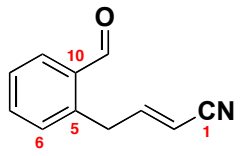


77

Indene (1.0 g, 8.6 mmol), *N*-methylmorpholine-*N*-oxide (1.3 g, 11.2 mmol) and osmium tetroxide (22 mg, 0.1 mmol) were stirred for 24 h in PEG (mw 400, 10 g). Diethyl ether (20 mL) was added to the reaction and stirred vigorously before allowing to settle and decanting the diethyl ether layer. This process was repeated twice, the organic layers were combined, concentrated *in vacuo* and purified by column chromatography (chloroform : methanol, 97 : 3) to afford compound **77** (1.29 g, 99 %) as a white solid. Data matches published data.

ν_{max} (neat): 3418 (br), 1642. δ_H (500 MHz, $CDCl_3$): 7.47 – 7.43 (1H, m, Ar-H), 7.32 – 7.23 (3H, m, Ar-H), 5.03 (1H, dd, *J* 7.0, *J* 5.3, OH), 4.57 – 4.51 (1H, m, OH), 3.15 (1H, dd, *J* 16.5, *J* 5.9, H3), 2.98 (1H, dd, *J* 16.5, *J* 3.7, H3), 2.42 (1H, d, *J* 7.4, H1), 2.35 (1H, d, *J* 6.0, H2). δ_C (125 MHz, $CDCl_3$): 141.9 (C4/C9), 140.1 (C4/C9), 128.9 (C5/C6/C7/C8), 127.2 (C5/C6/C7/C8), 125.4 (C5/C6/C7/C8), 125.0 (C5/C6/C7/C8), 76.0 (C1), 73.5 (C2), 38.7 (C3). LCMS (ES+): 173.1 $[M+Na]^+$. HRMS (ES+): found 173.0573; $C_9H_{10}O_2Na$ $[M+Na]^+$ requires 173.0573.

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



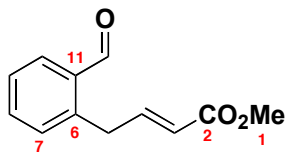
78

Diol **77** (1.3 g, 8.6 mmol) and sodium periodate (2.2 g, 10.3 mmol) were stirred in tetrahydrofuran (30 mL) and water (70 mL) for 6 h. The tetrahydrofuran was removed *in vacuo* and sodium chloride was added to the remaining mixture until saturated. The resulting solution was extracted with ethyl acetate (3 x 100 mL), the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude aldehyde obtained (218 mg, 1.5 mmol, 17 %) was stirred with 2-(triphenylphosphoranylidene)acetonitrile (443 mg, 1.5 mmol) in dichloromethane (3 mL) for 24 h. The reaction mixture was diluted with diethyl ether (10 mL), filtered to remove the solids formed, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 25 : 1) to afford *(E)*-**78** (91 mg, 35 %) and *(Z)*-**78** (32 mg, 13 %).

(E): ν_{max} (neat): 3057, 2925, 2859, 2360, 2342, 1697, 1631, 1601. 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, s, 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 (125 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). LCMS (ES+): 194.1 $[M+Na]^+$. HRMS (ES+): found 194.0575; $C_{11}H_9NNaO$ $[M+Na]^+$ requires 194.0576.

(Z): ν_{max} (neat): 3021, 2917, 2849, 2360, 2342, 1697, 1602. δ_H (500 MHz, $CDCl_3$): 10.15 (1H, s, H11), 7.83 (1H, dd, *J* 7.5, *J* 0.9, H6), 7.59 (1H, td, *J* 7.5, *J* 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, *J* 7.5, H3), 5.39 (1H, d, *J* 10.8, H2), 4.19 (2H, d, *J* 7.5, H4). δ_C (125 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). LCMS (ES+): 194.1 $[M+Na]^+$. HRMS (ES+): found 194.0578; $C_{11}H_9NNaO$ $[M+Na]^+$ requires 194.0576.

(*E*)-Methyl 4-(2-formylphenyl)but-2-enoate[68]

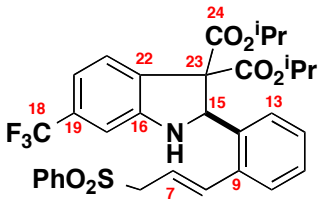


79

Diol **77** (1.3 g, 8.6 mmol) and sodium periodate (2.2 g, 10.3 mmol) were stirred in tetrahydrofuran (30 mL) and water (70 mL) for 6 h. The tetrahydrofuran was removed *in vacuo* and sodium chloride was added to the remaining mixture until saturated. The resulting solution was extracted with ethyl acetate (3 x 100 mL), the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude aldehyde obtained (205 mg, 1.4 mmol, 16 %) was stirred with methyl 2-(triphenylphosphoranylidene)acetate (463 mg, 1.4 mmol) in dichloromethane (3 mL) for 24 h. The reaction mixture was diluted with diethyl ether (10 mL), filtered to remove the solids formed, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 25 : 1) to afford compound **79** (90 mg, 37 %) as a pale oil. Data matches published data.

ν_{max} (neat): 2851, 2860, 2734, 1723, 1697, 1655, 1600, 1575. 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, *J* 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 (125 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). LCMS (ES+): 227.1 $[M+Na]^+$. HRMS (ES+): found 227.0679; $C_{12}H_{12}O_3Na$ $[M+Na]^+$ requires 227.0679.

(*R*,*E*)-diisopropyl 2-(2-(3-(phenylsulfonyl)prop-1-en-1-yl)phenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate

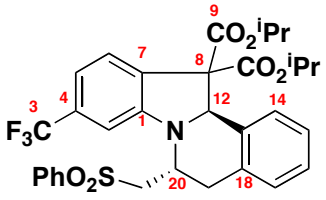


80

Aniline **8** (50 mg, 0.14 mmol), aldehyde **76** (47 mg, 0.14 mmol) and magnesium sulfate (87 mg, 0.73 mmol) were stirred for 12 h in toluene. The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (1 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (6 mg, 0.02 mmol) was added and the mixture was cooled to – 78 ˚C for 30 mins before adding anhydrous powdered potassium hydroxide (81 mg, 1.44 mmol). The reaction was stirred at – 78 ˚C for 16 h before being diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layer were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting mixture of diastereoisomers was separated by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford the compound **80** (91 mg, 99%) as a yellow oil.

ν_{max} (neat): 3066, 3026, 2984, 1728, 1618, 1596. δ_H (500 MHz, $CDCl_3$): 7.94 (2H, d, *J* 7.5, H3), 7.64 (1H, t, *J* 7.5, H1), 7.57 (2H, t, *J* 7.5 H2), 7.47 (1H, d, *J* 7.9, H21), 7.32 – 7.29 (1H, m, H13), 7.25 – 7.20 (2H, m, H11, H12), 7.19 – 7.14 (1H, m, H10), 7.04 (1H, d, *J* 7.9, H20), 6.96 (1H, d, *J* 15.6, H8), 6.85 (1H, s, H17), 5.99 (1H, dt, *J* 15.6, *J* 7.7, H7), 5.93 (1H, s, H15), 5.07 (1H, sept, *J* 6.3, H25), 4.49 (1H, sept, *J* 6.3, H25), 4.04 – 4.00 (2H, m, H6), 1.28 (3H, d, *J* 6.3, H26), 1.22 (3H, d, *J* 6.3, H26), 0.97 (3H, d, *J* 6.3, H26), 0.46 (3H, d, *J* 6.3, H26). δ_C (125 MHz, $CDCl_3$): 167.5 (C24), 166.6 (C24), 150.6 (C22), 138.6 (C4), 137.3 (C8), 137.3 (C14), 135.8 (C9), 133.7 (C1), 132.2 (q, *J* 32, C19), 129.2 (C2), 128.7 (C10/C11/C12), 128.6 (C10/C11/C12), 128.4 (C3), 128.1 (C21), 127.6 (C11/C12), 126.9 (C16), 126.6 (C10), 124.2 (q, *J* 273, C18), 118.6 (C7), 115.5 (q, *J* 4, C20), 105.3 (q, *J* 4, C2), 70.3 (C25), 69.7 (C25), 68.8 (C23), 62.4 (C15), 60.6 (C6), 21.5 (C26), 21.4 (C26), 21.2 (C26), 20.3 (C26). δ_F (376 MHz, $CDCl_3$): – 62.5. LCMS (ES+): 638.2 $[M+Na]^+$. HRMS (ES+): found 638.1795; $C_{32}H_{32}NF_3O_6SNa$ $[M+Na]^+$ requires 638.1795.

(6*R*,12a*R*)-Diisopropyl 6-((phenylsulfonyl)methyl)-9-(trifluoromethyl)-5,6-dihydroindolo[2,1-*a*]isoquinoline-12,12(12a*H*)-dicarboxylate



81

Asymmetric: Aniline **8** (50 mg, 0.14 mmol), aldehyde **76** (47 mg, 0.14 mmol) and magnesium sulfate (87 mg, 0.73 mmol) were stirred for 12 h in toluene. The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (1 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (6 mg, 0.02 mmol) was added and the mixture was cooled to – 78 ˚C for 30 mins before adding anhydrous powdered potassium hydroxide (81 mg, 1.44 mmol). The reaction was stirred at – 78 ˚C for 16 h and then allowed to warm to RT for 6 h before being diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layer were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting mixture of diastereoisomers was separated by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford the major diastereoisomer **81** (as drawn, 47 mg, 53 %, 83 % ee) as a yellow oil and the minor diastereoisomer **82** (34 mg, 38 %, 87 % ee) as a yellow oil.

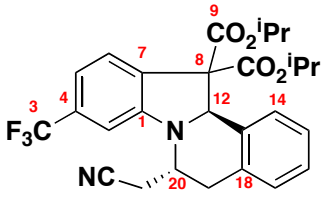
Racemic: Aniline **8** (50 mg, 0.14 mmol), aldehyde **76** (47 mg, 0.14 mmol) and magnesium sulfate (87 mg, 0.72 mmol) were stirred for 16 h at RT in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (1 mL), tetrabutylammonium chloride (3 mg, 0.01 mmol) and $CsOH{\cdot}H_2O$ (140 mg, 0.43 mmol) were added and the reaction left to stir for 6 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford the major diastereoisomer **81** (as drawn, 24 mg, 27 %) and the minor diastereoisomer **82** (13 mg, 15 %).

Major Diastereomer 81 (as drawn): ν_{max} (neat): 3070, 2983, 2933, 1724, 1667, 1614. $[\alpha]_D^{25}$ + 11 (*c* = 1.25, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.78 (2H, dd, *J* 8.0, *J* 0.8, H23), 7.57 (1H, t, *J* 7.4, H25), 7.46 – 7.37 (4H, m, H6, H17, H24), 7.22 – 7.16 (2H, m, H15, H16), 7.07 – 7.03 (1H, m, H14), 6.96 (1H, d, *J* 7.9, H5), 6.87 (1H, s, H2), 5.20 (1H, sept, *J* 6.3, H10), 5.11 (1H, s, H12),

4.63 – 4.56 (1H, m, H20), 4.39 (1H, sept, *J* 6.3, H10), 3.32 (1H, dd, *J* 14.8, *J* 8.4, H21), 3.16 (1H, dd, *J* 14.8, *J* 5.3, H21), 3.10 (1H, dd, *J* 15.5, *J* 5.5, H19), 2.72 (1H, d, *J* 15.5, H19), 1.38 (3H, d, *J* 6.3, H11), 1.36 (3H, d, *J* 6.3, H11), 0.76 (3H, d, *J* 6.3, H11), 0.61 (3H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 168.2 (C9), 166.9 (C9), 150.0 (C1), 139.4 (C7), 133.7 (C25), 132.7 (C18), 132.2 (C22), 131.4 (C13), 130.8 (q, *J* 263, C3), 130.2 (C4), 129.4 (C14), 129.0 (C24), 128.1 (C17), 127.9 (C15/C16), 127.5 (C23), 126.9 (C15/C16), 126.0 (C6), 115.4 (C5), 105.5 (C2), 70.3 (C10), 69.8 (C10), 68.1 (C8), 63.3 (C12), 57.8 (C21), 49.7 (C20), 33.1 (C19), 21.7 (C11), 21.5 (C11), 20.8 (C11), 20.7 (C11). δ_F (376 MHz, $CDCl_3$): – 62.6. LCMS (ES+): 638.2 $[M+Na]^+$. HRMS (ES+): found 616.1820; $C_{32}H_{33}NF_3O_6S$ $[M+H]^+$ requires 616.1981. Chiral HPLC (Chiralpak IA, 3 % IPA, 97 % hexane, 1.0 mL.min^{-1}, λ = 209) t_R (major) = 21.6, t_R (minor) = 17.4.

Minor Diastereomer 82: ν_{max} (neat): 2984, 2924, 1725, 1668. $[\alpha]_D^{25}$ + 36 (*c* = 1.85, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.91 (2H, d, *J* 8.6, H23), 7.72 (1H, t, *J* 7.5, H25), 7.64 – 7.58 (3H, m, H6, H24), 7.41 (1H, d, *J* 7.6, H17), 7.35 – 7.23 (3H, m, H14, H15, H16), 6.96 (1H, d, *J* 7.9, H5), 6.24 (1H, s, H2), 5.51 (1H, s, H12), 5.27 (1H, sept, *J* 6.3, H10), 4.77 (1H, sept, *J* 6.3, H10), 4.50 – 4.45 (1H, m, H20), 3.58 (1H, dd, *J* 15.2, *J* 1.9, H19), 3.18 (1H, dd, *J* 15.2, *J* 4.9, H19), 3.03 (1H, d, *J* 14.6, H21), 2.87 (1H, dd, *J* 14.6, *J* 10.3, H21), 1.39 (3H, d, *J* 6.3, H11), 1.37 (3H, d, *J* 6.3, H11), 0.91 (3H, d, *J* 6.3, H11), 0.80 (3H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 168.2 (C9), 167.0 (C9), 147.4 (C1), 139.1 (C7), 134.2 (C13/C22), 124.1 (C25), 132.5 (C13/C22), 132.2 (C18), 130.8 (C4), 129.6 (C24), 129.5 (C15), 127.8 (C23), 127.6 (C14), 126.8 (C16), 126.2 (C6), 125.3 (C17), 124.0 (q, *J* 272, C3), 115.3 (C5), 103.7 (C2), 70.5 (C10), 69.9 (C10), 65.7 (C8), 64.6 (C12), 56.0 (C21), 46.1 (C20), 32.9 (C19), 21.6 (C11), 21.6 (C11), 21.2 (C11), 21.2 (C11). δ_F (376 MHz, $CDCl_3$): – 62.5. LCMS (ES+): 638.2 $[M+Na]^+$. HRMS (ES+): found 638.1789; $C_{32}H_{32}NF_3O_6SNa$ $[M+Na]^+$ requires 638.1795. Chiral HPLC (Chiralpak IA, 4 % IPA, 96 % hexane, 1.0 mL.min^{-1}, λ = 335) t_R (major) = 14.8, t_R (minor) = 13.2.

(6*R*,12a*R*)-Diisopropyl 6-(cyanomethyl)-9-(trifluoromethyl)-5,6-dihydroindolo[2,1-*a*]isoquinoline-12,12(12a*H*)-dicarboxylate



84

Asymmetric: Aniline **8** (50 mg, 0.14 mmol), aldehyde **78** (25 mg, 0.14 mmol) and magnesium sulfate (87 mg, 0.73 mmol) were stirred for 12 h in toluene. The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (1 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (6 mg, 0.02 mmol) was added and the mixture was cooled to – 78 ˚C for 30 mins before adding anhydrous powdered potassium hydroxide (81 mg, 1.44 mmol). The reaction was stirred at – 78 ˚C for 16 h and then allowed to warm to RT for 6 h before being diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting mixture of diastereoisomers were separated by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford the major diastereoisomer **84** (as drawn, 41 mg, 57 %, 93 % ee) and the minor diastereoisomer **83** (30 mg, 42 %, 90 % ee).

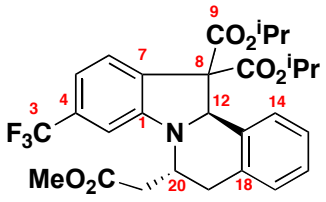
Racemic: Aniline **8** (24 mg, 0.07 mmol), aldehyde **78** (12 mg, 0.07 mmol) and magnesium sulfate (42 mg, 0.35 mmol) were stirred for 16 h at RT in toluene (0.4 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.7 mL), tetrabutylammonium chloride (3 mg, 0.01 mmol) and $CsOH{\cdot}H_2O$ (131 mg, 0.40 mmol) were added and the reaction left to stir for 6 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford the major diastereoisomer **84** (as drawn, 14 mg, 40 %) as a white solid and the minor diastereoisomer **83** (5 mg, 15 %) as a pale solid.

Major Diastereomer 84 (as drawn): ν_{max} (neat): 2984, 2934, 2360, 2342, 1731, 1699, 1668,1624. $[\alpha]_D^{25}$ – 11 (*c* = 0.95, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.57 (1H, d, *J* 7.0, H17), 7.53 (1H, d, *J* 7.9, H6), 7.29 – 7.22 (2H, m, H15, H16), 7.11 (1H, d, *J* 6.7, H14), 7.02 (1H, d, *J* 7.9, H5), 6.97 (1H, s, H2), 5.98 (1H, s, H12), 5.28 (1H, sept, *J* 6.3, H10), 4.47 (1H, sept, *J* 6.3, H10),

4.42 – 4.36 (1H, m, H20), 3.17 (1H, dd, *J* 15.5, *J* 5.2, H19), 2.76 (1H, d, *J* 15.5, H19), 2.55 (1H, dd, *J* 16.8, *J* 7.0, H21), 2.45 (1H, dd, *J* 16.8, *J* 7.3, H21) 1.42 (3H, d, *J* 6.3, H11), 1.38 (3H, d, *J* 6.3, H11), 0.85 (3H, d, *J* 6.3, H11), 0.63 (3H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 168.3 (C9), 167.0 (C9), 150.7 (C1), 132.5 (C7), 131.9 (C18), 131.0 (C13), 130.7 (C4), 129.6 (C17), 128.6 (C14), 128.1 (C15/C16), 127.1 (C15/C16), 126.2 (C6), 124.1 (q, *J* 273, C3), 117.8 (C22), 115.9 (C5), 105.6 (C2), 70.5 (C10), 69.9 (C10), 68.2 (C8), 63.9 (C12), 51.9 (C20), 32.4 (C19), 21.7 (C11), 21.6 (C11), 21.6 (C21), 21.0 (C11), 20.7 (C11). δ_F (376 MHz, $CDCl_3$): – 62.6. LCMS (ES+): 523.2 $[M+Na]^+$. HRMS (ES+): found 523.1816; $C_{27}H_{27}N_2F_3O_4Na$ $[M+Na]^+$ requires 523.1815. Chiral HPLC (Chiralpak OD-H, 3 % IPA, 97 % hexane, 1.0 mL.min^{-1}, λ = 219) t_R (major) = 12.8, t_R (minor) = 9.8. Mp: 93 – 95 ˚C (diethyl ether : petroleum ether).

Minor Diastereomer 83: ν_{max} (neat): 2986, 2936, 2851, 2360, 2339, 1792, 1646. $[\alpha]_D^{25}$ + 83 (*c* = 1.20, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.67 (1H, d, *J* 7.9, H6), 7.46 (1H, d, *J* 7.3, H17), 7.35 (1H, d, *J* 7.0, H14), 7.33 – 7.27 (2H, m, H15, H16), 7.02 (1H, d, *J* 7.9, H5), 6.74 (1H, s, H2), 5.52 (1H, s, H12), 5.29 (1H, sept, *J* 6.3, H10), 4.83 (1H, sept, *J* 6.3, H10), 4.50 – 4.46 (1H, m, H20), 3.28 (2H, br, H19), 2.57 (1H, dd, *J* 17.0, *J* 3.3, H21), 2.11 (1H, dd, *J* 17.0, *J* 10.6, H21), 1.41 (3H, d, *J* 6.3, H11), 1.39 (3H, d, *J* 6.3, H11), 1.02 (3H, d, *J* 6.3, H11), 0.92 (3H, d, *J* 6.3, H11). δ_C (125 MHz, $CDCl_3$): 168.2 (C9), 167.1 (C9), 147.7 (C7), 133.8 (C13), 132.6 (C1), 131.9 (C18), 130.7 (C4), 129.2 (C14), 127.7 (C15/C16), 127.0 (C15/C16), 126.4 (C6), 125.6 (C17), 125.1 (C3), 117.7 (C22), 115.6 (C5), 103.9 (C2), 70.5 (C10), 70.1 (C10), 65.5 (C12), 65.0 (C8), 48.1 (C20), 33.0 (C19), 21.7 (C11), 216 (C11), 21.3 (C11), 21.3 (C11), 20.1 (C21). δ_F (376 MHz, $CDCl_3$): – 61.0. LCMS (ES+): 523.2 $[M+Na]^+$. HRMS (ES+): found 523.1816; $C_{27}H_{27}N_2F_3O_4Na$ $[M+Na]^+$ requires 523.1815. Chiral HPLC (Chiralpak OD-H, 3 % IPA, 97 % hexane, 1.0 mL.min^{-1}, λ = 216) t_R (major) = 7.2, t_R (minor) = 19.0.

(6*R*,12a*R*)-Diisopropyl 6-(2-methoxy-2-oxoethyl)-9-(trifluoromethyl)-5,6-dihydroindolo[2,1-*a*]isoquinoline-12,12(12a*H*)-dicarboxylate



85

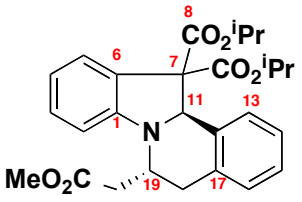
Asymmetric: Aniline **8** (50 mg, 0.14 mmol), aldehyde **79** (25 mg, 0.14 mmol) and magnesium sulfate (87 mg, 0.73 mmol) were stirred for 12 h in toluene. The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (1 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (6 mg, 0.02 mmol) was added and the mixture was cooled to – 78 ˚C for 30 mins before adding anhydrous powdered potassium hydroxide (81 mg, 1.44 mmol). The reaction was stirred at – 78 ˚C for 16 h and then allowed to warm to RT for 6 h before being diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **85** (68 mg, 88 %, 91 % ee), a single diastereoisomer, as a pale oil.

Racemic: Aniline **8** (25 mg, 0.07 mmol), aldehyde **79** (14 mg, 0.07 mmol) and magnesium sulfate (42 mg, 0.35 mmol) were stirred for 16 h at RT in toluene (0.4 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.7 mL), tetrabutylammonium chloride (3 mg, 0.01 mmol) and $CsOH \cdot H_2O$ (235 mg, 0.72 mmol) were added and the reaction left to stir for 16 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford compound **85** (29 mg, 57 %).

ν_{max} (neat): 2984, 2939, 1732, 1614. $[\alpha]_D^{25}$ + 8 (*c* = 1.10, $CHCl_3$). 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, sept, *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, *J* 5.2, H19), 3.04 (1H, dd, *J* 15.1, *J* 1.9, H19), 2.53 (1H, d, *J* 15.8, H21), 2.12 (1H, dd, *J* 15.9, *J* 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 (125

MHz, $CDCl_3$): 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, $CDCl_3$): – 62.6. LCMS (ES+): 556.2 $[M+Na]^+$. HRMS (ES+): found 556.1916; $C_{28}H_{30}NF_3O_6Na$ $[M+Na]^+$ requires 556.1917. Chiral HPLC (Chiralpak IC, 1 % IP, 99 % hexane, 1.0 $mL.min^{-1}$, λ = 288) t_R (major) = 12.5, t_R (minor) = 17.7.

(6*R*,12a*R*)-Diisopropyl 6-(2-methoxy-2-oxoethyl)-5,6-dihydroindolo[2,1-*a*]isoquinoline-12,12(12a*H*)-dicarboxylate



86

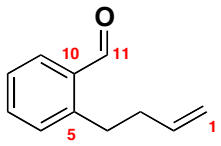
Asymmetric: Aniline **8** (50 mg, 0.18 mmol), aldehyde **79** (37 mg, 0.18 mmol) and magnesium sulfate (101 mg, 0.84 mmol) were stirred for 12 h in toluene (1 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was redissolved in toluene (1 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (6 mg, 0.02 mmol) was added and the mixture was cooled to – 78 ˚C for 30 mins before adding anhydrous powdered potassium hydroxide (101 mg, 1.80 mmol). The reaction was stirred at – 78 ˚C for 16 h and then allowed to warm to RT for 6 h before being diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford compound **86** (36 mg, 45 %, 80 % ee) as a pale oil.

Racemic: Aniline **8** (25 mg, 0.09 mmol), aldehyde **79** (18 mg, 0.09 mmol) and magnesium sulfate (54 mg, 0.45 mmol) were stirred for 16 h at RT in toluene (0.4 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.5 mL), tetrabutylammonium chloride (3 mg, 0.01 mmol) and potassium hydroxide (50 mg, 0.90 mmol) were added and the reaction left to stir for 16 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford compound **86** (15 mg, 36 %).

ν_{max} (neat): 2982, 2952, 1731, 1664, 1601. $[\alpha]_D^{25}$ + 6 (*c* = 0.3, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 7.56 (1H, d, *J* 7.7, H5), 7.48 – 7.43 (1H, m, H13), 7.27 – 7.18 (4H, m, H3, H14, H15, H16), 6.71 (1H, t, *J* 7.7, H4), 6.60 (1H, d, *J* 7.8, H2), 5.53 (1H, s, H11), 5.28 (1H, sept, *J* 6.3, H9), 4.81 (1H, sept, *J* 6.3, H9), 4.51 – 4.45 (1H, m, H19), 3.69 (3H, s, H22), 3.19 (1H, dd, *J* 15.0, *J* 5.2, H18), 3.01 (1H, dd, *J* 15.0, *J* 1.9, H18), 2.57 (1H, d, *J* 15.7, H20), 2.09 (1H, dd, *J* 15.7, *J* 10.6, H20), 1.40 (3H, d, *J* 6.3, H10), 1.38 (3H, d, *J* 6.3, H10), 0.93 (3H, d, *J* 6.3, H10), 0.80 (3H, d, *J* 6.3,

H10). δ_C (125 MHz, $CDCl_3$): 172.6 (C21), 169.2 (C8), 167.9 (C8), 148.2 (C1), 135.0 (C12), 133.5 (C17), 129.8 (C3), 128.9 (C14/C15/C16), 127.0 (C14/C15/C16), 126.9 (C6), 126.5 (C14/C15/C16), 126.0 (C5), 125.5 (C13), 117.7 (C4), 107.8 (C2), 69.9 (C9), 69.3 (C9), 66.1 (C7), 64.8 (C11), 51.6 (C22), 48.0 (C19), 36.6 (C20), 33.7 (C18), 21.7 (C10), 21.6 (C10), 21.3 (C10), 21.1 (C10). HRMS (ES+): 488.2038 found; $C_{27}H_{31}NO_6Na$ $[M+Na]^+$ requires 488.2044. Chiral HPLC (Chiralpak IA, 3 % IPA, 97 % hexane, 1.0 $mL.min^{-1}$, $\lambda = 272$) t_R (major) = 6.6, t_R (minor) = 7.0.

2-(But-3-en-1-yl)benzaldehyde[71]

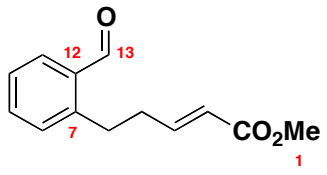


87

Allylmagnesium bromide (6.5 mL, 1 M in tetrahydrofuran, 6.56 mmol) was added dropwise over 30 minutes to a stirred solution of 2-bromobenzylbromide (1.0 g, 4.37 mmol) in tetrahydrofuran (3 mL). The resulting solution was heated to reflux for 2 h before being allowed to cool to RT. The reaction was quenched with ammonium chloride (sat. aq., 30 mL) and the aqueous layer was extracted with diethyl ether (3 x 50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The clear liquid was redissolved in tetrahydrofuran (4 mL) at – 78 ˚C and *n*-butyllithium (4.1 mL, 1.6 M in hexanes, 6.56 mmol) was added dropwise over 30 minutes followed by DMF (0.8 mL, 10.93 mmol) in tetrahydrofuran (1.5 mL) over 30 minutes. The resulting solution was allowed to warm to RT overnight before quenching with ammonium chloride (sat. aq., 50 mL), the aqueous layer was extracted with diethyl ether (3 x 50 mL), dried over magnsium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : diethyl ether, 50 : 1) to afford compound **87** (517 mg, 68 %) as a pale liquid. Data matches published data.

ν_{max} (neat): 3075, 2930, 1697, 1600. δ_H (400 MHz, $CDCl_3$): 10.28 (1H, s, H11), 7.84 (1H, d, *J* 7.7, H9), 7.52 (1H, td, *J* 7.5, *J* 1.2, H7), 7.39 (1H, t, *J* 7.5, H8), 7.29 (1H, d, *J* 7.5, H6), 5.94 – 5.90 (1H, m, H2), 5.10 – 4.97 (2H, m, H1), 3.15 (2H, t, *J* 7.6, H4), 2.43 – 2.34 (2H, m, H3). δ_C (100 MHz, $CDCl_3$): 192.4 (C11), 144.7 (C10), 137.4 (C2), 133.7 (C7), 132.0 (C9), 131.1 (C6), 130.1 (C5), 126.6 (C8), 115.5 (C1), 35.9 (C3), 32.0 (C4). HRMS (FI): found 160.0888; $C_{11}H_{12}O$ $[M]^+$ requires 160.0888.

Methyl 5-(2-formylphenyl)pent-2-enoate[72]

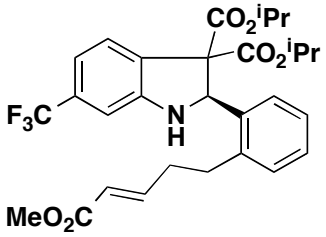


88

Hoveyda-Grubbs catalyst second generation (18 mg, 0.03 mmol) was added to a stirred solution of aldehyde **87** (100 mg, 0.58 mmol) and methyl acrylate (104 μL, 1.16 mmol) in dichloromethane (3 mL) and left to stir for 16 h at RT. The resulting solution was concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 25 : 1) to afford aldehyde **88** (121 mg, 90 %) as a pale oil. Data matches published data.

ν_{max} (neat): 2952, 2738, 1721, 1696, 1657. δ_H (400 MHz, $CDCl_3$): 10.14 (1H, s, H13), 7.79 (1H, d, *J* 7.6, H11), 7.50 (1H, t, *J* 7.4, H9), 7.39 (1H, t, *J* 7.4, H10), 7.25 (1H, d, *J* 7.5, H8), 7.00 (1H, dt, *J* 15.7, *J* 7.0, H4), 5.82 (1H, d, *J* 15.7, H3), 3.69 (3H, s, H1), 3.17 (2H, t, *J* 7.7, H6), 2.52 – 2.45 (2H, m, H5). δ_C (100 MHz, $CDCl_3$): 192.7 (C13), 166.9 (C2), 147.9 (C4), 143.1 (C12), 133.8 (C9), 133.8 (C11), 133.7 (C7), 131.1 (C10), 127.0 (C8), 121.7 (C3), 51.4 (C1), 33.8 (C5), 31.5 (C6). LCMS (ES+): 241.1 $[M+Na]^+$. HRMS (ES+): found 241.0830; $C_{13}H_{14}O_3Na$ $[M+Na]^+$ requires 241.0835.

(*R*,*E*)-Diisopropyl 2-(2-(5-methoxy-5-oxopent-3-en-1-yl)phenyl)-6-(trifluoromethyl)indoline-3,3-dicarboxylate



89

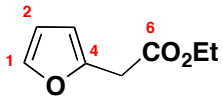
Asymmetric: Aniline **8** (15 mg, 0.04 mmol), aldehyde **88** (10 mg, 0.04 mmol) and magnesium sulfate (26 mg, 0.21 mmol) were stirred for 16 h at RT in toluene (0.5 mL). The resulting mixture was filtered and concentrated *in vacuo.* The imine was then redissolved in toluene (0.6 mL), (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride (4 mg, 0.01 mmol) was added and the solution was stirred at RT for 30 minutes. Potassium carbonate (33 % aq., 0.3 mL) was added to the reaction and allowed to stir for 70 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracting with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **89** (24 mg, 71 %) as a yellow oil.

Racemic: Aniline **8** (18 mg, 0.05 mmol), aldehyde **88** (12 mg, 0.05 mmol) and magnesium sulfate (32 mg, 0.27 mmol) were stirred for 16 h at RT in toluene (0.5 mL). The resulting mixture was filtered and concentrated *in vacuo*. The imine was then redissolved in toluene (0.6 mL), tetrabutylammonium chloride (2 mg, 0.01 mmol) and potassium carbonate (33 % aq., 3 mL) were added and the reaction left to stir for 16 h. The mixture was then diluted with ammonium chloride (sat. aq., 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford **89** (29 mg, 64 %).

ν_{max} (neat):3375, 2984, 2936, 1725, 1656, 1618. δ_H (500 MHz, $CDCl_3$): 7.51 (1H, d, *J* 8.0, ArH), 7.20 (2H, t, *J* 7.6, ArH), 7.15 – 6.98 (4H, m, ArH/H21), 6.86 (1H, s, H2), 6.14 (1H, s, H12), 5.92 (1H, d, *J* 15.7, H22), 5.14 – 5.04 (2H, m, H10), 3.75 (3H, s, H24), 3.18 – 3.09 (1H, m, H20),

2.87 – 2.77 (1H, m, H20), 2.66 – 2.49 (2H, m, H19), 1.31 – 1.20 (12H, m, H11). δ_C (125 MHz, $CDCl_3$): 167.8 (C9), 167.6 (C9), 167.1 (C23), 150.8 (C1/C7/C13/C18), 148.0 (C21), 146.0 (C1/C7/C13/C18), 139.1 (C1/C7/C13/C18), 138.1 (C1/C7/C13/C18), 132,2 (q, *J* 32, C4), 129.3 (C6/C14/C15/C16/C17), 128.8 (C6/C14/C15/C16/C17), 128.5 (C6/C14/C15/C16/C17), 127.4 (C6/C14/C15/C16/C17), 127.0 (C6/C14/C15/C16/C17), 124.2 (q, *J* 272, C3), 121.7 (C22), 115.4 (q, *J* 4, C5), 105.3 (q, *J* 4, C2), 70.3 (C10), 69.9 (C10), 69.0 (C8), 62.0 (C12), 51.5 (C24), 34.0 (C19), 31.4 (C20), 21.4 (C11), 21.3 (C11). δ_F (470 MHz, $CDCl_3$): – 62.6. LCMS (ES+): 570.2 $[M+Na]^+$. HRMS (ES+): found 548.2250; $C_{29}H_{33}F_3NO_6$ $[M+H]^+$ requires 548.2254. Chiral HPLC (Chiralpak OD-H, 4 % IPA, 96 % hexane, 1.0 mL.min^{-1}, λ = 209) t_R (major) = 17.9, t_R (minor) = 14.5.

Ethyl 2-(furan-2-yl)acetate[78]

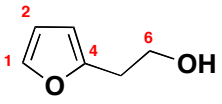


124

Hydrogen peroxide (33 % aq., 1.9 mL, 38.8 mmol) was added dropwise over 30 minutes to a stirring solution of furan (5.6 mL, 77.7 mmol), ethyl iodoacetate (0.5 mL, 4.3 mmol) and $FeSO_4 \cdot 7H_2O$ (0.6 g, 2.2 mmol) in dimethylsulfoxide (85 mL) at RT. The reaction was stirred for a further 2 h at RT before diluting with brine (sat. aq., 50 mL) and extracting with diethyl ether (2 x 100 mL). The combined organic layers were washed with brine (sat. aq., 50 mL), dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford ester **124** (0.4 g, 62 %) as a colourless oil. Data matches published data.

ν_{max} (neat): 2984, 1737. δ_H (400 MHz, $CDCl_3$): 7.36 (1H, d, *J* 1.8, H1), 6.34 (1H, dd, *J* 3.2, *J* 1.8, H2), 6.23 (1H, d, *J* 3.2, H3), 4.19 (2H, q, *J* 7.2, H7), 3.61 (2H, s, H5), 1.27 (3H, t, *J* 7.2, H8). δ_C (100 MHz, $CDCl_3$): 169.4 (C6), 147.8 (C4), 142.0 (C1), 110.5 (C2), 107.9 (C3), 61.1 (C7), 34.1 (C5), 14.1 (C8). LCMS (ES+): 177.1 $[M+Na]^+$. HRMS (ES+): found 177.0518; $C_8H_{10}O_3Na$ $[M+Na]^+$ requires 177.0522.

2-(furan-2-yl)ethanol[79]

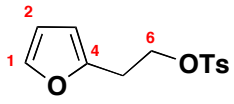


125

Lithium aluminium hydride (8 mL, 1 M in tetrahydrofuran) was added dropwise to a stirred solution of ester **124** (400 mg, 2.6 mmol) in tetrahydrofuran (20 mL) at 0 ˚C. The reaction was then heated to reflux for 1.5 h before cooling to RT and quenching by the dropwise addition of brine (sat. aq.). The resulting white precipitate was removed by filtration and the remaining fluid was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (sat. aq., 50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford **125** (230 mg, 79 %) as a colourless oil. Data matches published data.

ν_{max} (neat): 3294 (br), 2950, 2838, 1642. δ_H (400 MHz, $CDCl_3$): 7.35 (1H, dd, *J* 1.9, *J* 0.8, H1), 6.32 (1H, *J* 3.1, *J* 1.9, H2), 6.12 (1H, dd, *J* 3.1, *J* 0.8, H3), 3.89 (2H, br. s, H6), 2.91 (2H, t, *J* 6.3, H5), 1.62 (1H, br, OH). δ_C (100 MHz, $CDCl_3$): 152.8 (C4), 141.6 (C1), 110.3 (C2), 106.5 (C3), 61.1 (C6), 31.6 (C5). HRMS (FI+): found 112.0525; $C_6H_8O_2$ $[M]^+$ requires 112.0524.

2-(Furan-2-yl)ethyl 4-methylbenzenesulfonate[79]

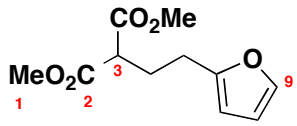


90

Alcohol **125** (230 mg, 2.1 mmol), pyridine (330 μL, 4.1 mmol) and tosyl chloride (588 mg, 3.1 mmol) were stirred in chloroform (3 mL) at RT for 3 h. The reaction was then diluted with sodium bicarbonate (sat. aq., 10 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 25 : 1) to afford **90** (274 mg, 50 %) as a pale oil.

ν_{max} (neat): 2960, 2925, 1598. δ_H (400 MHz, $CDCl_3$): 7.75 (2H, d, *J* 8.2, H8), 7.33 (2H, d, *J* 8.2, H9), 7.28 – 7.25 (1H, m, H1), 6.28 – 6.25 (1H, m, H2), 6.07 – 6.05 (1H, m, H3), 4.25 (2H, t, *J* 6.8, H6), 3.00 (2H, t, *J* 6.8, H5), 2.46 (3H, s, H11). δ_C (100 MHz, $CDCl_3$): 150.1 (C4/C7/C10), 144.8 (C4/C7/C10), 141.7 (C1), 132.9 (C4/C7/C10), 129.8 (C9), 127.9 (C8), 110.3 (C2), 107.1 (C3), 67.8 (C6), 28.0 (C5), 21.6 (C11). LCMS (ES+): 289.0 $[M+Na]^+$. HRMS (ES+): found 289.0502; $C_{13}H_{14}O_4SNa$ $[M+Na]^+$ requires 289.0505.

Dimethyl 2-(2-(furan-2-yl)ethyl)malonate

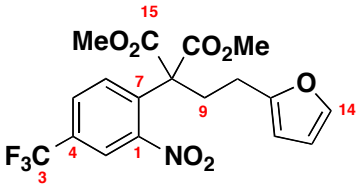


91

Tosylate **90** (606 mg, 2.28 mmol) and sodium iodide (683 mg, 4.46 mmol) were stirred in acetone (6 mL) at 35 ˚C for 2 h before cooling. The reaction was cooled to RT, filtered to remove the white precipitate and concentrated *in vacuo* to afford the corresponding iodide. Sodium hydride (100 mg, 2.51 mmol) was added in one portion to a stirring solution of dimethyl malonate (260 μL, 2.28 mmol) in DMF (4 mL) at 0 ˚C. The iodide was dissolved in DMF (4 mL) and then added to the stirred solution of dimethyl malonate at 0 ˚C. The resulting solution was allowed to warm to RT and stirred for a further 16 h before diluting with ammonium chloride (sat. aq., 20 mL) and extracting with dichloromethane (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 10 :1) to afford **91** (443 mg, 73 %) as a pale oil.

ν_{max} (neat): 2955, 1733, 1598. δ_H (400 MHz, $CDCl_3$): 7.33 – 7.30 (1H, m, H9), 6.29 – 6.25 (1H, m, H8), 6.07 – 6.01 (1H, m, H7), 3.75 (3H, s, H1), 3.42 (1H, t, *J* 7.4, H3), 2.71 (2H, t, *J* 7.4, H5), 2.26 (2H, q, *J* 7.4, H4). δ_C (100 MHz, $CDCl_3$): 169.6 (C2), 154.0 (C6), 129.8 (C9), 110.1 (C8), 105.8 (C7), 52.6 (C1), 50.7 (C3), 27.2 (C4), 25.6 (C5). LCMS (ES+): 249.1 $[M+Na]^+$. HRMS (ES+): found 249.0736; $C_{11}H_{14}O_5Na$ $[M+Na]^+$ requires 249.0733.

Dimethyl 2-(2-(furan-2-yl)ethyl)-2-(2-nitro-4-(trifluoromethyl)phenyl)malonate

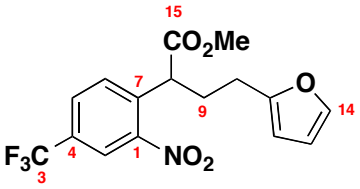


92

Malonate **91** (414 mg, 1.56 mmol) was added to a stirred slurry of potassium carbonate (240 mg, 1.74 mmol) in DMF at 90 ˚C. After 10 mins stirring, 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (222 μL, 1.56 mmol) was added in one portion and allowed to stir for 24 h at 90 ˚C. The reaction mixture was cooled to RT, diluted with dichloromethane (50 mL), washed with ammonium chloride (sat. aq., 50 mL) and extracted with dichloromethane (2 x 50 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether : ethyl acetate, 15 : 1) to afford compound **92** (304 mg, 43 % yield) as a yellow oil.

ν_{max} (neat): 3091, 3010, 2957, 2847, 1738, 1631. δ_H (500 MHz, $CDCl_3$): 8.30 (1H, s, H2), 7.89 (1H, d, *J* 8.4, H5), 7.60 (1H, d, *J* 8.4, H6), 7.28 (1H, dd, *J* 1.7, *J* 0.6, H14), 6.25 (1H, dd, *J* 3.2, *J* 1.7, H13), 5.98 (1H, dd, *J* 3.2, *J* 0.6, H12), 3.76 (6H, s, H16), 2.91 – 2.87 (2H, m, H9), 2.67 – 2.61 (2H, m, H10). δ_C (125 MHz, $CDCl_3$): 168.7 (C15), 153.7 (C11), 149.6 (C1), 141.3 (C14), 135.6 (C7), 131.4 (q, *J* 34, C4), 131.2 (C6), 129.3 (q, *J* 3, C5), 123.2 (q, *J* 4, C2), 122.5 (q, *J* 273, C3), 110.2 (C13), 105.4 (C12), 62.3 (C8), 55.3 (C16), 33.7 (C9), 24.2 (C10). δ_F (376 MHz, $CDCl_3$): – 63.1. LCMS (ES+): 438.1 $[M+Na]^+$. HRMS (ES+): found 438.0771; $C_{18}H_{16}F_3NO_7Na$ $[M+Na]^+$ requires 438.0771.

Methyl 4-(furan-2-yl)-2-(2-nitro-4-(trifluoromethyl)phenyl)butanoate

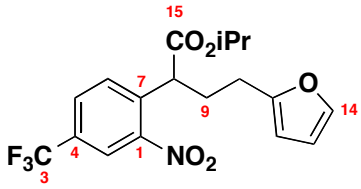


93

Nitro compound **92** (275 mg, 0.60 mmol), sodium chloride (106 mg, 1.81 mmol) and water (103 μL, 9.07 mmol) in dimethylsulfoxide (5 mL) were heated to 110 ˚C for 16 h. After cooling to RT the mixture was then washed with water (30 mL), extracted with dichloromethane (3 x 30 mL), dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 20 : 1) to afford compound **93** (151 mg, 63 %) as a yellow oil.

ν_{max} (neat): 3098, 2956, 1737, 1630. δ_H (500 MHz, $CDCl_3$): 8.17 (1H, s, H2), 7.84 (1H, d, *J* 8.3, H5), 7.68 (1H, d, *J* 8.3, H6), 7.29 – 7.28 (1H, m, H14), 6.26 (1H, dd, *J* 3.2, *J* 1.9, H13), 5.98 (1H, dd, *J* 3.2, *J* 0.7, H12), 4.27 (1H, t, *J* 7.3, H8), 3.69 (3H, s, H16), 2.71 – 2.65 (2H, m, H10), 2.62 – 2.54 (1H, m, H9), 2.27 – 2.17 (1H, m, H9). δ_C (125 MHz, $CDCl_3$): 172.0 (C15), 153.7 (C11), 149.3 (C1), 141.3 (C14), 137.1 (C7), 131.2 (C6), 130.8 (q, *J* 34, C4), 129.4 (q, *J* 3, C5), 122.7 (q, *J* 272, C3), 122.1 (q, *J* 4, C2), 110.2 (C13), 105.9 (C12), 52.6 (C16), 45.6 (C8), 31.1 (C9), 25.9 (C10). δ_F (376 MHz, $CDCl_3$): – 63.0. LCMS (ES+): 380.1 $[M+Na]^+$. HRMS (ES+): found 380.0706; $C_{16}H_{14}F_3NO_5Na$ $[M+Na]^+$ requires 380.0716.

Isopropyl 4-(furan-2-yl)-2-(2-nitro-4-(trifluoromethyl)phenyl)butanoate

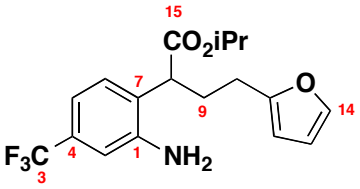


94

Methyl ester **93** (93 mg, 0.26 mmol), lithium bromide (101 mg, 1.16 mmol) and DBU (18 μL, 0.07 mmol) in isopropyl alcohol (1 mL) were stirred for 16 h at 80 ˚C. The resulting solution was then cooled to RT, diluted with ammonium chloride (sat. aq., 5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (petroleum ether : ethyl acetate, 40 : 1) to afford isopropyl ester **94** (61 mg, 61 %) as a pale yelow oil.

ν_{max} (neat): 3098, 2984, 2940, 1731, 1630. δ_H (500 MHz, $CDCl_3$): 8.16 (1H, s, H2), 7.83 (1H, d, *J* 8.2, H5), 7.69 (1H, d, *J* 8.2, H6), 7.29 (1H, dd, *J* 1.6, *J* 0.6, H14), 6.26 (1H, dd, *J* 3.1, *J* 1.6, H13), 5.99 (1H, dd, *J* 3.1, *J* 0.6, H12), 5.01 (1H, sept, *J* 6.3, H16), 4.21 (1H, t, *J* 7.2, H8), 2.70 (2H, qd, *J* 15.3, *J* 7.2, H10), 2.69 – 5.51 (1H, m, H9), 2.27 – 2.16 (1H, m. H9), 1.24 (3H, d, *J* 6.3, H17), 1.15 (3H, d, *J* 6.3, H17). δ_C (125 MHz, $CDCl_3$): 171.0 (C15), 153.8 (C11), 149.4 (C1), 141.3 (C14), 137.3 (C7), 131.1 (C6), 130.7 (q, *J* 35, C4), 129.3 (q, *J* 3, C5), 122.7 (q, *J* 272, C3), 122.0 (q, *J* 4, C2), 110.2 (C13), 105.8 (C12), 69.3 (C16), 46.0 (C8), 31.0 (C9), 26.0 (C10), 21.7 (C17), 21.4 (C17). LCMS (ES+): 408.1 $[M+Na]^+$. HRMS (ES+): found 386.1201; $C_{18}H_{19}F_3NO_5$ $[M+H]^+$ requires 386.1210.

Isopropyl 2-(2-amino-4-(trifluoromethyl)phenyl)-4-(furan-2-yl)butanoate

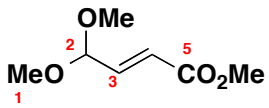


95

Palladium hydroxide (6 mg, 10 % palladium by weight) was added in one portion to a stirred solution of nitro compound **94** (60 mg, 0.21 mmol) and triethylamine (100 μL, 0.72 mmol) in ethyl acetate (3 mL). The solution was degassed three times with hydrogen using a pump-flood procedure and placed under hydrogen for 4 h. The mixture was filtered through Celite™, eluted with ethyl acetate (50 mL) and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether : ethyl acetate, 10 : 1) to afford compound **95** (54 mg, 98 %) as a pale yellow solid.

ν_{max} (neat): 3471, 3386, 2983, 2939, 1717, 1634. δ_H (500 MHz, $CDCl_3$): 7.33 – 7.31 (1H, m, H14), 7.22 (1H, d, *J* 8.0, H6), 6.99 (1H, d, *J* 8.0, H5), 6.91 (1H, s, H2), 6.30 (1H, dd, *J* 3.0, *J* 1.9, H13), 6.02 (1H, d, *J* 3.0, H12), 5.01 (1H, sept, *J* 6.3, H16), 4.20 (2H, br, NH), 3.62 (1H, t, *J* 7.6, H8), 2.65 (2H, t, *J* 7.4, H10), 2.55 – 2.46 (1H, m, H9), 2.22 – 2.13 (1H, m, H9), 1.23 (3H, d, *J* 6.3, H17), 1.18 (3H, d, *J* 6.3, H17). δ_C (125 MHz, $CDCl_3$): 172.6 (C15), 154.6 (C11), 145.3 (C7), 141.2 (C14), 130.3 (q, *J* 31, C4), 128.8 (C6), 126.2 (C1), 124.0 (q, *J* 272, C3), 115.2 (q, *J* 4, C5), 113.0 (q, *J* 4, C2), 110.2 (C13), 105.6 (C12), 68.8 (C16), 46.3 (C8), 28.6 (C9), 25.8 (C10), 21.7 (C17), 21.6 (C17). δ_F (376 MHz, $CDCl_3$): – 62.8. LCMS (ES+): 378.1 $[M+Na]^+$. HRMS (ES+): found 356.1458; $C_{18}H_{21}F_3NO_3$ $[M+H]^+$ requires 356.1468.

(*E*)-Methyl 4,4-dimethoxybut-2-enoate



96

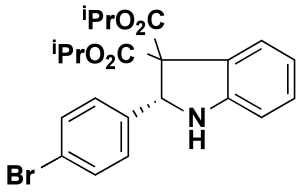
Potassium carbonate (0.99 g, 7.1 mmol) and dimethoxyactaldehyde (1.43 mL, 9.5 mmol, 60 % aq.) were added to a stirred solution of dimethylphosphonoacetate (0.89 mL, 4.6 mmol) in cyclohexane (12 mL) and left to stif for 1 h at 60 ˚C. The resulting solution was washed with ammonium chloride (sat. aq., 30 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with ammonium chloride (sat. aq., 50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford compound **96** (0.76 g, 90 %) as a colourless liquid.

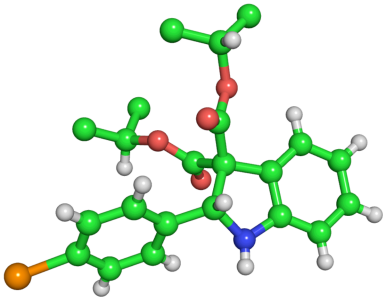
ν_{max} (neat): 2996, 2953, 2909, 2834, 1727. δ_H (400 MHz, $CDCl_3$): 6.77 (1H, dd, *J* 15.8, *J* 3.8, H3), 6.15 (1H, dd, *J* 15.8, *J* 1.3, H4), 4.95 (1H, dd, *J* 3.8, *J* 1.3, H2), 3.76 (3H, s, H6), 3.33 (6H, s, H1). δ_C (100 MHz, $CDCl_3$): 166.3 (C5), 142.9 (C3), 124.2 (C4), 100.4 (C2), 52.8 (C1), 51.8 (C6). HRMS (ES+): found 183.0629; $C_7H_{12}O_4Na$ $[M+Na]^+$ requires 183.0628.

5.3 X-ray crystallography data

futher data may be found on the attached CD for all structures. Key data and refinement for each structure are presented here.

(*R*)-Diisopropyl 2-(4-bromophenyl)indoline-3,3-dicarboxylate

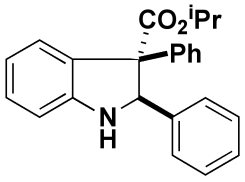


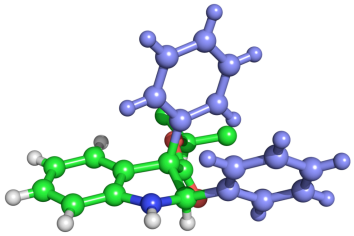


Key data and refinement for compound 28	
Empirical formula	$C_{22}H_{24}BrNO_4$
Formula weight	446.34
Temperature	150 K
Wavelength	0.71973 Å
Crystal system	Monoclinic
Space group	P 1 21 1
Unit cell dimensions	a = 9.9674(2) Å $\alpha = 90^\circ$
	b = 9.2807(2) Å $\beta = 93.4081(9)^\circ$
	c = 11.8745(3) Å $\gamma = 90^\circ$
Volume	1096.50(4) $Å^3$
Z	2
Density (calculated)	1.352 Mg/m^3
Absorption coefficient	1.900 mm^{-1}
F(000)	460

Crystal size	0.50 x 0.20 x 0.13 mm^3
Theta range for data collected	5.192 to 27.442°
Index ranges	-12<=h<=12, -11<=k<=12, -15<=l<=15
Reflections collected	4599
Independent reflections	4599 [R(int) = 0.056]
Completeness to theta = 75.913°	98.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.78 and 0.70
Refinement method	Full-matric least-squares on F^2
Data / restraint / parameters	4599 / 1 / 254
Goodness-of-fit on F^2	1.0000
Final R indices [I>2sigma(I)]	R1 = 0.0342, wR2 = 0.0869
R indices (all data)	R1 = 0.0364, wR2 = 0.0899
Absolute structure parameter	0.028(8)
Largest diff. peak hole	0.34 and -0.79 $e.Å^{-3}$

Isopropyl 2,3-diphenylindoline-3-carboxylate

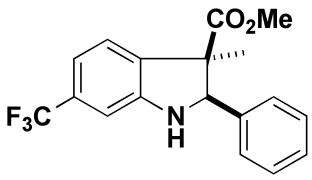


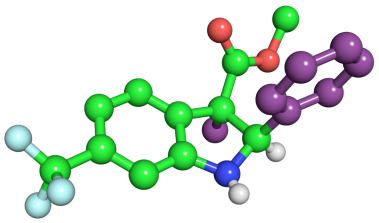


Key data and refinement for compound 50	
Empirical formula	$C_{24}H_{23}NO_2$
Formula weight	375.45
Temperature	150 K
Wavelength	0.71973 Å
Crystal system	Monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a = 9.8715(2) Å α = 90°
	b = 15.2884(3) Å β = 94.7782(6)°
	c = 25.8224(5) Å γ = 90°
Volume	3883.56(13) $Å^3$
Z	8
Density (calculated)	1.223 Mg/m^3
Absorption coefficient	0.077 mm^{-1}
F(000)	1520
Crystal size	0.400 x 0.400 x 0.400 mm^3
Theta range for data collected	5.104 to 27.498°
Index ranges	-12<=h<=12, -13<=k<=19, -33<=l<=33
Reflections collected	32816
Independent reflections	8771 [R(int) = 0.032]
Completeness to theta = 75.913°	98.6 %

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.97 and 0.86
Refinement method	Full-matric least-squares on F^2
Data / restraint / parameters	5774 / 0 / 487
Goodness-of-fit on F^2	0.9373
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.0998
R indices (all data)	R1 = 0.0697, wR2 = 0.1136
Largest diff. peak hole	0.33 and –0.30 e.$Å^{-3}$
Melting point	103 – 105 °C (dichloromethane : petroleum ether)

Methyl 3-methyl-2-phenyl-6-(trifluoromethyl)indoline-3-carboxylate

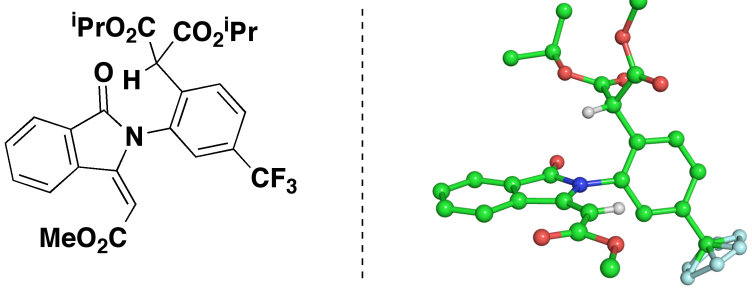




Key data and refinement for compound 59	
Empirical formula	$C_{18}H_{16}F_3NO_2$
Formula weight	335.32
Temperature	150 K
Wavelength	1.54180 Å
Crystal system	Monoclinic
Space group	P 1 21/n 1
Unit cell dimensions	a = 17.7908(2) Å α = 90°
	b = 9.85220(10) Å β = 91.7299(10)°
	c = 18.4426(6) Å γ = 90°
Volume	3231.12(6) $Å^3$
Z	8
Density (calculated)	1.379 Mg/m^3
Absorption coefficient	0.967 mm^{-1}
F(000)	1392
Crystal size	0.060 x 0.060 x 0.030 mm^3
Theta range for data collected	3.401 to 76.666°
Index ranges	-22<=h<=22, -12<=k<=12, -23<=l<=23
Reflections collected	66402
Independent reflections	6785 [R(int) = 0.038]
Completeness to theta = 75.913°	99.6 %

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.97 and 0.88
Refinement method	Full-matric least-squares on F^2
Data / restraint / parameters	6781 / 324 / 489
Goodness-of-fit on F^2	0.9743
Final R indices [I>2sigma(I)]	R1 = 0.0477, wR2 = 0.1268
R indices (all data)	R1 = 0.0573, wR2 = 0.1335
Largest diff. peak hole	0.67 and –0.67 e.$Å^{-3}$

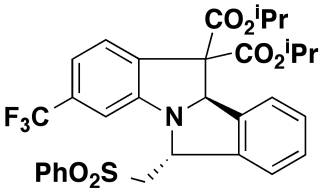
(*E*)-Diisopropyl 2-(2-(1-(2-methoxy-2-oxoethylidene)-3-oxoisoindolin-2-yl)-4-(trifluoromethyl)phenyl)malonate

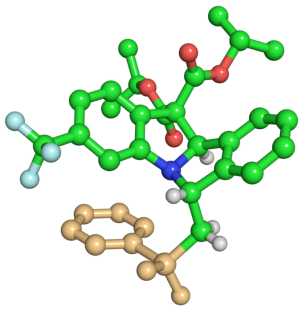


Key data and refinement for compound 126	
Empirical formula	$C_{28}H_{28.5}F_3NO_{7.25}$
Formula weight	552.03
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P - 1
Unit cell dimensions	a = 9.3027(3) Å α = 82.7658(15)°
	b = 11.0771(4) Å β = 76.1820(14)°
	c = 14.8761(6) Å γ = 77.2574(15)°
Volume	1447.56(9) $Å^3$
Z	2
Density (calculated)	1.266 Mg/m^3
Absorption coefficient	0.104 mm^{-1}
F(000)	577
Crystal size	0.350 x 0.290 x 0.170 mm^3
Theta range for data collected	5.254 to 26.435°

Index ranges	-11<=h<=11, -13<=k<=13, -17<=l<=18
Reflections collected	15021
Independent reflections	5842 [R(int) = 0.023]
Completeness to theta = 25.113°	98.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.92
Refinement method	Full-matric least-squares on F^2
Data / restraint / parameters	5842 / 176 / 390
Goodness-of-fit on F^2	0.9425
Final R indices [I>2sigma(I)]	R1 = 0.0732, wR2 = 0.1921
R indices (all data)	R1 = 0.0935, wR2 = 0.2190
Largest diff. peak hole	0.68 and -0.47 e.$Å^{-3}$

Diisopropyl 6-((phenylsulfonyl)methyl)-3-(trifluoromethyl)-6*H*-isoindolo[2,1-*a*]indole-11,11(10b*H*)-dicarboxylate

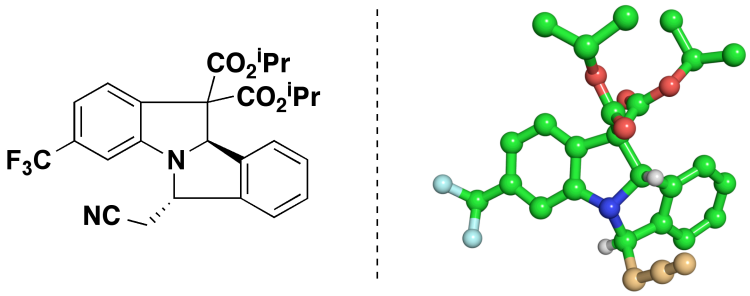




Key data and refinement for compound 65	
Empirical formula	$C_{31}H_{30}F_3NO_6S$
Formula weight	601.64
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a = 11.9727(3) Å α = 90°
	b = 24.2406(7) Å β = 107.339(1)°
	c = 10.4810(3) Å γ = 90°
Volume	2902.67(14) $Å^3$
Z	4
Density (calculated)	1.377 Mg/m^3
Absorption coefficient	0.176 mm^{-1}
F(000)	1256
Crystal size	0.140 x 0.120 x 0.120 mm^3
Theta range for data collected	5.174 to 26.562°
Index ranges	-14<=h<=14, -26<=k<=30, -13<=l<=13
Reflections collected	24515

Independent reflections	5858 [R(int) = 0.041]
Completeness to theta = 25.234°	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.89
Refinement method	Full-matric least-squares on F^2
Data / restraint / parameters	3945 / 0 / 379
Goodness-of-fit on F^2	0.9241
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1132
R indices (all data)	R1 = 0.0656, wR2 = 0.1327
Largest diff. peak hole	0.53 and –0.42 e.$Å^{-3}$

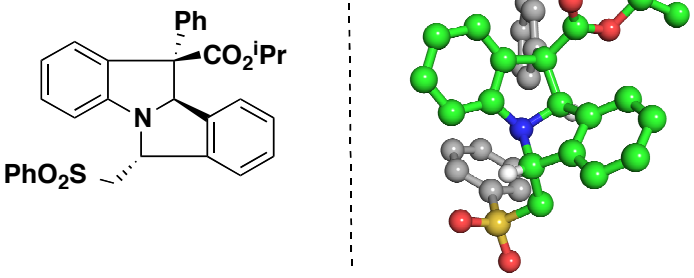
Diisopropyl 6-(cyanomethyl)-3-(trifluoromethyl)-6*H*-isoindolo[2,1-*a*]indole-11,11(10b*H*)-dicarboxylate



Key data and refinement for compound 66	
Empirical formula	$C_{26}H_{25}F_3N_2O_4$
Formula weight	486.49
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 8.6711(3) Å α = 90°
	b = 9.4306(4) Å β = 90°
	c = 29.5986(13) Å γ = 90°
Volume	2420.39(17) $Å^3$
Z	4
Density (calculated)	1.335 Mg/m^3
Absorption coefficient	0.105 mm^{-1}
F(000)	1016
Crystal size	0.340 x 0.120 x 0.030 mm^3
Theta range for data collected	5.111 to 26.023°

Index ranges	-10<=h<=10, -11<=k<=11, -36<=l<=36
Reflections collected	10506
Independent reflections	2566 [R(int) = 0.047]
Completeness to theta = 25.242°	94.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.92
Refinement method	Full-matric least-squares on F^2
Data / restraint / parameters	2015 / 306 / 381
Goodness-of-fit on F^2	0.9894
Final R indices [I>2sigma(I)]	R1 = 0.0835, wR2 = 0.1962
R indices (all data)	R1 = 0.1087, wR2 = 0.2219
Largest diff. peak hole	1.06 and -0.73 e.$Å^{-3}$

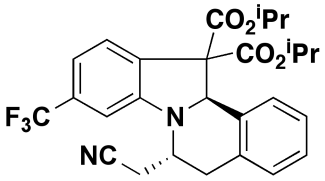
Isopropyl 11-phenyl-6-((phenylsulfonyl)methyl)-10b,11-dihydro-6*H*-isoindolo[2,1-*a*]indole-11-carboxylate

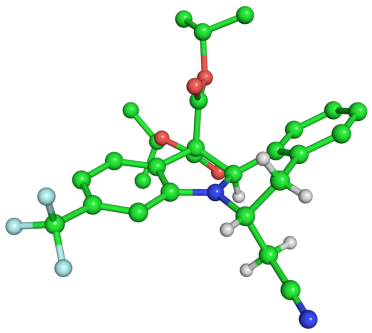


Key data and refinement for compound 71	
Empirical formula	$C_{32}H_{29}NO_4S$
Formula weight	523.65
Temperature	150 K
Wavelength	1.54180 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 9.3165(1) Å $\alpha = 90^\circ$
	b = 14.3322(1) Å $\beta = 90^\circ$
	c = 19.7050(1) Å $\gamma = 90^\circ$
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 collected	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 = 75.913°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.92 and 0.78
Refinement method	Full-matric least-squares on F^2
Data / restraint / 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
Largest diff. peak hole	0.26 and –0.41 e.$Å^{-3}$

(6*R*,12a*R*)-Diisopropyl 6-(cyanomethyl)-9-(trifluoromethyl)-5,6-dihydroindolo[2,1-*a*]isoquinoline-12,12(12a*H*)-dicarboxylate





Key data and refinement for compound 84	
Empirical formula	$C_{27}H_{27}F_3N_2O_4$
Formula weight	500.52
Temperature	150 K
Wavelength	1.54180 Å
Crystal system	Monoclinic
Space group	P 1 21 1
Unit cell dimensions	a = 10.8509(1) Å α = 90°
	b = 9.3445(1) Å β = 107.2971(15)°
	c = 12.7734(2) Å γ = 90°
Volume	1236.60(3) $Å^3$
Z	2
Density (calculated)	1.344 Mg/m^3
Absorption coefficient	0.890 mm^{-1}
F(000)	524
Crystal size	0.320 x 0.070 x 0.030 mm^3
Theta range for data collected	3.624 to 75.913°
Index ranges	-13<=h<=13, -11<=k<=11, -15<=l<=16
Reflections collected	29332

Independent reflections	5108 [R(int) = 0.031]
Completeness to theta = 75.913°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.97 and 0.71
Refinement method	Full-matric least-squares on F^2
Data / restraint / parameters	5106 / 1 / 326
Goodness-of-fit on F^2	0.9957
Final R indices [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0946
R indices (all data)	R1 = 0.0369, wR2 = 0.0957
Absolute structure parameter	0.01(10)
Largest diff. peak hole	0.29 and –0.21 e.$Å^{-3}$

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