DEVELOPMENTS IN CHIRAL COUNTERION-DIRECTED ASYMMETRIC REACTIONS

Alex Cavell

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

Doctor of Philosophy

of the

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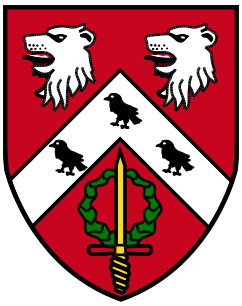

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Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between October 2012 and February 2016. This dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

Alex Cavell

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Abbreviations

°C	-	Degrees Celsius
3D	-	Three-dimensional
Ac	-	Acetyl
AIBN	-	Azobisisobutyronitrile
Anth	-	Anthracenyl
app.	-	Apparent
aq	-	Aqueous
Ar	-	Aryl / Aromatic
BINAP	-	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	-	[1,1'-Binaphthalene]-2,2'-diol
Bn	-	Benzyl
Boc	-	*tert*-Butyloxycarbonyl
br	-	Broad
Bu	-	Butyl
c	-	Centi-
c	-	Concentration
cal	-	Calories
cat.	-	Catalyst
CI	-	Chemical ionisation
COSY	-	^{1}H-^{1}H correlation spectroscopy
CRL	-	Chemistry Research Laboratory
d	-	Doublet / Deci-
DavePhos	-	2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	-	Dibenzylideneacetone
DCC	-	*N*,*N*'-Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
DEPT	-	Distortionless enhancement by polarisation transfer

DMA	-	*N*,*N*-Dimethylacetamide
DMAP	-	4-Dimethylaminopyridine
DMF	-	*N*,*N*-Dimethylformamide
DMSO	-	Dimethyl sulfoxide
d.r.	-	Diastereomeric ratio
DS	-	Diastereomer
δ	-	Chemical shift
EI	-	Electron impact ionisation
eq	-	Equivalents
e.r.	-	Enantiomeric ratio
ESI	-	Electrospray ionisation
Et	-	Ethyl
EWG	-	Electron-withdrawing group
FT	-	Fourier transform
g	-	Grams
G	-	Gibbs free energy
h	-	Hours
HIV	-	Human immunodeficiency virus
HMBC	-	Heteronuclear multiple-bond correlation
HMDS	-	Hexamethyldisilazane
HMQC	-	Heteronuclear multiple-quantum correlation
HPLC	-	High-performance liquid chromatography
HRMS	-	High-resolution mass spectrometry
HSQC	-	Heteronuclear single-quantum correlation
Hz	-	Hertz
i	-	Iso-
IPA	-	Isopropanol
IR	-	Infrared
IUPAC	-	International Union of Pure and Applied Chemistry

J	-	Joules
J	-	Coupling constant
k	-	Kilo-
k	-	Reaction rate constant
K	-	Kelvin
K_a	-	Acid dissociation constant
L	-	Litres
LRMS	-	Low-resolution mass spectrometry
λ	-	Wavelength
m	-	Metres / Milli- / Multiplet
m	-	Meta-
M	-	Mega- / Molar
maj	-	Major
max	-	Maximum
Me	-	Methyl
min	-	Minutes / Minor
mol	-	Moles
m.p.	-	Melting point
MRSA	-	Methicillin-resistant *Staphylococcus aureus*
m/z	-	Mass-to-charge ratio
μ	-	Micro-
n	-	Nano-
n	-	Normal
NBS	-	*N*-Bromosuccinimide
NMR	-	Nuclear magnetic resonance
NOE	-	Nuclear Overhauser effect
Nu	-	Generic nucleophile
v	-	Frequency
o	-	Ortho-

p	-	Para-
Petrol	-	Petroleum ether
Ph	-	Phenyl
ppm	-	Parts per million
Pr	-	Propyl
q	-	Quartet
Q	-	Generic quaternary ammonium or phosphonium
R	-	Generic group/substituent
®	-	Registered trademark
rac	-	Racemic
RT	-	Room temperature
s	-	Solid / Singlet
sat.	-	Saturated
sep	-	Septet
SM	-	Starting material
S_NAr	-	Nucleophilic aromatic substitution
t	-	Triplet
t	-	Tertiary
TBAB	-	Tetra-*n*-butylammonium bromide
tert	-	Tertiary
Tf	-	Trifluoromethanesulfonyl
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TLC	-	Thin-layer chromatography
Tol	-	Tolyl
TosMIC	-	Tosylmethyl isocyanide
t_R	-	Retention time
Ts	-	Tosyl
UV	-	Ultraviolet

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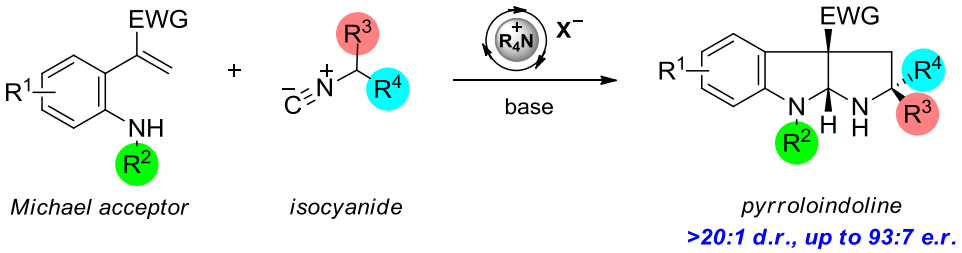
Abstract

The research outlined herein consists of two projects, each relating to the investigation and development of asymmetric phase-transfer catalysed reactions.

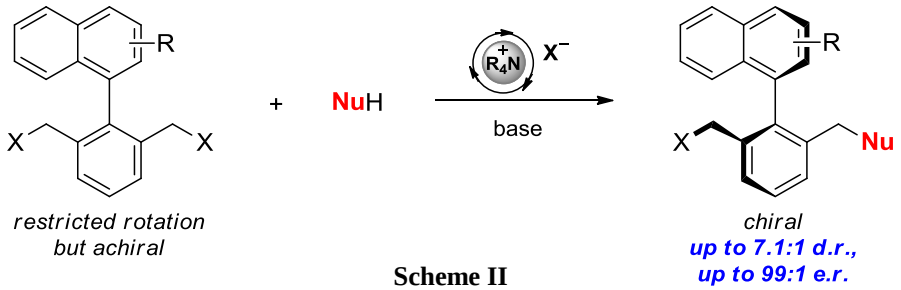
The aim of the first project was to develop a two-component cascade reaction that would assemble the valuable pyrroloindoline framework from simple and readily available starting materials, namely an isocyanide-containing substrate and a Michael acceptor. Successfully, we were able to synthesise a variety of pyrroloindolines containing up to three stereocentres with excellent diastereo- and enantioselectivity (Scheme I).

This rapid strategy uses a chiral ammonium salt to control the selectivity and exploits the remarkable reactivity profile of acidic isocyanides. A mechanistic proposal involving hydrogen-bond activation of the isocyanide is described, originating from the specific design of the Michael acceptor component.



Scheme I

Meanwhile, the objective of the second project was to develop a desymmetrising S_N2 reaction on achiral biaryl substrates under asymmetric phase-transfer conditions, offering a new pathway to axially chiral biaryls. We were able to generate such products, which can be subsequently derivatised, with tremendous enantioselectivity and pleasing diastereoselectivity (Scheme II), particularly when using a glycine Schiff base as the nucleophile.



Scheme II

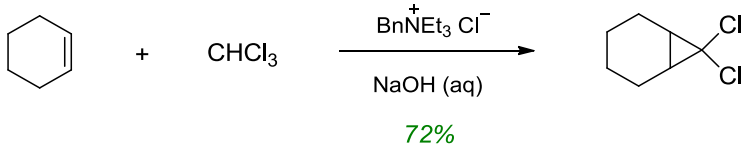
Contents

1. Introduction to Asymmetric Phase-Transfer Catalysis

1.1 Phase-Transfer Catalysis

The term "phase-transfer catalysis", which was devised in 1971 by Starks, describes the striking capability of quaternary ammonium or phosphonium salts to accelerate and influence reactions between two substances located in different immiscible phases.[1]

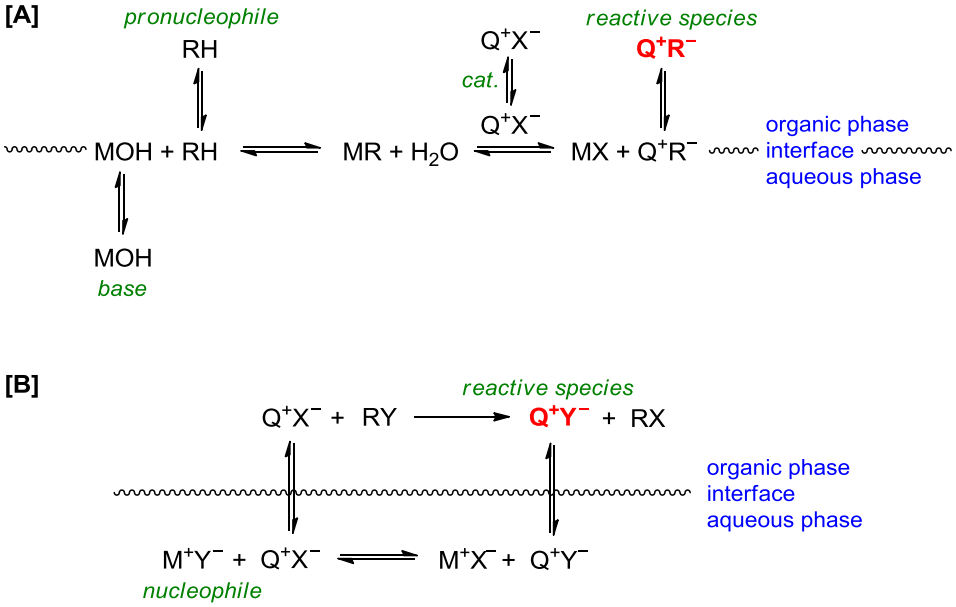
The first example of the commercial usage of phase-transfer catalysis was published in 1946, involving the *in situ* generation of benzyltriethylammonium chloride to catalyse the reaction between sodium benzoate and benzyl chloride, which was investigated due to a wartime shortage of benzaldehyde for the production of benzyl benzoate.[2] Then, in 1969, Mąkosza suggested the first mechanistic hypothesis for this concept, specifically proposing an ion exchange between a tetra-alkylammonium chloride and sodium hydroxide (in reactions including that depicted in Scheme 1), which generates the species that subsequently reacts in the organic phase.[3] This exchange enhances the organic-phase solubility and hence the nucleophilicity of the anion, owing to the lipophilicity and large ionic radius of the onium cation.[4]



Scheme 1. Preparation of dichlorocyclopropane derivatives, for which Mąkosza proposed the first mechanistic ideas for phase-transfer catalysis.

Since these pioneering studies, phase-transfer catalysis has rapidly become a powerful tool in organic synthesis, although the detailed mechanistic aspects remain somewhat uncertain.[5] It has been widely adopted due to the simplicity of the reactions and the versatility of its applications, requiring mild, metal-free reaction conditions and inexpensive,

environmentally benign reagents.[6] Moreover, phase-transfer catalysis has found an important role in a number of industrial processes, including in the commercial manufacture of more than $10 billion per year of chemicals,[7] due to the scalability and low energy demand of such "green" reactions. The ambiguity of the mechanistic pathways followed in asymmetric phase-transfer reactions is largely attributable to the difficulty of examining biphasic systems.[8] However, two approximate schemes that have been formulated have prevailed: the Mąkosza interfacial mechanism and the Starks extraction mechanism (Scheme 2).[5]



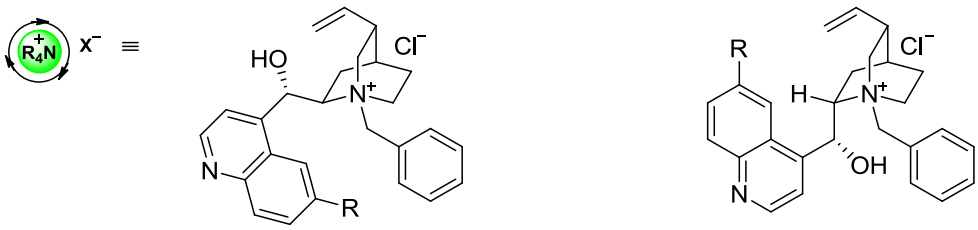
Scheme 2. The two main representative reaction systems for phase-transfer catalysed reactions: [A] the Mąkosza interfacial mechanism; [B] the Starks extraction mechanism. Q^+X^- denotes a general quaternary ammonium or phosphonium salt.

The Mąkosza interfacial mechanism is often followed by the most common system applied in this class of asymmetric catalysis, namely a biphasic mixture consisting of an electrophile and a prochiral acidic methylene or methine compound in the organic phase, together with an inorganic base (normally a metal hydroxide or carbonate) in the aqueous or solid phase.[9] Here, deprotonation of the acidic species by the base at the interface of the two layers generates a carbanion (typically an enolate or similar), which undergoes interfacial ion

exchange with the catalyst. This co-ordination increases the lipophilicity of the reactive species, allowing it to enter the organic phase, where the reaction takes place.

Meanwhile, the Starks extraction mechanism is generally followed when a nucleophilic anion without a prochiral centre attacks a prochiral electrophile, where the anion is employed in an aqueous solution or as a solid inorganic salt (at near-neutral pH).[1] In this system, the catalyst moves between the layers, and the anion is extracted from the aqueous to the organic phase as a tight ion pair with the catalyst's chiral onium cation.

In addition to quaternary ammonium and phosphonium salts, crown ethers (where the whole inorganic salt is transferred into the organic phase),[10] cryptates[11] and open-chain polyethers[12] are also viable phase-transfer catalysts. Frequently, the chiral tetra-alkylammonium salts utilised in asymmetric reactions are derived from cinchona alkaloids, following ground-breaking work in this field by a Merck research group in 1984 (Figure 1).[13] These chiral non-racemic catalysts are highly advantageous, as they are structurally well-defined but modifiable, and capable of inducing excellent selectivity in reactions.[14] This is due to the variety of potential modes of interaction with reacting species, including electrostatic and steric influences, π-π stacking and hydrogen bonding.



C1 R=H
C2 R=OMe

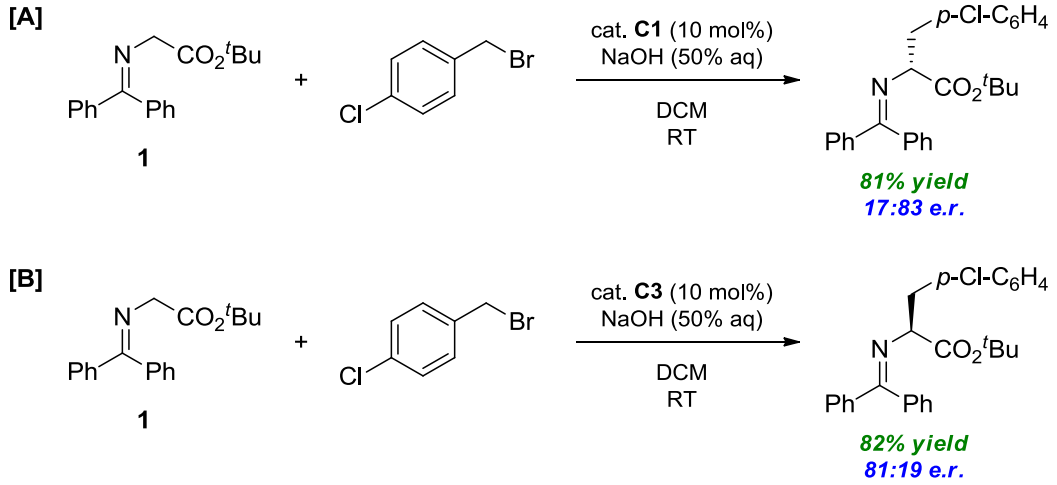
C3 R=H
C4 R=OMe

Figure 1. Simple cinchona alkaloid-derived phase-transfer catalysts: *N*-benzylcinchoninium chloride **C1**, -quinidinium chloride **C2**, -cinchonidinium chloride **C3** and -quininium chloride **C4**.

Consequently, such cinchona alkaloid-derived catalysts have been employed with impressive outcomes in a plethora of reactions, including alkylations,[15] Michael additions,[16] Mannich,[17] aldol[18] and Darzens reactions[19] and fluorinations.[20]

1.2 Asymmetric Phase-Transfer Reactions

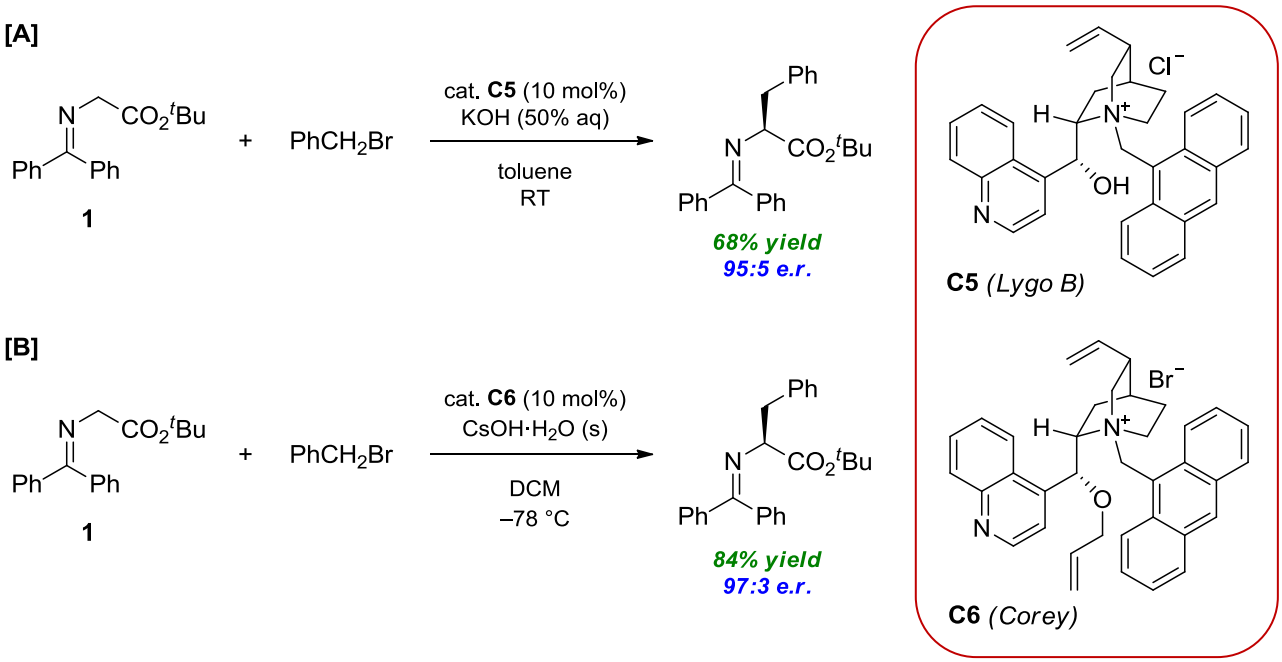
The asymmetric alkylation of glycinate Schiff bases is a valuable reaction for the synthesis of optically pure α-amino acids.[21] The first investigations into this route studied the reaction between *p*-chlorobenzyl bromide and Schiff base **1** (Scheme 3), using 50% aqueous sodium hydroxide as the base in DCM.[22] Both enantiomers of the alkylated product could be selectively accessed, with pseudoenantiomeric catalysts **C1** and **C3** generating opposite major products (in 17:83 and 81:19 e.r. respectively).



Scheme 3. Asymmetric alkylation reaction between *p*-chlorobenzyl bromide and Schiff base **1**, employing pseudoenantiomeric catalysts to generate opposite major products: [A] using cat. **C1**; [B] using cat. **C3**.

Subsequently, it was discovered that progressive improvements could be made to the enantioselectivity by modifying the catalyst. Second-generation catalysts were initially developed, featuring characteristic hydroxy-protection, before major advances by Lygo[23] and

Corey[24] led to the important introduction of third-generation phase-transfer catalysts, incorporating an *N*-anthracenylmethyl group (Scheme 4). Their distinctive cinchonidinium catalysts (Lygo B cat. **C5** and Corey cat. **C6**), together with accompanying optimised conditions, yielded tremendous enantioselectivity in the asymmetric alkylation of glycine Schiff base **1** with benzyl bromide (forming the product in 95:5 and 97:3 e.r. respectively).



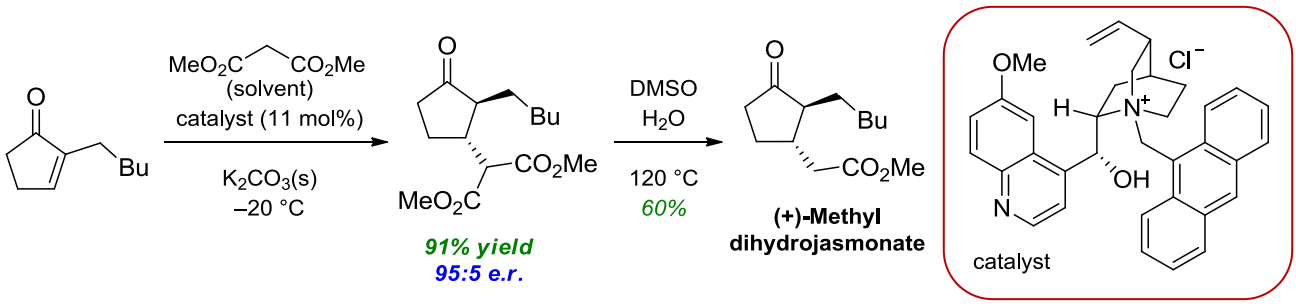
Scheme 4. Asymmetric alkylation reactions using the catalysts and conditions of: [A] Lygo; [B] Corey.

The reaction conditions applied by Lygo feature the use of 50% aqueous potassium hydroxide in toluene at room temperature, whereas Corey's alkylation was carried out at increased concentration with solid caesium hydroxide monohydrate in DCM at −78 °C. The Schiff base **1** employed in these reactions is particularly utile, as the remaining α-proton in the product of an alkylation reaction exhibits significantly reduced acidity compared with **1**, meaning that dialkylation of **1** is minimised.[25] Moreover, this ensures that racemisation of an alkylation product does not occur under basic phase-transfer reaction conditions.

Another prominent reaction that can be performed under asymmetric phase-transfer conditions is the Michael addition. Given that this classical carbon-carbon bond-forming

reaction commonly leads to the formation of a stereogenic centre, phase-transfer catalysis offers a valuable stereoselective pathway towards a variety of functionalised products, such as α-alkyl-α-amino acids.[26] The first successful asymmetric reaction of this type was reported by Cram in 1981, involving the addition of a β-keto ester to methyl vinyl ketone, utilising a chiral crown ether as the phase-transfer catalyst.[27] In this work, the Michael adducts could be generated efficiently with very good enantioselectivity, including an example impressively constructed in 99.5:0.5 e.r..

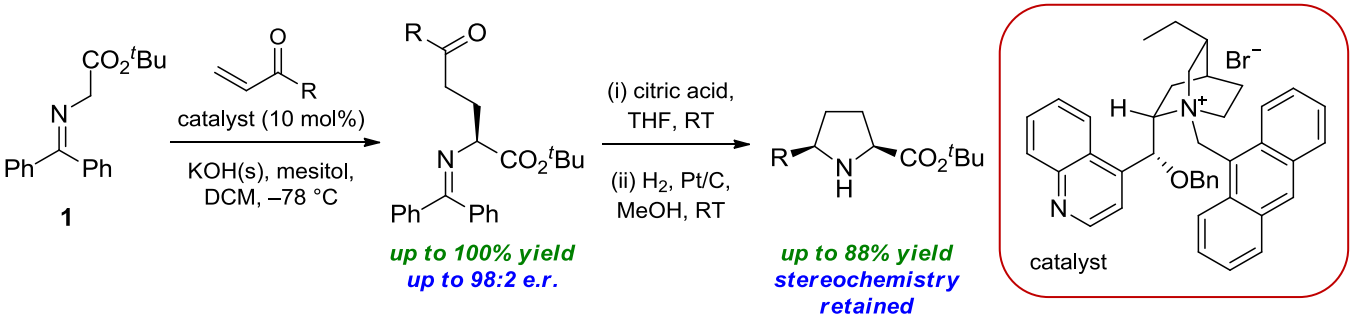
As aforementioned, cinchona alkaloid-derived catalysts can naturally also be utilised in asymmetric Michael additions. One particularly useful instance is in a simple enantioselective synthesis of the aroma compound, methyl dihydrojasmonate.[28] In this sequence, dimethyl malonate is added to 2-pentyl-2-cyclopentenone, where the use of a quininium (Scheme 5) or quinidinium catalyst achieves the selective generation of either enantiomer of an intermediate, upon which a Krapcho decarboxylation[29] is subsequently performed. Here, the catalysts again contain the eminent *N*-anthracenylmethyl group.



Scheme 5. Enantioselective synthesis of (+)-methyl dihydrojasmonate, featuring an asymmetric Michael addition.

The flagship glycine Schiff base **1** has also been recently exploited by Lygo in the enantioselective synthesis of *cis*-5-substituted proline esters, involving an asymmetric Michael addition (Scheme 6).[30] This route incorporates a conjugate addition of the Schiff base **1** to vinyl ketones in the presence of a dihydrocinchonidinium catalyst (containing an

N-anthracenylmethyl group), before acid-catalysed imine exchange and hydrogenation produce the amino acid derivatives in high yields and excellent enantioselectivity.



Scheme 6. Enantioselective synthesis of *cis*-5-substituted proline esters from Schiff base **1** under asymmetric phase-transfer conditions. Mesitol is used as a co-catalyst. Products formed as a single diastereomer.

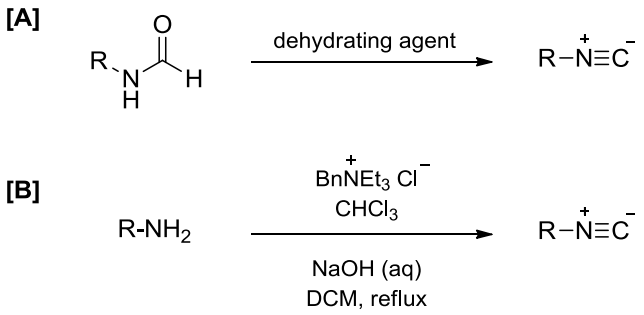
In conclusion, with an ever-growing library of successful asymmetric reactions effected by phase-transfer catalysis, the development of new catalysts with rational design modifications is an on-going topic of importance in synthetic organic chemistry.[26] The increasing versatility of this technique has steered it to the forefront of modern stereoselective approaches, and further studies may allow a more precise view of the mechanistic aspects of such reactions to be achieved.

1.3 Isocyanides

Isocyanides play a crucial role as building blocks in organic synthesis, with particularly widespread applications in heterocyclic chemistry.[31] This functional group displays remarkable versatility, with the ability to act as both a nucleophile and electrophile, and shows extensive ability to partake in multicomponent and cascade reactions.[32]

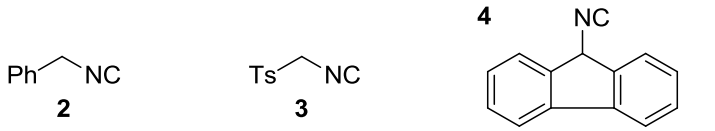
The synthetic power of isocyanides was largely underappreciated for around a century after their first recognition by Hofmann[33] and Gautier[34] in the 1860s, largely due to a

reluctance to carry out research on account of the exceptionally foul odour of the simplest compounds.[35] However, isocyanides became more accessible in the middle of the 20th century with the Ugi-led development of new, reliable synthetic methods, namely the dehydration of formamides[36] and the phase-transfer catalysed carbylamine reaction (Scheme 7).[37]



Scheme 7. Methods for the synthesis of isocyanides: [A] general dehydration of formamides; [B] Ugi's pioneering phase-transfer catalysed carbylamine reaction.

In aliphatic isocyanides, the electron-withdrawing effect of the isocyano-group augments the acidity of the α-H (Figure 2). This feature was first exploited in a carbonyl olefination reaction in 1968, where an isocyanide was demonstrated to be able to act akin to a Wittig reagent,[38] and was subsequently incorporated in the renowned van Leusen[39] and Barton-Zard[40] reactions.

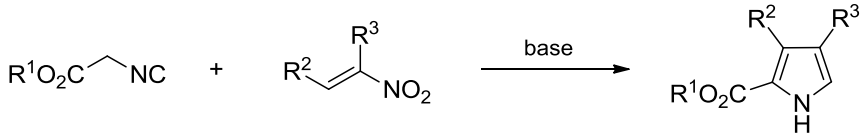


pK_a	*27.4*	*14*	*12.3*

Figure 2. Known equilibrium acidities of isocyanides in DMSO at 25 °C.[41,42]

The van Leusen reaction represents an attractive method to transform a ketone into a nitrile (with an additional carbon atom) using tosylmethyl isocyanide, a synthon with diverse functionality commonly known as TosMIC (**3** in Figure 2). Alternatively, if an aldehyde is utilised instead of a ketone, oxazoles are synthesised by this process because of earlier viable elimination of the excellent tosyl leaving group.[43] Meanwhile, the Barton-Zard reaction offers

a further route to nitrogen-containing heterocycles, as pyrrole derivatives are the outcome of the combination of an α-isocyanoacetate with a nitroalkene under basic conditions (Scheme 8). This elegant reaction consists of conjugate addition of the deprotonated isocyanide compound to the nitroalkene (facilitated by the electron-withdrawing group) and a 5-*endo-dig* cyclisation, followed by elimination of the nitro group and an aromatising [1,5]-H shift.

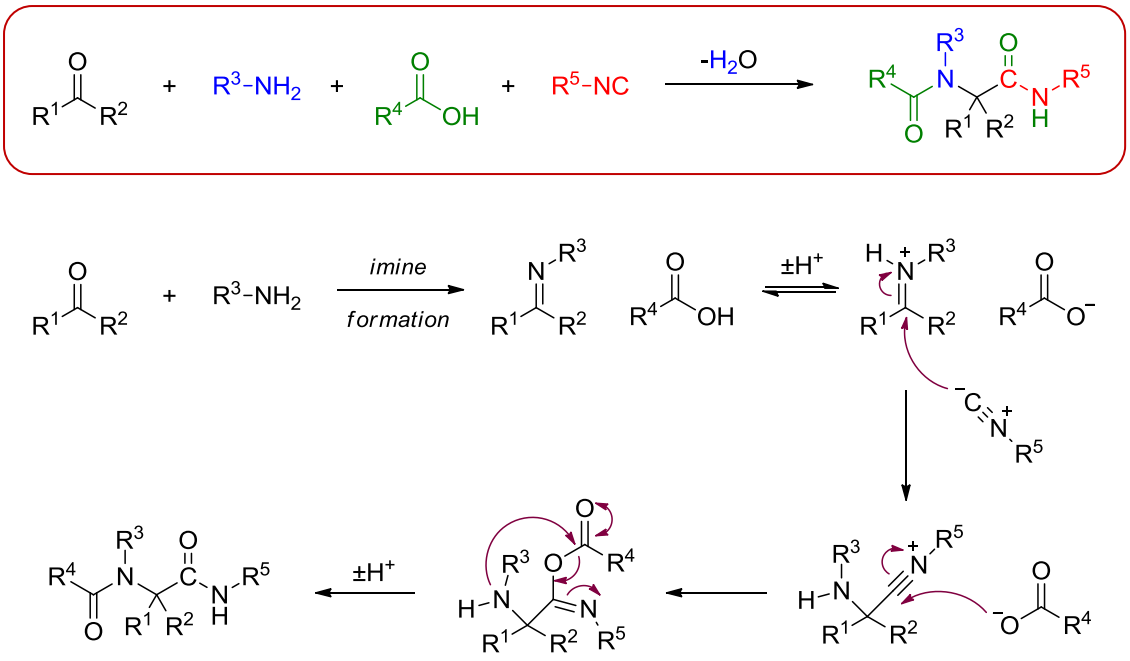


Scheme 8. The Barton-Zard pyrrole synthesis.

As described above, isocyanide-containing compounds take part in an array of multicomponent reactions, exploiting their dual functionality as both a nucleophile and electrophile. Generally, in order to operate as an electrophile, the isocyanide functional group must be activated.[44] This can be provided by a Brønsted acid,[45] hydrogen bonding (as isocyanides have been postulated to be strong hydrogen bond acceptors)[46] or a Lewis acid, such as a silver(I)[47] or zinc(II)[48] species. Multicomponent reactions are defined as processes in which three or more starting materials react in a sequential manner, forming a product that encompasses effectively all atoms of the reagents.[49] The ground-breaking reaction of this class was reported in 1921: a three-component process (the Passerini reaction) entailing the combination of an isocyanide, a carboxylic acid and a carbonyl compound (an aldehyde or ketone), allowing access to α-acyloxy carboxamides in a single step.[50]

In 1959, this was then extended to the four-component Ugi reaction, introducing an amine reactant to deliver an α-amido carboxamide as the final product in the simplest case (Scheme 9).[51] In the proposed mechanism, the first step is a condensation between the amine and carbonyl compound, forming an imine which is protonated by the acid.[52] Next the

isocyanide acts as a nucleophile, attacking the iminium ion, before the carboxylate oxygen adds at the carbon originating from the isocyanide. Finally, a Mumm rearrangement takes place to furnish the product. Both the Ugi and Passerini reactions have been extensively developed in recent years.[49]



Scheme 9. The classic Ugi reaction and mechanism.

The ability of isocyanide-containing compounds to participate in cascade reactions allows complex frameworks to be assembled in an ordered and rapid manner, and this quality is implemented in the construction of numerous natural products.[53] For instance, such derivatives have been employed in the total synthesis of the antitumour agent ecteinascidin 743,[54] the antimitotic peptide tubulysin,[55] and the prolyl endopeptidase inhibitor eurystatin A.[56]

1.4 Pyrroloindolines

Pyrroloindolines are components of a wide group of alkaloids, and compounds containing such structural motifs have been isolated from a variety of sources, including plants, amphibians, marine organisms and fungi.[57] Pyrroloindolines freqently exhibit biological activity and are prevalent in a multitude of pharmaceuticals.[58] For example, the natural product physostigmine is an anticholinergic agent and has been found to relieve symptoms of Alzheimer's disease,[59] flustramine acts as a muscle relaxant,[60] while 5-*N*-acetylardeemin efficiently reverses multi-drug resistance in cancer cells (Figure 3).[61]

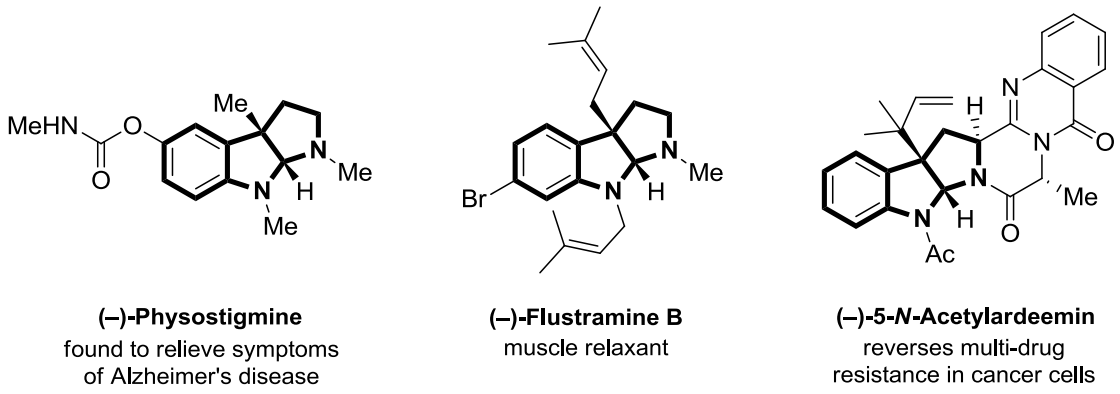


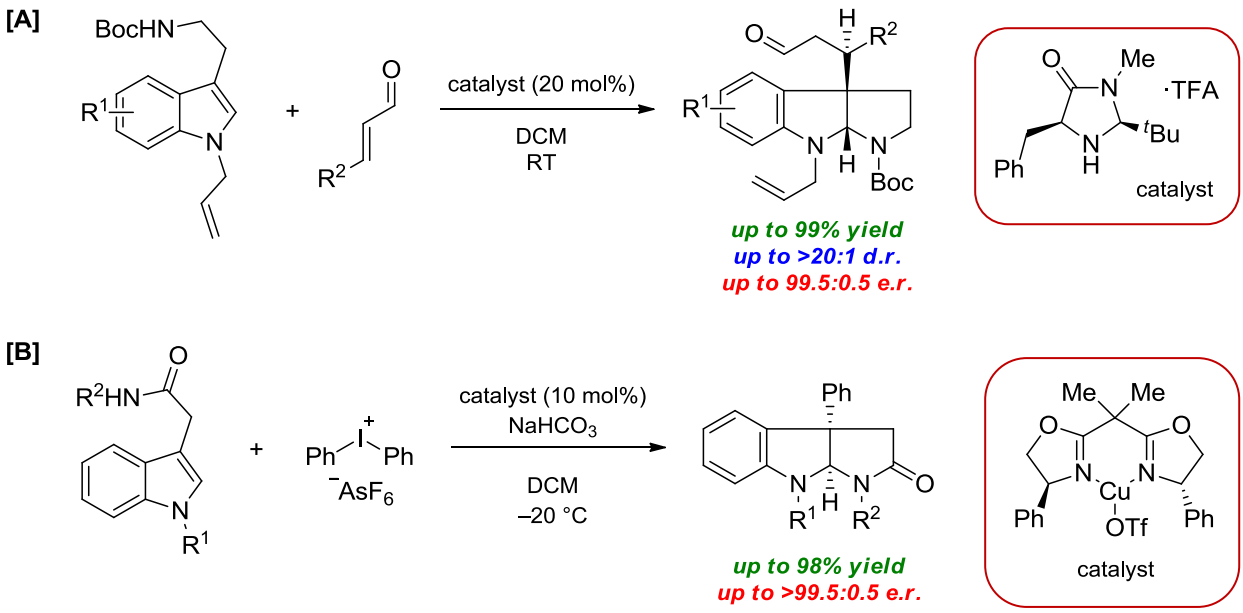
Figure 3. Examples of naturally occurring pyrroloindolines with significant biological properties.

Consequently, the formation of these structurally complex scaffolds has been the subject of much research, with the challenge of generating the ring system, installing quaternary stereocentres, and controlling diastereo- and enantioselectivity.[62] The most common strategies are biomimetic synthesis from a tryptophan or tryptamine derivative,[63] and the intramolecular cyclisation of an oxindole.[64] In these cases, part of the ring system is already intact in the substrate, leading to limited substitution patterns in the pyrroloindolines obtained.

The group of MacMillan has published recent reports on the highly enantioselective production of pyrroloindolines from tryptamines, using both organocatalysis[58] and metal-

catalysed arylation[65] respectively (Scheme 10). Specifically, the former involves an addition-cyclisation process with a chiral amine catalyst as part of the synthesis of (–)-flustramine B, while the latter utilises the coalition of a diaryliodonium salt and asymmetric copper catalysis in a cascade reaction.

These approaches are two of the relatively few enantioselective routes known. Though impressive, given the excellent selectivity, robustness and application in total synthesis, the scope of this and other current methodology is somewhat restricted, encouraging further research into the construction of this vital heterocyclic architecture.



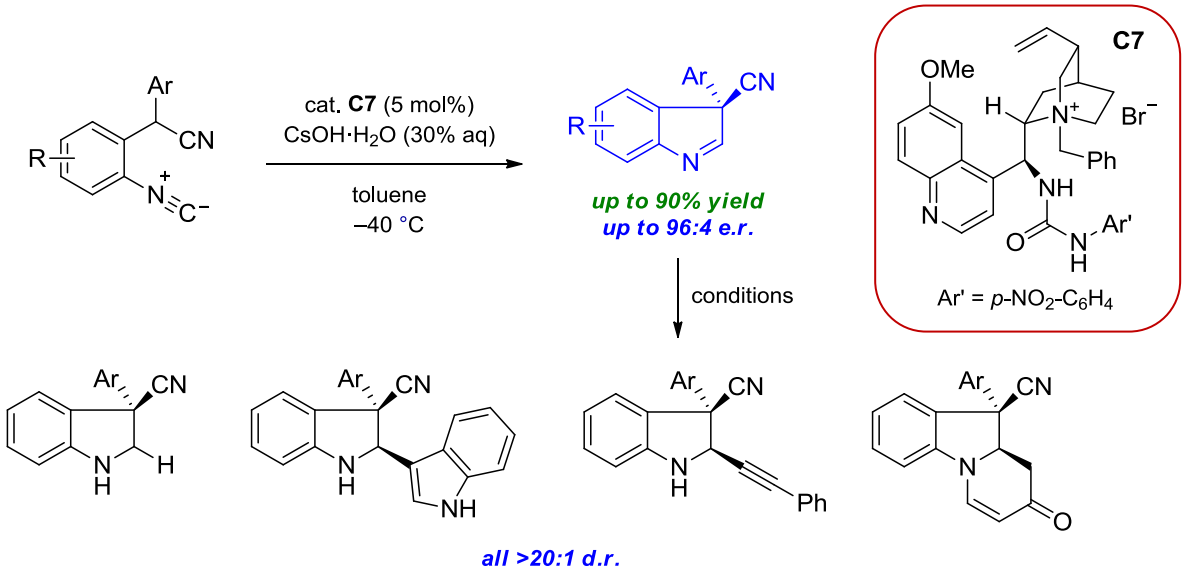
Scheme 10. Enantioselective synthesis of pyrroloindolines from tryptamines: [A] by an organocatalytic addition-cyclisation cascade; [B] by a copper-catalysed arylation-cyclisation cascade.

1.5 Previous Work in the Smith Group

As part of our research in phase-transfer catalysis, the Smith group have been interested in the combination of chiral cations with certain functional groups. In particular,

isocyanides were identified as a versatile chemical moiety which could act as a focal point in the synthesis of substituted and polycyclic indolines.

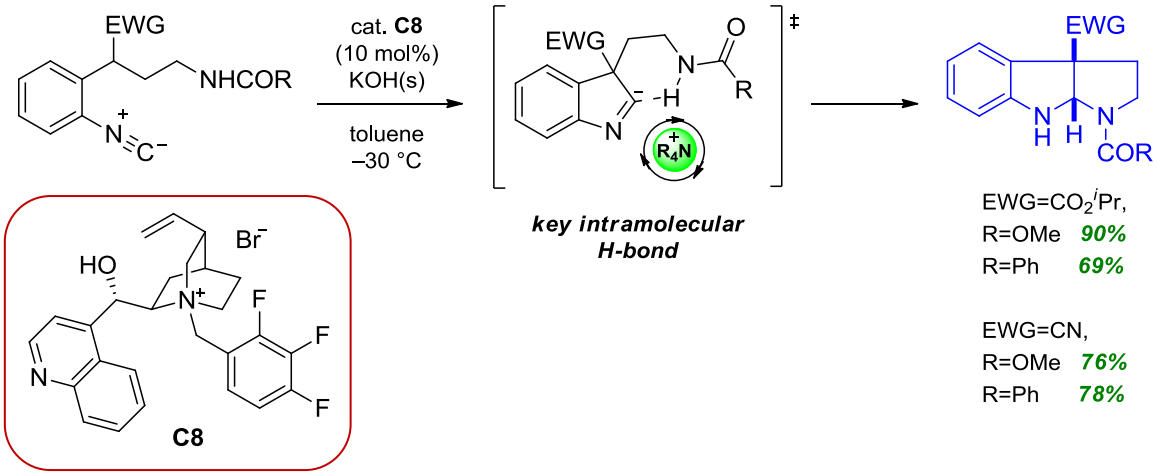
In the first studies involving this functional group, quaternary-substituted indolenines were synthesised *via* a 5-*endo-dig* cyclisation of a carbanion onto an isocyanide under phase-transfer conditions (Scheme 11).[44] These indolenines, which were delivered with excellent enantioselectivity, could subsequently be intercepted by a nucleophilic species to generate functionalised indolines as a single diastereomer. Due to enhanced outcomes from the use of phase-transfer catalysts containing a Brønsted acid functional group,[66] it was proposed that such bespoke catalysts both activate the isocyanide to act as an electrophile and pre-organise the catalyst-substrate complex by hydrogen bonding.



Scheme 11. Previous work in the Smith group involving the enantioselective synthesis of indolines.

This methodology was then developed further to a cascade process, incorporating an intramolecular nucleophile to trap the indolenine, resulting in the efficient synthesis of pyrroloindolines in a single operation (Scheme 12).[67] In this reaction, the crucial hydrogen bonding is provided by the N–H proton in the pendant carbamate or amide group instead of the catalyst. This theory was supported by replacing the key proton with a methyl group,

which led to the recovery of starting material and no generation of the indolenine intermediate.



Scheme 12. Previous work in the Smith group involving a H-bond-mediated cascade to produce pyrroloindolines.

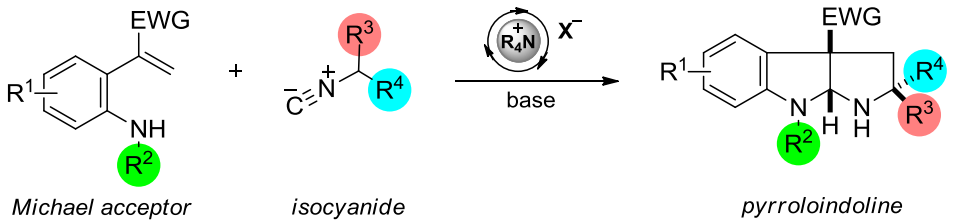
2. A Cation-Directed Two-Component Cascade Approach to Enantioenriched Pyrroloindolines

2.1 Project Aims

The aim of this project is to investigate and develop new asymmetric cascade reactions, which allow access to the pyrroloindoline framework from isocyanide-containing starting materials under phase-transfer conditions.

It was recognised that previous work involving the synthesis of pyrroloindolines within the Smith group (as detailed in Scheme 12) was limited in its applicability, as the reasonably complex substrates required several reaction steps to be prepared. Moreover, the substitution patterns and enantioselectivity could be enhanced by considering an alternative approach.

Therefore it was envisaged that this methodology could be improved by developing a two-component cascade process, with the aim of assembling pyrroloindolines containing three stereocentres (two of which would be quaternary) in a single operation from simple and readily available precursors (Scheme 13).



Scheme 13. Proposed cation-directed two-component cascade approach to pyrroloindolines.

The proposed phase-transfer catalysed reaction strategy exploits the great reaction diversity and synthetic utility of acidic isocyanides, which would be employed in conjunction

with a specifically engineered Michael acceptor. It was rationalised that asymmetric 1,4-addition to the Michael acceptor of a deprotonated isocyanide (co-ordinated to the chiral cation under basic phase-transfer conditions) would generate an anion, which would undergo a 5-*endo-dig* cyclisation. The design of the acceptor substrate would provide the crucial hydrogen bonding to activate the electrophilicity of the isocyanide group required for this step. Finally, the cascade process would be completed by nucleophilic attack of the pendant nitrogen in the amino group attached to the acceptor.

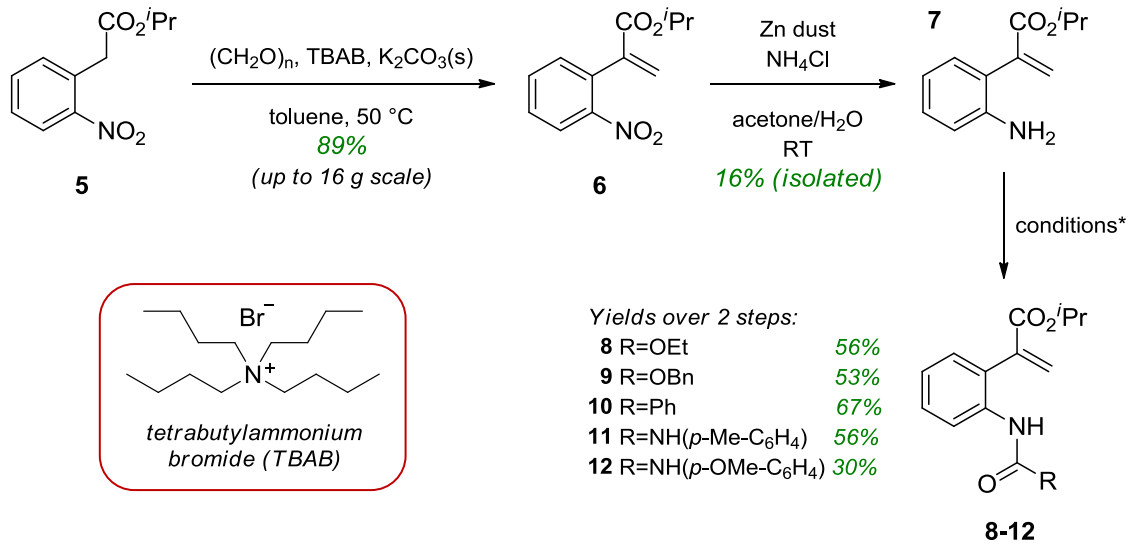
It was anticipated that the use of a chiral quaternary ammonium salt would allow the highly functionalised pyrroloindoline products to be generated with high diastereo- and enantioselectivity. General synthetic routes to suitable starting materials for these reactions would also be explored.

2.2 Synthesis of Starting Materials

2.2.1 Preparation of Michael Acceptors

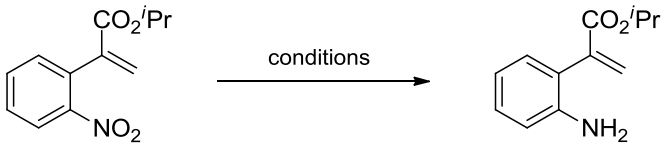
In order to prepare the Michael acceptor substrates, namely aminophenyl-substituted acrylates, a route from isopropyl 2-(2-nitrophenyl)acetate **5** was devised (Scheme 14). This entailed an initial reaction with paraformaldehyde under phase-transfer conditions in order to form the acrylate **6**, which proceeded in an excellent yield on a large scale. The subsequent step involved reduction of the nitro group. Although the product of this step **7** was isolated in a yield of only 16%, it was discovered that the desired protected Michael acceptors could be generated in greatly improved yields over 2 steps from **6**, if the aniline **7** was not isolated from the crude mixture. It was deduced that the aniline was unstable to column chromatography.

In the protection step, reaction with an alkyl chloroformate, acyl chloride or aryl isocyanate allowed Michael acceptors to be successfully constructed with carbamate **8-9**, amide **10** and urea moieties **11-12** respectively.



Scheme 14. Route for the preparation of Michael acceptor substrates. **Reagents and conditions for protection step:* RCOCl, pyridine, $CHCl_3$, 0 °C → RT (for **8-10**); ArNCO, DCM, RT (for **11-12**).

The reduction step was also investigated under different conditions (Table 1), but no improvement in isolated yield was observed on changing the solvent, and attempts with systems including Lindlar's catalyst, iron powder and tin(II) chloride dihydrate failed to give the aniline **7**.

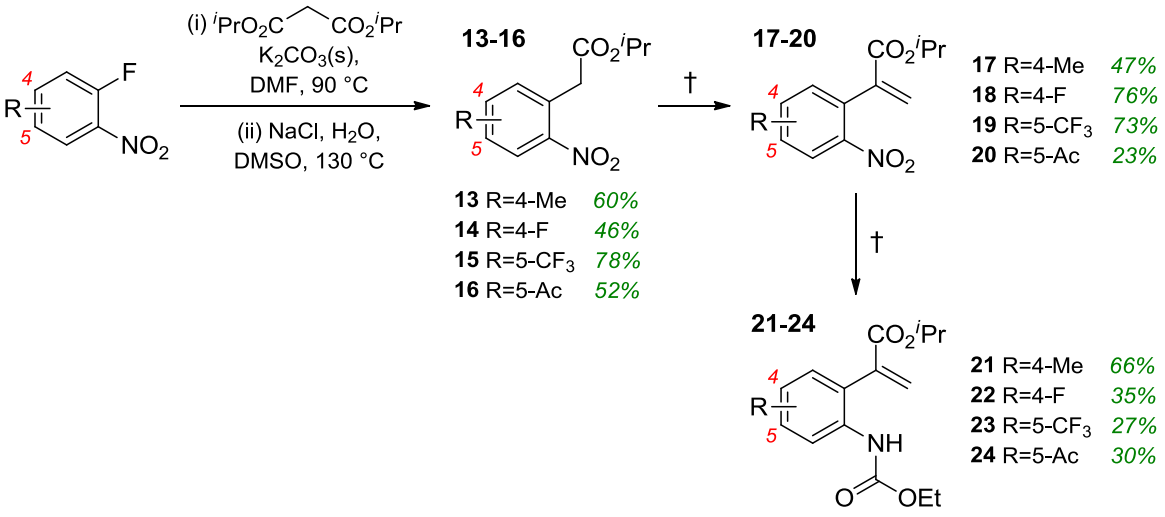


6 **7**

Entry	Conditions	Outcome
1	Zn, NH_4Cl, acetone/H_2O, RT	16% yield
2	Zn, NH_4Cl, MeOH/H_2O, RT	15% yield
3	H_2, Lindlar's cat., quinoline, Et_2O, RT	Returned starting materials
4	Fe, TFA, EtOH, RT	Returned starting materials and complex mixture
5	$SnCl_2 \cdot 2H_2O$, EtOH, 75 °C	Complex mixture of products

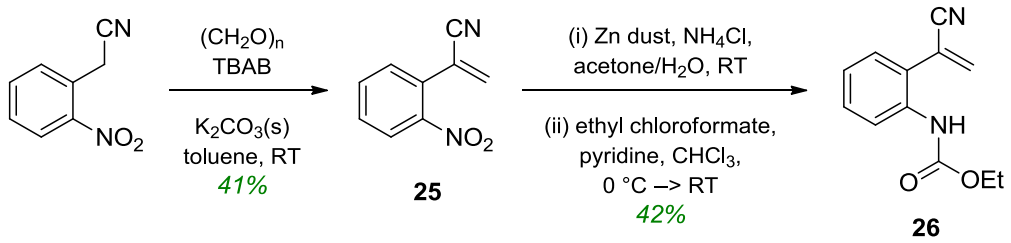
Table 1. Screening of reduction conditions. Isolated yield of **7** shown.

It was also decided to synthesise Michael acceptors with additional substituents on the core arene ring. Substrates **21**-**24** (featuring methyl, trifluoromethyl, fluoro and acyl groups) were prepared from the relevant 2-fluoronitrobenzene, starting with a nucleophilic aromatic substitution (S_NAr) reaction with diisopropyl malonate and subsequent Krapcho decarboxylation, before following the same route as previously (Scheme 15).



Scheme 15. Route for the preparation of Michael acceptors with additional substituents on the arene ring. †Conditions as in Scheme 14 for these reactions.

Finally, a Michael acceptor **26** with a nitrile in place of the isopropyl ester as the electron-withdrawing group (to facilitate the 1,4-addition) was generated from 2-nitrophenylacetonitrile (Scheme 16). The pathway to this substrate was almost identical, but the initial reaction with paraformaldehyde did not require heating above room temperature to proceed, while the reduction step was complete after just 1 minute (compared with 15 minutes for the previously detailed precursors).



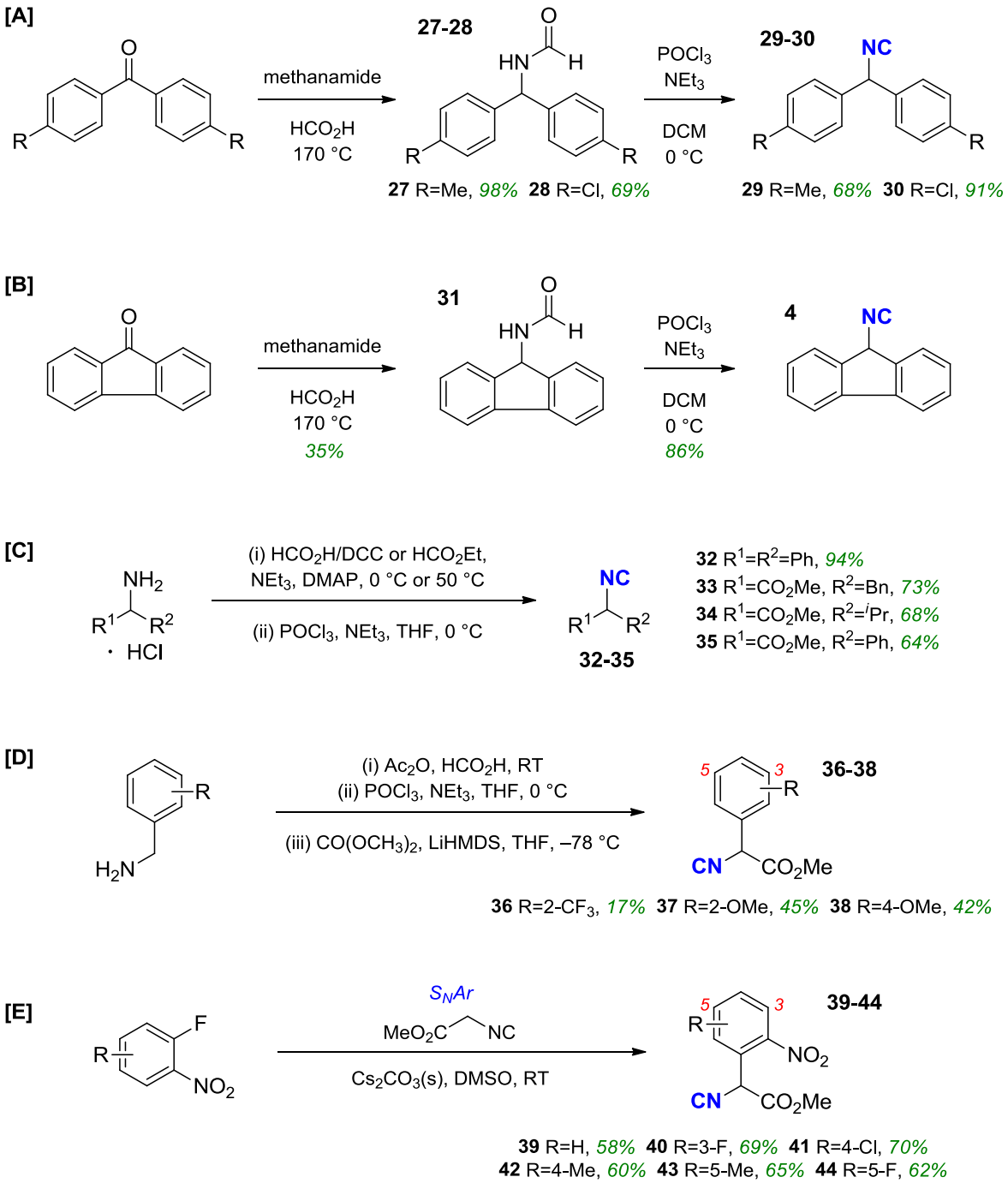
Scheme 16. Route for the preparation of Michael acceptor **26** featuring the nitrile electron-withdrawing group.

2.2.2 Preparation of Isocyanides

A range of isocyanide-containing compounds were also successfully prepared, in order to investigate the effect of steric and electronic diversity on the diastereomeric and enantiomeric ratios and yields in the reaction with Michael acceptors. The synthetic method employed was varied depending on the nature of the desired isocyanide (Scheme 17).

The most common general route involved the generation of a formamide, followed by dehydration with phosphorus oxychloride (as previously depicted in Scheme 7, equation [A]). In the synthesis of symmetrical α,α-diaryl isocyanides **29** and **30**, and additionally the fluorenyl isocyanide **4**, the initial formamides **27**, **28** and **31** were made by the reaction of the relevant diaryl ketone with methanamide in formic acid, before dehydration. Moreover, the non-substituted α,α-diphenyl isocyanide **32** and α-alkyl isocyanoacetates **33** and **34** were produced from the corresponding amine hydrochloride salts, which were converted to the formamide using ethyl formate or the combination of formic acid and

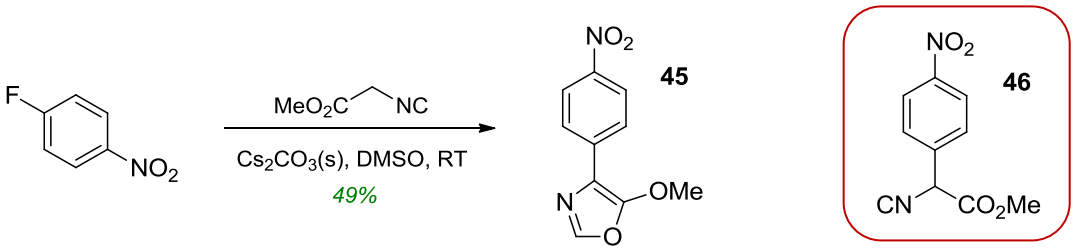
N,N'-dicyclohexylcarbodiimide (DCC). Lastly, the preparation of α-aryl isocyanoacetates **36-38** required an additional final step to introduce the ester group, following generation of the formamide from an amine (with acetic anhydride in formic acid) and dehydration. This was performed by reacting the intermediate with dimethyl carbonate in the presence of lithium bis(trimethylsilyl)amide (LiHMDS).



Scheme 17. Methods for the preparation of isocyanides.
Compounds **32-38** were prepared by Dr Matija Gredičak.

Meanwhile, an alternative approach was taken for the construction of the α-(*ortho*-nitroaryl) isocyanoacetates **39-44**, comprising an S_NAr reaction between a 2-fluoronitrobenzene and the commercially available methyl isocyanoacetate. This reaction led to the successful preparation of a number of further isocyanide-containing substrates.

It was observed that it was not possible to generate isocyanides with two ester groups in the α-position (where R^1=R^2=ester group in equation [C] of Scheme 17), as the product hydrolysed back to formamide. Furthermore, when an S_NAr reaction between methyl isocyanoacetate and 4-fluoronitrobenzene was attempted, an unexpected cyclisation took place (Scheme 18). Interestingly, the oxazole **45** was generated as the major product (in a yield of 49%) instead of the desired α-(*para*-nitroaryl) isocyanoacetate **46**.



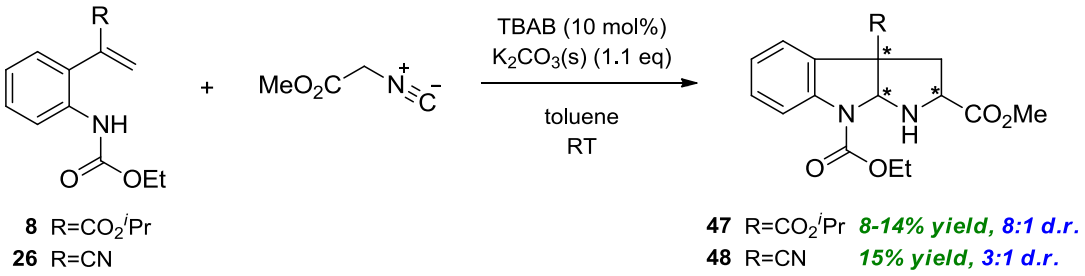
Scheme 18. Unexpected formation of oxazole **45** in the attempted preparation of isocyanide **46**.

2.3 Initial Reactions

2.3.1 Reactions of Methyl Isocyanoacetate

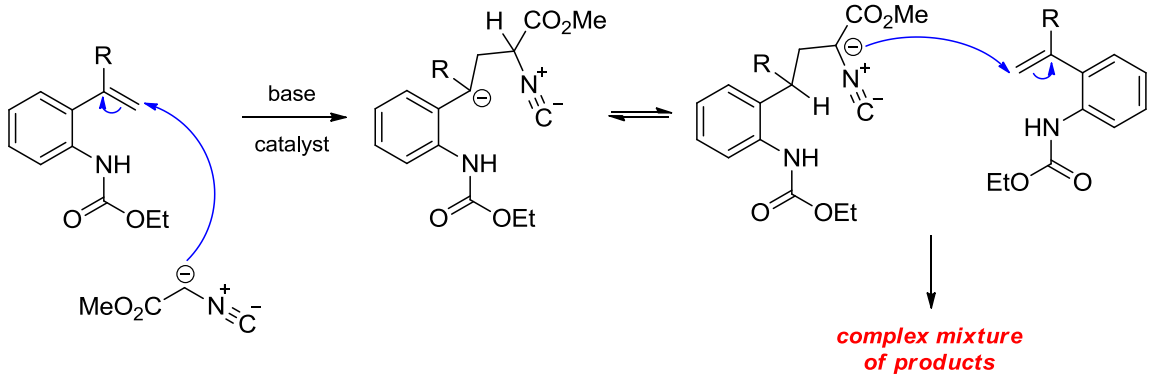
As a preliminary investigation, we began to explore the potential of the proposed reaction by examining the 1,4-addition of non-α-substituted methyl isocyanoacetate to Michael acceptors **8** and **26**, using the achiral phase-transfer catalyst tetrabutylammonium bromide (TBAB) and solid potassium carbonate as the base (Scheme 19).

The first desired pyrroloindoline product **47** was formed in 8% yield as a mixture of two inseparable diastereomers (in 8:1 d.r.). It was noted that the major product of the reaction corresponded to the addition of an isocyanide molecule to two acceptor molecules – this was isolated as a complex mixture of diastereomers that precluded detailed characterisation. The yield of **47** was augmented by slow addition of the acceptor to the reaction mixture and increasing the dilution, but only to 14%. Meanwhile, product **48** was generated in a yield of only 15% in this case (as a mixture of two inseparable diastereomers in 3:1 d.r.).



Scheme 19. Attempted cascade reactions with methyl isocyanoacetate.

It was hypothesised that the double addition occurred due to the greater acidity of the proton in the α-position to the isocyanide, within the intermediate that resulted from the first 1,4-addition. This could lead to intramolecular proton exchange, followed by conjugate addition to a second acceptor molecule (Scheme 20). It was therefore decided to employ isocyanides disubstituted at the α-position, in order to prevent the double addition.

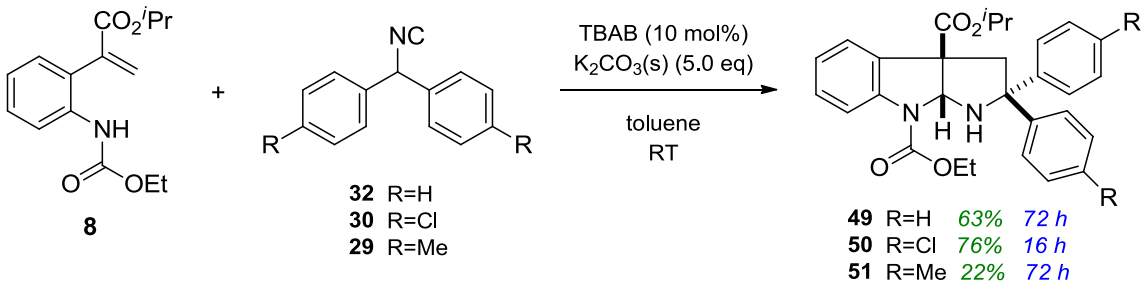


Scheme 20. Hypothesised major outcome of reactions with methyl isocyanoacetate. R is $CO_2{}^{i}Pr$ or CN.

2.3.2 Reactions of Symmetrical Isocyanides

The symmetrical α,α-diaryl isocyanides that had been synthesised were selected in order to assess our theory, and subjected to the same achiral phase-transfer conditions with Michael acceptor **8** (in 1:1 ratio). Pleasingly, these isocyanides readily and efficiently underwent the cascade to afford a single *cis*-fused diastereomer, presumably due to the ring strain associated with the alternative *trans*-5,5-ring junction (Scheme 21).

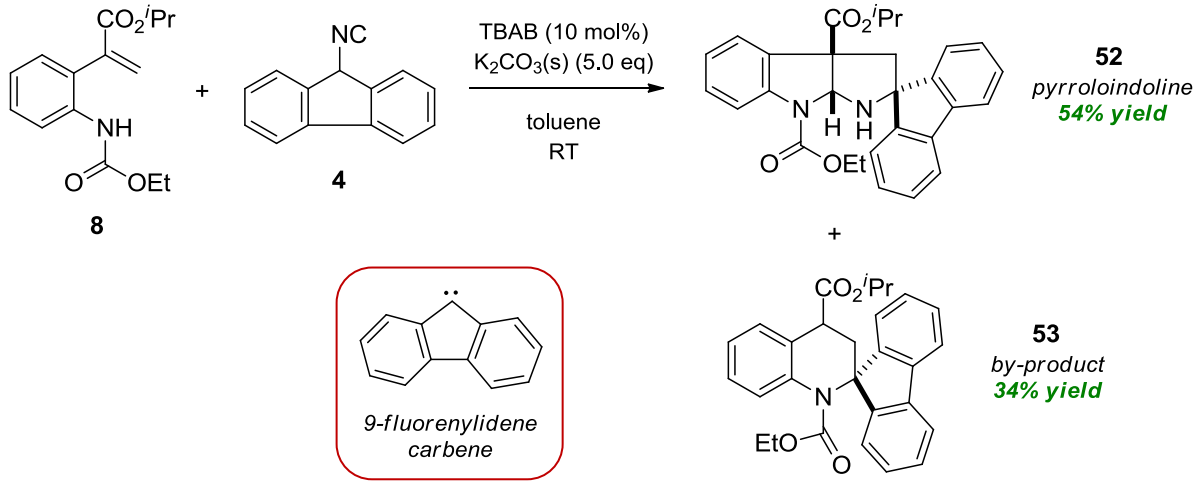
The isolated yields of the pyrroloindolines were generally good, considering the complexity of the reaction, but the isocyanide **29** (containing two electron-donating *p*-tolyl groups) showed comparatively sluggish reactivity. Here, the pyrroloindoline **51** was constructed in only 22% yield after 72 hours (with 30% conversion of the isocyanide). Meanwhile, the relatively electron-poor isocyanides **32** and **30** delivered pyrroloindolines **49** and **50** in yields of 63% and 76% respectively, indicating that the acidity of the isocyanide component would be an important factor to consider in this reaction. Specifically, it was deemed likely that the acidity would affect the concentration of the reactive isocyanocarbanion in the organic phase, influencing the rate of 1,4-addition.



Scheme 21. Reactions of symmetrical α,α-diaryl isocyanides with Michael acceptor **8**.

Michael acceptor **8** was also combined with fluorenyl isocyanide **4** under these achiral phase-transfer conditions, which furnished pyrroloindoline **52** in 54% yield (Scheme 22). Intriguingly, this was restricted by the significant formation of by-product **53**, which was generated in 34% yield. It was theorised that this by-product was obtained from the reaction

of the acceptor substrate with 9-fluorenylidene, a well-precedented and relatively stable carbene,[68-70] which could have been derived from the isocyanide under the basic reaction conditions.



Scheme 22. Reaction of fluorenyl isocyanide **4** with Michael acceptor **8**, generating unexpected by-product **53**.

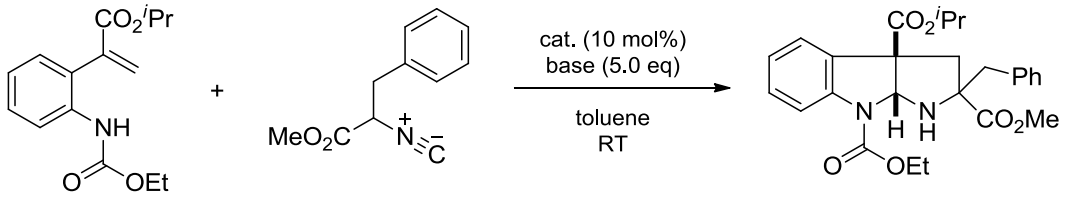
2.4 Diastereoselective Synthesis of Pyrroloindolines

2.4.1 Reactions of Alkyl-Substituted Methyl Isocyanoacetates

With a working cascade scheme underway and key observations noted concerning the relationship between isocyanide acidity and overall conversion, we advanced our investigations by studying non-symmetrical isocyanide starting materials. In this case, diastereoselectivity would become an issue, and we were interested to analyse how this could be controlled.

Given the significance of the acidity of the isocyanide component, α-substituted isocyanoacetates (containing an electron-withdrawing methyl ester group) were selected for the proposed cascade. Alkyl-substituted substrates **33** and **34**, derived from phenylalanine and valine respectively, were first employed under achiral phase-transfer conditions.

Isocyanide **33** and Michael acceptor **8** were subjected to basic phase-transfer conditions (as a 1:1 mixture), utilising the achiral catalyst TBAB and 50% aqueous potassium hydroxide as the base (to accelerate deprotonation of the isocyanide). Gratifyingly, the cascade now proceeded to generate *cis*-fused pyrroloindoline **56** as the major product of the reaction, but as a mixture of two diastereomers in 1:1 ratio. Subsequently, a base screen was performed to optimise the reaction (Table 2), and it was discovered that the reaction time was similar without TBAB when using 50% aqueous potassium hydroxide, demonstrating that the reaction did not depend on the catalyst in these conditions. Consequently, 25% aqueous potassium hydroxide was chosen as the optimal base for this set of reactions.

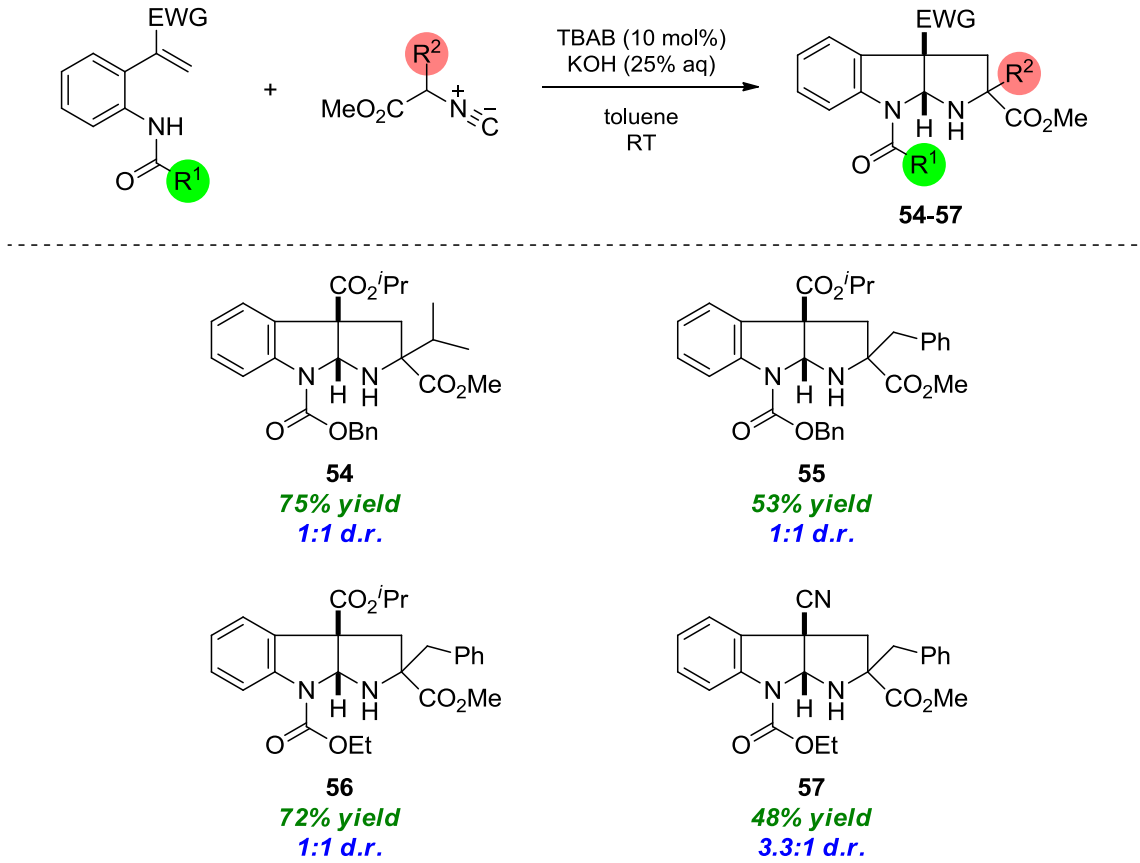


8 **33** **56**

Entry	Base	Catalyst	Time to Consume Acceptor
1	KOH (50% aq)	TBAB	10 min
2	KOH (50% aq)	–	10 min
3	KOH (25% aq)	TBAB	30 min
4	KOH (25% aq)	–	36 h
5	KOH (10% aq)	TBAB	3 h
6	KOH (10% aq)	–	>48 h
7	KOH (5% aq)	TBAB	8 h
8	KOH (5% aq)	–	>48 h

Table 2. Base screening in reaction to form pyrroloindoline **56**. Reactions carried out on 10 mg scale.

In the reactions of these α-alkyl-substituted isocyanoacetates (Scheme 23), the aniline *N*-substituent in the Michael acceptor was varied, in order to probe its ability to function as a hydrogen-bond donor. In all instances using an isopropyl ester-containing Michael acceptor (substrate **8** or **9**), it was observed that the pyrroloindolines **54**-**56** were synthesised in 1:1 d.r., while combination of the nitrile-containing acceptor **26** with isocyanide **33** afforded the appropriate pyrroloindoline **57** in 3.3:1 d.r.. However, the yield of this product (48%) was somewhat diminished in comparison to the yield of the corresponding pyrroloindoline **56** formed from the isopropyl ester-containing acceptor (72% yield).



Scheme 23. Reactions of α-alkyl-substituted methyl isocyanoacetates with Michael acceptors. Pyrroloindolines **54** and **55** were prepared by Dr Matija Gredičak.

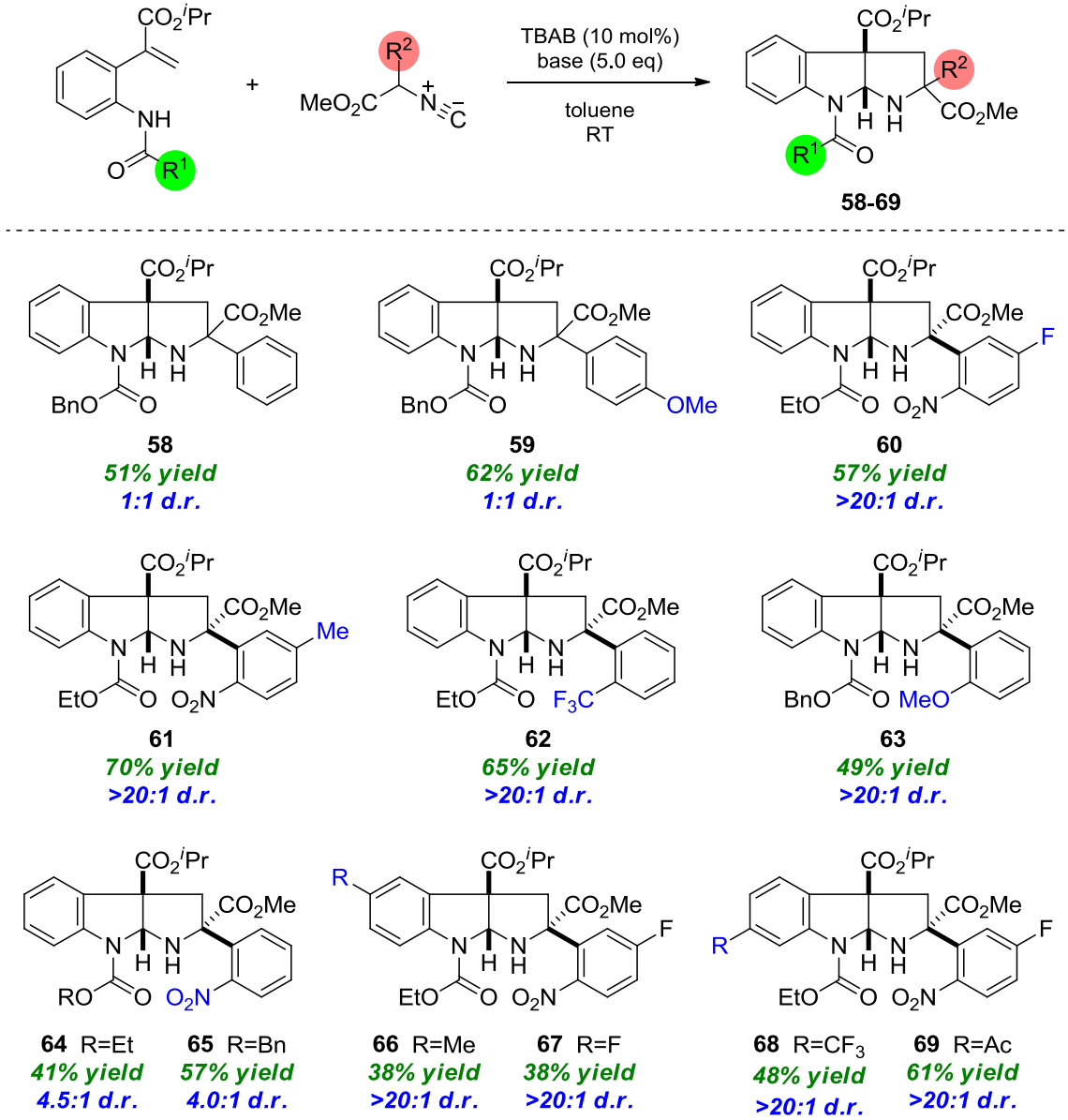
Moreover, it was noted that usage of a Michael acceptor with an ethyl ester as the aniline *N*-substituent delivered the pyrroloindoline **56** in greater yield (72%) than the acceptor with a benzyl ester (pyrroloindoline **55** obtained in 53% yield).

2.4.2 Reactions of Aryl-Substituted Methyl Isocyanoacetates

Next, α-aryl-substituted isocyanoacetates were assessed in the cascade reaction (Scheme 24), starting with the reaction of Michael acceptor **9** (1.0 eq) with the isocyanide **35** derived from the methyl ester of phenylglycine (1.0 eq). In this case, the pyrroloindoline **58** was again afforded as a 1:1 mixture of diastereomers – which was also the result when the *para*-methoxyphenyl-substituted isocyanide **38** was employed, giving the product **59** in 1:1 d.r..

However, we were delighted to observe that the introduction of an *ortho*-substituent on the arene ring of these isocyanides was rewarded with a dramatic increase in diastereoselectivity. Pyrroloindolines **60** and **61**, containing 2-nitro-5-fluoro and 2-nitro-5-methyl aromatic groups respectively, were isolated in good yields with three stereocentres as a single diastereomer (>20:1 d.r. by ^{1}H NMR spectroscopy). Furthermore, this outcome was achieved in the generation of pyrroloindoline **62**, featuring a 2-trifluoromethyl aromatic group.

For these reactions, involving aryl groups with an electron-withdrawing substituent, it was noticed that a milder base had to be used, as 25% and 10% aqueous potassium hydroxide led to decomposition of the isocyanide substrate. Through screening (Table 3), it was found that solid potassium carbonate, although giving a slower reaction time, was the most suitable base, with the reaction showing clean conversion from the starting materials to pyrroloindoline product (in >20:1 d.r.) *via* the imine intermediate.

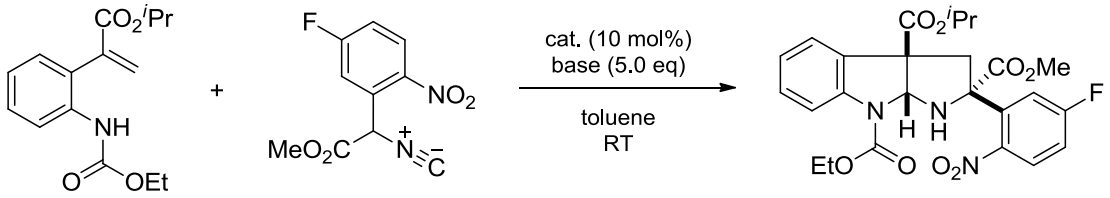


Scheme 24. Reactions of α-aryl-substituted methyl isocyanoacetates with Michael acceptors. *Base:* KOH (25% aq) for **58**-**59**, K_2CO_3(s) for **60**-**69**. Compound **59** was prepared by Dr Matija Gredičak.

Given the success shown in attaining diastereoselectivity with isocyanides containing 2-nitro- and 2-trifluoromethyl-substituted aromatic groups, we were interested in ascertaining whether this could be attributed to steric or electronic effects (namely whether this was a result of the extra bulk added to the arene at this position, or whether it was due to the electron-withdrawing nature of the substituent). Therefore an electron-donating group was examined: 2-methoxyphenyl-substituted isocyanide **37** was subjected to the cascade with

Michael acceptor **9** (with the ester varied to confirm the interchangeability of the acceptor component in reactions with α-aryl-substituted isocyanides), which yielded pyrroloindoline **63** as a single diastereomer. This indicated the predominance of steric factors in influencing the diastereoselectivity observed. Interestingly, pyrroloindolines **64** and **65**, featuring an aromatic group with only a 2-nitro-substituent, were generated in 4.5:1 and 4.0:1 d.r..

It was also observed that substitution on the Michael acceptor aryl ring was well-tolerated, with methyl, fluoro, trifluoromethyl and acyl groups all incorporated in pyrroloindolines **66**-**69**, which were each generated as a single diastereomer.



Entry	Base	Catalyst	Outcome
1	KOH (50% aq)	TBAB	Decomposition of isocyanide
2	KOH (25% aq)	TBAB	Decomposition of isocyanide
3	KOH (10% aq)	TBAB	Decomposition of isocyanide
4	K_2CO_3(s)	TBAB	Clean conversion to product **60** in 24 h
5	K_2CO_3(s)	–	Trace conversion to product **60** after 48 h
6	Cs_2CO_3(s)	TBAB	Conversion to **60** in 16 h with unidentified side-product
7	$CsOH·H_2O$(s)	TBAB	Conversion to **60** in 2 h with trace side-product
8	$CsOH·H_2O$(s)	–	Trace conversion to product **60** after 48 h

Table 3. Base screening in reaction to form pyrroloindoline **60**. Reactions carried out on 10 mg scale.

The relative stereochemistry of products **60** and **61** was unambiguously assigned by X-ray crystallographic analysis (Figure 4). This revealed that in both cases the smaller methyl ester group is orientated on the more hindered concave face of the pyrroloindoline framework (opposite the isopropyl ester group), rather than the larger aryl substituent.

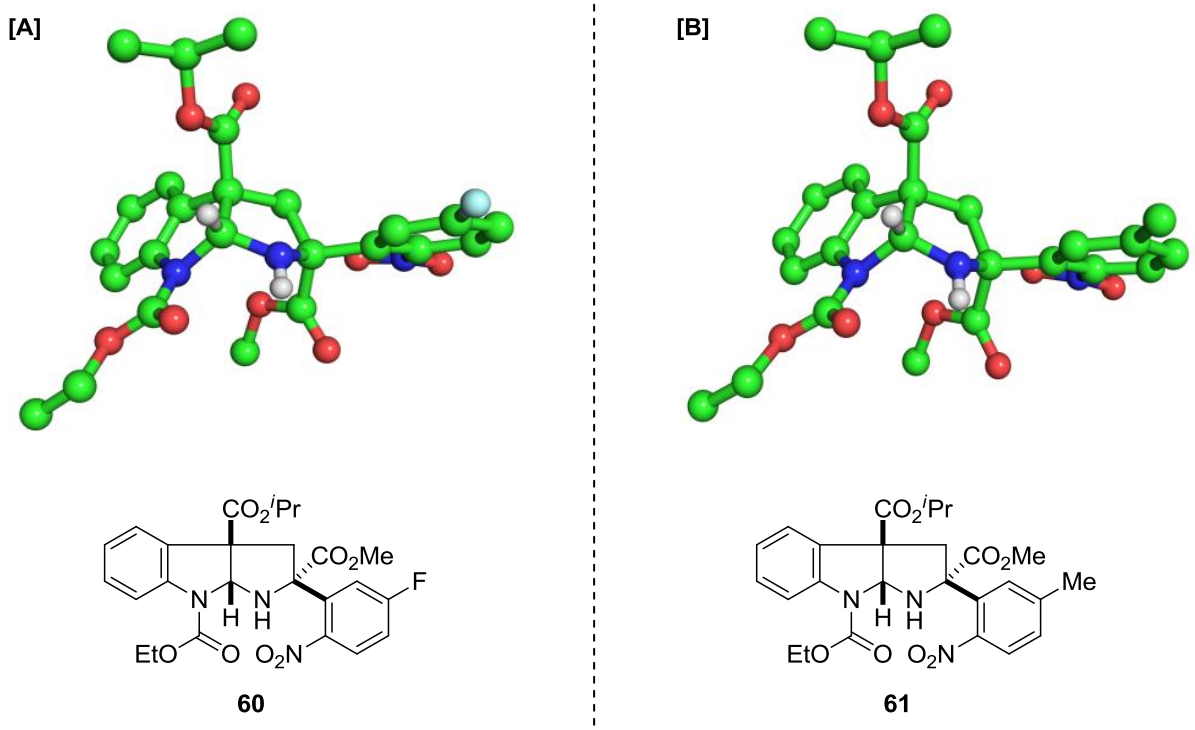
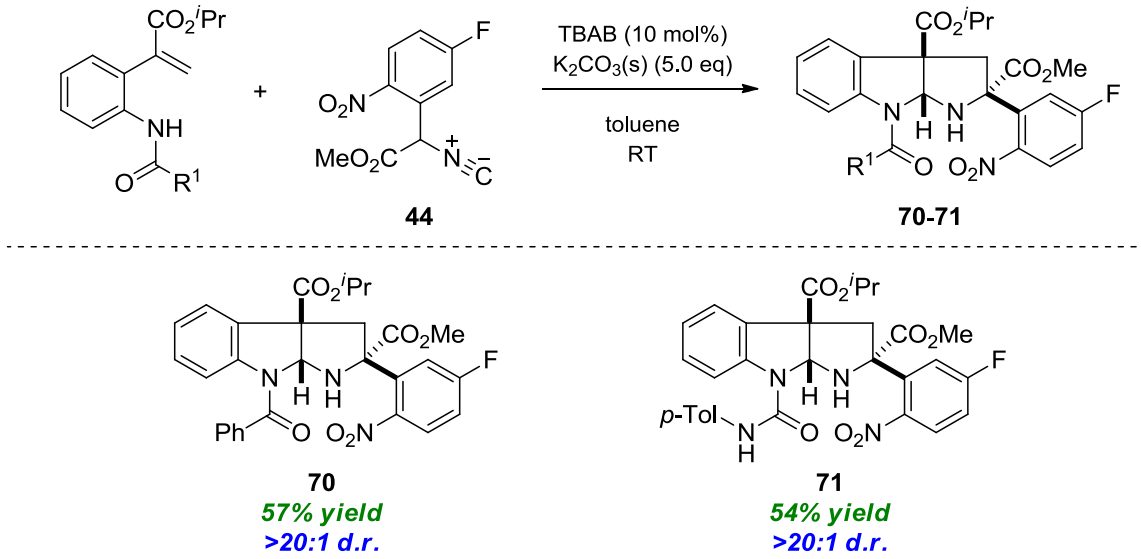


Figure 4. Crystal structures of the single diastereomer of pyrroloindolines **60** and **61**. X-ray diffraction data were collected and the structures solved by Dr Russell W. Driver (see Appendix I for full crystal data).

The relative stereochemistry of other compounds synthesised from α-aryl-substituted isocyanides was assigned by analogy to these X-ray structures, and further verification of the selectivity was obtained by a diagnostic chemical shift, specifically that of the 5,5-ring junction proton in the ^{1}H NMR spectra (see Appendix B).

Finally, in order to study the effect of altering the aniline *N*-substituent, isocyanide **44** was combined under the same phase-transfer conditions with Michael acceptors **10** and **11**, containing an amide and urea moiety respectively (instead of the carbamate employed previously). Here, pyrroloindolines **70** and **71** were assembled in similar yields and again as

single diastereomers (Scheme 25). Significantly, the reaction to form the urea-containing product **71** was complete in just 2 hours, compared with 16-24 hours for the majority of other products, and this compound was also less rotameric (other pyrroloindolines required use of variable temperature NMR to sharpen broad peaks in the ^{1}H spectra).



Scheme 25. Reactions of Michael acceptors containing different aniline *N*-substituents with isocyanide **44**.

The identity of this single diastereomer was confirmed by NOE analysis, and was found to exhibit stereochemistry that was consistent with the previous observations (Figure 5).

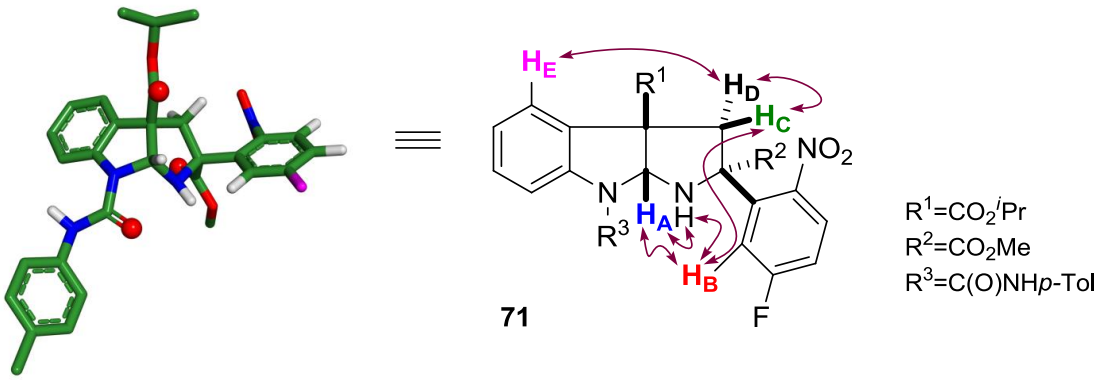


Figure 5. Computed structure of pyrroloindoline **71** with NOE interactions shown (see Appendix H for NOE NMR spectra; molecular model calculated by Dr Russell W. Driver).
The lowest energy conformation was calculated using Ascaleph Designer (open-source software) with an Amber94 force field, a Perdew-Burke-Erznerhof exchange-correlation functional and a PM3 basis set.

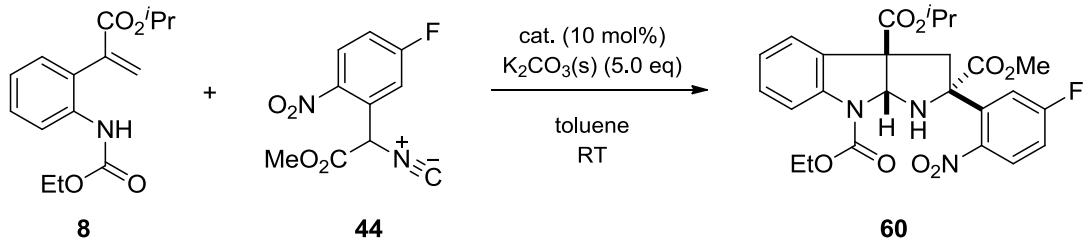
2.5 Enantioselective Synthesis of Pyrroloindolines

2.5.1 Catalyst Screening in the Reaction of an α-Aryl-Substituted Isocyanide

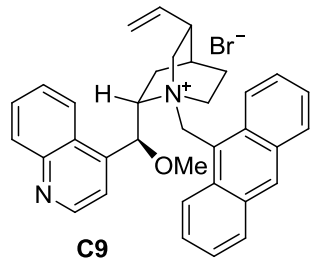
With conditions for the diastereoselective synthesis of pyrroloindolines found, we next decided to focus on developing an enantioselective catalytic cascade. As a starting point, the reaction between the carbamate-containing Michael acceptor **8** and the 5-fluoro-2-nitrophenyl-substituted isocyanoacetate **44** was selected for screening with an assortment of chiral, non-racemic tetra-alkylammonium phase-transfer catalysts. This reaction had produced pyrroloindoline **60** as a single diastereomer in 57% yield with the achiral catalyst, TBAB (Scheme 24).

Apart from changing the catalyst, the same conditions were applied in the screening trials as in the racemic reaction. However, although a large variety of chiral catalysts were assessed, in almost all cases a near-racemic mixture of the single diastereomer was generated. The most enantioselective results of the catalyst screen are depicted in Table 4 (a full list of results is in Appendix C). Attempts with the third-generation phase-transfer catalysts **C9** and **C10**, featuring an *N*-anthracenylmethyl group, afforded the product **60** in only 55:45 e.r. and 53:47 e.r. respectively (Table 4, Entries 1 and 2). The highest enantiomeric ratios were recorded with the renowned Lygo A catalyst **C11** (Entry 3, 66:34 e.r.), the monofluorinated cinchoninium catalyst **C12** (Entry 4, 65:35 e.r.) and the catalyst **C13** featuring a urea moiety (Entry 5, 33:67 e.r.).

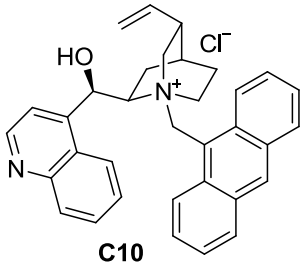
The Lygo A catalyst **C11** is non-cinchona alkaloid-derived and one of 40 valuable quaternary ammonium salts introduced by Lygo *et al.*, which were crafted by reacting commercially available chiral secondary amines with a range of conformationally flexible biaryl compounds containing *ortho*-benzylic bromide groups.[71]



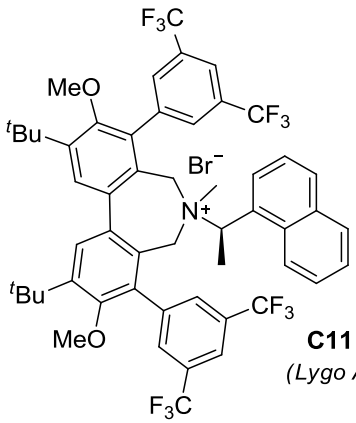
Entry	Catalyst	e.r. of 60
1	**C9**	55:45
2	**C10**	53:47
3	**C11** (Lygo A)	66:34
4	**C12**	65:35
5	**C13**	33:67
6	**C14**	61:39
7	**C15**	61:39



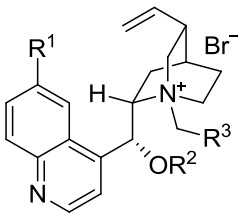
C9



C10

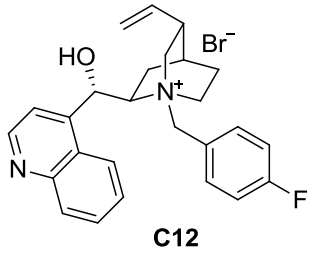


C11
(Lygo A)

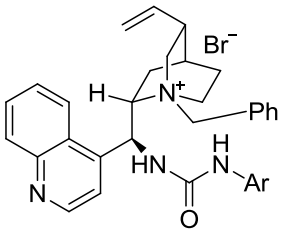


C14 R^1=R^2=H
R^3=4-CF_3-C_6H_4

C15 R^1=OH
R^2=Bn
R^3=Ph



C12



C13 Ar=4-NO_2-C_6H_4

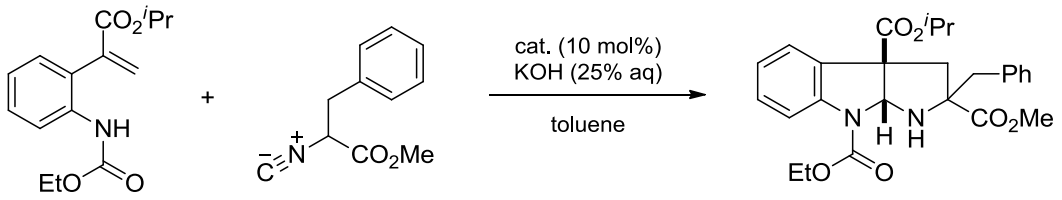
Table 4. Chiral catalyst screening in reaction of Michael acceptor **8** with isocyanide **44**. Reactions carried out on 10 mg scale. Single diastereomer observed in all cases.

Given the poor enantioselectivity observed across diverse catalyst scaffolds in this reaction scheme, no further optimisation was attempted and attention was turned to different systems.

2.5.2 Catalyst Screening in the Reaction of an α-Benzyl-Substituted Isocyanide

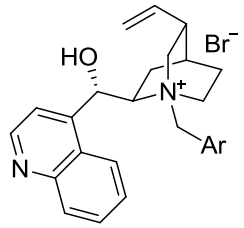
Next, the reaction between the carbamate-containing Michael acceptor **8** and isocyanide **33**, derived from the methyl ester of phenylalanine, was selected for catalyst screening. As this reaction had produced pyrroloindoline **56** (in 72% yield) as a 1:1 mixture of diastereomers with the achiral catalyst, TBAB (Scheme 23), it was not anticipated that changing the catalyst would markedly enhance the diastereoselectivity. However, it was considered that studying the results of these investigations could contribute to our understanding of the conditions required for a transformation that was both diastereo- and enantioselective.

As in the previous screening trials, apart from changing the catalyst, the same conditions were applied as in the racemic reaction. In the majority of examples, it was observed that one diastereomer was generated in good enantiomeric ratio, with the other almost racemic, but there were some notable exceptions (Table 5 shows the results with the greatest enantioselectivity, while a complete list is detailed in Appendix D). A trend was recognised that the catalysts generating the pyrroloindoline **56** in the highest e.r. featured an electron-poor benzylic group, with a nitro-, fluoro- or trifluoromethyl-substituted arene ring. Meanwhile, diastereomeric ratios remained at approximately 1:1, with some instances of enrichment raising the d.r. up to 2.3:1 at most.

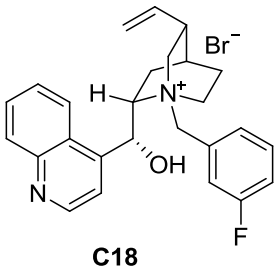


8 **33** **56**

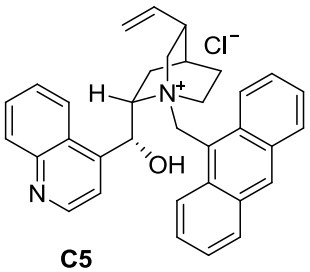
Entry	Catalyst	Temperature	e.r. of DS1	e.r. of DS2	d.r. (DS1:DS2)
1	**C8**	RT	88:12	55:45	1:1
2	**C12**	RT	90:10	52:48	1:1
3	**C16**	RT	91:9	55:45	1:1
4	**C17**	RT	89:11	41:59	1.0:1.5
5	**C18**	RT	16:84	52:48	1.0:2.3
6	**C5** (Lygo B)	RT	27:73	13:87	1.0:1.5
7	**C5** (Lygo B)	−20 °C	24:76	8:92	1.0:1.5
8	**C19**	RT	91:9	47:53	1:1
9	**C19**	−20 °C	95:5	58:42	1:1
10	**C20** (Maruoka)	RT	82:18	83:17	1:1



C8 Ar=2,3,4-F_3-C_6H_2
C16 Ar=3,5-$(CF_3)_2$-C_6H_3
C17 Ar=4-NO_2-C_6H_4
C19 Ar=4-CF_3-C_6H_4



C18



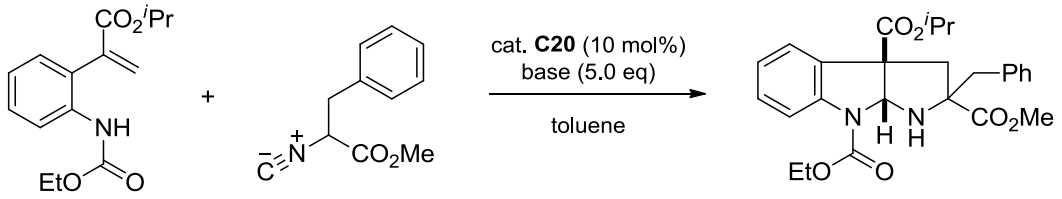
C5
(Lygo B)

Table 5. Chiral catalyst screening in reaction of substrate **8** with isocyanide **33**. DS1 and DS2 refer to each of the two diastereomers of pyrroloindoline **56**. Values for d.r. tentatively determined by chiral HPLC. Structures of catalysts **C12** and **C20** are found in Table 4 and Table 6 respectively.

The screening trials of three phase-transfer catalysts were chosen for further optimisation. Firstly, the reaction employing the third-generation Lygo B catalyst **C5** (see Scheme 4), which had generated both diastereomers in promising e.r. at room temperature (Table 5, Entry 6), was cooled to −20 °C (Entry 7). This led to improvements in enantioselectivity (from 13:87 to 8:92 e.r. for the major diastereomer and 27:73 to 24:76 e.r. for the minor diastereomer), while the diastereoselectivity remained unchanged (at 1.5:1 d.r.). Secondly, the reaction using catalyst **C19**, which had generated one diastereomer in impressive e.r. at room temperature (91:9 e.r., Entry 8) was also repeated at −20 °C, which resulted in an excellent e.r. of 95:5 (Entry 9). However, with this catalyst no diastereoselectivity was observed at either temperature (1:1 d.r.).

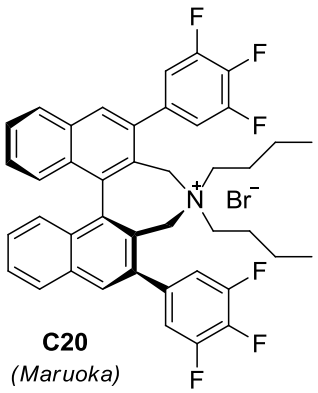
Finally, the reaction using the binaphthyl Maruoka catalyst **C20**, which had yielded both diastereomers in good e.r. at room temperature (82:18 and 83:17 e.r., 1:1 d.r., Entry 10) was subsequently repeated under a range of conditions (Table 6). It was found that lowering the temperature prompted a notable increase in the e.r. of one diastereomer, with slight erosion of the other (Table 6, Entry 2). Meanwhile, changing the base brought about no improvements in enantioselectivity, although utilising solid caesium hydroxide monohydrate led to a d.r. of 2.3:1 (Entry 4).

Akin to the Lygo A catalyst **C11**, the Maruoka catalyst **C20** has also demonstrated the ability to induce excellent enantioselectivity in a variety of reactions.[26,72,73] It similarly contains a biaryl core and is synthesised from simpler components (namely a chiral binaphthyl, an arylboronic acid and a secondary amine), rather than originating from a cinchona alkaloid.



8 **33** **56**

Entry	Base	Temperature	e.r. of DS1	e.r. of DS2	d.r. (DS1:DS2)
1	KOH (25% aq)	RT	82:18	83:17	1:1
2	KOH (25% aq)	−20 °C	95:5	79:21	1:1
3	KOH(s)	−20 °C	83:17	61:39	1:1
4	$CsOH·H_2O$(s)	−20 °C	67:33	65:35	2.3:1.0
5	Cs_2CO_3(s)	−20 °C	82:18	58:42	1:1



C20
(Maruoka)

Table 6. Base screening in reaction to form pyrroloindoline **56** with Maruoka catalyst **C20**.
DS1 and DS2 refer to each of the two diastereomers of **56**. Values for d.r. tentatively determined by chiral HPLC.

In summary, although the diastereoselectivity was generally difficult to control for this reaction, the pyrroloindoline **56** could be synthesised as a pair of diastereomers with excellent enantiomeric ratios of up to 95:5 and 79:21 simultaneously. The tendency of catalysts containing an electron-poor benzylic group to induce high enantioselectivity was also a valuable observation for the target of constructing a diastereo- and enantioselective cascade process.

2.5.3 Catalyst Screening in the Reaction of a Urea-Containing Michael Acceptor

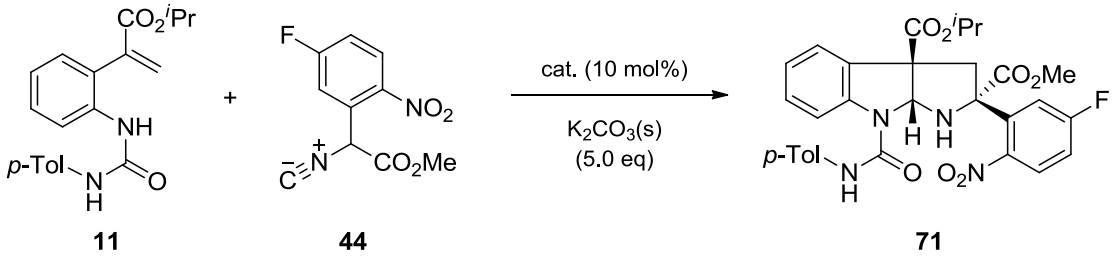
The third reaction selected for catalyst screening was the reaction between the urea-containing Michael acceptor **11** and the α-aryl-substituted isocyanoacetate **44**. With TBAB as the catalyst, this reaction had assembled the pyrroloindoline **71** as a single diastereomer in 54% yield and in a relatively fast reaction time (as previously depicted in Scheme 25). It was theorised that this reaction was accelerated by enhanced intramolecular hydrogen bonding provided by the urea moiety, activating the isocyanide group to act as an electrophile for the proposed 5-*endo-dig* cyclisation step in the cascade. This capability had been exhibited by a phase-transfer catalyst containing a urea group in previous research within the Smith group (Scheme 11). As in those studies, it was hoped that improved hydrogen bonding would increase the pre-organisation of the catalyst-substrate complex, leading to higher levels of stereocontrol.

A variety of different asymmetric conditions were trialled, with the effect of changing the catalyst, base and solvent investigated (Table 7). As a starting point, the racemic reaction conditions of solid potassium carbonate as the base and toluene as the solvent were employed at room temperature. Given the good enantioselectivity induced previously, the Lygo A cat. **C11** and Maruoka cat. **C20** were tested. These generated the pyrroloindoline **71** as a single diastereomer in 79:21 and 15:85 e.r. respectively (Entries 1 and 2), demonstrating that the enantiomer predominantly produced in the reaction could be selectively varied by changing the catalyst. The tremendous enantioselectivity observed with Maruoka cat. **C20** was augmented further to an e.r. of 11:89 by repeating the reaction at −20 °C (Entry 3).

Next, several cinchona alkaloid-derived catalysts were screened – with particular focus on those containing an electron-poor benzylic group, owing to our prior observations. Indeed, utilising cinchoninium catalysts with a pentafluorophenyl (cat. **C21**) and

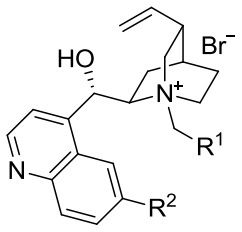
di(trifluoromethyl)phenyl group (cat. **C16**) respectively gave enantiomeric ratios of 77:23 (Entry 4) and 80:20 (Entry 5). The selectivity was then improved further by cooling the reaction with cat. **C16** to −20 °C, pleasingly causing the e.r. to rise to 88:12 (Entry 6). Performing the reaction with this catalyst in *m*-xylene at room temperature gave a similar e.r. (Entry 7), while changing the base to solid caesium carbonate resulted in a reduction in enantioselectivity (Entry 8). Furthermore, attempts with solid and 25% aqueous potassium hydroxide at −25 °C led to decomposition of the isocyanide substrate, while no reaction occurred with solid sodium carbonate as the base at room temperature (not listed in Table 7, performed by Dr Jamie R. Wolstenhulme). Increasing the equivalents of potassium carbonate from 5 to 10 for the reaction in *m*-xylene had no effect on the e.r. of the product.

Meanwhile, replacing two electron-withdrawing trifluoromethyl substituents in a quinidinium catalyst (cat. **C22**) with two electron-donating *tert*-butyl groups (cat. **C23**) resulted in a dramatic fall in e.r. from 81:19 (Entry 9) to 57:43 (Entry 10), vindicating our claim. Moreover, use of pseudoenantiomeric catalysts **C24** and **C25** allowed access to the opposite enantiomer of the pyrroloindoline **71** as the major product, but with slightly poorer selectivity (Entries 11 and 12). Finally, employing a quinidinium catalyst with a pentafluorophenyl group (cat. **C26**) induced the greatest enantioselectivity, with an e.r. of 87:13 attained at room temperature (Entry 13) and 91:9 at −20 °C (Entry 14). This excellent result was additionally achieved by adapting the solvent system to a 15:4:1 ratio of toluene, chloroform and water, aiding the solubility of the urea-containing starting material.

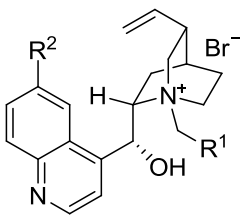


11 **44** **71**

Entry	Catalyst	Solvent	Temperature	e.r. of 71
1	**C11** (Lygo A)	Toluene	RT	79:21
2	**C20** (Maruoka)	Toluene	RT	15:85
3	**C20** (Maruoka)	Toluene	−20 °C	11:89
4	**C21**	Toluene	RT	77:23
5	**C16**	Toluene	RT	80:20
6	**C16**	Toluene	−20 °C	88:12
7	**C16**	*m*-Xylene	RT	82:18
8[a]	**C16**	*m*-Xylene	RT	65:35
9	**C22**	Toluene	RT	81:19
10	**C23**	Toluene	RT	57:43
11	**C24**	Toluene	RT	25:75
12	**C25**	Toluene	RT	23:77
13	**C26**	Toluene	RT	87:13
14[b]	**C26**	Tol/$CHCl_3$/H_2O	−20 °C	91:9



C16 R^1=3,5-$(CF_3)_2$-C_6H_3, R^2=H
C21 R^1=C_6F_5, R^2=H
C22 R^1=3,5-$(CF_3)_2$-C_6H_3, R^2=OMe
C23 R^1=3,5-^{t}Bu$_2$-C_6H_3, R^2=OMe
C26 R^1=C_6F_5, R^2=OMe



C24 R^1=3,5-$(CF_3)_2$-C_6H_3, R^2=H
C25 R^1=3,5-$(CF_3)_2$-C_6H_3, R^2=OMe

Table 7. Chiral catalyst screening in reaction of substrate **11** (1.0 eq) with isocyanide **44** (1.1 eq). Single diastereomer observed in all cases. Structures of catalysts **C11** and **C20** are found in Table 4 and Table 6 respectively. Base and solvent variations investigated by Dr Jamie R. Wolstenhulme.
[a]Cs_2CO_3(s) used as the base instead of K_2CO_3(s). [b]Solvent ratio 15:4:1 respectively.

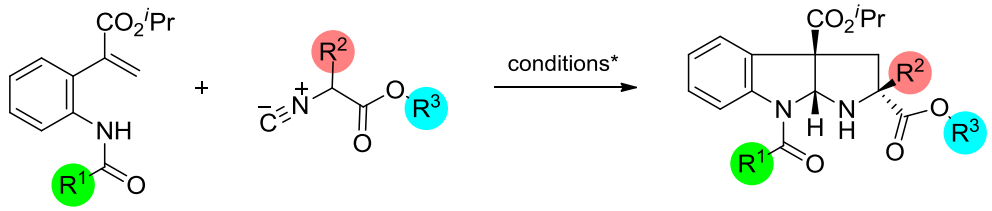
2.5.4 Scope of the Enantioselective Reaction

With conditions for the enantioselective preparation of the urea-containing pyrroloindoline **71** optimised, the scope of the cascade was explored. Initially, the Michael acceptor **11** was reacted with a range of α-aryl-substituted isocyanides, using the achiral catalyst TBAB to evaluate the reactivity. Subsequently, these reactions were repeated on a smaller screening scale, using the optimised asymmetric conditions (quinidinium catalyst **C26**, solid potassium carbonate as the base, and a 15:4:1 solvent system of toluene, chloroform and water at reduced temperature). This enabled enantiomeric ratios of the products to be acquired.

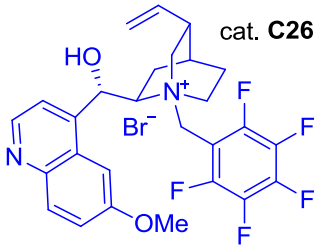
These results are presented in Table 8. For completeness, the yields and accurate diastereomeric ratios (by ^{1}H NMR spectroscopy) of the enantioenriched products are also included, which (except Entry 1) were obtained by Dr Jamie R. Wolstenhulme, who repeated these asymmetric reactions on 50-100 mg scales (following synthesis[74] of the catalyst **C26** in greater quantities). Wolstenhulme also generated and provided the isocyanide substrates employed for the preparation of pyrroloindolines **72** and **73**.

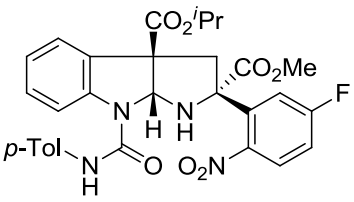
In investigating the scope of the enantioselective cascade, we were pleased to observe that the reaction was tolerant of different ester groups within the isocyanide component. Explicitly, the methyl isocyanoacetate could be changed to a benzyl (Entry 2) or isopropyl isocyanoacetate (Entry 3), affording pyrroloindolines **72** and **73** respectively as single diastereomers and with high levels of enantiocontrol (up to 93:7 e.r.). Moreover, replacing the 5-fluoro substituent in the aromatic ring of the isocyanide with a 4-chloro (Entry 5) or 4-methyl group (Entry 6) was also viable, with the products **75** and **76** obtained in similar e.r. (though in 10:1 d.r. in the case of **76**). However, moving this fluoro substituent from the 5- to

3-position resulted in a reduction in enantioselectivity from 90:10 (Entry 1) to 67:33 e.r. (**77**, Entry 7), along with diminished diastereoselectivity (from >20:1 to 8.1:1 d.r.).

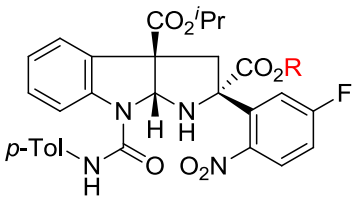


Entry	Product	Yield (racemic)	d.r. (racemic)	Yield (asymmetric)	d.r. (asymmetric)	e.r.
1	**71**	54%	>20:1	60%	>20:1	90:10
2	**72**	61%	>20:1	54%	>20:1	90:10
3	**73**	73%	>20:1	76%	>20:1	92:8
4	**74**	85%	7.0:1	46%	8.9:1	93:7
5	**75**	66%	>20:1	45%	>20:1	86:14
6	**76**	84%	6.4:1	83%	10:1	93:7
7	**77**	69%	5.1:1	49%	8.1:1	67:33
8	**78**	85%	>20:1	74%	>20:1	90:10

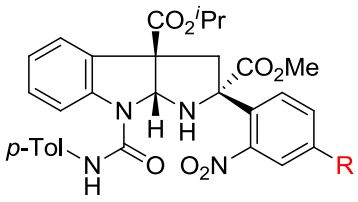




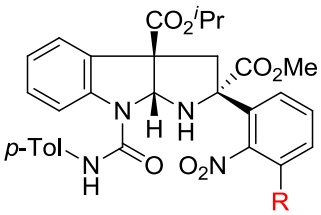
71



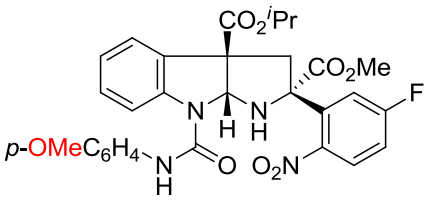
72 R=Bn, **73** R=^{i}Pr



75 R=Cl, **76** R=Me



74 R=H, **77** R=F



78

Table 8. Scope of enantioselective pyrroloindoline formation; e.r. reported for the major diastereomer. **Reagents and conditions:* racemic – Michael acceptor (1.0 eq), isocyanide (1.0 eq), TBAB (10 mol%), K_2CO_3(s) (5.0 eq), toluene, RT; asymmetric – Michael acceptor (1.0 eq), isocyanide (1.1 eq), cat. **C26** (10 mol%), K_2CO_3(s) (5.0 eq), toluene/chloroform/water (15:4:1), 0 °C [entries 2, 5, 7], −20 °C [entries 1, 3, 4, 6, 8].

It was also encouraging to discover that the *para*-tolyl *N*-substituent in the urea could be exchanged for a *para*-anisyl group (Entry 8), furnishing the product **78** as a single diastereomer once again with impressive enantioselectivity (90:10 e.r.).

In summary, the cascade reaction was considered to be very effective, synthesising pyrroloindolines in good yield, generally good to excellent diastereoselectivity and high enantioselectivity. Its scalability was also confirmed by the gram-scale asymmetric synthesis of **73** (Entry 3). However, a limitation of the enantioselective transformation is that an *ortho*-nitro group is necessary for superior outcomes. We hypothesised that the extra acidity engendered by this substituent was essential, as cinchona alkaloid-derived ammonium salts normally demonstrate reduced reactivity compared to simple tetra-alkylammonium salts in base-facilitated reactions.[8]

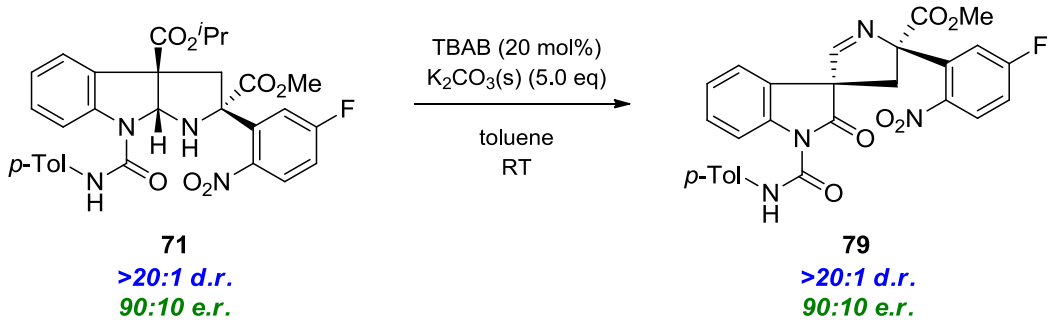
2.5.5 An Unanticipated Rearrangement

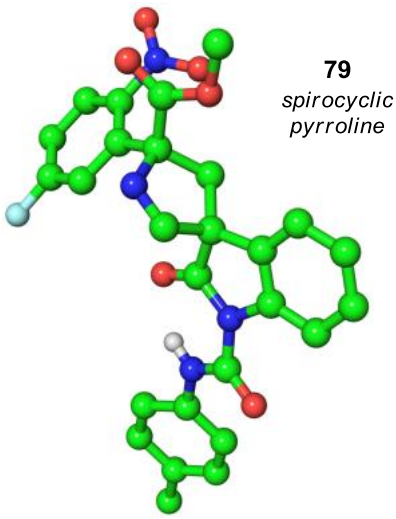
During completion of the asymmetric reactions, Wolstenhulme also noticed the general formation of a by-product in trace amounts, particularly with longer reaction times. In the synthesis of product **71**, this unexpected species was isolated in the same diastereomeric and enantiomeric ratios as the desired product. Therefore it was hypothesised that it most likely arose from an ensuing rearrangement of the pyrroloindoline itself.

Consequently, a sample of enantioenriched pyrroloindoline **71** (90:10 e.r.) was subjected to the racemic phase-transfer conditions, using TBAB as the catalyst, solid potassium carbonate as the base and toluene as the solvent at room temperature (Scheme 26). Over 48 hours, smooth conversion to the by-product **79** was observed, again with the d.r. and

e.r. remaining unchanged. Simultaneously, the pyrroloindoline was recovered with only a small degree of erosion in e.r. (88:12) witnessed.

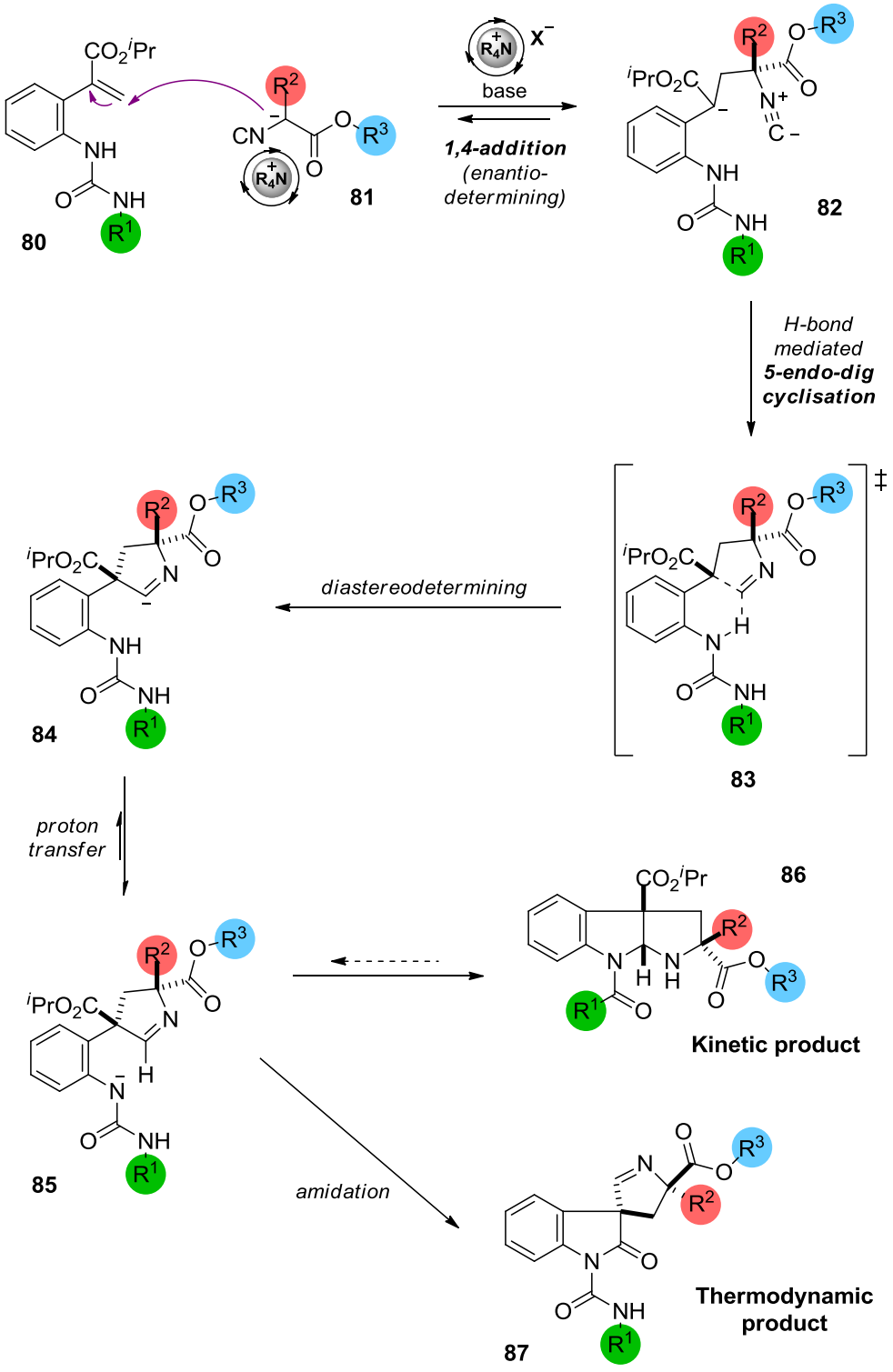
The identity of the side-product **79** was confirmed by X-ray crystallography, revealing it to be a spirocyclic pyrroline (Scheme 26). This implied that the nucleophilic attack of the aniline nitrogen atom (in the Michael acceptor) at the carbon originating from the isocyanide group could be reversible. This nitrogen atom could subsequently attack the isopropyl ester carbon instead to generate the spirocycle. Therefore we considered it to be the thermodynamic product of the reaction. These observations provided valuable insight into aspects of the reaction, contributing to our understanding of the mechanism of the cascade.





Scheme 26. Unanticipated rearrangement to spirocyclic pyrroline, with crystal structure of **79** shown. Reaction was performed by Dr Jamie R. Wolstenhulme. X-ray diffraction data were collected and the structure solved by Dr Russell W. Driver (see Appendix I for full crystal data).

2.6 Proposed Mechanistic Pathway



Scheme 27. Plausible mechanism for the phase-transfer catalysed cascade synthesis of pyrroloindolines from an isocyanide and Michael acceptor, together with the thermodynamic product of the reaction.

Based on the information obtained from our investigations, we were able to propose a plausible mechanism for the cascade reaction, which is depicted in Scheme 27.

Initially, under the basic phase-transfer conditions, the isocyanide is deprotonated at the α-position, generating a carbanion **81** that co-ordinates to the chiral cation of the catalyst. This species then reacts with the Michael acceptor **80** in an asymmetric 1,4-addition, forming an intermediate ester enolate **82** in the enantiodetermining step of the reaction. However, this step is reversible and, in order for good enantioselectivity to be observed, the subsequent step must be significantly faster than the retro-Michael addition.

The subsequent step is a 5-*endo*-*dig* cyclisation onto the isocyanide, which is activated to act as an electrophilic group by intramolecular hydrogen bonding from the specially designed acylated aniline (as in transition structure **83**). Therefore we attribute the excellent enantioselectivity observed with urea-containing substrates to enhanced hydrogen bonding provided by the urea moiety. Due to steric factors, this cyclisation preferentially orientates the smaller group originating from the isocyanide component (an ester) on the more hindered concave face of the forming bicycle (opposite the isopropyl ester group), while the larger (aryl) substituent is positioned away from the rest of the molecule. This is diastereodetermining and an irreversible step, and it would be a point of interest to discover whether the chiral cation is influential in this process – or if it is directed exclusively by the existing stereocentre.

It was observed that bulkier aromatic groups engendered excellent diastereoselectivity, regardless of the electronic properties of the substituents, whereas a non-substituted phenyl and the alkyl groups that were attempted yielded poorer diastereoselectivity. Unfortunately, we could not examine the reaction with the bulky α-alkyl isocyanide derived from the methyl ester of *tert*-leucine (R^2=*tert*-butyl), as this substrate could not be synthesised.

The 5-*endo*-*dig* cyclisation produces carbanion **84**, which undergoes an intramolecular N to C proton transfer to afford ureate **85**. At this point, ring closure can occur by nucleophilic attack at the unsaturated pyrroline carbon, forming the pyrroloindoline framework **86**, which is necessarily the *cis*-fused isomer due to the increased ring strain associated with the alternative *trans*-5,5-ring junction. The pyrroloindoline is the kinetic product of the cascade reaction, while the spirocyclic pyrroline **87** is the thermodynamic product. Given the identical diastereo- and enantioselectivity observed in both products, it is most likely that the spirocycle is generated by the reversal of the final ring closure and consequential trapping of the aniline nitrogen onto the benzylic isopropyl ester, forming an amide with loss of isopropanol in a condensation reaction.

This proposed mechanism is in part supported by computational modelling carried out in previous work published by the Smith group, concerning the synthesis of pyrroloindolines from the isocyanide functional group (Scheme 12).[67] The free-energy profile of the species involved in the intramolecular hydrogen bond-mediated cascade was studied by second-order perturbation theory of the basis set of natural bonding orbitals.[75] Herein, it was determined that the strength of the stabilising N–H···C hydrogen bond (shown in Figure 6, a transition structure akin to **83**) was 10.6 kcal mol^{-1}, a magnitude comparable to hydrogen-bonding interactions found in biological systems.[76] This provided strong evidence that the rapid carbocyclisation exhibited was a direct consequence of intramolecular hydrogen-bonding catalysis, and that the reaction rate should accelerate in the presence of a kinetically more labile proton donor. Moreover, the occurrence of the vinylic carbanion (similar to **84**) was endorsed by its surprising stability, being greater in energy than the starting material by only 5.4 kcal mol^{-1}.

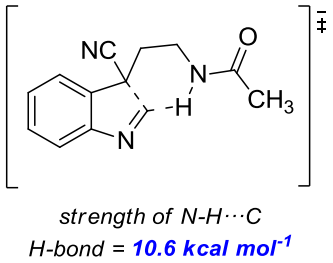
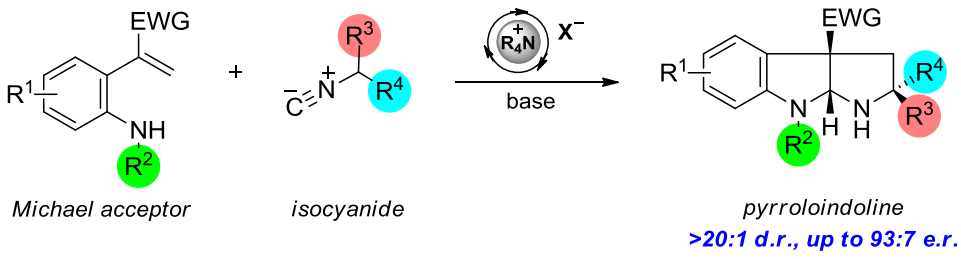


Figure 6. Transition structure studied by computational modelling in previous work by the Smith group.

2.7 Conclusions and Future Work

We have achieved the aim of this project, having developed a diastereo- and enantioselective two-component approach to the synthesis of pyrroloindolines under phase-transfer conditions (Scheme 28).[77] This cascade process offers a rapid and stereoselective pathway to highly functionalised frameworks from simple and readily available starting materials, namely an isocyanide-containing component and a Michael acceptor. The pyrroloindolines, which contain three stereocentres (two of which are all-carbon quaternary) are assembled in a single operation, and such compounds could potentially find application as natural product analogues or scaffolds for the discovery of bioactive species.



Scheme 28. Achieved cation-directed two-component cascade approach to pyrroloindolines.

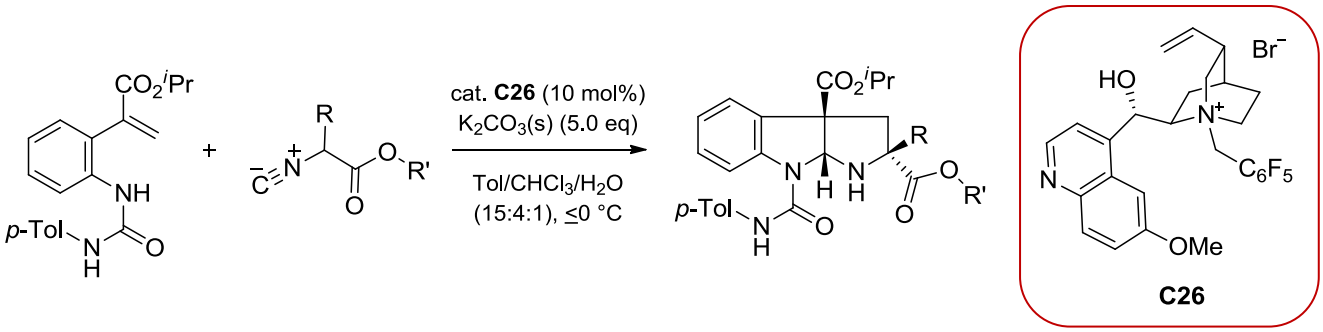
This reaction represents an enhancement on previous work within the Smith group involving the synthesis of pyrroloindolines (as detailed in Scheme 12), as the use of simpler substrates allows for wider substitution patterns and improved enantioselectivity. The cascade

takes advantage of the remarkable reactivity profile of acidic isocyanides, and provides a valuable example of how hydrogen bonding can activate the electrophilicity of this functional group. It was established that the hydrogen bond-donating group could be incorporated within the structure of the specifically engineered Michael acceptor.

After straightforward general synthetic routes to these starting materials were found, we discovered that symmetrical α,α-diaryl isocyanides (R^3=R^4=aryl in Scheme 28) readily underwent the cascade under achiral phase-transfer conditions, generating a single *cis*-fused diastereomer (Scheme 21). These early results revealed that the acidity of the isocyanide compound was an important factor to consider in the reaction.

Next, non-symmetrical isocyanide components ($R^3 \neq R^4$ in Scheme 28) were investigated under achiral phase-transfer conditions, where it was noted that the introduction of bulkier aromatic substituents in these substrates resulted in excellent product diastereoselectivity, irrespective of the electronic properties of the aromatic groups. Meanwhile, the isocyanides assessed with less bulky substituents yielded poorer diastereoselectivity (Schemes 23 and 24).

With conditions for the diastereoselective synthesis of pyrroloindolines found, an enantioselective catalytic cascade was subsequently developed under asymmetric phase-transfer conditions. Excellent enantioselectivity was observed when urea-containing Michael acceptor substrates were utilised, allowing a range of enantioenriched pyrroloindolines to be accessed (Table 8), attributed to enhanced hydrogen bonding provided by the urea moiety. The reaction conditions were varied, through which it was ascertained that the use of a cinchona alkaloid-derived catalyst **C26** containing an electron-poor benzylic group was optimal (Scheme 29), along with solid potassium carbonate as the base and a 15:4:1 solvent system of toluene, chloroform and water at reduced temperature.



Scheme 29. Optimised conditions for the enantioselective reaction.

A spirocyclic pyrroline side-product, which was considered to be the thermodynamic product of the reaction, was simultaneously generated by an unanticipated rearrangement of the pyrroloindoline (Figure 7).

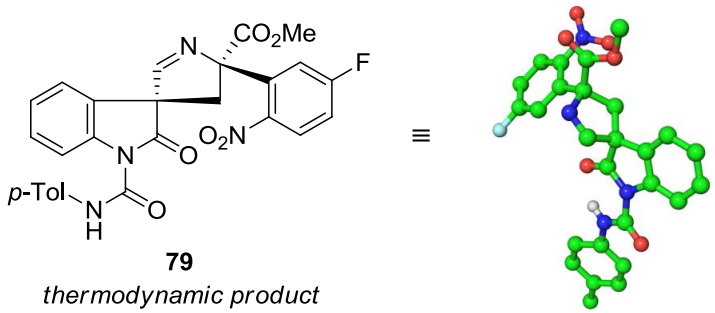


Figure 7. Spirocyclic pyrroline, generated by an unanticipated rearrangement.

Finally, a plausible mechanism for the cascade reaction was suggested (Scheme 27). We propose that the initial step is an enantiodetermining 1,4-addition, mediated by the chiral cation of the catalyst. This is followed by a diastereodetermining 5-*endo-dig* cyclisation onto the isocyanide, activated by intramolecular hydrogen bonding. After a proton transfer, ring closure to produce the pyrroloindoline (the kinetic product) takes place, although reversal of this final step can lead to the alternative generation of the thermodynamic product of the reaction.

In future, collaboration with a computational research group could provide a deeper insight into the mechanistic aspects of this specific reaction, including exploration of whether the chiral cation is influential in the diastereodetermining 5-*endo-dig* cyclisation. Moreover, further aniline *N*-substituents in the Michael acceptor could be investigated, in order to

discover which other groups can promote similar levels of enantioselectivity in the product. The inclusion of other α-substituents in the isocyanide component could also be studied, in order to probe the effect on the diastereoselectivity observed.

3. Introduction to Axially Chiral Biaryls

3.1 Atropisomerism

Atropisomerism describes the stereoisomerism observed due to hindered rotation about a σ-bond, where the energy barrier to rotation is sufficiently high to make the conformers isolable.[78] Most commonly, atropisomers are defined as physically separable species when, at a given temperature, they have a half-life of racemisation of at least 1000 seconds (16.7 min).[79] At 300 K this corresponds to a minimum free energy barrier ($\Delta G^{\ddagger}$) of 93.5 kJ mol^{-1}.[80]

The term "atropisomerism" was devised in 1933 by Kuhn, originating from the Greek word άτροπος (atropos), meaning "without turn".[78] Optical activity due to axial chirality had first been detected experimentally in 1922 by Christie and Kenner[81] in the tetrasubstituted biaryl, 6-6'-dinitro-2,2'-diphenic acid (Figure 8), shortly after evidence had been published disproving the hitherto widely-held belief that the two benzene nuclei in biphenyl are coplanar.[82]

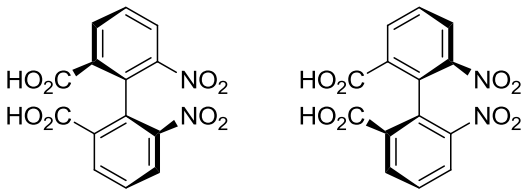
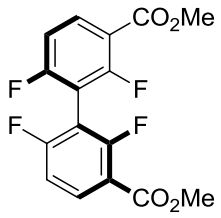


Figure 8. Atropisomers of 6,6'-dinitro-2,2'-diphenic acid.

Today it is understood that the lowest-energy conformation of a biaryl molecule is determined by the interplay of resonance stabilisation with the relief of strain.[83] As the former is optimal with coplanarity, whereas the latter most commonly favours a perpendicular orientation, the preferred conformation normally has an intermediate angle.

The two principal conditions for axial chirality to be observed in biaryl compounds are a rotationally stable axis and the presence of different substituents on both sides of the axis.[84] The rotational stability of biaryls is dependent on the nature, position and number of substituents. Specifically, while non-substituted biphenyl[85] has a torsional barrier of approximately only 6 kJ mol^{-1}, the majority of tetra-*ortho*-substituted biaryls have a sufficiently high barrier to exist as a pair of atropisomers at room temperature, due to increased steric interactions in the coplanar transition state. For example, in the case of the tetrafluorobiaryl **89** (Figure 9), $\Delta G^{\ddagger}_{358K}$ = 108 kJ mol^{-1}, even though the *ortho*-substituents are small.[86]



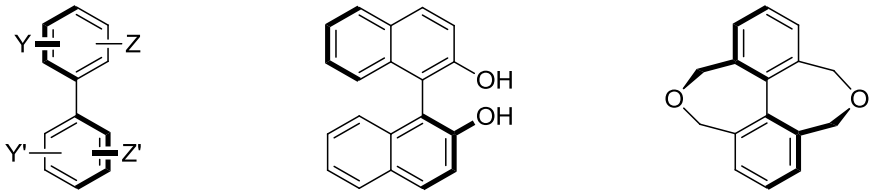
89

Figure 9. An atropisomeric tetrafluorobiaryl.

Meanwhile, atropisomeric tri-*ortho*-substituted biaryls often racemise above room temperature and, in di-*ortho*-substituted derivatives, it is required that both substituents are bulky for axial chirality to be observed.[84] Temperature has a marked effect on the rotational stability of the axis. For instance, a species with a lesser degree of steric hindrance may display restricted rotation at lower temperatures, while a compound which is axially chiral at room temperature may atropisomerise when heated, with full loss of chiral information.[80] In the case of the latter, distortion of the bonds to the *ortho*-substituents and the aryl rings can occur, producing a less rigid and non-planar transition state, which allows the substituents to move past each other on rotation about the axis.[87]

As aforementioned, the presence of different substituents on both sides of the axis is also logically a key requirement. Therefore in the molecule **90** (Figure 10), for optical activity

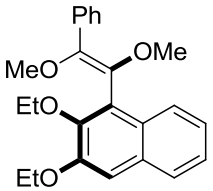
to be observed, it is necessary that Y ≠ Z and Y' ≠ Z'. If Y = Y' and Z = Z', the molecule is C_2-symmetric and still chiral, which is the case for the biaryl ligands BINAP and BINOL.[80] As an apparent exception to the rule, biaryls with four identical groups may be chiral if the two arene nuclei are connected by two bridges. This is illustrated by the D_2-symmetric compound **91** (Figure 10).



90 **BINOL** **91**

Figure 10. Examples of atropisomeric biaryls.

The phenomenon of atropisomerism is not exclusive to biaryls, as exemplified by the enol ether **92**, which was discovered to have a half-life of interconversion of around 1 hour at room temperature (Figure 11).[88]



92

Figure 11. A non-biaryl atropisomeric compound.

3.2 Prevalence of Axially Chiral Biaryls

Axial chirality is ubiquitous in nature: more than 1000 atropisomeric natural products have been isolated to date, and a multitude of these display significant biological activities.[89] For example, vancomycin is an antibiotic glycopeptide, which is included in the World Health Organization's Model List of Essential Medicines, a compilation of the most important medicines required in a basic health system.[90] Vancomycin is highly active *in vitro* against Gram-positive micro-organisms including MRSA,[91] and contains a chiral axis, as well as

several stereocentres and two chiral planes (Figure 12). Consequently, the molecule has a rigid 3D structure, allowing for effective binding to peptides in the cell walls of bacteria.

Meanwhile, the somewhat structurally simpler biaryl natural product, knipholone, and its derivatives have been found to deliver promising antiplasmodial activity against the most lethal parasitic carrier of malaria,[92] in addition to showing interesting anti-tumour activities.[93] Finally, the michellamines comprise a class of atropisomeric alkaloids that find important use in anti-HIV medications, due to their ability to inhibit HIV-induced cellular fusion and viral replication of protein kinase C.[94]

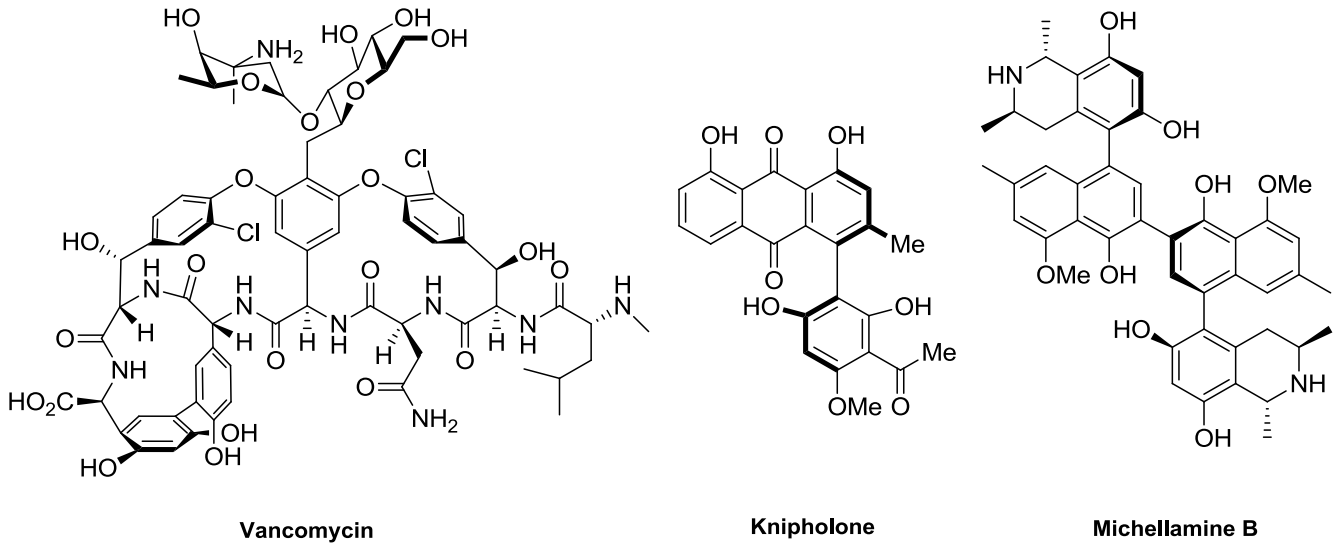
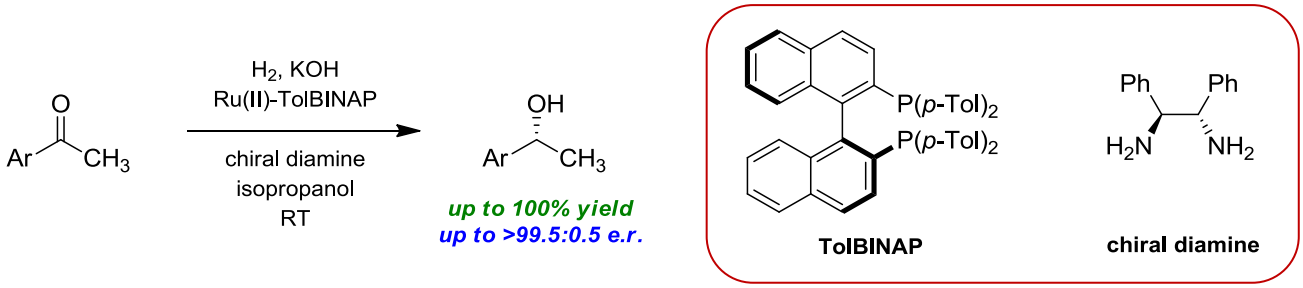


Figure 12. Examples of atropisomeric natural products.

The biaryl core is increasingly appearing in a wider range of pharmaceuticals too, as well as in other commercial applications, such as liquid crystals.[84] However, arguably the most notable usage of this motif is in asymmetric synthesis, where axial chirality is a fundamental property in a number of chiral auxiliaries, ligands and catalysts.[95] Two of the most valuable classes of ligands are BINOLs (Figure 10) and BINAPs, which have exhibited consistent success in a remarkable array of catalytic enantioselective reactions, including asymmetric hydrogenations,[96] Diels-Alder,[97] Michael[98] and aldol reactions,[99]

[2+2]-cycloadditions,[100] polymerisations[101] and Claisen rearrangements.[102] The ground-breaking significance of these discoveries was recognised by the co-awarding of the Nobel Prize in Chemistry to Ryōji Noyori in 2001 for hydrogenation reactions incorporating BINAP ligands in ruthenium complexes (Scheme 30).[103]

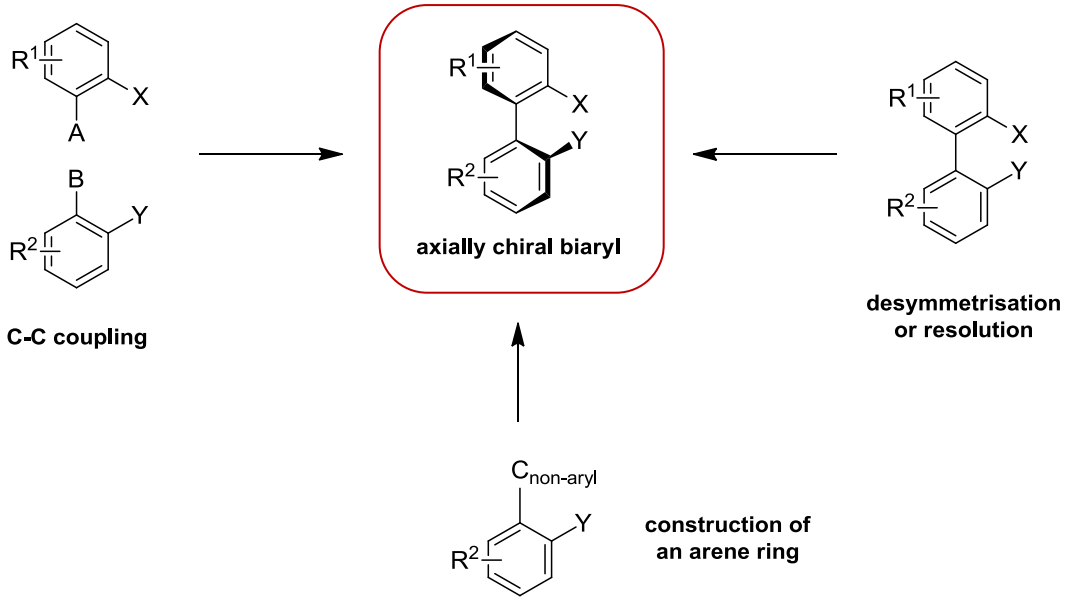


Scheme 30. Noyori asymmetric hydrogenation of ketones.

Moreover, chiral phosphoric acids derived from BINOL have been extensively employed as privileged Brønsted acid organocatalysts in Mannich, Diels-Alder and Friedel-Crafts reactions,[104] and the biaryl core is also a key feature in a variety of phase-transfer catalysts.[95]

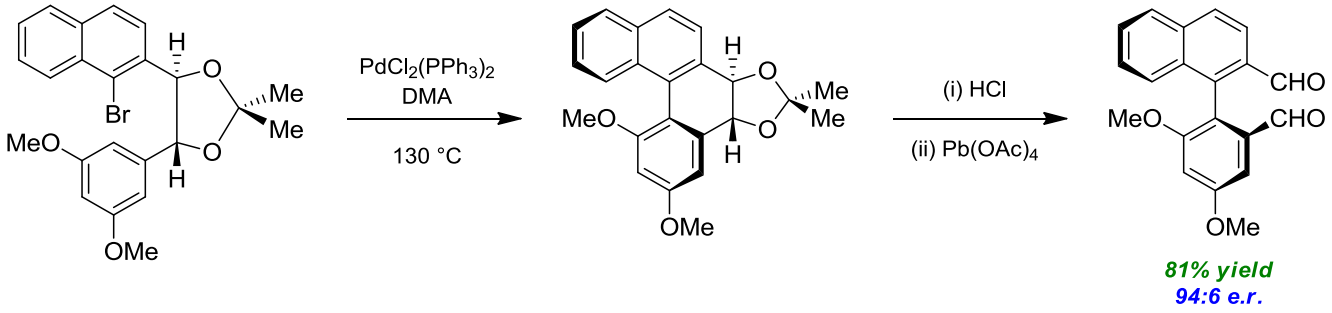
3.3 Atropselective Synthesis of Axially Chiral Biaryls

Although there is an ever-increasing number of known routes for the generation of axially chiral biaryls, there is still great potential for further research into the atropselective synthesis of such compounds, given their prevalence as described above.[89] These methods can be divided into three general strategies (Scheme 31): biaryl formation and asymmetric induction in a single step *via* C–C coupling; kinetic resolution or desymmetrisation of a ready-made prochiral biaryl; and asymmetric construction of the stereogenic axis from non-aryl substituents connected to an arene ring.[80]



Scheme 31. Synthetic approaches to axially chiral biaryls.

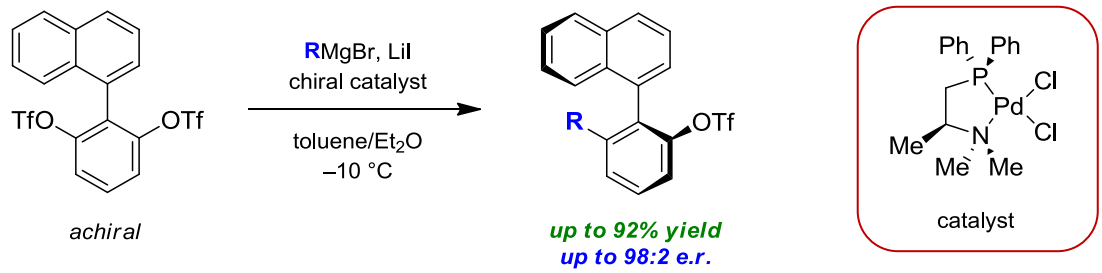
Transition metal-catalysed cross-coupling is the classic approach towards such scaffolds, although difficulty can be encountered when attempting to connect two bulky aromatic moieties, in order to generate tetrasubstituted biaryls.[105] The exact approach taken within this strategy differs depending on whether the desired synthesis is diastereo- or enantioselective. Diastereoselective couplings can be carried out by tethering the two aryl units with a chiral bridge, which results in a favoured intramolecular reaction. This linker can either be part of the final product, or act as an auxiliary that can be subsequently eliminated (Scheme 32).[106] Alternatively, a diastereoselective reaction can be performed using starting materials with a chiral auxiliary installed at a position *ortho* to the coupling carbon, or by incorporating a removable chiral element, such as a planar-chiral η^6-chromium complex.[80]



Scheme 32. Atropselective biaryl synthesis by cross-coupling, using a removable chiral bridge.

Meanwhile, Grignard coupling *via* a nucleophilic aromatic substitution reaction can be enantioselective if the leaving group is chiral.[107] Most other enantioselective approaches are based around the use of chiral ligands or additives, either in redox-neutral couplings[108] or oxidative homocoupling processes,[109] including a renowned laboratory method for the generation of BINOL derivatives from 2-naphthols.

The second strategy, specifically desymmetrisation or kinetic resolution of a prostereogenic biaryl compound, involves a step that establishes the absolute configuration at the axis of a pre-formed non-atropisomeric biaryl. This methodology can act as a more reliable approach to the synthesis of bulky tetrasubstituted biaryls than aryl-aryl coupling.[80] A rotationally stable but achiral biaryl can be desymmetrised by the modification of a group within the molecule, which results in an atropisomeric product. This can be achieved asymmetrically by employing a chiral catalyst (Scheme 33)[110] or by using an enzyme,[111] as each of the enantiotopic groups will consequently react at a different rate.

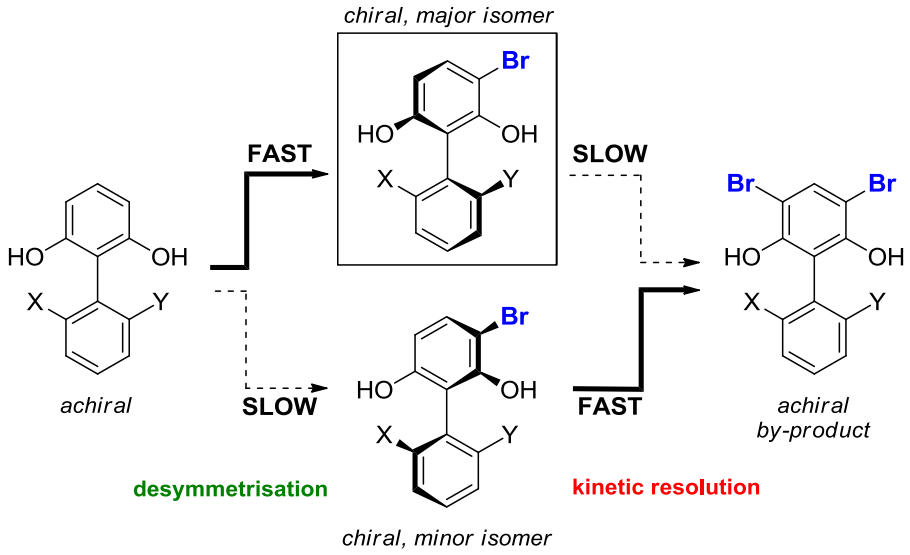


Scheme 33. Example of desymmetrisation of a prochiral biaryl.

On the other hand, biaryls which are substituted in such a way to permit chirality, but are configurationally unstable, can be locked as a pair of atropisomers by introducing further *ortho*-substitution in a dynamic kinetic resolution process.[112] In a simple catalytic kinetic resolution, two enantiomers react at different rates; therefore given an initial racemate of products, the faster-reacting atropisomer can be removed, leaving the other atropisomer to be obtained in an enantioenriched mixture. Here the theoretical yield can evidently only reach

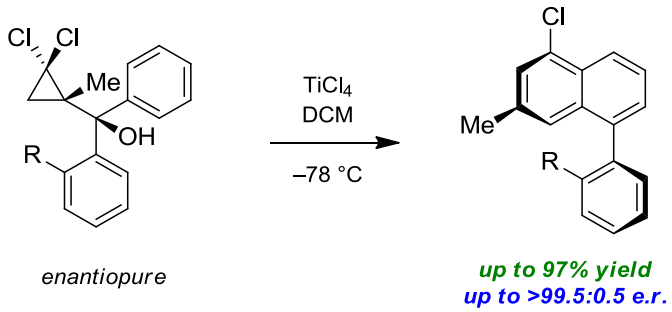
50% but contrastingly, in a dynamic kinetic resolution, a pair of enantiomers can be converted into a single enantiomer, allowing for full asymmetric acquisition of the product.[95]

Dynamic kinetic resolution can also be applied to establish axial chirality by formation of a bridge,[113] or by cleavage of a pre-existing tether,[114] between the two arene nuclei in a biaryl compound. A representative desymmetrisation/resolution sequence for the enantioselective synthesis of biaryls by Akiyama *et al.* is depicted in Scheme 34, which is based around asymmetric bromination, utilising a chiral phosphoric acid as the catalyst.[105]



Scheme 34. Representative desymmetrisation/resolution sequence.

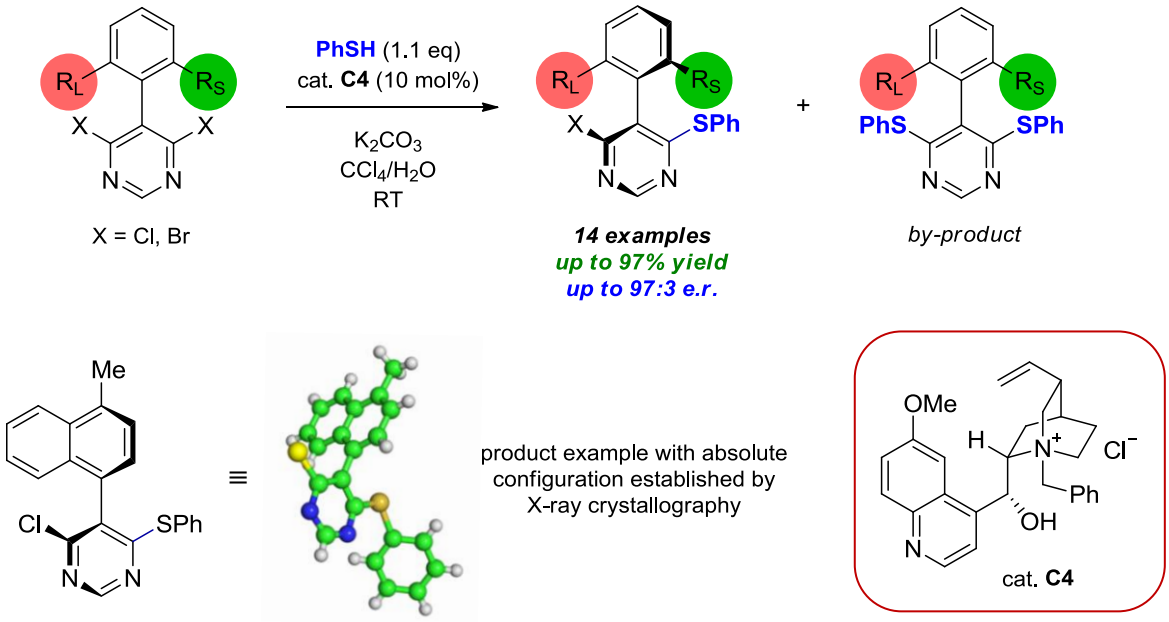
As an innovative approach that has been explored only relatively recently, there are fewer known examples of the final strategy for the generation of atropisomeric biaryls, namely the construction of an arene ring. In this method, a single bond between an aryl carbon and a non-aryl carbon is converted to a biaryl axis (Scheme 31), with chirality transfer to the axis ensuing from a pre-existing stereogenic centre or by enantioselective catalysis.[80] One excellent case of sp^3 point-to-axial conservation of chirality was reported in a benzannulation reaction by Nishii, Tanabe *et al.*, using a Lewis acid to transform an enantiopure substrate (Scheme 35).[115]



Scheme 35. Example of arene ring construction with point-to-axial chirality exchange.

3.4 Previous Work in the Smith Group

In previous research by the Smith group, atropisomeric biaryl compounds have been synthesised asymmetrically by a nucleophilic aromatic substitution reaction, directed by a chiral cation (Scheme 36).[116]



Scheme 36. Previous work in the Smith group involving the enantioselective synthesis of atropisomeric biaryls.

The biaryl products were furnished in excellent yields and with impressive enantioselectivity, and it was demonstrated that these compounds could be derivatised to a

variety of atropisomeric structures (by a second S_NAr reaction, oxidation of the sulfur or alkylation of the pyrimidine ring) without any reduction in enantioenrichment. Therefore this methodology provides a route to a range of unexplored atropisomeric scaffolds.

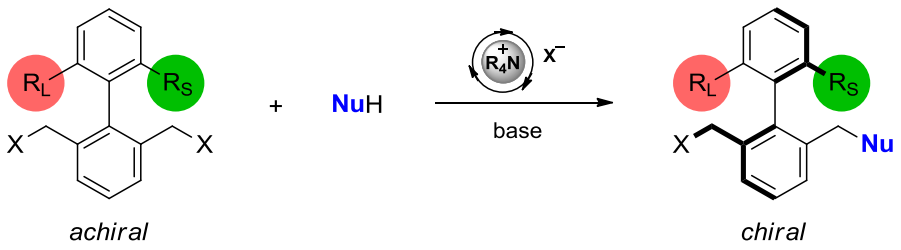
In this phase-transfer catalysed approach, prochiral dichloropyrimidines underwent a tandem desymmetrisation/kinetic resolution process (similar to that outlined in Scheme 34), using thiophenol as the nucleophile in basic conditions. It was explicitly observed that increasing the loading of thiol led to improved enantioselectivity, rationalised by preferential reaction of the excess nucleophile with the minor atropisomer to give the doubly substituted by-product.

4. Enantioselective Synthesis of Atropisomeric Biaryls *via* a Cation-Directed S_N2 Reaction

4.1 Project Aims

The aim of this project is to investigate a new enantioselective approach to axially chiral biaryls, with the objective of developing a desymmetrising S_N2 reaction on an achiral starting biaryl under asymmetric phase-transfer conditions. This builds on the aforementioned work involving a desymmetrising S_NAr reaction reported by the Smith group (Scheme 36).[116]

The proposed reaction to be explored herein is illustrated below (Scheme 37). In designing the reaction scheme, several factors were taken into consideration. Importantly, the electrophilic starting material should be straightforward to construct and contain a plane of symmetry through the biaryl axis, whilst being sufficiently sterically congested to restrict rotation. Moreover, the substrate should contain a leaving group that can be substituted under mild reaction conditions to give a configurationally stable, atropisomeric product.



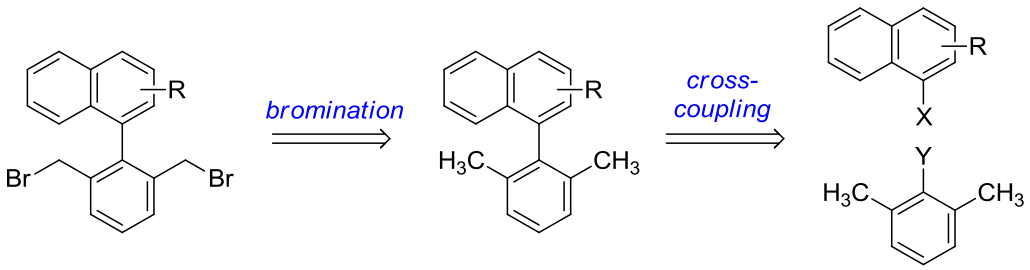
Scheme 37. Proposed asymmetric phase-transfer catalysed S_N2 reaction.

It was envisaged that, under asymmetric phase-transfer conditions, the tight ion pair formed between a deprotonated nucleophile and a chiral cation would induce discrimination in the displacement of enantiotopic leaving groups. If enantioselective, this transformation could offer valuable access to a myriad of chiral biaryl derivatives, an architecture with significant proven and potential utility.

4.2 Synthesis of Starting Materials

4.2.1 Retrosynthesis

Given the essential properties for the starting biaryl as described above, a suitable architecture was identified together with a route for its synthesis (Scheme 38). It was decided to attempt the construction of symmetrical biaryls consisting of naphthyl and *ortho*-di(bromomethyl)phenyl components, as this offered a reasonable degree of steric hindrance for restricted rotation whilst permitting feasible cross-coupling. Furthermore, it was hoped that the bromo groups could be readily installed and act as a good leaving group in the desired desymmetrisation reaction.



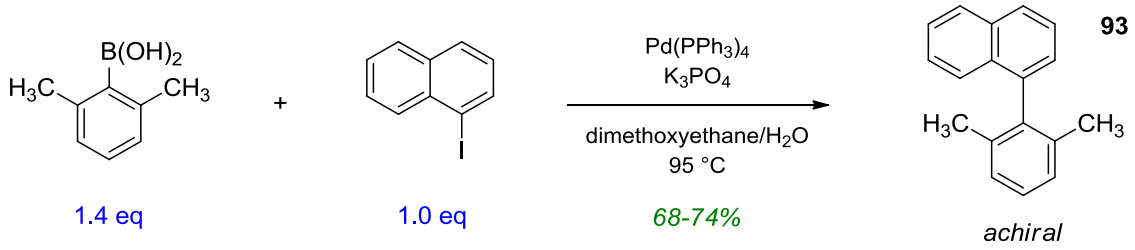
Scheme 38. Retrosynthetic analysis of biaryl starting material.

4.2.2 Suzuki-Miyaura Reactions

It was decided to perform a Suzuki-Miyaura reaction for the cross-coupling of the two aryl components, due to its broad scope, the wide commercial availability of the reagents and the relatively low toxicity of the boronic acids employed.[117]

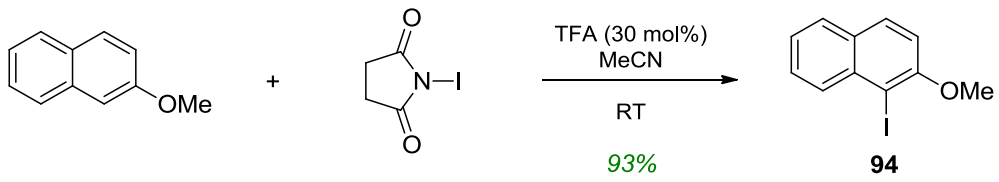
In the first C–C coupling reaction (Scheme 39), 1-iodonaphthalene was combined in a 1:1 ratio with (2,6-dimethylphenyl)boronic acid, using $Pd(PPh_3)_4$ as the catalyst. Gratifyingly, the coupling proceeded, but it was observed that a moderate amount of the iodonaphthalene

remained at the end of the reaction, which was difficult to separate by column chromatography from the biaryl product **93**. Accordingly, the reaction was repeated with a slight excess of the boronic acid (1.4 eq), successfully depleting the iodonaphthalene and generating the product **93** in 68% yield. This was subsequently expanded to a multi-gram scale, in which the yield was seen to improve to 74%.



Scheme 39. Suzuki coupling scales: (i) 250 mg of boronic acid, 10 mol% catalyst, 68% yield; (ii) 5.00 g of boronic acid, 6.5 mol% catalyst, 74% yield.

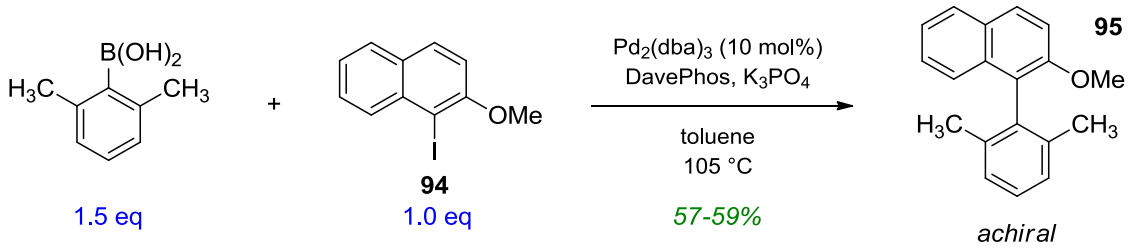
We were also interested to find out whether the Suzuki coupling could take place with enhanced steric encumbrance about the intended biaryl axis. Therefore it was decided to attempt to introduce a methoxy group in the *ortho*-position of the naphthyl component. The halide reagent **94** required for this Suzuki reaction was formed efficiently by regioselective iodination of 2-methoxynaphthalene with *N*-iodosuccinimide (Scheme 40).



Scheme 40. Iodination of 2-methoxynaphthalene to form Suzuki coupling reagent.

Unfortunately, it was discovered that the Suzuki reaction with 1-iodo-2-methoxynaphthalene did not proceed under the previously successful cross-coupling conditions, with starting materials returned and hydrodehalogenation observed. This was attributed to the increased hindrance. However, performing the reaction using a literature procedure by the Buchwald group[118] furnished the desired biaryl product **95** (Scheme 41),

initially in 57% yield and then 59% yield on a multi-gram scale. This modified method utilised $Pd_2(dba)_3$ as the catalyst with the phosphine ligand, DavePhos, at a slightly elevated temperature.

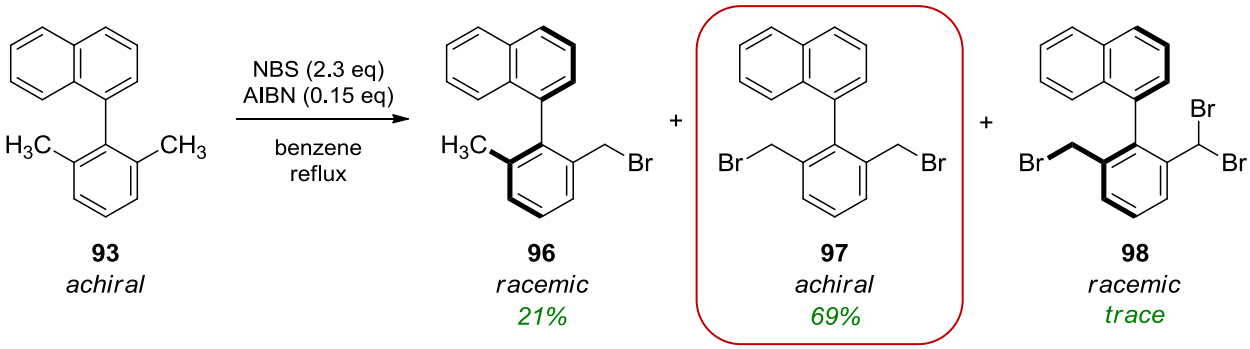


Scheme 41. Suzuki coupling scales: (i) 1.00 g of naphthalene, 57% yield; (ii) 4.00 g of naphthalene, 59% yield.

4.2.3 Bromination Reactions

Following the successful cross-coupling reactions, the final step to generate the biaryl starting materials was a benzylic bromination reaction, for which *N*-bromosuccinimide (NBS) was identified as an appropriate reagent.

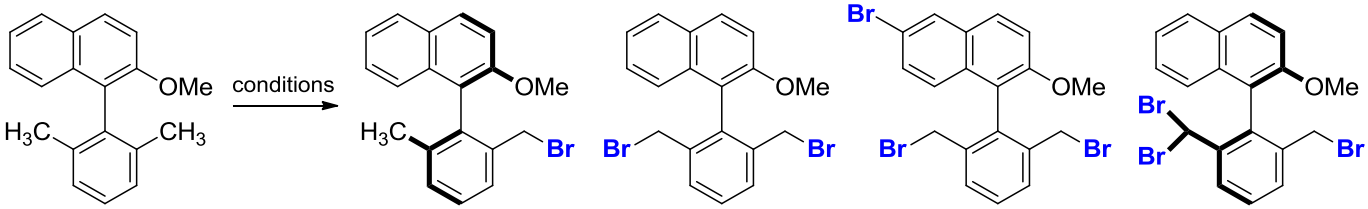
Refluxing precursor **93** in benzene with NBS and the radical initiator, AIBN, led to complete consumption of **93** in 4 hours, giving three products with varying degrees of bromination (Scheme 42). The desired dibrominated biaryl **97** was isolated as the major product in 69% yield, along with the chiral monobrominated compound **96** (in 21% yield) and a trace amount of the chiral tribrominated species **98** (both as racemates).



Scheme 42. Benzylic bromination of biaryl **93**.

Subsequently, the reaction was repeated under the same conditions with the methoxy-substituted precursor **95** and, after 6 hours, another trio of products was obtained (Table 9, Entry 1). However, in this instance, the monobrominated compound **99** was isolated as the major product in 46% yield (as a racemate), and the desired dibrominated molecule **100** was acquired in only 33% yield. Interestingly, the third compound **101** (which was obtained in a trace amount) was instead formed as a result of bromination of the naphthyl ring.

It was therefore recognised that more forcing conditions were necessary, in order to achieve a greater proportion of dibromination. As such, the equivalents of both NBS and AIBN were increased and the reaction time was extended (Table 9, Entry 2). This had a striking effect on the outcome of the reaction, with the dibrominated compound **100** now isolated as the major product (in 70% yield) and no monobrominated product **99** observed. Additionally, the ring-brominated product **101** was isolated in 10% yield, and the benzylically tribrominated product **102** was detected in a trace amount (inseparable from the major product).



95 **99** **100** **101** **102**

Entry	Mass of SM 95	Conditions	Yield of 99 (%)	Yield of 100 (%)	Yield of 101 (%)	Yield of 102 (%)
1	100 mg	NBS (2.3 eq), AIBN (0.15 eq), benzene, reflux, 6 h	46	**33**	trace	0
2	1.56 g	NBS (3.0 eq), AIBN (0.25 eq), benzene, reflux, 18 h	0	**70**	10	trace

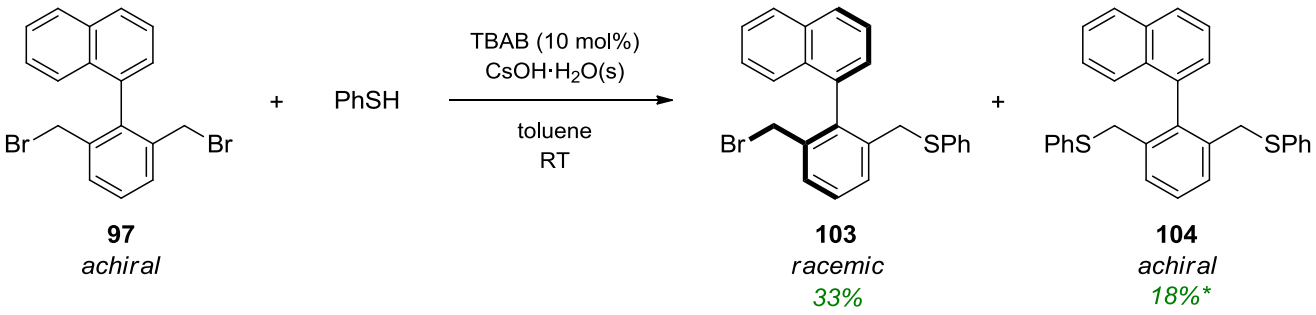
Table 9. Conditions for bromination of biaryl **95** and yields of products.

4.3 Desymmetrisation with a Thiol

4.3.1 Initial Reactions

Thiophenol was employed as the nucleophilic species in the work reported by the Smith group concerning the asymmetric synthesis of atropisomeric biaryls *via* an S_NAr reaction (Scheme 36). Inspired by these excellent results, we began our investigations into S_N2 reaction-induced desymmetrisation of the prepared prochiral biaryl substrates by selecting this nucleophile once again.

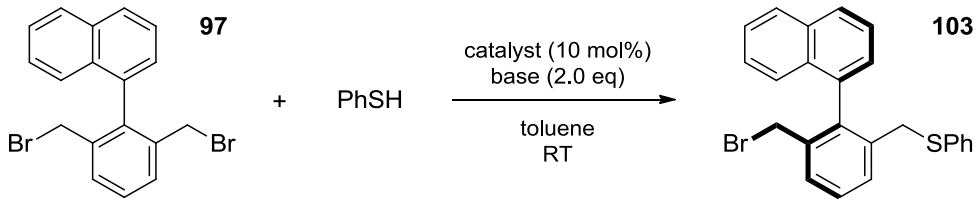
As a starting point, thiophenol was combined with the biaryl starting material **97** in toluene, using achiral TBAB as the phase-transfer catalyst and solid caesium hydroxide monohydrate as the base. The desired monosubstituted product **103** was generated as a racemic mixture in a modest yield of 26%, limited by the fact that a significant quantity of the disubstituted product **104** was also obtained (14% with respect to the biaryl substrate). As no thiophenol remained at the end of the reaction, it was also theorised that the yield may have been hindered by oxidation of this reagent to diphenyl disulfide, given the presence of oxygen and base.[119] Therefore the reaction was repeated in identical conditions, except under an atmosphere of argon (Scheme 43). However, the yield of the desired product **103** only rose to 33% (with 18% of the disubstituted compound **104** with respect to the biaryl substrate).



Scheme 43. Reaction of biaryl **97** (1.2 eq) with thiophenol (1.0 eq) in achiral phase-transfer conditions, using 2.0 eq of base, performed under an atmosphere of argon. *Yield with respect to biaryl substrate.

4.3.2 Catalyst and Base Screening

Next a catalyst screen was carried out on this reaction, whilst also studying the effect of changing the base (Table 10). Disappointingly, although a variety of chiral catalysts were assessed, in almost all cases a near-racemic mixture of the product **103** was generated.



Entry	Catalyst	Base	e.r.
1	**C1**	$CsOH \cdot H_2O$(s)	50:50
2	**C2**	$CsOH \cdot H_2O$(s)	49:51
3	**C2**	K_2CO_3(s)	39:61
4	**C3**	$CsOH \cdot H_2O$(s)	64:36
5	**C3**	K_2CO_3(s)	54:46
6	**C4**	$CsOH \cdot H_2O$(s)	62:38
7	**C4**	K_2CO_3(s)	52:48
8	**C6** (Corey)	$CsOH \cdot H_2O$(s)	55:45
9	**C11** (Lygo A)	$CsOH \cdot H_2O$(s)	44:56
10	**C27**	$CsOH \cdot H_2O$(s)	57:43

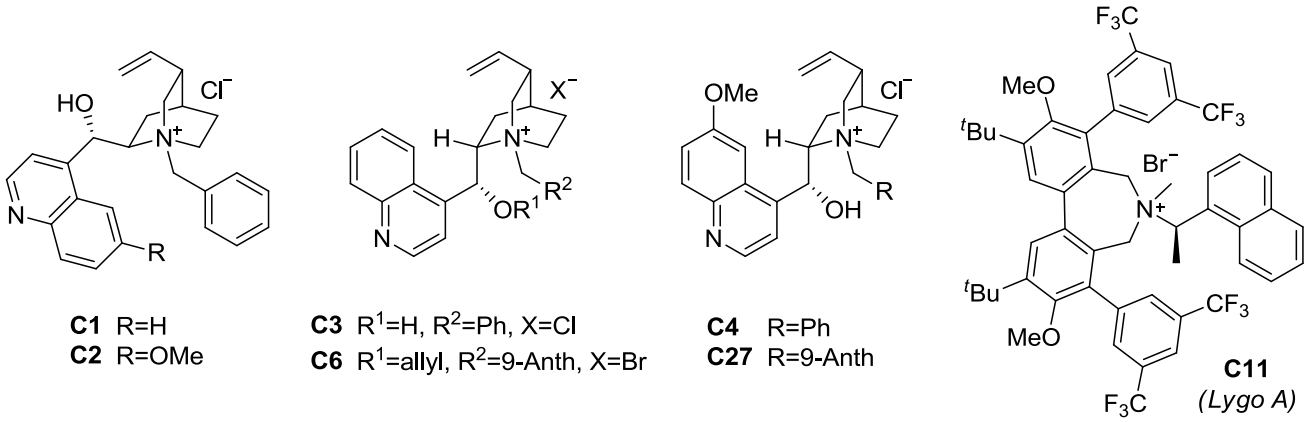
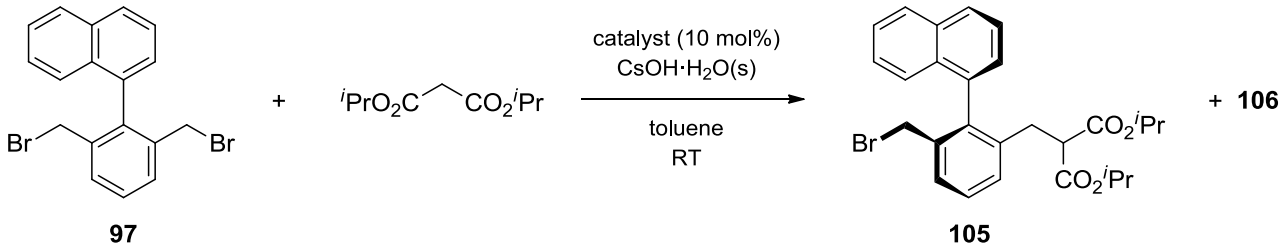


Table 10. Base and chiral catalyst screening in reaction of biaryl **97** (1.2 eq) with thiophenol (1.0 eq).

4.4 Desymmetrisation with a Malonate

4.4.1 Catalyst Screening

Given the modest yields and poor enantioselectivity observed when thiophenol was used as the nucleophilic species, attention was thus turned to a different reagent. Diisopropyl malonate was chosen and subjected to the same basic, achiral phase-transfer conditions as previously with the biaryl substrate **97**. More promisingly, the corresponding racemic monosubstituted product **105** was delivered in a yield of 47%, along with 18% of the disubstituted compound **106** (Table 11, Entry 1). Subsequently asymmetric catalyst screening was performed for this reaction (Table 11, Entries 2-7).



Entry	Catalyst	e.r. of 105
1*	TBAB	–
2	**C2**	36:64
3	**C4**	62:38
4	**C6** (Corey)	46:54
5	**C27**	53:47
6	**C5** (Lygo B)	43:57
7	**C11** (Lygo A)	72:28

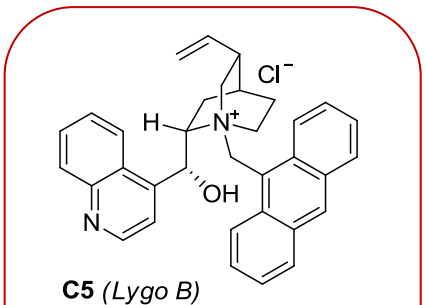
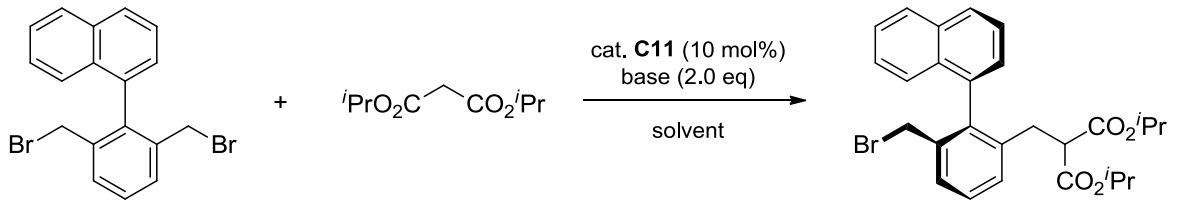


Table 11. Chiral catalyst screening in reaction of biaryl **97** (1.0 eq) with diisopropyl malonate (1.0 eq), using 2.0 eq of base. *Yield of **105** = 47%, yield of **106** (achiral disubstituted compound) = 18%.

Good preliminary atropselectivity was observed for the reaction with Lygo A catalyst **C11** (Table 11, Entry 7), and it was anticipated that this could be improved further. Additionally, the screening reactions in Entries 2 and 3 of Table 11 were repeated with solid potassium carbonate as the base, but inferior enantioselectivity was observed in both cases. However, the doubly alkylated compound **106** was not generated when using this base.

4.4.2 Optimisation

Variations in the base, solvent and temperature were monitored with Lygo A catalyst **C11**, in order to optimise the reaction (Table 12). It was ascertained that lowering the temperature enhanced the e.r. of the product **105** (from 72:28 at RT to 76:24 at −20 °C), while toluene was the most suitable solvent. Meanwhile, changing the base to potassium hydroxide led to a slight erosion in enantioselectivity.



97 **105**

Entry	Base	Solvent	Temperature	e.r. of 105
1	CsOH·H_2O(s)	Toluene	RT	72:28
2	CsOH·H_2O(s)	Toluene	−20 °C	76:24
3	CsOH·H_2O(s)	DCM	RT	52:48
4	KOH (50% aq)	Toluene	RT	71:29
5	KOH (25% aq)	Toluene	RT	70:30

Table 12. Optimisation of reaction for the asymmetric synthesis of biaryl **105** using Lygo A cat. **C11**.

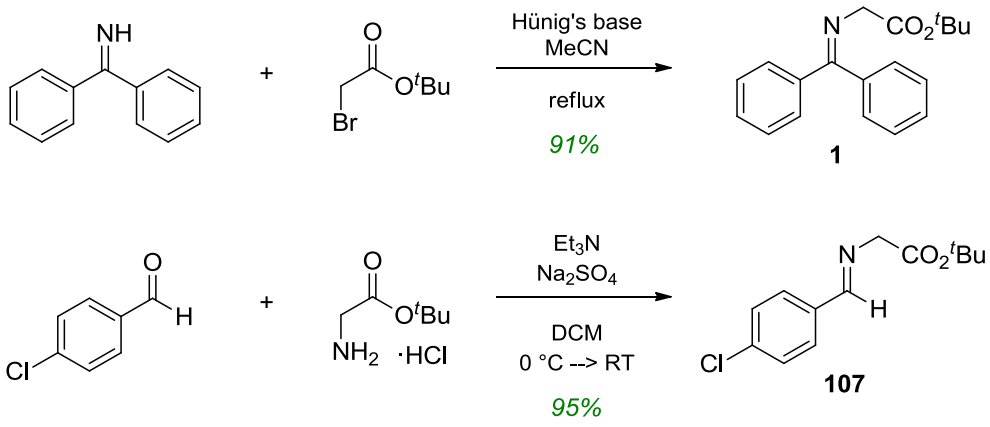
Consequently, the reaction was repeated under the optimised conditions detailed in Entry 2 of Table 12 on a larger scale (increasing from screening scale to 50 mg of biaryl starting material), which furnished the product **105** in 55% yield and 73:27 e.r..

4.5 Desymmetrisation with a Glycine Schiff Base

4.5.1 Synthesis of Glycine Schiff Bases

The good atropselectivity accomplished with the malonate nucleophile gave a foundation for optimism that a potent desymmetrisation reaction could be developed. On account of the impressive results for enantioselectivity obtained by Lygo[23] and Corey[24] in phase-transfer catalysed alkylations with a glycine Schiff base (as previously outlined in Scheme 4), we believed that this methodology could be successfully crafted for our reaction scheme.

In order to test this hypothesis, two glycine Schiff bases (**1** and **107**) were synthesised. These were obtained in excellent yields by simple one-step routes (Scheme 44).



Scheme 44. Synthesis of glycine Schiff bases. Hünig's base is ethyldiisopropylamine.

4.5.2 Initial Reactions

Initial alkylations were attempted using the benzophenone imine glycine ester **1** with biaryl **97**. Unlike the reactions with thiophenol and diisopropyl malonate, it was expected that with this pronucleophile the products would be yielded as a pair of diastereomers, each existing as a pair of enantiomers (Figure 13).

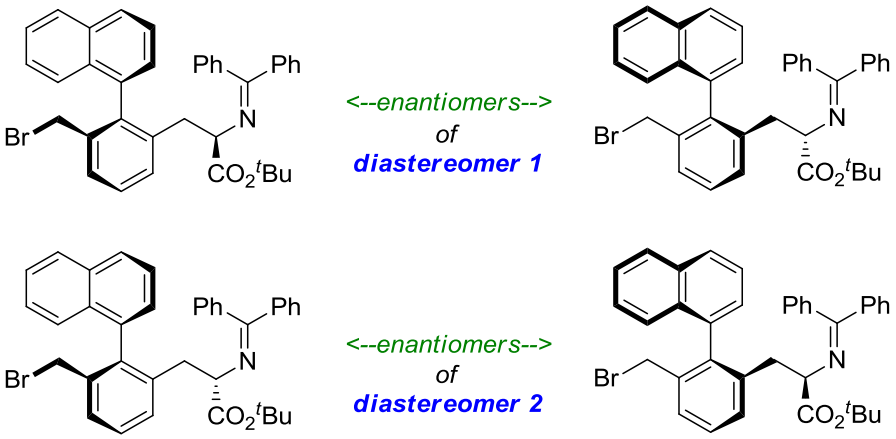
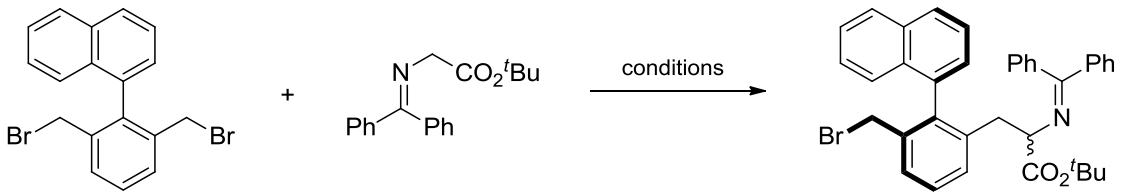


Figure 13. Expected products of alkylation of biaryl **97** with glycine Schiff base **1**.

In the first reactions performed to generate these products, conditions similar to those reported by the groups of Lygo and Corey were applied. As aforementioned, both groups had found great success in enantioselectivity when employing asymmetric phase-transfer catalysts bearing an *N*-anthracenylmethyl group – however, in order to study our new reaction, we began by using achiral TBAB in conjunction with the adapted literature conditions, generating the diastereomeric products racemically (Table 13).



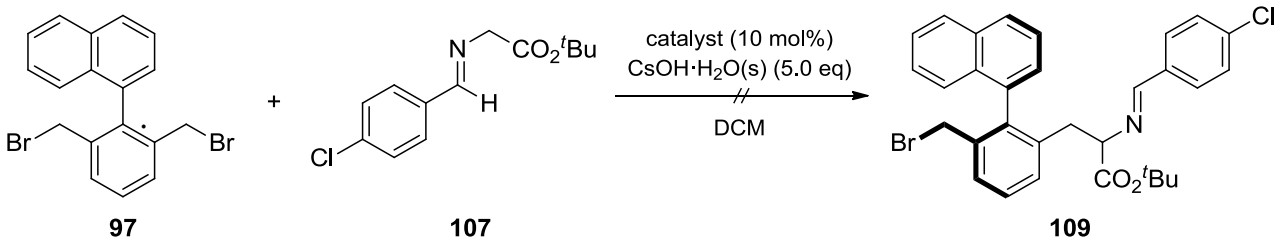
97 **1** **108**

Entry	Reagents and Conditions	d.r.	Yield* (%)
1 *(Lygo)*	**97** (1.0 eq), **1** (1.0 eq), TBAB (10 mol%), KOH (50% aq) (2.0 eq), toluene, RT	3.1:1	53
2 *(Corey)*	**97** (1.0 eq), **1** (1.0 eq), TBAB (10 mol%), $CsOH \cdot H_2O$(s) (5.0 eq), DCM, 0 °C	4.0:1	56

Table 13. Initial alkylation reactions and conditions. Wavy bond indicates unknown configuration at specified position. *Yield of both diastereomers combined; each diastereomer generated racemically.

It was encouraging to observe some diastereoselectivity in these early reactions. The yields were satisfactory, and found to be limited by the formation of a diastereomeric mixture of doubly alkylated products (specifically in 13% yield for Table 13, Entry 1). Hydrolysis of the glycine imine to benzophenone, both during the course of the reaction and the subsequent column chromatography purification, was also witnessed (it was noted that conversion of the biaryl starting material **97** was 81% for Table 13, Entry 1, using dibenzyl ether as an internal standard).

Next, the other synthesised glycine Schiff base **107** was subjected to the Corey-inspired conditions with biaryl **97** (Table 14). However, with TBAB as the catalyst at room temperature, a complex mixture of products was formed. Consequently, the reaction was repeated at −78 °C with Corey's asymmetric catalyst **C6**, so that the conditions were milder and more similar to those reported in the literature. At this temperature, no reaction was observed, but at 0 °C and RT the same unexpected major product **110** was furnished.



Entry	Catalyst	Temperature	Outcome
1	TBAB	RT	Complex mixture of products
2	**C6**	−78 °C	No reaction
3	**C6**	0 °C	No **109,** major product **110**
4	**C6**	RT	No **109,** major product **110**

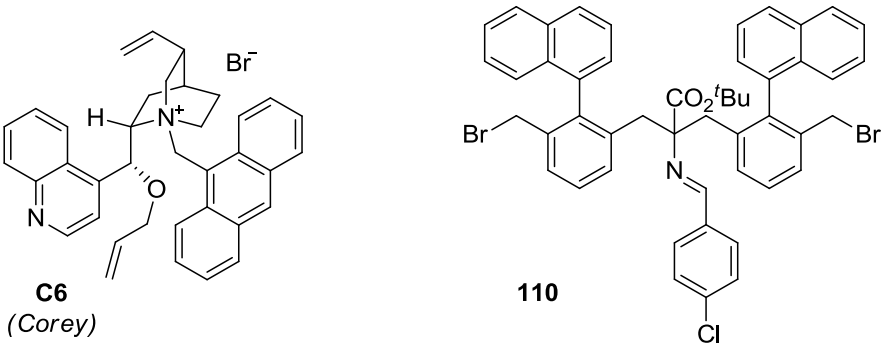


Table 14. Outcomes of attempted alkylation reactions of biaryl **97** with glycine Schiff base **107**.

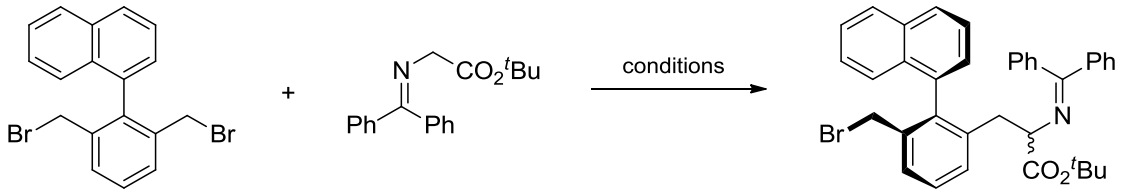
This unanticipated compound **110** (which could not be separated completely from a complex mixture, precluding detailed characterisation) was the result of one molecule of glycine Schiff base alkylating a biaryl substrate molecule, and the ensuing species then alkylating a second biaryl substrate molecule. The readiness of this glycine Schiff base **107** for dialkylation was found to be precedented,[120] and it was thus deemed unsuitable for the desired desymmetrisation. Further investigations would focus primarily on Schiff base **1**.

4.5.3 Catalyst Screening

Catalyst screening was then carried out for the reaction between glycine imine **1** and biaryl **97** under both sets of conditions from Table 13 in turn (with the modification that all tests were run at room temperature). An assortment of phase-transfer catalysts were trialled (Table 15), namely the simple *N*-benzylcinchoninium **C1**, -cinchonidinium **C3**, -quininium **C4** and -quinidinium **C2** chloride salts, along with catalysts bearing the effectual *N*-anthracenylmethyl group: the Lygo B cat. **C5** and the Corey cat. **C6**. The Lygo A cat. **C11**, which had induced good enantioselectivity in the reaction with diisopropyl malonate (Table 11), was also tested.

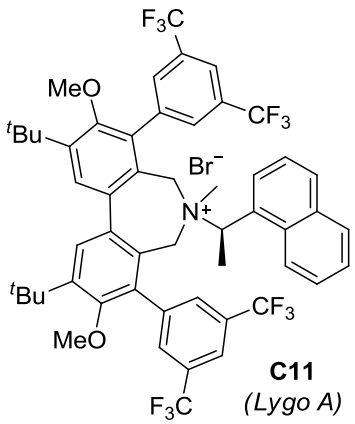
We were delighted to attain high levels of enantioselectivity under both sets of conditions, particularly with the *N*-anthracenylmethyl-containing catalysts. Notably, use of the Lygo A cat. **C11** delivered the diastereomeric products as essentially single enantiomers in one case, with an e.r. of 99:1 for the major diastereomer and 6:94 for the minor. As expected, excellent e.r. values for the major diastereomer were observed when the Corey cat. **C6** was utilised under the Corey reaction conditions (8:92 e.r.), and when the Lygo B cat. **C5** was employed under the Lygo reaction conditions (14:86 e.r.). The enantioselectivity for the minor diastereomer was not generally quite as high, though it was hoped that the generation of this product could be minimised through good simultaneous diastereoselectivity.

It was noticed that the d.r. values mostly lay between 2:1 and 3:1. However, using the Corey cat. **C6** in combination with the Lygo conditions pleasingly gave an improved d.r. of 4.6:1 (with an e.r. of 10:90 for the major diastereomer). It was therefore decided to screen the effect of varying the base, solvent and temperature within this set of conditions, in order to enhance the diastereoselectivity of the reaction – and indeed to fine-tune its enantioselectivity.

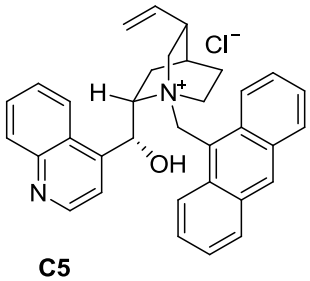


97 1 108

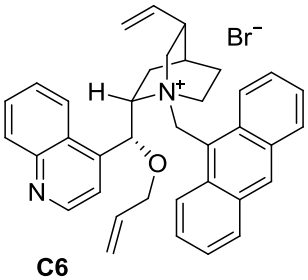
	Catalyst:	C1	C2	C3	C4	C11 *Lygo A*	C5 *Lygo B*	C6 *Corey*
Lygo conditions [a]	**e.r.$_{maj}$**	**87:13**	**61:39**	**18:82**	**38:62**	**99:1**	**14:86**	**10:90**
	e.r.$_{min}$	51:49	49:51	22:78	39:61	6:94	50:50	81:19
	d.r.[c]	**3.1:1**	**2.3:1**	**1.6:1**	**1.5:1**	**3.0:1**	**2.9:1**	**4.6:1**
Corey conditions [b]	**e.r.$_{maj}$**	**82:18**	**66:34**	**20:80**	**35:65**	**89:11**	**15:85**	**8:92**
	e.r.$_{min}$	27:73	42:58	75:25	28:72	17:83	68:32	89:11
	d.r.[c]	**2.7:1**	**2.4:1**	**2.3:1**	**1.2:1**	**3.0:1**	**2.8:1**	**2.4:1**



C11 *(Lygo A)*



C5 *(Lygo B)*



C6 *(Corey)*

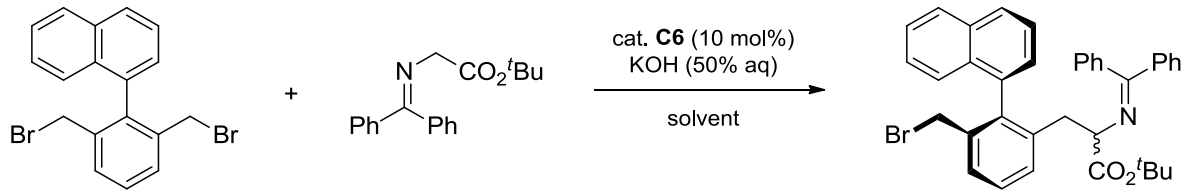
structures of other chiral phase-transfer catalysts shown in Figure 1

Table 15. Catalyst screening. Wavy bond indicates unknown configuration at shown position.
[a]*Lygo conditions:* phase-transfer cat. (10 mol%), KOH (50% aq) (2.0 eq), toluene, RT.
[b]*Corey conditions:* phase-transfer cat. (10 mol%), $CsOH \cdot H_2O$(s) (5.0 eq), DCM, RT.
[c]Values for d.r. tentatively determined by chiral HPLC at this stage. e.r.$_{maj}$ and e.r.$_{min}$ refer to the enantiomeric ratios of the major and minor diastereomers respectively.

A base screen revealed that KOH (50% aq) remained the optimal base, with none of the other bases assessed offering a better d.r. (see Appendix C). Changing the solvent to DCM (with KOH (50% aq) as the base) resulted in a slight increase in e.r. of the major diastereomer from 10:90 to 8:92, but with a reduction in d.r. from 4.6:1 to 2.6:1 (Table 16, Entry 3). However, lowering the temperature progressively boosted the selectivity – gratifyingly, at

−35 °C the d.r. reached 6.4:1 along with an e.r. of 3:97 for the major diastereomer (Table 16, Entry 5).

Next the screening reactions at room temperature and −35 °C were scaled up. At RT the product **108** was generated in 53% yield after 4 hours (Entry 2) with identical diastereoselectivity compared with the screening scale, together with 10% of a diastereomeric mixture of doubly alkylated products. Meanwhile, at −35 °C the product **108** was formed in 51% yield after 50 hours with a pleasing increased d.r. of 7.1:1 (Entry 6), along with double alkylation in only 9% yield. In both cases, minimal reductions in enantioselectivity were witnessed. Furthermore, it was noted that stirring each of the diastereomers of the product **108** in turn at 50 °C for 24 hours in toluene-d_8 led to no diastereomeric interconversion.



97 **1** **108**

Entry	Scale of 97	Solvent	Temperature	d.r.* of 108	e.r.$_{maj}$	e.r.$_{min}$
1	6 mg	Toluene	RT	4.6:1	10:90	81:19
2	60 mg	Toluene	RT	4.6:1	13:87	79:21
3	6 mg	DCM	RT	2.6:1	8:92	84:16
4	6 mg	Toluene	−20 °C	5.1:1	3:97	86:14
5	6 mg	Toluene	−35 °C	6.4:1	3:97	82:18
6	60 mg	Toluene	−35 °C	7.1:1	4:96	80:20

Table 16. Further screening of conditions. *For reactions on 6 mg scale, values for d.r. tentatively determined by chiral HPLC; for reactions on 60 mg scale, values for d.r. determined by analysis of ^{1}H NMR spectrum of the crude mixture. e.r.$_{maj}$ and e.r.$_{min}$ refer to the enantiomeric ratios of the major and minor diastereomers respectively.

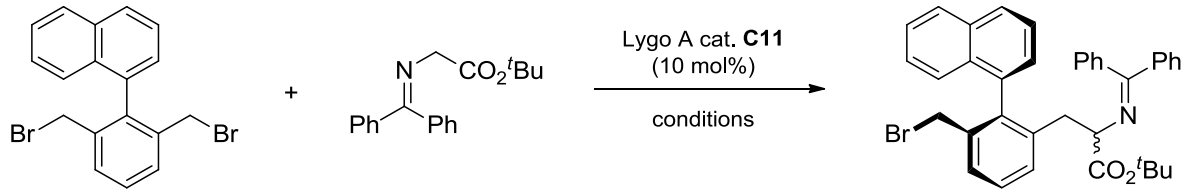
4.5.4 Additional Screening

The screening reactions in Table 15 that had been carried out under the Corey conditions were repeated with solid potassium carbonate as the base (instead of solid caesium hydroxide monohydrate), but no improvements in selectivity were recorded and the reactions were much slower.

Moreover, the room-temperature screening reaction in Table 15 using the Corey catalyst **C6** under the Corey reaction conditions (8:92 e.r.$_{maj}$, 89:11 e.r.$_{min}$, 2.4:1 d.r.) was performed again at −20 °C. As previously observed, lowering the temperature led to a rise in diastereoselectivity (7:93 e.r.$_{maj}$, 81:19 e.r.$_{min}$, 2.9:1 d.r.), but this result still fell short of that under the optimal conditions outlined in Table 16.

Finally, given the outstanding enantioselectivity induced by the Lygo A cat. **C11** (Table 15), further investigations were made into conditions involving this catalyst (Table 17). However, no other conditions were found to reach the previously acquired e.r. of 99:1 for the major diastereomer, while no appreciable increases in d.r. were seen. Interestingly, with this catalyst it was noticed that small decreases in temperature had a profound effect on the rate of the reaction and, contrary to previous observations, led to a loss of diastereoselectivity (Table 17, Entries 2 and 6).

Therefore, after these additional screening reactions, the conditions described in Entries 5 and 6 of Table 16 remained as those which were most encouraging (using Corey cat. **C6**, KOH (50% aq) as the base, and toluene as the solvent at −35 °C).



97 1 108

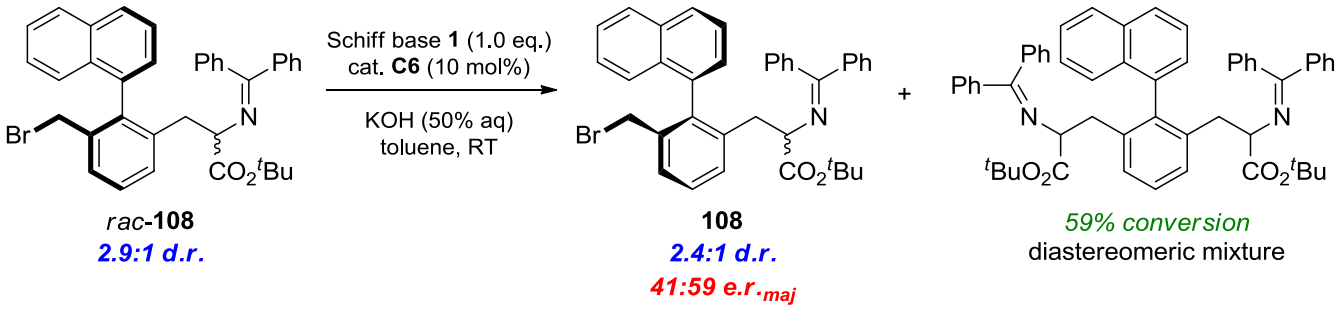
Entry	Base	Solvent	Temperature	d.r.* of 108	e.r.$_{maj}$	e.r.$_{min}$
1	KOH (50% aq)	Toluene	RT	3.0:1	99:1	6:94
2	KOH (50% aq)	Toluene	0 °C	1.2:1	81:19	3:97
3	KOH (50% aq)	DCM	RT	3.1:1	87:13	17:83
4	CsOH·H_2O (s)	DCM	RT	3.0:1	89:11	17:83
5	CsOH·H_2O (s)	Toluene	RT	2.6:1	96:4	5:95
6	CsOH·H_2O (s)	Toluene	−10 °C	1.1:1	96:4	3:97

Table 17. Screening of conditions using Lygo cat. **C11** and 2.0 eq of base.
*Values for d.r. tentatively determined by chiral HPLC.
e.r.$_{maj}$ and e.r.$_{min}$ refer to the enantiomeric ratios of the major and minor diastereomers respectively.

4.5.5 Attempted Kinetic Resolution

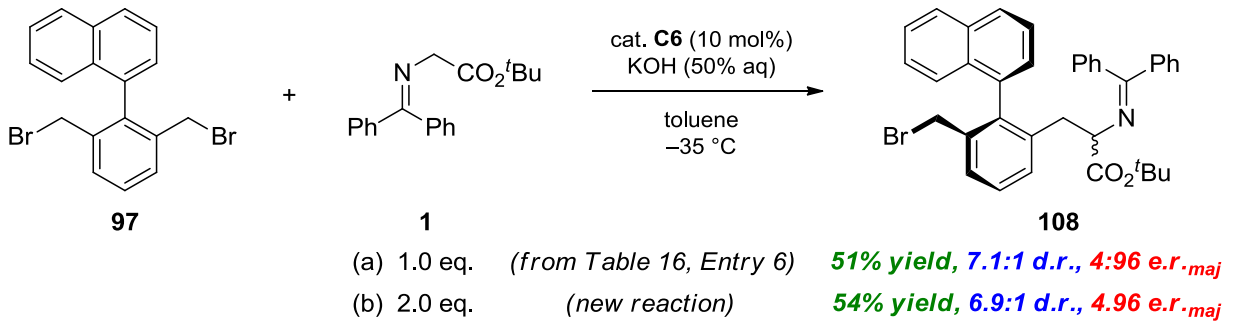
In order to make further enhancements to the selectivity from the optimal conditions, it was theorised that a tandem desymmetrisation/kinetic resolution process could be developed (similar to that outlined in Scheme 34). As aforementioned, this concept had been successfully implemented in previous work in the Smith group (Scheme 36),[116] where increasing the loading of the nucleophile resulted in improved selectivity, rationalised by preferential reaction of the excess reagent with the minor atropisomer to give the doubly substituted by-product.

In order to probe whether this could be applied to the reaction between glycine Schiff base **1** and biaryl **97**, a previously obtained racemic diastereomeric mixture of the monosubstituted product **108** (in 2.9:1 d.r.) was subjected to the optimised conditions (albeit at room temperature) with 1.0 equivalent of Schiff base **1** (Scheme 45).



Scheme 45. Attempted kinetic resolution of a racemic diastereomeric mixture of **108**.

It was encouraging to observe that the racemate became enantioenriched by submitting it to the asymmetric reaction conditions, indicating that one enantiomer was preferentially consumed. However, this mixture was less desirably retrieved in a slightly poorer diastereomeric ratio, eroded from 2.9:1 to 2.4:1. Nevertheless, given the fact that this trial had manifestly influenced the selectivity of the reaction, it was decided to carry out the S_N2 reaction between biaryl **97** and glycine imine **1** with 2.0 equivalents of **1** under the hitherto optimal asymmetric conditions. Thus a direct comparison could be made regarding the effect of employing an excess of the pronucleophile (Scheme 46).



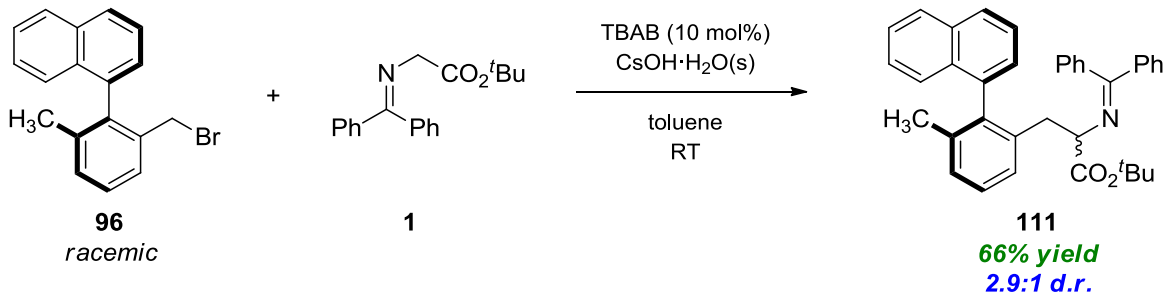
Scheme 46. Comparison of results when varying the loading of nucleophile in attempted desymmetrisation/kinetic resolution process. *Further results:* (a) 80:20 $e.r._{min}$, 9% double alkylation; (b) 74:26 $e.r._{min}$, 27% double alkylation. Values for d.r. determined by analysis of ^1H NMR spectrum of the crude mixture. Yields of both diastereomers combined.

Unfortunately, a slight decline in diastereoselectivity was witnessed once again (from 7.1:1 to 6.9:1) and, given the already excellent quality of the enantioselectivity, no further improvement in e.r. of the major diastereomer was made. It was therefore concluded that a tandem desymmetrisation/kinetic resolution process could not be effectively incorporated into this reaction under the present conditions. However, those conditions indeed generated highly pleasing results – producing the biaryl **108** in tremendous e.r. of 4:96 (for the major diastereomer) and in very good d.r. of 7.1:1.

4.6 Reactions of other Biaryls

4.6.1 Asymmetric Alkylation of Monobrominated Biaryl

We were also interested to examine the asymmetric alkylation of the chiral monobrominated biaryl **96**, which had been formed racemically as a by-product in the generation of the desired dibrominated species **97** (Scheme 42). As a starting point, this biaryl **96** was reacted with the glycine Schiff base **1** at room temperature under achiral phase-transfer conditions, using TBAB as the catalyst and solid caesium hydroxide monohydrate as the base in toluene. This produced the alkylated biaryl **111** in 66% yield (improved due to the absence of a competing dialkylation) and in 2.9:1 d.r. (Scheme 47).

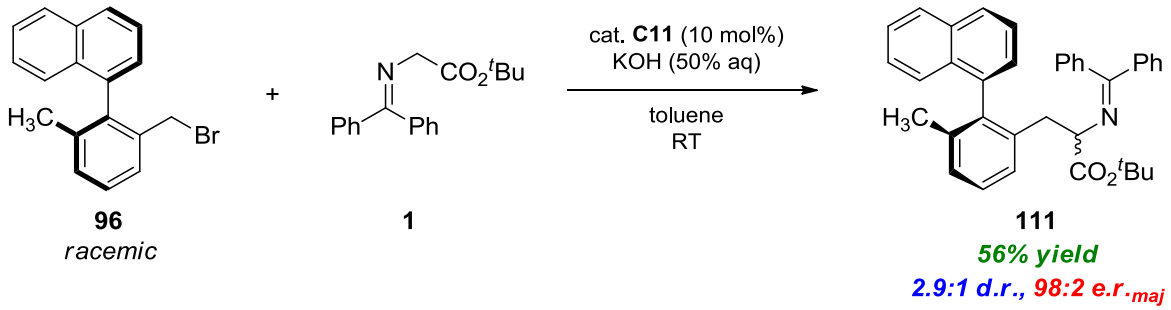


Scheme 47. Reaction of biaryl **96** (1.0 eq) with glycine Schiff base **1** (1.0 eq) in achiral phase-transfer conditions, using 2.0 eq of base. Yield of both diastereomers combined.

Screening of this reaction was then performed with a variety of different phase-transfer catalysts (see Appendix F). However, it became apparent that it was difficult to achieve both good diastereoselectivity and enantioselectivity simultaneously for this reaction. This was rationalised statistically due to the racemic nature of the starting material, unless one of the enantiomers reacted significantly faster than the other (which in the extreme case would limit the potential reaction yield to 50%), or unless atropisomeric interconversion could take place during the reaction (which had been shown to be very unlikely). Specifically, each equally abundant atropisomer of starting material could produce two diastereomers whose enantiomers, if produced in a relatively lesser quantity to give a good e.r., would limit the bias of one diastereomer over the other (giving a poorer d.r.), and vice versa.

However, amongst the screened catalysts, the Lygo A cat. **C11** distinctly engendered excellent enantioselectivity once more, with the product **111** generated in 98:2 e.r. (for the major diastereomer) and 3.0:1 d.r. (tentatively determined by chiral HPLC at this stage). By utilising 50% aqueous potassium hydroxide solution as the base, the d.r. improved slightly to 3.4:1 (with an $e.r._{maj}$ of 97:3). Meanwhile, as previously observed, cooling the temperature of the reaction with this catalyst led to slower reactivity and inferior selectivity.

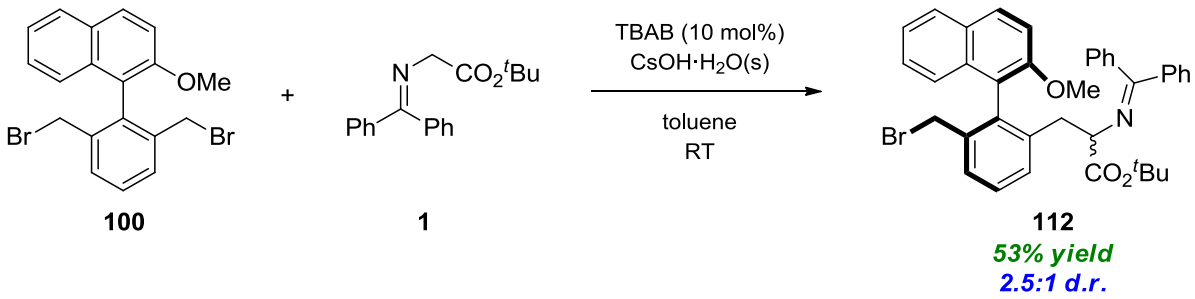
The reaction was subsequently enlarged to a 60 mg scale (of biaryl starting material **96**), whereby the alkylated product **111** was furnished in 56% yield, 2.9:1 d.r. and 98:2 $e.r._{maj}$ (Scheme 48). Statistical analysis suggested that, at this level of diastereoselectivity, such high enantioselectivity could not be achieved without a degree of bias in reactivity of one of the enantiomers of the biaryl substrate **96** under the asymmetric phase-transfer conditions. This hypothesis was subsequently confirmed, as the biaryl **96** recovered at the end of the reaction was found to be enantioenriched (29% recovered, 87:13 e.r.).



Scheme 48. Reaction of biaryl **96** (1.0 eq) with glycine Schiff base **1** (1.0 eq) in chiral phase-transfer conditions. Value for d.r. determined by analysis of ^{1}H NMR spectrum of the crude mixture. Yield of both diastereomers combined.

4.6.2 Alkylation of Methoxy-Substituted Biaryl

Lastly, we hoped that increasing the steric encumbrance about the biaryl axis could enhance the selectivity of asymmetric alkylation. Therefore the methoxy-substituted biaryl **100** was combined with the glycine Schiff base **1**, initially under achiral phase-transfer conditions, using TBAB as the catalyst and solid caesium hydroxide monohydrate as the base (Scheme 49). The desired alkylation product **112** was obtained, but in an inferior d.r. of 2.5:1 and a yield of 53%.



Scheme 49. Reaction of biaryl **100** (1.0 eq) with glycine Schiff base **1** (1.0 eq) in achiral phase-transfer conditions, using 2.0 eq of base. Yield of both diastereomers combined.

Despite the original hypothesis for this reaction, subsequent room-temperature catalyst screening supported the actual observation of poorer selectivity (see Appendix G). As consistently witnessed in previous experiments, the Lygo A cat. **C11** and Corey cat. **C6** delivered the best results in terms of enantioselectivity of the product **112**, which was made in 22:78 and 76:24 e.r. respectively for the major diastereomer, but in diminished

diastereoselectivity of only 1.1:1 and 2.5:1 d.r. respectively. For these screening trials, 50% aqueous potassium hydroxide was used as the base and toluene was selected as the solvent (and values for d.r. were tentatively determined by chiral HPLC). Given the limitations observed under a range of conditions, no further reactions were performed with this methoxy-substituted biaryl substrate **100**.

4.7 Attempted Determination of Stereochemistry

It was anticipated that the stereochemistry of the alkylated biaryl products could be determined by X-ray crystallography. However, despite numerous attempts with both racemic and enantioenriched samples, crystals could not be harvested for the major diastereomer of any of the three principal compounds **108**, **111** or **112** (Figure 14).

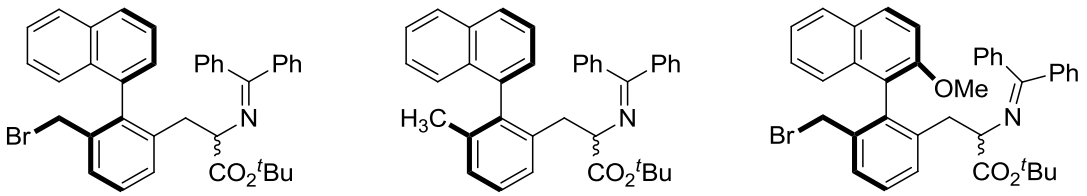
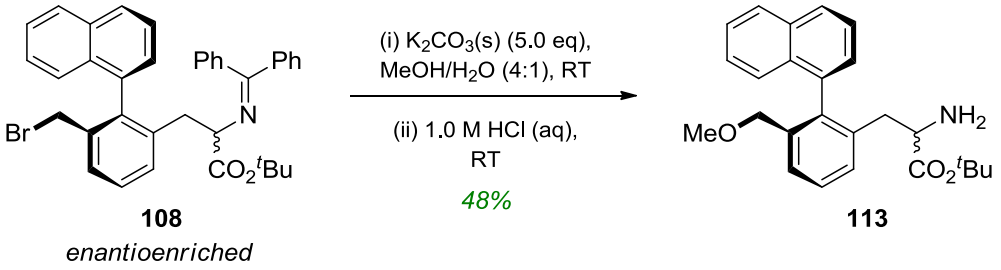


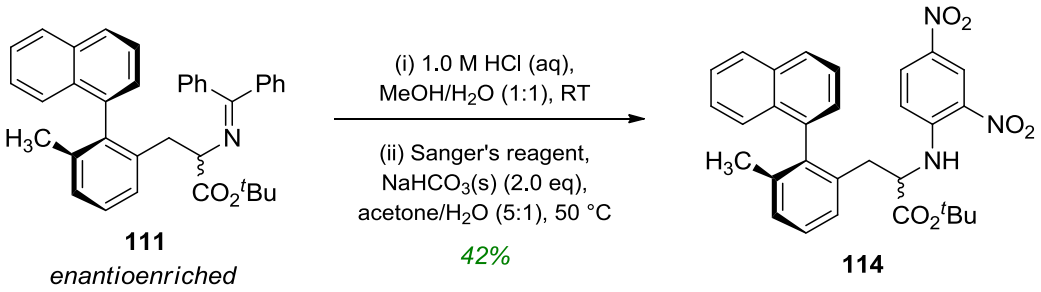
Figure 14. Alkylated biaryl products with undetermined stereochemistry.

Therefore it was decided to perform derivatisation reactions on these compounds, in order to obtain structures that would hopefully show greater crystallinity. Firstly, an enantioenriched sample of the major diastereomer of biaryl **108** was dissolved in methanol under mild basic conditions, resulting in substitution of the the bromide for a methoxy group (Scheme 50). On completion of this step, 1.0 M aqueous solution of hydrochloric acid was added directly to the reaction mixture, in order to hydrolyse the imine and afford the primary amine **113**. The initial S_N2 step was incorporated to inhibit polymerisation of the product.



Scheme 50. Derivatisation of an enantioenriched sample of the major diastereomer of biaryl **108**.

Unfortunately, neither the pure product nor the hydrochloride salt of derivative **113** was found to be crystalline, and subsequently further options were explored. An enantioenriched sample of the major diastereomer of biaryl **111** was thus taken and similarly hydrolysed in acid at pH 4 (Scheme 51). The resultant primary amine was combined with 1-fluoro-2,4-dinitrobenzene (Sanger's reagent)[121] under basic conditions, generating compound **114** by an S_NAr reaction.



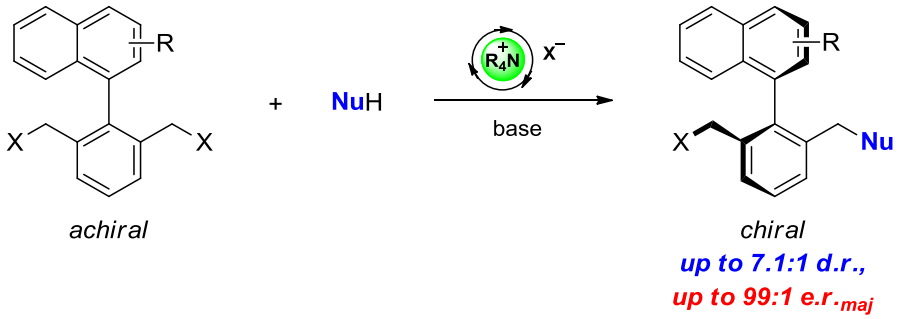
Scheme 51. Derivatisation of an enantioenriched sample of the major diastereomer of biaryl **111**. Sanger's reagent is 1-fluoro-2,4-dinitrobenzene.

However, once again the derivative **114** and primary amine intermediate were found to be amorphous. Consequently, due to time constraints, the stereochemistry of alkylated biaryl products **108**, **111** and **112** remains uncertain, and these compounds are drawn throughout this report with a wavy bond to indicate the undetermined configuration at the stereogenic centre. Nevertheless, the successful production of several derivatives of these biaryls proved to be a valuable exercise, demonstrating the utility of the enantioselective desymmetrisation reaction and the potential scope beyond it.

4.8 Conclusions and Future Work

4.8.1 Conclusions

In conclusion, we have developed a desymmetrising S_N2 reaction on achiral biaryl substrates under asymmetric phase-transfer conditions, offering a new pathway to axially chiral biaryls, which can be generated with excellent enantioselectivity and pleasing diastereoselectivity (Scheme 52).

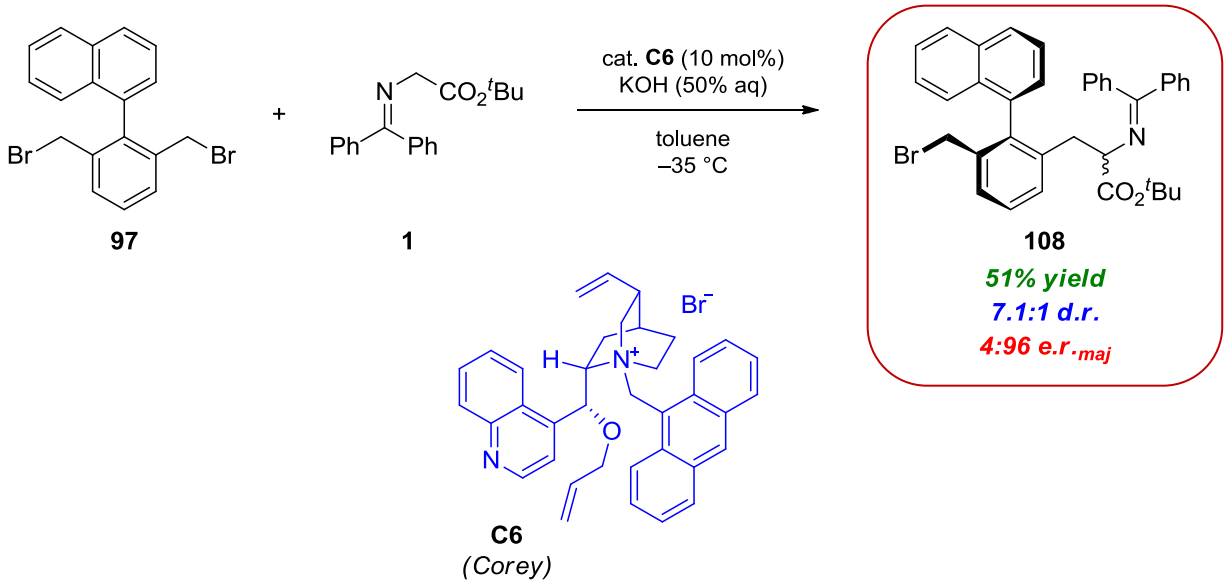


Scheme 52. Achieved asymmetric phase-transfer catalysed S_N2 reaction.

The starting biaryls, consisting of naphthyl and *ortho*-disubstituted phenyl components, are simple to construct and specifically designed to contain a plane of symmetry through the biaryl axis, whilst being sufficiently sterically congested to hinder rotation. Enantiotopic bromide leaving groups are incorporated, which can be substituted under mild reaction conditions to prepare configurationally stable, atropisomeric products. In the presence of an asymmetric phase-transfer catalyst, the tight ion pair formed between a deprotonated nucleophile and the chiral cation of the catalyst can induce discrimination in the displacement of these bromide groups.

We discovered that the benzophenone imine glycine ester **1** (a Schiff base) is a particularly effective pronucleophile for the desymmetrisation reaction, yielding alkylated products with impressive enantioselectivity. Diisopropyl malonate also afforded promising

enantioselectivity (Table 12), while results with thiophenol were less satisfactory (Table 10). The alkylation with glycine Schiff base **1** was found to be especially selective when employing the cinchona alkaloid-derived Corey catalyst **C6** (bearing an *N*-anthracenylmethyl group) with 50% aqueous potassium hydroxide as the base in toluene at −35 °C (Scheme 53).



Scheme 53. Optimised conditions for desymmetrisation by alkylation with glycine Schiff base **1**. Wavy bond indicates unknown configuration at specified position. Yield of both diastereomers combined

Additionally, the biaryl starting material can be varied such that the substrate is chiral but racemic (Scheme 48). In this case, one of the enantiomers of the substrate can react preferentially under the asymmetric phase-transfer conditions to generate the product in high e.r., although simultaneously the d.r. is somewhat limited. Moreover, an achiral biaryl starting material containing a methoxy substituent on the napthyl component was assessed, but resulted in reduced diastereo- and enantioselectivity (Scheme 49).

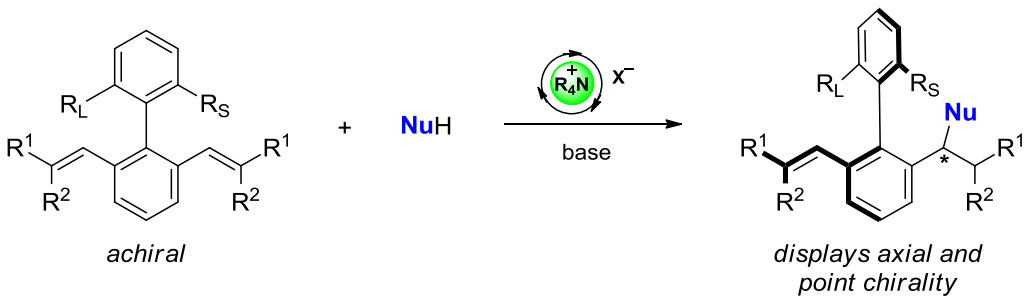
Unfortunately, the stereochemistry of the major biaryl products generated by alkylation with the glycine Schiff base **1** remains uncertain, due to difficulties in obtaining crystals of these compounds and their derivatives (Figure 14). However, the successful production of such derivatives from enantioenriched precursors has demonstrated that, from

the initial desymmetrisation reaction, a multitude of different enantioenriched compounds featuring the biaryl architecture could be accessed. This signifies the value of the developed desymmetrisation, due to the considerable prevalence of the framework in natural products, pharmaceuticals and ligands for asymmetric synthesis.

4.8.2 Future Work

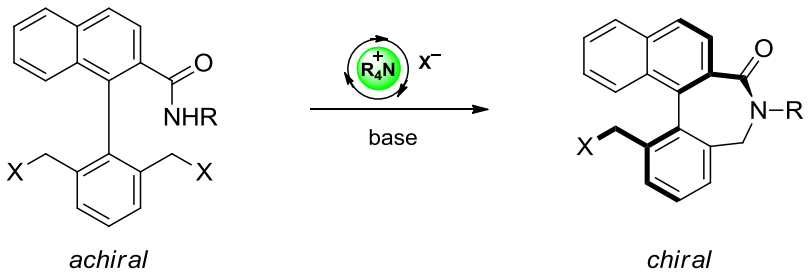
With more time, further derivatisation could be performed in order to synthesise compounds with practical applications, hopefully including structures showing greater crystallinity, so that the undetermined stereochemistry can be confirmed. Furthermore, a wider variety of nucleophiles could be investigated, in order to discover which alternatives can generate products with similar enantioselectivity and even higher diastereoselectivity. Additionally, the nature of the aryl components in the starting material could be varied, by introducing different substituents within the naphthyl ring or by replacing this group with other *ortho*-mono- or *ortho*-disubstituted aryl rings.

The S_N2 reaction strategy builds on previous work involving a desymmetrising S_NAr reaction reported by the Smith group (as detailed in Scheme 36).[116] In future, a desymmetrising 1,4-addition could even be explored under asymmetric phase-transfer conditions, utilising achiral biaryl starting materials containing *ortho*-alkenyl groups (Scheme 54).



Scheme 54. Proposed asymmetric phase-transfer catalysed 1,4-addition reaction. R^1 and/or R^2 are electron-withdrawing groups.

Research could also be carried out into desymmetrisation by an intramolecular S_N2 reaction, directed by a chiral cation. Here a biaryl substrate could be employed, containing enantiotopic leaving groups on one of the aryl components and a pendant nucleophilic group on the other (Scheme 55). This could potentially generate a series of atropisomeric products, in which the two arene nuclei are connected by a bridge.



Scheme 55. Example of the proposed intramolecular asymmetric phase-transfer catalysed S_N2 reaction.

5. Experimental

5.1 General Experimental

5.1.1 Naming and Numbering

Compounds have been named according to IUPAC recommendations. In assigning the NMR spectra, the atomic numbering system for compounds does not correspond to the IUPAC names but was chosen to allow for simpler and consistent assignment.

5.1.2 Reaction Conditions

Reactions were carried out under an atmosphere of argon or nitrogen in washed and oven-dried glassware unless stated otherwise. Reactions were stirred using a magnetic Teflon® stirrer bar and a stirrer hot plate. Room temperature refers to 20-25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures below 0 °C that had to be maintained for extended periods of time were obtained using an immersion cooler (HAAKE EK90).

5.1.3 Solvents and Reagents

Anhydrous dichloromethane, toluene, diethyl ether, methanol, acetonitrile and tetrahydrofuran were purified by filtration through activated alumina columns, employing the method of Grubbs *et al.*[122] Dimethyl sulfoxide was purchased as anhydrous solvent in Sure/Seal™ bottles from Sigma-Aldrich. Petroleum ether refers to the light petroleum boiling in the range 40-60 °C. Where mixtures of solvents are specified, the stated ratios are

volume:volume. Triethylamine was distilled over calcium hydride and stored over potassium hydroxide under an inert argon atmosphere. All water used experimentally was distilled. Brine refers to a saturated solution of sodium chloride in water. Unless otherwise indicated, all aqueous solutions used were saturated. Removal of solvents under reduced pressure was achieved using a Büchi rotary evaporator with bath temperatures of up to 50 °C. All other reagents and solvents (analytical or HPLC grade) were used as supplied without prior purification.

5.1.4 Chromatography

Thin layer chromatography was performed using commercially available Merck Kieselgel 60 F_{254} 0.25 mm precoated aluminium-backed plates. Visualisation was with UV fluorescence (254 nm) and/or staining with ceric ammonium molybdate solution, potassium permanganate solution or acidic ethanolic vanillin solution and heat. Flash column chromatography was performed using commercially available VWR silica gel: 230-400 mesh (40-63 μm) using head pressure by means of hand bellows or a nitrogen line. Analytical chiral HPLC was carried out using a Dionex Ultimate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler and TCC-3000 SD column compartment, fitted with the appropriate DAICEL Chiralpak column (0.46 cm × 25 cm) and corresponding guard column (0.4 cm × 1 cm).

5.1.5 NMR

^{1}H NMR spectra were recorded on a Bruker AVII 500 (500 MHz), AV400 (400 MHz) or DPX200 (200 MHz) spectrometer and were referenced to residual non-deuterated solvent

peaks. ^{13}C NMR spectra were recorded on a Bruker AVII 500 (126 MHz) or AV400 (101 MHz) spectrometer and were referenced to the residual non-deuterated solvent peak. ^{19}F NMR spectra were recorded on a Bruker AV400 (377 MHz) spectrometer and were referenced externally to $CFCl_3$ = 0 ppm. All spectra were recorded at ambient temperature unless stated otherwise, with chemical shifts (δ) quoted in parts per million (ppm). Coupling constants, *J*, are measured to the nearest 0.1 Hz. Assignment was aided by the use of DEPT, COSY, HMQC, HSQC, HMBC and NOESY experiments. Common abbreviations used are: br (broad), app. (apparent), Ar (aromatic), s (singlet), d (doublet), t (triplet), q (quartet), sep (septet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), td (triplet of doublets) and m (multiplet).

5.1.6 Mass Spectrometry

Low-resolution mass spectra were determined using electrospray ionisation (ESI^+), performed on a Micromass LCT Premier spectrometer. High-resolution mass spectra were recorded on a Bruker MicroTOF spectrometer under conditions of electrospray ionisation (ESI) or a Micromass GCT spectrometer under conditions of electron impact (EI) or chemical ionisation (CI). Values are reported as a ratio of mass to charge in Daltons.

5.1.7 IR Spectroscopy

Infrared spectroscopy was performed on a Bruker Tensor 27 FTIR spectrometer and analysed as thin films on sodium chloride plates. Only structurally important absorbances are quoted. Absorption maxima (λ_{max}) are quoted in wavenumbers (cm^{-1}).

5.1.8 Melting Points

Melting points were determined using a Reichert melting point apparatus and are uncorrected.

5.1.9 Polarimetry

Optical rotations were recorded on a PerkinElmer 341 polarimeter with a path length of 1 dm. Concentrations are reported in g/100 mL. Temperatures are reported in °C.

5.2 Experimental Procedures

General procedure A for the preparation of Michael acceptors

Zinc dust (10 eq) and ammonium chloride (15 eq) were added to a vigorously stirred RT solution of isopropyl 2-(2-nitrophenyl)acrylate **6** (1.0 eq) in acetone:water [4:1] (5.0 mL/mmol substrate). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 × 5.0 mL/mmol substrate) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (5.0 mL/mmol substrate), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in chloroform (3.0 mL/mmol substrate); pyridine (1.3 eq) was added, and the solution was cooled to 0 °C and stirred. The relevant chloroformate or chloride (1.2 eq) was added dropwise into the reaction mixture. The mixture was stirred for 3 h and allowed to warm to RT. The solution was then washed with

brine (2.0 mL/mmol substrate) and water (2 × 2.0 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

General procedure B for the preparation of Michael acceptors

Zinc dust (10 eq) and ammonium chloride (15 eq) were added to a vigorously stirred RT solution of isopropyl 2-(2-nitrophenyl)acrylate **6** (1.0 eq) in acetone:water [4:1] (5.0 mL/mmol substrate). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 × 5.0 mL/mmol substrate) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (5.0 mL/mmol substrate), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in chloroform (2.5 mL/mmol substrate), and the relevant isocyanate (1.0 eq) was added. The mixture was stirred for 12 h at RT.

General procedure C for the preparation of isopropyl acetates

Potassium carbonate (1.0 eq) and diisopropyl malonate (1.0 eq) were added to DMF (1.7 mL/mmol substrate), and stirred for 10 min at 90 °C. After allowing the reaction mixture to cool to RT, the relevant 2-fluoronitrobenzene (1.0 eq) was added, and then stirred for 3 h at 90 °C. After cooling to RT, the reaction mixture was diluted with 5% aqueous hydrochloric acid solution (2.5 mL/mmol substrate) and extracted with diethyl ether (3 × 5.0 mL/mmol substrate). The organic phases were combined, washed with brine (5.0 mL/mmol substrate) and water (5.0 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was then dissolved in DMSO (1.7 mL/mmol substrate), before sodium

chloride (1.0 eq) and water (2.0 eq) were added. The reaction mixture was stirred for 24 h at 130 °C. After cooling to RT, the mixture was diluted with water (2.5 mL/mmol substrate) and extracted with ethyl acetate (3 × 5.0 mL/mmol substrate). The organic phases were then combined, washed with brine (5.0 mL/mmol substrate) and water (5.0 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

General procedure D for the preparation of isopropyl acrylates

Paraformaldehyde (2.80 eq), tetrabutylammonium bromide (0.04 eq) and potassium carbonate (3.00 eq) were added to a stirred solution of the relevant isopropyl acetate (1.00 eq) in toluene (1.5 mL/mmol substrate), and the solution was heated to 50 °C. After 20 h the solution was allowed to cool to RT, water (3.5 mL/mmol substrate) was added and the aqeuous layer was extracted with toluene (3 × 2.0 mL/mmol). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

General procedure E for the preparation of Michael acceptors

Zinc dust (10 eq) and ammonium chloride (15 eq) were added to a vigorously stirred RT solution of the relevant isopropyl acrylate (1.0 eq) in acetone:water [4:1] (5.0 mL/mmol substrate). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 × 5.0 mL/mmol substrate) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (5.0 mL/mmol substrate), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in chloroform (3.0 mL/mmol substrate); pyridine (1.3 eq) was added, and the solution was cooled to 0 °C and stirred. Ethyl

chloroformate (1.2 eq) was added dropwise into the reaction mixture. The mixture was stirred for 3 h and allowed to warm to RT. The solution was then washed with brine (2.0 mL/mmol substrate) and water (2 × 2.0 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

General procedure F for the preparation of isocyanides

Triethylamine (2.5 eq) was added to a solution of the relevant formamide (1.0 eq) in DCM (1.4 mL/mmol substrate) at 0 °C. $POCl_3$ (1.0 eq) was then added dropwise, and the reaction mixture was left to stir at 0 °C for 90 min. The reaction was quenched with 10% aqueous sodium carbonate solution and stirred for a further 10 min. The mixture was then diluted with water (5.0 mL/mmol substrate) and extracted with DCM (3 × 5.0 mL/mmol substrate). The organic phases were combined, dried over K_2CO_3 and concentrated *in vacuo*.

General procedure G for the preparation of isocyanides

Formic acid (1.3 eq) was added dropwise to a solution of *N*,*N*'-dicyclohexylcarbodiimide (DCC) (1.3 eq) in DCM (2.0 mL/mmol substrate) at 0 °C. A precipitate formed upon addition. The reaction mixture was stirred for 10 min. The relevant methyl ester of an amino acid (1.0 eq), 4-dimethylaminopyridine (DMAP) (0.2 eq) and triethylamine (1.6 eq) were added, and the mixture was stirred at RT. After 16 h the crude mixture was concentrated *in vacuo*. The residue was suspended in ethyl acetate (2.0 mL/mmol substrate), filtered through a short silica column and then concentrated *in vacuo*. Under an atmosphere of argon, the crude mixture was then dissolved in THF (2.0 mL/mmol substrate) and cooled to 0 °C. Triethylamine (5.0 eq) was added, and then $POCl_3$ (1.5 eq) was added dropwise over 10 min.

The reaction mixture was left to stir at 0 °C for 2 h. The reaction was quenched with 10% aqueous sodium carbonate solution and stirred for a further 10 min. The mixture was then diluted with ethyl acetate (5.0 mL/mmol substrate), and washed with brine (5.0 mL/mmol substrate) and water (5.0 mL/mmol substrate). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

General procedure H for the preparation of isocyanides

Methyl isocyanoacetate (1.0 eq) was dissolved in DMSO (6.0 mL/mmol substrate) at RT. Caesium carbonate (1.5 eq) was added, and the reaction mixture was stirred for 10 min. The relevant fluoronitrobenzene (1.3 eq) was added, and the mixture was stirred for 16 h at RT. The mixture was then diluted with water (10 mL/mmol substrate) and extracted with ethyl acetate (3 × 10 mL/mmol substrate). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

General procedure I for the preparation of pyrroloindolines

The relevant Michael acceptor substrate (1.0 eq), isocyanide (1.0 eq) and tetrabutylammonium bromide (0.1 eq) were dissolved in toluene (10 mL/mmol substrate). The selected base (5.0 eq) was added, and the mixture was stirred at RT until both substrates were consumed according to thin layer chromatography (2-24 h). The reaction mixture was then diluted with DCM (20 mL/mmol substrate) and washed with brine (20 mL/mmol substrate) and water (20 mL/mmol substrate). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

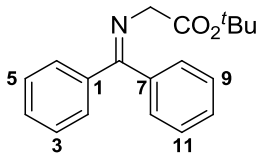
General procedure J for the preparation of pyrroloindolines

The relevant Michael acceptor substrate (1.0 eq), isocyanide (1.1 eq) and catalyst **C26** (0.1 eq) were dissolved in toluene:$CHCl_3$:H_2O [14:5:1] (10 mL/mmol substrate) at −20 °C. After 10 min, K_2CO_3 (5.0 eq) was added, and the mixture was stirred at −20 °C until both substrates were consumed according to thin layer chromatography (24-48 h). The reaction mixture was then diluted with DCM (20 mL/mmol substrate) and washed with brine (20 mL/mmol substrate) and water (20 mL/mmol substrate). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

Where compounds were prepared by co-workers in the Smith group, these are denoted as such. These compounds are included for reference purposes and completeness.

Method for assignment of stereochemistry of pyrroloindolines is found in Appendix B.

***tert*-Butyl 2-((diphenylmethylene)amino)acetate (1)**



tert-Butyl bromoacetate (10.6 mL, 72.0 mmol) was added to a solution of benzophenone imine (12.1 mL, 72.0 mmol) and *N*,*N*-diisopropylethylamine (12.5 mL, 72.0 mmol) in acetonitrile (80 mL). The mixture was stirred at reflux for 4 h. After allowing to cool to RT, the mixture was carefully concentrated under reduced pressure until the point of crystallisation. Diethyl ether (80 mL) and water (50 mL) were then added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Recrystallisation from diethyl ether afforded *tert*-butyl 2-((diphenylmethylene)amino)acetate **1** as a white solid (19.4 g, 91%).

IR (neat) ν_{max} 1737, 1626, 1446, 1393, 1150, 910, 781 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.67 (2H, m, *H*-9,11), 7.52-7.40 (4H, m, *H*-3,4,5,10), 7.39-7.33 (2H, m, *H*-8,12), 7.24-7.19 (2H, m, *H*-2,6), 4.15 (2H, s, $CH_2CO_2{}^tBu$), 1.49 (9H, s, $OC(CH_3)_3$).

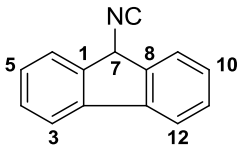
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 ($NCPh_2$), 169.9 ($CO_2{}^tBu$), 139.4 (*C*-1 or *C*-7), 136.2 (*C*-1 or *C*-7), 130.4 (*C*-4,10), 128.7 (*C*-9,11), 128.6 (C-3,5), 128.0 (*C*-8,12), 127.7 (*C*-2,6), 81.1 ($OC(CH_3)_3$), 56.4 ($CH_2CO_2{}^tBu$), 28.1 (($OC(CH_3)_3$).

m/z LRMS (ESI^+) 296.2 $[M+H]^+$.

m.p. 107-109 °C.

Data in accordance with literature.[a]

9-Isocyano-9*H*-fluorene (4)



Triethylamine (1.17 mL, 8.37 mmol) was added to a solution of *N*-(9*H*-fluoren-9-yl)formamide **31** (350 mg, 1.67 mmol) in THF (2.0 mL) at −78 °C, followed by $POCl_3$ (172 μL, 1.85 mmol) as a solution in THF (2.0 mL). The reaction mixture was allowed to warm to RT and stirred for 1 h, before ice water (40 mL) was added. The reaction was then extracted with diethyl ether, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [9:1]) afforded 9-isocyano-9*H*-fluorene **4** as a yellow solid (275 mg, 86%).

IR (neat) ν_{max} 2140, 1717, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.70 (4H, m, *H*-3,6,9,12), 7.49 (2H, t, *J* 7.4, *H*-4,11), 7.41 (2H, td, *J* 7.4, 1.0, *H*-5,10), 5.64 (1H, s, *H*-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (N*C*), 140.2, 139.6, 129.8, 128.3, 124.9, 120.4 [aromatics], 56.8 (t, *J* 6.8, *C*-7).

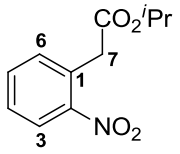
m/z LRMS (ESI^+) 214.1 $[M+Na]^+$.

m.p. 92-94 °C.

[a] P. Nun, V. Pérez, M. Calmès, J. Martinez, F. Lamaty, *Chem. Eur. J.* **2012**, *18*, 3773.

Data in accordance with literature.[a]

Isopropyl 2-(2-nitrophenyl)acetate (5)



Concentrated sulfuric acid (5.0 mL) was added to a stirred solution of 2-nitrophenylacetic acid (15.0 g, 82.8 mmol) in isopropanol (50 mL). The mixture was stirred at reflux for 4 h. After allowing to cool to RT, ethyl acetate (200 mL) was added. The mixture was washed with water (100 mL) and then with saturated aqueous sodium bicarbonate solution (2 × 100 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford isopropyl 2-(2-nitrophenyl)acetate **5** as an orange oil (17.2 g, 93%), which was used without further purification.

IR (neat) ν_{max} 2983, 2937, 1727, 1524, 1346, 1217, 1105 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* 8.1, *H*-3), 7.57 (1H, app. t, *J* 7.5, *H*-5), 7.49-7.41 (1H, m, *H*-4), 7.33 (1H, d, *J* 7.5, *H*-6), 5.01 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 3.97 (2H, s, *H*-7), 1.21 (6H, d, *J* 6.2, OCH(C*H*$_3)_2$).

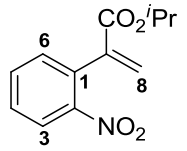
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (*C*$O_2{}^i$Pr), 148.8 (*C*-2), 133.5 (*C*-5), 133.3 (*C*-6), 130.0 (*C*-1), 128.5 (*C*-4), 125.2 (*C*-3), 68.8 (O*C*H$(CH_3)_2$), 40.1 (*C*-7), 21.7 (OCH(*C*H$_3)_2$).

m/z LRMS (ESI^+) 246.1 $[M+Na]^+$.

[a] R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Speck, R. V. A. Orru, *Org. Lett.* **2003**, *5*, 3759.

Data in accordance with literature.[a]

Isopropyl 2-(2-nitrophenyl)acrylate (6)



Paraformaldehyde (6.03 g, 201 mmol), tetrabutylammonium bromide (901 mg, 2.79 mmol) and potassium carbonate (29.7 g, 215 mmol) were added to a stirred solution of isopropyl 2-(2-nitrophenyl)acetate **5** (16.0 g, 71.8 mmol) in toluene (105 mL), and the solution was heated to 50 °C. After 20 h the solution was allowed to cool to RT, water (250 mL) was added and the aqeuous layer was extracted with toluene (3 × 150 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford isopropyl 2-(2-nitrophenyl)acrylate **6** as an orange oil (15.0 g, 89%), which was used without further purification.

IR (neat) ν_{max} 3071, 2983, 2937, 1716, 1526, 1350, 1207 cm^{-1}.

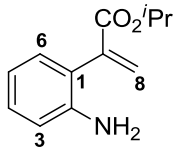
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* 8.1, *H*-3), 7.65 (1H, app. td, *J* 7.5, 1.5, *H*-4), 7.58-7.46 (1H, m, *H*-5), 7.39 (1H, dd, *J* 7.4, 1.5, *H*-6), 6.53 (1H, d, *J* 1.0, *H*-8), 5.86 (1H, d, *J* 1.0, *H*-8'), 5.05 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 1.21 (6H, d, *J* 6.2, OCH(C*H*$_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (*C*$O_2{}^i$Pr), 148.0 (*C*-2), 140.5 (*C*-7), 133.6 (*C*-5), 133.2 (*C*-1), 132.1 (*C*-6), 129.2 (*C*-4), 127.1 (*C*-8), 124.5 (*C*-3), 69.2 (O*C*H$(CH_3)_2$), 21.5 (OCH(*C*H$_3)_2$).

[a] P. Strazzolini, A. G. Giumanini, A. Runcio, M. Scuccato, *J. Org. Chem.* **1998**, *63*, 952.

m/z LRMS (ESI^+) 258.1 $[M+Na]^+$; HRMS (ESI^+) 258.0747 ($[M+Na]^+$, $C_{12}H_{13}NO_4Na$ requires 258.0742).

Isopropyl 2-(2-aminophenyl)acrylate (7)



Zinc dust (10.1 g, 416 mmol) and ammonium chloride (33.3 g, 623 mmol) were added to a vigorously stirred RT solution of isopropyl 2-(2-nitrophenyl)acrylate **6** (8.53 g, 41.6 mmol) in acetone:water [4:1] (200 mL). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 × 200 mL) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [4:1]) afforded isopropyl 2-(2-aminophenyl)acrylate **7** as a yellow oil (1.96 g, 23%).

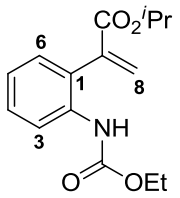
IR (neat) ν_{max} 3250, 2981, 1707, 1620, 1471, 1304, 1204, 1104, 936 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (1H, app. td, *J* 7.7, 1.5, *H*-4), 7.07 (1H, dd, *J* 7.6, 1.4, *H*-6), 6.80 (1H, app. t, *J* 7.5, *H*-5), 6.74 (1H, app. d, *J* 7.8, *H*-3), 6.42 (1H, d, *J* 1.6, *H*-8), 5.77 (1H, d, *J* 1.6, *H*-8'), 5.05 (1H, sep, *J* 6.3, $OCH(CH_3)_2$), 3.47 (2H, br s, NH_2), 1.21 (6H, d, *J* 6.3, $OCH(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (*C*$O_2{}^i$Pr), 140.3 (*C*-2), 130.6 (*C*-4), 129.4 (*C*-1), 129.2 (*C*-6), 129.1 (*C*-8), 124.01 (*C*-7), 118.6 (*C*-5), 116.2 (*C*-3), 68.8 (O*C*H(CH_3)$_2$), 21.8 (OCH(*C*H_3)$_2$).

m/z LRMS (ESI^+) 206.1 $[M+H]^+$; HRMS (ESI^+) 228.0995 ($[M+Na]^+$, $C_{12}H_{15}NO_2Na$ requires 228.1000).

Isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (8)



This compound was prepared according to general procedure A, using ethyl chloroformate (2.70 mL, 28.1 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the isopropyl 2-phenylacrylate **8** as an orange wax (3.61 g, 56%).

IR (neat) ν_{max} 3343, 2982, 1806, 1714, 1583, 1521, 1451, 1299, 1211, 1105, 1059 cm^{-1}.

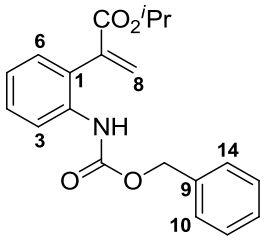
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, app. s, *H*-3), 7.41-7.35 (1H, m, *H*-4), 7.20-7.09 (2H, m, *H*-5,6), 6.93 (1H, br s, N*H*), 6.57 (1H, d, *J* 1.5, *H*-8), 5.85 (1H, d, *J* 1.5, *H*-8'), 5.15 (1H, sep, *J* 6.2, OC*H*(CH_3)$_2$), 4.21 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 1.34-1.28 (9H, m, OCH_2CH_3, OCH(CH_3)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (*C*$O_2{}^i$Pr), 153.9 (*C*O_2Et), 139.8 (*C*-2), 135.4 (*C*-1), 130.5 (*C*-8), 130.2 (*C*-6), 129.2 (*C*-4), 126.9 (*C*-7), 124.0 (*C*-5), 121.9 (*C*-3), 69.3 (O*C*H(CH_3)$_2$), 61.2 (O*C*$H_2$$CH_3$), 21.7 (OCH(*C*$H_3$)$_2$), 14.6 ($OCH_2$*C*$H_3$).

m/z LRMS (ESI^+) 300.1 $[M+Na]^+$; HRMS (ESI^+) 300.1208 ($[M+Na]^+$, $C_{15}H_{19}NO_4Na$ requires 300.1212).

m.p. 45-47 °C.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate (9)



This compound was prepared according to general procedure A, using benzyl chloroformate (1.46 mL, 10.2 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the isopropyl 2-phenylacrylate **9** as an orange solid (1.53 g, 53%).

IR (neat) v_{max} 3340, 2981, 1712, 1584, 1519, 1451, 1298, 1199, 1105, 1042, 937, 817 cm^{-1}.

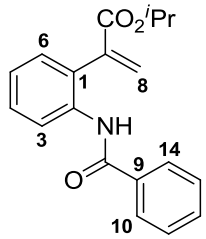
^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.84 (1H, m, *H*-3), 7.50-7.30 (6H, m, *H*-4,10,11,12,13,14), 7.21-7.11 (2H, m, *H*-5,6), 7.06 (1H, br s, N*H*), 6.56 (1H, d, *J* 1.4, *H*-8), 5.85 (1H, d, *J* 1.4, *H*-8'), 5.21 (2H, s, OCH_2Ph), 5.12 (1H, sep, *J* 6.3, $OCH(CH_3)_2$), 1.27 (6H, d, *J* 6.3, $OCH(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 ($CO_2{}^iPr$), 153.8 (CO_2Bn), 139.7 (*C*-2), 136.2 (*C*-9), 135.3 (*C*-1), 130.6 (*C*-8), 130.3 (*C*-6), 129.2 (*C*-4), 128.9 (*C*-7), 128.6 (*C*-11,13), 128.4 (*C*-12), 128.3 (*C*-10,14), 124.1 (*C*-5), 122.1 (*C*-3), 69.3 ($OCH(CH_3)_2$), 67.0 (CH_2Ph), 21.7 ($OCH(CH_3)_2$).

m/z LRMS (ESI^+) 362.1 $[M+Na]^+$; HRMS (ESI^+) 362.1356 ($[M+Na]^+$, $C_{20}H_{21}NO_4Na$ requires 362.1368).

m.p. 52-58 °C.

Isopropyl 2-(2-benzamidophenyl)acrylate (10)



Zinc dust (5.58 g, 85.0 mmol) and ammonium chloride (6.83 g, 128 mmol) were added to a vigorously stirred RT solution of isopropyl 2-(2-nitrophenyl)acrylate **6** (2.00 g, 8.50 mmol) in acetone:water [4:1] (50 mL). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 × 50 mL) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in DCM (30 mL); pyridine (826 μL, 10.2 mmol) was added, and the solution was cooled to 0 °C and stirred. Benzoyl chloride (983 μL, 8.50 mmol) was added dropwise into the reaction mixture. The mixture was stirred for 12 h and allowed to warm to RT. The solution was then washed with brine (30 mL) and water (2 × 30 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [5:1]) afforded the isopropyl 2-phenylacrylate **10** as a light yellow solid (1.76 g, 67%).

IR (neat) v_{max} 3321, 2982, 1665, 1580, 1518, 1449, 1303, 1199, 1100, 1079 cm^{-1}.

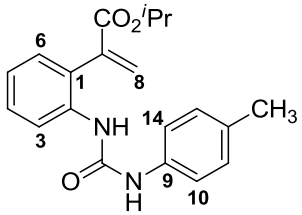
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (1H, br s, N*H*), 8.06 (1H, d, *J* 8.0, *H*-3), 7.90 (2H, d, *J* 7.6, *H*-10,14), 7.60-7.42 (4H, m, *H*-4,6,11,13), 7.28-7.18 (2H, m, *H*-5,12) 6.54 (1H, d, *J* 1.3, *H*-8), 5.91 (1H, d, *J* 1.3, *H*-8'), 5.16 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 1.30 (6H, d, *J* 6.3, OCH(C*H*$_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (*C*$O_2{}^{i}$Pr), 165.4 (*C*OPh), 140.3 (*C*-2), 135.3, 134.8 (*C*-1,9), 131.8 (*C*-6), 131.0 (*C*-8), 130.6 (*C*-12), 129.3 (*C*-4), 128.7 (*C*-11,13), 127.4 (*C*-7), 127.1 (*C*-10,14), 125.2 (*C*-5), 124.3 (*C*-3), 69.7 (O*C*H$(CH_3)_2$), 21.7 (OCH(*C*H$_3)_2$).

m/z LRMS (ESI^+) 332.1 $[M+Na]^+$; HRMS (ESI^+) 332.1259 ($[M+Na]^+$, $C_{19}H_{19}NO_3Na$ requires 332.1263).

m.p. 75-77 °C.

Isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (11)



This compound was prepared according to general procedure B, using *p*-tolyl isocyanate (1.07 mL, 8.50 mmol). The precipitate was filtered and washed with DCM (75 mL). The residue was dried *in vacuo* to afford the isopropyl 2-phenylacrylate **11** as a white solid (1.06 g, 37%), which was used without further purification.

IR (neat) ν_{max} 3300, 3024, 1704, 1642, 1549, 1375, 1230, 1209, 1106 cm^{-1}.

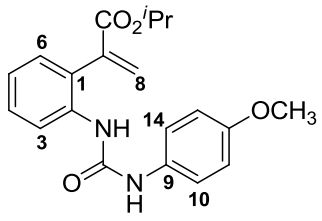
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* 8.1, *H*-3), 7.43-7.39 (1H, m, *H*-4), 7.25-7.16 (4H, m, *H*-5,6,10,14), 7.15-7.08 (2H, m, *H*-11,13), 6.94 (1H, br s, N*H*), 6.78 (1H, br s, N*H*), 6.47 (1H, d, *J* 1.4, *H*-8), 5.82 (1H, d, *J* 1.4, *H*-8'), 5.01 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 2.32 (3H, s, ArCH_3), 1.22 (6H, d, *J* 6.2, OCH(CH_3)$_2$).

^{13}C NMR (101 MHz) δ 166.5 (*C*$O_2{}^{i}$Pr), 153.8 (*C*(O)NH), 140.1 (*C*-2), 135.7 (*C*-9), 135.4 (*C*-1), 133.8 (*C*-12), 131.9 (*C*-7), 130.5 (*C*-6), 129.8 (*C*-8), 129.7 (*C*-11,13), 129.4 (*C*-4), 125.2 (*C*-5), 125.0 (*C*-3), 121.5 (*C*-10,14), 69.4 (O*C*H$(CH_3)_2$), 21.6 (OCH(*C*H_3)$_2$), 20.8 (Ar*C*H_3).

m/z LRMS (ESI^+) 361.2 $[M+Na]^+$; HRMS (ESI^+) 361.1521 ($[M+Na]^+$, $C_{20}H_{22}N_2O_3Na$ requires 361.1528).

m.p. 160-165 °C.

Isopropyl 2-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate (12)



This compound was prepared according to general procedure B, using 4-methoxyphenyl isocyanate (1.10 mL, 8.50 mmol). The precipitate was filtered and washed with DCM (75 mL). The residue was dried *in vacuo* to afford the isopropyl 2-phenylacrylate **12** as a white solid (817 mg, 27%), which was used without further purification.

IR (neat) ν_{max} 3319, 2986, 1712, 1650, 1552, 1510, 1297, 1227, 1106 cm^{-1}.

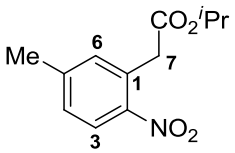
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (1H, d, *J* 8.0, *H*-3), 7.43-7.36 (1H, m, *H*-4), 7.24-7.15 (4H, m, *H*-5,6,10,14), 6.92 (1H, br s, N*H*), 6.89-6.83 (2H, m, *H*-11,13), 6.73 (1H, br s, N*H*), 6.46 (1H, d, *J* 1.4, *H*-8), 5.81 (1H, d, *J* 1.4, *H*-8'), 5.00 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 3.81 (3H, s, OCH_3), 1.22 (6H, d, *J* 6.3, OCH(C$H_3)_2$).

^{13}C NMR (101 MHz) δ 166.5 ($CO_2{}^{i}Pr$), 154.3 (*C*(O)NH), 148.1 (*C*-12), 140.1 (*C*-2), 135.7 (*C*-9), 135.4 (*C*-1), 131.8 (*C*-7), 130.4 (*C*-6), 129.8 (*C*-8), 129.3 (*C*-4), 125.0 (*C*-5), 124.8 (*C*-3), 124.1 (*C*-10,14), 114.4 (*C*-11,13), 69.4 (O*C*H$(CH_3)_2$), 55.5 (O*C*H_3), 21.6 (OCH(*C*$H_3)_2$).

m/z LRMS (ESI^+) 377.1 $[M+Na]^+$; HRMS (ESI^+) 377.1472 ($[M+Na]^+$, $C_{20}H_{22}N_2O_4Na$ requires 377.1477).

m.p. 137-140 °C.

Isopropyl 2-(5-methyl-2-nitrophenyl)acetate (13)



This compound was prepared according to general procedure C, using 2-fluoro-4-methylnitrobenzene (5.00 g, 32.3 mmol). Column chromatography (petrol:ethyl acetate [8:1]) afforded the isopropyl 2-phenylacetate **13** as an orange oil (4.60 g, 60%).

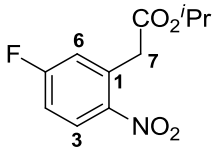
IR (neat) ν_{max} 2983, 1733, 1522, 1345, 1249, 1105, 841 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, d, *J* 8.4, *H*-3), 7.27 (1H, d, *J* 8.4, *H*-4), 7.16 (1H, s, *H*-6), 5.05 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 3.97 (2H, s, *H*-7), 2.45 (3H, s, ArCH_3), 1.26 (6H, d, *J* 6.3, OCH(C$H_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (*C*$O_2{}^i$Pr), 146.5 (*C*-2), 144.9 (*C*-5), 134.0 (*C*-6), 130.1 (*C*-1), 129.1 (*C*-4), 125.5 (*C*-3), 68.8 (O*C*H$(CH_3)_2$), 40.4 (*C*-7), 21.7 (OCH(*C*$H_3)_2$), 21.4 (Ar*C*H_3).

m/z LRMS (ESI$^+$) 260.1 $[M+Na]^+$; HRMS (ESI$^+$) 260.0897 ($[M+Na]^+$, $C_{12}H_{15}NO_4Na$ requires 260.0893).

Isopropyl 2-(5-fluoro-2-nitrophenyl)acetate (14)



This compound was prepared according to general procedure C, using 2,4-difluoronitrobenzene (2.00 g, 12.6 mmol). Column chromatography (petrol:ethyl acetate [8:1]) afforded the isopropyl 2-phenylacetate **14** as a yellow oil (1.40 g, 46%).

IR (neat) ν_{max} 2984, 1729, 1591, 1528, 1346, 1252, 1207, 1104, 842 cm^{-1}.

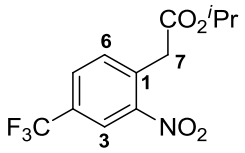
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, dd, *J* 9.1, 5.2, *H*-3), 7.20-7.14 (1H, m, *H*-4), 7.08 (1H, dd, *J* 8.6, 2.7, *H*-6), 5.06 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.00 (2H, s, *H*-7), 1.26 (6H, d, *J* 6.3, OCH(C$H_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9 (*C*$O_2{}^i$Pr), 164.7 (d, *J* 257.3, *C*-5), 144.9 (*C*-2), 133.6 (d, *J* 9.5, *C*-1), 128.2 (d, *J* 10.1, *C*-3), 120.2 (d, *J* 23.7, *C*-6), 115.4 (d, *J* 23.0, *C*-4), 69.2 (O*C*H(CH_3)$_2$), 40.3 (*C*-7), 21.7 (OCH(*C*H_3)$_2$).

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ −103.4.

m/z LRMS (ESI$^+$) 264.1 [M+Na]$^+$; HRMS (ESI$^+$) 264.0652 ([M+Na]$^+$, $C_{11}H_{12}FNO_4Na$ requires 264.0643).

Isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acetate (15)



This compound was prepared according to general procedure C, using 2-fluoro-5-(trifluoromethyl)nitrobenzene (1.34 mL, 9.56 mmol). Column chromatography (petrol:ethyl acetate [8:1]) afforded the isopropyl 2-phenylacetate **15** as a yellow oil (2.17 g, 78%).

IR (neat) ν_{max} 3096, 2987, 2851, 1715, 1630, 1575, 1538, 1503 cm^{-1}.

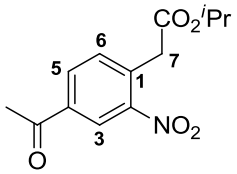
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, s, *H*-3), 7.77 (1H, d, *J* 8.0, *H*-5), 7.45 (1H, d, *J* 8.0, *H*-6), 4.95 (1H, sep, *J* 6.3, OC*H*(CH_3)$_2$), 3.98 (2H, s, *H*-7), 1.16 (6H, d, *J* 6.3, OCH(C*H*$_3$)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (*C*$O_2{}^i$Pr), 148.9 (*C*-2), 134.3 (*C*-6), 133.9 (*C*-1), 131.2 (q, *J* 34.3, *C*-4), 129.8 (q, *J* 3.5, *C*-5), 122.8 (q, *J* 272.4, *C*F_3), 122.5 (q, *J* 3.8, *C*-3), 69.4 (O*C*H(CH_3)$_2$), 40.0 (*C*-7), 21.6 (OCH(*C*H_3)$_2$).

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ −63.0.

m/z LRMS (ESI^+) 314.1 $[M+Na]^+$; HRMS (ESI^+) 314.0619 ($[M+Na]^+$, $C_{12}H_{12}F_3NO_4Na$ requires 314.0616).

Isopropyl 2-(4-acetyl-2-nitrophenyl)acetate (16)



This compound was prepared according to general procedure C, using 4'-fluoro-3'-nitroacetophenone (4.00 g, 21.8 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded the isopropyl 2-phenylacetate **16** as a yellow solid (3.01 g, 52%).

IR (neat) ν_{max} 2983, 1729, 1692, 1619, 1534, 1354, 1254, 1219, 1105 cm^{-1}.

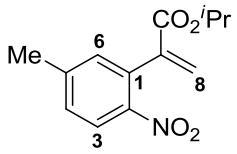
^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (1H, d, *J* 1.7, *H*-3), 8.16 (1H, dd, *J* 7.9, 1.7, *H*-5), 7.50 (1H, d, *J* 7.9, *H*-6), 5.04 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.06 (2H, s, *H*-7), 2.68 (3H, s, ArCOCH_3), 1.24 (6H, d, *J* 6.3, OCH(C$H_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4 (Ar*C*OMe), 168.7 (*C*$O_2{}^i$Pr), 149.0 (*C*-2), 137.3 (*C*-4), 133.9 (*C*-6), 132.4 (*C*-5), 132.0 (*C*-1), 125.0 (*C*-3), 69.3 (O*C*H$(CH_3)_2$), 40.1 (*C*-7), 26.7 (ArCO*C*H_3), 21.7 (OCH(*C*$H_3)_2$).

m/z LRMS (ESI^+) 288.1 $[M+Na]^+$; HRMS (ESI^+) 288.0853 ($[M+Na]^+$, $C_{13}H_{15}NO_5Na$ requires 288.0842).

m.p. 47-49 °C.

Isopropyl 2-(5-methyl-2-nitrophenyl)acrylate (17)



This compound was prepared according to general procedure D, using isopropyl 2-(5-methyl-2-nitrophenyl)acetate **13** (2.00 g, 8.43 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded the isopropyl 2-phenylacrylate **17** as a brown oil (988 mg, 47%).

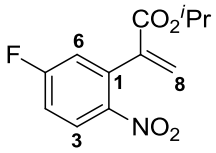
IR (neat) ν_{max} 2983, 1720, 1518, 1343, 1228, 1179, 1103, 838 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, d, *J* 8.4, *H*-3), 7.35-7.30 (1H, m, *H*-4), 7.19 (1H, s, *H*-6), 6.51 (1H, d, *J* 1.0, *H*-8), 5.85 (1H, d, *J* 1.0, *H*-8'), 5.07 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 2.48 (3H, s, ArC*H*$_3$), 1.23 (6H, d, *J* 6.2, OCH(C*H*$_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4 (*C*$O_2{}^i$Pr), 145.7, 144.9 (*C*-2,5), 140.9 (*C*-7), 133.3 (*C*-1), 132.8 (*C*-6), 129.7 (*C*-4), 126.6 (*C*-8), 124.7 (*C*-3), 69.2 (O*C*H$(CH_3)_2$), 21.6 (OCH(*C*H$_3)_2$), 21.4 (Ar*C*H$_3$).

m/z LRMS (ESI^+) 272.1 $[M+Na]^+$; HRMS (ESI^+) 272.0901 ($[M+Na]^+$, $C_{13}H_{15}NO_4Na$ requires 272.0893).

Isopropyl 2-(5-fluoro-2-nitrophenyl)acrylate (18)



This compound was prepared according to general procedure D, using isopropyl 2-(5-fluoro-2-nitrophenyl)acetate **14** (1.30 g, 5.39 mmol). The isopropyl 2-phenylacrylate **18** was afforded as a brown oil (1.04 g, 76%), which was used without further purification.

IR (neat) ν_{max} 2982, 1724, 1585, 1347, 1227, 1105, 928, 841 cm^{-1}.

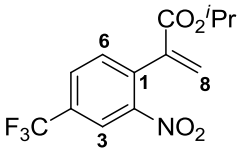
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, dd, *J* 9.1, 5.1, *H*-3), 7.12-7.07 (1H, m, *H*-4), 6.99 (1H, dd, *J* 8.5, 2.8, *H*-6), 6.45 (1H, d, *J* 0.7, *H*-8), 5.77 (1H, d, *J* 0.7, *H*-8'), 4.98 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 1.12 (6H, d, *J* 6.3, OCH(C*H*$_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (d, *J* 257.8, *C*-5), 163.8 (*C*$O_2{}^{i}$Pr), 144.1 (*C*-2), 139.8 (*C*-7), 136.3 (d, *J* 9.5, *C*-1), 127.6 (*C*-8), 127.4 (d, *J* 9.8, *C*-3), 119.2 (d, *J* 23.9, *C*-6), 116.0 (d, *J* 23.1, *C*-4), 69.5 (O*C*H$(CH_3)_2$), 21.5 (OCH(*C*H$_3)_2$).

^{19}F NMR (377 MHz, $CDCl_3$, $\{^{1}H\}$) δ −103.2.

m/z LRMS (ESI^+) 276.1 $[M+Na]^+$; HRMS (ESI^+) 276.0645 ($[M+Na]^+$, $C_{12}H_{12}FNO_4Na$ requires 276.0643).

Isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acrylate (19)



This compound was prepared according to general procedure D, using isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acetate **15** (2.00 g, 6.87 mmol). The isopropyl 2-phenylacrylate **19** was afforded as a brown oil (1.52 g, 73%), which was used without further purification.

IR (neat) ν_{max} 2940, 1714, 1541, 1352, 1134, 1087, 697 cm^{-1}.

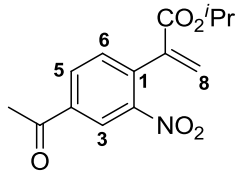
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, s, *H*-3), 7.83 (1H, app. ddd, *J* 8.0, 1.8, 0.6, *H*-5), 7.49 (1H, d, *J* 8.0, *H*-6), 6.54 (1H, d, *J* 0.6, *H*-8), 5.86 (1H, d, *J* 0.6, *H*-8’), 5.03 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 1.15 (6H, d, *J* 6.3, OCH(C*H*$_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (*C*$O_2{}^i$Pr), 148.0 (*C*-2), 139.5 (*C*-7), 136.6 (*C*-1), 133.1 (*C*-6), 131.8 (q, *J* 34.3, *C*-4), 130.1 (q, *J* 3.5, *C*-5), 128.4 (*C*-8), 122.7 (q, *J* 272.5, *C*F_3), 121.9 (q, *J* 3.8, *C*-3), 69.7 (O*C*H$(CH_3)_2$), 21.5 (OCH(*C*$H_3)_2$).

^{19}F NMR (377 MHz, $CDCl_3$, $\{^1H\}$) δ −62.9.

m/z LRMS (ESI^+) 326.1 $[M+Na]^+$; HRMS (ESI^+) 326.0600 ($[M+Na]^+$, $C_{13}H_{12}F_3NO_4Na$ requires 326.0611).

Isopropyl 2-(4-acetyl-2-nitrophenyl)acrylate (20)



This compound was prepared according to general procedure D, using isopropyl 2-(4-acetyl-2-nitrophenyl)acetate **16** (2.20 g, 8.29 mmol). Column chromatography (petrol:ethyl acetate [3:1]) afforded the isopropyl 2-phenylacrylate **20** as a yellow oil (529 mg, 23%).

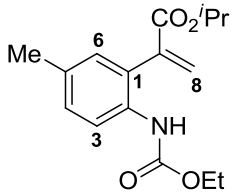
IR (neat) ν_{max} 3049, 2916, 1736, 1713, 1619, 1499, 1265 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (1H, s, *H*-3), 8.20 (1H, d, *J* 8.0, *H*-5), 7.52 (1H, d, *J* 8.0, *H*-6), 6.59 (1H, app. s, *H*-8), 5.93 (1H, app. s, *H*-8'), 5.04 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 2.68 (3H, s, ArCOCH_3), 1.20 (6H, d, *J* 6.2, OCH(C$H_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4 (Ar*C*OMe), 163.6 (*C*$O_2{}^{i}$Pr), 148.2 (*C*-2), 139.8 (*C*-7), 137.8 (*C*-4), 137.1 (*C*-1), 132.7 (*C*-6), 132.6 (*C*-5), 128.2 (*C*-8), 124.3 (*C*-3), 69.6 (O*C*H$(CH_3)_2$), 26.7 (ArCO*C*H_3), 21.5 (OCH(*C*$H_3)_2$).

m/z LRMS (ESI^+) 300.1 $[M+Na]^+$; HRMS (ESI^+) 300.0846 ($[M+Na]^+$, $C_{14}H_{15}NO_5Na$ requires 300.0848).

Isopropyl 2-(2-((ethoxycarbonyl)amino)-5-methylphenyl)acrylate (21)



This compound was prepared according to general procedure E, using isopropyl 2-(5-methyl-2-nitrophenyl)acrylate **17** (960 mg, 3.85 mmol). Column chromatography (petrol:ethyl acetate [6:1]) afforded the isopropyl 2-phenylacrylate **21** as a yellow solid (740 mg, 66%).

IR (neat) ν_{max} 3351, 2981, 1716, 1590, 1520, 1469, 1298, 1209, 1173, 1105, 1057 cm^{-1}.

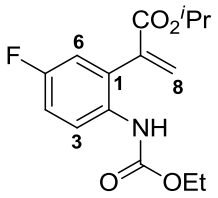
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, app. s, *H*-3), 7.08 (1H, dd, *J* 8.3, 1.7, *H*-4), 6.88 (1H, d, *J* 1.7, *H*-6), 6.72 (1H, br s, N*H*), 6.42 (1H, d, *J* 1.5, *H*-8), 5.73 (1H, d, *J* 1.5, *H*-8'), 5.05 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.10 (2H, q, *J* 7.1, OCH_2CH_3), 2.24 (3H, s, ArCH_3), 1.23-1.17 (9H, m, OCH_2CH_3, $OCH(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 ($CO_2^{i}Pr$), 154.2 (CO_2Et), 140.0 (*C*-2), 133.7, 132.8 (*C*-1,5), 130.7 (*C*-6), 130.1 (*C*-8), 129.8 (*C*-4), 127.9 (*C*-7), 122.5 (*C*-3), 69.2 ($OCH(CH_3)_2$), 61.1 (OCH_2CH_3), 21.7 ($OCH(CH_3)_2$), 20.8 ($ArCH_3$), 14.6 (OCH_2CH_3).

m/z LRMS (ESI^+) 314.1 $[M+Na]^+$; HRMS (ESI^+) 314.1361 ($[M+Na]^+$, $C_{16}H_{21}NO_4Na$ requires 314.1368).

m.p. 78-81 °C.

Isopropyl 2-(2-((ethoxycarbonyl)amino)-5-fluorophenyl)acrylate (22)



This compound was prepared according to general procedure E, using isopropyl 2-(5-fluoro-2-nitrophenyl)acrylate **18** (900 mg, 3.55 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded the isopropyl 2-phenylacrylate **22** as an orange oil (367 g, 35%).

IR (neat) ν_{max} 3338, 2983, 1719, 1522, 1376, 1307, 1223, 1105, 1056 cm^{-1}.

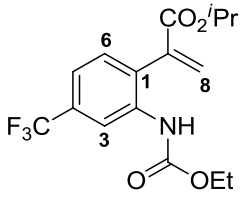
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, app. s, *H*-3), 6.99-6.92 (1H, m, *H*-4), 6.80 (1H, dd, *J* 8.8, 3.0, *H*-6), 6.73 (1H, br s, N*H*), 6.46 (1H, d, *J* 1.1, *H*-8), 5.75 (1H, d, *J* 1.1, *H*-8'), 5.04 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.08 (2H, q, *J* 7.1, OCH_2CH_3), 1.22-1.14 (9H, m, OCH_2CH_3, $OCH(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 ($CO_2{}^{i}Pr$), 159.1 (d, *J* 244.2, *C*-5), 154.1 (CO_2Et), 138.9 (*C*-2), 131.5 (*C*-1), 130.9 (*C*-8), 127.6 (*C*-7), 124.4 (app. br s, *C*-3), 116.8 (d, *J* 23.2, *C*-6), 115.6 (d, *J* 22.2, *C*-4), 69.5 (O*C*$H(CH_3)_2$), 61.2 (O*C*H_2CH_3), 21.6 ($OCH(CH_3)_2$), 14.5 (OCH_2CH_3).

^{19}F NMR (377 MHz, $CDCl_3$, $\{^{1}H\}$) δ −118.8.

m/z LRMS (ESI^+) 318.1 $[M+Na]^+$; HRMS (ESI^+) 318.1113 ($[M+Na]^+$, $C_{15}H_{18}FNO_4Na$ requires 318.1118).

Isopropyl 2-(2-((ethoxycarbonyl)amino)-4-(trifluoromethyl)phenyl)acrylate (23)



This compound was prepared according to general procedure E, using isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acrylate **19** (1.40 g, 4.62 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded the isopropyl 2-phenylacrylate **23** as a yellow oil (431 mg, 27%).

IR (neat) v_{max} 3341, 2985, 1719, 1584, 1534, 1471, 1333, 1214, 1127, 1095 cm^{-1}.

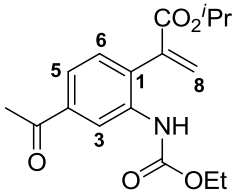
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.15 (1H, m, *H*-3), 7.29-7.22 (1H, m, *H*-5), 7.20-7.14 (1H, m, *H*-6), 6.94 (1H, br s, N*H*), 6.55 (1H, d, *J* 1.2, *H*-8), 5.79 (1H, d, *J* 1.2, *H*-8'), 5.06 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.13 (2H, q, *J* 7.1, OC*H*$_2CH_3$), 1.24-1.18 (9H, m, OCH_2CH_3, $OCH(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (*C*$O_2{}^{i}$Pr), 153.6 (*C*O_2Et), 138.7 (*C*-2), 136.2 (*C*-1), 131.6 (*C*-8), 131.3 (q, *J* 32.6, *C*-4), 130.7 (*C*-6), 127.9 (*C*-7), 123.8 (q, *J* 272.2, *C*F_3), 120.2 (app. br s, *C*-5), 118.3 (app. br s, *C*-3), 69.7 (O*C*H$(CH_3)_2$), 61.6 (O*C*H_2CH_3), 21.6 ($OCH(CH_3)_2$), 14.5 (OCH_2CH_3).

^{19}F NMR (377 MHz, $CDCl_3$, $\{^{1}H\}$) δ −62.8.

m/z LRMS (ESI^+) 368.1 $[M+Na]^+$; HRMS (ESI^+) 368.1086 ($[M+Na]^+$, $C_{16}H_{18}F_3NO_4Na$ requires 368.1068).

Isopropyl 2-(4-acetyl-2-((ethoxycarbonyl)amino)phenyl)acrylate (24)



This compound was prepared according to general procedure E, using isopropyl 2-(4-acetyl-2-nitrophenyl)acrylate **20** (500 mg, 1.80 mmol). Column chromatography (petrol:ethyl acetate [3:1]) afforded the isopropyl 2-phenylacrylate **24** as a yellow oil (172 mg, 30%).

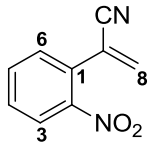
IR (neat) ν_{max} 3322, 2982, 1716, 1686, 1572, 1525, 1422, 1290, 1211, 1096, 1054 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, s, *H*-3), 7.63 (1H, dd, *J* 7.9, 1.7, *H*-5), 7.17 (1H, d, *J* 7.9, *H*-6), 6.89 (1H, br s, N*H*), 6.54 (1H, app. s, *H*-8), 5.79 (1H, app. s, *H*-8'), 5.06 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 4.14 (2H, q, *J* 7.1, OCH_2CH_3), 2.55 (3H, s, ArCOCH_3), 1.26-1.18 (9H, m, OCH_2CH_3, $OCH(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6 (Ar*C*OMe), 165.6 (*C*$O_2{}^{i}$Pr), 153.8 (*C*O_2Et), 139.1 (*C*-2), 137.8 (*C*-4), 135.9 (*C*-1), 131.3 (*C*-8), 130.6 (*C*-6), 125.3 (*C*-7), 123.3 (*C*-5), 122.1 (*C*-3), 69.6 (O*C*H$(CH_3)_2$), 61.5 (O*C*H_2CH_3), 26.8 (ArCO*C*H_3), 21.7 (OCH(*C*$H_3)_2$), 14.5 (OCH_2CH_3).

m/z LRMS (ESI^+) 342.1 $[M+Na]^+$; HRMS (ESI^+) 342.1310 ($[M+Na]^+$, $C_{17}H_{21}NO_5Na$ requires 342.1317).

2-(2-Nitrophenyl)acrylonitrile (25)



To a stirring RT solution of paraformaldehyde (2.25 g, 75.0 mmol), tetrabutylammonium bromide (385 mg, 1.19 mmol) and potassium carbonate (12.8 g, 92.5 mmol) in toluene (60 mL), a solution of 2-nitrophenylacetonitrile (4.90 g, 30.2 mmol) in toluene (60 mL) was added dropwise over 6 h. After a further 2 h, water (120 mL) was added and the aqeuous layer was extracted with toluene (3 × 100 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [3:1]) afforded 2-(2-nitrophenyl)acrylonitrile **25** as a light yellow solid (2.16 g, 41%).

IR (neat) ν_{max} 3021, 2232, 1519, 1398, 1348, 955, 855 cm^{-1}.

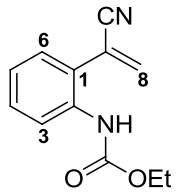
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, dd, *J* 8.1, 1.3, *H*-3), 7.65 (1H, app. td, *J* 7.6, 1.4, *H*-5), 7.56 (1H, app. td, *J* 7.9, 1.5, *H*-4), 7.39 (1H, dd, *J* 7.6, 1.5, *H*-6), 6.23 (1H, app. s, *H*-8), 5.99 (1H, app. s, *H*-8').

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (*C*-2), 134.1 (*C*-5), 133.3 (*C*-8), 131.7 (*C*-6), 130.9 (*C*-4), 129.6 (*C*-1), 125.3 (*C*-3), 121.1 (*C*N), 116.1 (*C*-7).

m/z LRMS (ESI^+) 197.0 $[M+Na]^+$; HRMS (ESI^+) 197.0324 ($[M+Na]^+$, $C_9H_6N_2O_2Na$ requires 197.0327).

m.p. 59 °C.

Ethyl (2-(1-cyanovinyl)phenyl)carbamate (26)



Zinc dust (6.89 g, 105 mmol) and ammonium chloride (8.40 g, 158 mmol) were added to a vigorously stirred RT solution of 2-(2-nitrophenyl)acrylonitrile **25** (1.83 g, 10.5 mmol) in acetone:water [4:1] (45 mL). After 1 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 × 50 mL) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in chloroform (35 mL); pyridine (1.08 mL, 13.7 mmol) was added and the solution was stirred at 0 °C. Ethyl chloroformate (1.21 mL, 12.6 mmol) was added dropwise into the reaction mixture. The mixture was stirred for 3 h and allowed to warm to RT. The solution was then washed with brine (30 mL) and water (2 × 30 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [4:1]) afforded ethyl (2-(1-cyanovinyl)phenyl)carbamate **26** as a yellow solid (954 mg, 42%).

IR (neat) ν_{max} 3305, 2984, 2237, 1723, 1583, 1522, 1452, 1375, 1219, 1061, 945 cm^{-1}.

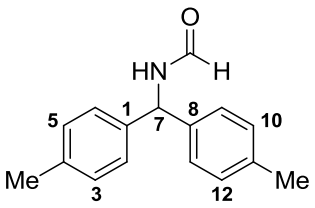
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, app. s, *H*-3), 7.42 (1H, app. t, *J* 7.8, *H*-4), 7.36-7.28 (1H, d, *J* 7.5, *H*-6), 7.20 (1H, app. t, *J* 7.5, *H*-5), 6.70 (1H, br s, N*H*), 6.32 (1H, app. s, *H*-8), 6.16 (1H, app. s, *H*-8'), 4.25 (2H, q, *J* 7.1, OCH_2CH_3), 1.33 (3H, t, *J* 7.1, OCH_2CH_3).

^{13}C NMR (101 MHz) δ 153.9 (*C*O_2Et), 134.8 (*C*-8), 134.7 (*C*-2), 130.6 (*C*-4), 129.3 (*C*-6), 129.0 (*C*-1), 125.1 (*C*-5), 123.6 (*C*-3), 120.5 (*C*N), 117.4 (*C*-7), 61.7 (O*C*H_2CH$_3$), 14.5 (OCH$_2$*C*H$_3$).

m/z LRMS (ESI$^+$) 239.1 [M+Na]$^+$; HRMS (ESI$^+$) 239.0792 ([M+Na]$^+$, $C_{12}H_{12}N_2O_2Na$ requires 239.0796).

m.p. 64-67 °C.

_N_-(Di-_p_-tolylmethyl)formamide (27)



Formic acid (1.12 mL, 29.7 mmol) was added to a solution of di-*p*-tolylmethanone (5.00 g, 23.8 mmol) in formamide (4.73 mL, 119 mmol), and the reaction was stirred at 170 °C. After 12 h, the reaction mixture was allowed to cool to RT and dissolved in ethyl acetate (25 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Recrystallisation from chloroform/hexanes afforded *N*-(di-*p*-tolylmethyl)formamide **27** as a colourless solid (5.57 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, s, C*H*O), 7.21-7.11 (8H, m, aromatics), 6.62 (1H, d, *J* 7.7, N*H*), 6.25 (1H, d, *J* 8.3, *H*-7), 2.36 (6H, ArCH_3).

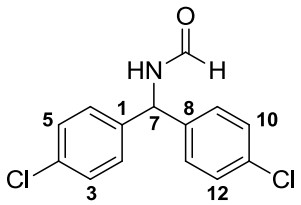
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (*C*HO), 138.3 (*C*-1,8), 137.2 (*C*-4,11), 129.4 (*C*-3,5,10,12), 127.3 (*C*-2,6,9,13), 55.2 (*C*-7), 21.1 (Ar*C*H$_3$).

m/z LRMS (ESI^+) 240.1 $[M+H]^+$.

m.p. 117-118 °C.

Data in accordance with literature.[a]

_N_-(Bis(4-chlorophenyl)methyl)formamide (28)



Formic acid (938 μL, 24.9 mmol) was added to a solution of bis(4-chlorophenyl)methanone (5.00 g, 19.9 mmol) in formamide (3.95 mL, 99.5 mmol), and the reaction was stirred at 170 °C. After 12 h, the reaction mixture was allowed to cool to RT and dissolved in ethyl acetate (25 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Recrystallisation from chloroform/hexanes afforded *N*-(bis(4-chlorophenyl)methyl)formamide **28** as a colourless solid (3.85 g, 69%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (1H, d, *J* 8.5, N*H*), 8.19 (1H, s, C*H*O), 7.42 (4H, d, *J* 8.4, *H*-3,5,10,12), 7.32 (4H, d, *J* 8.4, *H*-2,6,9,13), 6.23 (1H, d, *J* 8.7, *H*-7).

^{13}C NMR (101 MHz, DMSO-d_6) δ 160.8 (*C*HO), 141.2 (*C*-1,8), 132.4 (*C*-4,11), 129.5 (*C*-2,6,9,13), 129.0 (*C*-3,5,10,12), 53.8 (*C*-7).

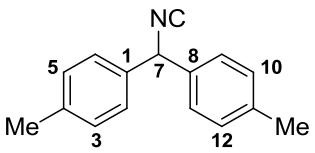
m/z LRMS (ESI^+) 280.0 $[M+H]^+$.

[a] A. A. Bakibaev, L. G. Tignibidina, V. D. Filimonov, A. V. Pustovoitov, V. K. Gorshkova, A. S. Saratikov, V. A. Krasnov, *Pharm. Chem. J.*, **1989**, *23*, 978.

m.p. 129-131 °C.

Data in accordance with literature.[a]

4,4'-(Isocyanomethylene)bis(methylbenzene) (29)



This compound was prepared according to general procedure F, using *N*-(di-*p*-tolylmethyl)formamide **27** (1.00 g, 4.18 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded 4,4'-(isocyanomethylene)bis(methylbenzene) **29** as a white solid (630 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (4H, d, *J* 8.0), 7.16 (4H, d, *J* 8.0) [aromatics], 5.83 (1H, s, *H*-7), 2.33 (6H, s, ArCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (N*C*), 138.3, 135.0, 129.6, 126.5 [aromatics], 61.6 (t, *J* 6.3, *C*-7), 21.1 (ArCH_3).

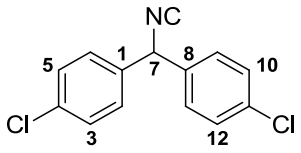
m/z LRMS (ESI^+) 244.1 $[M+Na]^+$.

m.p. 53-54 °C.

Data in accordance with literature.[b]

[a] A. A. Bakibaev, L. G. Tignibidina, V. D. Filimonov, A. V. Pustovoitov, V. K. Gorshkova, A. S. Saratikov, V. A. Krasnov, *Pharm. Chem. J.*, **1989**, *23*, 978.
[b] L. B. Engemyr, A. Martinsen, J. Songstad, *Acta Chem. Scand. A* **1974**, *28*, 255.

4,4'-(Isocyanomethylene)bis(chlorobenzene) (30)



This compound was prepared according to general procedure F, using *N*-(bis(4-chlorophenyl)methyl)formamide **28** (1.00 g, 3.57 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded 4,4'-(isocyanomethylene)bis(methylbenzene) **30** as a white solid (851 mg, 91%).

IR (neat) ν_{max} 2974, 2151, 1128, 875 cm^{-1}.

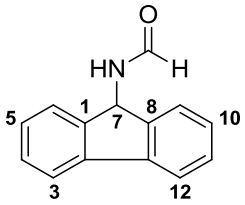
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (4H, d, *J* 8.4, *H*-3,5,10,12), 7.27 (4H, d, *J* 8.4, *H*-2,6,9,13), 5.86 (1H, s, *H*-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (N*C*), 135.6 (*C*-1,8), 134.8 (*C*-4,11), 129.3 (*C*-2,6,9,13), 128.0 (*C*-3,5,10,12), 60.7 (t, *J* 5.1, *C*-7).

m/z LRMS (ESI^+) 284.0 $[M+Na]^+$; HRMS (ESI^+) 284.0012 ([M+Na]+, $C_{14}H_9Cl_2NNa$ requires 284.0004).

m.p. 78-81 °C.

_N_-(9_H_-Fluoren-9-yl)formamide (31)



To a solution of 9-fluorenone (5.00 g, 27.7 mmol) in formamide (11.0 mL, 227 mmol), formic acid (1.31 mL, 34.7 mmol) was added, and the reaction was stirred at 170 °C for 12 h. The reaction was then removed from the heat source and solidified after 1 minute. The resulting solid was dissolved in hot ethyl acetate (500 mL), washed with brine (2 × 100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Recrystallisation from ethyl acetate afforded *N*-(9*H*-fluoren-9-yl)formamide **31** as a white solid (2.03 g, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (1H, s, C*H*O), 7.71 (2H, d, *J* 7.4, *H*-3,12), 7.59 (2H, dd, *J* 7.4, 0.6, *H*-6,9), 7.43 (2H, t, *J* 7.4, *H*-4,11), 7.34 (2H, td, *J* 7.4, 1.1, *H*-5,10), 6.30 (1H, d, *J* 9.0, *H*-7), 5.88 (1H, br s, N*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (*C*HO), 143.7 (*C*-1,8), 140.7 (*C*-2,13), 128.9 (*C*-6,9), 127.9 (*C*-5,10), 125.1 (*C*-4,11), 120.1 (*C*-3,12), 53.3 (*C*-7).

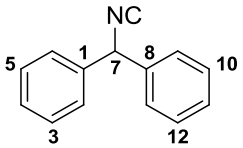
m/z LRMS (ESI$^+$) 210.1 $[M+H]^+$.

m.p. 191-194 °C.

Data in accordance with literature.[a]

[a] R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Speck, R. V. A. Orru, *Org. Lett.* **2003**, *5*, 3759.

(Isocyanomethylene)dibenzene (32)



This compound was prepared by Dr Matija Grdičak according to general procedure F, using *N*-benzhydrylformamide **88** (1.00 g, 4.74 mmol). Column chromatography (petrol:ethyl acetate [19:1]) afforded (isocyanomethylene)dibenzene **32** as a white solid (871 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.34 (10H, m, aromatics), 5.94 (1H, s, *H*-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (N*C*), 137.6, 129.0, 128.5, 126.6 [aromatics], 62.0 (t, *J* 6.6, *C*-7).

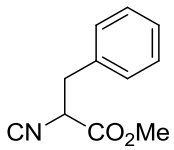
m/z LRMS (ESI^+) 216.1 $[M+Na]^+$.

m.p. 46-47 °C.

Data in accordance with literature.[a]

[a] M. Vamos, K. Welsh, D. Finlay, P. S. Lee, P. D. Mace, S. J. Snipas, M. L. Gonzalez, S. R. Ganji, R. J. Ardecky, S. J. Riedl, G. S. Salvesen, K. Vuori, J. C. Reed, N. D. P. Cosford, *ACS Chem. Biol.* **2013**, *8*, 725.

Methyl 2-isocyano-3-phenylpropanoate (33)



This compound was prepared by Dr Matija Gredičak according to general procedure G, using phenylalanine methyl ester hydrochloride (910 mg, 4.21 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded methyl 2-isocyano-3-phenylpropanoate **33** as a colourless oil (581 mg, 73%).

IR (neat) ν_{max} 2149, 1758, 1456, 1274, 1217, 747, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.15 (5H, m, aromatics), 4.39 (1H, dd, *J* 8.3, 4.8, C*H*CO_2Me), 3.72 (3H, s, OCH_3), 3.19 (1H, dd, *J* 13.9, 4.8, PhCH_2), 3.07 (1H, dd, *J* 13.8, 8.4, PhCH_2').

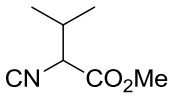
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 161.0 (*C*CO_2Me, N*C*), 134.4, 129.3, 128.9, 127.9 [aromatics], 58.0 (*C*HCO_2Me), 53.4 (O*C*H_3), 38.9 (Ph*C*H_2).

m/z LRMS (ESI^+) 212.1 $[M+Na]^+$.

Data in accordance with literature.[a]

[a] D. Seebach, G. Adam, T. Gees, M. Schiess, W. Weigand, *Chem. Ber.* **1988**, *121*, 507.

Methyl 2-isocyano-3-methylbutanoate (34)



This compound was prepared by Dr Matija Gredičak according to general procedure G, using valine methyl ester hydrochloride (1.00 g, 5.95 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded methyl 2-isocyano-3-methylbutanoate **34** as a colourless oil (570 mg, 68%).

IR (neat) ν_{max} 2972, 2148, 1751, 1438, 1261, 1210, 1130, 1010, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (1H, d, *J* 4.2, C*H*CO_2Me), 3.76 (3H, s, OC*H*$_3$), 2.35-2.19 (1H, m, C*H*$(CH_3)_2$), 1.04 (3H, d, *J* 6.8, CH(C*H*$_3$)), 0.94 (3H, d, *J* 6.7, CH(C*H*$_3$)').

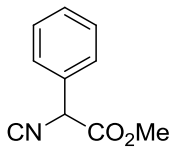
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 160.5 (*C*O_2Me, N*C*), 62.9 (*C*HCO_2Me), 53.2 (O*C*H$_3$), 31.2 (*C*H$(CH_3)_2$), 19.3 (CH(*C*H$_3$)).

m/z LRMS (ESI^+) 164.1 $[M+Na]^+$.

Data in accordance with literature.[a]

[a] A. Porcheddu, G. Giacomelli, M. Salaris, *J. Org. Chem.* **2005**, *70*, 2361.

Methyl 2-isocyano-2-phenylacetate (35)



This compound was prepared by Dr Matija Gredičak according to general procedure G, using phenylglycine methyl ester hydrochloride (1.00 g, 6.41 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded methyl 2-isocyano-2-phenylacetate **35** as a colourless oil (718 mg, 64%).

IR (neat) ν_{max} 2149, 1754, 1253, 1212, 1006, 731, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.23 (5H, m, aromatics), 5.30 (1H, s, C*H*CO_2Me), 3.71 (3H, s, OC*H*$_3$).

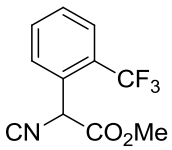
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 161.4 (*C*O_2Me, N*C*), 131.8, 129.6, 129.2, 126.7 [aromatics], 60.3 (*C*HCO_2Me), 53.8 (O*C*H$_3$).

m/z LRMS (ESI^+) 198.1 $[M+Na]^+$.

Data in accordance with literature.[a]

[a] R. S. Bon, C. Hong, M. J. Bouma, R. F Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Spek, R. V. A. Orru, *Org. Lett.* **2003**, *5*, 3759.

Methyl 2-isocyano-2-(2-(trifluoromethyl)phenyl)acetate (36)



This compound was prepared by Dr Matija Gredičak. To a solution of (2-(trifluoromethyl)phenyl)methanamine (1.20 g, 6.85 mmol) in ethyl formate (5.0 mL), triethylamine (1.10 mL, 7.54 mmol) was added, and the reaction mixture was stirred and heated to reflux for 48 h. The mixture was then allowed to cool to RT and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [1:1]) afforded *N*-(2-(trifluoromethyl)benzyl)formamide as a colourless oil. The formamide was dissolved in DCM (4.0 mL) at 0 °C, before triethylamine (1.14 mL, 8.22 mmol) was added and then $POCl_3$ (307 μL, 3.29 mmol) was added dropwise, and the reaction mixture was stirred. After 90 min, saturated sodium carbonate solution (5.0 mL) was added, and stirring was continued for 30 min, before water (8.0 mL) was added. The aqueous phase was then extracted with DCM (20 mL), and the combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was dissolved in THF (10 mL) and cooled to −78 °C, before LiHMDS (1.21 g, 7.24 mmol) in toluene (7.2 mL) was added dropwise. The reaction mixture was left to stir at −78 °C for 1 h, after which dimethyl carbonate (332 μL, 3.95 mmol) was added, and the reaction was allowed to warm to RT. The crude mixture was concentrated *in vacuo,* before the residue was diluted with ethyl acetate (35 mL) and washed with saturated aqueous ammonium chloride solution (35 mL), brine (35 mL) and water (35 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [9:1]) afforded the methyl isocyanoacetate **36** as a brown oil (283 mg, 17%).

IR (neat) ν_{max} 3025, 2157, 1612, 1487, 1046 cm^{-1}.

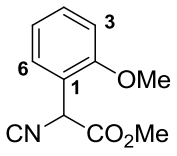
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* 7.6), 7.77 (1H, d, *J* 7.6), 7.71 (1H, t, *J* 7.6), 7.59 (1H, t, *J* 7.6) [aromatics], 5.78 (1H, s, C*H*CO_2Me), 3.84 (3H, s, OC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 161.6 (*C*O_2Me, N*C*), 133.1, 130.8, 130.0, 129.1, 128.2 (q, *J* 31.3), 126.5 (q, *J* 5.4) [aromatics], 123.6 (q, *J* 273.2, *C*F_3), 55.8 (*C*HCO_2Me), 54.0 (O*C*H_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ −58.4 (m).

m/z LRMS (ESI^+) 266.0 $[M+Na]^+$; HRMS (ESI^+) 266.0398 ($[M+Na]^+$, $C_{11}H_8F_3NO_2Na$ requires 266.0399).

Methyl 2-isocyano-2-(2-methoxyphenyl)acetate (37)



This compound was prepared by Dr Matija Gredičak. (2-Methoxyphenyl)methanamine (1.31 mL, 10.0 mmol) was dissolved in formic acid (20 mL) at RT. Acetic anhydride (1.42 mL, 15.0 mmol) was added dropwise over 2 h, and the mixture was stirred for 16 h. The crude mixture was concentrated *in vacuo*, and the residue was then dissolved in ethyl acetate (20 mL) and filtered through a short silica column. Under an atmosphere of argon, the mixture was dissolved in THF (20 mL) and cooled to 0 °C. Triethylamine (7.00 mL, 50.0 mmol) was added, and then $POCl_3$ (1.40 mL, 15.0 mmol) was added dropwise over 10 min. The reaction mixture left to stir at 0 °C. After 2 h, the reaction was quenched with 10% aqueous sodium carbonate solution, and stirred for a further 10 min. The mixture was concentrated *in vacuo*,

before column chromatography (petrol:ethyl acetate [8:1]) afforded 1-(isocyanomethyl)-2-methoxybenzene as a colourless oil. This isocyanide was dissolved in THF (28 mL) at −78 °C. LiHMDS (2.51 g, 15.0 mmol) in THF (15 mL) was added dropwise over 10 min, and the reaction mixture was left to stir at −78 °C. After 1 h dimethyl carbonate (685 μL, 8.15 mmol) was added, and the reaction was allowed to warm to RT. The crude mixture was concentrated *in vacuo*, before the residue was diluted with ethyl acetate (75 mL) and washed with saturated aqueous ammonium chloride solution (75 mL), brine (75 mL) and water (75 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [5:1]) afforded the methyl isocyanoacetate **37** as a light yellow oil (923 mg, 45%).

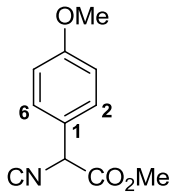
IR (neat) ν_{max} 3027, 2151, 1602, 1495, 1030, 726 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.37 (2H, m, *H*-4,6), 7.04 (1H, app. t, *J* 7.5, *H*-5), 6.96 (1H, d, *J* 8.3, *H*-3), 5.76 (1H, s, C*H*CO_2Me), 3.89 (3H, s, ArOCH_3), 3.80 (3H, s, CO_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (*C*O_2Me), 159.7 (N*C*), 156.2 (*C*-2), 131.4 (*C*-4), 128.3 (*C*-6), 121.2 (*C*-5), 121.1 (*C*-1), 111.3 (*C*-3), 55.9 (ArO*C*H_3), 54.8 (*C*HCO_2Me), 53.6 (CO_2CH_3).

m/z LRMS (ESI^+) 228.1 $[M+Na]^+$; HRMS (ESI^+) 228.0630 ($[M+Na]^+$, $C_{11}H_{11}NO_3Na$ requires 228.0637).

Methyl 2-isocyano-2-(4-methoxyphenyl)acetate (38)



This compound was prepared by Dr Matija Gredičak. (4-Methoxyphenyl)methanamine (261 μL, 2.00 mmol) was dissolved in formic acid (4.0 mL) at RT. Acetic anhydride (283 μL, 3.00 mmol) was added dropwise over 2 h, and the mixture was stirred for 16 h. The crude mixture was concentrated *in vacuo*, and the residue was then dissolved in ethyl acetate (4.0 mL) and filtered through a short silica column. Under an atmosphere of argon, the mixture was dissolved in THF (4.0 mL) and cooled to 0 °C. Triethylamine (1.40 mL, 10.0 mmol) was added, and then $POCl_3$ (280 μL, 3.00 mmol) was added dropwise over 10 min. The reaction mixture left to stir at 0 °C. After 2 h, the reaction was quenched with 10% aqueous sodium carbonate solution, and stirred for a further 10 min. The mixture was concentrated *in vacuo*, before column chromatography (petrol:ethyl acetate [8:1]) afforded 1-(isocyanomethyl)-4-methoxybenzene as a colourless oil. This isocyanide was dissolved in THF (3.7 mL) at −78 °C. LiHMDS (453 mg, 2.71 mmol) in THF (3.7 mL) was added dropwise over 10 min, and the reaction mixture was left to stir at −78 °C. After 1 h dimethyl carbonate (124 μL, 1.48 mmol) was added, and the reaction was allowed to warm to RT. The crude mixture was concentrated *in vacuo*, before the residue was diluted with ethyl acetate (15 mL) and washed with saturated aqueous ammonium chloride solution (15 mL), brine (15 mL) and water (15 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [8:1]) afforded the methyl isocyanoacetate **38** as a colourless oil (172 mg, 42%).

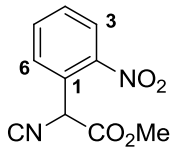
IR (neat) ν_{max} 2148, 1755, 1611, 1513, 1252, 1178, 1030, 832 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (2H, m, *H*-2,6), 6.89-6.82 (2H, m, *H*-3,5), 5.24 (1H, s, C*H*CO_2Me), 3.75 (3H, s, CO_2CH_3), 3.71 (3H, s, ArOCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 160.5 (*C*O_2Me, N*C*), 157.2, 128.1, 123.9, 114.6 [aromatics], 59.7 (*C*HCO_2Me), 55.4, 53.7 (CO_2CH_3, Ar*O*CH_3).

m/z LRMS (ESI$^+$) 228.1 [M+Na]$^+$; HRMS (ESI$^+$) 228.0633 ([M+Na]$^+$, $C_{11}H_{11}NO_3Na$ requires 228.0637).

Methyl 2-isocyano-2-(2-nitrophenyl)acetate (39)



This compound was prepared according to general procedure H, using 1-fluoro-2-nitrobenzene (1.37 mL, 13.0 mmol). Column chromatography (petrol:ethyl acetate [17:3]) afforded the methyl isocyanoacetate **39** as a brown oil (1.29 g, 58%).

IR (neat) ν_{max} 2148, 1758, 1530, 1347, 1225, 787, 741 cm^{-1}.

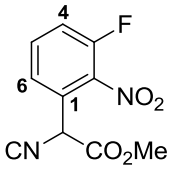
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (1H, dd, *J* 8.2, 1.2, *H*-3), 7.89 (1H, dd, *J* 7.8, 1.4, *H*-6), 7.83 (1H, td, *J* 7.8, 1.2, *H*-5), 7.68 (1H, ddd, *J* 8.2, 7.5, 1.4, *H*-4), 6.42 (1H, s, C*H*CO_2Me), 3.87 (3H, s, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 163.2 (*C*O_2Me, N*C*), 147.0, 134.6, 130.7, 129.3, 126.8, 125.8 [aromatics], 57.2 (*C*HCO_2Me), 54.2 (OCH_3).

m/z LRMS (ESI$^+$) 221.1 [M+Na]$^+$.

Data in accordance with literature.[a]

Methyl 2-(3-fluoro-2-nitrophenyl)-2-isocyanoacetate (40)



This compound was prepared according to general procedure H, using 2,6-difluoronitrobenzene (2.07 g, 13.0 mmol). Column chromatography (petrol:ethyl acetate [6:1]) afforded the methyl isocyanoacetate **40** as a brown oil (1.65 g, 69%).

IR (neat) ν_{max} 3001, 2146, 1589, 1335, 1256, 1222 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, td, *J* 8.2, 5.1, *H*-5), 7.62 (1H, d, *J* 8.0, *H*-6), 7.43 (1H, ddd, *J* 9.4, 8.5, 1.2, *H*-4), 6.01 (1H, s, C*H*CO_2Me), 3.85 (3H, s, OCH_3).

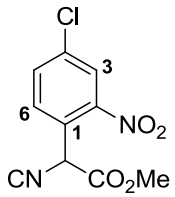
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 164.0 (*C*O_2Me, N*C*), 154.9 (d, *J* 262.2), 141.6, 133.6 (d, *J* 8.8), 127.0, 123.7 (d, *J* 3.8), 119.1 (d, *J* 20.0) [aromatics], 55.6 (*C*HCO_2Me), 54.4 (O*C*H_3).

^{19}F NMR (377 MHz, $CDCl_3$, $\{^{1}H\}$) δ −119.0.

m/z LRMS (ESI^+) 261.0 $[M+Na]^+$; HRMS (ESI^+) 261.0290 ($[M+Na]^+$, $C_{10}H_7FN_2O_4Na$ requires 261.0288).

[a] T. Buyck, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12714.

Methyl 2-(4-chloro-2-nitrophenyl)-2-isocyanoacetate (41)



This compound was prepared according to general procedure H, using 5-chloro-2-fluoronitrotoluene (1.53 mL, 13.0 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the methyl isocyanoacetate **41** as a brown oil (1.78 g, 70%).

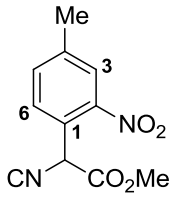
IR (neat) ν_{max} 2992, 2156, 1612, 1337, 1237, 1219, 827 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* 2.0, *H*-3), 7.84 (1H, d, *J* 8.4, *H*-6), 7.79 (1H, dd, *J* 8.4, 2.0, *H*-5), 6.38 (1H, s, C*H*CO_2Me), 3.87 (3H, s, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 163.8 (*C*O_2Me, N*C*), 147.3, 136.8, 134.5, 130.4, 126.0, 125.2 [aromatics], 56.8 (*C*HCO_2Me), 54.4 (O*C*H_3).

m/z LRMS (ESI^+) 277.0 $[M+Na]^+$; HRMS (ESI^+) 276.9990 ($[M+Na]^+$, $C_{10}H_7ClN_2O_4Na$ requires 276.9987).

Methyl 2-isocyano-2-(4-methyl-2-nitrophenyl)acetate (42)



This compound was prepared according to general procedure H, using 4-fluoro-3-nitrotoluene (2.02 g, 13.0 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the methyl isocyanoacetate **42** as a brown oil (1.46 g, 60%)

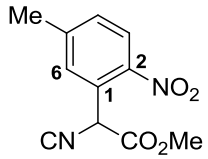
IR (neat) ν_{max} 2962, 2150, 1527, 1355, 1257, 1231, 989 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, app. s, *H*-3), 7.71 (1H, d, *J* 8.0, *H*-6), 7.60 (1H, app. d, *J* 8.0, *H*-5), 6.31 (1H, s, C*H*CO_2Me), 3.83 (3H, s, OCH_3), 2.51 (3H, s, ArCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 162.8 (*C*O_2Me, N*C*), 146.8, 141.6, 135.2, 129.2, 126.2, 123.9 [aromatics], 57.1 (*C*HCO_2Me), 54.1 (O*C*H_3), 21.0 (Ar*C*H_3).

m/z LRMS (ESI^+) 257.1 $[M+Na]^+$; HRMS (ESI^+) 257.0535 ($[M+Na]^+$, $C_{11}H_{10}N_2O_4Na$ requires 257.0538).

Methyl 2-isocyano-2-(5-methyl-2-nitrophenyl)acetate (43)



This compound was prepared according to general procedure H, using 3-fluoro-4-nitrotoluene (407 mg, 2.63 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded the methyl isocyanoacetate **43** as a yellow oil (187 mg, 40%).

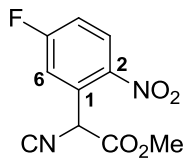
IR (neat) ν_{max} 2148, 1758, 1593, 1524, 1437, 1345, 1236, 1017, 837 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, d, *J* 8.4, *H*-3), 7.53 (1H, app. s, *H*-6), 7.34 (1H, app. d, *J* 8.4, *H*-4), 6.29 (1H, s, C*H*CO_2Me), 3.75 (3H, s, $CHCO_2CH_3$), 2.45 (3H, s, $ArCH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (*C*O_2Me), 162.8 (N*C*), 146.4 (*C*-2), 144.7 (*C*-5), 131.1 (*C*-4), 129.9 (*C*-6), 126.7 (*C*-1), 126.0 (*C*-3), 57.3 (*C*HCO_2Me), 54.1 (CO_2CH_3), 21.7 ($ArCH_3$).

m/z LRMS (ESI^+) 257.1 $[M+Na]^+$; HRMS (ESI^+) 257.0543 ($[M+Na]^+$, $C_{11}H_{10}N_2O_4Na$ requires 257.0538).

Methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (44)



This compound was prepared according to general procedure H, using 2,4-difluoronitrobenzene (1.33 mL, 11.9 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded the methyl isocyanoacetate **44** as a brown oil (1.07 g, 49%).

IR (neat) ν_{max} 2942, 2147, 1756, 1592, 1529, 1346, 1266, 1230, 877 cm^{-1}.

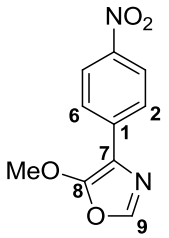
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (1H, dd, *J* 9.2, 5.0, *H*-3), 7.59 (1H, dd, *J* 8.8, 2.7, *H*-6), 7.38-7.31 (1H, m, *H*-4), 6.42 (1H, s, C*H*CO_2Me), 3.87 (3H, s, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (d, *J* 260.3, *C*-5), 164.2 (*C*O_2Me), 164.0 (N*C*), 141.8 (*C*-2), 130.3 (d, *J* 9.3, *C*-1), 128.9 (d, *J* 9.7, *C*-3), 117.6 (d, *J* 22.9, *C*-4), 116.9 (d, *J* 26.2, *C*-6), 57.3 (*C*HCO_2Me), 54.4 (O*C*H_3)

^{19}F NMR (377 MHz, $CDCl_3$, $\{^{1}H\}$) δ −99.7.

m/z LRMS (ESI^+) 261.0 $[M+Na]^+$; HRMS (ESI^+) 261.0280 ($[M+Na]^+$, $C_{10}H_7FN_2O_4Na$ requires 261.0288).

5-Methoxy-4-(4-nitrophenyl)oxazole (45)



This compound was prepared according to general procedure H, using 4-fluoronitrobenzene (1.68 g, 11.9 mmol). Column chromatography (petrol:ethyl acetate [9:2]) afforded 5-methoxy-4-(4-nitrophenyl)oxazole **45** as a yellow solid (990 mg, 49%), which was used without further purification.

IR (neat) ν_{max} 1742, 1633, 1600, 1502, 1385, 1351, 1066, 1022, 853 cm^{-1}.

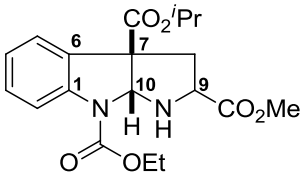
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (2H, d, *J* 9.0, *H*-3,5), 7.97 (2H, d, *J* 9.0, *H*-2,6), 7.54 (1H, s, *H*-9), 4.21 (3H, s, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (*C*-8), 145.7 (*C*-4), 141.5 (*C*-9), 137.9 (*C*-1), 124.9 (*C*-2,6), 124.1 (*C*-3,5), 123.8 (*C*-7), 59.6 (OCH_3).

m/z LRMS (ESI^+) 243.0 $[M+Na]^+$; HRMS (ESI^+) 243.0382 ($[M+Na]^+$, $C_{10}H_8N_2O_4Na$ requires 243.0382).

m.p. 126-128 °C.

(3a*R,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (47)**



Methyl isocyanoacetate (84 μL, 0.91 mmol), tetrabutylammonium bromide (28 mg, 0.091 mmol) and potassium carbonate (140 mg, 1.0 mmol) were dissolved in toluene (6.0 mL). The mixture was stirred at RT. A solution of isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (250 mg, 0.91 mmol) in toluene (3.0 mL) was added dropwise over 5 h. After a further 5 h the reaction mixture was diluted with DCM (10 mL), and then washed with brine (20 mL) and water (20 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [3:1]) afforded the pyrroloindoline **47** as a colourless oil (48 mg, 14%), and as a mixture of two inseparable diastereomers in 8:1 ratio (DS1:DS2).

IR (neat) ν_{max} 2963, 1732, 1570, 1487, 1387, 1263, 1105, 1044, 840, 821, 753 cm^{-1}.

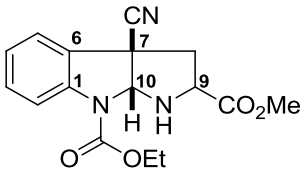
^{1}H NMR (500 MHz, toluene-d_8, 375 K) δ 7.96 (1H, app. s, *H*-2_{DS2}), 7.86 (1H, app. s, *H*-2_{DS1}), 7.30-7.22 (2H, m, *H*-$5_{DS1,DS2}$), 7.06 (1H, t, *J* 7.6, *H*-3_{DS1}), 6.88-6.77 (2H, m, *H*-$4_{DS1,DS2}$), 6.25 (1H, s, *H*-10_{DS2}), 6.16 (1H, s, *H*-10_{DS1}), 4.95-4.85 (2H, m, OC*H*$(CH_3)_{2\ DS1,DS2}$), 4.22-4.06 (6H, m, OCH_2CH$_{3\ DS1,DS2,}$ N*H* $_{DS1,DS2}$), 3.73-3.65 (1H, m, *H*-9_{DS1}), 3.59 (1H, t, *J* 7.2, *H*-9_{DS2}), 3.36 (3H, s, OC$H_{3\ DS2}$), 3.08 (3H, s, OC$H_{3\ DS1}$), 2.87-2.75 (2H, m, *H*-$8_{DS1,DS2}$), 2.64 (1H, app. d, *J* 12.9, *H*-8'$_{DS1}$), 2.42-2.35 (1H, m, *H*-8'$_{DS2}$), 1.16-1.10 (6H, m, $OCH_2CH_{3\ DS1,DS2}$), 1.00-0.95 (12H, m, $OCH(CH_3)_{2\ DS1,DS2}$). The signal for *H*-3_{DS2} is buried under toluene peaks.

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 173.2, 172.7 (CO_2Me), 170.9, 170.8 (CO_2^iPr), 154.3, 154.1 (CO_2Et), 147.1, 145.8, 143.0, 141.9, 129.8, 129.6, 123.6, 123.2, 123.0, 122.7,

115.3, 115.0 [aromatics], 82.5, 81.8 (*C*-10), 69.1, 69.0 (O*C*H(CH_3)$_2$), 61.9, 61.4, 61.1, 61.1 (*C*-7, O*C*H$_2$CH$_3$), 59.4, 58.4 (*C*-9), 53.2, 51.5 (CO_2*C*H$_3$), 40.8, 40.3 (*C*-8), 21.3, 21.3 (OCH(*C*H$_3$)$_2$), 14.6, 14.5 (OCH$_2$*C*H$_3$).

m/z LRMS (ESI$^+$) 399.2 [M+Na]$^+$; HRMS (ESI$^+$) 399.1534 ([M+Na]$^+$, $C_{19}H_{24}N_2O_6Na$ requires 399.1532).

(3a*R,8a*R**)-8-Ethyl 2-methyl 3a-cyano-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,8(2*H*)-dicarboxylate (48)**



Methyl isocyanoacetate (129 μL, 1.39 mmol), tetrabutylammonium bromide (42 mg, 0.14 mmol) and potassium carbonate (287 mg, 2.08 mmol) were dissolved in toluene (6.0 mL). The mixture was stirred at RT. A solution of ethyl (2-(1-cyanovinyl)phenyl)carbamate **26** (300 mg, 1.39 mmol) in toluene (6.0 mL) was added dropwise over 4 h. After a further 12 h the reaction mixture was diluted with DCM (25 mL), and then washed with brine (40 mL) and water (40 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [3:1]) afforded the pyrroloindoline **48** as a colourless oil (66 mg, 15%), and as a mixture of two separable diastereomers in 3:1 ratio.

Data are provided for the major diastereomer only.

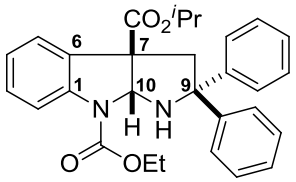
IR (neat) ν_{max} 2219, 1727, 1570, 1488, 1387, 1217, 1051, 840, 821, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, app. s), 7.41-7.30 (2H, m), 7.11 (1H, t, *J* 7.5) [aromatics], 6.07 (1H, s, *H*-10), 4.45-4.27 (2H, m, OCH_2CH_3), 3.83-3.74 (4H, m, *H*-9, OCH_3), 3.26 (1H, br s, N*H*), 2.79-2.63 (2H, m, *H*-8), 1.47-1.34 (3H, m, OCH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (CO_2Me), 152.0 (CO_2Et), 145.1, 141.8, 130.7, 124.0, 120.0, 115.2 [aromatics], 126.5 (*C*N), 82.6 (*C*-10), 62.3 (OCH_2CH_3), 57.9 (*C*-9), 52.6 (CO_2CH_3), 47.4 (*C*-7), 44.0 (*C*-8), 14.6 (OCH_2CH_3).

m/z LRMS (ESI^+) 338.1 $[M+Na]^+$; HRMS (ESI^+) 338.1119 ($[M+Na]^+$, $C_{16}H_{17}N_3O_4Na$ requires 338.1117).

(3a*R,8a*R**)-8-Ethyl 3a-isopropyl 2,2-diphenyl-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-3a,8(2*H*)-dicarboxylate (49)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (60 mg, 0.22 mmol) as the Michael acceptor, (isocyanomethylene)dibenzene **32** (42 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 72 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **49** as a yellow oil (64 mg, 63%), and as a single diastereomer.

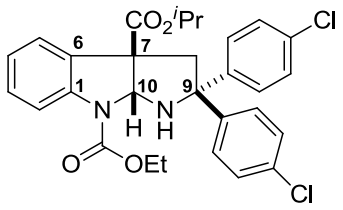
IR (neat) ν_{max} 1717, 1605, 1487, 1375, 1243, 1104, 905 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* 7.5), 7.33-7.25 (2H, m), 7.24-7.16 (3H, m), 7.11 (1H, app. s), 7.06-6.96 (3H, m), 6.96-6.88 (3H, m), 6.81 (1H, t, *J* 7.4) [aromatics], 6.08 (1H, s, *H*-10), 4.85 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 4.36-4.19 (2H, m, OC*H*$_2$CH$_3$), 3.74 (1H, br s, N*H*), 3.14 (1H, d, *J* 13.0, *H*-8), 3.01 (1H, d, *J* 13.0, *H*-8'), 1.39-1.27 (3H, m, OCH_2CH_3), 1.09 (6H, app. s, $OCH(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 ($CO_2{}^{i}Pr$), 152.5 (CO_2Et), 146.5, 140.7, 129.0, 128.4, 127.6, 126.8, 126.7, 126.3, 126.1, 125.9, 123.8, 123.6, 122.7, 114.7 [aromatics], 80.7 (*C*-10), 70.6 (*C*-9), 69.3 ($OCH(CH_3)_2$), 62.0 (*C*-7), 61.5 (OCH_2CH_3), 49.7 (*C*-8), 21.6 ($OCH(CH_3)_2$), 14.9 (OCH_2CH_3).

m/z LRMS (ESI^+) 493.2 $[M+Na]^+$; HRMS (ESI^+) 493.2098 ($[M+Na]^+$, $C_{29}H_{30}N_2O_4Na$ requires 493.2103).

(3a*R,8a*R**)-8-Ethyl 3a-isopropyl 2,2-bis(4-chlorophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-3a,8(2*H*)-dicarboxylate (50)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (60 mg, 0.22 mmol) as the Michael acceptor, 4,4'-(isocyanomethylene)bis(chlorobenzene) **30** (57 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column

chromatography (petrol:ethyl acetate [6:1]) afforded the pyrroloindoline **50** as a colourless oil (88 mg, 76%), and as a single diastereomer.

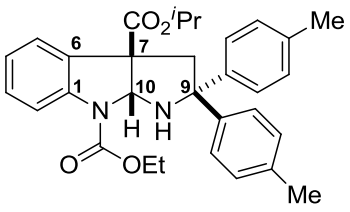
IR (neat) ν_{max} 1719, 1602, 1488, 1232, 1097, 904, 724 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, app. s), 7.26-7.11 (6H, m), 7.05-6.95 (2H, m), 6.93-6.78 (3H, m) [aromatics], 6.12-5.99 (1H, m, *H*-10), 4.88 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 4.36-4.10 (2H, m, OCH_2CH_3), 3.80 (1H, br s, N*H*), 2.98 (2H, app. br s, *H*-8), 1.37-1.27 (3H, m, OCH_2CH_3), 1.13-1.07 (6H, m, $OCH(CH_3)_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 ($CO_2{}^i$Pr), 152.4 (CO_2Et), 144.8, 143.5, 141.3, 136.2, 132.9, 132.3, 129.7, 128.5, 127.7, 127.5, 127.3, 123.8, 123.0, 114.7 [aromatics], 81.0 (*C*-10), 69.9 (*C*-9), 69.5 (O*C*$H(CH_3)_2$), 62.1 (*C*-7), 61.6 (O*C*H_2CH_3), 49.7 (*C*-8), 21.6 ($OCH(CH_3)_2$), 14.7 (OCH_2CH_3).

m/z LRMS (ESI^+) 561.1 $[M+Na]^+$; HRMS (ESI^+) 561.1323 ($[M+Na]^+$, $C_{29}H_{28}Cl_2N_2O_4Na$ requires 561.1324).

(3a*R,8a*R**)-8-Ethyl 3a-isopropyl 2,2-di-*p*-tolyl-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-3a,8(2*H*)-dicarboxylate (51)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (60 mg, 0.22 mmol) as the Michael acceptor, 4,4'-

(isocyanomethylene)bis(methylbenzene) **29** (48 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 72 h. Column chromatography (petrol:ethyl acetate [6:1]) afforded the pyrroloindoline **51** as a colourless oil (24 mg, 22%), and as a single diastereomer.

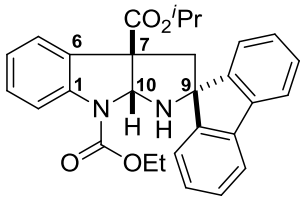
IR (neat) ν_{max} 2981, 1719, 1598, 1511, 1486, 1410, 1377, 1239, 1104, 1059, 908 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (1H, app. s), 7.34-7.22 (2H, m), 7.19-7.06 (4H, m), 7.00 (2H, d, *J* 8.2), 6.92 (1H, t, *J* 7.5), 6.84 (2H, d, *J* 7.4) [aromatics], 6.22-6.07 (1H, s, *H*-10), 4.93 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 4.56-4.18 (2H, m, OC*H*$_2CH_3$), 3.85 (1H, br s, N*H*), 3.26 (1H, d, *J* 13.1, *H*-8), 3.00 (1H, d, *J* 13.1, *H*-8'), 2.31 (3H, s, ArC*H*$_3$), 2.19 (3H, s, ArC*H*$_3$'), 1.34-1.27 (3H, m, OCH_2CH_3), 1.23-1.12 (6H, m, $OCH(CH_3)_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (*C*$O_2{}^{i}$Pr), 152.5 (*C*O_2Et), 143.4, 141.7, 140.6, 139.8, 136.4, 135.8, 129.5, 129.3, 129.0, 128.8, 128.3, 123.5, 122.7, 114.7 [aromatics], 80.4 (*C*-10), 70.0 (*C*-9), 69.2 (O*C*H$(CH_3)_2$), 62.0 (*C*-7), 61.5 (O*C*H_2CH_3), 49.8 (*C*-8), 21.7 (OCH(*C*$H_3)_2$), 20.9 (Ar*C*H_3), 20.8 (Ar*C*H_3'), 14.7 (OCH_2CH_3).

m/z LRMS (ESI^+) 521.2 $[M+Na]^+$; HRMS (ESI^+) 521.2421 ($[M+Na]^+$, $C_{31}H_{34}N_2O_4Na$ requires 521.2416).

(3a'*R,8a'*R**)-8'-Ethyl 3a'-isopropyl 3',3a'-dihydro-1'*H*-spiro[fluorene-9,2'-pyrrolo[2,3-*b*]indole]-3a',8'(8a'*H*)-dicarboxylate (52)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (60 mg, 0.22 mmol) as the Michael acceptor, 9-isocyano-9*H*-fluorene **4** (41 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **52** as a yellow oil (55 mg, 54%), and as a single diastereomer.

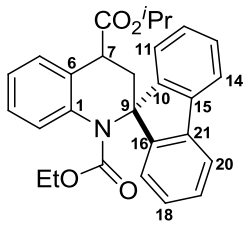
IR (neat) ν_{max} 1716, 1582, 1487, 1330, 1250, 1103, 905 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (1H, app. s), 7.66 (1H, d, *J* 7.5), 7.62-7.55 (2H, m), 7.43-7.35 (3H, m), 7.35-7.25 (2H, m), 7.17-7.07 (2H, m), 7.00 (1H, d, *J* 7.5) [aromatics], 6.62 (1H, s, *H*-10), 5.15 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.46-4.19 (2H, m, OCH_2CH_3), 3.22 (1H, d, *J* 13.9, *H*-8), 3.09 (1H, br s, N*H*), 2.78 (1H, d, *J* 13.9, *H*-8'), 1.34-1.23 (9H, m, OCH_2CH_3, $OCH(CH_3)_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9 ($CO_2{}^i$Pr), 154.4 (CO_2Et), 152.8, 151.7, 149.5, 141.2, 139.2, 139.1, 129.6, 128.4, 128.3, 128.2, 128.0, 124.6, 124.2, 124.1, 123.2, 119.9, 119.5, 115.5 [aromatics], 82.2 (*C*-10), 72.9 (*C*-9), 69.7 (O*C*H$(CH_3)_2$), 62.0 (*C*-7), 61.7 (O*C*H_2CH_3), 49.2 (*C*-8), 21.6 (OCH($CH_3)_2$), 14.7 (OCH_2CH_3).

m/z LRMS (ESI^+) 491.2 $[M+Na]^+$; HRMS (ESI^+) 491.1945 ($[M+Na]^+$, $C_{29}H_{28}N_2O_4Na$ requires 491.1947).

1'-Ethyl 4'-isopropyl 3',4'-dihydro-1'*H*-spiro[fluorene-9,2'-quinoline]-1',4'-dicarboxylate (53)



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (60 mg, 0.22 mmol) as the Michael acceptor, 9-isocyano-9*H*-fluorene **4** (41 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the product **53** as a light yellow oil (32 mg, 34%).

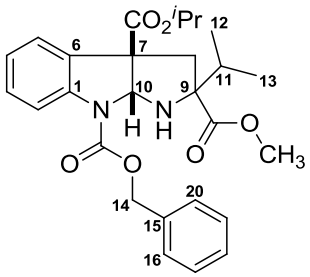
IR (neat) ν_{max} 2982, 2129, 1729, 1590, 1520, 1452, 1220, 1104, 1062, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64-7.57 (3H, m, *), 7.56 (1H, app. s, *H*-2), 7.42-7.29 (4H, m, *), 7.20 (1H, t, *J* 7.6, *), 7.08 (1H, td, *J* 7.7, 1.4, *H*-3), 6.83 (1H, t, *J* 7.4, *H*-4), 6.70 (1H, app. s, *H*-5), 4.52 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 4.14 (2H, q, *J* 7.1, OCH_2CH_3), 3.49 (1H, dd, *J* 13.9, 8.3, *H*-8), 2.98-2.89 (1H, m, *H*-7), 2.67 (1H, dd, *J* 13.9, 3.4, *H*-8'), 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 0.87 (3H, d, *J* 6.2, OCH$(CH_3)_2$), 0.85 (3H, d, *J* 6.2, OCH$(CH_3)_2$'). *Eight unassigned protons correspond to *H*-11,12,13,14,17,18,19,20.

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4 ($CO_2{}^{i}Pr$), 154.1 (CO_2Et), 157.1, 142.5, 141.9, 140.1, 139.7, 135.7, 130.2, 130.1, 129.0, 128.8, 128.6, 128.5, 128.2, 124.7, 123.8, 123.6, 120.5, 120.4 [aromatics], 69.6 (O*C*H$(CH_3)_2$), 67.0 (*C*-9), 61.3 (OCH_2CH_3), 43.6 (*C*-7), 42.1 (*C*-8), 21.5 (OCH$(CH_3)_2$), 21.2 (OCH$(CH_3)_2$'), 14.7 (OCH_2CH_3).

m/z LRMS (ESI^+) 442.2 $[M+H]^+$; HRMS (ESI^+) 442.2013 ($[M+H]^+$, $C_{28}H_{28}NO_4$ requires 442.2018).

(3a*R,8a*R**)-8-Benzyl 3a-isopropyl 2-methyl 2-isobutyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(8a*H*)-tricarboxylate (54)**



This compound was prepared by Dr Matija Grdičak according to general procedure I, using isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate **9** (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-isocyano-3-methylbutanoate **34** (21 mg, 0.15 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **54** as a colourless oil (53 mg, 75%), and as a mixture of two inseparable diastereomers in 1:1 ratio.

IR (neat) ν_{max} 2978, 1721, 1485, 1394, 1244, 1104, 752, 698 cm^{-1}.

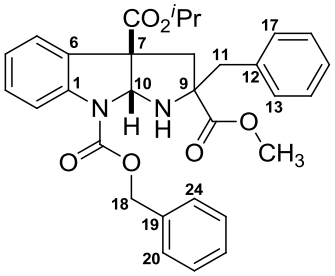
^1H NMR (500 MHz, toluene-d_8, 363 K) δ 8.08-7.83 (2H, m), 7.35-7.23 (6H, m), 7.19-6.98 (8H, m), 6.93-6.79 (2H, m) [aromatics], 6.32 (1H, s, *H*-10), 6.26 (1H, s, *H*-10'), 5.35-5.23 (2H, m, *H*-14), 5.12-5.01 (2H, m, *H*-14'), 4.97-4.85 (2H, m, OC*H*$(CH_3)_2$), 3.64 (1H, br s, N*H*), 3.45 (3H, s, OCH_3), 3.36 (1H, d, *J* 13.3, *H*-8a), 2.99 (3H, s, OCH_3'), 2.90 (1H, d, *J* 12.9, *H*-8a'), 2.59 (1H, d, *J* 12.9, *H*-8b), 2.13-2.09 (1H, m, *H*-8b'), 1.88-1.74 (2H, m, *H*-11),

1.03-0.95 (12H, m, OCH(CH_3)$_2$), 0.83 (6H, dd, *J* 16.1, 6.9, *H*-12,13), 0.74 (6H, dd, *J* 14.9, 6.9, *H*-12',13').

^{13}C NMR (126 MHz, toluene-d$_8$) δ 175.7, 174.7, 171.3, 171.1 (*C*O$_2^i$Pr, *C*O$_2$Me), 153.9, 152.1 (*C*O$_2$Bn), 142.9, 141.8, 137.2, 137.0, 132.5, 132.0, 131.1, 129.5, 129.2, 128.5, 127.6, 125.4, 124.3, 123.9, 123.2, 123.1, 115.7, 114.8 [aromatics], 82.0, 81.1 (*C*-10), 73.0, 72.5 (*C*-9), 69.2, 69.1 (O*C*H(CH$_3$)$_2$), 67.0, 66.8 (*C*-14), 61.2, 61.1 (*C*-7), 51.7, 51.3 (O*C*H$_3$), 44.9, 44.2 (*C*-8), 37.2, 35.4 (*C*-11), 21.4, 21.3 (OCH(*C*H$_3$)$_2$), 18.0, 18.0 (*C*-12,13).

m/z LRMS (ESI$^+$) 503.2 [M+Na]$^+$; HRMS (ESI$^+$) 503.2131 ([M+Na]$^+$, $C_{27}H_{32}N_2O_6Na$ requires 503.2153).

(3a*R,8a*R**)-8-Benzyl 3a-isopropyl 2-methyl 2-benzyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(8a*H*)-tricarboxylate (55)**



This compound was prepared by Dr Matija Gredičak according to general procedure I, using isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate **9** (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-isocyano-3-phenylpropanoate **33** (28 mg, 0.15 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded pyrroloindoline **55**

as a colourless oil (36 mg, 53%), and as a mixture of two inseparable diastereomers in 1:1 ratio.

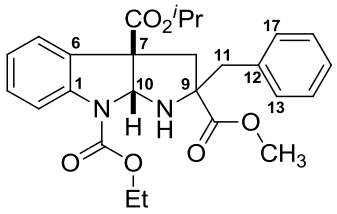
IR (neat) ν_{max} 2981, 1719, 1599, 1486, 1242, 1104, 747, 699 cm^{-1}.

^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.22-7.86 (2H, m), 7.26 (5H, ddd, *J* 23.2, 11.1, 7.1), 7.16-6.96 (19H, m), 6.91-6.83 (1H, m), 6.79 (1H, t, *J* 7.5) [aromatics], 6.32 (1H, s, *H*-10), 6.29 (1H, s, *H*-10'), 5.22 (2H, dd, *J* 31.4, 12.3, *H*-18), 5.08-4.96 (2H, m, H-18'), 4.95-4.80 (2H, m, OC*H*$(CH_3)_2$), 3.66 (2H, br s, N*H*), 3.36 (3H, s, OCH_3), 3.06-2.92 (4H, m, *), 2.88 (3H, s, OCH_3'), 2.81-2.71 (1H, m, *), 2.70-2.61 (1H, m, *), 2.57 (1H, d, *J* 13.2, *), 2.20-2.14 (1H, m, *), 0.97 (12H, dd, *J* 5.5, 3.7, OCH(C$H_3)_2$). *Eight unassigned protons correspond to *H*-8 and *H*-11.

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 174.7, 174.4, 170.7, 170.5 (*C*$O_2{}^{i}$Pr, *C*O_2Me), 152.4 (*C*O_2Bn), 142.4, 141.4, 136.8, 136.7, 136.6, 136.5, 132.5, 130.8, 129.5, 129.5, 129.1, 128.9, 127.9, 127.8, 124.0, 123.4, 122.6, 122.6, 115.4, 114.5 [aromatics†], 81.8, 81.3 (*C*-10), 70.3, 70.0 (*C*-9), 68.8, 68.6 (O*C*H$(CH_3)_2$), 66.9, 66.8 (*C*-18), 60.8 (*C*-7), 51.0, 50.7 (O*C*H_3), 46.4, 46.3, 46.1, 45.1 (*C*-8, *C*-11), 20.9, 20.8 (OCH(*C*$H_3)_2$). †Remaining aromatic signals are buried under toluene peaks.

m/z LRMS (ESI^+) 551.2 $[M+Na]^+$; HRMS (ESI^+) 551.2143 ($[M+Na]^+$, $C_{31}H_{32}N_2O_6Na$ requires 551.2153).

(3a*R,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-benzyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(8a*H*)-tricarboxylate (56)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (50 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyano-3-phenylpropanoate **33** (34 mg, 0.18 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded pyrroloindoline **56** as a colourless oil (61 mg, 72%), and as a mixture of two inseparable diastereomers in 1:1 ratio.

IR (neat) ν_{max} 2981, 1719, 1599, 1486, 1242, 1093, 750, 702 cm^{-1}.

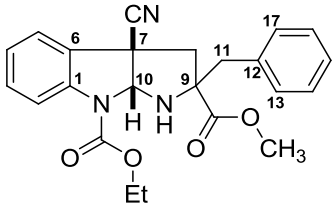
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.04 (1H, app. s), 7.85 (1H, app. s), 7.28 (2H, d, *J* 7.6), 7.17-6.96 (12H, m), 6.88 (1H, t, *J* 7.5), 6.81 (1H, t, *J* 7.5) [aromatics], 6.29 (1H, s, *H*-10), 6.26 (1H, s, *H*-10'), 4.96-4.83 (2H, m, OC*H*$(CH_3)_2$), 4.24-4.11 (2H, m, OCH_2CH_3), 4.10-3.98 (2H, m, OCH_2CH_3'), 3.58 (2H, br s, N*H*), 3.39 (3H, s, OCH_3), 3.05- 2.95 (4H, m, *), 2.94 (3H, s, OCH_3'), 2.81 (1H, d, *J* 13.1, *), 2.68 (1H, d, *J* 12.9, *), 2.60 (1H, d, *J* 13.2, *), 2.21 (1H, d, *J* 13.2, *), 1.11-1.05 (6H, m, OCH_2CH_3), 1.01-0.94 (12H, m, $OCH(CH_3)_2$). *Eight unassigned protons correspond to *H*-8 and *H*-11.

^{13}C NMR (500 MHz, toluene-d_8, 363 K) δ 175.3, 175.0, 171.3, 171.2 (CO_2^{i}Pr, CO_2Me), 152.5 (CO_2Et), 137.5, 137.4, 137.1, 130.1, 130.1, 129.6, 129.4, 128.4, 128.3, 127.1, 127.1, 124.6, 124.0, 123.0, 122.9, 115.9, 115.0 [aromatics†], 82.2, 81.8 (*C*-10), 70.8, 70.5 (*C*-9), 69.3, 69.2 ($OCH(CH_3)_2$), 61.5 (OCH_2CH_3), 61.3, 61.2 (*C*-7), 51.6, 51.2 (OCH_3), 47.1, 46.8, 46.7, 45.8

(*C*-8, *C*-11), 21.5, 21.4 (OCH(CH_3)$_2$), 14.6, 14.6 (OCH_2CH_3). †Remaining aromatic signals are buried under toluene peaks.

m/z LRMS (ESI^+) 489.2 $[M+Na]^+$; HRMS (ESI^+) 489.1986 ($[M+Na]^+$, $C_{26}H_{30}N_2O_6Na$ requires 489.1996).

(3a*R,8a*R**)-8-Ethyl 2-methyl 2-benzyl-3a-cyano-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,8(2*H*)-dicarboxylate (57)**



This compound was prepared according to general procedure I, using ethyl (2-(1-cyanovinyl)phenyl)carbamate **26** (39 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyano-3-phenylpropanoate **33** (34 mg, 0.18 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [5:1]) afforded the pyrroloindoline **57** as a colourless oil (35 mg, 48%), and as a mixture of two inseparable diastereomers in 3.3:1 ratio (DS1:DS2).

IR (neat) ν_{max} 2274, 2120, 1729, 1570, 1488, 1387, 1331, 1050, 840, 821, 754 cm^{-1}.

^1H NMR (500 MHz, toluene-d_8, 363 K) δ 7.98 (2H, app. s, $Ar_{DS1,DS2}$), 7.27 (2H, app. s, $Ar_{DS1,DS2}$), 7.14 (1H, app. s, Ar_{DS1}), 6.90 (2H, d, *J* 7.2, Ar_{DS1}), 6.81 (1H, t, *J* 7.5, Ar_{DS2}), 6.71 (1H, t, *J* 7.4, Ar_{DS1}), ‡, 5.91 (1H, s, *H*-10_{DS2}), 5.67 (1H, s, *H*-10_{DS1}), 4.20-3.94 (2H, m, $OCH_2CH_{3\ DS1}$), 3.92-3.74 (2H, m, $OCH_2CH_{3\ DS2}$), 3.49 (2H, br s, $NH_{\ DS1,DS2}$), 3.42 (3H, s,

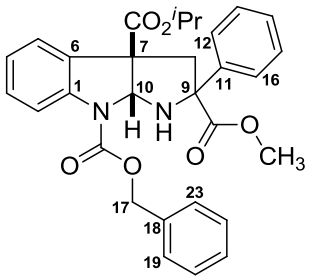
OC$H_{3\ DS2}$), 2.98-2.89 (2H, m, †), 2.85-2.71 (5H, m, OCH_3, *), 2.67 (1H, d, *J* 12.9, *), 2.43 (1H, d, *J* 12.9, *), 2.13 (1H, d, *J* 13.0, †), 1.90 (1H, d, *J* 13.1, †), 1.10-0.93 (6H, m, $OCH_2CH_{3\ DS1,DS2}$).

‡Remaining aromatic signals are buried under toluene peaks. †Four unassigned protons correspond to *H*-8_{DS2} and *H*-11_{DS2}. *Four unassigned protons correspond to *H*-8_{DS1} and *H*-11_{DS1}.

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 174.3, 174.0 (*C*O_2Me), 151.5 (*C*O_2Et), 137.3, 137.2, 136.5, 136.1, 129.7, 129.7, 129.2, 128.5, 128.5, 128.2, 127.4, 125.4, 124.1, 123.6, 123.5, 115.8, 114.9 [aromatics**], 120.6, 120.4 (*C*N), 82.8, 82.2 (*C*-10), 70.8, 69.8 (*C*-9), 62.2, 61.5 (O*C*H_2CH_3), 52.1, 51.5 (O*C*H_3), 48.7, 48.6 (*C*-8), 48.3, 47.5 (*C*-7), 46.0, 44.6 (*C*-11), 14.5, 14.4 (OCH_2CH_3). **Remaining aromatic signals are buried under toluene peaks.

m/z LRMS (ESI^+) 428.2 $[M+Na]^+$; HRMS (ESI^+) 428.1582 ($[M+Na]^+$, $C_{23}H_{23}N_3O_4Na$ requires 428.1586).

(3a*R,8a*R**)-8-Benzyl 3a-isopropyl 2-methyl 2-phenyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(8a*H*)-tricarboxylate (58)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate **9** (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-isocyano-2-phenylacetate **35** (26 mg, 0.15 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded pyrroloindoline **58** as a colourless oil (38 mg, 51%), and as a mixture of two inseparable diastereomers in 1:1 ratio.

IR (neat) ν_{max} 2981, 1724, 1486, 1244, 1104, 752, 698 cm^{-1}.

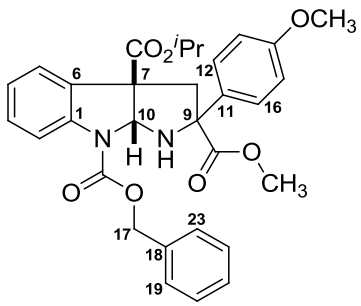
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.09-7.73 (2H, m), 7.49-7.25 (10H, m), 7.19-6.93 (14H, m), 6.87 (1H, t, *J* 7.5), 6.78 (1H, t, *J* 7.5) [aromatics], 6.46 (1H, s, *H*-10), 6.44 (1H, s, *H*-10'), 5.34-5.23 (2H, m, *H*-17), 5.16-5.06 (2H, m, *H*-17'), 4.99-4.83 (2H, m, OC*H*$(CH_3)_2$), 4.13 (2H, br s, N*H*), 3.78 (1H, d, *J* 13.0, *H*-8a), 3.43 (1H, d, *J* 12.8, *H*-8a'), 3.35 (3H, s, OCH_3), 2.98 (3H, s, OCH_3'), 2.78 (1H, d, *J* 12.8, *H*-8b), 2.45 (1H, d, *J* 13.0, *H*-8b'), 1.08-1.04 (6H, m, OCH(CH_3)$_2$), 0.96-0.92 (6H, m, OCH(CH_3)$_2$').

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 174.4, 174.3, 170.9, 170.7 (*C*$O_2{}^i$Pr, *C*O_2Me), 152.3, 152.1 (*C*O_2Bn), 141.8, 141.5, 137.2, 136.9, 131.7, 130.7, 129.7, 129.6, 129.2, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 125.9, 125.5, 125.4, 124.5, 124.2, 123.4, 123.2, 115.7, 114.9 [aromatics†], 81.7, 80.4 (*C*-10), 71.6, 71.5 (*C*-9), 69.3, 69.2 (O*C*H$(CH_3)_2$), 67.2,

67.0 (*C*-17), 60.6 (*C*-7), 52.3, 52.1 (O*C*H_3), 48.9, 48.2 (*C*-8), 21.4, 21.3 (OCH(*C*H_3)$_2$). †Remaining aromatic signals are buried under toluene peaks.

m/z LRMS (ESI$^+$) 537.2 [M+Na]$^+$; HRMS (ESI$^+$) 537.1993 ([M+Na]$^+$, $C_{30}H_{30}N_2O_6Na$ requires 537.1996).

(3a*R,8a*R**)-8-Benzyl 3a-isopropyl 2-methyl 2-(4-methoxyphenyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(8a*H*)-tricarboxylate (59)**



This compound was prepared by Dr Matija Gredičak according to general procedure I, using isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate **9** (41 mg, 0.12 mmol) as the Michael acceptor, methyl 2-isocyano-2-(4-methoxyphenyl)acetate **38** (25 mg, 0.12 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded pyrroloindoline **59** as a colourless oil (41 mg, 62%), and as a mixture of two inseparable diastereomers in 1:1 ratio.

IR (neat) ν_{max} 2971, 1728, 1486, 1351, 1249, 1105, 1037, 752 cm^{-1}.

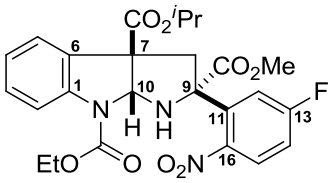
^{1}H NMR (500 MHz, toluene-d$_8$, 363 K) δ 8.02-7.82 (2H, m), 7.42-7.26 (8H, m), 7.19-6.99 (8H, m), 6.89 (2H, dd, *J* 13.8, 6.3), 6.81 (2H, dt, *J* 15.0, 7.7), 6.72-6.66 (2H, m), 6.62-6.56

(2H, m) [aromatics], 6.46 (1H, s, *H*-10), 6.44 (1H, s, *H*-10'), 5.29 (2H, d, *J* 12.3, *H*-17), 5.21-5.09 (2H, m, *H*-17'), 5.00-4.85 (2H, m, OC*H*$(CH_3)_2$), 4.12 (2H, br s, N*H*), 3.77 (1H, d, *J* 13.1, *H*-8a), 3.43 (1H, d, *J* 12.8, *H*-8a'), 3.39 (3H, s, CO_2CH_3), 3.38 (3H, s, ArOCH_3), 3.35 (3H, s, ArOCH_3'), 3.00 (3H, s, CO_2CH_3'), 2.79 (1H, d, *J* 12.8, *H*-8b), 2.46 (1H, d, *J* 13.1, *H*-8b'), 1.09-1.04 (6H, m, OCH(CH_3)$_2$), 0.97-0.94 (6H, m, OCH(CH_3)$_2$').

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 174.0, 171.0, 170.8 (*C*$O_2{}^i$Pr, *C*O_2Me), 159.2, 159.0 (*C*-14), 152.1 (*C*O_2Bn), 136.4, 132.4, 129.6, 129.2, 128.8, 128.7, 128.6, 128.4, 128.2, 127.0, 126.7, 126.4, 124.2, 123.9, 123.5, 123.1, 115.1, 114.3, 113.8, 113.6 [aromatics*], 80.9, 79.9 (*C*-10), 70.6, 70.5 (*C*-9), 69.6, 69.5 (O*C*H$(CH_3)_2$), 67.3, 67.1 (*C*-17), 61.0 (*C*-7), 55.3, 55.3 (ArO*C*H_3), 52.9, 52.5 (CO_2CH_3), 47.9, 47.4 (*C*-8), 21.6, 21.6 (OCH(*C*H_3)$_2$). *Remaining aromatic signals not observed due to low resolution of spectrum and signal overlapping.

m/z LRMS (ESI^+) 567.2 $[M+Na]^+$; HRMS (ESI^+) 567.2117 ($[M+Na]^+$, $C_{31}H_{32}N_2O_7Na$ requires 567.2107).

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (60)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (100 mg, 0.36 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (86 mg, 0.36 mmol) as the isocyanide

and potassium carbonate (250 mg, 1.8 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **60** as a yellow oil (110 mg, 57%), and as a single diastereomer.

IR (neat) ν_{max} 2972, 2212, 1729, 1533, 1487, 1387, 1257, 1104, 1046, 840, 821 cm^{-1}.

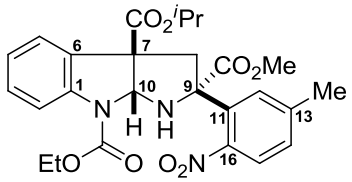
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 7.85 (1H, app. s), 7.68 (1H, d, *J* 9.0), 7.31 (1H, d, *J* 7.2), 7.29-7.20 (1H, m), 7.16-7.07 (1H, m), 6.87 (1H, t, *J* 7.5), 6.45-6.38 (1H, m) [aromatics], 6.33 (1H, s, *H*-10), 4.87 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.22-4.04 (2H, m, OC*H*$_2CH_3$), 3.99 (1H, br s, N*H*), 3.55 (1H, d, *J* 13.9, *H*-8), 3.13 (3H, s, CO_2CH_3), 3.09 (1H, d, *J* 13.9, *H*-8'), 1.12 (3H, t, *J* 7.1, OCH_2CH_3), 0.97 (3H, d, *J* 6.3, OCH$(CH_3)_2$), 0.91 (3H, d, *J* 6.3, OCH$(CH_3)_2$').

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 171.6 (CO_2Me), 170.2 ($CO_2{}^{i}$Pr), 164.0 (d, *J* 254.3, *C*-13), 152.5 (CO_2Et), 145.0, 141.8, 140.9, 131.3 (d, *J* 9.3), 129.4, 127.0 (d, *J* 9.5), 123.5, 122.8, 115.5 (d, *J* 26.0), 114.6 (d, *J* 24.0), 114.6 [aromatics], 82.4 (*C*-10), 71.1 (*C*-9), 69.1 (O*C*H$(CH_3)_2$), 61.3 (*C*-7), 60.9 (O*C*H_2CH_3), 51.7 (CO_2CH_3), 48.3 (*C*-8), 20.5 (OCH$(CH_3)_2$), 14.0 (OCH_2CH_3).

^{19}F NMR (377 MHz, toluene-d_8, $\{^{1}H\}$) δ −104.7.

m/z LRMS (ESI^+) 538.2 $[M+Na]^+$; HRMS (ESI^+) 538.1591 ($[M+Na]^+$, $C_{25}H_{26}FN_3O_8Na$ requires 538.1602).

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-(5-methyl-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (61)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (50 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyano-2-(5-methyl-2-nitrophenyl)acetate **43** (42 mg, 0.18 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 18 h. Column chromatography (petrol:ethyl acetate [7:2]) afforded the pyrroloindoline **61** as a yellow oil (64 mg, 70%), and as a single diastereomer.

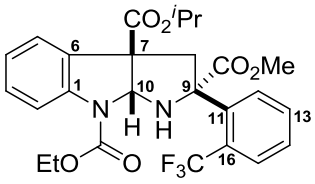
IR (neat) ν_{max} 2982, 1722, 1523, 1486, 1346, 1239, 1103, 830, 754 cm^{-1}.

^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 7.88 (1H, app. s), 7.66 (1H, app. s), 7.35 (1H, d, *J* 7.5), 7.31-7.24 (1H, m), 7.14-7.11 (1H, m), 6.87 (1H, t, *J* 7.4), 6.61 (1H, d, *J* 8.2) [aromatics], 6.40 (1H, s, *H*-10), 4.87 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.24-4.03 (3H, m, OC*H*$_2$CH$_3$, N*H*), 3.61 (1H, d, *J* 13.7, *H*-8), 3.21-3.13 (4H, m, *H*-8', CO_2CH_3), 1.98 (3H, s, ArCH_3), 1.15 (3H, t, *J* 7.1, OCH_2CH_3), 0.97 (3H, d, *J* 6.3, OCH$(CH_3)_2$), 0.91 (3H, d, *J* 6.3, OCH$(CH_3)_2$').

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 172.8 (CO_2Me), 170.3 ($CO_2{}^i$Pr), 152.5 (CO_2Et), 147.3, 142.2, 142.0, 139.1, 136.5, 131.4, 129.4, 126.8, 123.6, 122.8, 122.5, 114.6 [aromatics], 82.2 (*C*-10), 71.2 (*C*-9), 68.9 (O*C*H$(CH_3)_2$), 61.3 (*C*-7), 60.9 (OCH_2CH_3), 51.6 (CO_2CH_3), 48.4 (*C*-8), 20.7 (OCH$(CH_3)_2$), 20.5 (ArCH_3), 14.0 (OCH_2CH_3).

m/z LRMS (ESI$^+$) 534.2 [M+Na]$^+$; HRMS (ESI$^+$) 534.1855 ([M+Na]$^+$, $C_{26}H_{29}N_3O_8Na$ requires 534.1852).

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-(2-(trifluoromethyl)phenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (62)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (60 mg, 0.22 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-(trifluoromethyl)phenyl)acetate **36** (53 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 18 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **62** as a colourless oil (73 mg, 65%), and as single diastereomer.

IR (neat) ν_{max} 1731, 1564, 1487, 1311, 1244, 1105, 909 cm^{-1}.

^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.00-7.78 (2H, m), 7.51 (1H, d, *J* 7.7), 7.36 (1H, d, *J* 7.5), 7.16-7.06 (2H, m), 6.95 (1H, t, *J* 7.4), 6.88 (1H, t, *J* 7.4) [aromatics], 6.45 (1H, s, *H*-10), 4.85 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 4.25-4.05 (3H, m, OC*H*$_2$CH$_3$, N*H*), 3.59 (1H, d, *J* 13.6, *H*-8), 3.14 (3H, s, CO_2CH_3), 3.07 (1H, d, *J* 13.6, *H*-8'), 1.14 (3H, t, *J* 7.1, OCH_2CH_3), 0.96 (3H, d, *J* 6.2, OCH$(CH_3)_2$), 0.88 (3H, d, *J* 6.2, OCH$(CH_3)_2$').

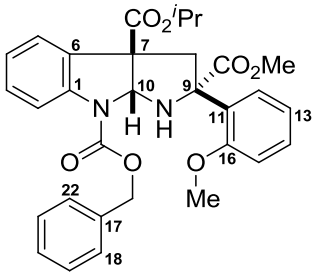
^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 172.8 (CO_2Me), 170.3 ($CO_2{}^{i}$Pr), 152.6 (CO_2Et), 142.0, 141.5, 131.7, 131.4, 129.1, 128.8, 127.5, 127.3, 123.5, 122.7, 114.6 [aromatics*], 124.6 (q, *J* 273.3, CF_3), 82.1 (*C*-10), 71.7 (*C*-9), 68.8 (OCH$(CH_3)_2$), 61.2 (OCH_2CH_3), 60.9 (*C*-7), 51.5 (CO_2CH_3), 48.5 (*C*-8), 20.8 (OCH$(CH_3)_2$), 20.7 (OCH$(CH_3)_2$'), 14.0 (OCH_2CH_3).

*Remaining aromatic signal is buried under toluene peaks.

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ −55.6.

m/z LRMS (ESI^+) 521.2 $[M+H]^+$; HRMS (ESI^+) 521.1877 ($[M+H]^+$, $C_{26}H_{28}F_3N_2O_6$ requires 521.1899).

(2*S,3a*R**,8a*R**)-8-Benzyl 3a-isopropyl 2-methyl 2-(2-methoxyphenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (63)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate **9** (70 mg, 0.21 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-methoxyphenyl)acetate **37** (43 mg, 0.21 mmol) as the isocyanide and potassium carbonate (140 mg, 1.0 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **63** as a colourless oil (55 mg, 49%), and as a single diastereomer.

IR (neat) ν_{max} 1728, 1602, 1480, 1352, 1247, 1105, 906 cm^{-1}.

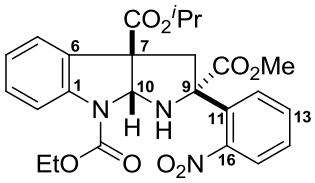
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 7.96 (1H, app. s, *H*-2), 7.59 (1H, d, *J* 7.6, *H*-12), 7.42 (1H, d, *J* 7.5, *H*-5), 7.32 (2H, d, *J* 7.4, *H*-18,22), 7.20-6.98 (5H, m, *H*-3,14,19,20,21), 6.87 (1H, t, *J* 7.5, *H*-4), 6.80 (1H, t, *J* 7.5, *H*-13), 6.59-6.47 (2H, m, *H*-10,15), 5.36-5.22 (1H, m, OCH_2Ph), 5.20-5.07 (1H, m, OCH_2Ph'), 4.86 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 4.41 (1H, br s,

N*H*), 3.61 (1H, d, *J* 13.1, *H*-8), 3.31 (3H, s, ArOCH_3), 3.04 (3H, s, CO_2CH_3), 2.99 (1H, d, *J* 13.1, *H*-8'), 0.96 (3H, d, *J* 6.2, OCH(CH_3)$_2$), 0.90 (3H, d, *J* 6.2, OCH(CH_3)$_2$').

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 173.6 (*C*O_2Me), 170.7 (*C*$O_2{}^i$Pr), 157.2 (*C*-16), 152.5 (*C*O_2Bn), 144.2, 142.3, 136.7, 131.9, 128.7, 128.4, 128.2, 127.9, 127.7, 126.7, 123.7, 122.6, 120.8, 114.7, 111.7 [aromatics], 81.9 (*C*-10), 69.8 (*C*-9), 68.6 (O*C*H(CH$_3$)$_2$), 67.0 (O*C*H$_2$Ph), 60.9 (*C*-7), 54.9 (ArO*C*H$_3$), 51.0 (CO_2CH_3), 46.8 (*C*-8), 20.9 (OCH(*C*H$_3$)$_2$).

m/z LRMS (ESI$^+$) 567.2 [M+Na]$^+$; HRMS (ESI$^+$) 567.2104 ([M+Na]$^+$, $C_{31}H_{32}N_2O_7Na$ requires 567.2107).

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-(2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (64)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate **8** (50 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-nitrophenyl)acetate **39** (40 mg, 0.18 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **64** as a yellow oil (37 mg, 41%), and as a mixture of two inseparable diastereomers in 4.5:1 ratio (DS1:DS2).

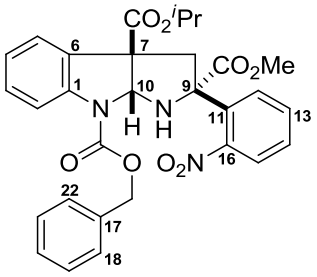
IR (neat) ν_{max} 1730, 1570, 1533, 1487, 1387, 1245, 1044, 840, 821, 753 cm^{-1}.

^{1}H NMR (500 MHz, toluene-d_8, 363K) δ 7.87 (1H, app. s, Ar_{DS1}), 7.69 (1H, d, *J* 8.0, Ar_{DS1}), 7.56 (1H, d, *J* 7.8, Ar_{DS2}), 7.40 (1H, d, *J* 8.0, Ar_{DS2}), 7.33 (1H, d, *J* 7.6, Ar_{DS1}), 7.27-7.19 (2H, m, $Ar_{DS1,DS2}$), 6.87 (1H, t, *J* 7.5, Ar_{DS1}), 6.84-6.75 (3H, m, $Ar_{DS1,DS2,DS2}$), 6.71 (1H, t, *J* 7.7, Ar_{DS2}), *, 6.45 (1H, s, *H*-10_{DS2}), 6.35 (1H, s, *H*-10_{DS1}), 4.99 (1H, sep, *J* 6.3, OC*H*$(CH_3)_{2\ DS2}$), 4.87 (1H, sep, *J* 6.2, OC*H*$(CH_3)_{2\ DS1}$), 4.25-4.02 (5H, m, OC*H*$_2$CH$_{3\ DS1,DS2}$, N*H* $_{DS1}$), 3.97 (1H, d, *J* 13.7, *H*-8_{DS2}), 3.78 (1H, br s, N*H* $_{DS2}$), 3.55 (1H, d, *J* 13.7, *H*-8_{DS1}), 3.40 (3H, s, CO_2CH_3 $_{DS2}$), 3.16-3.12 (4H, m, *H*-8'$_{DS1}$, $CO_2CH_{3\ DS1}$), 2.53 (1H, d, *J* 13.7, *H*-8'$_{DS2}$), 1.18-1.12 (6H, m, $OCH_2CH_{3\ DS1,DS2}$), 0.98 (6H, *J* 6.3, OCH(C*H*$_3)_{2\ DS1,DS2}$), 0.92 (6H, *J* 6.3, OCH(C*H*$_3)_2$' $_{DS1,DS2}$). *Remaining aromatic signals are buried under toluene peaks.

^{13}C NMR (126 MHz, toluene-d_8, 363K) δ 172.3, 172.1 (*C*O_2Me), 170.2, 170.2 (*C*$O_2{}^i$Pr), 152.5 (*C*O_2Et), 149.4, 148.9, 142.0, 142.0, 137.3, 136.6, 136.2, 131.2, 131.1, 129.0, 128.9, 128.3, 127.9, 124.2, 123.6, 123.2, 122.8, 122.5, 115.2, 114.6 [aromatics*], 82.1, 81.1 (*C*-10), 71.1, 70.5 (*C*-9), 69.0, 68.9 (O*C*H$(CH_3)_2$), 61.1, 61.1 (O*C*H_2CH_3), 60.9, 60.8 (*C*-7), 51.7, 51.6 (CO_2CH_3), 48.4, 47.2 (*C*-8), 21.0, 20.9 (OCH(*C*$H_3)_2$), 20.9, 20.8 (OCH(*C*$H_3)_2$'), 14.0, 14.0 (OCH_2CH_3). *Remaining aromatic signals are buried under toluene peaks.

m/z LRMS (ESI$^+$) 520.2 [M+Na]$^+$; HRMS (ESI$^+$) 520.1687 ([M+Na]$^+$, $C_{25}H_{27}N_3O_8Na$ requires 520.1696).

(2*S,3a*R**,8a*R**)-8-Benzyl 3a-isopropyl 2-methyl 2-(2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (65)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate **9** (70 mg, 0.21 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-nitrophenyl)acetate **39** (45 mg, 0.21 mmol) as the isocyanide and potassium carbonate (140 mg, 1.0 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **65** as a yellow oil (66 mg, 57%), and as a mixture of two inseparable diastereomers in 4.0:1 ratio (DS1:DS2).

IR (neat) ν_{max} 1725, 1600, 1530, 1486, 1394, 1351, 1246, 1134, 1104, 910 cm^{-1}.

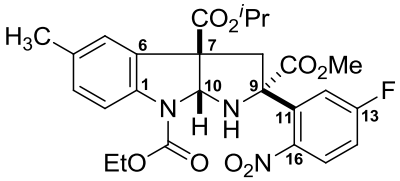
^{1}H NMR (500 MHz, toluene-d_8, 363K) δ 7.89 (1H, app. s, Ar_{DS1}), 7.72-7.62 (1H, m, Ar_{DS1}), 7.52 (1H, d, *J* 7.7, Ar_{DS2}), 7.41 (1H, d, *J* 7.9, Ar_{DS2}), 7.35-7.26 (5H, m, $Ar_{DS1,DS2}$), 7.25-6.94 (12H, m, $Ar_{DS1,DS2}$), 6.86 (1H, t, *J* 7.5, Ar_{DS1}), 6.83-6.73 (3H, m, $Ar_{DS1,DS2,DS2}$), 6.68 (1H, t, *J* 7.7, Ar_{DS2}), 6.47 (1H, s, *H*-10_{DS2}), 6.40 (1H, s, *H*-10_{DS1}), 5.30-5.05 (4H, m, $OCH_2Ph_{DS1,DS2}$), 5.02-4.94 (1H, m, $OCH(CH_3)_{2\ DS2}$), 4.86 (1H, sep, *J* 6.2, $OCH(CH_3)_{2\ DS1}$), 4.12-3.91 (2H, m, NH_{DS1}, *H*-8_{DS2}), 3.71 (1H, br s, NH_{DS2}), 3.56 (1H, d, *J* 13.7, *H*-8_{DS1}), 3.36 (3H, s, $CO_2CH_{3\ DS2}$), 3.21-3.04 (4H, m, *H*-8'$_{DS1}$, $CO_2CH_{3\ DS1}$), 2.52 (1H, d, *J* 13.7, *H*-8'$_{DS2}$), 1.07-0.88 (12H, m, $OCH(CH_3)_{2\ DS1,DS2}$).

^{13}C NMR (126 MHz, toluene-d_8, 363K) δ 172.1, 172.0 (CO_2Me), 170.1, 170.1 ($CO_2{}^i$Pr), 152.4 (CO_2Bn), 149.3, 148.9, 142.4, 142.3, 137.3, 136.8, 136.5, 136.3, 131.1, 131.1, 129.1,

129.0, 128.2, 128.0, 127.9, 127.8, 124.2, 123.6, 123.3, 122.9, 122.7, 115.3, 114.6 [aromatics*], 82.2, 81.1 (*C*-10), 71.1, 70.5 (*C*-9), 69.0, 68.9 (O*C*H(CH_3)$_2$), 67.2 (O*C*H_2Ph), 60.9, 60.8 (*C*-7), 51.6, 51.5 (CO_2*C*H_3), 48.2, 47.0 (*C*-8), 21.0, 20.8 (OCH(*C*H_3)$_2$), 20.9, 20.7 (OCH(*C*H_3)$_2$'). *Remaining aromatic signals are buried under toluene peaks.

m/z LRMS (ESI$^+$) 582.2 [M+Na]$^+$; HRMS (ESI$^+$) 582.1850 ([M+Na]$^+$, $C_{30}H_{29}N_3O_8Na$ requires 582.1852).

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-5-methyl-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (66)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)-5-methylphenyl)acrylate **21** (60 mg, 0.21 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (49 mg, 0.21 mmol) as the isocyanide and potassium carbonate (140 mg, 1.0 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **66** as a yellow oil (41 mg, 38%), and as a single diastereomer.

IR (neat) ν_{max} 1724, 1588, 1533, 1395, 1362, 1260, 1108, 906 cm^{-1}.

^{1}H NMR (500 MHz, toluene-d$_8$, 363 K) δ 7.87-7.66 (2H, m, *H*-2,15), 7.23-7.04 (2H, m, *H*-5,14), 7.04-6.98 (1H, m, *H*-12), 6.93 (1H, d, *J* 8.3, *H*-3), 6.33 (1H, s, *H*-10), 4.88 (1H, sep,

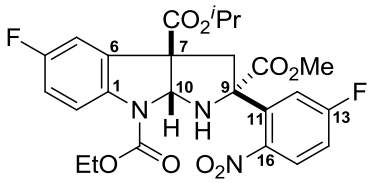
J 6.2, OC*H*(CH_3)$_2$), 4.27-3.94 (3H, m, OC$H_2$$CH_3$, N*H*), 3.58 (1H, d, *J* 14.1, *H*-8), 3.16 (3H, s, CO_2CH_3), 3.12 (1H, d, *J* 14.1, *H*-8'), 2.16 (3H, s, ArCH_3), 1.13 (3H, t, *J* 7.0, OCH_2CH_3), 0.99 (3H, d, *J* 6.2, OCH(CH_3)$_2$), 0.92 (3H, d, *J* 6.2, OCH(CH_3)$_2$').

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 171.6 (*C*O_2Me), 170.3 (*C*O_2^{i}Pr), 164.0 (d, *J* 256.1, *C*-13), 152.8 (*C*O_2Et), 145.0 (*C*-1), 141.3 (*C*-16), 141.2 (*C*-6), 132.3 (*C*-4), 131.4 (d, *J* 9.0, *C*-11), 129.6 (*C*-3), 127.1 (d, *J* 9.5, *C*-15), 124.0 (*C*-5), 115.6 (d, *J* 26.1, *C*-12), 114.7 (d, *J* 23.7, *C*-14), 114.6 (*C*-2), 82.6 (*C*-10), 71.1 (*C*-9), 69.0 (O*C*H(CH_3)$_2$), 61.2 (*C*-7), 60.9 (O*C*$H_2$$CH_3$), 51.7 ($CO_2$*C*$H_3$), 48.3 (*C*-8), 20.9 (OCH(*C*H_3)$_2$), 20.7 (Ar*C*H_3), 14.0 (OCH_2*C*H_3).

^{19}F NMR (377 MHz, toluene-d_8, {^{1}H}) δ −104.2.

m/z LRMS (ESI$^+$) 552.2 [M+Na]$^+$; HRMS (ESI$^+$) 552.1749 ([M+Na]$^+$, $C_{26}H_{28}FN_3O_8Na$ requires 552.1758).

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 5-fluoro-2-(5-fluoro-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (67)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)-5-fluorophenyl)acrylate **22** (60 mg, 0.20 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (48 mg, 0.20 mmol) as the isocyanide and potassium carbonate (140 mg, 1.0 mmol) as the base. Reaction time was 24 h.

Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **67** as a yellow oil (41 mg, 38%), and as a single diastereomer.

IR (neat) ν_{max} 1729, 1624, 1544, 1491, 1262, 1080, 909 cm^{-1}.

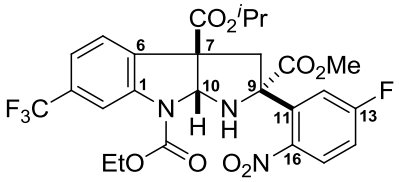
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 7.78-7.63 (2H, m), 7.29-7.22 (1H, m), 7.13-7.08 (1H, m), 6.79 (1H, td, *J* 8.9, 2.7), 6.44-6.38 (1H, m) [aromatics], 6.30 (1H, s, *H*-10), 4.84 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.18-3.99 (2H, m, OC*H*$_2CH_3$), 3.96 (1H, br s, N*H*), 3.51 (1H, d, *J* 14.0, *H*-8), 3.14 (3H, s, CO_2CH_3), 2.99 (1H, d, *J* 14.0, *H*-8'), 1.10 (3H, t, *J* 7.1, OCH_2CH_3), 0.95 (3H, d, *J* 6.3, OCH(C*H*$_3)_2$), 0.90 (3H, d, *J* 6.3, OCH(C*H*$_3)_2$').

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 171.5 (CO_2Me), 169.7 ($CO_2{}^{i}$Pr), 164.0 (d, *J* 254.2, *C*-13), 159.2 (d, *J* 241.3, *C*-4), 152.3 (CO_2Et), 145.0, 141.6, 140.7 (d, *J* 9.7), 132.6 (d, *J* 9.1), 127.0 (d, *J* 9.4), 115.4 (d, *J* 25.9), 115.3 (d, *J* 22.8), 115.3 (app. br s), 114.7 (d, *J* 23.4), 111.0 (d, *J* 24.7) [aromatics], 82.7 (*C*-10), 71.0 (*C*-9), 69.4 (O*C*H$(CH_3)_2$), 61.4 (*C*-7), 60.7 (O*C*H_2CH_3), 51.7 (CO_2CH_3), 48.3 (*C*-8), 20.8 (OCH(*C*$H_3)_2$), 20.7 (OCH(*C*$H_3)_2$'), 14.0 (OCH_2CH_3).

^{19}F NMR (470 MHz, toluene-d_8, {^{1}H}, 363 K) δ −104.6, −119.8.

m/z LRMS (ESI^+) 556.2 $[M+Na]^+$; HRMS (ESI^+) 556.1510 ($[M+Na]^+$, $C_{25}H_{25}F_2N_3O_8Na$ requires 556.1507).

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-6-(trifluoromethyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (68)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-((ethoxycarbonyl)amino)-4-(trifluoromethyl)phenyl)acrylate **23** (60 mg, 0.17 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (41 mg, 0.17 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **68** as a yellow oil (49 mg, 48%), and as a single diastereomer.

IR (neat) ν_{max} 1730, 1532, 1450, 1324, 1258, 1169, 1130, 1065, 909 cm^{-1}.

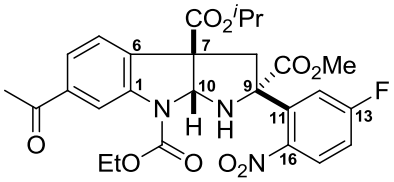
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.16 (1H, app. s), 7.72-7.62 (1H, m), 7.32-7.23 (2H, m), 7.16 (1H, d, *J* 7.9), 6.46-6.39 (1H, m) [aromatics], 6.31 (1H, s, *H*-10), 4.87 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.15-3.99 (2H, m, OCH_2CH_3), 3.95 (1H, br s, N*H*), 3.51 (1H, d, *J* 14.0, *H*-8), 3.11 (3H, s, CO_2CH_3), 3.03 (1H, d, *J* 14.0, *H*-8'), 1.09 (3H, t, *J* 7.1, OCH_2CH_3), 0.98 (3H, d, *J* 6.3, OCH(C$H_3)_2$), 0.92 (3H, d, *J* 6.3, OCH(C$H_3)_2$').

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 171.4 (CO_2Me), 169.6 ($CO_2{}^{i}$Pr), 164.1 (d, *J* 254.3, *C*-13), 152.3 (CO_2Et), 144.8, 142.2, 140.7, 131.7 (q, *J* 32.3), 131.3 (app. br s), 127.1 (d, *J* 9.3), 124.1, 119.8 (q, *J* 4.0), 115.3 (d, *J* 26.7), 114.8 (d, *J* 23.4), 111.4 (q, *J* 3.9) [aromatics], 124.4 (q, J 271.5, CF_3), 82.8 (*C*-10), 71.0 (*C*-9), 69.6 (OC$H(CH_3)_2$), 61.9 (*C*-7), 60.6 (OCH_2CH_3), 51.7 (CO_2CH_3), 48.3 (*C*-8), 20.8 (OCH($CH_3)_2$), 20.7 (OCH($CH_3)_2$'), 13.8 (OCH_2CH_3).

^{19}F NMR (377 MHz, toluene-d_8, {^{1}H}) δ −62.4, −102.5.

m/z LRMS (ESI$^+$) 584.2 [M+H]$^+$; HRMS (ESI$^+$) 584.1670 ([M+H]$^+$, $C_{26}H_{26}F_4N_3O_8$ requires 584.1656).

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 6-acetyl-2-(5-fluoro-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (69)**



This compound was prepared according to general procedure I, using isopropyl 2-(4-acetyl-2-((ethoxycarbonyl)amino)phenyl)acrylate **24** (60 mg, 0.19 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (44 mg, 0.19 mmol) as the isocyanide and potassium carbonate (130 mg, 0.94 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **69** as a yellow oil (64 mg, 61%), and as a single diastereomer.

IR (neat) ν_{max} 1731, 1668, 1539, 1437, 1255, 1094, 909 cm^{-1}.

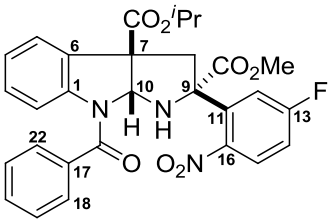
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.40 (1H, app. s), 7.70 (1H, d, *J* 10.0), 7.53 (1H, d, *J* 7.6), 7.34-7.27 (2H, m), 6.49-6.41 (1H, m) [aromatics], 6.34 (1H, s, *H*-10), 4.89 (1H, sep, *J* 6.2, OC*H*(CH$_3$)$_2$), 4.21-4.04 (2H, m, OC*H*$_2$CH$_3$), 3.99 (1H, br s, N*H*), 3.55 (1H, d, *J* 14.0, *H*-8), 3.13 (3H, s, CO$_2$C*H*$_3$), 3.09 (1H, d, *J* 14.0, *H*-8'), 2.26 (3H, s, ArCOC*H*$_3$), 1.14 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.00 (3H, d, *J* 6.2, OCH(C*H*$_3$)$_2$), 0.94 (3H, d, *J* 6.2, OCH(C*H*$_3$)$_2$').

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 195.0 (Ar*C*OMe), 171.4 (*C*O_2Me), 169.7 (*C*$O_2{}^i$Pr), 164.1 (d, *J* 254.1, *C*-13), 152.6 (*C*O_2Et), 144.9, 142.1, 140.8, 135.7, 131.1, 127.1 (d, *J* 9.4), 123.4, 123.2, 115.4 (d, *J* 26.2), 114.8 (d, *J* 23.7), 114.3 (*C*-2) [aromatics], 82.8 (*C*-10), 71.0 (*C*-9), 69.5 (O*C*H(CH_3)$_2$), 61.7 (*C*-7), 60.8 (O*C*$H_2$$CH_3$), 51.7 ($CO_2$*C*$H_3$), 48.2 (*C*-8), 25.5 (ArCO*C*H_3), 20.8 (OCH(*C*H_3)$_2$), 20.7 (OCH(*C*H_3)$_2$'), 13.9 (OCH_2*C*H_3).

^{19}F NMR (377 MHz, toluene-d_8, {^{1}H}) δ −104.3.

m/z LRMS (ESI$^+$) 558.2 [M+H]$^+$; HRMS (ESI$^+$) 558.1876 ([M+H]$^+$, $C_{27}H_{29}FN_3O_9$ requires 558.1888).

(2*S,3a*R**,8a*R**)-3a-Isopropyl 2-methyl 8-benzoyl-2-(5-fluoro-2-nitrophenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (70)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-benzamidophenyl)acrylate **10** (70 mg, 0.23 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (54 mg, 0.23 mmol) as the isocyanide and potassium carbonate (160 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **70** as a yellow oil (71 mg, 57%), and as a single diastereomer.

IR (neat) ν_{max} 1728, 1635, 1587, 1528, 1480, 1350, 1244, 1135, 1100, 909 cm^{-1}.

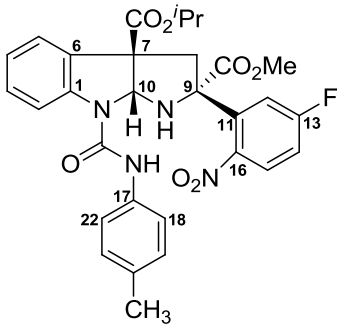
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-7.77 (2H, m), 7.59 (2H, app. d, *J* 7.1), 7.55-7.38 (4H, m), 7.23 (1H, d, *J* 7.1), 7.10-7.01 (1H, m), 7.00-6.82 (2H, m) [aromatics], 6.28 (1H, br s, *H*-10), 4.90 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 3.86 (1H, br s, N*H*), 3.52 (1H, d, *J* 14.4, *H*-8), 3.36 (3H, s, CO_2CH_3), 2.90 (1H, d, *J* 14.4, *H*-8'), 1.13 (3H, d, *J* 6.3, OCH(C$H_3)_2$), 1.02 (3H, d, *J* 6.3, OCH(C$H_3)_2$').

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (CO_2Me), 170.4 ($CO_2{}^{i}$Pr), 169.6 (*C*OPh), 164.2 (d, *J* 253.5, *C*-13), 143.7, 142.6, 140.9, 136.0, 132.0, 131.1, 128.9, 128.7, 128.1, 127.6, 127.4, 124.1, 123.9, 116.0 (d, *J* 26.2), 115.4 (d, *J* 23.1) [aromatics], 84.1 (*C*-10), 71.0 (*C*-9), 69.8 (O*C*H$(CH_3)_2$), 60.1 (*C*-7), 53.0 (CO_2CH_3), 47.5 (*C*-8), 21.5 (OCH($CH_3)_2$).

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ −101.6.

m/z LRMS (ESI^+) 570.2 $[M+Na]^+$; HRMS (ESI^+) 570.1646 ($[M+Na]^+$, $C_{29}H_{26}FN_3O_7Na$ requires 570.1652).

(2*S,3a*R**,8a*R**)-3a-Isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (71)**



Asymmetric: This compound was prepared according to general procedure J, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (39 mg, 0.16 mmol) as the isocyanide and potassium carbonate (100 mg, 0.74 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [9:2]) afforded the pyrroloindoline **71** as a colourless oil, and as a single diastereomer (52 mg, 60%, 90:10 e.r.).

Racemic: This compound was prepared according to general procedure I, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** (60 mg, 0.18 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (42 mg, 0.18 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [9:2]) afforded the pyrroloindoline **71** as a colourless oil (55 mg, 54%), and as a single diastereomer.

IR (neat) ν_{max} 2280, 1618, 1539, 1329, 1243, 812 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, dd, *J* 8.2, 5.1, *H*-15), 7.62 (1H, d, *J* 8.1, *H*-2), 7.49 (1H, dd, *J* 9.8, 2.7, *H*-12), 7.32 (2H, d, *J* 8.3, *H*-18,22), 7.28-7.20 (2H, m, *H*-3,5), 7.17 (1H, br s, N*H*), 7.13-7.03 (3H, m, *H*-14,19,21), 6.96 (1H, t, *J* 7.5, *H*-4), 5.68 (1H, s, *H*-10), 4.88 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 3.50 (3H, s, CO_2CH_3), 3.42 (1H, br s, N*H*), 3.37 (1H, d, *J* 14.2, *H*-8),

2.83 (1H, d, *J* 14.2, *H*-8'), 2.25 (3H, s, ArCH_3), 1.12 (3H, d, *J* 6.3, OCH(CH_3)$_2$), 1.09 (3H, d, *J* 6.3, OCH(CH_3)$_2$').

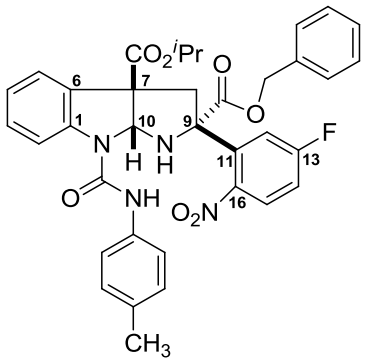
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (*C*O_2Me), 170.3 (*C*$O_2{}^i$Pr), 164.0 (d, *J* 256.3, *C*-13), 152.2 (*C*ON), 145.2 (*C*-1), 141.6 (*C*-16), 137.9 (*C*-6), 135.3 (*C*-17), 133.4 (*C*-20), 130.8 (d, *J* 9.3, *C*-11), 129.8 (*C*-3), 129.5 (*C*-19,21), 127.6 (d, *J* 9.5, *C*-15), 124.3 (*C*-5), 123.2 (*C*-4), 120.3 (*C*-18,22), 116.6 (d, *J* 25.9, *C*-12), 116.0 (d, *J* 23.4, *C*-14), 114.6 (*C*-2), 82.1 (*C*-10), 70.7 (*C*-9), 70.2 (O*C*H(CH_3)$_2$), 62.3 (*C*-7), 53.4 (CO_2*C*H_3), 47.8 (*C*-8), 21.5 (OCH(*C*H_3)$_2$), 21.5 (OCH(*C*H_3)$_2$'), 20.8 (Ar*C*H_3).

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ −103.4.

m/z LRMS (ESI$^+$) 599.2 [M+Na]$^+$; HRMS (ESI$^+$) 599.1910 ([M+Na]$^+$, $C_{30}H_{29}FN_4O_7Na$ requires 599.1918).

Chiral HPLC (Chiralpak IC, 25% IPA in hexane, 1.0 mL/min, λ = 270 nm) t_R(major) 18.2 min, t_R(minor) 23.9 min.

(2*S,3a*R**,8a*R**)-2-Benzyl 3a-isopropyl 2-(5-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (72)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** (68 mg, 0.20 mmol) as the Michael acceptor, benzyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (63 mg, 0.20 mmol) as the isocyanide and potassium carbonate (140 mg, 1.0 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [17:3]) afforded the pyrroloindoline **72** as a colourless oil (80 mg, 61%), and as a single diastereomer.

IR (neat) ν_{max} 3401, 3270, 2981, 1733, 1593, 1530, 1479, 1345, 1238, 1103 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, dd, *J* 8.9, 5.1), 7.63 (1H, d, *J* 7.7), 7.60 (1H, dd, *J* 9.0, 2.6), 7.41 (2H, d, *J* 8.4), 7.37-7.31 (2H, m), 7.31-7.29 (1H, m), 7.28-7.26 (1H, m), 7.23-7.11 (7H, m, incl. N*H*), 7.04 (1H, td, *J* 7.7, 0.8) [aromatics], 5.83 (1H, d, *J* 5.7, *H*-10), 5.06-4.98 (2H, m, OCH_2Ph), 4.98 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 3.53 (1H, d, *J* 5.7, N*H*), 3.44 (1H, d, *J* 14.2, *H*-8), 3.00 (1H, d, *J* 14.2, *H*-8'), 2.36 (3H, s, ArCH_3), 1.21 (3H, d, *J* 6.2, OCH(CH_3)$_2$), 1.19 (3H, d, *J* 6.2, OCH(CH_3)$_2$').

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 170.3 (*C*O_2Bn, *C*$O_2{}^{i}$Pr), 164.0 (d, *J* 254.8, *C*-13), 152.1 (*C*ON), 145.1, 141.5, 138.2, 135.4, 134.7, 133.3, 130.8, 129.8, 129.5, 128.5, 128.5, 128.2, 127.6 (d, *J* 9.5), 124.3, 123.1, 120.1, 116.6 (d, *J* 26.0), 116.0 (d, *J* 23.3), 114.3 [aromatics],

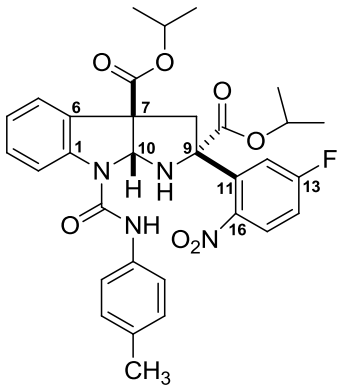
82.3 (*C*-10), 70.9 (*C*-9), 70.2 (O*C*H(CH_3)$_2$), 68.2 (OCH_2Ph), 62.2 (*C*-7), 47.8 (*C*-8), 21.5 (OCH(*C*H_3)$_2$), 20.9 (Ar*C*H_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ −103.3 (ddd, *J* 9.8, 6.7, 4.9).

m/z LRMS (ESI$^+$) 675.2 [M+Na]$^+$; HRMS (ESI$^+$) 675.2222 ([M+Na]$^+$, $C_{36}H_{33}FN_4O_7Na$ requires 675.2225).

This compound was also prepared according to general procedure J (using 10 mg [0.030 mmol] of isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** at 0 °C), by removal of an aliquot of the reaction mixture and purification by preparative TLC. The sample was analysed by chiral stationary phase HPLC to determine the e.r.: (Chiralpak IC, 15% IPA in hexane, 1.0 mL/min, λ = 264 nm) 90:10 e.r., t_R(major) 23.3 min, t_R(minor) 32.8 min.

(2*S,3a*R**,8a*R**)-Diisopropyl 2-(5-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (73)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** (68 mg, 0.20 mmol) as the Michael acceptor, isopropyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (63 mg, 0.20 mmol) as the isocyanide and

potassium carbonate (140 mg, 1.0 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [17:3]) afforded the pyrroloindoline **73** as a colourless oil (88 mg, 73%), and as a single diastereomer.

IR (neat) ν_{max} 2280, 1618, 1539, 1329, 1243, 812 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, dd, *J* 8.8, 5.1), 7.72 (1H, d, *J* 8.1), 7.56 (1H, dd, *J* 9.8, 2.7), 7.42 (2H, d, *J* 8.4), 7.37-7.28 (2H, m), 7.22-7.11 (4H, m, incl. N*H*), 7.04 (1H, td, *J* 7.5, 0.8) [aromatics], 5.76 (1H, d, *J* 6.0, *H*-10), 4.97 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 4.90 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 3.48 (1H, d, *J* 6.0, N*H*), 3.43 (1H, d, *J* 14.2, *H*-8), 2.92 (1H, d, *J* 14.2, *H*-8'), 2.34 (3H, s, ArCH_3), 1.21 (3H, d, *J* 6.2, OCH(C$H_3)_2$), 1.18 (3H, d, *J* 6.2, OCH(C$H_3)_2$'), 1.10 (3H, d, *J* 6.2, OCH(C$H_3)_2$), 1.05 (3H, d, *J* 6.2, OCH(C$H_3)_2$').

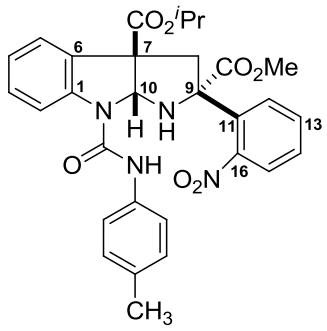
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (*C*$O_2{}^{i}$Pr), 170.0 (*C*$O_2{}^{i}$Pr), 163.9 (d, *J* 255.4, *C*-13), 152.1 (*C*ON), 145.2 (d, *J* 4.4), 141.7, 135.4, 133.2, 130.7, 129.8, 129.5, 128.5 (d, *J* 9.2), 127.4 (d, *J* 9.3), 124.3, 123.1, 120.2, 116.6 (d, *J* 25.8), 115.8 (d, *J* 23.1), 114.6 [aromatics], 82.3 (*C*-10), 71.0 (*C*-9), 70.7 (O*C*H$(CH_3)_2$), 70.2 (O*C*H$(CH_3)_2$), 62.4 (*C*-7), 47.9 (*C*-8), 21.5 (OCH(*C*$H_3)_2$), 21.2 (OCH(*C*$H_3)_2$), 20.8 (Ar*C*H_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ −103.5 (m).

m/z LRMS (ESI^+) 627.2 $[M+Na]^+$; HRMS (ESI^+) 627.2228 ($[M+Na]^+$, $C_{32}H_{33}FN_4NaO_7$ requires 627.2225).

This compound was also prepared according to general procedure J (using 10 mg [0.030 mmol] of isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11**), by removal of an aliquot of the reaction mixture and purification by preparative TLC. The sample was analysed by chiral stationary phase HPLC to determine the e.r.: (Chiralpak IC, 15% IPA in hexane, 1.0 mL/min, λ = 300 nm) 92:8 e.r., t_R(major) 16.0 min, t_R(minor) 24.0 min.

(2*S,3a*R**,8a*R**)-3a-Isopropyl 2-methyl 2-(2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (74)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-nitrophenyl)acetate **39** (33 mg, 0.15 mmol) as the isocyanide and potassium carbonate (100 mg, 0.74 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **74** as a colourless oil (70 mg, 85%), and as a mixture of two separable diastereomers in 7.0:1 ratio.

Data are provided for the major diastereomer only.

IR (neat) ν_{max} 3404, 3279, 1727, 1532, 1479, 1372, 1238, 1101 cm^{-1}.

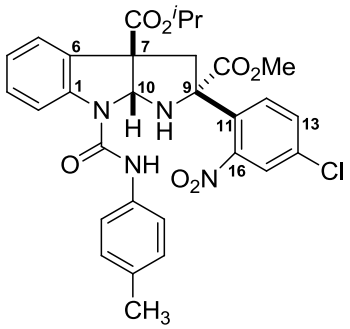
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* 8.1), 7.73 (1H, dd, *J* 7.9, 1.0), 7.68 (1H, dd, *J* 7.9, 1.3), 7.57 (1H, td, *J* 7.6, 1.3), 7.51-7.45 (3H, m), 7.36-7.28 (2H, m), 7.17 (2H, d, *J* 8.3), 7.03 (1H, td, *J* 7.6, 1.0) [aromatics], 7.43 (1H, br s, N*H*), 5.58 (1H, s, *H*-10), 4.90 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 3.69 (1H, d, *J* 14.0, *H*-8), 3.63 (3H, s, CO_2CH_3), 3.38 (1H, br s, N*H*), 2.75 (1H, d, *J* 14.0, *H*-8'), 2.34 (3H, s, ArCH_3), 1.16 (3H, d, *J* 6.2, OCH$(CH_3)_2$), 1.12 (3H, d, *J* 6.2, OCH$(CH_3)_2$').

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 170.3 (*C*O_2Me, *C*$O_2{}^i$Pr), 152.1 (*C*ON), 149.7, 141.9, 135.5, 133.2, 131.8, 130.5, 129.9, 129.5, 129.5, 129.4, 129.2, 124.8, 124.2, 123.2, 120.3, 115.4 [aromatics], 81.7 (*C*-10), 70.6 (*C*-9), 70.0 (O*C*H(CH_3)$_2$), 62.9 (*C*-7), 53.4 (CO_2CH_3), 47.8 (*C*-8), 21.5 (OCH(*C*H_3)$_2$), 21.5 (OCH(*C*H_3)$_2$'), 20.9 (Ar*C*H_3).

m/z LRMS (ESI^+) 581.2 $[M+Na]^+$; HRMS (ESI^+) 581.2018 ($[M+Na]^+$, $C_{30}H_{30}N_4O_7Na$ requires 581.2007).

This compound was also prepared according to general procedure J (using 10 mg [0.030 mmol] of isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11**), by removal of an aliquot of the reaction mixture and purification by preparative TLC. The sample was analysed by chiral stationary phase HPLC to determine the e.r. of the major diastereomer: (Chiralpak IC, 25% IPA in hexane, 1.0 mL/min, λ = 264 nm) 93:7 e.r., t_R(major) 30.1 min, t_R(minor) 44.5 min.

(2*S,3a*R**,8a*R**)-3a-Isopropyl 2-methyl 2-(4-chloro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (75)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-(4-

chloro-2-nitrophenyl)-2-isocyanoacetate **41** (38 mg, 0.15 mmol) as the isocyanide and potassium carbonate (100 mg, 0.74 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **75** as a colourless oil (61 mg, 66%), and as a single diastereomer.

IR (neat) ν_{max} 3401, 3269, 1728, 1531, 1485, 1364, 1240, 1105 cm^{-1}.

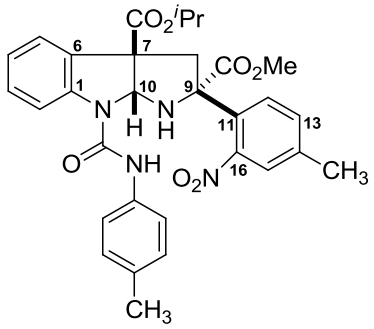
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, d, *J* 7.9), 7.72 (1H, d, *J* 8.5), 7.69 (1H, d, *J* 2.2), 7.54 (1H, dd, *J* 8.5, 2.2), 7.44 (2H, d, *J* 8.4), 7.34-7.28 (3H, m, incl. N*H*), 7.17 (2H, d, *J* 8.2), 7.04 (1H, td, *J* 7.5, 0.8) [aromatics], 5.64 (1H, s, *H*-10), 4.93 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 3.60 (3H, s, CO_2CH_3), 3.57 (1H, d, *J* 14.0, *H*-8), 3.33 (1H, br s, N*H*), 2.81 (1H, d, *J* 14.0, *H*-8'), 2.34 (3H, s, ArCH_3), 1.17 (3H, d, *J* 6.2, OCH$(CH_3)_2$), 1.15 (3H, d, *J* 6.2, OCH$(CH_3)_2$').

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.2 (CO_2Me, $CO_2{}^{i}$Pr), 152.0 (*C*ON), 149.8, 141.8, 135.4, 135.2, 133.3, 131.9, 131.7, 130.5, 130.4, 129.9, 129.5, 124.9, 124.2, 123.2, 120.3, 115.1 [aromatics], 81.9 (*C*-10), 70.4 (*C*-9), 70.1 (O*C*H$(CH_3)_2$), 62.7 (*C*-7), 53.5 (CO_2CH_3), 47.7 (*C*-8), 21.5 (OCH(CH_3)$_2$), 21.5 (OCH(CH_3)$_2$'), 20.9 (ArCH_3).

m/z LRMS (ESI^+) 615.2 $[M+Na]^+$; HRMS (ESI^+) 615.1610 ($[M+Na]^+$, $C_{30}H_{29}ClN_4O_7Na$ requires 615.1617).

This compound was also prepared according to general procedure J (using 10 mg [0.030 mmol] of isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** at 0 °C), by removal of an aliquot of the reaction mixture and purification by preparative TLC. The sample was analysed by chiral stationary phase HPLC to determine the e.r.: (Chiralpak IC, 40% IPA in hexane, 1.0 mL/min, λ = 264 nm) 86:14 e.r., t_R(minor) 19.7 min, t_R(major) 37.7 min.

(2*S,3a*R**,8a*R**)-3a-Isopropyl 2-methyl 2-(4-methyl-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (76)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-isocyano-2-(4-methyl-2-nitrophenyl)acetate **42** (35 mg, 0.15 mmol) as the isocyanide and potassium carbonate (100 mg, 0.74 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **76** as a colourless oil (75 mg, 84%), and as a mixture of two separable diastereomers in 6.4:1 ratio.

Data are provided for the major diastereomer only.

IR (neat) ν_{max} 3399, 3267, 1728, 1535, 1479, 1372, 1238, 1102 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, d, *J* 8.1), 7.56 (1H, d, *J* 8.1), 7.51-7.44 (4H, m), 7.38-7.27 (3H, m, incl. N*H*), 7.17 (2H, d, *J* 8.3), 7.02 (1H, td, *J* 7.5, 0.9) [aromatics], 5.55 (1H, s, *H*-10), 4.91 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 3.68 (1H, d, *J* 14.0, *H*-8), 3.63 (3H, s, CO_2CH_3), 3.31 (1H, br s, N*H*), 2.70 (1H, d, *J* 14.0, *H*-8'), 2.42 (3H, s, $C_6H_3NO_2CH_3$), 2.34 (3H, s, $NHC_6H_4CH_3$), 1.18 (3H, d, *J* 6.2, OCH$(CH_3)_2$), 1.13 (3H, d, *J* 6.2, OCH$(CH_3)_2$').

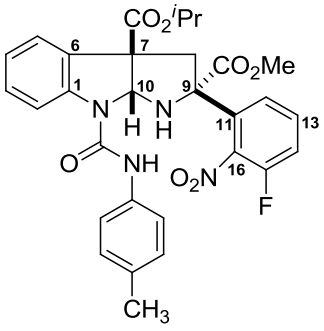
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.3 (CO_2Me, $CO_2{}^{i}$Pr), 152.1 (CON), 149.6, 141.9, 140.3, 135.6, 133.1, 132.3, 130.4, 129.8, 129.4, 129.4, 129.0, 125.2, 124.2, 123.2, 120.3,

115.5 [aromatics], 81.7 (*C*-10), 70.4 (*C*-9), 69.9 (O*C*H(CH_3)$_2$), 63.0 (*C*-7), 53.4 (CO_2CH_3), 47.8 (*C*-8), 21.5 (OCH(*C*H_3)$_2$), 21.5 (OCH(*C*H_3)$_2$'), 20.9 (Ar*C*H_3), 20.8 (Ar*C*H_3).

m/z LRMS (ESI^+) 595.2 $[M+Na]^+$; HRMS (ESI^+) 595.2174 ($[M+Na]^+$, $C_{31}H_{32}N_4O_7Na$ requires 595.2163).

This compound was also prepared according to general procedure J (using 10 mg [0.030 mmol] of isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11**), by removal of an aliquot of the reaction mixture and purification by preparative TLC. The sample was analysed by chiral stationary phase HPLC to determine the e.r. of the major diastereomer: (Chiralpak IC, 40% IPA in hexane, 1.0 mL/min, λ = 300 nm) 93:7 e.r., t_R(major) 17.0 min, t_R(minor) 29.8 min.

(2*S,3a*R**,8a*R**)-3a-Isopropyl 2-methyl 2-(3-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (77)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-(3-fluoro-2-nitrophenyl)-2-isocyanoacetate **40** (36 mg, 0.15 mmol) as the isocyanide and potassium carbonate (100 mg, 0.74 mmol) as the base. Reaction time was 2 h. Column

chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **77** as a colourless oil (59 mg, 69%), and as a mixture of two separable diastereomers in 5.1:1 ratio.

Data are provided for the major diastereomer only.

IR (neat) ν_{max} 3403, 3279, 2972, 1728, 1678, 1594, 1543, 1480, 1368, 1237, 1101 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* 8.0), 7.52 (2H, d, *J* 8.5), 7.47 (1H, dd, *J* 8.3, 5.3), 7.43-7.37 (2H, m), 7.30 (1H, td, *J* 7.8, 1.2), 7.27 (1H, td, *J* 8.3, 1.2), 7.18 (2H, d, *J* 8.3), 7.03 (1H, t, *J* 7.5) [aromatics], 7.32 (1H, br s, N*H*), 5.62 (1H, s, *H*-10), 4.94 (1H, sep, *J* 6.2, OC*H*$(CH_3)_2$), 3.64 (1H, d, *J* 13.8, *H*-8), 3.60 (3H, s, CO_2CH_3), 3.33 (1H, br s, N*H*), 2.76 (1H, d, *J* 13.8, *H*-8'), 2.34 (3H, s, ArCH_3), 1.20 (3H, d, *J* 6.2, OCH$(CH_3)_2$), 1.14 (3H, d, *J* 6.2, OCH$(CH_3)_2$').

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.2 (CO_2Me, $CO_2{}^{i}$Pr), 154.4 (d, *J* 258.6, *C*-15), 152.0 (*C*ON), 142.1, 135.5, 133.2, 132.9, 131.2 (d, *J* 8.1), 130.0, 129.8, 129.5, 129.4, 124.4 (d, *J* 3.2), 124.2, 123.2, 120.5, 117.5 (d, *J* 19.5), 115.6 [aromatics], 81.5 (*C*-10), 70.7 (*C*-9), 70.1 (O*C*H$(CH_3)_2$), 63.0 (*C*-7), 53.6 (CO_2CH_3), 48.1 (*C*-8), 21.5 (OCH$(CH_3)_2$), 21.5 (OCH$(CH_3)_2$'), 20.9 (ArCH_3).

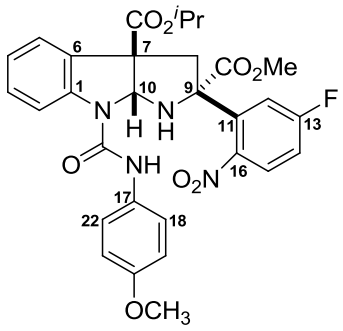
^{19}F NMR (377 MHz, $CDCl_3$) δ −122.9 (m).

m/z LRMS (ESI^+) 599.2 $[M+Na]^+$; HRMS (ESI^+) 599.1926 ($[M+Na]^+$, $C_{30}H_{29}FN_4O_7Na$ requires 599.1918).

This compound was also prepared according to general procedure J (using 10 mg [0.030 mmol] of isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **11** at 0 °C), by removal of an aliquot of the reaction mixture and purification by preparative TLC. The sample was analysed by chiral stationary phase HPLC to determine the e.r. of the major diastereomer:

(Chiralpak IC, 20% IPA in hexane, 1.0 mL/min, λ = 254 nm) 67:33 e.r., t_R(major) 16.1 min, t_R(minor) 40.3 min.

(2*S,3a*R**,8a*R**)-3a-Isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-8-((4-methoxyphenyl)carbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (78)**



This compound was prepared according to general procedure I, using isopropyl 2-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate **12** (50 mg, 0.14 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **44** (33 mg, 0.14 mmol) as the isocyanide and potassium carbonate (99 mg, 0.72 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [3:1]) afforded the pyrroloindoline **78** as a colourless oil (71 mg, 85%), and as a single diastereomer.

IR (neat) v_{max} 1730, 1514, 1235, 1102, 829, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (1H, dd, *J* 8.9, 5.1, *H*-15), 7.64 (1H, d, *J* 8.0, *H*-2), 7.48 (1H, dd, *J* 9.8, 2.6, *H*-12), 7.36 (2H, d, *J* 9.0, *H*-18,22), 7.28-7.21 (2H, m, *H*-3,5), 7.12 (1H, br s, N*H*), 7.11-7.05 (1H, m, *H*-14), 6.96 (1H, t, *J* 7.5, *H*-4), 6.83 (2H, d, *J* 9.0, *H*-19,21), 5.65 (1H, s, *H*-10), 4.88 (1H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 3.73 (3H, s, ArOCH_3), 3.51 (3H, s,

CO_2CH_3), 3.42-3.33 (2H, m, N*H*, *H*-8), 2.81 (1H, d, *J* 14.2, *H*-8'), 1.15-1.07 (6H, m, $OCH(CH_3)_2$).

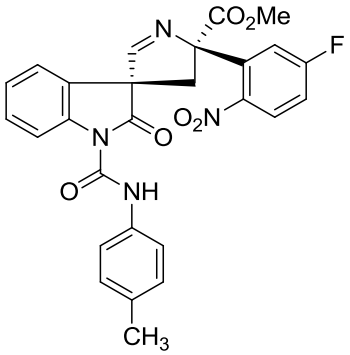
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (*C*O_2Me), 170.3 (*C*$O_2{}^i$Pr), 163.9 (d, *J* 255.4, *C*-13), 156.2 (*C*-20), 152.3 (*C*ON), 145.2 (*C*-1), 141.7 (*C*-16), 137.7 (*C*-6), 137.1 (*C*-17), 130.8 (d, *J* 9.5, *C*-11), 129.8 (*C*-3), 127.5 (d, *J* 9.5, *C*-15), 124.3 (*C*-5), 123.2 (*C*-4), 122.1 (*C*-18,22), 116.6 (d, *J* 26.1, *C*-12), 116.0 (d, *J* 23.2, *C*-14), 114.6 (*C*-2), 114.2 (*C*-19,21), 82.1 (*C*-10), 70.6 (*C*-9), 70.2 (O*C*H$(CH_3)_2$), 62.4 (*C*-7), 55.5 (ArO*C*H_3), 53.4 (CO_2CH_3), 47.8 (*C*-8), 21.5 ($OCH(CH_3)_2$), 21.5 ($OCH(CH_3)_2$').

^{19}F NMR (377 MHz, $CDCl_3$, $\{^1H\}$) δ −103.5.

m/z LRMS (ESI^+) 615.2 $[M+Na]^+$; HRMS (ESI^+) 615.1855 ($[M+Na]^+$, $C_{30}H_{29}FN_4O_8Na$ requires 615.1862).

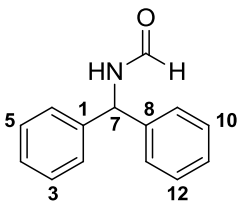
This compound was also prepared according to general procedure J (using 10 mg [0.028 mmol] of isopropyl 2-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate **12**), by removal of an aliquot of the reaction mixture and purification by preparative TLC. The sample was analysed by chiral stationary phase HPLC to determine the e.r.: (Chiralpak IC, 15% IPA in hexane, 1.0 mL/min, λ = 266 nm) 90:10 e.r., t_R(major) 64.9 min, t_R(minor) 71.8 min.

(3*R,5'*R**)-Methyl 5'-(5-fluoro-2-nitrophenyl)-2-oxo-1-(*p*-tolylcarbamoyl)-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (79)**



This thermodynamic product was synthesised by Dr Jamie R. Wolstenhulme. Pyrroloindoline **71** (>20:1 d.r., 90:10 e.r.) was redissolved in toluene, and TBAB (0.2 eq) and potassium carbonate (5.0 eq) were added. The reaction was stirred for 48 h, after which all of pyrroloindoline **71** had been consumed and a significant amount of an unidentified compound had been formed. This product was isolated (>20:1 d.r., 90:10 e.r.) and a single crystal was grown. The identity was revealed by X-ray crystallographic analysis as being pyrroline **79** (performed by Dr Russell W. Driver).

***N*-Benzhydrylformamide (88)**



To a suspension of diphenylmethanamine hydrochloride (2.20 g, 10.0 mmol) in ethyl formate (30 mL), triethylamine (2.79 mL, 20.0 mmol) and DMAP (100 mg, 0.819 mmol) were added.

The reaction mixture was stirred at 50 °C for 48 h. The mixture was then diluted with ethyl acetate (50 mL) and washed with 1 M aqueous hydrochloric acid solution (2 × 50 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford *N*-benzhydrylformamide **88** as a white solid (2.10 g, 99%), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s, C*H*O), 7.39-7.24 (10H, m, aromatics), 6.52 (1H, br s, N*H*), 6.34 (1H, d, *J* 8.2, *H*-7).

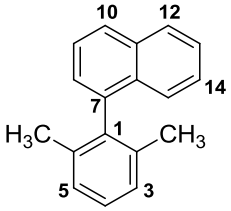
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (N*C*), 140.9, 128.8, 127.7, 127.4 [aromatics], 55.7 (*C*-7).

m/z LRMS (ESI$^+$) 212.1 $[M+H]^+$.

m.p. 132-133 °C.

Data in accordance with literature.[a]

1-(2,6-Dimethylphenyl)naphthalene (93)



Tripotassium phosphate (15.1 g, 71.1 mmol) was dissolved in water (80 mL), and argon was bubbled through the solution for 20 min at RT. Simultaneously, 1-iodonaphthalene (3.49 mL,

[a] M. Vamos, K. Welsh, D. Finlay, P. S. Lee, P. D. Mace, S. J. Snipas, M. L. Gonzalez, S. R. Ganji, R. J. Ardecky, S. J. Riedl, G. S. Salvesen, K. Vuori, J. C. Reed, N. D. P. Cosford, *ACS Chem. Biol.* **2013**, *8*, 725.

23.9 mmol) was added to a solution of (2,6-dimethylphenyl)boronic acid (5.00 g, 33.3 mmol) in 1,2-dimethoxyethane (240 mL), and argon was bubbled through this solution for 10 min at RT. Tetrakis(triphenylphosphine)palladium(0) (1.79 g, 1.55 mmol) was then added to the organic solution, and argon was bubbled through this solution for a further 10 min at RT. Next, the aqueous solution was added to the organic solution, and the mixture was stirred at 95 °C for 18 h under an atmosphere of argon. The reaction mixture was then allowed to cool to RT, diluted with diethyl ether (250 mL) and washed with water (200 mL). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 × 150 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol) afforded 1-(2,6-dimethylphenyl)naphthalene **93** as a white solid (4.11 g, 74%).

IR (neat) ν_{max} 1506, 1461, 906, 801, 778 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* 8.2, *H*-12), 7.91 (1H, d, *J* 8.3, *H*-10), 7.59 (1H, dd, *J* 8.3, 7.0, *H*-9), 7.53-7.49 (1H, m, *H*-13), 7.41-7.37 (2H, m, *H*-14,15), 7.33-7.28 (2H, m, *H*-4,8), 7.22 (2H, d, *J* 7.6, *H*-3,5), 1.95 (6H, s, ArCH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7 (*C*-1), 138.8 (*C*-7), 137.0 (*C*-2,6), 133.8 (*C*-11), 131.8 (*C*-16), 128.3 (*C*-12), 127.4 (*C*-4), 127.3 (*C*-3,5), 127.2 (*C*-10), 126.4 (*C*-8), 126.1 (*C*-15), 125.8 (*C*-13), 125.7 (*C*-9), 125.4 (*C*-14), 20.4 (Ar*C*H_3).

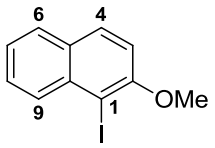
m/z HRMS (EI^+) 232.1245 ($[M]^+$, $C_{18}H_{16}$ requires 232.1252).

m.p. 56-58 °C.

Data in accordance with literature.[a]

[a] X.-X. Zhou, L.-X. Shao, *Synthesis* **2011**, *19*, 3138.

1-Iodo-2-methoxynaphthalene (94)



N-Iodosuccinimide (6.26 g, 27.8 mmol) was added to a solution of 2-methoxynaphthalene (4.00 g, 25.3 mmol) in acetonitrile (100 mL). Trifluoroacetic acid (581 μL, 7.59 mmol) was then added, and the mixture was stirred for 5 h at RT. The reaction mixture was then washed with aqueous sodium thiosulfate solution (100 mL) and water (2 × 100 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 1-iodo-2-methoxynaphthalene **94** as a light yellow solid (6.68 g, 93%), which was used without further purification.

IR (neat) ν_{max} 1619, 1499, 1296, 1082, 827 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (1H, d, *J* 8.7, *H*-9), 7.86 (1H, d, *J* 9.0, *H*-4), 7.77 (1H, d, *J* 8.1, *H*-6), 7.61-7.55 (1H, m, *H*-8), 7.45-7.38 (1H, m, *H*-7), 7.24 (1H, d, *J* 9.0, *H*-3), 4.06 (3H, s, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (*C*-2), 135.7 (*C*-10), 131.2 (*C*-9), 130.4 (*C*-4), 129.9 (*C*-5), 128.2 (*C*-6), 128.1 (*C*-8), 124.4 (*C*-7), 112.9 (*C*-3), 87.7 (*C*-1), 57.2 (*C*H_3).

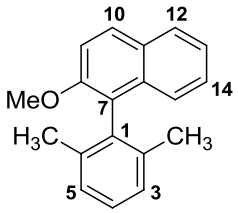
m/z HRMS (EI^+) 283.9700 ($[M]^+$, $C_{11}H_9IO$ requires 283.9698).

m.p. 79-81 °C.

Data in accordance with literature.[a]

[a] C.-Y. Zhou, J. Li, S. Peddibhotla, D. Romo, *Org. Lett.* **2010**, *12*, 2104.

1-(2,6-Dimethylphenyl)-2-methoxynaphthalene (95)



1-Iodo-2-methoxynaphthalene **94** (4.00 g, 14.1 mmol), (2,6-dimethyphenyl)boronic acid (3.17 g, 21.1 mmol), tripotassium phosphate (9.01 g, 42.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (645 mg, 0.704 mmol) and DavePhos (557 mg, 1.41 mmol) were added to a flame-dried flask, which was evacuated and filled with argon. Toluene (40 mL) was then added, and the mixture was heated to 105 °C and left to stir under an atmosphere of argon. After 40 h the reaction mixture was allowed to cool to RT, diluted with diethyl ether (120 mL) and filtered through Celite®. The filtrate was concentrated *in vacuo*, and column chromatography (pentane:diethyl ether [99.5:0.5]) afforded 1-(2,6-dimethylphenyl)-2-methoxynaphthalene **95** as a white solid (2.18 g, 59%).

IR (neat) ν_{max} 1593, 1507, 1270, 1256, 1178, 1093, 910, 807, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* 9.0, *H*-10), 7.90-7.86 (1H, m, *H*-12), 7.43 (1H, d, *J* 9.0, *H*-9), 7.40-7.28 (3H, m, *H*-4,13,14), 7.26-7.17 (3H, m, *H*-3,5,15), 3.89 (3H, s, OCH_3), 1.93 (6H, s, $ArCH_3$).

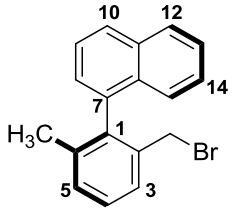
^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4 (*C*-8), 137.4 (*C*-2,6), 135.7 (*C*-1), 132.9 (*C*-16), 129.1 (*C*-11), 128.9 (*C*-10), 128.0 (*C*-12), 127.4 (*C*-4), 127.2 (*C*-3,5), 126.5 (*C*-14), 124.4 (*C*-15), 123.5 (*C*-13), 123.3 (*C*-7), 113.5 (*C*-9), 56.4 (OCH_3), 20.1 ($ArCH_3$).

m/z LRMS (ESI^+) 285.1 $[M+Na]^+$.

m.p. 87-90 °C.

Data in accordance with literature.[a]

1-(2-(Bromomethyl)-6-methylphenyl)naphthalene (96)



N-Bromosuccinimide (5.28 g, 29.7 mmol) was added to a stirred solution of 1-(2,6-dimethylphenyl)naphthalene **93** (3.00 g, 12.9 mmol) in benzene (120 mL). AIBN (330 mg, 2.01 mmol) was then added, and the mixture was heated to reflux. After 6 h the reaction mixture was cooled to 0 °C and a precipitate was formed. The precipitate was then removed by filtration, and the filtrate was concentrated *in vacuo*. Column chromatography (hexane) afforded 1-(2-(bromomethyl)-6-methylphenyl)naphthalene **96** as a colourless oil (843 mg, 21%).

IR (neat) ν_{max} 1506, 1211, 906, 802, 779, 760 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.92 (2H, m, *H*-10,12), 7.61 (1H, dd, *J* 8.3, 7.0, *H*-9), 7.55-7.47 (2H, m, *H*-3,13), 7.45 (1H, d, *J* 7.0, *H*-8), 7.42-7.37 (2H, m, *H*-4,14), 7.35-7.29 (2H, m, *H*-5,15), 4.28 (1H, d, *J* 10.0, CH_2Br), 4.00 (1H, d, *J* 10.0, CH_2Br'), 1.93 (3H, s, ArCH_3).

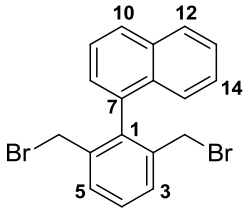
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7 (*C*-1), 138.0 (*C*-6), 136.7 (*C*-2), 136.2 (*), 133.7 (*), 131.9 (*), 130.1 (*C*-5), 128.4 (*C*-12), 128.1 (*C*-4), 128.0 (*C*-3), 128.0 (*C*-10), 127.1 (*C*-8),

[a] T. Tu, Z. Sun, W. Fang, M. Xu, Y. Zhou, *Org. Lett.* **2012**, *14*, 4250.

126.3 (*C*-14), 126.0 (*C*-13), 125.5 (*C*-9), 125.4 (*C*-15), 32.5 (CH_2Br), 20.3 ($ArCH_3$). *Three unassigned peaks correspond to *C*-7, *C*-11 and *C*-16.

m/z HRMS (EI^+) 310.0353 ($[M]^+$, $C_{18}H_{15}Br$ requires 310.0357).

1-(2,6-Bis(bromomethyl)phenyl)naphthalene (97)



N-Bromosuccinimide (5.28 g, 29.7 mmol) was added to a stirred solution of 1-(2,6-dimethylphenyl)naphthalene **93** (3.00 g, 12.9 mmol) in benzene (120 mL). AIBN (330 mg, 2.01 mmol) was then added, and the mixture was heated to reflux. After 6 h the reaction mixture was cooled to 0 °C and a precipitate was formed. The precipitate was then removed by filtration, and the filtrate was concentrated *in vacuo*. Column chromatography (hexane) afforded 1-(2,6-bis(bromomethyl)phenyl)naphthalene **97** as a white solid (3.47 g, 69%).

IR (neat) ν_{max} 1505, 1435, 1248, 907, 802, 779 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.03-7.95 (2H, m, *H*-10,12), 7.68-7.60 (3H, m, *H*-3,5,9), 7.59-7.49 (3H, m, *H*-4,8,13), 7.44-7.39 (1H, m, *H*-14), 7.28 (1H, d, *J* 8.3, *H*-15), 4.23 (2H, d, *J* 10.2, CH_2Br), 3.98 (2H, d, *J* 10.2, CH_2Br').

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6 (*C*-1), 137.5 (*C*-2,6), 133.7 (*), 133.6 (*), 132.0 (*), 130.8 (*C*-3,5), 129.0 (*C*-4), 128.7 (*C*-10), 128.4 (*C*-12), 128.0 (*C*-8), 126.5 (*C*-14), 126.2

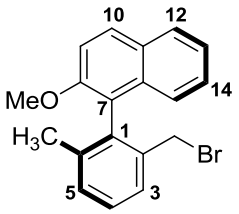
(*C*-13), 125.5 (*C*-15), 125.4 (*C*-9), 31.5 (*C*H_2Br). *Three unassigned peaks correspond to *C*-7, *C*-11 and *C*-16.

m/z LRMS (ESI$^+$) 389.0 $[M+H]^+$.

m.p. 67-69 °C.

Data in accordance with literature.[a]

1-(2-(Bromomethyl)-6-methylphenyl)-2-methoxynaphthalene (99)



N-Bromosuccinimide (160 mg, 0.88 mmol) was added to a stirred solution of 1-(2,6-dimethylphenyl)-2-methoxynaphthalene **95** (100 mg, 0.38 mmol) in benzene (4.0 mL). AIBN (9.7 mg, 0.057 mmol) was then added, and the mixture was heated to reflux. After 6 h the reaction mixture was cooled to 0 °C and a precipitate was formed. The precipitate was then removed by filtration, and the filtrate was concentrated *in vacuo*. Column chromatography (pentane:diethyl ether [99.5:0.5]) afforded the biaryl **99** as a white solid (60 mg, 46%).

IR (neat) ν_{max} 1579, 1495, 1174, 904, 810, 726, 650 cm^{-1}.

[a] Y. Ting, Y.-H. Lai, *J. Am. Chem. Soc.* **2004**, *126*, 909.

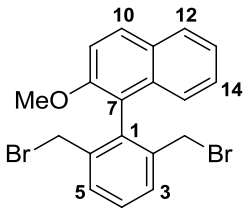
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.90 (1H, m), 7.77 (1H, d, *J* 9.1), 7.41-7.36 (1H, m), 7.35-7.20 (5H, m), 6.91 (1H, d, *J* 9.1) [aromatics], 4.05 (1H, d, *J* 10.0, C*H*$_2$Br), 3.97 (1H, d, *J* 10.0, C*H*$_2$Br'), 3.77 (3H, s, OC*H*$_3$), 1.79 (3H, s, ArC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 138.3, 136.8, 135.4, 131.6, 130.3, 130.0, 129.0, 128.9, 128.3, 128.1, 126.4, 124.5, 123.7, 117.5, 114.2 [aromatics], 56.3 (O*C*H$_3$), 32.3 (*C*H$_2$Br), 20.0 (Ar*C*H$_3$).

m/z LRMS (ESI$^+$) 363.0 [M+Na]$^+$; HRMS (ESI$^+$) 363.0355 ([M+Na]$^+$, $C_{19}H_{17}BrONa$ requires 363.0360).

m.p. 61-64 °C.

1-(2,6-Bis(bromomethyl)phenyl)-2-methoxynaphthalene (100)



N-Bromosuccinimide (3.18 g, 17.8 mmol) was added to a stirred solution of 1-(2,6-dimethylphenyl)-2-methoxynaphthalene **95** (1.56 g, 5.95 mmol) in benzene (72 mL). AIBN (116 mg, 1.49 mmol) was then added, and the mixture was heated to reflux. After 18 h the reaction mixture was cooled to 0 °C and a precipitate was formed. The precipitate was then removed by filtration, and the filtrate was concentrated *in vacuo*. Column chromatography (pentane:diethyl ether [99.5:0.5]) afforded the biaryl **100** as a yellow solid (1.75 g, 70%).

IR (neat) ν_{max} 1275, 921, 809, 725, 649 cm^{-1}.

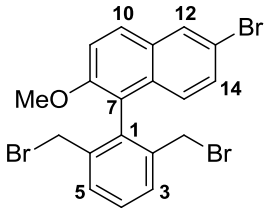
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (1H, d, *J* 9.1, *H*-10), 7.91-7.87 (1H, m, *H*-12), 7.63 (2H, d, *J* 7.7, *H*-3,5), 7.51 (1H, t, *J* 7.7, *H*-4), 7.44 (1H, d, *J* 9.1, *H*-9), 7.41-7.34 (2H, m, *H*-13,14), 7.13 (1H, d, *J* 8.3, *H*-15), 4.17 (2H, d, *J* 10.3, C*H*$_2$Br), 4.10 (2H, d, *J* 10.3, C*H*$_2$Br'), 3.90 (3H, s, OC*H*$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3 (*C*-8), 137.7 (*C*-2,6), 136.1 (*C*-1), 133.2 (*C*-16), 130.8 (*C*-3,5), 130.5 (*C*-10), 128.8 (*C*-11), 128.8 (*C*-4), 128.1 (*C*-12), 126.9 (*C*-14), 124.6 (*C*-15), 123.8 (*C*-13), 118.4 (*C*-7), 113.0 (*C*-9), 56.1 (O*C*H$_3$), 31.8 (*C*H$_2$Br).

m/z LRMS (ESI$^+$) 440.9 [M+Na]$^+$; HRMS (ESI$^+$) 440.9460 ([M+Na]$^+$, $C_{19}H_{16}Br_2ONa$ requires 440.9466).

m.p. 112-114 °C.

1-(2,6-Bis(bromomethyl)phenyl)-6-bromo-2-methoxynaphthalene (101)



N-Bromosuccinimide (3.18 g, 17.8 mmol) was added to a stirred solution of 1-(2,6-dimethylphenyl)-2-methoxynaphthalene **95** (1.56 g, 5.95 mmol) in benzene (72 mL). AIBN (116 mg, 1.49 mmol) was then added, and the mixture was heated to reflux. After 18 h the reaction mixture was cooled to 0 °C and a precipitate was formed. The precipitate was then removed by filtration, and the filtrate was concentrated *in vacuo*. Column chromatography (pentane:diethyl ether [99.5:0.5]) afforded the biaryl **101** as a yellow solid (250 mg, 10%).

IR (neat) v_{max} 1585, 1494, 1272, 1255, 1071, 922, 819, 730 cm^{-1}.

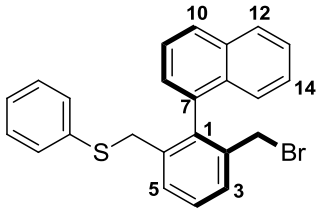
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (1H, d, *J* 2.0, *H*-12), 7.93 (1H, d, *J* 9.0, *H*-10), 7.62 (2H, d, *J* 7.7, *H*-3,5), 7.51 (1H, t, *J* 7.7, *H*-4), 7.45 (1H, d, *J* 9.0, *H*-9), 7.41 (1H, dd, *J* 9.0, 2.0, *H*-14), 7.02 (1H, d, *J* 9.0, *H*-15), 4.13 (2H, d, *J* 10.3, CH_2Br), 4.08 (2H, d, *J* 10.3, CH_2Br'), 3.89 (3H, s, OCH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5 (*C*-8), 137.7 (*C*-2,6), 135.5 (*C*-1), 131.7 (*C*-16), 130.9 (*C*-3,5), 130.2 (*C*-14), 130.0 (*C*-12), 129.9 (*C*-11), 129.7 (*C*-10), 129.1 (*C*-4), 126.6 (*C*-15), 118.8 (*C*-7), 117.7 (*C*-13), 114.0 (*C*-9), 56.2 (O*C*H_3), 31.5 (*C*H_2Br).

m/z LRMS (ESI^+) 518.9 $[M+Na]^+$; HRMS (ESI^+) 518.8566 ($[M+Na]^+$, $C_{19}H_{15}Br_3ONa$ requires 518.8571).

m.p. 80-82 °C.

(3-(Bromomethyl)-2-(naphthalen-1-yl)benzyl)(phenyl)sulfane (103)



Thiophenol (13 μL, 0.13 mmol), 1-(2,6-bis(bromomethyl)phenyl)naphthalene **97** (60 mg, 0.15 mmol) and tetrabutylammonium bromide (4.2 mg, 0.013 mmol) were dissolved in toluene (1.5 mL). Caesium hydroxide monohydrate (43 mg, 0.26 mmol) was added, and the mixture was stirred under an atmosphere of argon for 4 h at RT. The reaction mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The

organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:toluene [4:1]) afforded the biaryl **103** as a colourless oil (18 mg, 33%).

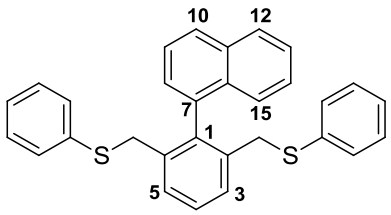
IR (neat) v_{max} 1479, 1392, 1213, 1174, 995, 965, 937, 735 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.83 (2H, m), 7.56-7.38 (5H, m), 7.36-7.27 (3H, m), 7.10-7.03 (3H, m), 6.97-6.93 (2H, m) [aromatics], 4.13 (1H, d, *J* 10.2, C*H*$_2$Br), 3.87 (1H, d, *J* 10.2, C*H*$_2$Br'), 3.64 (1H, d, *J* 13.4, C*H*$_2$SPh), 3.51 (1H, d, *J* 13.4, C*H*$_2$SPh').

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 137.2, 137.1, 136.2, 134.5, 133.6, 132.1, 130.1, 129.8, 129.6, 128.7, 128.5, 128.4, 128.4, 128.0, 126.4, 126.3, 126.1, 125.5, 125.4 [aromatics], 37.1 (*C*H_2SPh), 32.0 (*C*H_2Br).

m/z HRMS (CI^+) 419.0465 ($[M+H]^+$, $C_{24}H_{20}BrS$ requires 419.0465).

((2-(Naphthalen-1-yl)-1,3-phenylene)bis(methylene))bis(phenylsulfane) (104)



Thiophenol (13 μL, 0.13 mmol), 1-(2,6-bis(bromomethyl)phenyl)naphthalene **97** (60 mg, 0.15 mmol) and tetrabutylammonium bromide (4.2 mg, 0.013 mmol) were dissolved in toluene (1.5 mL). Caesium hydroxide monohydrate (43 mg, 0.26 mmol) was added, and the mixture was stirred under an atmosphere of argon for 4 h at RT. The reaction mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The

organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:toluene [4:1]) afforded the biaryl **104** as a colourless oil (12 mg, 18% with respect to biaryl starting material **97**).

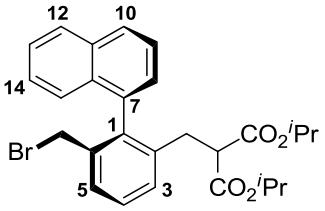
IR (neat) ν_{max} 1583, 1505, 1459, 1053, 831, 802, 760 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.78 (2H, m), 7.53-7.36 (4H, m), 7.35-7.24 (2H, m), 7.23-7.16 (2H, m), 7.10-7.01 (6H, m), 6.97-6.93 (4H, m) [aromatics], 3.65 (2H, d, *J* 13.3, CH_2SPh), 3.51 (2H, d, *J* 13.3, CH_2SPh').

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 136.7, 136.4, 135.2, 133.5, 132.2, 130.0, 128.7, 128.5, 128.4, 128.1, 128.0, 128.0, 126.3, 126.2, 126.0, 125.5, 125.4 [aromatics], 37.2 (*C*H_2SPh).

m/z LRMS (ESI^+) 471.1 $[M+Na]^+$; HRMS (ESI^+) 471.1213 ($[M+Na]^+$, $C_{30}H_{24}S_2Na$ requires 471.1217).

Diisopropyl 2-(3-(bromomethyl)-2-(naphthalen-1-yl)benzyl)malonate (105)



Asymmetric: Phase-transfer catalyst **C11** (13 mg, 0.013 mmol) and caesium hydroxide monohydrate (43 mg, 0.26 mmol) were added to a stirred solution of diisopropyl malonate (24 μL, 0.13 mmol) in toluene (1.2 mL). The mixture was cooled to −20 °C and, after 5 min, 1-(2,6-bis(bromomethyl)phenyl)naphthalene **97** (50 mg, 0.13 mmol) was added. The reaction mixture was stirred for 7 h at −20 °C. The mixture was then diluted with DCM (10 mL) and

washed with brine (10 mL) and water (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [14:1]) afforded the biaryl **105** as a colourless oil (35 mg, 55%, 73:27 e.r.).

Racemic: Diisopropyl malonate (29 μL, 0.15 mmol), 1-(2,6-bis(bromomethyl)phenyl)naphthalene **97** (60 mg, 0.15 mmol) and tetrabutylammonium bromide (5.0 mg, 0.015 mmol) were dissolved in toluene (1.0 mL). Caesium hydroxide monohydrate (52 mg, 0.31 mmol) was added, and the mixture was stirred for 4 h at RT. The reaction mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [14:1]) afforded the biaryl **105** as a colourless oil (36 mg, 47%).

IR (neat) ν_{max} 2981, 1738, 1391, 1215, 1147, 966, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.90-7.81 (2H, m), 7.52 (1H, dd, *J* 8.3, 7.0), 7.46-7.38 (3H, m), 7.34-7.24 (3H, m), 7.20-7.16 (1H, m) [aromatics], 4.77 (2H, sep, *J* 6.3, OC*H*$(CH_3)_2$), 4.13 (1H, d, *J* 10.0, C*H*$_2$Br), 3.84 (1H, d, *J* 10.0, C*H*$_2$Br'), 3.10 (1H, dd, *J* 8.4, 7.2, C*H*$(CO_2{}^i\text{Pr})_2$), 2.85 (1H, dd, *J* 14.2, 8.4, C*H*$_2$CH$(CO_2{}^i\text{Pr})_2$), 2.63 (1H, dd, *J* 14.2, 7.2, C*H*$_2$CH$(CO_2{}^i\text{Pr})_2$'), 1.07-1.00 (6H, m, OCH$(CH_3)_2$), 0.99-0.93 (6H, m, OCH$(CH_3)_2$').

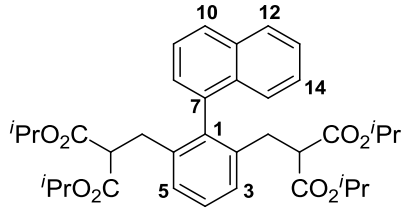
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3 ($CO_2{}^i$Pr), 168.3 ($CO_2{}^i$Pr'), 139.8, 137.8, 137.1, 134.9, 133.7, 132.0, 130.2, 129.2, 128.4, 128.4, 128.3, 127.8, 126.5, 126.1, 125.4, 125.4 [aromatics], 68.7 (O*C*H$(CH_3)_2$), 68.7 (O*C*H$(CH_3)_2$'), 52.8 (*C*H$(CO_2{}^i\text{Pr})_2$), 32.5 (*C*H$_2$CH$(CO_2{}^i\text{Pr})_2$), 32.1 (*C*H$_2$Br), 21.5 (OCH$(CH_3)_2$), 21.5 (OCH$(CH_3)_2$').

m/z LRMS (ESI^+) 497.1 $[M+H]^+$; HRMS (ESI^+) 497.1321 ($[M+H]^+$, $C_{27}H_{30}BrO_4$ requires 497.1327).

Chiral HPLC (Chiralpak IA, 2% IPA in hexane, 1.0 mL/min, λ = 250 nm) 73:27 e.r., t_R(major) 7.5 min, t_R(minor) 9.5 min.

$[\alpha]_D^{25}$ +7.5° (*c* 1.00, $CHCl_3$).

Tetraisopropyl 2,2'-((2-(naphthalen-1-yl)-1,3-phenylene)bis(methylene))dimalonate (106)



Diisopropyl malonate (29 μL, 0.15 mmol), 1-(2,6-bis(bromomethyl)phenyl)naphthalene **97** (60 mg, 0.15 mmol) and tetrabutylammonium bromide (5.0 mg, 0.015 mmol) were dissolved in toluene (1.0 mL). Caesium hydroxide monohydrate (52 mg, 0.31 mmol) was added, and the mixture was stirred for 4 h at RT. The reaction mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [14:1]) afforded the biaryl **106** as a colourless oil (17 mg, 18%).

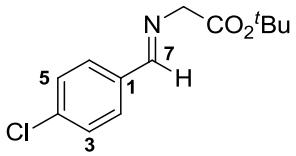
IR (neat) ν_{max} 1726, 1467, 1375, 1288, 1226, 1126, 906, 728 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* 8.3), 7.50 (1H, dd, *J* 8.3, 7.1), 7.44-7.38 (1H, m), 7.34-7.28 (2H, m), 7.24-7.15 (4H, m) [aromatics], 4.82-4.70 (4H, m, OC*H*$(CH_3)_2$), 3.07 (2H, app. t, *J* 7.8, C*H*$(CO_2{}^iPr)_2$), 2.83 (2H, dd, *J* 14.2, 8.2, CH_2), 2.62 (2H, dd, *J* 14.2, 7.2, CH_2'), 1.02 (12H, d, J 6.2, OCH(CH_3)$_2$), 0.99-0.93 (12H, m, OCH(CH_3)$_2$').

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 ($CO_2{}^{i}Pr$), 168.4 ($CO_2{}^{i}Pr$'), 139.9, 137.3, 136.1, 133.8, 132.0, 128.6, 128.4, 128.1, 127.7, 127.5, 126.6, 126.1, 125.5, 125.3 [aromatics], 68.6 ($OCH(CH_3)_2$), 68.6 ($OCH(CH_3)_2$'), 52.9 ($CH(CO_2{}^{i}Pr)_2$), 32.6 (CH_2), 21.5 ($OCH(CH_3)_2$), 21.5 ($OCH(CH_3)_2$').

m/z LRMS (ESI^+) 627.3 $[M+Na]^+$; HRMS (ESI^+) 627.2927 ($[M+Na]^+$, $C_{36}H_{44}O_8Na$ requires 627.2934).

(*E*)-*tert*-Butyl 2-((4-chlorobenzylidene)amino)acetate (107)



4-Chlorobenzaldehyde (1.12 g, 8.00 mmol) was added to a suspension of *tert*-butyl 2-aminoacetate hydrochloride (1.68 g, 10.0 mmol) and Na_2SO_4 (1.42 g, 10.0 mmol) in DCM (20 mL). The mixture was stirred at 0 °C and triethylamine (1.39 mL, 10.0 mmol) was added dropwise. The reaction was allowed to warm to RT and stirred for 16 h. Diethyl ether (20 mL) was then added, and the solution was filtered, before the filtrate was washed with water (3 × 40 mL) and then brine (30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the glycine imine **107** as a yellow wax (1.93 g, 95%), which was used without further purification.

IR (neat) ν_{max} 2918, 1733, 1650, 1597, 1490, 1393, 1152, 1089, 909, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, s, *H*-7), 7.65 (2H, d, *J* 8.4, *H*-2,6), 7.31 (2H, d, *J* 8.4, *H*-3,5), 4.24 (2H, s, $CH_2CO_2{}^{t}Bu$), 1.42 (9H, s, $OC(CH_3)_3$).

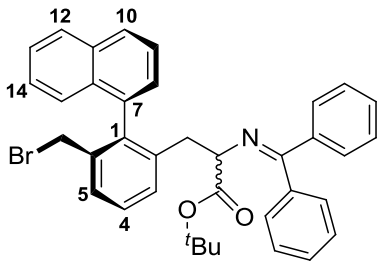
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (*C*$O_2{}^t$Bu), 163.8 (*C*-7), 137.1 (*C*-4), 134.2 (*C*-1), 129.6 (*C*-2,6), 128.9 (*C*-3,5), 81.6 (O*C*$(CH_3)_3$), 62.5 (*C*$H_2CO_2{}^t$Bu), 28.1 ((OC(*C*$H_3)_3$).

m/z LRMS (ESI^+) 254.1 $[M+H]^+$.

m.p. 30-34 °C.

Data in accordance with literature.[a]

***tert*-Butyl 3-(3-(bromomethyl)-2-(naphthalen-1-yl)phenyl)-2-((diphenylmethylene)amino)propanoate (108)**



Asymmetric: Phase-transfer catalyst **C6** (9.2 mg, 0.015 mmol) and 50% aqueous potassium hydroxide solution (1.0 mL) were added to a stirred solution of *tert*-butyl 2-((diphenylmethylene)amino)acetate **1** (45 mg, 0.15 mmol) in toluene (1.5 mL). The mixture was cooled to −35 °C and, after 5 min, 1-(2,6-bis(bromomethyl)phenyl)naphthalene **97** (60 mg, 0.15 mmol) was added. The reaction mixture was stirred for 50 h at −35 °C. The mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [18:1]) afforded the

[a] R. Lasch, M. R. Heinrich, *Tetrahedron* **2015**, *71*, 4282.

biaryl **108** as a colourless oil (48 mg, 51%, 96:4 e.r.), and as a mixture of two separable diastereomers in 7.1:1 ratio.

Racemic: Tetrabutylammonium bromide (5.0 mg, 0.015 mmol) and caesium hydroxide monohydrate (52 mg, 0.31 mmol) were added to a stirred solution of *tert*-butyl 2-((diphenylmethylene)amino)acetate **1** (45 mg, 0.15 mmol) in DCM (0.6 mL). The mixture was cooled to 0 °C and, after 5 min, 1-(2,6-bis(bromomethyl)phenyl)naphthalene **97** (60 mg, 0.15 mmol) was added. The reaction mixture was stirred for 18 h at 0 °C. The mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [18:1]) afforded the biaryl **108** as a colourless oil (52 mg, 56%), and as a mixture of two separable diastereomers in 4.0:1 ratio.

Data are provided for the major diastereomer.

IR (neat) ν_{max} 1730, 1660, 1446, 1368, 1278, 1170, 930, 803, 732 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.78-7.75 (2H, m), 7.53-7.49 (2H, m), 7.44-7.15 (12H, m), 6.98-6.93 (1H, m), 6.70-6.60 (3H, m) [aromatics], 4.06 (1H, d, *J* 10.0, C*H*$_2$Br), 3.82-3.76 (2H, m, C*H*$_2$Br', C*H*CO$_2^t$Bu), 2.86 (1H, dd, *J* 13.7, 4.1, C*H*$_2$CHCO), 2.76-2.67 (1H, m, C*H*$_2$CHCO'), 1.05 (9H, s, C(C*H*$_3$)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (*C*O$_2^t$Bu), 170.1 (N*C*Ph$_2$), 140.1, 138.5, 137.6, 136.9, 135.4, 133.5, 132.4, 132.1, 131.1, 130.3, 130.1, 128.9, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 126.2, 125.7, 125.4, 125.3 [aromatics], 80.7 (*C*(CH$_3$)$_3$), 67.3 (*C*HCO$_2^t$Bu), 37.1 (*C*H$_2$CHCO), 32.5 (*C*H$_2$Br), 27.7 (C(*C*H$_3$)$_3$).

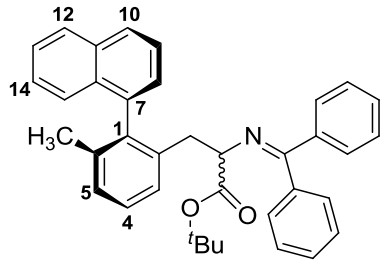
m/z LRMS (ESI^+) 604.2 $[M+H]^+$; HRMS (ESI^+) 604.1844 ($[M+H]^+$, $C_{37}H_{35}BrNO_2$ requires 604.1851).

Chiral HPLC (Chiralpak IA, 2% IPA in hexane, 1.0 mL/min, λ = 250 nm) 96:4 e.r., t_R(minor) 6.5 min, t_R(major) 7.9 min.

$[\alpha]_D^{25}$ −132° (*c* 1.00, $CHCl_3$).

Characteristic NMR peaks for the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76-3.62 (2H, m, CH_2Br, C*H*$CO_2{}^t$Bu), 2.56-2.47 (1H, m, CH_2CHCO).

***tert*-Butyl 2-((diphenylmethylene)amino)-3-(3-methyl-2-(naphthalen-1-yl)phenyl)propanoate (111)**



Asymmetric: *tert*-Butyl 2-((diphenylmethylene)amino)acetate **1** (57 mg, 0.19 mmol), 1-(2-(bromomethyl)-6-methylphenyl)naphthalene **96** (60 mg, 0.19 mmol) and phase-transfer catalyst **C11** (10 mg, 0.097 mmol) were dissolved in toluene (1.0 mL). 50% aqueous potassium hydroxide solution (1.0 mL) was added, and the mixture was stirred for 4 h at RT. The reaction mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [30:1]) afforded the biaryl **111** as a white solid (57 mg, 56%, 98:2 e.r.), and as a mixture of two separable diastereomers in 2.9:1 ratio.

Racemic: *tert*-Butyl 2-((diphenylmethylene)amino)acetate **1** (57 mg, 0.19 mmol), 1-(2-(bromomethyl)-6-methylphenyl)naphthalene **96** (60 mg, 0.19 mmol) and tetrabutylammonium bromide (6.2 mg, 0.019 mmol) were dissolved in toluene (1.0 mL). Caesium hydroxide monohydrate (65 mg, 0.39 mmol) was added, and the mixture was stirred for 4 h at RT. The reaction mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [30:1]) afforded the biaryl **111** as a white solid (67 mg, 66%), and as a mixture of two separable diastereomers in 2.9:1 ratio.

Data are provided for the major diastereomer.

IR (neat) ν_{max} 1725, 1628, 1255, 1152, 1053, 904, 724, 649 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.77-7.70 (2H, m), 7.54-7.50 (2H, m), 7.43-7.21 (8H, m), 7.15-7.06 (3H, m), 7.03 (1H, d, *J* 7.0), 6.98-6.92 (1H, m), 6.69 (1H, d, *J* 8.4), 6.64 (2H, d, *J* 7.3) [aromatics], 3.77 (1H, dd, *J* 9.0, 3.9, C*H*$CO_2{}^t$Bu), 2.90 (1H, dd, *J* 13.7, 3.9, ArCH_2), 2.72 (1H, dd, *J* 13.7, 9.0, ArCH_2'), 1.73 (3H, s, ArCH_3), 1.04 (9H, s, C(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (*C*$O_2{}^t$Bu), 169.7 (N*C*Ph_2), 140.1, 139.6, 138.0, 137.6, 137.2, 136.6, 133.6, 132.0, 130.1, 128.9, 128.2, 128.2, 128.1, 128.1, 127.9, 127.9, 127.7, 127.3, 127.2, 127.1, 126.0, 125.6, 125.5, 125.3 [aromatics], 80.5 (*C*$(CH_3)_3$), 67.7 (*C*H$CO_2{}^t$Bu), 37.2 (Ar*C*H_2), 27.7 (C(*C*H_3)$_3$), 20.5 (Ar*C*H_3).

m/z LRMS (ESI^+) 526.3 $[M+H]^+$; HRMS (ESI^+) 526.2738 ($[M+H]^+$, $C_{37}H_{36}NO_2$ requires 526.2746).

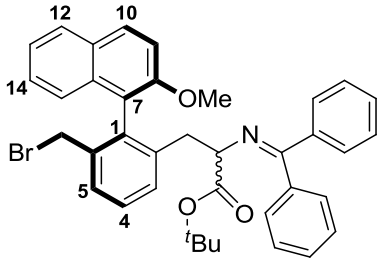
m.p. 96-97 °C.

Chiral HPLC (Chiralpak IC, 4% IPA in hexane, 1.0 mL/min, λ = 250 nm) 98:2 e.r., t_R(major) 6.9 min, t_R(minor) 10.2 min.

$[\alpha]_D^{25}$ +16.0° (*c* 1.00, $CHCl_3$).

Characteristic NMR peaks for the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (1H, dd, *J* 10.3, 2.7, C*H*$CO_2{}^t$Bu), 2.79 (1H, dd, *J* 13.3, 10.3, ArCH_2), 2.50 (1H, dd, *J* 13.3, 2.7, ArCH_2').

***tert*-Butyl 3-(3-(bromomethyl)-2-(2-methoxynaphthalen-1-yl)phenyl)-2-((diphenylmethylene)amino)propanoate (112)**



tert-Butyl 2-((diphenylmethylene)amino)acetate **1** (42 mg, 0.14 mmol), 1-(2,6-bis(bromomethyl)phenyl)-2-methoxynaphthalene **100** (60 mg, 0.14 mmol) and tetrabutylammonium bromide (4.6 mg, 0.014 mmol) were dissolved in toluene (1.0 mL). Caesium hydroxide monohydrate (48 mg, 0.29 mmol) was added, and the mixture was stirred for 4 h at RT. The reaction mixture was then diluted with DCM (10 mL) and washed with brine (10 mL) and water (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [18:1]) afforded the biaryl **112** as a white solid (48 mg, 53%), and as a mixture of two separable diastereomers in 2.5:1 ratio.

Data are provided for the major diastereomer.

IR (neat) ν_{max} 1725, 1623, 1595, 1257, 1150, 910, 847, 726, 649 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* 9.0), 7.75-7.70 (2H, m), 7.50-7.45 (2H, m), 7.44-7.38 (2H, m), 7.32-7.16 (8H, m), 7.15-7.10 (1H, m), 6.89 (1H, d, *J* 8.5), 6.52 (2H, d, *J* 7.3) [aromatics], 4.02 (1H, d, *J* 10.1, C*H*$_2$Br), 4.00-3.94 (1H, m, C*H*$CO_2{}^t$Bu), 3.86 (1H, d, *J* 10.1, C*H*$_2$Br'), 3.31 (3H, s, OC*H*$_3$), 2.97-2.84 (1H, m, C*H*$_2$CHCO), 2.77 (1H, dd, *J* 13.7, 3.7, C*H*$_2$CHCO'), 1.14 (9H, s, C(C*H*$_3$)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (*C*$O_2{}^t$Bu), 170.1 (N*C*Ph_2), 154.2, 139.9, 139.1, 137.6, 137.1, 136.6, 136.4, 132.4, 130.9, 130.1, 129.8, 128.8, 128.7, 128.6, 128.3, 128.2, 127.9, 127.7, 127.6, 126.7, 124.5, 123.5, 119.8, 112.7 [aromatics], 80.6 (*C*(CH$_3$)$_3$), 66.4 (*C*H$CO_2{}^t$Bu), 55.2 (OCH$_3$), 37.6 (*C*H$_2$CHCO), 32.7 (*C*H$_2$Br), 27.9 (C(*C*H$_3$)$_3$).

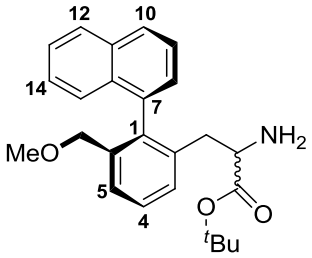
m/z LRMS (ESI^+) 634.2 $[M+H]^+$; HRMS (ESI^+) 634.1954 ($[M+H]^+$, $C_{38}H_{37}BrNO_3$ requires 634.1957).

m.p. 61-63 °C.

This compound was also prepared according to the above procedure, but using *tert*-butyl 2-((diphenylmethylene)amino)acetate **1** (4.2 mg, 0.014 mmol) and 1-(2,6-bis(bromomethyl)phenyl)-2-methoxynaphthalene **100** (6.0 mg, 0.014 mmol), together with phase-transfer catalyst **C6** (0.87 mg, 0.0014 mmol) and 50% aqueous potassium hydroxide solution (0.1 mL) as the base in toluene (0.15 mL). An aliquot of the reaction mixture was removed and purified by preparative TLC. The sample was analysed by chiral stationary phase HPLC to determine the e.r. of the major diastereomer: (Chiralpak IA, 1% IPA in hexane, 1.0 mL/min, λ = 250 nm) 76:24 e.r., t_R(major) 10.2 min, t_R(minor) 14.3 min.

Characteristic NMR peaks for the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74-3.68 (1H, m, C*H*$CO_2{}^t$Bu), 3.57 (3H, s, OCH_3), 1.03 (9H, s, C(CH_3)$_3$).

***tert*-Butyl 2-amino-3-(3-(methoxymethyl)-2-(naphthalen-1-yl)phenyl)propanoate (113)**



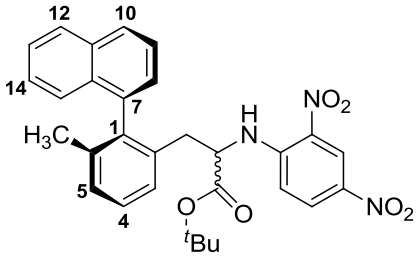
Potassium carbonate (22 mg, 0.16 mmol) was dissolved in water (180 μL), and this solution was added to a stirred solution of the enantioenriched major diastereomer of *tert*-butyl 3-(3-(bromomethyl)-2-(naphthalen-1-yl)phenyl)-2-((diphenylmethylene)amino)propanoate **108** (19 mg, 0.032 mmol) in methanol (720 μL). The reaction mixture was stirred for 120 h at RT, before 1.0 M aqueous solution of hydrochloric acid (250 μL) was added. The mixture was then stirred for a further 24 h at RT, and subsequently diluted with diethyl ether (5.0 mL) and washed with aqueous potassium carbonate (1.5 mL) and water (2 × 7.5 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [1:1]) afforded the biaryl **113** as a colourless oil (6.0 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.79 (2H, m), 7.53-7.33 (4H, m), 7.31-7.18 (4H, m) [aromatics], 3.94 (1H, d, *J* 12.6, CH_2OMe), 3.83 (1H, d, *J* 12.6, CH_2OMe'), 3.11-3.01 (4H, m, C*H*NH_2, OCH_3), 2.67 (1H, dd, *J* 13.6, 5.5, CH_2CHNH_2), 2.21 (1H, dd, *J* 13.6, 8.9, CH_2CHNH_2'), 1.44 (2H, app. br s, NH_2), 1.16 (9H, s, C(CH_3)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 ($CO_2{}^tBu$), 140.5, 138.7, 137.8, 137.0, 133.6, 132.9, 132.2, 129.3, 128.4, 128.0, 127.9, 127.5, 126.4, 126.0, 125.9, 125.3 [aromatics], 80.8 ($C(CH_3)_3$), 72.3 (CH_2OMe), 58.2 (OCH_3), 55.6 ($CHNH_2$), 39.7 (CH_2CHNH_2), 27.8 ($C(CH_3)_3$).

m/z LRMS (ESI^+) 392.2 $[M+H]^+$; HRMS (ESI^+) 392.2216 ($[M+H]^+$, $C_{25}H_{30}NO_3$ requires 392.2226).

tert-Butyl 2-((2,4-dinitrophenyl)amino)-3-(3-methyl-2-(naphthalen-1-yl)phenyl)propanoate (114)



1.0 M aqueous solution of hydrochloric acid (250 μL) was added to a solution of the enantioenriched major diastereomer of *tert*-butyl 2-((diphenylmethylene)amino)-3-(3-methyl-2-(naphthalen-1-yl)phenyl)propanoate **111** (19 mg, 0.037 mmol) in methanol:water [1:1] (1.4 mL). The reaction mixture was stirred for 24 h at RT. The mixture was then diluted with ethyl acetate (5.0 mL) and washed with aqueous potassium carbonate (1.5 mL) and water (2 × 7.5 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was subsequently dissolved in acetone:water [5:1] (1.2 mL), before 1-fluoro-2,4-dinitrobenzene (6.8 mg, 0.037 mmol) and sodium bicarbonate (6.1 mg, 0.073 mmol) were added. The reaction mixture was heated to 50 °C and stirred.

After 2 h, the mixture was diluted with ethyl acetate (5.0 mL) and washed with water (2 × 7.5 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [10:1]) afforded the biaryl **114** as an orange oil (8.2 mg, 42%).

IR (neat) ν_{max} 3306, 2892, 1722, 1611, 1584, 1518, 1336, 1274, 1133 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (1H, d, *J* 2.6), 8.74 (1H, d, *J* 7.2), 7.98-7.91 (2H, m), 7.62-7.53 (2H, m), 7.46-7.41 (1H, m), 7.38 (1H, d, *J* 7.0), 7.27-7.23 (2H, m), 7.22-7.18 (2H, m), 7.14-7.09 (1H, m) [aromatics], 4.99 (1H, d, *J* 9.5, N*H*), 3.89-3.80 (1H, m, C*H*$CO_2{}^t$Bu), 2.85-2.73 (2H, m, ArCH_2), 1.85 (3H, s, ArCH_3), 1.24 (9H, s, C(CH_3)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (*C*$O_2{}^t$Bu), 146.4, 139.5, 137.9, 137.6, 136.1, 134.0, 133.8, 131.8, 130.5, 129.7, 129.5, 128.7, 128.5, 128.0, 128.0, 127.5, 127.0, 126.6, 125.8, 124.9, 124.1, 113.2 [aromatics], 83.3 (*C*(CH$_3$)$_3$), 57.1 (*C*HCO$_2{}^t$Bu), 37.9 (Ar*C*H$_2$), 27.8 (C(*C*H$_3$)$_3$), 20.4 (Ar*C*H$_3$).

m/z LRMS (ESI^+) 550.2 $[M+Na]^+$; HRMS (ESI^+) 550.1948 ($[M+Na]^+$, $C_{30}H_{29}N_3O_6Na$ requires 550.1954).

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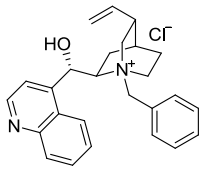
7. Appendices

7.1 **Appendix A –** Index of Phase-Transfer Catalysts Used

C1



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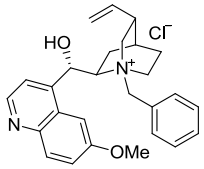

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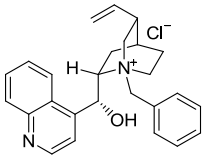

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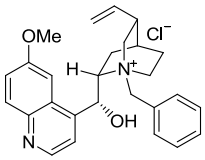

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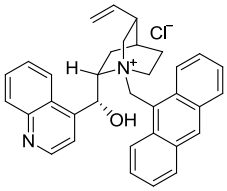

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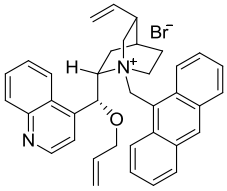

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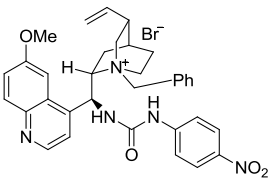

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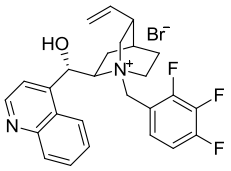

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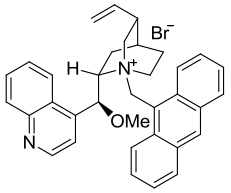

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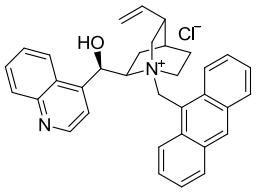

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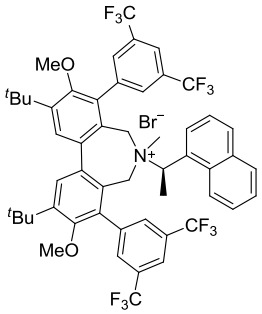

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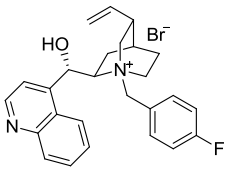

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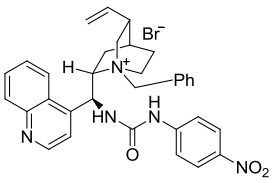

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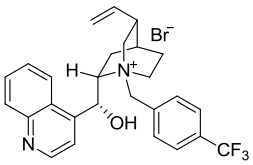

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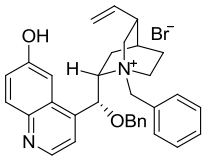
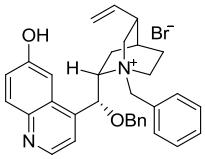
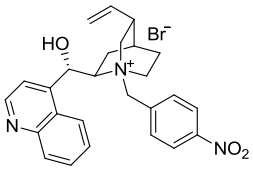


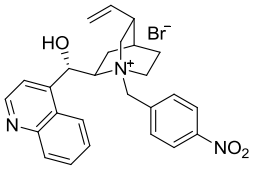
C16



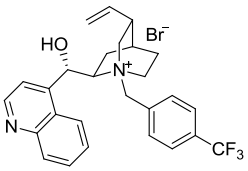
C17



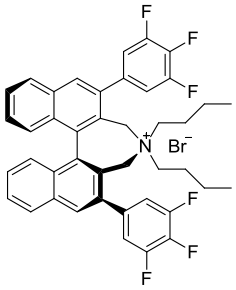
C18



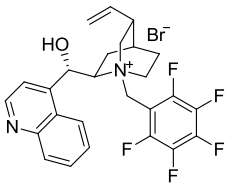
C19



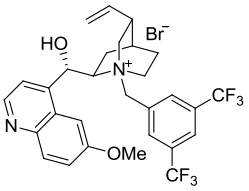
C20



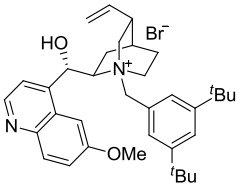
C21



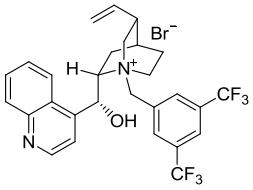
C22



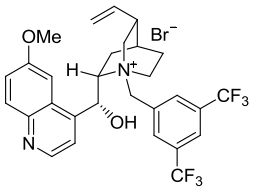
C23



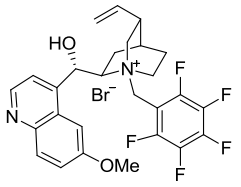
C24



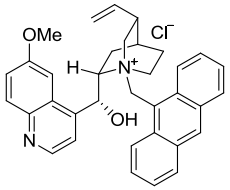
C25



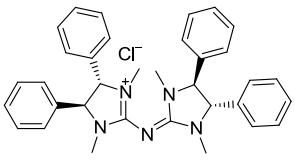
C26



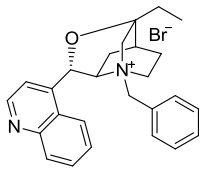
C27



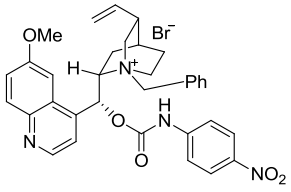
C28



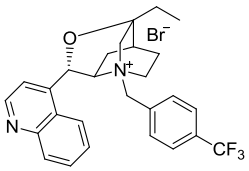
C29



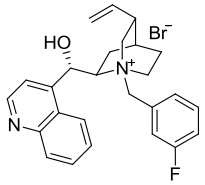
C30



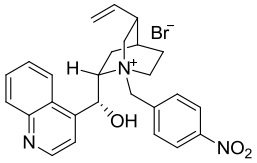
C31



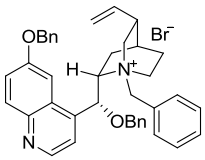
C32



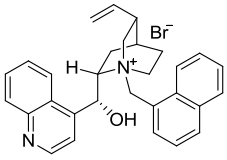
C33



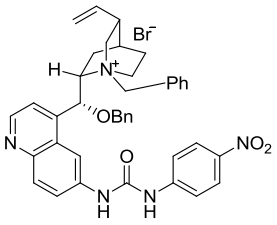
C34



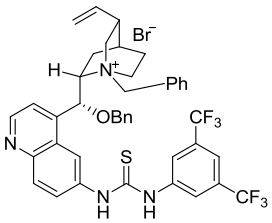
C35



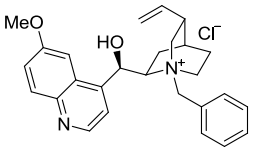
C36



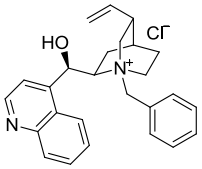
C37



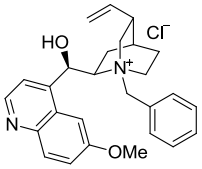
C38



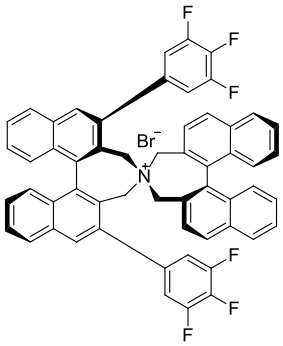
C39



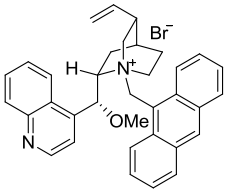
C40



C41

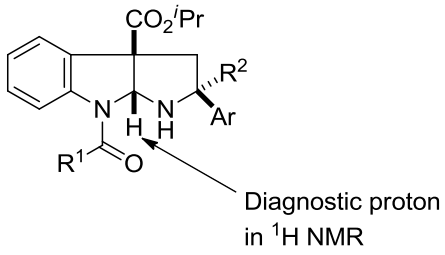


C42



7.2 **Appendix B –** Assignment of Stereochemistry of Pyrroloindolines

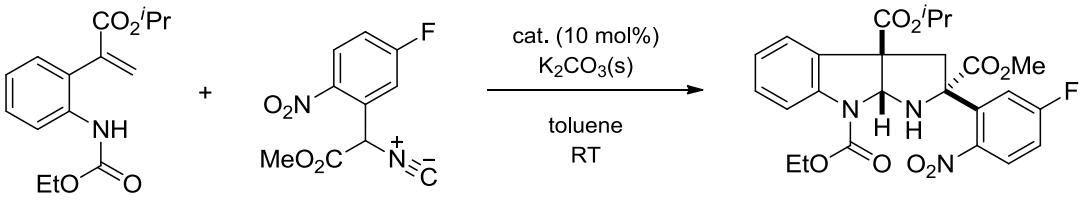
Assignment of relative stereochemistry of compounds was done by analogy to compounds **60** and **61**, whose relative stereochemistry was unambiguously assigned by X-ray crystallography. The ring junction proton was used as a diagnostic shift in the ^{1}H NMR spectra as follows:



As an illustration, a comparison of several compounds is shown below. The major diastereomer exhibits a peak with a lower chemical shift in the ^{1}H NMR spectra:

Compound	**^{1}H Shift (Major)**	**^{1}H Shift (Minor)**
60 (X-ray)	6.33	6.41
61 (X-ray)	6.40	6.50
64	6.35	6.45
74	5.58	6.12
76	5.55	6.11
77	5.62	6.13
	Lower δ	*Higher δ*

7.3 **Appendix C –** Catalyst Screening in Reaction to Form Pyrroloindoline **60**

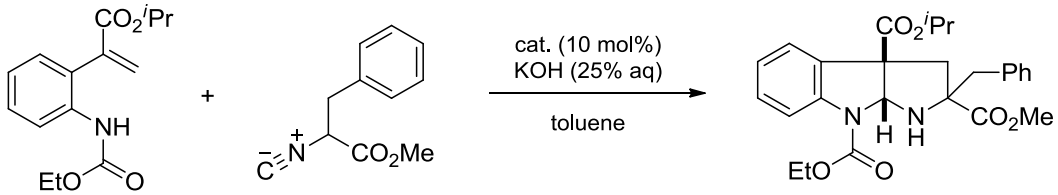


8 **44** **60**

Catalyst	e.r. of 60	Catalyst	e.r. of 60
C8	51:49	**C21**	54:46
C9	55:45	**C28**	52:48
C10	53:47	**C29**	54:46
C11	66:34	**C30**	52:48
C12	65:35	**C31**	48:52
C13	33:67	**C32**	57:43
C14	61:39	**C33**	55:45
C15	61:39	**C34**	48:52
C16	50:50	**C35**	56:44
C17	49:51	**C36**	53:47
C19	51:49	**C37**	56:44
C20	56:44	**C38**	52:48

Reactions carried out on 10 mg scale. Single diastereomer observed in all cases.
Reagents and conditions: phase-transfer cat. (10 mol%), K_2CO_3(s) (5.0 eq), toluene, RT.

7.4 **Appendix D –** Catalyst Screening in Reaction to Form Pyrroloindoline **56**

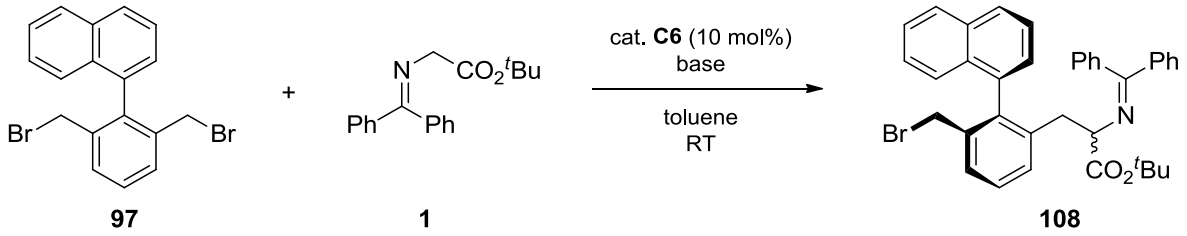


8 **33** **56**

Catalyst	e.r. of DS1	e.r. of DS2	d.r. (DS1:DS2)
C5	27:43	13:87	1.0:1.5
C5 *(at −20 °C)*	24:76	8:92	1.0:1.5
C8	88:12	55:45	1:1
C12	90:10	52:48	1:1
C14	25:75	56:44	1.0:2.0
C16	91:9	55:45	1:1
C17	89:11	41:59	1.0:1.5
C18	16:84	52:48	1.0:2.3
C19	91:9	47:53	1:1
C19 *(at −20 °C)*	95:5	58:42	1:1
C20	82:18	83:17	1:1
C21	84:16	37:63	1:1
C28	50:50	53:47	1.0:2.3
C29	45:55	50:50	1:1
C30	52:48	50:50	1.0:1.5
C31	43:57	50:50	1:1
C32	91:9	54:46	1:1
C34	16:84	18:82	1.0:2.0
C39	18:82	52:48	1.0:2.3
C40	45:55	40:60	1.0:2.3
C41	43:57	27:73	1:1

Reactions carried out on 10 mg scale. Values for d.r. tentatively determined by chiral HPLC.
Reagents and conditions: phase-transfer cat. (10 mol%), 25% KOH(aq) (5.0 eq), toluene, RT (unless otherwise stated).

7.5 **Appendix E –** Base Screening in Reaction to Form Biaryl **108**

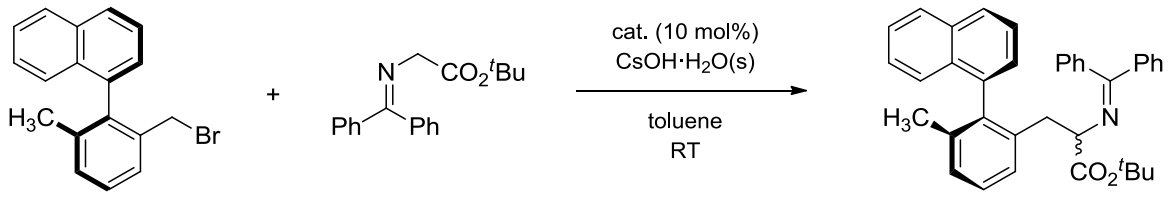


97 **1** **108**

Base	**d.r. of 108**	**e.r.$_{maj}$**	**e.r.$_{min}$**
KOH (50% aq)	4.6:1	10:90	81:19
KOH (25% aq)	4.2:1	10:90	78:22
KOH (5% aq)	2.4:1	9:91	75:25
KOH(s)	4.0:1	13:87	71:29
$CsOH{\cdot}H_2O$(s)	4.0:1	13:87	72:28
Cs_2CO_3(s)	2.4:1	12:88	56:44
K_3PO_4 (sat. aq)	3.8:1	14:86	70:30

Reactions carried out on 6 mg scale. Values for d.r. tentatively determined by chiral HPLC.
Reagents and conditions: Corey cat. **C6** (10 mol%), base (2.0 eq), toluene, RT.

7.6 **Appendix F –** Catalyst Screening in Reaction to Form Biaryl **111**

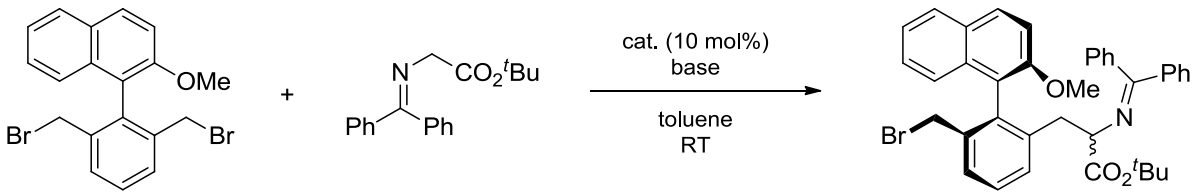


rac-**96** **1** **111**

Catalyst	d.r. of 111	e.r.$_{maj}$	e.r.$_{min}$
C2	1.9:1	57:43	52:48
C3	2.0:1	27:73	40:60
C4	1.3:1	48:52	57:43
C5	2.5:1	54:46	58:42
C6	3.7:1	16:84	12:88
C6 *[with KOH (50% aq) as base]*	2.1:1	15:85	6:94
C6 *[with DCM as solvent]*	1.6:1	13:87	5:95
C11	3.0:1	98:2	97:3
C11 *[with KOH (50% aq) as base]*	3.4:1	97:3	96:4
C42	3.1:1	49:51	36:64

Reactions carried out on 6 mg scale. Values for d.r. tentatively determined by chiral HPLC.
Reagents and conditions: phase-transfer cat. (10 mol%), CsOH·H_2O(s) (2.0 eq), toluene, RT (unless otherwise stated).

7.7 **Appendix G –** Screening in Reaction to Form Biaryl **112**



100 **1** **112**

Catalyst	Base	d.r. of 112	e.r.$_{maj}$	e.r.$_{min}$
C2	CsOH·H_2O(s)	1.0:1	48:52	50:50
C2	KOH (50% aq)	1.5:1	45:55	60:40
C3	CsOH·H_2O(s)	1.1:1	52:48	28:72
C3	KOH (50% aq)	1.1:1	46:54	38:62
C4	CsOH·H_2O(s)	1.3:1	47:53	48:52
C4	KOH (50% aq)	1.5:1	50:50	46:54
C6	KOH (50% aq)	2.5:1	76:24	8:92
C11	KOH (50% aq)	1.0:1	22:78	98:2

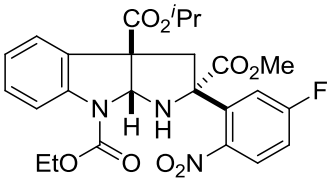
Reactions carried out on 6 mg scale. Values for d.r. tentatively determined by chiral HPLC.
Reagents and conditions: phase-transfer cat. (10 mol%), base (2.0 eq), toluene, RT.

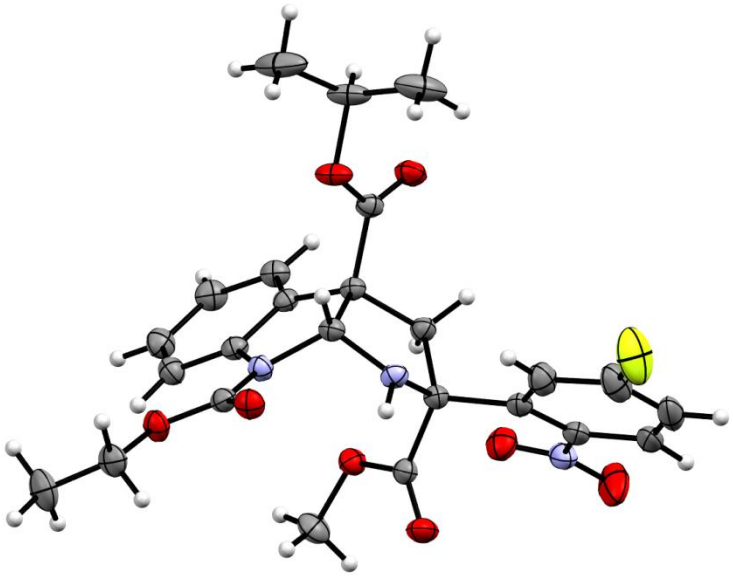
7.8 **Appendix H –** NOE NMR Spectra for Pyrroloindoline **71**

7.9 **Appendix I** – X-ray Crystallography Data

The crystallographic information files (.cif) for all X-ray structures provided can be found on the attached CD.

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (60)**



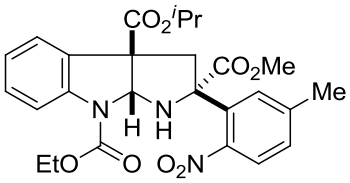


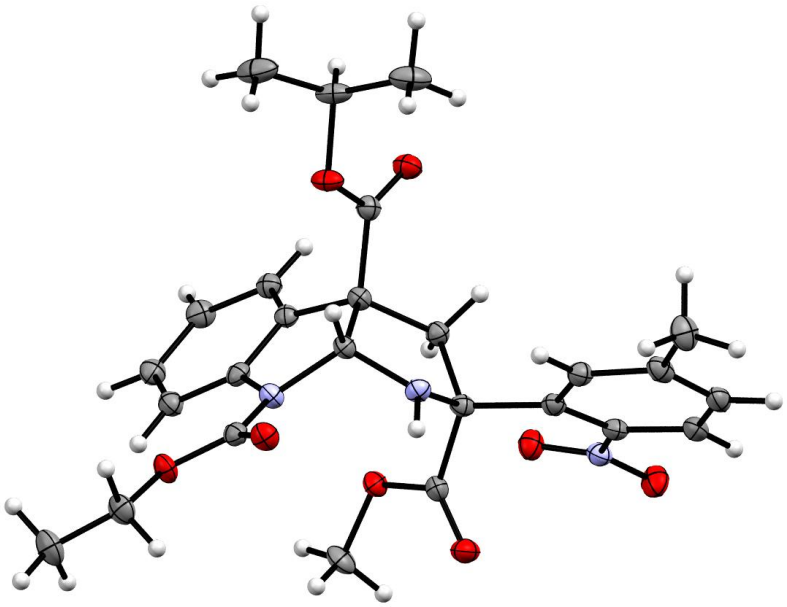
Key data and refinement for the crystal structure of compound **60**

Identification code	103RWD13	
Empirical formula	$C_{25}H_{26}FN_3O_8$	
Formula weight	515.49	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 13.9144 Å	α = 90°
	b = 7.4321 Å	β = 97.5321°
	c = 23.8094 Å	γ = 90°
Volume	2438.01 $Å^3$	
Z,Z'	Z: 4 Z': 0	
Density (calculated)	1.404 g cm^{-3}	
Absorption coefficient	0.937 mm^{-1}	
F(000)	1080.0	

Crystal size	0.10 × 0.10 × 0.10 mm^3
Theta range for data collection	3.204° to 76.757°
Reflections collected	87116
Independent reflections	5116
Absorption correction	Multi-scan
Refinement method	Full-matrix least squares on F^2
Goodness-of-fit on F^2	1.042
Final R indices [I>2σ(I)]	R^1 = 0.0376, wR^2 = 0.0964
R indices (all data)	R^1 = 0.0377, wR^2 = 0.0964

(2*S,3a*R**,8a*R**)-8-Ethyl 3a-isopropyl 2-methyl 2-(5-methyl-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (61)**



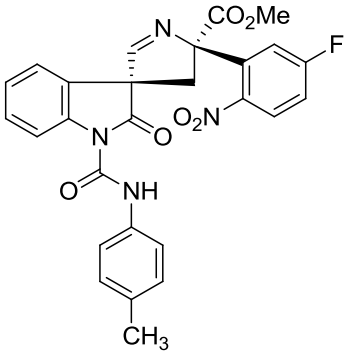


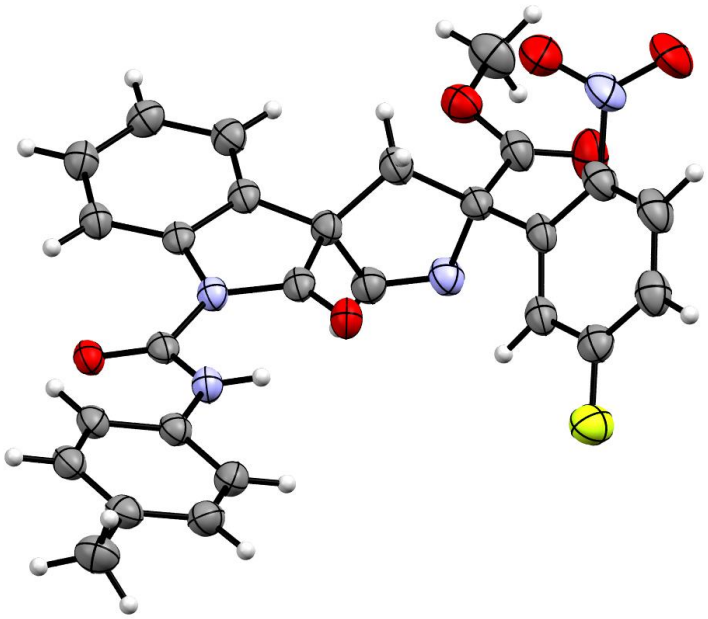
Key data and refinement for the crystal structure of compound **61**

Identification code	155RWD14	
Empirical formula	$C_{26}H_{29}N_3O_8$	
Formula weight	511.52	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 13.7695 Å	α = 90°
	b = 7.3850 Å	β = 97.695°
	c = 24.6016 Å	γ = 90°
Volume	2479.15 $Å^3$	

Z,Z'	Z: 4 Z': 0
Density (calculated)	1.370 g cm^{-3}
Absorption coefficient	0.095 mm^{-1}
F(000)	1080.0
Crystal size	0.01 × 0.03 × 0.05 mm^3
Theta range for data collection	1.619° to 26.468°
Reflections collected	29024
Independent reflections	5174
Absorption correction	Multi-scan
Refinement method	Full-matrix least squares on F^2
Goodness-of-fit on F^2	1.023
Final R indices [I>2σ(I)]	R^1 = 0.0377, wR^2 = 0.0963
R indices (all data)	R^1 = 0.0406, wR^2 = 0.1069

(3*R,5'*R**)-Methyl 5'-(5-fluoro-2-nitrophenyl)-2-oxo-1-(*p*-tolylcarbamoyl)-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (79)**





Key data and refinement for the crystal structure of compound **79**

Identification code	178RWD14
Empirical formula	$C_{27}H_{21}FN_4O_6$
Formula weight	516.48
Temperature	100 K
Wavelength	0.68890 Å
Crystal system	monoclinic
Space group	P $2_1/c$

Unit cell dimensions	a = 12.7056 Å	α = 90°
	b = 26.8163 Å	β = 95.887°
	c = 7.0360 Å	γ = 90°
Volume	2384.64 $Å^3$	
Z,Z'	Z: 4 Z': 0	
Density (calculated)	1.439 g m^{-3}	
Absorption coefficient	0.100 mm^{-1}	
F(000)	1072.0	
Crystal size	0.01 × 0.02 × 0.05 mm^3	
Theta range for data collection	2.146° to 26.703°	
Reflections collected	29242	
Independent reflections	4802	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.978	
Final R indices [I>2σ(I)]	R^1 = 0.0724, wR^2 = 0.1633	
R indices (all data)	R^1 = 0.0894, wR^2 = 0.1726	