Organic Brønsted Acid-Catalysed Enantioselective *N*-Acyliminium Cyclisation Cascades

Volume 1 – Introduction and Results and Discussion

A thesis submitted in partial fulfilment of the requirement for the degree of

Doctor of Philosophy (D. Phil.)

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Supervisor: Professor Darren J. Dixon

Content

Volume 1

Acknowledgements

I would like to take the opportunity to thank all the people who have participated in the realisation of this thesis. Because everything started back in Manchester, three years ago, this is where I shall start. I am very grateful to Wolfgang who was my mentor during the first year of my PhD, I have probably inherited his legendary clumsiness but I had a great time working next to the «Wolfypedia». Of course I have to mention my mates Johnny Boy and Chris Knox (a legend from the eastern point in Vietnam to the western point in Europe) for the good fun and great chats after a few pints! A special thank you to Adam, for his help during my first year.

September 2008 was the big move to Oxford. I would like to thank the labmates and friends I have (re)discovered or met there. I shall firstly thank our great batch of newbies (☺): the Toad, for his... stench? ... more seriously, for setting a good atmosphere in G6, for giving me the opportunity to discover **the** P.T. (never again!) and for being able to look in opposite directions the whole time; Dave, for being sarcastic and being able to accept my sarcasms; Ali, for her unalterable good mood and enthusiasm; Marta, for being there when I needed and for comforting me when I was sad. A special thank you to Chloe for her help, «viva» team *N*-acyliminium cyclisation cascades! I cannot forget to mention Dr. Pavol Jakubec a.k.a. Yoda, truly the greatest chemist I have had the chance to meet, an inspiration and mentor for the last couple of years of my PhD. Thank you very much for your help, for all the productive discussions and for showing all of us what it is to work for the group.

Thanks to all other members of the Dixon Group, past and present, for their help and for the laughter over the past three years.

Finally, I would like to thank Ian for being very helpful and for the nice chats down in Kent and Darren for giving me the opportunity to work in his group and for his help and support throughout the past three years.

This thesis is dedicated to my parents.

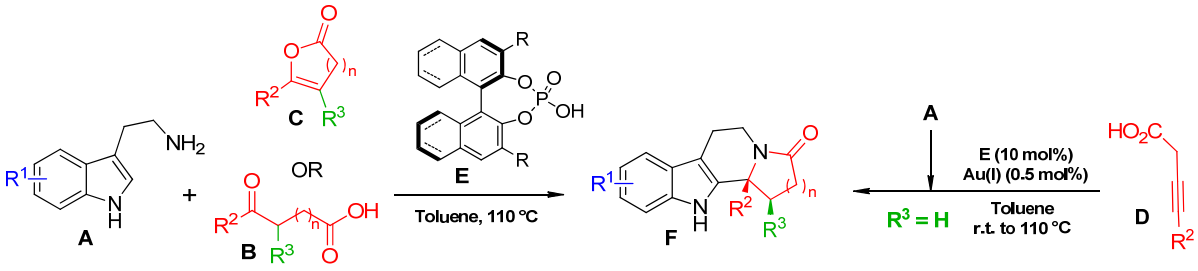
Ça n'a pas toujours été facile, mais vous avez toujours été derrière moi.

On y est finalement arrivé.

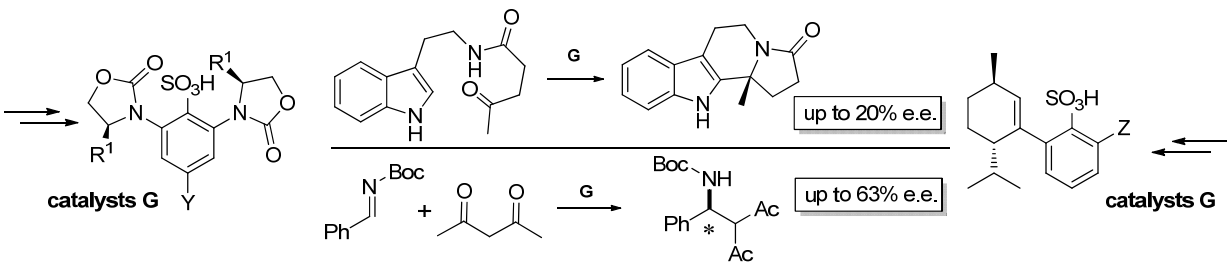
Merci d'être là.

This thesis concerns the development of the first BINOL phosphoric acid **E** (BPA) catalysed enantioselective *N*-acyliminium cyclisation reactions and their incorporation into domino sequences that allow for the construction of architecturally complex enantioenriched polycycles in a single step from easily accessible starting materials.

More specifically, this thesis deals with the discovery of a BPA-catalysed enantioselective *N*-acyliminium cyclisation cascade of enol lactones **C** and tryptamines **A**. Its extension to a doubly catalysed process involving gold(I) to cycloisomerise alkynoic acids **D** and a BPA to effect the enantioselective *N*-acyliminium cyclisation is presented. In addition, the exploitation of this method in highly diastereo- and enantioselective *N*-acyliminium cyclisations of oxoacids **B** and tryptamines **A** and in a site isolated base-catalysed Michael addition / acid-catalysed *N*-acyliminium cyclisation cascade is described.



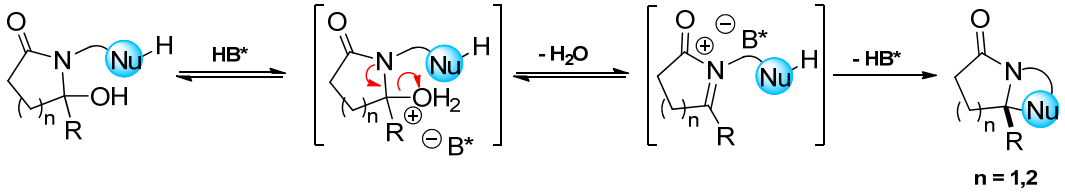
A study on the proposed mechanism and model for the origin of enantioselectivity is discussed, based on experimental data and a computational study. As a separate part of our programme, the development of a new class of stronger Brønsted acids, chiral benzenesulphonic acids **G**, is described. The optimisation of the synthetic routes as well as the synthesis of a library of acids is presented and their assessment in precedented reactions is discussed.



Introduction:

In the last decade, a myriad of methodologies using small organic molecules as viable alternatives for transition metal catalysts has been reported. Prominent amongst these is the emergence of chiral Brønsted acids to achieve enantioselective transformations.[1] In addition, the *one step-one vessel* approach to the synthesis of complex targets is very inefficient compared to cascade sequences. Therefore our work focuses on developing new methodologies and catalysts for asymmetric one-pot cyclisation cascades catalysed by Brønsted acids.

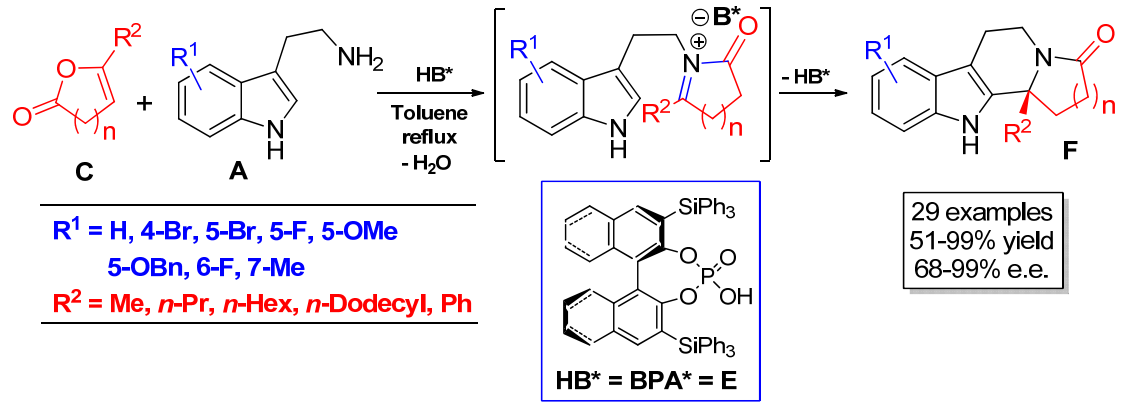
To date, we have investigated the feasibility of a cyclisation *via* a π-nucleophilic attack onto an *N*-acyliminium ion.[2] It is believed that in the transition state the pro-chiral *N*-acyliminium ion is associated to the chiral conjugate base of the Brønsted acid catalyst, and that tight ion pairing effectively shields one face of the planar intermediate giving rise to the preferential formation of one enantiomer.



Scheme 1: Concept of asymmetric Brønsted acid-catalysed cyclisation

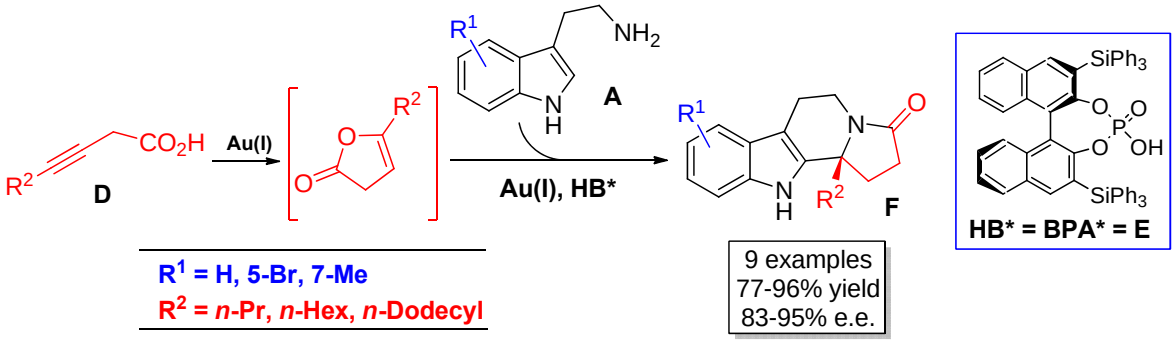
Discussion:

A Pictet-Spengler type cyclisation was developed using chiral BINOL derived phosphoric acids (BPAs) as organocatalysts. β-Carbolines **F** can be generated in excellent yields through a cascade sequence, from an enol lactone **C** and a substituted tryptamine **A** with high enantiocontrol over the stereochemistry of the newly formed quaternary centre (Scheme 2). The cascade is suitable for scale-up since the catalyst loading can be lowered to 1 mol% with only a slightly decreased enantiomeric excess (1 example, 99% e.e. with 10 mol% catalyst vs. 96% e.e. with 1 mol% catalyst loading).



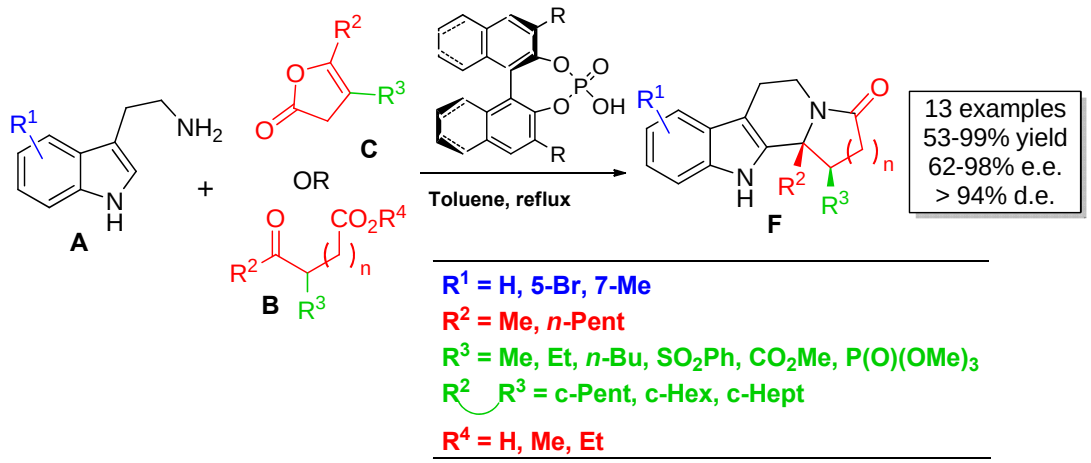
Scheme 2: Highly enantioselective Brønsted acid-catalysed cascades applied to the synthesis of β-carbolines

The impressive robustness of this cascade allowed us to combine it with another catalytic process, in a one-pot procedure, where an alkynoic acid **D** is used to generate an enol lactone *in situ*, and the chiral BPA **E** promotes the cyclisation, with no erosion being observed of the enantioselectivity. This last transformation constitutes a powerful and practically simple method to execute a four-bond forming cascade sequence, and is one of the very few examples of compatibility between a Lewis acid- and Brønsted acid-catalysed asymmetric transformation (Scheme 3).[2,4]



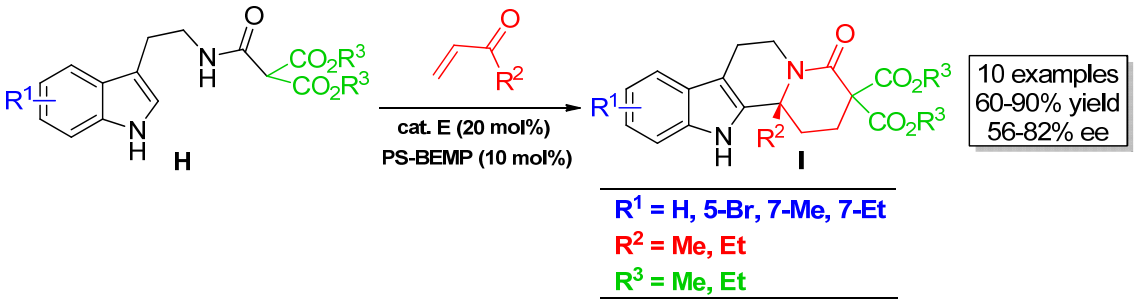
Scheme 3: Doubly catalysed highly enantioselective Brønsted acid-catalysed *N*-acyliminium cyclisation cascade

Furthermore, we discovered that when a disubstituted enol lactone **C** was used as reaction partner, β-carbolines **F** were obtained in high yields, high enantioselectivities and as single diastereoisomers. This powerful transformation was further extended to the use of simple oxoacid reaction partners **B** in a high yielding, highly diastereo- and enantioselective cascade (Scheme 4).[2,3]



Scheme 4: Highly diastereo- and enantioselective synthesis of complex β-carbolines

Recently an unanticipated reactivity was discovered in our laboratory. When a pro-nucleophile **H** was treated with both a polymer-supported base (PS-BEMP) and a bulky chiral phosphoric acid **E** in the presence of an excess amount of a vinyl ketone (Michael acceptor), a Michael addition occurred (> 90% conversion) followed by an enantioselective *N*-acyliminium cyclisation. This unprecedented one-pot (simultaneous addition of reagents) base-catalysed Michael addition / acid-catalysed *N*-acyliminium cyclisation was further investigated and is showing scope for the construction of complex functionalised β-carbolines **I** in good yields and moderate to good enantioselectivities (Scheme 5).[5]

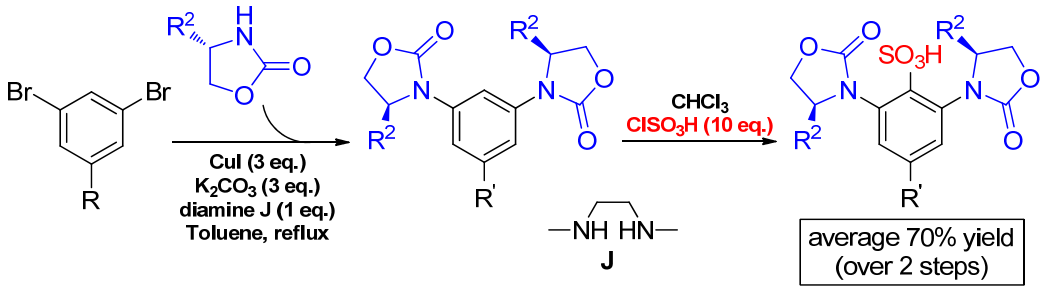


Scheme 5: Novel one-pot base-catalysed Michael addition / acid-catalysed enantioselective *N*-acyliminium cyclisation

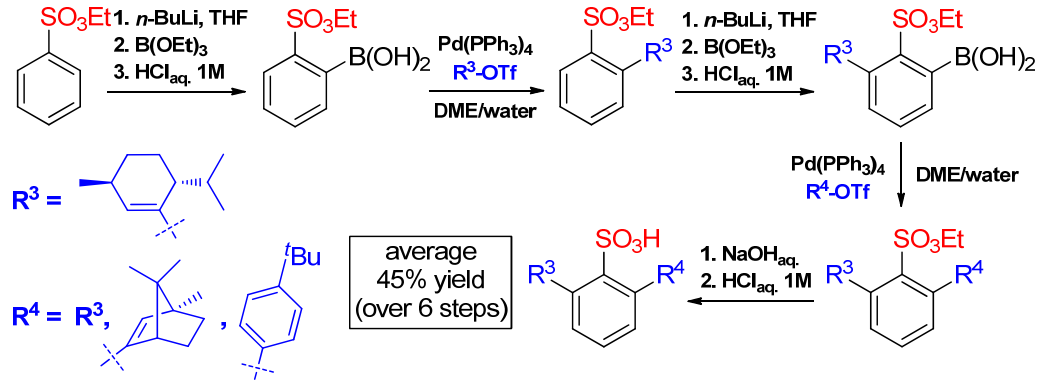
Although chiral phosphoric acids showed an impressive versatility in asymmetric organocatalysis, a clear limitation is their poor acidity which limits them to the catalysis of reaction between reactive moieties. To overcome this barrier we decided to develop a new

category of chiral organic Brønsted acids and our attention naturally turned to benzenesulphonic acid derivatives as they would be chiral mimics of *para*-toluenesulphonic acid.

We have developed two families of benzenesulphonic acids, one was based on chiral oxazolidinones as chiral auxiliaries and the other based on all-carbon chiral auxiliaries (derived from chiral pool ketones) (Schemes 6 and 7).

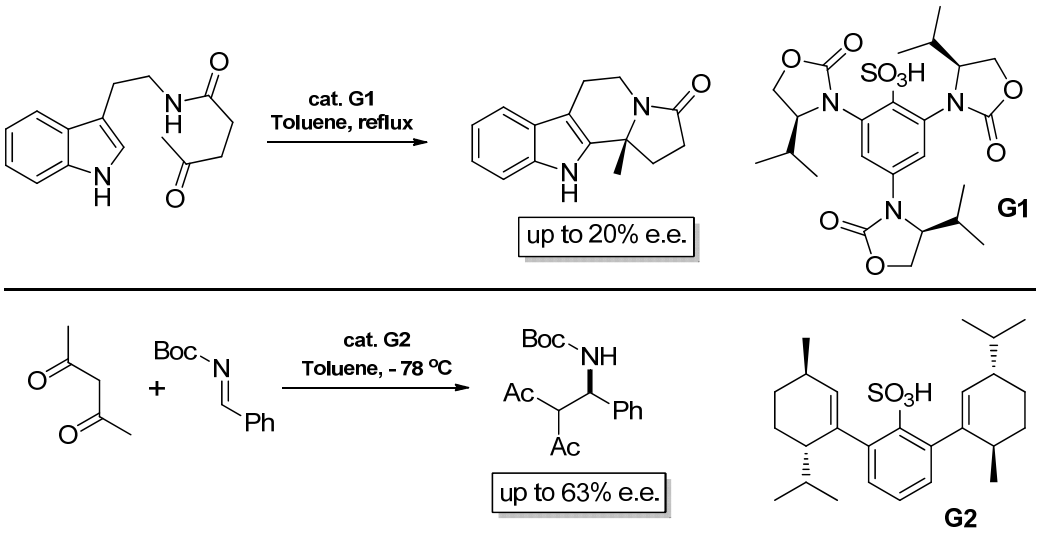


Scheme 6: Synthetic routes to new oxazolidinone-derived chiral benzenesulphonic acids



Scheme 7: Synthetic routes to new all-carbon auxiliary-substituted new chiral benzenesulphonic acids

Their enantioinduction was assessed in benchmark reactions and our preliminary results were very promising since up to 20% e.e. was obtained in our model *N*-acyliminium cyclisation and an impressive 63% e.e. was reached in the Mannich addition of acac to *N*-Boc benzaldimine (Scheme 8).



Scheme 8: Assessment of novel chiral benzenesulphonic acids

References:

[1] a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. & Cat.*, **2006**, *348*, 999; b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.*, **2007**, *107*, 5713.

[2] Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.*, **2009**, *131*, 10796.

[3] Holloway, C. A.; Muratore, M. E.; Storer, R. I; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720.

[4] Muratore M. E.; Holloway, C. A.; Shi, L.; Storer, R. I.; Dixon, D. J. *Full paper in preparation*

[5] Muratore M. E.; Storer, R. I.; Dixon, D. J. *Manuscript in preparation*

Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given a reference to a published source or a thesis. The results outlined have not previously been submitted for a degree, diploma, or other qualification at any University. Text taken from another source will be enclosed in quotation marks and a reference given.

Michaël E. Muratore 01 February 2011

Abbreviations

ºC: degrees Celsius

Å: angstrom

Ac: acetyl

Acac: acetylacetone

ADA or aza-DA: aza-Diels-Alder

Alk: alkyl

Ar: aryl, aromatic group, heteroaromatic group

BAMOL: 1,1′-biaryl-2,2′-dimethanol - family of axially chiral diols

BEMP: 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine

BINOL: 1,1′-binaphthalene-2,2′-diol

Bn: benzyl

Boc: *tert*-butyloxycarbonyl

BPA: BINOL phosphoric acid

br: broad

BSA: benzenesulphonic acid

Bu: butyl

CI: Chemical Ionisation

cm: centimetre

Conv or conv.: conversion

COSY: COrrelation SpectroscopY

d: doublet

dd: doublet of doublets

de or d.e.: diastereomeric excess

dr or d.r.: diastereomeric ratio

DEPT: Distortionless Enhancement by Polarization Transfer

DMAP: *N*,*N*-dimethylamino pyridine

DMF: *N*,*N*-dimethylformamide

DMSO: dimethylsulfoxide

DPEN or DPEDA: diphenylethylenediamine

EDG: electron-donating group

ee or e.e.: enantiomeric excess

e.g.: *exempli gratia* = for example

EI: Electron Impact

er or e.r.: enantiomeric ratio

eq.: equivalent(s)

ES: ElectroSpray

ESI: ElectroSpray Ionisation

Et: ethyl

et al.: *et alii* = and others

etc.: *et cetera* = and so on

EWG: electron-withdrawing group

g: gram(s)

h: hour(s)

HEH: Hantzsch ester: diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

HMBC: Heteronuclear Multiple Bond Correlation experiment

HMQC: Heteronuclear Multiple-Quantum Coherence experiment

HPLC: High Performance Liquid Chromatography

HRMS: High-Resolution Mass Spectrometry

HSQC: Heteronuclear Single-Quantum Coherence experiment

Hz: Hertz

i or ^{i}: iso

IPA: IsoPropyl Alcohol or isopropanol (propan-2-ol)

IR or I.R.: infra-red

LDA: lithium diisopropylamide

Lit.: literature

M: molar

m: meta

m: multiplet

m-xylyl: *meta*-xylyl or 3,5-dimethylphenyl

max: maximum

m/z: mass-to-charge ratio

Me: methyl

mg: milligram

MHz: megaHertz

min: minute(s)

mL: millilitre

µL: microlitre

mmol: millimole

mol: mole

MOM: methoxy methyl

m.p.: melting point

MS: mass spectrometry

M.S.: molecular sieves

n: normal, linear chain

N.B.: *nota bene*

NC: no conversion

nm: nanometre

NMR: Nuclear Magnetic Resonance

Nu: nucleophile

N.R.: no reaction

o: ortho

p: para

Ph: phenyl

PG or Pg: protecting group

ppm: parts per million

Pr: propyl

q: quartet

quat.: quaternary

quint: quintet

R: any group (alkyl, aryl, H *etc.*)

rac. or rac: racemic

r.t.: room temperature

s: singlet

sept: septet

sext: sextet

SR: specific rotation

t: triplet

TADDOL: trans-α,α′-(dimethyl-1,3-dioxolane-4,5-diyl)bis(diarylmethanol) /

(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane

TBDPS: *tert*-butyldiphenylsilyl (^{t}BuPh$_2$Si-)

TBME: *tert*-butyl methyl ether

TBS or TBDMS: *tert*-butyldimethylsilyl (^{t}BuMe$_2$Si-)

t-Bu or ^{t}Bu: *tert*-butyl

Temp.: temperature

TES: triethylsilyl (Et_3Si-)

TFA: trifluoroacetic acid

TFAA: trifluoroacetic anhydride

TIPS: triisopropylsilyl ($^{i}Pr_3Si$-)

THF: tetrahydrofuran

TLC: Thin Layer Chromatography

TMS: trimethylsilyl or trimethylsilane (Me_3Si-)

TPS BPA: 3,3′-triphenylsilyl BPA

TRIP BPA: 3,3′-(1,3,5-triisopropylphenyl) BPA

Trt: trityl ot triphenylmethyl (-CPh_3)

Ts: *para*-toluenesulphonyl

TS: transition structure

p-TsOH or *p*TSA: *para*-toluenesulphonic acid

USD: United States of America dollar

UV or U.V.: ultra-violet

Chapter One: General Introduction

1.1 General overview and project aims

For many years, one major challenge of organic chemistry has been to discover and develop new methodologies to create carbon-carbon bonds in a highly efficient and selective manner. Many efforts have been made to find new inventive and original methods to bind two carbons and particularly to create new ring systems. The aim of this project was to develop a new approach to various reactions, especially cyclisation reactions, involving formal stabilised carbocations that are trapped by nucleophiles.

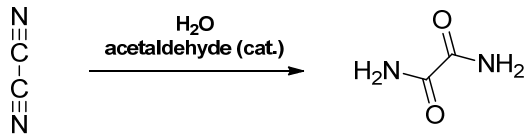
More specifically the development of methodologies to catalyse the enantioselective cyclisation of intramolecular π-nucleophiles onto *N*-acyliminium ions generated *in situ*, using organic Brønsted acid catalysts was pursued.

A major aim of our project was to develop attractive and general methods for these cyclisations. Taking advantage of their robustness and flexibility, the application to various domino sequences was studied. An effort was made to generalise the concept by developing new catalysts allowing for enantioselective transformations on a broader range of substrates.

1.2 History of organocatalysis

Organocatalysis can be defined as the use of a small organic molecule (less than a few thousands $g.mol^{-1}$) to increase the rate of a reaction or to activate a substrate.

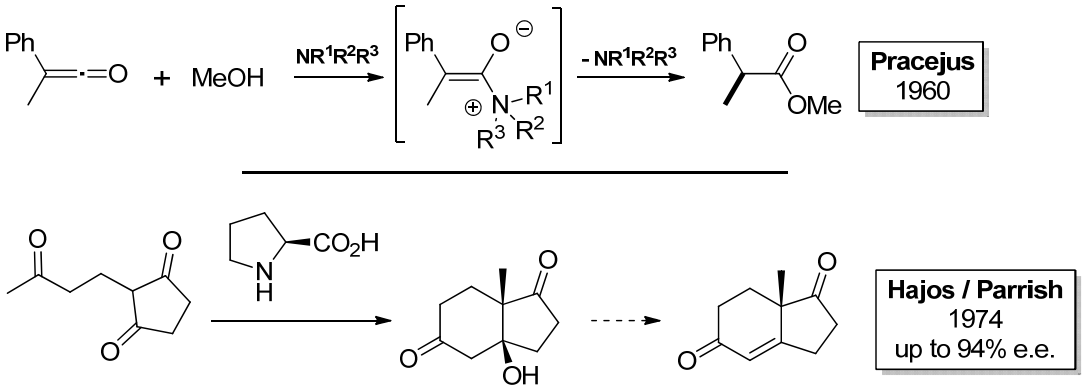
The first appearance of organocatalysis in the literature dates from the middle of the 19th century when Justus Liebig used acetaldehyde as a catalyst for oxamide formation from dicyan (Scheme 1.1).[1]



Scheme 1.1. Acetaldehyde as catalyst, first example of organocatalysis

Until the 1960s, very few examples of the use of organic molecules for catalysis can be found. Nevertheless, there is an early example of enantioselective organocatalysis dating from 1912; Bredig used alkaloids to synthesise cyanohydrins by the addition of cyanide to aldehydes observing moderate enantioselectivity also noting that quinine and quinidine gave opposite enantiomers of the product.[2]

This discovery was followed in 1960 by Pracejus who demonstrated the efficiency of using strychnine for the methanolysis of a ketene,[3] pioneering the use of organocatalysis for efficient enantioselective synthesis (Scheme 1.2). In 1974, Hajos and Parrish supported this work by developing a new methodology for a highly enantioselective Robinson annulation, leading to Wieland-Mieschler ketone, a reaction that is nowadays known by their names (Scheme 1.2).[4]



Scheme 1.2. First example of enantioselective organocatalysis

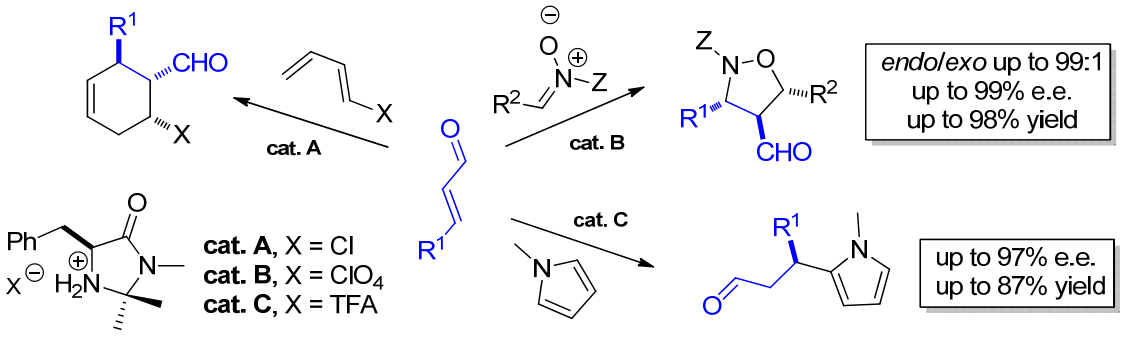
Despite this progress, for many years organocatalysis has been underestimated and poorly studied while transition metal catalysis was thoroughly investigated, leading to a shared Nobel Prize in 2001 for B. Sharpless for his contribution in asymmetric catalysis in oxidation

reactions and W. S. Knowles and R. Noyori for their contributions in the development of an asymmetric catalytic strategy for hydrogenation reactions.

Although metal catalysis is still often preferred and routinely employed in laboratories and industry, organocatalysis has been increasingly investigated and developed in the past decade. First of all, the very term organocatalysis (concatenation of organic and catalysis) was introduced in 2000 by D. W. C. MacMillan whose group has contributed greatly to this field. The "rediscovery" of this catalytic strategy opened the door to many asymmetric methodology developments and inspired many other research groups.

1.3 Organocatalysis applied to the formation of reactive iminium ions / enamine intermediates

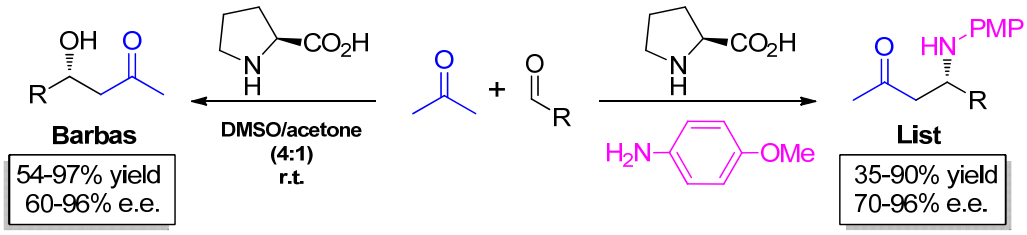
MacMillan and co-workers pioneered the work on iminium intermediates by showing that a chiral imidazolidinone was able to catalyse the Diels-Alder reaction with high enantioselectivity.[5] They demonstrated the efficiency of the same family of catalysts in asymmetric dipolar cycloadditions,[6] Friedel-Crafts alkylations[7] and Mukaiyama-Michael additions (Scheme 1.3).[8]



Scheme 1.3. Imidazolidinone-catalysed enantioselective reactions *via* iminium intermediates

Building up on the Hajos and Parrish work, Barbas *et al.* were the first to develop an asymmetric intermolecular aldol reaction using chiral prolines as catalysts to generate enamines

(Scheme 1.4).[9] Chiral enamine intermediates also proved to be efficient for asymmetric Mannich reactions[10] and Michael additions (Scheme 1.4).[11]



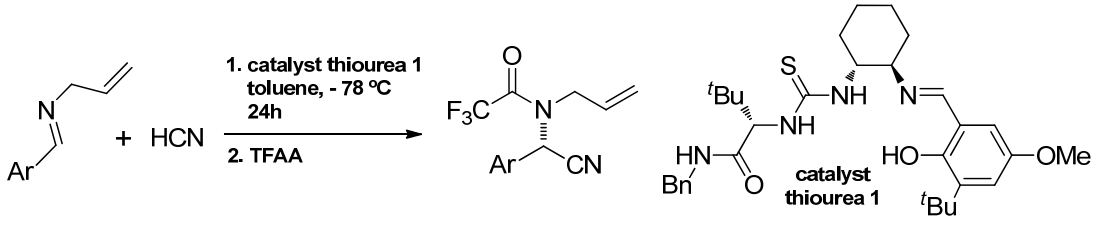
Scheme 1.4. Proline-catalysed enantioselective aldol and Mannich reactions

Another class of organocatalysts has led to a considerable amount of investigation: the use of chiral Brønsted acids in organocatalysis has truly become a major focus for researchers during the past decade.

1.4 Brønsted acids in asymmetric organocatalysis

1.4.1 Seminal research employing urea derivatives as Brønsted acid catalysts

Pioneering the work on organic Brønsted acid catalysis, Jacobsen *et al.* discovered that chiral urea and thiourea derivatives were efficient hydrogen bond (H-bond) donors and could induce high enantioselectivities through this interaction.[12] They applied this method to a highly enantioselective Strecker reaction (Scheme 1.5).



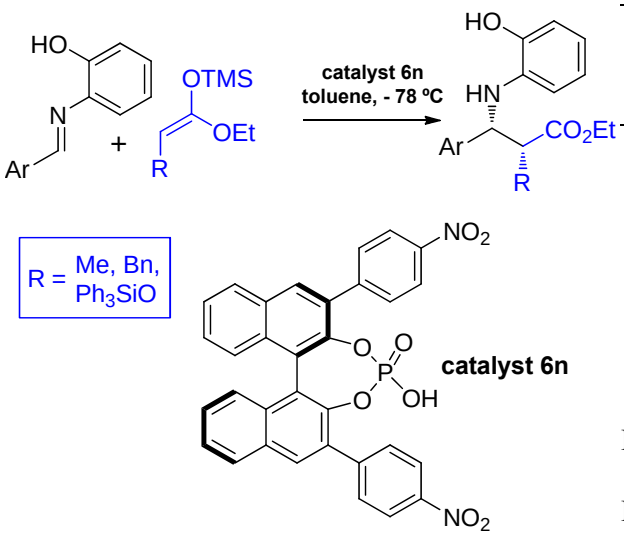
Scheme 1.5. Enantioselective urea-catalysed Strecker reaction

Inspired by these ground-breaking studies, new methodologies for asymmetric catalysis *via* H-bond formation or full protonation have emerged. The most recent development in Brønsted acid organocatalysis is without any doubt the use of stronger Brønsted acids such as phosphoric acids and sulphonic acids.

1.4.2 Pioneering work on asymmetric BINOL phosphoric acid organocatalysis

In 2004, the research groups of Prof. Akiyama and Terada independently discovered that enantiomerically pure phosphoric acids derived from BINOL were excellent catalysts in Mannich-type reactions. Employing various substituted BINOL phosphoric acids (BPAs) they were able to efficiently catalyse the addition of a carbon nucleophile onto a pre-formed imine with excellent enantioselectivities after optimisation (Tables 1.1 and 1.2).[13,14,15]

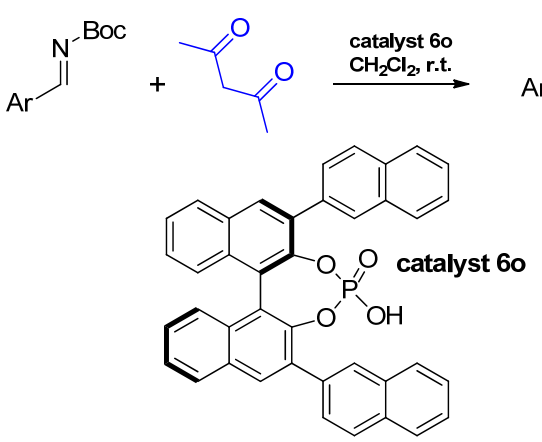
Table 1.1. Enantioselective BPA-catalysed Mannich-type reactions of *N*-aryl imines[13,16]



Ar	R	Yield (%)	*syn*/*anti*	e.e.[a] (%)
Ph	Me	100	87:13	96
p-Tol	Me	100	94:6	81
p-F-C_6H_4	Me	100	91:9	84
Ph	$PhCH_2$	100	93:7	91
PhCH=CH	Me	91	95:5	90
PhCH=CH	$PhCH_2$	65	95:5	90

[a] e.e. for the *syn* diastereoisomer

Table 1.2. Enantioselective BPA-catalysed Mannich-type reactions of *N*-Boc imines[14]



R	Yield (%)	e.e. (%)
Ph	99	95
p-MeO-C_6H_4	93	90
p-Tol	98	94
p-F-C_6H_4	94	96
1-Naphthyl	99	92

Following these original studies, various novel methods have been developed employing enantiomerically pure BPAs to induce enantioselectivities in a wide range of substrates. This class of catalysts has emerged as one of the most versatile and efficient in the field of Brønsted acid organocatalysis.

1.5 Chiral phosphoric acids: powerful catalysts for asymmetric transformations of iminium ions

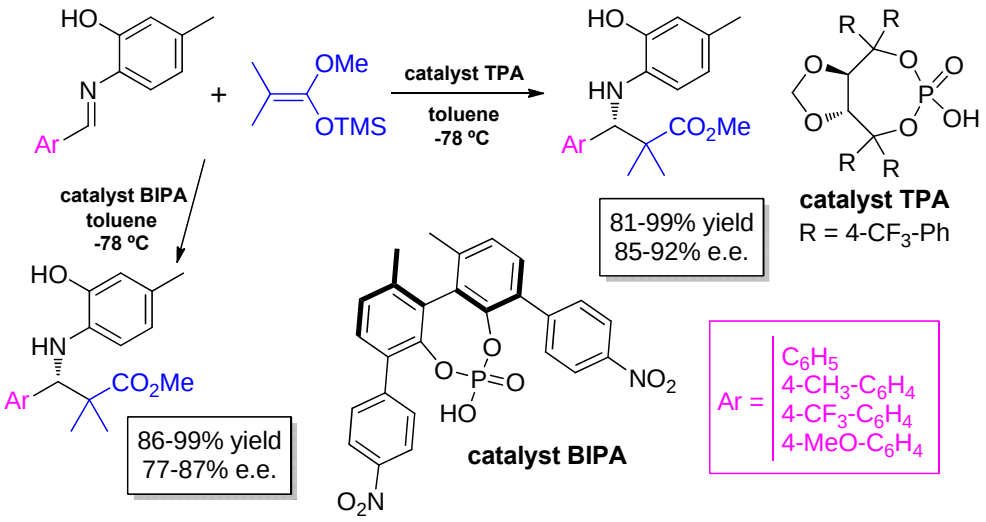
1.5.1 Enantioselective additions to iminium ions

1.5.1.1 Mannich-type reactions

The most studied BPA-catalysed reactions are arguably Mannich-type reactions. Inspired by the seminal work by Akiyama *et al.* and Terada and co-workers, various extensions and improvements have been developed.

Akiyama *et al.* proved that chiral phosphoric acids based on skeletons other than biphenyl were also capable of inducing high enantioselectivities; chiral phosphoric acids derived from TADDOL (prepared from the commercially available and inexpensive enantiomerically pure

diethyl tartrate) were prepared and assessed in the aforementioned indirect Mannich reaction of *N*-aryl imine and silyl enol ethers (see Table 1.1). After reaction optimisation by varying the *N*-aryl protecting group, Akiyama and co-workers achieved high enantiomeric excesses with various substrates (ranging from 85% to 92% e.e., Scheme 1.6).[17] Interestingly, they proposed that in both their studies, the presence of the hydroxyl group (hydrogen bond donor) was essential for high enantioselectivities.[18] The same research group demonstrated that smaller enantiomerically pure biphenyls were also efficient catalysts in their Mannich reaction (Scheme 1.6).[19]

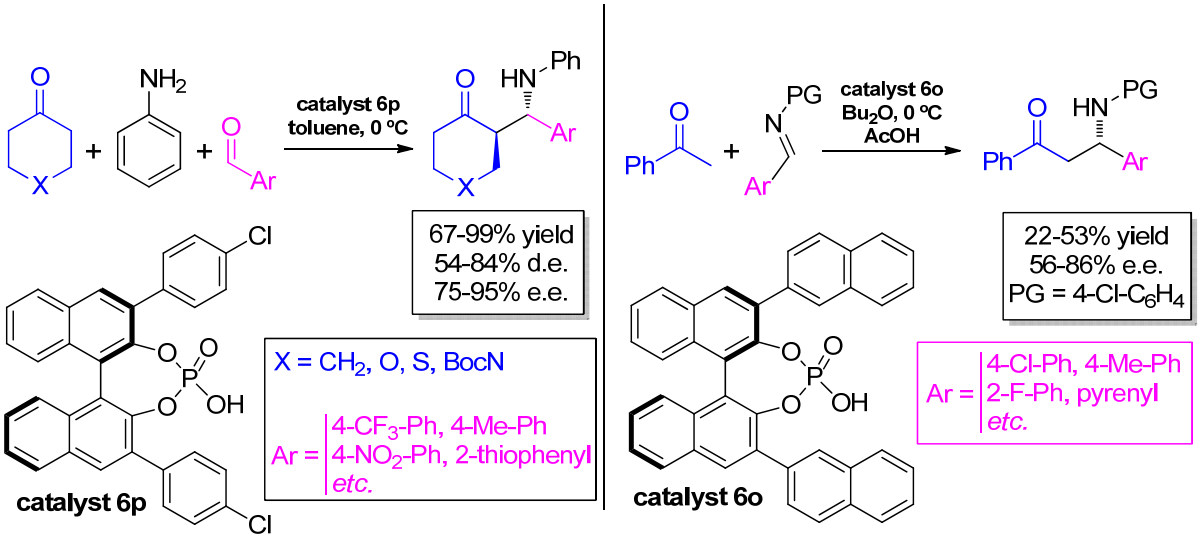


Scheme 1.6. TADDOL and biaryl-derived phosphoric acid-catalysed enantioselective Mannich reactions

More importantly, Gong *et al.*[20] and Rueping and co-workers[21] independently developed an enantioselective BPA-catalysed direct Mannich-type reaction of ketones. This was significant progress as the enol nucleophile was formed *in situ* avoiding the synthesis and isolation of protected enol ethers. In addition, Gong and co-workers succeeded in developing a three-component reaction where the imine pro-electrophile was formed *in situ*, preventing any instability issues (Scheme 1.7).

Gong *et al.*: Direct Mannich reaction of cyclic ketones and *in situ* imine formation

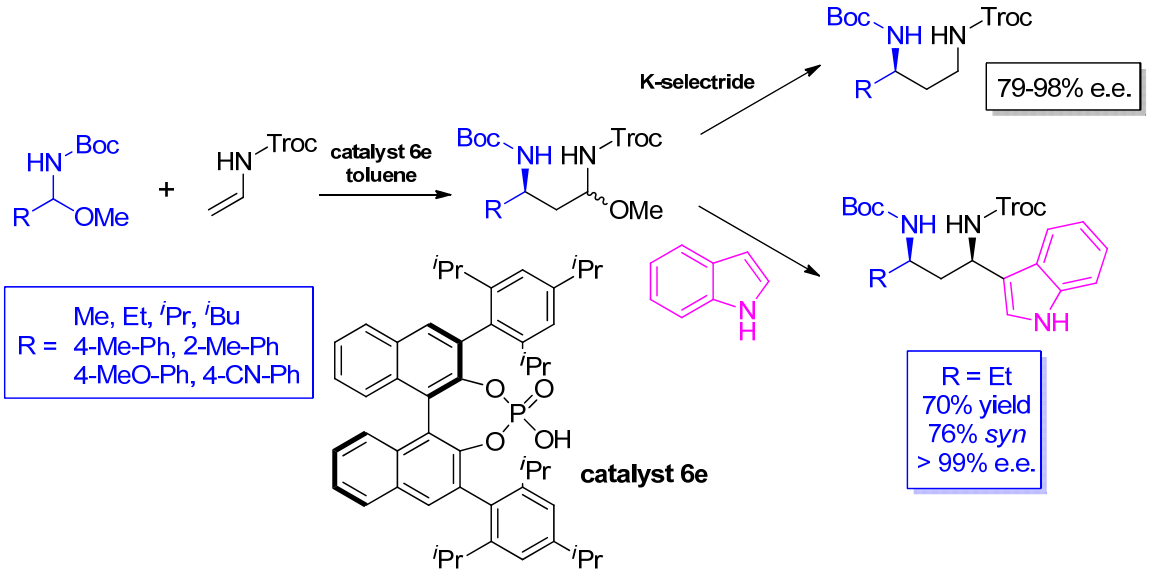
Rueping *et al.*: Direct Mannich reaction of acetophenone and pre-formed imines



Scheme 1.7. BPA-catalysed enantioselective direct Mannich-type reactions

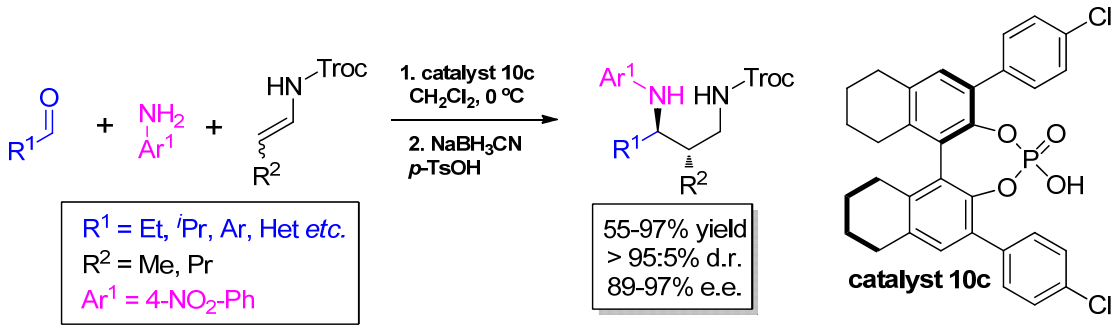
Using a different type of nucleophile, the Terada research group developed an asymmetric aza-ene reaction, which formally is the addition of a protected enamine to an activated imine (iminium ion). It can therefore be considered as a Mannich reaction between an activated carbonyl (enamine) and an iminium ion. This strategy enabled them to synthesise highly enantioenriched β-aminoketones as well as 1,3-diamines with good diastereoselectivity and excellent enantiomeric excesses. Notably, with this method the catalyst loading could be lowered to 0.05 mol% without a significant detrimental effect on the selectivity of the reaction.[22] Tsogoeva *et al.* discovered an elegant dimerisation (self-coupling) of enamides that allowed them to generate β-aminoketones bearing a quaternary chiral centre bonded to the protected primary amine with good to excellent enantiomeric excesses.[23] With the same initial strategy, Terada *et al.* have developed the condensation of a protected enamine onto an iminium ion generated *in situ* from an hemiaminal ether. Rather than hydrolysing the hemiaminal ether intermediates (moderate diastereomeric excesses), they either reduced them in the presence of K-selectride giving a chiral 1,3-diamine or intercepted them with an indole π-nucleophile

(Friedel-Craft-type reaction). They were able to form 1,3-diamines with high enantioselectivity and when the hemiaminal ether intermediate was treated with indole the chiral diamine was obtained with good diastereoselectivity and excellent enantiomeric excess (Scheme 1.8).[24]



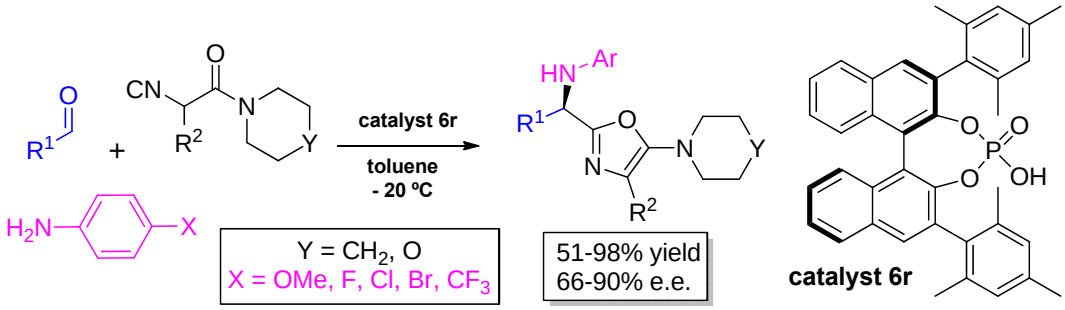
Scheme 1.8. BPA-catalysed enantioselective synthesis of 1,3-diamines *via a* Mannich-type reaction

Independently, Zhu and co-workers published a similar BPA-catalysed 1,3-diamine synthesis from a protected enamine and an imine formed *in situ*. Notably, their three-component methodology (the imine being formed from an aldehyde and an aniline) allowed them to form *anti*-1,3-diamines with high diastereo- and enantioselectivity, using a substituted protected enamine (Scheme 1.9).[25]



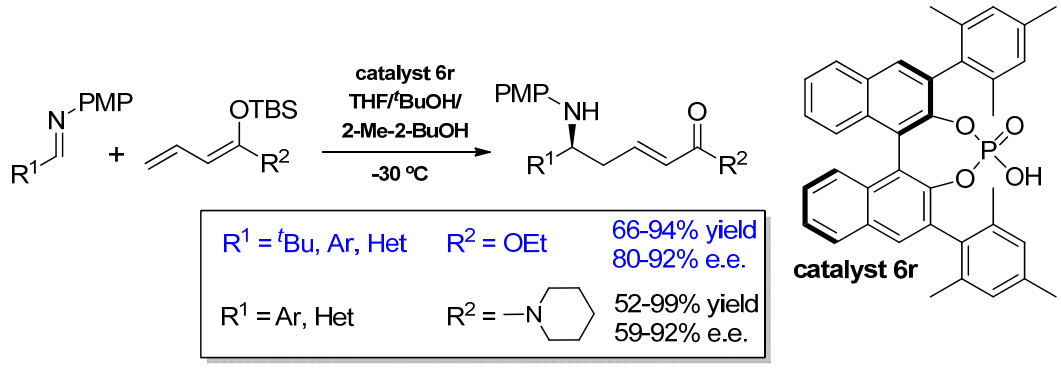
Scheme 1.9. BPA-catalysed enantio- and diastereoselective synthesis of 1,3-diamines *via* Mannich-type reaction

The same group also studied the Mannich reaction of an imine and a cyanoamide leading to the formation of a 5-aminoxazole bearing a chiral amine (Scheme 1.10). After hydrolysis under acidic conditions, dipeptides containing a glycine amino acid and either a natural or unnatural amino acid were accessible.[26]



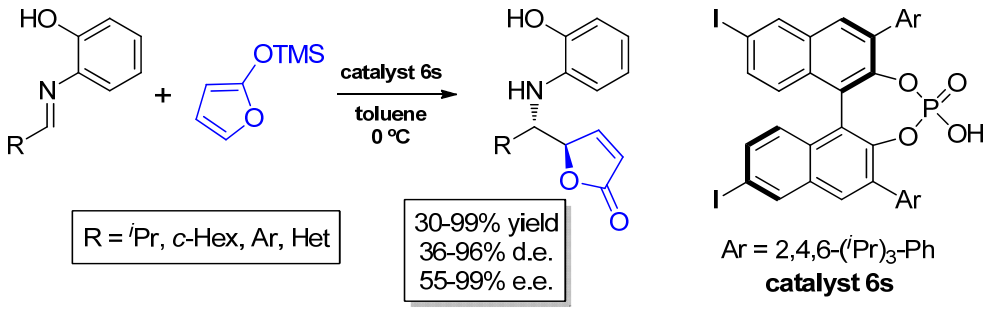
Scheme 1.10. BPA-catalysed enantioselective direct Mannich reaction of isocyanides

Further to these discoveries, an enantioselective BPA-catalysed vinylogous Mannich reaction was developed in the laboratory of C. Schneider. Although the vinylogous silyl enol ether had to be pre-formed, this strategy constituted a new powerful entry for the formation of highly enantioenriched δ-amino acids (Scheme 1.11).[27,28]



Scheme 1.11. BPA-catalysed enantioselective vinylogous Mannich reactions

Akiyama *et al.* independently developed a vinylogous Mannich-type reaction of an electron-rich furan onto an iminium ion. Interestingly, they were able to form a γ-butenolide with high diastereo- and enantiocontrol which also allowed them to further transform it into biologically relevant δ-lactams (Scheme 1.12).[29]



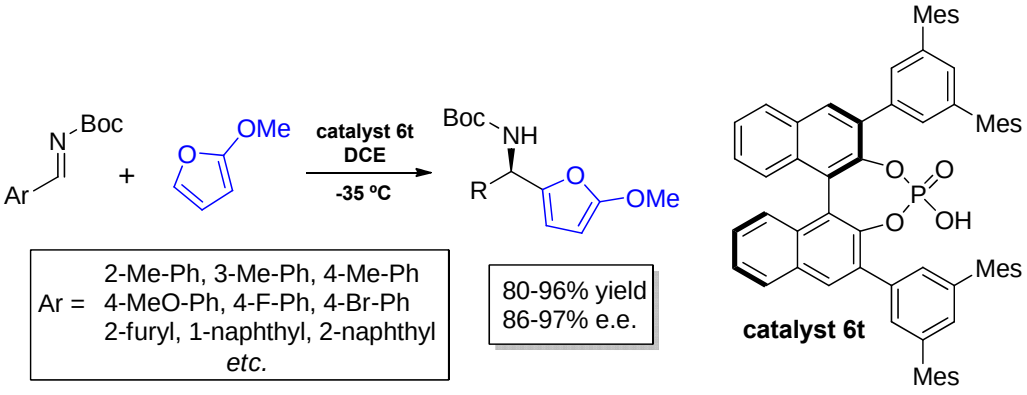
Scheme 1.12. BPA-catalysed enantioselective vinylogous Mannich reactions onto a furan derivative

More recently, other carbon nucleophiles have been employed in enantioselective Mannich-type reactions, including dihydropyrans,[30] dihydrofurans[31] and aza-enamines.[32]

The Mannich reaction is an extremely efficient tool for the formation of chiral amines and BPAs proved to be excellent and versatile catalysts to promote this type of transformation. If the nucleophile is exchanged for an aromatic compound, the same strategy can be expanded to Friedel-Craft reactions. This has led to significant research efforts during the past few years.

1.5.1.2 Friedel-Craft type additions onto iminium ions

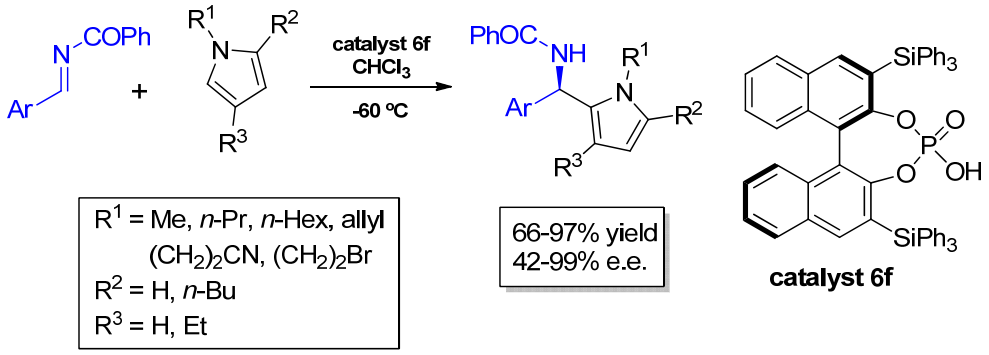
Terada *et al.* were the first to develop an enantioselective aza-Friedel-Craft alkylation. They successfully alkylated an electron-rich furan with various *N*-Boc aromatic imines (Scheme 1.13).[33]



Scheme 1.13. BPA-catalysed aza-Friedel-Craft alkylation of 1-methoxyfuran

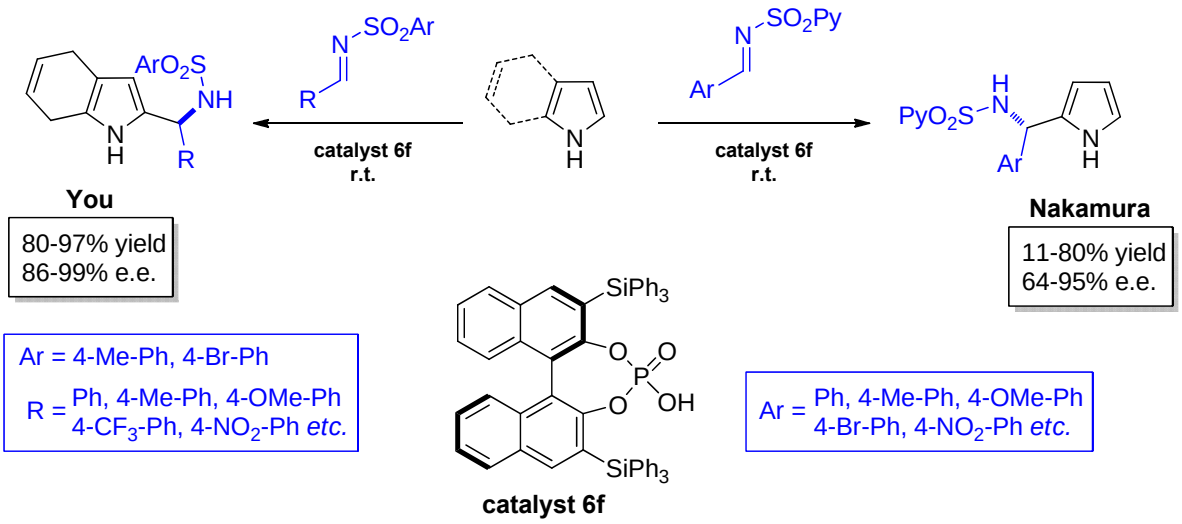
Further to this pioneering study, various electron-rich aromatic rings such as indoles, pyrroles and electron-rich aryls were used as π-nucleophiles and underwent highly enantioselective aza-Friedel-Craft alkylations.

Protected pyrroles, either substituted or naked have been successfully alkylated at the 2-position. Antilla and co-workers discovered that BPAs were efficient catalysts of an aza-Friedel-Craft alkylation of pyrroles onto aromatic imines (Scheme 1.14).[34]



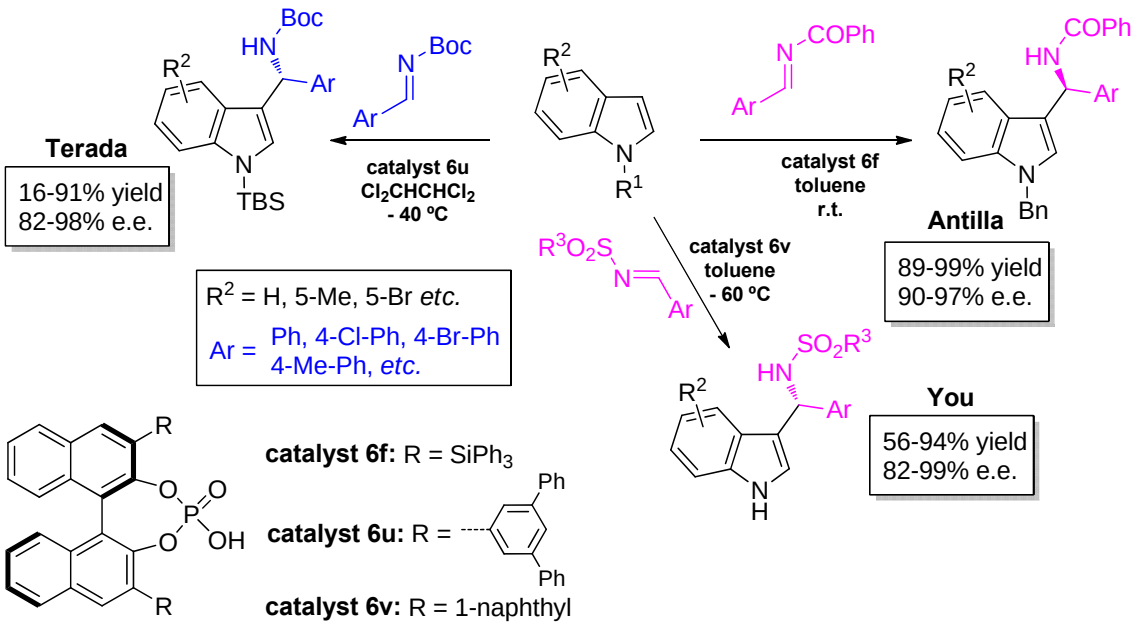
Scheme 1.14. BPA-catalysed aza-Friedel-Craft alkylation of pyrroles

Similarly, Nakamura *et al.* described a direct aza-Friedel-Craft alkylation of non-protected pyrroles, using a carefully designed protecting group on the aromatic imine reaction partner (2-pyridyl derivative able to coordinate *via* hydrogen bonding). They were able to form 2-substituted pyrroles with moderate to excellent enantioselectivities (64-95% e.e.).[35] The You research group developed an enantioselective Friedel-Craft type alkylation of unprotected 4,7-dihydroindoles (formally substituted pyrroles). This strategy allowed them to prepare tetrasubstituted pyrroles with good to excellent enantiomeric excesses for a broad range of aromatic *N*-tosyl imines (80-97% yield, 86-99% e.e., Scheme 1.15).[36]



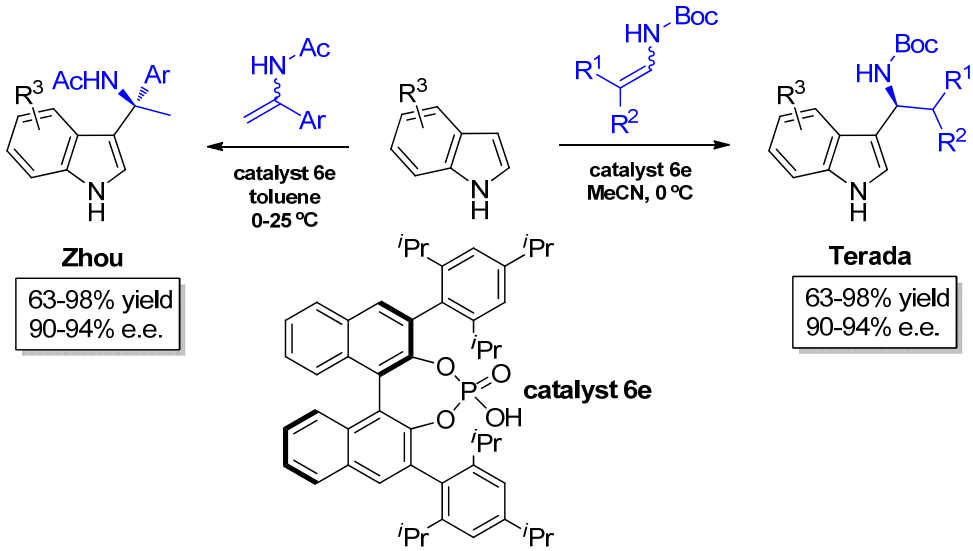
Scheme 1.15. BPA-catalysed aza-Friedel-Craft alkylation of unprotected pyrroles

The discovery that electron-rich aromatic rings can act as π-nucleophiles in aza-Friedel-Craft alkylations has led to considerable research focused on indole as a π-nucleophile. Pioneers in the field, Antilla *et al.* demonstrated that aromatic *N*-acylimines were good pro-electrophiles to alkylate *N*-benzyl indoles at the 3-position. They were able to employ electron-rich as well as electron-deficient aromatic imines and variously substituted indoles with yields and enantiomeric excesses consistently excellent (89-99% yield, 90-97% e.e.), 2-methyl indole being an exception and giving moderate enantioselectivity (Scheme 1.16).[37] Terada and co-workers observed a similar reactivity and selectivity for the addition of protected indoles onto aromatic *N*-Boc imines. Notably, they were unable to achieve satisfactory yields with *o*-substituted arylimines.[38] Aromatic *N*-tosyl imines were also found to be suitable pro-electrophiles for BPA-catalysed aza-Friedel-Craft alkylation of indoles (Scheme 1.16).[39]



Scheme 1.16. BPA-catalysed aza-Friedel-Craft alkylation of protected and unprotected indoles

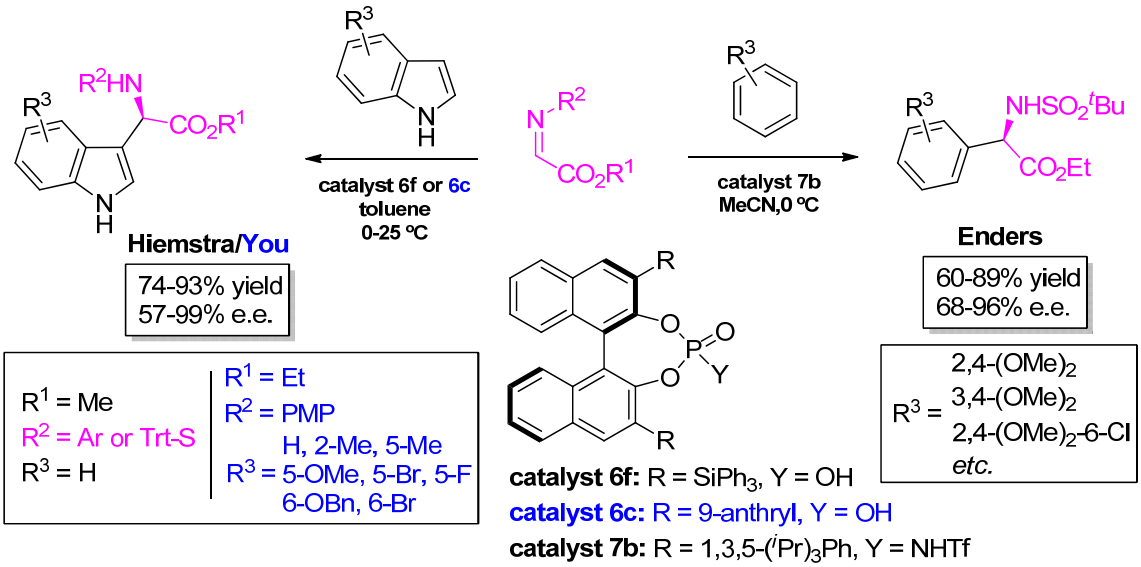
Interestingly, it was also found that non-protected indoles were alkylated by imines or iminium ions formed *in situ*, using enamines as precursors. This strategy was orthogonal to previously published work and of particular interest since it allowed for the formation of alkyl-substituted indoles (bearing an amine).[40] This strategy was also efficient for the preparation of indoles bearing a quaternary stereogenic centre (Scheme 1.17).[41]



Scheme 1.17. Enantioselective aza-Friedel-Craft alkylation indoles with enamines

Hiemstra *et al.* have developed an elegant alkylation of indoles with glyoxylate imine derivatives which allowed them to prepare enantiomerically enriched indolylglycine derivatives through this new entry to unnatural amino acids.[42] Later, You and co-workers improved this strategy by generating the glyoxylate imines *in situ* (Scheme 1.18).[43]

Although thus far only electron-rich heteroaromatics were successfully alkylated enantioselectively using BPA catalysis, Enders *et al.* proved that this approach was valid with electron-rich arenes (polymethoxy in most cases). In this study, the aza-Friedel-Craft alkylation of electron-rich arenes with glyoxylate imines led to the formation of unnatural arylglycine derivatives with enantiomeric excesses ranging from 68% to 96% (Scheme 1.18).[44]

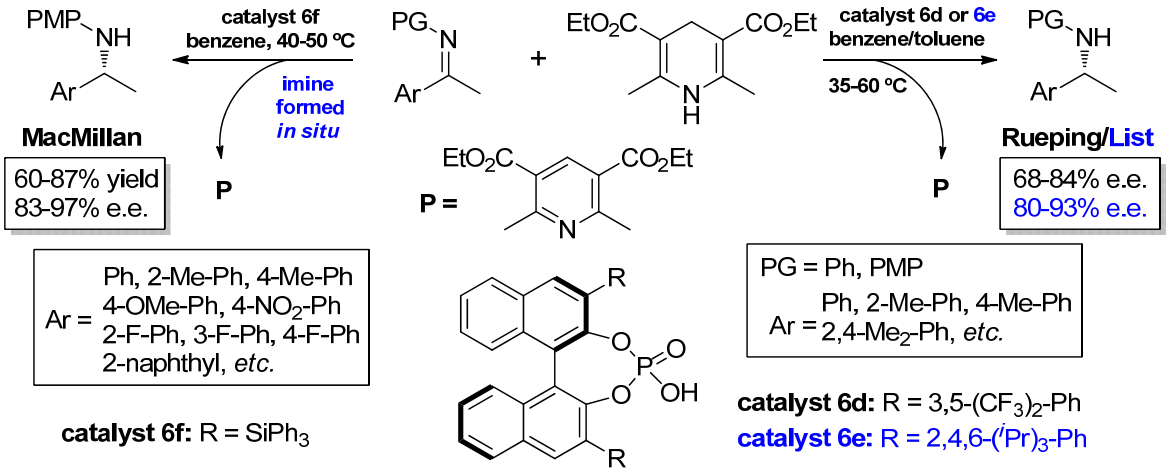


Scheme 1.18. Enantioselective aza-Friedel-Craft for the synthesis of unnatural α-aminoacid derivatives

Another field that has been explored and is of great importance in organic chemistry is the stereoselective reduction of imines to amines. In this case the nucleophile during the enantio-determining step can be considered formally as a hydride. Tremendous efforts have been made to develop novel and broad strategies for the enantioselective reduction of imines using BPA catalysis.

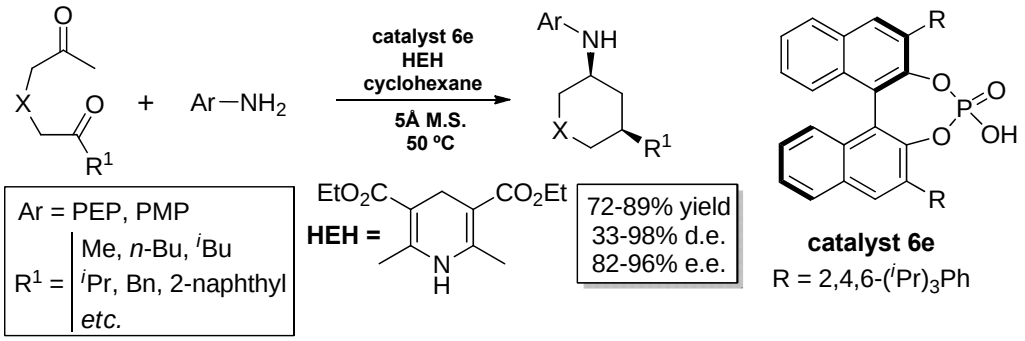
1.5.2 Enantioselective reduction of imines in the presence of a BPA and a hydride source

Inspired by bio-processes, List and co-workers and Rueping *et al.* independently developed the original idea of using an NADH mimic to partake in the reduction of imines in the presence of a BPA catalyst. The active part of this natural reducing agent is its dihydropyridine moiety. The Hantzsch ester, a simplified dihydropyridine derivative, was found to be an efficient hydride donor.[45,46] With this strategy, pre-formed imines were reduced to the corresponding protected primary amines with moderate to good enantioselectivities (Scheme 1.19).[47,48] This approach was further enhanced by the development of a one-pot reductive amination of various ketones and anilines (Scheme 1.19). Notably, this study also established that pro-chiral ketones bearing groups of similar steric hindrance also took part in the reaction with good levels of enantioselectivity.[49]



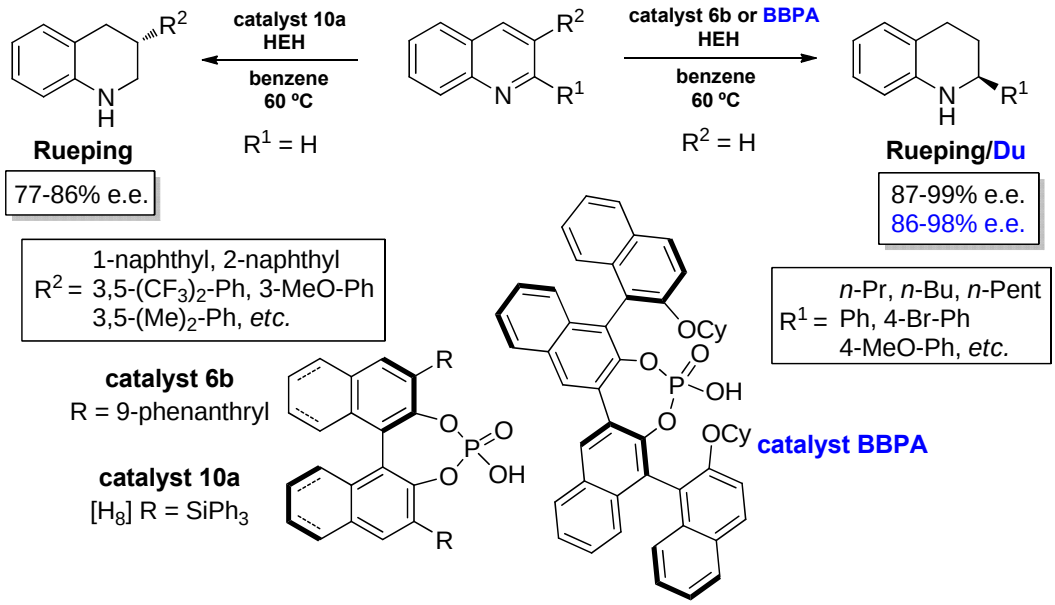
Scheme 1.19. Enantioselective reduction of imines in the presence of Hantzsch ester

This was exploited by List *et al.* to develop a powerful enamine-catalysed Robinson annulation/iminium reduction cascade to ultimately prepare 3-substituted cyclohexylamine derivatives with good diastereoselectivity (up to 98% d.e.) and good to excellent enantioselectivity (up to 96% e.e., Scheme 1.20).[50]



Scheme 1.20. Diastereo- and enantioselective Robinson annulations / imine reduction cascade

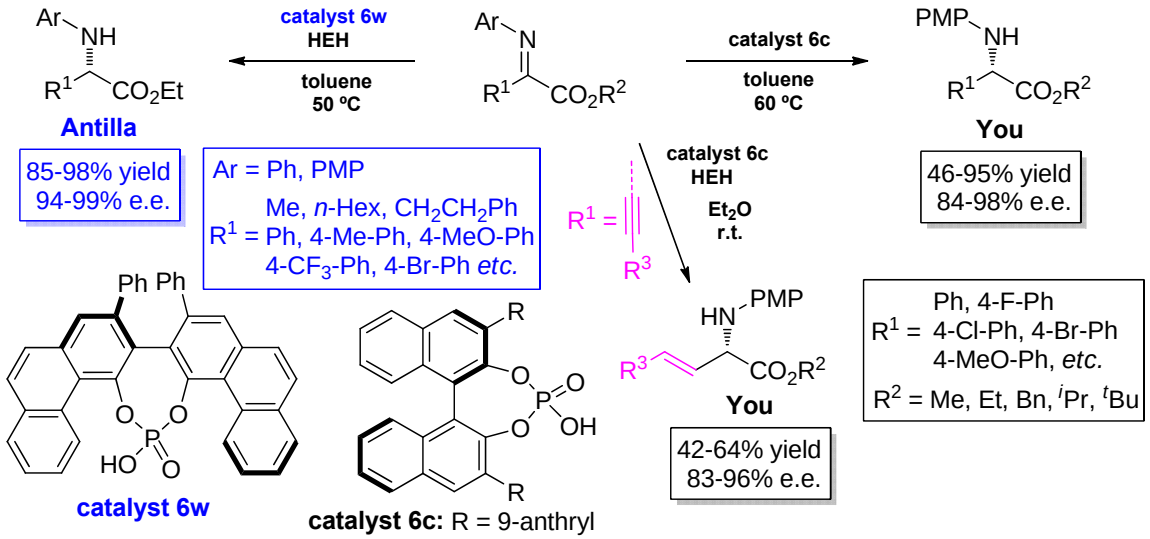
Later, this new approach to the reduction of imines was expanded to the saturation of heteroaromatic compounds such as pyridines,[51] 2-substituted quinolines[52,53,54] and 3-substituted quinolines (Scheme 1.21),[55] phenanthroline derivatives,[56] quinoxalines (and quinoxalinones)[57] or heterocycles such as benzoxazines, benzothiazines and benzoxazinones[58] and diazepine derivatives.[59]



Scheme 1.21. Reduction of 2- and 3-substituted quinolines into optically active tetrahydroquinolines

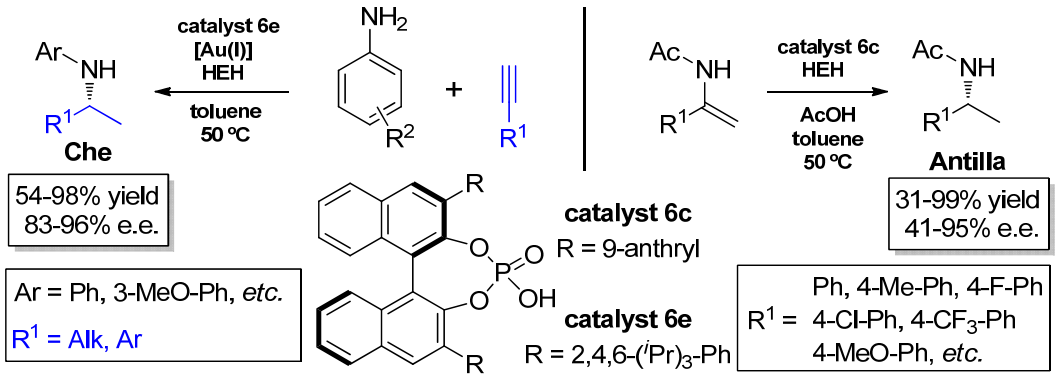
As an alternative to the existing syntheses of α-aminoacids, Antilla and co-workers and You *et al.* independently developed the asymmetric reduction of α-imino esters which proved to be

highly enantioselective for the formation of arylglycine derivatives (Antilla *et al.*: 94-99% e.e.; You *et al.*: 84-98% e.e., Scheme 1.22).[60,61] You and co-workers further expanded the scope of the reduction to alkynyl imines whereby a double reduction occurred to produce *trans*-alkenyl substituted α-aminoacid derivatives as single diastereoisomers with good to excellent enantiomeric excesses (83-96% e.e., Scheme 1.22).[62]



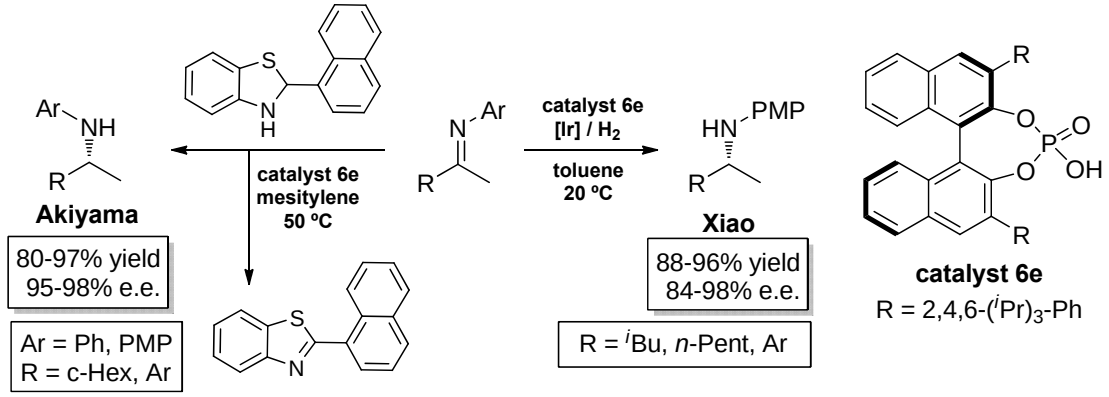
Scheme 1.22. Enantioselective reduction of imino esters and its application to a domino sequence

Utilising the tautomeric properties of imines/enamines, the Antilla group demonstrated that enamides were also suitable substrates that underwent a reduction in the presence of the Hantzsch ester and a chiral phosphoric acid (Scheme 1.23).[63] Interestingly, Che *et al.* took advantage of this discovery to develop a multi-catalysed one-pot procedure where gold(I) was used to effect the hydroamination of an alkyne by an aniline; the subsequently formed enamide underwent an enantioselective reduction in the presence of the Hantzsch ester and a BPA (Scheme 1.23).[64]



Scheme 1.23. Enantioselective reduction of enamines pre-formed or formed *in situ*

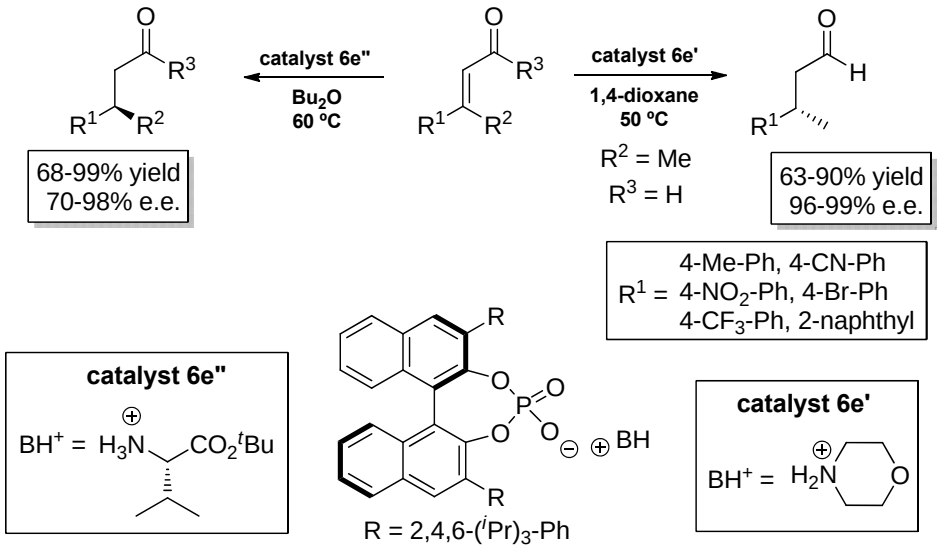
As an alternative to the use of Hantzsch ester, Xiao *et al.* developed an iridium-promoted hydrogenation where the chiral phosphoric acid was essential to activate the imine and to induce enantioselectivity (Scheme 1.24).[65] Akiyama *et al.* proposed the use of a benzothiazoline derivative as surrogate for the Hantzsch ester. With this strategy, the reduction of various imines was achieved with impressive levels of enantiocontrol (95-98% e.e., Scheme 1.24).[66]



Scheme 1.24. Enantioselective reduction of imines with surrogates for the Hantzsch ester

Employing the salt of a chiral BPA and a primary or secondary amine, List *et al.* discovered an enantioselective reduction of α,β-unsaturated aldehydes[67,68] and ketones[69] in the presence of the Hantzsch ester. Interestingly, although the reaction presumably proceeded *via* an iminium ion, only 1,4-reduction was observed and saturated aldehydes/ketones were recovered after hydrolysis. With this method, the control of a stereogenic centre at the β-position to the

carbonyl was achieved with high enantiomeric excess (70-99% e.e., Scheme 1.25). The same group found that non-symmetrical branched aldimines were also reduced enantioselectively giving rise to enantioenriched β-substituted amines. This highly selective transformation occurred *via* a dynamic kinetic reduction of the diastereomeric iminium ion pair in equilibrium with its enamine tautomer.[70]



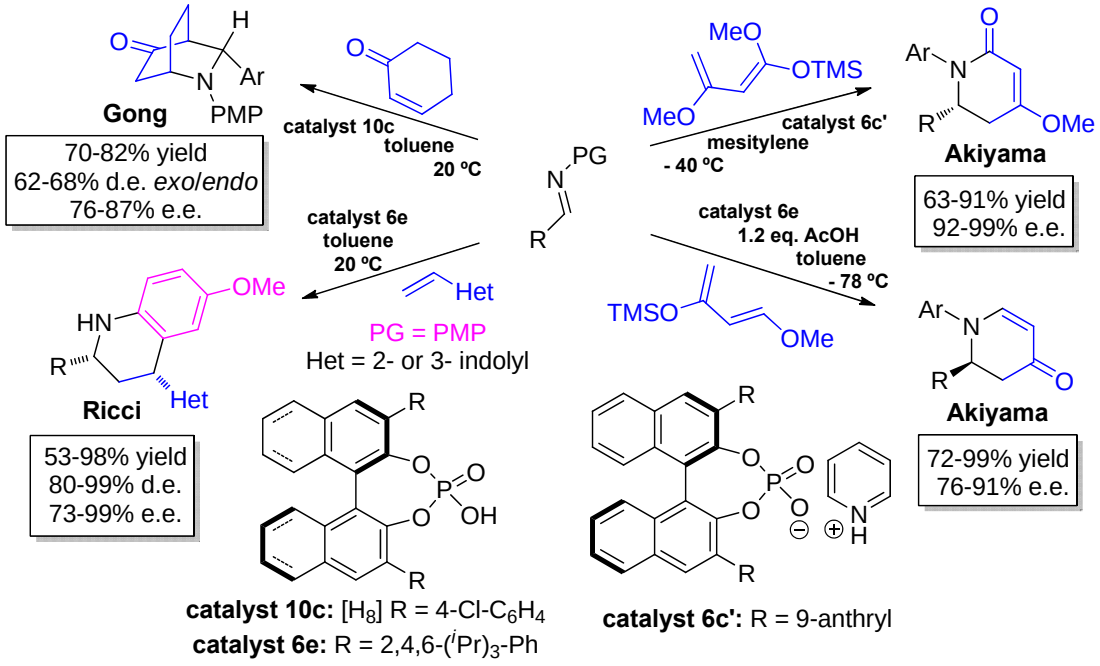
Scheme 1.25. Enantioselective reduction of carbonyls catalysed by ammonium BINOL phosphates

Computational studies have been performed to understand the origin of enantioselectivity. It is very likely that it arises from the activation of the imine *via* protonation by the catalyst (or strong hydrogen bonding) and a hydrogen bond between the phosphate and the reducing agent (dihydropyridine N-H).[71]

Although the aforementioned methods and strategies have proved to be highly efficient for the synthesis of acyclic amines, their application to the preparation of cyclic compounds has been limited. To address this, attention has turned towards the development of enantioselective BPA-catalysed cycloadditions and pericyclic reactions.

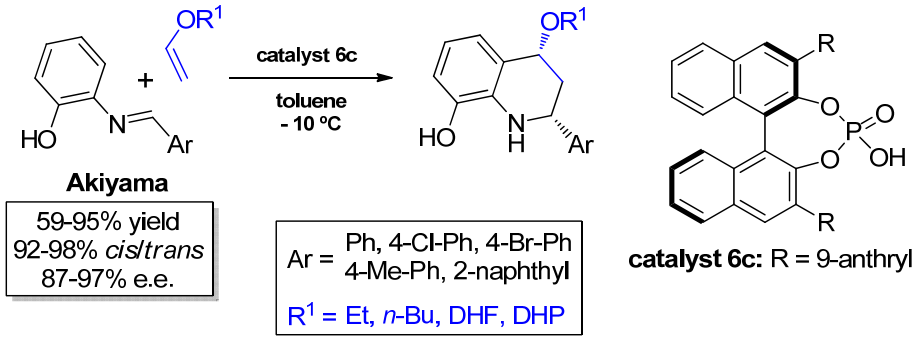
1.5.3 Enantioselective cycloadditions and pericyclic reactions

The Akiyama group has pioneered this field through the development of the first enantioselective aza-Diels-Alder (aza-DA) reaction of Brassard's diene with various imines. The use of an *o*-hydroxyarene protecting group was again essential for high enantiomeric excess. Interestingly, the authors found that the pyridinium salt of the BPA catalysed the reaction more efficiently (with regard to reactivity, due to the lability of Brassard's diene), however, the enantioselectivities remained very high in both cases. This strategy was efficient for the preparation of highly enantioenriched dihydropyridones (92-99% e.e.) which could be further derivatised (Scheme 1.26).[72] Similar results were reported employing Danishefsky's diene and various imines to prepare enantiomerically enriched dihydropyridones (Scheme 1.26).[73] Further studies expanded the scope of the BPA-catalysed aza-DA to less electron rich dienes such as cyclohex-2-en-1-one (*via* its enol form)[74] and later to a particular case of aza-DA: the Povarov reaction of *N*-aryl imines with an indole substituted ethylene (Scheme 1.26).[75]



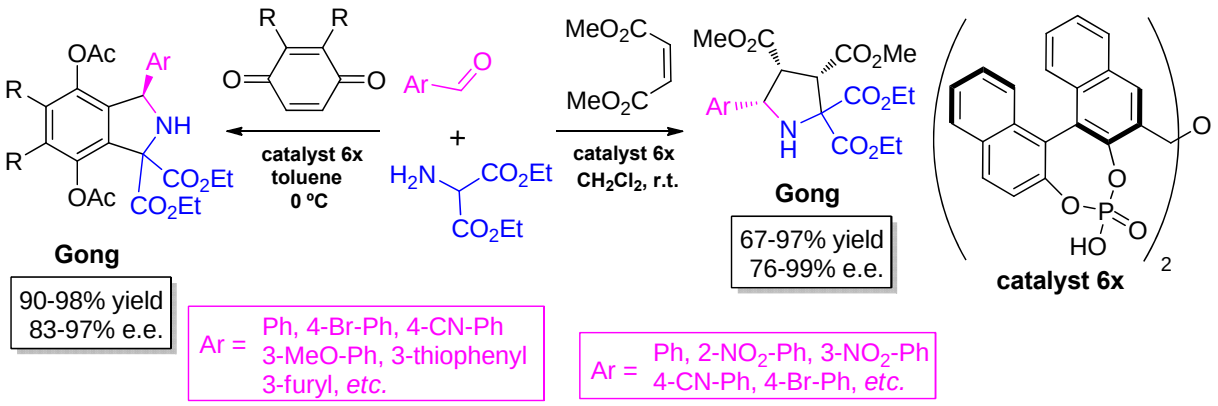
Scheme 1.26. Enantioselective aza-Diels-Alder cycloadditions catalysed by BPA derivatives

Akiyama and co-workers demonstrated that an enantioselective inverse-demand aza-DA could also be performed using an *N*-aryl benzaldimine derivative and an electron-rich enol ether. 2,4-Disubstituted tetrahydroquinolines were prepared with excellent *syn* diastereoselectivity and good to excellent enantiomeric excesses (87-97% e.e.).[76] The oxygenated fused bicycle was further manipulated to prepare the corresponding dihydro-4-quinolone and tetrahydroquinoline (Scheme 1.27).

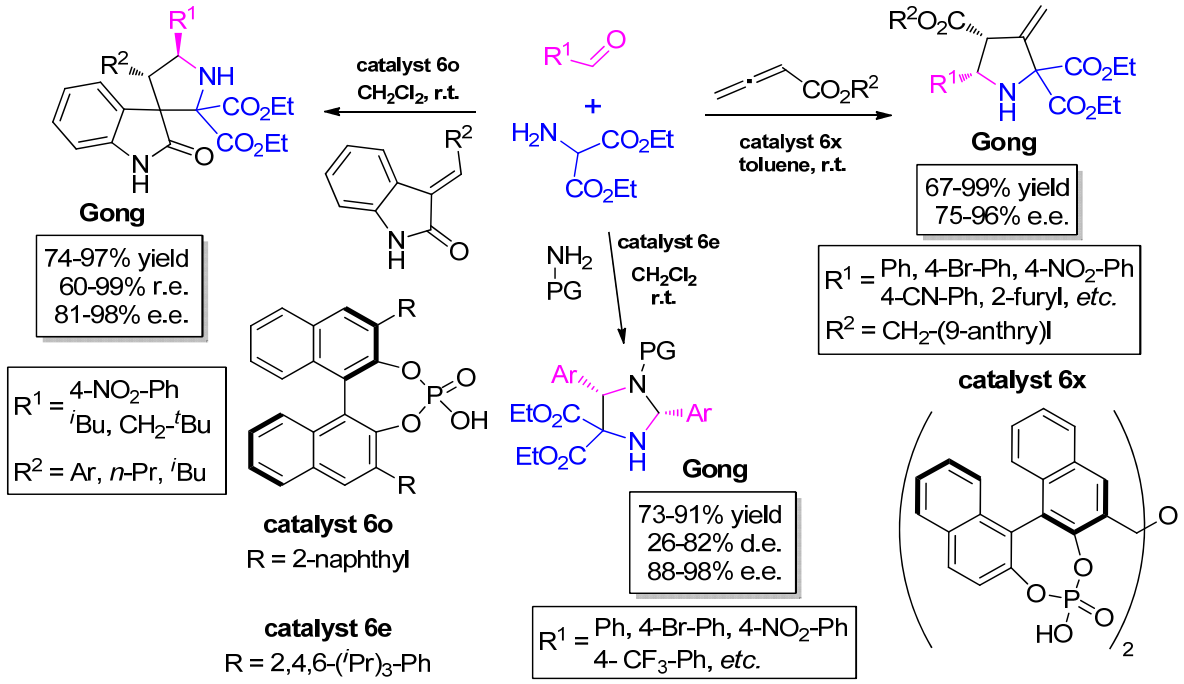


Scheme 1.27. Enantioselective inverse-demand aza-Diels-Alder reaction

To further expand the scope of application of BPAs, the feasibility of enantioselective 1,3-dipolar cycloadditions has also been studied in detail; it was found that aromatic imines generated with an amino malonate reacted readily with electron-poor alkenes[77] (Scheme 1.28) and allenes[78] (Scheme 1.29) to form pyrrolidines with up to four stereocentres[79] controlled during the enantio-determining step. The same strategy was applied to quinone derivatives to prepare isoindolines with high enantiomeric excesses as single diastereomers.[80] It was also exploited for the synthesis of spiro oxindoles controlling two tertiary and a quaternary stereocentre with excellent regioselectivity, as single diastereoisomer and with impressive levels of enantioselectivity (Scheme 1.28).[81] Interestingly, the use of an imine instead of the electron-poor alkene also proved to be efficient for the preparation of imidazolidines with up to two controlled stereocentres (Schemes 1.29).[82]



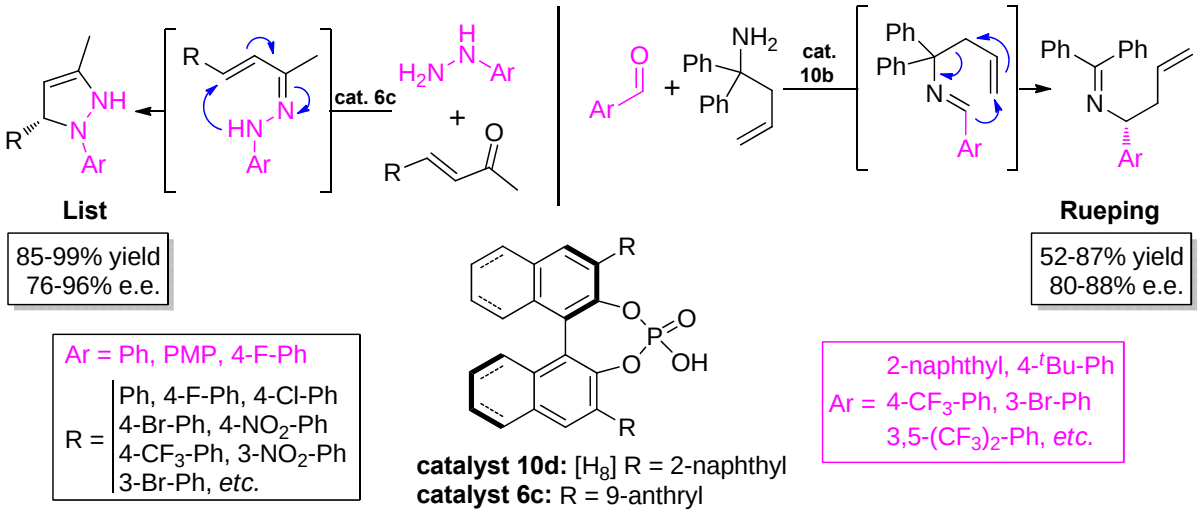
Scheme 1.28. Enantioselective BPA-catalysed 1,3-dipolar cycloadditions



Scheme 1.29. Enantioselective BPA-catalysed 1,3-dipolar cycloadditions

BPA derivatives were also applied to the catalysis of a sigmatropic rearrangement. An enantioselective [3,3]-sigmatropic 2-aza-Cope rearrangement was developed. Notably, the homo allylic imine precursor for cyclisation was generated *in situ* in what constituted a powerful cascade for the synthesis of a protected chiral amine (Scheme 1.30).[83]

Using a different strategy, List *et al.* demonstrated that α,β-unsaturated arylhydrazones cyclised readily in the presence of a BPA to form chiral pyrazolines with high enantioselectivity. They were able to develop a one-pot hydrazone formation/6π electrocyclisation cascade to prepare enantioenriched heterocycles directly from commercially available α,β-unsaturated aldehydes and arylhydrazines (Scheme 1.30).[84]



Scheme 1.30. Enantioselective BPA-catalysed pericyclic reactions

1.5.4 Miscellaneous applications of BPA in organocatalysis on iminium ions

BPAs have found many applications in a wide range of organic reactions, the most studied have been presented above, however chiral phosphoric acids have also been employed in the catalysis of various extremely useful organic transformations with high enantioselectivities.

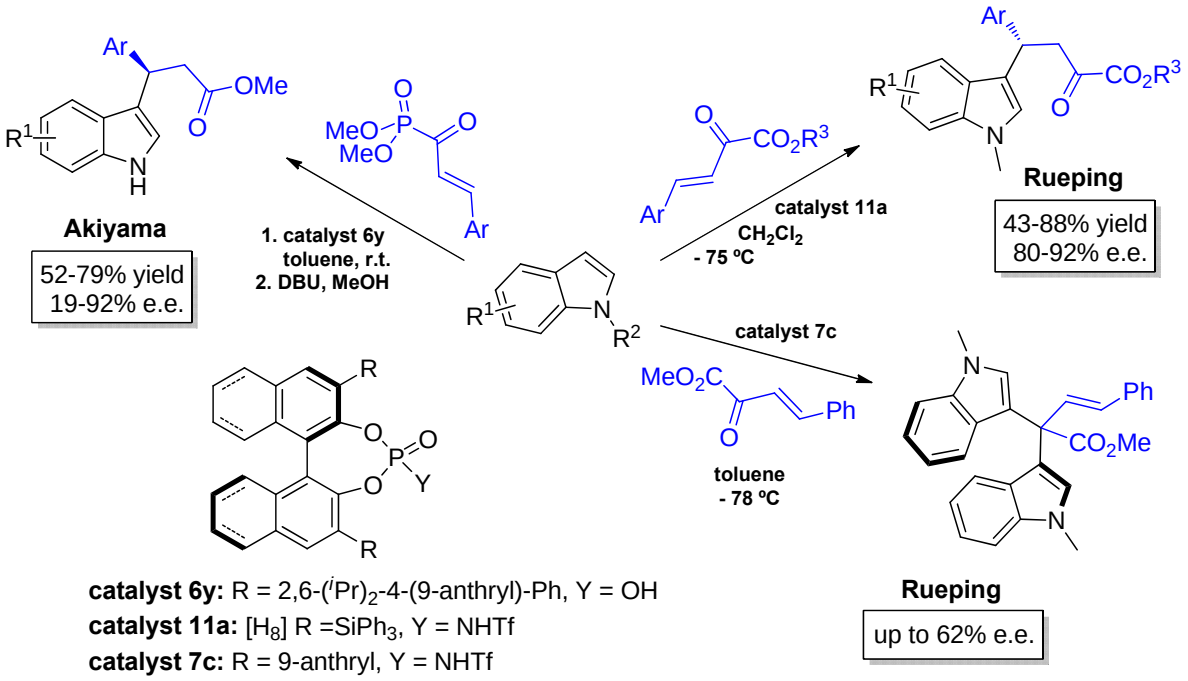
This includes the addition of nucleophilic heteroatoms across imines: nitrogen-based nucleophiles,[85,86,87,88] oxygen-based nucleophiles,[89] phosphorous-based nucleophiles (Kabachnik-Fields reaction)[90,91,92] and the addition of carbon-based nucleophiles: alkynes,[93] cyanide (Strecker reaction),[94] nitro alkanes,[95] and diazo compounds.[96,97,98]

1.6 Chiral phosphoric acid-catalysed additions to and reductions of formal oxonium ions

Recently, attention has turned to highly reactive species such as oxonium ions. Arguably, reactions of iminium ions have been thoroughly investigated because their formation or mode of activation is well-documented. In contrast, the chemistry of oxonium ions has not been widely explored especially in organocatalysis. Nevertheless, in the past few years, novel methods based on the exploitation of these highly reactive electrophiles have emerged.

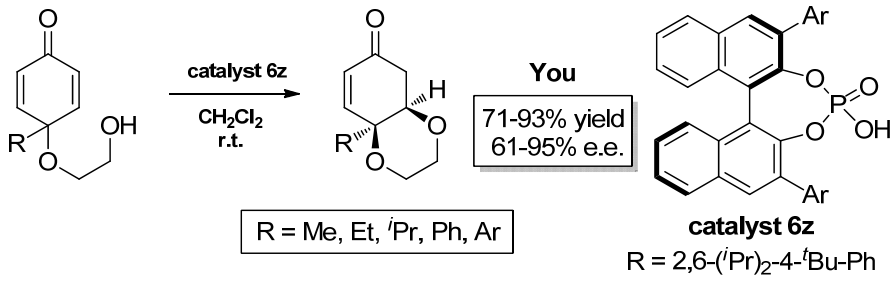
1.6.1 Michael additions onto activated α,β-unsaturated carbonyls

The development of enantioselective Michael addition reactions has been a major focus for the organocatalysis community. Zhou *et al.* described an enantioselective Michael addition of indole onto chalcones, catalysed by BPA, which proceeded in good yield, although it only afforded moderately enantioenriched alkylated indoles.[99] With more success, Rueping and co-workers studied an enantioselective Friedel-Craft type alkylation of indole with α,β-unsaturated pyruvates and found that depending on the nature of the catalyst used, 1,2-addition or 1,4-addition could be observed. When the controlled Michael addition was performed, chiral indoles were isolated in generally good yields and good enantioselectivities (80-92% e.e., Scheme 1.31). When the 1,2-addition was observed, the intermediate tertiary alcohol immediately dehydrated and the formal carbocation underwent a second indole addition to form an axially chiral bisindole with moderate enantiomeric excess (up to 62% e.e.).[100] Interestingly, the use of α,β-unsaturated acylphosphonates as Michael acceptors proved to be a viable alternative to enantioselectively alkylate indoles (Scheme 1.31).[101]



Scheme 1.31. Enantioselective BPA-catalysed additions to α,β-unsaturated carbonyls

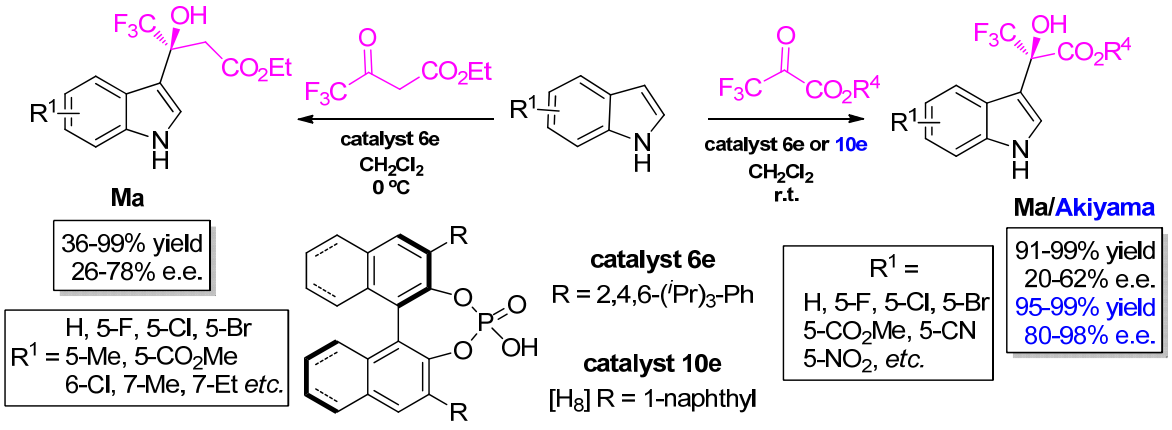
With a different approach, an intramolecular oxy-Michael addition was exploited to desymmetrise cyclohexadienone derivatives. Using a BPA, the 1,4-addition of an ethyleneglycol ether tether was directed on one side of the cyclohexadienone giving rise to substituted 1,4-dioxane derivatives as single diastereoisomers with moderate to high enantiomeric excesses (61-95% e.e., Scheme 1.32).[102]



Scheme 1.32. Desymmetrisation through BPA-catalysed oxy-Michael addition

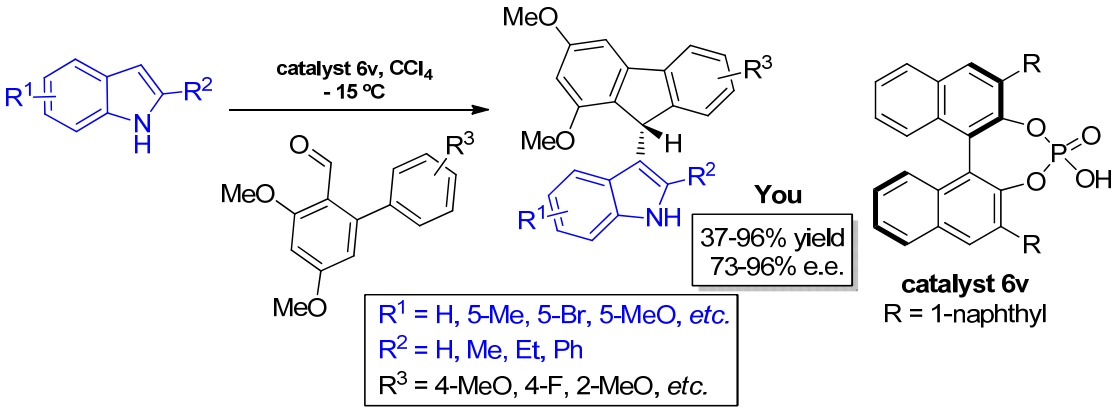
1.6.2 Direct additions onto activated carbonyls: Friedel-Craft-type alkylations, ene reactions and aldol-type reactions

A direct Friedel-Craft alkylation of indoles with trifluoromethylketones in the presence of catalytic amount of BPA has been studied; however, the newly formed quaternary alcohols were isolated with moderate enantioselectivities.[103] Reoptimising the conditions of the alkylation of indoles with methyl trifluoropyruvate, Akiyama *et al.* achieved high reactivity and selectivities (80-98% e.e., Scheme 1.33); pyrrole and 2-methylfuran also partook in the reaction although with lower enantioselectivities (70% and 82% e.e. respectively).[104]



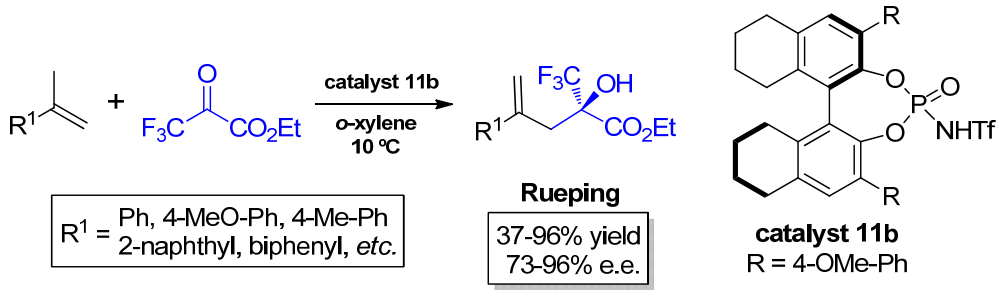
Scheme 1.33. Additions of indole π-nucleophiles onto trifluoroketones

Inspired by the bisindole formation uncovered by Rueping *et al.* (see Scheme 1.31),[100] You and co-workers developed an elegant double-Friedel-Craft alkylation of indoles using a 2-formylbiphenyl derivative. The addition of an indole derivative onto the activated aldehyde provided a tertiary alcohol that dehydrated readily to form a stabilised carbocation that subsequently underwent Friedel-Craft alkylation on the biaryl. Ultimately, an indole-substituted fluorene was formed in generally good yields (37-96% yield) and good to excellent enantioselectivities (73-96% e.e., Scheme 1.34).[105]



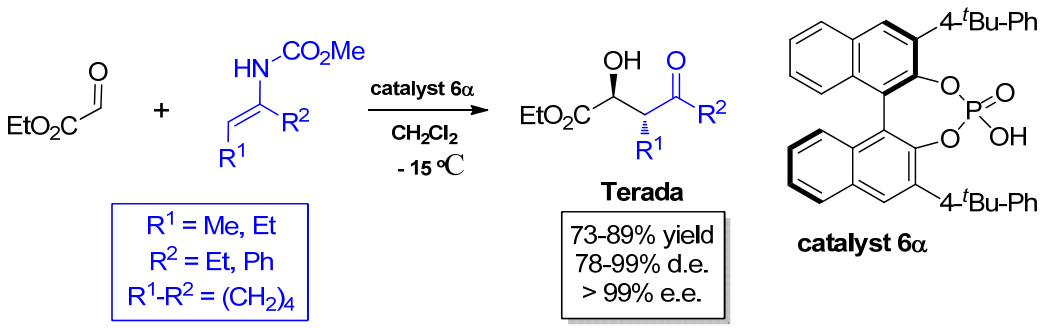
Scheme 1.34. Double additions of indole π-nucleophiles to activated carbonyls/carbocation

Using a different type of nucleophile, Rueping *et al.* developed an enantioselective carbonyl-ene reaction. By treating a pyruvate with a stryrene derivative in the presence of a chiral triflyl phosphoramide, quaternary homoallylic alcohols were prepared in generally high yields and excellent enantioselectivities (92-97% e.e., Scheme 1.35).[106]



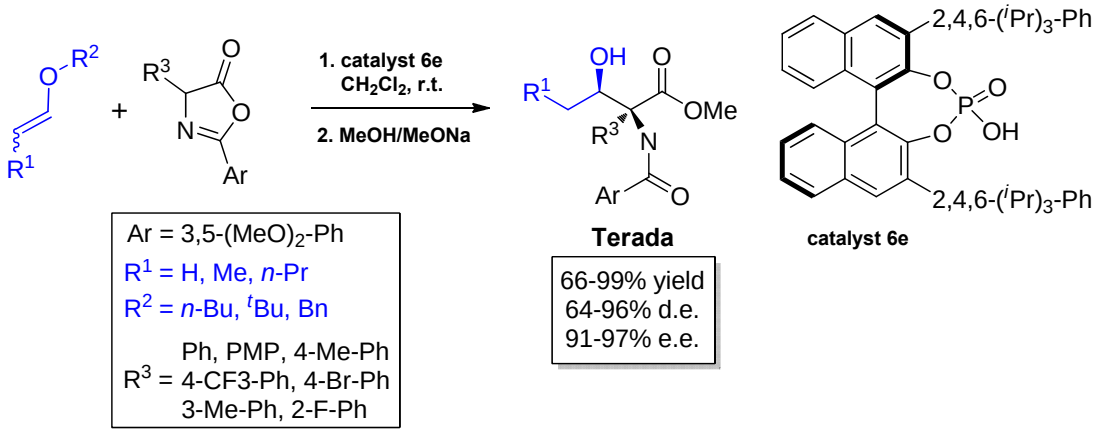
Scheme 1.35. Enantioselective carbonyl-ene reactions onto trifluoropyruvate

Glyoxylates also underwent nucleophilic addition when treated with an enamine in the presence of a chiral phosphoric acid (aza-ene reaction). This approach was employed to prepare α-hydroxy-γ-oxoesters with excellent diastereoselectivities (78-99% d.e.) and enantioselectivities (>99% e.e.) when *E*-enecarbamates were used (Scheme 1.36).[107]



Scheme 1.36. Aldol reaction of ene-carbamate onto activated carbonyls

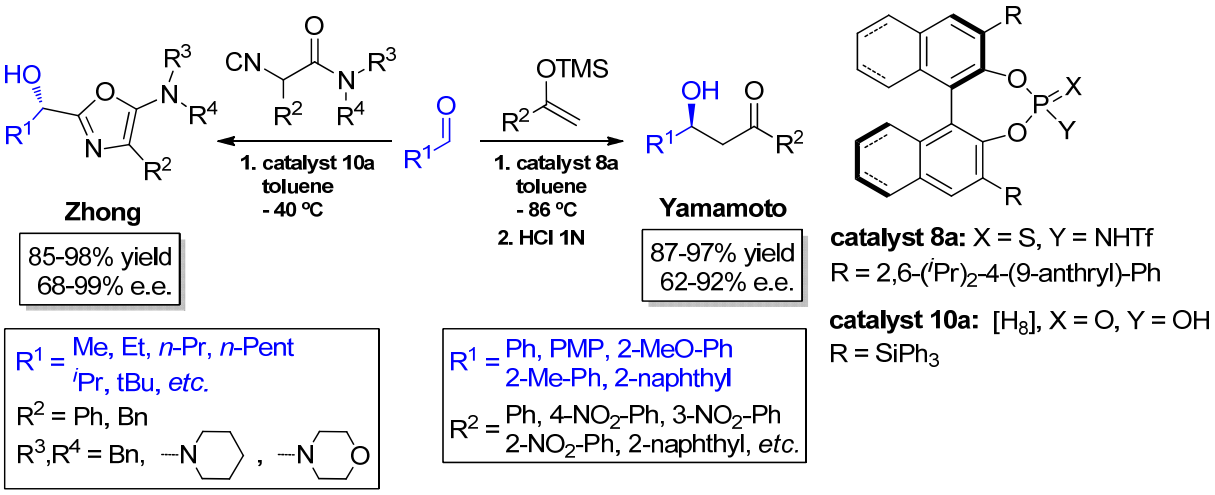
Interestingly, the same group also developed an aldol reaction between an azlactone (pro-nucleophile) and an enol ether (pro-oxonium ion). In the presence of a chiral phosphoric acid, they proposed that the azlactone tautomerised to form an aromatic oxazole bearing an enol moiety. This highly nucleophilic species would subsequently react with the activated enol ether in a high yielding, highly selective aldol reaction (64-96% d.e. and 91-97% e.e., Scheme 1.37).[108] The newly formed azlactones could be hydrolysed to form highly enantioenriched unnatural β-hydroxy-α-aminoacids.



Scheme 1.37. Aldol reaction of azlactones onto oxocarbenium ion generated *in situ*

Isocyanoacetamides proved to be suitable pro-nucleophiles for highly enantioselective aldol reactions. When they were treated with aliphatic aldehydes and 5 mol% of a BPA derivative, oxazoles bearing a chiral secondary alcohol were formed in good yield and high enantiomeric excesses (68-99% e.e., Scheme 1.38).[109] More importantly, a general enantioselective

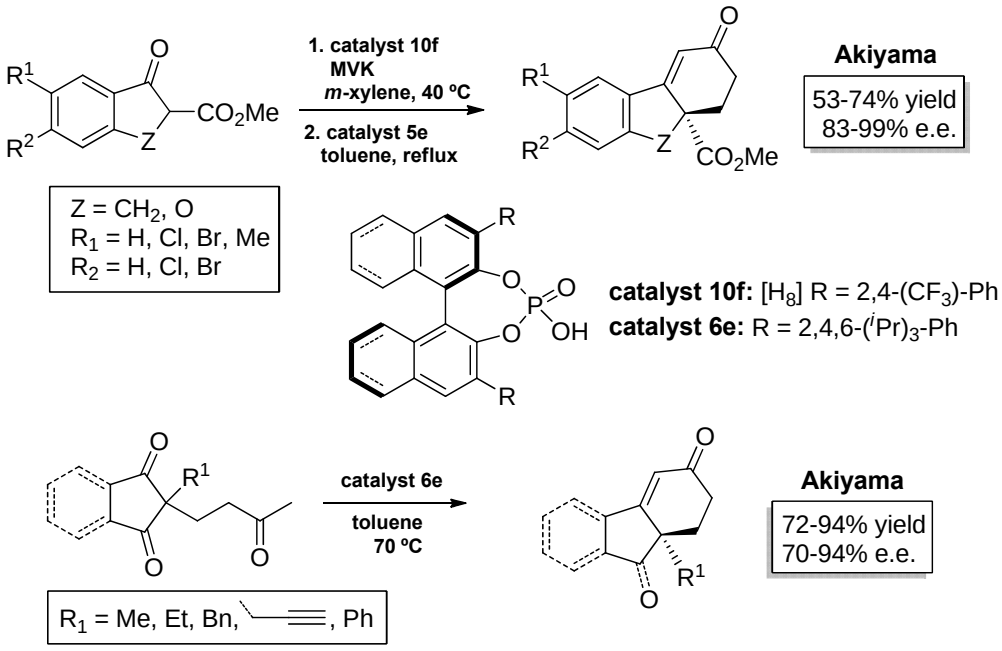
Mukaiyama aldol reaction was developed. Employing a BINOL triflyl thiophosphoramide derivative, TMS enol ethers reacted smoothly with conjugated aldehydes to form the desired aldol products with moderate to high enantioselectivities (62-92% e.e., Scheme 1.38).[110]



Scheme 1.38. BPA-catalysed aldol reaction of isocyanides and enol ethers

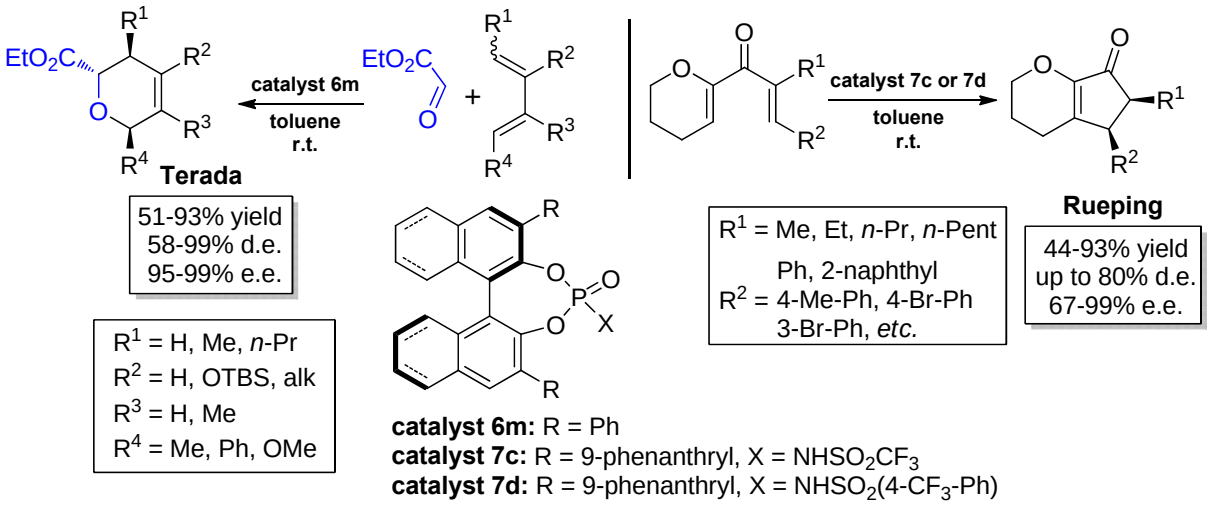
1.6.3 Miscellaneous

A tandem Michael addition/Robinson annulation was developed by Akiyama and co-workers. Indanone derivatives were added to vinyl ketones, in the presence of a BPA, with enantioselectivities ranging from 70% to 83% e.e. The enantioenriched adducts were then heated to promote the annulations that, due to the presence of a chiral phosphoric acid, proceeded with kinetic resolution of the enantiomeric mixture affording highly enantioenriched Robinson annulated products (Scheme 1.39, top).[111] Similar Robinson annulated products were prepared by desymmetrisation of *meso*-diketones through selective activation of one carbonyl with a chiral phosphoric acid (Scheme 1.39, bottom).[112]



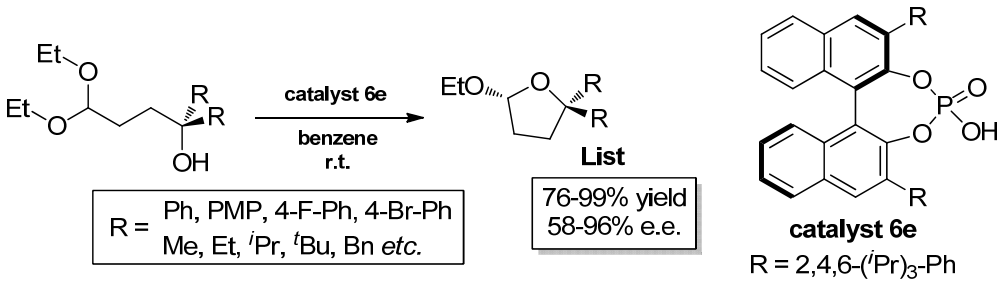
Scheme 1.39. BPA-catalysed formation of Robinson annulation products

Cycloadditions and pericyclic reactions have also drawn the attention of a number of research groups. The first BPA-catalysed enantioselective hetero-Diels-Alder (hetero-DA) reaction of electron-rich dienes and glyoxylate was developed. By using 5 mol% of a BPA derivative, the hetero-DA took place smoothly to afford dihydropyrones with up to two controlled stereocentres, with high diastereo- and enantioselectivity (typically > 80% d.e. and 95-99% e.e., Scheme 1.40).[113] Rueping and co-workers have been particularly involved in the study of BPA-catalysed enantioselective pericyclic reactions. An enantioselective Nazarov cyclisation methodology was successfully developed. They found that phosphoric triflimides were best suited for this type of reaction and achieved good to excellent enantioselectivities in their system although the diastereoselectivity remained low (Scheme 1.40).[114,115]



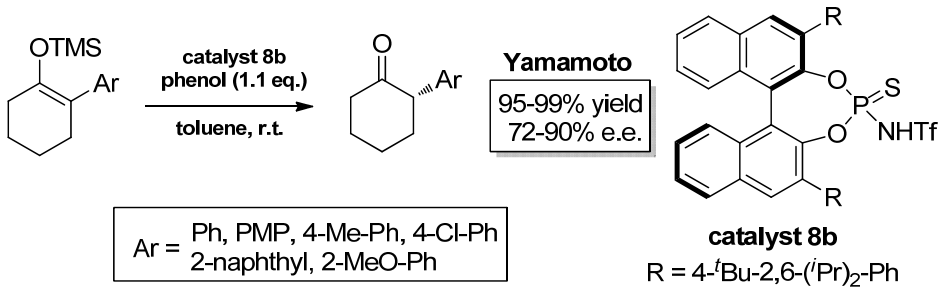
Scheme 1.40. BPA-catalysed hetero Diels-Alder and Nazarov reactions

List and co-workers have developed an enantioselective transacetalisation catalysed by a BPA. After activation by the catalyst, the initial acetal underwent a loss of alcohol to form an oxonium ion *in situ*. The intramolecular tertiary alcohol readily reacted with the strong electrophile to form a 2-alkoxy tetrahydrofuran derivative. Interestingly, although the reaction yielded highly enantioenriched tetrahydrofuran derivatives, the diastereocontrol was poor when the tertiary alcohol was chiral (Scheme 1.41).[116]



Scheme 1.41. BPA-catalysed desymmetrisation of acetals

In a significant development to the field, Yamamoto *et al.* developed an enantioselective protonation. A catalytic amount of BPA derivative in conjunction with stoichiometric phenol was used to desilylate TMS enol ethers to form enantioenriched α-substituted cyclohexanones in good yield and good enantioselectivities (72-90% e.e., Scheme 1.42).[117]



Scheme 1.42. Enantioselective protonation/deprotection of silyl enol ethers

Many efforts have been made to develop enantioselective versions of reactions of various nucleophiles onto formal iminium and oxonium ions. Research in this field has been very successful employing BPAs as catalysts and this is especially true for enantioselective reactions onto iminium ions. Yet, based on computational studies[18,49,92] as well as careful analysis of literature precedents (proposed model),[22,40,72] it appears that the activation of imines and/or formation of iminiums only proceeded *via* protonation (of the nitrogen) or stabilisation of a protonated iminium. The presence of a proton on the iminium was essential for high enantiocontrol and this was proved by different studies.

We believed this was a clear limitation of such a strategy that would only allow for the formation of certain motifs, particularly only primary or secondary amines. We therefore envisaged focusing on the chemistry of *N*-acyliminium ions since it would offer an alternative to prepare tertiary amides (and tertiary amines by reduction) enantioselectively.

1.7 Chiral phosphoric acid-catalysed Pictet-Spengler type cyclisations onto *N*-acyliminium ions

From the outset of this D. Phil., the aim of our project was to develop new methods of enantioselective cyclisation reactions. Many natural products possess backbones containing chiral pyrrolidines/pyrrolidinones or piperidines/piperidinones (Figure 1.1).

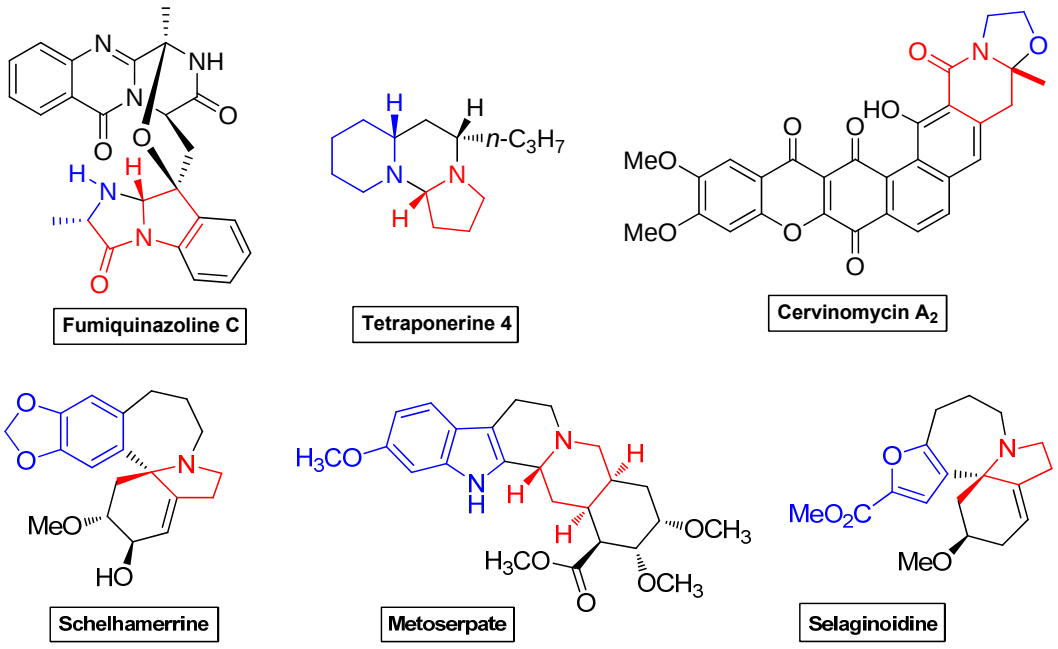
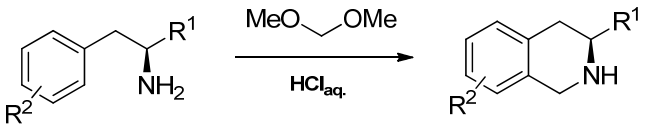


Figure 1.1. Selected examples of natural products presenting *N*-acyliminium cyclisation target motifs

In most of these natural products, we recognised that the chiral centre could result from the attack of an aromatic π-nucleophile on an iminium/*N*-acyliminium ion, in other words, from an enantioselective Pictet-Spengler type reaction. Arguably, amongst all cyclisation reactions involving iminium ions, the Pictet-Spengler reaction has been the most studied. It was discovered in 1911, when Pictet and Spengler treated phenylethylamine, phenylalanine and tyrosine with dimethoxymethane in the presence of aqueous HCl and isolated tetrahydroisoquinolines (Scheme 1.43).[118]



Scheme 1.43. Pictet-Spengler seminal publication: formation of tetrahydroisoquinolines

This discovery led to considerable research[119] and improvements, especially on various catalytic systems.[120,121] The most significant progress was probably the development of a highly

enantioselective *N*-acyl Pictet-Spengler reaction of tryptamine with various aliphatic aldehydes.[122]

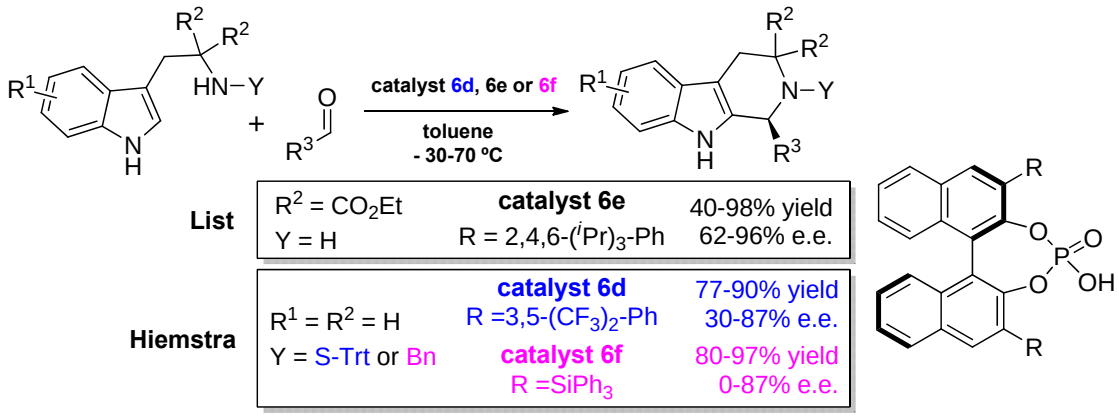
Since its discovery, the Pictet-Spengler reaction has been applied to many complex natural product syntheses;[123] recently our group has contributed to the field *via* the elegant synthesis of powelline and buphanidrine.[124,125]

This transformation was well documented and proved to be very efficient in complex target synthesis. In addition, the Pictet-Spengler reaction is relevant in biological systems (e.g. biosynthesis of complex antibiotics[126]). For these reasons, the use of π-nucleophiles in *N*-acyliminium cyclisation reactions emerged as our main focus. Moreover, since entire families of natural products present this type of backbone, developing an enantioselective *N*-acyliminium cyclisation methodology would give potential application to total synthesis.

When our program started, the only organocatalytic entry to Pictet-Spengler type products had been developed by Jacobsen *et al*.. During the course of our study, novel relevant methods of organocatalysed enantioselective Pictet-Spengler reactions have been disclosed and are outlined below.

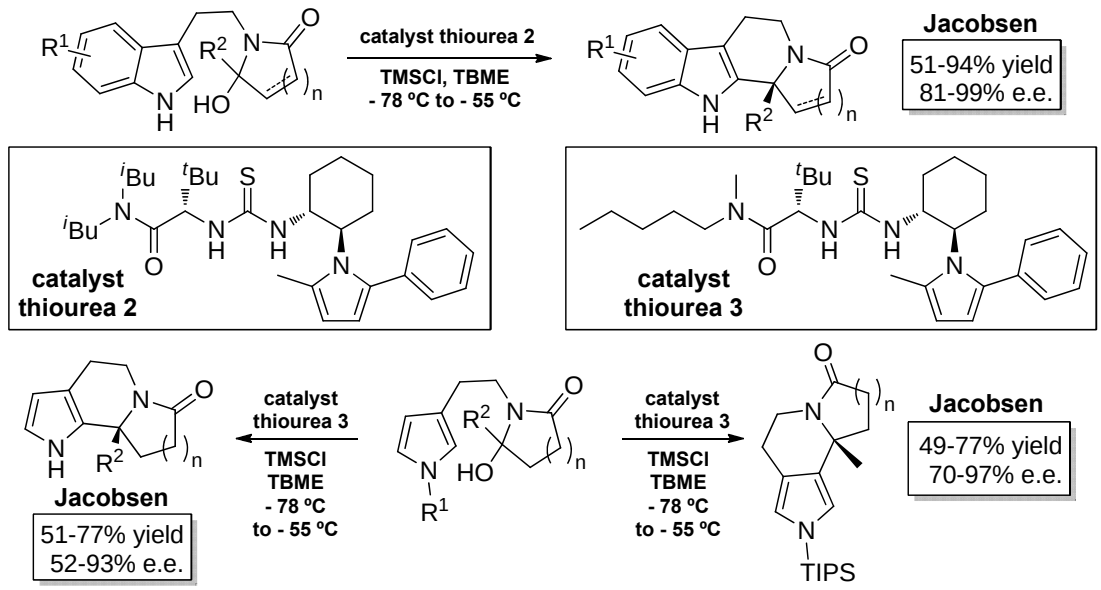
List and co-workers found that a tryptamine substituted by a geminal diester α to the amine underwent a clean and highly enantioselective Pictet-Spengler reaction in the presence of a BPA. Their strategy was however limited to these tryptamine derivatives bearing geminal diesters α to the amine nitrogen, since in the absence of any substitution, aldol condensation was observed (Scheme 1.44).[127] Overcoming this limitation, Hiemstra *et al.* found that a *N*-sulfenyl tryptamine reacted with aldehydes in the presence of a catalytic amount of BPA derivative to form *N*-sulfenyl iminium ion intermediates that readily cyclised to afford protected β-carbolines although with low to good levels of enantiocontrol (30-87% e.e.).[128] Later the same group reported the enantioselective Pictet-Spengler cyclisation of *N*-benzyl tryptamine with various aldehydes employing BPA catalysis, with enantiomeric excesses ranging from

racemic to 87% e.e. which were extremely dependant on the nature of the aldehyde (Scheme 1.44).[129]



Scheme 1.44. BPA-catalysed asymmetric Pictet-Spengler type reactions

Although these strategies generally provided moderately enantioenriched material, they differ significantly from the general approach described in Section 1.5. As a matter of fact, in Hiemstra's studies, enantioselectivity was still observed despite the fact there was no hydrogen-bond between the phosphate and the iminium ion; only the electrostatic interaction between the phosphate and the iminium ion can be the the origin of enantiocontrol. We believed similar behaviour could be observed with *N*-acyliminium ions as electrophiles as supported by literature precedent; Jacobsen and co-workers developed an enantioselective cyclisation of indoles onto intramolecular *N*-acyliminium ions. Employing a chiral thiourea-derived catalyst, they were able to prepare tri- and tetracyclic β-carbolines in good yield and good to excellent enantioselectivities (81-99% e.e., Scheme 1.45).[122,130,131] With a similar approach pyrroles also took part in an enantioselective *N*-acyliminium cyclisation, although with lower enantiomeric excesses being observed. Interestingly in the latter case, the regioselectivity of the cyclisation could be controlled by protecting the pyrrole nitrogen with a bulky silyl group (TIPS) preventing the cyclisation at the 2-position (Scheme 1.45).[132]



Scheme 1.45. Thiourea-catalysed asymmetric Pictet-Spengler reactions on *N*-acyliminium ions

The major drawback of the aforementioned methods (references 122 and 130-132) was to use a superstoichiometric amount of an activating agent (TMS-Cl) to observe the dehydration (formation of *N*-acyliminium ion) and subsequent cyclisation.

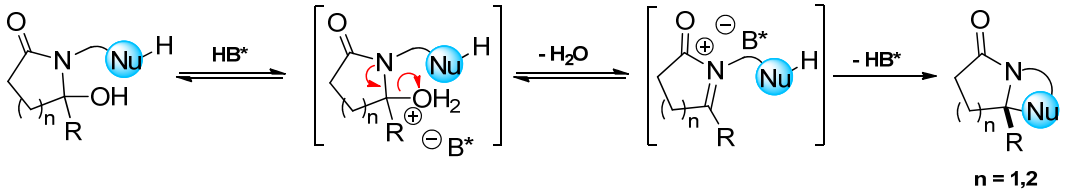
Our hope was to be able to adopt an approach similar to the one of Jacobsen and co-workers, however we believed that using stronger Brønsted acids such as BPAs and their derivatives, we would be able to promote the direct formation of *N*-acyliminium ions, without employing any activating agent.

Chapter 2:

A New Highly Enantioselective *N*-Acyliminium Cyclisation Cascade

2.1 Overview

The aim of the proposed project was initially to develop new enantioselective cyclisation reactions based on *N*-acyliminium ion intermediates in a first stage, a concept that could theoretically be expanded to more general stabilised carbocations. The principle was based on well documented reactivity (Pictet-Spengler type reaction), the originality was the development of an asymmetric and organocatalytic method, employing chiral Brønsted acids (especially BPAs), to impart enantioselectivity in the cyclisation. Such a method would be the first example of direct dehydrative formation of *N*-acyliminium ions in an enantioselective transformation (Scheme 2.1).



Scheme 2.1. Concept of a Brønsted acid catalysed enantioselective *N*-acyliminium cyclisation

The scope of such a methodology would be broad, and would allow access to various synthetic or natural product synthons (Figure 2.1).

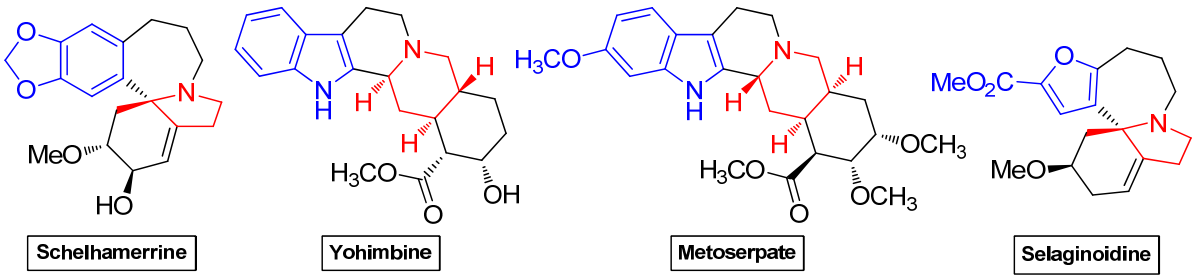
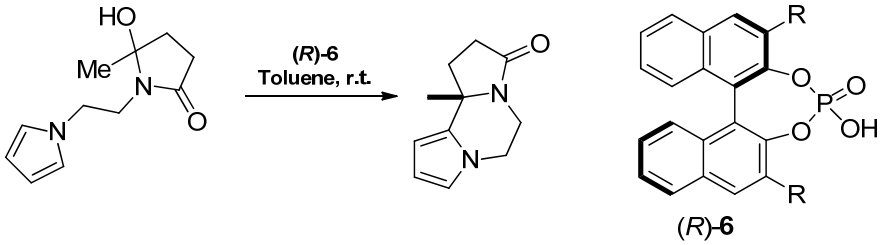


Figure 2.1. Natural products presenting polycyclic pyrrolidines/piperidines motifs

2.2 Proof of principle

A proof of principle of our concept was given by Dr. Adam W. Pilling and Christopher Knox in a short study concerning the cyclisation of a pyrrole nucleophile on a hydroxylactam substituent (Scheme 2.2).



Scheme 2.2. Brønsted acid catalysed enantioselective cyclisation of pyrrole on a hydroxylactam

After many efforts, very low enantioselectivities were achieved using this system, ranging from less than 5% to up to 12%. Despite these encouraging results, it was hoped that by employing a different nucleophile and exploring a wide range of reaction conditions, high levels of enantioselectivity might be reached. To be able to carry out these investigations, a library of catalysts needed to be synthesised.

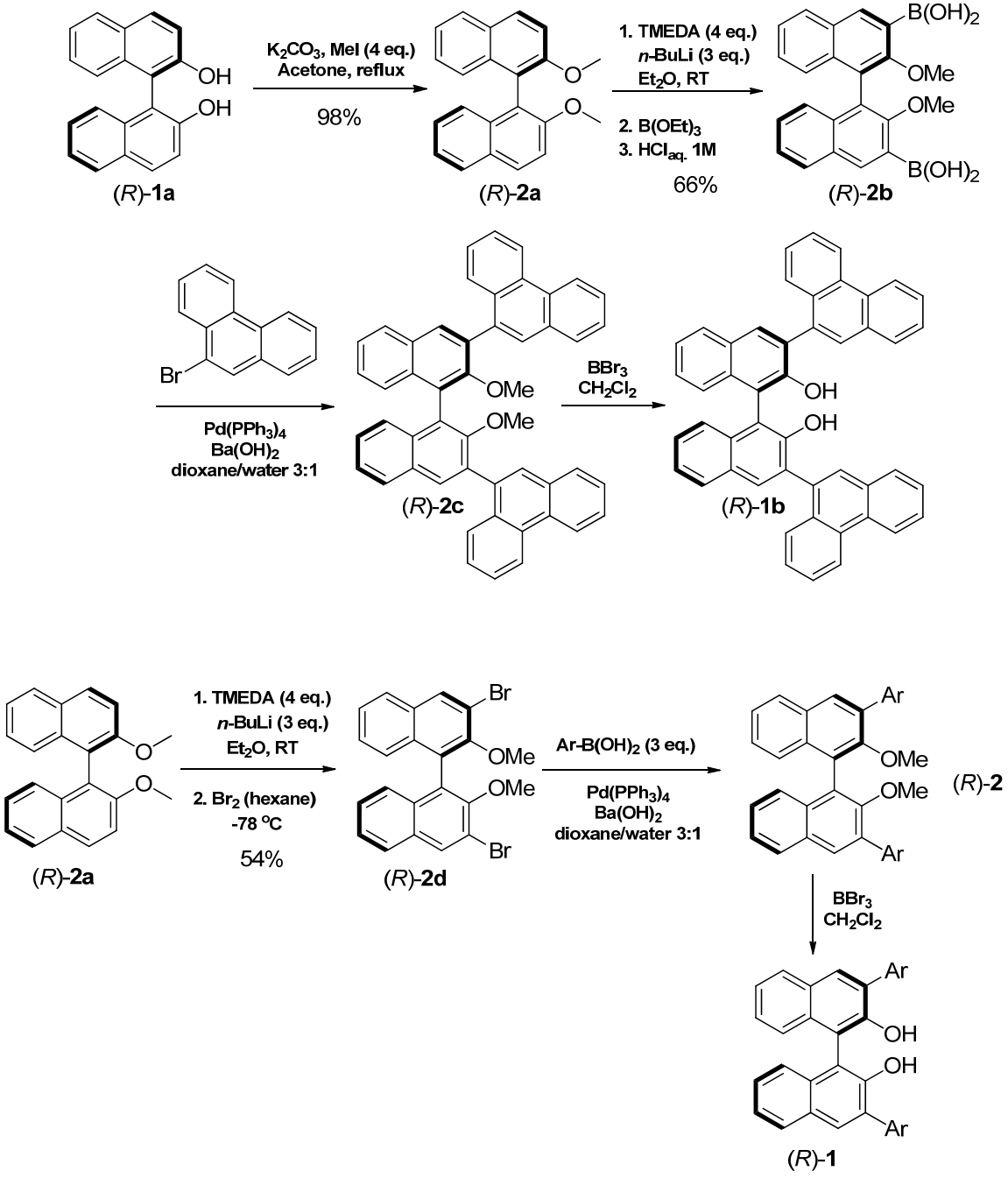
2.3 Catalyst synthesis

The synthesis of chiral BINOL-derived phosphoric acids followed three main strategies as outlined below.

2.3.1 Route 1: from dimethoxy BINOL (*R*)-**2a**

A methoxy-protected BINOL was used to synthesise either the diboronic acid BINOL-derivative (*R*)-**2b**, or the dibromo BINOL derivative (*R*)-**2d**, that were used in cross-coupling reactions to attach aromatic substituents at the 3 and 3′ position of the binaphthyl (mainly the Suzuki-Miyaura cross coupling or the Kumada-Tamao-Corriu cross coupling in the case of

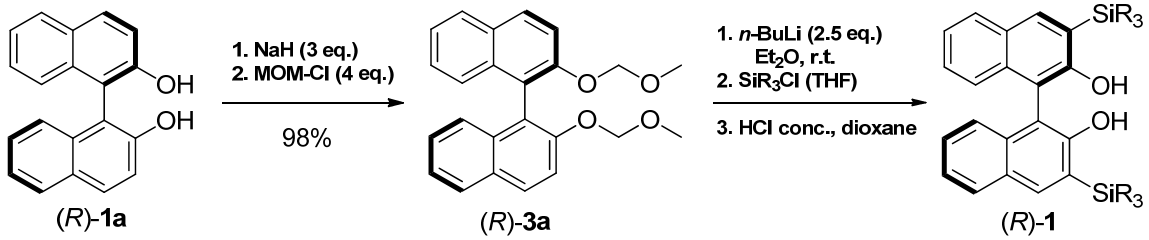
sterically congested aromatic groups). The subsequent deprotection of the methoxy groups with boron tribromide would afford the bulky BINOL derivatives (Scheme 2.3).[133]



Scheme 2.3. Synthesis of 3,3′-aryl disubstituted BINOLs

2.3.2 Route 2: from bis(methoxymethyl) BINOL (*R*)-**3a**

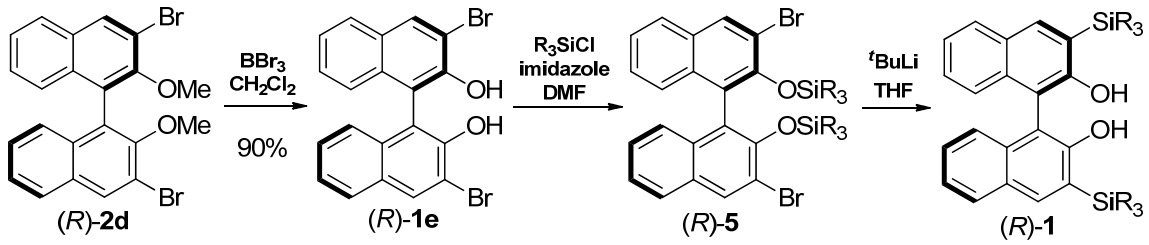
MOM-protected BINOL derivative (*R*)-**3a** was used to synthesise BINOLs silylated at the 3 and 3′ position *via* direct Snieckus *ortho*-metallation and quench with a chlorosilane. However this strategy was limited to the substitution by «small» silyl groups (highly sterically congested chlorosilanes such as TBDPS-Cl giving mainly monosubstitution). Subsequent deprotection in acidic conditions (typically concentrated aqueous HCl in dioxane) would afford the free substituted BINOLs (Scheme 2.4).[49]



Scheme 2.4. Synthesis of TMS, TES and TPS (Ph_3Si) substituted BINOLs

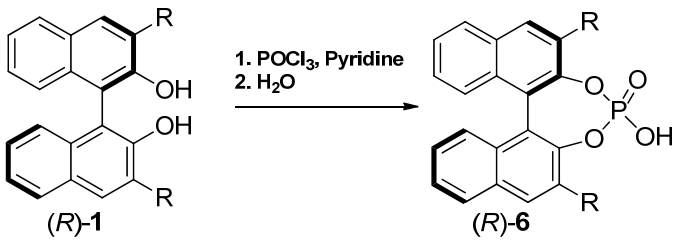
2.3.3 Route 3: from 3,3′-dibromo BINOL (*R*)-**1e**

Dibromo BINOL (*R*)-**1e** can be used as a precursor to synthesise BINOLs tethered to very bulky silyl groups (TBDPS, TIPS, TPS, (*m*-xylyl)$_3$Si *etc.*) through a bis-silylation of the hydroxyls and further retro-Brook rearrangement in the presence of ^{t}BuLi (Scheme 2.5).[134]



Scheme 2.5. Synthesis of bulky silyl substituted BPAs

A final phosphorylation of compounds (*R*)-**1** (from routes 1-3) using phosphorous oxychloride/pyridine followed by hydrolysis would give the desired substituted BINOL phosphoric acids (*R*)-**6** (Scheme 2.6).[49]



Scheme 2.6. Phosphorylation of BINOLs to form BPAs

With these three strategies, it was possible to efficiently generate a library of BINOLs and BINOL phosphoric acids (BPAs), although this work required meticulous purification to afford high purity material at each step.

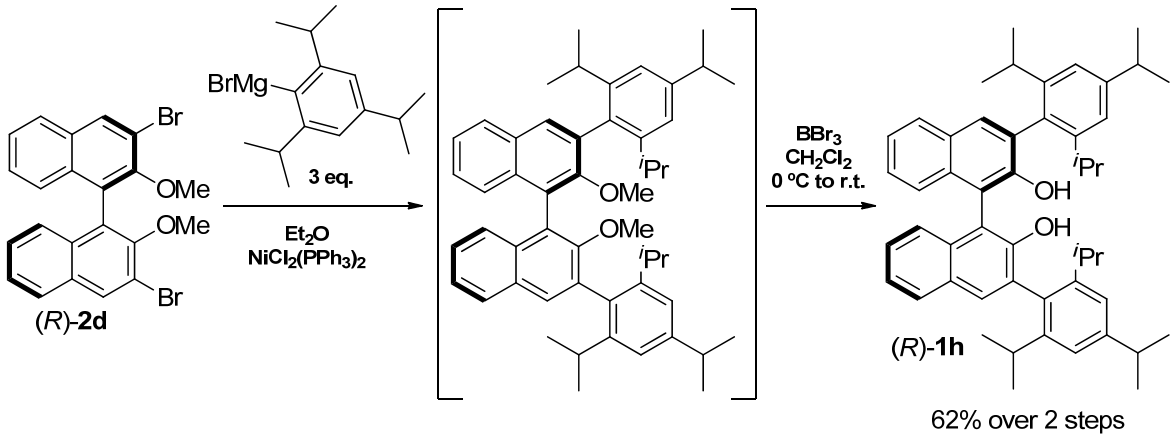
2.3.4 Synthesis of a library of catalysts

Catalyst (*R*)-**6b** was synthesised according to a literature procedure[133] from (*R*)-**2a** by firstly preparing the diboronic acid (*R*)-**2b** and then reacting it with 9-bromophenanthrene in a Suzuki-Miyaura coupling. The protected intermediate was not isolated, and deprotection of the crude material with boron tribromide in dichloromethane afforded BINOL derivative (*R*)-**1b** in good yield after purification by column chromatography (68%). The phosphoric acid (*R*)-**6b** was easily synthesised from the BINOL derivative in a standard, high yielding procedure (87%).[49]

Catalyst (*R*)-**6c** was synthesised according to a modified literature procedure[135] from (*R*)-**2d** *via* a Suzuki-Miyaura coupling with 9-anthrylboronic acid followed by deprotection to afford the BINOL derivative (*R*)-**1f**. A final standard phosphorylation/hydrolysis afforded the desired phosphoric acid (*R*)-**6c** in 58% yield.

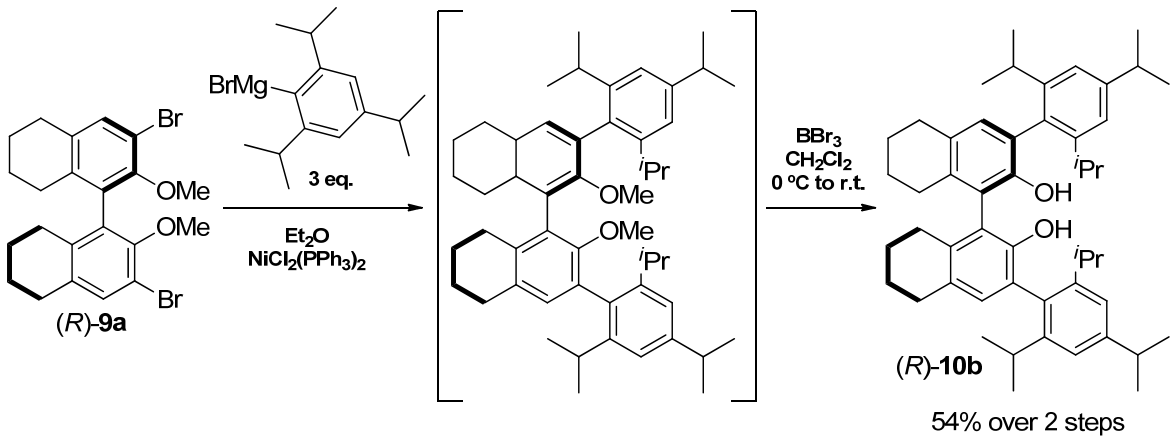
Catalyst (*R*)-**6d** was synthesised according to the previous route (for (*R*)-**6c**) in an overall 60% yield over 3 steps.

In the case of the sterically congested aryl groups at the 3,3′-positions, the Suzuki-Miyaura coupling approach showed its limitations. Indeed, attempting to synthesise 3,3′-(2,4,6-triisopropylphenyl) BINOL (*R*)-**1h** from (*R*)-**2b**, no coupling product was observed. To overcome this reactivity issue, the use of more activated coupling partners was necessary and as described in the literature[136], the use of (*R*)-**2d** and the aryl magnesium bromide, in the presence of $NiCl_2(PPh_3)_2$ led to the formation of the desired BINOL derivative (*R*)-**1h** after deprotection (BBr_3 in CH_2Cl_2) in 62% yield over 2 steps (Scheme 2.7).



Scheme 2.7. Synthesis of bulky aryl substituted BINOL (*R*)-**1h**

The same approach can be used to form octahydro BINOL derivatives (H_8 BINOL) and (*R*)-**10b** was synthesised according to the same strategy (Scheme 2.8).



Scheme 2.8. Synthesis of bulky aryl substituted H_8-BINOL (*R*)-**10b**

Catalyst (*R*)-**6f** was synthesised according to a procedure from MacMillan *et al.*[49] from (*R*)-**3a**. Snieckus direct *ortho*-lithiation followed by chlorotriphenylsilane quench afforded the crude MOM-protected BINOL that was deprotected and after careful purification gave (*R*)-**1c** in 66% yield over two steps (route 2, Scheme 2.4). The BINOL derivative was converted to the phosphoric acid in high yield by using the standard procedure (93%).

Catalyst (*R*)-**10a** was prepared from (*R*)-H_8 BINOL (*R*)-**4a**[137] following the same sequence used for the synthesis of (*R*)-**5f** (route 2, Scheme 2.4). Alternatively it can be prepared following route 3 (Scheme 2.5), in an overall good yielding 3-step procedure (52% yield over 3 steps).

Catalysts (*R*)-**6g** was prepared according to route 2 from (*R*)-**3a**. The deprotection (of the crude intermediate) had to be slightly modified because of the sensitivity of the TES group to acidic conditions and followed a modified procedure by Feringa *et al*.[138] Aqueous HCl (6M) in THF at 60 ºC was employed differing from previous conditions (see Scheme 2.4). The reaction took 48 hours to give satisfactory conversion and after column chromatography on silica gel, the desired TES substituted BINOL (*R*)-**1d** was isolated in 50% yield over 2 steps. The phosphorylation was carried out in conditions milder than the standard procedure (70 ºC instead of 95 ºC) to afford the desired acid in good yield (67%). Similarly, catalyst (*R*)-**6h** was prepared from the TMS BINOL derivative in good yield (88%, TMS BINOL was provided by Dr. A. W. Pilling). Catalysts (*R*)-**6i**, (*R*)-**6j** and (*R*)-**6k** were synthesised according to route 3 (Scheme 2.5), using the appropriate chlorosilane as a silyl source. All steps proceeded smoothly to afford the desired BINOLs that were converted to the catalysts in 36-83% yield over 3 steps.

Catalyst (*R*)-**6l** was synthesised according to route 3 (Scheme 2.5). The appropriate chlorosilane was synthesised following a literature procedure[139], in good overall yield (78% over 2 steps) and was used to prepare the BINOL derivative (see Scheme 2.5, R = (*m*-xylyl)$_3$Si) in good yield (64% yield over 2 steps). The phosphoric acid was prepared in a satisfactory 80% yield.

Catalyst (*R*)-**7a** was prepared according to a literature procedure[140] in good yield from the BINOL derivative (*R*)-**1c** (71%).

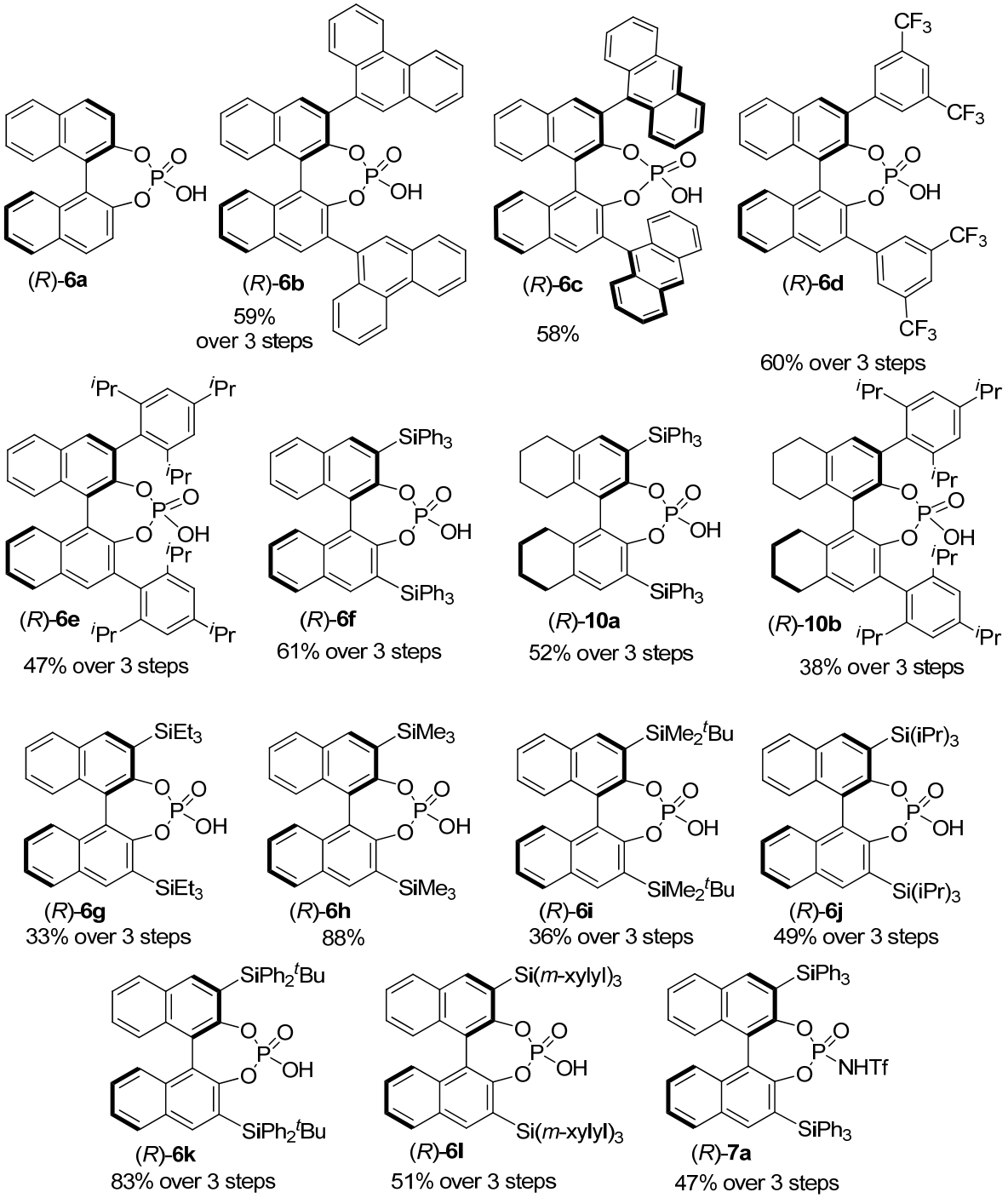
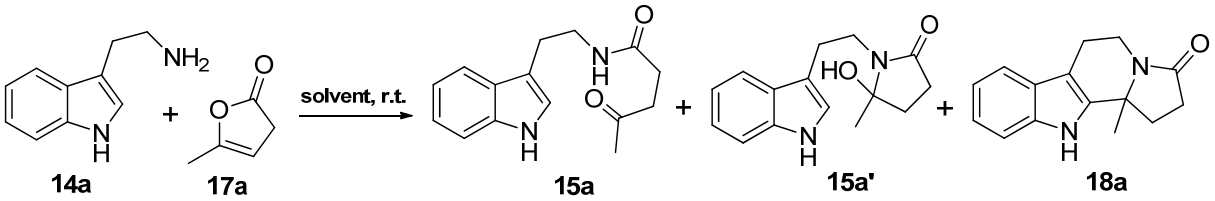


Figure 2.2. Library of catalysts synthesised for screening

2.4 Study of the cyclisation of hydroxylactams/oxoamides on indole

The synthesis of a system similar to the one studied by Dr. A. Pilling in his proof of concept, presenting both an indole core as the nucleophile and a hydroxylactam (tertiary alcohol) or masked hydroxylactam as its open form, was planned. It was hoped that the synthesis of such a precursor would be relatively straightforward by reacting tryptamine with α-angelica lactone (Scheme 2.9).[141]

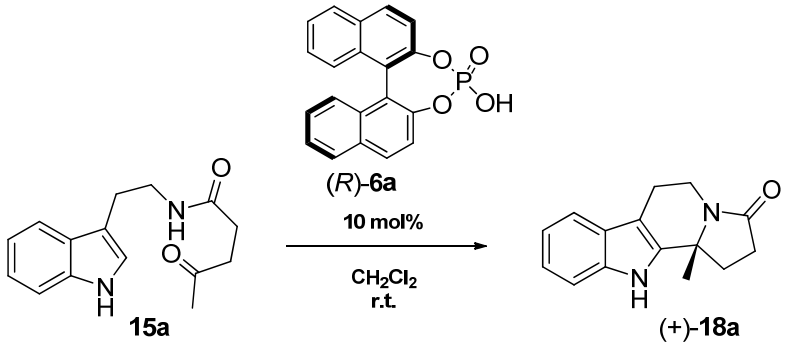


Scheme 2.9. Indole system synthesis from tryptamine and α-angelica lactone

A first synthesis attempt was carried out in water and led to the formation of a non-negligible amount of the tetracyclic β-carboline (±)-**18a**. Switching to a non-protic solvent (dichloromethane), **15a** was obtained as the major product (50% of the mixture) together with a minor product ((±)-**15a′**, 20% of the mixture) and some unreacted starting material. The open keto amide form **15a** could be isolated in 37-49% yield after purification and was preferred to the hydroxylactam due to its relative stability.

2.4.1 Proof of principle

The proof of both reactivity and enantioinduction was given by treating **15a** with (*R*)-BINOL phosphoric acid (*R*)-**6a**, in standard conditions (dichloromethane, 100 mM, room temperature, 10 mol% catalyst).



Scheme 2.10. Proof of principle of reactivity and enantioinduction

The reaction proceeded slowly (3 days) to afford the desired tetracycle (+)-**18a** in good yield (95%) and 8% enantiomeric excess. We believed this was a promising result that prompted us to investigate the use of more sterically demanding catalysts and run a preliminary screen of conditions. Notably, studying the influence of the solvent was of major importance.

2.4.2 Optimisation of the reaction conditions

2.4.2.1 Solvent and catalyst pre-screening

It was decided to first screen the library of BPA catalysts already synthesised within the group (Figure 2.3). These initial reactions were all performed at room temperature, utilising a variety of common solvents, to be able to define a trend (Table 2.1).

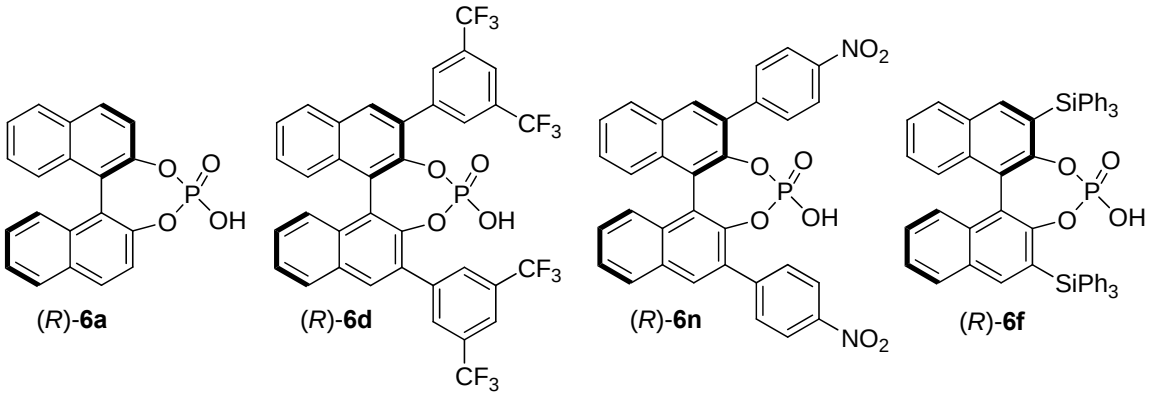
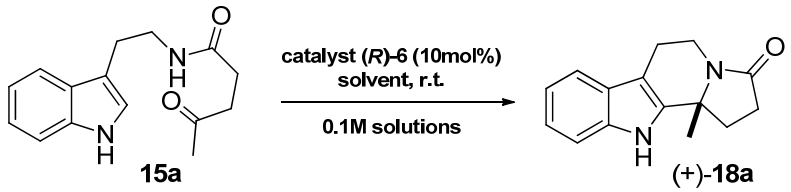


Figure 2.3. Catalysts used for preliminary screening

Table 2.1. Level of enantioselectivity for the cyclisation of **15a**



Catalyst (10 mol%)	Solvent	Temperature	Time	e.e. (%)
(*R*)-**6a**	acetone	r.t.	4 days	0
(*R*)-**6a**	diethyl ether	r.t.	48 hours	0
(*R*)-**6a**	acetonitrile	r.t.	48 hours	− 2
(*R*)-**6a**	tetrahydrofuran	r.t.	6 days	− 4
(*R*)-**6a**	dichloromethane	r.t.	3 days	8
(*S*)-**6a**	dichloromethane	r.t.	3 days	− 8
(*R*)-**6n**	dichloromethane	r.t.	36 hours	0
(*R*)-**6d**	dichloromethane	r.t.	10 days	15
(*R*)-**6f**	dichloromethane	r.t.	10 days	25
(*R*)-**6f**	toluene	r.t.	10 days	27

From these results, it was clear that (*R*)-**6f** was imparting the highest enantioselectivity. As well as this, apolar solvents showed moderate enantioselectivities while polar solvents mostly gave rise to racemates or poorly enantioenriched product. Dichloromethane and toluene gave similar results when (*R*)-**6f** was used, with up to 27% e.e. observed. It was decided that the reaction in toluene would be further explored due to its greater range of reaction temperatures and the possibility of using other aromatic solvents.

2.4.2.2 Temperature screening

The effect of the temperature was studied in toluene, in slightly more dilute conditions, for solubility reasons (Table 2.2).

Table 2.2. Influence of the temperature on enantioselectivity with 10 mol% catalyst (*R*)-**6f**

Concentration[a]	Temperature	Time[b]	e.e.[c] (%)
35 mM	50 ºC	6 days	50
35 mM	90 ºC	48 hours	68
35 mM	reflux (110 ºC)	2 hours	70

[a] relative to the substrate; [b] time to reach completion, monitored by TLC

[c] measured by HPLC using a Chiralpak OD column (*vide infra* for conditions)

Elevated temperatures, as well as providing dramatically enhanced reactivities, clearly gave higher enantioselectivities, with what seemed to be a plateau reached between 90 ºC and reflux (where enantiomeric excess was equal within error). This point is particularly interesting as in most of the reactions described in the literature (especially in the case of Brønsted acid organocatalysis), reactions are cooled to reach high enantiomeric excess. It was assumed that in our case, the reaction was proceeding under kinetic control therefore high temperatures were favouring the most stable transition state that was then leading to the formation of the major enantiomer. This fact was of particular interest from a mechanistic point of view, a topic that will be discussed in chapter four.

The utilisation of different aromatic solvents had little effect on the selectivity; their boiling points and nature did not seem to influence the enantiomeric excess (Table 2.3).

Table 2.3. Influence of aromatic solvents on enantioselectivity (with 10 mol% (*R*)-**6f**)

Solvent	Temperature	Concentration	e.e. (%)
Benzene	80 ºC	35 mM	72
Toluene	110 ºC	35 mM	73
Xylene	150 ºC	35 mM	74

It had been observed that at the concentration used (35 mM), high temperatures (usually > 70 ºC) were needed for both catalyst and substrate to be in solution. Therefore studying the effect of the concentration on the selectivity of the reaction was investigated.

2.4.2.3 Influence of the concentration on the enantioselectivity

The final variable in the reaction to be optimised was the substrate concentration (Table 2.4, Figure 2.4) and it was found that a narrow band of concentration was improving the enantioselectivity significantly. When the reaction was carried out at 7 mM, the highest selectivity was observed, with 6 mM and 10 mM giving similar selectivities within error.

Table 2.4. Effect of concentration on the level of enantioselectivity

Catalyst (10 mol%)	Solvent	Temperature	Concentration	Time	e.e. (%)
(*R*)-**6f**	Toluene	110 ºC	0.05 M	1 hour	67%
(*R*)-**6f**	Toluene	110 ºC	0.025 M	1 hour	71%
(*R*)-**6f**	Toluene	110 ºC	0.0167 M	1 hour	75%
(*R*)-**6f**	Toluene	110 ºC	0.01 M	1 hour	81%
(*R*)-**6f**	Toluene	110 ºC	0.007 M	1 hour	84%
(*R*)-**6f**	Toluene	110 ºC	0.00625 M	2 hours	82%
(*R*)-**6f**	Toluene	110 ºC	0.005 M	2 hours	70%

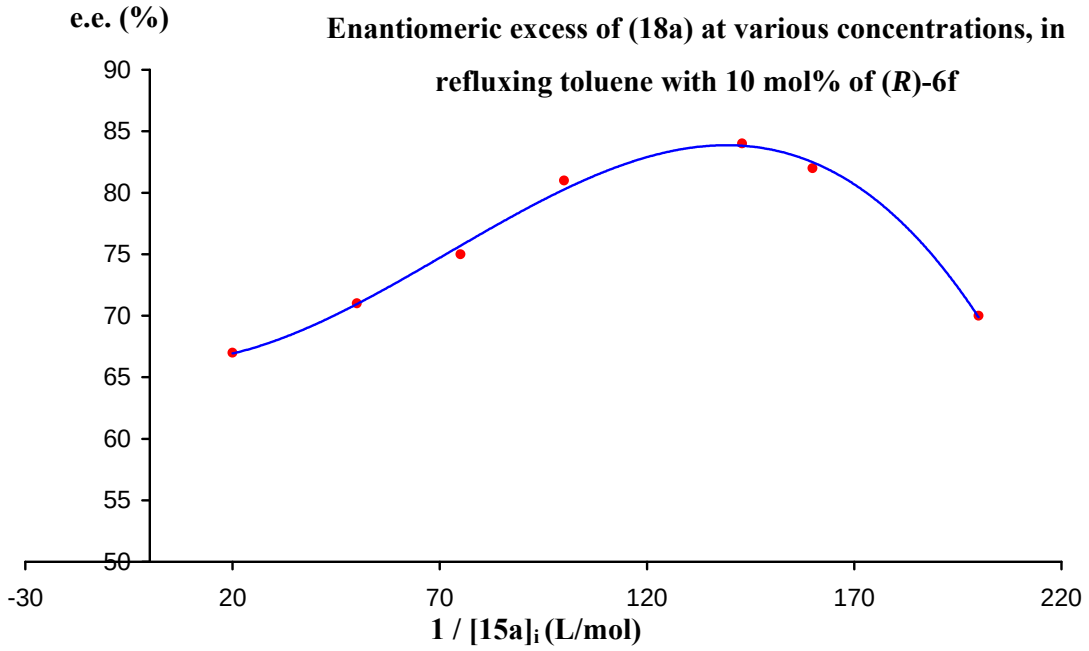


Figure 2.4. Influence of the concentration on the enantioselectivity of the *N*-acyliminium cyclisation of **15a**

2.4.2.4 Effect of catalyst loading

Now that an optimum substrate concentration had been found, attention turned to catalyst loading. Ideally, the lowest loading possible should be employed. When it was decreased to 5 mol% it was accompanied by a slight decrease in selectivity. Increasing the catalyst loading above 10 mol% had no effect (keeping the catalyst concentration identical) (Table 2.5).

Table 2.5. Catalyst loading influence on the enantioselectivity

Catalyst	Loading	Concentration[a]	Temperature	Time	e.e. (%)
(*R*)-**6f**	5 mol%	0.013 M	110 ºC	1 hour	80
(*R*)-**6f**	10 mol%	0.007 M	110 ºC	1 hour	83
(*R*)-**6f**	20 mol%	0.0035 M	110 ºC	1 hour	83
(*R*)-**6f**	40 mol%	0.0017 M	110 ºC	1 hour	83

[a] relative to the substrate

This was a significant result. If the catalyst loading can be decreased without major impact on the enantioselectivity, incorporating this cyclisation into a cascade sequence can be of a great interest for large scale reactions (industry *etc.*) and this will be discussed in section 2.5.6.

2.4.3 Cross-checking: catalysts assay in the optimum conditions, study of the influence of the temperature at the optimal concentration and evaluation of the benefit of additives

With these optimised conditions giving rise to the formation of tetracycle (+)-**18a** in good enantioselectivity, a series of cross-checking reactions were performed to confirm that the reaction conditions could not be optimised further.

2.4.3.1 Catalyst screening

Firstly, more catalysts in our primary library were reassessed in the model reaction (Table 2.6).

Table 2.6. Evaluation of different BPA catalysts in optimal conditions

Catalyst	Solvent	Loading	Concentration[a]	Temperature	e.e. (%)
(*R*)-**6f**	Toluene	10 mol%	0.007 M	110 ºC	84
(*R*)-**6b**	Toluene	10 mol%	0.007 M	110 ºC	55
(*R*)-**6c**	Toluene	10 mol%	0.007 M	110 ºC	39
(*R*)-**6e**	Toluene	10 mol%	0.007 M	110 ºC	50
(*R*)-**7a**	Toluene	10 mol%	0.007 M	110 ºC	60
(*R*)-**10a**	Toluene	10 mol%	0.007 M	110 ºC	84

[a] relative to the substrate

None of the catalysts synthesised improved the selectivity we had observed with (*R*)-**6f**. The H_8-BINOL derivative (*R*)-**10a** offered the same selectivity, but due to the higher cost of the catalyst, it was discarded in this particular study.

2.4.3.2 Effect of molecular sieves

As water was produced in stoichiometric amount in the reaction, molecular sieves (M.S.) were added to study whether the water had a deleterious effect on the reaction.[48,49,70,127] At the optimal concentration, it was noticed that molecular sieves did not improve the enantioselectivity (Table 2.7). In fact, 3Å M.S. clearly inhibited the reaction and a longer reaction time was needed to reach completion.

Table 2.7. Effect of M.S. and temperature on the level of enantioselectivity

Catalyst	Solvent	Concentration[a]	Temperature	Additive	Time	e.e. (%)
(*R*)-**6f**	Toluene	0.007 M	110 ºC	-	1 hour	84
(*R*)-**6f**	Toluene	0.007 M	110 ºC	3Å	48 hours	82
(*R*)-**6f**	Toluene	0.007 M	110 ºC	4Å	1 hour	84
(*R*)-**6f**	Toluene	0.007 M	110 ºC	5Å	1 hour	83

[a] relative to the substrate

2.4.3.3 Reassessment of the temperature influence

A final verification was carried out to find the optimal temperature for the reaction, using the previously optimised parameters. It was found that the enantioselectivities were improved when the reaction temperature was increased to approximately 70 ºC from room temperature. The reactivity was also improved dramatically on heating. Interestingly, the enantioselectivity remained unchanged when the temperature was increased above 70 ºC (Table 2.8, Figure 2.5).

Table 2.8. Influence of the temperature at the optimal concentration

Catalyst	Solvent	Concentration[a]	Temperature	Time	e.e. (%)
(*R*)-**6f**	Toluene	0.007 M	29 ºC	4 days	65
(*R*)-**6f**	Toluene	0.007 M	50 ºC	48 hour	74
(*R*)-**6f**	Toluene	0.007 M	70 ºC	24 hour	83
(*R*)-**6f**	Toluene	0.007 M	110 ºC	1 hour	84

[a] relative to the substrate

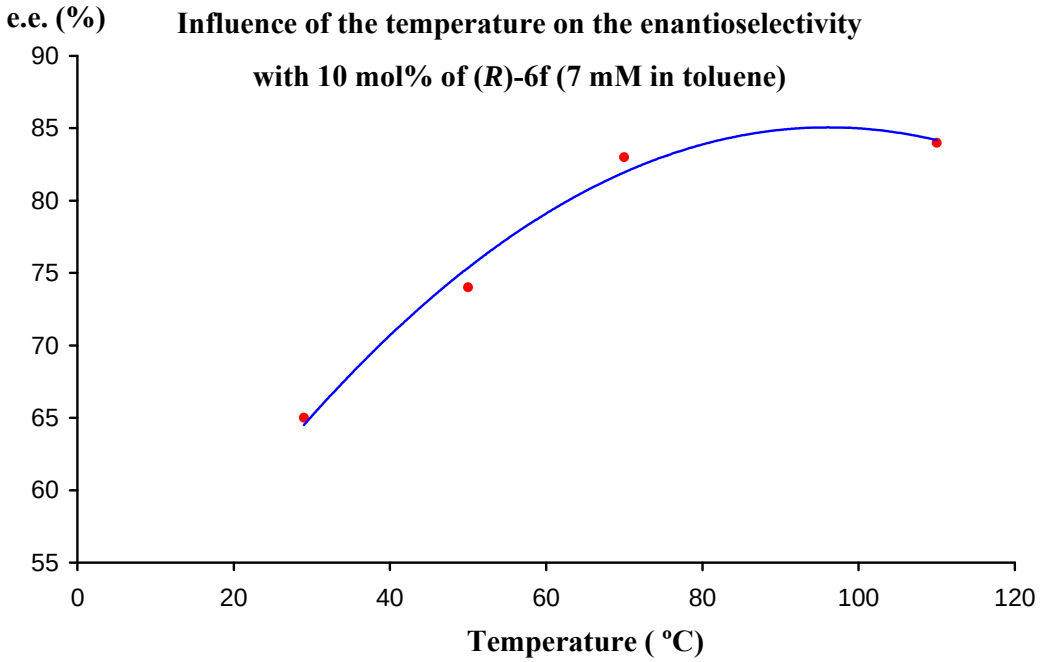


Figure 2.5. Influence of the temperature on the enantioselectivity in the *N*-acyliminium cyclisation of **15a** catalysed by 10 mol% of (*R*)-**6f** in toluene at 7 mM.

2.4.4 Optimal conditions

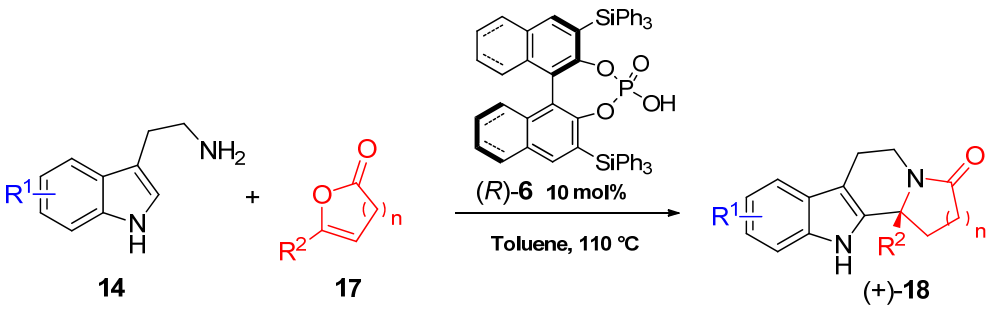
The optimal conditions were found to be 10 mol% of (*R*)-**6f** in refluxing toluene, with a critical 7 mM concentration. When the reaction was repeated on a 0.3 mmol scale, the desired β-carboline (+)-**18a** was isolated in essentially quantitative yield (99%) and 84% enantiomeric excess. It was envisaged to pursue the development of a practical method to synthesise related

tetracycles, the isolation of oxoamide intermediates (in moderate yield) was seen as a serious drawback for this method; it would be preferable to develop a one-pot cascade sequence from tryptamine and α-angelica lactone. Therefore a different strategy was investigated.

2.5 Cascade development and scope of reaction

2.5.1 Development of a new powerful cascade reaction

A one-pot procedure using a tryptamine derivative, an enol lactone and the BPA catalyst was studied. This method proved to be very efficient for the formation of (+)-**18a** in quantitative yield, with 84% enantiomeric excess, matching the selectivity obtained during the optimisation study. This showed that our one-pot cascade featuring a three-bond forming transformation (amide formation / dehydrative *N*-acyliminium formation / *N*-acyliminium cyclisation) did not suffer any erosion of selectivity due to the presence of unreacted starting material or intermediates of the reaction. This was a significant result that stimulated the study of the scope of this method (Scheme 2.11).

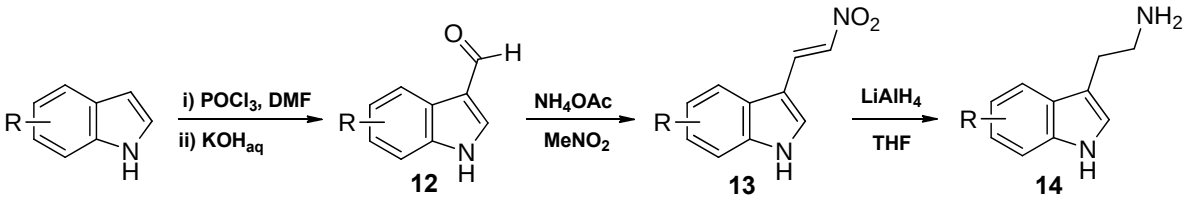


Scheme 2.11. Probing the scope of the *N*-acyliminium cyclisation cascade

2.5.2 Synthesis of starting materials

This work was carried out with the help of Dr. Adam Pilling and Dr. Lei Shi.

Different tryptamines were either synthesised (Scheme 2.12) or purchased and various enol lactones were prepared according to literature procedures (Scheme 2.13).



Scheme 2.12. Synthesis of substituted tryptamines

Commercially available substituted indoles were converted to the corresponding indole-3-carboxaldehydes using Vilsmeier-Haack conditions (*N,N*-dimethylformamide/phosphorous oxychloride followed by hydrolysis in basic conditions) in good to excellent yields (68-100%).[142] Treatment of these aldehydes with nitromethane in the presence of ammonium acetate led to the formation of the Henry adducts that collapsed to form the desired nitro-olefins in good yields (66-98%).[143] Finally, reduction of the nitro-olefins with six equivalents of lithium aluminium hydride provided substituted tryptamines in quantitative yields (Figure 2.6).[143a]

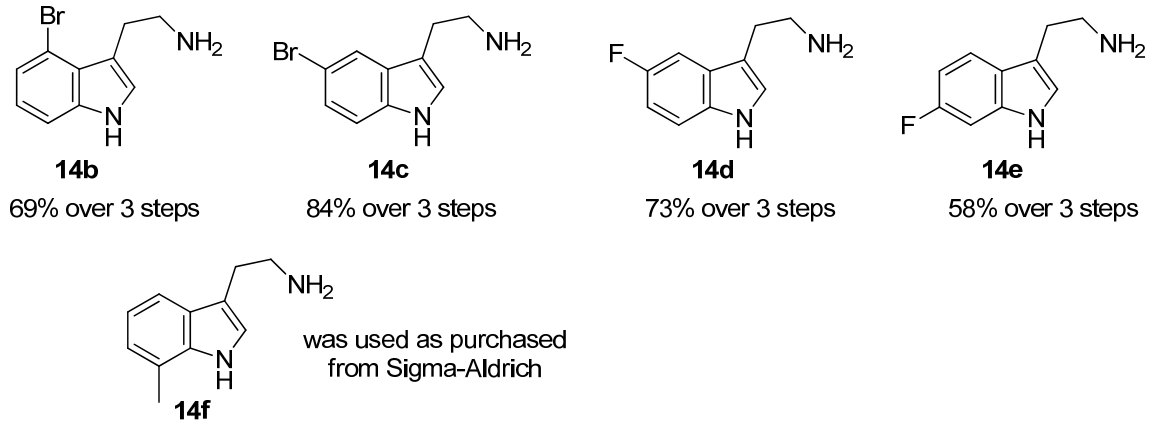
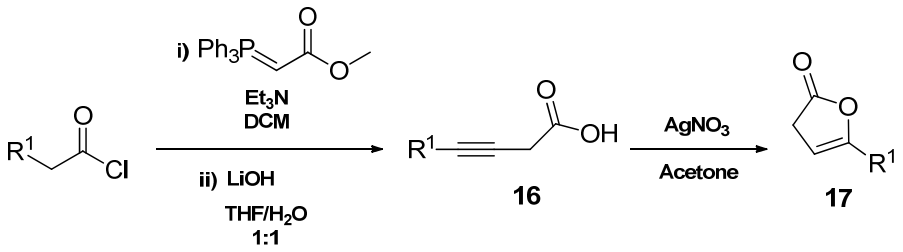


Figure 2.6. Synthesised substituted tryptamines

The synthesis of enol lactones from alkynoic acids using gold[144] or silver[145] catalysis, *via* 5-*endo*-dig or 6-*exo*-dig cyclisation, is well precedented in the literature. The desired 3-alkynoic acids were synthesised in two steps from commercially available acyl chlorides (Scheme 2.13).



Scheme 2.13. Synthesis of enol lactones

The starting acyl chlorides were converted to mixtures of methyl 3-alkynoate and methyl 2-allenoate *via* a Wittig-type reaction with methyl(triphenyphosphoranylidene) acetate that were saponified to afford the 3-alkynoic acids **16** (with little allenoic acid present). The 3-alkynoic acids were cycloisomerised using catalytic silver nitrate in acetone, in the dark, to give the desired enol lactones in good overall yields (32-50% over 3 steps, Figure 2.7).[145]

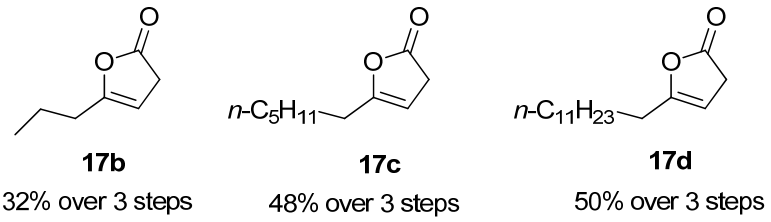
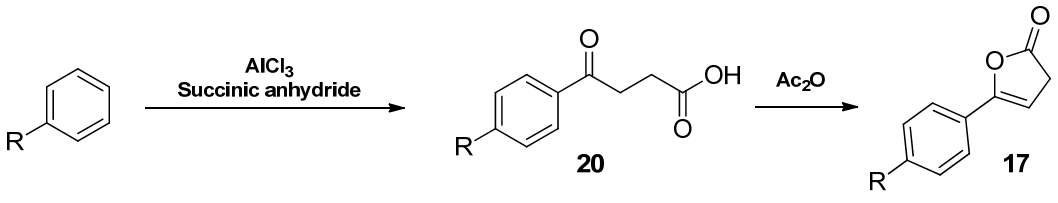


Figure 2.7. Synthesised enol lactones

Alternatively, enol lactones bearing an aryl group can be synthesised from 4-oxoacids in dehydrative conditions. Friedel-Craft acylation was used to prepare 4-oxo carboxylic acids by addition of succinic anhydride onto substituted aryls with high selectivity for the *para*-substitution (Scheme 2.14).



Scheme 2.14. Synthesis of aryl substituted enol lactones

Substituted aryls were treated with succinic anhydride in the presence of aluminium chloride. After neutralisation with aqueous hydrochloric acid, the 3-aroylpropionates **20** were isolated in good yields (62-78%).[146] Subsequent dehydrative cyclisation in the presence of acetic anhydride afforded the desired enol lactones **17** in moderate to good yields (50-88%, Figure 2.8).[147] The phenyl substituted enol lactone was prepared with slight modification, treating the commercially available 4-oxoacid with acetic anhydride and a catalytic amount of *para*-toluenesulphonic acid (Figure 2.8).[148]

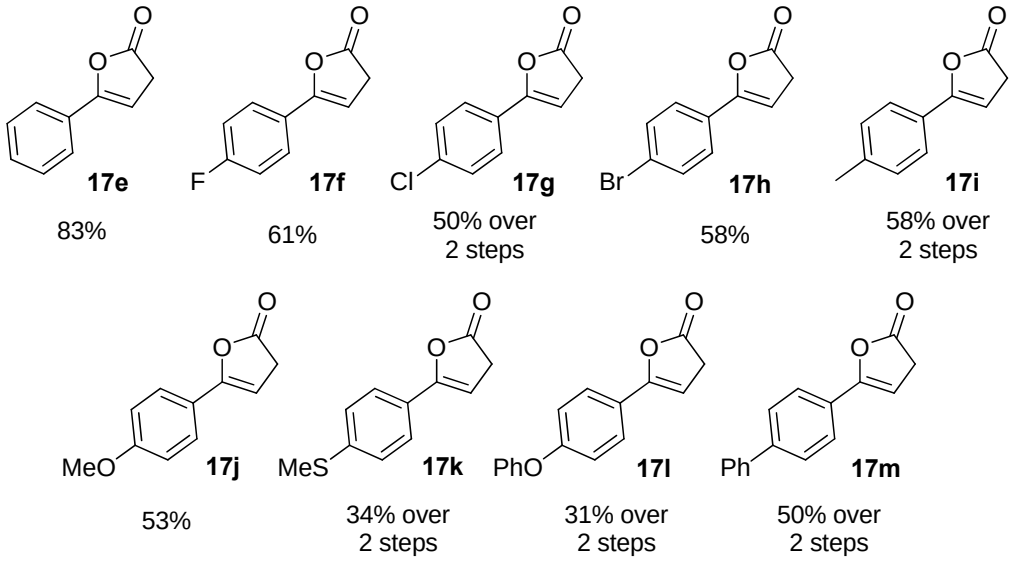
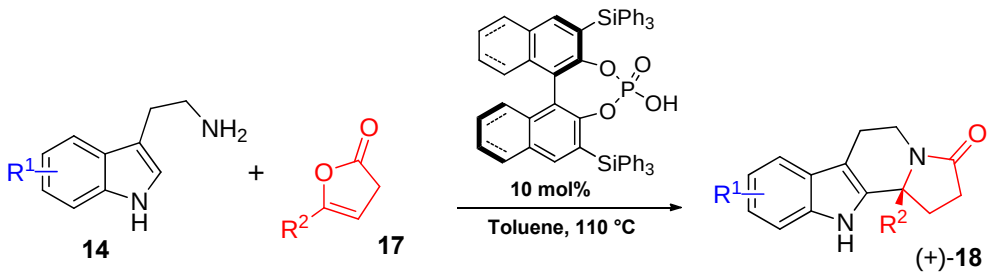
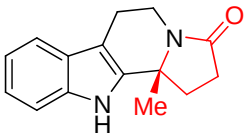


Figure 2.8. Synthesised arylated enol lactones

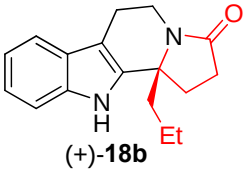
2.5.3 Scope of the novel enantioselective *N*-acyliminium cyclisation cascade

In order to assess the generality and efficiency of the newly developed cascade, different combinations of substituted tryptamines and enol lactones were used to generate a variety of tetracyclic β-carbolines. The results were the following:

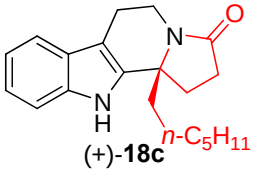




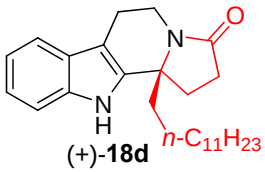
(+)-**18a**
2 hours
99% yield
84% e.e.



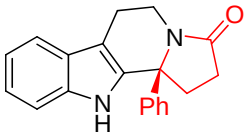
(+)-**18b**
24 hours
87% yield
84% e.e.



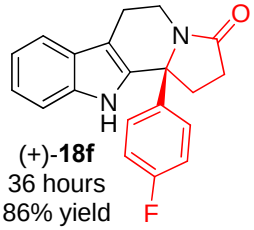
(+)-**18c**
12 hours
70% yield
83% e.e.



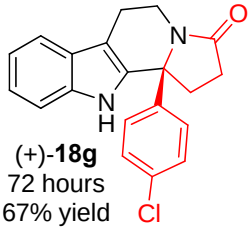
(+)-**18d**
12 hours
74% yield
83% e.e.



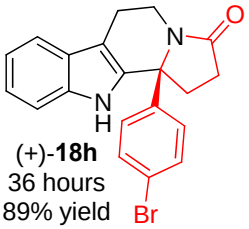
(+)-**18e**
36 hours
78% yield
87% e.e.



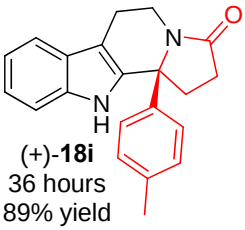
(+)-**18f**
36 hours
86% yield
71% e.e.



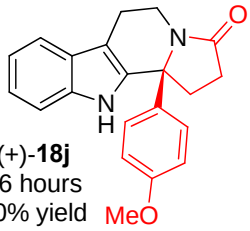
(+)-**18g**
72 hours
67% yield
86% e.e.



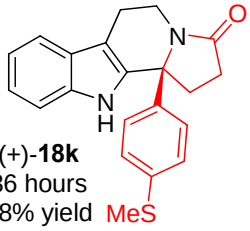
(+)-**18h**
36 hours
89% yield
86% e.e.



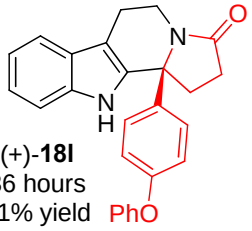
(+)-**18i**
36 hours
89% yield
87% e.e.



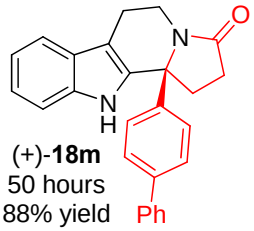
(+)-**18j**
36 hours
80% yield
71% e.e.



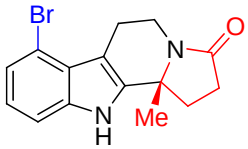
(+)-**18k**
36 hours
78% yield
78% e.e.



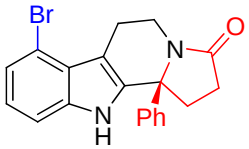
(+)-**18l**
36 hours
51% yield
90% e.e.



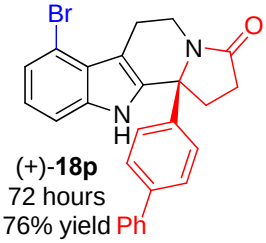
(+)-**18m**
50 hours
88% yield
94% e.e.



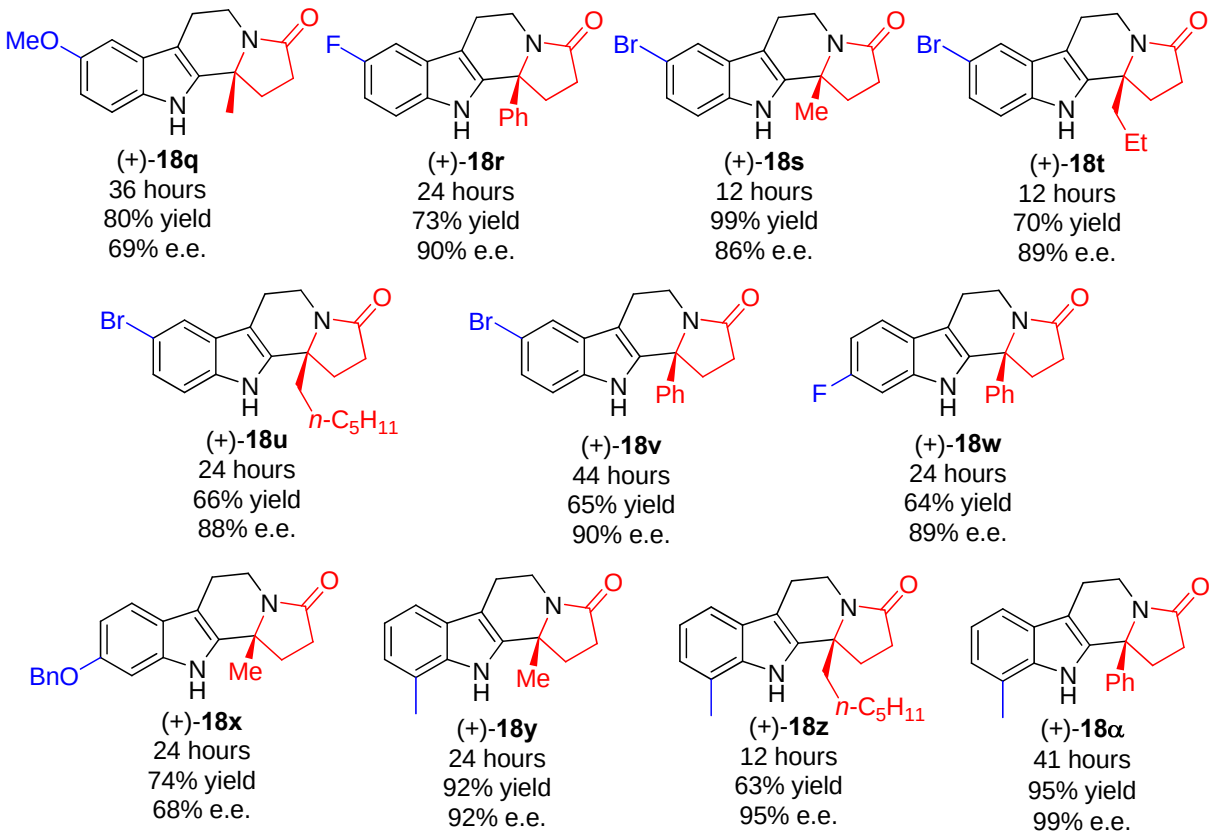
(+)-**18n**
26 hours
81% yield
92% e.e.



(+)-**18o**
36 hours
66% yield
94% e.e.



(+)-**18p**
72 hours
76% yield
82% e.e.



Scheme 2.15. Scope of the *N*-acyliminium cyclisation cascade

The cascade demonstrated an impressive robustness and efficiency. The target tetracyclic β-carbolines were formed in generally high yields, ranging from 51% to 99% (average 78%, 27 examples) and good to excellent enantiomeric excesses (68-99% e.e., average 86%).

Substituents were tolerated at all positions on the indole core and halides (4-, 5- and 6-position) as well as methyl (7-position) improved the enantioselectivity, with 4-bromo and 7-methyl substituents being particularly beneficial (see (+)-**18n-p** and (+)-**18y-α**). Electron-donating groups such as methoxy and benzyloxy at the 5- and 6-position ((+)-**18q** and (+)-**18x** respectively) decreased the selectivity compared to the unsubstituted indole counterpart (72% e.e. for (+)-**18q**, 68% e.e. for (+)-**18x** vs. 84% e.e. for (+)-**18a**).

Alkyl-substituted and aryl-substituted enol lactones were both suitable reaction partners and led to the formation of the desired products. The selectivity for the alkyl series (Me, *n*-Pr, *n*-Hex, *n*-dodecyl) was constant (*e.g.* 83-84% e.e. for (+)-**18a-d** and 86-89% e.e. for (+)-**18s-u**), however

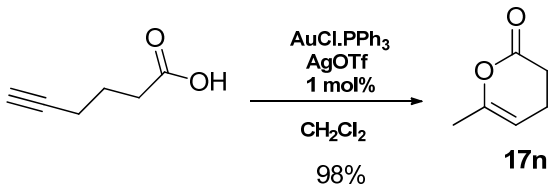
the selectivity for aryl-substituted enol lactones was slightly increased (87% e.e. for (+)-**18e** vs. 84% e.e. for (+)-**18a**; 99% e.e. for (+)-**18α** vs. 92% e.e. for (+)-**18y**). This increase in selectivity might be caused by subtle steric or electronic effects, in particular, aromatic rings might be able to create more interactions with the catalyst *via* π-stacking; we can also hypothesise that aromatic groups are able to stabilise the *N*-acyliminium ion thus providing different electronic properties and reactivities.

Different aryl-substituted enol lactones were assessed. Although arenes substituted at the *para* position with hydrogen, chlorine, bromine and methyl led to the same enantioselectivity in the *N*-acyliminium cyclisation ((+)-**18e** and (+)-**18g-i**, 86-87% e.e.). Arenes bearing an electron-donating group (methoxy and methylsulfide) as well as a fluorine at the 4-position led to significantly decreased enantiomeric excesses ((+)-**18f** and (+)-**18j-k**, 71-78% e.e.). Interestingly, *para*-phenoxyphenyl and biaryl substituents on the enol lactone had a beneficial influence on the enantioselectivity ((+)-**18l** and (+)-**18m**, 90% and 94% e.e. respectively).

To broaden the scope of the method, the same cascade was attempted with pyranone derivatives (6-membered ring enol lactones).

2.5.4 6-membered ring lactams vs. 5-membered ring lactams

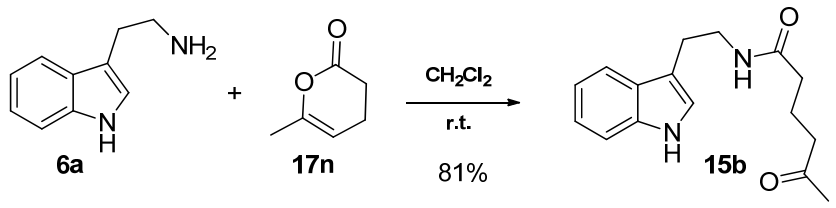
The 6-membered enol lactone **17n** was prepared from 5-hexynoic acid, using catalytic $AuCl.PPh_3$ / AgOTf to promote the cycloisomerisation.



Scheme 2.16. Synthesis of 6-methyl-3,4-dihydro-2*H*-pyran-2-one

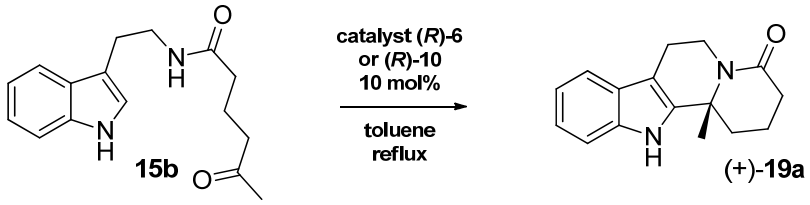
*2.5.4.1 Optimisation of the N-acyliminium cyclisation conditions to form piperidinone (**19a**)*

In order to expand the scope of the reaction further, oxoamide intermediate **15b** was synthesised (Scheme 2.17). Re-optimisation of the cyclisation conditions for this substrate was necessary to improve the enantiomeric excess from an initial 63% to 71% e.e. (Table 2.9).



Scheme 2.17. Synthesis of a precursor for 6-membered ring cyclic *N*-acyliminium cyclisation

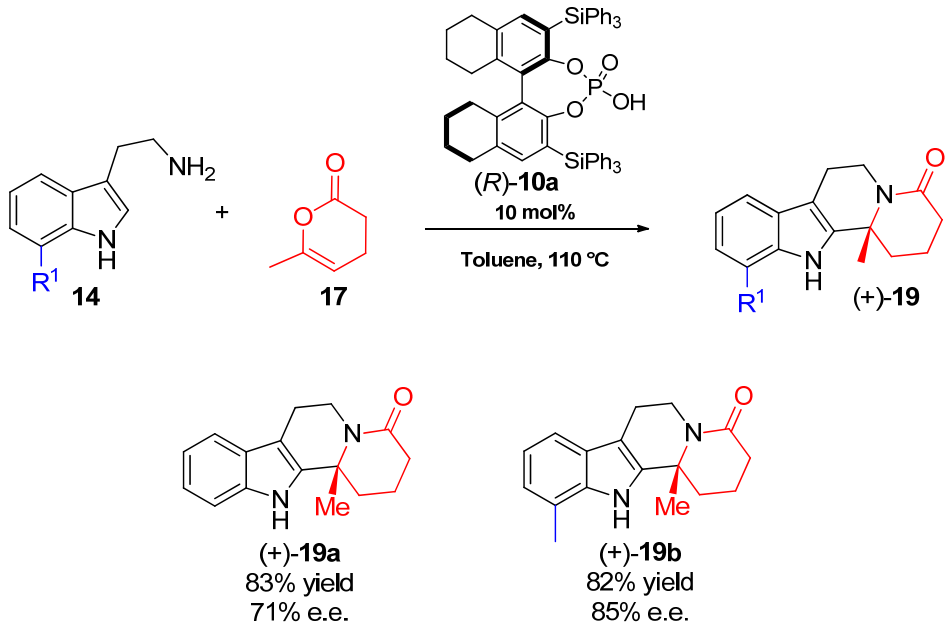
Table 2.9. Catalyst assay in the *N*-acyliminium cyclisation of **15b**



Entry	Catalyst	Time	Yield (%)	e.e. (%)
1	(*R*)-**6f**	4 hours	91	63
2	(*R*)-**6b**	16 hours	93	23
3	(*R*)-**6e**	4 hours	99	45
4	(*R*)-**6w**	48 hours	88	22
5	(*R*)-**10a**	28 hours	96	71

A definite decrease in enantioselectivity was observed when 6-membered ring lactams were formed with our methodology. For instance, when tryptamine was reacted with a methyl substituted enol lactone (**17a** or **17n**), in the presence of catalyst (*R*)-**10a**, the desired products were formed in good yields (99% and 91% respectively), however the enantioselectivity

decreased from 84% in the case of the 5-membered ring (+)-**18a** to 63% in the case of the 6-membered ring (+)-**19a**. This observation does not follow any simple explanation, nevertheless, modeling of both transition states might give more insight into this lower selectivity. By carefully choosing the reaction partners (**14f** and **17a**) and using (*R*)-**10a** as catalyst, we were able to reach a satisfactory level of enantioselectivity (85% for (+)-**19b**, Scheme 2.18).



Scheme 2.18. Scope of the *N*-acylimnium cyclisation cascade for the synthesis of fused piperidinones

2.5.5 Determination of the absolute stereochemistry

In order to assign the absolute stereochemistry, tetracycles (+)-**18t** and (+)-**18u** were recrystallised to enantiopurity from acetonitrile and single crystal X-ray crystallography of (+)-**18u** showed an unambiguous (*R*)-configuration at the quaternary centre. The stereochemistries of the other products were assigned by analogy as well as by comparison of the optical rotation of (+)-**18a** and (+)-**18e** with the same enantioenriched compounds synthesised by Jacobsen *et al.*[130]

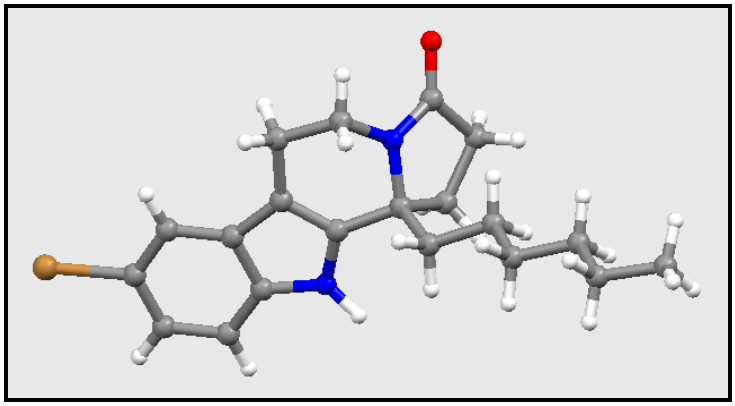
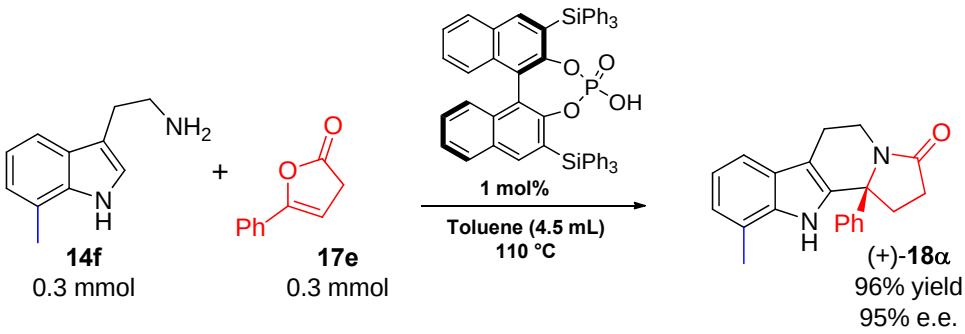


Figure 2.9. Single crystal X-ray crystal structure of (*R*)-(+)-**18u**

2.5.6 Potential for scale-up

During the development of our *N*-acyliminium cyclisation cascade, the catalyst loading was kept constant at 10 mol%. However, based on our optimisation studies, it was hoped that decreasing the catalyst loading would not harm the enantioselectivity or yield dramatically. Therefore, to prove that our strategy was efficient for use on large scale, for instance in industry, the reaction of 7-methyl tryptamine **14f** and phenyl enol lactone **17e** was carried out with 1 mol% of catalyst (*R*)-**6f** (Scheme 2.19)



Scheme 2.19. Preparation of (+)-**18α** with 1 mol% catalyst loading

As expected, the reaction took longer to reach completion, but the product was obtained in high yield (96%) and only a slight decrease of enantioselectivity was observed (95% e.e. vs. 99% e.e. when 10 mol% of catalyst was used). This experiment showed that our method exhibited good potential to transfer to large scale synthesis. It is particularly interesting for industry and

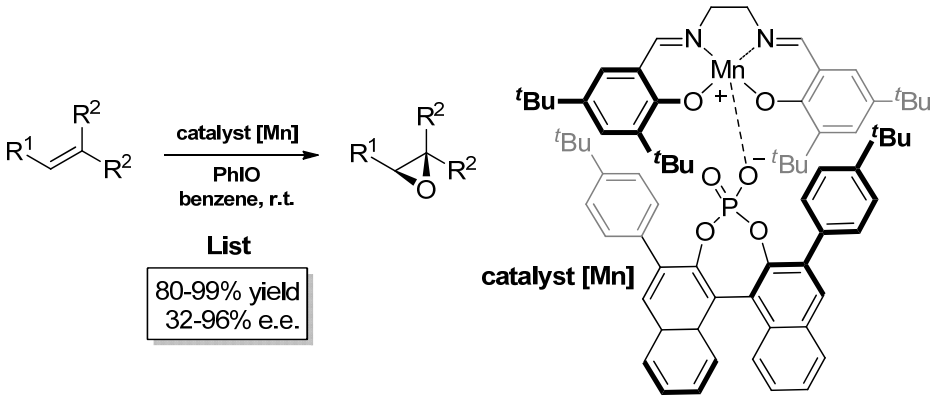
could also be applied in the total synthesis of a complex molecule (natural product or derivative).

2.6 Incorporation of the *N*-acyliminium cyclisation cascade into a doubly catalysed domino reaction

2.6.1 Overview

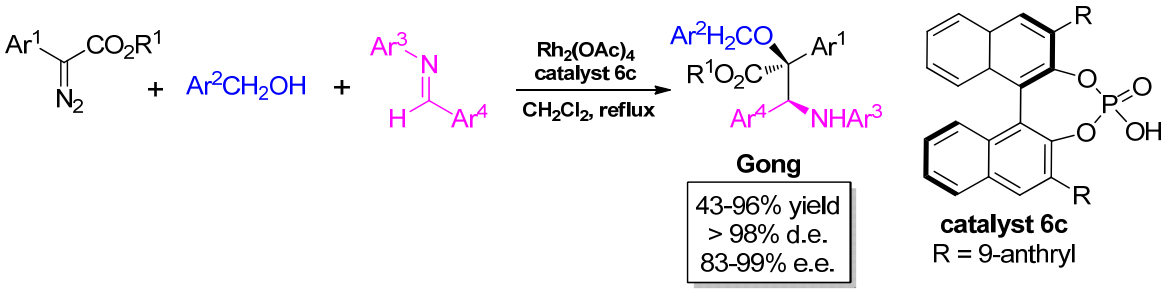
The observed robustness of our method was an asset we wanted to take advantage of further. It was hoped that our method could be associated to another catalytic process in a one-pot doubly catalysed cascade. Naturally, our attention turned to the use of metal catalysis in conjunction with organocatalysis as transition metal catalysed processes have attracted a lot of attention in the past few decades and their efficiency has been demonstrated and rewarded by Nobel prizes (Sharpless / Noyori / Knowles in 2001 for their work on asymmetric oxidations / reductions; Chauvin / Grubbs / Schrock in 2005 for their work on metathesis; Heck / Negishi / Suzuki in 2010 for developing palladium-catalysed cross-coupling reactions in organic synthesis).

Only a few studies to date have managed to combine metal catalysis and Brønsted acid organocatalysis successfully.[44,93,149] This can be explained by the fact that on the whole, transition metals also act as Lewis acids and in the majority of cases these Lewis acids are also capable of catalysing the racemic reaction. There is a subtle difference between using a metal coordinated by chiral ligands and exploiting both a transition metal and an organocatalyst synergetically. For instance, B. List *et al.* developed an enantioselective epoxidation of electron-rich alkenes using the well-precedented Mn(III)salen oxidation method (Jacobsen / Katsuki epoxidation[150,151]). The originality of their work lies in the use of a chiral BINOL phosphate as a ligand.[152] This method shows all the potential of BINOL phosphates as chiral ligands, however, the phosphate itself does not catalyse the epoxidation (Scheme 2.20).



Scheme 2.20. Enantioselective epoxidation in the presence of BPA-[Mn]salen complex

Contrary to this, L.-Z. Gong and co-workers have demonstrated the efficiency of a Rh(II) / BPA cooperative catalysis for the addition of an alcohol onto a carbenoid and subsequent Mannich-type reaction to form β-amino-α-hydroxy acid derivatives.[149a] In this case, if the rhodium salt was not present the reaction did not proceed. A direct activation of the imine reaction partner by the chiral phosphoric acid is necessary to justify the selectivity in the reaction (Scheme 2.21).

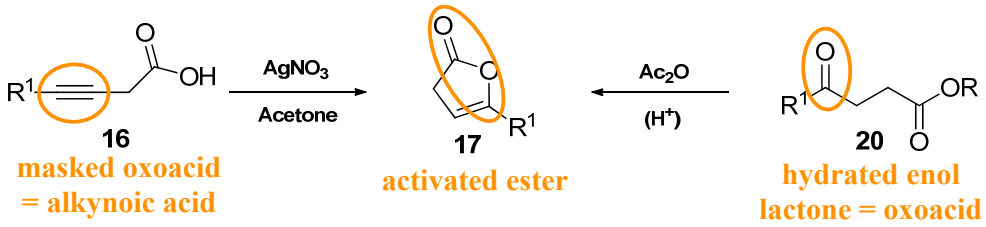


Scheme 2.21. Enantioselective alcohol addition / Mannich reaction cascade of a diazo compound, an alcohol and an imine

This shows that the metal and the chiral phosphoric acid both have their own catalytic role to play and it is therefore a cooperative catalysis. We wanted to take advantage of such reactivity by combining a metal-catalysed process with our *N*-acyliminium cyclisation cascade, bearing in mind that incompatibilities might be observed.

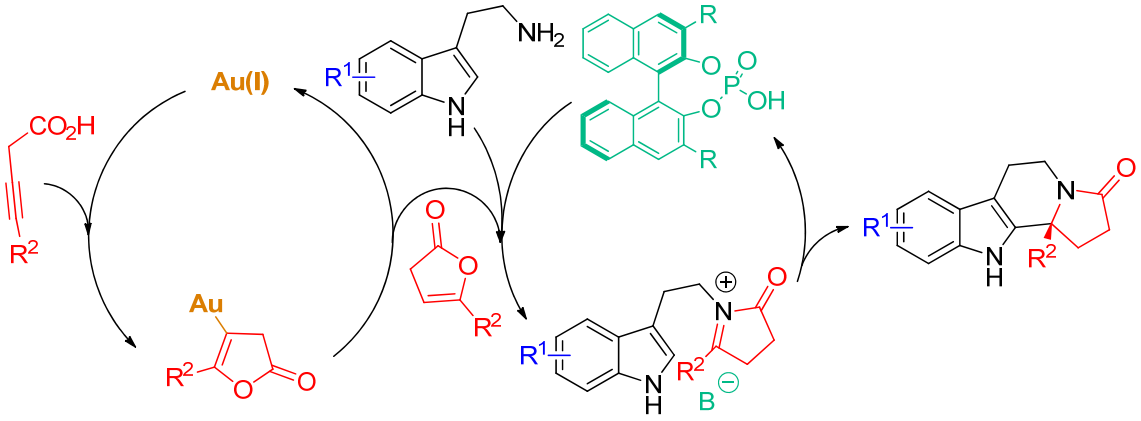
2.6.2 Proof of principle of reactivity

Analysing our previous strategy with enol lactones, we envisaged that the enol lactone reaction partner was effectively an activated ester, synthesised from the hydrated (therefore deactivated) oxoacid or its masked equivalent alkynoic acid (*via* silver nitrate catalysis) (Scheme 2.22).



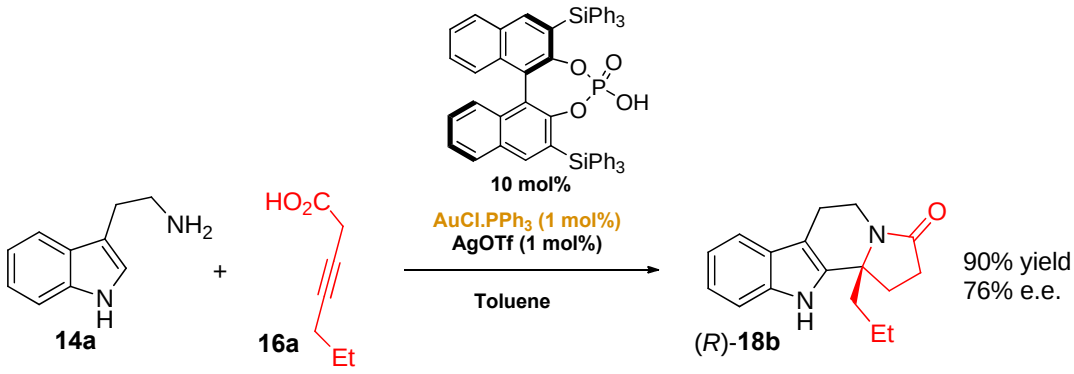
Scheme 2.22. Hydrated or masked enol lactones equivalents

This last approach using a masked oxoacid/enol lactone and a metal catalyst to generate the enol lactone was of particular interest and we hypothesised whether it would be possible to develop a method for the *in situ* formation of the enol lactone. Work previously carried out in the group,[144] as well as documented literature procedures,[153,154,155,156,157,158] pointed towards the use of a transition metal to promote the cycloisomerisation. Due to our experience in the field, we decided to investigate a gold(I)-catalysed *in situ* formation of enol lactones combined with our *N*-acyliminium cyclisation cascade (Scheme 2.23).



Scheme 2.23. Proposed doubly catalysed *N*-acyliminium cyclisation cascade of alkynoic acids and tryptamines

An experiment was designed to prove the concept of our doubly catalysed process: in the same pot, 1 mol% of $AuCl.PPh_3$ as well as 1 mol% of AgOTf were dissolved in toluene (volume based on the optimal concentration for the substrate/catalyst), alkynoic acid **16a** (1.2 equivalents) was added and the mixture stirred for 15 minutes. The organocatalyst (*R*)-**6f** (0.1 equivalents) and tryptamine **14a** (1 equivalent). The reaction mixture was heated at 80 ºC for 3 hours and then at reflux for another 24 hours.



Scheme 2.24. Proof of principle of reactivity for the doubly catalysed cascade

The desired product was isolated in good yield (90%) and only a slight erosion of enantioselectivity was observed compared to the enol lactone approach (76% vs. 84%). This promising result confirmed our hypothesis and motivated us to optimise the reaction conditions to reach the same level of enantioselectivity observed previously.

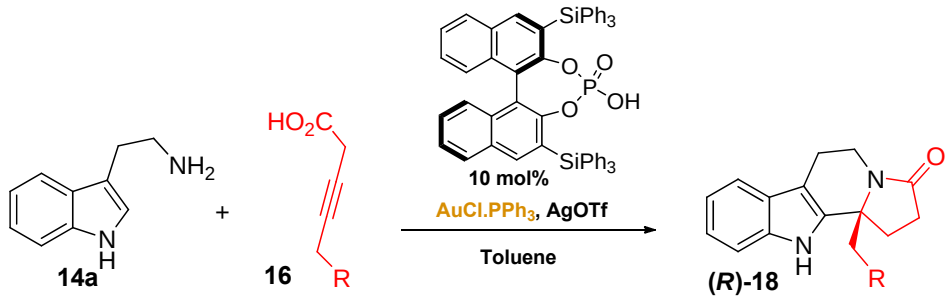
2.6.3 Optimisation of the doubly catalysed cascade conditions

Firstly, to decrease the background reaction observed (due to racemic gold-catalysed *N*-acyliminium cyclisation, as previously observed in the group[144]), the catalyst loading of the gold (I) salt as well as silver triflate was decreased to 0.5 mol%. This allowed us to form the desired tetracyle (*R*)-**18b** with a retained 83% e.e. although the yields obtained were inconsistent and usually low (38-56%, Table 2.10, entry 2). To tackle this lack of reproducibility, it was decided to premix the activated gold (I) catalyst and the alkynoic acid for

30 minutes at room temperature before adding the organocatalyst and tryptamine. As anticipated, when this modified procedure was carried out, (*R*)-**18c** was formed with 83% e.e. and the isolated yields were consistently between 75% and 87% (Table 2.10, entry 7).

Interestingly it was found that although silver was capable of catalysing the cycloisomerisation (to some extent), the presence of the gold (I) salt was essential to obtain the desired product (*R*)-**18c** in good yield and retain enantioselectivity. However, the presence of the silver salt was also necessary to guarantee good reactivity in the cycloisomerisation (Table 2.10, entries 5-7).

Table 2.10. Proof of the essential role of the gold (I) salt

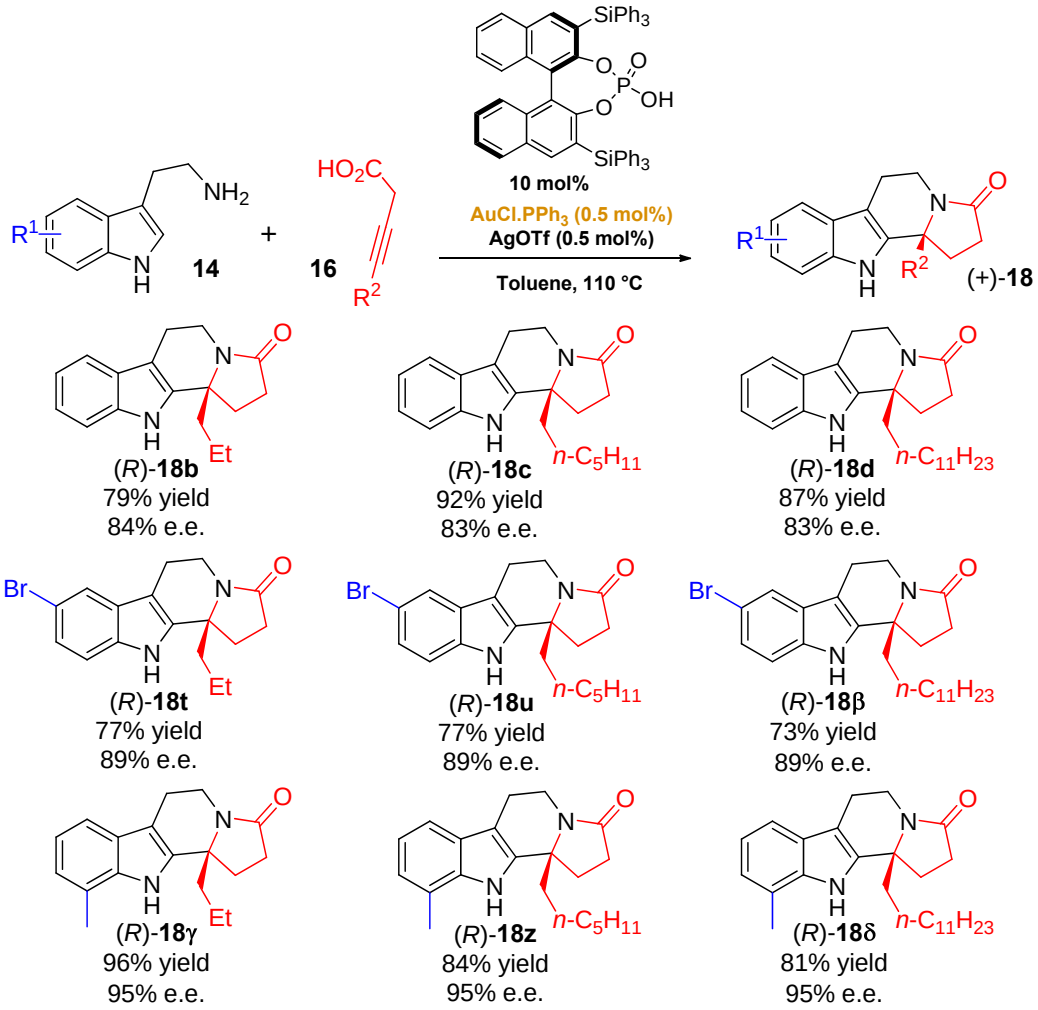


Entry	Catalyst (*R*)-**6f**	AgOTf	AuCl.PPh$_3$	R	Time (reflux)	Yield (%)	e.e. (%)
1	10 mol%	1 mol%	1 mol%	Et	20 hours	90	76
2	10 mol%	0.5 mol%	0.5 mol%	Et	24 hours	38-56	83
3	10 mol%	-	-	*n*-$C_{11}H_{23}$	72 hours	trace	-
4	10 mol%	5 mol%	-	*n*-$C_{11}H_{23}$	48 hours	60	34
5	10 mol%	0.5 mol%	-	*n*-$C_{11}H_{23}$	48 hours[a]	11	78
6	10 mol%	-	0.5 mol%	*n*-$C_{11}H_{23}$	48 hours[a]	45	83
7	10 mol%	0.5 mol%	0.5 mol%	*n*-$C_{11}H_{23}$	24 hours[a]	87	83

[a] Metal(s) and alkynoic acid premixed for 30 minutes before adding tryptamine and (*R*)-**6f**.

2.6.4 Scope of the doubly catalysed *N*-acyliminium cyclisation cascade

Tryptamine, 5-bromotryptamine **14c** and 7-methyltryptamine **14f** were reacted with either hept-3-ynoic acid **16a**, dec-3-ynoic acid **16b** or hexadec-3-ynoic acid **16c** in the presence of 0.5 mol% activated gold (I) catalyst, 10 mol% of (*R*)-**6f** in the optimal conditions previously developed (temperature ramping, concentration *etc.*). All reactions proceeded smoothly to afford the desired tetracycle in surprisingly good yields given the complexity of the transformation (73-96%) and high enantioselectivities (83-95%).



Scheme 2.25. Scope of the doubly catalysed gold (I)-induced enantioselective *N*-acyliminium cyclisation cascade

2.7 Conclusion

A novel *N*-acyliminium cyclisation cascade was developed allowing for the formation of tetracylic lactams in good to excellent yields (64-99%) and good to excellent enantioselectivities (71-99%). This method was practically simple to execute, did not require any particular precautions (HPLC grade toluene, no inert atmosphere) and showed a remarkably broad scope regarding the variables of the reaction (substituents on the indole, alkyl or aryl group on the enol lactone). To show the potential for scale-up, the catalyst loading was decreased to 1 mol% with only a slight decrease of enantioselectivity ((*R*)-**18α** was formed in 96% yield and 95% e.e.). This method was successfully combined to a gold (I)-catalysed process in a one-pot procedure where an alkynoic acid was used as a precursor to generate an enol lactone *in situ*. The enol lactone was subsequently trapped by the tryptamine and the resulting intermediate underwent a high yielding (73-96%), highly enantioselective *N*-acyliminium cyclisation cascade (83-95% e.e.). This strategy demonstrated the potential of synergetic action of metal catalysis and organocatalysis.

In light of these observations, it was planned to apply this method to the synthesis of a complex natural product. Work was ongoing in the group on the total synthesis of (−)-subincanadine B; the first approach was to use a chiral auxiliary to install the stereochemistry of the stereogenic centres. Unfortunately, this route led to an advanced intermediate on which the auxiliary could not be removed. It was hoped that our methodology could install the stereochemistry of the chiral centres, avoiding the use of a stoichiometric chiral auxiliary and at the same time decreasing the step count. This new approach would be a perfect example to show the potential of the enantioselective *N*-acyliminium cyclisation cascade and would permit a significant improvement in the route to (−)-subincanadine B. Although this work will not be discussed in this thesis, it led us to an intriguing discovery that is described in Chapter three.

Chapter Three:

Novel Highly Enantioselective *N*-Acyliminium Cyclisation Cascades

3.1 Aims of the project

It was hoped that the newly uncovered highly enantioselective *N*-acyliminium cyclisation cascade could be used to perform more complex transformations. In particular, it was believed that other type of reactions could be used to generate an oxoamide *in situ* (not only the condensation onto an enol lactone).

In the course of a total synthesis effort, a new reactivity was discovered. When a stereogenic centre was present adjacent to the *N*-acyliminium ion (neighbouring the positively charged carbon atom), it was found that the cyclisation in the presence of a chiral phosphoric acid in refluxing toluene led to the formation of a single product in high yield, with excellent diastereoselectivity and enantioselectivity. The aims of this project were to assess the generality of this transformation and to gain insight into the mechanistic pathway that was triggering such high selectivities.

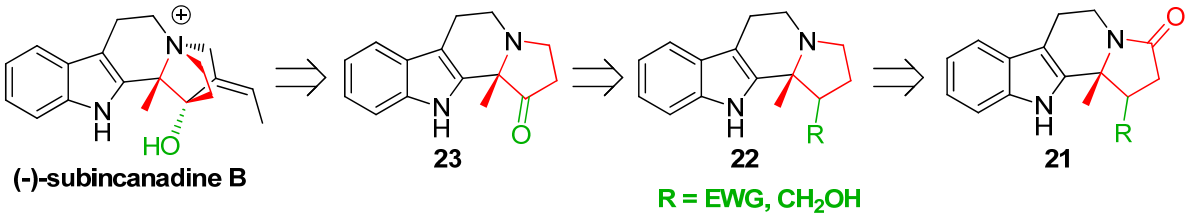
On another level, taking advantage of a surprising reactivity that was encountered during a control experiment, it was planned to optimise the first enantioselective one-pot base-catalysed Michael addition / acid-catalysed *N*-acyliminium cyclisation cascade that was taking advantage of site isolation without physically isolating the base and acid. Probing the scope of this complex and unprecedented transformation was the ultimate goal of this work.

3.2 Development of a highly diastereo- and enantioselective direct dehydrative *N*-acyliminium cyclisation cascade of oxoacids and tryptamines

3.2.1 Genesis of the highly diastereoselective and enantioselective *N*-acyliminium cyclisation cascade

The result that led to this methodological work was found during the studies towards the total synthesis of (−)-subincanadine B. It was hoped that the newly developed *N*-acyliminium cyclisation cascade of tryptamines and enol lactones could be employed to install the stereogenic centres on a precursor to the target. This study was carried out with the collaboration of Dr. Chloe A. Holloway from the Dixon group.

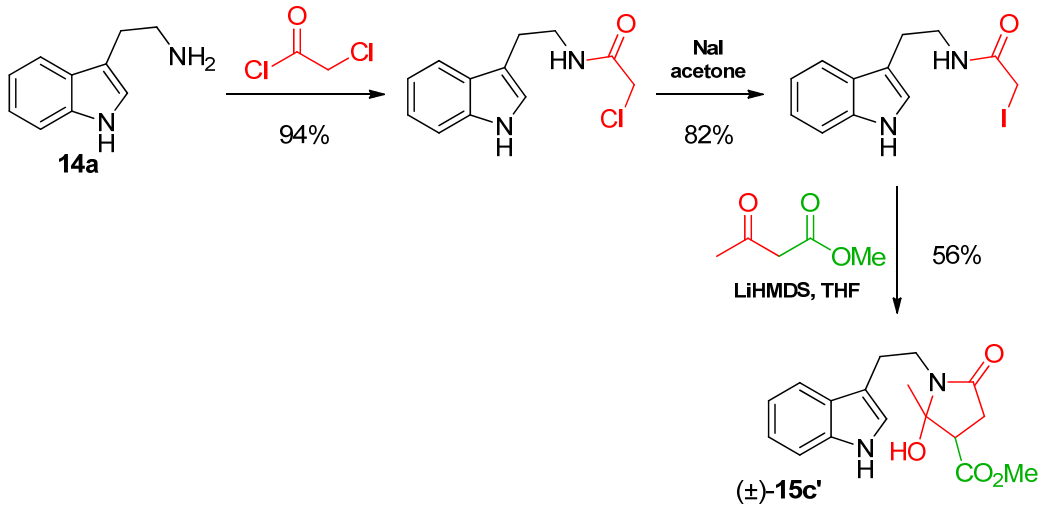
3.2.1.1 Retrosynthetic analysis of (−)-subincanadine B



Scheme 3.1. Retrosynthetic analysis of (−)-subincanadine B

It was our hope that (−)-subincanadine B could be prepared from the simple oxo β-carboline **23** through the addition of an organometallic (a vinylmagnesium bromide derivative was envisaged) followed by quaternisation of the amine. A functionalised tetracyclic β-carboline of type **22** would be a precursor for the desired ketone. It was believed that the functionalised β-carboline of type **22** could be prepared from the higher oxidation state lactam of type **21** that was a motif readily available with our methodology.

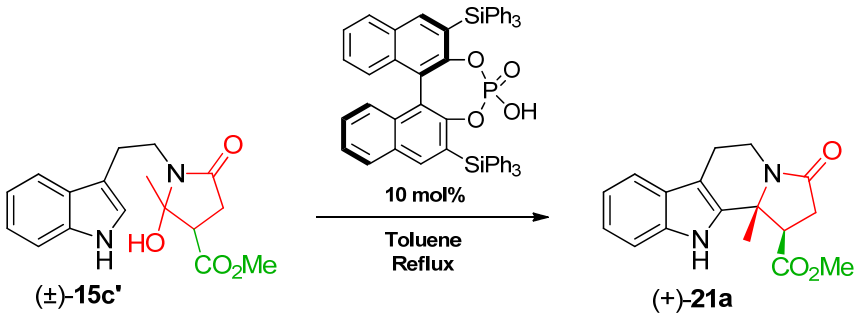
The synthesis of a precursor for *N*-acyliminium cyclisation was designed (Scheme 3.2).



Scheme 3.2. Synthesis of the key precursor for the synthesis of (−)-subincanadine B

Acylation of tryptamine with chloroacetyl chloride afforded tryptamine chloroacetamide in good yield (94%). The chloride was replaced by iodide *via* a Finkelstein reaction, for reactivity reasons (82%). Nucleophilic substitution of the iodide with the enolate of methyl acetoacetate (in the presence of LiHMDS in THF) afforded hydroxylactam (±)-**15c′** in moderate yield (56%). This substrate was ready to undergo a cyclisation under the previously developed conditions. We hoped that the formation of the tetracycle with high enantiomeric excess would be observed as well as kinetic resolution to some extent. Since the starting material was racemic, our hope was that one diastereomer would react faster leading to diastereomerically enriched material.

When (±)-**15c′** was treated with (*R*)-**6f** in refluxing toluene, it cyclised slowly (3 days) to form the desired tetracycle. The ^{1}H NMR spectrum of the crude mixture showed signals belonging to a single diastereoisomer. After purification, this observation was verified and the β-carboline (+)-**21a** had been formed in good yield (82%) with high enantioselectivity (92% e.e.) as a single diastereoisomer (after optimisation carried out by Dr. C. A. Holloway) (Scheme 3.3).

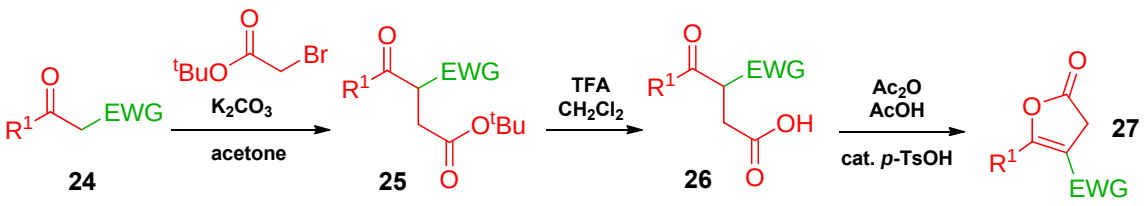


Scheme 3.3. Highly diastereo- and enantioselective cyclisation of (±)-**15c′**

The high yield, high diastereoselectivity (*vide infra* for assignment) and enantioselectivity of (+)-**21a** pointed towards the occurrence of the epimerisation of the tertiary stereogenic centre during the course of the reaction. This intriguing result led us to study the scope of such a transformation. Firstly, we sought a practically simple method to execute a cascade version of this new *N*-acyliminium cyclisation.

3.2.1.2 Direct enantioselective N-acyliminium cyclisation of disubstituted enol lactones and tryptamines

A new route to disubstituted enol lactones was designed, starting from commercially available ketones bearing an EWG at the α-position (Scheme 3.4).

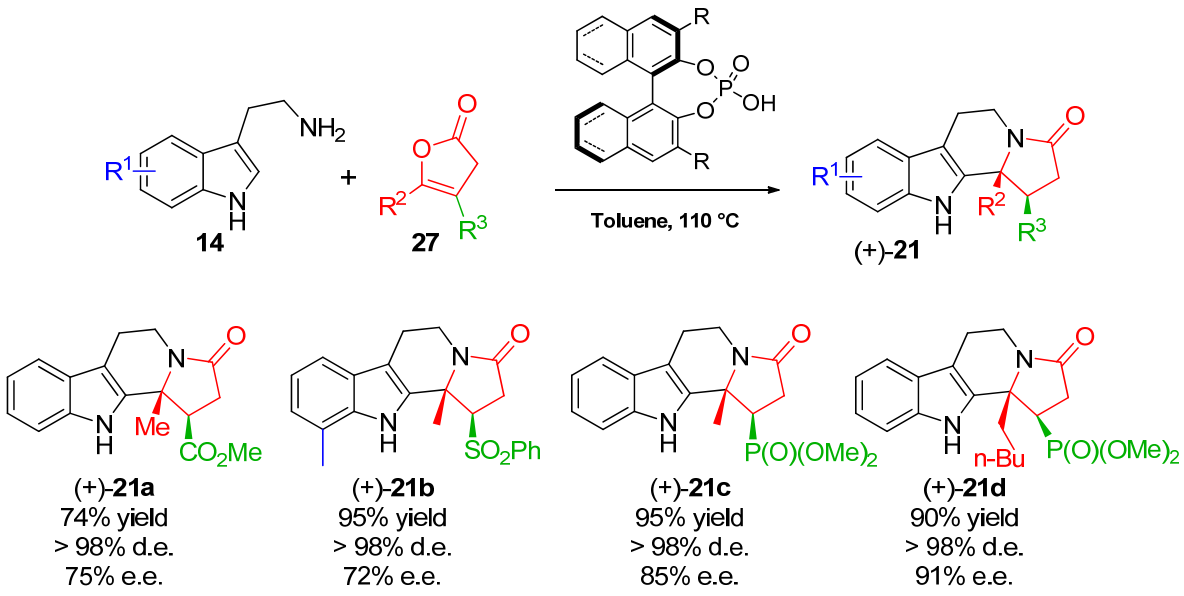


Scheme 3.4. Synthesis of disubstituted enol lactones

Alkylation of commercial pro-nucleophiles of type **24** was achieved using mild conditions (K_2CO_3 in refluxing acetone). The obtained 4-oxo *tert*-butyl esters **25** were then treated with TFA/CH_2Cl_2 1:1 to afford the free 4-oxo carboxylic acids **26** that, under dehydrative conditions (acetic anhydride in acetic acid), afforded the desired enol lactones **27**. The yield over three

steps was typically 25-30%. This route was not further optimised as sufficient quantities of the substrate enol lactones were isolated for our study.

Treatment of disubstituted enol lactones **27** with tryptamine derivatives **14** in the optimal conditions found for each transformation (optimisation carried out by Dr. C. A. Holloway) afforded the desired β-carboline in good to excellent yield (74-95%) and moderate to excellent enantioselectivities (72-91%) (Scheme 3.5).



Scheme 3.5. Enantioselective and diastereoselective *N*-acyliminium cyclisation of enol lactones and tryptamines

3.2.1.3 Assignement of relative and absolute stereochemistry

The nOe analysis of (+)-**21b** revealed that the methyl group at the quaternary centre and the phenylsulphone were *syn* (Figure 3.1).

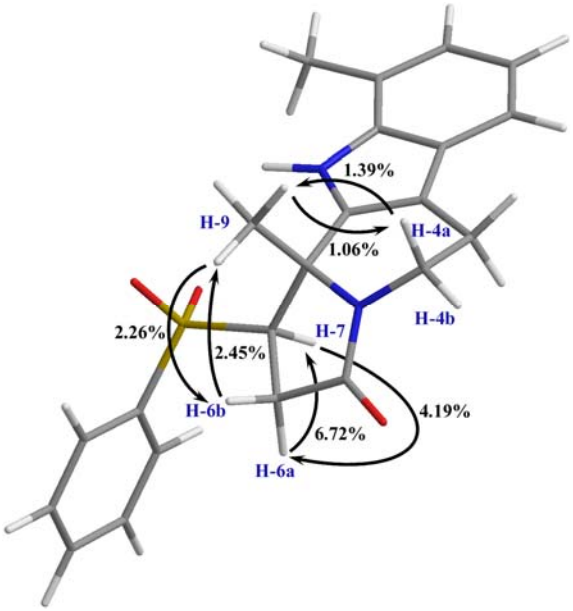
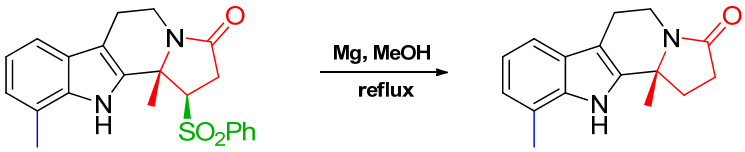


Figure 3.1. nOe responses of relevant protons on (+)-**21b**

Since H-9 is coupling through space with H-6b and since H-6a is coupling with H-7, the most plausible explanation is that H-7 and H-9 are *anti* and therefore the sulphone and methyl group (H-9) are *syn*. Moreover, (+)-**21b** was further manipulated and under conditions promoting the formation of radical species, desulphonylation was observed to ultimately form (+)-**18y** (Scheme 2.6).



(+)-**21b**
72% e.e.

(+)-**18y**
48% yield
72% e.e.

Scheme 3.6. Desulphonylation of (+)-**21b** in the presence of Mg/MeOH

The comparison of the optical rotation of (+)-**18y** obtained by desulphonylation of (+)-**21b** or *via* the cascade reaction between tryptamine **14e** and enol lactone **17a** gave us confidence that the configuration at the quaternary centre was identical ((*R*)-configuration, *vide supra* Section 2.5.3).

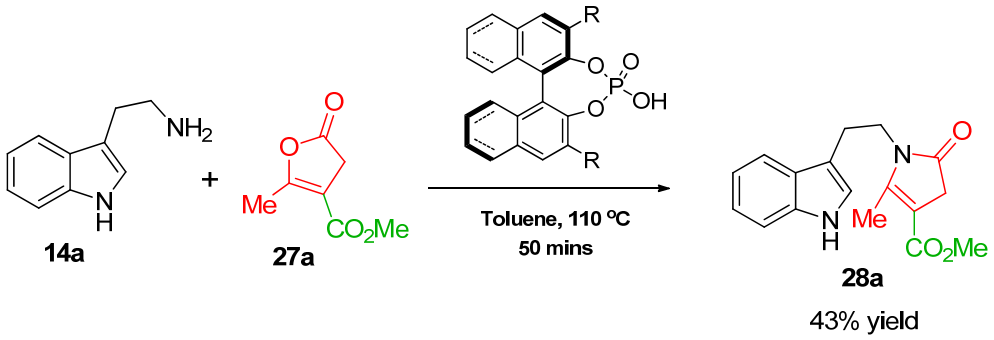
Further to this discovery, our endeavours focused on proposing a plausible mechanism for this transformation based on experimental evidence, as well as exploiting this likely general and powerful transformation.

3.2.2 Proposed mechanism and potential further applications

During the cyclisation of disubstituted enol lactones and tryptamines, the formation of an intermediate was observed (by thin layer chromatography). The amount of intermediate was increasing as the mixture was heated and then disappearing to form the expected tetracycle. The isolation of this intermediate was of major importance since we believed it could tell us more about how the reaction was proceeding.

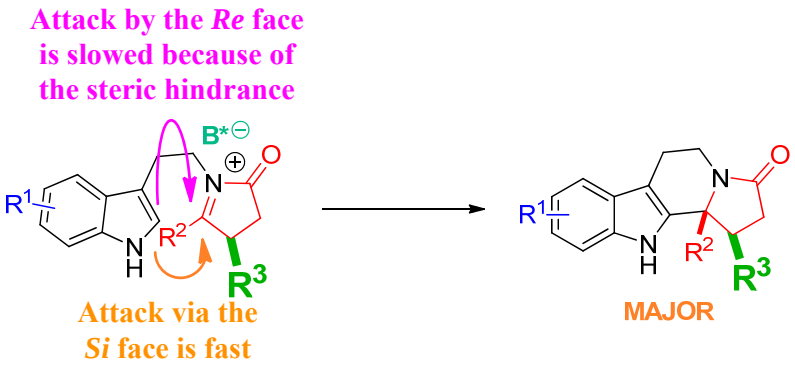
3.2.2.1 Proposed mechanism based on the isolation of an intermediate of the cyclisation

In an attempt to isolate the reaction intermediate previously observed by TLC, **14a** and **27a** partook in a cyclisation reaction that was stopped after a short reaction time (50 minutes). This allowed the intermediate to form in a large amount with little formation of the product being observed. The mixture was purified by column chromatography to isolate the pure intermediate. Full characterisation allowed us to identify this intermediate as an achiral (pro-chiral) ene-lactam **28a** (Scheme 3.7).



Scheme 3.7. Isolation of the key intermediate ene-lactam **28a**

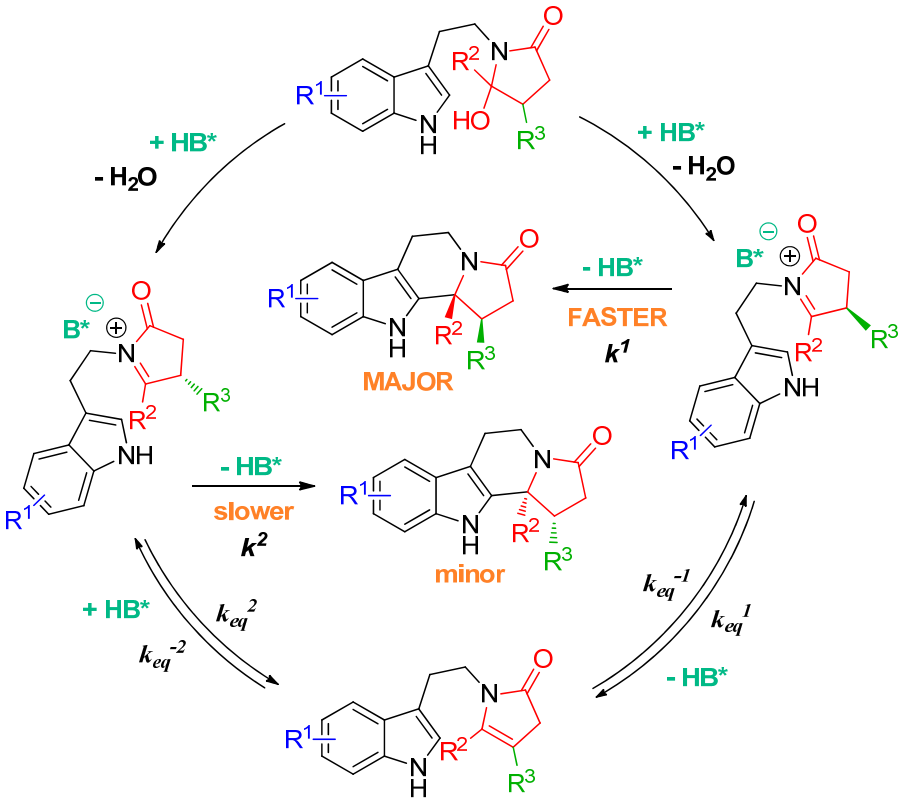
Interestingly, the same intermediate was observed during the non-enantioselective cyclisation, although it was not isolated in this case. In light of this, the envisaged reaction pathway displayed the formation of two diastereomeric *N*-acyliminium salts that deprotonated readily to form intermediate **28a**. We postulated that this step was reversible and therefore allowed for the efficient epimerisation of the tertiary stereogenic centre. Interestingly, even the non-enantioselective cyclisations led to the formation of a single diastereomer, which was interpreted as a strong substrate control over the cyclisation step: the substituent at the tertiary stereogenic centre would be hindering one face of the *N*-acyliminium ion very strongly, preventing the approach of the π-nucleophile from this face and therefore favouring the approach from the opposite face leading to the formation of the *syn* diastereomer only (Scheme 3.8).



Scheme 3.8. Favourable and unfavourable nucleophilic attacks on the *N*-acyliminium ion

Since, in the enantioselective reactions, the *N*-acyliminium salts are diastereomeric (because ion-paired with a chiral counter-ion), their behavior during the cyclisation will be differentiated. In one case, the chiral counter-ion and the substituent at the tertiary stereogenic centre will hinder the *Re* face of the *N*-acyliminium ion, leaving the *Si* face totally free and available to undergo the nucleophilic attack. This is a case of strongly matched catalyst/substrate control that triggers a fast cyclisation leading to the formation of the major enantiomer in the reaction. For the other diastereomer, the catalyst and the group at the tertiary centre hinder the opposite faces of the *N*-acyliminium ion. This is a case of mismatch catalyst/substrate control. Because

the substrate control is so high, the indole will still have to attack opposite to the substituent on the cyclic *N*-acyliminium ion and this position is hindered by the counter-ion, therefore this will be a slow process leading to the formation of the minor enantiomer in the reaction. This type of transformation is a typical example of **DY**namic **K**inetic **A**symmetric **T**ransformation (DYKAT).[159] In terms of kinetic constants, it is proposed that k_{eq}^{1}, k_{eq}^{2}, k_{eq}^{-1}, $k_{eq}^{-2} >> k^{1} >> k^{2}$ (Scheme 3.9).



Scheme 3.9. Explanation of the high selectivities observed *via* a *dynamic kinetic asymmetric transformation*

3.2.2.2 Further potential applications

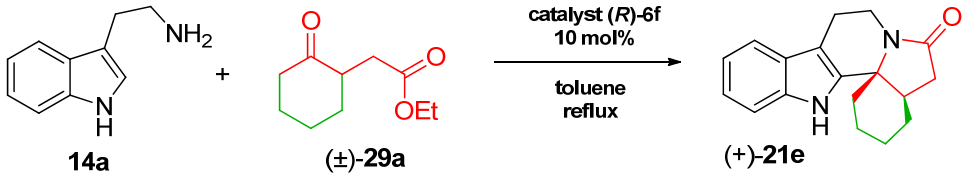
Motivated by the usefulness of such a highly diastereoselective and enantioselective transformation, it was reasoned that it might be possible to extend the scope to enol lactones bearing simple alkyl chains (or aryls), in order not to be limited to enol lactones only possessing

electron-withdrawing groups. In addition, the synthesis of enol lactones was convoluted and their very formation was most of the time low yielding and their stability low (moisture sensitive, air sensitive). Thus, it was hoped that precursors for the synthesis of these lactones would be suitable reaction partners. Once again, enol lactones are simply dehydrated, therefore activated oxoacids. Our hope was to be able to use these rather simple building blocks taking advantage of the previously uncovered DYKAT.

3.2.3 The first direct dehydrative diastereo- and enantioselective *N*-acyliminium cyclisation cascade of tryptamines and oxoacid derivatives

3.2.3.1 Proof of principle

The reaction between tryptamine **14a** and the commercially available, non-activated, (±)-ethyl 2-(2-oxocyclohexyl)acetate ((±)-**29**) was attempted in the presence of (*R*)-**6f** with conditions identical to the previously optimised for disubstituted enol lactones (Scheme 3.10).



Scheme 3.10. Proof of principle of a direct dehydrative *N*-acyliminium cyclisation between tryptamine and a non-activated oxoester

Under these conditions, the desired tetracycle was indeed formed in good yield (77%) and an impressive 82% e.e. in our first attempt and as a single diastereomer (the minor diastereomer cannot be observed in the crude ^{1}H NMR). This experiment proved that our hypothesis was verified and that the conditions previously developed were robust and applicable to this new system without further optimisation. Moreover the use of the methyl ester or the free carboxylic acid gave very similar results, the enantioselectivity being identical within error (83% and 81%

e.e. respectively) and with a consistent yield between 77% and 80%. The direct use of a carboxylic acid as a reaction partner was not anticipated. This important result prompted us to study this powerful cascade in further detail.

3.2.3.2 Catalyst screening in the reaction between tryptamine and (±)-2-(2-oxocyclohexyl)acetic acid

The influence of the different chiral phosphoric acid catalysts we had in hand was assessed. On one hand, another catalyst might be able to impart higher selectivities; on the other hand, assessing the selectivities of our acids might give us insight into the robustness of the reaction. In particular, we were worried that one catalyst might not be optimal in all cases with this strategy. Since the structural changes in the oxoacid reaction partners can have a great influence on the size of the transition structure we hypothesised that a different chiral pocket size might be needed to reach high levels of enantioselectivity.

Table 3.1. Assessment of selectivities in the *N*-acyliminium cyclisation between **14a** and (±)-**29a**

Entry	Catalyst	Temperature (ºC)	Time (h)	Yield (%)	e.e. (%)[a]
1	(*R*)-**6f**	110	24	77	81
2	(*R*)-**10a**	110	24	63	82
3	(*R*)-**6d**	110	24	95	63
4	(*R*)-**6e**	110	24	87	14
5	(*R*)-**6c**	110	24	95	43
6	(*R*)-**6b**	110	48	99	53
7	(*R*)-**6n**	110	24	86	57
8	(*R*)-**6h**	110	48	89	74

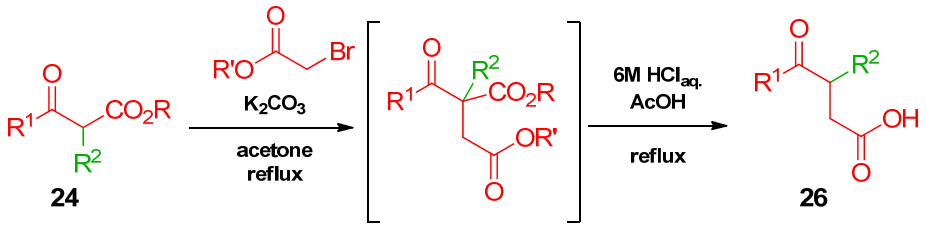
[a] Determined by chiral HPLC analysis using a chiral column

Our original catalyst (*R*)-**6f** imparted the highest selectivities for this example. It can be observed that the partially reduced catalyst (*R*)-**10a** promoted the reaction with an identical enantioselectivity. Interestingly the very bulky (*R*)-**6e** gave a poor enantiomeric excess in this case.

Based on this experiment, it was difficult to draw a conclusion regarding the catalyst effect on the reaction selectivity (qualitative predictive model). Therefore, we planned on assessing the selectivity of each catalyst for every substrate combination and select the catalyst inducing the highest selectivity in each case.

3.2.3.3 Synthesis of oxoacid substrates

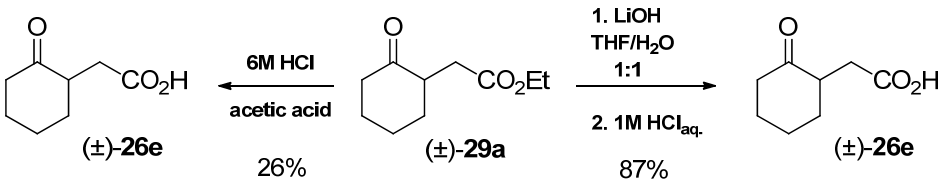
A set of substituted 4-oxo carboxylic acids was prepared by analogy with the route used to prepare disubstituted enol lactones (see section 3.2.1.2). A 1,3-keto ester was treated with methyl bromoacetate in the presence of excess potassium carbonate, in refluxing acetone. The resulting tricarbonyl was used crude for the decarboxylation in acidic conditions (Scheme 3.11).



Scheme 3.11. Synthesis of substituted 4-oxoacids

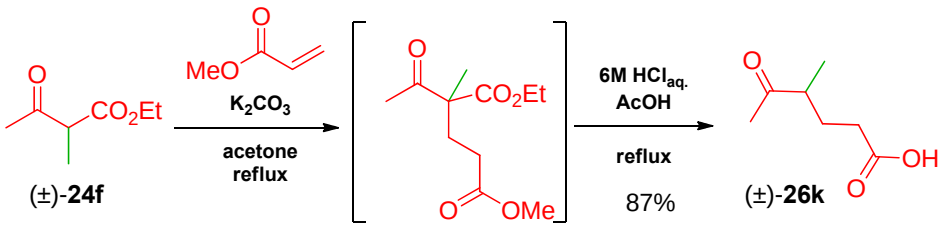
With this method a library of 4-oxoacids was synthesised efficiently and rapidly, in moderate to excellent overall yield (44-86%, Figure 3.2).

The cyclohexyl derivative (±)-**26e** was synthesised in one step from the commercially available ethyl ester (±)-**29a**, by hydrolysis either in acidic conditions or in better yield through saponification and acidification (Scheme 3.12).



Scheme 3.12. Synthesis of cyclohexyl derivative (±)-**26e**

By analogy with this strategy, a 5-oxo carboxylic acid was synthesised by treating a 1,3-keto ester with methyl acrylate in the presence of excess potassium carbonate, in refluxing acetone. The resulting tricarbonyl was used crude for the decarboxylation in acidic conditions (87% yield over 2 steps, Scheme 3.13).



Scheme 3.13. Synthesis of substituted 5-oxoacid (±)-**26k**

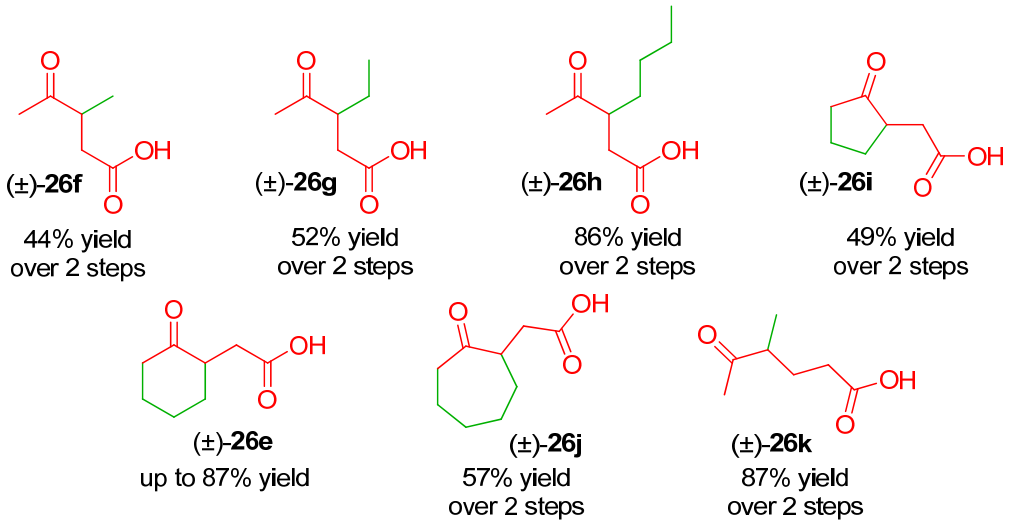
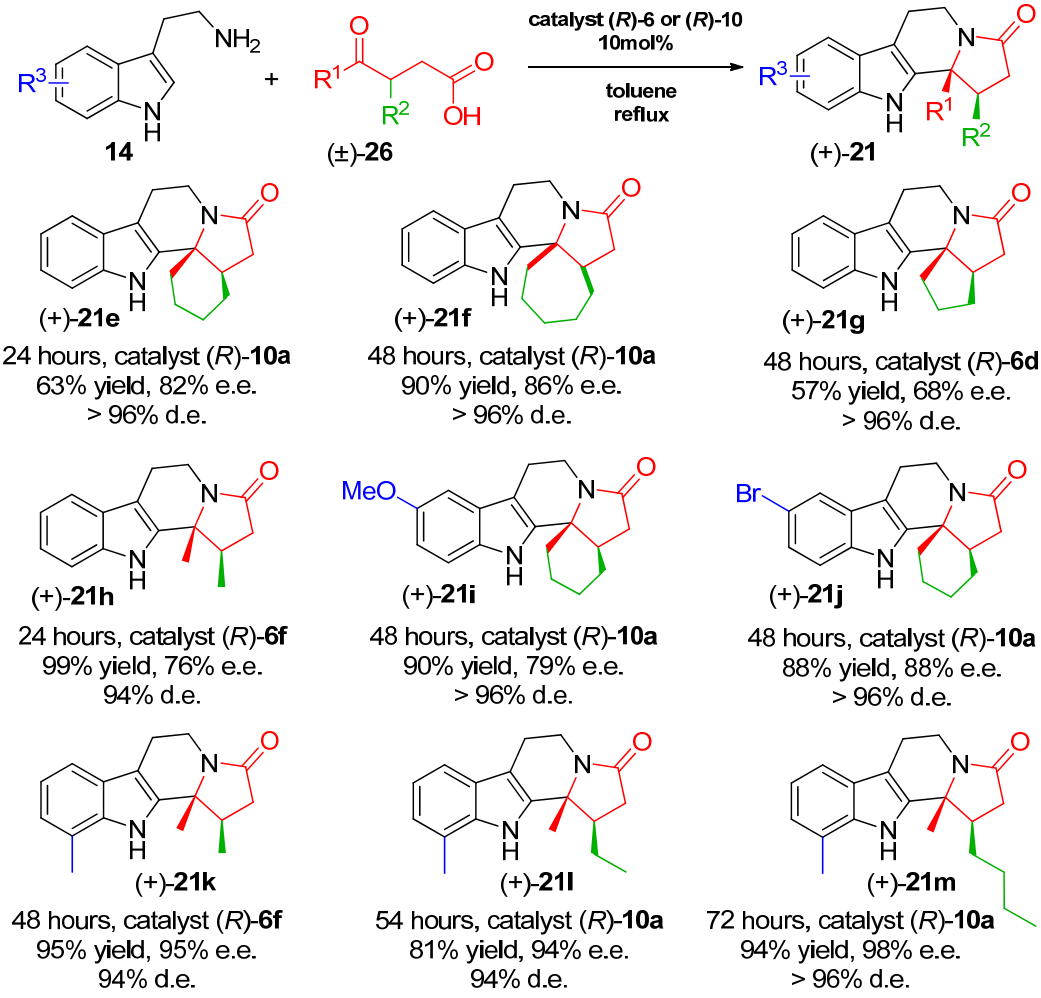
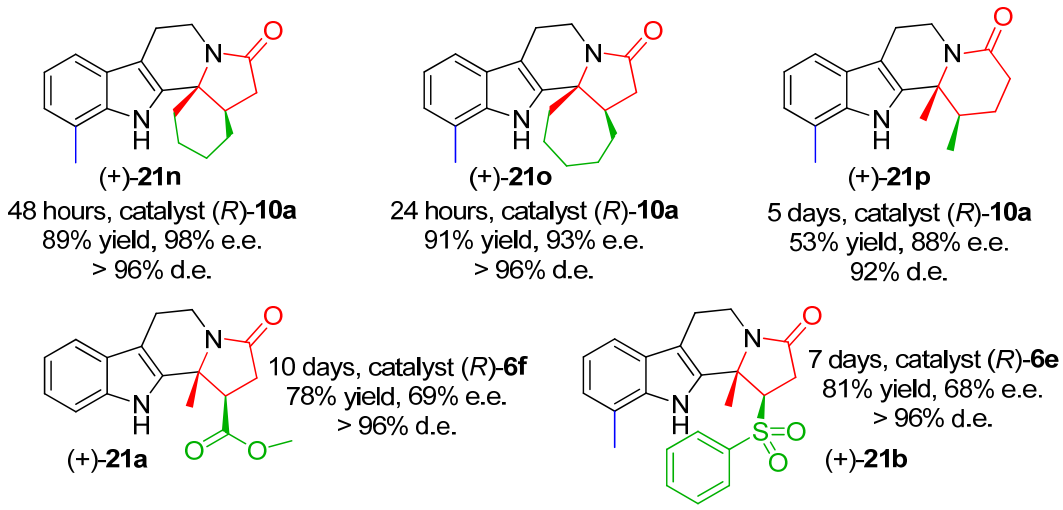


Figure 3.2. Library of oxoacids synthesised

3.2.3.4 Scope of the new direct dehydrative N-acyliminium cyclisation cascade of tryptamines and oxoacids

The previously synthesised 4- and 5-oxo carboxylic acids were reacted with tryptamine derivatives **14** (either available from commercial sources or prepared according to the procedures described in Chapter 2, Section 2.5.2) in the presence of a chiral phosphoric acid, in refluxing toluene, under the optimal conditions previously developed for the disubstituted enol lactone approach. For each condensative *N*-acyliminium cyclisation cascade, a range of acids were assessed and the optimal acid (with respect to enantioselectivity and diastereoselectivity) was reassessed in a larger scale reaction (0.2 mmol) to determine the yield of the reaction.





Scheme 3.14. Scope of the novel direct dehydrative *N*-acyliminium cyclisation cascade of tryptamines and oxoacids

The doubly dehydrative *N*-acyliminium cyclisation cascade with oxoacid derivatives proved to be general with respect to the substitution on the tryptamine and the substitution pattern on the oxoacid. Tryptamines bearing electron-donating substituents such as a methoxy group or alkyl chain were suitable reaction partners and led to the desired decorated β-carbolines in good yield and good to excellent enantioselectivities. As observed before, the presence of a bromo substituent (position 5 in these examples) or an alkyl (at the 7-position) significantly enhanced the enantioselectivities (7 examples, 88-98% e.e.).

The substitution pattern on the newly formed lactam can be as different as vicinal dialkyls (methyl/methyl; methyl/ethyl; methyl/butyl) and even spirocyclic lactams, using cyclic oxoacids. The latter is a particular feature of this transformation and allowed us to form pentaspirocyclic β-carbolines using cyclopentanone, cyclohexanone and cycloheptanone derived oxoacids ((±)-**26i**, (±)-**26e** and (±)-**26j**). When the cyclopentanone-derived γ-keto acid (±)-**26i** was used, the reaction was not as clean, with unidentified side products being formed. It is postulated that this is due to degradation of the starting material and/or product. As a result it led to the isolation of the desired product (+)-**21g** in lower yield and with a lower enantiomeric

excess (compared to the cyclohexyl and cycloheptyl derivatives, respectively (+)-**21e** and (+)-**21f**). Interestingly in this case a smaller catalyst (*R*)-**6d** was necessary to obtain the highest enantioselectivity. Cyclohexanone- and cycloheptanone-derived γ-keto acids were good reaction partners and generally furnished the β-carbolines in high yield (6 examples, average 85% yield) with good to excellent enantioselectivities (82-98% e.e.).

Importantly, γ-keto acids as well as δ-keto acids were good reaction partners, although δ-keto acids generally gave lower yields of the desired product. Interestingly, both the enantioselectivity and diastereoselectivity remained high when δ-keto acid (±)-**26k** was used. Notably in all cases, the diastereoselectivities were good to excellent, and in most cases the minor diastereomer could not even be observed in the crude ^{1}H NMR.

3.2.3.5 Proof of relative and absolute stereochemistry

All stereochemistries have been tentatively assigned based on our previous results:

- *syn* relationship between the quaternary and tertiary stereogenic centres assuming the previously observed DYKAT mechanism is still valid in this case.
- (*R*)-configuration at the quaternary centre when the (*R*)-enantiomer of the catalyst is used.
- Similar optical rotation (same sign, same order of magnitude) for all products in comparison with the one obtained with the enol lactone strategy.
- Match optical rotations for (+)-**21a** and (+)-**21b** obtained *via* the enol lactone strategy and oxoacid strategy.

To avoid any ambiguity, (+)-**21j** and (±)-**21k** were recrystallised ((+)-**21j** was recrystallised to enantiopurity) and an X-ray single crystal structure analysis was performed.

The crystal structure of (+)-**21j** allowed us to confirm the (*R*)-configuration at the quaternary centre as well as the *syn* relationship between the two chiral centres. However, due to the spirocyclohexyl ring strain, it was not obvious that this *syn* relationship would also be found in "non-strained" structures (with vicinal dialkyl chains for instance). The crystal structure of (±)-**21k** resolved this ambiguity proving that the *syn* relationship also existed in these products.

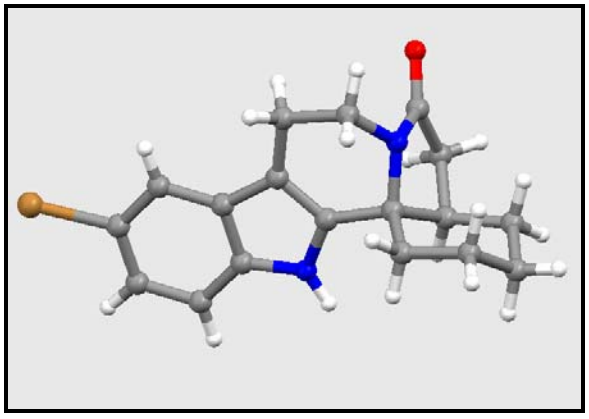


Figure 3.3. X-ray crystal structure of (+)-**21j**

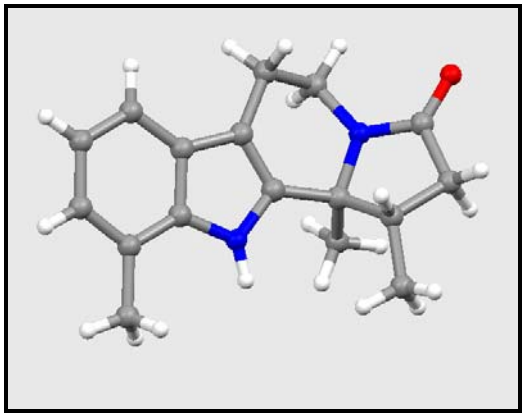
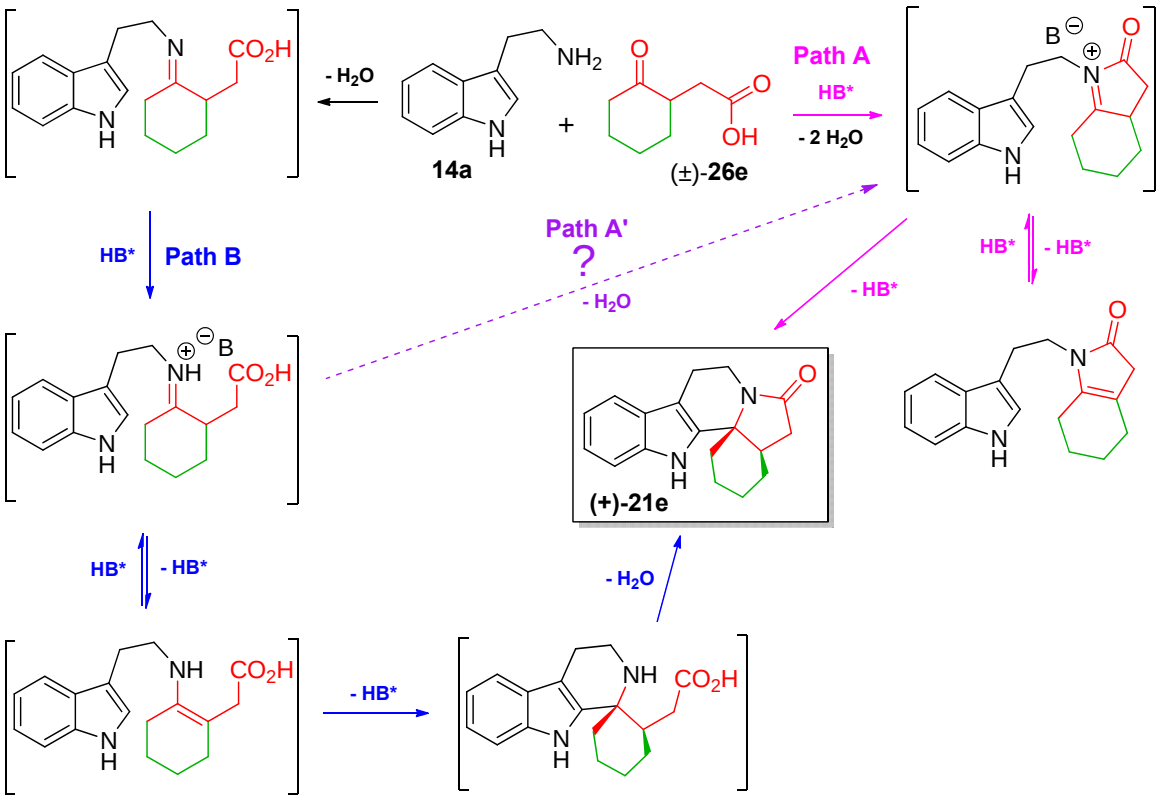


Figure 3.4. X-ray crystal structure of (±)-**21k**

3.2.3.6 Mechanistic study

Thus far, it has been assumed that the reaction was proceeding *via* the formation of an *N*-acyliminium ion. This was supported by the formation of a pro-chiral enamide for the enol lactone strategy. When oxoacids are used, many plausible mechanisms can be proposed for the course of reaction (Scheme 3.15).

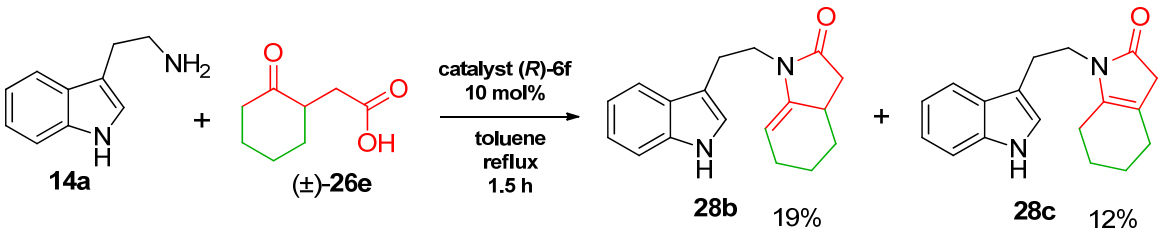


Scheme 3.15. Possible mechanistic pathways for the double dehydrative *N*-acyliminium cyclisation cascade of tryptamines and oxoacids

We were convinced that, due to the high selectivities observed and the scope of the reaction (that tolerates variations similar to the one operated for the enol lactone strategy), the cascade was proceeding *via* an *N*-acyliminium ion (paths A or A′). It was our wish to gather evidence to probe this hypothesis.

3.2.3.6.1 Isolation of enamide intermediates during the reaction

A series of experiments were run to isolate intermediates in the reaction. The most productive one led us to react tryptamine **14a** and the cyclohexanone derived keto acid (±)-**26e** in the presence of either *p*-TsOH or (*R*)-TPS BPA (*R*)-**6f**, stopping the reaction after a short time (2 hours and 1.5 hours respectively, Scheme 3.16).



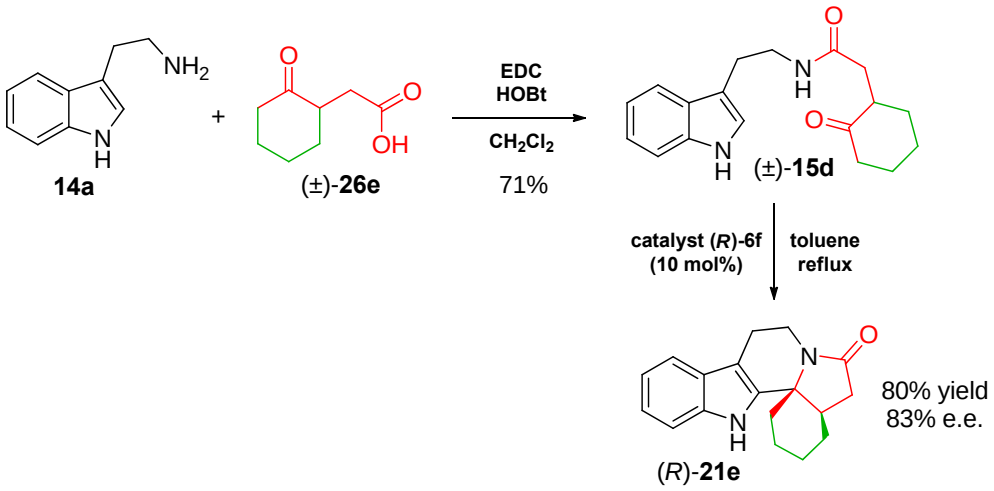
Scheme 3.16. Isolation of enamide intermediates in the reaction of **14a** and (±)-**26e**

In the case of the enantioselective version, it was possible to isolate two intermediates after purification by chromatography on silica gel. Full analysis proved that these intermediates were the isomeric cyclic enamides **28b** and **28c** (isolated in 19% and 12% yield respectively). Interestingly, **28c** is achiral, however, **28b** possesses a chiral centre and its enantiomeric excess was 7% e.e. The isolation of these intermediates and the negligible conversion to the product (only traces isolated), supported the formation of *N*-acyliminium ions during the reaction and their deprotonation to form **28b** and **28c**. This would also support that the *N*-acyliminium cyclisation is the rate-determining step in the cascade (because these intermediates form faster than the product). This would not invalidate but at least render unlikely the formation of an iminium ion that would cyclise and then lactamise (Scheme 3.15, path B).

In addition, when **28b** or **28c** were resubmitted to the optimal cyclisation conditions (for 24 hours), they both led to the formation of the expected pentacyclic lactam (*R*)-(+)-**21e** in good yield and an enantiomeric excess identical (within error) to the one obtained in the cascade (83% e.e. vs. 82% e.e.). This also supported the presence of an intermediate *N*-acyliminium ion in the cascade (paths A or A′).

3.2.3.6.2 Probing the presence of potential intermediates in the reaction

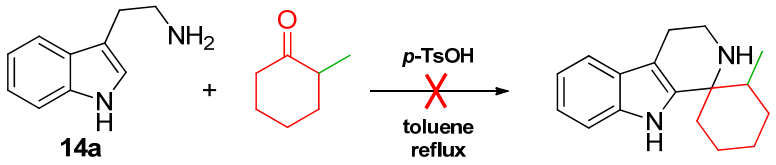
Interestingly, when oxoamide (±)-**15d** was prepared and submitted to the optimal cascade conditions, it also cyclised smoothly to form the expected pentacycle in good yield (80%) and 83% e.e. identical to the cascade within error (82% e.e., Scheme 3.17).



Scheme 3.17. Synthesis of a precursor oxoamide to probe the cascade mechanism

This result supported the initial formation of the *N*-acyliminium ion and further cyclisation; at least it supported the formation of the lactam (and amide bond) before the cyclisation event in the course of the cascade.

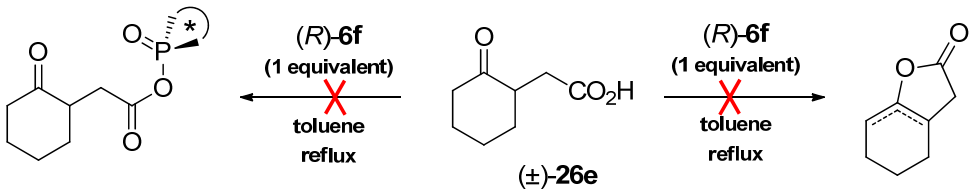
To gain further confidence that pathway B was unlikely to take place in the cascade, a reaction between tryptamine **14a** and 2-methyl cyclohexanone was performed, in the presence of *p*-TsOH. Theoretically, if pathway B was valid, an iminium ion should be formed leading to the cyclisation of the indole onto this electrophile. A free amine should be formed and observed by ^{1}H NMR. When this reaction was carried out, neither the imine intermediate nor the chiral amine was observed by careful ^{1}H NMR monitoring.



Scheme 3.18. Putting path B to the test

With this experiment being inconclusive, it did not allow us to discard path B but gave us confidence that path A (and to a lesser extent path A′) was the actual reaction pathway.

To elucidate whether an activated ester intermediate was formed during the reaction, oxoacid (±)-**26e** was treated with (*R*)-TPS BPA (*R*)-**6f** and the reaction monitored by ^{1}H NMR (Scheme 3.19).

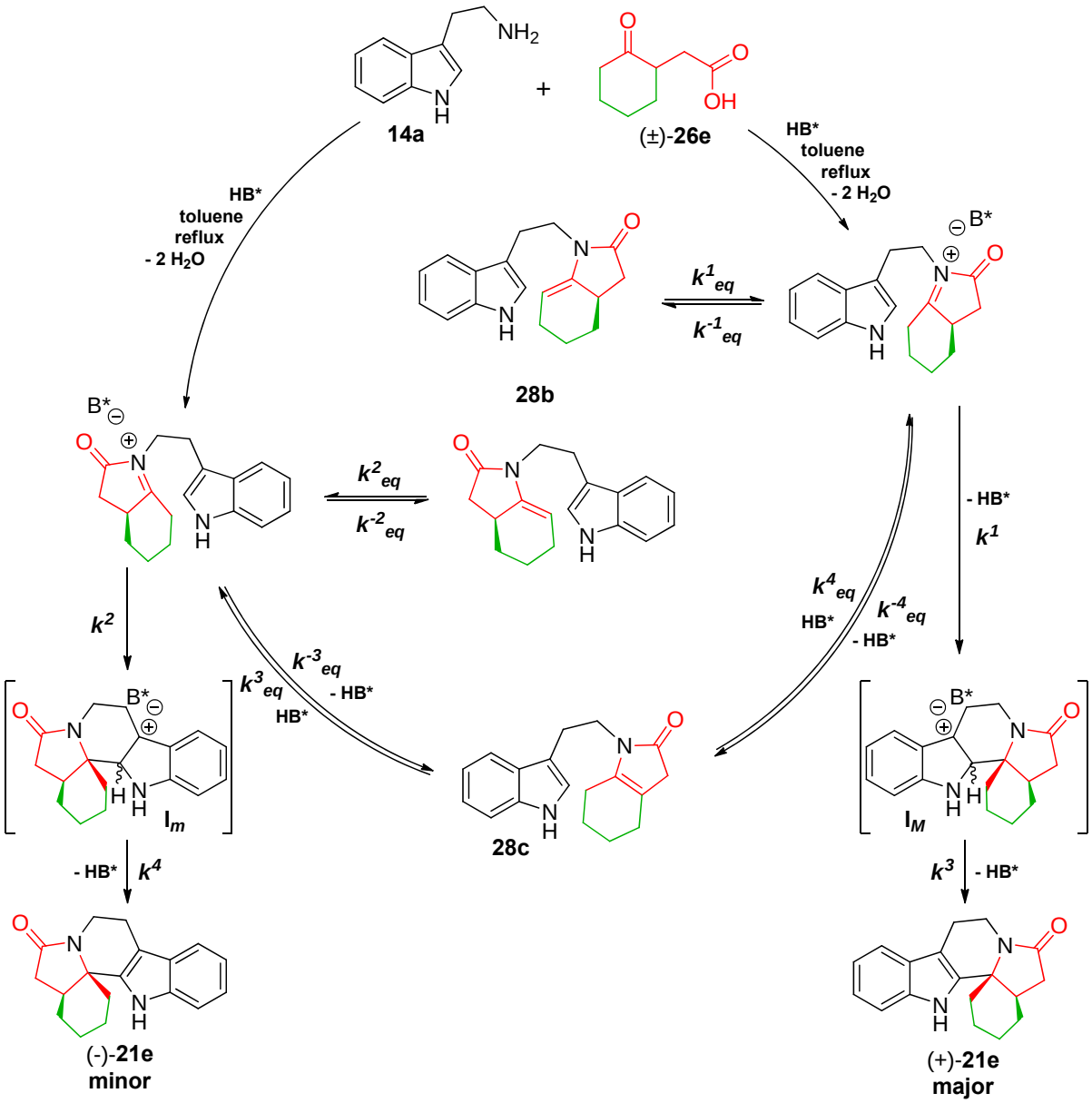


Scheme 3.19. Probing the potential formation of an activated ester

The formation of the activated enol lactone (through dehydration) as well as the formation of a mixed anhydride with the phosphate was envisaged. Heating (±)-**26e** to reflux in toluene in the presence of chiral phosphoric acid (*R*)-**6f** did not allow us to observe the formation of any intermediate even after an extensive reaction time (24 hours).

3.2.3.6.3 Proposed mechanism for the direct double dehydrative *N*-acyliminium cyclisation of tryptamines and oxoacids

We proposed a mechanism which takes into account all the evidence aforementioned; the reaction of **14a** and (±)-**26e** following path A should provide two diastereomeric *N*-acyliminium salts that very likely eliminate a proton to form the two enamides **28b** and **28c**. Although the achiral enamide **28c** is in equilibrium with both *N*-acyliminium salts, each enantiomer of **28b** can only be in equilibrium with its *N*-acyliminium ion counterpart. It is interesting to note that the enantiomeric excess of **28b** is negligible (after 1.5 hours at reflux, 7% e.e.) and cannot account for the selectivity observed during the cyclisation. The only way to reach a high level of enantioselectivity is if all chiral species epimerise *via* the formation of **28c** that is the key intermediate in this *dynamic kinetic asymmetric cyclisation* (Scheme 3.20).



Scheme 3.20. Mechanistic pathway of the dehydrative *N*-acyliminium cyclisation cascade of tryptamine **14a** and oxoacid (±)-**26e**

In terms of kinetic constants, our proposed mechanistic pathway implies that k^{1}_{eq}, k^{-1}_{eq}, k^{2}_{eq}, k^{-2}_{eq}, k^{3}_{eq}, k^{-3}_{eq}, k^{4}_{eq}, k^{-4}_{eq}, k^{3}, k^{4} >> k^{1} >> k^{2}. This is consistent with the cyclisation being under kinetic control and the C-C bond formation being the rate determining step.

It is possible to envisage another mechanism where the proton loss would be rate determining and the C-C bond formation (enantio-determining step) would be reversible. In this case the

reaction would be driven by the formation of the most stable 2*H*-indole cation/BPA ion pair intermediate ($\mathbf{I}_{M}$)and the enantioselectivity dictated by the relative amount of the favoured (most stable $\mathbf{I}_{M}$) and disfavoured (least stable $\mathbf{I}_{m}$) intermediates. To probe the latter mechanism, measurement of a kinetic isotopic effect (or its absence) during the cyclisation of a 2-deutero tryptamine derived substrate would be the key.

3.2.4 Conclusion

A chiral phosphoric acid-catalysed enantioselective *N*-acyliminium cyclisation cascade of oxoacid derivatives and tryptamines was developed. It allowed us to synthesise a library of highly decorated β-carbolines very rapidly, as single diastereomers (either due to an excellent selectivity during the reaction, or to the removal of the minor diastereoisomer by chromatography). The yields were good to excellent (53-99%) for this three-bond forming complex transformation and the enantioselectivities ranged from 68-98%. The absolute and relative stereochemistry was assigned unambiguously by X-ray crystallography. In an effort to understand the mechanistic pathway of the cyclisation, we discovered that two isomeric ene-amides were formed during the reaction. All experimental evidence pointed towards the cyclisation being the rate-limiting step and *N*-acyliminium ion intermediates forming. The high selectivities were attributed to a case of match/mismatch catalyst/substrate control during the *dynamic kinetic asymmetric cyclisation* (example of DYKAT).

3.3 Development of a novel base-catalysed Michael addition initiated enantioselective acid-catalysed *N*-acyliminium cyclisation cascade exploiting a new site isolation concept

3.3.1 Overview of the project

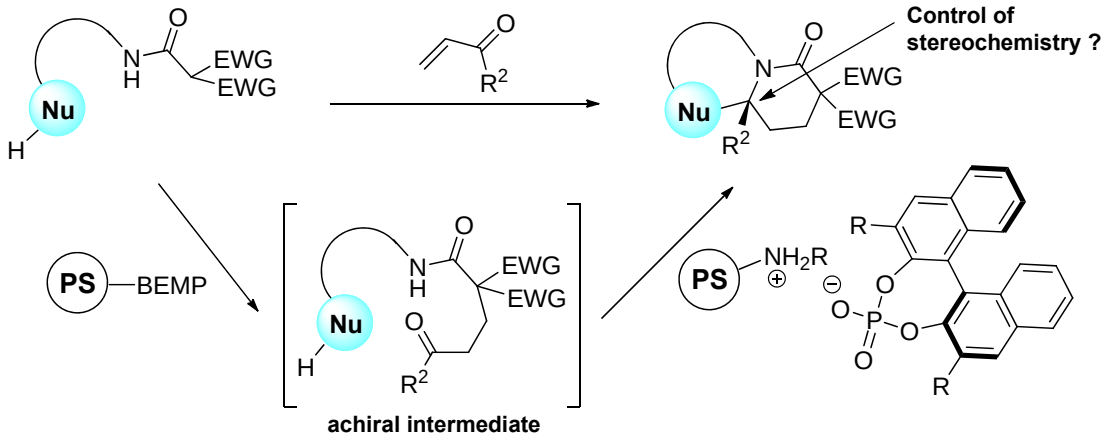
Starting with a different strategy, it was planned to combine a base-catalysed Michael addition (previously studied in the group) to our well-established acid-catalysed enantioselective *N*-acyliminium cyclisation. We envisaged to take advantage of site isolation to be able to run the doubly catalysed process in the same vessel in a powerful domino reaction. When this project started, the chemistry of polymer supported BPAs was very limited and mostly unknown (the chemistry of polymer supported BINOLs however was well-established[160]). Therefore our strategy was based on the anchoring of the phosphoric acid to another polymer supported species. Naturally, a weak base was our first choice since during our previous studies we learnt that BPAs tend to form stable ion pairs with bases such as pyridine and tertiary amines, keeping their catalytic power intact. The employment of ammonium phosphate salts had also been reported in asymmetric organocatalysed transformations by List *et al.*[67,68,161] and others.[72]

Our challenge was to prove that indeed this type of anchoring could be performed and that it would result in a new type of polymer supported BPA. Although this study was successful (*vide infra*), during a control experiment it was discovered that when a BPA bearing bulky group at the 3 and 3′ position was used in solution, in conjunction with a polymer supported base (in the same vessel), both catalytic activities were maintained and thus the anchoring was not necessary to observe site isolation.

Our new challenge became proving that we had a new site isolation concept in hand and that employing this new solution we would be able to develop our novel base-catalysed Michael addition-induced acid-catalysed enantioselective *N*-acyliminium cyclisation cascade.

3.3.2 Project genesis: study of the anchoring of a BPA onto a polymer supported amine

This strategy of ionic attachment of a BPA to a polymer supported amine was pursued because we believed it could be technically easy to perform and could prove to be efficient in site isolation. We already had a model reaction on which to test this concept, based on previous work carried out in the group by Dr. Adam Pilling (Scheme 3.21).



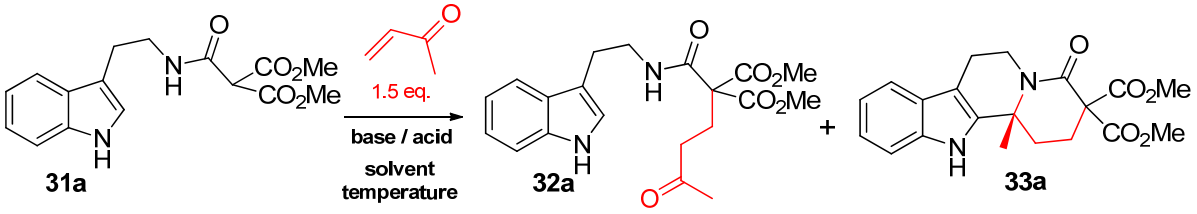
Scheme 3.21. Concept of the base-catalysed Michael addition-induced acid-catalysed enantioselective *N*-acyliminium cyclisation *via* anchoring of the phosphoric acid

A. W. Pilling successfully developed a one-pot PS-BEMP catalysed Michael addition / Amberlyst-15 catalysed *N*-acyliminium cyclisation to form fused polycycles taking advantage of site isolation to avoid catalyst annihilation.[162] Further to this study and our seminal work on enantioselective *N*-acyliminium cyclisation cascades, it was our wish to try and combine both these approaches.

3.3.3 Proof of principle of site isolation *via* anchoring and further discovery

A series of experiments was designed to assess whether an efficient site isolation could be reached by ionic anchoring of a phosphoric acid to a polymer-supported amine *via* formation of the ammonium salt (Table 3.2).

Table 3.2. Proof of principle experiments for the effective site isolation with PS-BEMP and anchored and non-anchored chiral phosphoric acids



Entry	Solvent	Base (10 mol%)	Acid (10 mol%)[a]	Time	Result	e.e. (%)
1	CH_2Cl_2	-	(*R*)-**6f**	24 hours	No reaction	-
2	CH_2Cl_2	PS-piperidine	-	24 hours	No reaction	-
3	CH_2Cl_2	PS-BEMP	-	6 hours	92% yield of **32a**	-
4	CH_2Cl_2	-	PS-piperidine + (*R*)-**6f**	24 hours	No reaction	-
5	CH_2Cl_2	PS-BEMP	PS-piperidine + (*R*)-**6f**	24 hours	100% conv. to **32a**	-
6	CH_2Cl_2	PS-BEMP	(*R*)-**6f**	24 hours	100% conv. to **32a**	-
7	CH_2Cl_2	liq. BEMP	-	24 hours	100% conv. to **32a**	-
8	CH_2Cl_2	liq. BEMP	(*R*)-**6f**	24 hours	No reaction	-
9	CH_2Cl_2	PS-BEMP	**DPP**	24 hours	No reaction	-
10	CH_2Cl_2	PS-BEMP	(*R*)-**6f**[b]	24 hours	100% conv. to **32a**	-
11	CH_2Cl_2	PS-BEMP	(*R*)-**6f**[c]	24 hours	100% conv. to **32a**	-
12	Toluene	PS-BEMP	(*R*)-**6f**[b]	48 hours	100% conv. to **32a**	-
13	Toluene	PS-BEMP	(*R*)-**6f**[b]	16 h[d] + 36 h[e]	25% yield of **33a**	51

[a] 10 mol% except when otherwise stated; [b] 20 mol% catalyst loading; [c] 30 mol% catalyst loading; [d] time at r.t. after addition of MVK; [e] time at reflux after r.t.

When the reaction was attempted solely in the presence of 10 mol% of chiral acid, no product formation was observed (entry 1). The presence of a stronger base was necessary for the Michael addition to occur. In our hands PS-piperidine was unable to catalyse the desired reaction (entry 2) whereas PS-BEMP led to full conversion after 6 hours (entry 3). As expected when (*R*)-**6f** was anchored to PS-piperidine, no Michael adduct was observed (entry 4). One key experiment was to combine PS-BEMP for its basic activity and PS-piperidine/(*R*)-**6f** to assess the strength of the anchoring (entry 5). In this experiement we observed the full conversion to the Michael adduct after 24 hours which proved that the base and the anchored acid did not quench each other on the reaction time scale and therefore that the anchoring was effective.

To our surprise, when acid (*R*)-**6f** was not anchored (free in solution) and in the presence of PS-BEMP, full conversion to the Michael adduct was still observed (entry 6). This was an unanticipated, significant and exciting result as it would mean that site isolation was achieved with a single polymer supported reagent. The same experiment was repeated to prove it was not a false positive and the same result was achieved. This is the first time that such an observation is reported.

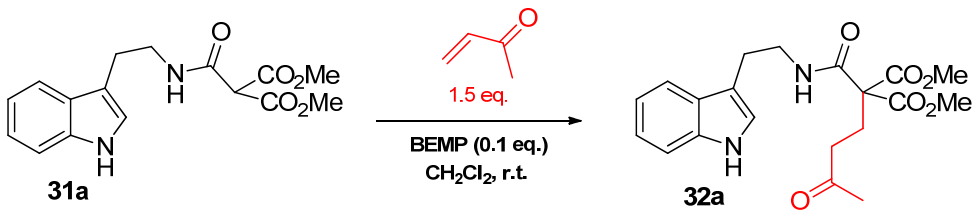
To ascertain whether we had a case of site isolation, control experiments were carried out. When PS-BEMP was replaced by liquid BEMP (which catalyses the reaction on its own, entry 7), in the presence of (*R*)-**6f**, no reaction was observed presumably due to the mutual acid/base quenching (entry 8). Interestingly, when the acid used was DPP (a small molecule), in the presence of PS-BEMP, no reaction was observed because of mutual acid/base quenching (entry 9). The conclusion drawn from this series of experiments was that site isolation must be created between PS-BEMP and (*R*)-**6f** because of the relative size of the acid (large molecule) and of the polymer pores. This is supported by entries 10 and 11 whereby even increasing the amount

of acid (up to 3 equivalents relative to the base) the basic catalytic activity remained and full conversion to the Michael adduct was observed.

The reaction proceeded similarly in toluene, where in the presence of PS-BEMP and (*R*)-**6f**, full conversion to the Michael adduct was observed at room temperature (after 48 hours, entry 12) and the formation of the desired tetracyclic β-carboline was achieved when the mixture was heated to reflux after ramping (r.t. for 16 hours). Although the isolated yield was low (25%), our concept was supported by hard data and in our first attempt 51% e.e. was reached (entry 13).

3.3.4 Optimisation of the *N*-acyliminium cyclisation conditions

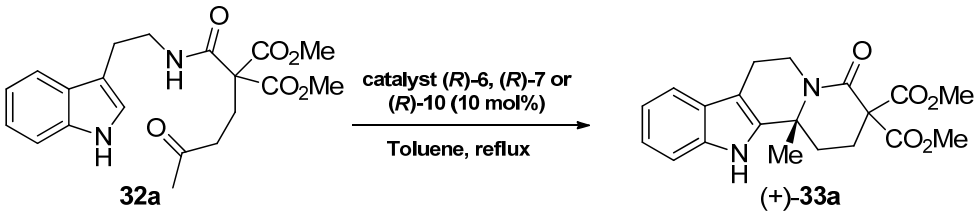
To optimise the cyclisation conditions with respect to enantioselectivity, the same strategy to optimise the seminal *N*-acyliminium cyclisation cascade was applied. The precursor oxoamide **32a** was prepared by liquid BEMP-catalysed Michael addition of **31a** onto methyl vinyl ketone (MVK) (Scheme 3.22).



Scheme 3.22. Preparation of **32a**, substrate for optimisation study

32a was subsequently exposed to a range of different conditions. Notably, a library of catalysts was assessed in an effort to increase the selectivity and the effect of the concentration was studied (Table 3.3).

Table 3.3. Catalysts screening in the *N*-acyliminium cyclisation of **32a**



Entry	$[32a]_i$ (mM)	Acid (10 mol%)	Time	Yield (%)	e.e. (%)
1	7 mM	(*R*)-**6f**	12 hours	99	52
2	7 mM	(*R*)-**10a**	24 hours	99	60
3	7 mM	(*R*)-**6g**	65 hours	76	35
4	7 mM	(*R*)-**6j**	18 hours	87	49
5	7 mM	(*R*)-**6k**	48 hours	81	38
6	7 mM	(*R*)-**6i**	12 hours	99	16
7	7 mM	(*R*)-**6l**	48 hours	99	27
8	7 mM	(*R*)-**6d**	12 hours	95	52
9	7 mM	(*R*)-**6e**	16 hours	92	58
10	7 mM	(*R*)-**10b**	30 hours	49	65
11	7 mM	(*R*)-**6c**	16 hours	98	29
12	7 mM	(*R*)-**6b**	16 hours	92	26
13	7 mM	(*R*)-**7a**	16 hours	99	45
14	5 mM	(*R*)-**10a**	20 hours	99	55
15	10 mM	(*R*)-**10a**	8 hours	99	55
16	16.67 mM	(*R*)-**10a**	7 hours	99	50

Amongst all the catalysts assessed in this optimisation study, (*R*)-**10a** and (*R*)-**10b** imparted the highest selectivities in the *N*-acyliminium cyclisation (entries 2 and 10). Although the enantiomeric excesses remained moderate, it was a significant improvement on the initial result

(51% e.e. in the cascade). Interestingly, a trend seemed to emerge: both (*R*)-**6f** and (*R*)-**6e** were good catalysts for the reaction but their reduced counterparts (*R*)-**10a** and (*R*)-**10b** both promoted the cyclisation with enhanced enantioselectivity (entries 1 and 9 vs. entries 2 and 10).

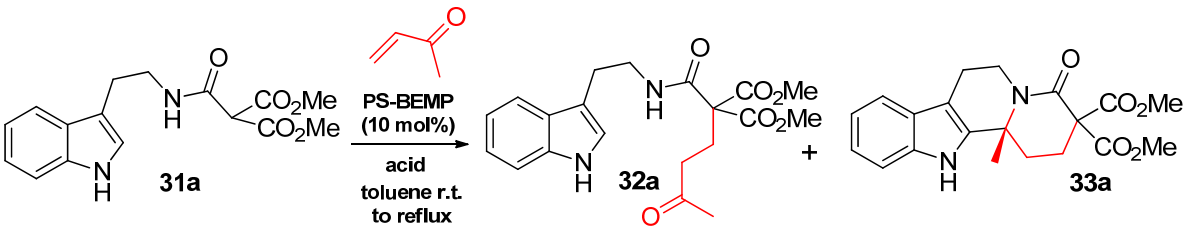
The effect of the concentration was measured using (*R*)-**10b** as a benchmark catalyst and the optimal concentration found for the original *N*-acyliminium cyclisation cascade with enol lactones also seemed to be optimal in this case (entries 1 and 14-16).

Accordingly, catalysts (*R*)-**10a** and (*R*)-**10b** were evaluated in the full cascade.

3.3.5 Development of an efficient base-catalysed Michael addition induced acid-catalysed enantioselective *N*-acyliminium cyclisation cascade

Firstly, the reaction conditions for the full cascade were optimised using (*R*)-**6f** as the acid since a reactivity issue was observed (*vide supra* Table 3.2, entry 13). Subsequently, the catalysts that were found to be optimal for the enantioselectivity were assessed in the optimised domino reaction (Table 3.4).

Table 3.4. Optimisation of the base-promoted Michael addition-induced enantioselective *N*-acyliminium cyclisation cascade



Entry	MVK (eq.)	Acid (20 mol%)	Time at r.t. + reflux	Result	e.e. (%)
1	1.5	(*R*)-**6f**	24 h	50% conv. to **32a**	-
2	1.5	(*R*)-**6f**	48 h + 36 h	25% yield of **33a**	51
3	2	(*R*)-**6f**	48 h	ratio **31a/32a/33a** 1:5:10	-
4	2	(*R*)-**6f**	48 h + 12 h	90% yield of **33a**	43
5	3	(*R*)-**6f**	48 h	ratio **31a/32a/33a** 0:3:5	-
6	3	(*R*)-**6f**	17 h	ratio **31a/32a/33a** 0:6:1	-
7	3	(*R*)-**6f**	17 h + 20 h	78% yield of **33a**	49
8	3	(*R*)-**10b**	20 h + 48 h	Only by-products[a], no **33a** observed	-
9	3	(*R*)-**10a**	24 h + 24 h	81% yield of **33a**	57

[a] The by-products come from the decarboxylation of one ester group and for some of them further Michael addition on the new pro-nucleophile.

To solve the reactivity issue (slow conversion to the Michael adduct, entries 1-2), the number of equivalents of MVK was increased up to 2 equivalents where a satisfactory reactivity was achieved (entries 1-3). Although the desired reactivity was obtained, conversion of **32a** to **33a** was observed even at room temperature (entry 3). This led to a significantly lower enantiomeric excess in the full cascade (43% e.e. vs. 52% e.e. expected, entry 4). To diminish the reaction time at room temperature and therefore limit the low selectivity cyclisation, the number of equivalents of MVK was increased to 3 equivalents. Interestingly, after 48 hours at room temperature in the presence of both catalysts, the Michael addition was complete but **33a** was again observed (entry 5). When the reaction time was only 17 hours, the Michael addition was again complete but the degree of cyclisation observed was negligible (entry 6) and indeed when the full cascade was attempted with these conditions (17 hours at room temperature followed by

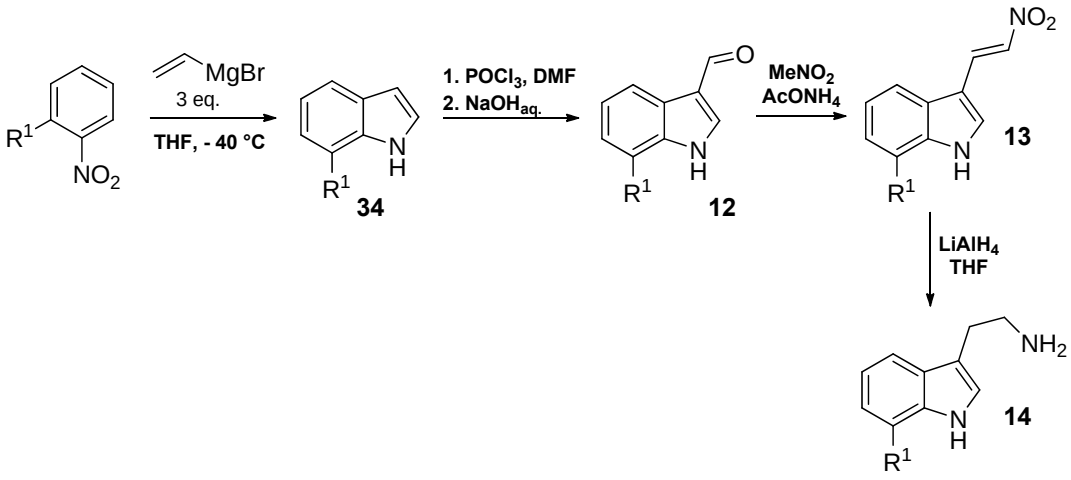
reflux), **33a** was isolated in good yield and an enantiomeric excess similar to the optimisation study within error (49% e.e. vs. 52% e.e.).

Under similar conditions, (*R*)-**10a** and (*R*)-**10b** were evaluated in the cascade. Surprisingly (*R*)-**10b** led to the formation of side products only, no **33a** was observed in this case. However, when (*R*)-**10a** was used as acid, the cascade proceeded to afford **33a** in good yield (81%) and with improved enantiomeric excess (57% e.e. vs. 60% e.e. for the optimisation).

3.3.6 Probing the scope of the cascade

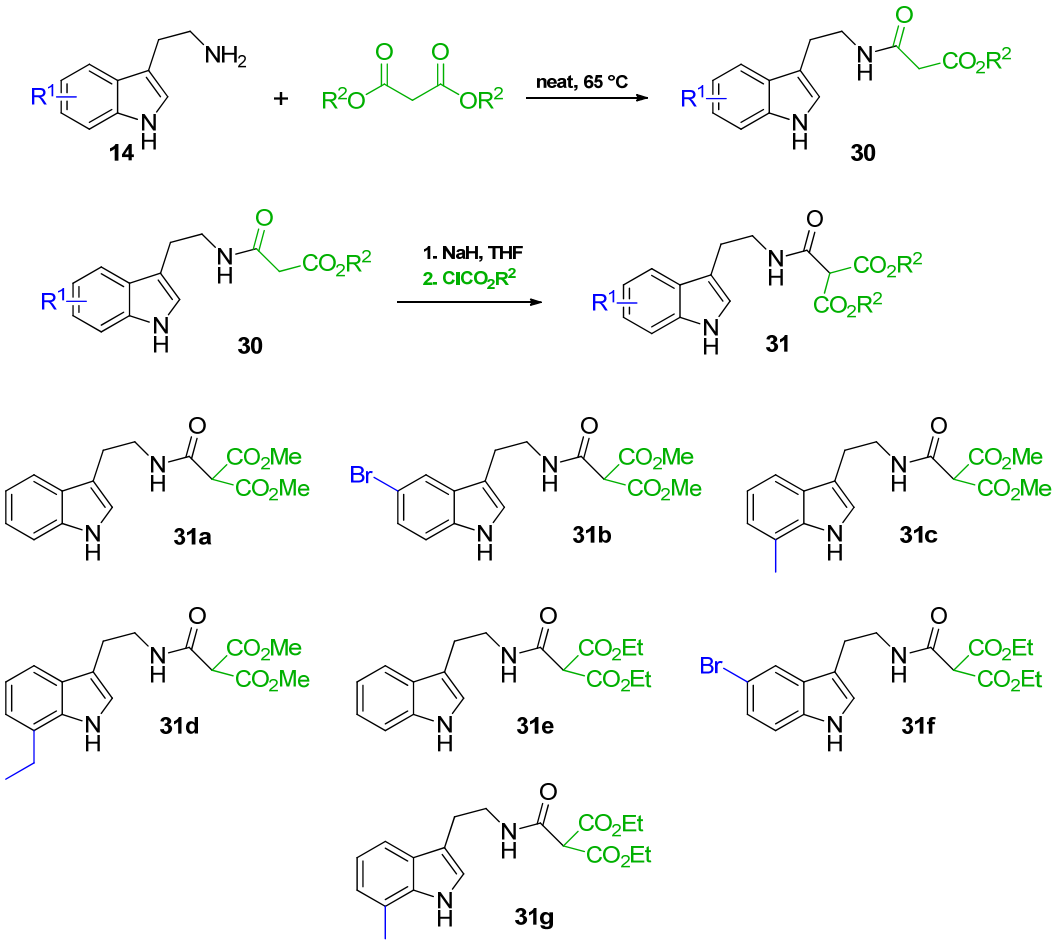
A series of pro-nucleophiles were synthesised to study the scope of the cascade with regards to the substitution pattern on the indole π-nucleophile and the ester substituents.

Indoles **34** with alkyl substituents at the 7-position (methyl or ethyl) were prepared according to the Bartoli synthesis.[163] They were converted to the indole-3-carbaldehydes **12** through a high yielding Vilsmeier-Haack formylation. The aldehydes were transformed to the corresponding nitro-olefins **13** and subsequently reduced to the corresponding tryptamines **14** (see Chapter 2, Section 2.5.2, Scheme 3.23).



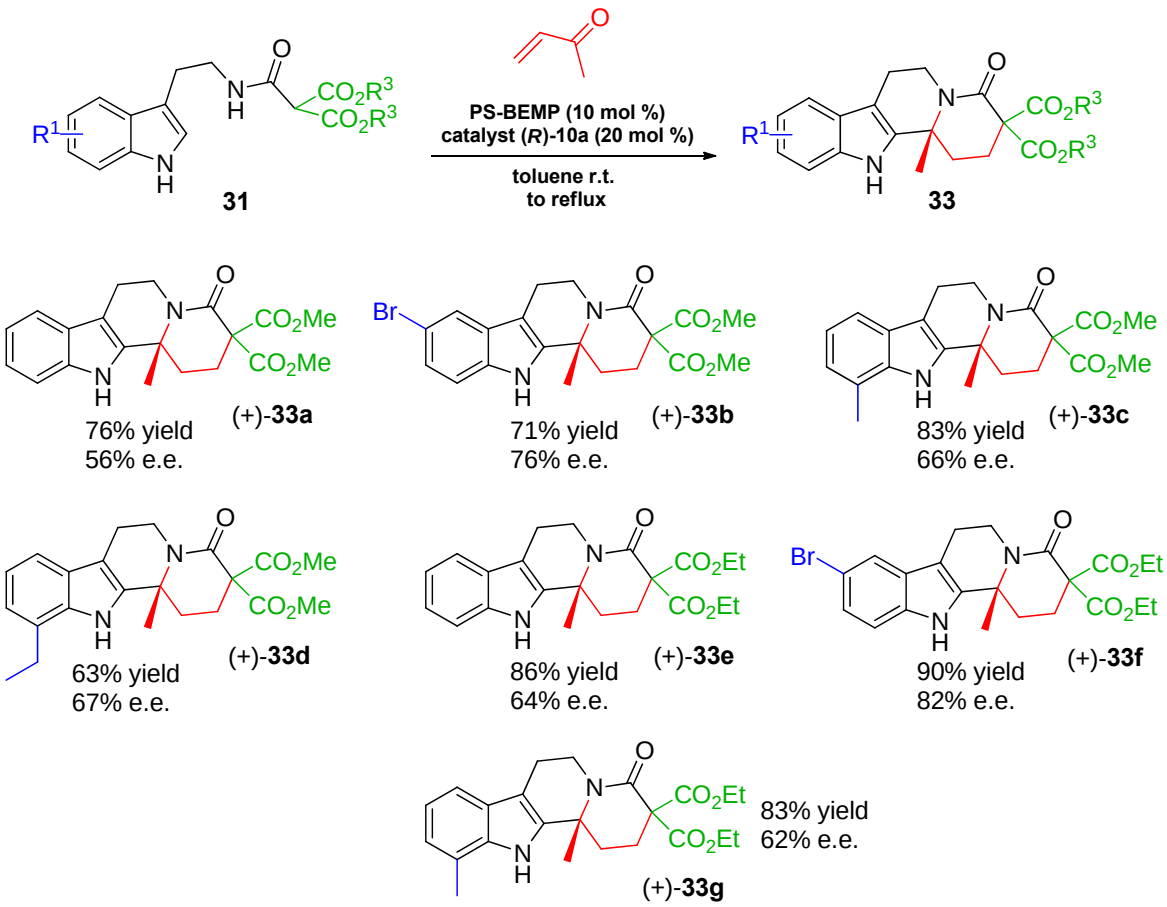
Scheme 3.23. Synthesis of 7-alkyl tryptamines

Commercially available and prepared tryptamine derivatives **14** were acylated by reaction with neat malonate esters (methyl or ethyl) at 65 ºC.[164] The resulting dicarbonyl compounds **30** were *C*-acylated a second time by deprotonation with sodium hydride and subsequent quenching with the desired chloroformate (Scheme 3.24).



Scheme 3.24. Synthesis of a library of pro-nucleophiles **31**

These pro-nucleophiles were employed in our base-induced acid-catalysed enantioselective *N*-acyliminium cyclisation with MVK as an electrophile, in the presence of PS-BEMP (10 mol%) and (*R*)-**10a** (20 mol%). All reactions proceeded smoothly to afford the expected tetracycles in good yields (63-90%) and enantiomeric excesses ranging from 56-82% e.e. (Scheme 3.25).



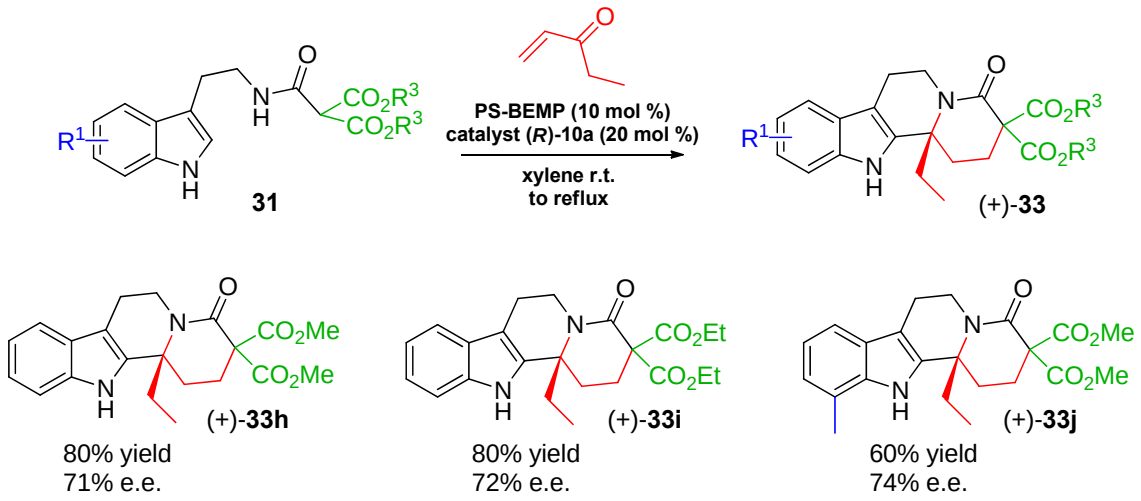
Scheme 3.25. Scope of the base-induced acid-catalysed enantioselective *N*-acyliminium cyclisation with MVK

Notably, the 5-bromo tryptamine-derived pro-nucleophiles improved the enantioselectivity compared to the unsubstituted indole derivatives [56% to 76% e.e. for the methyl ester derivatives (+)-**33a** and (+)-**33b**; 64% to 82% for the ethyl ester derivatives (+)-**33e** and **(+)-33f**]. The effect of the 7-alkyl substitutents on the indole was more subtle. Although a higher enantioselectivity was expected (based on our previous studies), the effect of the substituent was balanced by the improved reactivity of the indole nucleophile that started cyclising even at room temperature (giving rise to lower enantioselectivity). We managed to maintain a satisfactory level of enantioselectivity (compared to the model system (+)-**33a**) by heating to reflux as soon as full conversion to the Michael adduct was reached. The 7-methyl and 7-ethyl substitutents seemed to have an identical beneficial influence on the level of enantioselectivity

(66% and 67% e.e. respectively for (+)-**33c** and (+)-**33d**). Regarding the influence of the size of the ester moiety on the reactivity and enantioselectivity, no trend seem to emerge and both the methyl ester and ethyl ester pro-nucleophiles led to good reactivities and similar levels of enantioselectivity (except for the unsubstituted indole nucleophile where the ethyl ester led to significantly higher enantioselectivity: 64% e.e. vs. 57% e.e.).

This cascade was the first example of a site isolation method employing a single polymer supported reagent in conjunction with an incompatible reagent in solution.

It is not limited to the use of MVK and it was proved that EVK is also an effective electrophile in the cascade, although the reactions are significantly slower. To solve this problem, the cascade with EVK was run in higher boiling point aromatic solvents. The cascade in mesitylene resulted in extensive degradation, however, the cascade in xylene was clean and afforded the desired fused hetereocycles with an ethyl group at the quaternary centre (Scheme 3.26).



Scheme 3.26. Scope of the base-induced acid-catalysed enantioselective *N*-acyliminium cyclisation with EVK

Unfortunately, when vinyl ketones bearing a longer alkyl chain were tried in the cascade, the reaction became unconveniently slow, even in xylene and after extensive reaction times (over 10 days at reflux) completion was never observed with pentyl vinyl ketone. This is a clear

limitation of this method; however, we believe the concept displayed in this strategy will become increasingly popular as it circumvents the use of covalently attached polymer supported organocatalysts which are largely unknown to date.

3.3.7 Rationale for the observed site isolation

Beads of polymer supported BEMP can be considered as microporous beads where the basic sites can be either internal (inside the polymer network) or external (pointing outside the bead). When an acid is present in solution, the external basic sites will be immediately deactivated/quenched by acid molecules. This, we believe, decreases the size of the beads pores by creating a passivating crust, porous to small molecules such as vinyl ketones or our pro-nucleophiles, but impermeable to bigger molecules such as our catalysts (Figure 3.5).

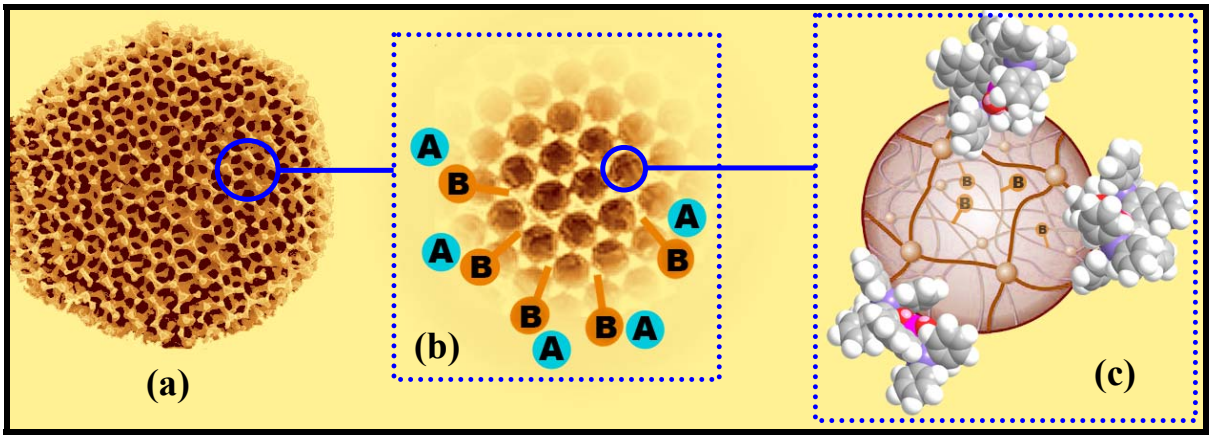


Figure 3.5. Representation of the interaction of PS-BEMP and (*R*)-**6f**: (a) Schematic representation of a bead of PS-BEMP; (b) Schematic representation of the surface of the bead quenched by the acid, B are basic sites and A are molecules of acid; (c) Schematic representation of the internal basic sites, the catalyst is too bulky to penetrate and thus quench them.

3.3.8 Conclusion

We have developed an efficient base-catalysed Michael addition-induced acid catalysed *N*-acyliminium cyclisation cascade taking advantage of an original case of site isolation. In our system, the base (BEMP) was polymer supported whereas the acid was in solution. Interestingly, this led to an effective site isolation of the base and acid which we postulate was due to the relative physical size of the catalyst and the polymer network.

Methyl vinyl ketone and ethyl vinyl ketone were good electrophiles in the cascade, however bulkier vinyl ketones did not react satisfactorily. Tetracyclic β-carbolines were obtained from pro-nucleophiles and vinyl ketones in generally high yield (average 77%) and moderate to good enantioselectivities (56-82%). Although this method clearly showed limitations in scope, we believe the concept of site isolation demonstrated with this approach, having a single polymer supported reagent, is of major importance. Our strategy provides a rapid and efficient alternative to the use of polymer supported BPAs whose chemistry and application is widely unknown.

Chapter Four:

Mechanistic aspect: a model for the origin of enantioselectivity and an explanation for the limitations

This work has been carried out in collaboration with Dr. Robert Paton from the University of Oxford, who modelled the intermediate and possible transitions states for the *N*-acyliminium cyclisation of **15a** into (+)-**18a**. Calculations were performed by Dr. Paton and supporting data were provided by myself.

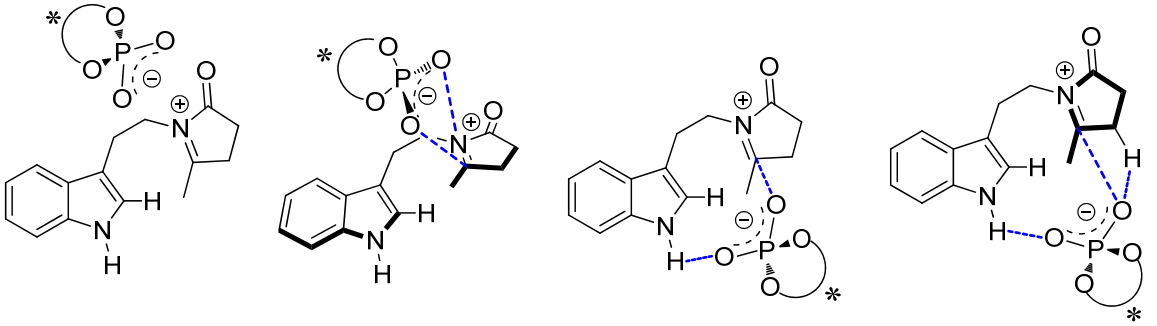
4.1 Aims of the project

We have developed a set of domino sequences based on a Brønsted acid-catalysed enantioselective *N*-acyliminium cyclisation, however, the origin of enantioselectivity remained unknown. It was desirable to test the limits of the *N*-acyliminium cyclisation and work in collaboration with a computational chemist to be able to answer some questions about fundamental aspects of this reaction. In particular, we were interested in determining a qualitative model to explain the selectivity observed and most importantly in performing high level calculations to model the transition states. Provided that our modeling reflects the genuine mechanistic pathway in the reaction, we should be able to establish a quantitative and predictive model for the enantioselective *N*-acyliminium cyclisation. It was our hope that this model could help us with understanding some of the limitations we have observed and also it could lead us to design new systems where we should expect high enantioselectivity.

4.2 A qualitative model to explain the origin of enantioselectivity

Although a few mechanistic studies and calculations have been carried out in the field of chiral phosphoric acid organocatalysis,[18,49,71,92] the origin of enantioselectivity in most of the published studies remains unknown. It was our wish to work in collaboration with a computational chemist to build a predictive model for the enantioselectivity observed in our *N*-acyliminium cyclisation reactions.

For this reason, a few models were studied and one of them emerged quickly as the most plausible interaction between the chiral acid and our substrate (Figure 4.1).



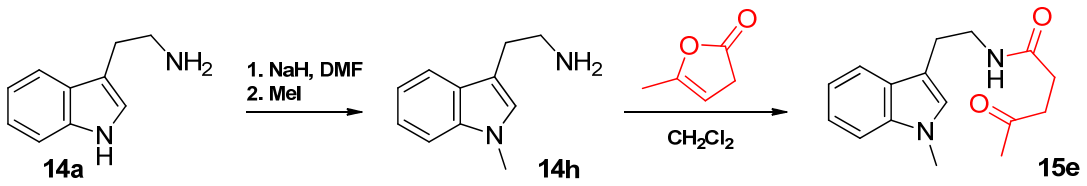
Model A	**Model B**	**Model C**	**Model D**
Simple ion pairing	Double electrostatic interaction P-O---N and P-O---C	Electrostatic interaction P-O---C and hydrogen bonding	Electrostatic interaction P-O---C and double hydrogen bonding

Figure 4.1. Proposed models to explain the origin of enatioselectivity

Firstly, models A and B were discarded because they were not in agreement with some of the experimental data we had gathered. In particular, they would not account for the low selectivities observed when the indole nitrogen was protected.

4.2.1 Behaviour of an *N*-methylated indole nucleophile in the *N*-acyliminium cyclisation

When we studied the scope of our primary method of the enantioselective *N*-acyliminium cyclisation cascade with enol lactones (described in chapter two), an *N*-methyl protected tryptamine was synthesised and the derived oxoamide was prepared (Scheme 4.1).

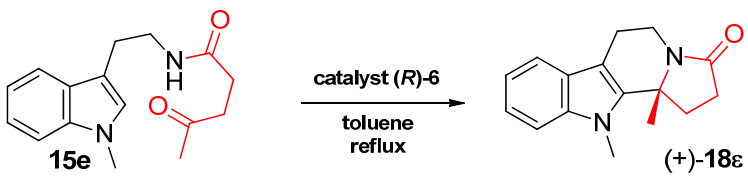


Scheme 4.1. Synthesis of an *N*-methyl protected precursor for cyclisation

A direct methylation of tryptamine **14a** using NaH in DMF as described by de Meijere[165] afforded *N*-methyl tryptamine **14h** in good yield (77%). The reaction of this *N*-methylated tryptamine with α-angelica lactone afforded the desired oxoamide **15e**, precursor for *N*-acyliminium cyclisation.

We hoped that the size of a small methyl group would have a negligible effect on the enantioselectivity during the cyclisation of **15e** into **18ε** under our optimal conditions. Actually, the presence of this methyl protecting group had a dramatic influence on the enantiomeric excess of the *N*-acyliminium cyclisation with a significantly decreased enantioselectivity being observed (Table 4.1).

Table 4.1. Study of the enantioselective cyclisation of **15e**

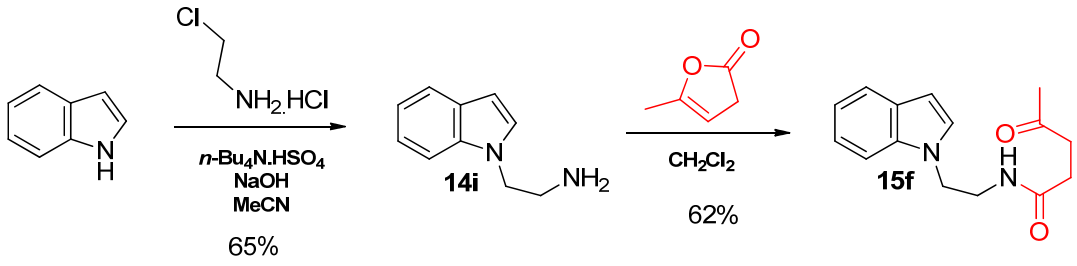


Entry	Catalyst	Yield (%)	e.e. (%)
1	(*R*)-**6f**	94	34
2	(*R*)-**6d**	89	23

Contrary to our initial hypothesis, the chiral phosphate seemed not only to act as a counter-ion, but also as a base or hydrogen-bond acceptor which would support models C and D. Our observation was supported by previously published studies that also postulated the presence of a hydrogen bonding interaction between the phosphate and the reaction partner. Notably in some studies, this interaction was crucial for high enantiocontrol.[13,17,72,90]

4.2.2 Probing the importance of hydrogen-bonding

To discriminate between a steric effect and hydrogen-bonding, a substrate for cyclisation having steric properties similar to **15a** but with no labile hydrogen was prepared. Instead of protecting the indole nitrogen, our strategy was to tether the oxoamide directly onto this nitrogen and not the indole C-3 (Scheme 4.2).



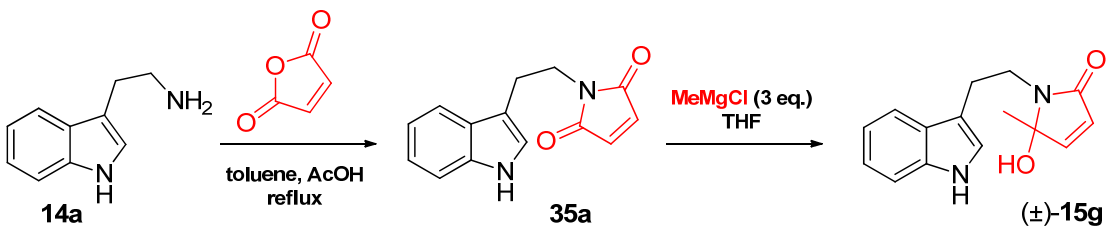
Scheme 4.2. Synthesis of a *N*-tethered oxoamide precursor for *N*-acyliminium cyclisation

14i was synthesised in a single step from indole and 2-chloroethylamine hydrochloric salt according to a literature procedure, in good yield (65%).[166] The precursor for cyclisation **15f** was prepared according to the standard procedure, treating the tryptamine with α-angelica lactone in dichloromethane (62%).

15f cyclised slowly (10 days) but cleanly in the presence of *p*-TsOH (racemate) at room temperature in dichloromethane. Surprisingly, when treated with catalyst (*R*)-**6f** under our optimised conditions, it led to extensive degradation and no desired tetracycle could be isolated. When **15f** was treated with catalyst (*R*)-**6f** in toluene at room temperature, it did not afford the expected fused heterocycle but a mixture of degradation products. All our efforts to promote an enantioselective *N*-acyliminium cyclisation with this substrate failed as it seemed too fragile to afford the product before degrading extensively. Unfortunately, these experiments did not allow us to differentiate between a possible steric effect and hydrogen-bonding. Nonetheless, based on our previous experiments with an *N*-methyl indole nucleophile and due to the peculiar behaviour of substrate **15f**, we postulated that a hydrogen-bonding was the most likely condition to observe high enantiomeric excess.

4.2.3 Unsaturated hydroxylactam precursor for *N*-acyliminium cyclisation

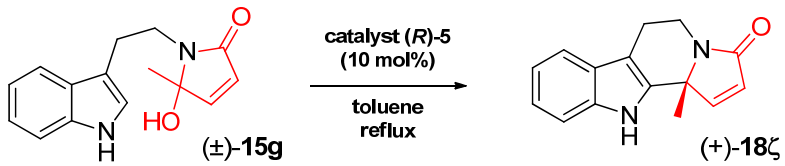
Of models C and D, the latter was particularly interesting since it would support both the necessary free N-H on the indole and the need for the presence of a labile hydrogen adjacent to the *N*-acyliminium carbon. That would explain why we observed the quick formation of enamides in the diastereo- and enantioselective cascades (*vide supra*). This model is supported by another experiment carried out to assess the scope. When a substrate identical to **15a** except for the presence of a conjugated amide (in its hydroxylactam cyclic form) was prepared (Scheme 4.3) and subjected to the optimal cyclisation conditions, only low enantioselectivities were achieved (Table 4.2).



Scheme 4.3. Synthesis of an unsaturated cyclic *N*-acyliminium precursor

(±)-**15g** was synthesised in an efficient two-step procedure from commercially available starting materials. Tryptamine **14a** was treated with maleic anhydride in a mixture toluene/acetic acid (1:2) at reflux. The resulting maleimide **35a** underwent a 1,2-addition by treatment with methyl magnesium chloride in tetrahydrofuran to give a stable hydroxylactam in good yield (69%).[130]

Table 4.2. Catalyst screening for the cyclisation of (±)-**15g**

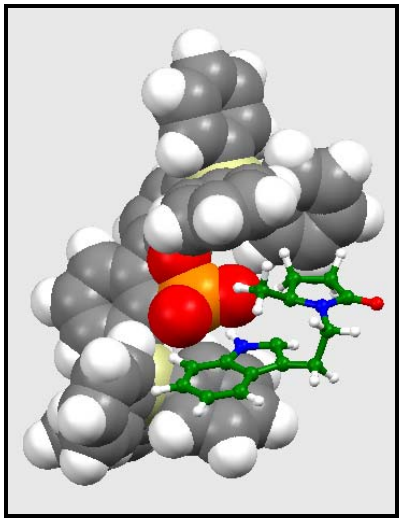


Entry	Catalyst	Yield (%)	e.e. (%)
1	(*R*)-**6f**	41	17
2	(*R*)-**6e**	50	17
3	(*R*)-**6d**	46	− 4
4	(*R*)-**6c**	38	0

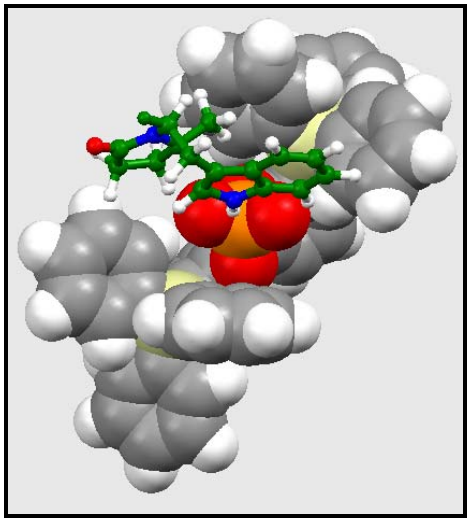
The highest enantioselectivity achieved in this cyclisation was 17% e.e, in the presence of (*R*)-**6e** or (*R*)-**6e**. Under the same conditions, when **15a** was treated with 10 mol% of (*R*)-**6f**, we observed the formation of (+)-**18a** in 84% e.e. If we assume the mechanism for the cyclisation remains unchanged, this result cannot be interpreted as a steric effect since (±)-**15g** and **15a** would have a similar size and only a hydrogen bonding effect can be invoked. It is thought that the presence of the unsaturation prevents the H-bond between the lactam moiety and the phosphate and therefore the mechanistic pathway for the reaction might differ in this case (going *via* different transition states). Model D would take into account all the previously discussed limitations; in particular it would account for the low enantioselectivities observed when no H-bond could be created between the catalyst and the nucleophile (indole N-H) and between the phosphate and the *N*-acyliminium ion (P=O---H-C).

4.2.4 Qualitative postulate for the transition structures

Based on our experiments, model D was adopted as it was supported by experimental data. With this model, it was possible to explain qualitatively why one of the enantiomers (most importantly the major enantiomer observed) was predominantly formed (Figure 4.2).



Disfavoured transition state with steric clash between the cyclic *N*-acyliminium ion and one of the TPS groups affording the (*S*)-enantiomer of **18a** (minor)



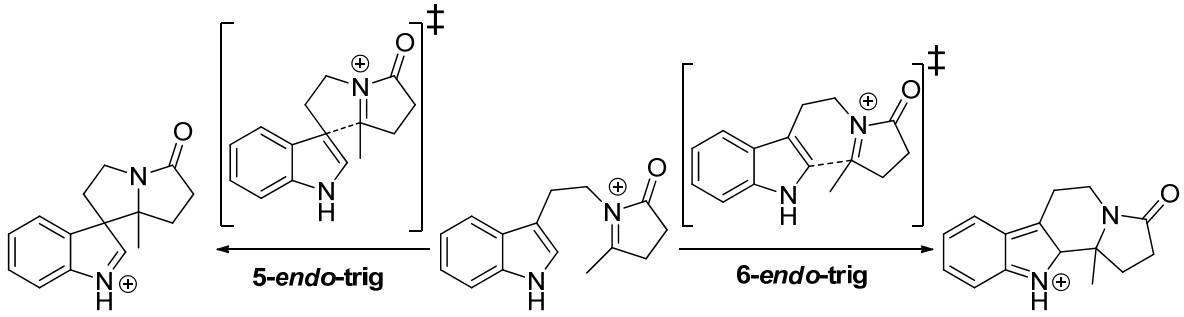
Favoured transition state with the cyclic *N*-acyliminium ion facing one of the sterically available sites giving the (*R*)-enantiomer of **18a** (MAJOR)

Figure 4.2. Representation of the favoured and disfavoured 3D models for the transition state during the cyclisation of **15a** into (*R*)-**18a**

4.3 Computational study: towards a quantitative model for the origin of enantioselectivity

4.3.1 Discussion on the mechanism of the cyclisation

Although thus far the *N*-acyliminium cyclisation has been considered to proceed through a 6-*endo*-trig mechanism, arguably it could also proceed *via* a 5-*endo*-trig pathway followed by [1,2]-alkyl shift (Scheme 4.4). It is of critical importance to know what the mechanistic pathway is, to be able to run high level calculations on this particular pathway. In addition, we can postulate that in the case of the 6-*endo*-trig mechanism, the rate-determining step and the enantiodetermining step are concurring. In the case of the 5-*endo*-trig mechanism, the enantiodetermining step is most probably the cyclisation step, however the rate-determining step can be either the cyclisation or the [1,2]-shift. The energies of the transition structures as well as intermediates for both pathways were computed (Scheme 4.4 and Figure 4.3)



Scheme 4.4. Calculated energies for the 5-*endo*-trig and 6-*endo*-trig pathways (with no counter-ion)

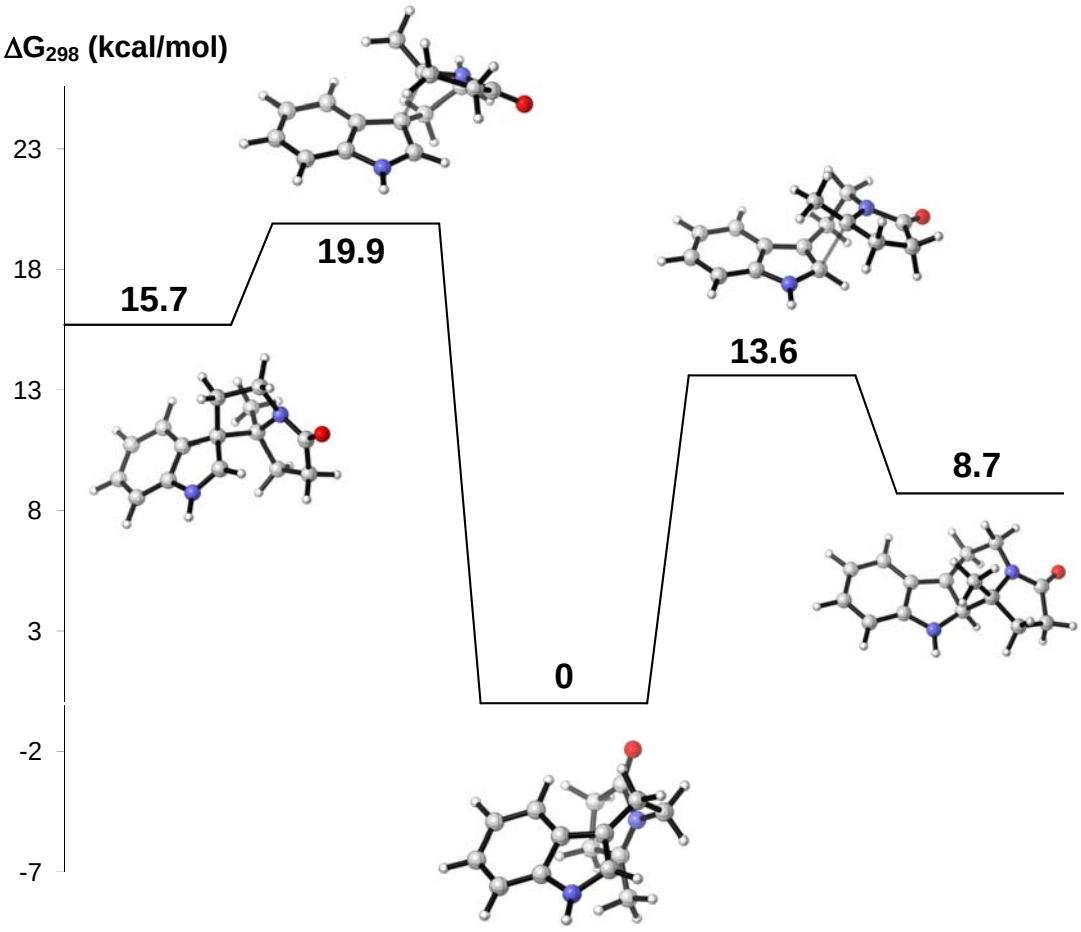


Figure 4.3. Energy diagram for the computed 5-*endo*-trig and 6-*endo*-trig pathways (with no counter-ion)

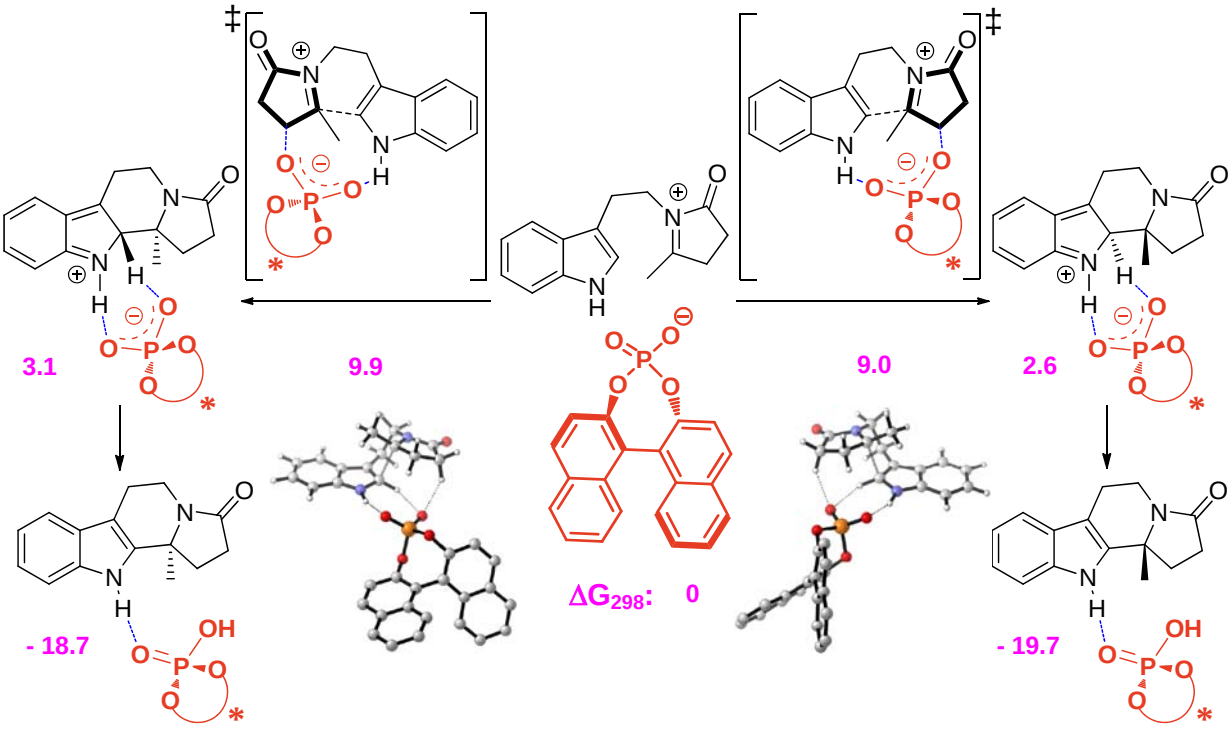
The difference of free energy calculated for the transition states involving a 5-*endo*-trig or 6-*endo*-trig cyclisation pathway is greater than 6 kcal/mol in favour of the 6-*endo*-trig mechanism. This difference of energy is significant, supporting a 6-*endo*-trig cyclisation as the sole reaction pathway. The mechanism featuring a 5-*endo*-trig cyclisation followed by [1,2]-shift thus can be discarded. Interestingly, Maresh and co-workers came to the same conclusion after a kinetic and computational study of the enzyme-catalysed Pictet-Spengler reaction of tryptamine and secologanine (synthesis of strictosidine catalysed by strictosidine synthase). Their study suggested that the difference of free energy between a spiroindolenine pathway (5-*endo*-trig) and a direct cyclisation at the 2-position (6-*endo*-trig) is greater that 4 kcal/mol for

their particular system; in addition their research for the [1,2]-shift transition-state from the spiroindolenine repeatedly resulted in the ring opening (back to the iminium).[167]

In conclusion, our study as well as the one published by Maresh *et al.* support a direct cyclisation at the 2-position *via* a 6-*endo*-trig pathway.

4.3.2 High level computation for our model system cyclisation through a 6-*endo*-trig pathway

The transition states leading to both enantiomers in the *N*-acyliminium cyclisation of **15a** were optimised and their free energies (relative to the *N*-acyliminium salt itself) were calculated in the case of the use of (*R*)-**6a** (Scheme 4.5 and Figure 4.4) and (*R*)-**6f** as catalyst (Scheme 4.6).



Scheme 4.5. Computed mechanistic pathways for the *N*-acyliminium cyclisation of **15a** catalysed by (*R*)-**6a**

Interestingly, for the cyclisation catalysed by (*R*)-**6a**, the difference of free energy between the two transition states is 0.9 kcal/mol (at 25 ºC) in favour of the transition state leading to the (*R*)-enantiomer, which would predict a 64% e.e. (*vide infra* for the calculations details).

More importantly, the energies computed in the presence of the phosphate counter-ion (it is actually more complex because the phosphate also provides stabilisation through hydrogen bonding, *vide infra*) are much lower than the one computed for the free *N*-acyliminium ion and subsequent intermediates and transition structures (*vide supra*, Scheme 4.3), which shows the beneficial effect of the presence of the phosphate (Figure 4.4).

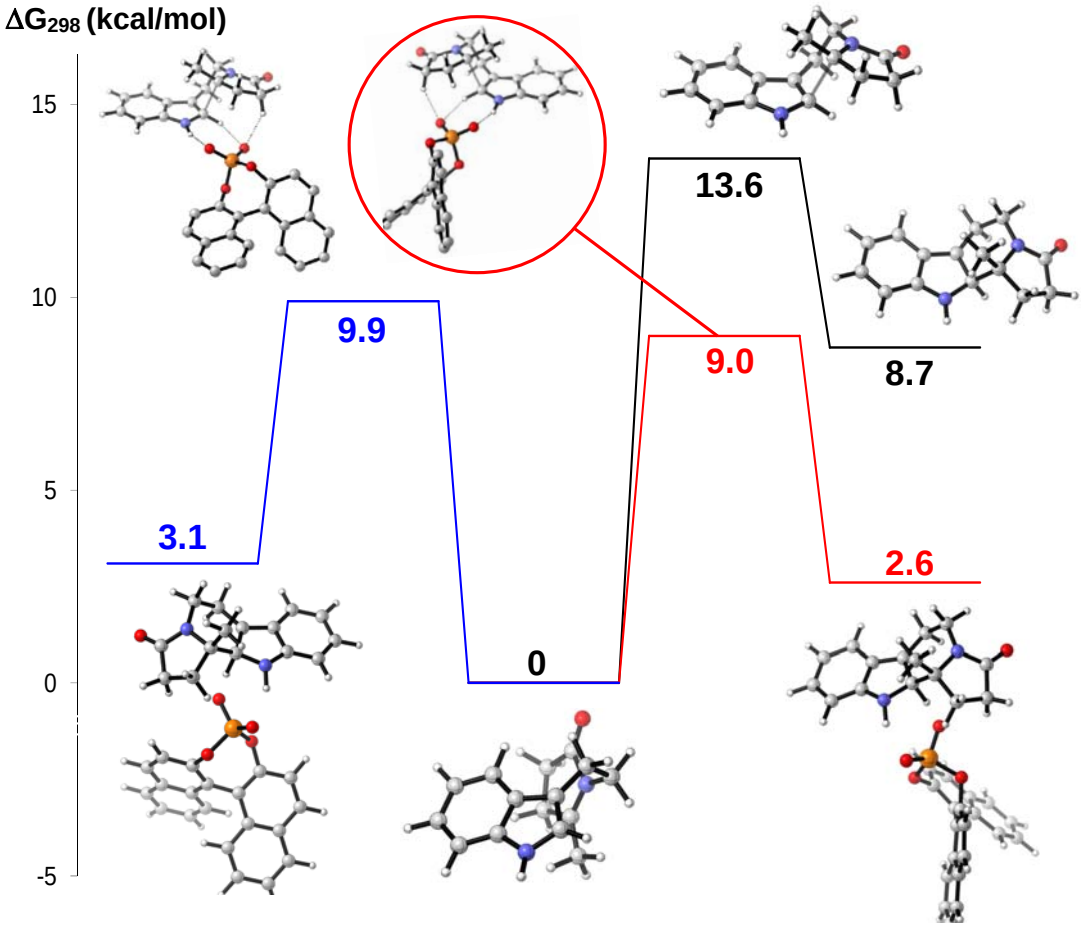
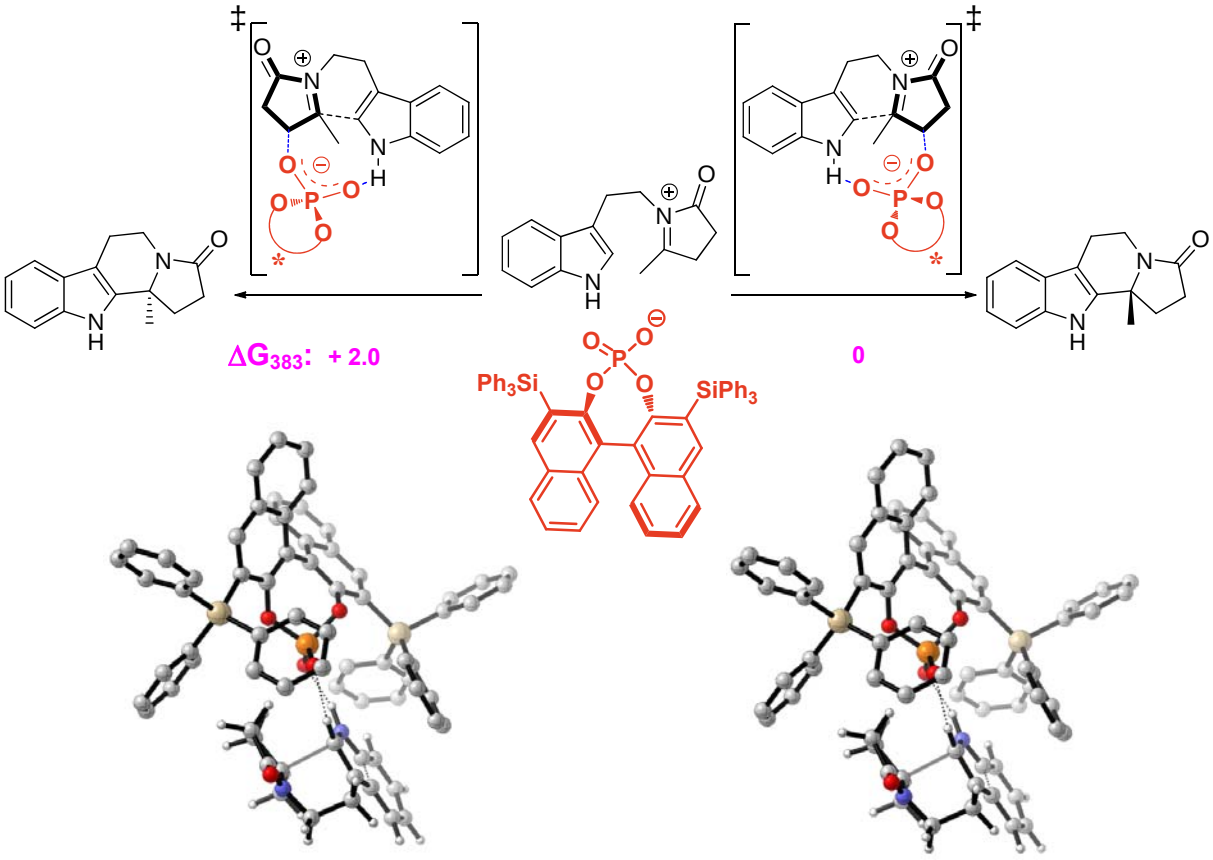


Figure 4.4. Energy diagram of the *N*-acyliminium cyclisation computed in the absence of counter-ion (black) and in the presence of (*R*)-**6a** (blue = formation of unfavoured (*S*)-enantiomer, red = formation of favoured (*R*)-enantiomer)

In the real system, because the size of the catalyst is prohibitive, only the transition structures were modelled, optimised and their free energies calculated (Scheme 4.6).



Scheme 4.6. Relative free energies of the transition states for the 6-*endo*-trig cyclisation of **15a** catalysed by (*R*)-**6f**

The difference of free energy between the favored transition state and its disfavoured counterpart was computed and equal to ΔG_{calc} = 2.0 kcal/mol. To calculate the theoretically observed enantiomeric excess, the relative free energies of both transition structures were used in the Eyring-Polanyi equation: $k = \frac{k_B T}{h} e^{-\frac{\Delta G}{RT}}$.

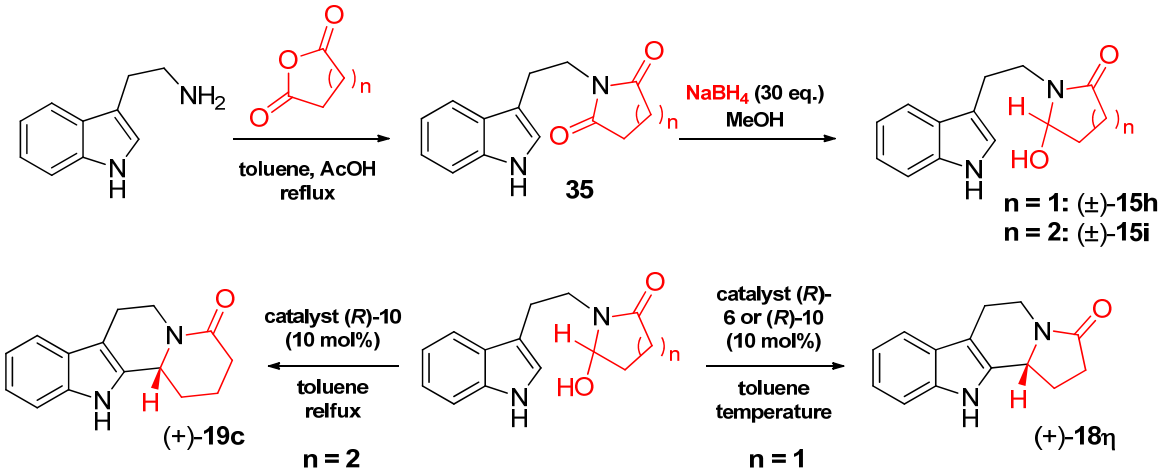
That translates to the (*R*)-enantiomer $k_R = \frac{k_B T}{h} e^{-\frac{\Delta G_R}{RT}}$ and (*S*)-enantiomer $k_S = \frac{k_B T}{h} e^{-\frac{\Delta G_S}{RT}}$.

Therefore, $\frac{k_R}{k_S} = \frac{\frac{k_B T}{h} e^{-\frac{\Delta G_R}{RT}}}{\frac{k_B T}{h} e^{-\frac{\Delta G_S}{RT}}} = e^{\frac{\Delta G_S - \Delta G_R}{RT}} = e^{\frac{\Delta G_{calc}}{RT}} = 13.845$ this means that $k_R(rel)$ = 13.845

while $k_S(rel)$ = 1, in other word we should observe a mixture of 93% of (*R*)-**18a** and 7% of (*S*)-**18a**, the selectivity that would be observed for the cyclisation of **15a** into **18a** in refluxing toluene should be 86% e.e. and it matches almost perfectly the experimental datum (84% e.e.).

4.3.3 Limitations of the *N*-acyliminium cyclisation methods compared to our model

One of the major limitations that we came across during our studies was the low enantioselectivities obtained during the cyclisation of substrates leading to β-carbolines having a proton at the stereogenic centre. Many efforts have been made to optimise the reaction conditions for these particular substrates, although they remained unsuccessful (Scheme 4.7).

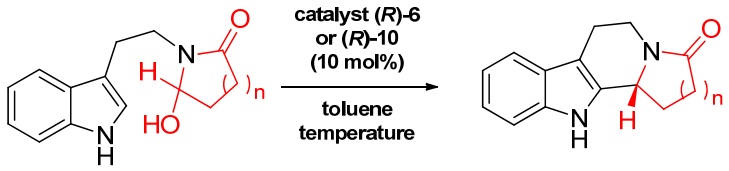


Scheme 4.7. Synthesis of hydroxylactams *via* reduction of cyclic imides and their *N*-acyliminium cyclisations

The precursors for cyclisation (±)-**15h** and (±)-**15i** were synthesised in two steps from tryptamine and a cyclic anhydride (reflux in toluene/acetic acid for 24-96 hours). The intermediate cyclic imides **35b** and **35c** were converted to the hydroxylactams *via* reduction with sodium borohydride in anhydrous methanol in high yield (75-97%).[130]

The precursors were then treated with a range of acids in toluene (reflux or room temperature) to assess the enantioinduction in these cyclisations (Table 4.3).

Table 4.3. *N*-acyliminium cyclisations of hydroxylactams (±)-**15h** and (±)-**15i**



Entry	n	Catalyst	Temperature	Yield (%)	e.e. (%)
1	1	(*R*)-**10a**	Reflux	42	39
2	1	(*R*)-**6e**	Reflux	88	26
3	1	(*R*)-**6k**	Reflux	99	32
4	1	(*R*)-**6l**	Reflux	80	25
5	1	(*R*)-**10a**	25 °C	99	15
6	2	(*R*)-**10a**	Reflux	92	49

As shown in Table 4.3, the highest enantiomeric excess observed for (+)-**18η** was 39% which can be compared to the 84% e.e. observed in the case of the parent β-carboline bearing a methyl group at the quaternary centre ((+)-**18a**). This significant decrease in enantioselectivity was also observed for a 6-membered ring example, although to a lesser extent, (+)-**19c** being formed in 49% e.e. compared to 71% e.e. for (+)-**19a**.

Unfortunately, the model that has been described above cannot explain this observation qualitatively. In the cyclisation transition states, the group on the *N*-acyliminium carbon and the catalyst are slightly interacting in the favoured transition state whereas they seem to be far apart

in the disfavoured transition state. In this context and considering only steric effects, having a proton instead of the methyl group should slightly increase the enantiomeric excess observed. What we observe is a significant decrease of enantioselectivity that might therefore be interpreted as an electronic effect. This could be supported by the increase in enantioselectivity observed for the series H < Me < Ph likely due to more stable *N*-acyliminium ions (see Chapter 2). To ascertain this hypothesis, high level calculations for all these systems would be key and will constitute our future work to fully understand this transformation.

4.4 Conclusion

In collaboration with Dr. Paton, we have been able to establish a qualitative and quantitative model to explain the origin of the enantioselectivity observed in our *N*-acyliminium cyclisation cascades. Our quantitative model, computed for the system used for the optimisation study (see chapter two) and the experimental data were in good agreement. Our model is supported by experimental evidence, however further calculations might be needed to gain a greater understanding of all the factors essential for high enantioselectivity. To date, high level calculations on a 6-membered ring lactam system have not been performed, however, it is postulated that the decrease in enantioselectivity observed between (+)-**18a** and (+)-**19a** (84% and 71% e.e. respectively) is likely due to a less favourable spatial organisation for the 6-membered ring. This could be either the consequence of a different steric hindrance on the *N*-acyliminium ion or a weaker hydrogen bonding effect (alignment of orbitals not as favourable).

Chapter Five:

Development of new chiral benzenesulphonic acids: chiral mimics of *para*-toluenesulphonic acid

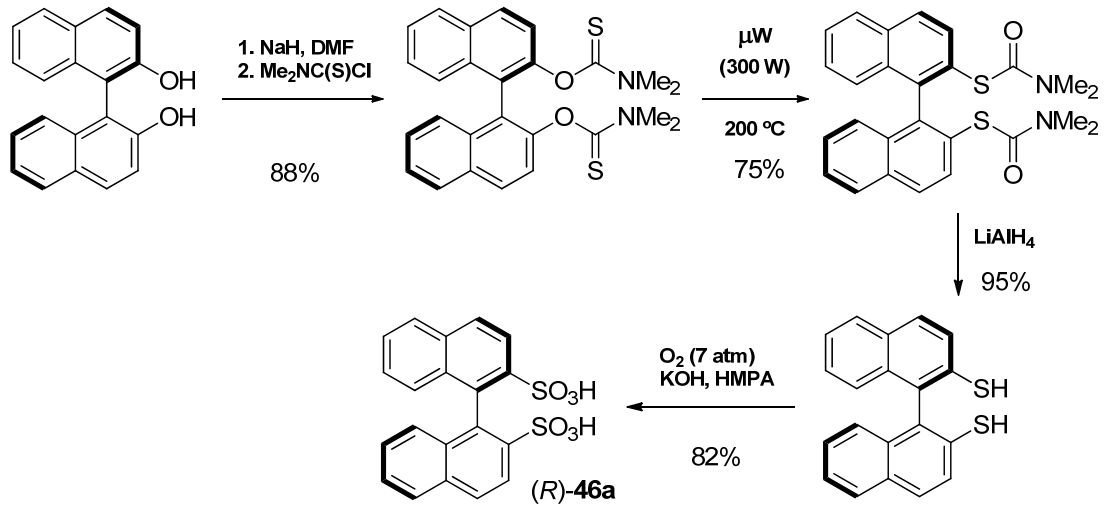
5.1 Overview on the synthesis and use of chiral sulphonic acid derivatives

Over the past decade, BPAs have proved to be very versatile catalysts, promoting a variety of acid-catalysed organic reactions.[168] Although few examples have displayed a direct activation of enones or the formation of a stabilised carbocation (see general introduction), BPAs have been mainly used to activate imines. Now with our new methodologies the scope of these acids has been extended to the formation of chiral *N*-acyliminium salts. The lack of examples on substrates other than imines is a clear limitation of these acids, which is likely due to their moderate acidity (pKa ~ 1 in water[169]). In light of this observation, it was decided that the development of a new class of stronger Brønsted acids could prove beneficial. Naturally, the creation of chiral mimics of *para*-toluenesulphonic acid (pKa ~ − 4 in water) was envisaged as this would provide a new entry to stronger chiral Brønsted acids.

The first successful synthesis of non-racemic sulphonic acid has been reported already in 1957.[170] Amarego and Turner successfully performed the resolution of a complex of racemic 1,1′-binaphthyl-2,2′-disulphonic acid (BINSA) with (−)-strychnyne and isolated the highly enantiomerically enriched (+)-BINSA sodium salt and (−)-BINSA sodium salt. They operated further transformations on these intermediates but never assessed their catalytic power or enantiomeric induction.

5.1.1 Recent progress on the synthesis of advanced chiral sulphonic acids

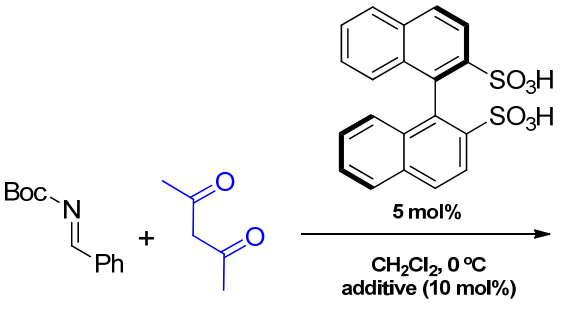
Despite this early work on the production of an optically active arylsulphonic acids, new methods to produce such compounds from enantiomerically pure precursors have only emerged in the past couple of years. Ishihara *et al.* developed an efficient route to synthesise optically pure BINSA from the corresponding single enantiomer of BINOL (Scheme 5.1).[171]



Scheme 5.1. Ishihara *et al.*'s synthesis of enantiomerically pure (*R*)-BINSA (*R*)-**46a**

Their synthesis displayed a microwave-promoted Newman-Kwart rearrangement followed by reduction to release optically pure 1,1′-binaphthalene-2,2′-thiol. The latter was converted to the desired sulphonic acid in the presence of oxygen in a pressurised vessel.

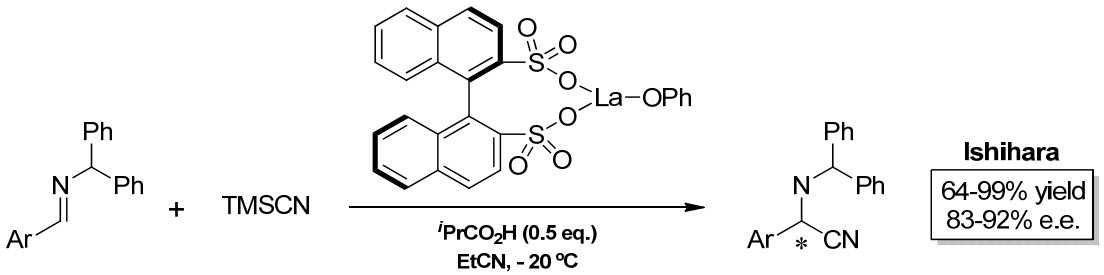
Interestingly, although (*R*)-BINSA efficiently catalysed the Mannich reaction of *N*-Boc benzaldimine with acac, only a poor level of enantioselectivity was achieved. The key to high enantioselectivity lied in the use of organic salts of BINSA. Several substituted pyridines were combined with (*R*)-BINSA and 2,6-di-*tert*-butylpyridine was found to be optimal in this reaction and gave a 92% e.e. (Scheme 5.2).



Additive	Yield (%)	e.e. (%)
-	81	17
C_5H_5N	8	5
2,6-^{t}Bu$_2$-C_5H_3N	32	76
2,6-Ph$_2$-C_5H_3N	74	92

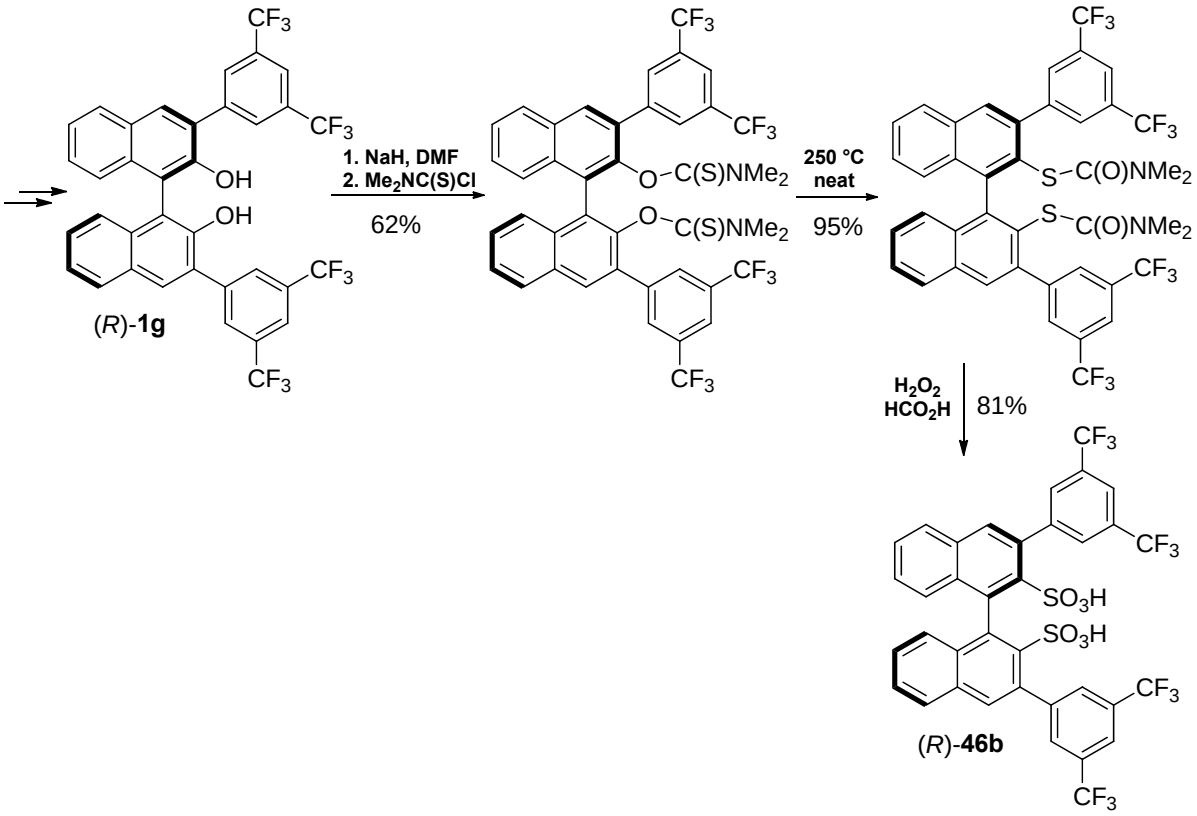
Scheme 5.2. (*R*)-BINSA/substituted pyridine salt-catalysed enantioselective Mannich reaction

The use of a metal complex with the dianion of BINSA also led to interesting results in the Strecker reaction of a protected imine.[172] A La(III)-BINSA complex was proved to efficiently catalyse the addition of TMS-CN across protected imines, with enantioselectivities ranging from 82% e.e. to 93% e.e. (for aromatic aldimines, Scheme 5.3).



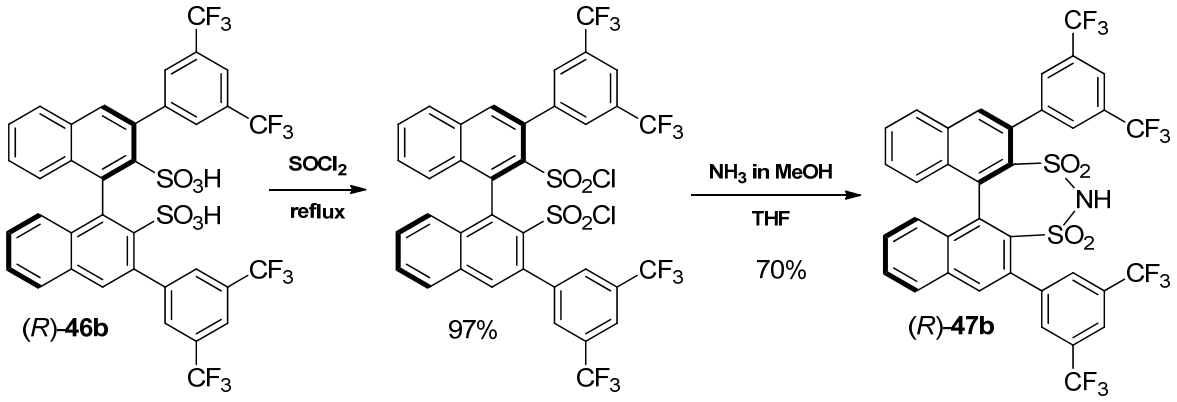
Scheme 5.3. Ishihara *et al.*'s BINSA-La(III) catalysed enantioselective Strecker reaction

More recently, List and co-workers described the synthesis of a 3,3′-substituted BINSA starting from the enantiomerically pure substituted BINOL precursor, through an improved route to the sulphonic acid. Instead of the previous microwave-promoted Newman-Kwart rearrangement, List and co-workers opted for a traditional thermal Newman-Kwart rearrangement and enhanced the overall route by omitting the reduction step and oxidising the thiocarbamate directly to the sulphonic acid using hydrogen peroxide/formic acid (Scheme 5.4).[173]



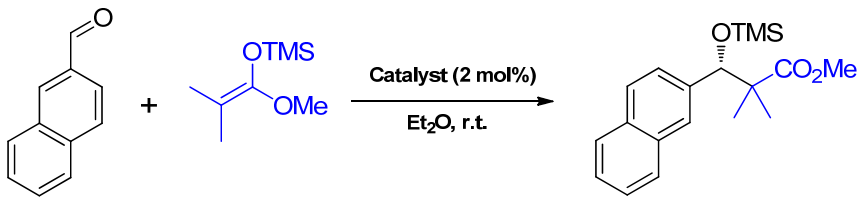
Scheme 5.4. List *et al.*'s synthesis of 3,3′-substituted BINSA

Interestingly, they found that this very acidic catalyst (*R*)-**46b** was unable to catalyse a Mukaiyama aldol reaction, whereas its disulphonimide derivative (*R*)-**47b** was a very efficient catalyst (Scheme 5.5, Table 5.1).



Scheme 5.5. List *et al.*'s synthesis of 3,3′-substituted BINSA disulphonimide (*R*)-**47b**

Table 5.1. 3,3′-substituted BINSA disulphonimide catalysed Mukaiyama aldol reaction



Entry	Catalyst	Yield (%)	e.e. (%)
1	(*R*)-**6d**	< 2	-
2	(*R*)-**7d**	< 2	-
3	(*R*)-**46b**	< 2	-
4	(*R*)-**47b**	> 99	80

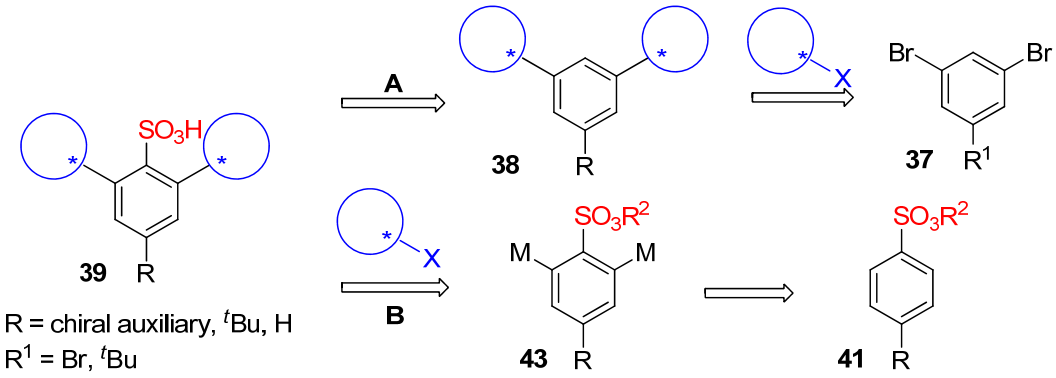
Although these recent examples demonstrated the potential of the BINSA scaffold and should be regarded as exemplary in the field of organocatalysis, they failed to show a direct catalysis of the free sulphonic acid with high enantioselectivity.

5.1.2 Aim of the project

Our project started prior to this newly developed chemistry of BINSA and derivatives. With a different approach, we envisaged to develop novel and robust routes towards new families of chiral sulphonic acids. Our aim was to focus on the synthesis of chiral mimics of toluenesulphonic acid and on the evaluation of their enantioinduction. Research in this area had been carried out in collaboration with Dr. Pavol Jakubec, with some success on new approaches to benzenesulphonic acids. Optimising the synthetic route to these acids as well as synthesising a library of structurally varied catalysts was our prime goal. The assessment of their potential for enantioinduction in benchmark reactions was also essential as a proof of concept.

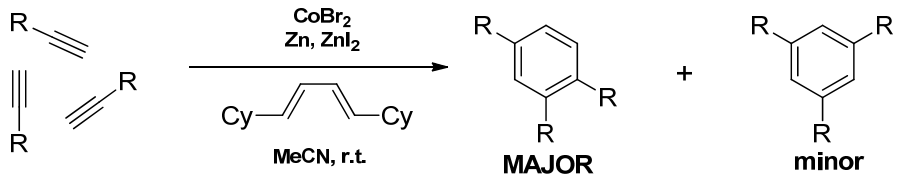
5.2 Background study towards the synthesis of new chiral benzenesulphonic acids

Two distinctive strategies were designed for the synthesis of novel chiral benzenesulphonic acids. The first strategy consisted in grafting chiral auxiliaries derived from amino acids to a benzene core and subsequently introducing the sulphonic acid functionality regioselectively. In the second strategy, the directing group properties of a sulphonate would be used to attach chiral auxiliaries presenting no heteroatom to the benzenesulphonate core regiospecifically (Scheme 5.6).



Scheme 5.6. Retrosynthetic analyses of a chiral benzenesulphonic acid

In strategy **A**, another route was first envisaged to reach **38**. In theory, the cyclotrimerisation of alkynes would enable the trisubstituted benzene core to be accessed. Unfortunately, literature precedent[174,175,176] and preliminary studies revealed that the unsymmetrical 1,2,4-trisubstituted benzenes were the predominant products in mixtures with the minor desired 1,3,5-trisubstituted benzenes (when bulky terminal alkynes were used, Scheme 5.7).



Scheme 5.7. General strategy envisaged for the cyclotrimerisation of alkynes into substituted arenes

It was therefore decided that the synthesis would be carried out with a suitably substituted arene cross-coupling partner **37** to remove any regioselectivity issues (Scheme 5.6, path **A**). With this approach, the chiral scaffold could be formed in a single step and would subsequently undergo the sulphonation. Three parameters were taken into account for the choice of the arene cross-coupling partner:

- the ease of access to a library of a family of chiral auxiliaries was our first concern.
- the availability of suitably substituted arenes, either from commercial sources or in few steps from commercially available chemicals was essential.
- the potential catalysts and the robustness (reliability, reproducibility) of the coupling method was also crucial.

Fortunately, copper-catalysed Ullmann-type couplings of aryl halides with chiral oxazolidinones were well-precedented in the literature and became our main focus to establish a route to **38**.[177] Substituted enantiomerically pure oxazolidinones **36** were commercially available or easily accessible from aminoacids. Their use in a copper-catalysed modern Goldberg-type coupling would afford C_3 and C_2 symmetrical *N*-aryloxazolidinones in a single operation. With these suitably electron-rich chiral scaffolds **38**, the application of a modified procedure for chlorosulphonation in an S_EAr reaction of 1,3,5-trisubstituted benzene would directly provide the desired chiral sulphonic acid (no hydrolysis needed unlike previously observed).[178] Our short 2-step synthesis of novel chiral sulphonic acids allowed us to produce significant quantities of a series of catalysts.

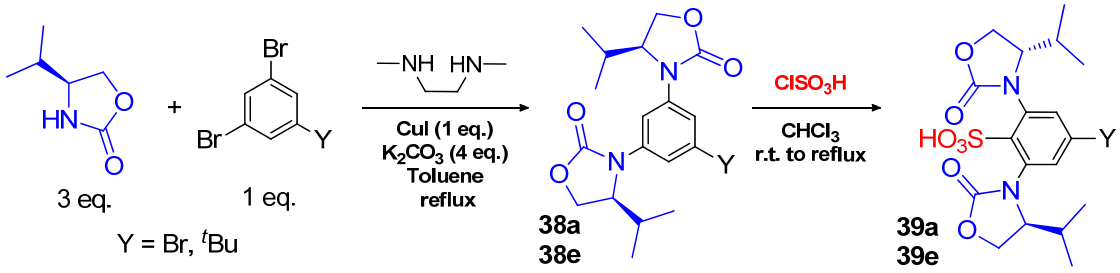
The second approach (path **B**) to the synthesis of new chiral benzenesulphonic acids relied upon the efficient tethering of an all-carbon chiral auxiliary (derived from the chiral pool) to suitable benzenesulphonates. Our plan was to take advantage of the directing properties of the sulphonate group to metallate the *ortho* position (Snieckus *ortho*-metallation[179]) and perform a subsequent cross-coupling with a suitable auxiliary derivative. Naturally abundant ketones such

as camphor and menthone/carvone were starting materials of choice for our study. In a single operation it would be possible to synthesise a cross-coupling partner (triflate). If the operation was to be repeated, it would afford a protected benzenesulphonic acid (ester) substituted at the 2- and 5- position by chiral auxiliaries.

5.3 First generation synthesis towards oxazolidinone-derived benzenesulphonic acids

5.3.1 Proof of principle

Two chiral benzenesulphonic acids were prepared following the aforementioned general strategy (Scheme 5.8)



Scheme 5.8. Proof of principle for the synthesis of chiral benzenesulphonic acids *via* strategy **A**

The synthesis of the *N*-aryloxazolidinone derivatives was achieved through a Goldberg-type coupling using a substoichiometric amount of copper iodide in conjunction with excess potassium carbonate and a catalytic amount of diamine.[180] The mixture was heated to reflux for 6 hours and the products isolated in 60-82% yield. The subsequent sulphonation was achieved with 17 equivalents of chlorosulphonic acid in chloroform at reflux (45-80% yield). Both acids were produced in minute quantities (< 50 mg). Interestingly, for **38e**, only the sulphonation at the least hindered position was observed to form **39e**, the ^{t}Bu group directing it through its steric bulk.

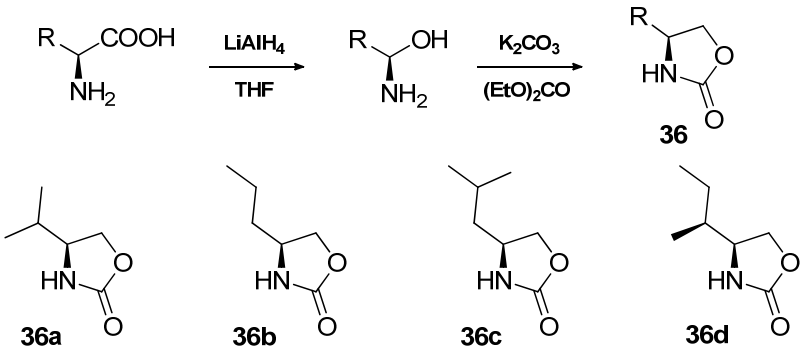
This proved that benzenesulphonic acids could be formed following this route. To be able to prepare a library, we wanted to optimise the conditions for each step.

5.3.2 Optimisation of the first generation synthesis of chiral oxazolidinone-derived benzenesulphonic acids

We aimed at synthesising a range of oxazolidinones, from amino acids (natural and unnatural), and optimise the Goldberg-type coupling to reliably achieve high yields. The chlorosulphonation proved to be an efficient method to synthesise the sulphonic acid, nonetheless, it was felt that using 17 equivalents of chlorosulphonic acid was certainly not necessary and optimisations could be implemented in this step as well.

5.3.3 Expedient synthesis of oxazolidinones from L-amino acids

The chiral oxazolidinones were synthesised in two steps from the commercially available amino acids. A reduction with LAH afforded the amino alcohol in essentially quantitative yield (lower yield for volatile amino alcohols).[181,182,183] The amino alcohols were used without purification and treated with diethylcarbonate in the presence of potassium carbonate, heating at 130 ºC and distilling off the ethanol formed during the reaction.[183,184] The chiral oxazolidinones were isolated in 38-89% yield after purification by column chromatography on silica gel or crystallisation (Scheme 5.9).

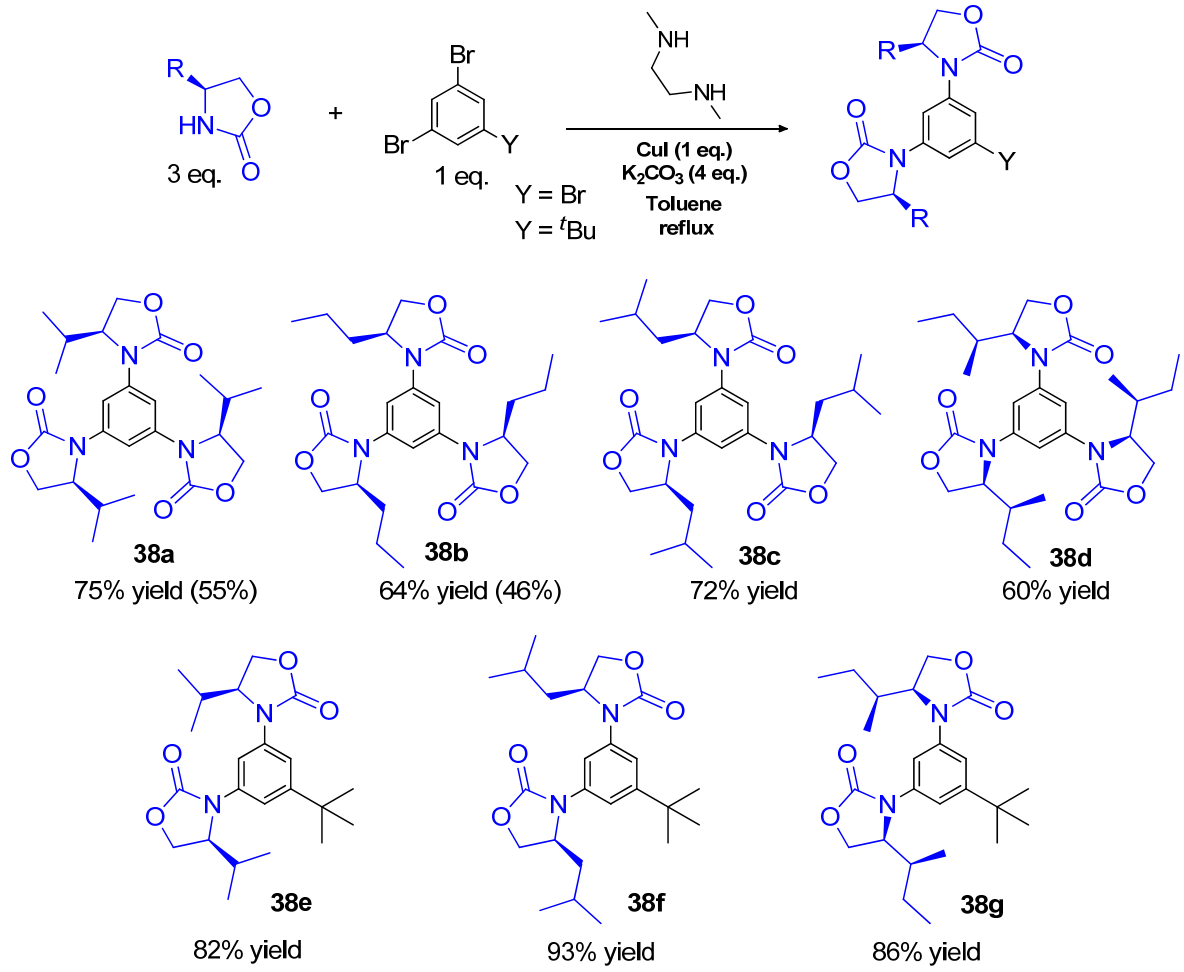


Scheme 5.9. Synthetic route to chiral oxazolidinones and synthesised library

The method was generally high yielding after chromatography. However, if purification was conducted by crystallisation, the yields were generally lower. This method was a robust and quick approach for the synthesis of natural or unnatural amino acid-derived oxazolidinones.

5.3.4 Optimisation of the Goldberg-type coupling

The method previously used for the proof of principle gave satisfactory yields, thus the same reagents were used in the optimisation studies. A slight improvement consisted in heating the reaction to reflux for 24 hours and adding supplementary amounts of catalyst, base, amine and oxazolidinone until full disappearance of the starting aryl halide (typically 1 equivalent of oxazolidinone was added as well as 1 equivalent of base, 0.3 equivalents of potassium carbonate and amine and further reflux for 24 hours). The *N*-aryloxazolidinones were isolated after column chromatography on silica gel in 60-93% yield (Scheme 5.10).



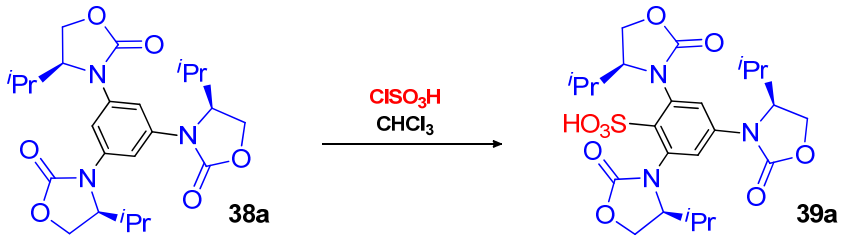
Scheme 5.10. Synthesis of a library of *N*-aryloxazolidinones

38b was recrystallised on 1.55 g scale (64% yield) to recover 1.12 g of pure material (46% yield). Seven *N*-aryloxazolidinones were synthesised, four presented a C_3 symmetry (circumventing any regioselectivity issue during the subsequent sulphonation) and three presenting a C_2 symmetry. It was hoped that the size of the ^{t}Bu group would prevent the sulphonation *ortho* to this group and that only the sulphonation *ortho* to both oxazolidinones would be observed (*vide supra*).

5.3.5 Optimisation of the sulphonation

In theory, a single equivalent of chlorosulphonic acid should be sufficient to efficiently form the sulphonic acid from the *N*-aryloxazolidinones. In previous reports of this type of reaction, two equivalents[185] to large excesses of chlorosulphonic acid were used either in solution[186] or neat.[187,188] It was felt that using 17 equivalents of this highly corrosive and toxic chemical was not necessary. A study was performed to determine the optimal number of equivalents of chlorosulphonic acid to have a satisfactory reactivity using the least amount of the reagent (Table 5.2).

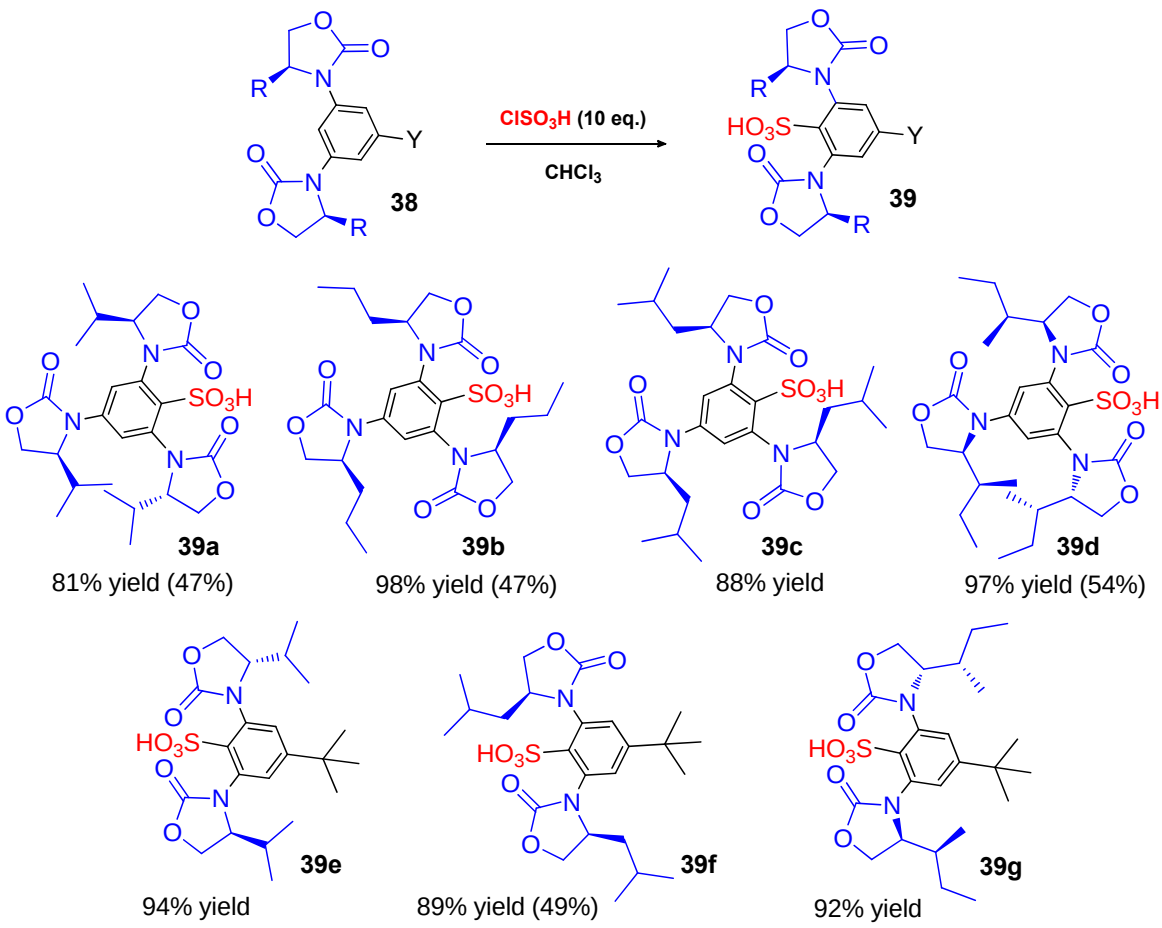
Table 5.2. Optimisation of the sulphonation of *N*-aryloxazolidinone **38a**



Entry	Eq. of $ClSO_3H$	Solvent	Observation	Yield (%)
1	17	$CHCl_3$	Full conversion after 24 hours	45%[a]
2	1	$CHCl_3$	Poor conversion after 24 hours	-
3	5	$CHCl_3$	Incomplete conversion after 24 hours	47%[b]
4	10	$CHCl_3$	Full conversion after 48 hours	81%[b] (47%[a])

[a] After recrystallisation from acetonitrile; [b] Isolated after column chromatography

The use of 10 equivalents of chlorosulphonic acid seemed to be a good compromise between reactivity (speed and conversion) and a clean/atom-economic process. Therefore, this method was used to generate the library of catalysts (Scheme 5.11).



Scheme 5.11. Library of new oxazolidinone-derived chiral benzenesulphonic acids

Seven acids were prepared with this method (five novel acids and the two acids prepared during the proof of principle study reprepared in quantities greater that 450 mg). The sulphonation was essentially a quantitative step, purification was tedious and recrystallisation was needed in most cases to obtain an analytically pure catalyst for our studies.

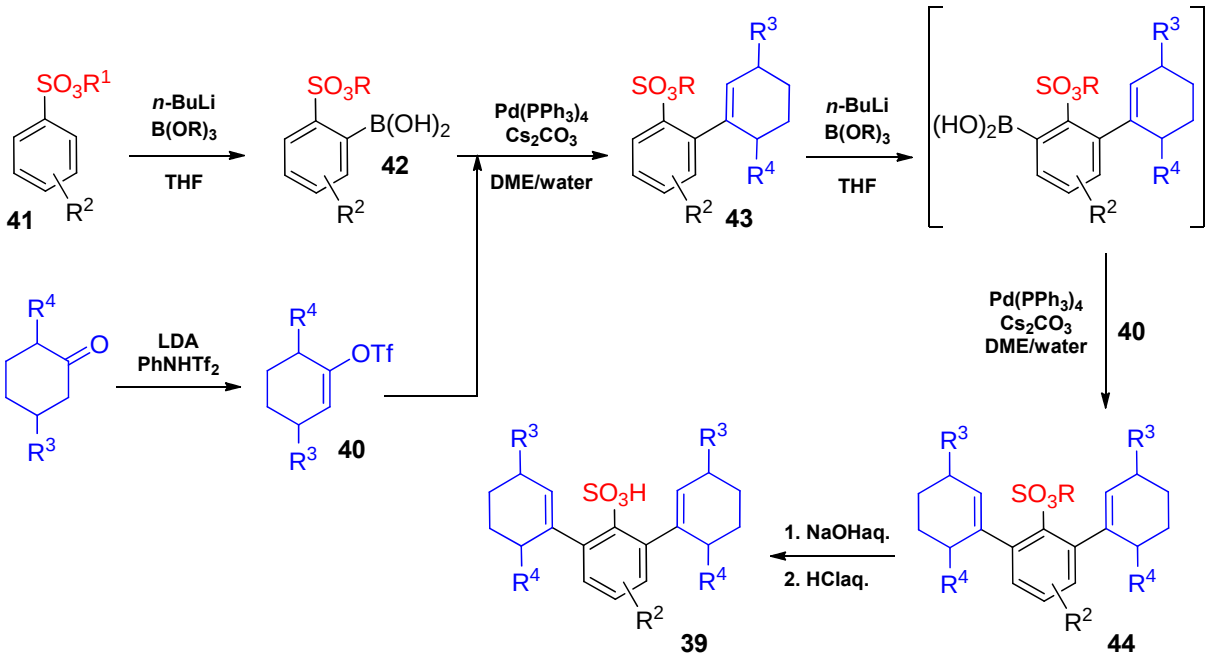
Notably, the leucine-derived catalysts were rotameric at room temperature. This was an interesting result as it meant that free-rotation would be altered, in agreement with a strong steric bulk around the sulphonic acid moiety. Thus, our aim was at least partially achieved by

synthesising benzenesulphonic acids presenting steric bulk *ortho* to the acid functionality as proved by their rotameric nature.

5.4 Development of a second generation of chiral benzenesulphonic acids

In our second strategy, we envisaged to *ortho*-lithiate a benzenesulphonate[179a,189,190] (masked benzenesulphonic acid) and subsequently quench this anion with a borate.[191,192] After hydrolysis, the isolation of the boronic acid would provide a suitable Suzuki-Miyaura cross-coupling partner. The triflation of camphor or menthone enol ethers using precedented literature procedures[179b,193,194] would afford the second Suzuki-Miyaura cross-coupling partner.

The whole strategy relied on the efficiency of the key cross-coupling reaction between the synthesised boronic acid(s) and triflate(s).[179b] Iteration of the same strategy would allow the formation of a symmetrically substituted benzenesulphonate which would only require hydrolysis in alkaline conditions to afford the designed chiral sulphonic acid (Scheme 5.12).



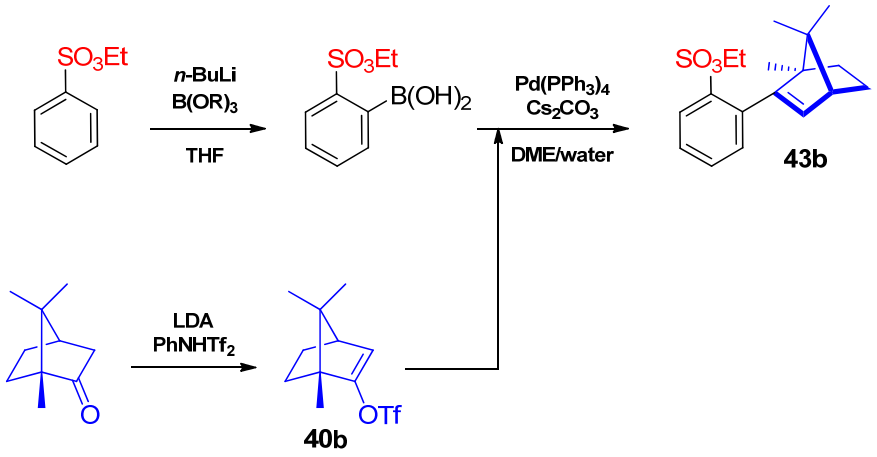
Scheme 5.12. Synthetic plan for the second generation chiral benzenesulphonic acids

5.4.1 Early stage synthesis and scale-up

The synthesis of ethyl benzenesulphonate boronic acid was carried out using *n*-BuLi in tetrahydrofuran, quenching with triethyl borate. The free boronic acid was obtained after hydrolysis in the presence of dilute aqueous hydrochloric acid (1M to 2M). The reaction was performed on 0.5 g to 10.5 g scale.

The preparation of camphor-derived enol triflate was straightforward by deprotonation of D-camphor with LDA in tetrahydrofuran and subsequent quench with *N*-Phenyl-trifluoromethanesulfonimide. The pure product was isolated after purification by chromatography on silica gel. It was typically synthesised on 1.0 g to 3.8 g.

The two fragments were attached via a classical Suzuki-Miyaura cross-coupling, in standard conditions[195] (tetrakis triphenylphosphine palladium(0) / cesium carbonate / mixture DME/water) using an excess of the boronic acid. Intermediate **43b** was prepared on up to 6.1 g scale (Scheme 5.13).

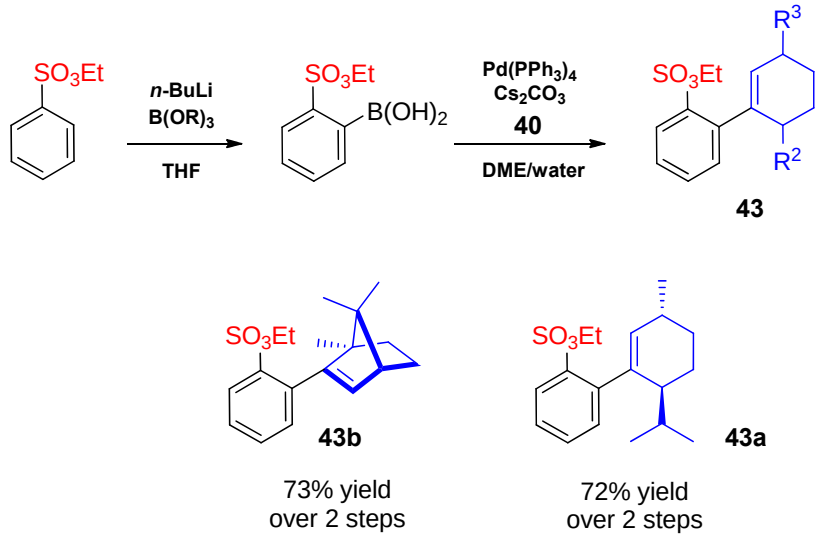


Scheme 5.13. Synthesis of intermediate benzenesulphonate **43b**

5.4.2 Late stage intermediate synthesis and novel chiral benzenesulphonic acids synthesis

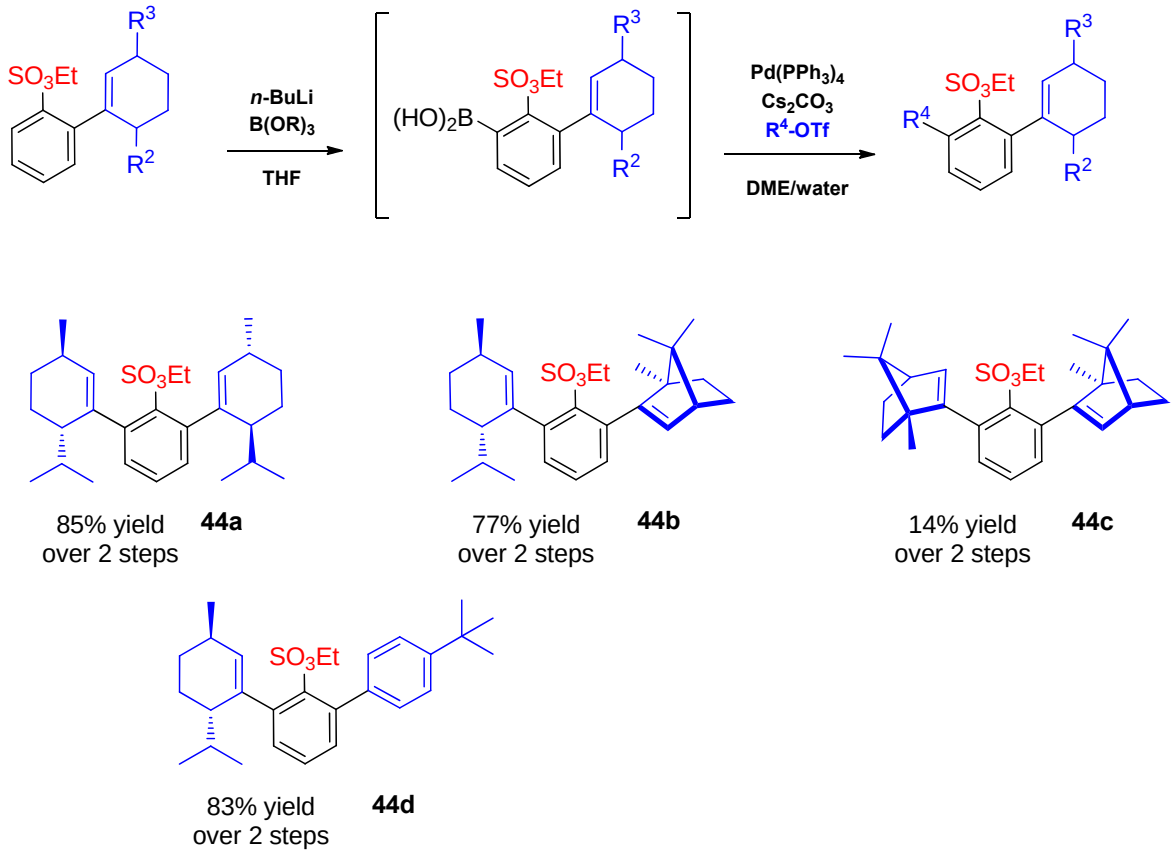
5.4.2.1 Late stage intermediates synthesis

Two substituted benzenesulphonate derivatives were synthesised following the aforementioned route (Scheme 5.14).



Scheme 5.14. Synthesis of benzenesulphonates **43**

Although the first lithiation/boronic acid synthesis/Suzuki-Miyaura cross coupling reaction proved to work in high and reliable yields. The second iteration was more challenging from a reactivity point of view. The lithiation/boronic acid synthesis usually proceeded in quantitative yield, however the cross-coupling showed a high dependence on the substrate and its steric bulk (Scheme 5.15).



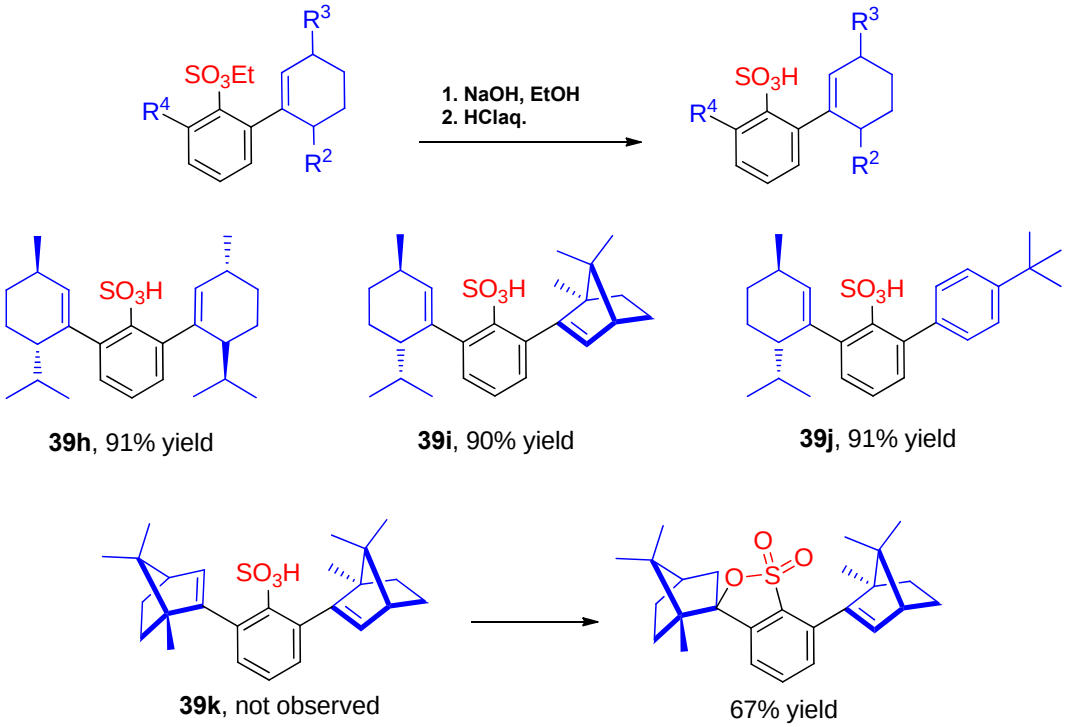
Scheme 5.15. Synthesis of symmetrical or unsymmetrical disubstituted benzenesulphonates

This route allowed us to synthesise four disubstituted benzenesulphonates in low to excellent yields. Notably, although this strategy is appealing to synthesise large libraries of catalysts, it still required optimisation work for low yielding cross-coupling and most importantly a higher reliability (more cross-couplings were performed, in some cases this led to products that could not be purified by classic and scalable methods).

5.4.2.2 Synthesis of the free chiral benzenesulphonic acids

The sulphonate ester was hydrolysed in alkaline conditions (reflux in ethanol). The free acid was formed by acidification with aqueous hydrochloric acid. Interestingly, due to the lypophilic nature of the chiral auxiliaries, these acids were highly soluble in organic solvents and it was easy to extract them in diethyl ether. Unfortunately, an unanticipated reactivity interefered with

our original plan. During the hydrolysis or acidification, in some cases, the free sulphonic acid or sulphonate ion was able to cyclise (*via* Markovnikov addition) on the auxiliary unsaturation (especially observed in the case of camphor-derived auxiliaries) leading to the formation of a cyclic sulphonate that could not be hydrolysed and was inert to various treatments (Scheme 5.16).



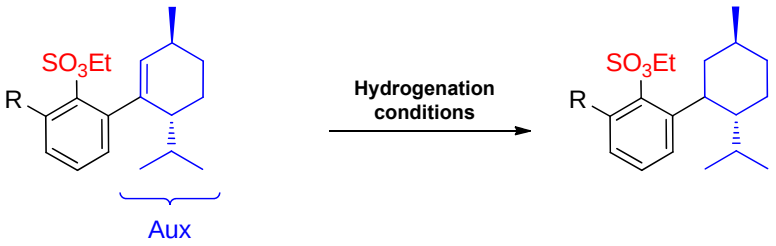
Scheme 5.16. Synthesis of three new chiral benzenesulphonic acids

Although the hydrolysis was efficient in some cases, it was clear that the uncontrollable reactivity of the olefin on the chiral auxiliaries was a limitation. To give strength to this second generation of chiral benzenesulphonic acids, it was necessary to investigate the possibility of diastereoselective reduction of this alkene.

5.4.3 Preliminary study on the reactivity of the chiral auxiliary unsaturation towards reduction

The diastereoselective reduction of the unsaturation would be a straightforward and very easy method to avoid the cyclisation of the sulphonate/sulphonic acid moiety. In addition it would provide an entry to new catalysts. Naturally, classic catalytic hydrogenation methods were tried to reduce this unsaturation (Table 5.3).

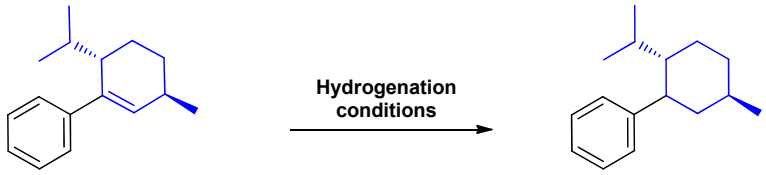
Table 5.3. Conditions screened for the reduction of **43a** or **44a**



Entry	Solvent	R	Conditions	Time	Result	d.e. (%)
1	EtOH	Aux	Pd/C (10%), H_2, 1 atm, r.t.	12 hours	No reaction	-
2	EtOH	Aux	Pd/C (10%), H_2, 1 atm, 60 ºC	16 hours	No reaction	-
3	EtOH	H	Raney Ni, H_2, 1 atm, r.t.	72 hours	No reaction	-
4	Toluene	H	$TsNHNH_2$, reflux	16 hours	No reaction	-
5	THF	H	B_2H_6 (10 eq.), r.t.	48 hours	No reaction	-

The reduction of the unsaturation seemed troublesome, although a similar reduction (metal-catalysed hydrogenation) was described on a substituted electron-rich arene with no sulphonate group.[179b] Our main concern was the possible deactivation of the catalyst due to the presence of the sulphonate. To test our hypothesis, a model system with no sulphonate was synthesised and subjected to reduction conditions (Table 5.4).

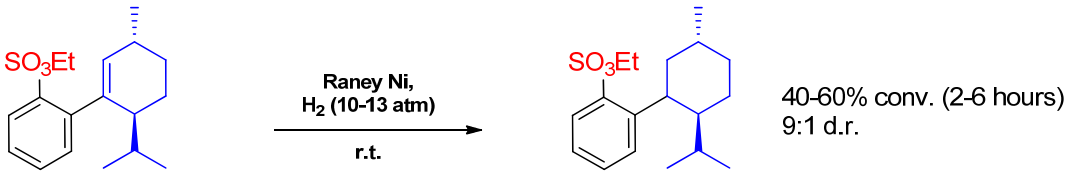
Table 5.4. Reduction of [(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]benzene



Entry	Solvent	Conditions	Time	Result[a]	d.r.[a]
1	EtOH	Pd/C, H_2, 1 atm, 60 ºC	24 hours	Full conversion	4:1
2	EtOH	Raney Ni, H_2, 1 atm, r.t.	16 hours	Full conversion	> 98:2[b]

[a] Measured by ^{1}H NMR on the crude mixture. [b]Minor isomer not detectable by ^{1}H NMR.

This substrate presented the desired reactivity. It was hoped that subjecting the real substrate to harsher conditions, would allow reduction to be achieved (especially under high pressure, Scheme 5.17 and Table 5.5).



43a

Scheme 5.17. Reduction of **43a** under high pressure hydrogenation

Interestingly, when **43a** was subjected to reduction in the presence of Raney nickel® the selectivity with was good, however, the H-Cube that was used for this study only allowed us to adjust the flow rate and temperature, therefore these results were difficult to reproduce.

Table 5.5. Reduction of **43b** in the presence of hydrogen/[M] under high pressure

Entry	Solvent	Conditions[a]	Time	Result	d.r.
1	EtOH	Pd/C (5%), 100 psi H_2	24 hours	< 10% conv.	-
2	AcOH	Pd/C (20%), 100 psi H_2	24 hours	100% conv.	100:41
3	EtOH	Pd/Al_2O_3 (5%), 100 psi H_2	24 hours	No reaction	-
4	AcOH	Pd/Al_2O_3 (5%), 100 psi H_2	24 hours	No reaction	-
5	EtOH	Rh/C (5%), 100 psi H_2	24 hours	No reaction	-
6	AcOH	Rh/C (5%), 100 psi H_2	24 hours	No reaction	-
7	EtOH	Rh/Al_2O_3 (5%), 100 psi H_2	24 hours	No reaction	-
8	AcOH	Rh/Al_2O_3 (5%), 100 psi H_2	24 hours	No reaction	-
9	EtOH	Pt/C (5%), 100 psi H_2	24 hours	No reaction	-
10	AcOH	Pd/C (5%), 100 psi H_2	24 hours	No reaction	-
11	EtOH	Pt/C (5%) ESCAT, 100 psi H_2	24 hours	No reaction	-
12	AcOH	Pt/C (5%) ESCAT, 100 psi H_2	24 hours	No reaction	-

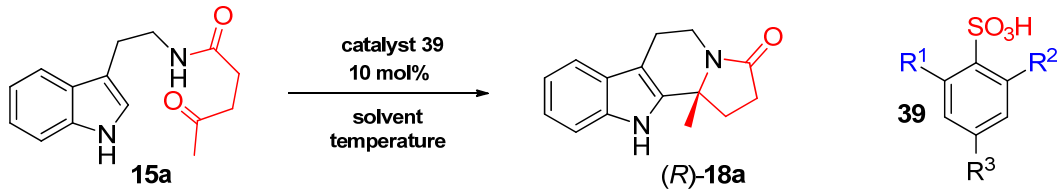
The most interesting result was achieved when Pd/C (20%) was used in acetic acid (entry 2). After 24 hours, full conversion was observed and the crude product was a mixture of diastereomers (d.r. 5:2). Although the diastereomeric excess was not satisfactory, it was the first time that a full reduction had been obtained.

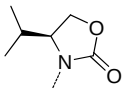
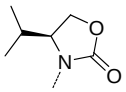
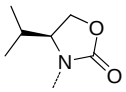
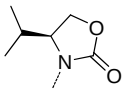
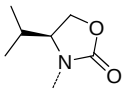
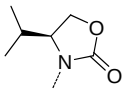
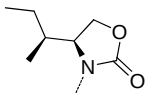
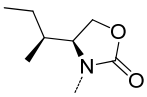
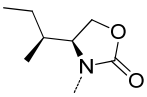
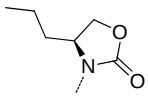
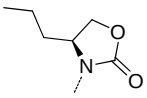
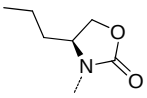
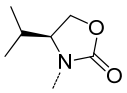
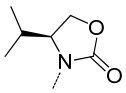
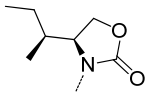
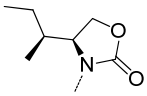
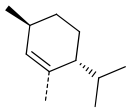
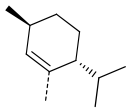
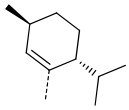
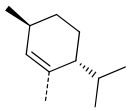
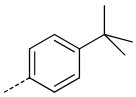
These results constitute a proof of principle that the unsaturation in the menthenyl/camphenyl-derived catalysts can be reduced diastereoselectively, although this required harsh conditions. In particular, a high pressure of hydrogen seemed essential to attain the desired reactivity. Future studies must include this type of reduction on fully parameterizable equipment and screening of conditions to obtain the reduced auxiliaries with excellent diastereomeric excesses. Other transformations of the alkene (addition of halides, radicals or other species) can also be envisaged to increase the potential for late-stage derivatisation.

5.5 Evaluation of the catalytic activity and enantioinduction of the novel chiral benzenesulphonic acids

Our library of sulphonic acids was utilised in two benchmark reactions: an *N*-acyliminium cyclisation reaction in which we had some expertise (see chapters 2-4) and the Mannich reaction of acac with *N*-Boc benzaldimine. For the latter, many organocatalytic methodologies have already been reported to form chiral amines with excellent enantioselectivities. Our primary aim was to evaluate the catalytic activity of our catalysts as well as determining their potential for enantioinduction. If high selectivities could be obtained, the application of our new sulphonic acids to a range of substrates would be particularly interesting to probe their scope of application (Tables 5.6 and 5.7).

Table 5.6. Evaluation of new benzenesulphonic acids in the *N*-acyliminium cyclisation reaction of **15a**

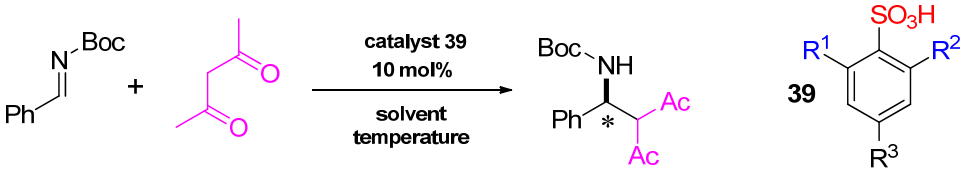


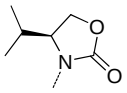
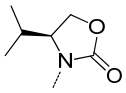
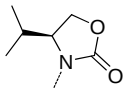
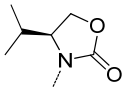
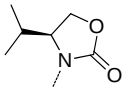
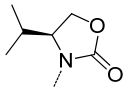
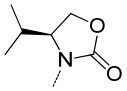
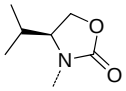
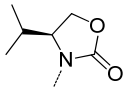
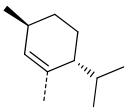
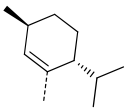
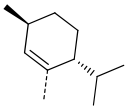
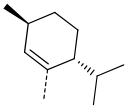
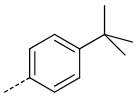
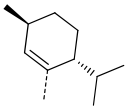
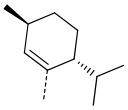
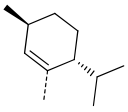
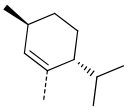
Entry	R^1	R^2	R^3	Acid	Temp. (°C)	Yield (%)	e.e. (%)
1				**39a**	Reflux	98	15
2				**39a**	60 °C	98	8
3				**39d**	Reflux	99	20
4				**39b**	Reflux	N.R.	-
5			^{t}Bu	**39e**	Reflux	N.R.	-
6			^{t}Bu	**39g**	Reflux	N.R.	-
7			H	**39h**	Reflux	98	− 7
8			H	**39i**	Reflux	N.R.	-
9			H	**39j**	Reflux	98	− 7

N.R. = no reaction was observed

Sulphonic acids bearing oxazolidinone chiral auxiliaries as well as chiral alkenes induced moderate enantioselectivity in the *N*-acyliminium cyclisation of **15a** to (*R*)-**18a** (up to 20%). Generally, the oxazolidinone-substituted benzenesulphonic acids promoted the reaction with greater enantioselectivity. Amongst those, the catalyst imparting the highest selectivity was substituted by bulky leucine-derived oxazolidinones.

Table 5.7. Evaluation of new chiral benzenesulphonic acids in the Mannich reaction of acac with *N*-Boc benzaldimine



Entry	R^1	R^2	R^3	Acid	Solvent	Temp. (ºC)	Yield (%)	e.e. (%)
1				**39a**	$CHCl_3$	r.t.	65	0
2				**39a**	$CHCl_3$	− 20 ºC	56	0
3				**39a**	$PhCH_3$	r.t.	62	6
4			H	**39h**	$PhCH_3$	− 20 ºC	12[a]	32
5			H	**39i**	$PhCH_3$	− 20 ºC	10[a]	7
6			H	**39j**	$PhCH_3$	− 20 ºC	8[a]	10
7			H	**39h** Na salt	$PhCH_3$	− 20 ºC	15[a]	− 15
8			H	**39h**	$PhCH_3$	− 78 ºC	11[a]	63

[a] Determined based on ^{1}H NMR analysis of the inseparable mixture of desired product and Boc-NH_2 obtained after column chromatography

More significantly, the Mannich reaction of acac and *N*-Boc benzaldimine was catalysed by our chiral acids. Screening a range of conditions, it was found that oxazolidinone-derived BSAs catalysed the reaction efficiently although they induced very low enantioselectivity. In contrast, the chiral alkene-derived BSAs imparted much greater enantioselectivities (up to 63% e.e.) but the reactivity was not entirely satisfactory and hydrolysis (of the imine) was a major issue with this family of catalysts.

5.6 Conclusion

In our efforts to develop a new class of stronger Brønsted acids, we have designed two robust routes towards two families of chiral toluenesulphonic acid mimics. One strategy consisted in grafting chiral oxazolidinones on to a benzene core; subsequent sulphonylation afforded the desired acids. With this approach, seven new chiral benzenesulphonic acids were prepared. Our second strategy was to use a cross-coupling reaction as the key step to introduce chiral auxiliaries onto a benzenesulphonate core; the Suzuki-Miyaura cross-coupling was found to be very efficient in attaching chiral alkenes derived from the chiral pool. After hydrolysis and acidification, three new chiral acids were synthesised.

As part of our program, we have assessed the enantioinduction of these acids in two reference reactions: our previously developed *N*-acyliminium cyclisation and the Mannich reaction of acac onto *N*-Boc benzaldimine. In the latter case, although the level of reactivity did not meet our expectations, obtaining 63% e.e. (not fully optimised) was significant progress in our endeavours to develop a new class of Brønsted acid. It proved that our concept was valid (enantioinduction by chiral benzenesulphonic acids) and that respectable levels of enantioselectivity could be reached with non-fully optimised conditions, with our first families of catalysts.

General conclusion and future work

During our studies, we have successfully developed an enantioselective *N*-acyliminium cyclisation cascade of enol lactones with tryptamine derivatives. From two very simple starting materials we have been able to build complexity in a single step, controlling the formation of a quaternary chiral centre with good to excellent enantioselectivities (68-99% e.e.).

This initial method has led us to study various extensions to synthesise complex β-carbolines from simple starting materials. A doubly-catalysed process has been developed allowing for the synthesis of tetracycles (+)-**18** from alkynoic acids and tryptamines taking advantage of the compatibility between a gold (I)-catalysed cycloisomerisation coupled and our BPA-catalysed *N*-acyliminium cyclisation. β-carbolines (+)-**18** were obtained in a one-pot four-bond forming transformation in good to excellent enantiomeric excesses (83-95% e.e.).

Since alkynoic acids were suitable reaction partners in our cascades as simple masked ketones, we investigated the feasibility of an *N*-acyliminium cyclisation between tryptamines and oxoacids. Our results indicate that BPA are capable of promoting the condensation of these starting materials to form *N*-acyliminium ions *in situ*. As observed previously, these intermediates underwent a Pictet-Spengler type cyclisation with high enantioselectivity. Interestingly, with this method, we have been able to control two contiguous stereogenic centres with exquisite diastereoselectivities and enantioselectivities (92 to >96 % d.e. and 68-98% e.e.). Mechanistic studies seem to indicate that the formation of the lactam moiety occurred prior to the Pictet-Spengler type cyclisation, therefore supporting that the reaction proceeded *via* an *N*-acyliminium ion intermediate. The high diastereo- and enantioselectivities were attributed to a match/mismatch case during a *dynamic kinetic asymmetric cyclisation*.

With a different strategy, the feasibility of a site isolated base-catalysed Michael addition-induced acid-catalysed enantioselective *N*-acyliminium cyclisation cascade was studied. We found that the anchoring of BPA catalysts to a polymer-supported amine was not necessary to

observe an efficient site isolation. Taking advantage of this unanticipated result, we have developed a one-pot PS-BEMP-catalysed Michael addition / BPA-catalysed enantioselective *N*-acyliminium cyclisation cascade leading to the formation of novel functionalised tetracyclic β-carbolines. Employing MVK and EVK as Michael acceptors, the cascade proceeded smoothly to afford the desired products (60-90% yield and 56-82% e.e.), however, bulkier vinyl ketones were not reactive enough to partake in the cascade. This in conjunction with the moderate enantioselectivities observed were the main limitations of this method; nevertheless, to the best of our knowledge, the very concept of observing site isolation with only one single polymer supported reagent had no precedent. It is our belief that much interest will arise from this discovery since the chemistry of polymer-supported organocatalysts is not well defined and this is especially true for BPAs.

Finally, because reactivity limitations were met during our studies, efforts were invested into developing a new class of stronger Brønsted acids, namely chiral benzenesulphonic acids. After establishing two robust synthetic routes, two families of chiral BSAs were prepared (ten catalysts in total) and assessed in reference reactions. As a proof of principle we established that oxazolidinone-derived chiral BSA efficiently catalysed our *N*-acyliminium cyclisation with up to 20% enantiomeric excess. More interestingly, using a chiral BSA derived from enantiopure menthone, we have been able to catalyse the addition of acac with *N*-Boc benzaldimine with a promising 63% enantiomeric excess.

Future work includes the application of BPAs and their derivatives to other types of cyclisation (directly on carbocations or with different nucleophiles), the exploitation of the uncovered site isolation behaviour of PS-BEMP and bulky BPAs to other systems and other types of reactions. The development of new families of chiral benzenesulphonic acids, their applications to known reactions and novel reactivities will be pursued. These projects are part of the ongoing Brønsted acid organocatalysis program in the Dixon group.

Organic Brønsted Acid-Catalysed Enantioselective *N*-Acyliminium Cyclisation Cascades

Volume 2 – Experimental Section

A thesis submitted in partial fulfilment of the requirement for the degree of

Doctor of Philosophy (D. Phil.)

Michael Eric Muratore

Supervisor: Professor Darren J. Dixon

Chapter Six: Experimental Section

6.1 General Experimental

All reactions were performed in open, round-bottom flasks, unless otherwise stated. All glass apparatus was oven dried and cooled under vacuum before use.

Solvents and Reagents

Bulk solutions were evaporated under reduced pressure using a Buchi rotary evaporator. Petroleum ether refers to distilled light petroleum ether of fraction 30-60 ºC. Solvents used are dry solvents. Dichloromethane was distilled over CaH_2; tetrahydrofuran, diethyl ether and toluene were distilled over sodium chips and benzophenone ketyl radical; dimethyl formamide was dried over molecular sieves. All other solvents were used as purchased. Commercial reagents were used as purchased without any further purification unless otherwise stated.

Chromatography

Chromatographic purification of products was carried out using Merck Kieselgel 60 silica gel (230-400 mesh) or using a Jones Flash Master where stated. Thin-layer chromatography was carried out using Merck Kieselgel 60 F_{254} (230-400 mesh) fluorescent treated silica which were visualised under UV light (250 nm) or by staining with aqueous potassium permanganate solutions or a *para*-anisaldehyde alcoholic solution. In all cases of chromatography, HPLC grade solvents or distilled solvents were used as eluents.

Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on a Hewlett-Packard 1050 Series system or Agilent 1200 Series system (column and solvent conditions are given with the compound).

Melting Points

Melting points were recorded on a Gallenkamp melting point apparatus with the sample contained in a thin glass tube or a Leica Galen III apparatus where the sample was placed between two cover glass windows, at ambient pressure and are uncorrected.

Infra-Red Spectroscopy

Infrared spectra were recorded on an ATI Mattson: Genesis Series FTIR spectrometer or a Bruker Tensor 27 FT-IR spectrometer, from a thin film deposited onto a sodium chloride plate. Only selected absorbances (ν_{max}) are reported.

NMR Spectroscopy

^{1}H NMR spectra were recorded in deuterated solvents on Bruker 500, 400 or 300 spectrometers 500 MHz, 400 MHz and 300 MHz respectively or on a Varian 300 MHz spectrometer, with residual protic solvent as the internal standard. ^{13}C NMR spectra were recorded in deuterated solvents on Bruker 500, 400 or 300 spectrometers at 125 MHz, 100 MHz and 75 MHz respectively or a Varian 300 MHz spectrometer, at 75 MHz, with the central peak of the deuterated solvent as the internal standard. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz) rounded to the nearest 0.5 Hz. The ^{1}H NMR spectra are reported as δ/ppm downfield from tetramethylsilane (multiplicity, number of protons, assignment, coupling constant *J*/Hz). The ^{13}C NMR spectra are reported as δ/ppm (multiplicity where needed, number of signals where needed, assignment, coupling constant *J*/Hz). Assignments were aided by the use of DEPT-135, COSY, HMQC and HMBC spectra where necessary.

Mass Spectrometry

Low resolution mass spectrometry (EI, CI, ESI) was recorded on a Fissions VG Trio 2000 quadropole mass spectrometer or a Bruker MicroTof mass spectrometer. High resolution mass

spectra (accurate mass) were recorded on a Thermo Finnigan Mat 95XP mass spectrometer or a Micromass GCT spectrometer.

Polarimetry (optical rotation)

Optical rotations were recorded using an Optical Activity AA-1000 polarimeter or a Perkin-Elmer 241 polarimeter; specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} deg.cm^2.g^{-1}; concentrations (*c*) are quoted in g/100 mL; *D* refers to the *D*-line of sodium (589 nm); Temperatures (*T*) are given in degrees Celsius (ºC).

X-Ray Crystallographic Data

X-Ray Crystallographic analyses were performed on a Bruker Smart Apex CCD diffractometer (crystals were mounted on top of fomblin (perfluoromethyl isopropyl ether) oil in a Hamilton Cryoloop) or an Enraf-Nonius KCCD diffractometer.

Numbering

All numbering used in this section is arbitrary and does not follow any particular convention.

Literature References

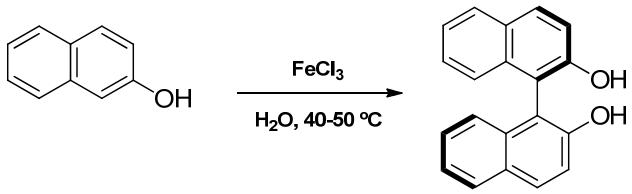
Known compounds are indicated by a reference to a previous literature report in their title line, commercially available chemicals are indicated by a double star (**). Any data that is referred to from a different source is noted separately in the characterisation text and the corresponding reference is given. If a literature procedure was followed, this is indicated explicitly in the method text.

6.2 Practical Experimental

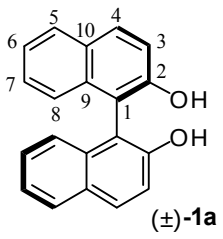
6.2.1 Experimental for Chapter 2

6.2.1.1 Catalysts synthesis

6.2.1.1.1 Synthesis and resolution of 1,1′-binaphthalene-2,2′-diol or BINOL (1a)[196,197]



In a round-bottom flask, 40.5 g of iron(III) chloride (0.25 mol, 0.5 equivalents) were dissolved in 1.25 L of warm water (40-50 ºC), the solution was stirred while 72 g of powdered 2-naphthol (0.5 mol, 1 equivalent) were added. The suspension was heated to 55 ºC for 12 hours and then allowed to cool to room temperature. The suspension was filtered. The solid was dissolved in hot toluene and the solvent was removed *in vacuo* (azeotropic removal of water). This operation can be repeated depending on the quantity of water to remove. The recovered brown solid was dissolved in the minimum amount of boiling toluene and crystallised allowing the mixture to cool to room temperature, then cooling to 0 ºC and finally to − 20 ºC. The crystals were filtered. The operation was repeated twice to recover (±)-**1a** (20 g, 28%) as a colourless crystalline solid. Spectral data were in agreement with the literature.[196a]

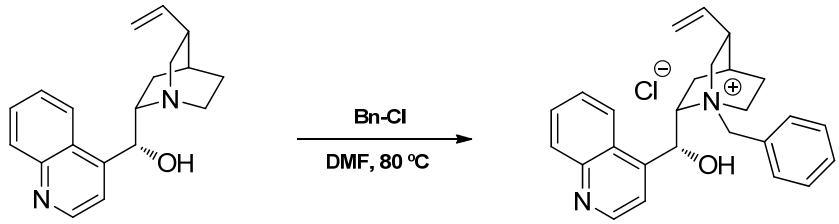


(±)-**1a**

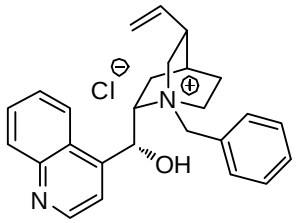
m.p. 217-220 ºC (lit.[196a] 216-218 ºC); **FT-IR** ν_{max}(NaCl): 3485 cm^{-1} (O-H), 1618 cm^{-1} (ArC=C), 1559 cm^{-1} (ArC=C); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 5.08 (s, 2H, OH), 7.17 (d, 2H, H-3, *J* 8.0 Hz), 7.31-7.34 (m, 2H, H-4), 7.36-7.45 (m, 4H, H-6, H-7), 7.91 (d, 2H, H-8, *J* 7.5 Hz), 7.99

(d, 2H, H-5, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 110.8 (C-1), 117.8 (C-3), 124.1 (C-6), 124.2 (C-8), 127.5 (C-7), 128.4 (C-5), 129.4 (C-10), 131.5 (C-4), 133.4 (C-9), 152.7 (C-2); ***m/z*** (ES−) 285 ($[M-H]^-$, 100%).

Synthesis of and characterisation of (9*R*)-1-benzyl-9-hydroxycinchonan-1-ium chloride or *N*-benzylcinchonidinium chloride[198]



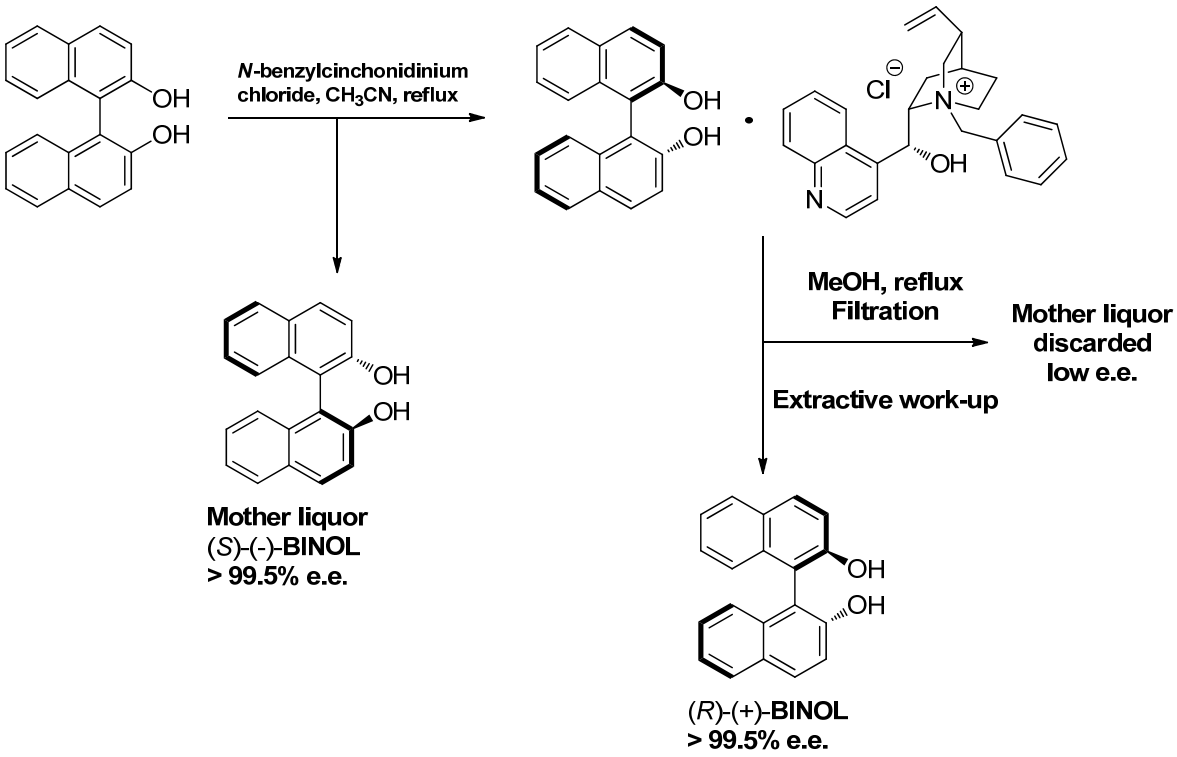
In a round-bottom flask, benzyl chloride (17.6 mL, 0.151 mol, 1.5 equivalents) was diluted with 200 mL of DMF and cinchonidine (30.0 g, 0.102 mol, 1 equivalent) was added. The suspension was stirred and heated at 80 ºC for 3 hours. The solvent was removed *in vacuo* and the residue dried for 24 hours. The residue was suspended in acetone and refluxed for 2 hours. Then the mixture was left to cool to room temperature and then cooled to 0 ºC, finally filtered through a sinter funnel. The pink solid was washed twice with 30 mL of acetone. After filtration, the title compound was isolated as a pale pink solid (35.45 g, 83%).



m.p. 249-253 ºC (dec.) (lit.[198] 256 ºC (dec.)); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.78-1.86 (m, 2H), 1.87-1.96 (m, 2H), 2.08-2.11 (m, 1H), 2.45-2.49 (m, 1H), 3.09-3.17 (m, 2H), 3.64-3.68 (m, 1H), 4.02 (t, 1H, *J* 8.6 Hz), 4.71-4.74 (m, 1H), 4.93 (d, 1H, *J* 10.5 Hz), 5.26 (d, 1H, *J* 17.3 Hz), 5.40-5.45 (m, 1H), 5.67 (d, 1H, *J* 12.0 Hz), 5.76 (d, 1H, *J* 12.0 Hz), 6.51-6.54 (m, 1H), 7.11-7.36 (m, 4H), 7.45 (d, 1H, *J* 5.9 Hz), 7.65 (d, 2H, *J* 7.2 Hz), 7.73 (d, 1H, *J* 7.9 Hz), 7.83 (d, 1H, H-2, *J* 4.4 Hz), 8.12 (d, 1H, *J* 8.0 Hz), 8.81 (d, 1H, H-1, *J* 4.4 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 22.2, 25.1, 26.5, 38.0, 50.3, 60.3, 64.9, 67.9, 117.8, 120.0, 122.7, 123.8, 127.1, 127.3, 128.6, 128.8, 129.7, 130.0, 134.0, 136.1,

149.6; ***m/z*** (ES+) 385 ([M−Cl]$^+$, 100%); $[\alpha]_D^{25}$ = + 167.6 (*c* 1.03, H_2O) (lit.[198] $[\alpha]_D^{27}$ = + 165.9 (*c* 0.50, H_2O)).

Resolution of racemic BINOL using *N*-benzylcinchonidinium chloride

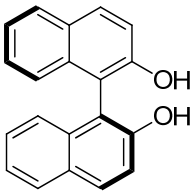


20 g of (±)-BINOL ((±)-**1a**, 70 mmol, 2 equivalents) and 16.14 g of *N*-benzylcinchonidinium chloride (38.30 mmol, 1.1 equivalents) were suspended in 260 mL of acetonitrile in a 500 mL round bottomed flask, stirring vigorously. The suspension was heated to reflux for 4 hours before allowing it to cool to room temperature, stirring for 16 hours. The suspension was cooled to 0 ºC and stirred for another 4 hours and finally it was filtered. The mother liquor was recovered and the solvent was removed *in vacuo* affording a pink gum. It was redissolved in the minimum amount of hot TBME/hexane (1:2) and recrystallised, leaving the solution to cool to room temperature, then cooling to 0 ºC and finally to − 20 ºC. This treatment gave 5.9 g of (*S*)-(−)-1,1'-binaphthalene-2,2'-diol ((*S*)-(−)-**1a**, 59%).

The previously filtered solid (containing (*R*)-**1a** inclusion complex with the cinchonidinium salt) was washed with acetonitrile (2 × 30 mL), the filtrate was discarded and the resulting white solid was suspended in methanol (200 mL) and refluxed for 24 hours. It was allowed to cool to room temperature and filtered again, washed once with 20 mL of methanol and the filtrate was discarded again while the white solid was suspended in ethyl acetate (100 mL) adding aqueous 1M HCl (100 mL) and the biphasic solution was stirred until complete dissolution of the solid (around 1 hour). The organic layer was recovered, the aqueous phase was washed once with ethyl acetate (20 mL). Organics were combined, washed once with 20 mL of 1M aqueous HCl and brine (20 mL), dried over magnesium sulphate and the solvent was removed under reduced pressure to give a yellow powder. The solid was recrystallised from hot TBME/hexane (2:1) to give 8.0 g of (*R*)-(+)-1,1'-binaphthalene-2,2'-diol ((*R*)-(+)-**1a**, 80%) as a colourless crystalline solid.

The spectral data of both enantiomers were identical to the ones of the racemate.

(*S*)-(−)-1,1′-binaphthalene-2,2′-diol



(*S*)-**1a**

^{1}H NMR purity > 98%

ee > 99.7%

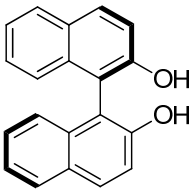
(Chiralpak AD column, 70:30 Hexane/propan-2-ol, 2 mL/min, t_R = 6.38 min)

m.p. 203-207 ºC (lit.[197] 207-210 ºC)

$[\alpha]_D^{23} = -34.1$ (*c* 1.02, THF)

[lit.[197] $[\alpha]_D^{21} = -34.0$ (*c* 1.0, THF)]

(*R*)-(+)-1,1′-binaphthalene-2,2′-diol



(*R*)-**1a**

^{1}H NMR purity > 98%

ee > 99.8%

(Chiralpak AD column, 70:30 Hexane/propan-2-ol, 2 mL/min, t_R = 9.06 min)

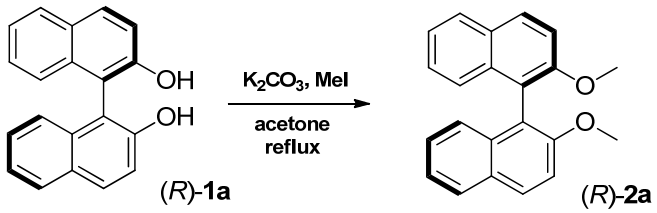
m.p. 210-213 ºC (lit.[197] 208-210 ºC)

$[\alpha]_D^{23} = +34.5$ (*c* 0.99, THF)

[lit.[197] $[\alpha]_D^{21} = +34.3$ (*c* 1.0, THF)]

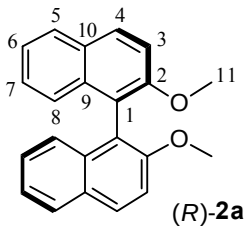
6.2.1.1.2 Synthesis and characterisation of (*R*)-2,2′-dimethoxy-1,1′-binaphthalene

(*R*)-2a[133,199]



(*R*)-**1a** (*R*)-**2a**

(*R*)-(+)-BINOL ((*R*)-**1a**, 4.55 g, 15.2 mmol, 1 equivalent) was suspended in 50 mL of acetone (in a 250 mL round bottomed flask) and potassium carbonate was added (7.47 g, 54.1 mmol, 3.4 equivalents). The mixture was stirred vigorously and iodomethane was added (4.16 mL, 66.8 mmol, 4.2 equivalents). The suspension was then heated to reflux for 16 hours. It was allowed to cool to room temperature and concentrated *in vacuo*. The residue was partitioned between dichloromethane and water. The aqueous layer was extracted once with dichloromethane and the organics combined, dried over magnesium sulphate and concentrated *in vacuo*. The residue was recrystallised from boiling dichloromethane, adding petroleum ether until having a slightly cloudy mixture, the mixture was shaken and placed at − 20 ºC for 24 hours and then the solid was filtered and washed with petroleum ether. The same procedure was repeated with the filtrate. Both crops were combined to give the title compound as a colourless crystalline solid (4.88 g, 98%). The spectral data were in agreement with the published ones.[133,199]



(*R*)-**2a**

m.p. 215-218 ºC (lit.[199] 224-225 ºC); **FT-IR** ν_{max}(NaCl) 1617 cm^{-1} (ArC=C), 1576 cm^{-1} (ArC=C), 1237 cm^{-1} (ArC-O); **^{1}H NMR** ($CDCl_3$, 500MHz) δ_H 3.80 (s, 6H, H-11), 7.15 (d, 2H, H-8, *J* 8.5 Hz), 7.25 (t, 2H, H-6, *J* 7.5 Hz), 7.35 (t, 2H, H-7, *J* 7.5 Hz,), 7.49 (d, 2H, H-3, *J* 9.0 Hz), 7.91 (d, 2H, H-5, *J* 8.0 Hz), 8.01 (d, 2H, H-4, *J* 9.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 56.9 (C-11), 114.2 (C-3), 119.6 (C-1), 123.5 (C-7), 125.3 (C-5), 126.3 (C-6), 128.0 (C-8), 129.2 (Ar-Cquat.), 129.4 (C-4), 134.0 (Ar-Cquat.), 155.0 (C-2); ***m/z*** (ES+) 337 ($[M+Na]^+$,

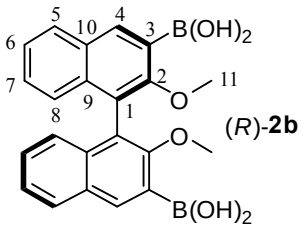
45%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{18}O_2Na^+$) requires ***m/z*** 337.1199, found ***m/z*** 337.1208; $[\alpha]_D^{25} = +50.3$ (*c* 1.05, $CHCl_3$) [lit.[199] $[\alpha]_D^{25} = +72.8$ (*c* 1.20, THF)].

6.2.1.1.3 Synthesis of (*R*)-(2,2'-dimethoxy-1,1'-binaphthalene-3,3'-diyl)diboronic acid (*R*)-2b[133]

(*R*)-**2a** (*R*)-**2b**

In a dry round-bottom flask (500 mL) under nitrogen, were placed 200 mL of freshly distilled ether and 5.77 mL of freshly distilled TMEDA (38.23 mmol, 3 equivalents) and *n*-BuLi (1.6 M, 23.9 mL, 38.24 mmol, 3 equivalents) was added dropwise at room temperature while stirring. The mixture was left stirring for 30 min and then 4.03 g of solid (*R*)-2,2'-dimethoxy-1,1'-binaphthalene (*R*)-**2a** (12.8 mmol, 1 equivalent) were added in one portion. The mixture was left stirring for 3 hours at room temperature, going from pale yellow to dark yellow and finally to a pale beige suspension (insoluble dianion). The complete lithiation was checked taking an aliquot of the suspension and quenching with deuterated methanol (CD_3OD), using ^1H NMR to confirm the complete disappearance of one proton signal. The suspension was cooled down to − 78 ºC, left for a couple of minutes and then triethylborate was added dropwise (15.1 mL, 88.7 mmol, 7 equivalents) over 15 minutes. When the addition was over, the mixture was allowed to warm to room temperature and stirred for 16 hours. 100 mL of a 1M aqueous solution hydrochloric acid was added, and the biphasic mixture stirred vigorously at room temperature for 3 hours. The organic layer was recovered, and the aqueous phase extracted with ether (2 × 30 mL). The organics were combined, washed with 1M aqueous HCl (30 mL) and brine (30 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a pale cream solid (4.2 g). It was purified by column chromatography on silica gel eluting with petroleum

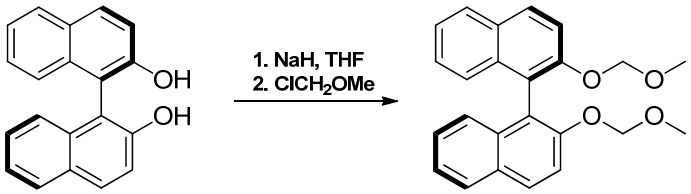
ether/diethyl ether (9:1 to 7:3) and then diethyl ether to give the pure boronic acid as a colourless solid (3.15 g, 66%). The spectral data were in agreement with the previously published ones.[133,200]



(*R*)-**2b**

m.p. 223-226 ºC (lit.[200] > 250 ºC); **FT-IR** ν_{max}(NaCl) 3447 cm^{-1} (O-H), 1617 cm^{-1} (ArC=C), 1588 cm^{-1} (ArC=C); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.32 (s, 6H, H-11), 6.19 (s, 4H, O-H), 7.19 (d, 2H, H-8, *J* 8.5 Hz), 7.34 (dd, 2H, H-6, *J* 8.5 Hz, 7.0 Hz), 7.48 (dd, 2H, H-7, *J* 8.0 Hz, 7.0 Hz), 7.99 (d, 2H, H-5, *J* 8.0 Hz), 8.66 (s, 2H, H-4); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 3.44 (s, 6H, H-11), 6.98 (d, 2H, H-8, *J* 8.5 Hz), 7.26 (ddd, 2H, H-7, *J* 8.5 Hz, 7.0 Hz, 1.5 Hz), 7.36-7.40 (m, 2H, H-6), 7.98 (d, 2H, H-5, *J* 8.0 Hz), 8.20 (s, 2H, H-4), 8.24 (s, 4H, OH); **^{13}C NMR** (d_6-DMSO, 500 MHz) δ_C 60.6 (C-11), 122.8 (C-1), 124.3 (C-6), 125.1 (C-8), 126.6 (C-7), 128.2 (C-5), 128.8 (C-3), 129.7 (C-10), 134.3 (C-9), 135.4 (C-4), 158.7 (C-1); ***m/z*** (ES−) 415 ([M+MeOH−H_2O−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M+MeOH−H_2O−H]$^-$ ($C_{23}H_{21}B_2O_6^-$) requires ***m/z*** 415.1538, found ***m/z*** 415.1531; $[\alpha]_D^{25}$ = − 111.0 (*c* 0.96, $CHCl_3$/MeOH 9:1) (lit.[200] $[\alpha]_D$ = − 153.4 (*c* 1.0, $CHCl_3$)).

6.2.1.1.4 Synthesis and characterisation of (R)-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (R)-3a[201]

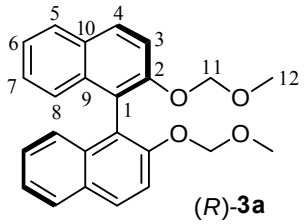


(*R*)-**1a** (*R*)-**3a**

(*R*)-**3a** was prepared according to a literature procedure.[201]

In a dry flask containing a magnetic stirrer bar, under nitrogen, 8.38 g of sodium hydride (60% suspension in mineral oil, 210 mmol, 3 equivalents) were suspended in 100 mL of anhydrous

tetrahydrofuran. The suspension was cooled to 0 ºC and a solution of 20.0 g of (*R*)-(+)-BINOL ((*R*)-**1a**, 69.8 mmol, 1 equivalent) in 400 mL of anhydrous tetrahydrofuran was canulated onto the sodium hydride suspension over 15 minutes. The resulting mixture was left stirring for 1 hour at 0 ºC. Chloromethyl methyl ether (16.1 mL, 279 mmol, 4 equivalents) was added over 30 minutes at 0 ºC. The mixture was left stirring for 16 hours at room temperature. The unreacted hydride was quenched with water, added slowly dropwise until effervescence ceased and another portion of 100 mL of DI water was added. The aqueous mixture was extracted with diethyl ether (3 × 100 mL). The organics were combined, dried over magnesium sulphate and filtered before removing the solvent *in vacuo*. The resulting light yellow solid was purified by column chromatography eluting with petroleum ether/diethyl ether 4:1 to afford (*R*)-**3a** as a colourless crystalline solid (25.8 g, 98%). The spectral data were in agreement with the literature.[201]

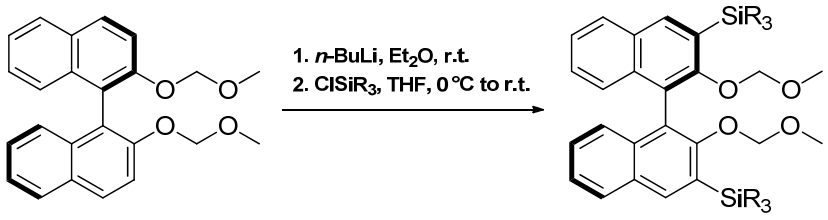


(*R*)-**3a**

m.p. 101-104 ºC (lit.[201] (*S*)-enantiomer 103-105 ºC); **FT-IR** ν_{max}(NaCl) 1622 cm^{-1} (ArC=C), 1592 cm^{-1} (ArC=C), 1507 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.16 (s, 6H, H-12), 5.00 (d, 2H, H-11a, *J* 7.0 Hz), 5.10 (d, 2H, H-11b, *J* 7.0 Hz), 7.17 (d, 2H, H-8, *J* 8.5 Hz), 7.24 (t, 2H, H-6, *J* 7.5 Hz), 7.36 (t, 2H, H-7, *J* 7.5Hz), 7.60 (d, 2H, H-3, *J* 9.0 Hz), 7.89 (d, 2H, H-5, *J* 8.0 Hz), 7.97 (d, 2H, H-4, *J* 9.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 55.8 (C-12), 95.2 (C-11), 117.3 (C-3), 121.3 (C-1), 124.1 (C-7), 125.5 (C-8), 126.3 (C-6), 127.9 (C-5), 129.4 (C-4), 129.9 (C-10), 134.0 (C-9), 152.6 (C-2); ***m/z*** (ES+) 397 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{22}O_4Na^+$) requires ***m/z*** 397.1410, found ***m/z*** 397.1409; $[\alpha]_D^{25}$ = + 92.1 (*c* 1.12, $CHCl_3$) (lit.[201] (*S*)-enantiomer $[\alpha]_D^{25}$ = – 96.6 (*c* 0.855, THF).

6.2.1.1.5 General methods for the bislithiation/silylation of 2,2′-methoxymethyl BINOL ((R)-3a) and preparation of 3,3′-silylated BINOLs

General method I for the bis-lithiation/silylation of (*R*)-3a



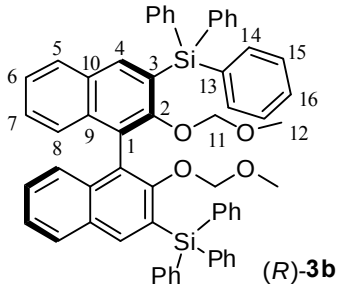
(*R*)-**3a** (*R*)-**3**

A dry tri-neck flask was charged with finely grounded (*R*)-**3a** (1 equivalent). The flask was then purged 3 times by a sequence vacuum / nitrogen. Freshly distilled diethyl ether (alternatively anhydrous ether purchased from Aldrich, SureSeal^{TM} bottle) was added (12.5 mL per mmol). The suspension was stirred vigorously at room temperature under nitrogen and *n*-BuLi (1.6 M in hexanes, 2.5 equivalents) was added in a quick dropwise addition. The mixture was stirred at room temperature for 3 to 5 hours (full lithiation monitored by ^{1}H NMR), during which time the di-lithium anion precipitated (thin beige suspension). The suspension was cooled to 0 ºC and anhydrous tetrahydrofuran was added (1.5 mL per 1 mmol). The solution was stirred for 15 minutes at 0 ºC before dropwise addition of the appropriate chlorosilane (2.6 equivalents) in anhydrous tetrahydrofuran (2.5 mL per mmol of chlorosilane) *via* canula, at 0 ºC, over 1 hour. The resulting mixture was stirred for a further 30 minutes at 0 ºC, and then allowed to warm to room temperature and stirred for 40 hours (the colour of the mixture usually fades from dark green/brown to yellow/pale yellow). The excess reagent was quenched by slow addition of a saturated solution of ammonium chloride (overall 3 mL per mmol) and the layers were separated. The aqueous phase was re-extracted twice with dichloromethane (1 mL per mmol). The organics were combined and dried over magnesium sulphate prior to concentration under reduced pressure.

Remark: The oily solid residue can be purified or used crude in the next step.

Preparation and characterisation of (*R*)-[2,2′-Bis(methoxymethoxy)-1,1′-binaphthalene-3,3′-diyl]bis (triphenylsilane) (*R*)-3b[49]

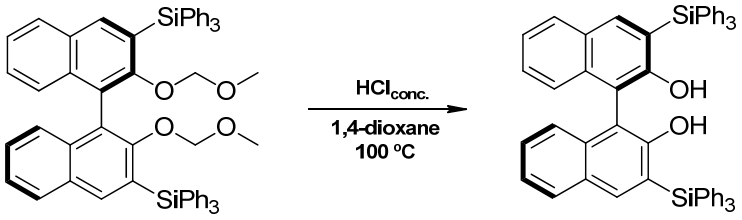
Prepared on a 94.8 mmol scale (35.5 g of (*R*)-**3a**). The product can be purified (chromatography on silica gel eluting with petroleum ether/dichloromethane/diethyl ether 9:1:0 to 85:14:1) or used without purification in the next step. Spectral data were matching the literature.[49]



(*R*)-**3b**

m.p. 139-141 ºC; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.27 (s, 6H, H-12), 3.76 (d, 2H, H-11a, *J* 5.0 Hz), 3.82 (d, 2H, H-11b, *J* 5.0 Hz), 7.25-7.30 (m, 12H, Ar-H), 7.30-7.45 (m, 6H, Ar-H), 7.46-7.51 (m, 6H, Ar-H), 7.69-7.74 (m, 14H, Ar-H), 7.89 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 56.1 (C-12), 97.7 (C-11), 123.0 (Ar-Cquat.), 124.5 (Ar-CH), 125.9 (Ar-CH), 127.3 (Ar-CH), 127.7 (Ar-CH), 127.7 (Ar-CH), 128.6 (Ar-CH), 129.1 (Ar-Cquat.), 129.3 (Ar-CH), 129.8 (Ar-CH), 130.0 (Ar-Cquat.), 135.0 (Ar-Cquat.), 135.2 (Ar-CH), 135.4 (Ar-Cquat.), 136.1 (Ar-Cquat.), 136.6 (Ar-CH); ***m/z*** (ES+) 913.4 ([M+Na]$^+$, 100%).

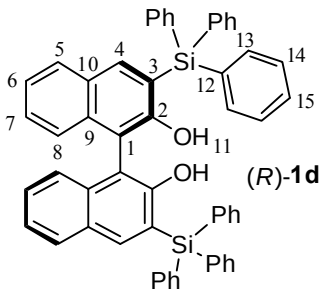
Preparation and characterisation of (*R*)-3,3′-bis(triphenylsilyl)-1,1'-binaphthalene-2,2'-diol (*R*)-1d[49]



(*R*)-**3b** (*R*)-**1d**

The crude mixture (from the previous reaction on 94.8 mmol scale) was dissolved in 1,4-dioxane (500 mL) and concentrated aqueous hydrochloric acid was added (25 mL). The solution was heated to 70 ºC for 24 hours (monitored by TLC). The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (200 mL) and DI water (100 mL).

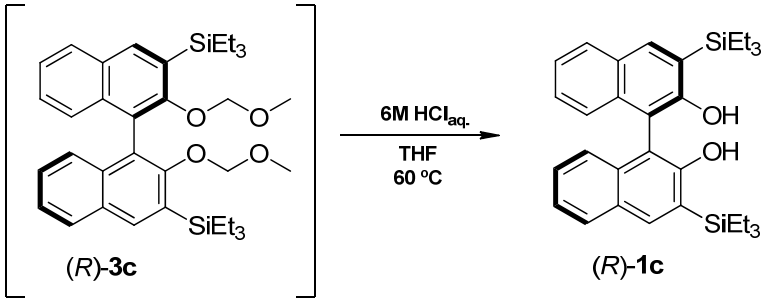
The layers were separated and the aqueous phase was re-extracted with dichloromethane (2 × 100 mL). The combined organics were dried over magnesium sulphate and adsorbed on silica gel (700 g). After purification by column chromatography on silica gel eluting with heptane / dichloromethane 85:15 to 7:3, the title product **(*R*)-1d** was obtained as a colourless solid (76.1 g, 66% over 2 steps). Spectral data were in agreement with the published ones.[49]



(*R*)-**1d**

m.p. 192-194 ºC; **FT-IR** ν_{max}(NaCl) 3520 cm^{-1} (O-H), 3069 cm^{-1} (ArC-H), 1617 cm^{-1} (ArC=C), 1581 cm^{-1} (ArC=C), 755 cm^{-1} (ArC-H OOP), 700 cm^{-1} (Ar-CH OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 5.39 (s, 2H, OH), 7.32 (d, 2H, H-8, *J* 8.0 Hz), 7.33-7.52 (m, 22H, H-6, H-7, H-14, H-15), 7.69-7.74 (m, 12H, H-13), 7.76 (d, 2H, H-5, *J* 8.5 Hz), 7.99 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 110.5 (Ar-Cquat.), 123.6 (Ar-Cquat.), 123.8 & 123.9 (C-7, C-8), 127.8 (C-14), 128.2 (C-6), 129.0 (C-5), 129.2 (Ar-Cquat.), 129.5 (C-15), 134.2 (C-12), 134.7 (Ar-Cquat.), 136.3 (C-13), 142.1 (C-4), 156.5 (C-2); ***m/z*** (ES−) 801 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+NH_4]^+$ ($C_{56}H_{46}NO_2Si_2^+$) requires ***m/z*** 820.3062, found ***m/z*** 820.3054; $[\alpha]_D^{25}$ = + 98.7 (*c* 1.00, $CHCl_3$) [lit.[49] $[\alpha]_D^{25}$ = + 102.7 (*c* 1.20, $CHCl_3$)].

Preparation and characterisation (*R*)-3,3′-bis(triethylsilyl)-1,1′-binaphthalene-2,2′-diol (*R*)-1c

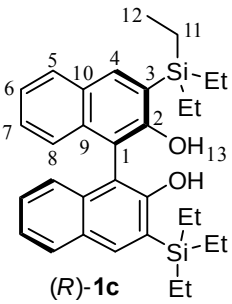


(*R*)-**3c** (*R*)-**1c**

MOM-protected TES BINOL (*R*)-**3c** was prepared according to general procedure **I** on 3.37 g (9 mmol, 1 equivalent) of (*R*)-**3a**. The crude oil was used for the deprotection.

With a slight modification of the previous procedure, (*R*)-**3c** (2 mmol, 1 equivalent) was dissolved in tetrahydrofuran (30 mL). 6M aqueous hydrochloric acid (30 mL) was added and the mixture was heated to 60 ºC for 48 hours (monitored by TLC). The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (50 mL) and water (50 mL). The aqueous was re-extracted with dichloromethane (25 mL). The combined organics were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The oily residue was purified by chromatography on silica gel eluting with petroleum ether to petroleum ether/diethyl ether 98.5:1.5 to afford the title product as a pale yellow solid (512 mg, 50 % over 2 steps).

Remark: the lower yield in this reaction is due to the relatively low stability of the TES group to acidic conditions, after 48 hours, deprotection of the silyl groups can be observed by TLC.

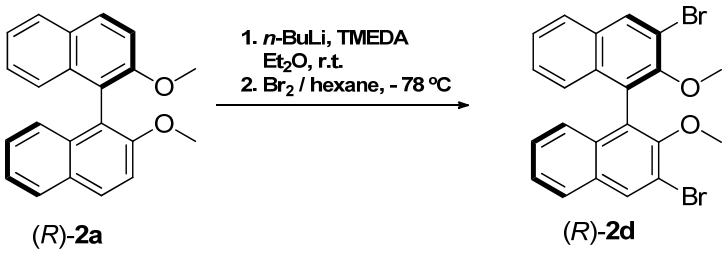


(*R*)-**1c**

m.p. 92-94 ºC; **FT-IR** ν_{max}(NaCl) 3524 cm^{-1} (O-H), 1616 cm^{-1} (ArC=C), 1580 cm^{-1} (ArC=C), 735 cm^{-1} (ArC-H OOP), 700 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.94-1.09 (m, 30H, H-11, H-12), 5.24 (s, 2H, H-13), 7.11 (d, 2H, H-8, *J* 8.3 Hz), 7.28-7.33 (m, 2H, H-7), 7.34-7.39 (m, 2H, H-6), 7.91 (d, 2H, H-5, *J* 7.8 Hz), 8.09 (d, 2H, H-4, *J* 8.6 Hz) ; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 3.5 (C-11), 7.7 (C-12), 109.4 (C-1), 123.6 (C-6), 123.9 (C-8), 126.2 (Ar-Cquat), 127.5 (C-7), 128.5 (C-5), 129.3 (Ar-Cquat), 134.2 (Ar-Cquat), 139.1 (C-4), 157.1 (C-2); ***m/z*** (ES−) 513 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{32}H_{41}O_2Si_2^-$) requires ***m/z*** 513.2651, found ***m/z*** 513.2642; $[\alpha]_D^{25}$ = + 100.9 (*c* 1.04, $CHCl_3$).

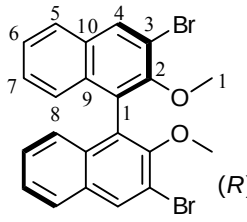
6.2.1.1.6 Preparation of aryl substituted BINOLs

Preparation and characterisation of (*R*)-3,3′-dibromo-2,2′-dimethoxy-1,1′-binaphthalene (*R*)-2d[133,199]



(*R*)-**2a** (*R*)-**2d**

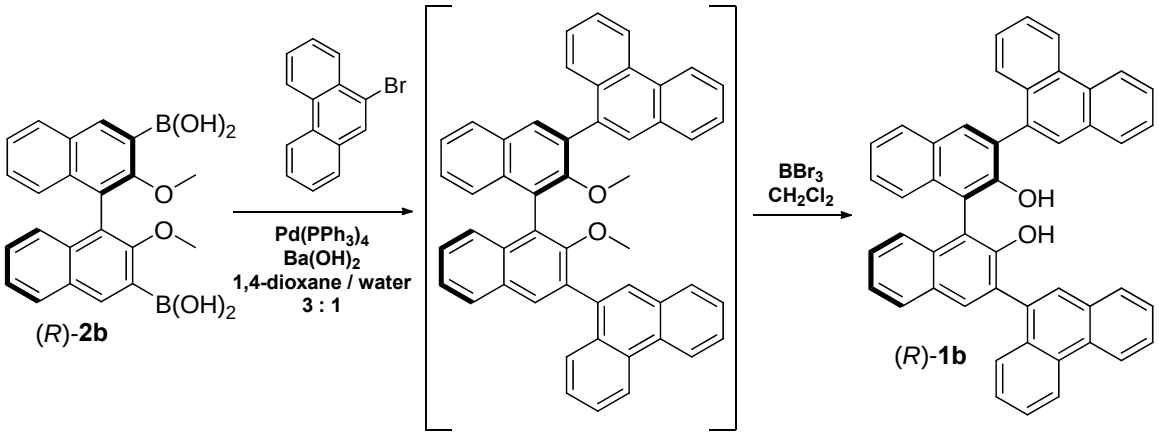
To a tri-neck dry round bottom flask under nitrogen were added sequentially: dry diethyl ether (700 mL), TMEDA (20.0 mL, 132.5 mmol, 3 equivalents) and, dropwise at room temperature, *n*-BuLi 1.6 M in hexanes (82.8 mL, 132.5 mmol, 3 equivalents). This mixture was left stirring at room temperature for 30 minutes, and then finely ground (*R*)-**2a** was added in one portion (13.88 g, 44.2 mmol, 1 equivalent). This suspension was left stirring at room temperature for 6 hours (completion of lithiation was followed by ^{1}H NMR). After completion (typically 3-6 hours), the suspension was cooled to − 78 °C, and a solution of bromine (6.81 mL, 132.5 mmol, 3 equivalents) in hexane (100 mL) was added dropwise over 1 hour. After addition, the mixture was allowed to warm to room temperature and was stirred for 1 hour. Completion was monitored by TLC (petroleum ether/diethyl ether 8:2 to 7:3). After completion, the excess reagent was quenched by addition of 250 mL of a saturated aqueous solution of sodium thiosulfate ($Na_2S_2O_3$). The resulting biphasic mixture was vigorously stirred for a few minutes, the layers were separated and the aqueous re-extracted with diethyl ether (200 mL) and then dichloromethane (100 mL). The organics were combined, dried over magnesium sulphate, filtered and the solvent was removed *in vacuo*. The slightly yellow solid residue was purified by chromatography on silica eluting with petroleum ether/diethyl ether 98:2 (dry load) to give (*R*)-**2d** as a colourless crystalline solid (11.3 g, 54%). The spectal data were in agreement with the literature.[199]



(*R*)-**2d**

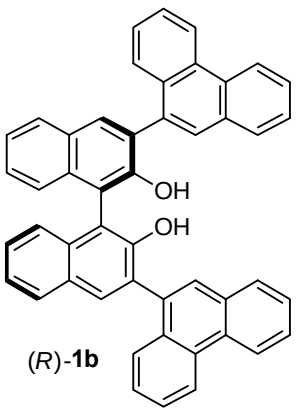
m.p. 180-183 ºC (lit.[199] 174-175 ºC); **FT-IR** ν_{max}(NaCl) 2935 cm^{-1} (ArC-H), 1461 cm^{-1} (CH_3), 755 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.52 (s, 6H, H-11), 7.09 (d, 2H, H-8, *J* 8.5 Hz), 7.28 (ddd, 2H, H-7, *J* 8.5 Hz, 7.0 Hz, 1.0 Hz), 7.43 (app td, 2H, H-6, *J* 7.5 Hz, 1.0 Hz), 7.83 (d, 2H, H-5, *J* 8.5 Hz), 8.28 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 61.1 (C-11), 117.5 (C-3), 125.8 (C-8), 125.9 (C-6), 126.5 (C-1), 126.9 (C-7), 127.1 (C-5), 131.4 (C-10), 133.0 (C-4), 133.1 (C-9), 152.5 (C-2); ***m/z*** (ES+) 488 (40%), 490 (80%), 492 (40%) ($[M+NH_4]^+$) and 493 (25%), 495 (50%), 497 (25%), ($[M+Na]^+$), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{16}O_2Br_2Na^+$) requires ***m/z*** 492.9409 (50%) & 494.9390 (100%) & 496.9374 (50%), found ***m/z*** 492.9406 (50%) & 494.9382 (100%) & 496.9359 (50%); $[\alpha]_D^{25} = +12.1$ (*c* 1.05, $CHCl_3$) (lit.[199] $[\alpha]_D^{25} = +13.2$ (*c* 1.2, $CHCl_3$)).

Preparation and characterisation of (*R*)-3,3′-di(9-phenanthryl)-1,1′-binaphthalene-2,2′-diol (*R*)-1b



Boronic acid (*R*)-**2b** (550 mg, 1.48 mmol, 1 equivalent), 9-bromophenanthrene (1.05 g, 4.08 mmol, 2.8 equivalents) and barium hydroxide (1.25 g, 3.8 mmol, 2.6 equivalents) were placed in a 50 mL round bottomed flask. 10 mL of a degassed dioxane/water 3:1 mixture was added. The suspension was stirred vigorously and nitrogen was bubbled through for 5 minutes. $Pd(Ph_3)_4$ (65.0 mg, 0.056 mmol, 0.04 equivalents) were rapidly introduced in the flask under

nitrogen. Nitrogen was bubbled through the resulting mixture for 2 minutes and it was then heated at reflux for 24 hours (Completion was monitored by TLC). The mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was partitioned between dichloromethane (30 mL) and 1M aqueous HCl (30 mL). The aqueous layer was extracted with dichloromethane (2 × 20 mL). The organics were combined, washed with 1M aqueous HCl (10 mL) and brine (10 mL), dried over magnesium sulphate, filtered and the solvent was removed under reduced pressure to give a brown gummy solid (1.25 g). It was redissolved in dry dichloromethane (25 mL) and a 1M colution of BBr_3 in dichloromethane (8.9 mL, 8.9 mmol, 6 equivalents) was added at 0 ºC. The mixture was stirred for 16 hours at room temperature. DI water (2 mL) was added dropwise at 0 ºC and the biphasic mixture was poured in a 1:1 mixture of dichloromethane/water (30 mL). The organic was separated and the aqueous layer re-extracted with dichloromethane (2 × 10 mL). The organics were combined, washed with brine (20 mL, dried over magnesium sulphate, filtered, and the solvent was removed *in vacuo*. The brown residue was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 9:1 to give the title BINOL (*R*)-**1b** as a colourless crystalline solid (640 mg, 68% over 2 steps).



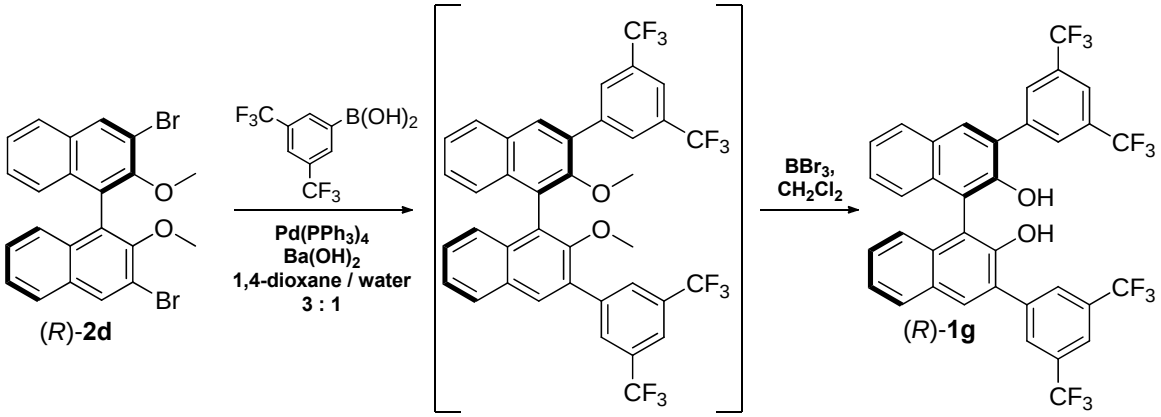
(*R*)-**1b**

m.p. 308-312 ºC (lit.[202] 192-202 ºC); **FT-IR** ν_{max}(NaCl) 3525 cm^{-1} (O-H), 3060 cm^{-1} (C-H), 1622 cm^{-1} (C=C), 749 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$:d_4-MeOD 9:1, 500 MHz) δ_H 5.25 (s, 2H, OH), 7.33-7.47 (m, 6H, Ar-H), 7.48-7.69 (m, 8H, Ar-H), 7.69-7.97 (m, 8H, Ar-H), 8.02-8.06 (m, 2H, Ar-H), 8.67-8.79 (m, 4H, Ar-H); **^{13}C NMR** ($CDCl_3$:d_4-MeOD 9:1, 125 MHz) δ_C 113.2, 113.3 (2 signals), 113.5, 122.5, 122.7, 122.8, 122.9 (2 signals), 124.0, 124.1 (2 signals), 124.4, 124.5, 124.7 (2 signals), 126.6, 126.7 (2 signals), 126.8, 127.1, 127.2 (2 signals), 128.2, 128.3, 128.7, 129.1, 129.2, 129.6 (2 signals), 129.7, 129.8, 130.3 (2

signals), 130.4 (2 signals), 131.1, 131.2 (2 signals), 131.4, 131.5, 131.8, 131.9, 133.7 (3 signals), 133.8, 134.1, 134.2, 134.4, 150.8 (2 signals); ***m/z*** (ES−) 1276 ($[2M-H]^-$, 80%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{48}H_{29}O_2F_{12}^-$) requires ***m/z*** 637-2173, found ***m/z*** 637.2160; $[\alpha]_D^{25}$ = + 52.1 (*c* 1.05, $CHCl_3$/MeOH 9:1) (lit.[202] $[\alpha]_D^{22}$ = + 62 (*c* 1.0, $CHCl_3$).

N.B. This compound is rotameric, therefore no assignment was attempted for the ^1H and ^{13}C spectra

Preparation and characterisation of 3,3′-bis[3,5-bis(trifluoromethyl)phenyl]-1,1′-binaphthalene-2,2′-diol (*R*)-1g[90]

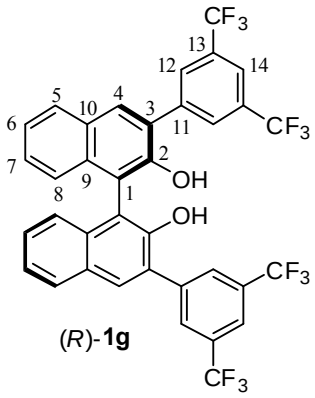


Prepared according to modified literature procedures from Wipf and Jung[133] and Akiyama *et al.*[90]

(*R*)-**2d** (4.72 g, 10.0 mmol, 1 equivalent), 3,5-bis(trifluoromethyl)phenylboronic acid (7.74 g, 30.0 mmol, 3 equivalents) and barium hydroxide (9.46 g, 30.0 mmol, 3 equivalents) were placed in a dry flask under nitrogen. Degassed 1,4-dioxane (18 mL) and degassed water (6 mL) were added through a septum. Nitrogen was bubbled through the vigorously stirred suspension for 5 minutes. $Pd(PPh_3)_4$ (1.16 g, 1.0 mmol, 0.1 equivalents) was added under nitrogen. Nitrogen was bubbled through the suspension for a further 2 minutes and the mixture was then heated to 110 ºC for 16 hours (monitored by TLC). After disappearance of the starting material, the mixture was partitioned between 1M aqueous HCl (150 mL) and dichloromethane (250 mL). The aqueous was re-extracted with dichloromethane (100 mL + 50 mL). The combined

organics were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The resulting brown oil was used without further purification in the next step.

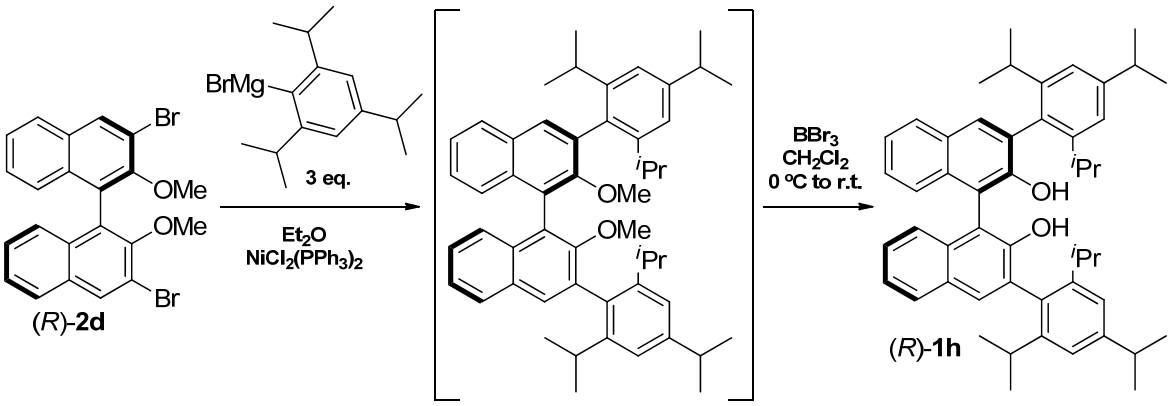
It was dissolved in dichloromethane (30 mL) and cooled to 0 ºC. A 1M solution of boron tribromide in dichloromethane (60 mL, 60 mmol, theoretical 6 equivalents) was then added slowly to the mixture, under nitrogen. After addition, the solution was stirred at room temperature for 16 hours. The excess reagent was carefully quenched by dropwise addition of ice-cold water to the solution, at 0 ºC. Once effervescence had ceased, 150 mL of water were added and the organics separated. The aqueous layer was re-extracted with dichloromethane (2 × 50 mL). The combined organics were dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with petroleum ether to petroleum ether/diethyl ether 98:2 to afford the title compound (*R*)-**1g** as a colourless solid (5.67 g, 80% over 2 steps). The spectral data matched the published ones.[90,135]



(*R*)-**1g**

m.p. 206-208 ºC; **FT-IR** ν_{max}(NaCl) 3529 cm^{-1} (O-H), 1622 cm^{-1} (ArC-H), 1377 cm^{-1}, 1279 cm^{-1}, 1173 cm^{-1}, 1133 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 5.49 (s, 2H, O-H), 7.32 (d, 2H, H-8, *J* 8.5 Hz), 7.48 (t, 2H, H-7, *J* 7.5 Hz), 7.54 (t, 2H, H-6, *J* 7.5 Hz), 8.00 (s, 2H, H-14), 8.07 (d, 2H, H-5, *J* 8.0 Hz), 8.20 (s, 2H, H-4), 8.33 (s, 4H, H-12); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 111.8 (Ar-Cquat.), 121.3 (app t, C-14, $J_{C\text{-}F}$ 3.5 Hz), 123.5 (q, CF_3, $J_{C\text{-}F}$ 272 Hz), 124.0 (C-8), 125.2 (C-6), 124.9 (C-8), 127.8 (Ar-Cquat.), 128.7 (C-7), 128.9 (C-5), 129.5 (Ar-Cquat.), 129.9 (d, C-12, $J_{C\text{-}F}$ 3.0 Hz), 131.6 (q, C-13, $J_{C\text{-}F}$ 33.0 Hz), 132.4 (C-4), 133.3 (Ar-Cquat.), 139.5 (Ar-Cquat.), 149.9 (C-2); ***m/z*** (ES−) 709 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{36}H_{17}O_2F_{12}^-$) requires ***m/z*** 709.1042, found ***m/z*** 709.1019; $[\alpha]_D^{25} = +48.3$ (*c* 0.99, $CHCl_3$) (lit.[90] $[\alpha]_D^{25} = +45.3$ (*c* 1.1, $CHCl_3$).

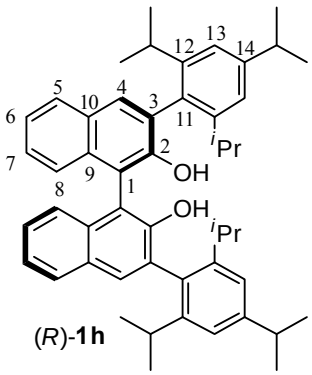
Preparation and characterisation of (*R*)-3,3′-bis-(2,4,6-triisopropylphenyl)-1,1′-binaphthalene-2,2′-diol (*R*)-1h[203]



Prepared according to a modified procedure from Schrock *et al*.[203]

In a dried tri-neck round bottom flask under nitrogen, (*R*)-**2d** (500 mg, 1.06 mmol, 1 equivalent) was suspended in dry diethyl ether (12.5 mL) and the suspension was stirred vigorously. $NiCl_2(PPh_3)_2$ was added (76.3 mg, 0.12 mmol, 0.11 equivalents) and the resulting mixture stirred for 1-2 minutes. Then, 2,4,6-triisopropylphenyl magnesiumbromide (0.7 M solution in Et_2O, 4 mL, 2.8 mmol, 2.4 equivalents) was added at room temperature over 10 minutes. The resulting mixture was stirred 10 minutes at room temperature before heating to reflux for 24 hours (the reaction can be monitored by TLC, eluent petroleum ether/diethyl ether 95:5). After completion the mixture was cooled to 0 ºC and quenched by slow addition of methanol and then water was added. The ethereal layer was collected and the aqueous re-extracted with dichloromethane (30 mL). The combined organics were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a green oil that was used without further purification. The green residue was dissolved in dry dichoromethane (20 mL). The mixture was stirred and cooled to 0 ºC before addition of a 1M solution of boron tribromide in dichloromethane (6.36 mL, 6.36 mmol, 6 equivalents) dropwise over 5 minutes. The mixture was then allowed to warm to room temperature and was stirred for 24 hours (completion was monitored by TLC, eluent petroleum ether/diethyl ether 95:5). The mixture was then cooled to

0 ºC and water was added dropwise very carefully (10 mL). The organic layer was separated and the aqueous re-extracted with dichloromethane (2 × 10 mL) dried over magnesium sulphate, filtered and concentrated *in vacuo*. The brown residue was purified by chromatography on silica gel eluting with petroleum ether/diethyl ether 99:1 to 98:2 to give (*R*)-**1h** as a pale brown foamy solid (458 mg, 62%). The spectral data were in agreement with the literature.[203]

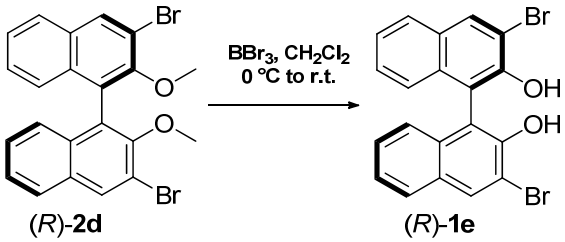


(*R*)-**1h**

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 1.02 (d, 6H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 1.08 (app. t, 12H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 1.18 (d, 6H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 1.30 (d, 12H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 2.67 (sept, 2H, $(CH_3)_2C\underline{H}$, *J* 7.0 Hz), 2.83 (sept, 2H, $(CH_3)_2C\underline{H}$, *J* 7.0 Hz), 2.89 (sept, 2H, $(CH_3)_2C\underline{H}$, *J* 7.0 Hz), 4.90 (s, 2H, O-H), 7.09-7.13 (m, 4H, Ar-H), 7.21-7.25 (m, 2H, Ar-H), 7.26-7.32 (m, 2H, Ar-H), 7.34-7.38 (m, 2H, Ar-H), 7.75 (s, 2H, H-4), 7.85 (d, 2H, Ar-H, *J* 8.0 Hz); ***m/z*** (ES−) 689 ([M−H]$^-$, 100%); $[\alpha]_D^{25}$ = + 86.9 (*c* 1.12, THF) (lit.[203] $[\alpha]_D^{25}$ = + 88.0 (*c* 3.0, THF).

6.2.1.1.7 Synthesis and characterisation of (*R*)-3,3′-dibromo-1,1′-binaphthalene-2,2′-diol

(*R*)-1e[204]

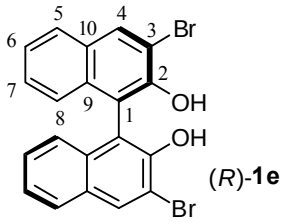


(*R*)-**2d** (*R*)-**1e**

Prepared according to a literature procedure from Yamamoto *et al.*[134]

(*R*)-**2d** (10.8 g, 22.9 mmol, 1 equivalent) was dissolved in dry dichloromethane (100 mL) and cooled to 0 ºC. A 1M solution of boron tribromide in dichloromethane (91.5 mL, 91.5 mmol, 4 equivalents) was added dropwise, at 0 ºC, to the stirred mixture, over 10 minutes. After addition

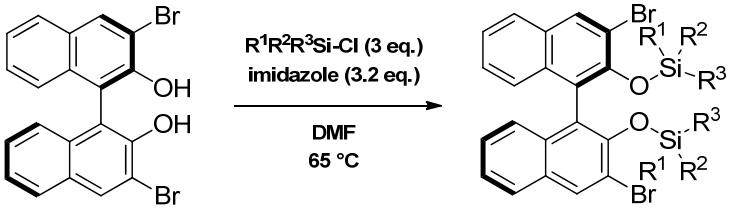
the mixture was allowed to warm to room temperature and stirred for 24 hours. The excess reagent was quenched by slow addition of water (very exothermic), and when all reagent was quenched, DI water (50 mL) was added to the biphasic mixture. The organic was separated, and the aqueous extracted twice with dichloromethane (2 × 40 mL). The organics were combined, washed once with water (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The resulting solid was purified by chromatography on a short path silica gel column eluting with petroleum ether/dichloromethane/diethyl ether 98:2:0 to 3:1:1 to afford (*R*)-**1e** as an off-white solid (12.9 g, 90 %). The spectral data were in agreement with the literature.[204]



(*R*)-**1e**

m.p.(CH_2Cl_2/petroleum ether 1:2) 239-242 ºC (lit.[204] 208-210 ºC); **FT-IR** ν_{max}(NaCl) 3496 cm^{-1} (O-H), 3055 cm^{-1} (ArC-H), 1616 cm^{-1} (ArC=C), 1577 cm^{-1} (ArC=C); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 5.57 (s, 2H, O-H), 7.12 (2H, d, H-8, *J* 8.5 Hz), 7.33 (app. t, 2H, H-6, *J* 7.0 Hz), 7.40 (app. t, 2H, H-7, *J* 7.5 Hz), 7.83 (d, 2H, H-5, *J* 8.0 Hz), 8.27 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 112.3 (C-3), 114.6 (C-1), 124.6 (C-8), 124.9 (C-7), 127.4 (C-6), 127.6 (C-5), 129.7 (C-10), 132.8 (2C, C-4 & C-9), 148.0 (C-2); ***m/z*** (ES−) 441 (80%), 443 (100%), 445 (70%) ($[M-H]^-$), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{12}O_2Br_2Na^+$) requires ***m/z*** 466.9077 found ***m/z*** 466.9066; $[\alpha]_D^{25}$ = + 64.6 (*c* 1.07, $CHCl_3$) (lit.[204] $[\alpha]_D^{22}$ = + 38.5 (*c* 0.1, THF)).

6.2.1.1.8 General procedure II for the preparation of (*R*)-5



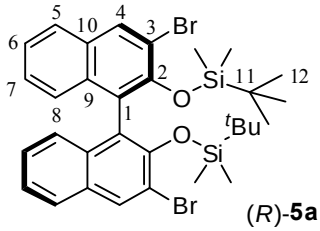
(*R*)-**1e** (*R*)-**5**

Prepared following a modified procedure from Yamamoto *et al.*[134]

(*R*)-**1e** (1 equivalent) and imidazole (3.2 equivalents) were suspended in anhydrous DMF (1 mL per 2 mmol) in a dry flask, under nitrogen. It was stirred at room temperature while the chlorosilane reaction partner was added (3 equivalents) in one portion. The resulting mixture was then heated to 65 ºC for 24 hours to 6 days (the completion was monitored by TLC). A saturated aqueous sodium bicarbonate was added (10 mL per 1 mmol) and the mixture was extracted with dichloromethane (4 × 15 mL per 1 mmol). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude solid was purified by column chromatography on silica gel.

Preparation and characterisation of(*R*)-[(3,3′-dibromo-1,1′-binaphthalene-2,2′-diyl)bis(oxy)]bis[*tert*-butyl(dimethyl)silane] (*R*)-5a

Synthesised on a 4 mmol scale (1.78 g of (*R*)-**1e**) according to general procedure **II**. Purified on silica gel eluting with petroleum ether to afford the title product (*R*)-**5a** as a colourless solid (2.60 g, 97%).

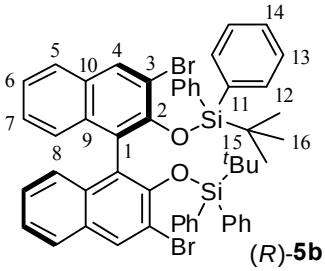


(*R*)-**5a**

m.p. 161-164 ºC; **FT-IR** ν_{max}(NaCl) 2941 cm^{-1} (ArC-H), 1493 cm^{-1} (ArC=C), 1253 cm^{-1} (Si-C), 851 cm^{-1} (ArC-H OOP/Si-C); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H – 1.06 (s, 6H, Si-C$\underline{H}_3$), 0.02 (s, 6H, Si-C$\underline{H}_3$), 0.85 (s, 18H, H-12), 7.13 (d, 2H, H-8, *J* 8.5 Hz), 7.23 (ddd, 2H, H-7, *J* 8.5 Hz, 7.5 Hz, 2.0 Hz), 7.35 (ddd, 2H, H-6, *J* 7.5 Hz, 7.0 Hz, 1.0 Hz), 7.76 (d, 2H, H-5, *J* 8.5 Hz), 8.24 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C − 4.0 (Si-$\underline{C}H_3$), − 3.0 (Si-$\underline{C}H_3$), 18.5 (C-11), 26.0 (C-12), 117.6 (Ar-Cquat.), 123.4 (Ar-Cquat.), 124.5 (C-6), 126.4 (C-8), 126.5 (C-7), 126.9 (C-5), 130.0 (Ar-Cquat.), 137.8 (C-4), 133.9 (Ar-Cquat.), 148.7 (C-2); ***m/z*** (ES+) 695 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{32}H_{40}O_2Si_2Br_2Na^+$) requires ***m/z*** 695.0808 found ***m/z*** 695.0812; $[\alpha]_D^{25}$ = − 237.1 (*c* 1.08, $CHCl_3$).

Preparation and characterisation of(*R*)-[(3,3′-dibromo-1,1′-binaphthalene-2,2′-diyl)bis(oxy)]bis[*tert*-butyl(diphenyl)silane] (*R*)-5b

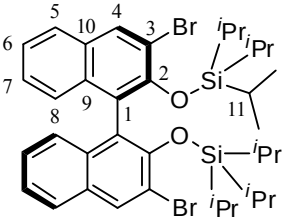
Synthesised on a 4 mmol scale (1.78 g of (*R*)-**1e**) according to general procedure **II**. Purified on silica gel eluting with petroleum ether/dichloromethane 96:4 to 9:1 to afford the title product (*R*)-**5b** as a colourless solid (3.45 g, 94 %).



(*R*)-**5b**

m.p. 297-301 ºC; **FT-IR** ν_{max}(NaCl) 3050 cm^{-1} (ArC-H), 1574 cm^{-1} (ArC=C), 1255 cm^{-1} (Si-C); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.44 (s, 18H, H-16), 7.20-7.25 (m, 6H, H-8, H-13a), 7.26-7.30 (m, 2H, H-7), 7.31-7.37 (m, 8H, H-6, H-8, H-13b, H-14a), 7.41-7.46 (m, 2H, H-14b), 7.52-7.56 (m, 4H, H-12a), 7.71 (d, 2H, H-5, *J* 8.0 Hz), 7.92-7.96 (m, 4H, H-12b), 8.03 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 19.4 (C-15), 25.6 (C-16), 116.1 (Ar-Cquat.), 123.7 (Ar-Cquat.), 124.7 (C-6), 126.0 (C-8), 126.5 (C-7), 126.9 (C-5), 127.1 (C-13b), 127.2 (C-13a), 129.1 (C-14a), 129.3 (C-14b), 130.2 (C-9), 133.3 (C-4), 133.9 (Ar-Cquat.), 134.4 (C-12a), 135.1 (Ar-Cquat.), 135.4 (C-12b), 149.1 (C-2); ***m/z*** (ES+) 941 (10%), 943 (20%), 945 (10%) ($[M+Na]^+$), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{52}H_{48}Br_2O_2Si_2Na^+$) requires ***m/z*** 943.1439 found ***m/z*** 943.1432; $[\alpha]_D^{25}$ = − 229.9 (*c* 1.02, $CHCl_3$).

Preparation and characterisation of(*R*)-[(3,3′-dibromo-1,1′-binaphthalene-2,2′-diyl)bis(oxy)]bis(triisopropylsilane)] (*R*)-5c



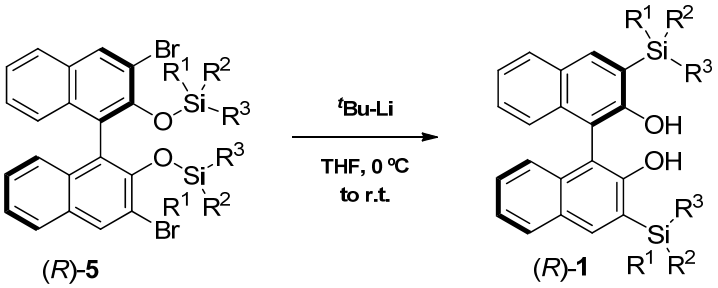
(*R*)-**5c**

Synthesised on a 4 mmol scale (1.78 g of (*R*)-**1e**) according to general procedure **II**. Purified on silica gel eluting with petroleum ether to afford the title product (*R*)-**5c** as a colourless solid (2.55 g, 84%).

m.p. 185-188 ºC; **FT-IR** ν_{max}(NaCl) 2945 cm^{-1} (ArC-H), 2866

cm^{-1} (Csp^3-H), 1449 cm^{-1} (CH_3), 1255 cm^{-1} (Si-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.59-0.72 (m, 6H, H-11), 0.81 (d, 18H, C<u>H</u>$_3$, *J* 7.3 Hz), 0.91 (d, 18H, C<u>H</u>$_3$, *J* 7.5 Hz), 7.11 (d, 2H, H-8, *J* 8.5 Hz), 7.20 (t, 2H, H-7, *J* 7.5 Hz), 7.34 (t, 2H, H-6, *J* 7.5 Hz), 7.77 (d, 2H, H-5, *J* 8.0 Hz), 8.25 (s, 2H, H-4) ; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.6 (C-11), 18.2 (<u>C</u>H$_3$), 18.2 (<u>C</u>H$_3$), 118.3 (Ar-Cquat.), 123.3 (Ar-Cquat.), 124.4 (C-6), 126.0 (C-7), 126.7 & 126.8 (C-5 & C-8), 129.6 (Ar-Cquat.), 132.6 (C-4), 133.2 (Ar-Cquat.), 150.3 (C-2); ***m/z*** (ES+) 779 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{38}H_{52}O_2Si_2Br_2Na^+$) requires ***m/z*** 779.1749 found ***m/z*** 779.1740; $[\alpha]_D^{25} = -246.3$ (*c* 1.10, $CHCl_3$).

6.2.1.1.9 General procedure III for the preparation of (*R*)-1 from (*R*)-5

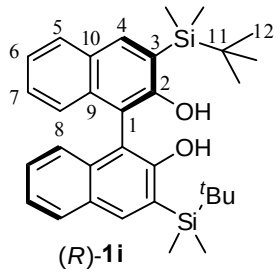


Prepared according to a literature procedure from Yamamoto *et al.*[134]

(*R*)-**5** (1 equivalent) was dissolved in freshly distilled tetrahydrofuran (10 mL per 1 mmol). The solution was cooled to 0 ºC and ^{t}BuLi (1.7 M in pentane, 4 equivalents) was added dropwise to the mixture, over 10 minutes. After addition, the solution was allowed to stir at room temperature for 1 hour (completion was monitored by TLC). The excess organolithium was quenched by addition of water (10 mL per 1 mmol) and the resulting biphasic mixture extracted with diethyl ether (4 × 10 mL per 1 mmol). The combined organics were dried over magnesium sulphate and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel.

Preparation and characterisation of(*R*)-3,3′-bis[*tert*-butyl(dimethyl)silyl]-1,1′-binaphthalene-2,2′-diol (*R*)-1i[134]

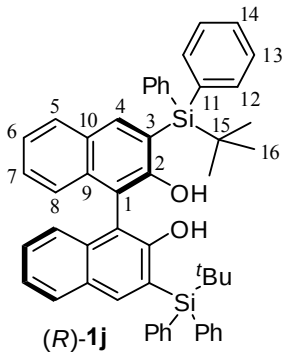
Synthesised on a 3.72 mmol scale (2.50 g of (*R*)-**5a**) according to general procedure **III**. Purified on silica gel eluting with petroleum ether to afford the title product (*R*)-**1i** as a colourless solid (1.84 g, 96%). Analytical data in agreement with the literature.[134]



(*R*)-**1i**

m.p. 87-90 ºC (lit.[134] 63-66 ºC); **FT-IR** ν_{max}(NaCl) 3522 cm^{-1} (O-H), 2954 cm^{-1} (ArC-H), 1618 cm^{-1} (ArC=C), 1580 cm^{-1} (ArC=C), 755 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.44 (s, 6H, Si-C$\underline{H}_3$), 0.45 (s, 6H, Si-C$\underline{H}_3$), 0.97 (s, 18H, H-12), 5.24 (s, 2H, OH), 7.10 (d, 2H, H-8, *J* 8.0 Hz), 7.30 (t, 2H, H-6, *J* 7.5 Hz), 7.36 (t, 2H, H-7, *J* 7.0 Hz), 7.90 (d, 2H, H-5, *J* 8.0 Hz), 8.10 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C − 4.6 (Si-$\underline{C}H_3$), − 4.5 (Si-$\underline{C}H_3$), 17.6 (C-11), 27.1 (C-12), 109.6 (C-1), 123.6 (C-7), 123.8 (C-8), 126.7 (Ar-Cquat.), 127.6 (C-6), 128.6 (C-5), 129.1 (ArC-quat.), 134.2 (Ar-Cquat.), 139.4 (C-4), 157.1 (C-2); ***m/z*** (ES+) 537 ([M+Na]$^+$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{32}H_{41}O_2Si_2^-$) requires ***m/z*** 513.2651 found ***m/z*** 513.2645; $[\alpha]_D^{25}$ = + 84.7 (*c* 1.02, $CHCl_3$) (lit.[134] $[\alpha]_D$ = + 136 (*c* 1.02, THF)).

Preparation and characterisation of(*R*)-3,3′-bis[*tert*-butyl(diphenyl)silyl]-1,1'-binaphthalene-2,2′-diol (*R*)-1j[134]



(*R*)-**1j**

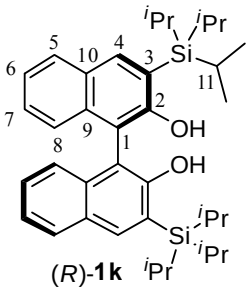
Synthesised on a 2 mmol scale (1.84 g of (*R*)-**5b**). Purified on silica gel eluting with petroleum ether/dichloromethane 95:5 to 85:15 to afford the title product (*R*)-**1j** as a colourless solid (1.53 g, 100%). The spectral data were in agreement with the literature.[134]

m.p. 148-151 ºC (lit.[134] 145-147 ºC); **FT-IR** ν_{max}(NaCl) 3517

cm^{-1} (O-H), 2933 cm^{-1} (ArC-H), 1616 cm^{-1} (ArC=C), 1579 cm^{-1} (ArC=C), 754 cm^{-1} (ArC-H OOP), 700 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.25 (s, 18H, H-16), 5.39 (s, 2H, OH), 7.24 (d, 2H, H-8, *J* 8.0 Hz), 7.30-7.47 (m, 16H, H-6, H-7, H-12, H-14), 7.65 (t, 8H, H-13, *J* 7.5 Hz), 7.73 (d, 2H, H-5, *J* 8.0 Hz), 7.98 (s, 2H, H-4) ; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 18.6 (C-15), 29.8 (C-16), 110.2 (C-1), 123.7 (4C, C-6, C-8), 124.2 (Ar-Cquat.), 127.6 (C-12), 128.1 (C-7), 129.0 (C-5), 129.1 (C-14), 134.5 (C-3), 135.1 (C-11), 136.2 (C-13), 142.5 (C-4), 156.5 (C-2); ***m/z*** (ES+) 785 ($[M+Na]^+$, 70%), **HRMS** (ES+) exact mass calculated for $[M+NH_4]^+$ ($C_{52}H_{54}NO_2Si_2^+$) requires ***m/z*** 780.3688 found ***m/z*** 780.3687; $[\alpha]_D^{25}$ = + 68.2 (*c* 1.03, $CHCl_3$) (lit.[134] $[\alpha]_D$ = + 111 (*c* 1.01, THF)).

Preparation and characterisation of(*R*)-3,3′-bis(triisopropylsilyl)-1,1′-binaphthalene-2,2′-diol (*R*)-1k

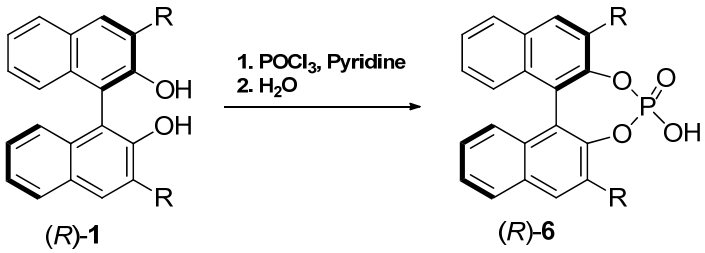
Synthesised on a 3 mmol scale (2.25 g, (*R*)-**5c**) according to general procedure **III**. Purified on silica gel eluting with petroleum ether to afford the title product (*R*)-**1k** as a pale yellow solid (1.75 g, 97%).



(*R*)-**1k**

m.p. 97-100 ºC; **FT-IR** ν_{max}(NaCl) 3519 cm^{-1} (O-H), 2943 cm^{-1} (ArC-H), 2865 cm^{-1} (Csp^3-H), 1617 cm^{-1} (ArC=C), 1579 cm^{-1} (ArC=C), 752 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.17-1.23 (m, 36H, CH_3), 1.64 (sept, 6H, H-11, *J* 7.5 Hz), 5.30 (s, 2H, OH), 7.17 (d, 2H, H-8, *J* 8.5 Hz), 7.33 (app. t, 2H, H-7, *J* 7.5 Hz), 7.40 (app. t, 2H, H-6, *J* 7.5 Hz), 7.95 (d, 2H, H-5, *J* 8.0 Hz), 8.20 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 11.7 (C-11), 19.0 (2 signals, $\underline{C}H_3$), 109.7 (C-1), 123.6 (C-6), 123.8 (C-8), 124.5 (Ar-Cquat.), 127.6 (C-7), 128.6 (C-5), 129.2 (Ar-Cquat.), 134.1 (C-3), 139.9 (C-4), 157.2 (C-2); ***m/z*** (ES+) 621 ($[M+Na]^+$, 30%), **HRMS** (ES+) exact mass calculated for $[M-H]^-$ ($C_{38}H_{53}O_2Si_2^-$) requires ***m/z*** 597.3590 found ***m/z*** 597.3592; $[\alpha]_D^{25}$ = + 70.5 (*c* 1.05, $CHCl_3$).

6.2.1.1.10 General procedure IV for the preparation of (R)-2,6-bis(aryl)dinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepin-4-ol 4-oxide (R)-6

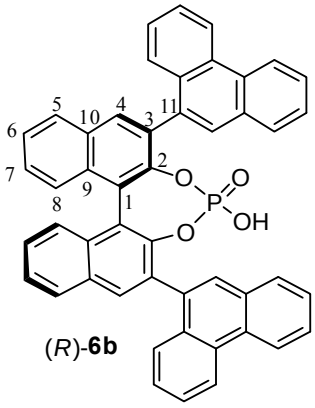


(*R*)-**1** (*R*)-**6**

BINOL (*R*)-**1** (1 equivalent) was suspended (dissolved) in pyridine (4 mL per 1 g) and stirred vigorously at room temperature while $POCl_3$ was added dropwise (2 equivalents). After addition the mixture was heated at 95 ºC for 6-48 hours (consumption of starter was monitored by TLC). The mixture was then allowed to cool to room temperature and was then cooled to 0 ºC. Water was added dropwise (1 mL per 1 g of diol). After addition, the mixture was heated at 95 ºC for 6-24 hours (consumption of intermediate monitored by TLC). The mixture was allowed to cool to room temperature, 4M aqueous hydrochloric acid was added (50 mL per 1 g of diol). To the resulting suspension was added dichloromethane (50 mL per 1 g of diol). The aqueous layer was washed four times with dichloromethane (50 mL per 1 g of diol), The organic layers were combined and washed twice with 4M aqueous HCl (50 mL per 1 g of diol). The organic layer was then dried over magnesium sulphate and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol (typically from 100:0 to 97:3) to afford the pure phosphoric acid.

Preparation and characterisation of(*R*)-2,6-di(9-phenanthryl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6b

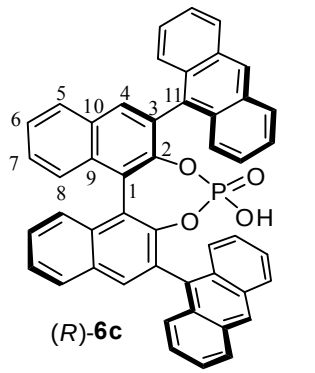
The product was synthesised according to general procedure **IV** on a 1.49 mmol scale (950 mg of (*R*)-**1b**) and purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/methanol 95:5 to afford the title phosphoric acid (*R*)-**6b** as a pale beige powder (912 mg, 87%).



(*R*)-**6b**

m.p. > 370 ºC (lit.[205] 390-400 ºC); **FT-IR** ν_{max}(NaCl) 3635 cm^{-1} (O-H), 3055 cm^{-1} (ArC-H), 1602cm^{-1} (ArC=C), 1260 cm^{-1} (P=O), 744 cm^{-1} (ArC-H OOP), 726 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 7.38-7.75 (m, 16H, Ar-H), 7.92-8.22 (m, 8H, Ar-H), 8.85-8.95 (m, 4H, Ar-H); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 122.2 (Ar-Cquat.), 122.8 (Ar-CH), 123.1 (Ar-Cquat.), 125.3 (Ar-CH), 126.2 (Ar-CH), 126.4 (2C, Ar-CH), 126.7 (Ar-CH), 126.8 (Ar-CH), 126.9 (Ar-CH), 126.9 (Ar-CH), 128.5 (Ar-Cquat.), 129.0 (Ar-CH), 129.3 (Ar-CH), 129.6 (Ar-Cquat.), 129.6 (Ar-Cquat.), 130.4 (Ar-Cquat.), 131.2 (Ar-Cquat.), 131.2 (Ar-Cquat.), 131.6 (Ar-CH), 132.2 (Ar-CH), 133.1 (Ar-Cquat.), 134.0 (Ar-Cquat.), 147.5 (d, C-2, $J_{C\text{-}P}$ 9.5 Hz); ***m/z*** (ES−) 701 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M−H]$^-$ ($C_{48}H_{28}O_4P$) requires ***m/z*** 699.1731 found ***m/z*** 699.1718; $[\alpha]_D^{25} = -66.2$ (*c* 1.05, $CHCl_3$/MeOH 9:1) (lit.[205] $[\alpha]_D^{22} = -44.0$ (*c* 1.00, DMSO).

Preparation and characterisation of (*R*)-2,6-di(9-anthryl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6c



(*R*)-**6c**

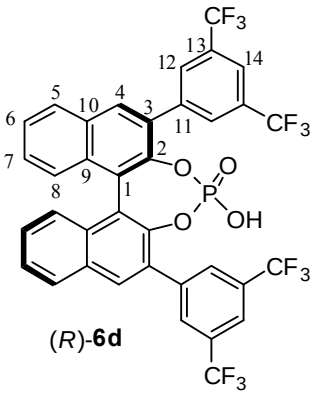
The product was synthesised according to general procedure **IV** on a 2.82 mmol scale (1.80 g of (*R*)-**1f** prepared by A. W. Pilling) and purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/methanol 98:2 to 95:5 to afford (*R*)-**6c** as a a pale beige powder (1.14 g, 58%). The spectral data were in agreement with the literature.[206]

m.p. 344-348 ºC; **FT-IR** ν_{max}(NaCl) 3601 cm^{-1} (O-H), 3028 cm^{-1} (C-H), 1598 cm^{-1} (ArC=C), 1110 cm^{-1} (P=O), 1110 cm^{-1} (P-O/C-O), 752 cm^{-1} (ArC-H OOP), 736cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 6.73 (t, 2H, Ar-H, *J* 7.0 Hz), 6.83 (t,

2H, Ar-H, *J* 7.5 Hz), 7.21-7.32 (m, 4H, Ar-H), 7.35-7.41 (d, 2H, Ar-H, *J* 8.0 Hz), 7.43-7.48 (m, 2H, Ar-H), 7.49-7.54 (m, 2H, Ar-H), 7.65 (d, 2H, Ar-H, *J* 8.5 Hz), 7.69-7.75 (m, 4H, Ar-H), 7.78 (d, 2H, Ar-H, *J* 8.5 Hz), 7.89-7.94 (m, 4H, Ar-H), 8.10 (s, 2H, Ar-H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 122.9 (Ar-Cquat.), 124.7 (Ar-CH), 125.0 (Ar-CH), 125.1 (Ar-CH), 125.4 (Ar-CH), 125.9 (Ar-CH), 126.6 (Ar-CH), 126.7 (Ar-CH), 126.8 (Ar-CH), 127.3 (Ar-CH), 127.4 (Ar-CH), 128.0 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 130.2 (Ar-Cquat.), 130.6 (Ar-Cquat.), 130.7 (Ar-Cquat.), 130.9 (Ar-Cquat.), 131.0 (2C, 2 × Ar-Cquat.), 132.6 (Ar-Cquat.), 133.0 (Ar-Cquat.), 133.3 (Ar-CH), 147.9 (d, C-2, $J_{C\text{-}P}$ 8.5 Hz); ***m/z*** (ES−) 699 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{48}H_{29}O_4PNa^+$) requires ***m/z*** 723.1696 found ***m/z*** 723.1701; $[\alpha]_D^{25} = +51.4$ (*c* 0.97, $CHCl_3$) (lit.[206] $[\alpha]_D^{16.6} = +64.9$ (*c* 1.00, EtOH)).

Preparation and characterisation of (*R*)-2,6-bis[3,5-bis(trifluoromethyl)phenyl] dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6d[90]

The product was synthesised according to general procedure **IV** on a 2.53 mmol scale (1.80 g of (*R*)-**1g**) and purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/methanol 97:3 to afford the title product (*R*)-**6d** as a colourless solid (1.96 g, 75%). The spectral data were in agreement with the literature.[90]



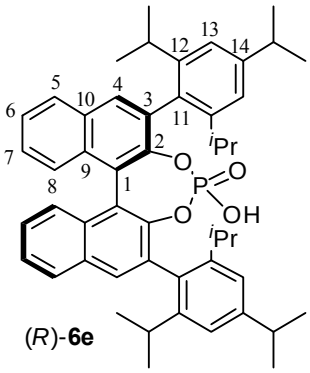
(*R*)-**6d**

m.p. 163-166 ºC (lit.[90] 163.5-180.0 ºC); **FT-IR** ν_{max}(NaCl) 3063 cm^{-1} (ArC-H), 1621 cm^{-1} (ArC=C), 1501 cm^{-1} (ArC=C), 1378 cm^{-1}, 1280 cm^{-1}, 1176 cm^{-1}, 1135 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 7.39-7.44 (m, 4H, Ar-H), 7.57-7.64 (m, 4H, Ar-H, H-14), 8.01-8.05 (m, 8H, Ar-H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 121.5 (m, C-14), 122.6 (d, Ar-Cquat., *J* 2.5 Hz), 123.1 (q, CF_3, $J_{C\text{-}F}$ 271.0), 126.7 (Ar-CH), 127.0 (Ar-Cquat.), 127.5 (Ar-CH), 128.6 (Ar-CH), 129.8 (d, Ar-CH, *J* 2.5 Hz), 131.1 (d, Ar-Cquat., *J* 3.0 Hz), 131.3 (Ar-Cquat.), 131.4 (q, C-CF_3, $J_{C\text{-}F}$ 33.0 Hz), 131.9 (Ar-CH), 132.3 (Ar-CH), 138.6 (Ar-Cquat.), 143.7 (d, C-

2, $J_{C\text{-}P}$ 9.5 Hz); ***m/z*** (ES−) 771 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{36}H_{17}O_4PF_{12}Na^+$) requires ***m/z*** 795.0565 found ***m/z*** 795.0557; $[\alpha]_D^{25}$ = − 197.3 (*c* 1.00, $CHCl_3$) (lit.[90] $[\alpha]_D^{25}$ = − 197.5 (*c* 0.97, $CHCl_3$)).

Preparation and characterisation of (*R*)-2,6-bis(2,4,6-triisopropylphenyl)dinaphtho [2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6e[127]

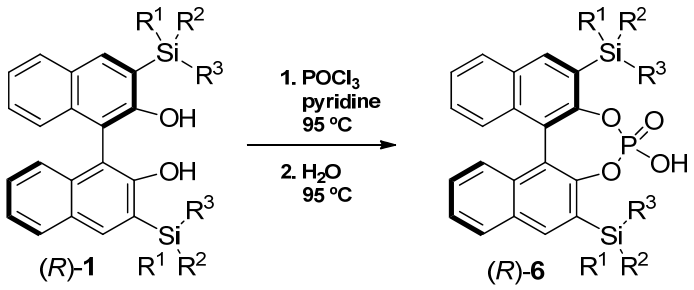
Synthesised according to general procedure **IV** on a 0.66 mmol scale (458 mg of (*R*)-**1h**) and purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/methanol 98:2 to afford (*R*)-**6e** as a colourless powder (372 mg, 75%). The spectral data were in agreement with the literature.[127]



(*R*)-**6e**

m.p. 238-242 ºC; **FT-IR** ν_{max}(NaCl) 3611 cm^{-1} (O-H), 2961 cm^{-1} (ArC-H), 1605 cm^{-1} (ArC=C), 1214 cm^{-1} (P=O), 1280 cm^{-1}, 752 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 0.86 (d, 6H, (C$\underline{H}_3$)$_2$CH, *J* 7.0 Hz), 1.08 (d, 6H, (C$\underline{H}_3$)$_2$CH, *J* 7.0 Hz), 1.14-1.18 (m, 12H, (C$\underline{H}_3$)$_2$CH), 1.27 (d, 12H, (C$\underline{H}_3$)$_2$CH, *J* 7.0 Hz), 2.58 (q, 2H, (CH$_3$)$_2$C$\underline{H}$, *J* 7.0 Hz), 2.86-3.01 (m, 4H, (CH$_3$)$_2$C$\underline{H}$), 7.01 (d, 2H, Ar-H, *J* 1.5 Hz), 7.04 (d, 2H, H-8, *J* 8.5 Hz), 7.11 (d, 2H, Ar-H, *J* 1.5 Hz), 7.27 (t, 2H, Ar-H, *J* 8.0 Hz), 7.39 (t, 2H, Ar-H, *J* 8.0 Hz), 7.77 (s, 2H, H-4), 7.98 (d, 2H, H-5, *J* 8.0 Hz); ***m/z*** (ES−) 751 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{50}H_{57}O_4PNa^+$) requires ***m/z*** 775.3887 found ***m/z*** 775.3883; $[\alpha]_D^{25}$ = − 55.7 (*c* 1.13, $CHCl_3$).

6.2.1.1.11 General procedure V for the preparation of silylated phosphoric acids (*R*)-6

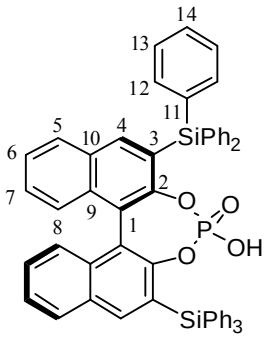


BINOL (*R*)-**1** (1 equivalent) was suspended (dissolved) in pyridine (4 mL per 1 g) and stirred vigorously at room temperature while $POCl_3$ was added dropwise over 10 minutes (2 equivalents). After addition the mixture was heated at 95 ºC for 6-48 hours (consumption of starter was monitored by TLC). The mixture was then allowed to cool to room temperature and was then cooled to 0 ºC while water was added dropwise (1 mL per 1 g of diol). After addition, the mixture was heated at 95 ºC for 6-24 hours (consumption of intermediate monitored by TLC). The mixture was allowed to cool to room temperature, 2M aqueous hydrochloric acid was added (50 mL per 1 g of diol). To the resulting suspension was added dichloromethane (50 mL per 1 g of diol). The aqueous layer was washed four times with dichloromethane (50 mL per 1 g of diol), The organic layers were combined and washed twice with 4M aqueous HCl (50 mL per 1 g of diol). The organic layer was then dried over magnesium sulphate and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel, eluting with dichloromethane/methanol (typically from 99:1 to 95:5) to afford the pure phosphoric acid.

Preparation and characterisation of (*R*)-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1′,2′-*f*] [1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6f[49]

Prepared according to general procedure **V** on a 12.45 mmol scale ((*R*)-**1c**, 10.00 g, 1 equivalent). The formation of the phosphoryl chloride intermediate was complete after 6 hours at 95 ºC. The hydrolysis was carried out over 6 hours at 95 ºC. The crude acid was purified by column chromatography on silica gel eluting with dichloromethane/methanol 99:1 to 97:5 to

afford the title compound as a colourless solid (10.77 g, 93%). The analytical data were in agreement with the literature.[49]



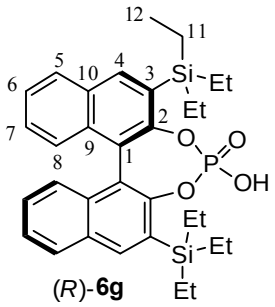
(*R*)-**6f**

m.p. 310-315 ºC; **FT-IR** ν_{max}(NaCl) 3608 cm^{-1} (O-H), 3070 cm^{-1} (ArC-H), 753 cm^{-1} (ArC-H OOP), 702 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.28-7.42 (m, 22H, H-7, H-8, H-13, H-14), 7.42-7.48 (m, 2H, H-6), 7.70 (app d, 12H, H-12, *J* 7.5 Hz), 7.82 (d, 2H, *J* 8.0 Hz, H-5), 8.14 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 121.5 (d, Ar-Cquat., $J_{C\text{-}P}$ 1.5 Hz), 125.3 (C-6), 126.0 (d, Ar-Cquat., $J_{C\text{-}P}$ 3.5 Hz), 126.8 & 127.4 (C-7, C-8), 127.7 (C-13), 128.6 (C-5), 129.5 (C-14), 130.6 (Ar-Cquat.), 134.0 (C-11), 134.2 (Ar-Cquat.), 136.7 (C-12), 142.0 (C-4), 151.4 (d, C-2, $J_{C\text{-}P}$ 9.0 Hz); ***m/z*** (ES−) 863 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{56}H_{40}O_4PSi_2^-$) requires ***m/z*** 863.2208 found ***m/z*** 863.2206; $[\alpha]_D^{25}$ = − 173.3 (*c* 1.06, $CHCl_3$) (lit.[49] $[\alpha]_D^{23}$ = − 156.0 (*c* 1.02, $CHCl_3$)).

Preparation and characterisation of (*R*)-2,6-bis(triethylsilyl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2] dioxaphosphepin-4-ol 4-oxide (*R*)-6g

The title product was prepared according to a slight modification of general procedure **V**. (*R*)-**1d** (220 mg, 0.43 mmol, 1 equivalent) was dissolved in pyridine (1.5 mL). The solution was cooled to 0 ºC and $POCl_3$ (78 µL, 0.86 mmol, 2 equivalents) was added slowly dropwise. After addition, the solution was warmed to 60 ºC for 6 hours (conversion monitored by TLC). It was then cooled to 0 ºC and water (0.5 mL) was added dropwise slowly. After addition, the solution was heated to 60 ºC for 6 hours. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (25 mL) and 1M aqueous hydrochloric acid (40 mL). The aqueous was re-extracted with dichloromethane (2 × 15 mL). The combined organics were washed with 1M aqueous hydrochloric acid (2 × 25 mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica

gel eluting with dichloromethane to dichloromethane/methanol 97:3 to afford the title product as a colourless powder (170 mg, 67%).



(*R*)-**6g**

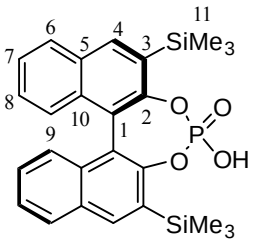
m.p. 364-365 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3358 cm^{-1} (O-H), 2953 cm^{-1} (ArC-H), 1247 cm^{-1} (P=O), 1111 cm^{-1} (P-O/C-O), 1091 cm^{-1} (P-O/C-O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.85-1.05 (m, 30H, H-11, H-12), 7.03 (d, 2H, H-8, *J* 8.5 Hz), 7.14-7.20 (m, 2H, H-7), 7.39 (app. t, 2H, H-6, *J* 7.5 Hz), 7.90 (d, 2H, H-5, *J* 8.0 Hz), 8.00 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 3.5 (C-11), 7.5 (C-12), 121.1 (C-1), 124.6 (C-6), 126.3 (C-7), 126.7 (C-8), 128.0 (C-5), 128.9 (d, C-3, J_{C-P} 3 Hz), 130.5 (C-10), 133.8 (C-9), 137.9 (C-4), 152.5 (d, C-2, J_{C-P} 10 Hz); ***m/z*** (ES−) 575 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M-H]$^-$ ($C_{32}H_{40}O_4Si_2P^-$) requires ***m/z*** 575.2208 found ***m/z*** 575.2208; $[\alpha]_D^{25} = -328.5$ (*c* 0.98, $CHCl_3$).

Preparation and characterisation of (*R*)-2,6-bis(trimethylsilyl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6h

N.B. 3,3′-TMS substituted BINOL was synthesised by Dr. Adam Pilling according to a literature procedure.[138]

3,3′-TMS substituted BINOL (430 mg, 1 mmol, 1 equivalent) was dissolved in pyridine (3 mL) and the solution was cooled to 0 ºC. $POCl_3$ (183 µL, 2 mmol, 2 equivalents) was added dropwise at 0 ºC. After addition the solution was heated to 65 ºC for 16 hours (monitored by TLC). It was then cooled to 0 ºC and DI water (1 mL) was added carefully, dropwise. After addition, the solution was heated for 6 hours to 65 ºC (monitored by TLC). The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (20 mL) and 1M aqueous HCl (20 mL). The aqueous was re-extracted with 2 × 10 mL of dichloromethane. The combined organics were washed with 2M aqueous HCl (2 × 10 mL, shaking vigorously), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The

pale brown residue was purified by column chromatography on silica gel eluting with dichloromethane/methanol 100:0 to 49:1 to afford the title phosphoric acid (*R*)-**6h** as a colourless crystalline solid (433 mg, 88 %).

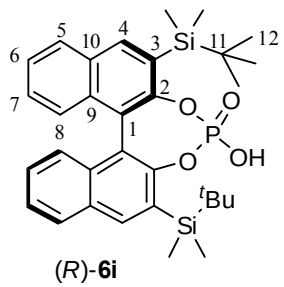


(*R*)-**6h**

m.p. 213-219 ºC; **FT-IR** ν_{max}(NaCl) 3070 cm^{-1} (O-H), 2956 cm^{-1} (ArC-H), 1252 cm^{-1} (Si-C), 1022 cm^{-1} , 839 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.63 (s, 18H, H-11), 7.21-7.32 (m, 4H, H-8, H-9), 7.49 (t, 2H, H-7, *J* 7.5 Hz), 7.99 (d, 2H, H-5, *J* 7.5 Hz), 8.22 (s, 2H, H-4), 11.31 (br s, 1H, O-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 0.11 (C-11), 120.6 (2 signals, C-1), 125.5 (C-7), 126.9 (4C, C-8, C-9), 131.3 (Ar-Cquat.), 131.5 (rotameric C-3), 133.4 (Ar-Cquat.), 138.0 (C-4), 150.5 & 150.6 (rotameric C-2); ***m/z*** (ES−) 491 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{29}O_4PSi_2Na^+$) requires ***m/z*** 515.1234, found ***m/z*** 515.1233; $[\alpha]_D^{25} = -247.4$ (*c* 1.06, $CHCl_3$).

Preparation and characterisation of (*R*)-2,6-bis[*tert*-butyl(dimethyl)silyl]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6i

Synthesised according to general procedure **V** on a 3.11 mmol scale ((*R*)-**1i**, 1.60 g). Purified on silica gel eluting with dichloromethane/methanol 100:0 to 93:7 to afford the title product (*R*)-**6i** as a colourless powder (0.70 g, 39% [94% brsm]).



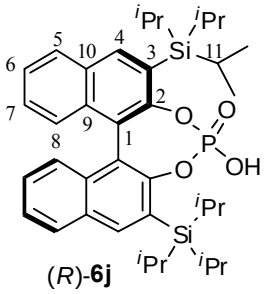
(*R*)-**6i**

m.p. 270-275 ºC; **FT-IR** ν_{max}(NaCl) 3494 cm^{-1} (O-H), 2931 cm^{-1} (ArC-H), 2855 cm^{-1} (Csp^3-H), 1615 cm^{-1} (ArC=C), 1577 cm^{-1} (ArC=C), 753 cm^{-1} (ArC-H OOP), 700 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.19 (br s, 6H, Si-C<u>H</u>$_3$), 0.57 (s, 6H, Si-C<u>H</u>$_3$), 0.79 (s, 18H, H-12), 7.02 (d, 2H, H-8, *J* 8.5 Hz), 7.21 (t, 2H, H-7, *J* 7.5 Hz), 7.44 (app. br s, 2H, H-6), 7.94 (app. br s, 4H, H-4, H-5); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C – 5.31 (br, Si-<u>C</u>H$_3$), − 2.91 (br, Si-<u>C</u>H$_3$), 17.5 (C-11), 26.8 (C-12), 121.1 (C-1),

124.9 (C-6), 126.6 (C-7), 126.7 (C-8), 128.2 (C-5), 128.8 (br, Ar-Cquat.), 130.5 (Ar-Cquat.), 133.8 (Ar-Cquat.), 138.2 (C-4), 151.8 (d, C-2, $J_{C\text{-}P}$ 7.5 Hz); ***m/z*** (ES−) 575 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{32}H_{40}O_4PSi_2^-$) requires ***m/z*** 575.2208 found ***m/z*** 575.2202; $[\alpha]_D^{25} = -332.6$ (*c* 0.96, $CHCl_3$/MeOH 50:1).

Preparation and characterisation of (*R*)-2,6-bis(triisopropylsilyl)dinaphtho[2,1-d:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6j

Synthesised according to general procedure **V** on a 2.75 mmol scale (1.65 g of (*R*)-**1k**). Purified on silica gel eluting with dichloromethane/methanol 100:0 to 93:7 to afford the title product (*R*)-**6j** as an off-white powder (1.07 g, 60%).



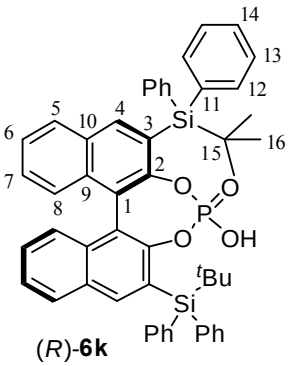
(*R*)-**6j**

m.p. 265-268 ºC; **FT-IR** ν_{max}(NaCl) 3382 cm^{-1} (br, O-H), 2964 cm^{-1} (ArC-H), 2866 cm^{-1} (Csp^3-H), 1619 cm^{-1} (ArC=C), 1219 cm^{-1}, 1090 cm^{-1}, 749 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 0.79 (d, 18H, C<u>H</u>$_3$, *J* 7.0 Hz), 0.85 (d, 18H, C<u>H</u>$_3$, *J* 7.0 Hz), 1.49 (app. quint, 6H, H-11, *J* 7.0 Hz), 6.50 (d, 2H, H-8, *J* 8.5 Hz), 6.87 (app. t, 2H, H-7, *J* 7.5 Hz), 7.02 (app. t, 2H, H-6, *J* 7.5 Hz), 7.67 (d, 2H, H-5, *J* 8.0 Hz), 7.78 (s, 2H, H-4); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 11.6 (C-11), 19.3 (<u>C</u>H$_3$), 19.4 (<u>C</u>H$_3$), 120.9 (Ar-Cquat.), 124.0 (C-6), 125.4 (C-8), 126.4 (C-7), 128.3 (C-5), 128.6 (Ar-Cquat.), 129.6 (Ar-Cquat.), 133.3 (Ar-Cquat.), 137.6 (C-4), 153.8 (br, C-2); ***m/z*** (ES−) 659 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{38}H_{52}O_4PSi_2^-$) requires ***m/z*** 659.3147 found ***m/z*** 659.3143; $[\alpha]_D^{25} = -175.6$ (*c* 0.90, $CHCl_3$).

Preparation and characterisation of (*R*)-2,6-bis[*tert*-butyl(dimethyl)silyl]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6k

Synthesised according to general procedure **V** on a 2 mmol scale (1.53 g of (*R*)-**1j**). Purified on silica gel eluting with dichloromethane/methanol 100:0 to 95:5 to afford the title product (*R*)-**6k**

as a colourless powder (1.45 g, 88%). The analytical data were in agreement with the literature.[49]

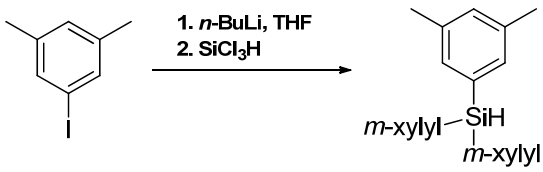


(*R*)-**6k**

m.p. 211-216 ºC; **FT-IR** ν_{max}(NaCl) 3610 cm^{-1} (O-H), 2937 cm^{-1} (ArC-H), 2860 cm^{-1} (Csp^3-H), 1618 cm^{-1} (ArC=C), 1562 cm^{-1} (ArC=C), 755 cm^{-1} (ArC-H OOP), 703 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.18 (m, 18H, H-16), 7.15-7.25 (m, 8H, H-6, H-8, H-13a), 7.27 (ddd, 2H, H-7, *J* 7.5 Hz, 6.5 Hz, 1.0 Hz), 7.31-7.36 (m, 4H, H-13b), 7.36-7.41 (m, 4H, H-7, H-14), 7.52-7.56 (m, 4H, H-12b), 7.60-7.64 (m, H-12a), 7.75 (d, 2H, H-5, *J* 8.0 Hz), 8.07 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 18.9 (C-15), 29.4 (C-16), 121.3 (C-1, $J_{C\text{-}P}$ 2.0 Hz), 126.5 (C-8), 126.7 (C-3, $J_{C\text{-}P}$ 4.0 Hz), 127.4 (C-7), 127.5 (C-13a), 127.6 (C-13b), 128.6 (C-5), 129.1 (C-6, C-14a), 130.5 (C-10), 134.0 (C-9), 134.3 (C-11a), 136.4 (C-11b), 136.5 (C-12b), 136.9 (C-12a), 142.4 (C-4), 151.1 (C-2, $J_{C\text{-}P}$ 9.5 Hz); ***m/z*** (ES−) 823 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{52}H_{48}O_4PSi_2^-$) requires ***m/z*** 823.2834 found ***m/z*** 823.2842; $[\alpha]_D^{25} = -181.8$ (*c* 1.03, $CHCl_3$) (lit.[49] $[\alpha]_D^{23} = -171.5$ (*c* 0.42, $CHCl_3$).

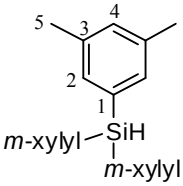
6.2.1.1.12 Synthesis of 2,6-bis[tris(3,5-dimethylphenyl)silyl]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2] dioxaphosphepin-4-ol 4-oxide

Preparation and characterisation of tri-(*m*-xylyl)silane[139]



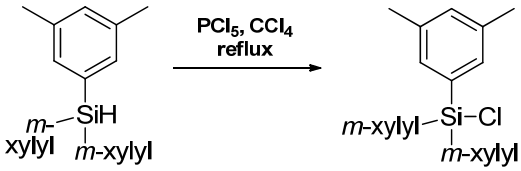
1-Iodo-3,5-dimethylbenzene (11.5 mL, 18.6 g, 80 mmol, 3 equivalents) was dissolved in 250 mL of dry diethyl ether and stirred in a round-bottomed flask and cooled to 0 ºC. *n*-BuLi 1.6 M

in hexanes (100 mL, 160 mmol, 6 equivalents) was added dropwise over 15 minutes. The resulting bright yellow solution was left stirring for 4 hours at 0 ºC (after the first hour, a white suspension had formed). Then trichlorosilane (freshly distilled) was added dropwise over 10 minutes at 0 ºC (2.7 mL, 3.61 g, 26.7 mmol, 1 equivalent). The resulting white suspension was allowed to warm to room temperature and stirred for 36 hours. The mixture was quenched with methanol (15 mL) and then a saturated aqueous solution of $NaHCO_3$ was added (150 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL), the organics were combined, washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over magnesium sulphate and the solvent was removed *in vacuo*. The resulting yellow oil was left standing at room temperature for 1 hour and it crystallised. The product was recrystallised from the minimum volume of boiling diethyl ether then cooled to room temperature and finally – 20 ºC. The title product was obtained after filtration as an off-white crystalline solid (9.03 g, 98%). The spectral data were in agreement with the literature.[139]



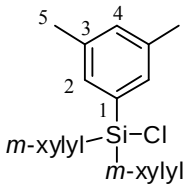
m.p. 117 ºC; **FT-IR** ν_{max}(NaCl) 3014 cm^{-1} (Ar-C-H), 2117 cm^{-1} (Si-H) , 864 cm^{-1} (Ar-C-H), 790 cm^{-1} (Si-C); **^{1}H NMR** ($CDCl_3$, 300MHz) δ_H 2.32 (s, 18H, H-5), 5.35 (s, 1H, Si-H), 7.08 (s, 3H, H-4), 7.22 (s, 6H, H-2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 21.4 (C-5), 131.5 (C-4), 133.5 (C-1 & C-2), 137.3 (C-3).

Preparation of and characterisation of tri-(*m*-xylyl)chlorosilane



Tri-(*m*-xylyl)silane (5.17 g, 15.0 mmol, 1 equivalent) was dissolved in carbon tetrachloride (75 mL) at room temperature. Phosphorus pentachloride (3.75 g, 18.0 mmol, 1.2 equivalents) was added portionwise over 5 minutes. The resulting suspension was heated at reflux for 2 hours. After completion (monitored by disappearance of the starting material by TLC), the mixture

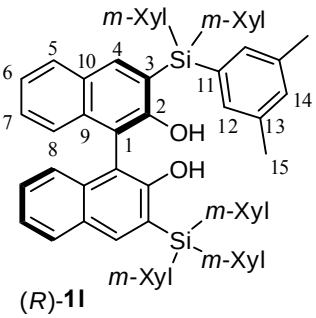
was allowed to cool to room temperature before removing the solvent *in vacuo*. The obtained solid was triturated with petroleum ether (2 × 15 mL) to afford the desired chlorosilane as an off-white solid that was used without further purification (4.80 g, 84%).



m.p. 137 ºC; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.33 (s, 18H, H-5), 7.13 (s, 3H, H-4), 7.26 (s, 6H, H-2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 21.4 (C-5), 132.4 (C-4), 132.8 (C-2), 133.0 (C-1), 137.4 (C-3); ***m/z*** (CI+) 378 (M^+, 55%), (EI+) 378 (M^+, 30%).

Preparation and characterisation of (*R*)-3,3′-bis[tris(3,5-dimethylphenyl)silyl]-1,1′-binaphthalene-2,2′-diol (*R*)-1l

The silyloxy precursor (*R*)-**5d** was synthesised according to general procedure **II** using the previously formed tri(*m*-xylyl)chlorosilane, on a 2.00 mmol scale of dibromo BINOL (*R*)-**1e** (888 mg). The crude mixture was then treated in the conditions described in general procedure **III**. The title product was purified by column chromatography on silica gel eluting with petroleum ether/dichloromethane/diethyl ether 90:10 to 85:15:1 to afford the title product (*R*)-**1l** as a pale yellow solid (1.25 g, 64 % over 2 steps). The spectral data were in agreement with the literature.[134,139]



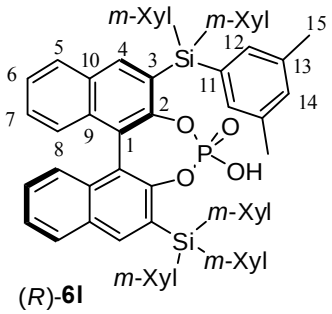
(*R*)-**1l**

m.p. 281-284 ºC (lit.[134] 285-286 ºC); **FT-IR** ν_{max}(NaCl) 3524 cm^{-1} (O-H), 3014 cm^{-1} (ArC-H), 2918 cm^{-1} (ArC-H), 1617 cm^{-1} (ArC=C), 1584 cm^{-1} (ArC=C), 755 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.31 (s, 36H, H-15), 5.34 (s, 2H, OH), 7.12 (s, 6H, H-14), 7.30-7.44 (m, 18H, H-12, H-6, H-7, H-8), 7.80 (d, 2H, H-5, *J* 7.5 Hz), 7.98 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 21.4 (C-15), 111.0 (C-1), 123.6 (ArC-H), 123.9 (Ar-CH), 124.4 (Ar-Cquat.), 127.8 (Ar-CH), 129.0 (C-5), 129.2 (Ar-Cquat.), 131.2 (C-14), 133.9 (C-13), 134.1 (C-11), 134.8 (Ar-Cquat.), 136.9 (C-12), 141.8 (C-4), 156.6 (C-2); ***m/z*** (ES+) 994 ($[M+Na]^+$,

100%), **HRMS** (ES+) exact mass calculated for $[M+NH_4]^+$ ($C_{68}H_{70}NO_2Si_2^+$) requires ***m/z*** 988.4940 found ***m/z*** 988.4934; $[\alpha]_D^{25}$ = + 99.5 (*c* 1.05, $CHCl_3$) (lit.[139] (*S*)-enantiomer $[\alpha]_D^{27}$ = − 132 (*c* 1.00, THF)).

Preparation and characterisation of 2,6-bis[tris(3,5-dimethylphenyl)silyl]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-6l

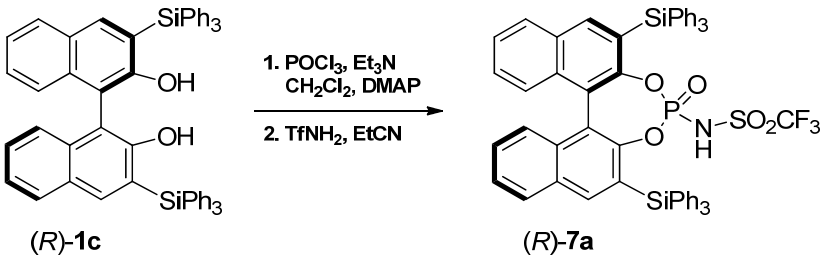
The phosphoric acid (*R*)-**6l** was prepared according to general procedure **V**, on a 0.5 mmol scale. The product was purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/methanol 97:3 to obtain the title acid as a pale pink powder (400 mg, 80 %).



(*R*)-**6l**

m.p. 176-181 ºC; **FT-IR** ν_{max}(NaCl) 3436 cm^{-1} (O-H), 3015 cm^{-1} (Ar-C-H), 2919 cm^{-1} (Ar-C-H), 2858 cm^{-1} (Csp^3-H), 1595 cm^{-1} (ArC=C), 1584 cm^{-1} (ArC=C), 1217 cm^{-1} (P=O), 1139 cm^{-1} (P-O/C-O); **^{1}H NMR** (C_6D_6, 400 MHz) δ_H 2.09 (s, 36H, H-15), 6.81 (ddd, 2H, H-7, *J* 8.0 Hz, 7.5 Hz, 1.0 Hz), 6.87 (s, 6H, H-14), 6.99 (app. t, 2H, H-6, *J* 7.5 Hz), 7.30 (d, 2H, H-8, *J* 8.5 Hz), 7.37 (d, 2H, H-5, *J* 8.0 Hz), 7.68 (s, 12H, H-12), 8.48 (s, 2H, H-4); **^{13}C NMR** (C_6D_6, 100 MHz) δ_C 21.8 (C-15), 122.4 (d, Ar-Cquat., $J_{C\text{-}P}$ 2.0 Hz), 126.0 (C-6), 127.5 (C-8), 128.1 (C-7), 128.3 (Ar-Cquat.), 129.5 (C-5), 131.8 (Ar-Cquat.), 132.1 (C-14), 134.9 (Ar-Cquat.), 135.1 (C-11), 135.6 (C-12), 137.6 (C-13), 142.8 (C-4), 152.4 (d, C-2, $J_{C\text{-}P}$ 9.0 Hz); ***m/z*** (ES−) 1033 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{68}H_{65}O_4PSi_2^+$) requires ***m/z*** 1055.4051 found ***m/z*** 1055.4030; $[\alpha]_D^{25}$ = − 143.5 (*c* 1.03, $CHCl_3$).

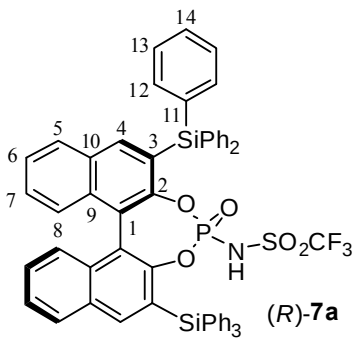
6.2.1.1.13 Synthesis and characterisation of (*R*)-1,1,1-trifluoro-*N*-[4-oxido-2,6-bis (triphenylsilyl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yl]methanesulfonamide (*R*)-7a



(*R*)-**1c** (*R*)-**7a**

Prepared according to a literature procedure from Yamamoto and co-workers.[140]

TPS BINOL (*R*)-**1c** (802 mg, 1.00 mmol, 1 equivalent) was dissolved in dry dichloromethane (5 mL). Triethylamine (1.0 mL, 7.2 mmol, 7.2 equivalents) was added and the solution cooled to 0 ºC. $POCl_3$ (110 µL, 1.20 mmol, 1.2 equivalents) was added slowly dropwise followed by addition of DMAP (244 mg, 2.00 mmol, 2 equivalents) in one portion. After addition, the solution was warmed to room temperature and stirred for 3 hours (conversion monitored by TLC). Anhydrous propionitrile (5 mL) was added followed by $CF_3SO_2NH_2$ (298 mg, 2 mmol, 2 equivalents). The solution was heated to 100 ºC for 16 hours. DI water was added (10 mL) and the biphasic mixture extracted with dichloromethane (3 × 15 mL). The combined organics were washed with a saturated solution of sodium bicarbonate (2 × 10 mL), then a 4M aqueous solution of HCl (2 × 15 mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 9:1 to 4:1 to afford the title product as a colourless solid (704 mg, 71%).



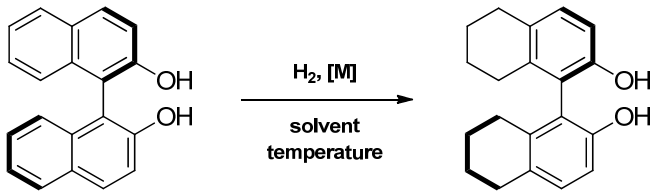
(*R*)-**7a**

m.p. > 365 ºC; **FT-IR** ν_{max}(NaCl) 3227 cm^{-1} (N-H), 3071 cm^{-1} (ArC-H), 1618 cm^{-1} (ArC=C), 1587 cm^{-1} (ArC=C), 1201 cm^{-1} (P=O), 755 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.19 (d, 1H, H-8), 7.23-7.53 (m, 23H, H-8', H-6, H-7, H-13, H-14), 7.63-7.68 (m, 6H, H-12), 7.68-7.72 (m, 6H,

H-12'), 7.77 (d, 1H, H-5, *J* 8.0 Hz), 7.88 (d, 2H, H-5', *J* 8.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 121.0, 121.3 (d, $J_{C\text{-}P}$ 2.5 Hz), 125.3 (d, $J_{C\text{-}P}$ 3.0 Hz), 125.7 (d, $J_{C\text{-}P}$ 4.0 Hz), 126.0 & 126.0 (Ar-CH), 126.7 (2C, Ar-CH), 127.7, 127.8, 127.8, 127.9, 128.0, 128.3, 128.7 (C-4), 128.9 (C-4'), 129.5, 129.7, 131,1, 133.3 (C-11), 133.4 (C-11'), 134.0, 134.2, 135.0, 136.5(C-12), 136.7, 136.9 (C-12'), 142.1 (C-4'), 142.7 (C-4), 150.2 (d, $J_{C\text{-}P}$ 9.5 Hz), 150.3 (d, $J_{C\text{-}P}$ 10.5 Hz); ***m/z*** (ES−) 994, 996 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M+Na]^+$ ($C_{57}H_{41}NSO_5Si_2PF_3Na^+$) requires ***m/z*** 1018.1826 found ***m/z*** 1018.1833; $[\alpha]_D^{25} = -157.6$ (*c* 0.67, $CHCl_3$).

6.2.1.1.14 Preparation and characterisation of (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-3,3′-substituted BPAs (*R*)-10

Preparation of and characterisation (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalene-2,2′-diol (*R*)-4a



(*R*)-**1a** (*R*)-**4a**

Method A: small scale synthesis in flow reactor

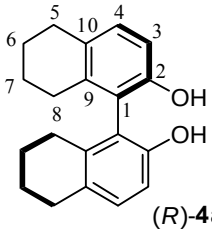
This method was inspired by the work of Börner and co-workers.[207]

(*R*)-BINOL (*R*)-**1a** (2.00 g, 6.98 mmol, 1 equivalent) was dissolved in 100 mL of ethanol (heating if necessary). This solution was hydrogenated using an H-Cube, recycling the solution (input and output are in the same vessel). Hydrogenation was performed with a Pd/C 10% cartridge under 50 bars and at 70 ºC. The solution was passed through the hydrogenator for 12 hours and the completion monitored by ^{1}H NMR. Ethanol was removed *in vacuo* and the resulting white solid was purified by column chromatography on silica gel eluting with

petroleum ether/dichloromethane 1:1 to neat dichloromethane to give (*R*)-**4a** as a white crystalline solid (1.81 g, 90%).

Method B: batch reactor synthesis[137]

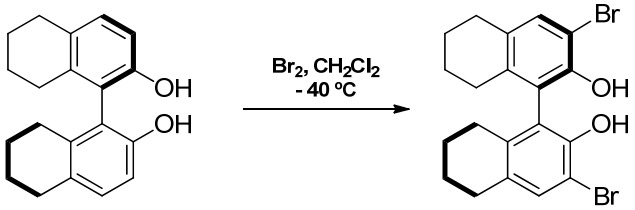
(*R*)-BINOL (*R*)-**1a** (100 g, 0.349 mol, 1 equivalent) was dissolved in 1 L of acetic acid. The solution was stirred while platinum(IV) oxide (12.7 g, 0.056 mol, 0.16 equivalents) was added. The reactor was then pressurised with 100 psi of hydrogen and the mixture stirred for 24 hours (LC-MS showed complete consumption of starting material). The catalyst was filtered off on celite and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel eluting with petroleum ether/dichloromethane 4:1 to 7:3 to afford the title product as a colourless solid (94.1 g, 92%). Analytical data in agreement with previous report.[137]



(*R*)-**4a**

m.p. 155-159 ºC (lit.[137] 165-166 ºC); **FT-IR** ν_{max}(NaCl) 3477 & 3389 cm^{-1} (O-H), 1587 cm^{-1} (Ar-C=C), 1435 cm^{-1} (CH_2), 1198 cm^{-1} (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.68-1.78 (m, 8H, H-6, H-7), 2.18 (dt, 2H, H-8a, *J* 17.0 Hz, 6.5 Hz), 2.32 (dt, 2H, H-8b, *J* 17.0 Hz, 6.0 Hz), 2.78 (t, 2H, H-5, *J* 6.0 Hz), 4.61 (s, 2H, OH), 6.85 (d, 1H, H-3, *J* 8.5 Hz), 7.09 (d, 1H, H-4, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 23.0 (C-6 & C-7), 27.1 (C-8), 29.2 (C-5), 113.0 (C-3), 118.8 (C-1), 130.1 (C-10), 131.1 (C-4), 137.1 (C-9), 151.4 (C-2); ***m/z*** (ES−) 293 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{22}O_2Na^+$) requires ***m/z*** 317.1512 found ***m/z*** 317.1517; **HPLC** - Chiralpak AD column - hexane/isopropanol 70:30, 2 mL/min, t_R = 2.89 min (*S*), t_R = 7.58 min (*R*), 99.5% e.e.; $[\alpha]_D^{25}$ = + 37.0 (*c* 1.06, $CHCl_3$) (lit.[137] $[\alpha]_D^{25}$ = + 52.8 (*c* 1.1, $CHCl_3$)).

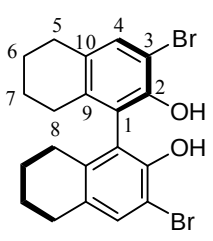
Preparation and characterisation of (*R*)-3,3′-dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalene-2,2′-diol (*R*)-4b[137]



(*R*)-**4a** (*R*)-**4b**

Prepared according to a literature procedure.[137]

(*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalene-2,2′-diol (*R*)-**4a** (8.82 g, 30 mmol, 1 equivalent) was dissolved in anhydrous dichloromethane (300 mL), and the solution was cooled to − 40 ºC and stirred under nitrogen while bromine was added quickly at − 40 ºC (3.54 mL, 69 mmol, 2.3 equivalents). The solution was stirred at − 40 ºC for 30 minutes (complete consumption of starting material monitored by TLC). A saturated solution of sodium thiosulphate was first added slowly at − 40 ºC (~ 15 mL), ~ 135 mL of the same solution were then added in one portion. The biphasic mixture was allowed to warm to room temperature and stirred vigorously for 5 minutes. The organic layer was collected and the aqueous layer extracted with 2 × 50 mL of dichloromethane. The combined organic phases were dried over magnesium sulphate and concentrated *in vacuo*. Column chromatography on silica gel eluting with petroleum ether/dichloromethane/diethyl ether 4:1:0 to 80:20:7 afforded the title product (*R*)-**4b** as an of-white crystalline solid (13.5 g, 99%). The spectral data were in agreement with the published ones.[137]

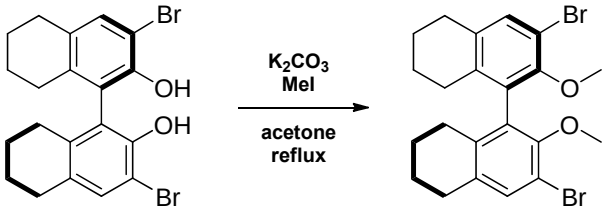


(*R*)-**4b**

m.p. 141-143 ºC (lit.[137] 142-143 ºC); **FT-IR** ν_{max}(NaCl) 3516 cm^{-1} (O-H), 2933 cm^{-1} (ArC-H), 2858 cm^{-1} (Csp^3-H), 1578 cm^{-1} (ArC=C), 1452 cm^{-1} (CH_2), 757 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.61-1.80 (m, 8H, H-6, H-7), 2.12 (dt, 2H, H-8a, *J* 17.5 Hz, 6.0 Hz), 2.32 (dt, 2H, H-8b, *J* 17.5 Hz, 6.0 Hz), 2,77 (app t, 4H, H-5, *J*

5.5 Hz), 5.12 (s, 2H, OH), 7.31 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 22.7 (2C, C-6, C-7), 26.8 (C-8), 29.0 (C-5), 107.1 (C-1), 122.1 (Ar-Cquat.), 131.4 (Ar-Cquat.), 132.5 (C-4), 136.7 (Ar-Cquat.), 147.1 (C-2); ***m/z*** (ES−) 449 (50%), 451 (100%), 453 (50%) ($[M-H]^-$), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{20}O_2Br_2Na^+$) requires ***m/z*** 472.9722 & 474.9703 & 476.9682 found ***m/z*** 472.9716 (45%) & 474.9684 (100%) & 476.9670 (45%); $[\alpha]_D^{25}$ = + 25.7 (*c* 1.03, $CHCl_3$) (lit.[137] $[\alpha]_D^{25}$ = + 29.2 (*c* 1.05, $CHCl_3$)).

Preparation and characterisation of (*R*)-3,3′-dibromo-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalene (*R*)-9a

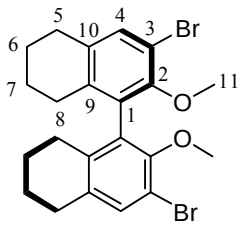


(*R*)-**4b** (*R*)-**9a**

Prepared by analogy to the procedure carried out for the methylation of BINOL[199] as described by Jia *et al.*[208]

(*R*)-3,3′-dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalene-2,2′-diol (*R*)-**4b** (9.04 g, 20 mmol, 1 equivalent) was dissolved in HPLC grade acetone (60 mL). The solution was vigorously stirred at room temperature while potassium carbonate (9.40 g, 68 mmol, 3.4 equivalents) was added in one portion. To the resulting suspension was added iodomethane (5.4 mL, 86 mmol, 4.3 equivalents), and the mixture was heated at reflux for 16 hours. The suspension was concentrated under reduced pressure and the residue partitioned between dichloromethane (200 mL) and water (200 mL). The aqueous was re-extracted with 2 × 100 mL of dichloromethane. The combined organics were dried over magnesium sulphate and concentrated *in vacuo*. The obtained solid was dissolved in the minimum amount of hot dichloromethane and a double amount of petroleum ether was added to the solution which started crystallizing on standing. It was then cooled to – 20 ºC for 16 hours to afford the title

compound as a colourless crystalline solid (9.20 g, 96 %). The analytical data were in agreement with the previous reports.[208,209]

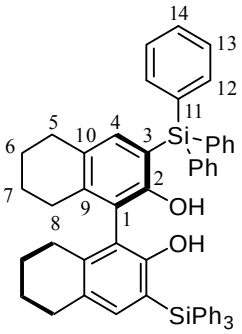


(*R*)-**9a**

m.p. 144-146 ºC; **FT-IR** ν_{max}(NaCl) 2936 cm^{-1} (ArC-H), 2858 cm^{-1} (Csp^3-H), 1461 cm^{-1} (CH_2), 757 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.62-1.71 (m, 4H, H-7), 1.71-1.79 (m, 4H, H-6), 2.09 (dt, 2H, H-8a, *J* 17.5 Hz, 6.5 Hz), 2.29 (dt, 2H, H-8b, *J* 17.5 Hz, 6.5 Hz), 2,78 (app. t, 4H, H-5, *J* 6.5 Hz), 3.59 (s, 6H, H-11), 7.34 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 22.6 & 22.7 (C-6, C-7), 27.3 (C-8), 29.2 (C-5), 60.4 (C-11), 113.9 (C-1), 132.0 (Ar-Cquat.), 133.0 (C-4), 134.8 (Ar-Cquat.), 136.1 (Ar-Cquat.), 151.7 (C-2); ***m/z*** (ES+) 498 ($[M+Na]^+$, 45%), 503 ($[M+Na]^+$, 40%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{24}O_2Br_2Na^+$) requires ***m/z*** 501.0035 & 503.0016 & 404.9995 found ***m/z*** 501.0032 (45%) & 503.0000 (100%) & 504.9986 (45%); $[\alpha]_D^{25} = -19.7$ (*c* 1.02, $CHCl_3$).

Preparation and characterisation of (*R*)-3,3′-bis(triphenylsilyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalene-2,2′-diol (*R*)-4c

Prepared according to general procedures **II** and **III** using (*R*)-**4b** as substrate, on a 15 mmol scale (6.78 g of (*R*)-**4b**, 1 equivalent). The intermediate triphenylsilyl ether was used without purification for the Brook rearrangement (procedure **III**) as described by Hiemstra *et al.*[129] The obtained mixture was purified by chromatography on silica gel eluting with petroleum ether/dichloromethane/diethyl ether 9:1:0 to 85:15:1 to afford the title compound as a colourless solid (9.30 g, 77 % over 2 steps). The analytical data were in agreement with the literature.[129]

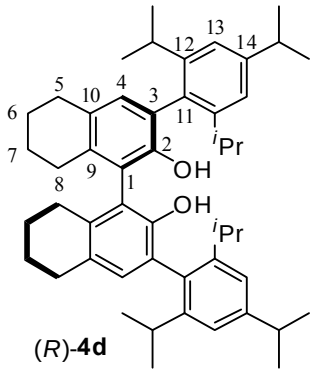


(*R*)-**4c**

m.p. 144-148 ºC (lit.[129] 127-130 ºC); **FT-IR** ν_{max}(NaCl) 3522 cm^{-1} (O-H), 3087 cm^{-1} (ArC-H), 2933 cm^{-1} (Csp^3-H), 1588 cm^{-1} (Ar-C=C), 758 cm^{-1} (ArC-H OOP), 701 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.72-1.85 (m, 8H, H-6, H-7), 2.35-2.55 (m, 4H, H-8), 2.61-2.74 (m, 4H, H-5), 4.99 (s, 2H, OH), 7.05 (s, 2H, H-4), 7.39-7.45 (m, 12H, H-13), 7.45-7.52 (m, 6H, H-14), 7.66-7.72 (m, 12H, H-12); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 22.9 (C-6, C-7), 27.4 (C-8), 29.1 (C-5), 118.9 (Ar-Cquat.), 127.7 (C-13), 129.3 (C-14), 130.0 (Ar-Cquat.), 134.6 (C-11), 136.2 (C-12), 139.6 (C-4), 140.0 (Ar-Cquat.), 156.1 (C-2); ***m/z*** (ES−) 809 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+NH_4]^+$ ($C_{56}H_{54}NO_2Si_2^+$) requires ***m/z*** 828.3688 found ***m/z*** 828.3686; $[\alpha]_D^{25}$ = + 42.4 (*c* 1.07, $CHCl_3$).

Preparation and characterisation of (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalene-2,2′-diol (*R*)-4d

Prepared by analogy with the procedure described by Schrock *et al.*[209], on a 2.17 mmol scale of (*R*)-**9a** (1.04 g, 1 equivalent). The intermediate substituted methoxy H_8-BINOL was used without purification for the deprotection (see section 6.2.1.1.7). The obtained mixture was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 100:0 to 97:3 to afford the title product as a colourless solid (0.81 g, 54 % over 2 steps).



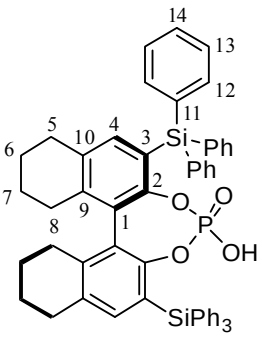
(*R*)-**4d**

m.p. 330-335 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3508 cm^{-1} (O-H), 2961 cm^{-1} (C-H), 1607 cm^{-1} (C=C), 1586 cm^{-1} (C=C), 1311 cm^{-1}, 759 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.16 (d, 6H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 1.21 (d, 6H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 1.27 (d, 6H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 1.31 (d, 6H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 1.44 (d, 12H, $(C\underline{H}_3)_2CH$, *J* 7.0 Hz), 1.86-1.98 (m, 8H,

H-6, H-7), 2.45-2.62 (m, 4H, H-8), 2.81 (sept, 2H, $(CH_3)_2C\underline{H}$, *J* 7.0 Hz), 2.87-3.01 (m, 6H, H-5, $(CH_3)_2C\underline{H}$, *J* 7.0 Hz), 3.07 (sept, 2H, $(CH_3)_2C\underline{H}$, *J* 7.0 Hz), 4.58 (s, 2H, O-H), 6.99 (s, 2H, H-4), 7.22 (dd, 4H, H-13, *J* 9.0 Hz, 1.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 23.1 & 23.2 (C-6, C-7), 23.8 ($\underline{C}H_3$), 24.0 ($\underline{C}H_3$), 24.0 ($\underline{C}H_3$), 24.1 ($\underline{C}H_3$), 24.2 ($\underline{C}H_3$), 24.3 ($\underline{C}H_3$), 26.9 (C-8), 29.2 (C-5), 30.5 ($\underline{C}H(CH_3)_2$), 30.6 ($\underline{C}H(CH_3)_2$), 34.3 ($\underline{C}H(CH_3)_2$), 120.4 (Ar-Cquat.), 120.8 & 120.9 (C-13, C-15), 124.1 (Ar-Cquat.), 129.1 (Ar-Cquat.), 131.2 (C-4), 131.2 (Ar-Cquat.), 135.8 (Ar-Cquat.), 147.5 (Ar-Cquat.), 147.7 (Ar-Cquat.), 148.3 (Ar-Cquat.), 148.5 (Ar-Cquat.); ***m/z*** (ES−) 697 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{50}H_{66}O_2Na^+$) requires ***m/z*** 721.4955 found ***m/z*** 721.4960; $[\alpha]_D^{25} = -10.2$ (*c* 1.02, $CHCl_3$).

Preparation and characterisation of (*R*)-2,6-bis(triphenylsilyl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-10a

Prepared according to general procedure **V**, on a 11 mmol scale (8.9 g of (*R*)-**4c**, 1 equivalent). The obtained mixture was purified by column chromatography on silica gel eluting with petroleum dichloromethane/methanol 99:1 to 96:4 to afford the desired acid (*R*)-**10a** as a colourless solid (6.8 g, 71 %). The analytical data were in agreement with the literature.[129]



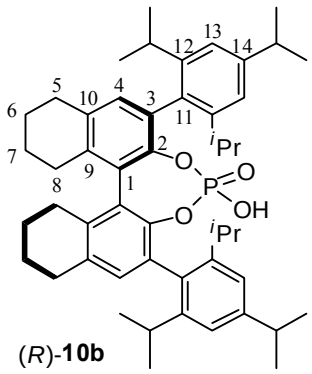
(*R*)-**10a**

m.p. 196-200 ºC (lit.[129] > 264 ºC (dec.)); **FT-IR** ν_{max}(NaCl) 3613 cm^{-1} (O-H), 2934 cm^{-1} (C-H), 1587 cm^{-1} (Ar-C=C), 1215 cm^{-1} (P=O), 757 cm^{-1} (ArC-H OOP), 703 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.65-1.90 (m, 8H, H-6, H-7), 2.32-2.44 (m, 2H, H-8a), 2.65-2.86 (m, 6H, H-5, H-8b), 7.22 (s, 2H, H-4), 7.32-7.42 (m, 18H, H-13, H-14), 7.62-7.69 (m, 12H, H-12); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 22.4 & 22.6 (C-6, C-7), 27.9 (C-8), 29.1 (C-5), 122.1 (d, C-1, J_{C-P} 4.0 Hz), 126.6 (d, C-3, J_{C-P} 1.5 Hz), 127.5 (C-13), 129.3 (C-14), 134.1 (br, Ar-Cquat.), 134.4 (C-11), 136.6 (C-12), 139.3 (C-4), 140.4 (Ar-Cquat.), 151.5 (d, C-2, J_{C-P} 9.0 Hz); ***m/z*** (ES−) 873

([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{56}H_{49}O_4PNaSi_2^+$) requires ***m/z*** 895.2799 found ***m/z*** 895.2810; $[\alpha]_D^{25} = -152.5$ (*c* 1.10, $CHCl_3$).

Preparation and characterisation of (*R*)-2,6-bis(triphenylsilyl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-ol 4-oxide (*R*)-10b

Phosphoric acid (*R*)-**10b** was prepared according to general procedure **V** on a 0.215 mmol scale (150 mg of (*R*)-**4d**, 1 equivalent). The precursor (*R*)-**4d** was heated at 95 ºC for 24 hours in the presence of phosphorous oxychloride and was then heated at 95 ºC for 24 hours after hydrolysis. The acid was purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/methanol 96:4 to afford the title product as a pale brown solid (115 mg, 71 %).



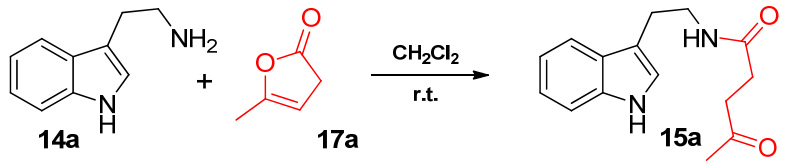
(*R*)-**10b**

m.p. 247-251 ºC; **FT-IR** ν_{max}(NaCl) 3616 cm^{-1} (O-H), 2961 cm^{-1} (ArC-H), 2867 cm^{-1} (Csp^3-H), 1605 cm^{-1} (ArC=C), 1237 cm^{-1} (P=O), 1095 cm^{-1} (P-O/C-O), 757 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.92 (d, 6H, 2 × C<u>H</u>$_3$, *J* 7.0 Hz), 0.97 (br d, 6H, 2 × C<u>H</u>$_3$, *J* 5.0 Hz), 1.08 (d, 6H, 2 × C<u>H</u>$_3$, *J* 6.5 Hz), 1.13 (d, 6H, 2 × C<u>H</u>$_3$, *J* 6.5 Hz), 1.23 (d, 12H, 4 × C<u>H</u>$_3$, *J* 7.0 Hz), 1.66-1.76 (m, 2H, C<u>H</u>aHb), 1.80-1.91 (m, 6H, CHa<u>H</u>b, C<u>H</u>$_2$), 2.26 (td, 2H, C<u>H</u>cHd, *J* 16.5 Hz, 6.5 Hz), 2.58-2.92 (m, 12H, CHc<u>H</u>d, CH_2, 6 × $CH(CH_3)_2$), 6.87 (s, 2H, H-13), 6.94 (s, 2H, H-13′), 6.96 (s, 2H, H-4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 23.0 (4C, 2 × <u>C</u>HaHb, 2 × <u>C</u>H$_2$), 23.3 (2 × <u>C</u>H$_3$), 23.5 (2 × <u>C</u>H$_3$), 24.0 (2 × <u>C</u>H$_3$), 24.2 (2 × <u>C</u>H$_3$), 24.8 (2 × <u>C</u>H$_3$), 26.4 (2 × <u>C</u>H$_3$), 27.7 (2 × <u>C</u>HcHd), 29.2 (2 × <u>C</u>H$_2$), 30.4 (2 × <u>C</u>H), 30.5 (2 × <u>C</u>H), 34.2 (2 × <u>C</u>H), 119.8 (C-13′), 120.7 (C-4), 127.5 (Ar-Cquat.), 128.7 (Ar-Cquat.), 131.8 (C-13), 132.5 (Ar-Cquat.), 133.1 (Ar-Cquat.), 136.1 (Ar-Cquat.), 145.4 (d, C-2, $J_{C\text{-}P}$ 8.5 Hz), 147.2 (Ar-Cquat.), 147.7 (Ar-Cquat.), 148.2 (Ar-Cquat.); ***m/z*** (ES−) 759, 761 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass

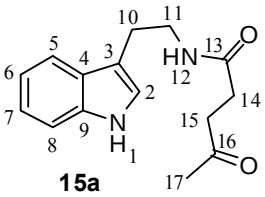
calculated for $[M-H]^-$ ($C_{50}H_{64}O_4P^-$) requires ***m/z*** 759.4548 found ***m/z*** 759.4532; $[\alpha]_D^{25} = -57.8$ (*c* 2.00, $CHCl_3$).

6.2.1.2 Synthesis of substrate for the optimisation study and the N-acyliminium cyclisation cascade

6.2.1.2.1 Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-4-oxopentanamide 15a



The oxoamide **15a** was prepared according to a modified procedure published by Padwa *et al.*[141] Tryptamine **14a** (2.50 g, 15.6 mmol, 1 equivalent) was suspended in dichloromethane (50 mL) in a round-bottom flask, the suspension was stirred at room temperature and α-angelica lactone was added in one portion (1.40 mL, 15.6 mmol, 1 equivalent). The mixture was left stirring for 5 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel, eluting with dichloromethane/acetone/Et_3N (90:9:1) to afford the title compound **15a** as a colourless powder (1.96 g, 49%).

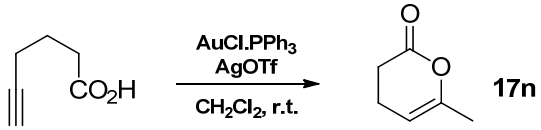


m.p. 83-85 ºC; **FT-IR** ν_{max}(NaCl) 3396 cm^{-1} (N-H), 2927 cm^{-1} (ArC-H), 1712 cm^{-1} (C=O ketone), 1652 cm^{-1} (C=O amide), 1545 cm^{-1} (ArC=C), 746 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.17 (s, 3H, H-17), 2.36 (t, 2H, H-14, *J* 6.5 Hz), 2.78 (t, 2H, H-15, *J* 6.5 Hz), 2.97 (t, 2H, H-10, *J* 6.5 Hz), 3.58 (dt, 2H, H-11, *J* 13.0 Hz, 6.5 Hz), 5.70 (br s, 1H, H-12), 7.07 (s, 1H, H-2), 7.11-7.16 (m, 1H, H-6), 7.19-7.24 (m, 1H, H-7), 7.39 (d, 1H, H-8, *J* 8.0 Hz), 7.62 (d, 1H, H-5, *J* 8.0 Hz), 8.21 (br s, 1H, H-1); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 25.2 (C-10), 29.9 (C-17), 29.9 (C-14), 38.5 (C-15), 39.7 (C-11), 111.3 (C-8), 112.9

(C-3), 118.7 (C-5), 119.5 (C-6), 122.2 (C-2), 122.2 (C-7), 127.3 (C-4), 136.4 (C-9), 171.8 (C-13), 207.9 (C-16); ***m/z*** (ES−) 257 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{15}H_{19}N_2O_2^+$) requires ***m/z*** 259.1441, found ***m/z*** 259.1445.

6.2.1.2.2 Preparation of and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-5-oxohexanamide 15b

Preparation and characterisation of 6-methyl-3,4-dihydro-2*H*-pyran-2-one 17n

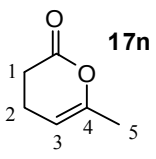


$AuCl.PPh_3$ was prepared according to a literature procedure.[210]

In a dry flask under nitrogen, gold chloride triphenylphosphine complex (49 mg, 0.10 mmol, 0.01 equivalents) and silver trifluoromethanesulfonate (26 mg, 0.10 mmol, 0.01 equivalents) were dissolved in dry dichloromethane (20 mL) and stirred under nitrogen for a few minutes (2-5 minutes). 5-Hexynoic acid (1.12 g, 10.0 mmol, 1 equivalent) was added in one portion. The resulting mixture was stirred at room temperature for 12 hours, in a sealed flask.

Remark: The mixture became slightly brown within the first hours, because of silver chloride precipitating and silver being reduced by day light.

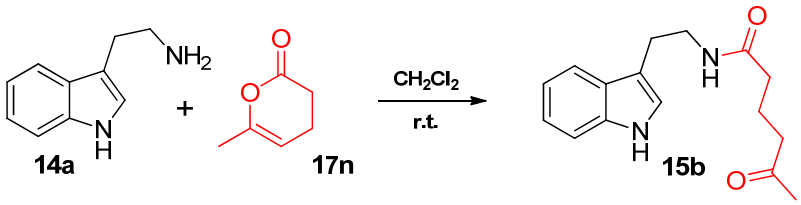
The progress of the reaction was monitored by TLC (eluent dichloromethane), after 12 hours the mixture was concentrated *in vacuo* giving a light brown oil which was purified by column chromatography on silica gel (short path column) eluting with dichloromethane to give the title compound **17n** as a pale yellow oil (1.10 g, 98%). The analytical data were in agreement with the literature.[153a,211]



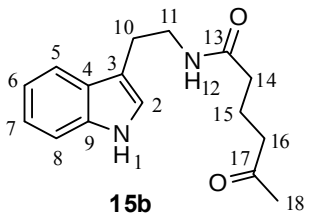
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.89 (d, 3H, H-5, *J* 1.5 Hz), 2.29 (m, 2H, H-2), 2.58 (t, 2H, H-1, *J* 7.5 Hz), 5.01 (t, 1H, H-3, *J* 4.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 18.7 (C-2, C-5), 28.3 (C-1), 99.8 (C-3), 150.0 (C-4), 169.3

(C=O); ***m/z*** (CI+) 130 ($[M+NH_4]^+$ ($C_6H_{12}O_2N^+$), 100%).

Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-5-oxohexanamide 15b



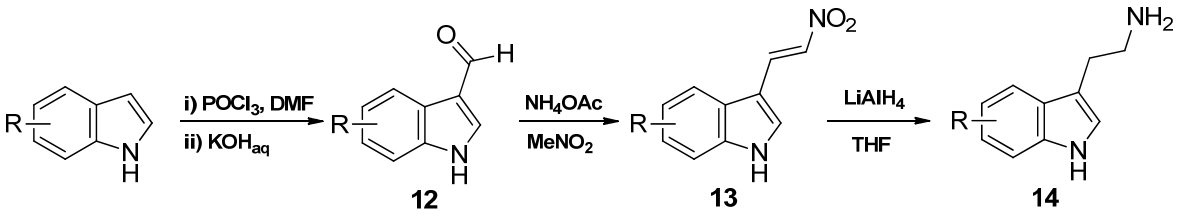
In a dry flask, tryptamine **14a** (0.8 g, 5 mmol, 1 equivalent) was dissolved in dry dichloromethane (50 mL) and 6-methyl-3,4-dihydro-2*H*-pyran-2-one **17n** (561 mg, 5.00 mmol, 1 equivalent) was added in one portion. The mixture was stirred at room temperature until a precipitate started to form (about 5 hours at room temperature). The progress was monitored by TLC (eluent dichloromethane/acetone 3:1). After 6 hours at room temperature, dichloromethane was removed *in vacuo* to give a light brown solid that was purified by column chromatography on silica (eluent dichloromethane/acetone 9:1 to 8:2) to afford the title product **15b** as a colourless solid (1.10 g, 81%).



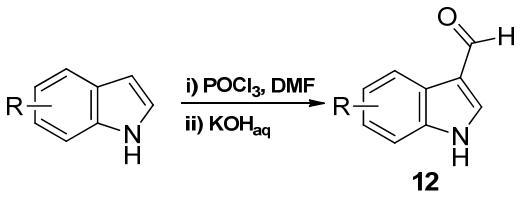
m.p. 123-125 ºC; **FT-IR** ν_{max}(NaCl) 3348 cm^{-1} (N-H), 3318 cm^{-1} (N-H), 1700 cm^{-1} (C=O ketone), 1625 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.87 (quint., 2H, H-15, *J* 7.0 Hz), 2.12 (s, 3H, H-18), 2.13 (t, 2H, H-14, *J* 7.0 Hz), 2.48 (t, 2H, H-16, *J* 7.0 Hz), 2.99 (t, 2H, H-10, *J* 7.0 Hz), 3.61 (dt, 2H, H-11, *J* 13.0 Hz, 6.5 Hz), 5.59 (br s, 1H, H-12), 7.07 (d, 1H, H-2, *J* 2.0 Hz), 7.15 (dd, 1H, H-6, *J* 8.0 Hz, 7.0 Hz), 7.23 (dd, 1H, H-7, *J* 8.0 Hz, 7.0 Hz), 7.40 (d, 1H, H-8, *J* 8.0 Hz), 7.62 (d, 1H, H-5, *J* 8.0 Hz), 8.14 (br s, 1H, H-1); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 19.7 (C-15), 25.3 (C-10), 29.9 (C-18), 35.5 (C-14), 39.6 (C-11), 42.4 (C-16), 111.3 (C-8), 113.0 (C-3), 118.7 (C-5), 119.5 (C-6), 122.04 (Ar-CH), 122.3(Ar-CH), 127.3 (C-4), 136.4 (C-9), 172.3 (C-13), 208.7 (C-17); ***m/z*** (ES+) 295 ($[M+Na]^+$,

100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}N_2O_2^+$) requires ***m/z*** 273.1598, found ***m/z*** 273.1601.

6.2.1.2.3 Preparation and characterisation of tryptamine derivatives 14

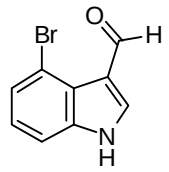


General procedure VI for the synthesis of indole carbaldehydes 12[142]



Phosphorus oxychloride (2.5 equivalents) was added dropwise to dimethyl formamide (5 mL per 1 mL of $POCl_3$) with ice-bath cooling. The mixture was stirred for 5 minutes before the chosen indole (1 equivalent) was added as a dimethyl formamide solution (10 mL per 1 g of indole). The mixture was then allowed to warm to room temperature and stirred for 3 hours. The reaction became a heavy suspension that required vigorous stirring. 3.8 M aqueous potassium hydroxide (10 equivalents) was added v*ia* a dropping funnel and the mixture was heated at reflux overnight. It was cooled to room temperature before adding saturated aqueous sodium hydrogen carbonate and ethyl acetate until the mixture became clear and the organic layer separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to furnish the desired aldehyde **12** that required no further purification.

Preparation and characterisation of 4-bromo-1*H*-indole-3-carbaldehyde 12b

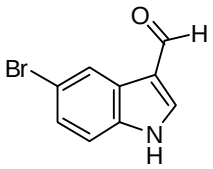


12b

The title compound was synthesised according to general procedure **VI** in 100% yield as an off-white powder. The spectral data were in agreement with the literature.[212,213]

m.p. 168-170 ºC (lit.[212] 185-187 ºC); **FT-IR** ν_{max}(NaCl) 1633 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 300 MHz) δ_H 7.18 (t, 1H, Ar-H, *J* 8.0 Hz), 7.48 (d, 1H, Ar-H, *J* 8.0 Hz), 7.57 (d, 1H, Ar-H, *J* 8.0 Hz), 8.32 (s, 1H, Ar-H), 9.87 (s, 1H, CHO), 10.68 (br s, 1H, NH); **^{13}C NMR** (d_6-DMSO, 75 MHz) δ_C 112.3 (Ar-Cquat.), 112.4 (Ar-CH), 117.8 (Ar-Cquat.), 123.8 (Ar-CH), 124.7 (Ar-Cquat.), 126.0 (Ar-CH), 133.8 (Ar-CH), 138.2 (Ar-Cquat.), 184.5 (C=O); ***m/z*** (ES−) 222, 224 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_7BrNO^+$) requires *m/z* 223.9706 & 225.9685, found *m/z* 223.9707 & 225.9684.

Preparation and characterisation of 5-bromo-1*H*-indole-3-carbaldehyde 12c[143a]

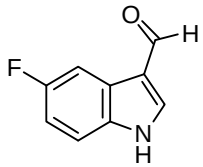


12c

The title compound was synthesised according to general procedure **VI** in 100% yield as a colourless powder. The spectral data were in agreement with the literature.[143a]

m.p. 187-191 ºC (lit.[143a] 204-205 ºC); **FT-IR** ν_{max}(NaCl) 1651 cm^{-1} (C=O); **^{1}H NMR** (d_4-MeOD, 400 MHz) δ_H 7.37 (m, 2H, 2 × Ar-H), 8.12 (s, 1H, Ar-H), 8.29 (s, 1H, Ar-H), 9.87 (s, 1H, CHO); **^{13}C NMR** (d_4-MeOD, 100 MHz) δ_C 114.8 (Ar-CH), 116.9 (Ar-Cquat.), 119.5 (Ar-Cquat.), 125.0 (Ar-CH), 127.4 (Ar-Cquat.), 127.9 (Ar-CH), 137.5 (Ar-Cquat.), 140.3 (Ar-CH), 187.3 (C=O); ***m/z*** (ES+) 224, 226 ($[M+H]^+$, 40%), 246, 248 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_7BrNO^+$) requires ***m/z*** 223.9706, found ***m/z*** 223.9712.

Preparation and characterisation of 5-fluoro-1*H*-indole-3-carbaldehyde 12d

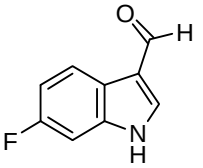


12d

The title compound was synthesised according to general procedure **VI** in 98% yield as a colourless powder.

m.p. 143-146 ºC (lit.[214] 170-171 °C); **FT-IR** ν_{max}(NaCl) 1648 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 7.13 (dt, 1H, Ar-H, *J* 9.0 Hz, 2.5 Hz), 7.54 (dd, 1H, Ar-H, *J* 9.0 Hz, 4.5 Hz), 7.76 (dd, 1H, Ar-H, *J* 9.0 Hz, 2.5 Hz), 8.36 (s, 1H, Ar-H), 9.93 (s, 1H, CHO), 12.26 (s, 1H, NH); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 105.6 (d, $J_{C,F}$ 25.0 Hz, Ar-CH), 111.5 (d, $J_{C,F}$ 26.5 Hz, Ar-CH), 113.7 (d, $J_{C,F}$ 10.0 Hz, Ar-CH), 118.0 (d, $J_{C,F}$ 5.0 Hz, Ar-Cquat.), 124.6 (d, $J_{C,F}$ 15.0 Hz, Ar-Cquat.), 133.6 (Ar-Cquat.), 139.7 (Ar-CH), 158.6 (d, $J_{C,F}$ 235 Hz, Ar-Cquat.), 185.0 (C=O); ***m/z*** (ES−) 162 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_7FNO^+$) requires ***m/z*** 164.0506, found ***m/z*** 164.0510.

Preparation and characterisation of 6-fluoro-1*H*-indole-3-carbaldehyde 12e

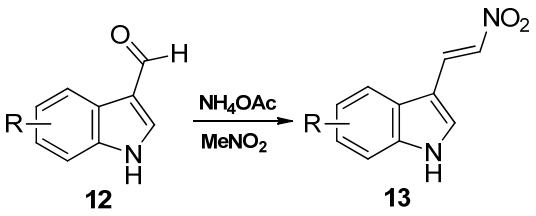


12e

The title compound was synthesised according to general procedure **VI** in 96% yield as a colourless powder. Analytical data in agreement with the literature.[215]

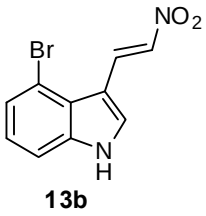
m.p. 165-168 ºC (lit.[214] 178-179 °C); **FT-IR** ν_{max}(NaCl) 1647 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 7.09 (td, 1H, Ar-H, *J* 9.5 Hz, 2.5 Hz), 7.32 (dd, 1H, Ar-H, *J* 5.5 Hz, 2.5 Hz), 8.08 (dd, 1H, Ar-H, *J* 9.5 Hz, 5.5 Hz), 8.31 (s, 1H, Ar-H), 9.92 (s, 1H, CHO), 12.20 (s, 1H, NH); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 98.7 (d, $J_{C,F}$ 25.0 Hz, Ar-CH), 110.4 (d, $J_{C,F}$ 25.5 Hz, Ar-CH), 118.0 (Ar-Cquat.), 120.7 (Ar-Cquat.), 121.9 (d, $J_{C,F}$ 22.5 Hz, Ar-CH), 137.1 (d, $J_{C,F}$ 12.0 Hz, Ar-Cquat.), 139.2 (Ar-CH), 159.5 (d, $J_{C,F}$ 235 Hz, Ar-Cquat.), 184.9 (C=O); ***m/z*** (ES+) 164 ($[M+H]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_7FNO^+$) requires ***m/z*** 164.0506, found ***m/z*** 164.0506.

General procedure VII for the synthesis of nitro-olefins



Aldehyde (1 equivalent) and dry ammonium acetate (3 equivalents) were heated at reflux in nitromethane (20 mL per 1 g of aldehyde) for 1 hour. The solvent was removed *in vacuo* and the residue washed with water and filtered. The residue was pre-absorbed onto silica and purified by flash chromatography eluting with 2:1 petroleum ether/ethyl acetate to furnish the desired nitro-olefin.

Preparation and characterisation of 4-bromo-3-((*E*)-2-nitrovinyl)-1*H*-indole 13b

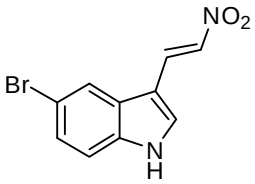


13b

The title compound was synthesised from **12b** according to general procedure **VII** in 88% yield as a red amorphous solid. Analytical data in agreement with previous report.[213]

m.p. 220 ºC (dec.)(lit.[213] > 200 °C (dec.)); **FT-IR** ν_{max}(NaCl) 1613 cm^{-1} (C=C), 1293 cm^{-1} (NO_2), 1269 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 400 MHz) δ_H 7.19 (t, 1H, Ar-H, *J* 8.0 Hz), 7.45 (dd, 1H, Ar-H, *J* 8.0 Hz, 1.0 Hz), 7.61 (dd, 1H, Ar-H, *J* 8.0 Hz, 1.0 Hz), 7.90 (d, 1H, alkene-H, *J* 13.5 Hz), 8.42 (d, 1H, Ar-H, *J* 3.0 Hz), 9.25 (d, 1H, alkene-H, *J* 13.5 Hz), 11.56 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 100 MHz) δ_C 109.0 (Ar-Cquat.), 113.3 (Ar-CH), 113.9 (Ar-Cquat.), 124.9 (Ar-CH), 125.5 (Ar-Cquat.), 127.0 (Ar-CH), 130.9 (Ar-CH), 133.5 (alkene-C), 133.7 (alkene-C), 139.4 (Ar-Cquat.); ***m/z*** (ES−) 264, 266 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{10}H_6BrN_2O_2^-$) requires ***m/z*** 264.9618 & 266.9598, found ***m/z*** 264.9628 & 266.9608.

Preparation and characterisation of 5-bromo-3-((*E*)-2-nitrovinyl)-1*H*-indole 13c[143a]

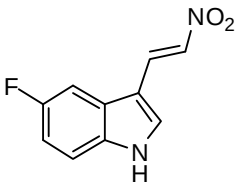


13c

The title compound was synthesised from **12c** according to general procedure **VII** in 93% yield as an orange amorphous solid. The analytical data were in agreement with the literature.[143a]

m.p. 178-181 ºC (dec.) (lit.[143a] 192-193 ºC); **FT-IR** ν_{max}(NaCl) 1613 cm^{-1} (C=C), 1298 cm^{-1} (NO_2), 1227 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 500 MHz) δ_H 7.42 (dd, 1H, Ar-H, *J* 8.5 Hz, 2.0 Hz), 7.54 (d, 1H, Ar-H, *J* 8.5 Hz), 7.98 (d, 1H, alkene-H, *J* 13.5 Hz), 8.18 (s, 1H, Ar-H), 8.20 (d, 1H, Ar-H, *J* 2.0 Hz), 8.35 (d, 1H, alkene-H, *J* 13.5 Hz), 11.40 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 125 MHz) δ_C 109.1 (Ar-Cquat.), 115.3 (Ar-CH), 115.8 (Ar-Cquat.), 123.7 (Ar-CH), 127.2 (Ar-CH), 127.7 (Ar-Cquat.), 133.6 **(**alkene-C**),** 133.8 (alkene-C), 136.3 (Ar-CH), 137.6 (Ar-Cquat.); ***m/z*** (ES−) 265, 267 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{10}H_6BrN_2O_2^-$) requires ***m/z*** 266.9598, found ***m/z*** 266.9598.

Preparation and characterisation of 5-fluoro-3-((*E*)-2-nitrovinyl)-1*H*-indole 13d



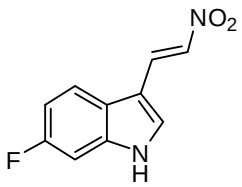
13d

The title compound was synthesised from **12d** according to general procedure **VII** in 98% yield as an orange solid. Analytical data in agreement with previous report.[216]

m.p. 158-160 ºC (dec.); **FT-IR** ν_{max}(NaCl) 1613 cm^{-1} (C=C), 1304 cm^{-1} (NO_2), 1256 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 500 MHz) δ_H 6.98 (td, 1H, Ar-H, *J* 9.0 Hz, 2.5 Hz), 7.47 (dd, 1H, Ar-H, *J* 9.0 Hz, 4.5 Hz), 7.62 (dd, 1H, Ar-H, *J* 6.0 Hz, 2.5 Hz), 7.79 (d, 1H, alkene-H, *J* 13.5 Hz), 8.09 (s, 1H, Ar-H), 8.23 (d, 1H, alkene-H, *J* 13.5 Hz), 11.22 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 125 MHz) δ_C 106.6 (d, $J_{C,F}$ 24.5 Hz, Ar-CH), 109.6 (Ar-Cquat.), 112.4 (d, $J_{C,F}$ 26.0 Hz, Ar-CH), 114.7 (d, $J_{C,F}$ 9.5 Hz, Ar-CH), 126.5 (Ar-Cquat.), 133.1 (alkene-C), 134.2 (alkene-C), 135.4 (Ar-Cquat.), 136.9 (Ar-CH), 160.0 (d, $J_{C,F}$ 237 Hz, Ar-

Cquat.); ***m/z*** (ES−) 205 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{10}H_6FN_2O_2^-$) requires ***m/z*** 205.0419, found ***m/z*** 205.0418.

Preparation and characterisation of 6-fluoro-3-((*E*)-2-nitrovinyl)-1*H*-indole 13e

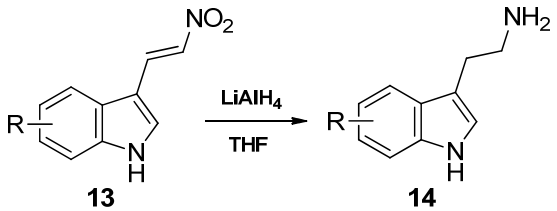


13e

The title compound was synthesised from **12e** according to general procedure **VII** in 66% yield as a red powder.

m.p. 170-172 ºC (dec.); **FT-IR** ν_{max}(NaCl) 1616 cm^{-1} (C=C), 1320 cm^{-1} (NO_2), 1229 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 500 MHz) δ_H 7.09 (td, 1H, Ar-H, *J* 9.5 Hz, 2.0 Hz), 7.33 (dd, 1H, Ar-H, *J* 9.5 Hz, 2.0 Hz), 7.91 (d, 1H, alkene-H, *J* 13.5 Hz), 7.97 (dd, 1H, Ar-H, *J* 9.5 Hz, 5.0 Hz), 8.16 (s, 1H, Ar-H), 8.35 (d, 1H, alkene-H, *J* 13.5 Hz), 11.32 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 500 MHz) δ_C 99.9 ($J_{C,F}$ 26.0 Hz, Ar-CH), 109.7 (Ar-Cquat.), 110.9 ($J_{C,F}$ 24.5 Hz, Ar-CH), 122.4 ($J_{C,F}$ 10.0 Hz, Ar-CH), 133.2 (alkene-C), 134.2 (alkene-C), 136.3 (Ar-CH), 139.1 (Ar-Cquat.), 139.2 (Ar-Cquat.), 161.2 ($J_{C,F}$ 237 Hz, Ar-Cquat.); ***m/z*** (ES−) 205 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{10}H_6FN_2O_2^-$) requires ***m/z*** 205.0419, found ***m/z*** 205.0419.

General procedure VIII for the synthesis of tryptamines



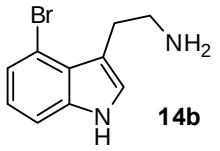
13 **14**

Under an inert nitrogen atmosphere, a tetrahydrofuran solution (10 mL per 1 mmol of nitro olefin) of nitro olefin (1 equivalent) was added to a stirred slurry of lithium aluminium hydride powder (6 equivalents) in tetrahydrofuran (equal volume) at 0 ºC. The mixture was allowed to warm to room temperature and stirred for 36 hours. The reaction was quenched by dropwise addition of water until effervescence ceased. The mixture was then diluted with diethyl ether before addition of a saturated aqueous solution of Rochelle's salt and the subsequent biphasic

mixture was stirred for 24 hours. The layers were separated and the organic layer was extracted with 1 M aqueous hydrochloric acid. The aqueous phase was basified with 3 M aqueous potassium hydroxide, extracted with diethyl ether, dried over sodium sulphate, filtered and concentrated *in vacuo* to furnish the desired tryptamine which required no further purification.

Remark: the work-up can be simplified by using sodium sulphate decahydrate to quench the excess LAH. $Na_2SO_4.10H_2O$ was added slowly by portion until ≈ 2.5 g of salt was added per 1 g of LAH used. The mixture was then stirred vigorously for 6 hours (colour faded to pale yellow / colourless) and the suspension filtered over celite. The flask and resulting cake were washed thoroughly with diethyl ether (volume identical to tetrahydrofuran used) and then dichloromethane (volume identical to tetrahydrofuran used). The combined organics were concentrated to afford the desired tryptamine that did not require any further purification.

Preparation and characterisation of 2-(4-bromo-1*H*-indol-3-yl)ethanamine 14b

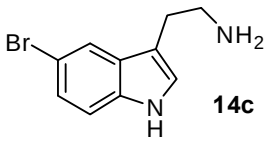


14b

The title compound was synthesised from **13b** according to general procedure **VIII** in 78% yield as a pale brown powder. Analytical data in agreement with the literature.[213]

m.p. 113-115 ºC; **FT-IR** ν_{max}(NaCl) 3405 cm^{-1} (N-H, broad); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.47 (br s, 2H, NH_2), 3.05-3.11 (m, 2H, $ArCH_2CH_2NH_2$), 3.12-3.18 (m, 2H, $ArCH_2CH_2NH_2$), 7.00 (t, 1H, Ar-H, *J* 7.5 Hz), 7.05 (d, 1H, Ar-H, *J* 1.5 Hz), 7.27 (dd, 1H, Ar-H, *J* 7.5 Hz, 1.0 Hz), 7.29 (dd, 1H, Ar-H, *J* 7.5 Hz, 1.0 Hz), 8.75 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 30.3 ($ArCH_2CH_2NH_2$), 43.7 ($ArCH_2CH_2NH_2$), 110.6 (Ar-CH), 114.4 (Ar-Cquat.), 114.5 (Ar-Cquat.), 122.7 (Ar-CH), 123.9 (Ar-CH), 124.0 (Ar-CH), 125.5 (Ar-Cquat.), 137.9 (Ar-Cquat.); ***m/z*** (ES−) 237, 239 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}BrN_2^+$) requires ***m/z*** 239.0178 & 241.0158, found ***m/z*** 239.0178 & 241.0157.

Preparation and characterisation of 2-(5-bromo-1*H*-indol-3-yl)ethanamine 14c[143a]



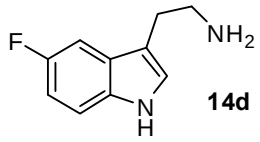
14c

The title compound was synthesised from **13c** according to general procedure **VIII** in 90% yield as a brown oil. The analytical data were in agreement with the literature.[143a]

FT-IR ν_{max}(NaCl) 3140 cm^{-1} (N-H, broad); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.76 (br s, 2H, NH_2), 2.90 (t, 2H, $ArC\underline{H}_2CH_2NH_2$, *J* 6.5 Hz), 3.06 (t, 2H, $ArCH_2C\underline{H}_2NH_2$, *J* 6.5 Hz), 7.05 (s, 1H, Ar-H), 7.24-7.32 (m, 2H, 2 × Ar-H), 7.77 (d, 1H, Ar-H, *J* 1.5 Hz), 8.83 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 29.1 ($Ar\underline{C}H_2CH_2NH_2$), 42.1 ($ArCH_2\underline{C}H_2NH_2$), 112.5 (Ar-Cquat.), 112.7 (Ar-<u>C</u>H), 113.2 (Ar-Cquat.), 121.4 (Ar-<u>C</u>H), 123.5 (Ar-<u>C</u>H), 124.7 (Ar-<u>C</u>H), 129.3 (Ar-Cquat.), 135.1 (Ar-Cquat.); ***m/z*** (ES−) 237, 239 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}BrN_2^+$) requires ***m/z*** 239.0178 & 241.0158, found ***m/z*** 239.0178 & 241.0158.

Preparation and characterisation of 2-(5-fluoro-1*H*-indol-3-yl)ethanamine 14d

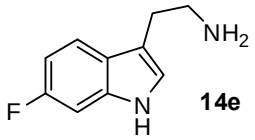
The title compound was synthesised from **13d** according to general procedure **VIII** in 76% yield as a brown oil. Analytical data in agreement with previous reports.[217,218]



14d

FT-IR ν_{max}(NaCl) 3176 cm^{-1} (N-H, broad); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.53 (br s, 2H, NH_2), 2.87 (t, 2H, $ArC\underline{H}_2CH_2NH_2$, *J* 6.5 Hz), 3.03 (t, 2H, $ArCH_2C\underline{H}_2NH_2$, *J* 6.5 Hz), 6.93 (td, 1H, Ar-H, *J* 9.0 Hz, 2.5 Hz), 7.04 (s, 1H, Ar-H), 7.22-7.26 (m, 2H, 2 × Ar-H), 8.94 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 29.3 ($Ar\underline{C}H_2CH_2NH_2$), 42.1 ($ArCH_2\underline{C}H_2NH_2$), 103.6 (d, $J_{C,F}$ 23.0 Hz, Ar-<u>C</u>H), 110.2 (d, $J_{C,F}$ 26.0 Hz, Ar-<u>C</u>H), 111.8 (d, $J_{C,F}$ 9.5 Hz, Ar-<u>C</u>H), 113.5 (d, $J_{C,F}$ 5.0 Hz, Ar-Cquat.), 124.0 (Ar-<u>C</u>H), 127.7 (d, $J_{C,F}$ 9.5 Hz, Ar-Cquat.), 133.0 (Ar-Cquat.), 157.6 (d, $J_{C,F}$ 233 Hz, Ar-Cquat.); ***m/z*** (ES−) 177 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}FN_2^+$) requires ***m/z*** 179.0979, found ***m/z*** 179.0974.

Preparation and characterisation of 2-(6-fluoro-1*H*-indol-3-yl)ethanamine 14e



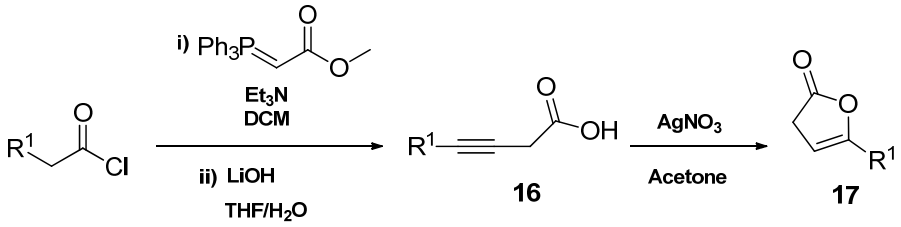
14e

The title compound was synthesised from **13e** according to general procedure **VIII** in 90% yield as an off-white solid.

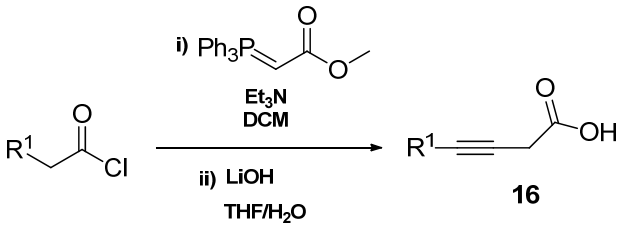
m.p. 75-77 ºC; **FT-IR** ν_{max}(NaCl) 3195 cm^{-1} (N-H, broad); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.42 (br s, 2H, NH_2), 2.89 (t, 2H, $ArCH_2CH_2NH_2$, *J* 6.5 Hz), 3.04 (t, 2H, $ArCH_2CH_2NH_2$, *J* 6.5 Hz), 6.89 (td, 1H, Ar-H, *J* 9.5 Hz, 2.0 Hz), 6.99 (s, 1H, Ar-H), 7.03 (dd, 1H, Ar-H, *J* 9.5 Hz, 2.0 Hz), 7.51 (dd, 1H, Ar-H, *J* 9.5 Hz, 5.5 Hz), 8.61 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 29.4 ($ArCH_2CH_2NH_2$), 42.3 ($ArCH_2CH_2NH_2$), 97.4 (d, $J_{C,F}$ 26.0 Hz, Ar-CH), 107.9 (d, $J_{C,F}$ 24.5 Hz, Ar-CH), 113.7 (Ar-Cquat.), 119.5 (d, $J_{C,F}$ 10.0 Hz, Ar-CH), 122.3 (Ar-CH), 124.1 (Ar-Cquat.), 136.3 (Ar-Cquat.), 159.9 (d, $J_{C,F}$ 236 Hz, Ar-Cquat.); ***m/z*** (ES−) 177 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}FN_2^+$) requires ***m/z*** 179.0979, found ***m/z*** 179.0979.

N.B. 6-OBn tryptamine was prepared by a co-worker and used without further purification.

6.2.1.2.4 Preparation of substituted enol lactones from alkynoic acids



General procedure IX for the synthesis of alkynoic acids 16 (R^1 = alkyl)[145]



Methyl (triphenylphosphoranylidene)acetate (1 equivalent) was stirred with triethylamine (1 equivalent) in dry dichloromethane (10 mL per 1 g of acetate) with ice-bath cooling. Acyl

chloride (1 equivalent) was added dropwise and the mixture was allowed to warm to room temperature then stirred for 24 hours. Approximately half of the solvent was removed *in vacuo* and the residue was passed through a short plug of silica eluting with dichloromethane. The solvent was removed *in vacuo* and the residue purified by flash column chromatography eluting with 6:1 petroleum ether/ethyl acetate. The material obtained was dissolved in tetrahydrofuran (10 mL per mmol of ester) and saponified by treatment with aqueous lithium hydroxide (5 equivalents, 10 mL of water per mmol of ester) for 15-30 minutes (completion followed by TLC). The mixture was then diluted with diethyl ether and water and the layers were separated. The aqueous layer was acidified with 1 M aqueous hydrochloric acid to < pH 1 and extracted with diethyl ether twice (2 × 10 mL per mmol of material). The combined organic layers were dried over sodium sulphate and concentrated *in vacuo* to furnish the desired alkynoic acid that did not require further purification.

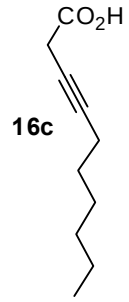
Preparation and characterisation of hept-3-ynoic acid 16b

16b

The title compound was synthesised according to general procedure **IX** from valeroyl chloride as a colourless oil in 55% yield over 2 steps. Analytical data in agreement with previous report.[219]

FT-IR ν_{max}(NaCl) 1719 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.99 (t, 3H, CH_3, *J* 7.5 Hz), 1.54 (quint, 2H, C≡CCH_2CH_2, *J* 7.5 Hz), 2.20 (tt, 2H, C≡CCH_2CH_2, *J* 7.5 Hz, 2.5 Hz), 3.35 (t, 2H, C≡CCH_2CO_2H, *J* 2.5 Hz), 8.13 (br s, 1H, COOH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.4 (CH_3), 20.7 (CH_2), 22.0 (CH_2), 25.9 (CH_2), 70.7 (C≡C), 84.4 (C≡C), 174.8 (C=O); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_7H_{14}NO_2^+$) requires ***m/z*** 144.1025, found ***m/z*** 144.1026 (100%).

Preparation and characterisation of dec-3-ynoic acid 16c

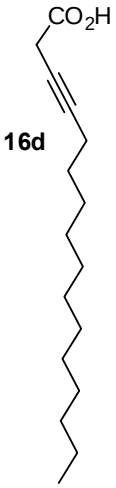


16c

The title compound was synthesised according to general procedure **IX** from octanoyl chloride as a pale yellow oil in 71% yield over 2 steps. Analytical data in agreement with the literature.[220]

FT-IR ν_{max}(NaCl) 1708 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.87 (t, 3H, CH_3, *J* 7.0 Hz), 1.22-1.39 (m, 6H, 3 × CH_2), 1.47 (quint, 2H, C≡CCH$_2$C$\underline{H}_2$, *J* 7.0 Hz), 2.17 (tt, 2H, C≡CC$\underline{H}_2$CH$_2$, *J* 7.0 Hz, 2.5 Hz), 3.31 (t, 2H, C≡CC$\underline{H}_2$CO$_2$H, *J* 2.5 Hz), 11.14 (br s, 1H, COOH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 ($\underline{C}H_3$), 18.6 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 28.4 ($\underline{C}H_2$), 28.5 ($\underline{C}H_2$), 32.2 ($\underline{C}H_2$), 70.5 (C≡C), 84.4 (C≡C), 175.5 (C=O); ***m/z*** (ES−) 167 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{10}H_{15}O_2^-$) requires ***m/z*** 167.1078, found ***m/z*** 167.1078.

Preparation and characterisation of hexadec-3-ynoic acid 16d

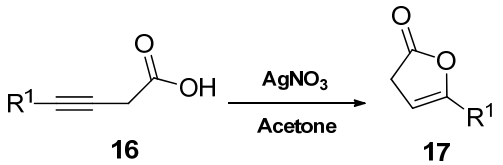


16d

The title compound was synthesised according to general procedure **IX** from myristoyl chloride as a colourless solid in 81% yield over 2 steps. Analytical data in agreement with previous report.[221]

m.p. 61-62 ºC (lit.[221] 66-68 °C); **FT-IR** ν_{max}(NaCl) 1691 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.89 (t, 3H, CH_3, *J* 7.0 Hz), 1.25-1.39 (m, 18H, 9 × CH_2), 1.51 (quint, 2H, C≡CCH$_2$C$\underline{H}_2$, *J* 7.0 Hz), 2.20 (tt, 2H, C≡CC$\underline{H}_2$CH$_2$, *J* 7.0 Hz, 2.5 Hz), 3.34 (t, 2H, C≡CC$\underline{H}_2$CO$_2$H, *J* 2.5 Hz), 9.07 (br s, 1H, COOH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.1 ($\underline{C}H_3$), 18.7 ($\underline{C}H_2$), 22.7 ($\underline{C}H_2$), 25.9 ($\underline{C}H_2$), 28.6 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 29.1 ($\underline{C}H_2$), 29.4 ($\underline{C}H_2$), 29.5 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.7 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 70.5 (C≡C), 84.7 (C≡C), 175.1 (C=O); ***m/z*** (ES−) 251 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ $(C_{16}H_{27}O_2)^-$ requires ***m/z*** 251.2017, found ***m/z*** 251.2017.

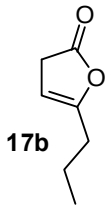
General procedure X for the synthesis of enol lactones 17 (R^1 = alkyl, R^2 = H)



16 17

Alkynoic acid (1 equivalent) was stirred in acetone (10 mL per 1 g of acid) in a foil-covered round-bottom flask and treated with silver nitrate (0.2 equivalents). After 24 hours the mixture was dried over sodium sulphate, filtered and concentrated *in vacuo*. Purification by column chromatography eluting with 4:1 petroleum ether/diethyl ether furnished the desired lactone.

Preparation and characterisation of 5-propylfuran-2(3*H*)-one 17b

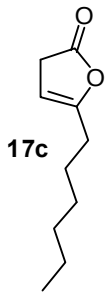


17b

The title compound was synthesised from **16b** according to general procedure **X** as a colourless oil in 58% yield.

FT-IR ν_{max}(NaCl) 1797 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.96 (t, 3H, CH_3, *J* 7.5 Hz), 1.58 (quint, 2H, *J* 7.5 Hz), 2.21-2.31 (m, 2H, CH_2), 3.16-3.19 (m, 2H, $C\underline{H}_2CO_2$), 5.09-5.14 (m, 1H, alkene-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.5 ($\underline{C}H_3$), 19.0 ($\underline{C}H_2$), 30.1 ($\underline{C}H_2$), 33.9 ($\underline{C}H_2$), 98.3 (alkene-$\underline{C}$H), 157.0 (alkene-Cquat.), 177.1 (C=O); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_7H_{14}NO_2^+$) requires ***m/z*** 144.1025, found ***m/z*** 144.1026 (100%).

Preparation and characterisation of 5-hexylfuran-2(3*H*)-one 17c



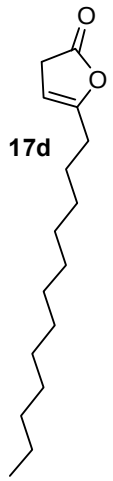
17c

The title compound was synthesised from **16c** according to general procedure **X** as a colourless oil in 67% yield.

FT-IR ν_{max}(NaCl) 1797 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.89 (t, 3H, CH_3, *J* 7.0 Hz), 1.28-1.36 (m, 6H, 3 × CH_2), 1.56 (quint, 2H, CH_2, *J* 7.5 Hz), 2.25-2.33 (m, 2H, CH_2), 3.16-3.20 (m, 2H, $C\underline{H}_2CO_2$), 5.09-5.13 (m, 1H, alkene-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.0 ($\underline{C}H_3$), 22.5 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 28.2 ($\underline{C}H_2$), 28.7

(<u>C</u>H$_2$), 31.4 (<u>C</u>H$_2$), 33.9 (<u>C</u>H$_2$), 98.1 (alkene-<u>C</u>H), 157.3 (alkene-Cquat.), 177.8 (C=O); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_{10}H_{20}NO_2^+$) requires ***m/z*** 186.1494, found ***m/z*** 186.1495 (100%).

Preparation and characterisation of 5-dodecylfuran-2(3*H*)-one 17d

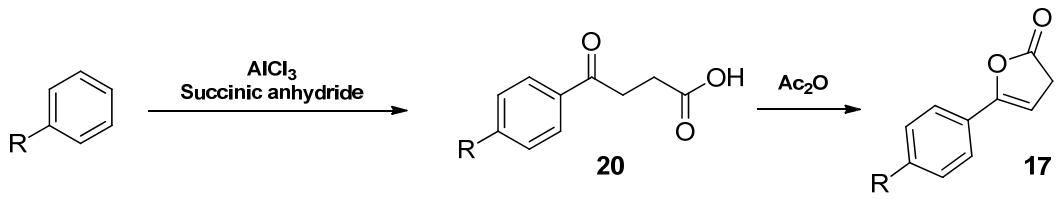


17d

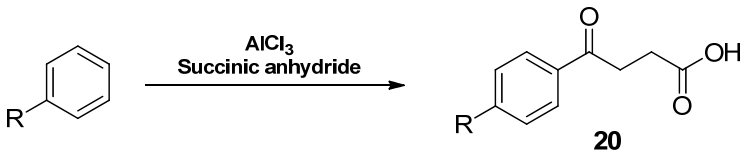
The title compound was synthesised from **16d** according to general procedure **X** as a colourless solid in 62%. Analytical data in agreement with previous report.[222]

m.p. 55-57 ºC; **FT-IR** ν_{max}(NaCl) 1786 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.88 (t, 3H, CH_3, *J* 7.0 Hz), 1.24-1.34 (m, 18H, 9 × CH_2), 1.54 (quint, 2H, CH_2), 2.27 (m, 2H, CH_2), 3.17 (m, 2H, C<u>H</u>$_2$CO$_2$), 5.09-5.12 (m, 1H, alkene-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.1 (<u>C</u>H$_3$), 22.6 (<u>C</u>H$_2$), 25.7 (<u>C</u>H$_2$), 28.2 (<u>C</u>H$_2$), 29.0 (<u>C</u>H$_2$), 29.2 (<u>C</u>H$_2$), 29.3 (<u>C</u>H$_2$), 29.4 (<u>C</u>H$_2$), 29.6 (<u>C</u>H$_2$), 29.6 (<u>C</u>H$_2$), 29.7 (<u>C</u>H$_2$), 31.9 (<u>C</u>H$_2$), 33.9 (<u>C</u>H$_2$), 98.1 (alkene-<u>C</u>H), 157.3 (alkene-Cquat.), 177.0 (C=O); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_{16}H_{32}NO_2^+$) requires ***m/z*** 270.2433, found ***m/z*** 270.2428 (100%).

6.2.1.2.5 Preparation of 5-arylfuran-2(3*H*)-one (R^1 = alkyl, R^2= H) 17



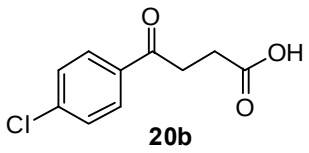
General procedure XI for the preparation of 3-aroylpropionic acids[146]



To a solution of succinic anhydride (2.0 g, 20 mmol, 1 equivalent) in dry dichloromethane (40 mL) in a round-bottom flask fitted with an addition funnel was added aluminum chloride (4.0 g, 30 mmol, 1.5 equivalents). The reaction mixture was cooled under stirring to 0 ºC. Aromatic compound (1 equivalent) in dry dichloromethane (10 mL per 1 g of aromatic compound) was added dropwise to the reaction mixture, maintaining the same temperature, and then the reaction mixture was stirred at room temperature. The reaction was monitored by TLC, and after completion the reaction mixture was poured onto a mixture of ice and concentrated hydrochloric acid (200 g : 20 mL) under stirring; the precipitated solid was filtered, washed with cold petroleum ether (100 mL), dried *in vacuo* to give the desired product which was used without further purification.

*N.B. for R = F, Br and OMe, the substituted propionic acids (**20a**, **20c** and **20e** respectively) were used as purchased.*

Preparation and characterisation of 3-(4-chloro-benzoyl) propionic acid 20b



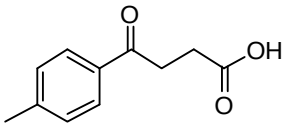
20b

The title compound was synthesised according to general procedure **XI** as a colourless solid (2.63 g, 62%). Analytical data in agreement with the literature.[223]

m.p. 119-121 ºC (lit.[224] 131 °C; lit.[223] 124 °C); **FT-IR** ν_{max}(NaCl) 3091 cm^{-1} (OH), 1694 cm^{-1} (C=O), 1680 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.82 (t, 2H, CH_2, *J* 6.5 Hz), 3.28 (t, 2H, CH_2, *J* 6.5 Hz), 7.45 (d, 2H, 2 × Ar-H, *J* 8.5 Hz), 7.92 (d, 2H, 2 × Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 27.9 ($\underline{C}H_2$), 33.1 ($\underline{C}H_2$), 129.0 (2 × Ar-$\underline{C}$H), 129.5 (2 × Ar-$\underline{C}$H), 134.7 (Ar-Cquat.), 139.8 (Ar-Cquat.), 178.7 (C=O), 196.6 (C=O); ***m/z*** (ES+) 235 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_9ClO_3Na^+$) requires ***m/z*** 235.0132, found ***m/z*** 235.0132.

Preparation and characterisation of 3-(4-methyl-benzoyl) propionic acid 20d

The title compound was synthesised according to general procedure **XI** as a colourless solid (2.54 g, 66%). Analytical data in agreement with the literature.[225]

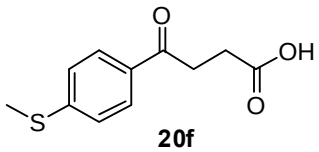


20d

m.p. 111-113 ºC (lit.[226] 127-129 °C); **FT-IR** ν_{max}(NaCl) 3029 cm^{-1} (OH), 1694 cm^{-1} (C=O), 1682 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.41 (s, 3H, CH_3), 2.81 (t, 2H, CH_2, *J* 6.5 Hz), 3.29 (t, 2H, CH_2, *J* 6.5 Hz), 7.27 (d, 2H, 2 × Ar-H, *J* 8.0 Hz), 7.88 (d, 2H, 2 × Ar-H, *J* 8.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 21.7 ($\underline{C}H_3$), 28.1 ($\underline{C}H_2$), 33.0 ($\underline{C}H_2$), 128.2 (2 × Ar-$\underline{C}$H), 129.3 (2 × Ar-$\underline{C}$H), 133.9 (Ar-Cquat.), 144.2 (Ar-Cquat.), 179.1 (C=O), 197.5 (C=O); ***m/z*** (ES+) 215 ($[M+Na]^+$, 70%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{12}O_3Na^+$) requires ***m/z*** 215.0679, found ***m/z*** 215.0677.

Preparation and characterisation of 3-(4-methylthio-benzoyl) propionic acid 20f

The title compound was synthesised according to general procedure **XI** as a colourless solid (3.05 g, 68%).

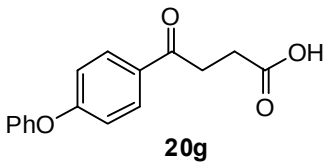


20f

m.p. 119-122 ºC; **FT-IR** ν_{max}(NaCl) 3030 cm^{-1} (OH), 1699 cm^{-1} (C=O), 1672 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.53 (s, 3H, CH_3), 2.82 (t, 2H, CH_2, *J* 6.5 Hz), 3.29 (t, 2H, CH_2, *J* 6.5 Hz), 7.28 (d, 2H, 2 × Ar-H, *J* 8.5 Hz,), 7.90 (d, 2H, 2 × Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.7 ($\underline{C}H_3$), 27.9 ($\underline{C}H_2$), 32.9 ($\underline{C}H_2$), 125.0 (2 × Ar-$\underline{C}$H), 128.4 (2 × Ar-$\underline{C}$H), 132.6 (Ar-Cquat.), 146.2 (Ar-Cquat.), 177.7 (C=O), 196.8 (C=O); ***m/z*** (ES+) 247 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{12}O_sSNa^+$) requires ***m/z*** 247.0399, found ***m/z*** 247.0398.

Preparation and characterisation of 3-(4-phenoxy-benzoyl) propionic acid 20g

The title compound was synthesised according to general procedure **XI** as a colourless solid (3.35 g, 62%). Analytical data in agreement with the literature.[227]

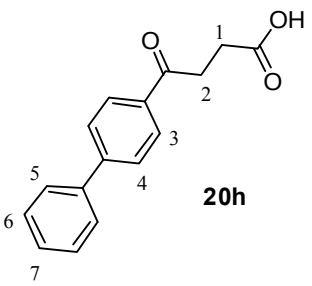


20g

m.p. 167-169 ºC (lit.[227] 172 °C); **FT-IR** ν_{max}(NaCl) 3041 cm^{-1} (OH), 1706 cm^{-1} (C=O), 1676 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.82 (t, 2H, CH_2, *J* 6.5 Hz), 3.28 (t, 2H, CH_2, *J* 6.5 Hz), 7.01 (d, 2H, Ar-H, *J* 8.5 Hz), 7.05-7.11 (m, 2H, Ar-H), 7.18-7.25 (m, 1H, Ar-H), 7.37-7.45 (m, 2H, Ar-H), 7.97 (d, 2H, Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 28.1 ($\underline{C}H_2$), 32.9 ($\underline{C}H_2$), 117.3 (2 × Ar-$\underline{C}$H), 120.2 (2 × Ar-$\underline{C}$H), 124.7 (Ar-$\underline{C}$H), 130.1 (2 × Ar-$\underline{C}$H), 130.3 (2 × Ar-$\underline{C}$H), 131.0 (Ar-Cquat.), 155.4 (Ar-Cquat.), 162.2 (Ar-Cquat.), 178.9 ($\underline{C}O_2H$), 196.4 (C=O); ***m/z*** (ES+) 293 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{14}O_4Na^+$) requires ***m/z*** 293.0784, found ***m/z*** 293.0783.

Preparation and characterisation of 3-(4-phenyl-benzoyl) propionic acid 20h

The title compound was synthesised according to general procedure **XI** as a colourless solid (3.96 g, 78%). Analytical data in agreement with previous report.[228]



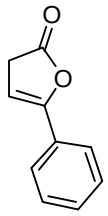
20h

m.p. 189-190 ºC (lit.[228] 180 °C); **FT-IR** ν_{max}(NaCl) 3040 cm^{-1} (OH), 1715 cm^{-1} (C=O), 1680 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.86 (t, 2H, CH_2, *J* 6.5 Hz), 3.37 (t, 2H, CH_2, *J* 6.5 Hz), 7.38-7.43 (m, 1H, H-7), 7.45-7.52 (m, 2H, H-6), 7.64 (d, 2H, H-5, *J* 7.5 Hz), 7.71 (d, 2H, 2 × Ar-H, *J* 8.5 Hz), 8.07 (d, 2H, 2 × Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 27.8 ($\underline{C}H_2$), 33.2 ($\underline{C}H_2$), 127.2 (2 × Ar-$\underline{C}$H), 127.3 (2 × Ar-$\underline{C}$H), 128.3 (Ar-$\underline{C}$H), 128.6 (2 × Ar-$\underline{C}$H), 129.0 (2 × Ar-$\underline{C}$H), 135.1 (Ar-Cquat.), 139.8 (Ar-Cquat.), 146.0 (Ar-Cquat.), 177.0 (C=O), 197.5 (C=O); ***m/z*** (ES+) 277

([M+Na]$^+$, 90%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{16}H_{14}O_3Na^+$) requires ***m/z*** 277.0835, found ***m/z*** 277.0836.

Preparation and characterisation of of 5-phenylfuran-2(3*H*)-one 17e[148]

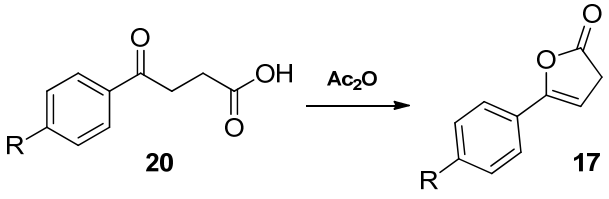
4-Oxo-4-phenyl-butyric acid (8.30 g, 46.6 mmol) was added to a stirred solution of acetic anhydride (10 mL) and acetic acid (5 mL) with a catalytic amount of *para*-toluenesulfonic acid (50 mg). The mixture was heated to 55 ºC for 16 hours, cooled to room temperature, diluted with water (25 mL) and stirred for a further 30 minutes during which time the product precipitated. The product was filtered from the solution, washed with water (3 × 50 mL) and dried *in vacuo* to give the desired product as an orange solid which can be used without further purification (6.19 g, 83%). Analytical data in agreement with previous report.[229]



17e

m.p. 82-83 ºC (lit.[230] 91-92 ºC); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ_H 3.43 (d, 2H, CH_2, *J* 2.5 Hz), 5.80 (t, 1H, alkene-H, *J* 2.5 Hz), 7.39-7.45 (m, 3H, 3 × Ar-H), 7.60 (m, 2H, 2 × Ar-H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ_C 34.7 ($\underline{C}H_2$), 97.7 (alkene-$\underline{C}$H), 124.8 (Ar-$\underline{C}$H), 128.4 (Ar-$\underline{C}$H), 128.7 (Ar-$\underline{C}$H), 129.6 (Ar-Cquat.), 154.0 (alkene-Cquat.), 175.9 (C=O); **HRMS** (CI+) exact mass calculated for [M+H]$^+$ ($C_{10}H_9O_2^+$) requires ***m/z*** 161.0603, found ***m/z*** 161.0596 (100%).

General procedure XII for the preparation of 5-arylfuran-2(3*H*)-ones[147]



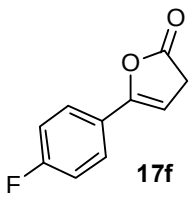
20 **17**

A mixture of 3-aroylpropionic acid **20** (10 mmol, 1 equivalent) and acetic anhydride (2.04 g, 20 mmol, 2 equivalents) was warmed at 100 ºC for 1 hour. After cooling, the reaction mixture was poured onto a cold 10% aqueous solution of potassium carbonate and stirred for a further 30 minutes during which time the product precipitated. It was filtered, washed with water (3 × 20

mL) and dried *in vacuo* to give the desired product as a solid which was used without further purification.

Preparation and characterisation of 5-(4-fluorophenyl)furan-2(3*H*)-one 17f

The title compound was prepared according to general procedure **XII** and obtained as an orange solid (1.09 g, 61%).

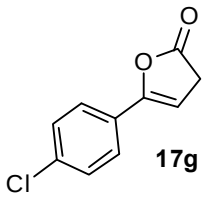


17f

m.p. 104-107 ºC; **FT-IR** ν_{max}(NaCl) 1783 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.41 (d, 2H, CH_2, *J* 2.5 Hz), 5.72 (t, 1H, alkene-H, *J* 2.5 Hz), 7.02-7.13 (m, 2H, 2 × Ar-H), 7.52-7.63 (m, 2H, 2 × Ar-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 34.6 ($\underline{C}H_2$), 97.3 (d, alkene-$\underline{C}$H, $J_{C,F}$ 9.0 Hz), 115.8 (d, 2 × Ar-$\underline{C}$H, $J_{C,F}$ 22.5 Hz), 124.7 (d, Ar-Cquat., $J_{C,F}$ 3.0 Hz), 126.7 (d, 2 × Ar-$\underline{C}$H, $J_{C,F}$ 22.5 Hz), 153.0 (alkene-Cquat.), 163.3 (d, $\underline{C}$-F, $J_{C,F}$ 250.0 Hz), 175.7 (C=O); ***m/z*** (ES+) 179 ($[M+H]^+$, 75%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{10}H_7FO_2^-$) requires ***m/z*** 177.0356, found ***m/z*** 177.0353.

Preparation and characterisation of 5-(4-chlorophenyl)furan-2(3*H*)-one 17g

The title compound was prepared according to general procedure **XII** and obtained as a brown solid (1.55 g, 80%).

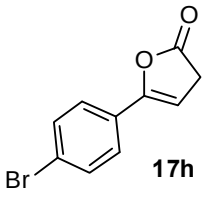


17g

m.p. 101-102 ºC; **FT-IR** ν_{max}(NaCl) 1801 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.43 (d, 2H, CH_2, *J* 2.5 Hz), 5.79 (t, 1H, alkene-H, *J* 2.5 Hz), 7.38 (d, 2H, 2 × Ar-H, *J* 8.5 Hz), 7.54 (d, 2H, 2 × Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 34.7 ($\underline{C}H_2$), 98.2 (alkene-$\underline{C}$H), 126.0 (2 × Ar-$\underline{C}$H), 126.9 (Ar-Cquat.), 129.0 (2 × Ar-$\underline{C}$H), 135.5 (Ar-Cquat.), 153.0 (alkene-Cquat.), 175.5 (C=O); ***m/z*** (ES−) 193 ($[M-H]^-$, 50%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_8ClO_2^+$) requires ***m/z*** 195.0207, found ***m/z*** 195.0208.

Preparation and characterisation of 5-(4-bromophenyl)furan-2(3*H*)-one 17h

The title compound was prepared according to general procedure **XII** and obtained as an orange solid (1.38 g, 58%). Analytical data in agreement with previous report.[231]

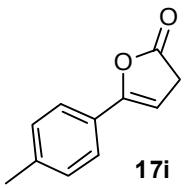


17h

m.p. 124-126 ºC (lit.[231] 124-127 °C); **FT-IR** ν_{max}(NaCl) 1777 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.38 (d, 2H, $\underline{C}H_2$, *J* 1.0 Hz), 5.79 (t, 1H, alkene-H, *J* 1.0 Hz), 7.42 (d, 2H, 2 × Ar-H, *J* 8.5 Hz), 7.50 (d, 2H, 2 × Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 34.7 ($\underline{C}H_2$), 98.5 (alkene-$\underline{C}$H), 123.7 (Ar-Cquat.), 126.2 (2 × Ar-$\underline{C}$H), 127.3 (Ar-Cquat.), 131.9 (2 × Ar-$\underline{C}$H), 152.9 (alkene-Cquat.), 175.5 (C=O); ***m/z*** (ES−) 237 ($[M-H]^-$, 35%), 475 ($[2M-H]^-$, 95%), **HRMS** (ES+) exact mass calculated for $[M+Na+CH_3OH]^+$ ($C_{11}H_{11}BrO_3Na^+$) requires ***m/z*** 292.9789, found ***m/z*** 292.9784.

Preparation and characterisation of 5-(4-methylphenyl)furan-2(3*H*)-one 17i

The title compound was prepared according to general procedure **XII** and obtained as an orange solid (1.53 g, 88%).

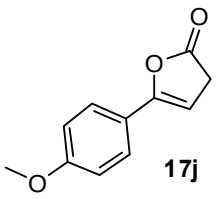


17i

m.p. 100-102 ºC; **FT-IR** ν_{max}(NaCl) 1803 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.38 (s, 3H, CH_3), 3.40 (d, 2H, CH_2, *J* 2.5 Hz), 5.72 (t, 1H, alkene-H, *J* 2.5 Hz), 7.21 (d, 2H, 2 × Ar-H, *J* 8.5 Hz), 7.50 (d, 2H, 2 × Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 21.4 ($\underline{C}H_3$), 34.6 ($\underline{C}H_2$), 98.7 (alkene-$\underline{C}$H), 124.7 (2 × Ar-$\underline{C}$H), 125.7 (Ar-Cquat.), 129.4 (2 × Ar-$\underline{C}$H), 139.8 (Ar-Cquat.), 154.1 (alkene-Cquat.), 176.1 (C=O); ***m/z*** (ES+) 197 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{10}O_2Na^+$) requires ***m/z*** 197.0573, found ***m/z*** 197.0574.

Preparation and characterisation of 5-(4-methoxyphenyl)furan-2(3*H*)-one 17j

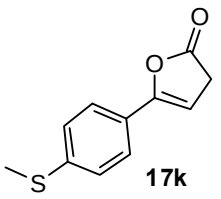
The title compound was prepared according to general procedure **XII** and obtained as a pale orange solid (1.01 g, 53%). Analytical data in agreement with previous report.[232]



m.p. 100-101 ºC (lit. 110-111 °C); **FT-IR** ν_{max}(NaCl) 1799 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.32 (d, 2H, CH_2, *J* 2.5 Hz), 3.77 (s, 3H, CH_3), 5.57 (t, 1H, alkene-H, *J* 2.5 Hz), 6.87 (d, 2H, 2 × Ar-H, *J* 8.5 Hz), 7.47 (d, 2H, 2 × Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 34.6 ($\underline{C}H_2$), 55.3 ($\underline{C}H_3$), 95.6 (Aalkene-$\underline{C}$H), 114.0 (2 × Ar-$\underline{C}$H), 121.1 (Ar-Cquat.), 126.2 (2 × Ar-$\underline{C}$H), 153.6 (alkene-Cquat.), 160.5 (Ar-Cquat.), 176.2 (C=O); ***m/z*** (ES+) 213 ([M+Na]$^+$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{11}H_{10}O_3Na^+$) requires ***m/z*** 213.0522, found ***m/z*** 213.0521.

Preparation and characterisation of 5-(4- methylthiophenyl)furan-2(3*H*)-one 17k

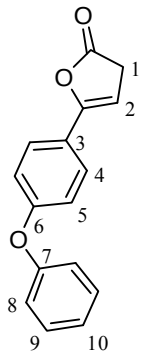
The title compound was prepared according to general procedure **XII** and obtained as a brown solid (1.03 g, 50%).



m.p. 108-110 ºC; **FT-IR** ν_{max}(NaCl) 1796 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.51 (s, 3H, CH_3), 3.42 (d, 2H, CH_2, *J* 2.5 Hz), 5.74 (t, 1H, alkene-H, *J* 2.5 Hz), 7.26 (d, 2H, 2 × Ar-H, *J* 8.5 Hz), 7.51 (d, 2H, 2 × Ar-H, *J* 8.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 15.3 ($\underline{C}H_3$), 34.6 ($\underline{C}H_2$), 96.9 (alkene-$\underline{C}$H), 124.9 (Ar-Cquat.), 125.1 (2 × Ar-$\underline{C}$H), 126.0 (2 × Ar-$\underline{C}$H), 140.8(Ar-Cquat.), 153.6 (alkene-Cquat.), 175.9 (C=O); ***m/z*** (ES−) 205 ([M−H]$^-$, 85%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{11}H_{11}O_2S^+$) requires ***m/z*** 207.0474, found ***m/z*** 207.0474.

Preparation and characterisation of 5-(4-phenoxyphenyl)furan-2(3*H*)-one 17l

The title compound was prepared according to general procedure **XII** and obtained as a pale orange solid (1.31 g, 52%).

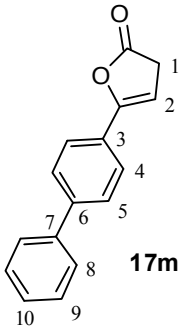


17l

m.p. 101-103 ºC; **FT-IR** ν_{max}(NaCl) 1805 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.42 (d, 2H, H-1, *J* 2.5 Hz), 5.70 (t, 1H, H-2, *J* 2.5 Hz), 6.95-7.03 (m, 2H, 2 × Ar-H), 7.04-7.11 (m, 2H, 2 × Ar-H), 7.13-7.21 (m, 1H, H-10), 7.33-7.42 (m, 2H, 2 × Ar-H), 7.55-7.59 (m, 2H, 2 × Ar-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 34.7 (C-1), 96.4 (C-2), 118.4 (2 × Ar-CH), 119.5 (2 × Ar-CH), 123.2 (Ar-Cquat.), 124.0 (Ar-CH), 126.4 (2 × Ar-CH), 129.9 (2 × Ar-CH), 153.6 (alkene-Cquat.), 156.3 (Ar-Cquat.), 158.7 (Ar-Cquat.), 175.9 (C=O); ***m/z*** (ES+) 275 ($[M+Na]^+$, 65%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{12}O_3Na^+$) requires ***m/z*** 275.0679, found ***m/z*** 275.0678.

Preparation and characterisation of 5-(biphenyl-4-yl)furan-2(3*H*)-one 17m

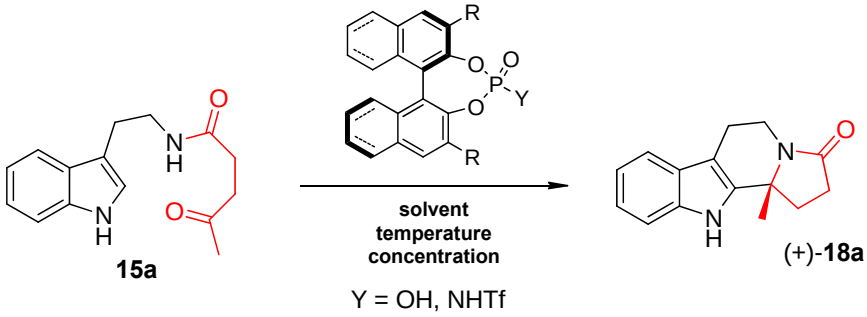
The title compound was prepared according to general procedure **XII** and obtained as a pale yellow solid (1.82 g, 77%).



17m

m.p. 180-181 ºC (lit.[233] 182-184 °C); **FT-IR** ν_{max}(NaCl) 1797 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.45 (d, 2H, H-1, *J* 3.0 Hz), 5.83 (t, 1H, H-2, *J* 3.0 Hz), 7.32-7.42 (m, 1H, H-10), 7.42-7.53 (m, 2H, 2 × Ar-H), 7.59-7.64 (m, 2H, 2 × Ar-H), 7.64-7.74 (m, 4H, 4 × Ar-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 34.7 (C-1), 97.7 (C-2), 125.2 (2 × Ar-CH), 127.0 (2 × Ar-CH), 127.2 (Ar-Cquat.), 127.3 (2 × Ar-CH), 127.8 (C-10), 128.9 (2 × Ar-CH), 140.1 (Ar-Cquat.), 142.3 (Ar-Cquat.), 153.8 (alkene-Cquat.), 175.9 (C=O); ***m/z*** (ES−) 235 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{12}O_2Na^+$) requires ***m/z*** 259.0730, found ***m/z*** 259.0730.

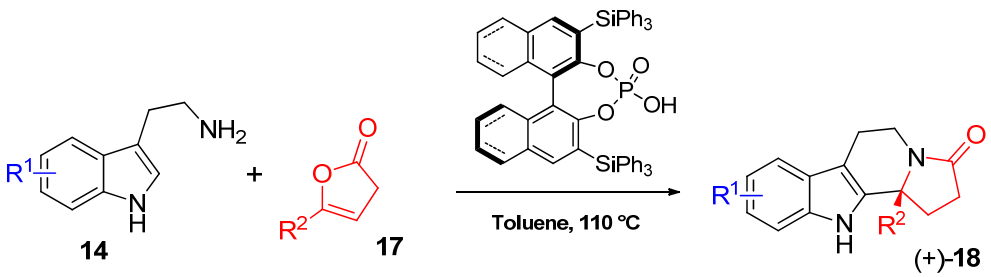
6.2.1.2.6 Enantioselective *N*-acyliminium cyclisation: general procedure XIII for optimisation studies



In a dry flask, catalyst (*R*)-**6**, (*R*)-**7** or (*R*)-**10** (0.005 mmol, 0.1 equivalents) was dissolved/suspended in the desired solvent. This suspension was stirred and if necessary heated to the desired temperature for the experiment. **15a** (12.9 mg, 0.05 mmol, 1 equivalent) was added to the mixture. The mixture was stirred at the desired temperature until complete formation of the tetracycle (monitored by TLC and confirmed by ^{1}H NMR). The mixture was purified by column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 4:1. The yield of reaction was determined after the purity was confirmed by ^{1}H NMR. The enantiomeric excess was measured by chiral HPLC using an OD column and eluting with hexane/isopropanol 80:20, 2 mL/min. The maximum of absorption was observed at 220 nm and $t_R(1) = 4.0$ min, $t_R(2) = 5.3$ min.

6.2.1.3 N-Acyliminium cyclisation cascade from enol lactones

General method XIV for the cascade cyclisation from lactones

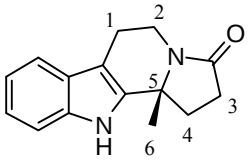


A tryptamine derivative (**14**, 0.3 mmol, 1 equivalent) was suspended in dry toluene (45 mL) and an enol lactone (**17**, 0.3 mmol, 1 equivalent) was added in one portion at room temperature, immediately followed by the addition of catalyst (*R*)-**6f** or (*R*)-**10a** (0.1 equivalents) in one portion. The resulting suspension was heated at reflux until completion (monitored by TLC / ^{1}H NMR). The solvent was removed *in vacuo*, and the residue redissolved in the minimum amount of dichloromethane and purified by column chromatography on silica gel.

Preparation and characterisation of (11b*R*)-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18a

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 4:1 as a colourless powder (71 mg, 99%). Analytical data in agreement with the literature.[130]

84% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 4.0 min, minor t_R = 5.3 min); $[\alpha]_D^{28}$ = + 99.5 (*c* 0.88, $CHCl_3$) (lit.[130] for (*R*)-enantiomer at 96% e.e., $[\alpha]_D^{23}$ = + 179.0 (*c* 1.0, $CHCl_3$)).



(*R*)-**18a**

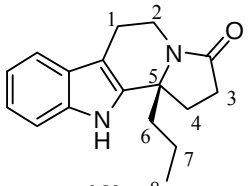
m.p. 243 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3255 cm^{-1} (N-H), 1664 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.62 (s, 3H, H-6), 2.20 (dt, 1H, H-4a, *J* 12.0 Hz, 9.5 Hz), 2.30 (ddd, 1H, H-4b, *J* 12.0 Hz, 9.5 Hz, 2.5 Hz), 2.50 (ddd, 1H, H-3a, *J* 17.0 Hz, 9.5 Hz, 2.5 Hz), 2.65-2.77 (m, 1H, H-3b), 2.77-2.91 (m, 2H, H-1), 3.07-3.17 (m, 1H, H-2a), 4.49 (ddd, 1H, H-2b, *J* 13.0 Hz, 5.5 Hz, 1.5 Hz), 7.14 (ddd, 1H, Ar-H, *J* 8.0 Hz, 7.0 Hz, 1.5 Hz), 7.20 (ddd, 1H, Ar-H, *J* 8.0 Hz, 7.0 Hz, 1.5 Hz), 7.35 (d, 1H, Ar-H, *J* 8.0 Hz), 7.50 (d, 1H, Ar-H, *J* 8.0 Hz), 7.89 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 21.1 (C-1), 25.5 (C-6), 30.6 (C-4), 32.8 (C-3), 34.9 (C-2), 59.4 (C-5), 107.1 (Ar-Cquat.), 110.9 (Ar-CH), 118.6 (Ar-CH), 119.9 (Ar-CH), 122.2 (Ar-CH), 126.7 (Ar-Cquat.), 136.0 (Ar-Cquat.), 137.6 (Ar-Cquat.), 172.7 (C=O); ***m/z*** (ES−)

239 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{15}H_{17}N_2O^+$) requires ***m/z*** 241.1335, found ***m/z*** 241.1337.

Preparation and characterisation of (11b*R*)-11b-propyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18b

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as a colourless amorphous solid (70 mg, 87%).

84% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 3.7 min, minor t_R = 6.1 min); the sample was further purified by crystallisation from methanol; $[\alpha]_D^{27}$ = + 172.9 (*c* 1.30, $CHCl_3$, 92% e.e. sample).



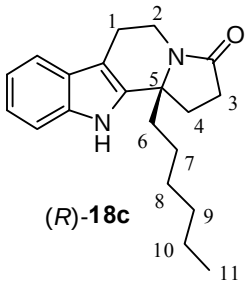
(*R*)-**18b**

m.p. 241-247 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3261 cm^{-1} (N-H), 1669 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.95 (t, 3H, H-8, *J* 7.5 Hz), 1.36-1.54 (m, 2H, H-7), 1.83-2.00 (m, 2H, H-6), 2.18 (dt, 1H, H-4a, *J* 12.5 Hz, 10.0 Hz), 2.37 (ddd, 1H, H-4b, *J* 12.5 Hz, 10.0 Hz, 2.5 Hz), 2.46 (ddd, 1H, H-3a, *J* 17.0 Hz, 10.0 Hz, 2.5 Hz), 2.67 (dt, 1H, H-3b, *J* 17.0 Hz, 10.0 Hz), 2.76-2.92 (m, 2H, H-1), 3.16 (td, 1H, H-2a, *J* 12.5 Hz, 5.5 Hz), 4.52 (dd, 1H, H-2b, *J* 12.5 Hz, 5.5 Hz), 7.14 (t, 1H, Ar-H, *J* 7.5 Hz), 7.20 (t, 1H, Ar-H, *J* 7.5 Hz), 7.35 (d, 1H, Ar-H, *J* 7.5 Hz), 7.50 (d, 1H, Ar-H, *J* 7.5 Hz), 7.89 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.4 (C-8), 17.8 (C-7), 21.0 (C-1), 30.6 (C-4), 31.1 (C-3), 35.5 (C-2), 42.4 (C-6), 62.4 (C-5), 107.4 (Ar-Cquat.), 110.9 (Ar-CH), 118.5 (Ar-CH), 119.9 (Ar-CH), 122.2 (Ar-CH), 126.7 (Ar-Cquat.), 136.0 (Ar-Cquat.), 137.4 (Ar-Cquat.), 173.5 (C=O); ***m/z*** (ES−) 267 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{17}H_{21}N_2O^+$) requires ***m/z*** 269.1648, found ***m/z*** 269.1651.

Preparation and characterisation of (11b*R*)-11b-hexyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18c

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as a colourless powder (65 mg, 70%).

83% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.9 min, minor t_R = 5.7 min); $[\alpha]_D^{29}$ = + 130.9 (*c* 1.03, $CHCl_3$).



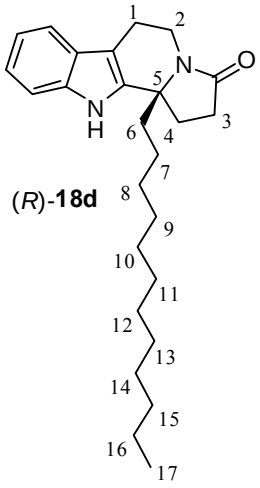
(*R*)-**18c**

m.p. 138-139 ºC; **FT-IR** ν_{max}(NaCl) 3248 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.87 (t, 3H, H-11, *J* 7.0 Hz), 1.25-1.45 (m, 8H, H-7, H-8, H-9, H-10), 1.84-1.99 (m, 2H, H-6), 2.18 (dt, 1H, H-4a, *J* 12.5 Hz, 10.0 Hz), 2.36 (ddd, 1H, H-4b, *J* 12.5 Hz, 10.0 Hz, 2.5 Hz), 2.45 (ddd, 1H, H-3a, *J* 17.0 Hz, 10.0 Hz, 2.5 Hz), 2.61-2.72 (m, 1H, H-3b), 2.78 (ddd, 1H, H-1a, *J* 15.5 Hz, 5.5 Hz, 1.0 Hz), 2.87 (ddd, 1H, H-1b, *J* 15.5 Hz, 11.0 Hz, 6.0 Hz), 3.09-3.19 (m, 1H, H-2a), 4.51 (ddd, 1H, H-2b, *J* 13.0 Hz, 6.0 Hz, 1.0 Hz), 7.13 (ddd, 1H, Ar-H, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.20 (ddd, 1H, Ar-H, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.35 (d, 1H, Ar-H, *J* 8.0 Hz), 7.49 (d, 1H, Ar-H, *J* 8.0 Hz), 7.82 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.0 (C-11), 21.0 (C-1), 22.6 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 30.5 (C-4), 31.1 (C-3), 31.7 ($\underline{C}H_2$), 35.5 (C-2), 40.1 (C-6), 62.4 (C-5), 107.4 (Ar-Cquat.), 110.9 (Ar-$\underline{C}$H), 118.5 (Ar-$\underline{C}$H), 119.9 (Ar-$\underline{C}$H), 122.2 (Ar-$\underline{C}$H), 126.7 (Ar-Cquat.), 136.0 (Ar-Cquat.), 137.5 (Ar-Cquat.), 173.5 (C=O); ***m/z*** (ES−) 309 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{27}N_2O^+$) requires ***m/z*** 311.2118, found ***m/z*** 311.2113.

Preparation and characterisation of (11b*R*)-11b-dodecyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18d

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 as a pale brown gum (87 mg, 74%).

83% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.7 min, minor t_R = 5.3 min); $[\alpha]_D^{29}$ = + 102.4 (*c* 1.52, $CHCl_3$).



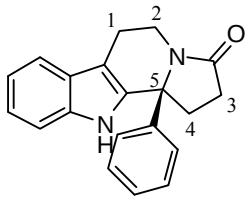
(*R*)-**18d**

FT-IR ν_{max}(NaCl) 3239 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.90 (t, 3H, H-17, *J* 7.0 Hz), 1.21-1.33 (m, 20H, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16), 1.86-2.02 (m, 2H, H-6), 2.20 (dt, 1H, H-4a, *J* 12.5 Hz, 10.0 Hz), 2.35-2.50 (m, 2H, H-4b, H-3a), 2.67 (dt, 1H, H-3b, *J* 17.0 Hz, 9.5 Hz), 2.76-2.92 (m, 2H, H-1), 3.16 (td, 1H, H-2a, *J* 12.5 Hz, 5.0 Hz), 4.52 (dd, 1H, H-2b, *J* 12.5 Hz, 5.5 Hz), 7.13 (ddd, 1H, Ar-H, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.19 (ddd, 1H, Ar-H, *J* 8.0 Hz, 7.0 Hz, 1.3 Hz), 7.34 (d, 1H, Ar-H, *J* 8.0 Hz), 7.49 (d, 1H, Ar-H, *J* 8.0 Hz), 8.42 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.0 (C-17), 21.1 (C-1), 22.7 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$), 29.4 ($\underline{C}H_2$), 29.5 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 30.0 ($\underline{C}H_2$), 30.5 (C-4), 31.2 (C-3), 31.7 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 35.6 (C-2), 40.1 (C-6), 62.6 (C-5), 107.0 (Ar-Cquat.), 111.0 (Ar-$\underline{C}$H), 118.5 (Ar-$\underline{C}$H), 119.7 (Ar-$\underline{C}$H), 122.1 (Ar-$\underline{C}$H), 126.7 (Ar-Cquat.), 136.1 (Ar-Cquat.), 137.7 (Ar-Cquat.), 173.7 (C=O); ***m/z*** (ES−) 393 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{26}H_{39}N_2O^+$) requires ***m/z*** 395.3057, found ***m/z*** 395.3053.

Preparation and characterisation of (11b*S*)-11b-phenyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18e

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as an off-white powder (70 mg, 78%). Analytical data in agreement with the literature.[130]

87% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 4.0 min, minor t_R = 10.9 min); $[\alpha]_D^{29}$ = + 70.6 (*c* 1.55, $CHCl_3$) (lit.[130] for (*S*)-enantiomer at 85% ee, $[\alpha]_D^{23}$ = + 89.5 (*c* 1.0, $CHCl_3$)).



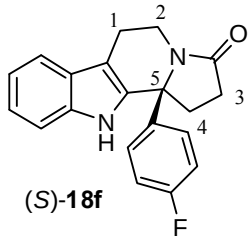
(*S*)-**18e**

m.p. 225 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3256 cm^{-1} (N-H), 1668 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.57-2.64 (m, 2H), 2.68-2.80 (m, 2H), 2.81-2.87 (m, 1H), 2.87-3.04 (m, 2H), 4.41 (dd, 1H, H-2b, *J* 12.5 Hz, 6.0 Hz), 7.17 (t, 1H, Ar-H, *J* 7.5 Hz), 7.23-7.28 (m, 3H, 3 × Ar-H), 7.29-7.36 (m, 3H, 3 × Ar-H), 7.40 (d, 1H, Ar-H, *J* 8.0 Hz), 7.54 (d, 1H, *J* 8.0 Hz), 8.12 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.8 (C-1), 31.2 (C-4), 33.1 (C-3), 33.6 (C-2), 65.4 (C-5), 109.3 (Ar-Cquat.), 111.2 (Ar-CH), 118.7 (Ar-CH), 120.0 (Ar-CH), 122.5 (Ar-CH), 126.2 (Ar-CH), 126.7 (Ar-Cquat.), 128.1 (Ar-CH), 128.8 (Ar-CH), 135.2 (Ar-Cquat.), 136.3 (Ar-Cquat.), 143.5 (Ar-Cquat.), 173.6 (C=O); ***m/z*** (ES−) 301 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{19}N_2O^+$) requires ***m/z*** 303.1492, found ***m/z*** 303.1494.

Preparation and characterisation of (11b*S*)-(4-fluorophenyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18f

The title product was prepared according to general method **XIV** in the presence of (*R*)-**10a** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as a a pale pink solid (83 mg, 86%).

71% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 6.6 min, minor t_R = 13.8 min); $[\alpha]_D^{25}$ = + 102.1 (*c* 1.13, $CHCl_3$).



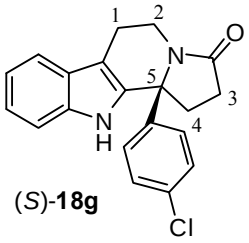
(*S*)-**18f**

m.p. 105-109 ºC; **FT-IR** ν_{max}(NaCl) 3259 cm^{-1} (N-H), 1668 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.41-2.58 (m, 1H, H-4a), 2.59-2.70 (m, 2H, H-4b, H-3a), 2.70-2.82 (m, 2H, H-3b, H-1a), 2.85-3.06 (m, 2H, H-1b, H-2a), 4.34-4.41 (m, 1H, H-2b), 6.98 (app. t, 2H, Ar-H, *J* 8.5 Hz), 7.17 (t, 1H, Ar-H, *J* 7.5 Hz), 7.20-7.33 (m, 3H, Ar-H), 7.42 (d, 1H, Ar-H, *J* 8.0 Hz), 7.17 (d, 1H, Ar-H, *J* 8.0 Hz), 9.38 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.8 (C-1), 31.1 (C-4), 33.6 (C-3), 35.4 (C-2), 65.3 (C-5), 108.9 (Ar-Cquat.), 111.4 (Ar-CH), 115.5 (d, 2 × Ar-CH, $J_{C\text{-}F}$ 21.5 Hz), 118.7 (Ar-CH), 119.9 (Ar-CH), 122.5 (Ar-CH), 126.5 (Ar-Cquat.), 128.1 (d, 2 × Ar-CH, $J_{C\text{-}F}$ 9.0 Hz), 134.9 (Ar-Cquat.), 136.5 (Ar-Cquat.), 139.5 (d, Ar-Cquat., $J_{C\text{-}F}$ 3.0 Hz), 162.3 (d, Ar-Cquat., $J_{C\text{-}F}$ 248.0 Hz), 173.4 (C=O); ***m/z*** (ES−) 319 ([M−H]$^-$, 95%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{20}H_{17}ON_2FNa^+$) requires ***m/z*** 343.1217, found ***m/z*** 343.1216.

Preparation and characterisation of 11b*S*-(4-chlorophenyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18g

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as an off-white solid (68 mg, 67%).

86% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 6.2 min, minor t_R = 13.7 min); $[\alpha]_D^{25}$ = + 70.5 (*c* 1.82, $CHCl_3$).



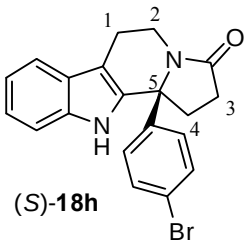
(*S*)-**18g**

m.p. 193-197 ºC; **FT-IR** ν_{max}(NaCl) 3262 cm^{-1} (N-H), 1669 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.45-2.59 (m, 1H, H-4a), 2.59-2.70 (m, 2H, H-4b, H-3a), 2.71-2.82 (m, 2H, H-3b, H-1a), 2.82-3.08 (m, 2H, H-1b, H-2a), 4.37 (dd, 1H, H-2b, *J* 12.5 Hz, 6.0 Hz), 7.14-7.23 (m, 3H, Ar-H), 7.23-7.32 (m, 3H, Ar-H), 7.40 (d, 1H, *J* 8.0 Hz, Ar-H), 7.53 (d, 1H, *J* 8.0 Hz, Ar-H), 8.82 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 20.7 (C-1), 29.7 (C-4), 31.0 (C-3), 33.4 (C-2), 64.9 (C-5), 109.6 (Ar-Cquat.), 111.2 (Ar-CH), 118.8 (Ar-CH), 120.1 (Ar-CH), 122.7 (Ar-CH), 126.6 (Ar-Cquat.), 127.7 (2 × Ar-CH), 128.9 (2 × Ar-CH), 134.0 (Ar-Cquat.), 134.5 (Ar-Cquat.), 136.2 (Ar-Cquat.), 142.1 (Ar-Cquat.), 173.5 (C=O); ***m/z*** (ES+) 359 ($[M+Na]^+$, 75%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{17}ON_2ClNa^+$) requires ***m/z*** 359.0922, found ***m/z*** 359.0922.

Preparation and characterisation of 11b*S*-(4-bromophenyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18h

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as a pale-orange solid (102 mg, 89%).

86% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 6.6 min, minor t_R = 14.8 min); $[\alpha]_D^{25}$ = + 79.3 (*c* 1.00, $CHCl_3$).



(*S*)-**18h**

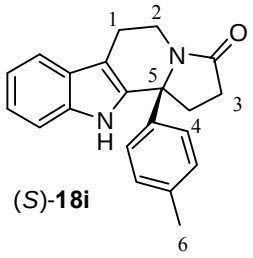
m.p. 146-149 ºC; **FT-IR** ν_{max}(NaCl) 3228 cm^{-1} (N-H), 1652 cm^{-1} (C=O); **^{1}H NMR** (d_6-acetone, 400 MHz) δ_H 2.30-2.49 (m, 1H, H-4a), 2.60-2.76 (m, 3H, H-4b, H-3), 2.79-3.06 (m, 3H, H-1, H-2a), 4.32 (dd, 1H, H-2b, *J* 11.0 Hz, 4.5 Hz), 7.06 (t, 1H, Ar-H, *J* 7.5 Hz), 7.15 (t, 1H,

Ar-H, *J* 7.5 Hz), 7.30 (d, 2H, Ar-H, *J* 8.5 Hz), 7.43 (d, 1H, Ar-H, *J* 8.0 Hz), 7.48 (d, 1H, Ar-H, *J* 8.0 Hz), 7.52 (d, 2H, Ar-H, *J* 8.5 Hz), 10.59 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 100 MHz) δ_C 20.8 (C-1), 30.6 (C-4), 33.9 (C-3), 35.5 (C-2), 65.3 (C-5), 108.6 (Ar-Cquat.), 111.7 (Ar-CH), 118.7 (Ar-CH), 119.7 (Ar-CH), 121.5 (Ar-Cquat.),122.3 (Ar-CH), 127.1 (Ar-Cquat.), 128.8 (2 × Ar-CH), 132.0 (2 × Ar-CH), 135.7 (Ar-Cquat.), 137.2 (Ar-Cquat.), 144.2 (Ar-Cquat.), 173.7 (C=O); ***m/z*** (ES−) 379 ([M−H]$^-$, 80%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{20}H_{17}ON_2BrNa^+$) requires ***m/z*** 403.0416, found ***m/z*** 403.0414.

Preparation and characterisation of 11b*S*-(*p*-tolyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18i

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as a pale-yellow solid (84 mg, 89%).

87% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 5.7 min, minor t_R = 14.2 min); $[\alpha]_D^{25} = +88.9$ (*c* 1.08, $CHCl_3$).



(*S*)-**18i**

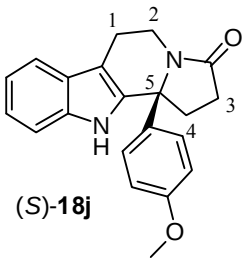
m.p. 225 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3254 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.31 (s, 3H, H-6), 2.41-2.63 (m, 2H, H-4), 2.64-2.85 (m, 3H, H-3, H-1a), 2.85-3.08 (m, 2H, H-1b, H-2a), 4.39 (dd, 1H, H-2b, *J* 12.0 Hz, 5.5 Hz), 7.0-7.27 (m, 6H, Ar-H), 7.41 (d, 1H, Ar-H, *J* 8.0 Hz), 7.53 (d, 1H, Ar-H, *J* 7.5 Hz), 8.90 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.8 (C-1), 20.9 (C-6), 31.2 (C-4), 33.6 (C-3), 35.4 (C-2), 65.3 (C-5), 108.8 (Ar-Cquat.), 111.2 (Ar-CH), 118.6 (Ar-CH), 119.8 (Ar-CH), 122.3 (Ar-CH), 126.1 (2 × Ar-CH), 126.6 (Ar-Cquat.), 129.4 (2 × Ar-CH), 135.5 (Ar-Cquat.), 136.4 (Ar-Cquat.), 137.8 (Ar-Cquat.), 140.5 (Ar-Cquat.), 173.7 (C=O); ***m/z*** (ES−) 315

([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{21}H_{20}ON_2Na^+$) requires ***m/z*** 339.1468, found ***m/z*** 339.1468.

Preparation and characterisation of 11b*S*-(4-methoxyphenyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-b]indol-3-one (*S*)-18j

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as an off-white solid (80 mg, 80%).

71% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 8.3 min, minor t_R = 17.4 min); $[\alpha]_D^{25}$ = + 135.7 (*c* 1.36, $CHCl_3$).



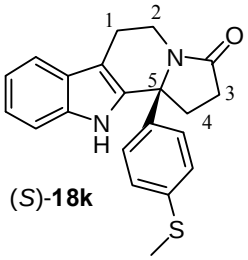
(*S*)-**18j**

m.p. 225 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3254 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.38-2.54 (m, 1H, H-4a), 2.56-2.71 (m, 2H, H-4b, H-3a), 2.71-2.85 (m, 2H, H-3b, H-1a), 2.90-3.10 (m, 2H, H-1b, H-2a), 3.74 (s, 3H, OC<u>H</u>$_3$), 4.31-4.47 (m, 1H, H-2b), 6.83 (d, 2H, Ar-H, *J* 8.5 Hz), 7.13-7.28 (m, 4H, Ar-H), 7.45 (d, 1H, Ar-H, *J* 8.0 Hz), 7.56 (d, 1H, Ar-H, *J* 8.0 Hz), 9.71 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.9 (C-1), 31.3 (C-4), 33.6 (C-3), 35.4 (C-2), 55.3 (O<u>C</u>H$_3$), 65.4 (C-5), 108.4 (Ar-Cquat.), 111.4 (Ar-<u>C</u>H), 113.9 (2 × Ar-<u>C</u>H), 118.5 (Ar-<u>C</u>H), 119.7 (Ar-<u>C</u>H), 122.3 (Ar-<u>C</u>H), 126.6 (Ar-Cquat.), 127.6 (2 × Ar-<u>C</u>H), 135.6 (Ar-Cquat.), 135.7 (Ar-Cquat.), 136.5 (Ar-Cquat.), 159.2 (Ar-Cquat.), 173.7 (C=O); ***m/z*** (ES+) 355 ([M+Na]$^+$, 55%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{21}H_{20}O_2N_2Na^+$) requires ***m/z*** 355.1417, found ***m/z*** 355.1417.

Preparation and characterisation of 11b*S*-(4-(methylthio)phenyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18k

The title product was prepared according to general method **XIV** in the presence of (*R*)-**10a** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as a pale-yellow powder (81 mg, 78%).

78% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 mL/min, 220 nm, major t_R = 8.2 min, minor t_R = 17.1 min); $[\alpha]_D^{25}$ = + 52.0 (*c* 1.08, $CHCl_3$).



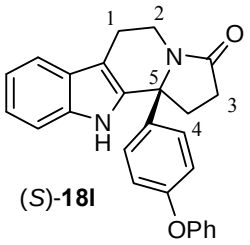
(*S*)-**18k**

m.p. 118-120 ºC; **FT-IR** ν_{max}(NaCl) 3255 cm^{-1} (N-H), 1667 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.44 (s, 3H, SC<u>H</u>$_3$), 2.47-2.71 (m, 3H, H-4, H-3a), 2.71-2.85 (m, 2H, H-3b, H-1a), 2.85-3.04 (m, 2H, H-1b, H-2a), 4.35-4.42 (m, 1H, H-2b), 7.12-7.19 (m, 5H, Ar-H), 7.20-7.25 (m, 1H, Ar-H), 7.39 (d, 1H, Ar-H, *J* 8.0 Hz), 7.53 (d, 1H, Ar-H, *J* 8.0 Hz), 8.42 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 15.5 (S<u>C</u>H$_3$), 20.8 (C-1), 31.1 (C-4), 33.4 (C-3), 35.3 (C-2), 65.0 (C-5), 109.3 (Ar-Cquat.), 111.2 (Ar-<u>C</u>H), 118.7 (Ar-<u>C</u>H), 120.0 (Ar-<u>C</u>H), 122.5 (Ar-<u>C</u>H), 126.4 (2 × Ar-<u>C</u>H), 126.6 (Ar-Cquat.), 126.7 (2 × Ar-<u>C</u>H), 135.0 (Ar-Cquat.), 136.2 (Ar-Cquat.), 138.7 (Ar-Cquat.), 140.2 (Ar-Cquat.), 173.5 (C=O); ***m/z*** (ES−) 347 ($[M-H]^-$, 50%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{20}ON_2SNa^+$) requires ***m/z*** 371.1189, found ***m/z*** 371.1188.

Preparation and characterisation of 11b*S*-(4-phenoxyphenyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18l

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as a pale-yellow solid (60 mg, 51%).

90% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, minor t_R = 35.7 min, major t_R = 95.3 min); $[\alpha]_D^{25}$ = + 95.8 (*c* 1.07, $CHCl_3$).

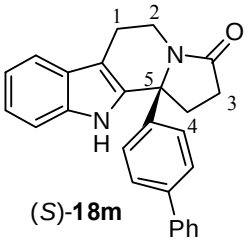


(*S*)-**18l**

m.p. 113-117 ºC; **FT-IR** ν_{max}(NaCl) 3258 cm^{-1} (N-H), 1667 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.46-2.58 (m, 1H, H-4a), 2.59-2.85 (m, 4H, H-4b, H-3, H-1a), 2.91-3.06 (m, 2H, H-1b, H-2a), 4.37-4.46 (m, 1H, H-2b), 6.93 (d, 2H, Ar-H, *J* 8.5 Hz), 6.99-7.04 (m, 2H, Ar-H), 7.09-7.29 (m, 5H, Ar-H), 7.31-7.44 (m, 3H, Ar-H), 7.54 (d, 1H, Ar-H, *J* 8.0 Hz), 9.02 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.8 (C-1), 31.2 (C-4), 33.6 (C-3), 35.4 (C-2), 65.2 (C-5), 108.9 (Ar-Cquat.), 111.3 (Ar-CH), 118.5 (2 × Ar-CH), 118.7 (Ar-CH), 119.2 (2 × Ar-CH), 119.9 (Ar-CH), 122.4 (Ar-CH), 123.8 (Ar-CH), 126.6 (Ar-Cquat.), 127.8 (2 × Ar-CH), 129.9 (2 × Ar-CH), 135.2 (Ar-Cquat.), 136.4 (Ar-Cquat.), 138.1 (Ar-Cquat.), 156.6 (Ar-Cquat.), 157.2 (Ar-Cquat.), 173.8 (C=O); ***m/z*** (ES+) 417 ($[M+Na]^+$, 75%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{22}O_2N_2Na^+$) requires ***m/z*** 417.1753, found ***m/z*** 417.1753.

Preparation and characterisation of 11b*S*-(biphenyl-4-yl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18m

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as an off-white solid (100 mg, 88%).



(*S*)-**18m**

94% e.e. (Chiralcel OD, 70:30 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 6.4 min, minor t_R = 11.0 min); $[\alpha]_D^{25}$ = + 38.3 (*c* 1.51, $CHCl_3$).

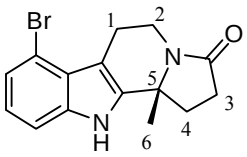
m.p. 153-155 ºC; **FT-IR** ν_{max}(NaCl) 3259 cm^{-1} (N-H), 1668 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.49-2.69 (m, 2H, H-4), 2.69-

2.90 (m, 3H, H-3, H-1a), 2.91-3.07 (m, 2H, H-1b, H-2a), 4.39-4.48 (m, 1H, H-2b), 7.14-7.21 (m, 1H, Ar-H), 7.22-7.29 (m, 1H, Ar-H), 7.30-7.40 (m, 3H, Ar-H), 7.41-7.45 (m, 3H, Ar-H), 7.50-7.56 (m, 5H, Ar-H), 8.83 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 20.9 (C-1), 31.2 (C-4), 33.6 (C-3), 35.5 (C-2), 65.3 (C-5), 109.1 (Ar-Cquat.), 111.3 (Ar-CH), 118.7 (Ar-CH), 119.9 (Ar-CH), 122.4 (Ar-CH), 126.6 (Ar-Cquat.), 126.7 (2 × Ar-CH), 127.0 (2 × Ar-CH), 127.4 (2 × Ar-CH), 127.6 (Ar-CH), 128.9 (2 × Ar-CH), 135.2 (Ar-Cquat.), 136.4 (Ar-Cquat.), 140.1 (Ar-Cquat.), 140.9 (Ar-Cquat.), 142.4 (Ar-Cquat.), 173.7 (C=O); ***m/z*** (ES+) 401 ($[M+Na]^+$, 95%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{22}ON_2Na^+$) requires ***m/z*** 401.1624, found ***m/z*** 401.1624.

Preparation and characterisation of (11b*R*)-7-bromo-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18n

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as a colourless powder (78 mg, 81%).

92% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 18.8 min, minor t_R = 28.4 min); $[\alpha]_D^{28}$ = + 117.5 (*c* 1.52, $CHCl_3$).



(*R*)-**18n**

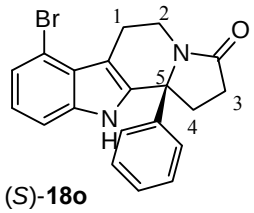
m.p. 225 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3254 cm^{-1} (N-H), 1667 cm^{-1} (C=O); **^{1}H NMR** (d_4-MeOD, 400 MHz) δ_H 1.62 (s, 3H, H-6), 2.09-2.20 (m, 1H, H-4a), 2.38 (ddd, 1H, H-4b, *J* 9.0 Hz, 7.0 Hz, 2.0 Hz), 2.42 (ddd, 1H, H-3a, *J* 12.5 Hz, 9.5 Hz, 2.0 Hz), 2.65-2.76 (m, 1H, H-3b), 2.94 (ddd, 1H, H-1a, *J* 15.5 Hz, 12.5 Hz, 6.0 Hz), 3.13 (td, 1H, H-2a, *J* 12.5 Hz, 4.5 Hz), 3.35 (dd, 1H, H-1b, *J* 15.5 Hz, 4.5 Hz), 4.31 (dd, 1H, H-2b, *J* 12.5 Hz, 6.0 Hz), 6.92 (t, 1H, Ar-H, *J* 8.0 Hz), 7.11 (dd, 1H, Ar-H, *J* 8.0 Hz, 0.5 Hz), 7.27 (dd, 1H, Ar-H, *J* 8.0 Hz, 0.5 Hz); **^{13}C NMR** (d_4-MeOD, 100 MHz) δ_C 24.4 (C-1), 25.2 (C-6), 31.5 (C-3), 33.9 (C-4), 36.0 (C-2), 61.4

(C-5), 107.1 (Ar-Cquat.), 111.5 (Ar-CH), 114.6 (Ar-Cquat.), 123.4 (Ar-CH), 124.0 (Ar-CH), 126.6 (Ar-Cquat.), 139.1 (Ar-Cquat.), 140.7 (Ar-Cquat.), 175.3 (C=O); ***m/z*** (ES−) 317, 319 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}BrN_2O^+$) requires ***m/z*** 319.0441 & 321.0421, found ***m/z*** 319.0439 & 321.0423.

Preparation and characterisation of (11b*S*)-7-bromo-11b-phenyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18o

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 as a brown gum (75 mg, 66%).

94% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 8.2 min, minor t_R = 28.9 min); $[\alpha]_D^{28}$ = + 103.6 (*c* 1.16, $CHCl_3$).



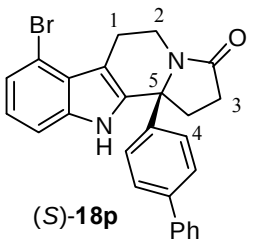
(*S*)-**18o**

FT-IR ν_{max}(NaCl) 3249 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 2.37 (ddd, 1H, H-4a, *J* 13.5 Hz, 8.5 Hz, 4.5 Hz), 2.53-2.70 (m, 3H, H-4b, H-3), 2.75 (td, 1H, H-2a, *J* 12.0 Hz, 6.0 Hz), 2.97 (ddd, 1H, H-1a, *J* 16.0 Hz, 12.0 Hz, 6.0 Hz), 3.13 (dd, 1H, H-1b, *J* 16.0 Hz, 6.0 Hz), 4.16 (dd, 1H, H-2b, *J* 12.0 Hz, 6.0 Hz), 7.00 (t, 1H, Ar-H, *J* 8.0 Hz), 7.17 (dd, 1H, Ar-H, *J* 8.0 Hz, 0.5 Hz), 7.25-7.32 (m, 3H, Ar-H), 7.35-7.40 (m, 3H, Ar-H), 11.78 (br s, 1H, NH); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 22.3 (C-1), 30.1 (C-4), 33.5 (C-3), 34.7 (C-2), 64.6 (C-5), 107.1 (Ar-Cquat.), 111.0 (Ar-CH), 112.8 (Ar-Cquat.), 122.5 (Ar-CH), 124.6 (Ar-Cquat.), 125.9 (Ar-CH), 127.7 (Ar-CH), 128.6 (2 × Ar-CH), 137.3 (Ar-Cquat.), 137.5 (Ar-Cquat.), 143.6 (Ar-Cquat.), 173.0 (C=O); ***m/z*** (ES−) 379, 381 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{18}BrN_2O^+$) requires ***m/z*** 381.0597 & 383.0579, found ***m/z*** 381.0597 & 383.0579.

Preparation and characterisation of (11b*S*)-7-bromo-11b(biphenyl-4-yl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18p

The title product was prepared according to general method **XIV** in the presence of (*R*)-**10a** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as a pale-yellow powder (104 mg, 76%).

82% e.e. (Chiralcel OD, 85:15 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 10.9 min, minor t_R = 27.4 min); $[\alpha]_D^{25}$ = + 105.5 (*c* 0.75, $CHCl_3$).



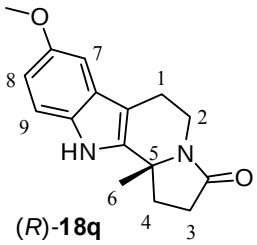
(*S*)-**18p**

m.p. 225 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3240 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.53-2.68 (m, 2H, H-4), 2.70-2.81 (m, 1H, H-3a), 2.81-3.02 (m, 2H, H-3b, H-1a), 3.17-3.43 (m, 2H, H-2a, H-1b), 4.39 (dd, 1H, H-2b, *J* 13.5 Hz, 6.0 Hz), 7.05 (t, 1H, Ar-H, *J* 8.0 Hz), 7.27-7.39 (m, 5H, Ar-H), 7.39-7.46 (m, 2H, Ar-H), 7.51-7.58 (m, 4H, Ar-H), 8.44 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 22.9 (C-1), 31.1 (C-4), 33.6 (C-3), 35.5 (C-2), 64.9 (C-5), 110.2 (Ar-Cquat.), 110.3 (Ar-CH), 114.4 (Ar-Cquat.), 123.3 (Ar-CH), 124.1 (Ar-CH), 125.6 (Ar-Cquat.), 126.6 (2 × Ar-CH), 127.0 (2 × Ar-CH), 127.5 (2 × Ar-CH), 127.7 (Ar-CH), 128.9 (2 × Ar-CH), 136.1 (Ar-Cquat.), 137.2 (Ar-Cquat.), 140.1 (Ar-Cquat.), 141.2 (Ar-Cquat.), 142.1 (Ar-Cquat.), 173.3 (C=O); ***m/z*** (ES−) 455 ($[M-H]^-$, 75%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{21}ON_2BrNa^+$) requires ***m/z*** 479.0729, found ***m/z*** 479.0733.

Preparation and characterisation of (11b*R*)-8-methoxy-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18q

The title product was prepared according to general method **XIV** in the presence of (*R*)-**10a** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 4:1 as a tan solid (65 mg, 80%).

69% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 7.7 min, minor t_R = 9.6 min); $[\alpha]_D^{25}$ = + 65.9 (*c* 1.70, $CHCl_3$).

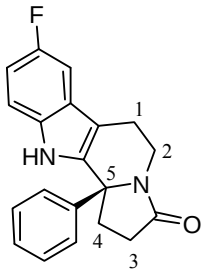


(*R*)-**18q**

m.p. 73-75 ºC; **FT-IR** ν_{max}(NaCl) 3260 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.62 (s, 3H, H-6), 2.17-2.36 (m, 2H, H-4), 2.42-2.59 (m, 1H, H-3a), 2.60-2.71 (m, 1H, H-3b), 2.72-2.95 (m, 2H, H-1), 3.13 (td, 1H, H-2a, *J* 12.0 Hz, 5.5 Hz), 3.87 (s, 3H, O<u>C</u>H_3), 4.49 (dd, 1H, H-2b, *J* 13.0 Hz, 5.5 Hz), 6.84 (dd, 1H, H-8, *J* 8.5 Hz, 2.0 Hz), 6.95 (d, 1H, H-7, *J* 2.0 Hz), 7.22 (d, 1H, H-9, *J* 8.5 Hz), 8.83 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 21.3 (C-1), 25.4 (C-6), 30.8 (C-4), 32.8 (C-3), 35.1 (C-2), 56.0 (O<u>C</u>H_3), 59.8 (C-5), 100.6 (Ar-<u>C</u>H), 106.3 (Ar-Cquat.), 111.8 (Ar-<u>C</u>H), 111.9 (Ar-<u>C</u>H), 127.0 (Ar-Cquat.), 131.3 (Ar-Cquat.), 138.8 (Ar-Cquat.), 154.2 (Ar-Cquat.), 173.0 (C=O); ***m/z*** (ES−) 269 ([M−H]$^-$, 80%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}O_2N_2Na^+$) requires ***m/z*** 293.1260, found ***m/z*** 293.1262.

Preparation and characterisation of (11b*S*)-8-fluoro-11b-phenyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18r

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as a brown amorphous solid (70 mg, 73%).



(*S*)-**18r**

90% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 3.5 min, minor t_R = 9.0 min); $[\alpha]_D^{28}$ = + 72.9 (*c* 1.10, $CHCl_3$).

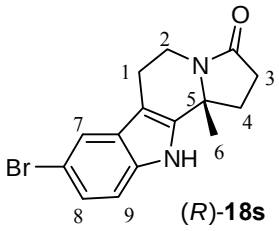
m.p. 226-231 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3260 cm^{-1} (N-H), 1659 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.51 (ddd, 1H, *J* 15.5 Hz, 9.0 Hz, 3.0 Hz, H-4a), 2.55-2.75 (m, 3H, H-3, H-4b), 2.77 (dt, 1H, *J* 15.5 Hz, 7.5 Hz, H-1a), 2.86-2.95 (m, 2H, H-1b, H-2a), 4.27 (dt, 1H, H-2b, *J* 11.5 Hz,

7.5 Hz), 6.95 (td, 1H, Ar-H, *J* 9.0 Hz, 2.5 Hz), 7.15 (dd, 1H, Ar-H, *J* 9.0 Hz, 2.5 Hz), 7.22-7.33 (m, 6H, 6 × Ar-H), 8.86 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.8 (C-1), 31.1 (C-4), 33.6 (C-3), 35.3 (C-2), 65.5 (C-5), 103.7 (d, Ar-CH *ortho*, $J_{C,F}$ 23.5 Hz), 109.2 (d, Ar-Cquat. *para*, $J_{C,F}$ 4.5 Hz), 110.6 (d, Ar-CH *ortho*, $J_{C,F}$ 26.0 Hz), 111.8 (d, Ar-CH *meta*, $J_{C,F}$ 9.5 Hz), 126.1 (2 × Ar-CH), 127.0 (d, Ar-Cquat. *meta*, $J_{C,F}$ 9.5 Hz), 128.2 (2 × Ar-CH), 128.8 (Ar-CH), 132.8 (Ar-Cquat.), 137.1 (Ar-Cquat.), 143.3 (Ar-Cquat.), 158.0 (d, C-F *ipso*, $J_{C,F}$ 235 Hz), 173.7 (C=O); ***m/z*** (ES−) 319 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{18}FN_2O^+$) requires ***m/z*** 321.1398, found ***m/z*** 321.1396.

Preparation and characterisation of (11b*R*)-8-bromo-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18s

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as an off-white solid (96 mg, 99%).

86% e.e. (Chiralcel OD, 85:15 hexane/isopropanol, 1.5 ml/min, 220 nm, major t_R = 8.5 min, minor t_R = 10.5 min); $[\alpha]_D^{28}$ = + 110.9 (*c* 1.16, $CHCl_3$).



(*R*)-**18s**

m.p. 220 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3247 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.64 (s, 3H, H-6), 2.15-2.23 (m, 1H, H-4a), 2.30 (ddd, 1H, H-4b, *J* 11.0 Hz, 9.0 Hz, 2.5 Hz), 2.49 (ddd, 1H, H-3a, *J* 17.0 Hz, 9.5 Hz, 2.5 Hz), 2.64-2.85 (m, 3H, H-3b, H-1), 3.04-3.14 (m, 1H, H-2a), 4.48 (ddd, 1H, H-2b, *J* 13.0 Hz, 6.0 Hz, 1.0 Hz), 7.22 (d, 1H, H-9, *J* 8.5 Hz), 7.28 (dd, 1H, H-8, *J* 8.5 Hz, 2.0 Hz), 7.61 (d, 1H, H-7, *J* 2.0 Hz), 8.05 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 21.0 (C-1), 25.5 (C-6), 30.6 (C-4), 32.7 (C-3), 34.8 (C-2), 59.3 (C-5), 106.9 (Ar-Cquat.), 112.4 (Ar-CH), 113.1 (Ar-Cquat.), 121.3 (Ar-CH), 125.0 (Ar-CH), 128.6 (Ar-Cquat.), 134.7 (Ar-Cquat.), 139.0

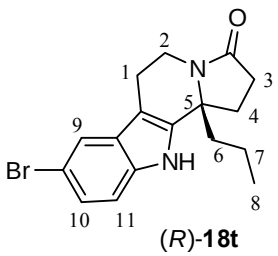
(Ar-Cquat.), 172.6 (C=O); ***m/z*** (ES−) 317, 319 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{15}H_{16}BrN_2O^+$) requires ***m/z*** 319.0441 & 321.0421, found ***m/z*** 319.0438 & 321.0425.

Preparation and characterisation of (11b*R*)-8-bromo-11b-propyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18t

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 as an amorphous pale brown solid (73 mg, 70%).

89% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 3.1 min, minor t_R = 5.7 min).

The sample was triturated with Et_2O and then crystallised from acetonitrile to reach > 99.5% e.e., $[\alpha]_D^{28}$ = + 107.8 (*c* 1.20, $CHCl_3$).



(*R*)-**18t**

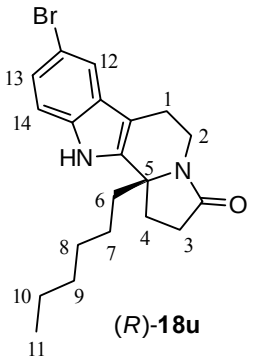
m.p. 290-295 ºC; **FT-IR** ν_{max}(NaCl) 3253 cm^{-1} (N-H), 1667 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.94 (t, 3H, H-8, *J* 7.5 Hz), 1.34-1.52 (m, 2H, H-7), 1.82-1.99 (m, 2H, H-6), 2.17 (dt, 1H, H-4a, *J* 12.0 Hz, 10.0 Hz), 2.36 (ddd, 1H, H-4b, *J* 12.0 Hz, 10.0 Hz, 2.0 Hz), 2.45 (ddd, 1H, H-3a, *J* 17.0 Hz, 10.0 Hz, 2.0 Hz), 2.66 (dt, 1H, H-3b, *J* 17.0 Hz, 10.0 Hz), 2.73 (dd, 1H, H-1a, *J* 15.5 Hz, 5.0 Hz), 2.81 (ddd, 1H, H-1b, *J* 15.5 Hz, 12.5 Hz, 6.5 Hz), 3.13 (td, 1H, H-2a, *J* 12.5 Hz, 5.0 Hz), 4.50 (dd, 1H, H-2b, *J* 12.5 Hz, 6.5 Hz), 7.20 (d, 1H, H-11, *J* 9.0 Hz), 7.27 (d, 1H, H-10, *J* 9.0 Hz), 7.60 (s, 1H, H-9), 8.09 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.3 (C-8), 17.7 (C-7), 20.9 (C-1), 30.5 (C-4), 31.0 (C-3), 35.4 (C-2), 42.3 (C-6), 62.4 (C-5), 107.0 (Ar-Cquat.), 112.3 (Ar-CH), 113.0 (Ar-Cquat.), 121.2 (Ar-CH), 124.9 (Ar-CH), 128.6 (Ar-Cquat.), 134.7 (Ar-Cquat.), 138.8 (Ar-Cquat.), 173.4 (C=O); ***m/z*** (ES−) 345, 347 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass

calculated for $[M+H]^+$ ($C_{17}H_{20}BrN_2O^+$) requires ***m/z*** 347.0754 & 349.0734, found ***m/z*** 347.0751 & 349.0727.

Preparation and characterisation of (11b*R*)-8-bromo-11b-hexyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18u

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 as a colourless crystalline solid (77 mg, 66%).

88% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 3.0 min, minor t_R = 5.7 min); the sample was triturated in Et_2O and then recrystallised from acetonitrile to reach > 99.5% e.e., $[\alpha]_D^{28}$ = + 117.2 (*c* 1.21, $CHCl_3$).



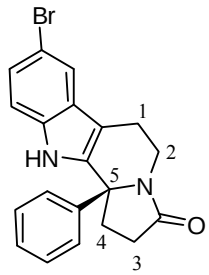
(*R*)-**18u**

m.p. 183-185 ºC; **FT-IR** ν_{max}(NaCl) 3259 cm^{-1} (N-H), 1671 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.87 (t, 3H, H-11, *J* 6.5 Hz), 1.24-1.45 (m, 8H, H-7, H-8, H-9, H-10), 1.84-1.99 (m, 2H, H-6), 2.18 (dt, 1H, H-4a, *J* 12.5 Hz, 9.5 Hz), 2.36 (ddd, 1H, H-4b, *J* 12.5 Hz, 9.5 Hz, 2.5 Hz), 2.45 (ddd, 1H, H-3a, *J* 17.5 Hz, 9.5 Hz, 2.5 Hz), 2.66 (dt, 1H, H-3b, *J* 17.5 Hz, 9.5 Hz), 2.70-2.76 (m, 1H, H-1a), 2.82 (ddd, 1H, H-1b, *J* 15.5 Hz, 12.0 Hz, 6.0 Hz), 3.13 (td, 1H, H-2a, *J* 12.0 Hz, 5.0 Hz), 4.50 (dd, 1H, H-2b, *J* 12.0 Hz, 6.0 Hz), 7.21 (d, 1H, H-14, *J* 8.5 Hz), 7.26 (dd, 1H, H-13, *J* 8.5 Hz, 1.5 Hz), 7.60 (d, 1H, H-12, *J* 1.5 Hz), 8.12 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.0 (C-11), 20.9 (C-1), 22.6 ($\underline{C}H_2$), 24.2 ($\underline{C}H_2$), 29.5 ($\underline{C}H_2$), 30.4 (C-4), 31.1 (C-3), 31.7 ($\underline{C}H_2$), 35.4 (C-2), 40.0 (C-6), 62.4 (C-5), 107.0 (Ar-Cquat.), 112.3 (Ar-$\underline{C}$H), 113.0 (Ar-Cquat.), 121.2 (Ar-$\underline{C}$H), 124.9 (Ar-$\underline{C}$H), 128.5 (Ar-Cquat.), 134.6 (Ar-Cquat.), 138.9 (Ar-Cquat.), 173.4 (C=O); ***m/z*** (ES−) 387, 389 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}BrN_2O^+$) requires ***m/z*** 389.1223 & 391.1205, found ***m/z*** 389.1225 & 391.1207.

Preparation and characterisation of (11b*S*)-8-bromo-11b-phenyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18v

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 as a brown amorphous solid (74 mg, 65%).

90% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 4.0 min, minor t_R = 11.6 min); $[\alpha]_D^{28}$ = + 89.0 (*c* 0.93, $CHCl_3$).



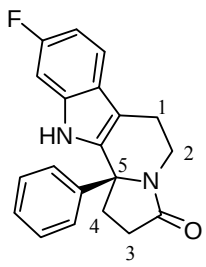
(*S*)-**18v**

m.p. 90-93 ºC; **FT-IR** ν_{max}(NaCl) 3256 cm^{-1} (N-H), 1668 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.48-2.82 (m, 4H, H-3, H-4), 2.88 (td, 1H, H-2a, *J* 12.0 Hz, 6.0 Hz), 3.20 (ddd, 1H, H-1a, *J* 16.0 Hz, 12.0 Hz, 6.0 Hz), 3.26 (dt, 1H, H-1b, *J* 16.0 Hz, 6.0 Hz), 4.31 (dd, 1H, H-2b, *J* 12.0 Hz, 6.0 Hz), 6.99 (t, 1H, Ar-H, *J* 8.0 Hz), 7.20-7.34 (m, 8H, 7 × Ar-H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 22.8 (C-1), 31.0 (C-4), 33.4 (C-3), 35.4 (C-2), 65.7 (C-5), 108.8 (Ar-Cquat.), 110.4 (Ar-CH), 113.9 (Ar-Cquat.), 122.8 (Ar-CH), 123.3 (Ar-CH), 125.3 (Ar-Cquat.), 125.9 (2 × Ar-CH), 128.0 (Ar-CH), 128.7 (2 × Ar-CH), 136.3 (Ar-Cquat.), 137.5 (Ar-Cquat.), 143.2 (Ar-Cquat.), 174.2 (C=O); ***m/z*** (ES−) 379, 381 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{18}BrN_2O^+$) requires ***m/z*** 381.0597 & 383.0579, found ***m/z*** 381.0600 & 383.0580.

Preparation and characterisation of (11b*S*)-9-fluoro-11b-phenyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*S*)-18w

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as a brown gum (63 mg, 64%).

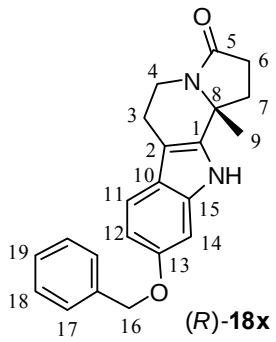
89% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 3.6 min, minor t_R = 6.4 min); $[\alpha]_D^{28}$ = + 90.0 (*c* 1.32, $CHCl_3$).



(*S*)-**18w**

FT-IR ν_{max}(NaCl) 3253 cm^{-1} (N-H), 1664 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.46-2.80 (m, 5H, H-3, H-4, H-1a), 2.83-2.95 (m, H-1b, H-2a), 4.35 (dt, 1H, H-2b, *J* 13.0 Hz, 8.0 Hz), 6.89 (ddd, 1H, Ar-H, *J* 9.5 Hz, 8.5 Hz, 2.5 Hz), 7.06 (dd, 1H, Ar-H, *J* 9.5 Hz, 2.0 Hz), 7.19-7.31 (m, 5H, 5 × Ar-H), 7.39 (dd, 1H, Ar-H, *J* 8.5 Hz, 5.5 Hz), 8.65 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.8 (C-1), 31.1 (C-4), 33.6 (C-3), 35.3 (C-2), 65.4 (C-5), 97.8 (d, Ar-CH *ortho*, $J_{C,F}$ 26.0 Hz), 108.5 (d, Ar-CH *ortho*, $J_{C,F}$ 24.5 Hz), 109.2 (Ar-Cquat.), 119.4 (d, Ar-CH *meta*, $J_{C,F}$ 10.0 Hz), 123.3 (Ar-Cquat.), 126.1 (2 × Ar-CH), 128.1 (Ar-CH), 128.9 (2 × Ar-CH), 135.4 (d, Ar-Cquat. *para*, $J_{C,F}$ 3.5 Hz), 136.3 (d, Ar-Cquat. *meta*, $J_{C,F}$ 12.5 Hz), 143.4 (Ar-Cquat.), 160.1 (d, C-F *ipso*, $J_{C,F}$ 238 Hz), 173.7 (C=O); ***m/z*** (ES−) 319 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{18}FN_2O^+$) requires ***m/z*** 321.1398, found ***m/z*** 321.1401.

Preparation and characterisation of 9-(Benzyloxy)-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18x



(*R*)-**18x**

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 4:1 as an off-white solid (77 mg, 74%).

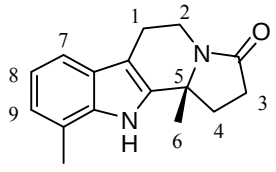
68% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 7.0 min, minor t_R = 10.1 min); $[\alpha]_D^{28}$ = + 51.9 (*c* 1.07, $CHCl_3$).

m.p. 88-92 ºC; **FT-IR** ν_{max}(NaCl) 3258 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.60 (s, 3H, H-9), 2.13-2.24 (m, 1H, H-7a), 2.28 (ddd, 1H, H-7b, *J* 11.5 Hz, 8.5 Hz, 2.5 Hz), 2.48 (ddd, 1H, H-6a, *J* 17.0 Hz, 10.0 Hz, 2.0 Hz), 2.63-2.87 (m, 3H, H-3, H-6b), 3.09 (ddd, 1H, H-4a, *J* 13.0 Hz, 11.0 Hz, 5.5 Hz), 4.47 (dd, 1H, H-4b, *J* 13.0 Hz, 5.5 Hz), 5.11 (s, 2H, H-16), 6.93 (dd, 1H, H-12, *J* 8.5 Hz, 2.5 Hz), 7.03 (d, 1H, H-14, *J* 2.5 Hz), 7.24 (d, 1H, H-11, *J* 8.5 Hz), 7.30-7.36 (m, 1H, H-19), 7.36-7.43 (m, 2H, H-18), 7.46-7.51 (m, 2H, H-17), 7.68 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 21.2 (C-3), 25.5 (C-9), 30.6 (C-6), 32.8 (C-7), 34.9 (C-4), 59.4 (C-8), 71.0 (C-16), 102.4 (C-14), 107.1 (C-2), 111.6 (C-12), 112.9 (C-11), 127.2 (Ar-Cquat.), 127.5 (2C, C-17), 127.8 (C-19), 128.5 (2C, C-18), 131.2 (Ar-Cquat.), 137.6 (Ar-Cquat.), 138.6 (Ar-Cquat.), 153.6 (Ar-Cquat.), 172.6 (C=O); ***m/z*** (ES−) 345 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{22}N_2O_2Na^+$) requires ***m/z*** 369.1573, found ***m/z*** 369.1570.

Preparation and characterisation of (11b*R*)-10,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18y

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 4:1 as a colourless powder (70 mg, 92%).

92% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1.5 ml/min, 220 nm, major t_R = 10.8 min, minor t_R = 14.4 min); $[\alpha]_D^{21} = +215.6$ (*c* 1.25, $CHCl_3$).



(*R*)-**18y**

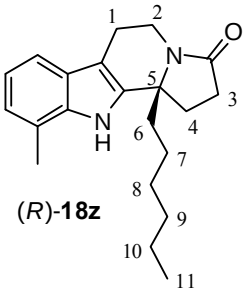
m.p. 194-197 ºC; **FT-IR** ν_{max}(NaCl) 3262 cm^{-1} (N-H), 1664 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.63 (s, 3H, H-6), 2.20 (dt, 1H, H-4a, *J* 11.5 Hz, 10.0 Hz), 2.34 (ddd, 1H, H-4b, *J* 11.5 Hz, 9.0 Hz, 2.0 Hz), 2.47 (ddd, 1H, H-3a, *J* 17.0 Hz, 10.0 Hz, 2.0 Hz), 2.51 (s, 3H, Ar-C$\underline{H}_3$), 2.65-2.74 (m, 1H, H-3b), 2.79 (ddd, 1H, H-1a, *J* 15.5 Hz, 6.0 Hz, 1.5 Hz),

2.85 (ddd, 1H, H-1b, *J* 15.5 Hz, 10.5 Hz, 5.5 Hz), 3.05-3.16 (m, 1H, H-2a), 4.48 (ddd, 1H, H-2b, *J* 13.0 Hz, 5.5 Hz, 1.5 Hz), 7.01 (d, 1H, Ar-H, *J* 7.5 Hz), 7.07 (t, 1H, H-8, *J* 7.5 Hz), 7.35 (d, 1H, Ar-H, *J* 7.5 Hz), 7.79 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.7 (Ar-$\underline{C}H_3$), 21.3 (C-1), 25.5 (C-6), 30.7 (C-4), 32.9 (C-3), 35.0 (C-2), 59.5 (C-5), 107.6 (Ar-Cquat.), 116.3 (Ar-$\underline{C}$H), 120.2 (2C, Ar-$\underline{C}$H, Ar-Cquat.), 123.0 (Ar-$\underline{C}$H), 126.3 (Ar-Cquat.), 135.6 (Ar-Cquat.), 137.4 (Ar-Cquat.), 172.7 (C=O); ***m/z*** (ES−) 253 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}N_2O^+$) requires ***m/z*** 255.1492, found ***m/z*** 255.1491.

Preparation and characterisation of (11b*R*)-11b-hexyl-10-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18z

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 as an off-white gum (61 mg, 63%).

95% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.7 min, minor t_R = 4.8 min); $[\alpha]_D^{28}$ = + 102.8 (*c* 2.26, $CHCl_3$).



(*R*)-**18z**

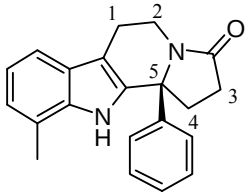
FT-IR ν_{max}(NaCl) 3255 cm^{-1} (N-H), 1667 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.87 (t, 3H, H-11, *J* 7.0 Hz), 1.20-1.46 (m, 8H, H-7, H-8, H-9, H-10), 1.86-2.02 (m, 2H, H-6), 2.21 (dt, 1H, H-4a, *J* 12.5 Hz, 10.0 Hz), 2.38 (ddd, 1H, H-4b, *J* 12.5 Hz, 10.0 Hz, 2.5 Hz), 2.45 (ddd, 1H, H-3a, *J* 17.0 Hz, 10.0 Hz, 2.5 Hz), 2.50 (s, 3H, Ar-$\underline{C}H_3$), 2.67 (dt, 1H, H-3b, *J* 17.0 Hz, 10.0 Hz), 2.77 (ddd, 1H, H-1a, *J* 15.5 Hz, 5.5 Hz, 1.0 Hz), 2.86 (ddd, 1H, H-1b, *J* 15.5 Hz, 11.0 Hz, 6.0 Hz), 3.08-3.19 (m, 1H, H-2a), 4.50 (ddd, 1H, H-2b, *J* 13.0 Hz, 6.0 Hz, 1.0 Hz), 7.00 (d, 1H, Ar-H, *J* 7.0 Hz), 7.05 (t, 1H, Ar-H, *J* 7.0 Hz), 7.34 (d, 1H, Ar-H, *J* 7.0 Hz), 7.93 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.1 (C-11), 16.8 (Ar-$\underline{C}H_3$), 21.1 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$), 24.2 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 30.6 ($\underline{C}H_2$), 31.2 ($\underline{C}H_2$), 31.7 ($\underline{C}H_2$),

35.6 (C-2), 40.1 (C-6), 62.6 (C-5), 107.7 (Ar-Cquat.), 116.2 (Ar-CH), 120.1 (Ar-CH), 120.2 (Ar-Cquat.), 122.9 (Ar-CH), 126.3 (Ar-Cquat.), 135.5 (Ar-Cquat.), 137.4 (Ar-Cquat.), 173.6 (C=O); ***m/z*** (ES−) 323 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{21}H_{29}N_2O^+$) requires ***m/z*** 325.2274, found ***m/z*** 325.2274.

Preparation and characterisation of (11b*S*)-10-methyl-11b-phenyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-b]indol-3-one (*S*)-18α

The title product was prepared according to general method **XIV** in the presence of (*R*)-**6f** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as an off-white powder (90 mg, 95%).

99% e.e. (Chiralcel OD, 70:30 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.4 min, minor t_R = 9.4 min); $[\alpha]_D^{28}$ = + 98.9 (*c* 1.42, $CHCl_3$).



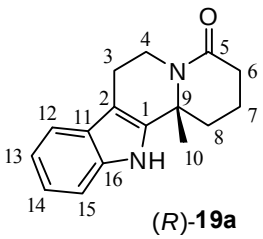
(*R*)-**18α**

m.p. 140 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3259 cm^{-1} (N-H), 1668 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.53 (s, 3H, Ar-C$\underline{H}_3$), 2.58-2.67 (m, 2H, H-4), 2.73-2.81 (m, 2H, H-3), 2.84-2.94 (m, 2H, H-1), 2.96-3.03 (m, 1H, H-2a), 4.39 (dd, 1H, H-2b, *J* 13.0 Hz, 6.0 Hz), 7.06 (d, 1H, Ar-H, *J* 7.5 Hz), 7.10 (t, 1H, *J* 7.5 Hz), 7.24-7.27 (m, 2H, Ar-H), 7.30-7.35 (m, 3H, Ar-H), 7.39 (d, 1H, Ar-H, *J* 7.5 Hz), 7.92 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.8 (C$\underline{H}_3$), 20.9 (C-1), 31.3 (C-4), 33.5 (C-3), 35.3 (C-2), 65.3 (C-5), 110.1 (Ar-Cquat.), 116.4 (Ar-CH), 120.3 (2C, Ar-CH, Ar-Cquat.), 123.3 (Ar-CH), 126.2 (Ar-Cquat.), 126.3 (2 × Ar-CH), 128.2 (Ar-CH), 128.8 (2 × Ar-CH), 134.8 (Ar-Cquat.), 135.8 (Ar-Cquat.), 143.6 (Ar-Cquat.), 173.4 (C=O); ***m/z*** (ES−) 315 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{21}H_{21}N_2O^+$) requires ***m/z*** 317.1648, found ***m/z*** 317.1648.

Preparation and characterisation of (12b*R*)-12b-methyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (*R*)-19a

The title product prepared according to general method **XIV** in the presence of (*R*)-**10a** and was obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as a pale brown solid (63 mg, 83%). Analytical data in agreement with the literature.[130]

70% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 7.7 min, minor t_R = 8.9 min); $[\alpha]_D^{25}$ = + 176.3 (*c* 0.98, $CHCl_3$/MeOH 9:1) (lit.[130] (*R*)-enantiomer at 92% e.e. $[\alpha]_D^{23}$ = + 201.8 (*c* 0.225, $CHCl_3$)).



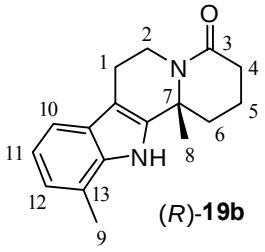
(*R*)-**19a**

m.p. 258-260 ºC; **FT-IR** ν_{max}(NaCl) 3256 cm^{-1} (NH), 1609 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.69 (s, 3H, H-10), 1.85-2.06 (m, 3H, H-7, H-8a), 2.24-2.30 (m, 1H, H-8b), 2.45 (ddd, 1H, H-6a, *J* 18.0 Hz, 10.5 Hz, 7.5 Hz), 2.60-2.67 (m, 1H, H-6b), 2.75 (app. dd, 1H, H-3a, *J* 16.0 Hz, 4.5 Hz), 2.85 (ddd, 1H, H-3b, *J* 16.0 Hz, 11.0 Hz, 4.5 Hz), 3.03 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 5.11 (app. dd, 1H, H-4b, *J* 12.5 Hz, 4.5 Hz), 7.13 (ddd, 1H, H-13, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.19 (ddd, 1H, H-14, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.34 (d, 1H, H-15, *J* 8.0 Hz), 7.51 (d, 1H, H-12, *J* 8.0 Hz), 7.89 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 16.6 (C-7), 21.2 (C-3), 26.1 (C-10), 31.8 (C-6), 35.5 (C-8), 36.7 (C-4), 56.8 (C-9), 108.2 (C-2), 110.9 (C-15), 118.5 (C-12), 119.8 (C-13), 122.2 (C-14), 126.7 (C-11), 136.0 (C-16), 138.1 (C-1), 169.6 (C=O); ***m/z*** (ES−) 253 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{16}H_{17}N_2O^-$) requires ***m/z*** 253.1346, found ***m/z*** 253.1340.

Preparation and characterisation of (12b*R*)-11,12b-dimethyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (*R*)-19b

The title product was prepared according to general method **XIV** in the presence of (*R*)-**10a** and obtained after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as a colourless crystalline solid (66 mg, 82%).

85% e.e. (Chiralcel AD, 90:10 hexane/isopropanol, 1.5 ml/min, 220 nm, major t_R = 4.7 min, minor t_R = 6.6 min); $[\alpha]_D^{21}$ = + 201.0 (*c* 1.02, $CHCl_3$).

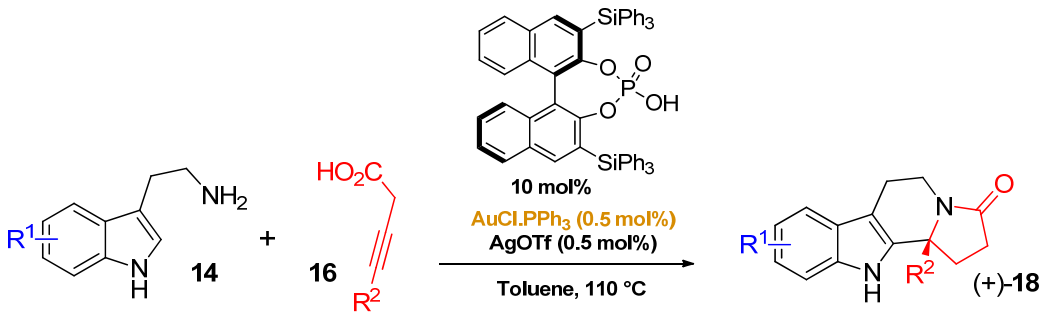


(*R*)-**19b**

m.p. 261-264 ºC; **FT-IR** ν_{max}(NaCl) 3273 cm^{-1} (N-H), 1608 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 1.62 (s, 3H, H-8), 1.67-1.77 (m, 2H, H-5a, H-6a), 1.83-2.00 (m, 1H, H-5b), 2.19-2.41 (m, 2H, H-4), 2.46 (s, 3H, H-9), 2.52-2.67 (m, 3H, H-1, H-6b), 2.91 (td, 1H, H-2a, *J* 12.0 Hz, 4.0 Hz), 4.85 (dd, 1H, H-2b, *J* 13.0 Hz, 4.0 Hz), 6.82-6.92 (m, 2H, H-11, H-12), 7.21 (d, 1H, H-10, *J* 7.0 Hz), 10.54 (br s, 1H, NH); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 17.1 (C-5), 17.9 (C-9), 22.0 (C-1), 26.0 (C-8), 32.6 (C-4), 35.5 (C-6), 36.4 (C-2), 57.4 (C-7), 107.2 (Ar-Cquat.), 116.3 (C-10), 119.6 (C-11), 121.1 (C-13), 122.5 (C-12), 126.7 (Ar-Cquat.), 136.3 (Ar-Cquat.), 140.4 (Ar-Cquat.), 168.8 (C=O); ***m/z*** (ES−) 267 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{21}N_2O^+$) requires ***m/z*** 269.1648, found ***m/z*** 269.1641.

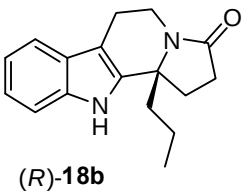
6.2.1.4 *N-acyliminium cyclisation cascade combined with gold(I)-catalysed cycloisomerisation of alkynoic acids*

General procedure XV for the doubly catalysed cyclisation cascade



A 15 mM solution of $AuCl.PPh_3$ in toluene (100 µL, 15.0 µmol, 0.5 mol%) and a 15 mM solution of AgOTf in toluene (100 µL, 15.0 µmol, 0.5 mol%) were added to 10 mL of toluene. Alkynoic acid **16** (0.36 mmol, 1.2 equivalents) was added in one portion at room temperature and the resulting solution was stirred for 60 minutes in a sealed vessel. The solution was diluted with 35 mL of toluene and a tryptamine derivative **14** (0.3 mmol, 1 equivalent) was added in one portion, immediately followed by (*R*)-**6f** (26 mg, 0.03 mmol, 0.1 equivalents) in one portion. The suspension was then heated at 80 ºC for 24 hours and at reflux for a further 24 hours. The solvent was removed *in vacuo*. The residue was redissolved in dichloromethane and purified by column chromatography on silica gel.

Preparation and characterisation of (11b*R*)-11b-propyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18b



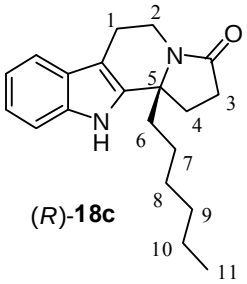
(*R*)-**18b**

The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 85:15 as a colourless amorphous solid (63 mg, 79%).

84% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 3.7 min, minor t_R = 6.1 min); $[\alpha]_D^{27}$ = + 172.9 (*c* 1.30, $CHCl_3$, 92% e.e. sample).

Spectral data identical to (*R*)-**18b** obtained from the condensation of preformed enol **17b** lactone and tryptamine **14a**.

Preparation and characterisation of (11b*R*)-11b-hexyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18c

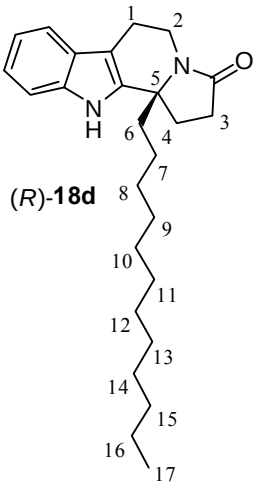


(*R*)-**18c**

The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 9:1 as a colourless powder (86 mg, 92%).

83% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.9 min, minor t_R = 5.7 min); $[\alpha]_D^{29}$ = + 130.9 (*c* 1.03, $CHCl_3$). Spectral data identical to (*R*)-**18c** obtained from the condensation of preformed enol lactone **17c** and tryptamine **14a**.

Preparation of characterisation of (11b*R*)-11b-dodecyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18d

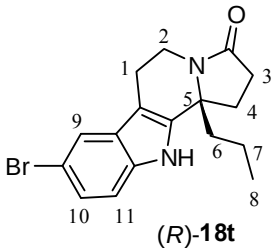


(*R*)-**18d**

The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 95:5 to 93:7 as a colourless foamy solid (103 mg, 87%).

83% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.7 min, minor t_R = 5.3 min); $[\alpha]_D^{29}$ = + 102.4 (*c* 1.52, $CHCl_3$). Spectral data identical to (*R*)-**18d** obtained from the condensation of preformed enol lactone **17d** and tryptamine **14a**.

Preparation and characterisation of (11b*R*)-8-bromo-11b-propyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18t

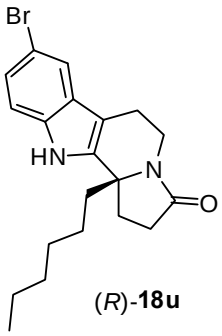


(*R*)-**18t**

The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 7:1 as a pale brown amorphous solid (80 mg, 77%).

89% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 3.1 min, minor t_R = 5.7 min); $[\alpha]_D^{28}$ = + 107.8 (*c* 1.20, $CHCl_3$, > 99.5% e.e. sample). Spectral data identical to (*R*)-**18t** obtained from the condensation of preformed enol lactone **17b** and **14c**.

Preparation and characterisation of (11b*R*)-8-bromo-11b-hexyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18u



(*R*)-**18u**

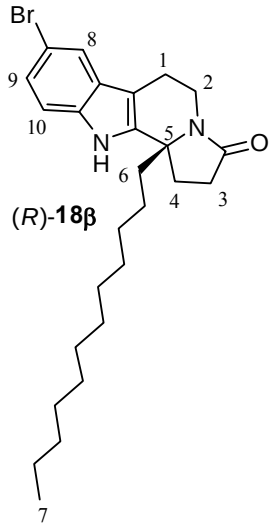
The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 12:1 to 10:1 as a colourless crystalline solid (90 mg, 77%).

88% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 3.0 min, minor t_R = 5.7 min). $[\alpha]_D^{28}$ = + 117.2 (*c* 1.21, $CHCl_3$, > 99.5 % e.e. sample). Spectral data identical to (*R*)-**18u** obtained from the condensation of preformed enol lactone **17c** and **14c**.

Preparation and characterisation of (11b*R*)-8-bromo-11b-dodecyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18β

The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 15:1 to 12:1 as a pale yellow crystalline solid (117 mg, 82%).

89% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 2.5 min, minor t_R 4.8 min), $[\alpha]_D^{24}$ = + 82.2 (*c* 1.0, $CHCl_3$).



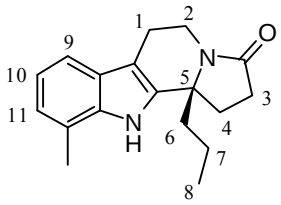
(*R*)-**18β**

m.p. 88-89 ºC; **FT-IR** ν_{max}(NaCl) 3253 cm^{-1} (N-H), 2924 cm^{-1} (ArC-H), 2853 cm^{-1} (Csp^3-H), 1662 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.88 (t, 3H, H-7, *J* 7.0 Hz), 1.22-1.45 (m, 20H, 10 × C<u>H</u>$_2$), 1.84-1.99 (m, 2H, H-6), 2.18 (dt, 1H, H-4a, *J* 12.5 Hz, 9.5 Hz), 2.37 (ddd, 1H, H-4b, *J* 12.5 Hz, 9.5 Hz, 2.5 Hz), 2.45 (ddd, 1H, H-3a, *J* 18.0 Hz, 9.5 Hz, 2.5 Hz), 2.66 (dt, 1H, H-3b, *J* 18.0 Hz, 9.5 Hz), 2.73 (dd, 1H, H-1a, *J* 15.5 Hz, 5.0 Hz), 2.82 (ddd, 1H, H-1b, *J* 15.5 Hz, 12.5 Hz, 5.0 Hz), 3.13 (td, 1H, H-2a, *J* 12.5 Hz, 6.0 Hz), 4.50 (dd, 1H, H-2b, *J* 12.5 Hz, 6.0 Hz), 7.20 (d, 1H, H-10, *J* 8.5 Hz), 7.25 (dd, 1H, H-9, *J* 8.5 Hz, 2.0 Hz), 7.60 (d, 1H, H-8, *J* 2.0 Hz), 8.09 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.0 (C-7), 20.9 (C-1), 22.7 (<u>C</u>H$_2$), 24.3 (<u>C</u>H$_2$), 29.3 (<u>C</u>H$_2$), 29.5 (<u>C</u>H$_2$), 29.6 (<u>C</u>H$_2$), 29.6 (<u>C</u>H$_2$), 29.6 (<u>C</u>H$_2$), 29.9 (<u>C</u>H$_2$), 30.4 (C-4), 31.1 (C-3), 31.9 (<u>C</u>H$_2$), 31.9 (<u>C</u>H$_2$), 35.4 (C-2), 40.0 (C-6), 62.4 (C-5), 106.8 (Ar-Cquat.), 112.4 (Ar-<u>C</u>H), 112.9 (Ar-Cquat.), 121.2 (Ar-<u>C</u>H), 124.8 (Ar-<u>C</u>H), 128.5 (Ar-Cquat.), 134.7 (Ar-Cquat.), 139.0 (Ar-Cquat.), 173.5 (C=O); ***m/z*** (ES−) 471, 473 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{37}BrN_2ONa^+$) requires ***m/z*** 495.1981 & 497.1962, found ***m/z*** 495.1976 & 497.1971.

Preparation and characterisation of (11b*R*)-10,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18γ

The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 10:1 to 7:1 as a colourless crystalline solid (81 mg, 96%).

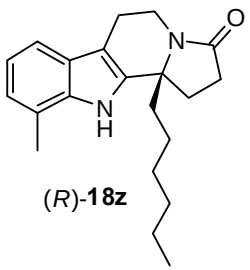
95% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.9 min, minor t_R = 4.7 min); $[\alpha]_D^{24}$ = + 168.1 (*c* 1.0, $CHCl_3$).



(*R*)-**18γ**

m.p. 181-185 ºC; **FT-IR** ν_{max}(NaCl) 3272 cm^{-1} (N-H), 1665 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.95 (t, 3H, H-8, *J* 7.5 Hz), 1.34-1.56 (m, 2H, H-7), 1.90 (ddd, 1H, H-6a, *J* 14.0Hz, 12.5 Hz, 4.5 Hz), 1.98 (ddd, 1H, H-6b, *J* 14.0 Hz, 12.0 Hz, 5.0 Hz), 2.21 (dt, 1H, H-4a, *J* 12.0 Hz, 10.0 Hz), 2.39 (ddd, 1H, H-4b, *J* 12.0 Hz, 10.0 Hz, 2.5 Hz), 2.46 (ddd, 1H, H-3a, *J* 17.0 Hz, 10.0 Hz, 2.5 Hz), 2.51 (s, 3H, Ar-C$\underline{H}_3$), 2.62-2.72 (m, 1H, H-3b), 2.79 (dd, 1H, H-1a, *J* 15.5 Hz, 5.5 Hz), 2.87 (ddd, 1H, H-1b, *J* 15.5 Hz, 11.5 Hz, 6.0 Hz), 3.15 (ddd, 1H, H-2a, *J* 13.0 Hz, 11.5 Hz, 5.5 Hz), 4.51 (dd, 1H, H-2b, *J* 13.0 Hz, 6.0 Hz), 7.01 (d, 1H, Ar-H, *J* 7.5 Hz), 7.06 (t, 1H, H-10, *J* 7.5 Hz), 7.34 (d, 1H, Ar-H, *J* 7.5 Hz), 7.80 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.3 (C-8), 16.7 (Ar-$\underline{C}H_3$), 17.7 (C-7), 21.1 (C-1), 30.6 (C-4), 31.1 (C-3), 35.5 (C-2), 42.4 (C-6), 62.5 (C-5), 107.8 (Ar-Cquat.), 116.2 (Ar-$\underline{C}$H), 120.1 (2C, C-9, Ar-Cquat.), 122.9 (Ar-$\underline{C}$H), 126.3 (Ar-Cquat.), 135.6 (Ar-Cquat.), 137.2 (Ar-Cquat.), 173.5 (C=O); ***m/z*** (ES−) 281 ($[M-H]^-$, 95%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2ONa^+$) requires ***m/z*** 305.1624, found ***m/z*** 305.1628.

Preparation and characterisation of (11b*R*)-11b-hexyl-10-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18z



(*R*)-**18z**

The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 12:1 to 9:1 as an off-white foamy solid (82 mg, 84%).

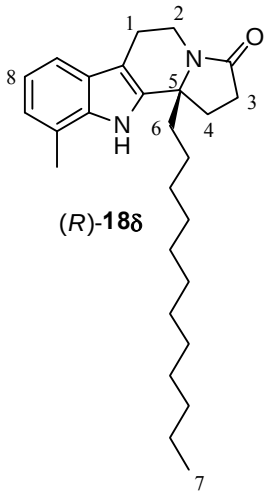
95% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.7 min, minor t_R = 4.8 min); $[\alpha]_D^{28}$ = + 102.8 (*c* 2.26,

$CHCl_3$). Spectral data identical to (*R*)-**18z** obtained from the condensation of preformed enol lactone **17c** and **14f**.

Preparation and characterisation of (11b*R*)-11b-dodecyl-10-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (*R*)-18δ

The title product was obtained after purification by column chromatography on silica gel eluting with dichloromethane/acetone 15:1 to 12:1 as a pale yellow gum (99 mg, 81%).

95% e.e. (Chiralcel OD, 80:20 hexane/isopropanol, 2.0 ml/min, 220 nm, major t_R = 2.5 min, minor t_R = 4.3 min); $[\alpha]_D^{28}$ = + 65.2 (*c* 1.23, $CHCl_3$).



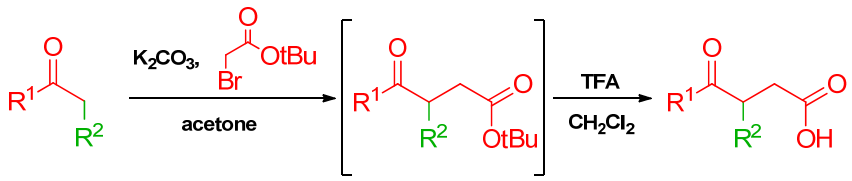
(*R*)-**18δ**

FT-IR ν_{max}(NaCl) 3264 cm^{-1} (N-H), 1667 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.88 (t, 3H, H-7, *J* 7.0 Hz), 1.22-1.45 (m, 20H, 10 × C$\underline{H}_2$), 1.86-2.03 (m, 2H, H-6), 2.21 (dt, 1H, H-4a, *J* 11.5 Hz, 10.5 Hz), 2.39 (ddd, 1H, H-4b, *J* 11.5 Hz, 10.5 Hz, 2.0 Hz), 2.45 (ddd, 1H, H-3a, *J* 17.0 Hz, 10.5 Hz, 2.0 Hz), 2.50 (s, 3H, Ar-C$\underline{H}_3$), 2.67 (dt, 1H, H-3b, *J* 17.0 Hz, 10.5 Hz), 2.78 (dd, 1H, H-1a, *J* 15.5 Hz, 5.0 Hz), 2.84 (ddd, 1H, H-1b, *J* 15.5 Hz, 12.0 Hz, 6.0 Hz), 3.14 (td, 1H, H-2a, *J* 12.0 Hz, 5.0 Hz), 4.50 (dd, 1H, H-2b, *J* 12.0 Hz, 6.0 Hz), 7.00 (d, 1H, Ar-H, *J* 7.5 Hz), 7.05 (t, 1H, H-8, *J* 7.5 Hz), 7.34 (d, 1H, Ar-H, *J* 7.5 Hz), 7.98 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.2 (C-7), 16.8 (Ar-$\underline{C}H_3$), 21.1 (C-1), 22.7 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$), 29.4 ($\underline{C}H_2$), 29.5 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.9 ($\underline{C}H_2$), 30.6 (C-4), 31.2 (C-3), 31.9 ($\underline{C}H_2$), 35.6 (C-2), 40.1 (C-6), 62.6 (C-5), 107.6 (Ar-Cquat.), 116.2 (Ar-$\underline{C}H$), 120.1 (Ar-$\underline{C}H$), 120.2 (Ar-Cquat.), 122.8 (Ar-$\underline{C}H$), 126.3 (Ar-Cquat.), 135.5 (Ar-Cquat.), 137.4 (Ar-Cquat.), 173.6 (C=O); ***m/z*** (ES−) 407 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{27}H_{41}N_2O^+$) requires ***m/z*** 409.3213, found ***m/z*** 409.3212.

6.2.2 Experimental for Chapter 3

6.2.2.1 Preparation of disubstituted enol lactones

General procedure XVI for the preparation of 4-oxo carboxylic acids



To a solution of ketone (1 equivalent) in acetone (3 mL per 1 mmol of ketone) was added anhydrous potassium carbonate (5 equivalents) followed by *tert*-butyl bromoacetate (1 equivalent). The heterogeneous mixture was heated at reflux for 16 hours. It was allowed to cool to room temperature and water was added (volume identical to acetone). The solution was extracted with diethyl ether (3 × volume of water added). The combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the crude *tert*-butyl 4-oxo carboxylate.[234]

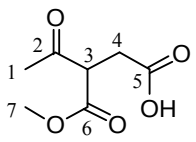
Remark: For R^2 = $PhSO_2$, the *tert*-butyl ester was isolated and purified by column chromatography. The dehydrative cyclisation to the enol lactone was carried out on the corresponding crude 4-oxo carboxylic acid.

The crude *tert*-butyl oxo ester mixture was dissolved in dichloromethane (3 mL per 1 g of mixture) and trifluoroacetic acid was added. The solution was stirred at room temperature for 30 minutes and the solvents were removed under a stream of nitrogen. The residue was purified by column chromatography on silica gel to afford the title compound.

Preparation and characterisation of (±)-3-(methoxycarbonyl)-4-oxopentanoic acid (±)-26a

Synthesised on a 43.0 mmol scale (5.00 g) of methyl acetoacetate. The product was purified eluting with dichloromethane/ethyl acetate 9:1 to 4:1 to give the title acid as a colourless

crystalline solid (2.98 g, 40% over 2 steps). Analytical data in agreement with previous report.[235]

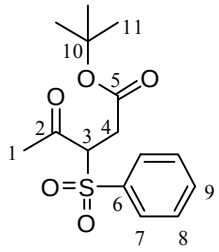


(±)-**26a**

m.p. 46-49 ºC; **FT-IR** ν_{max}(NaCl) 3209 cm^{-1} (O-H), 1739 cm^{-1} (C=O), 1718 cm^{-1} (C=O), 1270 cm^{-1} (C-O), 1163 cm^{-1} (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.35 (s, 3H, H-1), 2.88 (dd, 1H, H-4a, *J* 18.0 Hz, 6.5 Hz), 3.03 (dd, 1H, H-4b, *J* 18.0 Hz, 8.0 Hz), 3.76 (s, 3H, H-7), 3.96 (app. t, 1H, H-3, *J* 7.0 Hz), 10.19 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 29.9 (C-1), 32.0 (C-4), 52.9 (C-7), 54.1 (C-3), 168.6 (C=O), 177.1 (C=O), 201.4 (C-2); ***m/z*** (ES+) 197 ($[M+Na]^+$, 50%), 387 ($[2M+K]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_7H_{10}O_5Na^+$) requires ***m/z*** 197.0420, found ***m/z*** 197.0413.

Preparation and characterisation of (±)-*tert*-butyl 4-oxo-3-(phenylsulfonyl)pentanoate (±)-26b

Synthesised on a 5 mmol scale of *tert*-butyl bromo acetate and 1-(phenylsulfonyl)acetone. The product was purified eluting with petroleum ether/ethyl acetate 9:1 to give the title oxoester **26b** as a colourless solid (891 mg, 57%).

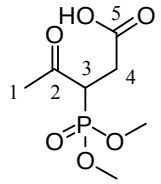


(±)-**26b**

m.p. 116-118 ºC; **FT-IR** ν_{max}(NaCl) 1724 cm^{-1} (C=O), 1322 cm^{-1} (SO_2), 1149 cm^{-1} (SO_2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.38 (s, 9H, H-11), 2.52 (s, 3H, H-1), 2.77-2.94 (m, 2H, H-4), 4.58 (dd, 1H, H-3, *J* 11.5 Hz, 3.5 Hz), 7.59 (t, 2H, H-8, *J* 7.5 Hz), 7.71 (tt, 1H, H-7, *J* 7.5 Hz, 1.0 Hz), 7.78 (dd, 2H, H-7, *J* 7.5 Hz, 1.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 27.9 (C-11), 32.2 (C-1), 33.5 (C-4), 70.7 (C-3), 82.4 (C-10), 129.3 (Ar-CH), 129.4 (Ar-CH), 134.6 (C-9), 135.9 (C-6), 168.7 (C-5), 199.0 (C-2); ***m/z*** (ES+) 335 ($[M+Na]^+$, 50%), 647 ($[2M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}O_5SNa^+$) requires ***m/z*** 335.0924, found ***m/z*** 335.0917.

Preparation and characterisation of (±)-3-(dimethoxyphosphoryl)-4-oxopentanoic acid (±)-26c

Synthesised on a 9.0 mmol scale of dimethyl (2-oxopropyl)phosphonate (1.5 g). The product was purified eluting with dichloromethane/ethyl acetate 3:2 to give the title compound as a colourless crystalline solid (415 mg, 46% over 2 steps).

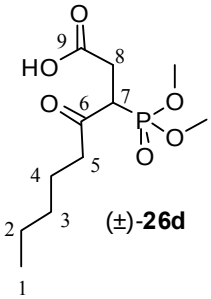


(±)-**26c**

m.p. 97-100 ºC; **FT-IR** ν_{max}(NaCl) 3412 cm^{-1} (O-H), 1792 cm^{-1} (C=O), 1720 cm^{-1} (C=O), 1238 cm^{-1} (P=O), 1209 cm^{-1} & 1052 cm^{-1} & 1033 cm^{-1} (C-O / P-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.40 (s, 3H, H-1), 2.73 (ddd, 1H, H-4a, *J* 18.0 Hz, 3.0 Hz, J_{H-P} 9.5 Hz), 3.16 (ddd, 1H, H-4b, *J* 18.0 Hz, 11.0 Hz, J_{H-P} 7.5 Hz), 3.72 (ddd, 1H, H-3, *J* 11.0 Hz, 3.0 Hz J_{H-P} 25.0 Hz,), 3.77 (d, 3H, OCH_3, J_{H-P} 2.0 Hz), 3.80 (d, 3H, OCH_3, J_{H-P} 2.0 Hz), 9.44 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 30.8 (d, C-4, J_{C-P} 3 Hz), 31.2 (C-1), 47.7 (d, C-3, J_{C-P} 127 Hz), 53.5 (d, O<u>C</u>H_3, J_{C-P} 7 Hz), 53.8 (d, O<u>C</u>H_3, J_{C-P} 7.0 Hz), 175.0 (d, C-5, J_{C-P} 19 Hz), 199.8 (d, C-2, J_{C-P} 5 Hz); ***m/z*** (ES−) 223 ($[M-H]^-$, 80%), 469 ($[2(M-H)+K]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_7H_{13}O_6PNa^+$) requires ***m/z*** 247.0342, found ***m/z*** 247.0344.

Preparation and characterisation of (±)-3-(dimethoxyphosphoryl)-4-oxononanoic acid (±)-26d

Synthesised on a 5.00 mmol scale of dimethyl (2-oxoheptyl)phosphonate (1.03 mL). The product wass purified eluting with dichloromethane/ethyl acetate 9:1 to give the title acid as a colourless oil (922 mg, 65% over 2 steps).



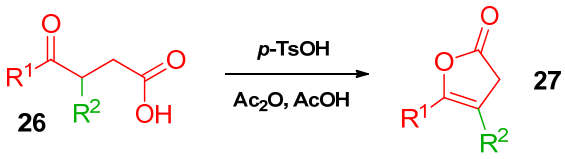
(±)-**26d**

FT-IR ν_{max}(NaCl) 3413 cm^{-1} (O-H), 1719 cm^{-1} (C=O), 1238 cm^{-1} (P=O), 1034 cm^{-1} (C-O / P-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.89 (t, 3H, H-1, *J* 7.0 Hz), 1.20-1.40 (m, 4H, H-2, H-3), 1.60 (quint., 2H, H-4, *J* 7.0 Hz), 2.63 (dt, 1H, H-5a, *J* 18.0 Hz, 7.0 Hz), 2.75 (ddd, 1H, H-8a, *J* 18.0 Hz, 3.0 Hz, J_{H-P} 9.5 Hz), 2.85 (dt, 1H, H-5b, *J* 18.0 Hz, 7.5 Hz, J_{H-P} 7.5 Hz), 3.20 (ddd, 1H, H-8b, *J* 18.0 Hz, 11.0 Hz, 7.5 Hz), 3.69 (ddd,

1H, H-7, *J* 11.0 Hz, 3.0 Hz, $J_{H\text{-}P}$ 25.0 Hz), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 7.57 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 (C-1), 22.4 (C-2), 23.0 (C-4), 30.8 (C-8), 31.0 (C-3), 43.9 (C-5), 47.2 (d, C-7, *J* 128 Hz), 53.4 (d, O<u>C</u>H$_3$, *J* 7 Hz), 53.7 (d, O<u>C</u>H$_3$, *J* 7 Hz), 175.2 (d, C-9, *J* 19 Hz), 204.2 (d, C-6, *J* 5 Hz); ***m/z*** (ES−) 279 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{21}O_6PNa^+$) requires ***m/z*** 303.0968, found ***m/z*** 303.0969.

6.2.2.2 N-acyliminium cyclisation cascade of disubsituted enol lactones and tryptamines

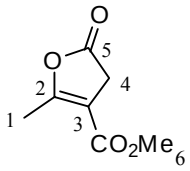
General procedure XVII for the preparation of enol lactones 27 ($R^2 \neq H$)



To a solution of 4-oxo carboxylic acid **26** (1 equivalent) in acetic anhydride (1 mL per 0.5 mmol of substrate) and acetic acid (1 mL per 0.5 mmol of substrate) was added *para*-toluenesulfonic acid (0.1 equivalents) and the solution was heated at 60 ºC for 45 minutes to 5 hours (completion followed by TLC) and allowed to cool to room temperature. Water was added (10 mL per 1 mmol of starting material). The solution was extracted with ethyl acetate (3 × 20 mL per 1 mmol of starting material). The combined organic layers were dried over sodium sulphate and the solvent concentrated *in vacuo*. The product was purified by column chromatography on silica gel.

Preparation and characterisation of methyl 2-methyl-5-oxo-4,5-dihydrofuran-3-carboxylate 27a

The title compound was synthesised according to general procedure **XVII** on a 4.05 mmol of **26a** and isolated as a colourless crystalline solid after column chromatography on silica gel eluting with dichloromethane (45 minutes at 60 ºC, 469 mg, 74%).

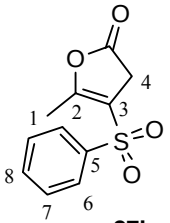


27a

m.p. 61-63 ºC; **FT-IR** ν_{max}(NaCl) 1807 cm^{-1} (C=O), 1713 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.41 (t, 3H, H-1, *J* 2.5 Hz), 3.43-3.46 (m, 2H, H-4), 3.78 (s, 3H, H-6); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-1), 33.6 (C-4), 51.6 (C-6), 105.9 (C-3), 163.5 (C-2), 163.7 ($\underline{C}O_2Me$), 172.8 (C-5); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_7H_{12}NO_4^+$) requires ***m/z*** 174.0766, found ***m/z*** 174.0767 (100%).

Preparation and characterisation of 5-methyl-4-(phenylsulfonyl)furan-2(3*H*)-one 27b

The title compound was synthesised according to general procedure **XVII** on a 1.56 mmol of corresponding *tert*-butyl oxoester **26b** and isolated as a colourless solid after column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 (45 minutes at 60 ºC, 56 mg, 15% yield over 2 steps).

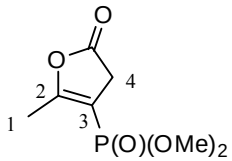


27b

m.p. 102-105 ºC; **FT-IR** ν_{max}(NaCl) 1821 cm^{-1} (C=O), 1319 cm^{-1} (SO_2), 1165 cm^{-1} (SO_2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.48 (t, 3H, H-1, *J* 2.5 Hz), 3.36-3.41 (m, 2H, H-4), 7.59 (t, 2H, H-7, *J* 7.5 Hz), 7.68 (t, 1H, H-8, *J* 7.5 Hz), 7.88 (d, 2H, H-6, *J* 7.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.0 (C-1), 33.8 (C-4), 114.3 (C=C), 127.2 (2 × Ar-$\underline{C}$H), 129.7 (2 × Ar-$\underline{C}$H), 134.0 (C-8), 140.3 (C-5), 161.4 (C=C), 170.3 (C=O); ***m/z*** (ES+) 293 ($[M+Na+MeOH]^+$, 60%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{14}O_5SNa^+$) requires ***m/z*** 293.0454, found ***m/z*** 293.0465.

Preparation and characterisation of dimethyl (5-oxo-2-methyl-4,5-dihydrofuran-3-yl)phosphonate 27c

The title compound was synthesised according to general procedure **XVII** on a 1.44 mmol of **26c** and isolated as a colourless oil after column chromatography on silica gel eluting with dichloromethane/acetone 4:1 (5 hours at 60 ºC, 191 mg, 64%).

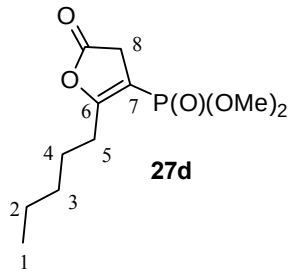


27c

FT-IR ν_{max}(NaCl) 1816 cm^{-1} (C=O), 1238 cm^{-1} (P=O), 1034 cm^{-1} (C-O / P-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.30-2.34 (m, 3H, H-1), 3.28-3.32 (m, 2H, H-4), 3.73 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-1), 34.9 (d, C-4, $J_{C\text{-}P}$ 9.0 Hz), 52.4 (2 × O<u>C</u>H_3), 99.1 (d, C-3, $J_{C\text{-}P}$ 220 Hz), 165.0 (d, C-2, $J_{C\text{-}P}$ 25 Hz), 173.6 (d, C=O, $J_{C\text{-}P}$ 18 Hz); ***m/z*** (ES+) 229 ($[M+Na]^+$, 40%, 435 ($[2M+Na]^+$, 90%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_7H_{11}O_5PNa^+$) requires ***m/z*** 229.0236, found ***m/z*** 229.0239.

Preparation and characterisation of dimethyl (5-oxo-2-pentyl-4,5-dihydrofuran-3-yl)phosphonate 27d

The title compound was synthesised according to general procedure **XVII** on a 0.58 mmol of **26d** and isolated as a colourless oil after column chromatography on silica gel eluting with dichloromethane/acetone 9:1 (3 hours at 60 ºC, 63 mg, 41%).

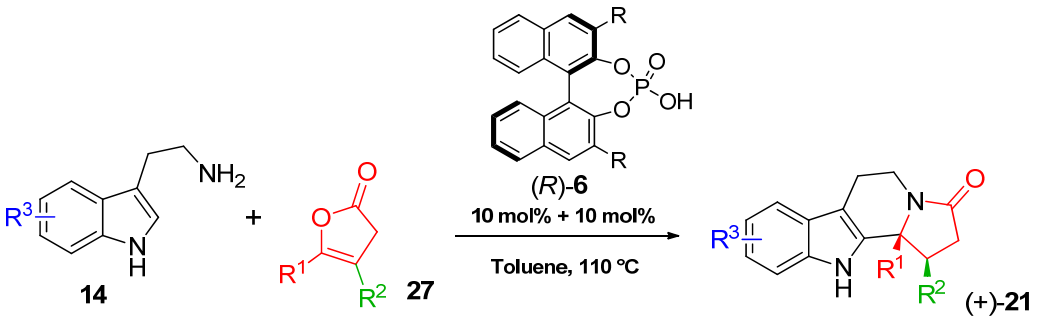


27d

FT-IR ν_{max}(NaCl) 1814 cm^{-1} (C=O), 1235 cm^{-1} (P=O), 1030 cm^{-1} (C-O / P-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.89 (t, 3H, H-1, *J* 7.0 Hz), 1.30-1.37 (m, 4H, H-2, H-3), 1.61 (quint., 2H, H-4, *J* 7.5 Hz), 2.67-2.75 (m, 2H, H-5), 3.29-3.33 (m, 2H, H-8), 3.73 (s, 1H, 3H, OCH_3), 3.76 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 (C-1), 22.2 (C-2), 26.3 (d, C-4, $J_{C\text{-}P}$ 2 Hz), 27.5 (C-5), 31.1 (C-3), 34.9 (d, C-8, $J_{C\text{-}P}$ 9 Hz), 52.4 (2 × O<u>C</u>H_3), 98.8 (d, C-7, $J_{C\text{-}P}$ 221 Hz), 168.7 (d, C-6, $J_{C\text{-}P}$ 26 Hz), 173.9 (d, C=O, $J_{C\text{-}P}$ 18

Hz); ***m/z*** (ES+) 285 ([M+Na]$^+$, 40%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{11}H_{19}O_5PNa^+$) requires ***m/z*** 285.0862, found ***m/z*** 285.0860.

General procedure XVIII for the preparation of cyclised β-carbolines 21 ($R^2 \neq H$)



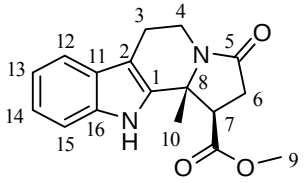
Enol lactone **27** (0.2 mmol, 1 equivalent) was dissolved in toluene (42 mL) and a tryptamine derivative **14** (0.2 mmol, 1 equivalent) was added in one portion at room temperature, immediately followed by the addition of phosphoric acid catalyst (*R*)-**6** (0.02 mmol, 0.1 equivalents) in one portion. The resulting suspension was heated at reflux for 34 hours. Another portion of catalyst (0.02 mmol, 0.1 equivalents) was then added to the hot mixture and the solution was heated to reflux for 2 to 6 days (48 to 144 hours). The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel.

Note: All racemates were prepared using *para*-toluenesulfonic acid (catalytic amount) in refluxing toluene. A single diastereomer was obtained in all cyclization reactions.

Preparation and characterisation of methyl (1*R*,11b*R*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-1-carboxylate (+)-21a

Heated at reflux in toluene for 34 + 96 hours in the presence of (*R*)-**6f**. The title product was isolated after column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 to ethyl acetate as a colourless crystalline solid (44 mg, 74%).

75% e.e. (Chiralcel IB, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 12.3 min, minor t_R = 18.9 min); $[\alpha]_D^{25}$ = + 56.6 (*c* 1.00, $CHCl_3$).

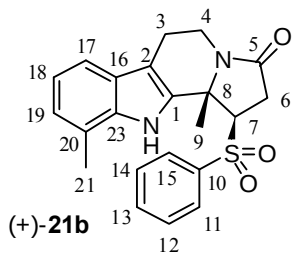

(+)-**21a**

m.p. 205-207 ºC; **FT-IR** ν_{max}(NaCl) 3388 cm^{-1} (N-H), 1741 cm^{-1} (C=O), 1678 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 1.48 (s, 3H, H-10), 2.41-2.55 (m, 1H, H-6a), 2.62 (ddd, 1H, H-3a, *J* 15.5 Hz, 11.5 Hz, 6.0 Hz), 2.74 (dd, 1H, H-3b, *J* 15.5 Hz, 4.0 Hz), 2.88 (dd, 1H, H-6b, *J* 16.5 Hz, 11.0 Hz), 3.04 (td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 3.41 (dd, 1H, H-7, *J* 10.5 Hz, 9.0 Hz), 3.85 (s, 3H, H-9), 4.25 (dd, 1H, H-4b, *J* 13.0 Hz, 5.5 Hz), 7.00 (t, 1H, H-13, *J* 7.5 Hz), 7.10 (t, 1H, H-14, *J* 7.5 Hz), 7.42 (d, 1H, H-15, *J* 7.5 Hz), 7.48 (d, 1H, H-12, *J* 7.5 Hz), 10.25 (s, 1H, NH); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ_C 20.4 (C-3), 20.4 (C-10), 32.2 (C-6), 34.0 (C-4), 47.6 (C-7), 52.0 (C-7), 59.5 (C-8), 105.5 (C-2), 111.3 (C-12), 117.5 (C-15), 118.2 (C-14), 120.8 (C-13), 125.4 (C-11), 135.4 (C-16), 136.4 (C-1), 168.9 (C=O), 170.6 (C=O); ***m/z*** (ES+) 357 ([M+MeCN+NH_4]$^+$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{17}H_{18}N_2O_3Na^+$) requires ***m/z*** 321.1210, found ***m/z*** 321.1206.

Preparation and characterisation of (1*R*,11b*S*)-10,11b-dimethyl-1-(phenylsulfonyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*] indol-3-one (+)-21b

Heated at reflux in toluene for 34 + 72 hours in the presence of (*R*)-**6e**. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 2:3 to afford the title product as a colourless crystalline solid (75 mg, 95%).

72% e.e. (Chiralcel OD-H, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 17.1 min, minor t_R = 14.3 min); $[\alpha]_D^{21} = +222.3$ (*c* 0.53, $CHCl_3$).


(+)-**21b**

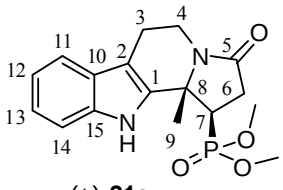
m.p. 112-116 ºC; **FT-IR** ν_{max}(NaCl) 3401 cm^{-1} (N-H), 1698 cm^{-1} (C=O amide), 1148 cm^{-1} (OMe); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.02 (s, 3H, H-9), 2.41 (dd, 1H, H-6a, *J* 16.0 Hz, 8.0 Hz), 2.61 (s, 3H, H-21), 2.71-2.90 (m, 2H, H-3), 3.15 (ddd, 1H, H-4a, *J* 11.5 Hz, 4.5 Hz, 1.0 Hz), 3.24 (ddd, 1H, H-6b, *J* 16.0 Hz, 12.0 Hz, 1.5

Hz), 3.79 (dd, 1H, H-7, *J* 12.0 Hz, 8.0 Hz), 4.48 (ddd, 1H, H-4b, *J* 13.0 Hz, 6.0 Hz, 1.0 Hz), 7.05-7.13 (m, 2H, H-18, H-19), 7.36 (dd, 1H, H-17, *J* 5.5 Hz, 3.0 Hz), 7.58-7.64 (m, 2H, H-11, H-15), 7.72 (tt, 1H, H-13, *J* 8.0 Hz, 1.0 Hz), 7.87-7.93 (m, 2H, H-12, H-14), 9.42 (br s, 1H, H-16); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.7 (C-21), 21.2 (C-3), 21.6 (C-9), 33.5 (C-6), 35.0 (C-4), 61.7 (C-8), 66.8 (C-7), 107.7 (C-2), 116.4 (C-17), 120.2 (C-18), 120.9 (Ar-Cquat.), 123.3 (C-19), 125.7 (Ar-Cquat.), 128.1 (2C, C-12, C-14), 129.8 (2C, C-11, C-15), 134.8 (Ar-Cquat.), 135.6 (Ar-Cquat.), 138.7 (Ar-Cquat.), 167.0 (C=O); ***m/z*** (ES+) 448 ($[M+MeCN+NH_4]^+$, 65%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{22}N_2O_3SNa^+$) requires ***m/z*** 417.1243, found ***m/z*** 417.1234.

Preparation and characterisation of dimethyl [(1*R*,11b*S*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl] phosphonate (+)-21c

Heated at reflux in toluene for 34 + 48 hours in the presence of (*R*)-**6e**. The crude residue was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 to furnish the title product as a colourless crystalline solid (63 mg, 95%).

85% e.e. (Chiralcel OJ, 60:40 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 6.9 min, minor t_R = 14.5 min); $[\alpha]_D^{21} = +31.9$ (*c* 0.92, $CHCl_3$).



(+)-**21c**

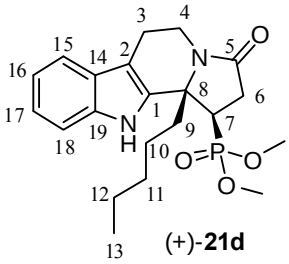
m.p. 174-177 ºC; **FT-IR** ν_{max}(NaCl) 3300 cm^{-1} (N-H), 1696 cm^{-1} (C=O), 1220 cm^{-1} (P=O), 1033 cm^{-1} (P-O); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 1.62 (s, 3H, H-9), 2.45-2.82 (m, 4H, H-3, H-6), 2.99 (ddd, 1H, H-7, *J* 17.0 Hz, 12.0 Hz, 8.5 Hz), 3.10 (td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 3.71 (d, 3H, OCH_3, *J* 11.0 Hz), 3.82 (d, 3H, OCH_3, *J* 10.5 Hz), 4.22 (dd, 1H, H-4b, *J* 13.0 Hz, 6.0 Hz), 6.96-7.03 (m, 1H, H-13), 7.05-7.12 (m, 1H, H-12), 7.41 (d, 1H, H-14, *J* 8.0 Hz), 7.44 (d, 1H, H-11, *J* 8.0 Hz), 10.15 (br s, 1H, H-18); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 20.2 (C-3), 21.1 (C-9), 31.1 (C-6), 33.4 (C-4), 39.7 (d, C-7, *J* 147 Hz), 52.3 (d, O<u>C</u>H_3,

J 7 Hz), 52.4 (d, O<u>C</u>H$_3$, *J* 7 Hz), 58.7 (C-8), 104.8 (C-2), 111.2 (C-11), 117.6 (C-14), 118.4 (C-13), 121.0 (C-12), 125.5 (C-12), 134.9 (C-15), 136.6 (C-1), 166.2 (d, C=O, *J* 18 Hz); ***m/z*** (ES+) 407 ([M+MeCN+NH$_4$]$^+$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{17}H_{21}N_2O_4PNa^+$) requires ***m/z*** 371.1131, found ***m/z*** 371.1131.

Preparation and characterisation of dimethyl [(1*R*,11b*S*)-3-oxo-11b-pentyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl] phosphonate (+)-21d

Heated at reflux in toluene for 34 + 144 hours in the presence of (*R*)-**6e**. The crude residue was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 to furnish the title product as a colourless crystalline solid (73 mg, 90%).

91% e.e. (Chiralcel AD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 9.1 min, minor t_R = 13.9 min); $[\alpha]_D^{21} = +48.8$ (*c* 0.33, $CHCl_3$).



(+)-**21d**

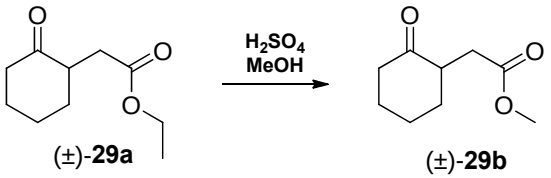
FT-IR ν_{max}(NaCl) 3317 cm^{-1} (OH), 1695 cm^{-1} (C=O), 1061 cm^{-1} (OMe), 1033 cm^{-1} (OMe); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.79-0.87 (m, 3H, H-13), 1.15-1.33 (m, 5H, H-10a, H-11, H-12), 1.38-1.52 (m, 1H, H-10b), 2.12-2.27 (m, 2H, H-9), 2.58 (dd, 1H, H-6a, *J* 16.0 Hz, 8.0 Hz), 2.68-2.98 (m, 3H, H-6b, H-3), 3.14-3.25 (m, 1H, H-4a), 3.76 (d, 3H, OCH$_3$, *J* 11.0 Hz), 3.93 (d, 3H, OCH$_3$, *J* 11.0 Hz), 4.57 (dd, 1H, H-4b, *J* 13.5 Hz, 6.5 Hz), 7.12 (td, 1H, H-16, *J* 7.5 Hz, 1.0 Hz), 7.20 (td, 1H, H-17, *J* 7.5 Hz, 1.0 Hz), 7.42 (d, 1H, H-18, *J* 7.5 Hz), 7.50 (d, 1H, H-15, *J* 7.5 Hz), 9.88 (s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.1 (C-13), 20.9 (C-3), 22.5 (CH_2), 24.7 (CH_2), 32.4 (CH_2), 33.1 (C-6), 37.0 (C-4), 37.7 (C-9), 42.4 (d, C-7, *J* 152 Hz), 52.8 (d, O<u>C</u>H$_3$, *J* 7 Hz), 53.2 (d, O<u>C</u>H$_3$, *J* 7 Hz), 63.3 (d, C-8, *J* 5 Hz), 106.5 (C-2), 111.7 (C-15), 118.5 (C-18), 119.5 (C-17), 122.1 (C-16), 126.4 (C-14), 135.6 (C-19), 136.1 (C-1), 170.6 (d, C=O, *J* 19 Hz); ***m/z*** (ES+) 463 ([M+MeCN+NH$_4$]$^+$,

100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{29}N_2O_4PNa^+$) requires ***m/z*** 427.1757, found ***m/z*** 427.1748.

6.2.2.3 Direct dehydrative N-acyliminium cyclisation of oxoacids and tryptamines

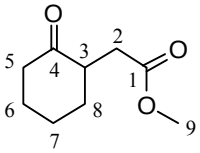
6.2.2.3.1 Preparation of starting materials – 4-oxo carboxylic acids (±)-26

Preparation and characterisation of (±)-methyl 2-(2-oxocyclohexyl)acetate (±)-29b



(±)-**29a** (±)-**29b**

To a solution of (±)-ethyl 2-(2-oxocyclohexyl)acetate (±)-**29a** (11 mmol, 2.03 g, 2.00 mL) in DME (30 mL) was added 5% aqueous H_2SO_4 solution (30 mL) and the solution was heated at reflux for 2 days before quenching with water (30 mL) and extracting with dichloromethane (3 × 30 mL). The combined organic layers were dried over sodium sulphate and concentrated *in vacuo* to afford the crude oxoacid. It was dissolved in methanol (20 mL) and cooled to 0 ºC before adding thionyl chloride dropwise (12 mmol, 1.43 g, 0.88 mL). The solution was heated at reflux for 1 hour before cooling, evaporating the solution *in vacuo* and adding a saturated solution of $NaHCO_3$ (20 mL). The solution was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried over sodium sulphate and concentrated *in vacuo* to afford the crude oxoester. The product was purified by column chromatography on silica gel eluting with dichloromethane/ethyl acetate 9:1 to give the title ester as a colourless oil (1.58 g, 84%).



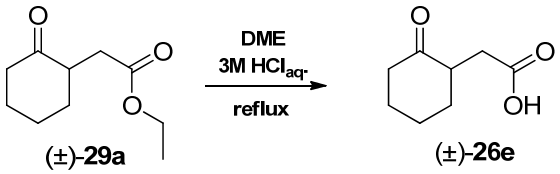
(±)-**29b**

FT-IR ν_{max}(NaCl) 1739 cm^{-1} (C=O), 1712 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.34-1.47 (m, 1H, H-8a), 1.56-1.79 (m, 2H, H-6a, H-7a), 1.84-

1.92 (m, 1H, H-7b), 2.06-2.18 (m, 3H, H-2a, H-6b, H-8b), 2.31-2.45 (m, 2H, H-5), 2.73-2.81 (m, 1H, H-2b), 2.81-2.91 (m, 1H, H-3), 3.66 (s, 1H, H-9); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 25.2 (C-7), 27.8 (C-6), 33.9 (C-8), 34.0 (C-2), 41.8 (C-5), 47.0 (C-3), 51.7 (C-9), 173.1 (C-1), 211.1 (C-4); ***m/z*** (ES+) 193 ($[M+Na]^+$, 50%), 363 ($[2M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_9H_{14}O_3Na^+$) requires ***m/z*** 193.0835, found ***m/z*** 193.0842.

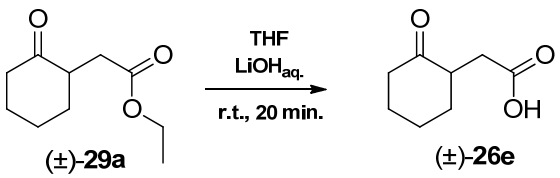
Preparation and characterisation of (±)-2-(2-oxocyclohexyl)acetic acid (±)-26e

Method A:



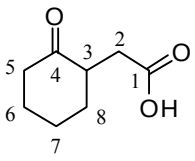
To a solution of (±)-ethyl 2-(2-oxocyclohexyl)acetate (±)-**29a** (10.8 mmol, 2.00 g, 1.96 mL) in DME (10 mL) was added 3 M aqueous HCl (10 mL) and the solution was heated to reflux for 2 days. It was allowed to cool to room temperature and a saturated solution of Na_2CO_3 (20 mL) was added. The solution was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with a saturated solution of Na_2CO_3 (2 × 20 mL). The combined aqueous layers were acidified to pH < 1 with 6 M aqueous HCl and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over sodium sulphate and concentrated *in vacuo* to afford the crude oxoacid. The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9:1 to give 431 mg of colourless oil (26%).

Method B:



(±)-Ethyl 2-(2-oxocyclohexyl)acetate (±)-**29a** (3.0 mmol, 0.56 g, 0.54 mL, 1 equivalent) was diluted with tetrahydrofuran (7 mL). A solution of lithium hydroxide (0.63 g, 15 mmol, 5

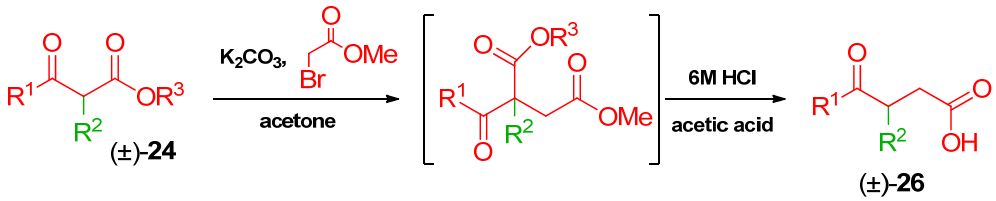
equivalents) in DI water (7 mL) was added in one portion to the stirred mixture. The resulting cloudy solution was stirred vigorously for 20 minutes (completion was followed by TLC). The solution was poured onto 40 mL of a 1M solution of HCl and extracted with diethyl ether (4 × 20 mL). The combined ethereal layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 4:1 to 1:2 to afford the title acid as a colourless oil (0.41 g, 87%).



(±)-**26e**

FT-IR ν_{max}(NaCl) 3095 cm^{-1} (O-H), 1709 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.36-1.49 (m, 1H, H-8a), 1.57-1.79 (m, 2H, H-6a, H-7a), 1.85-1.93 (m, 1H, H-7b), 2.07-2.25 (m, 3H, H-2a, H-8b, H-6b), 2.31-2.48 (m, 2H, H-5), 2.77-2.89 (m, 2H, H-3, H-2b), 10.01 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 25.1 (C-7), 27.7 (C-6), 33.8 (C-8), 34.3 (C-2), 41.8 (C-5), 46.9 (C-3), 178.5 (C-1), 211.1 (C-4); ***m/z*** (ES−) 155 ($[M-H]^-$, 90%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_8H_{12}O_3Na^+$) requires ***m/z*** 179.0679, found ***m/z*** 179.0679.

General procedure XIX for the preparation of 4-oxoacids (±)-26f-k

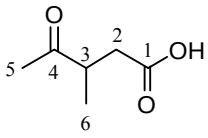


To a solution of ketone **(±)-24** (1 equivalent) in acetone (3 mL per 1 mmol of ketone) was added anhydrous potassium carbonate (5 equivalents) followed by methyl 2-bromoacetate (1 equivalent). The heterogeneous mixture was heated at reflux for 16 hours. It was allowed to cool to room temperature and water was added (volume identical to acetone). The solution was extracted with diethyl ether (3 × volume of water added). The combined organic layers were concentrated *in vacuo* to afford the crude 2-alkylsuccinate.

The crude 2-alkylsuccinate mixture was dissolved in aqueous 6M HCl (3 mL per 1 g of mixture) and acetic acid (3 mL per 1 g of mixture). The biphasic mixture was heated at reflux for 2 days. It was allowed to cool to room temperature and water was added (volume identical to the combined volume of 6M HCl and acetic acid). The solution was extracted with dichoromethane (3 × volume of water added). The combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude acid was purified by column chromatography on silica gel to afford the pure 4-oxo carboxylic acid.[236]

Preparation and characterisation of (±)-3-methyl-4-oxopentanoic acid (±)-26f

Synthesised on a 70 mmol scale of ethyl 2-methyl-3-oxobutanoate (10 g). The product was purified by chromatography on silica gel eluting with petroleum ether/diethyl ether 1:1 to diethyl ether to give the title acid as a colourless oil (4.0 g, 44% over 2 steps). Analytical data in agreement with the literature.[237]

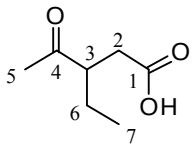


(±)-**26f**

FT-IR ν_{max}(NaCl) 3350 cm^{-1} (O-H), 1713 cm^{-1} (C=O), 1279 cm^{-1} (C-O), 1171 cm^{-1} (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.19 (d, 3H, H-6, *J* 8.0 Hz), 2.22 (s, 3H, H-5), 2.34 (dd, 1H, H-2a, *J* 17.0 Hz, *J* 5.0 Hz), 2.81 (dd, 1H, H-2b, *J* 17.0 Hz, *J* 8.5 Hz), 2.94-3.05 (m, 1H, H-3), 9.30 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.5 (C-6), 28.3 (C-5), 36.5 (C-2), 42.5 (C-3), 178.1 (C=O), 210.7 (C=O); ***m/z*** (ES−) 129 ($[M-H]^-$, 50%).

Preparation and characterisation of (±)-3-ethyl-4-oxopentanoic acid (±)-26g

Synthesised on a 20 mmol scale of methyl 2-ethyl-3-oxobutanoate (3.0 g). The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9:1 to give the title acid as a colourless oil (1.49 g, 52% over 2 steps).

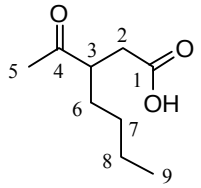


(±)-**26g**

FT-IR ν_{max}(NaCl) 3150 cm^{-1} (O-H), 1712 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.91 (t, 3H, H-7, *J* 7.5 Hz), 1.45-1.58 (m, 1H, H-6a), 1.63-1.75 (m, 1H, H-6b), 2.22 (s, 3H, H-5), 2.38 (dd, 1H, H-2a, *J* 17.0 Hz, *J* 4.0 Hz), 2.79 (dd, 1H, H-2b, *J* 17.0 Hz, *J* 10.0 Hz), 2.88-2.97 (m, 1H, H-3), 10.17 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 11.1 (C-7), 24.2 (C-6), 29.4 (C-5), 34.3 (C-2), 48.9 (C-3), 178.5 (C=O), 210.8 (C=O); ***m/z*** (ES−) 143 ($[M-H]^-$, 40%), 309 ($[2(M-H)+Na]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_7H_{12}O_3Na^+$) requires ***m/z*** 167.0679, found ***m/z*** 167.0686.

Preparation and characterisation of (±)-3-acetylheptanoic acid (±)-26h

Synthesised on a 26.9 mmol scale of methyl 2-ethyl-3-oxobutanoate (5.00 g). The product was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate 6:1 to 1:1 to give the title compound as a colourless oil (3.9 g, 86% over 2 steps).

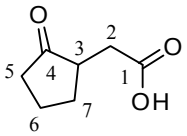


(±)-**26h**

FT-IR ν_{max}(NaCl) 2200 cm^{-1} (O-H), 1712 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.86 (t, 3H, H-9, *J* 7.0 Hz), 1.17-1.33 (m, 4H, H-7 & H-8), 1.34-1.45 (m, 1H, H-6a), 1.54-1.64 (m, 1H, H-6b), 2.19 (s, 3H, H-5), 2.36 (dd, 1H, H-2a, *J* 17.0 Hz, *J* 4.0 Hz), 2.76 (dd, 1H, H-2b, *J* 17.0 Hz, *J* 10.0 Hz), 2.89-2.87 (m, 1H, H-3), 11.14 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-9), 22.6 & 28.9 (C-8, C-7), 29.4 (C-5), 30.8 (C-6) 34.8 (C-2), 47.6 (C-3), 178.5 (C=O), 210.8 (C=O) ; ***m/z*** (ES+) 195 ($[M+Na]^+$, 55%), 367 ($[2M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_9H_{16}O_3Na^+$) requires ***m/z*** 195.0992, found ***m/z*** 195.0997.

Preparation and characterisation of (±)-2-(2-oxocyclopentyl)acetic acid (±)-26i

Synthesised on a 19 mmol scale of ethyl 2-oxocyclopentanecarboxylate (3.0 g). The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9:1 to give the title acid as a colourless crystalline solid (1.06 g, 49% over 2 steps).

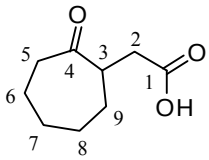


(±)-**26i**

m.p. 43-45 ºC (lit.[238] 50-53 ºC); **FT-IR** ν_{max}(NaCl) 3250 cm^{-1} (O-H), 1734 cm^{-1} (C=O), 1273 cm^{-1} (C-O), 1163 cm^{-1} (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.57-1.70 (m, 1H, CHaHb), 1.75-1.89 (m, 1H, CHaHb), 2.02-2.23 (m, 2H, CH_2) , 2.29-2.51 (m, 4H, CH_2, H-2a, H-3), 2.74-2.83 (m, 1H, H-2b), 10.67 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.6 (CH_2), 29.2 (CH_2), 33.7 (C-2), 37.4 (CH_2), 45.4 (C-3), 178.1 (C=O), 219.3 (C=O); ***m/z*** (ES+) 165 ([M+Na]$^+$, 80%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_7H_{10}O_3Na^+$) requires ***m/z*** 165.0522, found ***m/z*** 165.0521.

Preparation and characterisation of (±)-2-(2-oxocycloheptyl)acetic acid (±)-26j

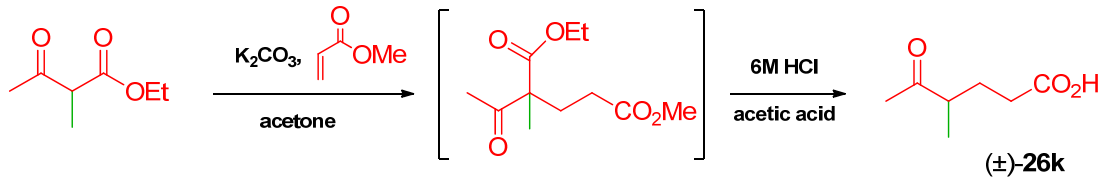
Synthesised on a 19 mmol scale of methyl 2-oxocycloheptanecarboxylate (3.0 g). The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9:1 to give the title acid as a colourless oil (1.87 g, 57% over 2 steps).



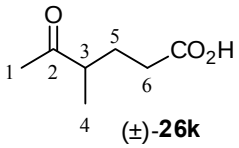
(±)-**26j**

FT-IR ν_{max}(NaCl) 3095 cm^{-1} (O-H), 1699 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.23-1.44 (m, 2H, CH_2), 1.50-1.62 (m, 1H, CHaHb), 1.68-1.96 (m, 5H, 2 × CH_2, CHaHb), 2.34 (dd, 1H, H-2a, *J* 17.0 Hz, *J* 6.5 Hz), 2.40-2.50 (m, 1H, H-5a), 2.63 (dt, 1H, H-5b, *J* 9.0 Hz, *J* 4.0 Hz), 2.85 (dd, 1H, H-2b, *J* 17.0 Hz, *J* 8.5 Hz), 3.04-3.12 (m, 1H, H-3), 10.33 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 23.4 & 28.9 & 29.3 & 31.1 (C-6, C-7, C-8, C-9), 36.4 (C-2), 43.3 (C-5), 47.2 (C-3), 178.4 (C-1), 214.3 (C-4); ***m/z*** (ES−) 169 ([M−H]$^-$, 60%), 361 ([2(M−H)+Na]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M−H+2Na]$^+$ ($C_9H_{13}O_3Na_2^+$) requires *m/z* 215.0655, found *m/z* 215.0655.

Preparation and characterisation of (±)-4-methyl-5-oxohexanoic acid (±)-26k



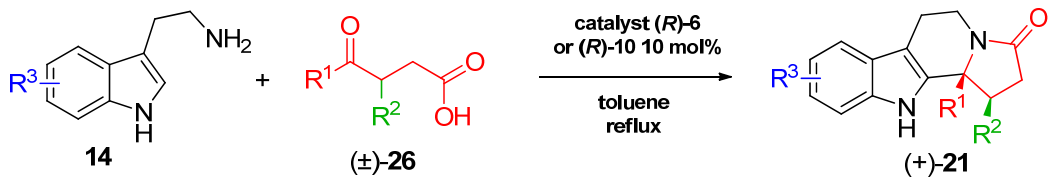
To a solution of (±)-ethyl 2-methyl-3-oxobutanoate (0.71 mL, 5 mmol, 1 equivalent) in acetone (20 mL) was added potassium carbonate (3.45 g, 25 mmol, 5 equivalents) followed by methyl acrylate (0.54 mL, 6 mmol, 1.2 equivalents). The solution was stirred vigorously and heated to reflux for 3 hours. The solvent was removed *in vacuo* and the resulting heterogeneous mixture partitioned between water (30 mL) and diethyl ether (40 mL). The aqueous was re-extracted with diethyl ether (2 × 40 mL). The combined organics were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude oil was diluted in a mixture 1:1 of acetic acid and 6M aqueous HCl (6 mL) and heated at 100 ºC for 24 hours. The solvent was removed under reduced pressure and the resulting biphasic mixture extracted with diethyl ether (5 × 20 mL). The organics were washed with water (15 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude oil was purified by column chromatography on silica gel eluting with petroleum ether / diethyl ether 3:1 to 1:1 to afford the title acid as a colourless oil (550 mg, 88% over 2 steps). Analytical data in agreement with previous report.[239]



(±)-**26k**

FT-IR ν_{max}(NaCl) 3454 cm^{-1} (O-H), 1708 cm^{-1} (2 bands with shoulder, C=O), 1361 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.14 (d, 3H, H-4, *J* 7.0 Hz), 1.67 (app. dq, 1H, H-5a, *J* 14.0 Hz, 7.0 Hz), 2.01 (app. dq, 1H, H-5b, *J* 14.0 Hz, 7.0 Hz), 2.17 (s, 3H, H-1), 2.29-2.44 (m, 2H, H-6), 2.61 (sext., 1H, H-3, *J* 7.0 Hz), 10.97 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.3 (C-4), 27.1 (C-5), 28.3 (C-1), 31.4 (C-6), 45.9 (C-3), 178.9 ($\underline{C}O_2H$), 211.8 (C-2); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_7H_{16}O_3N^+$) requires ***m/z*** 162.1130, found ***m/z*** 162.1128.

6.2.2.3.2 General procedure XX for the preparation of cyclised β-carbolines (+)-21



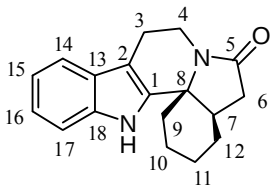
4-Oxo carboxylate (±)-**26** (0.2 mmol, 1 equivalent) was dissolved in toluene (42 mL) and a tryptamine derivative **14** (0.2 mmol, 1 equivalent) was added in one portion at room temperature, immediately followed by the addition of phosphoric acid catalyst (*R*)-**6** or (*R*)-**10** (0.02 mmol, 0.1 equivalents) in one portion. The resulting suspension was heated at reflux until complete consumption of starters (TLC monitoring). The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel.

Note: All racemates were prepared using *para*-toluenesulfonic acid (0.1 equivalents) in refluxing toluene, in conditions similar to the enantioselective cascade (identical concentration, same reagents purity *etc.*).

Preparation and characterisation of (4a*R*,14b*R*)-1,2,3,4,4a,5,9,14-octahydro-6*H*,8*H*-pyrido[3,4-*b*:2,1-*i*′]diindol-6-one (+)-21e

Heated at reflux in toluene for 24 hours in the presence of (*R*)-**6f**. The crude mixture was purified by column chromatography on silica gel eluting with ethyl acetate to afford the title compound as a colourless crystalline solid (45 mg, 80%).

82% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 5.7 min, minor t_R = 10.7 min), > 98:2 d.r.; $[\alpha]_D^{25}$ = + 116.1 (*c* 1.0, $CHCl_3$).



(+)-**21e**

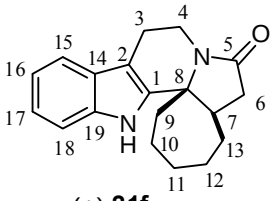
m.p. 241-244 ºC; **FT-IR** ν_{max}(NaCl) 3305 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.55-1.68 (m, 2H, CH_2), 1.73-1.85 (m, 3H, H-9a, CH_2), 1.87-2.04 (m, 2H, H-12), 2.19-2.26 (m, 1H, H-9b), 2.37-2.45 (m, 1H, H-6a), 2.48-2.59 (m, 2H, H-6b,

H-7), 2.78-2.94 (m, 2H, H-3), 3.09-3.17 (m, 1H, H-4a), 4.46 (dd, 1H, H-4b, *J* 13.0 Hz, *J* 5.5 Hz), 7.14 (t, 1H, Ar-H, *J* 7.5 Hz), 7.21 (t, 1H, Ar-H, *J* 7.5 Hz), 7.39 (d, 1H, Ar-H, *J* 7.5 Hz), 7.51 (d, 1H, Ar-H, *J* 7.5 Hz), 8.36 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.3 & 21.1 (C-10, C-11), 22.0 (C-3), 26.2 (C-12), 34.2 (C-9), 34.7 (C-4), 35.6 (C-6), 38.0 (C-7), 60.2 (C-8), 107.1 (Ar-Cquat.), 111.1 & 118.5 (C-14, C-17), 119.9 & 122.2 (C-15, C-16), 126.5 (Ar-Cquat.), 135.9 (Ar-Cquat.), 138.0 (Ar-Cquat.), 172.0 (C-5); ***m/z*** (ES−) 279 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}N_2ONa^+$) requires ***m/z*** 303.1468, found ***m/z*** 303.1467.

Preparation and characterisation of (5a*R*,15b*R*)-2,3,4,5,5a,6,10,15-octahydro-9*H*-cyclohepta[1,8a]indolizino[8,7-*b*]indol-7(1*H*)-one (+)-21f

Heated at reflux in toluene for 48 hours in the presence of (*R*)-**10a**. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 to afford the title product as a colourless crystalline solid (53 mg, 90%).

86% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 4.6 min, minor t_R = 9.7 min), > 98:2 d.r.; $[\alpha]_D^{25}$ = + 58.2 (*c* 0.86, $CHCl_3$).



(+)-**21f**

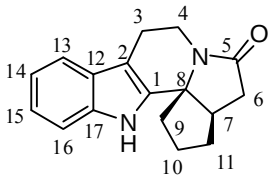
m.p. 244-247 ºC; **FT-IR** ν_{max}(NaCl) 3264 cm^{-1} (N-H), 1662 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 1.21-1.47 (m, 2H, H-10a, H-12a), 1.55-1.81 (m, 5H, H-10b, H-13a, H-11, H-12a), 1.95-2.13 (m, 2H, H-9), 2.14-2.32 (m, 2H, H-6a, H-13b), 2.44-2.52 (m, 1H, H-6b), 2.56-2.66 (m, 2H, H-3), 2.67-2.77 (m, 1H, H-7), 2.97-3.07 (m, 1H, H-4a), 4.22 (dd, 1H, H-4b, *J* 13.0 Hz *J* 4.5 Hz), 6.96 (t, 1H, Ar-H, *J* 7.5 Hz), 7.05 (t, 1H, Ar-H, *J* 7.5 Hz), 7.32-7.36 (m, 2H, 2 × Ar-H), 10.90 (s, 1H, NH); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 21.3 (C-3), 23.8 (C-10), 25.1 (C-11), 29.1 (C-13), 31.3 (C-12), 35.4 & 35.5 (C-4 & C-6), 38.3 (C-9), 41.6 (C-7), 66.6 (C-8), 105.3 (Ar-Cquat.), 112.1 (Ar-CH), 118.7 (Ar-CH), 119.4 (Ar-CH), 121.8

(Ar-CH), 127.1 (Ar-Cquat.), 136.9 (Ar-Cquat.), 141.4 (Ar-Cquat.), 173.8 (C-5); ***m/z*** (ES−) 293 ([M−H]$^-$, 80%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{19}H_{22}N_2ONa^+$) requires ***m/z*** 317.1624, found ***m/z*** 317.1624.

Preparation and characterisation of (3a*R*,13b*R*)-2,3,3a,4,8,13-hexahydro-7*H*-cyclopenta [1,8a]indolizino[8,7-*b*]indol-5(1*H*)-one (+)-21g

Heated at reflux in toluene for 48 hours in the presence of (*R*)-**6d**. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:4 to afford the title product as a colourless crystalline solid (30 mg, 57%).

68% e.e. (Chiralcel AD, 85:15 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 8.9 min, minor t_R = 17.3 min), > 98:2 d.r.; $[\alpha]_D^{25}$ = + 31.8 (*c* 1.03, $CHCl_3$).



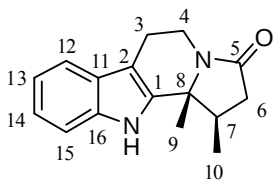
(+)-**21g**

m.p. 80-85 ºC; **FT-IR** ν_{max}(NaCl) 3260 cm^{-1} (N-H), 1665 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.75-1.95 (m, 4H, H-9, H-10), 2.06-2.22 (m, 2H, H-11), 2.28 (dd, 1H, H-6a, *J* 17.5 Hz, *J* 4.0 Hz), 2.71-2.84 (m, 2H, H-3a, H-6b), 2.87-2.96 (m, 2H, H-3b, H-7), 3.10 (app. td, 1H, H-4a, *J* 12.5 Hz, *J* 5.0 Hz), 4.51 (dd, 1H, H-4b, *J* 12.5 Hz, *J* 5.5 Hz), 7.10-7.14 (m, 1H, Ar-H), 7.16-7.21 (m, 1H, Ar-H), 7.34 (d, 1H, Ar-H, *J* 8.0 Hz), 7.47 (d, 1H, Ar-H, *J* 7.5 Hz), 8.21 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.9 (C-3), 24.6 & 35.2 (C-9, C-10), 36.8 (C-4), 39.0 (C-6), 40.2 (C-11), 41.3 (C-7), 71.0 (C-8), 108.1 (Ar-Cquat.), 111.0 (Ar-CH), 118.3 (Ar-CH), 119.8 (Ar-CH), 122.1 (Ar-CH), 126.7 (Ar-Cquat.), 136.3 (Ar-Cquat.), 136.7 (Ar-Cquat.), 174.2 (C-5); ***m/z*** (ES−) 265 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{17}H_{18}N_2ONa^+$) requires ***m/z*** 289.1311, found ***m/z*** 289.1312.

Preparation and characterisation of (1*R*,11b*R*)-1,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (+)-21h

Heated at reflux in toluene for 24 hours in the presence of (*R*)-**6f**. The crude mixture was purified by column chromatography on silica gel eluting with ethyl acetate to afford the title product as a colourless oil (54 mg, 99%).

76% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, minor t_R = 25.3 min, major t_R = 30.9 min), 97:3 d.r.; $[\alpha]_D^{25}$ = + 66.6 (*c* 0.94, $CHCl_3$).



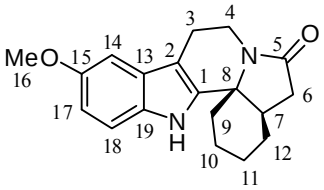
(+)-**21h**

FT-IR ν_{max}(NaCl) 3271 cm^{-1} (N-H), 1664 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.42 (d, 3H, H-10, *J* 6.5 Hz), 1.51 (s, 3H, H-9), 2.34-2.41 (m, 1H, H-6a), 2.50-2.62 (m, 2H, H-6b, H-7), 2.85-2.89 (m, 2H, H-3), 3.05-3.12 (m, 1H, H-4a), 4.53-4.58 (m, 1H, H-4b), 7.17-7.21 (m, 1H, Ar-H), 7.24-7.28 (m, 1H, Ar-H), 7.41 (d, 1H, Ar-H, *J* 8.0 Hz), 7.55 (d, 1H, Ar-H, *J* 8.0 Hz), 8.01 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.8 (C-10), 19.3 (C-9), 21.5 (C-3), 35.0 (C-4), 38.8 (C-6), 39.2 (C-7), 61.6 (C-8), 107.1 (Ar-Cquat.), 111.0 (Ar-CH), 118.5 (Ar-CH), 119.9 (Ar-CH), 122.2 (Ar-CH), 126.6 (Ar-Cquat.), 136.1 (Ar-Cquat.), 137.9 (Ar-Cquat.), 171.9 (C-5); ***m/z*** (ES−) 253 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}N_2ONa^+$) requires ***m/z*** 277.1311, found ***m/z*** 277.1312.

Preparation and characterisation of (4a*R*,14b*R*)-11-methoxy-1,2,3,4,4a,5,9,14-octahydro-6*H*,8*H*-pyrido[3,4-*b*:1,2-*i*']diindol-6-one (+)-21i

Heated at reflux in toluene for 24 hours in the presence of (*R*)-**10a**. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:4 to afford the title compound as a colourless crystalline solid (56 mg, 90%).

79% e.e. (Chiralcel AD , 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 7.4 min, minor t_R = 11.5 min), > 98:2 d.r.; $[\alpha]_D^{25}$ = + 66.6 (*c* 1.11, $CHCl_3$).



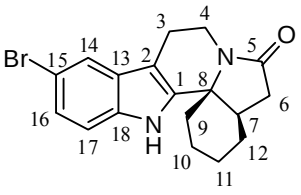
(+)-**21i**

m.p. 102-107 ºC; **FT-IR** ν_{max}(NaCl) 3306 cm^{-1} (N-H), 1664 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.55-1.70 (m, 2H, CHaHb, CHaHb), 1.79-1.90 (m, 3H, CHaHb, CHaHb, CHaHb), 1.95-1.99 (m, 2H, H-6), 2.24-2.29 (m, 1H, CHaHb), 2.43 (dd, 1H, CHaHb, *J* 14.0Hz, *J* 6.5 Hz), 2.51-2.62 (m, 2H, H-7, CHaHb), 2.81 (dd, 1H, H-3a, *J* 15.5 Hz, *J* 5.0 Hz), 2.90 (ddd, 1H, H-3b, *J* 15.5 Hz, *J* 12.5 Hz, *J* 6.0 Hz), 3.16 (app. td, 1H, H-4a, *J* 12.5 Hz, *J* 5.0 Hz), 3.91 (s, 3H, H-16), 4.49 (dd, 1H, H-4b, *J* 12.5 Hz, *J* 6.0 Hz), 6.91 (dd, 1H, H-17, *J* 9.0 Hz, *J* 2.5 Hz), 6.99 (d, 1H, H-14, *J* 2.5 Hz), 7.32 (m, 1H, H-18), 7.96 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.7 (C-3), 21.6 (CH_2), 22.6 (CH_2), 26.7 (C-6), 34.6 (CH_2), 35.1 (C-4), 35.9 (CH_2), 38.6 (C-7), 56.4 (C-16), 60.6 (C-8), 101.0 (Ar-CH), 107.6 (Ar-Cquat.), 112.2 (Ar-CH), 112.6 (Ar-CH), 127.5 (Ar-Cquat.), 131.3 (Ar-Cquat.), 139.4 (Ar-Cquat.), 154.8 (Ar-Cquat.), 173.1 (C-5); ***m/z*** (ES−) 309 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{22}N_2ONa^+$) requires ***m/z*** 333.1573, found ***m/z*** 333.1573.

Preparation and characterisation of (4a*R*,14b*R*)-11-bromo-1,2,3,4,4a,5,9,14-octahydro-6*H*,8*H*-pyrido[3,4-*b*:1,2-*i*']diindol-6-one (+)-21j

Heated at reflux in toluene for 48 hours in the presence of (*R*)-**10a**. The crude mixture was purified by column chromatography on silica gel eluting with ethyl acetate to afford a the title compound as a colourless crystalline solid (64 mg, 88%).

88% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 7.1 min, minor t_R = 21.5 min), > 98:2 d.r.; $[\alpha]_D^{25}$ = + 75.8 (*c* 0.91, $CHCl_3$).



(+)-**21j**

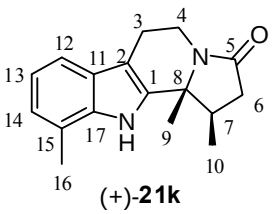
m.p. 275-277 ºC; **FT-IR** ν_{max}(NaCl) 3283 cm^{-1} (N-H), 1665 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.50-1.67 (m, 3H, H-10a, H-11), 1.74-1.87 (m, 2H, H-9a, H-10b), 1.90-1.96 (m, 2H, H-12), 2.17-2.25 (m, 1H, H-9b), 2.38 (dd, 1H, H-6a, *J* 13.0 Hz *J* 5.5 Hz),

2.45-2.59 (m, 2H, H-6b, H-7), 2.71-2.88 (m, 2H, H-3), 3.10 (td, 1H, H-4a, *J* 12.5 Hz, *J* 5.5 Hz), 4.44 (dd, 1H, H-4b, *J* 12.5 Hz, *J* 6.0 Hz), 7.23-7.30 (m, 2H, 2 × Ar-H), 7.62 (s, 1H, H-14), 8.09 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.2 (C-11), 20.9 (C-3), 22.0 (C-10), 26.1 (C-12), 34.1 (C-4), 34.5 (C-9), 35.4 (C-6), 37.9 (C-7), 60.1 (C-8), 106.9 (Ar-Cquat.), 112.5 (Ar-CH), 113.1 (Ar-Cquat.), 121.1 (C-14), 124.9 (Ar-CH), 128.3 (Ar-Cquat.), 134.5 (Ar-Cquat.), 139.3 (Ar-Cquat.), 172.8 (C-5); ***m/z*** (ES−) 357, 359 ($[M-H]^-$, 70%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{19}N_2OBrNa^+$) requires ***m/z*** 381.0573 and 383.0553, found ***m/z*** 381.0573 and 383.0555.

Preparation and characterisation of (1*R*,11b*R*)-1,10,11b-trimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (+)-21k

Heated at reflux in toluene for 48 hours in the presence of (*R*)-**6f**. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 to afford the title product as a colourless crystalline solid (62 mg, 95%).

95% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, minor t_R = 18.0 min, major t_R = 23.2 min), 97:3 d.r.; $[\alpha]_D^{25}$ = + 161.3 (*c* 1.12, $CHCl_3$).



(+)-**21k**

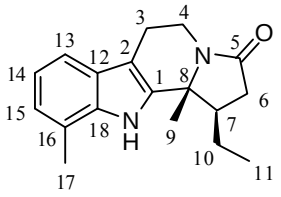
m.p. 190-196 ºC; **FT-IR** ν_{max}(NaCl) 3292 cm^{-1} (N-H), 1667 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.41 (d, 3H, H-10, *J* 6.5 Hz), 1.49 (s, 3H, H-9), 2.27-2.39 (m, 1H, H-7), 2.45-2.59 (m, 5H, H-6, H-16), 2.80-2.85 (m, 2H, H-3), 3.04 (m, 1H, H-4a), 4.50 (ddd, 1H, H-4b, *J* 13.0 Hz, *J* 4.5 Hz, *J* 3.0 Hz), 7.02 (d, 1H, Ar-H, *J* 7.5 Hz), 7.08 (t, 1H, Ar-H, *J* 7.5 Hz), 7.37 (d, 1H, Ar-H, *J* 7.5 Hz), 8.03 (br s, 1H, NH). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 15.0 (C-10), 16.8 (C-16), 19.3 (C-9), 21.7 (C-3), 35.0 (C-4), 38.8 (C-6), 39.2 (C-7), 61.7 (C-8), 107.8 (Ar-Cquat.), 116.2 (Ar-CH), 120.2 (Ar-CH), 120.3 (Ar-Cquat.), 123.0 (Ar-CH), 126.3 (Ar-Cquat.), 135.6 (Ar-Cquat.), 137.8 (Ar-Cquat.), 171.9 (C-5); ***m/z*** (ES−) 267 ($[M-H]^-$,

100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2ONa^+$) requires ***m/z*** 291.1468, found ***m/z*** 291.1469.

Preparation and characterisation of (1*R*,11b*R*)-1-ethyl-10,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (+)-21l

Carried out on a 0.3 mmol scale. Heated at reflux in toluene for 54 hours in the presence of (*R*)-**10a**. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 2:3 to afford the title compound as a colourless crystalline solid (69 mg, 81%).

94% e.e. (Chiralcel OD, 85:15 hexane/isopropanol, 1 ml/min, 220 nm, minor t_R = 8.4 min, major t_R = 18.6 min), 97:3 d.r.; $[\alpha]_D^{25}$ = + 161.2 (*c* 1.06, $CHCl_3$).

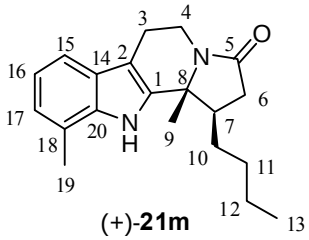


(+)-**21l**

m.p. 107-111 ºC; **FT-IR** ν_{max}(NaCl) 3290 cm^{-1} (N-H), 1667 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.07 (t, 3H, H-11, *J* 7.5 Hz), 1.48 (s, 3H, H-9), 1.62-1.74 (m, 1H, H-10a), 1.89-2.00 (m, 1H, H-10b), 2.23-2.36 (m, 2H, H-6a, H-7), 2.52 (s, 3H, H-17), 2.58-2.68 (m, 1H, H-6b), 2.79-2.84 (m, 2H, H-3), 3.03 (dt, 1H, H-4a, *J* 12.5 Hz, *J* 8.5 Hz), 4.50 (dt, 1H, H-4b, *J* 12.5 Hz, *J* 4.0 Hz), 7.02 (d, 1H, Ar-H, *J* 7.1 Hz), 7.08 (t, 1H, Ar-H, *J* 7.4 Hz), 7.36 (d, 1H, Ar-H, *J* 7.7 Hz), 7.85 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 12.8 (C-11), 16.8 (C-17), 19.8 (C-9), 21.6 (C-3), 23.7 (C-10), 34.8 (C-4), 36.5 (C-6), 46.5 (C-7), 61.6 (C-8), 107.9 (Ar-Cquat.), 116.2 (Ar-CH), 120.2 (2C, Ar-CH, Ar-Cquat.), 123.0 (Ar-CH), 126.2 (Ar-Cquat.), 135.5 (Ar-Cquat.), 137.7 (Ar-Cquat.), 171.7 (C=O); ***m/z*** (ES−) 281 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2ONa^+$) requires ***m/z*** 305.1624, found ***m/z*** 305.1626.

Preparation and characterisation of (1*R*,11b*R*)-1-butyl-10,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (+)-21m

Heated at reflux in toluene for 72 hours in the presence of (*R*)-**10a**. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 to afford a the title compound as a colourless crystalline solid (58 mg, 94%).



(+)-**21m**

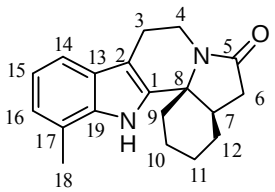
98% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, minor t_R = 6.6 min, major t_R = 12.9 min), > 98:2 d.r.; $[\alpha]_D^{25}$= + 100.9 (*c* 0.91 , $CHCl_3$).

m.p. 208-210 ºC; **FT-IR** ν_{max}(NaCl) 3296 cm^{-1} (N-H), 1668 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.97 (t, 3H, *J* 6.5 Hz, H-13), 1.27-1.47 (m, 4H, H-11, H-12), 1.49 (s, 3H, H-9), 1.61-1.72 (m, 1H, H-10a), 1.82-1.91 (m, 1H, H-10b), 2.23-2.42 (m, 2H, H-6a, H-7), 2.53 (s, 3H, H-19), 2.60 (dd, 1H, H-6b, *J* 15.0 Hz, *J* 7.0 Hz), 2.79-2.84 (m, 2H, H-3), 2.98-3.07 (m, 1H, H-4a), 4.47-4.53 (m, 1H, H-4b), 7.02 (d, 1H, Ar-H, *J* 7.5 Hz), 7.08 (t, 1H, Ar-H, *J* 7.5 Hz), 7.37 (d, 1H, Ar-H, *J* 7.5 Hz), 7.91 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.0 (C-13), 16.8 (C-19), 19.7 (2C, C-9, $\underline{C}H_2$), 21.7 ($\underline{C}H_2$), 22.8 (C-3), 30.4 (C-10), 34.9 (C-4), 36.9 (C-6), 44.7 (C-7), 61.6 (C-8), 107.9 (Ar-Cquat.), 116.2 (Ar-$\underline{C}$H), 120.2 (2C, Ar-$\underline{C}$H, Ar-Cquat.), 123.0 (Ar-$\underline{C}$H), 126.2 (Ar-Cquat.), 135.5 (Ar-Cquat.), 137.8 (Ar-Cquat.), 171.7 (C-5); ***m/z*** (ES−) 309 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{26}N_2ONa^+$) requires ***m/z*** 333.1937, found ***m/z*** 333.1937.

Preparation and characterisation of (4a*R*,14b*R*)-13-methyl-1,2,3,4,4a,5,9,14-octahydro-6*H*,8*H*-pyrido[3,4-*b*:1,2-*i*']diindol-6-one (+)-21n

Heated at reflux in toluene for 48 hours in the presence of (*R*)-**10a**. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 2:3 to afford the title compound as a colourless crystalline solid (52 mg, 89%).

98% e.e. (Chiralcel AD, 95:5 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 10.9 min, minor t_R = 16.0 min), > 98:2 d.r.; $[\alpha]_D^{25}$ = + 24.6 (*c* 0.89, $CHCl_3$).



(+)-**21n**

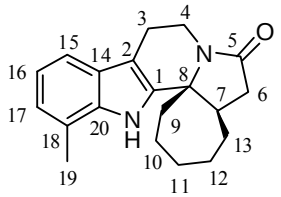
m.p. 113-117 ºC; **FT-IR** ν_{max}(NaCl) 3293 cm^{-1} (N-H), 1669 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.50-1.70 (m, 2H, CHaHb, CHaHb), 1.76-1.88 (m, 3H, CHaHb, CHaHb, CHaHb), 1.90-1.96 (m, 2H, H-6), 2.17-2.24 (m, 1H, CHaHb), 2.35-2.44 (m, 1H, CHaHb), 2.48-2.52 (m, 5H, H-7, H-18, CHaHb), 2.79 (dd, 1H, H-3a, *J* 15.5 Hz, *J* 5.0 Hz), 2.84-2.93 (m, 1H, H-3b), 3.11 (td, 1H, H-4a, *J* 12.5 Hz, *J* 5.5 Hz), 4.44 (dd, 1H, H-4b, *J* 12.5 Hz, *J* 6.0 Hz), 7.02 (d, 1H, Ar-H, *J* 7.5 Hz), 7.08 (t, 1H, Ar-H, *J* 7.5 Hz), 7.36 (d, 1H, Ar-H, *J* 7.5 Hz), 7.70 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 17.1 (C-18), 20.9 (CH_2), 21.4 (C-3), 22.4 (CH_2), 27.1 (C-6), 34.5 (CH_2), 35.3 (C-4), 36.3 (CH_2), 38.0 (C-7), 61.2 (C-8), 108.3 (Ar-Cquat.), 116.5 (Ar-CH), 120.5 & 120.6 (Ar-CH, Ar-Cquat.), 123.3 (Ar-CH), 126.6 (Ar-Cquat.), 135.7 (Ar-Cquat.), 138.2 (Ar-Cquat.), 174.5 (C=O); ***m/z*** (ES−) 293 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{22}N_2ONa^+$) requires ***m/z*** 317.1624, found ***m/z*** 317.1619.

Preparation and characterisation of (5a*R*,15b*R*)-14-methyl-2,3,4,5,5a,6,10,15-octahydro-9*H*-cyclohepta[1,8a]indolizino[8,7-*b*]indol-7(1*H*)-one (+)-21o

Carried out on a 0.3 mmol scale. Heated to reflux in toluene for 48 hours in the presence of (*R*)-**10a**. The crude mixture was purified by column chromatography on silica gel eluting with

petroleum ether/ethyl acetate 1:1 to afford the title compound as a colourless crystalline solid (84 mg, 91%).

93% e.e. (Chiralcel AD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 7.5 min, minor t_R = 9.9 min), > 98:2 d.r.; $[\alpha]_D^{25}$ = + 15.1 (*c* 0.67, $CHCl_3$).



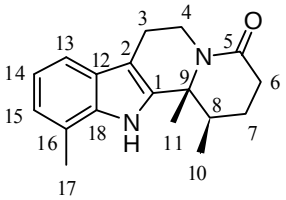
(+)-**21o**

m.p. 128-133 ºC; **FT-IR** ν_{max}(NaCl) 3279 cm^{-1} (N-H), 1662 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.46-1.58 (m, 2H, C$\underline{H}_2$), 1.69-1.76 (m, 1H, C$\underline{Ha}$Hb), 1.80-1.88 (m, 2H, C$\underline{H}_2$), 1.90-1.96 (m, 1H, C$\underline{Ha}$Hb), 2.03-2.13 (m, 3H, C$\underline{H}_2$, CHa$\underline{Hb}$), 2.28 (dd, 1H, CHa$\underline{Hb}$, *J* 15.0 Hz, *J* 9.0 Hz), 2.49-2.55 (m, 4H, H-6a, H-19), 2.68-2.79 (m, 2H, H-3a, H-6b), 2.92-3.01 (m, 2H, H-3b, H-7), 3.15 (td, 1H, H-4a, *J* 12.5 Hz, *J* 4.5 Hz), 4.56 (dd, 1H, H-4b, *J* 12.5 Hz, *J* 6.5 Hz), 7.05 (d, 1H, Ar-H, *J* 7.5 Hz), 7.10 (t, 1H, Ar-H, *J* 7.5 Hz), 7.38 (d, 1H, Ar-H, *J* 7.5 Hz), 7.90 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 17.2 (C-19), 21.4 (C-3), 23.9 (C$\underline{H}_2$), 25.3 (C$\underline{H}_2$), 30.3 (C$\underline{H}_2$), 31.5 (C$\underline{H}_2$), 35.5 & 35.8 (C-4, C-6), 38.5 (C$\underline{H}_2$), 41.6 (C-7), 66.9 (C-8), 107.7 (Ar-Cquat.), 116.6 (Ar-C$\underline{H}$), 120.6 (2C, Ar-C$\underline{H}$, Ar-Cquat.), 123.3 (Ar-C$\underline{H}$), 126.7 (Ar-Cquat.), 135.8 (Ar-Cquat.), 139.8 (Ar-Cquat.), 174.1 (C-5); ***m/z*** (ES−) 307 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{20}H_{24}N_2ONa^+$) requires ***m/z*** 331.1781, found ***m/z*** 331.1780.

Preparation and characterisation of (1*R*,12b*R*)-1,11,12b-trimethyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (+)-21p

Heated at reflux in toluene for 54 hours before addition of an additional equivalent of ketoacid and 10 mol% of catalyst (*R*)-**10a**, heated at reflux for further 48 hours. The crude mixture was purified by column chromatography on silica gel eluting with diethyl ether to diethyl ether/ethyl acetate 4:1 to afford the title compound as a pale tan solid (30 mg, 53%).

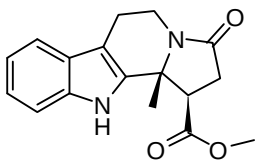
88% e.e. (Chiralcel OD, 85:15 hexane/isopropanol, 0.7 ml/min, 220 nm, minor t_R = 12.8 min, major t_R = 25.6 min), 96:4 d.r.; $[\alpha]_D^{26}$ = + 137.1 (*c* 0.98, $CHCl_3$).



(+)-**21p**

m.p. 255-260 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3293 cm^{-1} (N-H), 1612 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.41 (d, 3H, H-10, *J* 6.5 Hz), 1.60 (s, 3H, H-11), 1.68-1.76 (m, 1H, H-7a), 1.78-1.90 (m, 1H, H-7b), 2.12-2.21 (m, 1H, H-8), 2.46-2.54 (m, 4H, H-6a, H-11), 2.60 (ddd, 1H, H-6b, *J* 18.0 Hz, 6.5 Hz, 3.0 Hz), 2.71 (ddd, 1H, H-3a, *J* 15.0 Hz, 3.5 Hz, 1.5 Hz), 2.84 (ddd, 1H, H-3b, *J* 15.0 Hz, 12.5 Hz, 4.5 Hz), 2.95 (td, 1H, H-4a, *J* 12.5 Hz, 3.5 Hz), 5.11 (ddd, 1H, H-4b, *J* 12.5 Hz, 4.5 Hz, 1.5 Hz), 7.01 (d, 1H, Ar-H, *J* 7.5 Hz), 7.07 (t, 1H, H-14, *J* 7.5 Hz), 7.37 (d, 1H, Ar-H, *J* 7.5 Hz), 7.65 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 16.8 (C-17), 18.4 (C-10), 21.2 (C-11), 21.8 (C-3), 25.9 (C-7), 31.4 (C-6), 37.8 (C-4), 38.5 (C-8), 61.0 (C-9), 111.0 (C-2), 116.3 (Ar-CH), 120.0 (Ar-Cquat.), 120.2 (C-14), 123.0 (Ar-CH), 126.1 (C-12), 135.3 (Ar-Cquat.), 138.0 (Ar-Cquat.), 169.8 (C-5); ***m/z*** (ES−) 281([M−H]$^-$, 90%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{23}N_2O^+$) requires ***m/z*** 283.1805, found ***m/z*** 283.1804.

Preparation and characterisation of methyl (1*R*,11b*R*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-1-carboxylate (+)-21a



(+)-**21a**

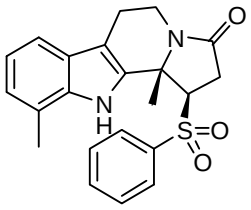
Heated at reflux in toluene for 10 days in the presence of (*R*)-**6f**. The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 then ethyl acetate to afford the title compound as a colourless crystalline solid (47 mg, 78%).

69% e.e. (Chiralcel IB, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 12.6 min, minor t_R = 20.1 min), > 98:2 d.r. ; $[\alpha]_D^{25}$ = + 56.6 (*c* 1.0, $CHCl_3$).

Analytical data identical to (+)-**21a** obtained from the condensation of preformed enol lactone **27a** and tryptamine **14a**.

Preparation and characterisation of (1*R*,11b*S*)-10,11b-dimethyl-1-(phenylsulfonyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*] indol-3-one (+)-21b

Heated at reflux in toluene for 7 days in the presence of (*R*)-**6e**. The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate 2:3 to afford the title product as a colourless crystalline solid (64 mg, 81%).



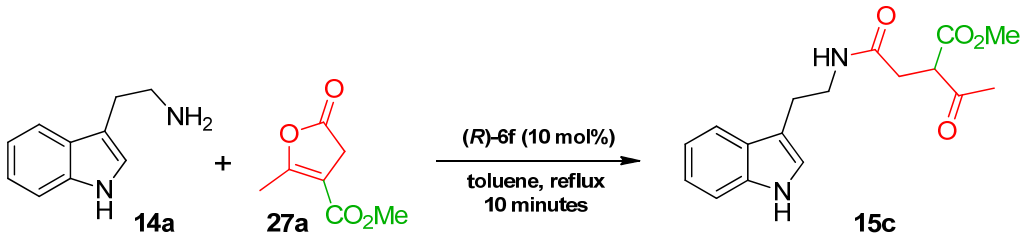
(+)-**21b**

68% e.e. (Chiralcel OD-H, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, minor t_R = 14.7 min, major t_R = 17.4 min), >98:2 dr; $[\alpha]_D^{21}$ = + 222.3 (*c* 0.528, $CHCl_3$).

Analytical data identical to (+)-**21b** obtained from the condensation of preformed enol lactone **27b** and tryptamine **14f**.

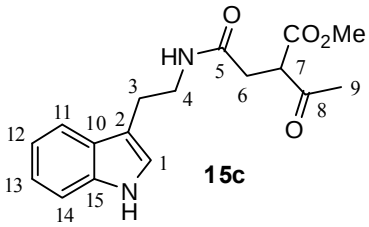
6.2.2.3.3 Elucidation of mechanism in the diastereoselective and enantioselective *N*-acyliminium cyclisation cascades

Isolation and characterisation of methyl 2-acetyl-4-{[2-(1*H*-indol-3-yl)ethyl]amino}-4-oxobutanoate 15c



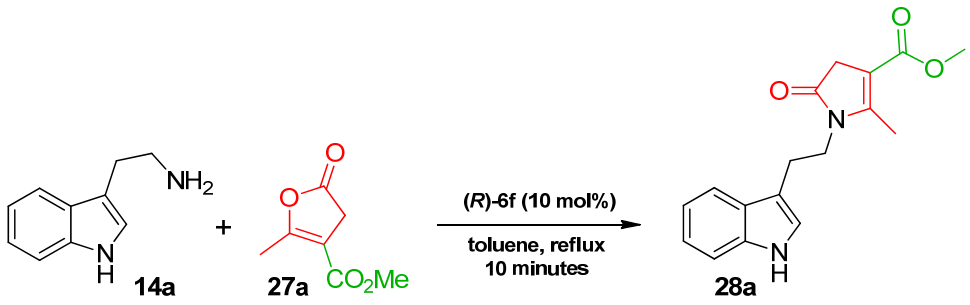
A cyclisation reaction between tryptamine **14a** and **27a** was performed under the optimal cyclisation conditions for doubly substituted lactones (see section 6.2.2.2), on a 0.2 mmol scale, but the reaction was stopped after 10 minutes. The solvent was removed *in vacuo* and the residue immediately purified by column chromatography on silica gel eluting with

dichloromethane/acetone 9:1 to afford oxoamide intermediate **15c** as a colourless oil (41 mg, 65%).



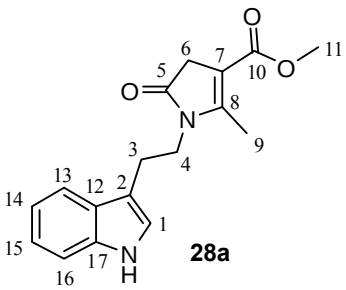
FT-IR ν_{max}(NaCl) 3396 cm^{-1} (N-H), 3309 cm^{-1} (N-H), 1740 cm^{-1} (C=O ketone), 1715 cm^{-1} (C=O ester), 1653 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.35 (s, 3H, H-9), 2.61 (dd, 1H, H-6a, *J* 16.0 Hz, 6.5 Hz), 2.73 (dd, 1H, H-6b, *J* 16.0 Hz, 8.0 Hz), 2.93 (t, 2H, H-3, *J* 7.0 Hz), 3.54 (m, 2H, H-4), 3.72 (s, 3H, OMe), 4.12 (dd, 1H, H-7, *J* 8.0 Hz, 6.5 Hz), 5.77 (br t, 1H, NH amide, *J* 5.0 Hz), 7.01 (d, 1H, H-1, *J* 1.5 Hz), 7.12 (td, 1H, H-12, *J* 8.0 Hz, 1.0 Hz), 7.20 (td, 1H, H-13, *J* 8.0 Hz, 1.0 Hz), 7.37 (d, 1H, H-14, *J* 8.0 Hz), 7.58 (d, 1H, H-11, *J* 8.0 Hz), 8.33 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 25.2 (C-3), 30.2 (C-9), 34.2 (C-6), 39.8 (C-4), 52.7 ($O\underline{C}H_3$), 54.5 (C-7), 111.3 (C-14), 112.6 (C-2), 118.6 (C-11), 119.4 (C-12), 122.1 (C-13), 122.3 (C-1), 127.2 (C-10), 136.4 (C-15), 169.4 (C=O), 169.9 (C=O), 202.7 (C-8); ***m/z*** (ES+) 339 ($[M+Na]^+$, 60%), 655 ($[2M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2O_4Na^+$) requires ***m/z*** 339.1315, found ***m/z*** 339.1316.

Isolation and characterisation of methyl 1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate 28a



A cyclisation reaction between tryptamine and **14a** was performed under the optimal cyclisation conditions for doubly substituted lactones **27a** (see section 6.2.2.2), on a 0.2 mmol scale. The reaction was stopped after 50 minutes and quenched with triethylamine (150 µL for 0.2 mmol

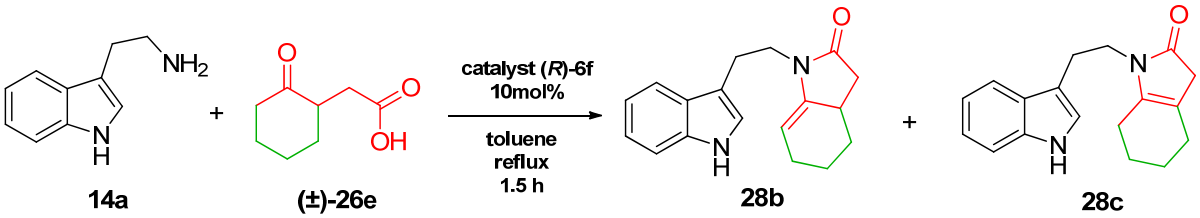
scale reaction). The solvent was removed *in vacuo* and the residue immediately purified by column chromatography on deactivated silica gel (1% triethylamine in the eluent), eluting with petroleum ether/ethyl acetate/triethylamine 60:40:1 to afford enamide intermediate **28a** as a colourless solid (26 mg, 43%).



28a

m.p. 158-160 ºC; **FT-IR** ν_{max}(NaCl) 3337 cm^{-1} (N-H), 1688 cm^{-1} (C=O), 1628 cm^{-1} (C=C); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 2.16 (t, 3H, H-9, *J* 2.5 Hz), 2.90 (t, 2H, H-3, *J* 7.5 Hz), 3.22 (q, 2H, H-6, *J* 2.5 Hz), 3.61 (s, 3H, H-11), 3.70 (t, 2H, H-4, *J* 7.5 Hz), 6.99 (td, 1H, H-15, *J* 7.5 Hz, 1.0 Hz), 7.07 (td, 1H, H-16, *J* 7.5 Hz, 1.0 Hz), 7.15 (d, 1H, H-1, *J* 2.0 Hz), 7.34 (d, 1H, H-17, *J* 7.5 Hz), 7.54 (d, 1H, H-14, *J* 7.5 Hz), 10.87 (br s, 1H, H-12); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 12.5 (C-9), 25.1 (C-3), 37.8 (C-6), 41.5 (C-4), 51.5 (C-11), 102.2 (C-7), 111.4 (C-2), 112.3 (C-17), 118.9 (C-14), 119.3 (C-15), 121.9 (C-16), 124.1 (C-1), 127.9 (C-13), 137.0 (C-18), 156.1 (C-8), 165.8 (C-10), 176.0 (C-5); ***m/z*** (ES+) 357 ($[M+MeCN+NH_4]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{18}N_2O_3Na^+$) requires ***m/z*** 321.1210, found ***m/z*** 321.1210.

Preparation and isolation of the two isomeric enamides 28b and 28c

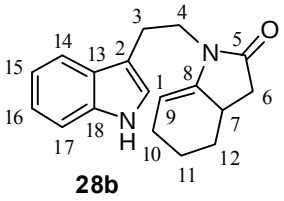


14a (±)-26e **28b** **28c**

The cyclisation of tryptamine and oxoacid **14a** under the optimised cyclisation conditions (reflux in toluene in the presence of 10 mol % of (*R*)-**6f**, 0.0048 mM concentration, 0.2 mmol scale, see section 6.2.2.3.2) was carried out and the reaction was stopped after 1.5 hours. Little product was formed (according to TLC) however two intermediates were isolated, respectively **28b** (16 mg, 19%) and **28c** (10 mg, 12%) as pale brown solids.

Characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]-1,3,3a,4,5,6-hexahydro-2*H*-indol-2-one (−)-28b

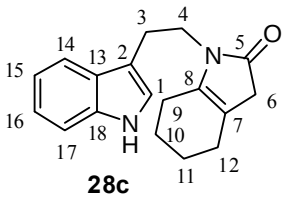
7% e.e. (Chiralcel IA, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 5.7 min, minor t_R = 10.7 min), $[\alpha]_D^{25} = -10.3$ (*c* 1.40, $CHCl_3$).



28b

m.p. 172-177 ºC; **FT-IR** ν_{max}(NaCl) 3306 cm^{-1} (N-H), 1713 cm^{-1}, 1671 cm^{-1} (C=O lactam); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.29-1.39 (m, 1H, H-12a), 1.52-1.63 (m, 1H, H-11a), 1.88-1.96 (m, 1H, H-11b), 2.05 (app. ddd, 1H, H-12b, *J* 11.5 Hz, 7.5 Hz, 3.5 Hz), 2.09-2.19 (m, 2H, H-6a, H-10a), 2.21-2.30 (m, 1H, H-10b), 2.53 (dd, 1H, H-6b, *J* 16.0 Hz, *J* 9.0 Hz), 2.61-2.71 (m, 1H, H-7), 2.97-3.09 (m, 2H, H-3), 3.60 (ddd, 1H, H-4a, *J* 14.0 Hz, *J* 9.0 Hz, *J* 5.5 Hz), 3.91 (ddd, 1H, H-4b, *J* 14.0 Hz, *J* 9.5 Hz, *J* 7.0 Hz), 4.90-4.95 (m, 1H, H-9), 7.08 (d, 1H, H-1, *J* 2.0 Hz), 7.13 (t, 1H, H-15, *J* 7.5 Hz), 7.20 (t, 1H, H-16, *J* 7.5 Hz), 7.36 (d, 1H, H-17, *J* 7.5 Hz), 7.65 (d, 1H, H-14, *J* 7.5 Hz), 8.17 (br s, 1H, N-H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 22.4 (C-11), 22.7 (C-3), 23.2 (C-10), 27.9 (C-12), 34.7 (C-7), 36.9 (C-6), 40.2 (C-4), 96.9 (C-9), 111.2 (C-17), 112.9 (C-2), 118.7 (C-14), 119.3 (C-15), 121.9 (C-1), 122.0 (C-16), 127.5 (C-13), 136.2 (C-18), 142.1 (C-8), 174.5 (C-5); ***m/z*** (ES-) 279 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}N_2ONa^+$) requires ***m/z*** 303.1468, found ***m/z*** 303.1469.

Characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]-1,3,4,5,6,7-hexahydro-2*H*-indol-2-one 28c

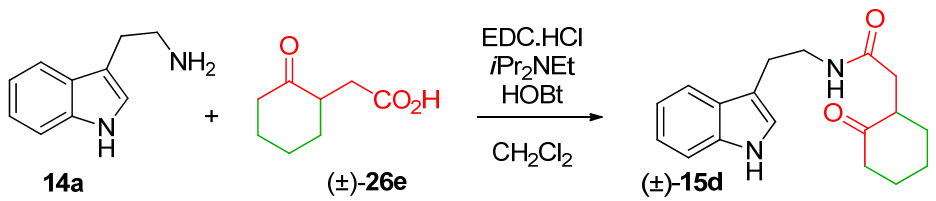


28c

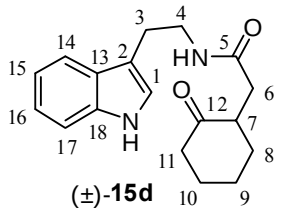
m.p. 158-163 ºC; **FT-IR** ν_{max}(NaCl) 3287 cm^{-1} (N-H), 1692 cm^{-1}, 1666 cm^{-1} (C=O lactam); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.58-1.71 (m, 4H, H-10, H-11), 1.97-2.07 (m, 4H, H-9, H-12), 2.90-2.94 (m, 2H, H-6), 2.99-3.04 (m, 2H, H-3), 3.65-3.70 (m, 2H, H-4), 7.04 (d, 1H, H-1, *J* 2.0 Hz), 7.12 (ddd, 1H, H-15, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.19 (ddd, 1H, H-16, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.37 (d, 1H, H-17, *J* 8.0 Hz), 7.60 (d, 1H, H-14, *J* 8.0 Hz), 8.15

(br s, 1H, N-H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 21.4 (C-9 or C-12), 22.3 & 22.6 (C-10, C-11), 23.3 (C-9 or C-12), 25.3 (C-3), 39.8 (C-6), 40.7 (C-4), 110.7 (C-7), 111.1 (C-17), 113.0 (C-2), 118.6 (C-14), 119.3 (C-15), 122.0 & 122.1 (C-1, C-16), 127.4 (C-13), 136.2 (C-18), 137.3 (C-8), 177.2 (C-5); ***m/z*** (ES−) 279 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{18}H_{20}N_2ONa^+$) requires ***m/z*** 303.1468, found ***m/z*** 303.1471.

Preparation and characterisation of (±)-*N*-[2-(1*H*-indol-3-yl)ethyl]-2-(2-oxocyclohexyl) acetamide (±)-15d



Tryptamine **14a** (1 mmol, 160 mg, 1 equivalent) and oxoacid (±)-**26e** (1 mmol, 156 mg, 1 equivalent) were dissolved in 30 mL of dry dichloromethane. The solution was cooled to 0 ºC and HOBt (1 mmol, 135 mg, 1 equivalent) was added, followed by addition of EDC.HCl (1 mmol, 192 mg, 1 equivalent) and *i*Pr_2NEt (2 mmol, 0.35 mL, 2 equivalents) in one portion. The suspension was stirred at 0 ºC for 1 hour and then at room temperature for 48 hours (the solution became clear after a few hours at room temperature). 30 mL of water were added to the solution. The organic layer was separated and the aqueous phase was re-extracted with ethyl acetate (2 × 30 mL). The combined organics were washed with a saturated aqueous solution of $NaHCO_3$, dried over magnesium sulphate and concentrated *in vacuo*. The crude oil was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether to afford oxoamide (±)-**15d** as a colorless gummy oil (213 mg, 71%).



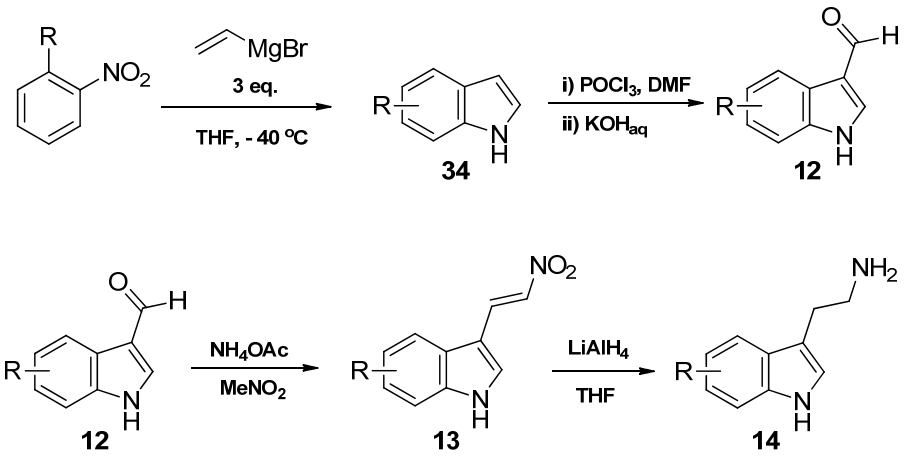
FT-IR ν_{max}(NaCl) 3305 cm^{-1} (N-H), 1666 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.23-1.36 (m, 1H, H-8a), 1.48-1.73 (m, 2H, H-9a, H-10a), 1.77-1.86 (m, 1H, H-10b), 1.95 (dd, 1H, H-

6a, *J* 14.5 Hz, 5.5 Hz), 2.01-2.14 (m, 2H, H-8b, H-9b), 2.21-2.39 (m, 2H, H-11), 2.55 (dd, 1H, H-6b, *J* 14.5 Hz, 7.5 Hz), 2.82-2.92 (m, 1H, H-7), 2.94 (t, 2H, H-3, *J* 7.0 Hz), 3.48-3.63 (m, 2H, H-4), 6.02 (br s, 1H, N-H amide), 7.01 (br s, 1H, H-1), 7.08-7.13 (m, 1H, H-15), 7.18 (t, 1H, H-16, *J* 7.5 Hz), 7.35 (d, 1H, H-17, *J* 7.5 Hz), 7.59 (d, 1H, H-14, *J* 7.5 Hz), 8.64 (br s, 1H, N-H indole); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 25.2 & 25.3 (C-3, C-12), 28.0 (C-9), 34.4 (C-8), 36.5 (C-6), 39.8 (C-4), 42.0 (C-11), 47.7 (C-7), 111.4 (C-17), 112.7 (C-2), 118.6 (C-14), 119.3 (C-15), 121.9 (C-16), 122.3 (C-1), 127.4 (C-13), 136.5 (C-18), 172.0 (C-5), 212.7 (C-12); ***m/z*** (ES−) 279 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}N_2ONa^+$) requires ***m/z*** 303.1468, found ***m/z*** 303.1467.

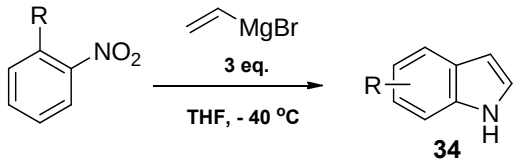
6.2.2.4 Site isolated polymer supported base-catalysed Michael addition / chiral phosphoric acid N-acyliminium cyclisation cascade

6.2.2.4.1 Preparation of starting materials

Preparation of substituted tryptamines 14



General procedure XXI for the preparation of substituted indoles



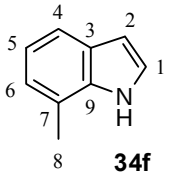
34

According to a modified literature procedure.[163]

The desired *ortho*-substituted nitro benzene substrate (1 equivalent) was dissolved in anhydrous tetrahydrofuran (4 mL per mmol of substrate) in a dry flask under nitrogen. The solution was cooled to − 40 ºC and a 1M solution of vinylmagnesium bromide in tetrahydrofuran was added quickly to the vigorously stirred solution, at − 40 ºC. The dark brown mixture was left stirring for 1 hour at − 40 ºC and then quenched by the addition of a saturated aqueous solution of ammonium chloride (at − 40 ºC, 3 mL per 1 mmol). The suspension was then allowed to warm to room temperature and stirred vigorously for 5 minutes. Ethyl acetate (2 mL per 1 mmol) was added and the organic layer separated. The aqueous layer was re-extracted with ethyl acetate (4 × 1 mL per 1 mmol). The combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. The brown residue was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 95:5 to 9:1.

Preparation and characterisation of 7-methyl-1*H*-indole 34f

The title compound was synthesised according to general procedure **XXI**, on a 90.0 mmol scale (12.4 g of 2-nitrotoluene) and isolated as a pale brown solid (4.0 g, 34%). Analytical data in agreement with the literature.[240]



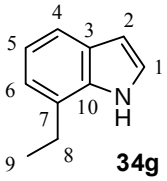
34f

m.p. 69-72 ºC (lit.[163] 80-82 °C); **FT-IR** ν_{max}(NaCl) 3402 cm^{-1} (N-H), 1590 cm^{-1} (ArC=C), 1340 cm^{-1} (CH_3), 782 cm^{-1} (ArC-H OOP), 722 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.28 (s, 3H, H-8), 6.52 (app. dd, 1H, H-2, *J* 3.0 Hz, 2.5 Hz), 6.81 (t, 1H, H-1, *J* 3.0 Hz), 7.00 (d, 1H, Ar-H, *J* 7.0 Hz), 7.09 (t, 1H, H-5, *J* 7.5 Hz), 7.45 (br s, 1H, NH), 7.54 (d, 1H, Ar-H, *J* 7.5 Hz); **^{13}C NMR**

($CDCl_3$, 100 MHz) δ_C 16.3 (C-8), 102.5 (C-2), 118.2 (Ar-CH), 119.8 (C-5), 120.2 (C-7), 122.2 (Ar-CH), 124.0 (C-1), 127.1 (C-3), 135.1 (C-9); ***m/z*** (ES−) 130 ($[M-H]^-$, 30%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_9H_8N^-$) requires ***m/z*** 130.0662, found ***m/z*** 130.0661.

Preparation and characterisation of 7-ethyl-1*H*-indole 34g

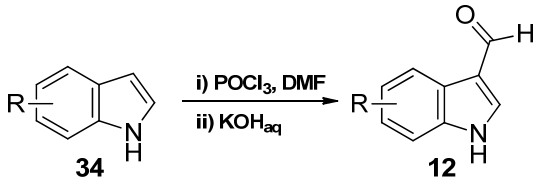
The title compound was synthesised according to general procedure **XXI**, on a 50.0 mmol scale (7.56 g of 1-ethyl-2-nitrobenzene) and isolated as a pale yellow oil (3.0 g, 41%). Analytical data in agreement with previous report.[241]



34g

FT-IR ν_{max}(NaCl) 3420 cm^{-1} (N-H), 2966 cm^{-1} (C-H), 1608 cm^{-1} (C=C), 1590 cm^{-1} (C=C), 1431 cm^{-1} (CH_2), 1342 cm^{-1} (CH_3), 728 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.49 (t, 3H, H-9, *J* 7.5 Hz), 2.93 (q, 2H, H-8, *J* 7.5 Hz), 6.72 (app. dd, 1H, H-2, *J* 3.0 Hz, 2.0 Hz), 7.17-7.23 (m, 2H, H-1, Ar-H), 7.28 (t, 1H, H-5, *J* 7.5 Hz), 7.70 (d, 1H, Ar-H, *J* 8.0 Hz), 7.98 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.7 (C-9), 23.9 (C-8), 102.8 (C-2), 118.3 (Ar-CH), 120.0 (C-5), 120.3 (Ar-CH), 123.8 (C-1), 126.4 (Ar-Cquat.), 127.5 (Ar-Cquat.), 134.5 (C-10); **HRMS** (CI+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}N^+$) requires ***m/z*** 146.0970, found ***m/z*** 146.0966.

General procedure XXII for the preparation of substituted indole-3-carbaldehydes 12



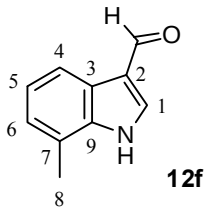
34 **12**

Phosphorus oxychloride (1.2 equivalents) was added dropwise to dimethyl formamide (4.4 equivalents) with ice-bath cooling. The mixture was stirred for 1.5 hours, then the chosen indole (1 equivalent) was added as a dimethyl formamide solution (0.5 mL per 1 mmol of indole). The mixture was then allowed to warm to room temperature and stirred for 10 minutes

(the mixture became a heavy suspension that required vigorous stirring). 3.8 M aqueous potassium hydroxide (10 equivalents) was added v*ia* a dropping funnel and after addition the mixture was heated to 105 ºC for 1 hour. It was cooled to room temperature before adding saturated aqueous ammonium chloride (5 mL per 1 mmol of indole) and ethyl acetate (10 mL per 1 mmol of indole). The aqueous layer was re-extracted with ethyl acetate (4 × 5 mL per 1 mmol of indole) and the combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to furnish the desired aldehyde that was further purified by column chromatography on short-path silica gel column.

Preparation and characterisation of 7-methyl-1*H*-indole-3-carbaldehyde 12f

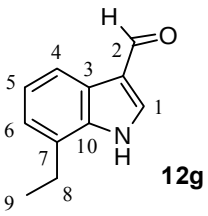
The title compound was prepared according to general procedure **XXII**, on a 30 mmol scale and isolated after chromatography eluting with dichloromethane/acetone 9:1 to 3:1 as a pale brown solid (82% yield, 3.91 g). Analytical data in agreement with the literature.[242]



12f

m.p. 209-211 ºC; **FT-IR** ν_{max}(NaCl) 3243 cm^{-1} (N-H), 3243 cm^{-1} (C=O), 1649 cm^{-1} (C=O); **^{1}H NMR** (d_6-acetone, 400 MHz) δ_H 2.54 (s, 3H, H-8), 7.09 (d, 1H, Ar-H, *J* 7.5 Hz), 7.16 (t, 1H, H-5, *J* 7.5 Hz), 8.07 (d, 1H, Ar-H, *J* 7.5 Hz), 8.16 (d, 1H, H-1, *J* 3.0 Hz), 10.03 (s, 1H, C(O)H), 11.18 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 100 MHz) δ_C 16.8 (C-8), 119.8 (Ar-CH), 120.5 (Ar-Cquat.), 122.4 (Ar-Cquat.), 123.3 (C-5), 125.1 (Ar-CH), 125.2 (Ar-Cquat.), 137.6 (C-1), 185.4 (C=O); ***m/z*** (ES−) 158 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{10}NO^+$) requires ***m/z*** 160.0757, found ***m/z*** 160.0758.

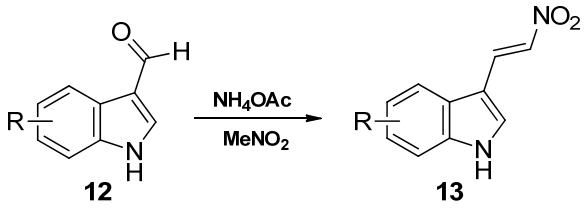
Preparation of 7-ethyl-1*H*-indole3-carbaldehyde 12g



12g

The title compound was prepared according to general procedure **XXII**, on a 17.2 mmol scale and used without further purification in the next reaction (3.50 g, 84% yield crude).

General procedure XXIII for the preparation of substituted indole nitro-olefins 13

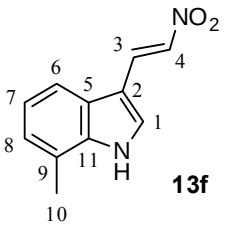


12 **13**

Indole-3-carbaldehyde **12** (1 equivalent) was suspended in nitromethane (2.5 mL per 1 mmol of aldehyde). Dry ammonium acetate (0.7 equivalents) was added to the vigorously stirred suspension. The mixture was heated at reflux for 1-5 hours (disappearance of the starting material monitored by ^{1}H NMR) and the reaction was stopped immediatedly after full consumption (to avoid Michael addition of nitromethane to the nitroolefin). The solvent was removed under reduced pressure and the residue partitioned between water (5 mL per 1 mmol) and ethyl acetate (20 mL per 1 mmol). The aqueous was re-extracted with ethyl acetate (4 × 10 mL per 1 mmol) and the combined organics dried over magnesium sulphate, filtered and concentrated *in vacuo*. The residue was purified by chromatography on short-path silica gel column.

Preparation and characterisation of 7-methyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole 13f

The title compound was synthesised according to general procedure **XXIII** on a 25 mmol scale and was obtained as an orange solid after purification by column chromatography on short-path silica gel column eluting with dichloromethane (4.85 g, 98%).

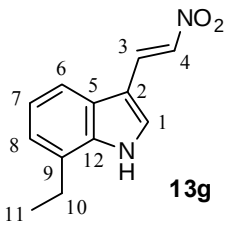


13f

m.p. 226-230 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3263 cm^{-1} (N-H), 1611 cm^{-1} (C=C), 1587 cm^{-1} (C=C), 1522 cm^{-1} (NO_2), 1301 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 400 MHz) δ_H 2.54 (s, 3H, H-10), 7.11 (d, 1H, Ar-H, *J* 7.0 Hz), 7.20 (t, 1H, H-7, *J* 7.5 Hz), 7.76 (d, 1H, Ar-H, *J* 8.0 Hz), 7.89 (d, 1H, H-4, *J* 13.5 Hz), 8.11 (d, 1H, H-1, *J* 3.0 Hz), 8.36 (d, 1H, H-3, *J* 13.5 Hz), 11.24 (br s, 1H, NH); **^{13}C NMR** (d_6-acetone, 100 MHz) δ_C 16.8 (C-10), 110.0 (C-2), 118.9 (C-6), 123.0 (Ar-Cquat.), 123.1 (C-7), 125.1 (C-8), 125.6 (Ar-Cquat.), 132.7 (C-4), 134.8 (C-3), 135.3 (C-1), 138.3 (C-11); ***m/z*** (ES+) 225 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{10}N_2O_2Na^+$) requires ***m/z*** 225.0634, found ***m/z*** 225.0636.

Preparation and characterisation of 7-ethyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole 13g

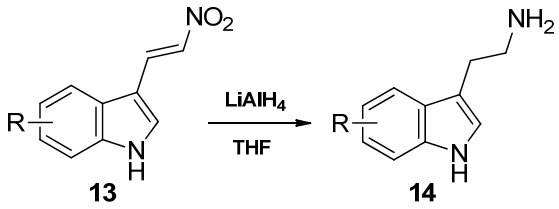
The title compound was synthesised according to general procedure **XXIII** on a 10 mmol scale (theoretical) and was obtained as an orange solid after purification by column chromatography on short-path silica gel column eluting with dichloromethane (2.50 g, 60% over 2 steps).



13g

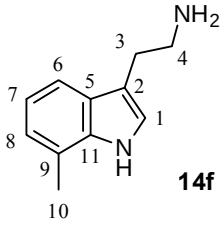
m.p. 203-206 ºC; **FT-IR** ν_{max}(NaCl) 3333 cm^{-1} (N-H), 1615 cm^{-1} (C=C), 1553 cm^{-1} (C=C), 1523 cm^{-1} (NO_2), 1302 cm^{-1} (NO_2); **^{1}H NMR** (d_4-MeOD, 500 MHz) δ_H 1.32 (t, 3H, H-11, *J* 7.5 Hz), 2.91 (q, 2H, H-10, *J* 7.5 Hz), 7.11 (d, 1H, H-8, *J* 7.5 Hz), 7.21 (t, 1H, H-7, *J* 7.5 Hz), 7.63 (d, 1H, H-6, *J* 8.0 Hz), 7.86 (d, 1H, H-4, *J* 13.0 Hz), 7.89 (app. s, 1H, H-1), 8.37 (d, 1H, H-3, *J* 13.0 Hz); **^{13}C NMR** (d_4-MeOD, 125 MHz) δ_C 14.9 (C-11), 25.0 (C-10), 110.4 (C-2), 118.9 (C-6), 123.5 (2 signals, C-7, C-8), 126.2 (C-5), 129.8 (C-9), 132.4 (C-4), 135.8 (2C, C-1, C-3), 138.0 (C-12); ***m/z*** (ES+) 239 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}N_2O_2Na^+$) requires ***m/z*** 239.0791, found ***m/z*** 239.0788.

Preparation of substituted tryptamines 14



According to general procedure **VIII**.

Preparation and characterisation of 2-(7-methyl-1*H*-indol-3-yl)ethanamine 14f

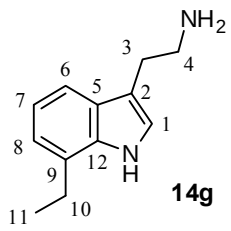


The title compound was synthesised according to general procedure **VIII** on a 24 mmol scale and was isolated as a brown gum that was used without further purification (4.40 g, 99%).

FT-IR ν_{max}(NaCl) 3338 cm^{-1} (N-H), 3286 cm^{-1} (N-H), 1588 cm^{-1} (C=C), 741 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 2.44 (s, 3H, H-10), 2.88 (br s, 4H, H-3, H-4), 6.84 (br s, 2H, 2 × Ar-H), 7.13 (br s, 1H, H-1), 7.35 (br s, 1H, Ar-H), 10.84 (br s, 1H, NH indole); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 16.8 (C-10), 27.7 (C-3), 41.8 (C-4), 112.3 (C-2), 116.0 (Ar-CH), 118.4 (Ar-CH), 120.5 (C-9), 121.4 (Ar-CH), 122.6 (C-1), 126.9 (C-5), 135.9 (C-11); ***m/z*** (ES−) 173 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{11}H_{13}N_2^-$) requires ***m/z*** 173.1084, found ***m/z*** 173.1077.

Preparation and characterisation of 2-(7-ethyl-1*H*-indol-3-yl)ethanamine 14g

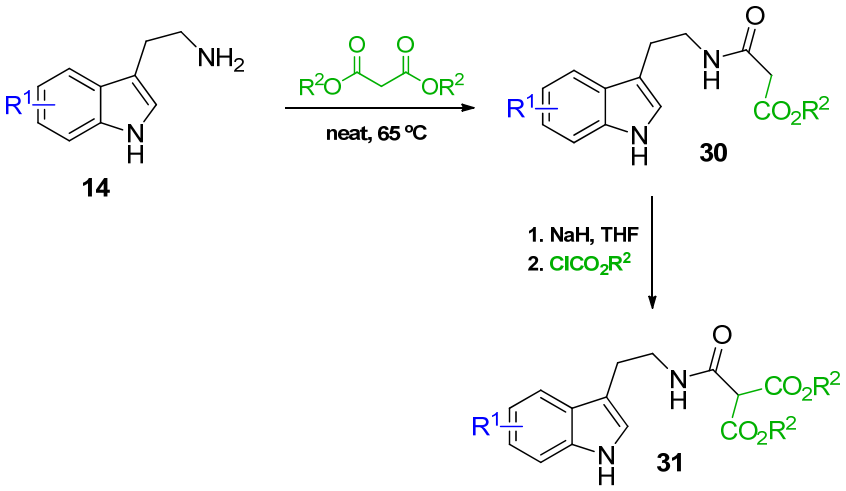
The title compound was synthesised according to general procedure **VIII** on a 11.6 mmol scale and was isolated as a pale brown solid that was used without further purification (2.20 g, 99%).



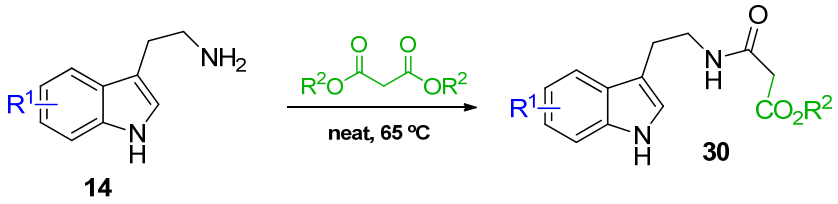
m.p. 203-205 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3398 cm^{-1} (N-H), 3282 cm^{-1} (N-H), 1586 cm^{-1} (C=C), 1473 cm^{-1} (CH_2), 743 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 1.26 (t, 3H, H-11, *J* 7.5 Hz), 2.86 (q, 2H, H-10, *J* 7.5 Hz), 3.07 (app. s, 4H, H-3, H-4), 6.88-6.98 (m, 2H, H-7, Ar-H), 7.24 (d, 1H, H-1, *J* 2.5 Hz), 7.42 (d, 1H, Ar-H, *J* 7.5 Hz), 11.05 (br s, 1H, NH

indole); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 14.5 (C-11), 23.3 (C-10), 23.8 (C-3), 39.3 (C-4), 110.1 (C-2), 115.9 (Ar-CH), 118.8 (Ar-CH), 118.9 (Ar-CH), 123.1 (C-1), 126.8 (Ar-Cquat.), 127.1 (Ar-Cquat.), 135.1 (C-12); ***m/z*** (ES−) 223 ($[M+Cl]^-$, 35%), **HRMS** (ES−) exact mass calculated for $[M+Cl]^-$ ($C_{12}H_{16}N_2Cl^-$) requires ***m/z*** 223.1007, found ***m/z*** 223.1001.

Preparation of pro-nucleophiles 31



General procedure XXIV for the preparation of malonate monoamide 30

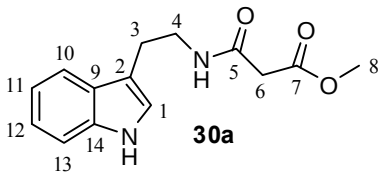


Prepared *via* a slight modification of a literature procedure.[164]

A tryptamine derivative **14** (1 equivalent) was suspended in the corresponding neat malonate (5 equivalents). The suspension was heated at 65 ºC for 48 to 96 hours. The brown viscous solution was loaded on silica gel and the mixture was eluted with petroleum ether/ethyl acetate to afford the desired dicarbonyl **30**.

Preparation and characterisation of methyl 3-{[2-(1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 30a

Synthesised according to general procedure **XXIV** on a 30 mmol scale of **14a** (4.8 g). Purified by column chromatography eluting with petroleum ether/ethyl acetate 2:1 to 2:3 to give the title compound as a pale yellow solid (5.75 g, 74%). Analytical data in agreement with the literature.[243]

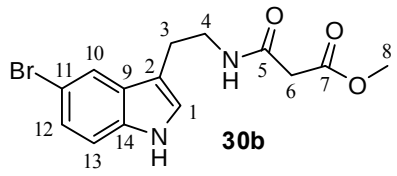


30a

m.p. 105-108 ºC; **FT-IR** ν_{max}(NaCl) 3353 cm^{-1} (br with shoulder, N-H), 1734 cm^{-1} (C=O ester), 1652 cm^{-1} (C=O amide), 742 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.29 (s, 2H, H-6), 3.65 (app. q, 2H, H-4, *J* 7.0 Hz), 3.70 (s, 3H, H-8), 7.04 (br s, 1H, NH amide), 7.08 (d, 1H, H-1, *J* 2.5 Hz), 7.14 (t, 1H, H-11, *J* 7.5 Hz), 7.22 (t, 1H, H-12, *J* 7.5 Hz), 7.39 (d, 1H, H-13, *J* 7.5 Hz), 7.62 (d, 1H, H-10, *J* 7.5 Hz), 8.09 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 25.1 (C-3), 40.0 (C-4), 41.2 (C-6), 52.3 (C-8), 111.3 (C-13), 112.6 (C-2), 118.6 (C-12), 119.3 (C-11), 122.0 (C-10), 122.1 (C-1), 127.3 (C-9), 136.4 (C-14), 164.9 (C-5), 169.7 (C-7); ***m/z*** (ES+) 283 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}N_2O_3Na^+$) requires ***m/z*** 283.1053, found ***m/z*** 283.1063.

Preparation and characterisation of methyl 3-{[2-(5-bromo-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 30b

Synthesised according to general procedure **XXIV** on a 8.4 mmol scale of **14c** (2.0 g). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to give the title compound as a pale yellow oil (2.0 g, 70%).



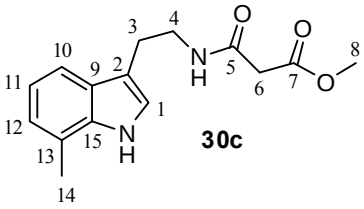
30b

FT-IR ν_{max}(NaCl) 3303 cm^{-1} (br with shoulder, N-H), 1738 cm^{-1} (C=O ester), 1654 cm^{-1} (C=O amide), 754

cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.95 (t, 2H, H-3, *J* 7.0 Hz), 3.30 (s, 2H, H-6), 3.60 (app. q, 2H, H-4, *J* 7.0 Hz), 3.70 (s, 3H, H-8), 7.06 (s, 1H, H-1), 7.15 (br s, 1H, NH amide), 7.24 (d, 1H, H-13, *J* 8.5 Hz), 7.27 (dd, 1H, H-12, *J* 8.5 Hz, 1.5 Hz), 7.72 (d, 1H, H-10, *J* 1.5 Hz), 8.33 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.9 (C-3), 39.9 (C-4), 40.9 (C-6), 52.4 (C-8), 112.6 & 112.7 (C-2 & C-11), 112.7 (Ar-CH), 121.3 (C-10), 123.3 (C-1), 124.9 (Ar-CH), 129.1 (C-9), 134.9 (C-14), 164.9 (C-5), 169.8 (C-7); ***m/z*** (ES−) 337, 339 ($[M-H]^-$, 100%, **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}N_2O_3BrNa^+$) requires ***m/z*** 361.0158, found ***m/z*** 361.0161.

Preparation and characterisation of methyl 3-{[2-(7-methyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 30c

Synthesised according to general procedure **XXIV** on a 10.0 mmol scale of **14f** (1.74 g). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:2 to give the title compound as a pale brown crystalline solid (1.9 g, 69%).

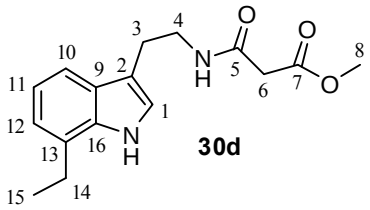


30c

m.p. 106-108 ºC; **FT-IR** ν_{max}(NaCl) 3387 cm^{-1} (N-H), 3301 cm^{-1} (N-H), 1739 cm^{-1} (C=O ester), 1656 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.49 (s, 3H, H-14), 3.01 (t, 2H, H-3, *J* 7.0 Hz), 3.25 (s, 2H, H-6), 3.63 (app. q, 2H, H-4, *J* 7.0 Hz), 3.69 (s, 3H, H-8), 7.00-7.15 (m, 4H, 3 × Ar-H, NH amide), 7.48 (d, 1H, Ar-H, *J* 7.5 Hz), 8.62 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.6 (C-14), 25.2 (C-3), 40.1 (C-4), 41.7 (C-6), 52.4 (C-8), 113.0 (C-2), 116.3 (Ar-CH), 119.6 (Ar-CH), 120.6 (C-13), 122.0 (Ar-CH), 122.6 (Ar-CH), 126.9 (C-9), 136.0 (C-15), 165.1 (C-5), 169.6 (C-7); ***m/z*** (ES+) 297 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_3Na^+$) requires ***m/z*** 297.1210, found ***m/z*** 297.1207.

Preparation and characterisation of methyl 3-{[2-(7-ethyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 30d

Synthesised according to general procedure **XXIV** on a 5.85 mmol scale of **14g** (1.1 g). Purified by column chromatography on silica gel eluting with diethyl ether to diethyl ether/ethyl acetate 3:1 to give the title product as a pale brown oil (1.2 g, 71%).

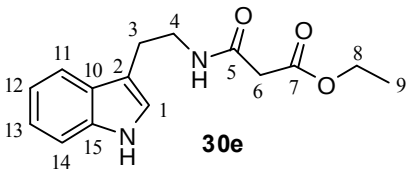


30d

FT-IR ν_{max}(NaCl) 3383 cm^{-1} (N-H), 3310 cm^{-1} (N-H), 1741 cm^{-1} (C=O ester), 1659 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.37 (t, 3H, H-15, *J* 7.5 Hz), 2.87 (q, 2H, H-14, *J* 7.5 Hz), 3.01 (t, 2H, H-3, *J* 7.0 Hz), 3.28 (s, 2H, H-6), 3.64 (app. q, 2H, H-4, *J* 6.5 Hz), 3.70 (s, 3H, H-8), 7.03-7.13 (m, 4H, H-1, 2 × Ar-H, NH amide), 7.47 (dd, 1H, Ar-H, *J* 7.5 Hz, 1.0 Hz), 8.28 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-15), 23.9 (C-14), 25.1 (C-3), 39.9 (C-4), 41.2 (C-6), 52.3 (C-8), 113.1 (C-2), 116.3 (Ar-CH), 119.7 (Ar-CH), 120.6 (Ar-CH), 121.7 (Ar-CH), 126.7 (Ar-Cquat.), 127.0 (Ar-Cquat.), 135.2 (C-13), 164.9 (C-5), 169.6 (C-7); ***m/z*** (ES−) 287 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}N_2O_3Na^+$) requires ***m/z*** 311.1366, found ***m/z*** 311.1366.

Preparation and characterisation of ethyl 3-{[2-(1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 30e

Synthesised according to general procedure **XXIV** on a 30 mmol scale of **14a** (4.8 g). Purified by column chromatography eluting with petroleum ether/ethyl acetate 2:1 to 1:2 to give the title product as a pale yellow oil (6.0 g, 73%). Analytical data in agreement with previous report.[243]



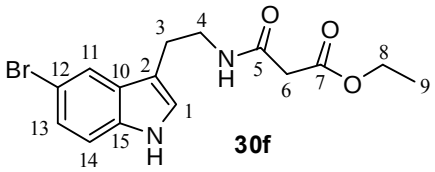
30e

FT-IR ν_{max}(NaCl) 3393 cm^{-1} (N-H), 3309 cm^{-1} (N-H), 1732 cm^{-1} (C=O ester), 1658 cm^{-1} (C=O amide), 746 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H

1.25 (t, 3H, H-9, *J* 7.0 Hz), 3.00 (t, 2H, H-3, *J* 7.0 Hz), 3.25 (s, 2H, H-6), 3.63 (app. q, 2H, H-4, *J* 7.0 Hz), 4.14 (q, 2H, H-8, *J* 7.0 Hz), 7.01 (s, 1H, H-1), 7.09-7.17 (m, 2H, H-12, NH amide), 7.20 (app. t, 1H, H-13, *J* 7.5 Hz), 7.36 (d, 1H, H-14, *J* 7.5 Hz), 7.61 (d, 1H, H-11, *J* 7.5 Hz), 8.56 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 (C-9), 25.0 (C-3), 39.9 (C-4), 41.3 (C-6), 61.4 (C-8), 111.2 (C-14), 112.4 (C-2), 118.4 (C-11), 119.1 (C-12), 121.8 (C-13), 122.1 (C-1), 127.1 (C-10), 136.3 (C-15), 165.2 (C-5), 169.1 (C-7); ***m/z*** (ES+) 129 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_3Na^+$) requires ***m/z*** 297.1210, found ***m/z*** 297.1211.

Preparation and characterisation of ethyl 3-{[2-(5-bromo-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 30f

Synthesised according to general procedure **XXIV** on a 10 mmol scale of **14c** (2.4 g). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 7:2 to 1:1 to give the title product as a pale yellow oil (2.03 g, 58%).

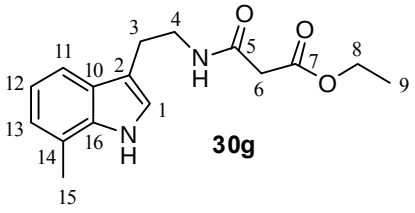


30f

FT-IR ν_{max}(NaCl) 3313 cm^{-1} (br with shoulder, N-H), 1725 cm^{-1} (C=O ester), 1653 cm^{-1} (C=O amide), 750 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.25 (t, 3H, H-9, *J* 7.0 Hz), 2.94 (t, 2H, H-3, *J* 7.0 Hz), 3.28 (s, 2H, H-6), 3.59 (app. q, 2H, H-4, *J* 7.0 Hz), 4.15 (q, 2H, H-8, *J* 7.0 Hz), 7.03 (d, 1H, H-1, *J* 2.0 Hz), 7.18-7.28 (m, 3H, H-13, H-14, NH amide), 7.71 (d, 1H, H-11, *J* 1.5 Hz), 8.49 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.0 (C-9), 24.9 (C-3), 39.9 (C-4), 41.1 (C-6), 61.5 (C-8), 112.5 & 112.6 (C-2 & C-12), 112.7 (Ar-CH), 121.2 (C-11), 123.3 (C-1), 124.8 (Ar-CH), 129.1 (C-10), 134.9 (C-15), 165.1 (C-5), 169.4 (C-7); ***m/z*** (ES−) 351, 353 ($[M-H]^-$, 100%, **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{17}N_2O_3BrNa^+$) requires ***m/z*** 375.0315 & 377.0295, found ***m/z*** 375.0316 & 377.0294.

Preparation and characterisation of ethyl 3-{[2-(7-methyl-1*H*-indol-3-yl)ethyl]amino}-3-oxopropanoate 30g

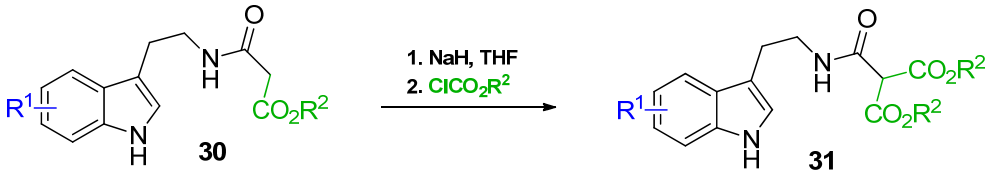
Synthesised according to general procedure **XXIV** on a 11.2 mmol scale of **14f** (1.95 g). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1 to give the title compound as an off-white solid (2.08 g, 64%).



30g

m.p. 82-84 ºC; **FT-IR** ν_{max}(NaCl) 3383 cm^{-1} (N-H), 3306 cm^{-1} (N-H), 1734 cm^{-1} (C=O ester), 1658 cm^{-1} (C=O amide), 750 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.26 (t, 3H, H-9, *J* 7.0 Hz), 2.49 (s, 3H, H-15), 3.00 (t, 2H, H-3, *J* 7.0 Hz), 3.27 (s, 2H, H-6), 3.64 (app. q, 2H, H-4, *J* 6.5 Hz), 4.15 (q, 2H, H-8, *J* 7.0 Hz), 6.99-7.09 (m, 3H, H-1, H-12, Ar-H), 7.12 (br s, 1H, N-H amide), 7.46 (d, 1H, Ar-H, *J* 8.0 Hz), 8.22 (br s, 1H, N-H indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 (C-9), 16.5 (C-15), 25.2 (C-3), 39.9 (C-4), 41.3 (C-6), 62.4 (C-8), 113.2 (C-2), 116.3 (Ar-CH), 119.6 (Ar-CH), 120.4 (C-14), 121.8 (Ar-CH), 122.6 (Ar-CH), 126.8 (C-10), 135.9 (C-16), 165.0 (C-5), 169.3 (C-7); ***m/z*** (ES−) 287 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}N_2O_3Na^+$) requires ***m/z*** 311.1366, found ***m/z*** 311.1367.

General procedure XXV for the preparation of pro-nucleophiles 31

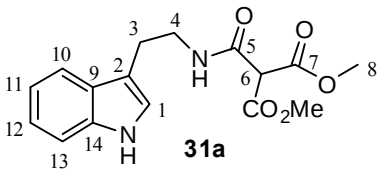


Sodium hydride (1 equivalent) was suspended in tetrahydrofuran (5 mL per 1 mmol of dicarbonyl), and the suspension was cooled to 0 ºC. Dicarbonyl **30** was added dropwise as a solution in tetrahydrofuran (2 mL per 1 mmol). The suspension was stirred for 1.5 hours at 0 ºC (it became clear meanwhile) and the relevant chloroformate was added in one portion to the

vigorously stirred mixture. The resulting solution was stirred for 1 hour at 0 ºC and further 30 minutes at room temperature. It was quenched with a saturated aqueous solution of ammonium chloride (3 mL per 1 mmol of substrate). The aqueous layer was diluted with water (3 mL per 1 mmol), and ethyl acetate was added (3 mL per 1 mmol). The layers were separated and the aqueous was re-extracted with ethyl acetate (2 × 3 mL per 1 mmol). The combined organics were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel eluting with petroleum ether / diethyl ether (see eluent conditions for each compound).

Preparation and characterisation of dimethyl {[2-(1*H*-indol-3-yl)ethyl] carbamoyl}malonate 31a

Synthesised according to general procedure **XXV** on a 22.1 mmol scale of **30a** (5.75 g). The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether and then diethyl ether/ethyl acetate 9:1 to give the title product as an off-white solid (2.96 g, 84%).

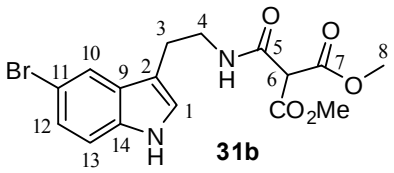


31a

m.p. 82-84 ºC; **FT-IR** ν_{max}(NaCl) 3389 cm^{-1} (N-H), 3321 cm^{-1} (N-H), 1740 cm^{-1} (C=O ester), 1663 cm^{-1} (C=O amide), 747 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.01 (t, 2H, H-3, *J* 7.0 Hz), 3.64 (app. q, 2H, H-4, *J* 7.0 Hz), 3.74 (s, 6H, H-8), 4.36 (s, 1H, H-6), 7.04 (d, 1H, H-1, *J* 2.5 Hz), 7.12 (ddd, 1H, H-11, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.20 (ddd, 1H, H-12, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.33-7.40 (m, 2H, H-13, NH amide), 7.61 (d, 1H, H-10, *J* 8.0 Hz), 8.44 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.8 (C-3), 40.2 (C-4), 53.3 (C-8), 58.6 (C-6), 111.2 (C-13), 112.2 (C-2), 118.5 (C-10), 119.2 (C-11), 121.9 (C-12), 122.3 (C-1), 127.1 (C-9), 136.3 (C-14), 161.9 (C-5), 165.9 (C-7); ***m/z*** (ES+) 341 ($[M+Na]^+$, 80%), 659 ($[2M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}N_2O_5Na^+$) requires ***m/z*** 341.1108, found ***m/z*** 341.1108.

Preparation and characterisation of dimethyl {[2-(5-bromo-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 31b

Synthesised according to general procedure **XXV** on a 2.2 mmol scale of **30b** (730 mg). The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether to give the title compound as a pale yellow oil (280 mg, 65%).

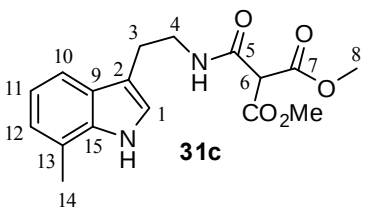


31b

FT-IR ν_{max}(NaCl) 3374 cm^{-1} (N-H), 3308 cm^{-1} (N-H), 1739 cm^{-1} (C=O ester), 1662 cm^{-1} (C=O amide), 756 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.96 (t, 2H, H-3, *J* 7.0 Hz), 3.62 (app. q, 2H, H-4, *J* 7.0 Hz), 3.76 (s, 6H, H-8), 4.35 (s, 1H, H-6), 7.07 (d, 1H, H-1, *J* 1.0 Hz), 7.26 (d, 1H, H-13, *J* 8.5 Hz), 7.27 (dd, 1H, H-12, *J* 8.5 Hz, 1.5 Hz), 7.39 (br s, 1H, NH amide), 7.72 (d, 1H, H-10, *J* 1.5 Hz), 8.30 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.8 (C-3), 40.2 (C-4), 53.4 (C-8), 58.5 (C-6), 112.3 (C-2), 112.7 (2C, C-11, Ar-CH), 121.2 (C-10), 123.5 (C-1), 124.9 (Ar-CH), 129.1 (C-9), 134.9 (C-14), 161.9 (C-5), 166.0 (C-7); ***m/z*** (ES−) 395, 397 ($[M-H]^-$, 90%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{17}N_2O_5BrNa^+$) requires ***m/z*** 419.0213 & 421.0193, found ***m/z*** 419.0211 & 421.0192.

Preparation and characterisation of dimethyl {[2-(7-methyl-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 31c

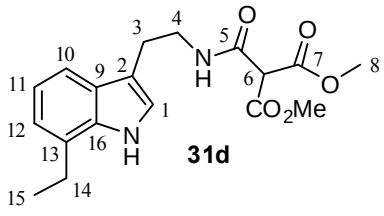
Synthesised according to general procedure **XXV** on a 7.3 mmol scale of **30c** (2.00 g). The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/diethyl ether 3:1 to 95:5 to give the title compound as a colourless crystalline solid (650 mg, 54% [92% brsm]).



m.p. 86-89 ºC; **FT-IR** ν_{max}(NaCl) 3385 cm^{-1} (N-H), 3313 cm^{-1} (N-H), 1739 cm^{-1} (C=O ester), 1664 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.49 (s, 3H, H-14), 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.65 (app. q, 2H, H-4, *J* 7.0 Hz), 3.76 (s, 6H, H-8), 4.35 (s, 1H, H-6), 7.00-7.10 (m, 3H, 3 × Ar-H), 7.31-7.38 (m, 1H, N-H amide), 7.47 (d, 1H, Ar-H, *J* 7.5 Hz), 8.16 (br s, 1H, N-H indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.6 (C-14), 25.1 (C-3), 40.3 (C-4), 53.4 (C-8), 58.7 (C-6), 113.0 (C-2), 116.4 (Ar-CH), 119.7 (Ar-CH), 120.5 (C-13), 122.0 (C-1), 122.6 (C-11), 126.8 (C-9), 136.0 (C-15), 161.8 (C-5), 166.1 (C-7); ***m/z*** (ES−) 331 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2O_5Na^+$) requires ***m/z*** 355.1264, found ***m/z*** 355.1264.

Preparation and characterisation of dimethyl {[2-(7-ethyl-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 31d

Synthesised according to general procedure **XXV** on a 3.82 mmol scale of **30d** (1.1 g). The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/diethyl ether 2:1 to 1:1 to give the title product as a pale yellow oil (0.44 g, 67%, 91% brsm).

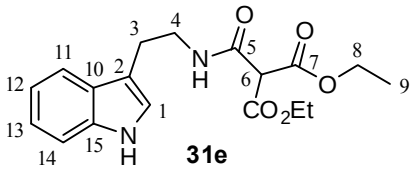


FT-IR ν_{max}(NaCl) 3384 cm^{-1} (N-H), 3324 cm^{-1} (N-H), 1740 cm^{-1} (C=O ester), 1663 cm^{-1} (C=O amide), 752 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.37 (t, 3H, H-15, *J* 7.5 Hz), 2.87 (q, 2H, H-14, *J* 7.5 Hz), 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.65 (app q, 2H, H-4, *J* 7.0 Hz), 3.75 (s, 6H, H-8), 4.36 (s, 1H, H-6), 7.03-7.13 (m, 3H, H-1, H-11, Ar-H), 7.34 (br s, 1H, NH amide), 7.48 (d, 1H, Ar-H, *J* 8.0 Hz), 8.17 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-15), 23.9 (C-14), 25.0 (C-3),

40.2 (C-4), 53.3 (C-8), 58.7 (C-6), 113.0 (C-2), 116.3 (Ar-CH), 119.7 (ArC-H), 120.6 (Ar-CH), 121.8 (Ar-CH), 126.6 (Ar-Cquat.), 126.9 (Ar-Cquat.), 135.2 (C-16), 161.8 (C-5), 166.0 (C-7); ***m/z*** (ES+) 369 ($[M+Na]^+$, 90%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2O_5Na^+$) requires ***m/z*** 369.1421, found ***m/z*** 369.1422.

Preparation and characterisation of diethyl {[2-(1*H*-indol-3-yl)ethyl]carbamoyl}malonate 31e

Synthesised according to general procedure **XXV** on a 10 mmol scale of **30e** (2.74 g). The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 5:1 to 3:2 to give the title compound as a pale yellow oil (860 mg, 50%).



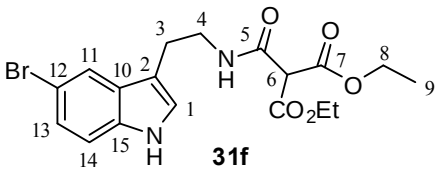
31e

FT-IR ν_{max}(NaCl) 3384 cm^{-1} (N-H), 3314 cm^{-1} (N-H), 1734 cm^{-1} (C=O ester), 1662 cm^{-1} (C=O amide), 746 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.26 (t, 6H, H-9, *J* 7.0 Hz), 3.02 (t, 2H, H-3, *J* 7.0 Hz), 3.65 (app. q, 2H, H-4, *J* 7.0 Hz), 4.22 (q, 4H, H-8, *J* 7.0 Hz), 4.32 (s, 1H, H-6), 7.06 (s, 1H, H-1), 7.13 (ddd, 1H, H-12, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.20 (ddd, 1H, H-13, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.35-7.43 (m, 2H, H-14, NH amide), 7.62 (d, 1H, H-11, *J* 8.0 Hz), 8.28 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-9), 24.9 (C-3), 40.2 (C-4), 59.1 (C-6), 62.5 (C-8), 111.2 (C-13), 112.5 (C-2), 118.6 (C-11), 119.3 (C-12), 122.0 (C-13), 122.2 (C-1), 127.2 (C-10), 136.3 (C-14), 162.1 (C-5), 165.6 (C-7); ***m/z*** (ES−) 345 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2O_5Na^+$) requires ***m/z*** 369.1421, found ***m/z*** 369.1421.

Preparation and characterisation of diethyl {[2-(5-bromo-1*H*-indol-3-yl)ethyl]carbamoyl}malonate 31f

Synthesised according to general procedure **XXV** on a 5.7 mmol scale of **30f** (2.0 g). The crude mixture was purified by column chromatography on silica gel eluting with petroleum

ether/diethyl ether 1:4 to diethyl ether to give the title product as a pale yellow oil (510 mg, 41%).

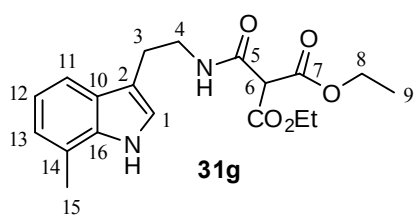


31f

FT-IR ν_{max}(NaCl) 3372 cm^{-1} (N-H), 3311 cm^{-1} (N-H), 1733 cm^{-1} (C=O ester), 1661 cm^{-1} (C=O amide), 755 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.26 (t, 6H, H-9, *J* 7.0 Hz), 2.95 (t, 2H, H-3, *J* 7.0 Hz), 3.61 (app. q, 2H, H-4, *J* 7.0 Hz), 4.21 (q, 4H, H-8, *J* 7.0 Hz), 4.31 (s, 1H, H-6), 7.06 (d, 1H, H-1, *J* 2.0 Hz), 7.23 (d, 1H, H-14, *J* 8.5 Hz), 7.25 (dd, 1H, H-13, *J* 8.5 Hz, 1.5 Hz), 7.44 (br s, 1H, NH amide), 7.71 (d, 1H, H-11, *J* 1.5 Hz), 8.43 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-9), 24.8 (C-3), 40.2 (C-4), 59.0 (C-6), 62.6 (C-8), 112.2 & 112.6 (C-2 & C-12), 112.7 (Ar-CH), 121.2 (C-11), 123.5 (C-1), 124.8 (Ar-CH), 129.0 (C-10), 134.9 (C-15), 162.2 (C-5), 165.6 (C-7); ***m/z*** (ES−) 423, 425 ($[M-H]^-$, 55%), 847, 849, 851 ($[2M-H]^-$, 50%, 100%, 50%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{21}N_2O_5BrNa^+$) requires ***m/z*** 447.0526 & 449.0506, found ***m/z*** 447.0524 & 449.0504.

Preparation and characterisation of diethyl {[2-(7-methyl-1*H*-indol-3-yl)ethyl] carbamoyl}malonate 31g

Synthesised according to general procedure **XXV** on a 7.2 mmol scale of **30g** (2.08 g). The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 1:4 to diethyl ether and then diethyl ether/ethyl acetate 4:1 to give the title compound as an off-white solid (1.0 g, 77%).

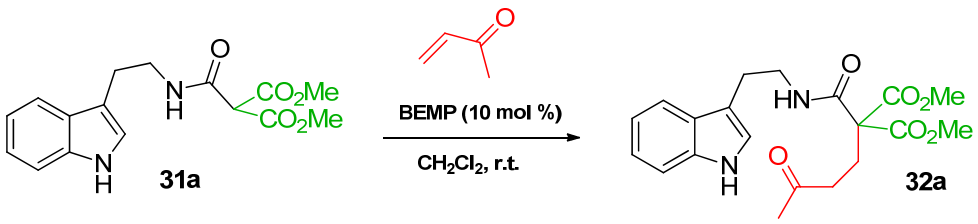


31g

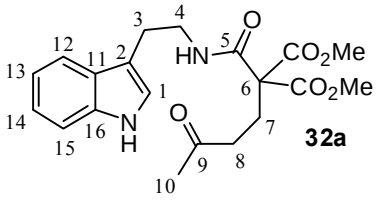
m.p. 83-87 ºC; **FT-IR** ν_{max}(NaCl) 3384 cm^{-1} (N-H), 3319 cm^{-1} (N-H), 1733 cm^{-1} (C=O ester), 1662 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.27 (t, 6H, H-9, *J* 7.0 Hz), 2.49 (s, 3H, H-15), 3.02 (t, 2H, H-3,

J 7.0 Hz), 3.65 (app. q, 2H, H-4, *J* 7.0 Hz), 4.22 (q, 4H, H-8, *J* 7.0 Hz), 4.32 (s, 1H, H-6), 6.99-7.10 (m, 3H, 3 × Ar-H), 7.35-7.42 (m, 1H, N-H amide), 7.48 (d, 1H, Ar-H, *J* 8.0 Hz), 8.17 (br s, 1H, N-H indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.9 (C-9), 16.6 (C-15), 25.2 (C-3), 40.2 (C-4), 59.1 (C-6), 62.6 (C-8), 113.1 (C-2), 116.4 (Ar-CH), 119.6 (Ar-CH), 120.4 (C-14), 122.0 (C-1), 122.6 (C-12), 126.8 (C-10), 136.0 (C-16), 162.1 (C-5), 165.7 (C-7); ***m/z*** (ES−) 359 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{24}N_2O_5Na^+$) requires ***m/z*** 383.1577, found ***m/z*** 383.1576.

Preparation and characterisation of dimethyl {[2-(1*H*-indol-3-yl)ethyl]carbamoyl}(3-oxobutyl)malonate 32a (substrate for optimisation)



Pro-nucleophile **31a** (520 mg, 1.63 mmol, 1 equivalent) was dissolved in dichloromethane (5 mL) and stirred vigorously at room temperature. Liquid BEMP (45 µL, 0.16 mmol, 0.1 equivalents) was added to the solution immediately followed by the addition of MVK (0.41 mL, 4.90 mmol, 3 equivalents). The mixture was left stirring at room temperature for 16 hours (completion confirmed by TLC and LC-MS). The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 4:1 to 1:2 to afford the title product as as colourless gum (420 mg, 84%).



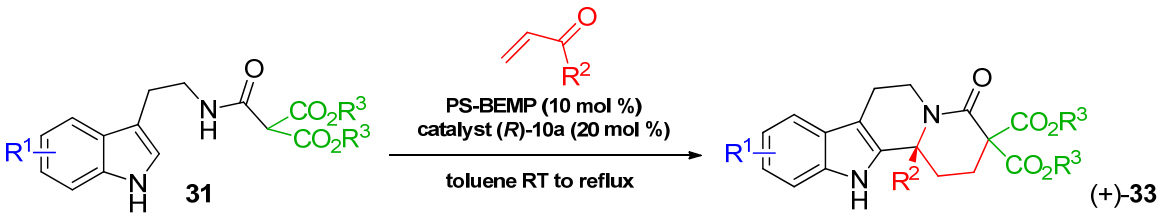
FT-IR ν_{max}(NaCl) 3386 cm^{-1} (N-H), 3352 cm^{-1} (N-H), 1731 cm^{-1} (C=O ester), 1659 cm^{-1} (C=O amide), 749 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.99 (s, 3H, H-10), 2.39 (t, 2H, H-7, *J* 7.5 Hz), 3.49 (t, 2H, H-8, *J* 7.5 Hz), 3.06 (t, 2H, H-3, *J* 7.0 Hz), 3.68-3.77 (m, 8H, H-4, 2 × CO_2CH_3), 7.09 (s, 1H, H-1), 7.14

(t, 1H, H-13, *J* 7.5 Hz), 7.21 (t, 1H, H-14, *J* 7.5 Hz), 7.39 (d, 1H, H-15, *J* 8.0 Hz), 7.65 (d, 1H, H-12, *J* 8.0 Hz), 8.16 (t, 1H, NH amide), 8.88 (br s, 1H, NH indole); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.7 (C-3), 28.1 (C-8), 29.4 (C-10), 38.2 (C-7), 39.8 (C-4), 53.0 ($CO_2\underline{C}H_3$), 62.8 (C-6), 111.1 (C-15), 111.8 (C-2), 118.3 (C-12), 118.9 (C-13), 121.6 (C-14), 122.2 (C-1), 127.0 (C-11), 136.2 (C-16), 165.6 (C-5), 168.9 (2 × C=O ester), 206.7 (C-9); ***m/z*** (ES−) 387 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{24}N_2O_6Na^+$) requires ***m/z*** 411.1527, found ***m/z*** 411.1527.

6.2.2.4.2 Procedure for the *N*-acyliminium cyclisation of 32a (optimisation study)

32a (19.9 mg, 0.1 mmol, 1 equivalent) was dissolved in toluene (14 mL). The stirred mixture was heated to reflux and the catalyst (*R*)-**6**, (*R*)-**7** or (*R*)-**10** was added (0.01 mmol, 0.1 equivalents). The mixture was heated at reflux for 16-48 hours (completion monitored by TLC and LC-MS (ES+)). The solvent was removed, the residue redissolved in the minimum amount of dichloromethane and the product purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1. The enantiomeric excess of the combined collected fractions was measured.

6.2.2.4.3 General procedure XXVI for the base-catalysed Michael addition / acid-catalysed enantioselective *N*-acyliminium cyclisation cascade



Pro-nucleophile **31** (0.2 mmol, 1 equivalent), PS-BEMP (0.02 mmol, 0.1 equivalents, 9.0 mg) and catalyst (*R*)-**10a** (0.04 mmol, 0.2 equivalents, 34.9 mg) were placed in a dry flask and dry toluene (28 mL) was added immediately followed by the addition of vinyl ketone (0.6 mmol, 3 equivalents) in one portion. The resulting suspension was stirred at room temperature until full

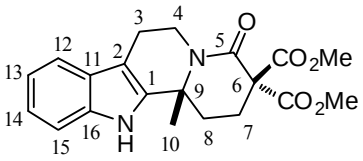
conversion to the Michael adduct (**32**) (LC-MS (ES+) monitoring). The mixture was then heated at reflux until full conversion to the tetracycle **33** (monitoring by LC-MS and TLC). The solvent was removed *in vacuo*, and the residue purified by column chromatography on silica gel.

Note: All racemates were prepared in a one pot procedure using BEMP (0.1 equivalents) followed by addition of *para*-toluenesulfonic acid (0.2 equivalents) when the Michael addition was complete.

Preparation and characterisation of dimethyl (12b*R*)-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33a

Prepared according to general procedure **XXVI**. Stirred at room temperature for 17 hours then heated at reflux in toluene for 36 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1 to afford the title product as an off-white solid (56 mg, 76%).

56% e.e. (Chiralcel OD, 85:15 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 16.7 min, minor t_R = 13.7 min); $[\alpha]_D^{25}$ = + 53.0 (c 1.0, $CHCl_3$).



(+)-**33a**

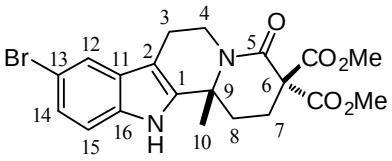
m.p. 232-237 ºC; **FT-IR** ν_{max}(NaCl) 3305 cm^{-1} (N-H), 1748 cm^{-1} (C=O ester), 1735 cm^{-1} (C=O ester), 1628 cm^{-1} (C=O amide), 749 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.73 (s, 3H, H-10), 2.00 (ddd, 1H, H-8a, *J* 14.0 Hz, 12.0 Hz, 3.0 Hz), 2.20 (ddd, 1H, H-8b, *J* 14.0 Hz, 6.0 Hz, 3.0 Hz), 2.55 (ddd, 1H, H-7a, *J* 14.0 Hz, 6.0 Hz, 3.5 Hz), 2.65 (ddd, 1H, H-7b, *J* 13.5 Hz, 12.0 Hz, 3.0 Hz), 2.76 (ddd, 1H, H-3a, *J* 15.5 Hz, 4.5 Hz, 1.5 Hz), 2.87 (ddd, 1H, H-3b, *J* 15.5 Hz, 11.5 Hz, 5.5 Hz), 3.12 (ddd, 1H, H-4a, *J* 12.5 Hz, 11.5 Hz, 4.5 Hz), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 5.09 (ddd, 1H, H-4b, *J* 12.5 Hz, 5.0 Hz, 1.0 Hz), 7.14 (app. td, 1H, H-13, *J* 7.5 Hz, 1.0 Hz), 7.21 (app. td, 1H,

H-14, *J* 7.5 Hz, 1.5 Hz), 7.35 (d, 1H, H-15, *J* 8.0 Hz), 7.51 (d, 1H, H-12, *J* 7.5 Hz), 7.79 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$:d_4-MeOD 19:1, 100 MHz) δ_C 21.0 (C-3), 25.0 (C-8), 26.5 (C-10), 31.7 (C-7), 37.6 (C-4), 53.2 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 57.7 (C-9), 63.5 (C-6), 107.4 (C-2), 111.0 (C-15), 118.1 (C-12), 119.2 (C-13), 121.7 (C-14), 126.3 (C-11), 136.3 (C-1), 137.4 (C-16), 163.4 (C-5), 168.4 ($\underline{C}O_2Me$), 168.7 ($\underline{C}O_2Me$); ***m/z*** (ES−) 369 ([M−H]$^-$, 80%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{20}H_{22}N_2O_5Na^+$) requires ***m/z*** 393.1421, found ***m/z*** 393.1420.

Preparation and characterisation of dimethyl (12b*R*)-9-bromo-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33b

Prepared according to general procedure **XXVI**. Stirred at room temperature for 48 hours then heated at reflux in toluene for 72 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 3:1 to 1:1 to afford the title product as an off-white solid (71 mg, 79%).

77% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 14.1 min, minor t_R = 43.8 min); $[\alpha]_D^{25}$ = + 41.1 (*c* 1.20, $CHCl_3$).



(+)-**33b**

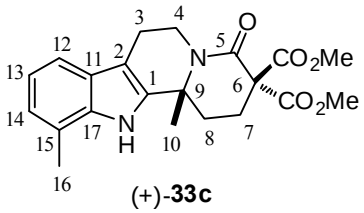
m.p. 241-247 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3291 cm^{-1} (N-H), 1748 cm^{-1} (C=O ester), 1735 cm^{-1} (C=O ester), 1628 cm^{-1} (C=O amide), 756 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$:d_4-MeOD 19:1, 400 MHz) δ_H 1.69 (s, 3H, H-10), 1.96 (ddd, 1H, H-8a, *J* 14.5 Hz, 12.5 Hz, 3.0 Hz), 2.25 (ddd, 1H, H-8b, *J* 14.0 Hz, 6.0 Hz, 3.0 Hz), 2.49 (ddd, 1H, H-7a, *J* 14.0 Hz, 6.0 Hz, 3.5 Hz), 2.60 (app. td, 1H, H-7b, *J* 13.0 Hz, 3.0 Hz), 2.68 (dd, 1H, H-3a, *J* 15.5 Hz, 3.5 Hz), 2.79 (ddd, 1H, H-3b, *J* 17.0 Hz, 11.5 Hz, 5.0 Hz), 3.08 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.0 Hz), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 3.80 (s, 3H, $CO_2C\underline{H}_3$), 5.02 (dd, 1H, H-4b, *J* 13.0 Hz, 4.5 Hz), 7.17 (d, 1H, H-15, *J* 8.5 Hz), 7.21 (dd, 1H, H-14, *J* 8.5 Hz,

1.5 Hz), 7.57 (d, 1H, H-12, *J* 1.5 Hz), 9.28 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.9 (C-3), 25.9 (C-7), 26.7 (C-10), 31.8 (C-8), 37.5 (C-4), 53.3 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 57.5 (C-9), 63.5 (C-6), 107.5 (C-2), 112.5 (C-15), 112.6 (C-13), 120.9 (C-12), 124.6 (C-14), 128.2 (C-11), 134.8 (C-16), 138.6 (C-1), 163.3 (C-5), 168.4 (CO_2Me), 168.6 (CO_2Me); ***m/z*** (ES+) 471, 473 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{22}N_2O_5Br^+$) requires ***m/z*** 449.0707 & 451.0687, found ***m/z*** 449.0703 & 451.0686.

Preparation and characterisation of dimethyl (12b*R*)-11,12b-dimethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33c

Prepared according to general procedure **XXVI**. Stirred at room temperature for 12 hours then heated at reflux in toluene for 72 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as an off-white solid (69 mg, 90%).

66% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 31.6 min, minor t_R = 25.6 min); $[\alpha]_D^{25}$ = + 56.5 (*c* 1.15, $CHCl_3$).



(+)-**33c**

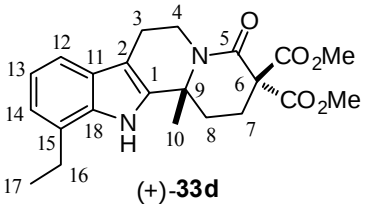
m.p. 216-223 ºC; **FT-IR** ν_{max}(NaCl) 3321 cm^{-1} (N-H), 1736 cm^{-1} (2 signals with a shoulder, 2 × CO_2Me), 1629 cm^{-1} (C=O amide), 750 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$:d_4-MeOD 9:1, 500 MHz) δ_H 1.77 (s, 3H, H-10), 2.02-2.11 (m, 1H, H-7a), 2.31-2.40 (m, 1H, H-7b), 2.50 (s, 3H, H-16), 2.56 (ddd, 1H, H-8a, *J* 13.5 Hz, 9.0 Hz, 3.0 Hz), 2.67 (app. td, 1H, H-8b, *J* 13.0 Hz, 2.5 Hz), 2.77 (dd, 1H, H-3a, *J* 16.0 Hz, 4.0 Hz), 2.89 (ddd, 1H, H-3b, *J* 16.0 Hz, 12.5 Hz, 5.5 Hz), 3.16 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.0 Hz), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 3.83 (s, 3H, $CO_2C\underline{H}_3$), 5.10 (dd, 1H, H-4b, *J* 12.5 Hz, 5.5 Hz), 7.02 (d, 1H, H-14, *J* 7.0 Hz), 7.08 (app. t, 1H, H-13, *J* 7.5 Hz), 7.37 (d, 1H, H-12, *J* 7.5 Hz), 8.39 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$:d_4-MeOD 9:1, 125 MHz) δ_C 16.6 (C-16), 21.2 (C-3), 25.2 (C-8),

26.9 (C-10), 31.9 (C-7), 37.5 (C-4), 53.2 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 57.6 (C-9), 63.5 (C-6), 108.7 (C-2), 115.9 (C-12), 119.9 (C-13), 120.4 (C-15), 122.8 (C-14), 126.1 (C-11), 135.6 (C-17), 137.0 (C-1), 163.2 (C-5), 168.4 ($\underline{C}O_2Me$), 168.6 ($\underline{C}O_2Me$); ***m/z*** (ES+) 407 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}N_2O_5Na^+$) requires ***m/z*** 407.1577, found ***m/z*** 407.1577.

Preparation and characterisation of dimethyl (12b*R*)-11-ethyl-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33d

Prepared according to general procedure **XXVI**. Stirred at room temperature for 24 hours then heated at reflux in toluene for 72 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as a pale yellow gum (50 mg, 63%).

68% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 23.1 min, minor t_R = 18.7 min); $[\alpha]_D^{25}$ = + 78.3 (*c* 1.50, $CHCl_3$).



(+)-**33d**

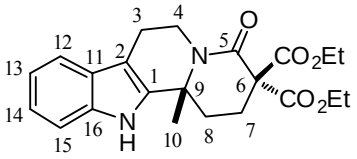
FT-IR ν_{max}(NaCl) 3325 cm^{-1} (N-H), 1749 cm^{-1} (C=O ester), 1736 cm^{-1} (C=O ester), 1630 cm^{-1} (C=O amide), 752 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.37 (t, 3H, H-17, *J* 7.5 Hz), 1.75 (s, 3H, H-10), 2.02 (app. td, 1H, H-8a, *J* 14.0 Hz, 3.0 Hz), 2.30 (ddd, 1H, H-8b, *J* 14.0 Hz, 6.0 Hz, 3.0 Hz), 2.56 (ddd, 1H, H-7a, *J* 14.0 Hz, 6.0 Hz, 3.5 Hz), 2.66 (ddd, 1H, H-7b, *J* 13.5 Hz, 12.5 Hz, 3.0 Hz), 2.76 (dd, 1H, H-3a, *J* 15.5 Hz, 3.5 Hz), 2.82-2.92 (m, 3H, H-3b, H-16), 3.13 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 5.09 (dd, 1H, H-4b, *J* 13.0 Hz, 4.5 Hz), 7.06 (d, 1H, H-12, *J* 7.5 Hz), 7.11 (app. t, 1H, H-13, *J* 7.5 Hz), 7.37 (d, 1H, H-14, *J* 7.5 Hz), 8.01 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-17), 21.3 (C-3), 23.9 (C-16), 25.2 (C-7), 27.0 (C-10), 32.2 (C-8), 37.6 (C-4), 53.4 ($CO_2\underline{C}H_3$), 53.5 ($CO_2\underline{C}H_3$), 57.6 (C-9), 63.6 (C-6),

109.1 (C-2), 116.2 (Ar-CH), 120.3 (C-13), 120.9 (Ar-CH), 126.5 (Ar-Cquat.), 134.9 (Ar-Cquat.), 136.9 (Ar-Cquat.), 163.2 (C-5), 168.5 (CO_2Me), 168.7 (CO_2Me); ***m/z*** (ES+) 421 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}N_2O_5Na^+$) requires ***m/z*** 421.1734, found ***m/z*** 421.1734.

Preparation and characterisation of diethyl (12b*R*)-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33e

Prepared according to general procedure **XXVI**. Stirred at room temperature for 17 hours then heated at reflux in toluene for 46 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as an off-white solid (69 mg, 86%).

67% e.e. (Chiralcel IA, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 26.3 min, minor t_R = 46.5 min); $[\alpha]_D^{25}$ = + 62.4 (*c* 1.76, $CHCl_3$).



(+)-**33e**

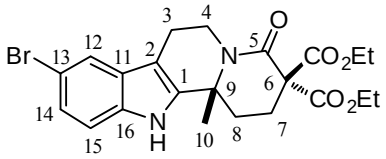
m.p. 93-98 ºC; **FT-IR** ν_{max}(NaCl) 3303 cm^{-1} (N-H), 1745 cm^{-1} (C=O ester), 1731 cm^{-1} (C=O ester), 1629 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.17 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.5 Hz), 1.32 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.5 Hz), 1.73 (s, 3H, H-10), 2.01 (app. td, 1H, H-8a, *J* 14.0 Hz, 3.0 Hz), 2.25 (ddd, 1H, H-8b, *J* 14.0 Hz, 6.0 Hz, 3.0 Hz), 2.53 (ddd, 1H, H-7a, *J* 13.5 Hz, 5.5 Hz, 3.0 Hz), 2.65 (app. td, 1H, H-7b, *J* 13.0 Hz, 3.0 Hz), 2.76 (ddd, 1H, H-3a, *J* 15.5 Hz, 4.0 Hz, 1.5 Hz), 2.87 (ddd, 1H, H-3b, *J* 15.5 Hz, 12.0 Hz, 5.5 Hz), 3.12 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 4.13-4.38 (m, 4H, 2 × $CO_2C\underline{H}_2CH_3$), 5.10 (dd, 1H, H-4b, *J* 13.0 Hz, 4.5 Hz), 7.13 (app. td, 1H, H-13, *J* 8.0 Hz, 1.0 Hz), 7.20 (app. td, 1H, H-14, *J* 8.0 Hz, 1.0 Hz), 7.34 (d, 1H, H-15, *J* 8.0 Hz), 7.50 (d, 1H, H-12, *J* 8.0 Hz), 8.02 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.8 ($CO_2CH_2\underline{C}H_3$), 13.9 ($CO_2CH_2\underline{C}H_3$), 21.2 (C-3), 25.1 (C-7), 26.9 (C-10), 32.0 (C-8), 37.6 (C-4), 57.5 (C-9), 62.3

($CO_2\underline{C}H_2CH_3$), 62.4 ($CO_2\underline{C}H_2CH_3$), 63.6 (C-6), 108.2 (C-2), 111.1 (C-15), 118.4 (C-12), 119.7 (C-13), 122.1 (C-14), 126.6 (C-11), 136.1 (C-16), 137.4 (C-1), 163.5 (C-5), 168.0 ($\underline{C}O_2Et$), 168.2 ($\underline{C}O_2Et$); ***m/z*** (ES−) 397 ($[M-H]^-$, 80%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{27}N_2O_5^+$) requires ***m/z*** 399.1914, found ***m/z*** 399.1913.

Characterisation of diethyl (12b*R*)-9-bromo-12b-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33f

Prepared according to general procedure **XXVI**. Stirred at room temperature for 31 hours then heated at reflux in toluene for 72 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as an off-white solid (86 mg, 90%).

82% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 30.3 min, minor t_R = 19.9 min); $[\alpha]_D^{25} = +43.5$ (*c* 1.08, $CHCl_3$).



(+)-**33f**

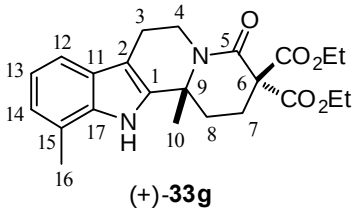
m.p. 186-190 ºC; **FT-IR** ν_{max}(NaCl) 3287 cm^{-1} (N-H), 1731 cm^{-1} (2 signals with shoulder, CO_2Me), 1628 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.16 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.30 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.74 (s, 3H, H-10), 1.94-2.04 (m, 1H, H-7a), 2.24-2.33 (m. 1H, H-7b), 2.52 (ddd, 1H, H-8a, *J* 13.5 Hz, 5.5 Hz, 3.0 Hz), 2.60-2.73 (m, 2H, H-3a, H-8b), 2.81 (ddd, 1H, H-3b, *J* 16.0 Hz, 12.0 Hz, 5.5 Hz), 3.05-3.15 (m, 1H, H-4a), 4.13-4.35 (m, 4H, 2 × $CO_2C\underline{H}_2CH_3$), 5.07 (dd, 1H, H-4b, *J* 13.0 Hz, 4.5 Hz), 7.18-7.27 (m, 2H, H-14, H-15), 7.60 (s, 1H, H-12), 8.76 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.8 & 13.9 (2 × $CO_2CH_2\underline{C}H_3$), 21.0 (C-3), 25.0 (C-8), 26.9 (C-10), 32.0 (C-7), 37.5 (C-4), 57.4 (C-9), 62.4 (2 signals, 2 × $CO_2C\underline{H}_2CH_3$), 63.6 (C-6), 108.0 (C-2), 112.6 (C-14), 112.9 (C-13), 121.1 (C-12), 124.9 (C-15), 128.4 (C-11), 134.8 (C-16), 138.7 (C-1), 163.5 (C-5), 167.9 ($\underline{C}O_2Et$), 168.1 ($\underline{C}O_2Et$); ***m/z*** (ES−) 475, 477 ($[M-H]^-$,

20%), 511, 513 ([M+Cl]$^-$, 40%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{22}H_{25}N_2O_5BrNa^+$) requires ***m/z*** 499.0839 & 501.0820, found ***m/z*** 499.0836 & 501.0814.

Characterisation of diethyl (12b*R*)-11,12b-dimethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33g

Prepared according to general procedure **XXVI**. Stirred at room temperature for 20 hours then heated at reflux in toluene for 60 hours. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:1 to afford the title product as an off-white solid (69 mg, 83%).

62% e.e. (Chiralcel AD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 19.6 min, minor t_R = 26.0 min); $[\alpha]_D^{25}$ = + 71.3 (*c* 2.23, $CHCl_3$).



(+)-**33g**

m.p. 101-106 ºC; **FT-IR** ν_{max}(NaCl) 3318 cm^{-1} (N-H), 1744 cm^{-1} (C=O ester), 1732 cm^{-1} (C=O ester), 1630 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.18 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.32 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.75 (s, 3H, H-10), 1.97-2.10 (m, 1H, H-8a), 2.32 (ddd, 1H, H-8b, *J* 14.0 Hz, 5.5 Hz, 2.5 Hz), 2.46-2.59 (m, 4H, H-16, H-7a), 2.66 (app. td, 1H, H-7b, *J* 13.5 Hz, 2.5 Hz), 2.75 (app. dd, 1H, H-3a, *J* 15.5 Hz, 3.5 Hz), 2.86 (ddd, 1H, H-3b, *J* 16.5 Hz, 11.5 Hz, 5.0 Hz), 3.12 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.0 Hz), 4.15-4.38 (m, 4H, 2 × $CO_2C\underline{H}_2CH_3$), 5.09 (dd, 1H, H-4b, *J* 12.5 Hz, 4.5 Hz), 7.00 (d, 1H, H-14, *J* 7.0 Hz), 7.07 (app. t, 1H, H-13, *J* 7.0 Hz), 7.36 (d, 1H, H-12, *J* 7.5 Hz), 8.11 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.8 ($CO_2CH_2\underline{C}H_3$), 13.9 ($CO_2CH_2\underline{C}H_3$), 16.7 (C-16), 21.2 (C-3), 25.1 (C-7), 27.0 (C-10), 32.1 (C-8), 37.5 (C-4), 57.5 (C-9), 62.2 ($CO_2\underline{C}H_2CH_3$), 62.3 ($CO_2\underline{C}H_2CH_3$), 63.6 (C-6), 108.9 (C-2), 116.1 (C-12), 120.0 (C-13), 120.2 (C-15), 122.8 (C-14), 126.2 (C-11), 135.6 (C-17), 137.1 (C-

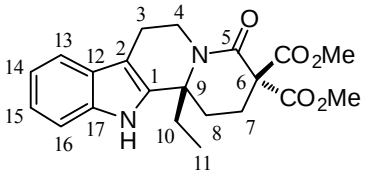
1), 163.4 (C-5), 167.9 (<u>C</u>O_2Et), 168.2 (<u>C</u>O_2Et); ***m/z*** (ES−) 411 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{23}H_{29}N_2O_5^+$) requires ***m/z*** 413.2071, found ***m/z*** 413.2074.

Characterisation of dimethyl (12b*R*)-12b-ethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33h

Prepared according to general procedure **XXVI**. <u>Remark</u>: xylene was used as solvent instead of toluene.

Stirred at room temperature for 48 hours then heated at reflux in xylene for 7 days. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as a pale yellow oil (64 mg, 83%).

71% e.e. (Chiralcel IA, 85:15 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 12.6 min, minor t_R = 21.6 min); $[\alpha]_D^{25}$ = + 78.9 (*c* 0.96, $CHCl_3$).



(+)-**33h**

FT-IR ν_{max}(NaCl) 3308 cm^{-1} (N-H), 1749 cm^{-1} (C=O ester), 1737 cm^{-1} (C=O ester), 1628 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.99 (t, 3H, H-11, *J* 7.5 Hz), 1.96-2.14 (m, 3H, H-8a, H-10), 2.22 (ddd, 1H, H-8b, *J* 13.5 Hz, 10.5 Hz, 3.0 Hz), 2.32 (ddd, 1H, H-7a, *J* 13.5 Hz, 10.5 Hz, 3.0 Hz), 2.51 (ddd, 1H, H-7b, *J* 13.5 Hz, 8.0 Hz, 3.0 Hz), 2.73 (dd, 1H, H-3a, *J* 15.5 Hz, 3.5 Hz), 2.97 (ddd, 1H, H-3b, *J* 15.5 Hz, 12.0 Hz, 6.0 Hz), 3.20 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 3.72 (s, 3H, $CO_2C\underline{H}_3$), 3.86 (s, 3H, $CO_2C\underline{H}_3$), 5.01 (dd, 1H, H-4b, *J* 13.0 Hz, 5.0 Hz), 7.13 (app. td, 1H, H-14, *J* 7.5 Hz, 1.0 Hz), 7.20 (app. td, 1H, H-15, *J* 7.5 Hz, 1.0 Hz), 7.35 (d, 1H, H-16, *J* 8.0 Hz), 7.51 (d, 1H, H-13, *J* 8.0 Hz), 8.15 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 8.7 (C-11), 20.8 (C-3), 25.0 (C-7), 27.8 (C-8), 33.4 (C-10), 37.4 (C-4), 53.3 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 61.3 (C-9), 63.8 (C-6), 109.3 (C-2), 111.0 (C-16), 118.4 (C-13), 119.8 (C-14), 122.2 (C-15), 126.9 (C-12), 135.1 (C-17), 136.5 (C-1), 164.4 (C-5), 168.3 (<u>C</u>O_2Me), 168.7 (<u>C</u>O_2Me);

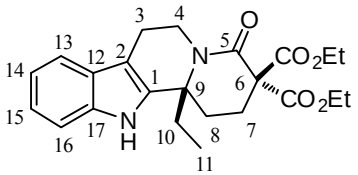
m/z (ES−) 383 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{21}H_{27}N_2O_5Na^+$) requires ***m/z*** 407.1577, found ***m/z*** 407.1576.

Characterisation of diethyl (12b*R*)-12b-ethyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33i

Prepared according to general procedure **XXVI**. Remark: xylene was used as solvent instead of toluene.

Stirred at room temperature for 48 hours then heated at reflux in xylene for 4 days. The crude mixture was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 2:1 to afford the title product as a pale yellow oil (60 mg, 73%).

76% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 8.1 min, minor t_R = 18.8 min); $[\alpha]_D^{25}$ = + 86.6 (*c* 1.12, $CHCl_3$).



(+)-**33i**

FT-IR ν_{max}(NaCl) 3308 cm^{-1} (N-H), 1746 cm^{-1} (C=O ester), 1733 cm^{-1} (C=O ester), 1629 cm^{-1} (C=O amide), 748 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.00 (t, 3H, H-11, *J* 7.5 Hz), 1.19 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.34 (t, 3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 1.94-2.13 (m, 3H, H-8a, H-10), 2.23 (ddd, 1H, H-8b, *J* 13.0 Hz, 10.0 Hz, 3.0 Hz), 2.31 (ddd, 1H, H-7a, *J* 13.0 Hz, 10.0 Hz, 3.0 Hz), 2.51 (ddd, 1H, H-7b, *J* 13.0 Hz, 8.5 Hz, 3.0 Hz), 2.72 (app. dd, 1H, H-3a, *J* 15.5 Hz, 4.0 Hz), 2.95 (ddd, 1H, H-3b, *J* 15.5 Hz, 12.0 Hz, 6.0 Hz), 3.18 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 4.14-4.22 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.30-4.36 (m, 2H, $CO_2C\underline{H}_2CH_3$), 5.02 (dd, 1H, H-4b, *J* 13.0 Hz, 5.0 Hz), 7.13 (app. td, 1H, H-14, *J* 7.5 Hz, 1.0 Hz), 7.20 (app. td, 1H, H-15, *J* 7.5 Hz, 1.0 Hz), 7.34 (d, 1H, H-16, *J* 8.0 Hz), 7.50 (d, 1H, H-13, *J* 8.0 Hz), 7.87 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 8.9 (C-11), 13.8 ($CO_2CH_2\underline{C}H_3$), 14.0 ($CO_2CH_2\underline{C}H_3$), 20.8 (C-3), 24.9 (C-7), 28.0 (C-8), 33.5 (C-10), 37.4 (C-4), 61.1 (C-9), 62.3 ($CO_2\underline{C}H_2CH_3$), 62.4 ($CO_2\underline{C}H_2CH_3$), 63.8 (C-6), 109.5 (C-

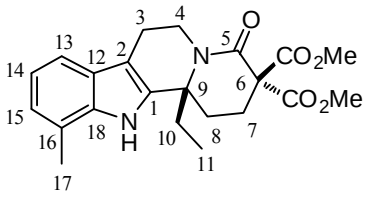
2), 110.9 (C-16), 118.4 (C-13), 119.8 (C-14), 122.2 (C-15), 126.9 (C-12), 135.8 (C-17), 136.6 (C-1), 164.4 (C-5), 167.8 ($\underline{C}O_2Et$), 168.3 ($\underline{C}O_2Et$); ***m/z*** (ES−) 411 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{23}H_{28}N_2O_5Na^+$) requires ***m/z*** 435.1890, found ***m/z*** 435.1891.

Characterisation of dimethyl (12b*R*)-12b-ethyl-11-methyl-4-oxo-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3,3(4*H*)-dicarboxylate (+)-33j

Prepared according to general procedure **XXVI**. Remark: xylene was used as solvent instead of toluene.

Stirred at room temperature for 48 hours then heated at reflux in xylene for 10 days. The crude mixture was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to 3:2 to afford the title product as a pale yellow oil (48 mg, 60%).

74% e.e. (Chiralcel AD, 80:20 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 7.8 min, minor t_R = 12.5 min); $[\alpha]_D^{25}$ = + 112.4 (*c* 1.40, $CHCl_3$).



(+)-**33j**

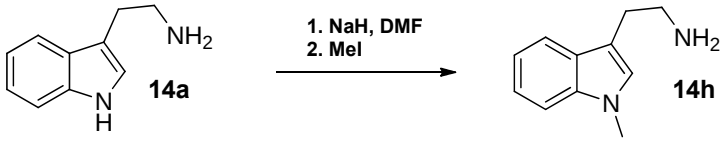
FT-IR ν_{max}(NaCl) 3327 cm^{-1} (N-H), 1748 cm^{-1} (C=O ester), 1737 cm^{-1} (C=O ester), 1629 cm^{-1} (C=O amide), 751 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.00 (t, 3H, H-11, *J* 7.5 Hz), 1.99 (dq, 1H, H-10a, *J* 14.5 Hz, 7.5 Hz), 2.06-3.14 (m, 2H, H-8a, H-10b), 2.23 (ddd, 1H, H-8b, *J* 13.5 Hz, 10.5 Hz, 3.0 Hz), 2.32 (ddd, 1H, H-7a, *J* 13.5 Hz, 10.5 Hz, 3.0 Hz), 2.47-2.55 (m, 4H, H-7b, H-17), 2.71 (dd, 1H, H-3a, *J* 15.5 Hz, 4.0 Hz), 2.97 (ddd, 1H, H-3b, *J* 15.5 Hz, 12.0 Hz, 6.0 Hz), 3.18 (app. td, 1H, H-4a, *J* 12.5 Hz, 4.5 Hz), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 3.87 (s, 3H, $CO_2C\underline{H}_3$), 5.01 (dd, 1H, H-4b, *J* 13.0 Hz, 5.5 Hz), 7.02 (d, 1H, H-15, *J* 7.5 Hz), 7.07 (t, 1H, H-14, *J* 7.5 Hz), 7.36 (d, 1H, H-13, *J* 8.0 Hz), 7.65 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 8.7 (C-11), 16.7 (C-17), 20.9 (C-3), 25.0 (C-7), 27.9 (C-8), 33.5 (C-10), 37.4 (C-4), 53.3 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 61.3 (C-9),

63.8 (C-6), 110.1 (C-2), 116.1 (C-13), 120.1 (2C, C-14, C-16), 123.0 (C-15), 126.5 (C-12), 135.3 (C-18), 136.2 (C-1), 164.3 (C-5), 168.3 ($\underline{C}O_2Me$), 168.7 ($\underline{C}O_2Me$); ***m/z*** (ES−) 397 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}N_2O_5Na^+$) requires ***m/z*** 421.1734, found ***m/z*** 421.1727.

6.2.3 Experimental for Chapter 4

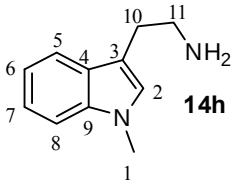
6.2.3.1 Synthesis of a methylated indole-tethered oxoamide

Preparation and characterisation of 2-(1-methyl-1*H*-indol-3-yl)ethanamine 14h



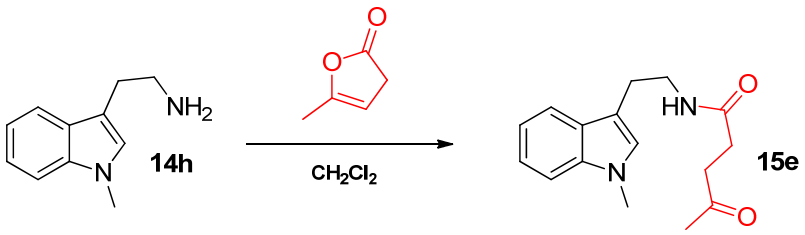
N-methyl tryptamine **14h** was synthesised according to a literature procedure.[165]

Sodium hydride (0.44 g, 11 mmol, 1.1 equivalents) was suspended in anhydrous DMF (30 mL). A solution of tryptamine (1,6 g, 10 mmol, 1 equivalent) in anhydrous DMF (20 mL) was added to the suspension, dropwise over 15 minutes. After addition, the mixture was stirred for 30 minutes at room temperature and then cooled to 0 ºC. Iodomethane (0.68 mL, 11 mmol, 1.1 equivalents) was added dropwise over 15 minutes. The ice-bath was removed and the mixture stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue partitioned between water (100 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous re-extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude oil was purified by column chromatography on silica gel eluting with dichloromethane/methanol/triethylamine 85:10:5 to afford the pure methylated tryptamine **14h** as a yellow oil (1.35 g, 77%). The spectral data were in agreement with the literature.[165]

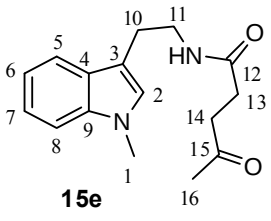


FT-IR ν_{max}(NaCl) 3443 cm^{-1} (N-H), 2976 cm^{-1} (C-H), 1615 cm^{-1} (C=C), 1474 cm^{-1}, 759 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 2.99-3.11 (m, 4H, H-10, H-11), 3.72 (s, 3H, H-1), 7.02-7.08 (m, 1H, H-6), 7.16 (app. td, 1H, H-7, *J* 7.5 Hz, 1.0 Hz), 7.20 (s, 1H, H-2), 7.38 (d, 1H, H-8, *J* 8.5 Hz), 7.59 (d, 1H, H-5, *J* 8.0 Hz); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 23.3 (C-10), 32.3 (C-1), 39.7 (C-11), 109.1 (C-3), 109.8 (C-8), 118.4 (C-5), 118.7 (C-6), 121.4 (C-7), 127.3 (C-4), 127.8 (C-2), 136.8 (C-9); **HRMS** (FI+) exact mass calculated for $[M]^+$ ($C_{11}H_{14}N_2^+$) requires ***m/z*** 174.1157, found ***m/z*** 174.1156.

Synthesis of *N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]-4-oxopentanamide 15e



N-Me tryptamine **14h** (500 mg, 2.87 mmol, 1 equivalent) was suspended in dichloromethane (10 mL) in a round-bottom flask, the suspension was stirred at room temperature and α-angelica lactone was added in one portion (336 µL, 3.74 mmol, 1.3 equivalents). The mixture was left stirring 5 hours at room temperature. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel, eluting with dichloromethane and then dichloromethane/acetone (9:1). The obtained pale brown solid was triturated in a mixture petroleum ether/diethyl ether 1:1 and filtered to give the pure title product as a colourless solid (180 mg, 23 %).

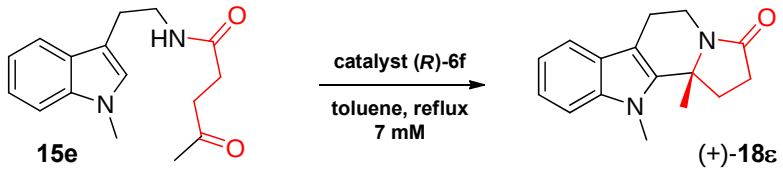


m.p. 76-78 ºC; **FT-IR** ν_{max}(NaCl) 3311 cm^{-1} (N-H), 1715 cm^{-1} (C=O ketone), 1649 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 2.18 (s, 3H, H-16), 2.37 (t, 2H, H-13, *J* 6.5 Hz), 2.79 (t, 2H, H-14, *J* 6.5 Hz), 2.96 (t, 2H, H-10, *J* 6.5 Hz), 3.58 (dd, 2H, H-

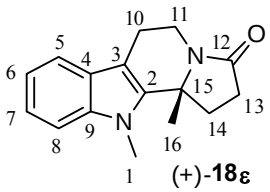
11, *J* 12.5 Hz, 6.5 Hz), 3.79 (s, 3H, H-1), 5.70 (br s, 1H, NH), 6.94 (s, 1H, H-2), 7.14 (ddd, 1H, H-6, *J* 8.0 Hz, 7.0 Hz, 1.5 Hz), 7.26 (ddd, 1H, H-7, *J* 8.0 Hz, 6.0 Hz, 1.0 Hz), 7.33 (app. dt, 1H, H-8, *J* 8.5 Hz, 1.0 Hz), 7.61 (app. dt, 1H, H-5, *J* 8.0 Hz, 1.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 25.2 (C-10), 29.9 (C-16), 29.9 (C-13), 32.7 (C-1), 38.5 (C-14), 39.9 (C-11), 109.3 (C-8), 111.4 (C-3), 118.8 (C-5), 118.9 (C-6), 121.7 (C-7), 127.0 (C-2), 127.8 (C-4), 137.1 (C-9), 171.7 (C-12), 207.8 (C-15); ***m/z*** (ES+) 295 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}N_2O_2Na^+$) requires ***m/z*** 295.1417, found ***m/z*** 295.1415.

6.2.3.2 N-acyliminium cyclisation of N-methylated oxoamide 15e

Synthesis and characterisation of (11b*R*)-11,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (+)-18ε



The catalyst (*R*)-**6f** (17.3 mg, 0.02 mmol, 0.1 equivalents) was suspended in toluene (30 mL). The mixture was heated to reflux, and the oxoamide substrate **15e** was added to the hot mixture (51.6 mg, 0.2 mmol, 1 equivalent). The solution was stirred vigorously at reflux for 2 hours. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 2:1 to 1:2 to afford the title product as a colourless gum (88-93% yield).



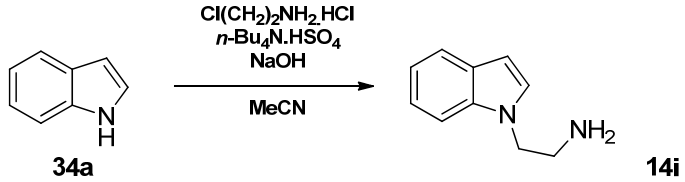
FT-IR ν_{max}(NaCl) 2973 cm^{-1} (ArC-H), 2925 cm^{-1} (Csp^3-H), 1682 cm^{-1} (C=O amide), 744 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.65 (s, 3H, H-16), 2.37 (app. q, 1H, H-14a, *J* 11.5 Hz), 2.45-2.57 (m, 2H, H-14b, H-13a), 2.72 (app. dddd, 1H, H-13b, *J* 17.0 Hz, 10.0 Hz, 8.0 Hz, 1.5 Hz), 2.80-2.90 (m, 2H, H-10), 3.05-3.14 (m, 1H, H-11a), 3.77 (s,

3H, H-1), 4.46-4.52 (m, 1H, H-11b), 7.14 (app. td, 1H, H-6, *J* 7.5 Hz, 0.5 Hz), 7.25 (app. td, 1H, H-7, *J* 7.5 Hz, 1.0 Hz), 7.31 (d, 1H, H-8, *J* 8.0 Hz), 7.50 (d, 1H, H-5, *J* 8.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 21.2 (C-10), 24.8 (C-16), 30.5 (C-13), 31.0 (C-1), 32.5 (C-14), 34.5 (C-11), 59.8 (C-15), 106.6 (C-3), 108.8 (C-8), 118.5 (C-5), 119.5 (C-6), 121.9 (C-7), 126.2 (C-4), 137.3 (C-9), 138.6 (C-2), 171.8 (C-12); ***m/z*** (ES+) 255 ($[M+H]^+$, 40%), 277 ($[M+Na]^+$, 50%), 531 ($[2M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}N_2ONa^+$) requires ***m/z*** 277.1311, found ***m/z*** 277.1316.

34% e.e. (Chiralcel AD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 11.0 min, minor t_R = 13.8 min); $[\alpha]_D^{25}$ = + 71.0 (*c* 1.28, $CHCl_3$).

6.2.3.3 Preparation and characterisation of N-[2-(1H-indol-1-yl)ethyl]-4-oxopentanamide 15f

Preparation and characterisation of 2-(1*H*-indol-1-yl)ethanamine 14i

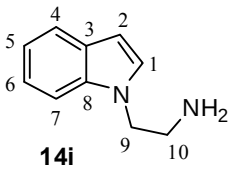


34a **14i**

Prepared according to a literature procedure.[166]

Indole (5.85 g, 50.0 mol, 1 equivalent), *n*-$Bu_4N.HSO_4$ (679 mg, 2 mmol, 0.04 equivalents) and sodium hydroxide (8.00 g, 200 mmol, 4 equivalents) were suspended in acetonitrile (175 mL). The suspension was stirred at room temperature and 2-chloroethanamine hydrochloride was added in one portion (6.38 g, 55 mmol, 1.1 equivalents). The mixture was heated at reflux for 16 hours. The mixture was allowed to cool to room temperature and the solid was filtered off. The clear solution was concentrated *in vacuo*. The residue was dissolved in dichloromethane (200 mL) and extracted with a 1M aqueous solution of HCl (5 × 75 mL). The organic layer was discarded and the combined aqueous layers were washed with dichloromethane (20 mL) and

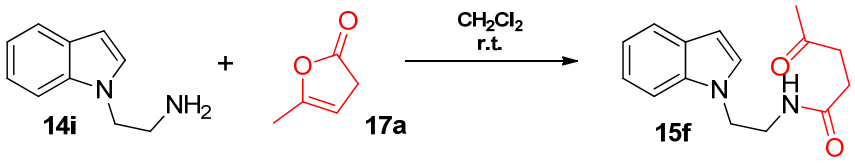
basified with potassium carbonate until pH > 10. The suspension was extracted with dichloromethane (4 × 75 mL). The combined organics were dried over potassium carbonate, filtered and concentrated under reduced pressure to give a pale brown gum (5.2 g, 65 %).



14i

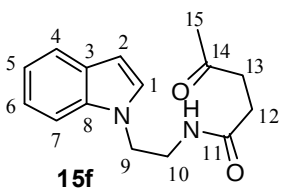
FT-IR ν_{max}(NaCl) 3367 cm^{-1} (N-H), 2934 cm^{-1} (C-H), 1611 cm^{-1} (C=C), 1589 cm^{-1} (C=C), 1463 cm^{-1}, 1314 cm^{-1}, 743 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.06 (br s, 2H, NH_2), 3.09 (t, 2H, H-9, *J* 6.0 Hz), 4.15 (t, 2H, H-10, *J* 6.0 Hz), 6.60 (d, 1H, H-2, *J* 3.0 Hz), 7.17 (d, 1H, H-1, *J* 3.0 Hz), 7.19-7.24 (m, 1H, H-5), 7.31 (t, 1H, H-6, *J* 7.5 Hz), 7.42 (d, 1H, H-7, *J* 8.5 Hz), 7.75 (d, 1H, H-4, *J* 8.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 42.1 (C-9), 49.7 (C-10), 101.4 (C-2), 109.5 (C-7), 119.5 (C-5), 121.1 (C-4), 121.6 (C-6), 128.2 (C-1), 128.8 (C-3), 136.1 (C-8); **HRMS** (FI+) exact mass calculated for $[M]^+$ ($C_{10}H_{12}N_2^+$) requires ***m/z*** 160.1000, found ***m/z*** 160.1001.

Preparation and characterisation of *N*-[2-(1*H*-indol-1-yl)ethyl]-4-oxopentanamide 15f



14i **17a** **15f**

2-(1*H*-Indol-1-yl)ethanamine **14i** (1.60 g, 10 mmol, 1 equivalent) was suspended in dichloromethane (10 mL) in a round-bottom flask, the suspension was stirred at room temperature and α-angelica lactone was added in one portion (900 µL, 10 mmol, 1 equivalent). The mixture was left stirring 12 hours at room temperature. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with petroleum ether/acetone (9:1 to 7:3) to give the title compound as a colourless solid (1.61 g, 62 %).



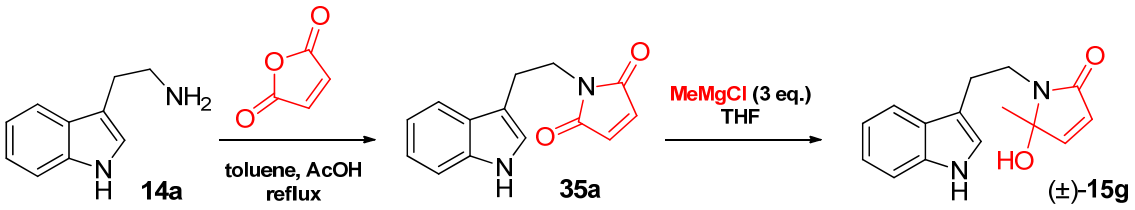
15f

m.p. 83-85 ºC; **FT-IR** ν_{max}(NaCl) 3307 cm^{-1} (N-H), 1714 cm^{-1} (C=O ketone), 1655 cm^{-1} (C=O amide); **^{1}H NMR** ($CDCl_3$, 400

MHz) δ_H 2.13 (s, 3H, H-15), 2.28 (t, 2H, H-12, *J* 6.5 Hz), 2.72 (t, 2H, H-13, *J* 6.5 Hz), 3.58 (app. q, 2H, H-10, *J* 6.0 Hz), 4.26 (t, 2H, H-9, *J* 6.0 Hz), 5.77 (br s, 1H, NH), 6.52 (d, 1H, H-2, *J* 3.0 Hz), 7.08-7.15 (m, 2H, H-1, H-5), 7.22 (ddd, 1H, H-6, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.35 (app. d, 1H, H-7, *J* 8.0 Hz), 7.63 (app. d, 1H, H-4, *J* 8.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 29.6 (C-12), 29.8 (C-15), 38.2 (C-13), 39.8 (C-10), 45.3 (C-9), 101.6 (C-2), 109.2 (C-7), 119.5 (C-5), 121.0 (C-4), 121.7 (C-6), 128.0 (C-1), 128.6 (C-3), 136.0 (C-8), 172.3 (C-11), 207.7 (C-14); ***m/z*** (ES+) 281 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_2Na^+$) requires ***m/z*** 281.1260, found ***m/z*** 281.1261.

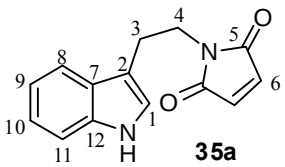
*6.2.3.4 Preparation of hydroxylactams **15g-i**[130]*

Preparation of 5-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (±)-15g



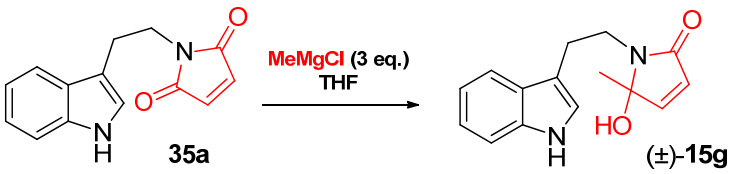
Prepared according to a modified literature procedure.[130]

Maleic anhydride (1.96 g, 20.0 mmol, 1 equivalent) was dissolved in glacial acetic acid/toluene (2:1, 60 mL). Tryptamine **14a** (3.20 g, 20.0 mmol, 1 equivalent) was added and the mixture stirred vigorously at room temperature. The mixture was heated at reflux for 6 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane afford the title product as a yellow solid (1.63 g, 34%). The spectral data were in agreement with the literature.[130,244]

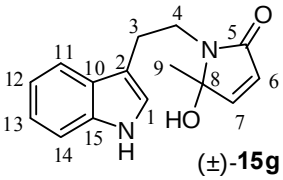


m.p. 110-114 ºC (lit.[244] 116-118 ºC); **FT-IR** ν_{max}(NaCl) 3387 cm^{-1} (N-H), 1700 cm^{-1} (C=O conjugated); **^{1}H NMR** ($CDCl_3$, 400 MHz)

δ_H 3.07 (t, 2H, H-3, *J* 7.5 Hz), 3.85 (t, 2H, H-4, *J* 7.5 Hz), 6.67 (s, 2H, H-6), 7.07 (s, 1H, H-1), 7.15 (app. t, 1H, H-9, *J* 7.0 Hz), 7.21 (app. t, 1H, H-10, *J* 7.5 Hz), 7.36 (d, 1H, H-11, *J* 8.0 Hz), 7.68 (d, 1H, H-8, *J* 8.0 Hz), 8.01 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.3 (C-3), 38.4 (C-4), 111.1 (C-11), 112.3 (C-2), 118.7 (C-8), 119.5 (C-9), 122.0 (C-1), 122.1 (C-10), 127.3 (C-7), 134.0 (C-6), 136.1 (C-12), 170.7 (C-5); ***m/z*** (ES−) 239 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{12}N_2O_2Na^+$) requires ***m/z*** 263.0791, found ***m/z*** 263.0793.

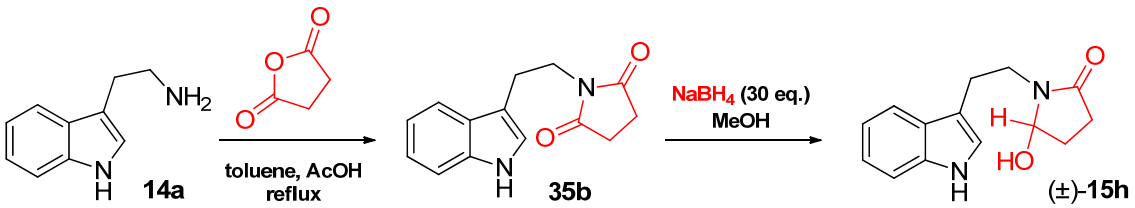


Maleimide **35a** (360 mg, 1.50 mmol, 1 equivalent) was dissolved in anhydrous tetrahydrofuran (150 mL) and stirred vigorously under nitrogen. It was cooled to − 78 ºC and a 3M solution of methylmagnesium chloride (1.1 mL, 3.3 mmol, 2.2 equivalents) was added in one portion at − 78 ºC. The mixture was stirred at − 78 ºC for 20 minutes (monitored by TLC). The cold bath was removed and the mixture immediately quenched by addition of a saturated aqueous solution of sodium bicarbonate (7.5 mL). The suspension was stirred for 3 minutes at room temperature and poured onto a biphasic mixture of dichloromethane (150 mL) and a saturated aqueous solution of $NaHCO_3$ (75 mL). The layers were separated and the aqueous re-extracted with dichloromethane (2 × 45 mL). The combined organics were dried over sodium sulphate, filtered and concentrated under reduced pressure to afford a pale yellow foamy solid that was purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/methanol 97:3 to give the title compound as a colourless foamy solid (265 mg, 69%). The spectral data were in agreement with the literature.[130]


(±)-15g

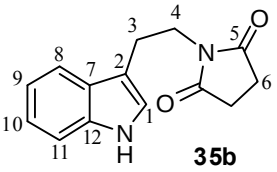
m.p. 102-106 ºC; **FT-IR** ν_{max}(NaCl) 3407 cm^{-1} & 3333 cm^{-1} (N-H / O-H), 1691 cm^{-1} (C=O conjugated); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 1.43 (s, 3H, H-9), 2.94-3.12 (m, 2H, H-3), 3.40-3.60 (m, 2H, H-4), 6.08 (d, 1H, H-6, *J* 6.0 Hz), 6.10 (s, 1H, OH), 7.00-7.08 (m, 2H, H-7, H-12), 7.11 (app. td, 1H, H-13, *J* 7.5 Hz, 1.0 Hz), 7.23 (d, 1H, H-1, *J* 2.0 Hz), 7.39 (d, 1H, H-14, *J* 8.0 Hz), 7.65 (d, 1H, H-11, *J* 7.5 Hz), 10.85 (br s, 1H, NH); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 23.5 (C-9), 24.9 (C-3), 38.8 (C-4), 89.2 (C-8), 111.5 (C-14), 111.9 (C-2), 118.3 (C-11), 118.4 (C-12), 121.0 (C-13), 122.8 (C-1), 125.0 (C-6), 127.3 (C-10), 136.3 (C-15), 151.7 (C-7), 168.6 (C-5); ***m/z*** (ES+) 279 ([M+Na]$^+$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{15}H_{16}N_2O_2Na^+$) requires ***m/z*** 279.1104, found ***m/z*** 279.1105.

Preparation of 5-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]pyrrolidin-2-one (±)-15h



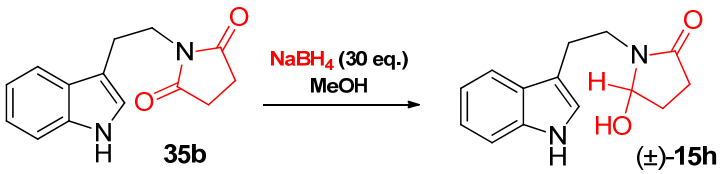
Prepared according to a modified literature procedure.[130]

Succinic anhydride (1.0 g, 10 mmol, 1 equivalent) was dissolved in glacial acetic acid (20 mL). Tryptamine **14a** (1.6 g, 10 mmol, 1 equivalent) was added and the mixture stirred vigorously at room temperature. DMAP (12 mg, 0.1 mmol, 0.01 equivalents) was added and the mixture was heated at reflux for 24 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/methanol 98:2 to afford the title compound as a pale brown crystalline solid (1.46 g, 60%). The spectral data were in agreement with the literature.[130]


35b

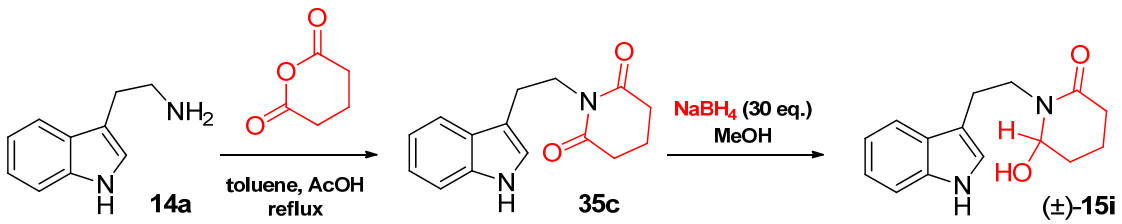
m.p. 167-170 ºC (lit.[245] 163-166 ºC); **FT-IR** ν_{max}(NaCl) 3363 cm^{-1} (N-H), 1693 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.62 (s,

4H, H-6), 3.04-3.09 (m, 2H, H-3), 3.81-3.86 (m, 2H, H-4), 7.09 (d, 1H, H-1, *J* 2.0 Hz), 7.14 (ddd, 1H, H-9, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.20 (ddd, 1H, H-10, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.34-7.38 (m, 1H, H-11), 7.68 (app. d, 1H, H-8, *J* 8.0 Hz), 8.09 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 23.3 (C-3), 28.1 (C-6), 39.5 (C-4), 111.1 (C-11), 112.1 (C-2), 118.6 (C-8), 119.5 (C-9), 122.1 & 122.1 (C-1, C-10), 127.1 (C-7), 136.1 (C-12), 177.3 (C-5); ***m/z*** (ES−) 241 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{14}N_2O_2Na^+$) requires ***m/z*** 265.0947, found ***m/z*** 265.0951.



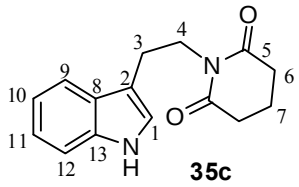
Succinimide **35b** (726 mg, 3.00 mmol, 1 equivalent) was suspended in anhydrous methanol (150 mL), the mixture was stirred vigorously under nitrogen. It was cooled to 0 ºC and $NaBH_4$ (3.41 g, 90.0 mmol, 30 equivalents) was added portionwise over 15 minutes at 0 ºC. The mixture was stirred at 0 ºC for 2 hours (monitored by TLC) and quenched by addition of a saturated aqueous solution of sodium bicarbonate (150 mL) at 0 ºC. The suspension was stirred for 2 minutes at room temperature and poured onto a biphasic mixture of dichloromethane (150 mL) and a saturated aqueous solution of $NaHCO_3$ (100 mL). The layers were separated and the aqueous re-extracted with dichloromethane (2 × 100 mL). The combined organics were dried over sodium sulphate, filtered and concentrated under reduced pressure to afford a foamy solid which was used without further purification for the cyclisation (550 mg, 75%).

Preparation of 6-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]piperidin-2-one (±)-15i



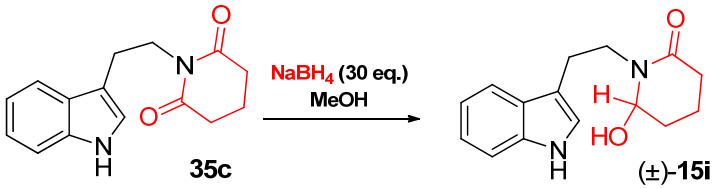
Prepared according to a modified literature procedure.[130]

Glutaric anhydride (1.14 g, 10.0 mmol, 1 equivalent) was dissolved in glacial acetic acid/toluene (2:1, 30 mL). Tryptamine **14a** (1.60 g, 10.0 mmol, 1 equivalent) was added and the mixture stirred vigorously at room temperature. The mixture was heated at reflux for 96 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/acetone 97:3 to afford the title product as an off-white crystalline solid (0.80 g, 31%). The spectral data were in agreement with the literature.[130]



35c

m.p. 172-176 ºC (lit.[246] 173-175 ºC); **FT-IR** ν_{max}(NaCl) 3331 cm^{-1} (N-H), 1666 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.87 (quint, 2H, H-7, *J* 6.5 Hz), 2.62 (t, 4H, H-6, *J* 6.5 Hz), 2.97-3.03 (m, 2H, H-3), 4.06-4.12 (m, 2H, H-4), 7.04 (d, 1H, H-1, *J* 1.5 Hz), 7.15 (app. td, 1H, H-10, *J* 7.5 Hz, 1.0 Hz), 7.20 (app. td, 1H, H-11, *J* 7.5 Hz, 1.0 Hz), 7.34 (app. d, 1H, H-12, *J* 7.5 Hz), 7.79 (app. d, 1H, H-9, *J* 7.5 Hz), 8.19 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 17.0 (C-7), 23.6 (C-3), 32.7 (C-6), 40.2 (C-4), 111.0 (C-12), 112.6 (C-2), 119.0 (C-9), 119.3 (C-10), 121.8 (C-11), 122.1 (C-1), 127.5 (C-8), 136.1 (C-13), 172.5 (C-5); ***m/z*** (ES+) 279 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{16}N_2O_2Na^+$) requires ***m/z*** 279.1104, found ***m/z*** 279.1105.



Glutarimide **35c** (128 mg, 0.50 mmol, 1 equivalent) was suspended in anhydrous methanol (25 mL), the mixture was stirred vigorously under nitrogen. It was cooled to 0 ºC and $NaBH_4$ (567 mg, 15.0 mmol, 30 equivalents) was added portionwise over 10 minutes at 0 ºC. The mixture was stirred at 0 ºC for 18 hours (monitored by TLC) and quenched by addition of a saturated

aqueous solution of sodium bicarbonate (25 mL) at 0 ºC. The suspension was stirred for 2 minutes at room temperature and poured onto a biphasic mixture of dichloromethane (25 mL) and a saturated aqueous solution of $NaHCO_3$ (25 mL). The layers were separated and the aqueous re-extracted with dichloromethane (2 × 20 mL). The combined organics were dried over sodium sulphate, filtered and concentrated under reduced pressure to afford a foamy solid that was used without purification in the cyclisation (125 mg, 97%).

*6.2.3.5 N-acyliminium cyclisation of oxoamide substrates and hydroxylactams **15g-i***

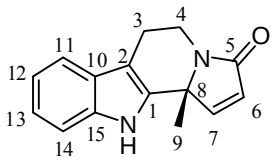
6.2.3.5.1 General procedure XXVII for the enantioselective cyclisation

Catalyst (*R*)-**6**, (*R*)-**7** or (*R*)-**10** (0.02 mmol, 0.1 equivalents) was suspended/dissolved in toluene (30 mL). The mixture was heated to reflux and the oxo amide/hydroxylactam substrate **15** was added to the hot mixture (0.2 mmol, 1 equivalent). The solution was heated at reflux for 2-16 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel.

Preparation and characterisation of (11b*R*)-methyl-5,6,11,11b-tetrahydro-3*H*-indolizino [8,7-*b*]indol-3-one (+)-18ζ

Prepared according to general procedure **XXVII** on a 0.19 mmol scale of (±)-**15g**. Heated at reflux for 16 hours in the presence of (*R*)-**6f**. Purified by column chromatography on silica gel eluting with dichloromethane to dichloromethane/acetone 85:15 to afford a colourless solid (19 mg, 40%). The spectral data were in agreement with the literature.[130]

17% e.e. (Chiralcel AD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 13.8 min, minor t_R = 32.0 min); $[\alpha]_D^{25}$ = + 45.0 (*c* 1.25, $CHCl_3$:MeOH 19:1) (lit.[130] 88% e.e. sample $[\alpha]_D^{25}$ = + 222.3 (*c* 0.75, $CHCl_3$).



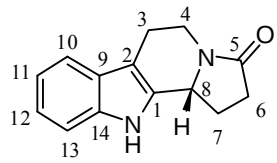
(+)-**18ζ**

m.p. 245-250 ºC; **FT-IR** ν_{max}(NaCl) 3253 cm^{-1} (N-H), 1664 cm^{-1} (C=O conjugated), 747 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.70 (s, 3H, H-9), 2.82 (ddd, 1H, H-3a, *J* 15.5 Hz, 5.0 Hz, 0.5 Hz), 2.90 (ddd, 1H, H-3b, *J* 15.5 Hz, 11.5 Hz, 6.5 Hz), 3.29 (ddd, 1H, H-4a, *J* 13.5 Hz, 11.5 Hz, 5.0 Hz), 4.62 (dd, 1H, H-4b, *J* 13.0 Hz, 6.0 Hz), 6.17 (d, 1H, H-6, *J* 5.5 Hz), 7.12 (ddd, 1H, H-12, *J* 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.19 (ddd, 1H, H-13, *J* 8.0 Hz, 7.5 Hz, 1.0 Hz), 7.34 (d, 1H, H-14, *J* 8.0 Hz), 7.42 (d, 1H, H-7, *J* 5.5 Hz), 7.49 (d, 1H, H-11, *J* 7.5 Hz), 8.61 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 21.9 (C-3), 24.5 (C-9), 35.6 (C-4), 64.3 (C-8), 107.7 (C-2), 111.0 (C-14), 118.8 (C-11), 119.9 (C-12), 122.5 (C-13), 126.0 (C-6), 126.6 (C-10), 133.8 (C-15), 136.2 (C-1), 151.3 (C-7), 171.1 (C-5); ***m/z*** (ES−) 237 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{15}N_2O^+$) requires ***m/z*** 239.1179, found ***m/z*** 239.1186.

Preparation and characterisation of (11b*R*)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (+)-18η

Prepared according to general procedure **XXVII** from (±)-**15i**. Heated at reflux for 2 hours in the presence of (*R*)-**10a**. Purified by column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 3:1 to afford a pale brown crystalline solid (19 mg, 42%). The spectra data were in agreement with the literature.[130]

39% e.e. (Chiralcel AD, 85:15 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 5.9 min, minor t_R = 8.4 min); $[\alpha]_D^{25}$ = + 56.3 (*c* 0.97, $CHCl_3$:MeOH 9:1) (lit.[130] 97% e.e. sample $[\alpha]_D^{25}$ = + 249.5 (*c* 1.00, $CHCl_3$)).



(+)-**18η**

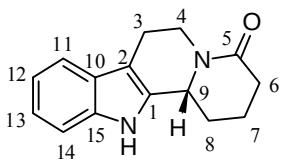
m.p. 250-252 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3255 cm^{-1} (N-H), 1667 cm^{-1} (C=O), 745 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 1.70-1.80 (m, 1H, H-7a), 2.19-2.27 (m, 1H, H-6a), 2.40-

2.54 (m, 2H, H-6b, H-7b), 2.59 (app. dddd, 1H, H-3a, *J* 13.0 Hz, 11.5 Hz, 6.0 Hz, 2.0 Hz), 2.70 (dd, 1H, H-3b, *J* 15.0 Hz, 4.5 Hz), 2.93 (app. td, 1H, H-4a, *J* 12.0 Hz, 4.5 Hz), 4.23 (dd, 1H, H-4b, *J* 13.0 Hz, 6.0 Hz), 4.86 (app. t, 1H, H-8, *J* 7.5 Hz), 6.93 (app. td, 1H, H-11, *J* 8.0 Hz, 0.5 Hz), 7.02 (app. td, 1H, H-12, *J* 8.0 Hz, 1.0 Hz), 7.29 (d, 1H, H-13, *J* 8.0 Hz), 7.35 (d, 1H, H-10, *J* 8.0 Hz), 10.99 (br s, 1H, NH); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 20.8 (C-3), 25.5 (C-7), 31.1 (C-6), 36.9 (C-4), 53.7 (C-8), 106.0 (C-2), 111.2 (C-13), 117.9 (C-10), 118.6 (C-11), 121.0 (C-12), 126.5 (C-9), 134.6 (C-1), 136.1 (C-14), 172.4 (C-5); ***m/z*** (ES−) 225 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{14}H_{14}N_2ONa^+$) requires ***m/z*** 249.0998, found ***m/z*** 249.0999.

Preparation and characterisation of (12b*R*)-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*] quinolizin-4(1*H*)-one (+)-19c

Prepared according to general procedure **XXVII** from (±)-**15i**. Heated at reflux for 18 hours in the presence of (*R*)-**10a**. Purified by column chromatography on silica gel eluting with dichloromethane/acetone 9:1 to 4:1 to afford a colourless solid (38 mg, 79%). The spectral data were in agreement with the literature.[130]

48% e.e. (Chiralcel AD, 90:10 hexane/isopropanol, 1 ml/min, 220 nm, major t_R = 13.8 min, minor t_R = 32.0 min); $[\alpha]_D^{25}$ = + 89.5 (*c* 0.62, $CHCl_3$) (lit.[130] 81% e.e. sample $[\alpha]_D^{25}$ = + 166.3 (*c* 0.96, $CHCl_3$).



(+)-**19c**

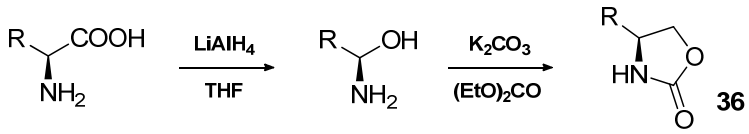
m.p. 219-224 ºC; **FT-IR** ν_{max}(NaCl) 3256 cm^{-1} (N-H), 1616 cm^{-1} (C=O), 741 cm^{-1} (ArC-H OOP); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.70-1.93 (m, 2H, H-7a, H-8a), 1.93-2.03 (m, 1H, H-7b), 2.36-2.52 (m, 2H, H-6a, H-8b), 2.60 (ddd, 1H, H-6b, *J* 16.5 Hz, 5.0 Hz, 2.5 Hz), 2.75-2.94 (m, 3H, H-3, H-4a), 4.75-4.84 (m, 1H, H-9), 5.14-5.24 (m, 1H, H-4b), 7.13 (app. td, 1H, H-12, *J* 7.0 Hz, 1.0 Hz), 7.19 (app. td, 1H, H-13, *J* 7.0 Hz, 1.0 Hz), 7.35 (d, 1H, H-14, *J*

8.0 Hz), 7.52 (d, 1H, H-11, *J* 8.0 Hz), 8.14 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 19.4 (C-7), 21.0 (C-3), 29.1 (C-8), 32.4 (C-6), 40.2 (C-4), 54.4 (C-9), 109.6 (C-2), 110.9 (C-14), 118.4 (C-11), 119.9 (C-12), 122.2 (C-13), 126.9 (C-10), 133.2 (C-1), 136.2 (C-15), 169.3 (C-5); ***m/z*** (ES−) 239 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{16}N_2ONa^+$) requires ***m/z*** 263.1155, found ***m/z*** 263.1163.

6.2.4 Experimental for Chapter 5

6.2.4.1 Synthesis of oxazolidinone-derived chiral benzenesulphonic acids

6.2.4.1.1 General procedure XXVIII for the synthesis of oxazolidinones 36



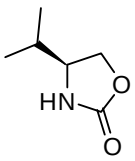
36

In a dry flask under nitrogen, lithium aluminium hydride (5.44 equivalents) was suspended in tetrahydrofuran (1.7 mL per mmol of amino acid). The suspension was cooled to 0 ºC by immersion in an ice-water bath, and the amino acid (1 equivalent) was added in small portions. Once all the amino acid was added, the suspension was stirred at 0 ºC for 15 minutes and then left at room temperature for 1 hour. The flask was then mounted with a condenser and the mixture was heated at reflux for 16 hours. The suspension was allowed to cool to room temperature. It was diluted with diethyl ether (1.5 mL per mmol of starting material amino acid) and the excess hydride was quenched by slow addition of sodium sulfate decahydrate (100 milligrams per mmol of amino acid) and stirred for 1 hour at room temperature. The suspension was then filtered through a pad of silica gel, washing thoroughly with ethyl acetate. The filtrate was concentrated *in vacuo* to afford the crude amino alcohol that was used in the next step without further purification.

In a round-bottom flask fitted up with a distillation apparatus, the crude amino alcohol (1 equivalent) was suspended/dissolved in diethyl carbonate (2 equivalents) at room temperature and potassium carbonate was added (0.1 equivalents). The resulting suspension was stirred vigorously and heated at 130 ºC for 4 hours to distill off the forming ethanol. It was then allowed to cool to room temperature and 50 mL of water were added. The biphasic mixture was extracted with dichloromethane (3 mL per mmol of substrate). The aqueous was extracted once more with dichloromethane (3 mL per mmol of substrate). The organics were combined and dried over magnesium sulphate and concentrated *in vacuo* to afford the crude oxazolidinone which was further purified by column chromatography on silica gel or by crystallisation.

Preparation and characterisation of (4*S*)-4-isopropyl-1,3-oxazolidin-2-one (*S*)-36a

Prepared according to general procedure **XXVIII** on 100 mmol of *L*-valine. The crude material was crystallised from a hot mixture of diethyl ether/petroleum ether 1:1 (120 mL) to afford (*S*)-**36a** as a pale yellow crystalline solid (7.20 g, 56% over 2 steps). Analytical data in agreement with the literature.[247]

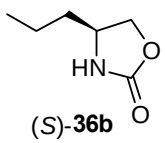


(*S*)-**36a**

m.p. 64-67 ºC; **FT-IR** ν_{max}(NaCl) 3270 cm^{-1} (N-H), 2963 cm^{-1} (C-H), 1751 cm^{-1} (C=O), 1245 cm^{-1} (C-O/C-N); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.90 (d, 3H, $C\underline{H}_3CH$, *J* 7.0 Hz), 0.96 (d, 3H, $CHC\underline{H}_3$, *J* 7.0 Hz), 1.68-1.78 (m, 1H, $(CH_3)_2C\underline{H}$), 3.57-3.65 (m, 1H, $NC\underline{H}$), 4.10 (dd, 1H, $OC\underline{H}_AH_B$, *J* 8.5 Hz, 6.5 Hz), 4.44 (t, 1H, $OCH_A\underline{H}_B$, *J* 8.5 Hz), 6.51 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 17.6 ($\underline{C}H_3$), 18.0 ($\underline{C}H_3$), 32.7 ($C\underline{H}(CH_3)_2$), 58.3 ($N\underline{C}H$), 68.6 ($O\underline{C}H_2$), 160.3 (C=O); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_6H_{15}N_2O_2^+$) requires ***m/z*** 147.1134, found ***m/z*** 147.1131; $[\alpha]_D^{25}$ = + 6.6 (*c* 1.0, $CHCl_3$) (lit.[247] $[\alpha]_D^{24}$ = + 8 (*c* 1.68, $CHCl_3$)).

Preparation and characterisation of (4*S*)-4-propyl-1,3-oxazolidin-2-one (*S*)-36b

Prepared according to general procedure **XXVIII** on 24.3 mmol of *L*-norvaline. The crude material was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 2:1 to 1:1 to afford (*S*)-**36b** as a pale yellow gum (2.80 g, 89% over 2 steps).

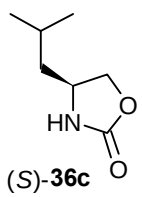


(*S*)-**36b**

FT-IR ν_{max}(NaCl) 3274 cm^{-1} (N-H), 2961 cm^{-1} (C-H), 1768 cm^{-1} (C=O), 1235 cm^{-1} (C-O/C-N); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.90-0.97 (m, 3H, CH_3), 1.21-1.44 (m, 2H, $CH_3C\underline{H}_2$), 1.45-1.64 (m, 2H, $CH_3CH_2C\underline{H}_2$), 3.81-3.91 (m, 1H, NC<u>H</u>), 4.00 (ddd, 1H, $OC\underline{H}_AH_B$, *J* 8.5 Hz, 6.0 Hz, 3.0 Hz), 4.41-4.51 (m, 1H, $OCH_A\underline{H}_B$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 ($\underline{C}H_3$), 18.6 ($CH_3\underline{C}H_2$), 37.4 ($CH_3CH_2\underline{C}H_2$), 52.3 (N<u>C</u>H), 70.4 (O<u>C</u>H$_2$), 160.4 (C=O); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_6H_{15}N_2O_2^+$) requires ***m/z*** 147.1134, found ***m/z*** 147.1128; $[\alpha]_D^{25} = +4.1$ (*c* 1.0, $CHCl_3$).

Preparation and characterisation of (4*S*)-4-isobutyl-1,3-oxazolidin-2-one (*S*)-36c

Prepared according to general procedure **XXVIII** on 40.0 mmol of *L*-leucine. The reduction of the amino acid afforded a yellow oil (4.70 g, quantitative - crude) which was used without purification in the next step. The oxazolidinone synthesis was carried out on 2.34 g of crude amino alcohol. After purification by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (1:1) and recrystallisation from 20 mL of ethyl acetate/petroleum ether 1:2 the title product was obtained as a colourless crystalline solid (1.10 g, 38% over two steps). Analytical data in agreement with the literature.[248]



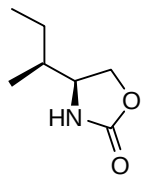
(*S*)-**36c**

m.p. 28-31 ºC; **FT-IR** ν_{max}(NaCl) 3278 cm^{-1} (NH), 2960 cm^{-1} (C-H aliph.), 1769 cm^{-1} (C=O), 1235 cm^{-1} (C-O / C-N); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.93 (app. t, 6H, $(C\underline{H}_3)_2CH$, *J* 6.0 Hz), 1.33-1.43 (m, 1H, $(CH_3)_2C\underline{H}$), 1.52-1.71 (m, 2H, $CHC\underline{H}_2CH$), 3.90-4.02 (m, 2H, $NHC\underline{H}C\underline{H}_AH_B$), 4.47-4.53 (m, 1H, $OCH_A\underline{H}_B$), 6.35 (br s, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 22.1 ($\underline{C}H_3$), 22.9 ($\underline{C}H_3$),

25.0 ((CH$_3$)$_2$CH), 44.4 (CHCH$_2$CH), 51.0 (NHCH), 70.7 (OCH$_2$), 160.3 (C=O); **HRMS** (CI+) exact mass calculated for [M+NH$_4$]$^+$ (C$_7$H$_{17}$N$_2$O$_2^+$) requires ***m/z*** 161.1290, found ***m/z*** 161.1283; $[\alpha]_D^{25} = -11.6$ (*c* 1.0, CHCl$_3$) (lit.[248] $[\alpha]_D^{16} = -11.6$ (*c* 1.0, CHCl$_3$)).

Preparation and characterisation of (4*S*)-4-[(2*S*)-butan-2-yl]-1,3-oxazolidin-2-one (*S*,*S*)-36d

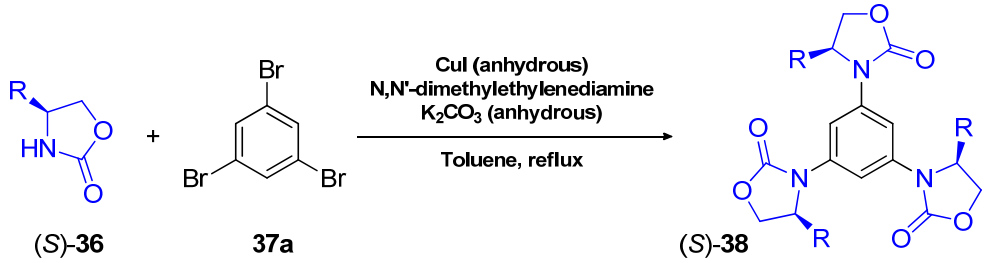
Prepared according to general procedure **XXVIII** on 40.0 mmol of L-isoleucine. The reduction of the amino acid afforded a pale yellow oil (3.80 g, 81% - crude) which was used without purification for the next step. The oxazolidinone synthesis was carried out on 2.34 g of crude amino alcohol. After purification by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (2:1 to 2:3) the title compound was obtained as a colourless crystalline solid (1.08 g, 38% over two steps). Analytical data in agreement with the literature.[247]



(*S*,*S*)-**36d**

m.p. 44-46 ºC; **FT-IR** ν_{max}(NaCl) 3278 cm^{-1} (N-H), 2969 cm^{-1} (C-H), 1769 cm^{-1} (C=O), 1235 cm^{-1} (C-O / C-N); **^{1}H NMR** (CDCl$_3$, 400 MHz) δ_H 0.88 (d, 3H, CH$_3$CH, *J* 6.5 Hz), 0.93 (t, 3H, CH$_3$CH$_2$, *J* 7.5 Hz), 1.08-1.22 (m, 1H, CH$_3$CH$_A$H$_B$), 1.43-1.60 (m, 2H, CH$_3$CH$_A$H$_B$, CH$_3$CH), 3.66-3.74 (m, 1H, NCH), 4.10 (dd, 1H, OCH$_A$H$_B$, *J* 8.5 Hz, 6.5 Hz), 4.43 (t, 1H, OCH$_A$H$_B$, *J* 8.5 Hz), 6.44 (br s, 1H, NH); **^{13}C NMR** (CDCl$_3$, 100 MHz) δ_C 11.0 (CH$_3$CH$_2$), 13.7 (CH$_3$CH), 25.1 (CH$_3$CH$_2$), 39.0 (CH$_3$CH), 57.1 (NCH), 68.4 (OCH$_2$), 160.3 (C=O); **HRMS** (CI+) exact mass calculated for [M+NH$_4$]$^+$ (C$_7$H$_{17}$N$_2$O$_2^+$) requires ***m/z*** 161.1290, found ***m/z*** 161.1289; $[\alpha]_D^{25} = +3.4$ (*c* 1.0, CHCl$_3$) (lit.[247] $[\alpha]_D^{27} = +6$ (*c* 6.50, CHCl$_3$).

6.2.4.1.2 General procedure XXIX for the preparation of C-3 symmetrical *N*-aryloxazolidinones (*S*)-38

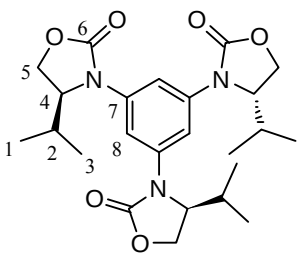


(*S*)-**36** **37a** (*S*)-**38**

1,3,5-Tribromobenzene **37a** (1 equivalent), potassium carbonate (4 equivalents), copper (I) iodide (1 equivalent) and an oxazolidinone (*S*)-**36** (4 equivalents) were placed in a dry flask and 2 sequences vacuum / nitrogen were applied. Under nitrogen, dry toluene was added (2 mL per mmol), and the suspension was stirred vigorously while *N*,*N'*-dimethylethylenediamine was added in one portion (1 equivalent). The resulting dark suspension was heated at reflux for 18 hours (turned blue after few minutes heating). When the conversion was not complete, another portion of copper (I) iodide (0.5 equivalents), oxazolidinone (1 equivalent) as well as amine (0.5 equivalents) was added, and the suspension heated at reflux for 4 to 24 hours. The mixture was allowed to cool to room temperature and purified by column chromatography on silica gel (the large amount of solid can be filtered on celite prior to purification, washing with ethyl acetate thoroughly).

Preparation and characterisation of (4*S*,4'*S*,4''*S*)-3,3',3''-benzene-1,3,5-triyltris(4-isopropyl-1,3-oxazolidin-2-one) (*S*)-38a

Prepared according to general procedure **XXIX** on a 3 mmol scale. Heated at reflux for 18 hours + 4 hours (with additional reagents). Purified on silica gel eluting with petroleum ether/ethyl acetate (1:1 to 2:3) to give the title product as a colourless crystalline solid (1.03 g, 75%). The product can be recystallised from dichloromethane/petroleum ether 1:2 to afford the analytically pure product (> 99% purity) as a crystalline solid (757 mg, 55%).

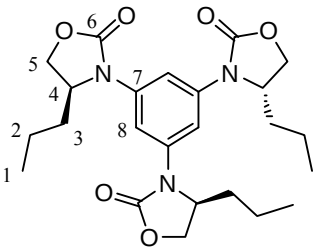


(*S*)-**38a**

m.p. 158-161 ºC; **FT-IR** ν_{max}(NaCl) 1745 cm^{-1} (C=O), 1603 cm^{-1} (C=C), 1473 cm^{-1} (CH_2), 1402 cm^{-1} & 1393 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.88 (d, 9H, 3 × C$\underline{H}_3$CH, *J* 7.0 Hz), 0.95 (d, 9H, 3 × CHC$\underline{H}_3$, *J* 7.0 Hz), 2.22 (td, 3H, H-2, *J* 7.0 Hz, 3.5 Hz), 4.27 (dd, 3H, H-5a, *J* 8.0 Hz, 3.5 Hz), 4.38-4.50 (m, 6H, H-4, H-5b), 7.62 (s, 3H, H-8); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.4 ($\underline{C}H_3$), 17.7 ($\underline{C}H_3$), 27.7 (C-2), 60.2 (C-4), 62.5 (C-5), 109.7 (C-8), 138.4 (C-7), 155.6 (C=O); ***m/z*** (ES+) 482 ([M+Na]$^+$, 100%), **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{24}H_{33}N_3O_6Na^+$) requires ***m/z*** 482.2262, found ***m/z*** 482.2262; $[\alpha]_D^{25}$ = + 101.4 (*c* 1.0, $CHCl_3$).

Preparation and characterisation of (4*S*,4'*S*,4''*S*)-3,3',3''-benzene-1,3,5-triyltris(4-propyl-1,3-oxazolidin-2-one) (*S*)-38b

Prepared according to general procedure **XXIX** on a 5.22 mmol scale. Heated at reflux for 30 hours. Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (1:1) and the recovered solid (1.55 g, 64%) was recrystallised from dichloromethane/petroleum ether (2:3) to give the analytically pure compound as a colourless crystalline solid (1.12 g, 46%).



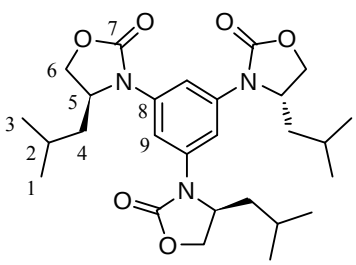
(*S*)-**38b**

m.p. 83-86 ºC; **FT-IR** ν_{max}(NaCl) 1746 cm^{-1} (C=O), 1603 cm^{-1} (C=C), 1471 cm^{-1} (CH_2), 1399 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.96 (t, 9H, H-1, *J* 7.5 Hz), 1.27-1.47 (m, 6H, H-2), 1.58-1.72 (m, 3H, H-3a), 1.76-1.87 (m, 3H, H-3b), 4.17 (dd, 3H, H-5a, *J* 8.0 Hz, 4.0 Hz), 4.41-4.49 (m, 3H, H-4), 4.49-4.56 (m, 3H, H-5b), 7.60 (s, 3H, H-8); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.8 (C-1), 17.4 (C-2), 33.8 (C-3), 55.9 (C-4), 66.9 (C-5), 108.2 (C-8), 138.4 (C-7), 155.7 (C=O); ***m/z*** (ES+) 482 ([M+Na]$^+$, 45%), 941 ([2M+Na]$^+$, 100%), **HRMS** (ES+) exact mass

calculated for $[M+Na]^+$ ($C_{24}H_{33}N_3O_6Na^+$) requires ***m/z*** 482.2262, found ***m/z*** 482.2255; $[\alpha]_D^{25} = +142.0$ (*c* 1.0, $CHCl_3$).

Preperation and characterisation of (4*S*,4'*S*,4''*S*)-3,3',3''-benzene-1,3,5-triyltris(4-isobutyl-1,3-oxazolidin-2-one) (*S*)-38c

Prepared according to general procedure **XXIX** on a 1.75 mmol scale. Heated at reflux for 24 hours. Purified by column chromatography on silica gel eluting with petroleum ether / ethyl acetate (1:1). The recovered solid was further purified by recrystallisation from ethyl acetate/petroleum ether (1:1) to give the analytically pure product as a colourless crystalline solid (630 mg, 72%).



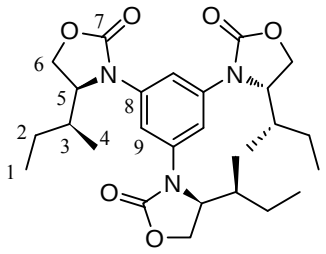
(*S*)-**38c**

m.p. 170-174 ºC; **FT-IR** ν_{max}(NaCl) 1754 cm^{-1} (C=O), 1603 cm^{-1} (C=C), 1471 cm^{-1} (CH_2), 1398 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.96 (d, 9H, 3 × C$\underline{H}_3$CH, *J* 6.5 Hz), 1.02 (d, 9H, 3 × CHC$\underline{H}_3$, *J* 6.5 Hz), 1.50-1.60 (m, 3H, H-4a), 1.62-1.74 (m, 3H, H-2), 1.79 (ddd, 3H, H-4b, *J* 13.0 Hz, 9.0 Hz, 1.5 Hz), 4.17 (dd, 3H, H-6a, *J* 8.0 Hz, 4.0 Hz), 4.47 (ddd, 3H, H-5, *J* 10.5 Hz, 7.5 Hz, 3.0 Hz), 4.53 (t, 3H, H-6b, *J* 8.0 Hz), 7.63 (s, 3H, H-9); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 21.7 ($\underline{C}H_3CH$), 23.6 ($CH\underline{C}H_3$), 24.8 (C-2), 40.7 (C-4), 54.9 (C-5), 67.3 (C-6), 107.3 (C-9), 138.5 (C-8), 155.2 (C=O); ***m/z*** (ES+) 519 ($[M+NH_4]^+$, 95%), 560 ($[M+CH_3CN+NH_4]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{27}H_{39}N_3O_6Na^+$) requires ***m/z*** 524.2731, found ***m/z*** 524.2735; $[\alpha]_D^{25} = +171.9$ (*c* 1.0, $CHCl_3$).

Characterisation of (4*S*,4'*S*,4''*S*)-3,3',3''-benzene-1,3,5-triyltris{4-[(2*S*)-butan-2-yl]-1,3-oxazolidin-2-one} (*S*)-38d

Prepared according to general procedure **XXIX** on a 1.4 mmol scale. Heated at reflux for 20 hours (complete conversion). Purified by column chromatography on silica gel eluting with

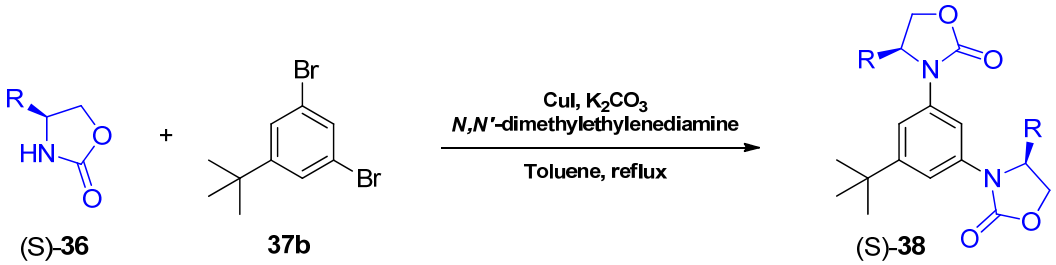
petroleum ether/ethyl acetate (3:2 to 2:3). The recovered solid was further purified by recrystallisation from ethyl acetate/petroleum ether (1:2) to give the analytically pure compound as a colourless crystalline solid (420 mg, 60%).



(*S*)-**38d**

m.p. 139-143 ºC; **FT-IR** ν_{max}(NaCl) 1748 cm^{-1} (C=O), 1603 cm^{-1} (C=C), 1472 cm^{-1} (CH_2), 1400 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.87 (d, 9H, H-4, *J* 7.0 Hz), 0.97 (t, 9H, H-1, *J* 7.5 Hz), 1.16-1.29 (m, 3H, H-2a), 1.29-1.40 (m, 3H, H-2b), 1.91-2.03 (m, 3H, H-3), 4.25 (dd, 3H, H-6a, *J* 9.0 Hz, 4.0 Hz), 4.41 (t, 3H, H-6b, *J* 9.0 Hz), 4.57 (dt, 3H, H-5, *J* 9.0 Hz, 4.0 Hz), 7.63 (s, 3H, H-9); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 11.8 (C-4), 11.9 (C-1), 25.3 (C-2), 34.3 (C-3), 59.0 (C-5), 62.5 (C-6), 109.4 (C-9), 138.3 (C-8), 155.7 (C=O); ***m/z*** (ES+) 519 ($[M+NH_4]^+$, 95%) 560 ($[M+CH_3CN+NH_4]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{27}H_{39}N_3O_6Na^+$) requires ***m/z*** 524.2731 found ***m/z*** 524.2737; $[\alpha]_D^{25}$ = + 121.1 (*c* 1.0, $CHCl_3$).

6.2.4.1.3 General procedure XXX for the preparation of C-2 symmetrical *N*-aryloxazolidinones (*S*)-38

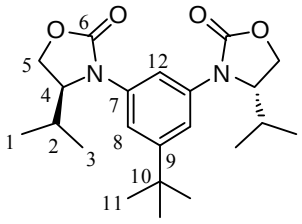


1,3-Dibromo-5-*tert*-butylbenzene **37b** (1 equivalent), potassium carbonate (3 equivalents), copper (I) iodide (1 equivalent) and an oxazolidinone (*S*)-**36** (3 equivalents) were placed in a dry flask, and 2 sequences vacuum / nitrogen were applied. Under nitrogen, dry toluene was added (2 mL per mmol) and the suspension was stirred vigorously while *N,N'*-

dimethylethylenediamine was added in one portion (1 equivalent). The resulting dark suspension was heated to reflux for 24 hours (turned blue after few minutes heating). The mixture was allowed to cool to room temperature and purified by column chromatography on silica gel (the large amount of solid can be filtered on celite prior to purification, washing with ethyl acetate thoroughly).

Preparation and characterisation of (4*S*,4'*S*)-3,3'-(5-*tert*-butyl-1,3-phenylene)bis(4-isopropyl-1,3-oxazolidin-2-one) (*S*)-38e

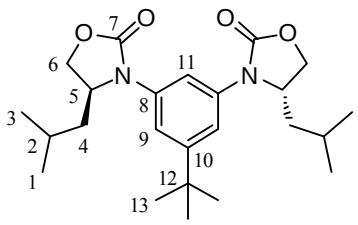
Prepared according to general procedure **XXX** on a 3.4 mmol scale. Heated at reflux for 18 hours. Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 to afford the title product as a colourless crystalline solid (1.09 g, 82%).



(*S*)-**38e**

m.p. 61-63 ºC; **FT-IR** ν_{max}(NaCl) 1746 cm^{-1} (C=O), 1601 cm^{-1} (C=C), 1457 cm^{-1} (CH_2), 1393 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.87 (d, 6H, 2 × C<u>H</u>$_3$CH, *J* 7.0 Hz), 0.92 (d, 6H, 2 × CHC<u>H</u>$_3$, *J* 7.0 Hz), 1.33 (s, 9H, H-11), 2.14 (sept d, 2H, H-2, *J* 7.0 Hz, 3.5 Hz), 4.21-4.29 (m, 2H, H-4), 4.38-4.46 (m, 4H, H-5), 7.35 (d, 2H, H-8, *J* 2.0 Hz), 7.37-7.41 (m, 1H, H-12); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.4 (<u>C</u>H$_3$CH), 17.7 (CH<u>C</u>H$_3$), 27.8 (C-2), 31.2 (C-11), 35.1 (C-10), 60.7 (C-4), 62.5 (C-5), 113.1 (C-12), 116.4 (C-8), 137.2 (C-7), 153.3 (C=O), 155.9 (C-9); ***m/z*** (ES+) 411 ([M+Na]$^+$, 40%), 799 ([2M+Na]$^+$), 100%, **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{22}H_{32}N_2O_4Na^+$) requires ***m/z*** 411.2254, found ***m/z*** 411.2252; $[\alpha]_D^{25}$ = + 71.7 (*c* 1.0, $CHCl_3$).

Preparation and characterisation of (4*S*,4'*S*)-3,3'-(5-*tert*-butyl-1,3-phenylene)bis(4-isobutyl-1,3-oxazolidin-2-one) (*S*)-38f



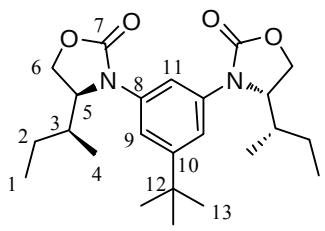
(*S*)-**38f**

Prepared according to general procedure **XXX** on a 1.63 mmol scale. Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 7:3 to 1:1 to afford the title product as a colourless crystalline solid (633 mg, 93%).

m.p. 138-141 ºC; **FT-IR** ν_{max}(NaCl) 1754 cm^{-1} (C=O), 1603 cm^{-1} (C=C), 1471 cm^{-1} (CH_2), 1398 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.94 (d, 6H, 2 × C$\underline{H}_3$CH, *J* 6.5 Hz), 0.98 (d, 6H, 2 × CHC$\underline{H}_3$ *J* 6.5 Hz), 1.33 (s, 9H, H-13), 1.51 (ddd, 2H, H-4a, *J* 13.0 Hz, 10.0 Hz, 4.5 Hz), 1.56-1.68 (m, 2H, H-2), 1.73 (ddd, 2H, H-4b, *J* 13.0 Hz, 10.0 Hz, 3.0 Hz), 4.13 (dd, 2H, H-6a, *J* 8.0 Hz, 5.0 Hz), 4.45 (dddd, 2H, H-5, *J* 10.0 Hz, 8.0 Hz, 5.0 Hz, 3.0 Hz), 4.55 (t, 2H, H-6b, *J* 8.0 Hz), 7.25 (d, 2H, H-9, *J* 2.0 Hz), 7.54 (t, 1H, H-11, *J* 2.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 21.7 (C$\underline{H}_3$CH), 23.6 (CH$\underline{C}H_3$), 24.8 (C-2), 31.2 (C-13), 35.1 (C-12), 41.1 (C-4), 55.0 (C-5), 67.6 (C-6), 111.9 (C-11), 114.8 (C-9), 137.3 (C-8), 153.3 (C=O), 155.5 (C-10); ***m/z*** (ES+) 439 ($[M+Na]^+$, 40%), 855 ($[2M+Na]^+$, 100%, **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{36}N_2O_4Na^+$) requires ***m/z*** 439.2567, found ***m/z*** 439.2566; $[\alpha]_D^{25} = +108.9$ (*c* 1.0, $CHCl_3$).

Preparation and characterisation of (4*S*,4'*S*)-3,3'-(5-*tert*-butyl-1,3-phenylene)bis{4-[(2*S*)-butan-2-yl]-1,3-oxazolidin-2-one} (*S*)-38g

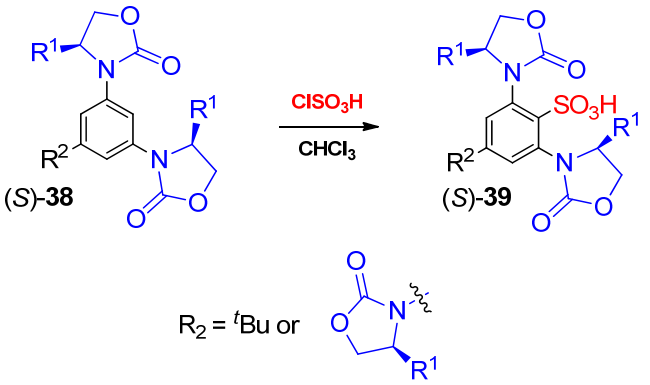
Prepared according to general procedure **XXX** on a 1.47 mmol scale. Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 7:3 to 1:1 to give a solid that was crystallised from ethyl acetate/diethyl ether/petroleum ether (1:2:4, 7 mL) to afford the title product as a colourless crystalline solid (525 mg, 86%).



(*S*)-**38g**

m.p. 123-125 ºC; **FT-IR** ν_{max}(NaCl) 1748 cm^{-1} (C=O), 1601 cm^{-1} (C=C), 1458 cm^{-1} (CH_2), 1399 cm^{-1} (CH_3); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.87 (d, 6H, H-4, *J* 6.5 Hz), 0.95 (t, 6H, H-1, *J* 7.5 Hz), 1.17-1.37 (m, 13H, H-2, H-13), 1.85-1.95 (m, 2H, H-3), 4.24 (dd, 2H, H-6a, *J* 9.0 Hz, 4.5 Hz), 4.41 (t, 2H, H-6b, *J* 9.0 Hz), 4.51-4.57 (m, 2H, H-5), 7.34 (d, 2H, H-9, *J* 2.0 Hz), 7.44 (t, 1H, H-11, *J* 2.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 11.7 (C-4), 11.9 (C-1), 25.3 (C-2), 31.2 (C-13), 34.3 (C-3), 35.1 (C-12), 59.2 (C-5), 62.4 (C-6), 112.6 (C-11), 115.9 (C-9), 137.1 (C-8), 153.3 (C=O), 155.9 (C-10); ***m/z*** (ES+) 439 ($[M+Na]^+$, 40%), 855 ($[2M+Na]^+$, 100%, **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{36}N_2O_4Na^+$) requires ***m/z*** 439.2567, found ***m/z*** 439.2569; $[\alpha]_D^{25}$ = + 76.2 (*c* 1.0, $CHCl_3$).

6.2.4.1.4 General procedure XXXI for the preparation of sulphonic acids (*S*)-39

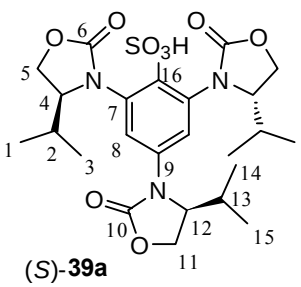


In a dry flask under nitrogen, the substituted *N*-aryl oxazolidinone (*S*)-**38** (1 equivalent) was dissolved in dry chloroform (30-50 mL per mmol). The solution was stirred vigorously at room temperature while chlorosulphonic acid (10 equivalents) was added dropwise. The cloudy solution was then heated at reflux, with a reverse Dean-Starck apparatus (heavy solvent recycled back to the flask) for 24 to 48 hours. The resulting brown biphasic mixture was allowed to cool to room temperature and poured onto ice (50 mL per mmol), washing the flask twice with dichloromethane (5 mL per mmol each time) and three times with DI water (10 mL

per mmol each time). The aqueous was collected and the organic layer was extracted with DI water (5 × 20 mL per mmol). Aqueous layers were combined and concentrated under reduced pressure to give a brown oily residue which was purified by column chromatography on silica gel.

Preparation and characterisation of 2,4,6-tris[(4*S*)-4-isopropyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulphonic acid (*S*)-39a

Prepared according to general procedure **XXXI** on a 1.85 mmol scale. Heated at reflux for 48 hours. Purified by column chromatography on silica gel eluting with dichloromethane/methanol 9:1. The resulting pale yellow solid (813 mg, 81%) was dissolved in dichloromethane/methanol 9:1 (60 mL), the insoluble part was filtered off and the filtrate concentrated and recrystallised from hot acetonitrile (30 mL) to afford the pure acid as a colourless crystalline solid (470 mg, 47 %).

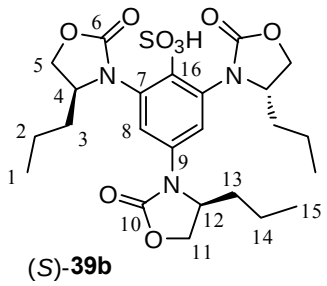


(*S*)-**39a**

m.p.(acetonitrile) 130-133 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3400 cm^{-1} (O-H), 2965 cm^{-1} (C-H), 1752 cm^{-1} (C=O), 1395 cm^{-1} (CH_3), 1202 cm^{-1} (SO_3), 1056 cm^{-1} (SO_3); **^{1}H NMR** (d_4-MeOD, 400 MHz) δ_H 0.86 (d, 3H, H-14, *J* 7.0 Hz), 0.90 (d, 6H, H-1, *J* 7.0 Hz), 0.98 (d, 3H, H-15, *J* 7.0 Hz), 1.09 (d, H-3, *J* 7.0 Hz), 1.93-2.05 (m, 2H, H-2), 2.11-2.24 (m, 1H, H-13), 4.31-4.42 (m, 3H, H-5a, H-11a), 4.43-4.60 (m, 5H, H-4, H-5b, H-11b), 4.72 (dt, 1H, H-12, *J* 8.5 Hz, 3.5 Hz), 7.63 (s, 2H, H-8); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 13.5 (C-14), 14.2 (C-1), 16.8 (C-15), 17.2 (C-3), 28.0 (C-13), 28.9 (C-2), 59.7 (C-12), 63.2 (C-11), 64.2 (C-4), 64.8 (C-5), 124.3 (C-8), 136.4 (C-7), 138.1 (C-16), 139.2 (C-9), 156.4 (C-6), 159.4 (C-10); ***m/z*** (ES−) 538 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{24}H_{32}N_3O_9S^-$) requires ***m/z*** 538.1865, found ***m/z*** 538.1871; $[\alpha]_D^{25}$ = + 42.1 (*c* 1.0, MeOH).

Preparation and characterisation of 2,4,6-tris[(4*S*)-4-propyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulphonic acid (*S*)-39b

Prepared according to general procedure **XXXI** on a 2.17 mmol scale. Heated at reflux for 36 hours. Purified by column chromatography on silica gel eluting with dichloromethane/methanol 9:1 to give a light brown solid (1.15 g, 98%) that was crystallised from hot water (30 mL) to afford the title acid as a colourless crystalline solid (540 mg, 47 %). The crystals were a 2:1 mixture of rotamers (according to ^{1}H NMR at room temperature).



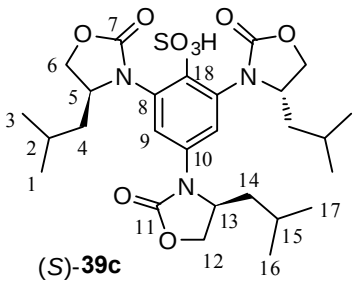
(*S*)-**39b**

m.p.(water) 231-235 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3430 cm^{-1} (O-H), 2962 cm^{-1} (C-H), 1745 cm^{-1} (C=O), 1200 cm^{-1} (SO_3), 1064 cm^{-1} (SO_3); **^{1}H NMR** (d_6-DMSO, 500 MHz, 373K) δ_H 0.87 (t, 6H, H-1, *J* 7.0 Hz), 0.90 (t, 3H, H-15, *J* 7.0 Hz), 1.16-1.41 (m, 6H, H-2, H-14), 1.45-1.74 (m, 6H, H-3, H-13), 4.04 (dd, 2H, H-5a, *J* 8.0 Hz, 4.5 Hz), 4.19 (dd, 1H, H-11a, *J* 8.5 Hz, 4.5 Hz), 4.47 (t, 2H, H-5b, *J* 8.0 Hz), 4.56 (t, 1H, H-11b, *J* 8.5 Hz), 4.60-4.69 (m, 3H, H-4, H-12), 7.35 (s, 2H, H-8); **^{13}C NMR** (d_6-DMSO, 500 MHz, 373K) δ_C 13.0 (C-15), 13.2 (C-1), 16.2 (C-2), 16.7 (C-14), 32.9 (C-3), 34.2 (C-13), 54.3 (C-4), 57.4 (C-12), 66.3 (C-11), 67.2 (C-5), 123.7 (C-8), 135.3 (C-7), 136.4 (C-9), 141.0 (C-16), 154.2 (C-10), 155.6 (C-6); ***m/z*** (ES−) 538 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{24}H_{32}N_3O_9S^-$) requires ***m/z*** 538.1865, found ***m/z*** 538.1854; $[\alpha]_D^{25} = +26.2$ (*c* 1.0, MeOH).

Preparation and characterisation of 2,4,6-tris[(4*S*)-4-isobutyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulphonic acid (*S*)-39c

Prepared according to general procedure **XXXI** on a 1.26 mmol scale. Heated at reflux for 48 hours. Purified by column chromatography on silica gel eluting with dichloromethane/methanol

9:1 to give the title acid as a light yellow amorphous solid (640 mg, 88%). The acid exists as different rotamers at room temperature (confirmed by VT NMR in DMSO at 100 ºC).



(*S*)-**39c**

m.p. 242-245 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3468 cm^{-1} (O-H), 2958 cm^{-1} (C-H), 1751 cm^{-1} (C=O), 1201 cm^{-1} (SO_3), 1087 cm^{-1} (SO_3), 758 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 500 MHz, 298K) δ_H 0.66 (app. t, '6H', H-1 minor rotamer, *J* 6.0 Hz), 0.73 (app. d, '3H', H-16 minor rotamer, *J* 6.5 Hz), 0.76 (d, '6H', H-1 major rotamer, *J* 6.5 Hz), 0.78 (d, '3H', H-17 minor rotamer, *J* 6.5 Hz), 0.84 (app. t, '6H', H-3 minor rotamer, *J* 6.0 Hz), 0.85 (d, '6H', H-3 major rotamer, *J* 6.5 Hz), 0.88 (d, '3H', H-16 major rotamer, *J* 6.5 Hz), 0.95 (d, '3H', H-17 major rotamer, *J* 6.5 Hz), 1.35-1.60 (m, '8H', H-2, H-4, H-14 both rotamers), 1.61-1.72 (m, '1H', H-15 major rotamer), 1.73-1.83 (m, '1H', H-15 minor rotamer), 3.80-3.87 (m, '1H', H-12a minor rotamer), 3.98-4.03 (m, '2H', H-6a minor rotamer), 4.07 (dd, '2H', H-6a major rotamer, *J* 8.0 Hz, 5.0 Hz), 4.21 (dd, '1H', H-12a major rotamer, *J* 8.5 Hz, 4.5 Hz), 4.43-4.53 (m, '2H+2H', H-6b both rotamers, H-12b minor rotamer), 4.58 (t, '1H', H-12b major rotamer, *J* 8.0 Hz), 4.65 (app. tt, '2H', H-5 major rotamer, *J* 9.0 Hz, 4.5 Hz), 4.66-4.76 (m, '1H', H-13 major rotamer), 5.00-5.09 (m, '1H', NCH minor rotamer), 7.27 (s, '2H', H-9 minor rotamer), 7.31 (s, '2H', H-9 major rotamer), 7.51 (s, '2H', H-9 minor rotamer); **^{13}C NMR** (d_6-DMSO, 125 MHz, 298K) δ_C 21.6 (C-16 major rotamer), 21.8 (C-1 major rotamer), 22.0 (br, C-1 minor rotamer), 22.8 (C-3 minor rotamer), 23.1 (C-16 minor rotamer), 23.3 (C-17 minor rotamer), 23.4 (C-3 major rotamer), 23.5 (C-17 major rotamer), 23.8 (C-15 minor rotamer), 23.9 (C-15 major rotamer), 24.0 (C-2 major rotamer), 24.1 (C-2 minor rotamer), 40.2 (C-14 major rotamer), 40.3 (C-14 minor rotamer), 41.9 (C-4 major rotamer), 42.6 (br, C-4 minor rotamer), 53.3 (C-13 major rotamer), 53.9 (br, C-13 minor rotamer), 54.9 (C-13 minor rotamer), 55.5 (br, C-5 minor rotamer), 56.6 (C-5 major rotamer), 58.3 (C-5 minor rotamer), 67.1 (C-12 major rotamer), 67.2 (C-12 minor rotamer),

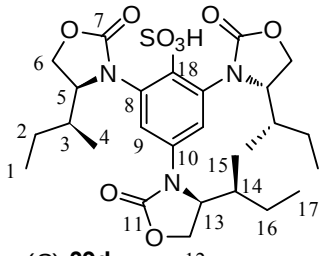
68.1 (C-6 major rotamer), 68.7 (br, C-6 minor rotamer), 68.8 (br, C-6 minor rotamer), 123.0 (br, C-9 minor rotamer), 124.5 (C-9 major rotamer), 125.0 (br, C-9 minor rotamer), 135.4 (C-8 major rotamer), 135.9 (br, C-8 minor rotamer), 136.3 (br, ArC-N minor rotamer), 136.7 (C-10 major rotamer), 137.2 (br, C-10 minor rotamer), 140.7 (C-18 major rotamer), 142.2 (br, C-18 minor rotamer), 154.6 (br, C-11 minor rotamer), 154.6 (C-11 major rotamer), 156.0 (br, C-7 minor rotamer), 156.1 (br, C-7 minor rotamer), 156.2 (C-7 major rotamer); ; ***m/z*** (ES−) 580 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{27}H_{38}N_3O_9S^-$) requires ***m/z*** 580.2334, found ***m/z*** 580.2323; $[\alpha]_D^{25}$ = + 30.7 (c 1.0, MeOH).

VT NMR:

^{1}H NMR (d_6-DMSO, 500 MHz, 373K) δ_H 0.79 (d, 6H, 2 × CH_3, *J* 6.0 Hz), 0.85 (d, 6H, 2 × CH_3, *J* 5.5 Hz), 0.91 (d, 3H, CH_3, *J* 6.5 Hz), 0.96 (d, 3H, CH_3, *J* 6.5 Hz), 1.40-1.62 (m, 8H, H-2, H-4, H-14), 1.63-1.74 (m, 1H, H-15), 4.02 (m, 2H, H-6a), 4.19 (dd, 1H, H-12a, *J* 8.5 Hz, 4.5 Hz), 4.51 (t, 2H, H-6b, *J* 8.0 Hz), 4.60 (t, 1H, H-12b, *J* 8.0 Hz), 4.66 (ddd, 1H, H-13, *J* 13.0 Hz, 8.5 Hz, 4.5 Hz), 4.76 (br, 2H, H-5), 7.31 (s, 2H, H-9); **^{13}C NMR** (d_6-DMSO, 125 MHz, 373K) δ_C 22.3 (C-1), 22.5 (C-16), 23.5 (C-3), 23.7 (C-17), 24.5 (C-15), 24.7 (C-2), 40.5 (C-14), 42.6 (br, C-4), 54.4 (C-13), 67.8 (C-12), 68.9 (br, C-6), 125.2 (br, C-9), 136.4 (Ar-Cquat.), 155.1 (C-11), 156.7 (C-7) *the other carbons were not detected at high temperature*.

Preparation and characterisation of (2,4,6-tris{(4*S*)-4-[(2*S*)-butan-2-yl]-2-oxo-1,3-oxazolidin-3-yl}benzenesulphonic acid (*S*)-39d

Prepared according to general procedure **XXXI** on a 0.80 mmol scale. Heated at reflux for 24 hours. Purified by column chromatography on silica gel eluting with dichloromethane/methanol 95:5 to 93:7 to give a pale brown amorphous solid (450 mg, 97%) that was crystallised from dichloromethane to afford the title acid as a light tan crystalline solid (250 mg, 54%).

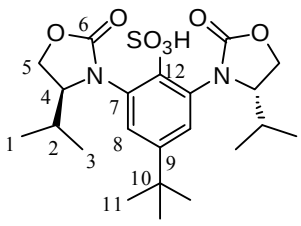


(*S*)-**39d**

m.p. 166-168 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3435 cm^{-1} (O-H), 2965 cm^{-1} (C-H), 1749 cm^{-1} (C=O), 1200 cm^{-1} (SO_3), 1053 cm^{-1} (SO_3); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 0.75 (d, 3H, H-15, *J* 6.5 Hz), 0.82 (t, 6H, H-1, *J* 7.5 Hz), 0.90 (t, 3H, H-17, *J* 7.5 Hz), 0.97 (d, 6H, H-4, *J* 6.5 Hz), 1.06-1.26 (m, 5H, H-2, H-16a), 1.27-1.39 (m, 1H, H-16b), 1.47-1.58 (m, 2H, H-3), 1.72-1.81 (m, 1H, H-14), 4.18 (dd, 2H, H-6a, *J* 8.5 Hz, 3.0 Hz), 4.32 (app. t, 3H, H-6b, H-12a, *J* 8.5 Hz), 4.42 (t, 1H, H-12b, *J* 8.5 Hz), 4.52 (dt, 2H, H-5, *J* 8.5 Hz, 3.0 Hz), 4.80-4.85 (m, 1H, H-13), 7.39 (s, 2H, H-9); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 11.1 (C-15), 11.7 (2 signals, 5C, C-1, C-4, C-17), 24.3 (C-16), 24.7 (C-2), 33.9 (C-14), 35.2 (C-3), 57.5 (C-13), 62.0 (C-5), 62.4 (C-12), 63.6 (C-6), 123.5 (C-9), 135.7 (C-8), 136.8 (C-10), 140.4 (C-18), 154.9 (C-11), 156.7 (C-7); ***m/z*** (ES−) 580 ($[M-H]^-$,100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{27}H_{38}N_3O_9S^-$) requires ***m/z*** 580.2334 found ***m/z*** 580.2341; $[\alpha]_D^{25} = +38.4$ (*c* 1.0, MeOH).

Preparation and characterisation of 4-*tert*-butyl-2,6-bis[(4*S*)-4-isopropyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulphonic acid (*S*)-39e

Prepared according to general procedure **XXXI** on a 1.0 mmol scale. Heated at reflux for 48 hours. Purified by column chromatography on silica gel eluting with dichloromethane/methanol 9:1 to afford the title acid as an off-white foamy solid (440 mg, 94%).



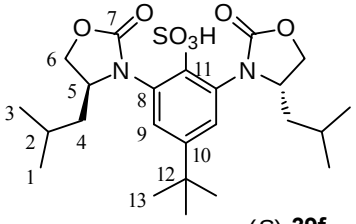
(*S*)-**39e**

m.p. 260-262 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3437 cm^{-1} (O-H), 2965 cm^{-1} (C-H), 1733 cm^{-1} (C=O), 1229 cm^{-1} (SO_3), 1079 cm^{-1} (SO_3), 1035 cm^{-1} (SO_3); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 0.80 (d, 6H, H-1, *J* 7.0 Hz), 0.98 (d, 6H, H-3, *J* 7.0 Hz), 1.27 (s, 9H, H-11), 1.71-1.79 (m, 2H, H-2), 4.18 (dd, 2H, H-5a, *J* 8.5 Hz, 3.0 Hz), 4.30 (t, 2H, H-5b, *J* 8.5 Hz), 4.40 (dt, 2H, H-4, *J* 8.5 Hz, 3.0 Hz), 7.09 (s, 2H, H-8); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 14.7 (C-3), 17.6 (C-1), 28.3 (C-2), 30.6 (C-11), 34.0 (C-10),

62.4 (C-4), 63.4 (C-5), 129.1 (C-8), 134.9 (C-7), 142.0 (C-12), 151.4 (C-9), 156.8 (C-6); ***m/z*** (ES−) 467 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{22}H_{31}N_2O_7S^-$) requires ***m/z*** 467.1857, found ***m/z*** 467.1860; $[\alpha]_D^{25}$ = + 56.7 (*c* 1.0, MeOH).

Preparation and characterisation of 4-*tert*-butyl-2,6-bis[(4*S*)-4-isobutyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulphonic acid (*S*)-39f

Prepared according to general procedure **XXXI** on a 1.44 mmol scale. Heated at reflux for 24 hours. Purified by column chromatography on silica gel eluting with dichloromethane/methanol 95:5 to 93:7 to give a light tan foamy solid (633 mg, 89%) that was redissolved in dichloromethane (1 mL) and diethyl ether was added slowly (2 mL) and the solid acid started precipitating (350 mg, 49%). The acid exists as different rotamers at room temperature (confirmed by VT NMR in DMSO at 100 ºC).



(*S*)-**39f**

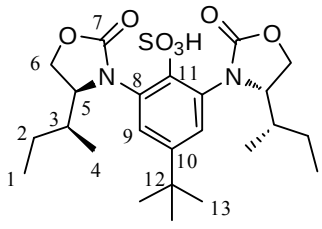
m.p. 223-226 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3437 cm^{-1} (O-H), 2958 cm^{-1} (C-H), 1740 cm^{-1} (C=O), 1227 cm^{-1} (SO_3), 1077 cm^{-1} (SO_3), 1029 cm^{-1} (SO_3), 755 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 500 MHz, 298K) δ_H 0.60-0.66 (m, '3H', H-1 minor rotamer), 0.69 (d, '3H' minor rotamer, H-1, *J* 6.0 Hz), 0.72-0.78 (m, '3H'+'3H', H-1 major rotamer + H-3 minor rotamer), 0.82 (d, '3H', H-3 major rotamer, *J* 6.5 Hz), 0.96-1.06 (m, '1H', H-2 minor rotamer), 1.26 (s, '9H', H-13 minor rotamer), 1.28 (s, '9H', H-13 major rotamer), 1.29-1.53 (m, '2H+4H', H-2 major rotamer, H-4 major rotamer), 1.73-1.82 (m, '4H', H-4 minor rotamer), 3.78-3.84 (m, '2H', H-6a minor rotamer), 3.93-3.97 (m, '2H', H-6b minor rotamer), 4.03 (dd, '2H', H-6a major rotamer, *J* 8.0 Hz, 4.5 Hz), 4.31-4.39 (m, '2H', H-5 minor rotamer), 4.42-4.50 (m, '2H', H-6b major rotamer), 4.60 (tt, '2H', H-5 major rotamer, *J* 8.5 Hz, 4.5 Hz), 4.90-4.96 (m, '2H', H-5 minor rotamer), 7.12 (s, '2H', H-9 major rotamer), 7.37 (s, '2H', H-9 minor rotamer) ; **^{13}C NMR** (d_6-DMSO, 125 MHz, 298K) δ_C 21.7 ($\underline{C}H_3$-CH minor rotamer), 21.9 (C-1 major rotamer), 22.3 ($\underline{C}H_3$-CH

minor rotamer), 22.8 ($\underline{C}H_3$-CH minor rotamer), 23.3 (C-3 major rotamer), 24.0 (C-2 major rotamer), 30.6 (C-13 both rotamers), 34.0 (C-12 major rotamer), 34.2 (C-12 minor rotamer), 40.0 (C-4 minor rotamer), 41.8 (C-4 major rotamer), 42.8 (C-4 minor rotamer), 55.4 (C-5 minor rotamer), 56.4 (C-5 major rotamer), 57.9 (C-5 minor rotamer), 68.0 (C-6 major rotamer), 68.7 (C-6 minor rotamer), 68.8 (C-6 minor rotamer), 126.6 (C-9 minor rotamer), 129.8 (C-9 minor rotamer), 130.0 (C-9 major rotamer), 134.6 (C-8 major rotamer), 134.9 (C-8 minor rotamer), 135.4 (C-8 minor rotamer), 141.9 (C-11 major rotamer), 142.7 (C-11 minor rotamer), 151.2 (C-10 major rotamer), 151.8 (C-10 minor rotamer), 156.3 (C-7 minor rotamer), 156.3 (C-7 major rotamer); ***m/z*** (ES−) 495 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{24}H_{35}N_2O_7S^-$) requires ***m/z*** 495.2170, found ***m/z*** 495.2173; $[\alpha]_D^{25} = +44.4$ (*c* 1.0, MeOH).

VT NMR:

^{1}H NMR (DMSO-d_6, 500 MHz, 373K) δ_H 0.74-0.80 (br m, 6H, H-1), 0.80-0.86 (br m, 6H, H-3), 1.31 (s, 9H, H-13), 1.36-1.60 (br m, 6H, H-2, H-4), 3.95-4.02 (br m, 2H, H-6a), 4.49 (t, 2H, H-6b, *J* 8.0 Hz), 4.60-4.90 (br m, 2H, H-5), 7.14 (br s, 2H, H-9); **^{13}C NMR** (d_6-DMSO, 125 MHz, 373K) δ_C 23.1 (C-1), 23.7 (br, unassigned), 25.0 (C-2 and/or C-4), 31.5 (C-3), 34.8 (br, unassigned), 69.2 (br, C-6), 130.5 (br, C-9), 135.9 (Ar-Cquat.), 157.1 (C-7), *the other carbons were not detected at high temperature*.

Preparation and characterisation of 2,6-bis{(4*S*)-4-[(2*S*)-butan-2-yl]-2-oxo-1,3-oxazolidin-3-yl}-4-*tert*-butylbenzenesulfonic acid (*S*)-39g



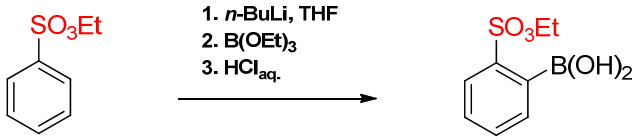
(*S*)-**39g**

Prepared according to general procedure **XXXI** on a 1.22 mmol scale. Heated at reflux for 24 hours. Purified by column chromatography on silica gel eluting with dichloromethane/methanol 95:5 to 93:7 to give the title acid as a colourless amorphous solid (556 mg, 92%).

m.p. 233-236 °C (dec.); **FT-IR** ν_{max}(NaCl) 3436 cm^{-1} (O-H), 2965 cm^{-1} (C-H), 1739 cm^{-1} (C=O), 1227 cm^{-1} (SO_3), 1078 cm^{-1} (SO_3), 1033 cm^{-1} (SO_3); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 0.82 (t, 6H, H-1, *J* 7.5 Hz), 0.99 (d, 6H, H-4, *J* 7.0 Hz), 1.07-1.21 (m, 4H, H-2), 1.28 (s, 9H, H-13), 1.42-1.56 (m, 2H, H-3), 4.16 (dd, 2H, H-6a, *J* 8.5 Hz, 3.0 Hz), 4.31 (t, 2H, H-6b, *J* 8.5 Hz), 4.51 (dt, 2H, H-5, *J* 8.5 Hz, 3.0 Hz), 7.09 (s, 2H, H-9); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 11.7 (4C, C-1, C-4), 24.8 (C-2), 30.5 (C-13), 34.0 (C-12), 35.0 (C-3), 61.7 (C-6), 63.4 (C-5), 129.0 (C-9), 134.8 (C-8), 142.0 (C-11), 151.3 (C-10), 156.8 (C-7); ***m/z*** (ES−) 495 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{24}H_{35}N_2O_7S^-$) requires ***m/z*** 495.2170, found ***m/z*** 495.2176; $[\alpha]_D^{25} = +74.2$ (*c* 1.0, MeOH).

6.2.4.2 Synthesis of second generation all-carbon auxiliary-derived chiral sulphonic acids

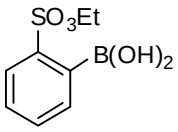
6.2.4.2.1 Synthesis of [2-(ethoxysulphonyl)phenyl]boronic acid 42a



41a **42a**

To a solution of ethyl benzenesulphonate **41a** (56.0 mmol, 10.5 g, 1 equivalent) in THF (84 mL) was added dropwise 1.6 M *n*-BuLi in hexanes (73 mmol, 45.6 mL, 1.1 equivalents) at − 78 ºC. The resulting yellow solution was stirred for 5 hours before being quenched with $B(OEt)_3$ (15.3 mL, 90.0 mmol, 1.6 equivalents) at − 78 °C. The resulting mixture was warmed to room temperature over 1 hour and a 1M aqueous solution of HCl (200 mL) was added. The resulting mixture was stirred at room temperature for 12 hours. The organic phase was separated and the water phase was extracted with diethyl ether (4 × 60 mL). The combined organics were dried over magnesium sulphate, filtered and concentrated *in vacuo* and the residue was purified by

column chromatography on silica gel eluting with petroleum ether/diethyl ether 1:1 to 1:3 to afford **42a** as a colourless crystalline solid (7.58 g, 60%).

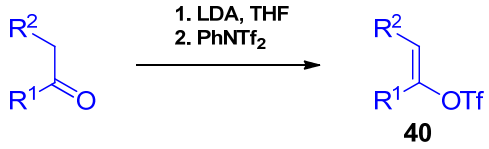


42a

m.p. 62-65 ºC; **FT-IR** ν_{max}(NaCl) 2956 cm^{-1} (C-H), 2932 cm^{-1} (C-H), 2869 cm^{-1} (C-H), 1356 cm^{-1} (SO_3Et), 1182 cm^{-1} (SO_3Et); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.33 (t, 3H, $OCH_2C\underline{H}_3$, *J* 7.0 Hz), 4.15 (q, 2H, $OC\underline{H}_2CH_3$, *J* 7.0 Hz), 4.88 (br s, 2H, $B(O\underline{H})_2$), 7.61 (td, 1H, Ar-H, *J* 7.5 Hz, 1.5 Hz), 7.69 (td, 1H, Ar-H, *J* 7.5 Hz, 1.0 Hz), 8.04-8.08 (m, 2H, Ar-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.6 ($OCH_2\underline{C}H_3$), 67.7 ($O\underline{C}H_2CH_3$), 128.8 (Ar-$\underline{C}$H), 130.3 (2C, Ar-$\underline{C}$H, Ar-Cquat.), 133.3 (Ar-$\underline{C}$H), 136.8 (Ar-$\underline{C}$H), 138.9 (Ar-Cquat.); ***m/z*** (ES−) 229 ($[M-H]^-$, 100%), **HRMS** (FI+) exact mass calculated for $[M-H_2O]^+$ ($C_8H_9BO_4S^+$) requires ***m/z*** 212.0315, found ***m/z*** 212.9883.

6.2.4.2.2 Synthesis of triflate coupling partners

General procedure XXXII for the synthesis of enol triflates 40



40

According to a modified literature procedure.[194]

In a dry flask under nitrogen, DIPA (1.1 equivalents) was diluted with anhydrous tetrahydrofuran (2.2 mL per 1 mmol of ketone). The solution was cooled to − 78 ºC and a 1.6 M solution of *n*-BuLi in hexanes (1.1 equivalents) was added dropwise over 3-5 minutes. The solution was left stirring for 5 minutes at − 78 ºC and warmed to 0 ºC for 5 minutes. It was then cooled to − 78 ºC and a chiral ketone (1 equivalent) was added as a solution in anhydrous tetrahydrofuran (1.2 mL per 1 mmol of ketone). The mixture was stirred at − 78 ºC for 2.5 hours and quenched by dropwise addition of a solution of $PhNTf_2$ (1.05 equivalents) in anhydrous tetrahydrofuran (1.2 mL per 1 mmol of ketone). The resulting suspension was stirred at − 78 ºC for 30 minutes and warmed to 0 ºC for 1 hour. The solvent was concentrated *in*

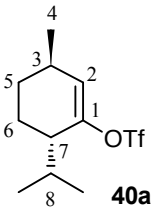
vacuo until approximately half of its initial volume. The mixture was quenched with DI water (2 mL per 1 mmol) and extracted with diethyl ether (4 × 6 mL per 1 mmol). The organics were combined, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel eluting with petroleum ether.

Preparation of (3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl trifluoromethanesulphonate

40a

40a

Prepared according to general procedure **XXXII** on a 25 mmol scale of (−)-menthone (1.54 g, 10 mmol). After purification the title product was obtained as a colourless liquid (2.12 g, 74%). The ^{1}H NMR data matched the published ones.[193,194]



40a

FT-IR ν_{max}(NaCl) 2964 cm^{-1} (C-H), 2876 cm^{-1} (C-H), 1675 cm^{-1}, 1418 cm^{-1}, 1210 cm^{-1}, 1145 cm^{-1}, 896 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.83 (d, 3H, C$\underline{H}_3$, *J* 7.0 Hz), 0.95 (d, 3H, C$\underline{H}_3$, *J* 7.0 Hz), 1.04 (d, 3H, H-4, *J* 7.5 Hz), 1.09-1.19 (m, 1H, H-5a), 1.37-1.49 (m, 1H, H-6a), 1.78-1.88 (m, 2H, H-5b, H-6b), 2.16 (app. dtd, 1H, H-8), 2.28-2.38 (m, 1H, H-3), 2.45-2.55 (m, 1H, H-7), 5.64 (s, 1H, H-2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 16.3 (C$\underline{H}_3$), 19.7 (C$\underline{H}_3$), 21.1 (C-4), 22.4 (C-5), 27.3 (C-8), 29.9 (C-6), 30.6 (C-3), 43.1 (C-7), 118.6 (q, CF_3, $J_{C\text{-}F}$ 319.6 Hz), 125.9 (C-2), 151.8 (C-1); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_{11}H_{21}NO_3SF_3^+$) requires ***m/z*** 304.1194 found ***m/z*** 304.1207; $[\alpha]_D^{25} = +54.1$ (*c* 2.02, CH_2Cl_2) (lit.[194] $[\alpha]_D^{20} = +56.3$ (*c* 1.9, CH_2Cl_2).

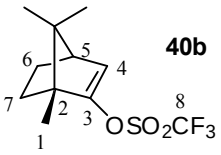
Preparation of (1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl trifluoromethanesulfonate

40b

40b

Prepared according to general procedure **XXXII** on a 25 mmol scale of D-camphor (3.81 g). After purification the pure title product was obtained as a colourless liquid (6.77 g, 87%).

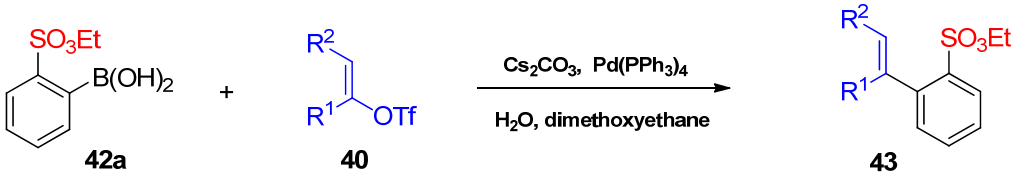
The ^{1}H NMR data matched the published ones.[249]



FT-IR ν_{max}(NaCl) 2964 cm^{-1} (C-H), 2880 cm^{-1} (C-H), 1624 cm^{-1}, 1423 cm^{-1}, 1208 cm^{-1}, 1143 cm^{-1}, 880 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.80 (s, 3H, C$\underline{H}_3$), 0.93 (s, 3H, C$\underline{H}_3$), 1.04 (s, 3H, H-1), 1.16 (ddd, 1H, H-6a, *J* 12.5 Hz, 9.0 Hz, 3.5 Hz), 1.34 (ddd, 1H, H-7a, *J* 12.5 Hz, 9.0 Hz, 3.5 Hz), 1.66 (ddd, 1H, H-7b, *J* 12.5 Hz, 9.0 Hz, 3.5 Hz), 1.94 (ddt, 1H, H-6b, *J* 12.5 Hz, 9.0 Hz, 3.5 Hz), 2.46 (t, 1H, H-5, *J* 3.5 Hz), 5.67 (d, 1H, H-4, *J* 3.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 9.4 (C-1), 18.9 (C$\underline{H}_3$), 19.6 (C$\underline{H}_3$), 25.3 (C-6), 30.8 (C-7), 50.1 (C-5), 53.8 (Cquat.), 57.0 (Cquat.), 117.7 (C-4), 118.6 (q, C-8, $J_{C\text{-}F}$ 321 Hz), 155.3 (C-3); **HRMS** (CI+) exact mass calculated for $[M+NH_4]^+$ ($C_{11}H_{19}NO_3SF_3^+$) requires ***m/z*** 302.1038 found ***m/z*** 302.1034; $[\alpha]_D^{25}$ = + 8.4 (*c* 0.98, $CHCl_3$) (lit.[249] $[\alpha]_D^{23}$ = + 8.63 (*c* 1.07, $CHCl_3$)).

6.2.4.2.3 Synthesis of monosubstituted chiral benzenesulphonates 43

General procedure XXXIII for the Suzuki-Miyaura cross-coupling of 42a and an enol triflate 40

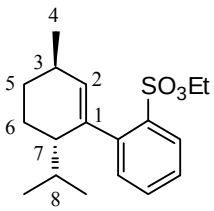


42a **40** **43**

Boronic acid **42a** (1.2 equivalents), triflate **40** (1 equivalent) and cesium carbonate (1.2 equivalents) were charged in a round-bottom flask. Degassed DME (3.6 mL per 1 mmol of triflate) was added and the mixture stirred vigorously for 2 minutes. Degassed DI water (0.6 mL per 1 mmol of triflate) was added to the vigorously stirred mixture. A sequence vacuum/nitrogen was applied and nitrogen was bubbled through the suspension for 5 minutes. $Pd(PPh_3)_4$ (0.05 equivalents) was finally added to the suspension, under nitrogen. Nitrogen was bubbled through the suspension for 2 minutes and the mixture was heated at 60 ºC for 2 hours (monitoring the disappearance of the triflate by TLC). The biphasic mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel.

Preparation and characterisation of ethyl 2-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]benzenesulphonate (+)-43a

Prepared according to general procedure **XXXIII** on a 8.70 mmol of triflate **40a** (2.50 g). The residue was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 95:5 to 9:1 and the title product was obtained as a colourless oil (2.19 g, 78%).



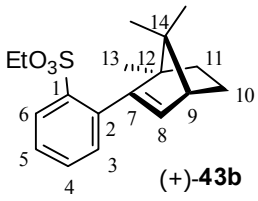
(+)-**43a**

FT-IR ν_{max}(NaCl) 2958 cm^{-1} (C-H), 2932 cm^{-1} (C-H), 2869 cm^{-1} (C-H), 1356 cm^{-1} (SO_3Et), 1182 cm^{-1} (SO_3Et); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.70 (d, 3H, C$\underline{H}_3$CHCH$_3$, *J* 7.0 Hz), 0.84 (d, 3H, C$\underline{H}_3$CHCH$_3$, *J* 7.0 Hz), 1.01 (d, 3H, H-4, *J* 7.0 Hz), 1.27-1.45 (m, 5H, OCH$_2$C$\underline{H}_3$, H-5a, H-6a), 1.48-1.56 (m, 1H, H-8), 1.77-1.86 (m, 2H, H-5b, H-6b), 2.22-2.29 (m, 1H, H-3), 2.97 (br s, 1H, H-7), 3.99-4.12 (m, 2H, OC$\underline{H}_2$CH$_3$), 5.48 (s, 1H, H-2), 7.30 (dd, 1H, Ar-H, *J* 7.5 Hz, 1.5 Hz), 7.37 (td, 1H, Ar-H, *J* 7.5 Hz, 1.5 Hz), 7.53 (td, 1H, Ar-H, *J* 7.5 Hz, 1.5 Hz), 7.98 (dd, 1H, Ar-H, *J* 8.0 Hz, 1.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 14.7 (OCH$_2$$\underline{C}H_3$), 16.2 ($\underline{C}H_3$CHCH$_3$), 20.9 (CH$_3CH\underline{C}H_3$), 21.4 (C-6), 21.6 (C-4), 28.4 (C-8), 30.5 (C-5), 31.4 (C-3), 43.0 (C-7), 66.6 (O$\underline{C}$H$_2$CH$_3$), 126.7 (Ar-$\underline{C}$H), 129.7 (Ar-$\underline{C}$H), 132.5 (Ar-$\underline{C}$H), 133.0 (Ar-

CH), 134.0 (Cquat.), 136.6 (C-2), 141.1 (Cquat.), 143.9 (Cquat.); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}NaO_3S^+$) requires ***m/z*** 345.1495, found ***m/z*** 345.1497; $[\alpha]_D^{25} = +50.7$ (*c* 4.02, $CHCl_3$).

Preparation and characterisation of ethyl 2-[(1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzenesulphonate (+)-43b

Prepared according to general procedure **XXXIII** on a 22 mmol scale of triflate **40b** (6.25 g). The residue was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether 95:5 to 9:1 and the title product obtained as a colourless crystalline solid (5.80 g, 82%).

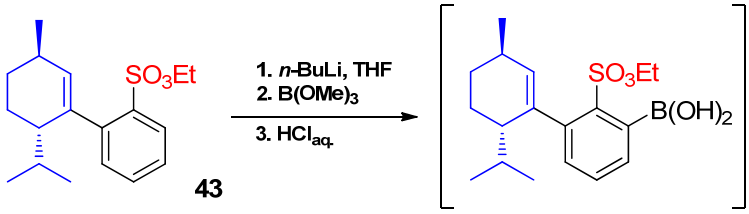


(+)-**43b**

m.p. 67-69 ºC; **FT-IR** ν_{max}(NaCl) 2955 cm^{-1} (C-H), 1591 cm^{-1} (C=C), 1562 cm^{-1} (C=C), 1357 cm^{-1} (SO_3Et), 1183 cm^{-1} (SO_3Et); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.86 (s, 3H, C$\underline{H}_3$), 0.99 (s, 3H, H-13), 1.04 (s, 3H, C$\underline{H}_3$), 1.21 (ddd, 1H, H-10a, *J* 12.0 Hz, 7.5 Hz, 5.0 Hz), 1.34 (t, 3H, $OCH_2C\underline{H}_3$, *J* 7.0 Hz), 1.61-1.70 (m, 2H, H-11), 1.91-1.99 (m, 1H, H-10b), 2.48 (t, 1H, H-9, *J* 3.5 Hz), 4.05-4.19 (m, 2H, $OC\underline{H}_2CH_3$), 6.26 (d, 1H, H-8, *J* 3.5 Hz), 7.32-7.37 (m, 2H, H-3, H-5), 7.54 (app. td, 1H, H-4, *J* 7.5 Hz, 1.5 Hz), 8.07 (dd, 1H, H-6, *J* 8.0 Hz, 1.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 12.6 ($\underline{C}H_3$), 14.8 ($OCH_2\underline{C}H_3$), 19.6 ($\underline{C}H_3$), 20.0 ($\underline{C}H_3$), 24.9 (C-10), 32.0 (C-11), 52.5 (C-9), 56.9 (C-14), 57.6 (C-12), 66.6 ($O\underline{C}H_2CH_3$), 126.2 (C-5), 130.3 (C-6), 130.6 (C-3), 132.3 (C-4), 134.5 (C-1), 137.6 (C-8), 138.8 (C-2), 142.6 (C-7); ***m/z*** (ES+) 663 ($[2M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{24}O_3SNa^+$) requires ***m/z*** 343.1338 found ***m/z*** 343.1334; $[\alpha]_D^{25} = -41.3$ (*c* 1.15, $CHCl_3$).

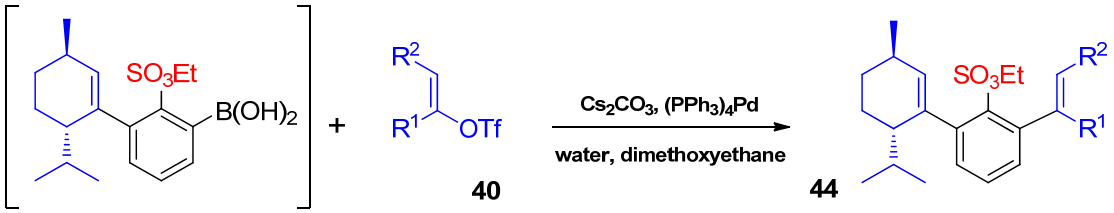
6.2.4.2.4 Synthesis of disubstituted benzenesulphonates 44

General procedure XXXIV for the synthesis of benzenesulphonates 44



43

To a solution of bezensulphonate **43** (1 equivalent) in tetrahydrofuran (4 mL per 1 mmol) was added dropwise *n*-BuLi (1.1 equivalents, 1.6 M in hexanes) at − 78 ºC. The resulting yellow-orange solution was stirred for 6.5 hours at − 78 ºC before being quenched with $B(OMe)_3$ (1.5 equivalents) at − 78 ºC. The resulting mixture was warmed to room temperature over 1 hour, 1M aqueous HCl (15 mL per 1 mmol) was added and the mixture was stirred at room temperature for 1 hour. The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 10 mL per 1 mmol). The combined organics were washed (brine, 3 mL per 1 mmol), dried (Na_2SO_4) and concentrated *in vacuo* to afford the title product as a mixture of boronic acid and anhydride, which was used in next step without further purification.



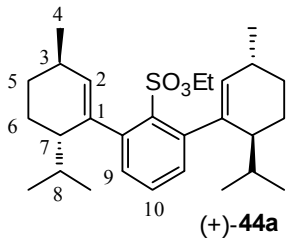
40 **44**

A mixture of the previously prepared boronic acid (2 equivalents), Cs_2CO_3 (2 equivalents), triflate **40** (1 equivalent) in dimethoxyethane/water (5:1, 2.0 mL per 1 mmol of **40**) was degassed and filled with nitrogen. $Pd(PPh_3)_4$ (0.05 equivalents) was added and the mixture was stirred at 70 ºC. When the starting material **40** was fully consumed (TLC monitoring, typically 1-2 hours) the mixture was cooled to room temperature concentrated *in vacuo*. DI water (8.4 mL per mmol of **40**) was added and the mixture was extracted with diethyl ether (3 × 8.4 mL per mmol of **40**). The combined organics were dried (Na_2SO_4), concentrated *in vacuo* and the

residue was purified by column chromatography on silica gel eluting with petroleum ether to petroleum ether/diethyl ether 95:5 to yield the disubstituted benzenesulphonate **44**.

Preparation and characterisation of ethyl 2,6-bis[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]benzenesulfonate (+)-44a

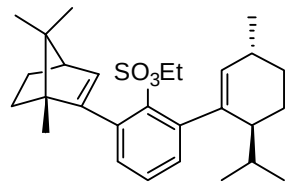
Prepared according to general procedure **XXXIV** on a 0.59 mmol scale of triflate **40a** (0.170 g). Heated at 70 ºC for 1 hour. **(+)-44a** was obtained as a colourless oil (0.205 g, 76%).



(+)-**44a**

FT-IR ν_{max}(NaCl) 2957 cm^{-1} (C-H), 2931 cm^{-1} (C-H), 2869 cm^{-1} (C-H), 1355 cm^{-1} (SO_3Et), 1179 cm^{-1} (SO_3Et); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 0.77 (d, 6H, 2 × $C\underline{H}_3CHCH_3$, *J* 7.0 Hz), 0.86 (d, 6H, 2 × $C\underline{H}_3CHCH_3$, *J* 7.0 Hz), 1.04 (d, 6H, H-4, *J* 7.0 Hz), 1.30-1.50 (m, 7H, $OCH_2C\underline{H}_3$, H-5a, H-6a), 1.58-1.65 (m, 2H, H-8), 1.79-1.84 (m, 4H, H-5b, H-6b), 2.19-2.30 (m, 2H, H-3), 2.96 (br s, 2H, H-7), 4.05-4.17 (m, 2H, $OC\underline{H}_2CH_3$), 5.48 (s, 2H, H-2), 7.15 (d, 2H, H-9, *J* 7.5 Hz), 7.35 (t, 1H, H-10, *J* 7.5 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 15.2 ($OCH_2\underline{C}H_3$), 16.9 ($\underline{C}H_3CHCH_3$), 21.3 & 21.4 & 21.6 ($CH_3CH\underline{C}H_3$, C-4, C-6), 28.3 (C-8), 30.3 (C-5), 31.2 (C-3), 43.2 (C-7), 65.6 ($O\underline{C}H_2CH_3$), 130.7 (Ar-$\underline{C}$H), 131.4 (Ar-$\underline{C}$H), 134.2 (Cquat.), 135.1 (C-2), 142.5 (Cquat.), 144.6 (Cquat.); **HRMS** (EI/FI) exact mass calculated for $[M]^+$ ($C_{28}H_{42}O_3S^+$) requires ***m/z*** 458.2855, found ***m/z*** 458.2859; $[\alpha]_D^{25} = +78.6$ (*c* 0.22, $CHCl_3$).

Preparation and characterisation of ethyl 2-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]-6-[(1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzenesulfonate (+)-44b



(+)-**44b**

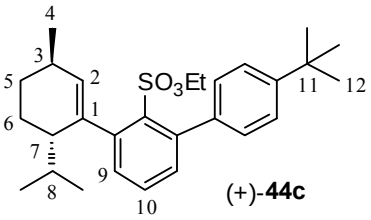
Prepared according to general procedure **XXXIV** on a 0.29 mmol scale of triflate **40b** (82 mg). Heated at 70 ºC for 2 hours. **(+)-44b** was obtained as a colourless oil (0.101 g, 77%).

FT-IR ν_{max}(NaCl) 2955 cm^{-1} (C-H), 2870 cm^{-1} (C-H), 1354 cm^{-1}

(SO_3Et), 1177 cm^{-1} (SO_3Et); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.58 (d, 3H, C<u>H</u>$_3$, *J* 7.0 Hz), 0.85-0.86 (m, 6H), 1.02-1.06 (m, 9H), 1.07-1.09 (m, 1H), 1.27-1.53 (m, 6H), 1.68 (br s, 2H), 1.81-1.85 (m, 2H), 1.90-1.96 (m, 1H), 2.23-2.34 (m, 1H), 2.46 (br s, 1H), 2.98-3.08 (m, 1H), 3.99 (q, 2H, OC<u>H</u>$_2$CH$_3$, *J* 7.5 Hz), 5.60 (s, 1H), 6.16 (br s, 1H), 7.13 (d, 1H, Ar-H, *J* 7.5 Hz), 7.23 (d, 1H, Ar-H, *J* 7.5 Hz), 7.36 (t, 1H, Ar-H, *J* 7.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 12.1, 15.2, 16.3, 19.7, 20.3, 20.9, 21.7, 21.8, 25.3, 28.8, 30.3, 31.5, 32.2, 43.4, 52.4, 56.8, 66.2, 128.0, 130.7, 130.9, 133.2, 134.4, 140.8, 144.3, 145.0; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{28}H_{40}NaO_3S^+$) requires ***m/z*** 479.2590, found ***m/z*** 479.2590; $[\alpha]_D^{25}$ = + 10.5 (*c* 1.22, $CHCl_3$).

Preparation and characterisation of ethyl 4'-*tert*-butyl-3-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]biphenyl-2-sulfonate (+)-44c

Prepared according to general procedure **XXXIV** on a 0.50 mmol scale of triflate **40c** (provided by Dr. P. Jakubec). Heated at 70 ºC for 1 hour. (+)-**44c** was obtained as a colourless oil (0.142 g, 83%).

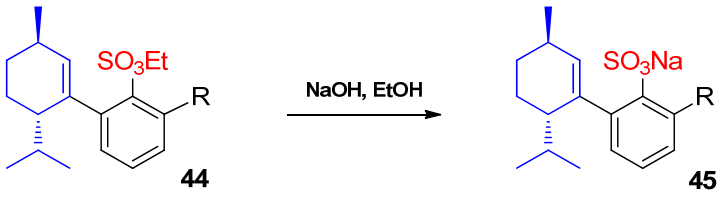


(+)-**44c**

FT-IR ν_{max}(NaCl) 2958 cm^{-1} (C-H), 2933 cm^{-1} (C-H), 2869 cm^{-1} (C-H), 1354 cm^{-1} (SO_3Et), 1177 cm^{-1} (SO_3Et); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.68 (d, 3H, C<u>H</u>$_3$CHCH$_3$, *J* 6.5 Hz), 0.92 (d, 3H, CH$_3$CHC<u>H</u>$_3$, *J* 7.0 Hz), 1.03 (t, 3H, OCH$_2$C<u>H</u>$_3$, *J* 7.0 Hz), 1.06 (d, 3H, H-4, *J* 7.0 Hz), 1.33-1.49 (m, 11H, H-12, H-5a, H-6a), 1.60-1.67 (m, 1H, H-8), 1.85-1.89 (m, 2H, H-5b, H-6b), 2.24-2.35 (m, 1H, H-3), 3.03-3.12 (m, 1H, H-7), 3.72-3.84 (m, 2H, OC<u>H</u>$_2$CH$_3$), 5.63 (s, 1H, H-2), 7.25 (d, 1H, Ar-H, *J* 7.5 Hz), 7.29 (d, 1H, Ar-H, *J* 7.5 Hz), 7.37 (br s, 2H, Ar-H), 7.42-7.48 (m, 3H, Ar-H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.5 (OCH$_2$<u>C</u>H$_3$), 16.4 (<u>C</u>H$_3$CHCH$_3$), 21.0 (CH$_3$CH<u>C</u>H$_3$), 21.7 (2 signals, C-4, C-6), 28.8 (C-8), 30.3 (C-5), 31.4 & 31.5 (C-3, C-12), 34.6 (C-11), 43.4 (C-7), 65.7 (O<u>C</u>H$_2$CH$_3$), 124.6 (Ar-<u>C</u>H), 128.6 (br, Ar-<u>C</u>H), 131.4 (Ar-<u>C</u>H), 131.4 (Ar-<u>C</u>H), 131.7 (Ar-<u>C</u>H), 133.7

(Cquat.), 135.3 (C-2), 138.4 (Cquat.), 142.9 (Cquat), 143.4 (Cquat.), 145.2 (Cquat.), 150.5 (Cquat.); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{28}H_{38}NaO_3S^+$) requires ***m/z*** 477.2434, found ***m/z*** 477.2438; $[\alpha]_D^{25} = +78.1$ (*c* 1.12, $CHCl_3$).

General procedure XXXV for the hydrolysis of benzenesulfonates 45

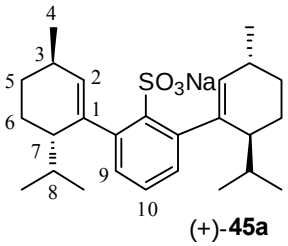


44 **45**

A mixture of ester **44** (0.100 g) in EtOH (10 mL) 1M aqueous NaOH (10 mL) was stirred and heated at reflux. After 14 hours the mixture was cooled to room temperature and concentrated *in vacuo*. DI water (30 mL) was added and the suspension was stirred at room temperature for 10 minutes. The insoluble solid was filtered off, washed with water and dried to yield the sodium sulfonate **45** as a colourless solid.

Preparation and characterisation of sodium 2,6-bis[(3*R*,6I)-6-isopropyl-3-methylcyclohex-1-en-1-yl]benzenesulfonate (+)-45a

Prepared according to general procedure **XXXV** on a 1.07 mmol scale of (+)-**44a** (490 mg). The title salt was obtained as a colourless solid (480 mg, 99%).



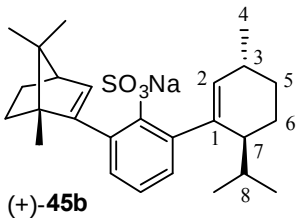
(+)-**45a**

m.p. 152-156 ºC; **FT-IR** ν_{max}(NaCl) 2957 cm^{-1} (C-H), 2929 cm^{-1} (C-H), 2868 cm^{-1} (C-H), 1366 cm^{-1} (SO_2), 1191 cm^{-1} (SO_2); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 0.69 (d, 6H, 2 × C<u>H</u>$_3$CHCH$_3$, *J* 7.0 Hz), 0.76 (d, 6H, 2 × C<u>H</u>$_3$CHCH$_3$, *J* 7.0 Hz), 0.94 (d, 6H, H-4, *J* 7.0 Hz), 1.27-1.35 (m, 4H, H-5a, H-6a), 1.57-1.71 (m, 6H, H-5b, H-6b, H-8), 2.06-2.17 (m, 2H, H-3), 3.15 (br s, 2H, H-7), 5.15 (s, 2H, H-2), 6.82 (d, 2H, H-9, *J* 7.5 Hz), 7.04 (t, 1H, H-10, *J* 7.5 Hz); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 16.9 (<u>C</u>H$_3$CHCH$_3$), 21.1 (C-6), 21.3 (CH$_3$CH<u>C</u>H$_3$), 21.9 (C-4), 27.7 (C-8), 29.9 (C-5), 30.6 (C-3), 42.1 (C-7), 125.8

(Ar-CH), 129.5 (Ar-CH), 130.4 (C-2), 141.6 (Cquat.), 144.8 (Cquat.).145.1 (Cquat.); **HRMS** (ES+) exact mass calculated for $[M-Na]^-$ ($C_{26}H_{37}O_3S^-$) requires ***m/z*** 429.2469, found ***m/z*** 429.2477; $[\alpha]_D^{25} = +51.3$ (*c* 1.18, MeOH).

Preparation and characterisation of sodium 2-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]-6-[(1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzenesulfonate (+)-45b

Prepared according to general procedure **XXXV** on a 0.21 mmol scale of (+)-**44b** (95 mg). The title salt was obtained as a colourless solid (85 mg, 90%).

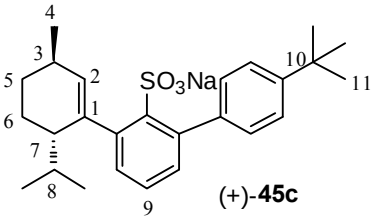


(+)-**45b**

m.p. 181-193 ºC; **FT-IR** ν_{max}(NaCl) 2954 cm^{-1} (C-H), 2869 cm^{-1} (C-H), 1384 cm^{-1} (SO_2), 1186 cm^{-1} (SO_2); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 0.51 (d, 3H, *J* 6.5 Hz), 0.74 (d, 3H, *J* 7.0 Hz), 0.76 (s, 3H), 0.89 (br s, 3H), 0.94 (d, 3H, *J* 7.0 Hz), 1.00-1.11 (m, 4H), 1.23-1.32 (m, 2H) 1.45-1.54 (m, 2H), 1.64-1.71 (m, 2H), 1.78-1.84 (m, 1H), 1.85-2.04 (br s, 1H), 2.10-2.21 (m, 1H), 3.31 (t, 1H, *J* 3.5 Hz) 3.38 (br s, 1H), 5.23 (s, 1H), 6.05 (br s, 1H), 6.84 (d, 1H, *J* 7.5 Hz), 6.94 (d, 1H, *J* 7.5 Hz), 7.08 (t, 1H, *J* 7.5 Hz); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 12.1, 16.5, 20.2, 20.4, 20.9, 21.4, 22.0, 25.6, 28.2, 29.9, 30.9, 31.4, 41.8, 51.3, 56.0, 57.1, 126.4, 126.9, 128.9, 129.5, 137.9, 142.8, 144.2, 147.2; **HRMS** (ES−) exact mass calculated for $[M-Na]^-$ ($C_{26}H_{35}O_3S^-$) requires ***m/z*** 427.2312, found ***m/z*** 427.2321; $[\alpha]_D^{25} = -14.2$ (*c* 1.0, $CHCl_3$).

Preparation and characterisation of sodium 4'-tert-butyl-3-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]biphenyl-2-sulfonate (+)-45c

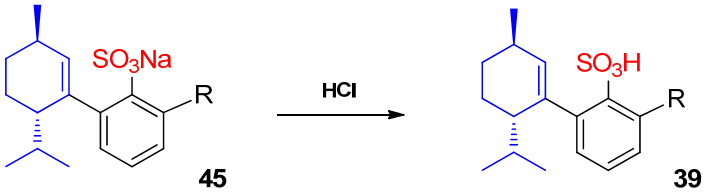
Prepared according to general procedure **XXXV** on a 0.22 mmol scale of (+)-**44c** (102 mg). The title salt was obtained as a colourless solid (94 mg, 91%).



(+)-**45c**

m.p. 288-290 ºC; **FT-IR** ν_{max}(NaCl) 2957 cm^{-1} (C-H), 2931 cm^{-1} (C-H), 2868 cm^{-1} (C-H), 1364 cm^{-1} (SO_2), 1218 cm^{-1} (SO_2); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 0.57 (d, 3H, C<u>H</u>$_3$CHCH$_3$, *J* 7.0 Hz), 0.79 (d, 3H, CH$_3$CHC<u>H</u>$_3$, *J* 7.0 Hz), 0.94 (d, 3H, H-4, *J* 7.0 Hz), 1.24-1.31 (m, 11H, H-5a, H-6a, H-11), 1.53-1.63 (m, 1H, H-8), 1.64-1.76 (m, 2H, H-5b, H-6b), 2.12-2.23 (m, 1H, H-3), 3.42-3.51 (m, 1H, H-7), 5.26 (br s, 1H, H-2), 6.91 (d, 1H, Ar-H, *J* 7.5 Hz), 6.99 (d, 1H, Ar-H, *J* 7.5 Hz), 7.17 (t, 1H, H-9, *J* 7.5 Hz), 7.25 (d, 2H, Ar-H, *J* 8.5 Hz), 7.35 (d, 2H, Ar-H, *J* 8.5 Hz); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ 16.4 (<u>C</u>H$_3$CHCH$_3$), 21.0 (CH$_3$CH<u>C</u>H$_3$), 21.4 (C-6), 22.0 (C-4), 28.3 (C-8), 30.0 (C-5), 30.9 (CH$_2$<u>C</u>HCH$_3$), 31.4 (C-11), 34.0 (C-10), 41.7 (C-7), 123.3 (Ar-<u>C</u>H), 127.1 (Ar-<u>C</u>H), 128.7 (Ar-<u>C</u>H), 129.9 (Ar-<u>C</u>H), 130.3 & 130.4 (Ar-<u>C</u>H, C-2), 141.0 (Cquat.), 142.0 (Cquat.), 142.7 (Cquat.), 144.0 (Cquat.), 146.6 (Cquat.), 147.1 (Cquat.); **HRMS** (ES−) exact mass calculated for $[M-Na]^-$ ($C_{26}H_{33}O_3S^-$) requires ***m/z*** 425.2156, found ***m/z*** 425.2164; $[\alpha]_D^{25}$ = + 55.5 (*c* 0.55, MeOH).

General procedure XXXVI for the acidification of sodium benzenesulfonates

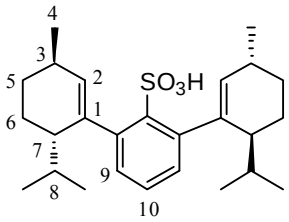


45 **39**

A suspension of **45** in 0.5 M aqueous HCl (10 mL per 0.100 g) was stirred for 2 minutes and extracted with diethyl ether (10 mL). The organic layer was dried ($MgSO_4$) and concentrated by a stream of nitrogen affording the free acid **39** as a colourless solid.

Preparation and characterisation of 2,6-Bis[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]benzenesulfonic acid (+)-39h

Prepared according the general procedure **XXXVI** on a 0.07 mmol scale. **(+)-39h** was obtained as a colourless solid (0.025 g, 86%).

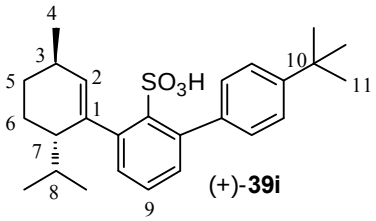


(+)-**39h**

m.p. 76-81 ºC; **FT-IR** ν_{max}(NaCl) 2958 cm^{-1} (C-H), 2932 cm^{-1} (C-H), 2870 cm^{-1} (C-H), 1367 cm^{-1} (SO_2), 1173 cm^{-1} (SO_2); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 0.70 (d, 6H, 2 × C<u>H</u>$_3$CHCH$_3$, *J* 6.5 Hz), 0.77 (d, 6H, 2 × CH$_3$CHC<u>H</u>$_3$, *J* 7.0 Hz), 0.94 (d, 6H, H-4, *J* 7.0 Hz), 1.23-1.36 (m, 4H, H-5a, H-6a), 1.56-1.69 (m, 6H, H-5b, H-6b, H-8), 2.08-2.18 (m, 2H, H-3), 3.00-3.13 (m, 2H, H-7), 5.19 (br s, 2H, H-2), 6.87 (d, 2H, Ar-H, *J* 7.5 Hz), 7.11 (t, 1H, Ar-H, *J* 7.5 Hz); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 16.9 (<u>C</u>H$_3$CHCH$_3$), 21.1 (C-6), 21.3 (CH$_3$CH<u>C</u>H$_3$), 21.8 (C-4), 27.7 (C-8), 29.9 (C-5), 30.6 (C-3), 42.4 (C-7), 126.6 (Ar-<u>C</u>H), 129.7 (Ar-<u>C</u>H), 131.2 (C-2), 141.8 (Cquat.), 143.6 (Cquat.).144.1 (Cquat.); ***m/z*** (ES−) 429 ([M−H]$^-$, 100%), **HRMS** (ES−) exact mass calculated for [M−H]$^-$ ($C_{26}H_{37}O_3S^-$) requires ***m/z*** 429.2469, found ***m/z*** 429.2469; $[\alpha]_D^{25}$ = + 52.9 (*c* 0.38, MeOH).

Preparation and characterisation of 4'-*tert*-Butyl-3-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]biphenyl-2-sulfonic acid (+)-39i

Prepared according to general procedure **XXXVI** on a 0.20 mmol scale. **(+)-39i** was obtained as a colourless solid (0.086 g, 97%).



(+)-**39i**

m.p. 78-84 ºC; **FT-IR** ν_{max}(NaCl) 3358 cm^{-1} (O-H), 2957 cm^{-1} (C-H), 2868 cm^{-1} (C-H), 1450 cm^{-1} (SO_2), 1188 cm^{-1} (SO_2); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 0.57 (d, 3H, C<u>H</u>$_3$CHCH$_3$, *J* 6.5 Hz), 0.79 (d, 3H, CH$_3$CHC<u>H</u>$_3$, *J* 6.5 Hz), 0.94 (d, 3H, H-4, *J* 7.0 Hz), 1.23-1.33 (m, 11H, H-5a, H-6a, H-11), 1.53-1.61 (m, 1H, H-8),

1.65-1.71 (m, 2H, H-5b, H-6b), 2.14-2.22 (m, 1H, H-3), 3.44 (br s, 1H, H-7), 5.27 (br s, 1H, H-2), 6.92 (d, 1H, Ar-H, *J* 7.5 Hz), 7.00 (d, 1H, Ar-H, *J* 7.5 Hz), 7.19 (t, 1H, Ar-H, *J* 7.5 Hz), 7.25 (d, 2H, Ar-H, *J* 8.5 Hz), 7.34 (d, 2H, Ar-H, *J* 8.0 Hz); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 16.4 ($\underline{C}H_3CHCH_3$), 21.0 ($CH_3CH\underline{C}H_3$), 21.4 (C-6), 22.0 (C-4), 28.3 (C-8), 30.0 (C-5), 31.0 (C-3), 31.4 (C-11), 34.1 (C-10), 41.7 (C-7), 123.4 (Ar-$\underline{C}$H), 127.3 (Ar-$\underline{C}$H), 128.7 (Ar-$\underline{C}$H), 130.0 & 130.4 & 130.6 (2 × Ar-$\underline{C}$H, C-2), 141.0 (Cquat.), 141.9 (Cquat.), 142.7 (Cquat.), 143.6 (Cquat.), 146.5 (Cquat.), 147.2 (Cquat.); ***m/z*** (ES−) 426 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-Na]^-$ ($C_{26}H_{33}O_3S^-$) requires ***m/z*** 425.2156, found ***m/z*** 425.2164; $[\alpha]_D^{25}$ = + 57.5 (*c* 0.16, MeOH).

[1] Liebig, J. *Liebigs Ann. Chem.* **1860**, *113*, 246.

[2] Bredig, G.; Fiske, P. S. *Bichem. Z.* **1912**, *46*, 7.

[3] (a) Pracejus, H. *Liebigs Ann. Chem.* **1960**, *634*, 9. (b) Pracejus, H. *Liebigs Ann. Chem.* **1960**, *634*, 23.

[4] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

[5] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[6] (a) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (b) Karlsson, S.; Hogberg, H. E. *Tetrahedron: Asymmetry* **2002**, *13*, 923.

[7] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

[8] Brown, S. P.; Goodwin, N. C.; MacMillan, D. C. W. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

[9] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[10] List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

[11] List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

[12] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

[13] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.

[14] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

[15] Terada, M.; Tanaka, H.; Sorimachi, K. *Synlett* **2008**, *11*, 1661.

[16] Itoh, J.; Fuchibe, K.; Akiyama, T. *Synthesis* **2008**, *8*, 1319.

[17] Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523.

[18] Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756.

[19] Akiyama, T.; Katoh, T.; Mori, K.; Kanno, K. *Synlett* **2009**, *10*, 1664.

[20] Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790.

[21] Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2007**, *9*, 1441.

[22] Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2257.

[23] Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. *Chem. Commun. 2008*, 4637.

[24] Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 2553.

[25] Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546.

[26] Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6717.

[27] Sickert, M.; Schneider, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3631.

[28] Giera, D. S.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10*, 4259.

[29] Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399.

[30] Li, G.; Kaplan, M. J.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2010**, *12*, 1960.

[31] Rueping, M.; Lin, M.-Y. *Chem. Eur. J.* **2010**, *16*, 4169.

[32] Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Köckritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065.

[33] Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.

[34] Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065.

[35] Nakamura, S.; Sakurai, Y.; Nakashima, H.; Shibata, N.; Toru, T. *Synlett* **2009**, *10*, 1639.

[36] Kang, Q.; Zheng, X.-J.; You, S.-L. *Chem. Eur. J.* **2008**, *14*, 3539.

[37] Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, 9, 2609.

[38] Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synt. Catal.* **2007**, *349*, 1863.

[39] Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484.

[40] Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292.

[41] Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5565.

[42] Wanner, M. J.; Hauwert, P.; Schoemaker, H. E.; Gelder (de), R.; Maarseveen (van), J. H.; Hiemstra, H. Eur. *J. Org. Chem*. **2008**, 180.

[43] Kang, Q.; Zhao, Z.-A.; You, S.-L. *Tetrahedron* **2009**, *65*, 1603.

[44] Enders, D.; Seppelt, M.; Beck, T. *Adv. Synth. Catal.* **2010**, *352*, 1413.

[45] Yang, J. W.; Hechevarria Fonseca, M. T.; List, B. *Angew. Chem. Int. Ed.* **2004**, *43*, 6660.

[46] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

[47] Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781.

[48] Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.

[49] Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

[50] Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498.

[51] Rueping, M.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4562.

[52] Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3683.

[53] Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 759.

[54] Rueping, M.; Sugiono, E.; Steck, A.; Theissmann, T. *Adv. Synth. Catal.* **2010**, *352*, 281.

[55] Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001.

[56] Metallinos, C.; Barrett, F. B.; Xu, S. *Synlett* **2008**, *5*, 720.

[57] Rueping, M.; Tato, F.; Schoepke, F. R. *Chem. Eur. J.* **2010**, *16*, 2688.

[58] Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6751.

[59] Gong, L.-Z.; Xiao, H.; Han, Z.-Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3729.

[60] Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830.

[61] Kang, Q.; Zhao, Z.-A.; You, S.-L. *Adv. Synth. Catal.* **2007**, *349*, 1657.

[62] Kang, Q.; Zhao, Z.-A.; You, S.-L. *Org. Lett.* **2008**, *10*, 2031.

[63] Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075.

[64] Che, C.-M.; Liu, X.-Y. *Org. Lett.* **2009**, *11*, 4204.

[65] Li, C.; Wang, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 14450.

[66] Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180.

[67] Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193.

[68] Stadler, M.; List, B. *Synlett* **2008**, *4*, 597.

[69] Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.

[70] Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.

[71] Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.

[72] Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796.

[73] Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, *1*, 141.

[74] Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 6023.

[75] Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327.

[76] Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070.

[77] Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652.

[78] Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946.

[79] Li, N.; Song, J.; Tu, X.-F..; Chen, X.-H.; Gong, L.-Z. *Org. Biomol. Chem.* **2010**, *8*, 2016.

[80] Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 1275.

[81] Chen, X.-H.; Qiang, W.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *11*, 13819.

[82] Liu, W.-J.; Chen, X.-H.; Gong, L.-Z. *Org. Lett.* **2008**, *10*, 5357.

[83] Rueping, M.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 10090.

[84] Müller, S.; List. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9975.

[85] Rowland, B. G.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696.

[86] Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, *43*, 4477.

[87] Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786.

[88] Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 908.

[89] Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216.

[90] Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583.

[91] Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 5079.

[92] Akiyama, T.; Morita, H.; Bachu, P.; Mori, K.; Yamanaka, M.; Hirata, T. *Tetrahedron* **2009**, *65*, 4950.

[93] Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6903.

[94] Rueping, M.; Sugiono, E.; Moreth, S. A. *Adv. Synth. Catal.* **2007**, *349*, 759.

[95] Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.

[96] Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360.

[97] Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445.

[98] Zeng, X.; Zeng, X.; Xu, Z.; Lu, M.; Zhong, G. *Org. Lett.* **2009**, *11*, 3036.

[99] Tang, H.-Y.; Lu, A.-D.; Zhou, Z.-H. ; Zhao, G.-F. ; He, L.-N.; Tang, C.-C. *Eur. J. Org. Chem.* **2008**, *8*, 1406.

[100] Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 593.

[101] Bachu, P.; Akiyama, T. *Chem. Commun.* **2010**, *46*, 4112.

[102] Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056.

[103] Nie, J.; Zhang, G.-W.; Wang, L.; Zheng, D.-H.; Zheng, Y.; Ma, J.-A. *Eur. J. Org. Chem.* **2009**, *9*, 3145.

[104] Kashikura, W.; Itoh, J.; Mori, K.; Akiyama, T. *Chem. Asian J.* **2010**, *5*, 470.

[105] Sun, F.-L.; Zeng, M.; Gu, Q.; You, S.-L. *Chem. Eur. J.* **2009**, *15*, 8709.

[106] Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6798.

[107] Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4122.

[108] Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430.

[109] Zeng, X.; Ye, K.; Lu, M.; Chua, P. J.; Tan, B.; Zhong, G. *Org. Lett.* **2010**, *12*, 2414.

[110] Cheon, C. H.; Yamamoto, H. *Org. Lett.* **2010**, *12*, 2476.

[111] Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4226.

[112] Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 9652.

[113] Momiyama, N.; Tabuse, H.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 12882.

[114] Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2097.

[115] Rueping, M.; Ieawsuwan, W. *Adv. Synth. Catal.* **2009**, *351*, 78.

[116] Čorić, I.; Vellalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536.

[117] Hong, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246.

[118] Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030.

[119] For a review see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

[120] Srinivasan, N.; Ganesan, A. *Chem. Commun.* **2003**, 916.

[121] Hegedüs, A.; Hell, Z. *Tetrahedron Lett.* **2004**, *45*, 8553.

[122] Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

[123] For recent examples see: (a) Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishevsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 8506. (b) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148. (c) Wu, Y.-C.; Zhu, J. *Org. Lett.* **2009**, *11*, 5558.

[124] Bogle, K. M.; Hirst, D. J.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 1252.

[125] Bogle, K. M.; Hirst, D. J.; Dixon, D. J. *Tetrahedron* **2010**, *66*, 6399.

[126] Koketsu, K.; Watanabe, K.; Suda, H.; Oguri, H.; Oikawa, H. *Nat. Chem. Biol.* **2010**, *6*, 408.

[127] Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086.

[128] Wanner, M. J.; Haas (van der), R. N. S.; Cuba (de), R.; Maarseveen (van) J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 7485.

[129] Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; Gelder (de), R.; Maarseveen (van) J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405.

[130] Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.

[131] Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745.

[132] Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577.

[133] Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2006**, *65*, 6319.

[134] Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975.

[135] Singh, R.; Czekelius, C.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *Organometallics*, **2007**, *26*, 2528.

[136] (a) Dolman, S. J.; Hultzsch, K. C.; Pezet, F.; Teng, X.; Hoveyda, A. H.; Schrock R. R. *J. Am. Chem. Soc.* **2004**, *126*, 10945. (b) Gribkhov, D. V.; Hultzsch, K. C.; Hampel, F. *Chem. Eur. J.* **2003**, *9*, 4796.

[137] Cram, D. J. ; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeieer, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. *J. Org. Chem.* **1978**, *43*, 1930.

[138] Fernández-Ibáñez, M. Á.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2008**, 2571.

[139] Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190.

[140] Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

[141] Padwa, A.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 5139.

[142] Modified procedure from Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, *8*, 5287.

[143] Modified procedure from (a) Still, I. W.; Strautmanis, J. R. *Can. J. Chem.*, **1990**, *68*, 1408. (b) Palmer, F. N.; Lach, F.; Poriel, C.; Pepper, A. G.; Bagley, M. C.; Slawin, A. M. Z.; Moody, C. J. *Org. Biomol. Chem.* **2005**, *3*, 3805. (c) Davies, J. R.; Kane, P. D.; Moody, C. J. *J. Org. Chem.* **2005**, *70*, 7305.

[144] Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070.

[145] Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem*. **1997**, *62*, 367.

[146] Modified procedure from (a) Høg, S. ; Wellendorph, P.; Nielsen, B.; Frydenvang, K.; Dahl, I. F.; Bräuner-Osborne, H.; Brehm, L.; Frølund, B.; Clausen, R. P. *J. Med. Chem.* **2008**, *51*, 8088. (b) Srinivas, C.; Raju, C. M. H.; Acharyulu, P. V. R. *Org. Process Res. Dev.* **2004**, *8*, 291.

[147] Modified procedure from Tamura, Y.; Shirouchi, Y.; Minamikawa, J.-I.; Haruta, J.-I. *Chem. Pharm. Bull.* **1985**, *33*, 551.

[148] Jones, D. J.; Gibson, V. C. *Heterocycles* **2006**, *68*, 1121.

[149] (a) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (b) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org.*

Lett. **2010**, *12*, 2266. (c) Lu, J.; Zhong, L.; Luo, S.; Cheng, J.-P. *Org. Lett.* **2010**, *12*, 1096.

[150] Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

[151] Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron: Asymmetry* **1991**, *2*, 481.

[152] Liao, S.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 628.

[153] Rhodium-promoted cycloisomerisation of alkynoic acids: (a) Chan, D. M. T.; Marder, T. B.; Milstein, D.; Taylor, N. J. *J. Am. Chem. Soc.* **1987**, *109*, 6385. (b) Elgafi, S.; Field, L. D.; Messerle, B. A. *J. Organomet. Chem.* **2000**, *607*, 97. (c) Lim, S.-G.; Kwon, B.-I.; Choi, M.-G.; Jun, C.-H. *Synlett* **2005**, *7*, 1113.

[154] Ruthenium-promoted cycloisomerisation of alkynoic acids: (a) Melis, K.; Verpoort, F. *J. Mol. Catal. A: Chem.* **2003**, *194*, 39.

[155] Mercury- promoted cycloisomerisation of alkynoic acids: (a) Imagawa, H.; Fujikawa, Y.; Tsuchihiro, A.; Kinoshita, A.; Yoshinaga, T.; Takao, H.; Nishizawa, M. *Synlett* **2006**, *4*, 639.

[156] Molybdenum-promoted cycloisomerisation of alkynoic acids: (a) Takei, I.; Wakebe, Y.; Suzuki, K.; Enta, Y.; Suzuki, T.; Mizobe, Y.; Hidai, M. *Organometallics* **2003**, *22*, 4639. (a) Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2123.

[157] Palladium-promoted cycloisomerisation of alkynoic acids: (a) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. (b) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753.

[158] Silver-promoted cycloisomerisation of alkynoic acids: Jong, T.-T.; Williard, P. G.; Porwoll J. P. *J. Org. Chem.* **1984**, *49*, 735.

[159] For relevant discussions on DYKAT, see: (a) Steinreiber, J.; Faber, K.; Griengl, H. *Chem. Eur. J.* **2008**, *14*, 8060. See also, (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543.

[160] (a) Jayaprakash, D.; Sasai, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2589. (b) Kobayashi, S.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225. (c) Lipshutz, B. H.; Shin, Y.-J. *Tetrahedon Lett.* **2000**, *41*, 9515. (d) Sellner, H.; Faber, C.; Rheiner, P. B.; Seebach, D. *Chem. Eur. J.* **2000**, *6*, 3692.

[161] Wang, X. ; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 1119.

[162] Pilling, A. W.; Boehmer, J.; Dixon, D. J. *Angew. Chem . Int. Ed.* **2007**, *46*, 5428.

[163] Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129.

[164] Franzén, J.; Fischer, A. *Angew. Chem. Int. Ed.* **2008**, *48*, 787.

[165] Lygin, A. V.; Meijere (de), A. *Eur. J. Org. Chem.* **2009**, *30*, 5138.

[166] Cuadro, A. M.; Matia, M. P.; Garcia, J. L.; Vaquero, J. J.; Alvarez-Builla, J. *Synth. Commun.* **1991**, *21*, 535.

[167] Maresh, J. J. ; Giddings, L.-A.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stöckigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 710.

[168] Reviews : (a) Akiyama, T. *Chem. Rev.*, **2007**, *107*, 5745. (b) Terada, M. *Synthesis* **2010**, *12*, 1929.

[169] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

[170] Armarego, W. L. F., Turner, E. E. *J. Chem. Soc.* **1957**, 13.

[171] Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858.

[172] Hatano, M.; Hattori, Y.; Furuya, Y.; Kazuaki, I. *Org. Lett.* **2009**, *11*, 2321.

[173] García-García, P; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 4363.

[174] Yong, L.; Butenschön, H. *Chem. Commun.* **2002**, 2852.

[175] Sigman, M. S.; Fatland, A. W.; Eaton, B. E. *J. Am. Chem. Soc.* **1998**, *120*, 5130.

[176] Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

[177] (a) Ghosh, A.; Sieser, J. E.; Caron, S.; Couturier, M.; Dupont-Gaudet, K.; Girardin, M. *J. Org. Chem.* **2006**, *71*, 1258. (b) Tatsumi, R.; Fujio, M.; Satoh, H.; Katayama, J.; Takanashi, S.-I.; Hashimoto, K.; Tanaka, H. *J. Med. Chem.* **2005**, *48*, 2678. (d) G. D. Holl. *Boronic Acids*, WILEY-VCH Verlag Gmbh & Co. KGaA, Weinheim, **2005**. (e) D. Brillon, P. Deslongchamps, *Can. J. Chem*., 1987, **65**, 43.

[178] Newton, A. *J. Am. Chem. Soc.* **1943**, *65*, 2439.

[179] For selected examples, see: (a) Blanchet, J.; Macklin, T.; Ang, P.; Metallinos, C.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 3199. (b) Oishi, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1. (c) Spangler, L.A. *Tetrahedron Lett.* **1996**, *37*, 3639.

[180] Our method was inspired by a thorough study on copper(I)-catalysed coupling of amine and amide onto aryl halides: Klapars, R.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

[181] Feng, D.-Z.; Song, Y.-L.; Jiang, X.-H.; Chen, L.; Long, Y.-Q. *Org. Biomol. Chem.* **2007**, *5*, 2690.

[182] Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586.

[183] Lu, C.-D.; Zakarian, A. *Org. Synth.* **2008**, *85*, 158.

[184] Benoit, D.; Coulbeck, E.; Eames, J.; Motevalli, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1068.

[185] Jarboe, S. G.; Terrazas, M. S. ; Beak, P. *J. Org. Chem.* **2008**, *73*, 9627.

[186] Samanta, S.; Srikanth, K.; Banerjee, S.; Debnath, B.; Gayen, S.; Jha, T. *Bioorg. Med. Chem.* **2004**, *12*, 1413.

[187] Gopalsamy, A.; Shi, M.; Stauffer, B.; Bahat, R.; Billiard, J.; Ponce-de-Leon, H.; Seestaller-Wehr, L.; Fukuyama, S.; Mangine, A.; Moran, R.; Krishnamurthy, G.; Bodine, P. *J. Med. Chem.* **2008**, *51*, 7670.

[188] Andersen, K. K.; Malver, O. *J. Org. Chem.* **1983**, *48*, 4803.

[189] Alo, B.; Familoni, O. B. *J. Chem. Soc., Perkin Trans 1* **1990**, 1611.

[190] Bonfiglio, J. N. *J. Org. Chem.* **1986**, *51*, 2833.

[191] Sekine, M.; Aoyagi, M.; Ushioda, M.; Ohkubo, A.; Seio, K. *J. Org. Chem.* **2005**, *70*, 8400.

[192] Liu, S.-J.; Zhao, Q.; Fan, Q.-L.; Huang, W. *Eur. J. Inorg. Chem.* **2008**, 2177.

[193] Paquette, L. A.; Ra, C. S.; Edmonson, S. D. *J. Org. Chem.* **1990**, *55*, 2443.

[194] Scheiper, B.; Bonnekessel, M.; Krause, H.; Furstner, A. *J. Org. Chem.* **2004**, *69*, 3943.

[195] Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419.

[196] (a) Ding, K.; Wang, Y.; Zhang, L.; Wu, Y. *Tetrahedron* **1996**, *52*, 1005. (b) Toda, K.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007.

[197] Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991.

[198] Wang, Y.; Sun, J.; Ding, K. *Tetrahedron* **2000**, *56*, 4447.

[199] Lingenfelter, D. S.; Hegelson, R. S.; Cram, D. J. *J. Org. Chem.* **1981**, *46*, 393.

[200] Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536.

[201] Tani, F.; Matsu-ura, M.; Nakayama, S. ; Ichimura, M.; Nakamura, N. ; Naruta, Y. *J. Am. Chem. Soc.* **2001**, *123*, 1133.

[202] Sigma-Aldrich®; http://www.sigmaaldrich.com/catalog/ProductDetail.do?N4=700673|ALDRICH&N5=SEARCH_CONCAT_PNO|BRAND_KEY&F=SPEC (accessed 15 December 2010).

[203] Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251.

[204] Xu, Y.; Larkson, G. C.; Docherty, G. ; North, C. L.; Woodward, G.; Wills, M. *J. Org. Chem.* **2005**, *70*, 8079.

[205] Sigma-Aldrich®; http://www.sigmaaldrich.com/catalog/ProductDetail.do?N4=700665|ALDRICH&N5=SEARCH_CONCAT_PNO|BRAND_KEY&F=SPEC (accessed 15 December 2010).

[206] Inanaga, J. Eur. Pat. Appl. EP-A1-134209, 2001.

[207] Korostylev, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Borner, A. *J. Org. Chem.* **2004**, *69*, 3220.

[208] Ouyang, X.; Chen, Z.; Liu, X.; Yang, Y.; Deng, M.; Weng, L.; Zhou, Y.; Jia, Y. *Inorg. Chem. Commun.* **2008**, *11*, 948.

[209] Schrock, R. R.; Jamieson, J. Y.; Dolman, S. J.; Miller, S. A.; Bonitatebus (Jr.), P. J.; Hoveyda, A. H.; *Organometallics* **2002**, *21*, 409.

[210] Al-Sa'Ady, A. K.; McAuliffe, C. A; Parish, R. V.; Sandeank, J. A. *Inorg. Synth.*, **1985**, 191.

[211] Belmont, D. T.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 4102.

[212] Somei, M.; Kizu, K.; Kunimoto, M.; Yamada, F. *Chem. Pharm. Bull.* **1985**, *33*, 3696.

[213] Kalinin, A. V.; Chauder, B. A. ; Rakhit, S. ; Snieckus, V. *Org. Lett.* **2003**, *5*, 3519.

[214] Kalir, A.; Szara, S. *J. Med. Chem.* **1963**, *6*, 716.

[215] Pedras, M. S.; Ahiahonu, P. W. K. *Bioorg. Med. Chem.* **2002**, *10*, 3307.

[216] Mor, M.; Rivara, S.; Silva, C.; Bordi, F.; Plazzi, P. V. *J. Med. Chem.* **1998**, *41*, 3831.

[217] Nicolaou, K. C.; Krasovskiy, A.; Trépanier, V. É.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.*, **2008**, *47*, 4217.

[218] Guo, W.; Wong, T. C. *Mag. Res. Chem.* **1986**, *24*, 75.

[219] Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; Leon (de), P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843.

[220] Henderson, B. S.; Larsen, B. S.; Schwab, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 5025.

[221] Camps, F.; Hospital, S.; Rosell, G.; Delgado, A.; Guerrero, A. *Chem. Phys. Lipids* **1992**, *61*, 157.

[222] Auria (D'), M.; Mico (De), A.; Piancatelli, G.; Scettri, A. *Tetrahedron* **1982**, *38*, 1661.

[223] Alam, M. M.; Husain, A.; Hasan, S. M.; Suruchi; Anwer, T. *Eur. J. Med. Chem.* **2009**, *44*, 2636.

[224] Skraup, S. ; Schwamberger, E. *Liebigs Ann. Chem.* **1928**, *462*, 135.

[225] Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 2217.

[226] Reinheimer, J. D.; Taylor, S. *J. Org. Chem.* **1954**, *19*, 802.

[227] Husain, A.; Khan, M. S. Y.; Hasan, S. M.; Alam, M. M. *Eur. J. Med. Chem.* **2005**, *40*, 1394.

[228] Husain, A.; Ahmad, A.; Alam, M. M.; Ajmal, M.; Ahuja, P. *Eur. J. Med. Chem.* **2009**, *44*, 3798.

[229] Knochel, P.; Rao, C. J. *Tetrahedron* **199**3, *49*, 29.

[230] Pelter, A. *Tetrahedron Lett.*, **1987**, *28*, 1203.

[231] Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

[232] Bartlett, P. A. *J. Am. Chem. Soc.* **1976**, *98*, 3305.

[233] Child, R. G.; Osterberg, A. C.; Sloboda, A. E.; Tomcufcik, A. S. *J. Pharm. Sci.* **1977**, *66*, 466.

[234] Modified procedure from: Lash, T. D.; Mani, U. N.; Lyons, E. A.; Thientanavanich, P.; Jones, M. A. *J. Org. Chem.* **1999**, *64*, 478.

[235] Lopez Aparicio, F. J.; Lopez Herrera, F. J.; Sanchez Ballesteros, J. *Carbohydr. Res.* **1979**, *69*, 55.

[236] According to a modified procedure: Brooks, D. W.; Bevinakatti, H. S.; Kennedy, E.; Hathaway, J. *J. Org. Chem.* **1985**, *50*, 628.

[237] Koul, S.; Crout, D. H. G.; Errington, W.; Tax, J. *J. Chem. Soc. Perkin Trans. I*, **1995**, *23*, 2969.

[238] Kötz, A. *Liebigs Ann.* Chem. **1906**, *350*, 229; Linstead, R. P.; Meade, E. M. *J. Chem. Soc.* **1934**, 935.

[239] Boers, R. B.; Gast, P.; Hoff, A. J.; Groot (de), H. J. M.; Lugtenburg, J. Eur. *J. Org. Chem.* **2002**, 189.

[240] Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899.

[241] Cho, C. S.; Kim, J. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2001**, *57*, 3321.

[242] Sako, K.; Aoyama, H.; Sato, S.; Hashimoto, Y.; Baba, M. *Bioorg. Med. Chem.* **2008**, *16*, 3780.

[243] Torisawa, Y.; Hashimoto, A.; Nakagawa, M.; Seki, H.; Hara, R.; Hino, T. *Tetrahedron* **1991**, *47*, 8067.

[244] Pal, B.; Pradhan, P. K.; Jaisankar, P.; Giri, V. S. *Synthesis* **2003**, *10*, 1549.

[245] Morrison, G. C.; Cetenko, W.; Shavel (Jr.), J. *J. Org. Chem.* **1964**, *49*, 2771.

[246] Paz, J.; Pérez-Baldo, C.; Iglesias, B.; Muñoz, L. *J. Org. Chem.* **2010**, *75*, 3037.

[247] Bégis, G.; Cladingboel, D. E.; Jerome, L.; Motherwell, W. B.; Sheppard, T. D. *Eur. J. Org. Chem.* **2009**, 1532.

[248] Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941.

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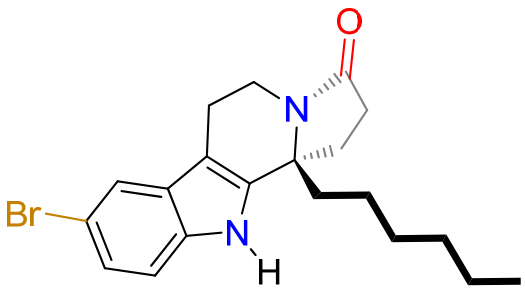
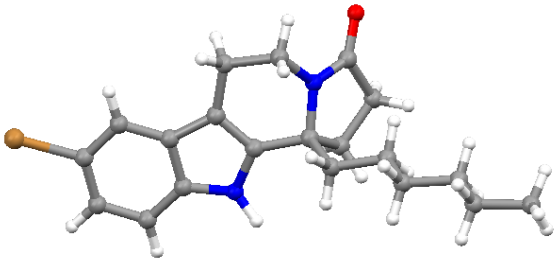
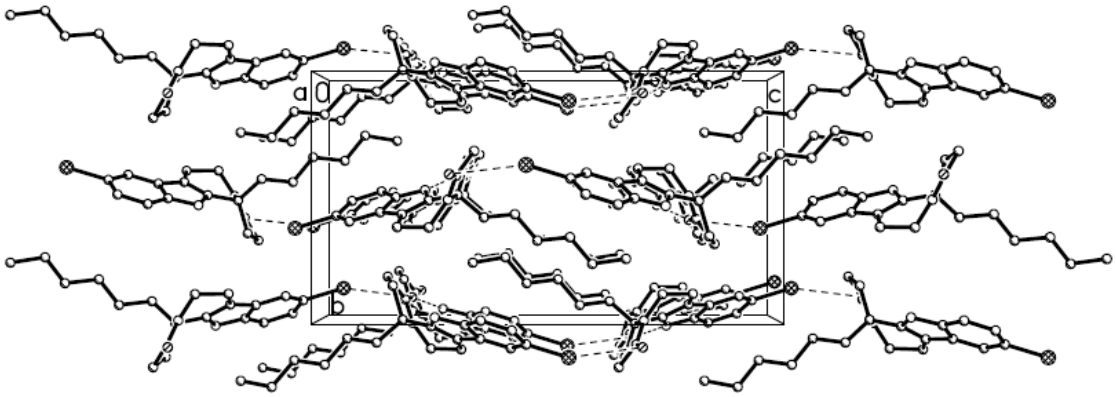
Chapter Four: Mechanistic Apsect: a model for the origin of enantioselectivity and an explanation for the limitations

Chapter Five: Development of new chiral benzenesulphonic acids: chiral mimics of *para*-toluenesulfonic acid







Crystal data and structure refinement for (+)-18u

Empirical formula	$C_{20}H_{25}BrN_2O$
Formula weight	389.33
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 8.010(2) Å alpha = 90°
	b = 10.902(2) Å beta = 90°
	c = 20.373(5) Å gamma = 90°
Volume	1779.0(7) $Å^3$
Z, Calculated density	4, 1.454 Mg/m^3

Absorption coefficient	2.320 mm^{-1}
F(000)	808
Crystal size	0.30 x 0.25 x 0.10 mm
Theta range for data collection	2.00 to 26.38°
Limiting indices	$-9 \leq h \leq 9, -13 \leq k \leq 12, -25 \leq l \leq 15$
Reflections collected / unique	10334 / 3620 [R(int) = 0.0520]
Completeness to theta = 26.38	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.704
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3620 / 0 / 219
Goodness-of-fit on F^2	0.969
Final R indices [I > 2sigma(I)]	R1 = 0.0399, wR2 = 0.0699
R indices (all data)	R1 = 0.0535, wR2 = 0.0733
Absolute structure parameter	0.017(9)
Largest diff. peak and hole	0.568 and − 0.364 $e.A^{-3}$

Atomic coordinates (× 10^4) and equivalent isotropic Displacement parameters (A^2 × 10^3) for (*R*)-18u

U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

	x	y	z	U(eq)
Br(1)	-1964(1)	6228(1)	-437(1)	24(1)
O(1)	5765(3)	4115(2)	3004(1)	19(1)
N(1)	-1125(3)	4696(2)	2375(2)	15(1)
N(2)	3223(3)	5077(2)	2938(1)	14(1)
C(1)	-1761(4)	5723(3)	456(2)	18(1)
C(2)	-3120(5)	5131(3)	750(2)	18(1)
C(3)	-3022(5)	4748(3)	1394(2)	18(1)
C(4)	-1559(4)	4980(3)	1738(2)	14(1)
C(5)	-176(4)	5579(3)	1439(2)	14(1)
C(6)	-290(4)	5941(3)	783(2)	14(1)
C(7)	494(4)	5107(3)	2487(2)	13(1)
C(8)	1100(4)	5647(3)	1932(2)	13(1)
C(9)	2847(4)	6134(3)	1878(2)	15(1)
C(10)	3708(4)	6141(3)	2550(2)	15(1)
C(11)	1447(4)	4884(3)	3109(2)	15(1)
C(12)	1423(4)	3518(3)	3322(2)	14(1)
C(13)	3234(4)	3200(3)	3477(2)	17(1)
C(14)	4257(4)	4159(3)	3117(2)	14(1)
C(15)	906(4)	5771(3)	3655(2)	17(1)
C(16)	1827(5)	5649(3)	4309(2)	19(1)

C(17)	1374(4)	6678(3)	4780(2)	20(1)
C(18)	2130(4)	6540(3)	5460(2)	18(1)
C(19)	1679(4)	7583(3)	5927(2)	20(1)
C(20)	2316(4)	7375(3)	6624(2)	21(1)

Bond lengths (Å) and angles (°) for (*R*)-18u

Bond lengths

Br(1)-C(1)	1.907(4)	C(11)-C(15)	1.536(5)
O(1)-C(14)	1.231(4)	C(11)-C(12	1.552(5)
N(1)-C(4)	1.378(5)	C(12)-C(13)	1.525(5)
N(1)-C(7)	1.391(4)	C(12)-H(12A)	0.9900
N(1)-H(1N)	0.9598	C(12)-H(12B)	0.9900
N(2)-C(14)	1.349(4)	C(13)-C(14)	1.518(4)
N(2)-C(10)	1.456(4)	C(13)-H(13A)	0.9900
N(2)-C(11)	1.480(4)	C(13)-H(13B)	0.9900
C(1)-C(6)	1.374(5)	C(15)-C(16)	1.530(5)
C(1)-C(2)	1.400(5)	C(15)-H(15A)	0.9900
C(2)-C(3)	1.380(5)	C(15)-H(15B)	0.9900
C(2)-H(2)	0.9500	C(16)-C(17)	1.519(5)
C(3)-C(4)	1.389(5)	C(16)-H(16A)	0.9900
C(3)-H(3)	0.9500	C(16)-H(16B)	0.9900
C(4)-C(5)	1.423(4)	C(17)-C(18)	1.519(5)
C(5)-C(6)	1.396(5)	C(17)-H(17A)	0.9900
C(5)-C(8)	1.435(5)	C(17)-H(17B)	0.9900
C(6)-H(6)	0.9500	C(18)-C(19)	1.527(4)
C(7)-C(8)	1.364(5)	C(18)-H(18A)	0.9900
C(7)-C(11)	1.499(5)	C(18)-H(18B)	0.9900
C(8)-C(9)	1.500(4)	C(19)-C(20)	1.524(5)
C(9)-C(10)	1.533(4)	C(19)-H(19A)	0.9900

C(9)-H(9A)	0.9900	C(19)-H(19B)	0.9900
C(9)-H(9B)	0.9900	C(20)-H(20A)	0.9800
C(10)-H(10A)	0.9900	C(20)-H(20B)	0.9800
C(10)-H(10B)	0.9900	C(20)-H(20C)	0.9800

Angles

C(4)-N(1)-C(7)	108.5(3)	H(15A)-C(15)-H(15B)	107.4
C(4)-N(1)-H(1N)	131.8	N(2)-C(11)-C(7)	105.5(3)
C(7)-N(1)-H(1N)	116.4	N(2)-C(11)-C(15)	110.6(3)
C(14)-N(2)-C(10)	125.0(3)	C(7)-C(11)-C(15)	111.5(3)
C(14)-N(2)-C(11)	114.9(3)	N(2)-C(11)-C(12)	102.3(2)
C(10)-N(2)-C(11)	119.8(3)	C(7)-C(11)-C(12)	112.7(3)
C(6)-C(1)-C(2)	122.6(3)	C(15)-C(11)-C(12)	113.4(3)
C(6)-C(1)-Br(1)	119.1(3)	C(13)-C(12)-C(11)	105.3(3)
C(2)-C(1)-Br(1)	118.3(3)	C(13)-C(12)-H(12A)	110.7
C(3)-C(2)-C(1)	120.1(3)	C(11)-C(12)-H(12A)	110.7
C(3)-C(2)-H(2)	119.9	C(13)-C(12)-H(12B)	110.7
C(1)-C(2)-H(2)	119.9	C(11)-C(12)-H(12B)	110.7
C(2)-C(3)-C(4)	118.3(3)	H(12A)-C(12)-H(12B)	108.8
C(2)-C(3)-H(3)	120.9	C(14)-C(13)-C(12)	104.9(3)
C(4)-C(3)-H(3)	120.9	C(14)-C(13)-H(13A)	110.8
N(1)-C(4)-C(3)	130.3(3)	C(12)-C(13)-H(13A)	110.8
N(1)-C(4)-C(5)	108.1(3)	C(14)-C(13)-H(13B)	110.8
C(3)-C(4)-C(5)	121.6(3)	C(12)-C(13)-H(13B)	110.8
C(6)-C(5)-C(4)	119.3(3)	H(13A)-C(13)-H(13B)	108.9

C(6)-C(5)-C(8)	134.6(3)	C(17)-C(16)-C(15)	111.7(3)
C(4)-C(5)-C(8)	106.2(3)	C(17)-C(16)-H(16A)	109.3
C(1)-C(6)-C(5)	118.1(3)	C(15)-C(16)-H(16A)	109.3
C(1)-C(6)-H(6)	120.9	C(17)-C(16)-H(16B)	109.3
C(5)-C(6)-H(6)	120.9	C(15)-C(16)-H(16B)	109.3
C(8)-C(7)-N(1)	109.6(3)	H(16A)-C(16)-H(16B)	107.9
C(8)-C(7)-C(11)	126.1(3)	C(16)-C(17)-C(18)	114.0(3)
N(1)-C(7)-C(11)	124.1(3)	C(16)-C(17)-H(17A)	108.8
C(7)-C(8)-C(5)	107.7(3)	C(18)-C(17)-H(17A)	108.8
C(7)-C(8)-C(9)	123.0(3)	C(16)-C(17)-H(17B)	108.8
C(5)-C(8)-C(9)	129.2(3)	C(18)-C(17)-H(17B)	108.8
C(8)-C(9)-C(10)	110.8(3)	H(17A)-C(17)-H(17B)	107.6
C(8)-C(9)-H(9A)	109.5	C(17)-C(18)-C(19)	113.7(3)
C(10)-C(9)-H(9A)	109.5	C(17)-C(18)-H(18A)	108.8
C(8)-C(9)-H(9B)	109.5	C(19)-C(18)-H(18A)	108.8
C(10)-C(9)-H(9B)	109.5	C(17)-C(18)-H(18B)	108.8
H(9A)-C(9)-H(9B)	108.1	C(19)-C(18)-H(18B)	108.8
N(2)-C(10)-C(9)	111.1(3)	H(18A)-C(18)-H(18B)	107.7
N(2)-C(10)-H(10A)	109.4	C(20)-C(19)-C(18)	113.0(3)
C(9)-C(10)-H(10A)	109.4	C(20)-C(19)-H(19A)	109.0
N(2)-C(10)-H(10B)	109.4	C(18)-C(19)-H(19A)	109.0
C(9)-C(10)-H(10B)	109.4	C(20)-C(19)-H(19B)	109.0
H(10A)-C(10)-H(10B)	108.0	C(18)-C(19)-H(19B)	109.0
O(1)-C(14)-N(2)	125.6(3)	H(19A)-C(19)-H(19B)	107.8

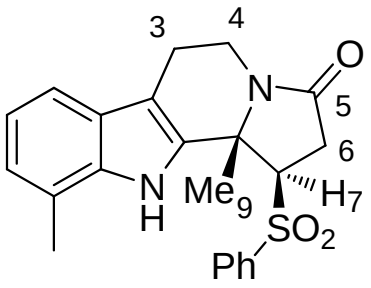
O(1)-C(14)-C(13)	126.3(3)	C(19)-C(20)-H(20A)	109.5
N(2)-C(14)-C(13)	108.1(3)	C(19)-C(20)-H(20B)	109.5
C(16)-C(15)-C(11)	116.1(3)	H(20A)-C(20)-H(20B)	109.5
C(16)-C(15)-H(15A)	108.3	C(19)-C(20)-H(20C)	109.5
C(11)-C(15)-H(15A)	108.3	H(20A)-C(20)-H(20C)	109.5
C(16)-C(15)-H(15B)	108.3	H(20B)-C(20)-H(20C)	109.5
C(11)-C(15)-H(15B)	108.3		

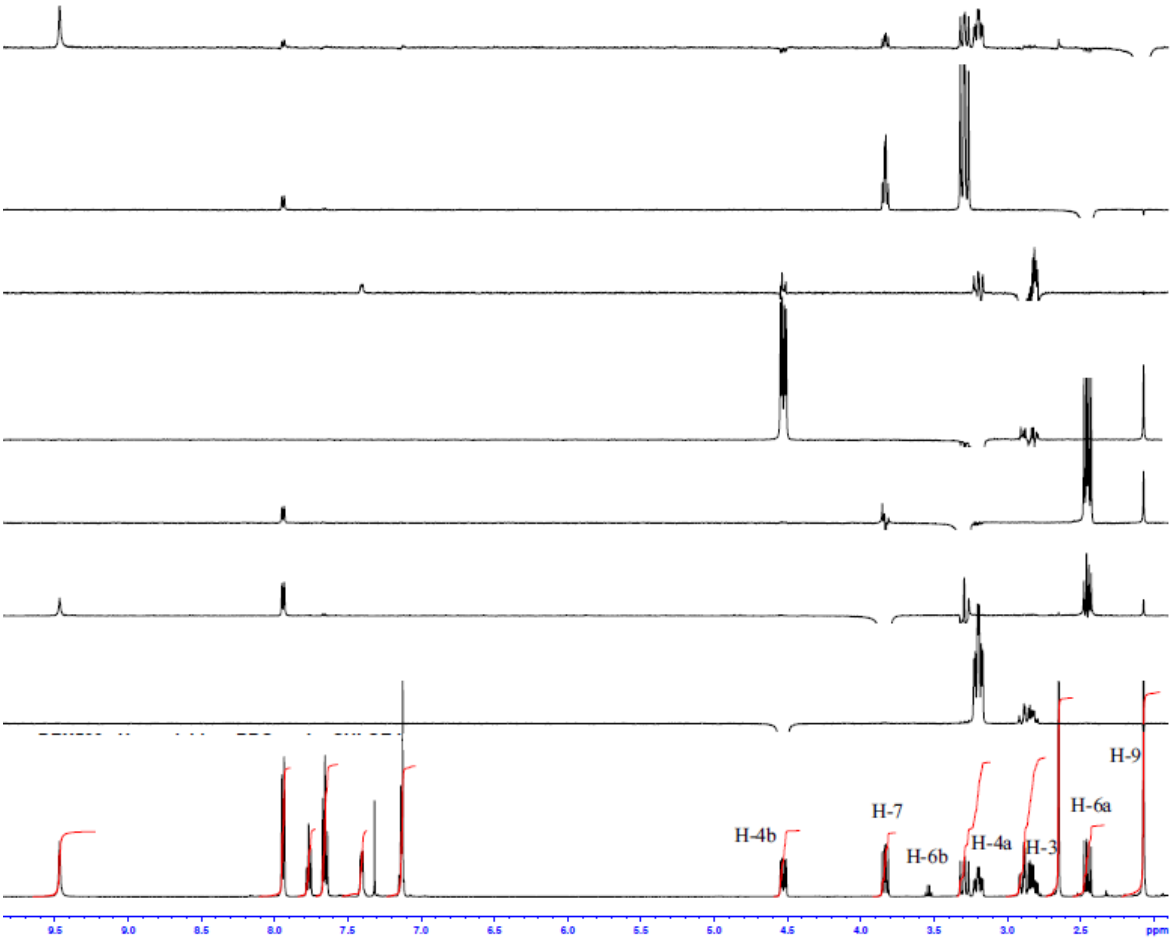
Hydrogen bonds for (+)-18u [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)^{i}	0.96	2.07	2.872(4)	139.6

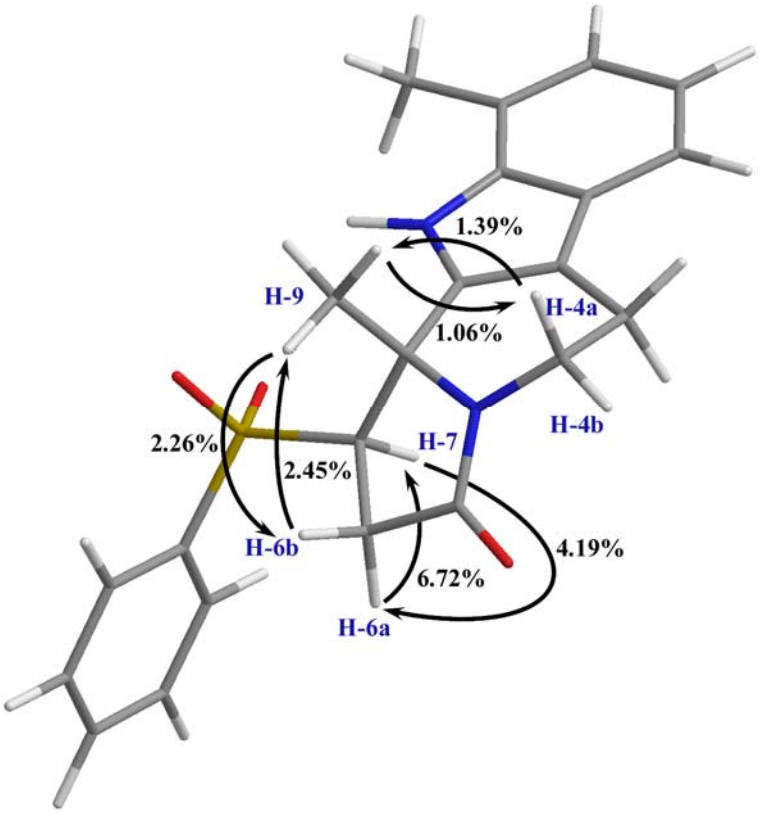
Symmetry code: (i) x-1,y,z

nOe experiments performed on (+)-21b:



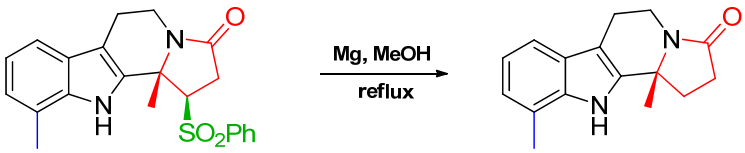


Summary of the relevant nOe responses observed for (+)-21b



3D model obtained with ChemDraw (no energy minimization performed)

Desulphonylation of (+)-21b:



(+)-**21b**
72% e.e.

(+)-**18y**
48% yield
72% e.e.

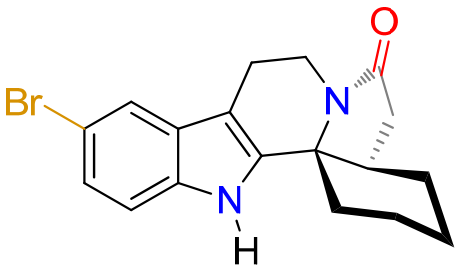
To a solution of (+)-**21b** (72% e.e., 54 mg, 0.136 mmol, 1 equivalent) in anhydrous methanol (15 mL) were added magnesium turnings (108 mg, 4.46 mmol). The solution was heated to 50 C before cooling to room temperature and stirring for 40 minutes. The mixture was then brought to reflux for 3 hours before cooling to room temperature and pouring onto 2M aqueous HCl solution (20 mL). The mixture was extracted with diethyl ether 3 × 20 mL) and the

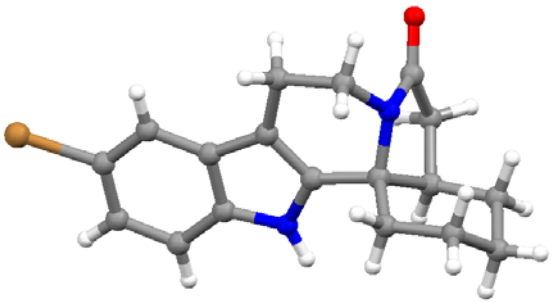
combined organic layers dried over sodium sulphate. The solvent was removed in vacuo aaand the residue purified by chromatography on silica gel eluting with ethyl acetate to yield (+)-**18y** (17 mg, 48%).

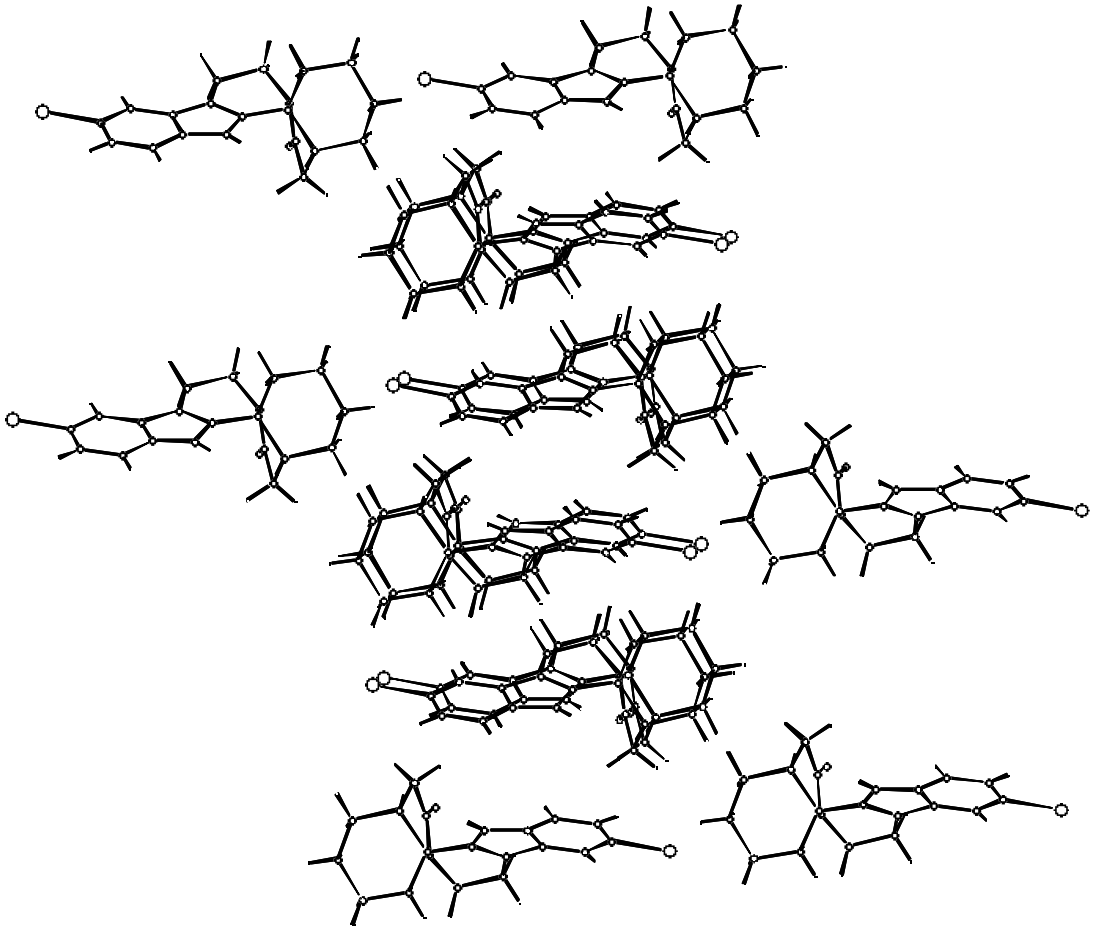
The spectroscopic data were identical to the one collected previously.

72% e.e. (Chiralcel OD, 90:10 hexane/isopropanol, 1.5 mL/min, 220 nm, major t_R = 10.6 min, minor t_R = 13.9 min); $[\alpha]_D^{21}$ = + 176.7 (*c* 1.25, $CHCl_3$).

The HPLC retention times as well as the specific rotation of this sample confirmed the (*R*)-configuration at the quaternary centre, hence confirming the (1*R*, 11b*S*) configuration of (+)-**21b**.


Br
O
N
N
H





Crystal data and structure refinement for (+)-21j

Empirical formula	$C_{18}H_{19}BrN_2O$
Formula weight	359.27
Temperature	150 K
Wavelength	Mo *K*α radiation, λ = 0.71073 Å
Crystal system, space group	Monoclinic, *C*2
Unit cell dimensions	*a* = 18.7232 (4) Å
	b = 6.9539 (2) Å β = 120.2197 (13)°
	c = 14.1450 (4) Å
Volume	*V* = 1591.39 (8) Å^3
Z	4
Absorption coefficient	μ = 2.59 mm^{-1}
Crystal size	0.17 × 0.06 × 0.05 mm

Data collection

Area diffractometer	3391 independent reflections
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski	2808 reflections with $I > 2.0\sigma(I)$
T_{min} = 0.80, T_{max} = 0.89	R_{int} = 0.068
7601 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039	No H atoms present
$wR(F^2)$ = 0.081	$\Delta\rho_{max}$ = 0.70 e Å^{-3}
S = 0.93	$\Delta\rho_{min}$ = −1.07 e Å^{-3}
3391 reflections	Absolute structure: Flack (1983), 0

Friedel-pairs

200 parameters

Flack parameter: −0.030 (11)

1 restraint

Atomic coordinates (× 10^4) and equivalent isotropic Displacement parameters (A^2 × 10^3) for (+)-21j

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	0.54156 (2)	0.17418 (13)	0.90615 (3)	0.0346
C2	0.49056 (19)	0.2133 (5)	0.7522 (3)	0.0225
C3	0.5049 (2)	0.3891 (5)	0.7156 (3)	0.0263
C4	0.4657 (2)	0.4278 (5)	0.6047 (3)	0.0262
C5	0.4124 (2)	0.2886 (5)	0.5327 (3)	0.0212
N6	0.36376 (19)	0.2918 (4)	0.4200 (3)	0.0223
C7	0.3211 (2)	0.1207 (5)	0.3862 (3)	0.0191
C8	0.3403 (2)	0.0051 (5)	0.4749 (3)	0.0187
C9	0.3998 (2)	0.1112 (5)	0.5702 (3)	0.0183
C10	0.4400 (2)	0.0734 (5)	0.6827 (3)	0.0219
C11	0.3018 (2)	−0.1877 (5)	0.4672 (3)	0.0237
C12	0.2318 (2)	−0.2248 (5)	0.3499 (3)	0.0235
N13	0.25123 (18)	−0.1432 (4)	0.2708 (2)	0.0184
C14	0.2592 (2)	0.0691 (5)	0.2696 (3)	0.0181
C15	0.2929 (2)	0.0929 (5)	0.1890 (3)	0.0212
C16	0.3487 (2)	−0.0830 (5)	0.2168 (3)	0.0231
C17	0.3079 (3)	−0.2327 (6)	0.2523 (4)	0.0215
O18	0.3257 (2)	−0.4046 (4)	0.2678 (3)	0.0311

C19	0.17817 (17)	0.1764 (8)	0.2337 (2)	0.0238
C20	0.1126 (2)	0.1505 (8)	0.1131 (3)	0.0317
C21	0.1482 (2)	0.2061 (7)	0.0413 (3)	0.0328
C1	0.2230 (2)	0.0820 (5)	0.0684 (3)	0.0258

Bond lengths (Å) and angles (°) for (+)-21j

Bond lengths (Å)

Br1—C2	1.907 (3)	C11—C12	1.532 (5)
C2—C3	1.405 (5)	C12—N13	1.455 (4)
C2—C10	1.368 (5)	N13—C14	1.484 (4)
C3—C4	1.383 (5)	N13—C17	1.364 (5)
C4—C5	1.395 (5)	C14—C15	1.566 (5)
C5—N6	1.383 (5)	C14—C19	1.530 (5)
C5—C9	1.408 (5)	C15—C16	1.525 (5)
N6—C7	1.377 (4)	C15—C1	1.543 (5)
C7—C8	1.377 (5)	C16—C17	1.518 (5)
C7—C14	1.506 (5)	C17—O18	1.230 (4)
C8—C9	1.445 (5)	C19—C20	1.530 (4)
C8—C11	1.500 (5)	C20—C21	1.519 (5)
C9—C10	1.401 (5)	C21—C1	1.521 (5)

Angles (°)

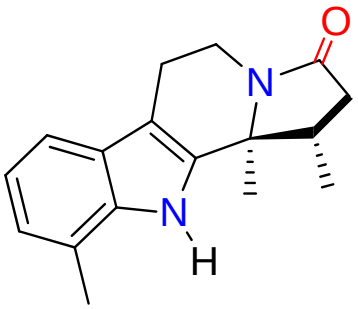
Br1—C2—C3	117.8 (3)	C12—N13—C14	117.5 (3)
Br1—C2—C10	119.1 (3)	C12—N13—C17	119.3 (3)
C3—C2—C10	123.1 (3)	C14—N13—C17	111.1 (3)
C2—C3—C4	119.7 (3)	C7—C14—N13	104.5 (3)
C3—C4—C5	118.0 (3)	C7—C14—C15	113.7 (3)
C4—C5—N6	130.1 (3)	N13—C14—C15	101.1 (3)
C4—C5—C9	121.8 (3)	C7—C14—C19	109.6 (3)
N6—C5—C9	108.1 (3)	N13—C14—C19	113.6 (3)

C5—N6—C7	108.4 (3)	C15—C14—C19	113.8 (3)
N6—C7—C8	110.4 (3)	C14—C15—C16	101.6 (3)
N6—C7—C14	125.3 (3)	C14—C15—C1	111.8 (3)
C8—C7—C14	124.3 (3)	C16—C15—C1	109.6 (3)
C7—C8—C9	106.1 (3)	C15—C16—C17	104.1 (3)
C7—C8—C11	124.1 (3)	C16—C17—N13	108.6 (3)
C9—C8—C11	129.9 (3)	C16—C17—O18	126.1 (4)
C8—C9—C5	107.0 (3)	N13—C17—O18	125.2 (4)
C8—C9—C10	133.2 (3)	C14—C19—C20	114.7 (3)
C5—C9—C10	119.7 (3)	C19—C20—C21	109.8 (3)
C9—C10—C2	117.7 (3)	C20—C21—C1	110.2 (3)
C8—C11—C12	110.3 (3)	C15—C1—C21	114.3 (3)
C11—C12—N13	111.0 (3)		

Hydrogen bonds for (+)-21j [Å and º]

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H61···O18^{i}	0.87	1.98	2.838 (6)	171

Symmetry code: (i) *x*, *y*+1, *z*.


O
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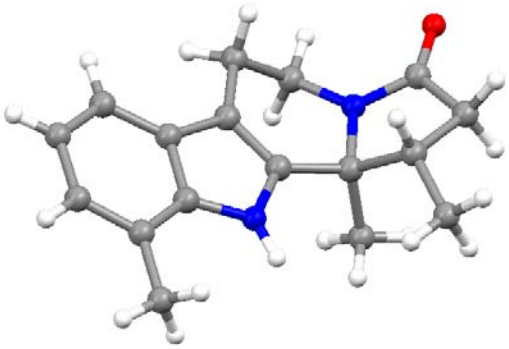

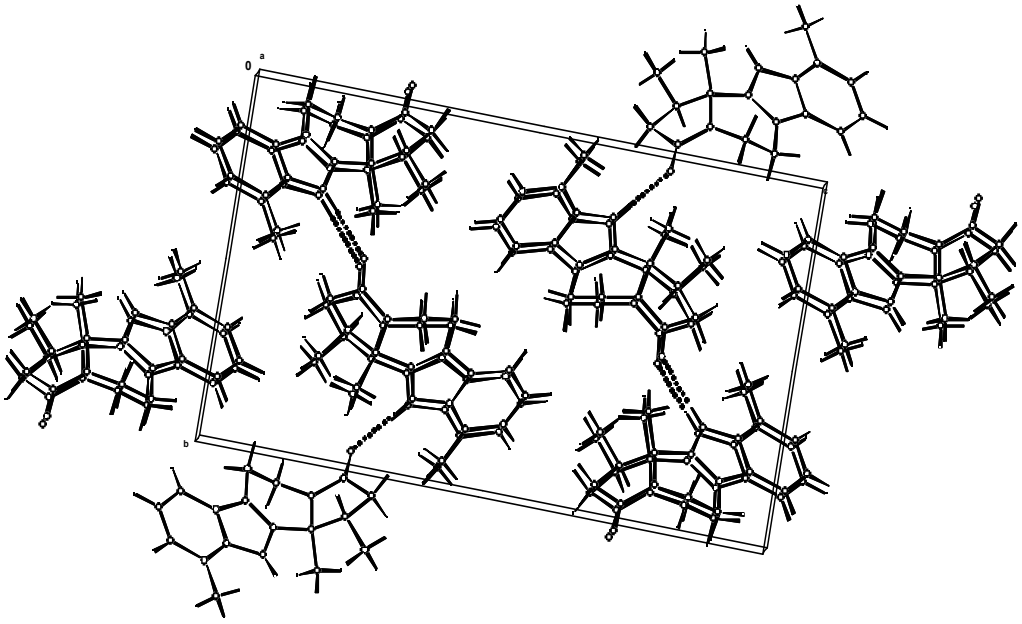

Crystal data and structure refinement for (±)-21k

Empirical formula	$C_{17}H_{20}N_2O$
Formula weight	268.36
Temperature	150 K
Wavelength	Mo *K*α radiation, λ = 0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	*a* = 5.7927 (1) Å
	b = 12.1783 (2) Å β = 94.4916 (8)°
	c = 20.5935 (5) Å
Volume	1448.31 (5) Å^3
Z	4
Absorption coefficient	μ = 0.08 mm^{-1}
Crystal size	0.20 × 0.18 × 0.05 mm
Data collection	
Area diffractometer	3315 independent reflections
Absorption correction: Multi-scan	
DENZO/*SCALEPACK* (Otwinowski	2036 reflections with $I > 2.0\sigma(I)$
T_{min} = 0.94, T_{max} = 1.00	R_{int} = 0.041
24984 measured reflections	
Refinement	
$R[F^2 > 2\sigma(F^2)]$ = 0.055	0 restraints
$wR(F^2)$ = 0.189	No H atoms present
S = 0.99	$\Delta\rho_{max}$ = 0.45 e Å^{-3}
3315 reflections	$\Delta\rho_{min}$ = −0.43 e Å^{-3}

181 parameters

Atomic coordinates (× 10^4) and equivalent isotropic Displacement parameters (A^2 × 10^3) for (±)-21k

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	1.1138 (3)	0.45198 (14)	0.23180 (9)	0.0345
C2	0.9784 (4)	0.52985 (19)	0.23688 (12)	0.0289
N3	0.9728 (3)	0.59531 (16)	0.28904 (10)	0.0281
C4	1.1118 (4)	0.5776 (2)	0.35052 (12)	0.0325
C5	0.9529 (5)	0.5593 (2)	0.40517 (13)	0.0372
C6	0.7670 (4)	0.6455 (2)	0.40027 (12)	0.0307
C7	0.7077 (4)	0.70408 (18)	0.34494 (11)	0.0267
C8	0.8047 (4)	0.68664 (19)	0.28007 (11)	0.0265
C9	0.9248 (4)	0.7902 (2)	0.25753 (13)	0.0327
C10	0.6324 (4)	0.6378 (2)	0.22569 (11)	0.0286
C11	0.7922 (4)	0.5675 (2)	0.18683 (12)	0.0313
C12	0.4848 (4)	0.7187 (2)	0.18452 (13)	0.0381
N13	0.5468 (3)	0.78416 (17)	0.35712 (9)	0.0279
C14	0.4964 (4)	0.7754 (2)	0.42158 (11)	0.0293
C15	0.6315 (4)	0.6881 (2)	0.44966 (12)	0.0323
C16	0.6077 (5)	0.6590 (3)	0.51490 (13)	0.0440
C17	0.4493 (5)	0.7158 (3)	0.54896 (13)	0.0484
C18	0.3179 (5)	0.8016 (3)	0.51951 (13)	0.0456
C19	0.3379 (5)	0.8344 (2)	0.45567 (12)	0.0356
C20	0.1948 (6)	0.9264 (3)	0.42557(14)	0.0510

Bond lengths (Å) and angles (°) for (±)-21k

Bond lengths (Å)

O1—C2	1.240 (3)	C8—C10	1.559 (3)
C2—N3	1.340 (3)	C10—C11	1.532 (3)
C2—C11	1.504 (3)	C10—C12	1.519 (3)
N3—C4	1.462 (3)	N13—C14	1.385 (3)
N3—C8	1.480 (3)	C14—C15	1.416 (3)
C4—C5	1.525 (4)	C14—C1	91.398 (3)
C5—C6	1.502 (3)	C15—C16	1.407 (4)
C6—C7	1.365 (3)	C16—C17	1.384 (4)
C6—C15	1.430 (3)	C17—C18	1.402 (4)
C7—C8	1.505 (3)	C18—C19	1.388 (4)
C7—N13	1.385 (3)	C19—C20	1.498 (4)
C8—C9	1.530 (3)		

Angles (°)

O1—C2—N3	125.3 (2)	C9—C8—C10	112.2 (2)
O1—C2—C11	126.8 (2)	C8—C10—C11	102.08 (18)
N3—C2—C11	107.9 (2)	C8—C10—C12	117.0 (2)
C2—N3—C4	124.1 (2)	C11—C10—C12	114.1 (2)
C2—N3—C8	113.82 (19)	C10—C11—C2	104.04 (19)
C4—N3—C8	122.08 (19)	C7—N13—C14	108.31 (19)
N3—C4—C5	109.7 (2)	N13—C14—C15	107.3 (2)
C4—C5—C6	108.6 (2)	N13—C14—C19	129.6 (2)
C5—C6—C7	123.6 (2)	C15—C14—C19	123.0 (2)

C5—C6—C15	129.5 (2)	C6—C15—C14	107.4 (2)
C7—C6—C15	106.7 (2)	C6—C15—C16	133.5 (2)
C6—C7—C8	125.5 (2)	C14—C15—C16	119.1 (2)
C6—C7—N13	110.2 (2)	C15—C16—C17	118.5 (3)
C8—C7—N13	124.3 (2)	C16—C17—C18	120.9 (3)
C7—C8—N3	106.45 (18)	C17—C18—C19	122.8 (3)
C7—C8—C9	111.31 (19)	C14—C19—C18	115.7 (2)
N3—C8—C9	110.32 (18)	C14—C19—C20	122.7 (2)
C7—C8—C10	115.39 (19)	C18—C19—C20	121.5 (2)
N3—C8—C10	100.42 (18)		

Hydrogen bonds for (±)-21k [Å, º]

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4—H41···C14^{i}	0.99	2.57	3.521 (4)	161
C12—H122···O1^{ii}	0.97	2.55	3.395 (4)	146
N13—H131···O1^{ii}	0.88	1.97	2.851 (4)	178

Symmetry codes: (i) x+1, y, z; (ii) −x+3/2, y+1/2, −z+1/2